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Part A: The Application of Fluorescence Resonance Energy Transfer to Reaction Discovery, Part B: The Stereodefined Synthesis of Tetrasubstituted Olefins

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Part A. The Application of Fluorescence Resonance Energy Transfer to Reaction Discovery

Part B. The Stereodefined Synthesis of Tetrasubstituted Olefins

by

Alison B. Flynn

A thesis submitted to the School of Graduate Studies and Research

In partial fulfillment of the requirements for the degree of
Philosophiae Doctor in Chemistry

Ottawa-Carleton Chemistry Institute
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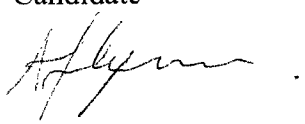
June 2007

Candidate



Alison B. Flynn

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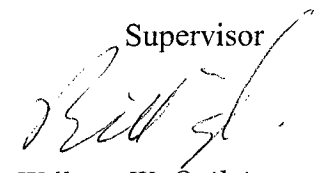

Dr. William W. Ogilvie

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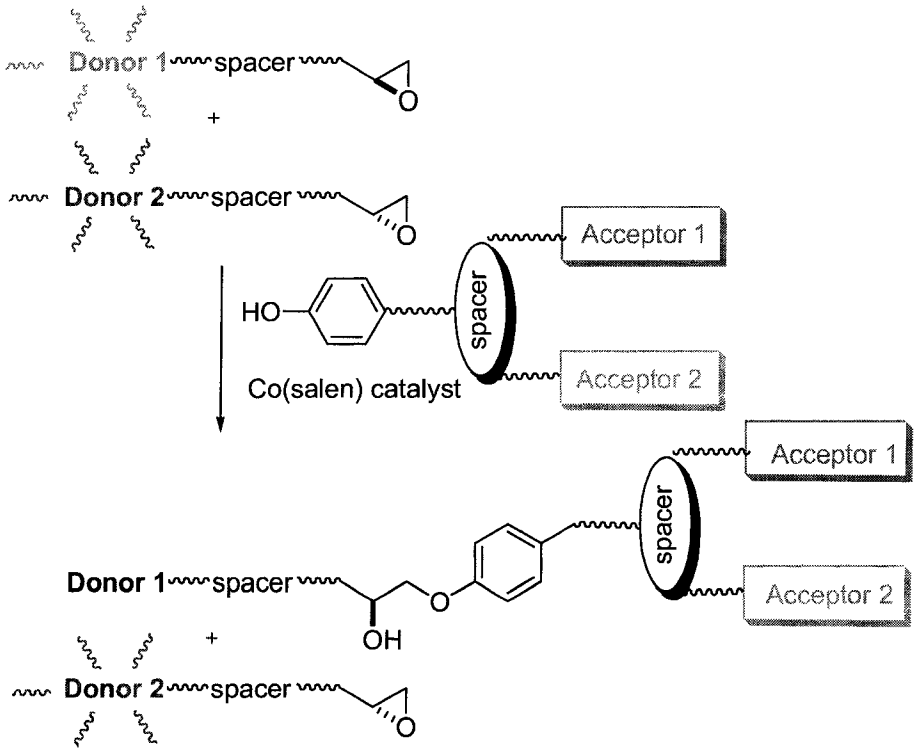
List of Abbreviations

Ac	acetyl
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPE	1,2-bis(diphenylphosphino)ethane
DPPP	1,3-bis(diphenylphosphino)propane
DPPB	1,4-bis(diphenylphosphino)butane
BBN	borabicyclo[3.3.1]nonane
Bu	butyl
CSA	camphorsulfonic acid
CI	chemical ionization
Cy	cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	dibenzylideneacetone
DCM	dichloromethane
DIPEA	diisopropylethylamine or Hünig's base
EI	electron impact ionization
ee	enantiomeric excess
EtOH	ethanol
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Et	ethyl
GC	gas chromatography
HPLC	high performance liquid chromatography
HTS	high-throughput screening
HOBT	1-hydroxybenzotriazole
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
NMM	*N*-methylmorpholine
NR	no reaction
NOE	nuclear Overhauser effect

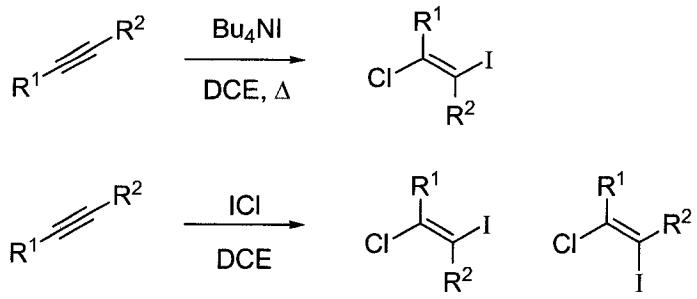
NOESY	nuclear Overhauser effect spectroscopy
TsOH	*para*-toluenesulfonic acid
Ph	phenyl
pin	pinacol
PrOH	propanol
Pr	propyl
r.t.	room temperature
SDS	sodium dodecyl sulfate
SM	starting material
Temp.	temperature
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl
TEBA	triethylbenzylammonium chloride
TFA	trifluoroacetic acid
Tf	trifluoromethansulfonyl
TMS	trimethylsilyl

Abstract

In part A, the development of methodology for enantioselective reaction monitoring using Fluorescence Resonance Energy Transfer (FRET) is described. The syntheses of enantiomeric epoxides bearing different fluorescent donors and a phenol that bore fluorescence acceptor were explored.

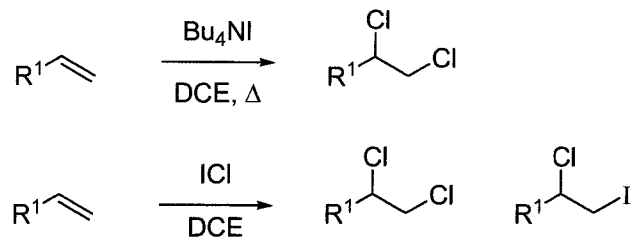


Part B describes the stereodefined synthesis of tetrasubstituted olefins. 2-Alkynyl esters were selectively converted to *E*-β-chloro-α-iodo-α,β-unsaturated esters by exposure to Bu_4NI in refluxing dichloroethane. These products were produced cleanly, regio- and stereoselectively, and in high yields. The treatment of the same substrates with ICl produced mixtures of isomers. Mechanistic studies indicated that ICl was the most plausible intermediate and that a Bu_4NI-ICl complex was likely responsible for the high selectivity observed in the Bu_4NI/DCE system.

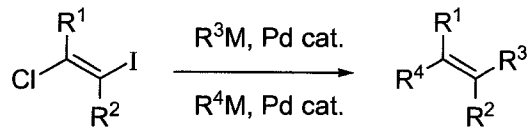


R^1 = H, alkyl, aryl
R^2 = ester, amide, alkyl

The Bu_4NI/DCE system was shown to be selective for the chlorination of alkenes. The treatment of the same alkenes with ICl returned a mixture of chlorinated and iodochlorinated products. In addition, the Bu_4NI/DCE system was chemoselective in substrates bearing both aromatic and olefinic moieties, reacting at the alkenyl functionality exclusively. Exposure of these substrates to ICl produced a mixture of products.



The halogenated olefins produced in the initial study were employed as olefin templates for the formation of tetrasubstituted olefins. Regioselective and stereospecific palladium-catalyzed cross-coupling reactions were employed to incorporate a wide variety of substituents into the highly congested olefins, affording single isomer products in good yields.



R^3 = alkynyl, aryl, vinyl
R^4 = alkynyl, aryl, vinyl, alkyl

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and I've learned that it pays to be that organized in this profession—you have saved me much time in the writing of my thesis! Ami, I loved having you as a bench mate and I'm lucky to have met you. Without a doubt, you are the kindest and most generous person that I've ever met. Thanks also to our undergrads Myra, Joe #2, Liz, and John, who are now all pursuing graduate studies in chemistry.

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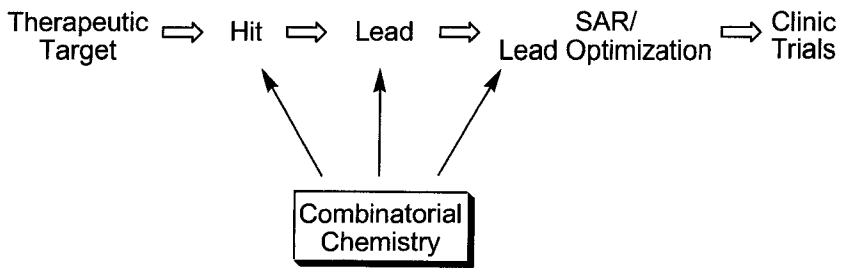
A. The Application of Fluorescence Resonance Energy Transfer to Reaction Discovery

CHAPTER 1. INTRODUCTION

1.1 Combinatorial chemistry

The basic goal of combinatorial chemistry is to generate a large number of compounds very quickly. The use of combinatorial chemistry can accelerate the drug discovery process in several ways (Figure 1), including the identification of a hit or lead compound and lead optimization steps. Combinatorial approaches have also been employed in material sciences to facilitate the identification of new superconducting ceramics and to identify materials with desirable structure or electronic properties.[1]

Figure 1. Combinatorial chemistry benefits key steps in the drug discovery process.



Orthodox chemistry involves the individual synthesis of chemical compounds in a fully purified and characterized state (Figure 2). The testing of compounds is straightforward because the identity of each compound is known and therefore compounds showing desired properties can be immediately analyzed further. The synthesis process is time-consuming, however, and it is futile to have this level of purification if the compound proves to be inactive against the chosen target.

[1] (a) Dagani, R. *Chem. Eng. News* **1999**, *77*, 51. (b) Xiang, X. D.; Sun, X.; Briceno, G.; Lou, Y.; Wang, K.-A.; Chang, H.; Wallace-Freedman, W. G.; Chen, S.-W.; Schultz, P. G. *Science* **1995**, *268*, 1738.

Figure 2. Orthodox synthesis of a library

The synthetic process can be accelerated by using combinatorial chemistry methods. Two main strategies, split-and-pool synthesis and parallel synthesis, are employed to generate large libraries of compounds, whether the goal of the combinatorial chemistry process is to identify a potential drug or to optimize a lead. The compounds or mixtures generated are tested, and those that show desired properties are identified and pursued.

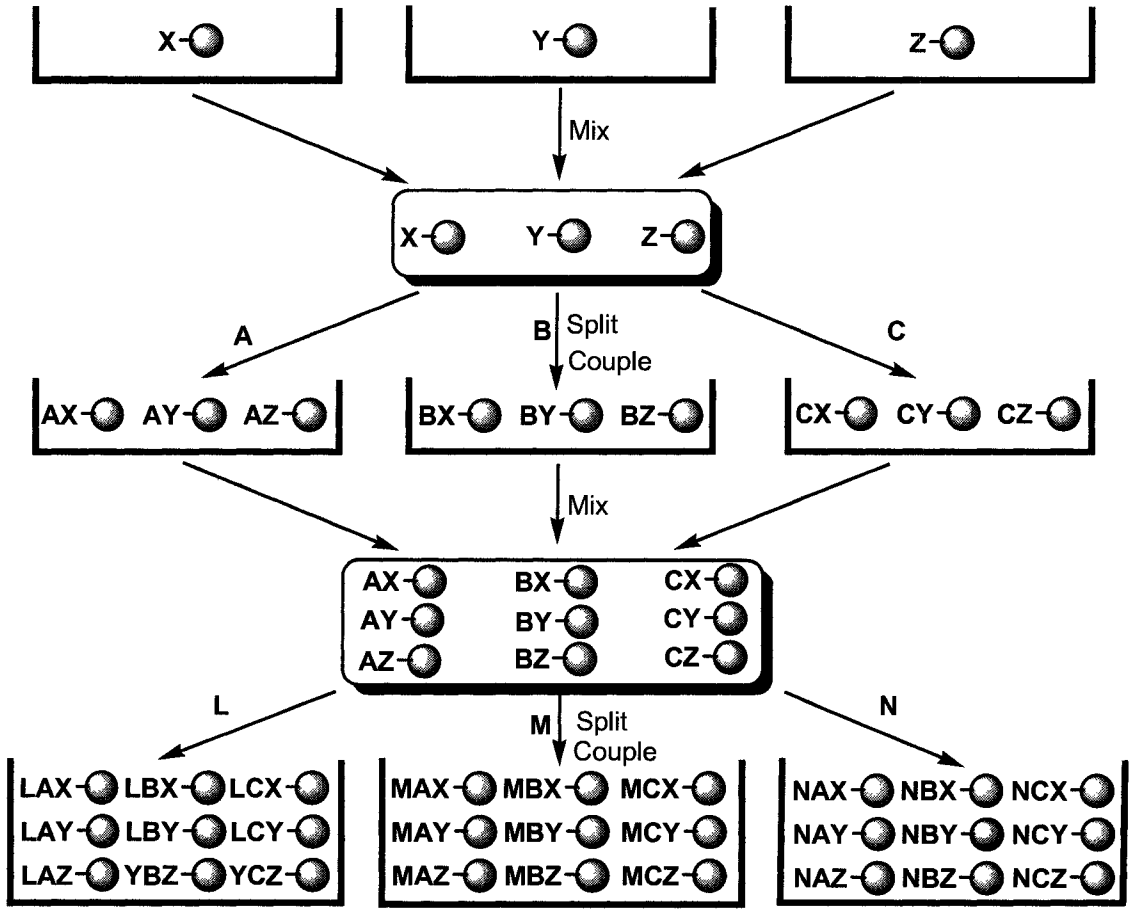
In split and pool synthesis, mixtures of compounds are deliberately generated using solid phase synthesis. An enormous number of compounds can be quickly generated and tested using this method. Mixtures that do not show desired properties can be immediately set aside. This carries with it the disadvantage that active compounds must be identified and isolated from mixtures that show activity. This separation can be extremely difficult.

Split-pool (or mix and split) synthesis is a simple and commonly used technique that takes advantage of solid-phase synthetic methods. The technique itself is iterative: split, couple, pool, and repeat (Figure 3). For example, compounds **X**, **Y**, and **Z** (amino acids, for example) are bound to polymer beads in separate reaction flasks.[2] The beads are mixed together into a single vessel, and the homogenized mixture is split equally into three separate reaction vessels. The result is three new reaction vessels that each contain equal mixtures of polymer-bound **X**, **Y**, *and* **Z**. To the first of the three vessels is added reactant **A**, to the second, **B**, and to the third, **C**, generating three separate mixtures of

[2] The majority of combinatorial syntheses use solid phase techniques. See: (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; Wiley-Interscience: New York, 2000.

beads and a total of nine compounds. The contents of each reaction vessel are again mixed, or pooled, together into a single vessel to generate a homogeneous mixture of the beads. This mixture is split into three new vessels that now each contain all nine compounds. To the first vessel is added reactant **L**, to the second, **M**, and to the third, **N**. By doing this, nine distinct compounds are generated in each reaction vessel, for a total of twenty seven members in what is now called a library. The compounds can be generated in only three chemical steps and from only nine different building blocks in this case.

Figure 3. Split-pool synthesis of a 27-member library



Following this process, each mixture would be tested for activity. Only those vessels that showed desired activity would be further investigated; there would be no need to identify the inactive compounds. A major issue at this stage is the identification of an active compound from the mixtures present in the vessel. Compound separation is

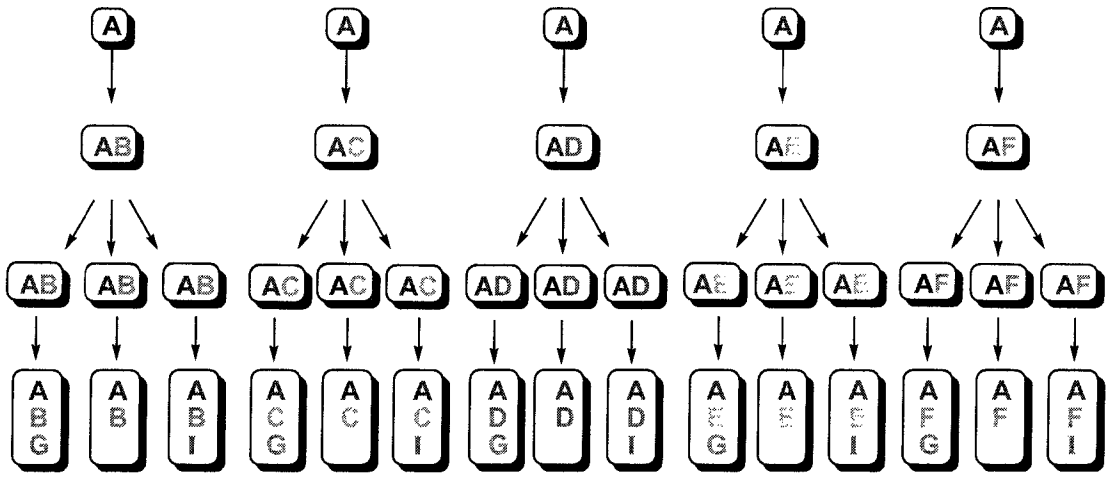
typically not easy, and re-synthesis of all the members of the mixture can be time-consuming. For this reason, split-pool methods are less-frequently employed in industry in which parallel synthesis is normally the preferred method.

In parallel synthesis, a single compound is produced in each reaction flask, either by a manual or an automated technique. The reactions are commonly performed in reaction wells in a grid-like fashion but can also be performed in micro-compartments in which the interchange of intermediates is prevented during the process. Reactions can be performed in solution or on solid phase.[3] Reactants (**B–F**) are added in grid-like fashion to different reaction vessels that each contain a common starting material **A** (Figure 4). Each vessel is processed or purified in parallel. The product of each vessel is split again and to each new vessel in introduced a new reactant. For example, a solution of **AB** is split into three vessels that each contain only starting material **AB**. To the first vessel is added **G**, to the second, **H**, and to the third, **I**. This process is repeated for **AC–AF**. In the end, many different compounds are obtained, one per reaction flask or well (fifteen in the case shown).[2b]

Parallel synthesis is much more efficient than the orthodox method in which each compound must be synthesized, purified, and characterized one at a time. The major difference between this method and the split-and-pool method is that single products of known identity are generated in each reaction flask. The products from each vessel are never pooled together. Parallel synthesis is the principal method used during structure-activity relationship (SAR) analysis and lead compound optimization, and is overtaking mixed synthesis protocols in other stages of drug development as expectations for high compound purity grow.

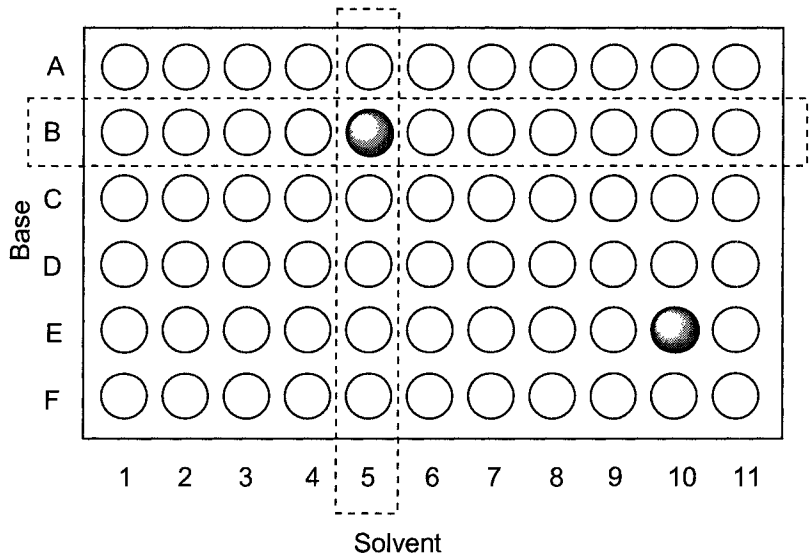
[3] Pirrung, M. C. *Chem. Rev.* **1997**, *97*, 473.

Figure 4. Parallel synthesis of a fifteen-member library



Chemists have taken advantage of these techniques for high-throughput *reaction* discovery and development. Parallel synthesis in well-plates is frequently used to examine a selection of reaction variables simultaneously (Figure 5). For example, one variable (a base) could be changed along a row of the well-plate, while another component (the solvent) could be varied along the columns. This would allow the identification of optimal base "B" and solvent "5." It could also enable the identification of combinations such as base "E" and solvent "10," a combination that otherwise might not have been attempted. High-throughput methods have enabled chemists to identify the most advantageous reaction conditions for a variety of different processes.

Figure 5. Application of high-throughput techniques to reaction discovery



1.2 High throughput screening

Combinatorial chemistry may seem to offer a solution to synthetic difficulties and time constraints encountered by chemists; however it is not only the synthesis of compounds that must be efficient: a bottle neck must also be avoided at the testing stage, in which massive amounts of data are generated from the enormous libraries that have been created. This is the point at which high-throughput screening (HTS) comes into play. In fact, HTS was developed before combinatorial synthesis, and was one of the pressures to develop faster synthetic techniques. A typical goal for HTS is to analyze 500 to 1000 compounds per day. Many techniques exist and generally employ a combination of robotics, microplates (96-, 384- and more well-plate formats) and computers for data processing.

These HTS methods have recently been adapted to the problem of monitoring the progress of *reactions*.[4] Common analysis methods such as gas chromatography, high performance liquid chromatography and nuclear magnetic resonance spectrometry have been adapted to this purpose. In addition, many techniques commonly used in biology and biochemistry have been adapted to the screening of organic reagents and catalysts.

[4] Reetz, M. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1335.

Fewer techniques exist for the identification of an *enantioselective* reaction and methods for the *quantification* of enantioselective reactions are rare. The selection of the automated technique is critical, and is highly dependent on the type of compounds being generated. Constant monitoring of the reaction is desirable as opposed to the testing of products after a pre-determined time. This would allow the yield of the target to be maximized and the reaction to be halted before side products begin to form in significant quantities.

Herein the focus is placed on high-throughput screening (HTS) techniques for determining *enantioselectivity* and for quantitative reaction discovery.[5] Our research is concentrated in this area, owing to the need for the development of more general *enantioselective* HTS techniques.

1.2.1 Chromatography

Thin-layer chromatography (TLC) has been investigated because of its potential as a high-throughput analysis tool. This is not surprising considering TLC occupies a front-line position in the daily life an organic chemist due to the simplicity, reliability, and speed of the technique. The high-throughput versions of TLC offer the same advantages. Automated multichannel pipetters can be used, and compounds can be detected visually with a UV lamp, by mass spectroscopy, or using visualization stains such as ninhydrin,[6] bromophenol blue,[7] and nitrophenyl isothiocyanate-*O*-trityl.[8] This method cannot be used for chiral compounds and it remains challenging and often impractical to quantify the results.

Perhaps the two most commonly employed techniques for the enantioselective HTS of organic compounds are gas chromatography (GC) and high-performance liquid chromatography (HPLC). These methods are popular because of their reliability and accuracy, but the time required for the analysis of each compound can be quite high for library screening. GC has nevertheless been used by numerous researchers, such as

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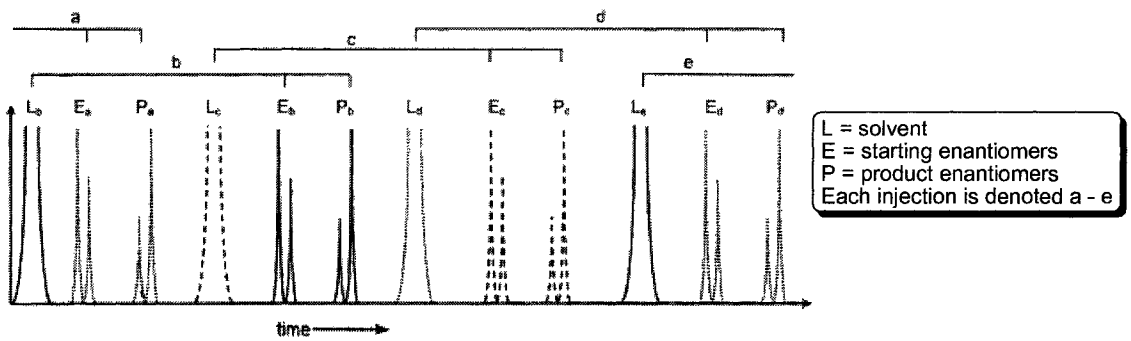
[5] Charbonneau, V.; Ogilvie, W. W. *Mini-Rev. Org. Chem.* **2006**, *4*, 313.
[6] Brown, W. D.; Green, S. *Anal. Biochem.* **1970**, *34*, 593.
[7] Flegel, M.; Sheppard, R. C. *J. Chem. Soc. Chem. Comm.* **1990**, 536.
[8] Chu, S. S.; Reich, S. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1053.

Gennari,[9] Liskamp,[10] Burgess,[11] Wolf,[12] and Jacobsen,[13] to analyze libraries generated by parallel synthesis. Although the fifteen minutes typically required per sample precludes the designation of these analyses as truly high-throughput, a high number of samples were efficiently analyzed in each report. Reetz described a significant contribution to enantioselective reaction monitoring by GC techniques in 2001.[14] Two chiral CG instruments were connected to a sample manager (autosampler) and to a computer. Injections were timed so that the chromatograms became interlocked, and injections could be performed one block at a time, or continuously (Figure 6). The sample manager was able to inject samples from 96 or 384 microtiter plates; therefore, over 3000 samples could be handled without manual intervention. Using this system, approximately 700 samples could be run each day. The data acquired was organized in an Excel® spreadsheet and could be presented in table or microtiter formats.

Figure 6. Schematic representation of interlocked chromatograms[14]



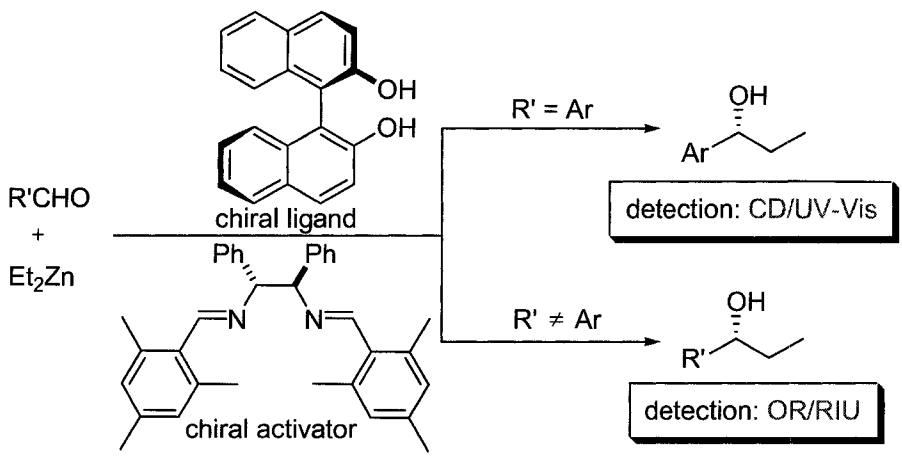
HPLC is a relatively low-throughput process, as each sample analysis can require periods of ten to forty-five minutes, however, enantioselectivity can usually be quantified. Analogous high-throughput methods are very desirable. In 1999, the Mikami group proposed a method to speed up processing time, in which an achiral column with a

[9] (a) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. (b) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 916. (c) Chataigner, I.; Gennari, C.; Ongeri, S.; Piarulli, U.; Ceccarelli, S. *Chem. Eur. J.* **2001**, *7*, 2628. (d) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, *2001*, 803.
[10] Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 1750.
[11] Burgess, K.; Porte, A. M. *Tetrahedron Asymm.* **1998**, *9*, 2465.
[12] Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727.
[13] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
[14] Reetz, M. T.; Kuhling, K. M.; Wilensek, S.; Husmann, H.; Hausig, U. W.; Hermes, M. *Cat. Today* **2001**, *67*, 389.

circular dichroism (CD) or UV-VIS detection system was used to monitor the asymmetric reduction of aldehydes with chiral zinc catalysts (Scheme 1).[15] Because of the detection system used, only molecules possessing a chromophore could be detected.

This Mikami report was based on previous work by Mason,[16] Salvadori[17] and Mannschreck[18] and has been employed by Reetz *et al.*[19] to monitor the asymmetric reduction of prochiral ketones with mutant reductases. Mikami subsequently published a method in which an optical rotation (OR) and refractive index unit (RIU) replaced the CD/UV-VIS detector, enabling the monitoring of simple aliphatic compounds (Scheme 1).[20]

Scheme 1. HTS-screening of the asymmetric reduction of aldehydes by chiral zinc catalysts

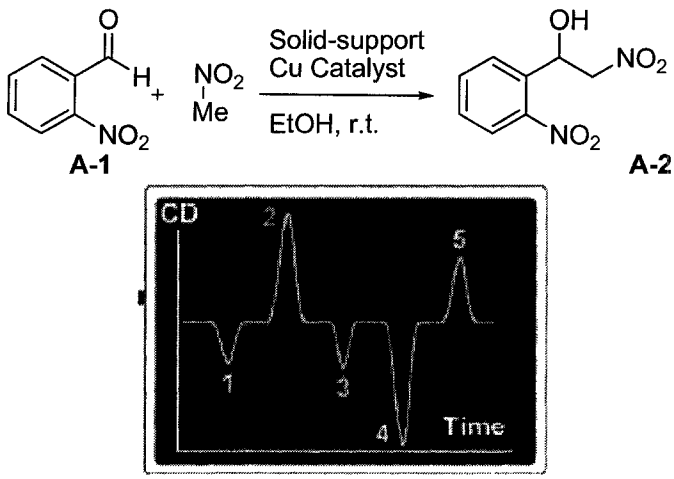


The direct monitoring of the asymmetric Henry reaction using circular dichroism (CD) was recently reported (Scheme 2).[21] Because any two enantiomers have exactly the opposite CD values at a given wavelength, the CD detector analyzed a single appropriate wavelength and recorded a positive or negative signal that corresponded to the amount of

[15] Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 497.
[16] Drake, A. F.; Gould, J. M.; Mason, S. F. *J. Chromatogr. A* **1980**, *202*, 239.
[17] Salvadori, P.; Bertucci, C.; Rosini, C. *Chirality* **1991**, *3*, 376.
[18] Mannschreck, A. *Trends Anal. Chem.* **1993**, *12*, 220.
[19] Reetz, M. T.; Kühling, K. M.; Hinrichs, H.; Deege, A. *Chirality* **2000**, *12*, 479.
[20] (a) Angelaud, R.; Matsumoto, Y.; Korenaga, T.; Kudo, K.; Senda, M.; Mikami, K. *Chirality* **2000**, *12*, 544. (b) Mikami, K.; Angelaud, R.; Ding, K.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K.; Senda, M. *Chem. Eur. J.* **2001**, *7*, 730.
[21] Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5978.

excess enantiomer. Peak intensity was proportional to the product of the yield (%) and the *ee* (%). The method could not distinguish between a reaction that was high-yielding and non-selective and one that was low-yielding but highly-selective, however it could identify highly successful catalysts that gave both high yields and selectivity.

Scheme 2. Catalysts for the asymmetric Henry reaction identified using CD[21]

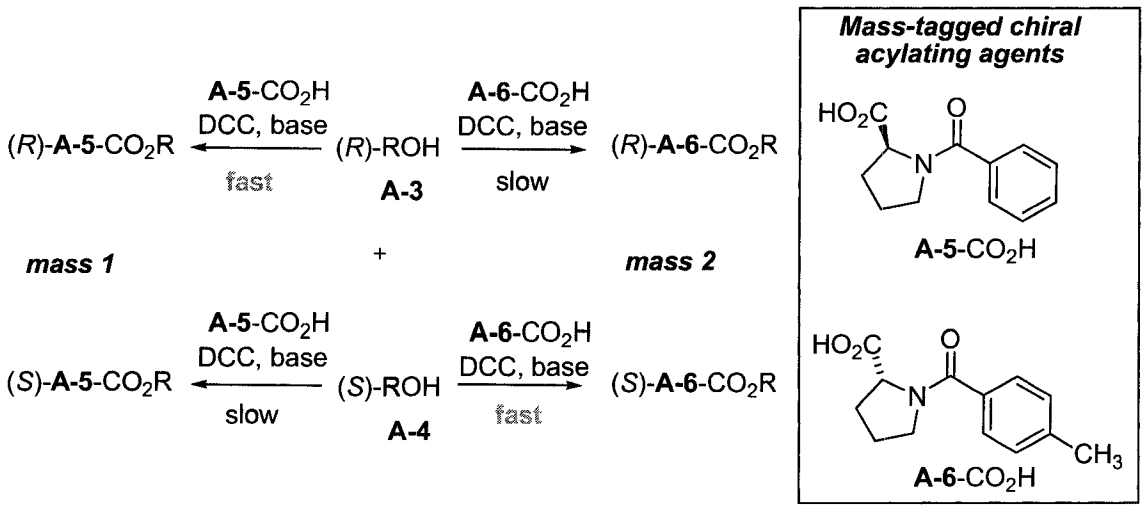


1.2.2 Mass spectroscopy

Mass spectrometry can be used in combinatorial chemistry, particularly when diastereomeric products are formed. Thus, Suizdak and Finn used automated electrospray ionization mass spectrometry (ESI-MS) to determine the enantiomeric excess of alcohols or amines in a mixture (Scheme 3).[22] Substrates containing an unknown enantiomeric ratio were treated with a pseudo-enantiomeric mixture of mass-tagged carboxylic acids in the presence of DCC and a base. The "mass-tag" was a small substituent – methyl in this example – located far from the chiral centre. One enantiomer reacted faster with the **A-5** carboxylic acid, while the other enantiomer reacted faster with the **A-6** carboxylic acid. The ratio of the pseudo-diastereomers was determined by mass spectroscopy and the ratio of the original enantiomers could then be calculated. While the samples could be analyzed quickly, the need for derivatization of the enantiomeric products significantly limited the utility and generality of the method.

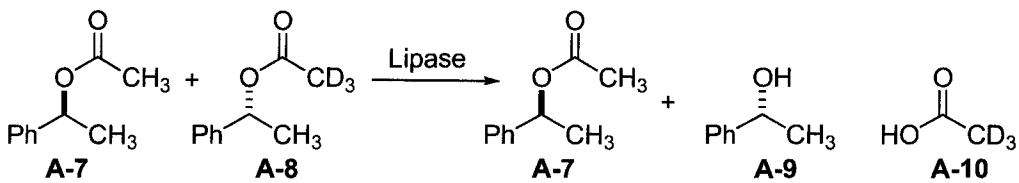
[22] Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1755.

Scheme 3. Reaction of chiral alcohols with mass-tagged enantiopure carboxylic acids



Mass spectroscopy can be used for the HTS of isotopically labeled substrates (Scheme 4).[23] Pseudo-enantiomeric esters, in which one substrate was deuterium-labeled (**A-8**), underwent enantioselective hydrolysis in the presence of a catalyst. Kinetic studies of the substrates were performed to ensure that no secondary kinetic isotope effect existed. Reetz showed that over one thousand enantioselective catalysts could be screened per day, giving exact *ee*-determinations, however the assay was limited to reactions of chiral or prochiral substrates and the reaction yield could not be directly calculated.

Scheme 4. Isotopically labeled substrates used for kinetic resolution reaction monitoring



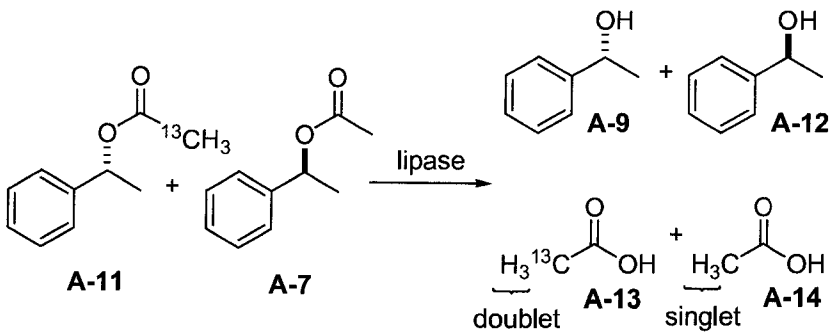
Mass spectrometry is a relatively laborious, equipment intensive and destructive process that frequently requires product derivatization prior to analysis. The technique does permit the direct analysis of reaction mixture composition and enables precise structure identification.

[23] Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stöckigt, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 1758.

1.2.3 Nuclear Magnetic Resonance (NMR)

NMR, a chemist's best-friend, is routinely used for solution-phase chemistry and can even be used for on-bead reaction monitoring using some very creative NMR experiments and probes.[2] Enantioselective reaction-monitoring is more challenging, however. Various techniques have been investigated, including the derivatization of products using chiral reagents such as Mosher's ester, to prepare diastereomers which can be differentiated by NMR. The ^{13}C-labelling of one enantiomer has been investigated together with ^{1}H detection (Scheme 5).[24] The ^{13}C-labelled methyl protons would appear as a doublet, while the non-labelled methyl protons would be a singlet. This particular method works very well for testing reactions in which chiral alcohols or amines are present, since these can be easily acylated.

Scheme 5. ^{13}C-labeling enables differentiation of enantiomers in ^{1}H NMR spectra



These screening methods are very precise, but are still rather low-throughput, require relatively large quantities of sample, and typically require sample manipulation before analysis. The use of an autosampler or flow cells[25] can increase throughput, however large amount of products are required.

1.2.4 Infrared and colorimetric methods

James Morken reported that infrared thermography (IRT) could be used to measure the rates of reactions.[26] Solid-phase bound acylation catalysts (3150 distinct compounds)

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[24] Reetz, M. T.; Eipper, A.; Tielmann, P.; Mynott, R. *Adv. Synth. Catal.* **2002**, *344*, 1008.
[25] Hamper, B. C.; Snyderman, D. M.; Owen, T. J.; Scates, A. M.; Owsley, D. C.; Kesselring, A. S.; Chott, R. C. *J. Comb. Chem* **1999**, *1*, 140.
[26] Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267.

were generated by split-pool techniques. In this method, an IR camera was used to monitor the heat evolved by acylation reactions (Figure 7). The temperature change in the catalytic reaction was proportional to the product of the turnover frequency and the enthalpy of reaction ($\Delta T \propto$ turnover frequency $\times \Delta H_r°$). Thus, the most active catalysts caused the largest temperature changes.

Figure 7. IR thermographic images of acylation catalyst beads[26]

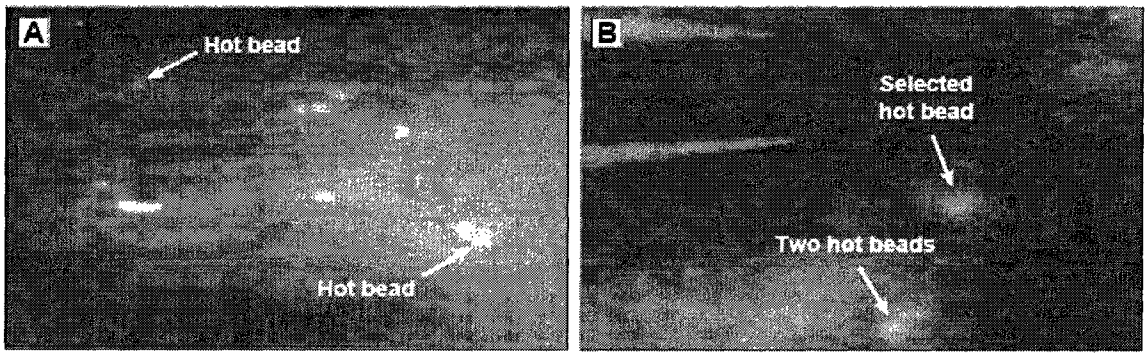
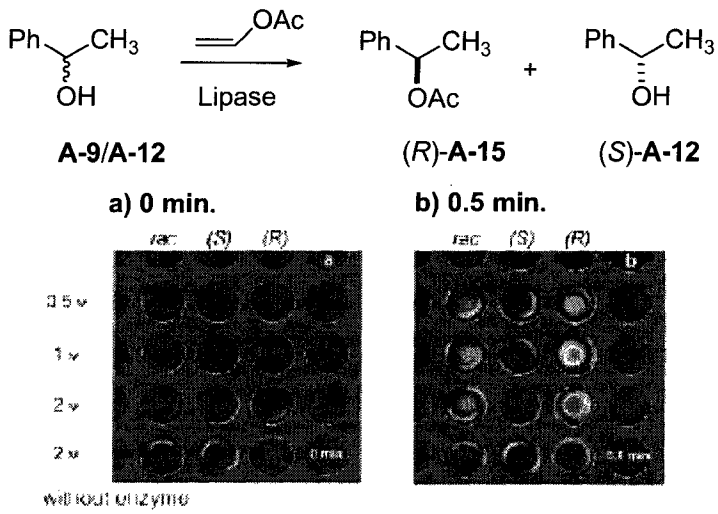


Fig. 2. (**A**) Infrared thermographic image of ~20 catalyst beads in the presence of ~3000 noncatalyst beads. Arrows indicate 2 of the 14 visible hot beads. (**B**) Closeup IR thermographic image of the trimeric catalyst library in the presence of acylation reagents, showing one hot bead being selected for decoding (tweezers in upper left).

Reetz expanded on the method by performing and screening the reactions in microtiter plates.[27] As a proof of the method, he examined both the lipase-catalyzed enantioselective acylation of 1-phenylethanol with vinyl acetate (Figure 8) and the enantioselective ring-opening hydrolysis of epoxides using Jacobsen's salen catalysts. Images were obtained with an IR camera at specified time intervals. Enantioselective reactions could be readily identified by the appearance of red spots which corresponded to a significant rise in temperature.

[27] Reetz, M. T.; Becker, M. H.; Kühling, K. M.; Holzwarth, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2647.

Figure 8. IR thermographic imaging of the enantioselective acylation of (±)-1-phenylethanol[27]



The feasibility of this method was shown by researchers at GlaxoSmithKline who used the technique to screen *Candida antarctica* lipase for substrate specificity using 96-well microtiter plates.[28] It was found that in many cases investigated, the results obtained by the IRT method correlated well with chiral GC or HPLC results. The major advantage is the non-invasiveness of the method, although the applicability must be tested for each catalyst system, and in some cases, alternative HTS methods are required.

Colorimetric methods can provide a rapid and reliable qualitative assay for certain specific systems.[29] Frequently encountered drawbacks include interference when strongly coloured reagents, such as organometallic catalysts, are employed and the usual need for derivatization of the products prior to analysis.

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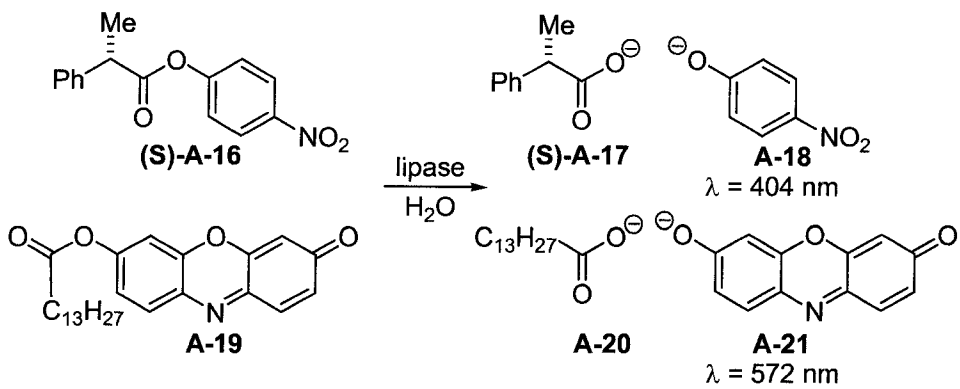
[28] Millot, N.; Borman, P.; Anson, M. S.; Campbell, I. B.; Macdonald, S. J. F.; Mahmoudian, M. *Org. Proc. Res. Dev.* **2002**, *6*, 463.

[29] (a) Weingarten, M. D.; Sekanina, K.; Still, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 9112. (b) Cooper, A. C.; McAlexander, L. H.; Lee, D. H.; Torres, M. T.; Crabtree, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 9971. (c) Lavastre, O.; Morken, J. P. *Angew. Chem. Int. Ed.* **1999**, *38*, 3163. (d) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (e) Banerjee, A.; Kaul, P.; Sharma, R.; Banerjee, U. C. *J. Biomol. Screening* **2003**, *8*, 559.

1.2.5 Biological methods

A variety of biological methods exist for enantioselective reaction monitoring, such as the quick-E test[30] and various enzymatic methods.[31] During the development of the quick-E test, an enantiopure solution of an ester such as **(*S*)-A-16** was hydrolyzed using various enzymes and the initial rates of hydrolysis were measured (Scheme 6). This procedure was repeated for the *R*-enantiomer. It was found that these initial rates of hydrolysis could not be used to estimate the enantiomeric ratio, E. This was due to the fact that when a racemic mixture of enantiomers was subjected to the reaction conditions, competition existed between the enantiomers for binding to the enzyme. This competition altered the rate of hydrolysis that was observed when only the pure compound was present in the solution. To account for this competition, the rate studies with the pure enantiomers were repeated, however this time a reference compound (**A-19**) was introduced to the reactions. This reference compound simulated competition for the enzyme. The initial rates of hydrolysis of both compounds were monitored and from these data the selectivity of the hydrolase for **(*S*)-A-16** over the reference compound (**A-19**) could be calculated. The experiment was repeated using **(*R*)-A-16**, and the ratio of these two selectivities reliably gave the enantiomeric ratio, E.

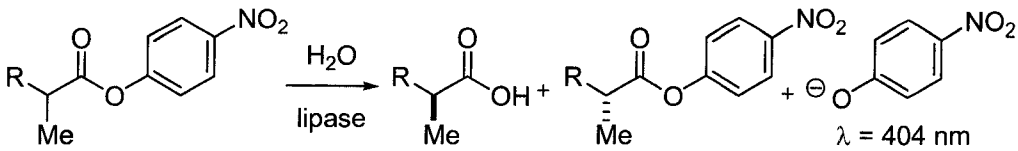
Scheme 6. The rates of hydrolysis of *enantiopure* esters were determined using the Quick-E test



[30] Janes, L. E.; Kazlauskas, R. J. *J. Org. Chem.* **1997**, *62*, 4560.
[31] (a) Baumann, M.; Stürmer, R.; Bornscheuer, U. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 4201. (b) Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206.

A lipase-catalyzed hydrolytic kinetic resolution of chiral *p*-nitrophenol esters was subsequently devised (Scheme 7).[32] In this method, the UV-Vis absorption of the *p*-nitrophenolate (404 nm) was monitored as a function of time. Of the 400–600 samples that were screened per day, the 3–5 hits identified by the initial "crude" technique were analyzed quantitatively by chiral GC. These methods can be quite efficient for the HTS of specific targets but have limited generality.

Scheme 7. Hydrolytic kinetic resolution of chiral *p*-nitrophenol esters



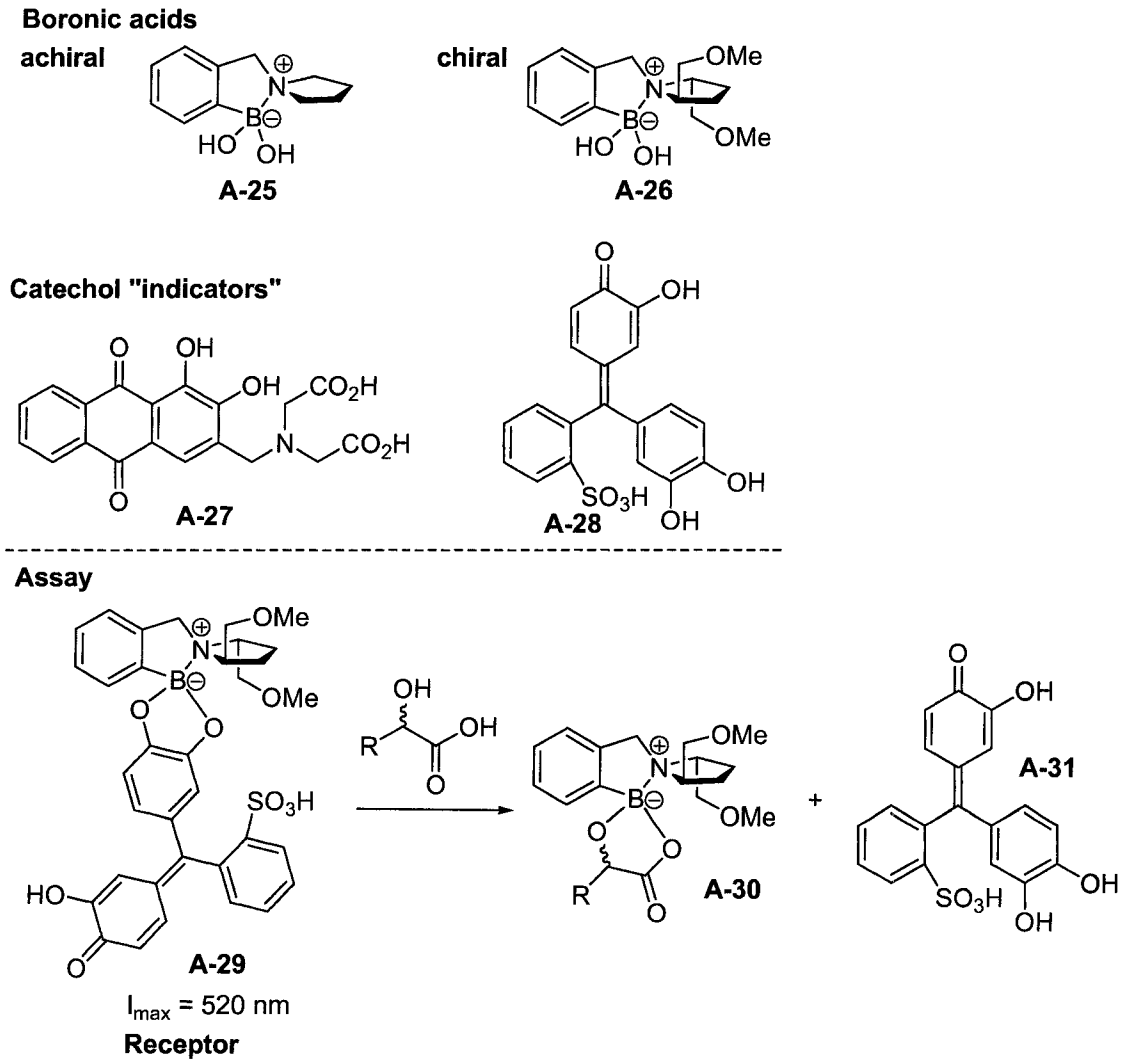
A-22 **A-23** **A-24** **A-18**

Anslyn has reported a high-throughput indicator-displacement assay (IDA) that was used for the analysis of enantiomeric excess of α-hydroxyacids (Scheme 8).[33] Boronic acids bound to catechols served as "receptors" for α-hydroxyacids. When achiral boronic acids such as **A-25** were used, the receptors bound both α-hydroxyacid enantiomers without preference. When chirality was introduced into the receptor, the displacement of indicator catechols **A-27** and **A-28** from D- and L-**A-29** was enantioselective and the selectivity was correlated with the UV absorbance of the receptor-indicator complexes. In solutions containing a mixture of the two enantiomers, the difference in absorbance could be correlated with the enantiomeric excess. Two independent measurements were necessary to obtain the concentration and *ee* of the products. First, an IDA was performed with an *achiral* receptor, a combination of **A-25** and **A-28**, and the concentration of the α-hydroxyacid was calculated from the solution absorbance using the Beer-Lambert law.[34] Then, a second IDA was done using a *chiral* receptor, **A-29**. The enantiomeric excess

[32] Reetz, M. T.; Zonta, A.; Schimossek, K.; Jaeger, K.-E.; Liebeton, K. *Angew. Chem. Int. Ed.* **1997**, *36*, 2830.
[33] Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676.
[34] The Beer-Lambert law relates transmission of light through a substance with the concentration of that substance: $A = \alpha lc$, where A = absorbance, α = molar absorptivity coefficient, l = path length, c = concentration. The molar absorptivity is given by: $\alpha = 4\pi k/\lambda$ where k = extinction coefficient, λ = wavelength of light.

could then be calculated without the need for a calibration curve. The calculated concentrations were within 10% and *ee* values within 20% of the actual values.

Scheme 8. Indicator-displacement assay for analysis of α-hydroxyacids

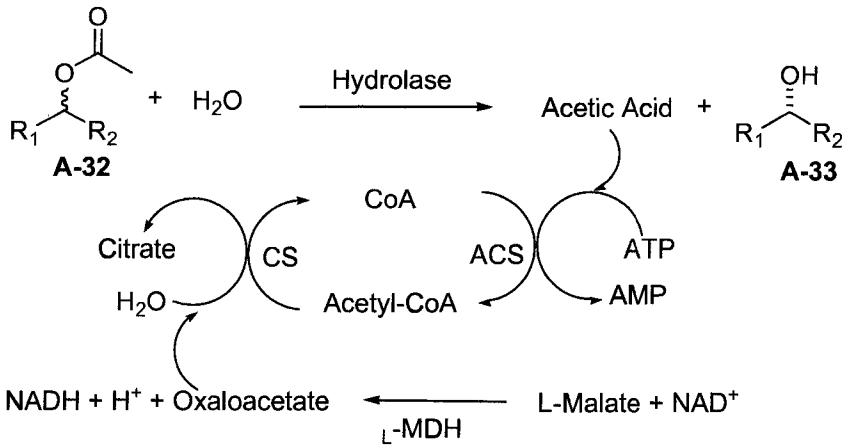


The activity and enantioselectivity of hydrolases (lipases and esterases) were determined by Bornscheuer using a method that coupled the reaction with enzymatic conversion (Scheme 9).[35] Racemic mixtures of esters (**A-32**) were subjected to various hydrolases, and the acetic acid produced in the process entered a cascade of enzymatic reactions generated by a cheap test-kit used for food analysis. The initial rates of acetic

[35] Baumann, M.; Stürmer, R.; Bornscheuer, U. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 4201.

acid formation could be calculated from the change in concentration of NADH, which was measured by its absorption at 340 nm. Although the technique was restricted to reactions that produce acetic acid, the enantiomeric ratios obtained by this method correlated well with values measured by GC and each reaction could be analyzed quickly—approximately 7 seconds per reaction.

Scheme 9. Concentration of NADH produced by coupled enzymatic conversion was correlated to *ee*



Biological methods are very efficient, reliable, and highly selective for screening specific systems. The drawback of these methods for applications in organic chemistry is that they are limited to specific systems.

1.2.6 Fluorescence

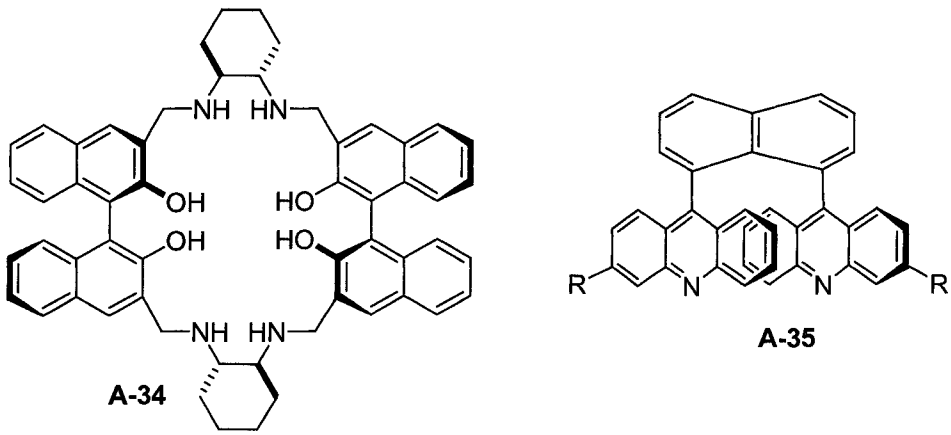
Fluorescence-based assays are well-proven in biological applications. These assays are reliable, sensitive, rapid and facile. Fairly recently, organic chemists have begun to explore the potential of fluorescence-based assays for the HTS screening of enantioselective reactions.

Fluorescent "sensors" such as **A-34** have been employed to determine the enantiomeric excess of mandelic acid and derivatives (Figure 8).[36] The Wolf group has developed a fluorescent sensor (**A-35**) that underwent stereoselective interactions with

[36] (a) Li, Z. B.; Lin, J.; Qin, Y. C.; Pu, L. *Org. Lett.* **2005**, *7*, 3441. (b) Zi-Bo Li, J. L. L. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1690.

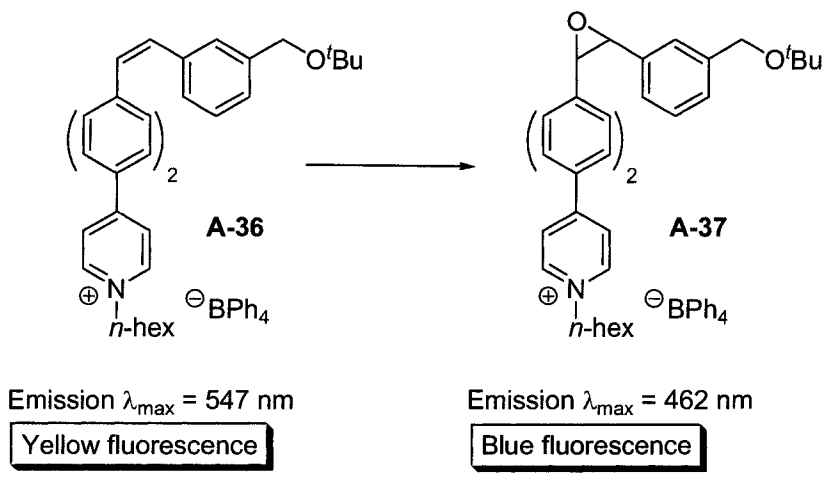
chiral carboxylic acids, resulting in fluorescence quenching (Figure 9).[37] These methods permitted immediate analysis of the enantiomeric composition of a mixture, but were not applied to reaction discovery.

Figure 9. Enantioselective fluorescent recognition groups



The Sames group reported the HTS assay of fluorogenic probes for the monitoring of atom transfer catalysis (Scheme 10).[38] It was found that the fluorescence profiles of the probes changed upon reaction, a consequence of the increase or decrease in the extent of π-conjugation in terphenyl systems.

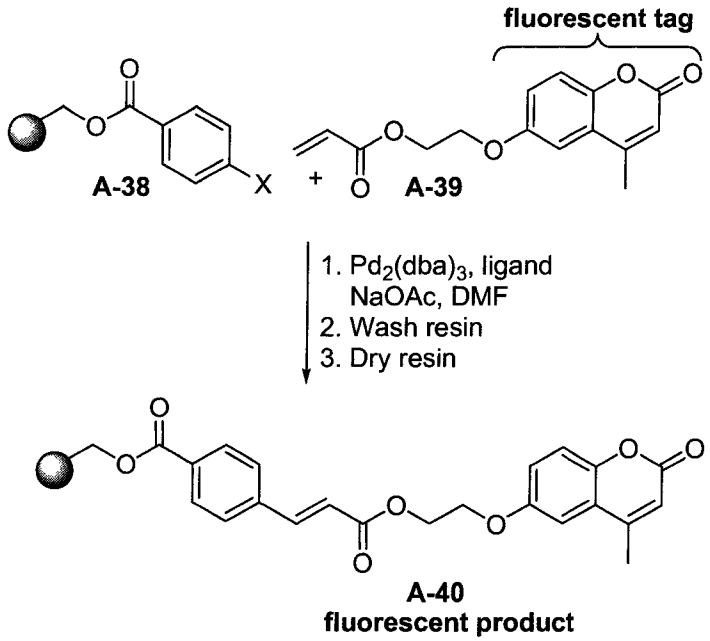
Scheme 10. Fluorescence-based assay for atom transfer catalysis



[37] Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736.
[38] Havranek, M.; Moreira, R.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 3927.

Hartwig and co-workers reported one of the first fluorescence-based screening methods in organic chemistry which was applied to ligand optimization in a Heck coupling reaction (Scheme 11).[39] Aryl halides were bound to a solid support and an acrylate was substituted with a fluorescent tag. The substrates were exposed to $Pd_2(dba)_3$, a ligand, and sodium acetate in DMF. The reactions were run in parallel for four hours at 100 °C, and the resin was subsequently washed, dried, and analyzed manually under UV light. Reaction wells showing strong fluorescence were further analyzed by GC to generate yields. Although the method was many orders of magnitude faster than GC or HPLC techniques, the reaction progress could neither be monitored nor quantified, and provided no information about selectivity. In addition, the use of resins could also become problematic in some cases as there is always the risk that the resin or other species in the solution could cause fluorescence quenching.

Scheme 11. Heck coupling reaction on solid support monitored by fluorescence

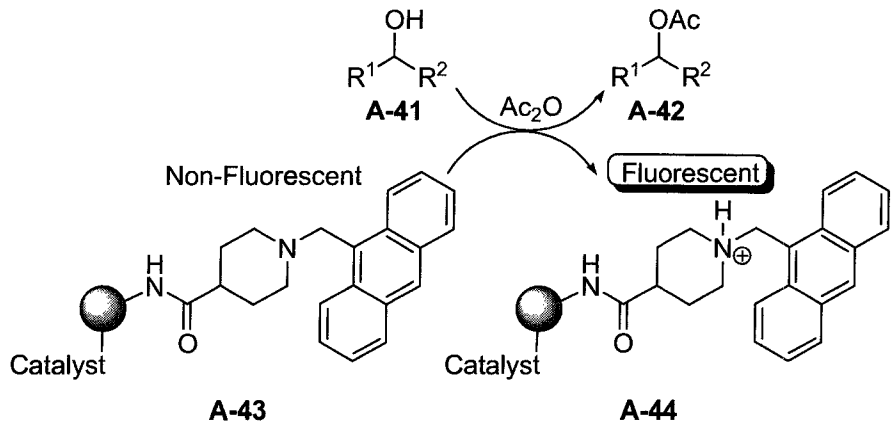


Miller has extensively investigated fluorescence-based screening techniques,[40] and a highlight of his research is the development of a catalyst linked on solid support to a

[39] Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123.
[40] (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306. (b) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (c) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.

fluorescent sensor (Scheme 12).[41] The assay design depended on proton-activated fluorescence within a resin bead. The acylation reaction of an alcohol, which produces one proton per catalytic cycle, was monitored. The fluorescence signal was directly coupled with catalyst activity and not enantioselectivity, but the group hypothesized that a catalyst that provided rate acceleration was also an enantioselective catalyst. This proved to be true in most cases investigated, and this methodology facilitated the discovery of several general and selective peptide catalysts for the kinetic resolution of alcohols.[40,42]

Scheme 12. Proton-activated fluorescence was used to monitor an acylation reaction



While many screening techniques exist such as GC, HPLC, MS, NMR, and colorimetric and fluorescence-based assays, many of these are not truly high-throughput. Many are criticized because they are strictly qualitative or require substrate derivatization prior to analysis. Few can identify enantioselective reactions and fewer still can quantify such processes.

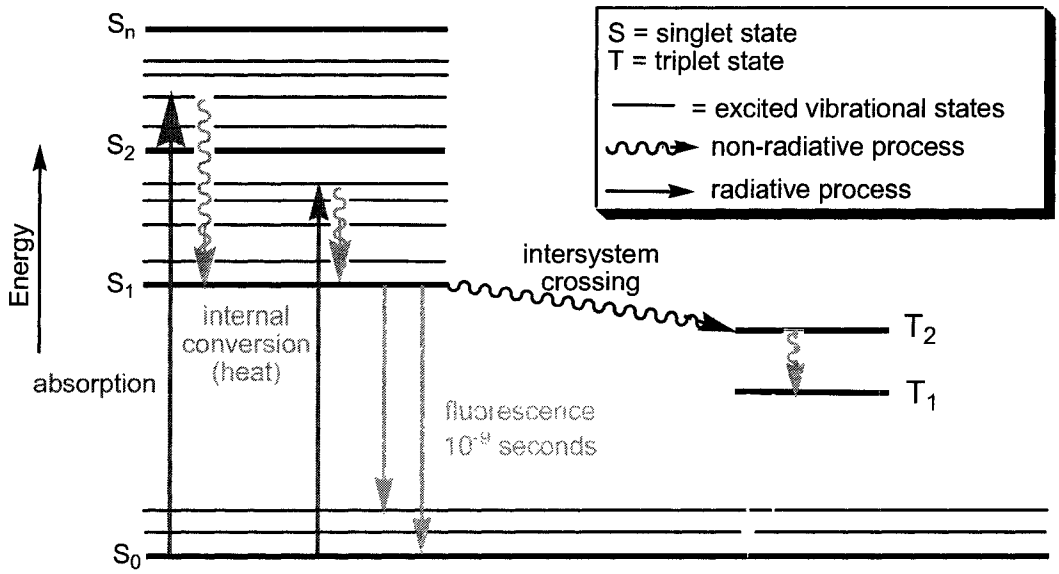
1.3 Fluorescence Resonance Energy Transfer Principle

Fluorescence is the emission of light caused by the electronic excitation and subsequent relaxation of a photon between singlet states. When a fluorophore absorbs light, it is excited to a higher energy electronic state, and subsequently relaxes back to the ground state by several different processes. Radiative processes such as fast photon

[41] Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.
[42] (a) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522. (b) Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 11270.

emission by fluorescence or slower phosphorescent emissions are possible. Non-radiative processes such as internal conversion of energy into heat and intersystem crossing also occur. These processes are depicted in the Jablonski diagram below (Figure 10).

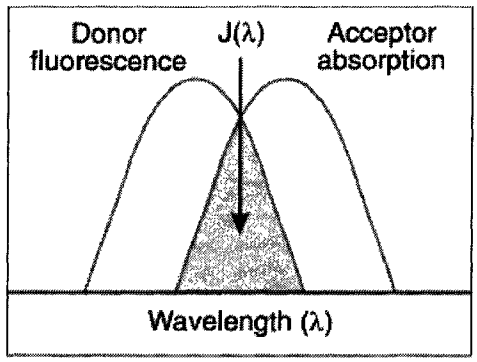
Figure 10. Jablonski diagram



Fluorescence Resonance Energy Transfer, or FRET, involves the non-radiative transfer of energy from a fluorophore, called a donor, to another molecule, called an acceptor. This process occurs when the emission spectrum of the donor overlaps with the absorption spectrum of the acceptor (Figure 11).[43] This transfer is due to the coupling of the donor and acceptor dipole moments. The extent of resonance energy transfer is inversely related to the separation distance between the donor and acceptor pair, and a separation of 10 to 100 angstroms is required. Fluorescence is detected with a spectrofluorometer, and can be quantified.

[43] The acceptor does not need to be fluorescent for the energy transfer to occur.

Figure 11. Emission band of a fluorophore overlaps with the absorption band of an acceptor



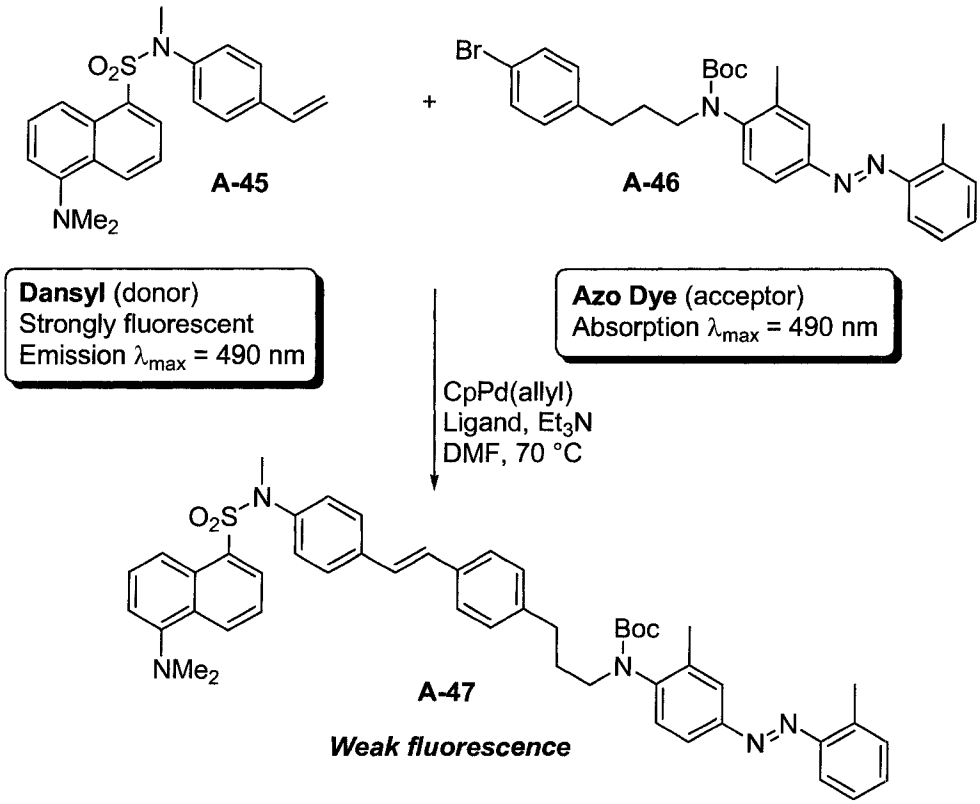
1.4 FRET Background

FRET is often used in studies of biological systems, such as in the study of proteins and DNA.[44] The method is applicable to both inter- and intramolecular systems, although one must take care when studying the latter that intermolecular interactions do not interfere with the analysis.

Hartwig developed a general, rapid, and quantitative screening assay using FRET.[45] In order to screen for active ligands in solution-phase Heck reactions, a dansyl fluorophore (donor) was covalently tethered to a styrenyl group and an azodye quencher (acceptor) was tethered to an aryl bromide (Scheme 13). The donor and acceptor pair was chosen such that the emission wavelength of the dansyl group overlapped with the absorption wavelength of the azodye. At the start of the reaction, the solution was strongly fluorescent. This fluorescence decreased in intensity as the reaction proceeded, due to the proximity of the donor and acceptor moieties to each other in the coupled products.

[44] Rasnik, I.; McKinney, S. A.; Ha, T. *Acc. Chem. Res.* **2005**, *38*, 542.
[45] Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677.

Scheme 13. Identification of effective ligands using FRET



In one phosphine ligand scan, reactions were performed in a 96-well plate. After 15 hours at 70 °C, an aliquot was taken from each well, diluted and the results were analyzed on an automated fluorescent plate reader, which took approximately one second per well. The emission intensity was converted to a reaction yield by using a linear plot that correlated emission intensity to the mole fraction of coupled product. The results correlated well with HPLC yields obtained from individual runs. Hartwig's method was also applied to other organometallic coupling reactions, such as the arylation of cyanoacetates[46] and the amination of aryl halides.[47]

These FRET results were obtained much more quickly than those obtained by GC, HPLC, or NMR, and the results could be accurately quantified, unlike the results obtained by TLC, IR and colorimetric techniques. The FRET reaction monitoring method should prove ideal for the high-throughput screening of many organic reactions.

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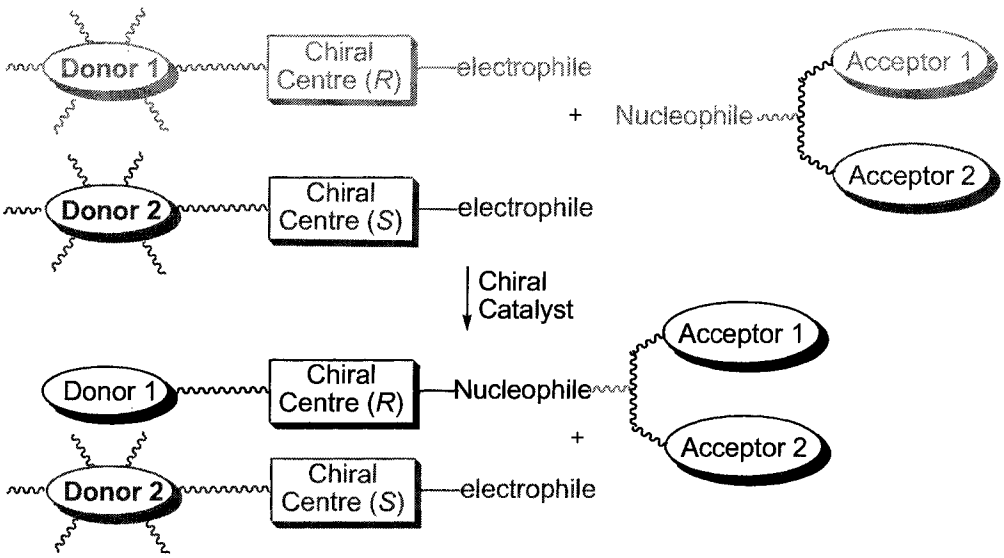
[46] Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641.
[47] Stauffer, S. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6977.

1.5 Project Objective

The goal of this project was to develop a general, quantitative, high-throughput assay for ***enantioselective*** reaction discovery using Fluorescence Resonance Energy Transfer (FRET).

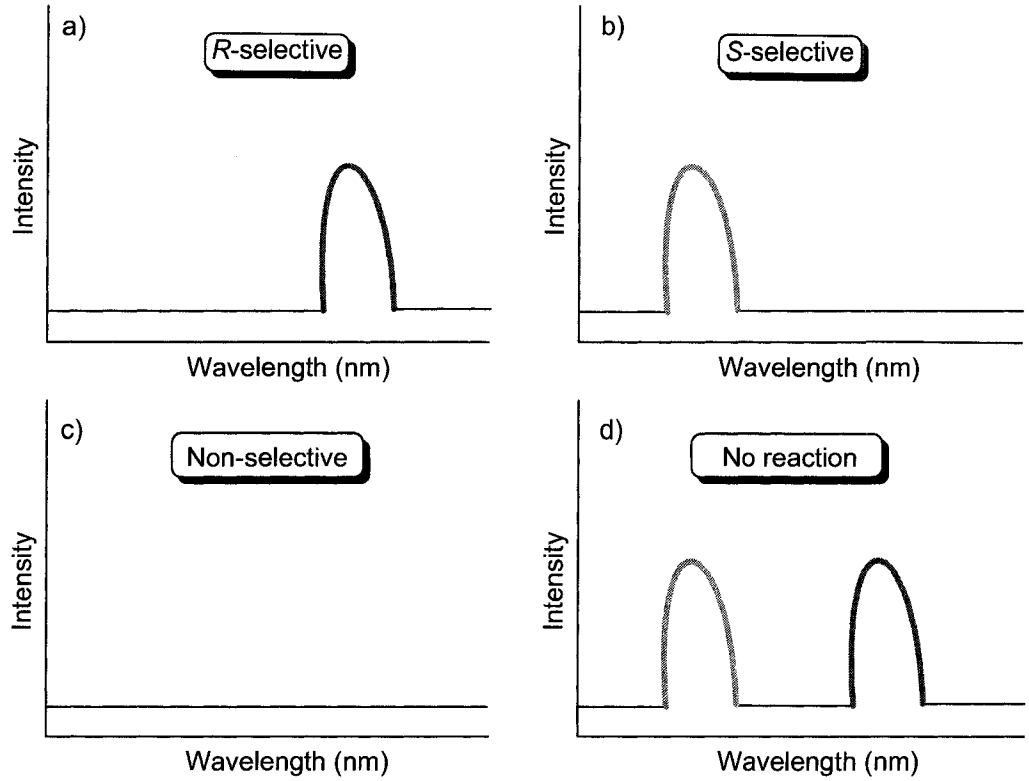
The general design ensured that the methodology could be easily modified to suit the needs of different research groups. A fluorescent donor moiety would be tethered to an electrophile bearing a defined chiral centre and a second fluorescent donor moiety to an electrophile bearing the opposite chiral centre (Scheme 14). These donors would each fluoresce at a different wavelength. A nucleophile would be tethered to two fluorescence quenchers (acceptors), each of whose absorption spectrum would overlap with the emission spectrum of one of the donors.

Scheme 14. General principle for a FRET-identified enantioselective reaction.



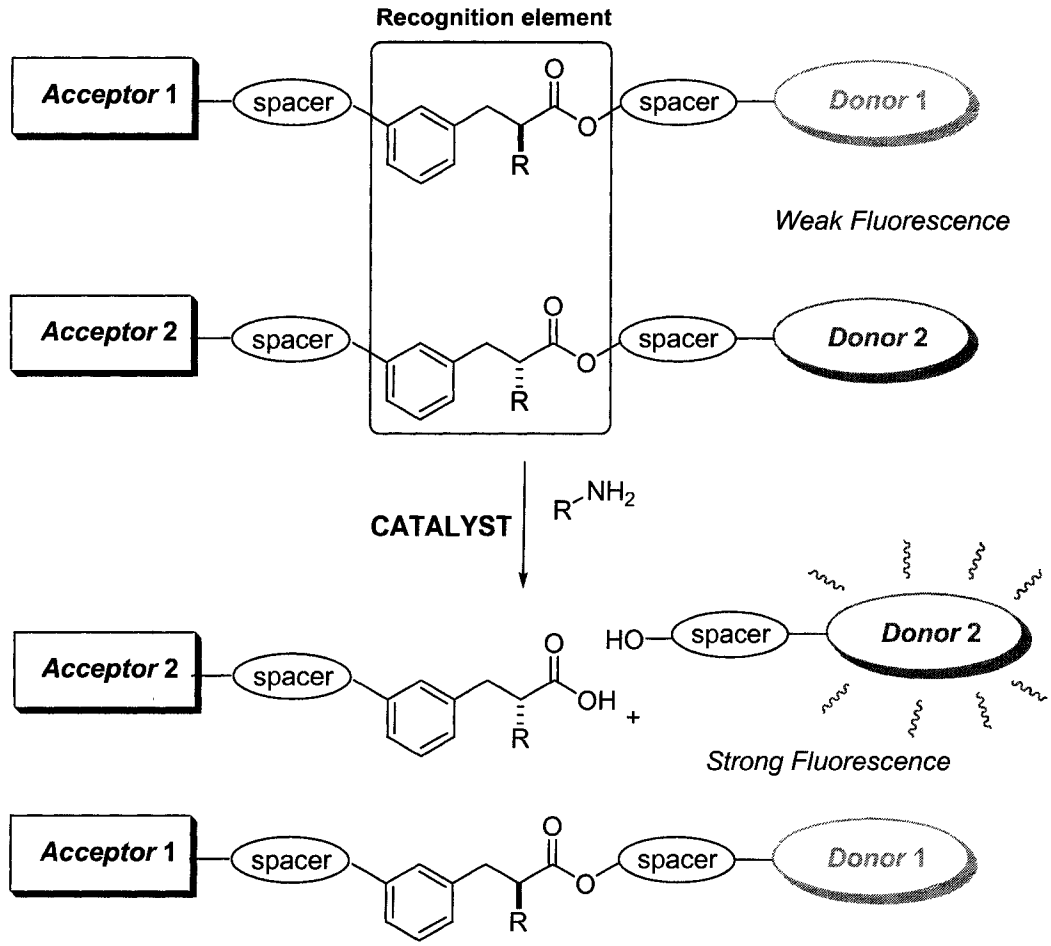
As the reaction proceeded in the presence of a chiral catalyst, the various possible outcomes would be quantified (Figure 12). The nucleophile may react selectively with the *R* enantiomer over the other (Figure 12a), which would result in the quenching of Donor 1's fluorescence; Donor 2's fluorescence (blue) would still be observed. The opposite result would be obtained for an *S*-selective reaction (Figure 12b). The fluorescence of both donors would be quenched in a non-selective reaction (Figure 12c) and would remain unchanged in the presence of an ineffective catalyst (Figure 12d).

Figure 12. Potential FRET results



One could also envision the opposite strategy being employed that would use bond-breaking reactions such as hydrolysis (Figure 13). If enantioselective ester hydrolysis was to be monitored, Donor 1 would be linked through one chiral centre to Acceptor 1, and Donor 2 would be linked through the opposite chiral centre to Acceptor 2. Fluorescence would not be observed until a reaction occurred, and the enantioselectivity of the reaction would be measured through fluorescence analysis.

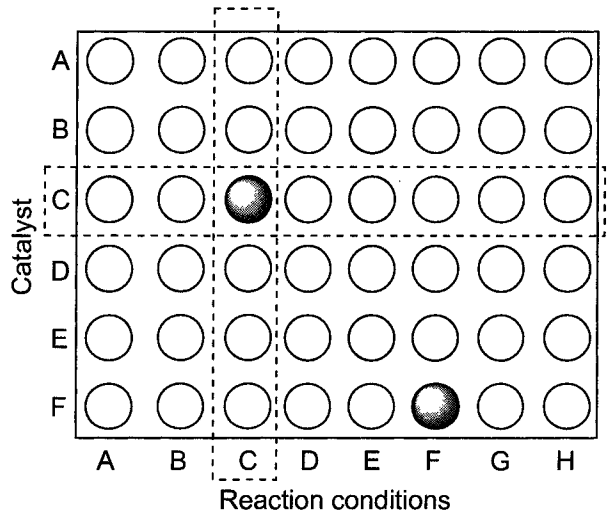
Figure 13. Application of FRET to enantioselective ester hydrolysis



A long-range goal for this research would be to link some or all of the substrates to solid support, which would facilitate isolation and purification procedures.

A key advantage of our proposed methodology over those previously mentioned is that *enantioselective* reactions would be *identified* and *quantified prior* to purification, isolation and characterization. Both catalysts and reaction conditions could simultaneously be tested using well plates (Figure 14) and reactions could be rapidly analyzed using a spectrofluorometer equipped with an autosampler.[45]

Figure 14. Identification of successful catalysts and reaction conditions in a well-plate



There were a number of factors to be addressed the method was designed:

1. The donor and acceptor moieties must be in close proximity to each other in the product molecule for fluorescence to be effectively quenched (typically 10–100 Å).

2. The absorption spectrum of the acceptor must overlap with the fluorescence emission spectrum of the donor.

3. Detection sensitivity can be severely compromised by background signals.

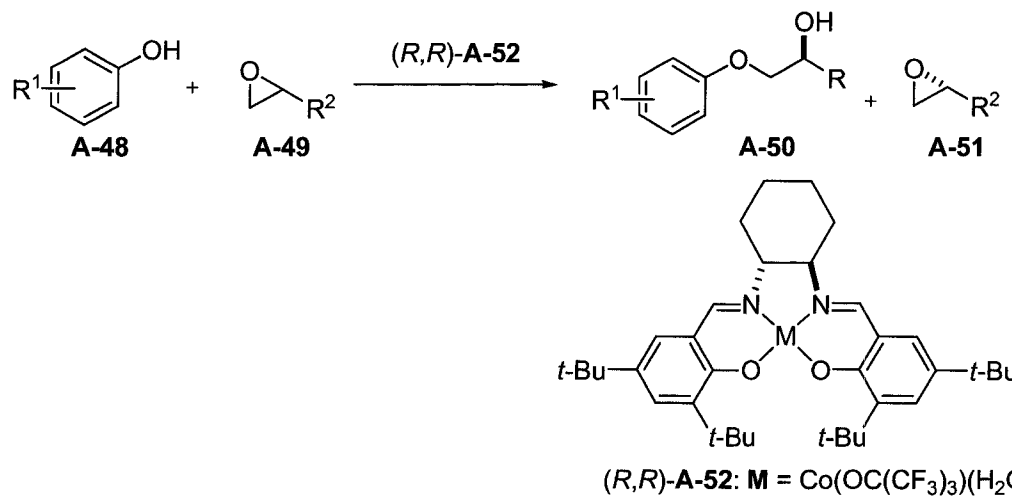
4. Concentrated solutions can result in self-absorption or the "inner-filter" effect.

5. The donor and acceptor moieties must not interfere with the catalyst.

6. The donor and acceptor moieties must not hinder reaction near the chiral centre.

Our studies would begin with a proof of principle using the Jacobsen's reliable kinetic resolution of terminal epoxides with phenols (Scheme 15).[48] Using the knowledge garnered from their work on hydrolytic kinetic resolution of terminal epoxides with Co(salen) catalysts,[49] the Jacobsen group explored the analogous kinetic resolution of epoxides with phenols as nucleophiles. Terminal epoxides could successfully be resolved in nearly quantitative yield when reactions were run in *tert*-butyl methyl ether (TBME) (5M) in the presence of 3Å molecular sieves using Co(salen) catalyst **A-52**. The use of perfluoro-*tert*-butoxide as the counter ion was key, and the reactions displayed a strong temperature dependence. Reactions providing only moderate *ee*'s at room temperature could be rendered significantly more selective upon lowering of the reaction temperature. Oligomeric variants of the Co(salen) catalyst **A-52** were superior to the monomeric catalyst in many cases. The selectivities and yields of previously unreactive epoxide-phenol combinations, such as *ortho*-allyl-substituted phenols and phenyl-substituted epoxides, were greatly improved using the oligomeric catalyst variants.[48c] A polymer-supported chiral Co(salen) complex facilitated the isolation of reaction products from the reaction mixtures and enabled the recycling of the catalyst.[48b]

Scheme 15. Enantioselective ring-opening of terminal epoxides with phenols

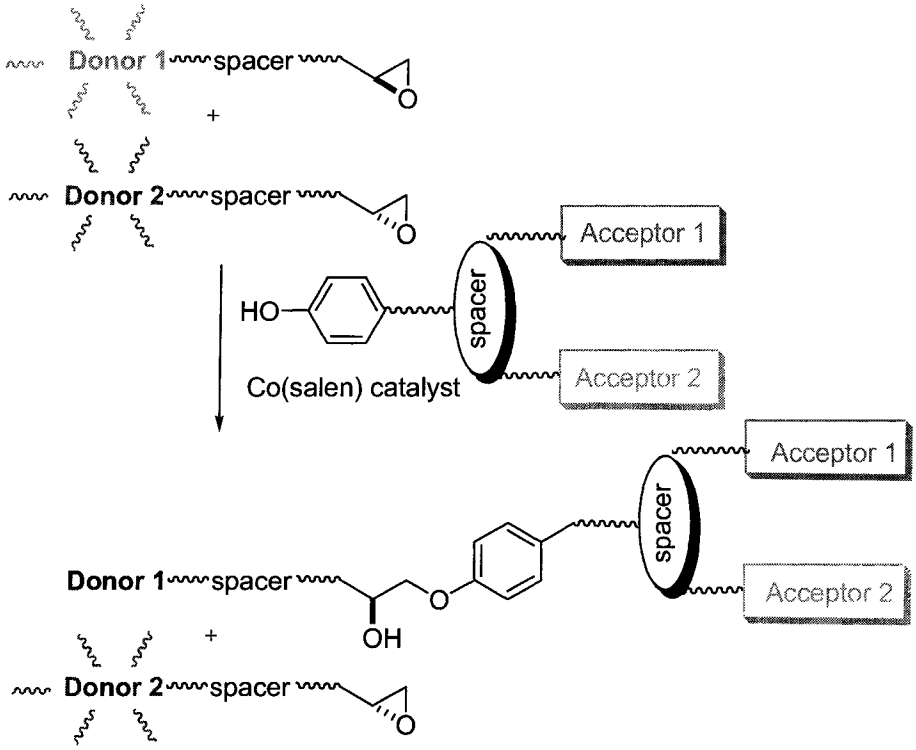


[48] (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086. (b) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (c) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.Ready; Jacobsen.

[49] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

The selectivity and simplicity of the method, in addition to the potential for catalyst recycling suggested that this system would be the perfect starting point to prove the utility and efficiency of FRET for high-throughput enantioselective reaction discovery. Each epoxide enantiomer would be tethered to a different fluorescence donor and the phenol would be tethered to complimentary fluorescence quenchers (Scheme 16). Spacers would be installed between the recognition elements (the epoxides) from the fluorescent groups to avoid any interference from the latter. Flexible aliphatic spacers would be employed in this first proof of principle. These linkers would not be expected to interfere with the catalyst because of their simplicity, inertness, and greater solubility compared to larger molecules. By using this type of spacer, functionalities that could hydrogen bond, π-stack, or otherwise hamper the catalyst would be avoided.

Scheme 16. Design of proof-of-principle enantioselective ring-opening of epoxides with phenols



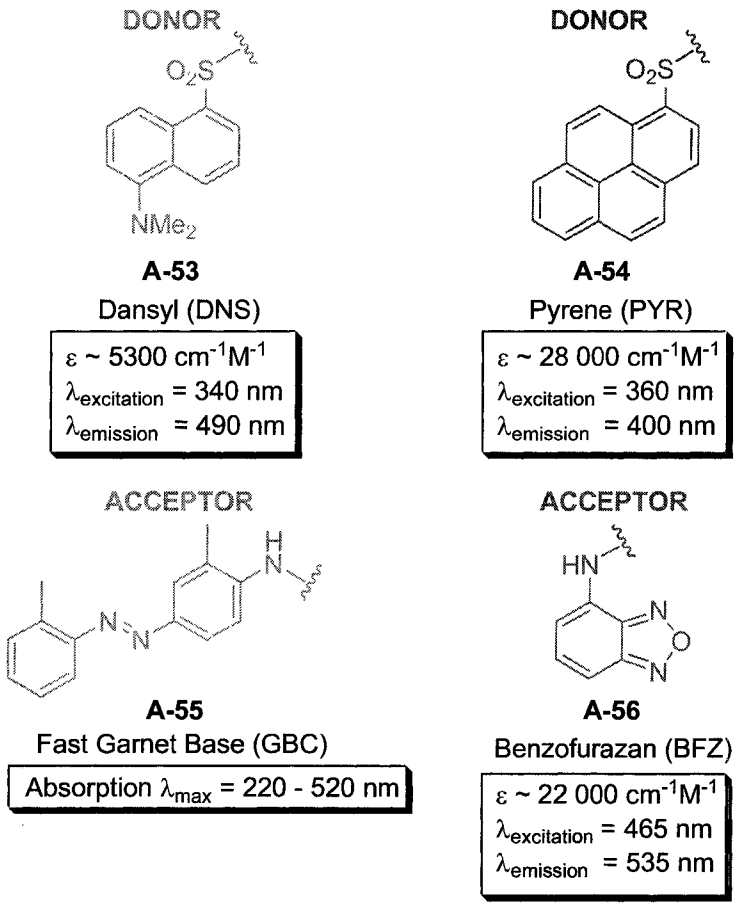
To address other potential issues, control reactions would be performed to ensure that the fluorescent moieties would not affect the catalyst. Dilute solutions would be employed to avoid the inner-filter effect and calibration curves would be generated to

account for background signals. Overall, the size of our system would be designed such that the donor and acceptor groups would be between 10 and 100 Å apart when located on the same molecule.

Chapter 2. Results and Discussion

The first important undertaking was the selection of the donor/acceptor pairs and we would examine a number of potential partners for this project. Reports from the Hartwig group suggested that dansyl moiety **A-53** and Fast Garnet Base **A-55** would be one suitable donor/acceptor pair (Figure 15).[45] Investigation of a variety of other potential donor/acceptor pairs suggested that pyrene moiety **A-54** would be suitable as the second fluorescent donor and that benzofurazan moiety **A-56** could be employed as the acceptor.

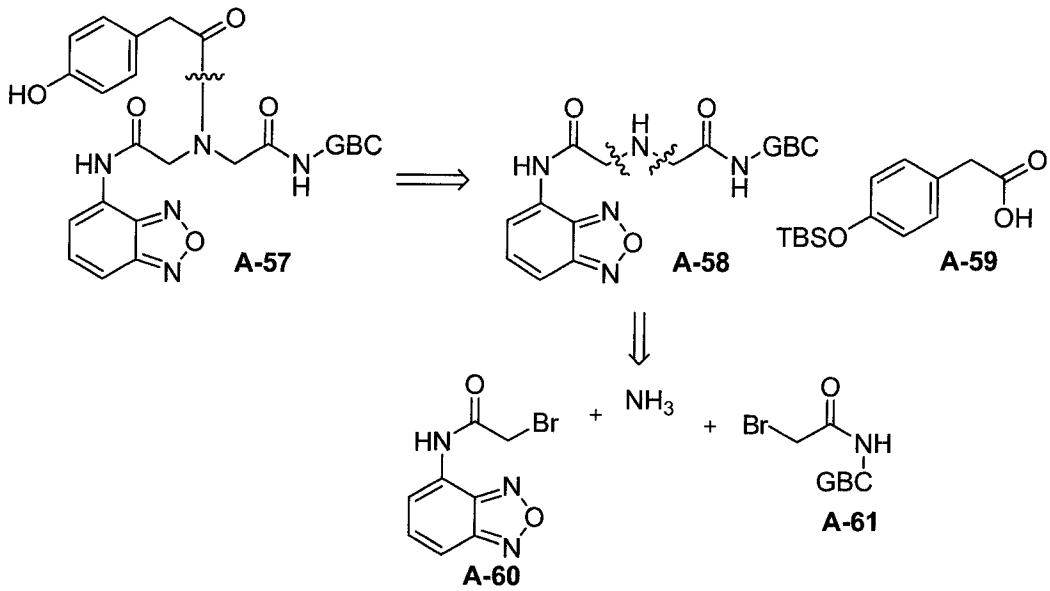
Figure 15. Donor/acceptors pairs for the FRET assay



2.1 Design of the phenol-acceptor moiety

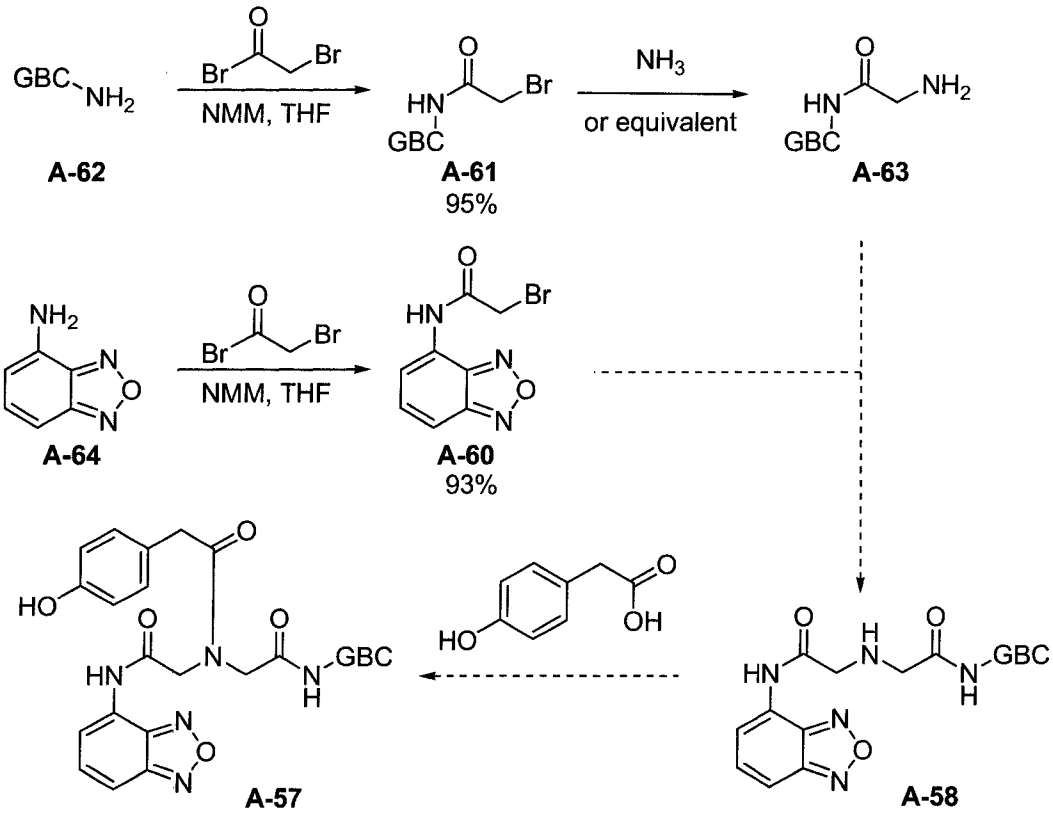
Our initial target saw tethered together the GBC, BFZ, and phenol moieties This target would ge synthesized using displacement and peptide coupling reactions to give derivative **A-57** (Scheme 17). Care was taken to ensure that no chiral centre was incorporated into the molecule. Phenol **A-57** would arise from the peptide coupling reaction between **A-58** and **A-59**. The two acceptor moieties would arise from electrophiles **A-60** and **A-61** and would be linked in **A-58** via an amine or amine equivalent.

Scheme 17. Retrosynthetic analysis of the phenol synthesis



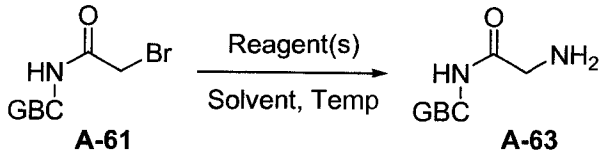
The generation of electrophiles **A-60** and **A-61** was accomplished by the reaction of the appropriate amine with bromoacetyl bromide (Scheme 18). Exposure of GBC **A-62** to bromoacetyl bromide in the presence of *N*-methylmorpholine (NMM) provided bromide **A-61** in 95% yield. Exposure of benzofurazan **A-64** to bromoacetyl bromide in THF using NMM as a base gave bromide **A-60** in 93% yield.

Scheme 18. Initial design of the phenol moiety



The direct amination of bromide **A-61** was next investigated (Table 1). The use of ammonia in THF gave a mixture of products (entry 1) and a similar result was observed in DMF at 80 °C (entry 2). No reaction took place with ammonia in ethanol (entry 3) and the use of ammonia as the solvent gave another mixture of products (entry 4). The use of ammonium chloride as an alternate amine source was attempted in various solvents in the presence of DIPEA. Reactions in DMF at room temperature (entry 5) and at 80 °C (entry 6) gave intractable mixtures. When acetone was attempted as the solvent, a similar mixture of products was observed (entry 7).

Table 1. Direct amination was unsuccessful

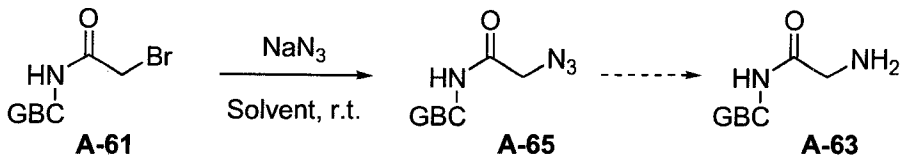


A-61 A-63

Entry	Reagent(s)	Solvent	Temp	Result
1	NH_3	THF	r.t	mixture
2	NH_3	DMF	80 °C	mixture
3	NH_3	EtOH	r.t.	NR
4	NH_3	NH_3	r.t.	mixture
5	NH_4Cl, DIPEA	DMF	r.t.	mixture
6	NH_4Cl, DIPEA	DMF	80 °C	mixture
7	NH_4Cl, DIPEA	acetone	r.t.	mixture

These results were not surprising, as direct amination is known to give mixtures of products. This is because the product of the initial amination is also a nucleophilic amine that can react with another electrophilic molecule. An indirect route to the desired amine product was therefore explored. Azide, a small and potent nucleophile would be employed and had the added advantage that once a first displacement had occurred, no further reaction would occur, thereby minimizing side product formation. The azide would need to be reduced once the product had formed, but numerous methods were available to accomplish this task, such as catalytic hydrogenation or the Staudinger reaction. The use of sodium azide in DMF gave a mixture of products (Table 2, entry 1). Ethanol (entry 2) and THF (entry 3) were no better as solvents; the reaction gave a mixture of products each time.

Table 2. An indirect method to install the amine

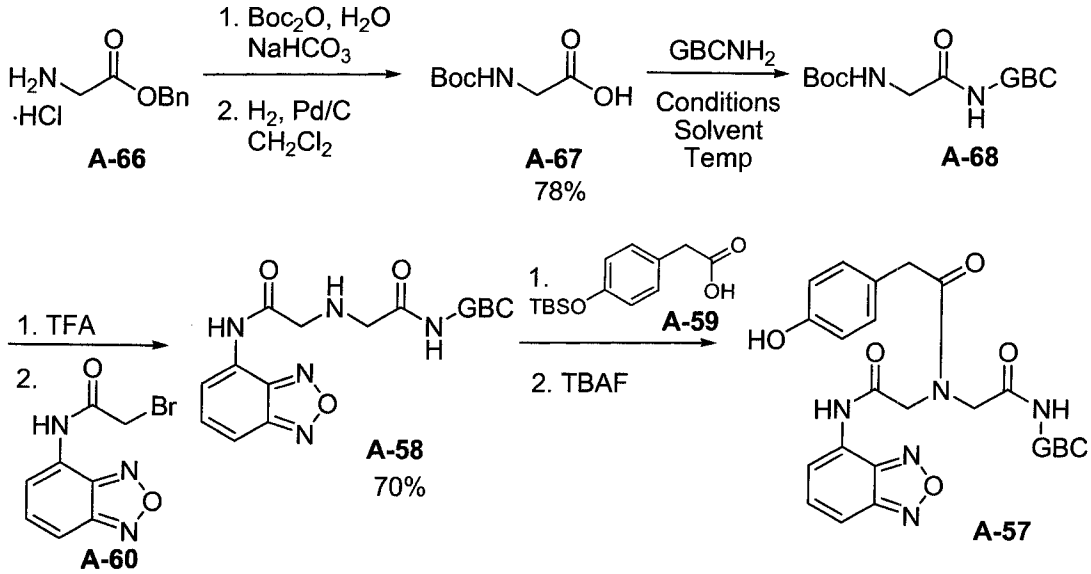


A-61 A-65 A-63

Entry	Solvent	Result
1	DMF	mixture
2	EtOH	mixture
3	THF	mixture

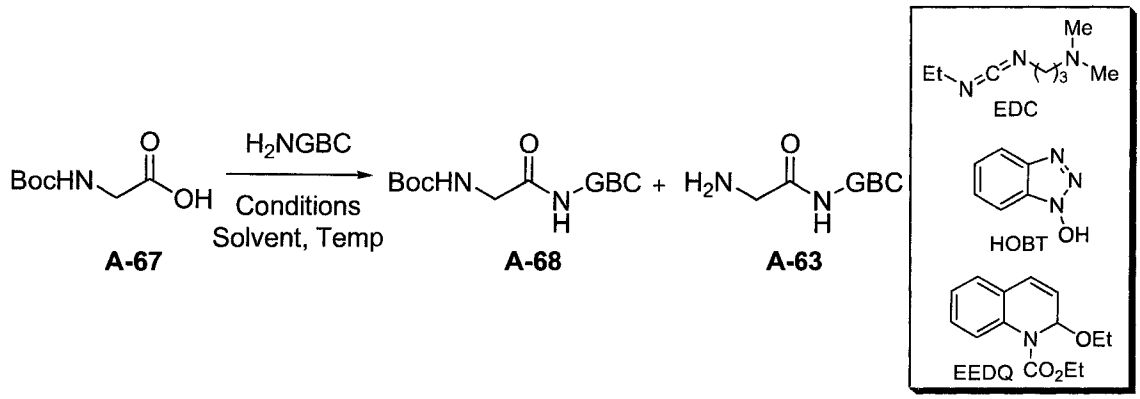
The acceptor design was slightly modified to generate an early intermediate in which the amine was already installed in the molecule in protected form (Scheme 19). The requisite carboxylic acid (**A-67**) was prepared by the protection of the primary amine as the Boc-carbamate, and the ester was deprotected via hydrogenation.

Scheme 19. Design modification incorporated the required amine in the starting material



A series of conditions were investigated in an attempt to generate protected amine **A-68** (Table 3). The use of oxalyl chloride in CH_2Cl_2 with a catalytic amount of DMF provided the deprotected product **A-63** (Table 3, entry 1). The reaction medium had evidently become too acidic during the reaction conditions. Attempts to protect the amine present in the crude reaction mixture using BOC-anhydride resulted in a mixture of products. Exposure of carboxylic acid **A-67** and $GBCNH_2$ to EDC, HOBT, and DIPEA in THF at reflux generated the desired product **A-68** in 40% yield (entry 2). This yield was improved to 60% when DMF was employed at 100 °C (entry 3). CH_2Cl_2 proved to be the optimal solvent, giving an 85% yield of the desired product in a reaction conducted at room temperature (entry 4). A final coupling reagent, EEDQ, was tested but gave only a 69% yield of the desired product (entry 5).

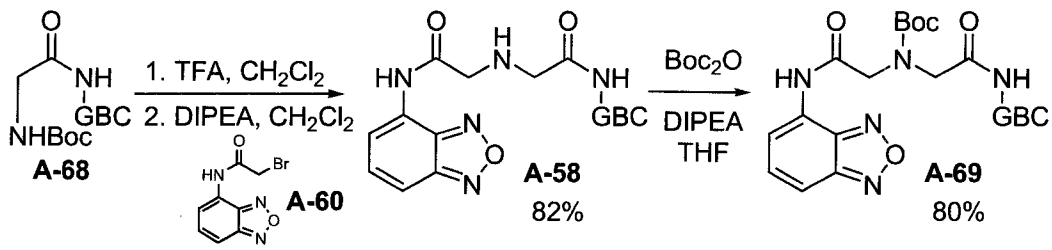
Table 3. Coupling conditions investigated



Entry	Conditions	Solvent	Temp	Yield A-68 (%)
1	$(COCl)_2$, DMF	CH_2Cl_2	r.t.	**A-63**
2	EDC, HOBT, DIPEA	THF	reflux	40
3	EDC, HOBT, DIPEA	DMF	100 °C	60
4	**EDC, HOBT, DIPEA**	**CH_2Cl_2**	**r.t.**	**85**
5	EEDQ	CH_2Cl_2	r.t.	69

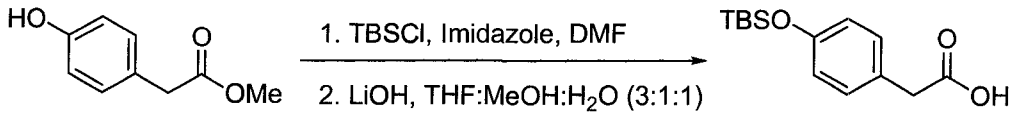
Deprotection of the amine proceeded smoothly using TFA in CH_2Cl_2 and exposure of the crude product to bromide **A-60** in the presence of DIPEA gave amine **A-58** in 82% yield (Scheme 20). This compound was protected as the BOC-carbamate (**A-69**) to simplify the purification and storage of the product. Having installed the two acceptor moieties on the same molecule, the obstacle remained to incorporate the phenol that would act as the nucleophile in the Jacobsen process.

Scheme 20. Final steps in the synthesis of the phenolic moiety



The phenol coupling partner was generated from the silylation of the phenolic oxygen of **A-70** using *tert*-butyldimethylsilyl chloride (TBSCl) (Scheme 21). Saponification of the ester with LiOH provided the target carboxylic acid **A-59** in quantitative yield.

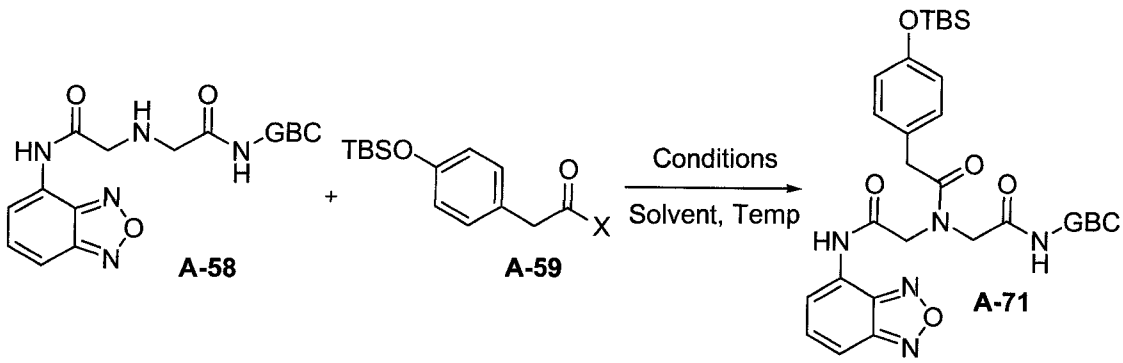
Scheme 21. Preparation of the phenol coupling partner



A-70 **A-59**
99% (2 steps)

The generation of tertiary amide **A-71** proved to be more difficult than expected. The exposure of amine **A-58** to carboxylic acid **A-59** in the presence of EEDQ in DMF resulted in decomposition (Table 4, entry 1). The acid chloride of **A-59** was generated using oxalyl chloride. Exposure of secondary amine **A-58** to the acid chloride of **A-59** in the presence of DIPEA and DMAP at 0 °C (entry 2) and at room temperature (entry 3) again resulted in decomposition or multiple reactions.

Table 4. Attempted generation of a tertiary amide



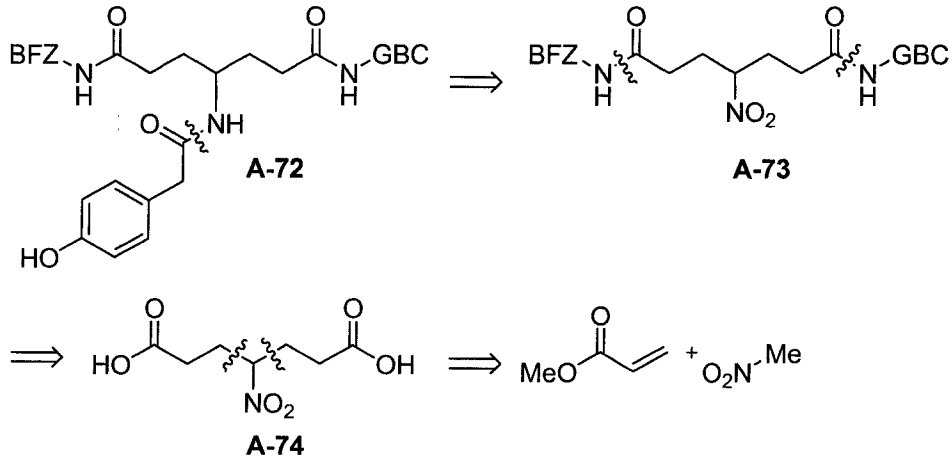
A-58 **A-59** **A-71**

Entry	X	Conditions	Solvent	Temp	Yield (%)
1	OH	EEDQ	DMF	r.t.	mixture
2	Cl	DIPEA, DMAP	CH_2Cl_2	0 °C	mixture
3	Cl	DIPEA, DMAP	CH_2Cl_2	r.t.	mixture

The generation of the tertiary amide (**A-71**) was clearly severely impeded by the crowding around the amine in **A-58**. The phenol moiety was therefore redesigned to link the three required pieces at a tertiary carbon atom that would be generated early in the synthesis. The target phenol **A-72** would arise from the reduction of a nitro group and subsequent coupling to a carboxylic acid (Scheme 22). Diamide **A-73** would come from the coupling of the two acceptor moieties with **A-74**. Diacid **A-74** would be obtained

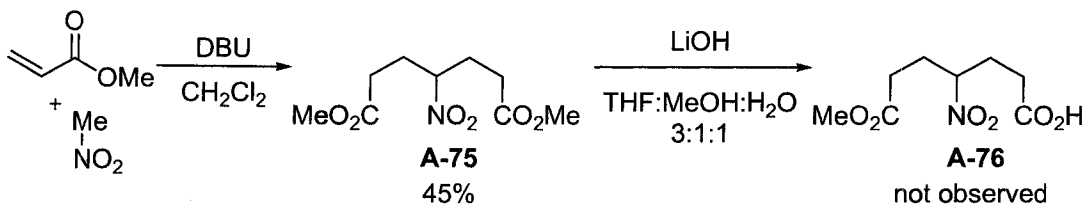
from two Michael additions of nitromethane with methyl acrylate followed by saponification.

Scheme 22. Alternate design of the phenol moiety



The initial double Michael addition proceeded very cleanly to give diester **A-75** in 45% yield (Scheme 23).[50] Unfortunately, the attempted monosaponification of **A-75** gave complete conversion of the starting material to an unidentified product. No trace of the desired carboxylic acid **A-76** was observed.

Scheme 23. Attempted generation of carboxylic acid R gave an unanticipated product

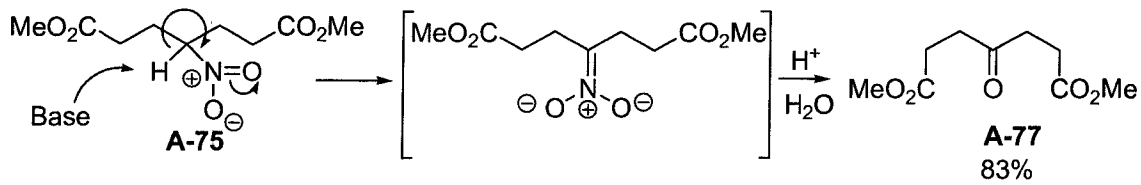


We discovered that an unanticipated, competing process was occurring; this process was identified as the Nef reaction.[51] In this process, the proton alpha to the nitro group was first deprotonated in the presence of a base (Scheme 24). Subsequent exposure of this intermediate to aqueous acid, such as in the workup of our saponification reaction, resulted in the formation of ketone **A-77**. The Nef reaction has also been reported to take place using DBU in acetonitrile, however that transformation required higher

[50] For the preparation of this compound, see: Chasar, I. *Synthesis* **1982**, 841.
[51] Pinnick, H. W. *Org. React.* **1990**, *38*, 655.

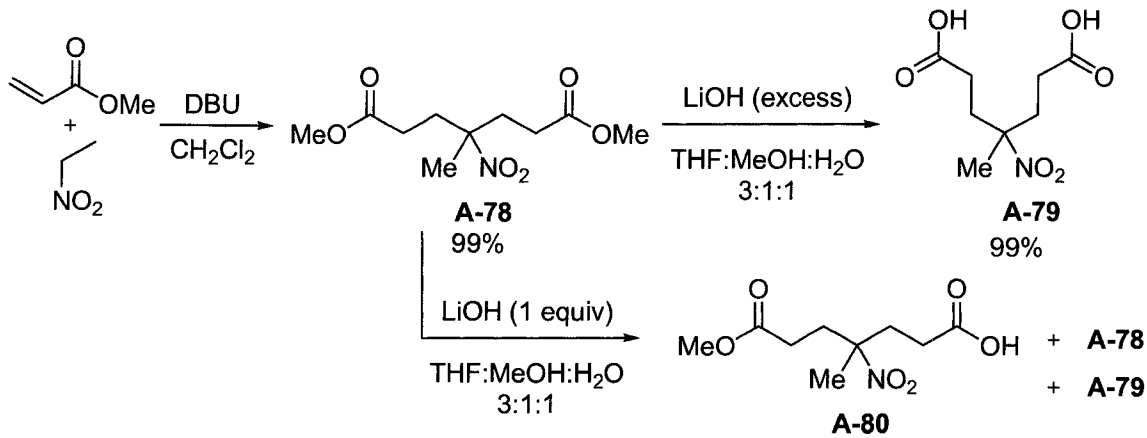
temperatures and longer reaction times.[52] A Nef reaction was in fact likely occurring as a side process in the initial generation of **A-75**, which would explain the low yield of only 45% that had been obtained.

Scheme 24. The Nef reaction



To avoid this problem, nitro*ethane* was employed for the Michael addition step in the place of nitro*methane* so that no proton would be available α to the nitro group for this undesired deprotonation to proceed. Exposure of nitroethane to methyl acrylate and DBU in CH_2Cl_2 provided diester **A-78** in quantitative yield (Scheme 25). The monosaponification of **A-78**,[50] which would allow us to couple first the GBC moiety followed by the BFZ moiety, resulted in mixtures of unreacted starting material, monoacid, and diacid products (**A-78**, **A-80**, and **A-79**). The full saponification of diester **A-78** proceeded in excellent yield, however, to give diacid **A-79**.[53]

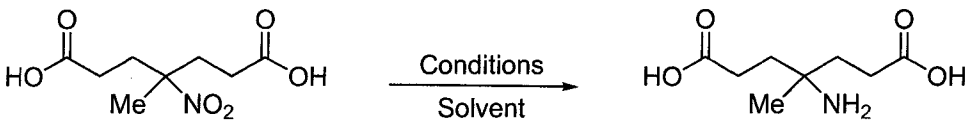
Scheme 25. Nitro*ethane* was substituted for nitro*methane* to prevent a Nef reaction



[52] (a) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Letters* **2002**, *43*, 5233. (b) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**.
[53] Patterson, J. M.; Barnes, M. W.; Johnson, R. L. *J. Org. Chem.* **1966**, *31*, 3103.

Efforts were then focused on the incorporation of the two acceptor moieties to diacid **A-79**. We felt that this would be most easily accomplished if the nitro group was first reduced, and a number of reduction methods were investigated. A high-pressure hydrogenation reaction was conducted for 5 days but showed no product (Table 5, entry 1). The use of zinc in concentrated HCl gave a single, new product, however it could not be isolated (entry 2). The same reaction was repeated, and upon consumption of starting material, the mixture was basified and Boc_2O was introduced (entry 3). Unfortunately, no identifiable products were observed.

Table 5. Reduction of the nitro substituent



A-79 **A-81**

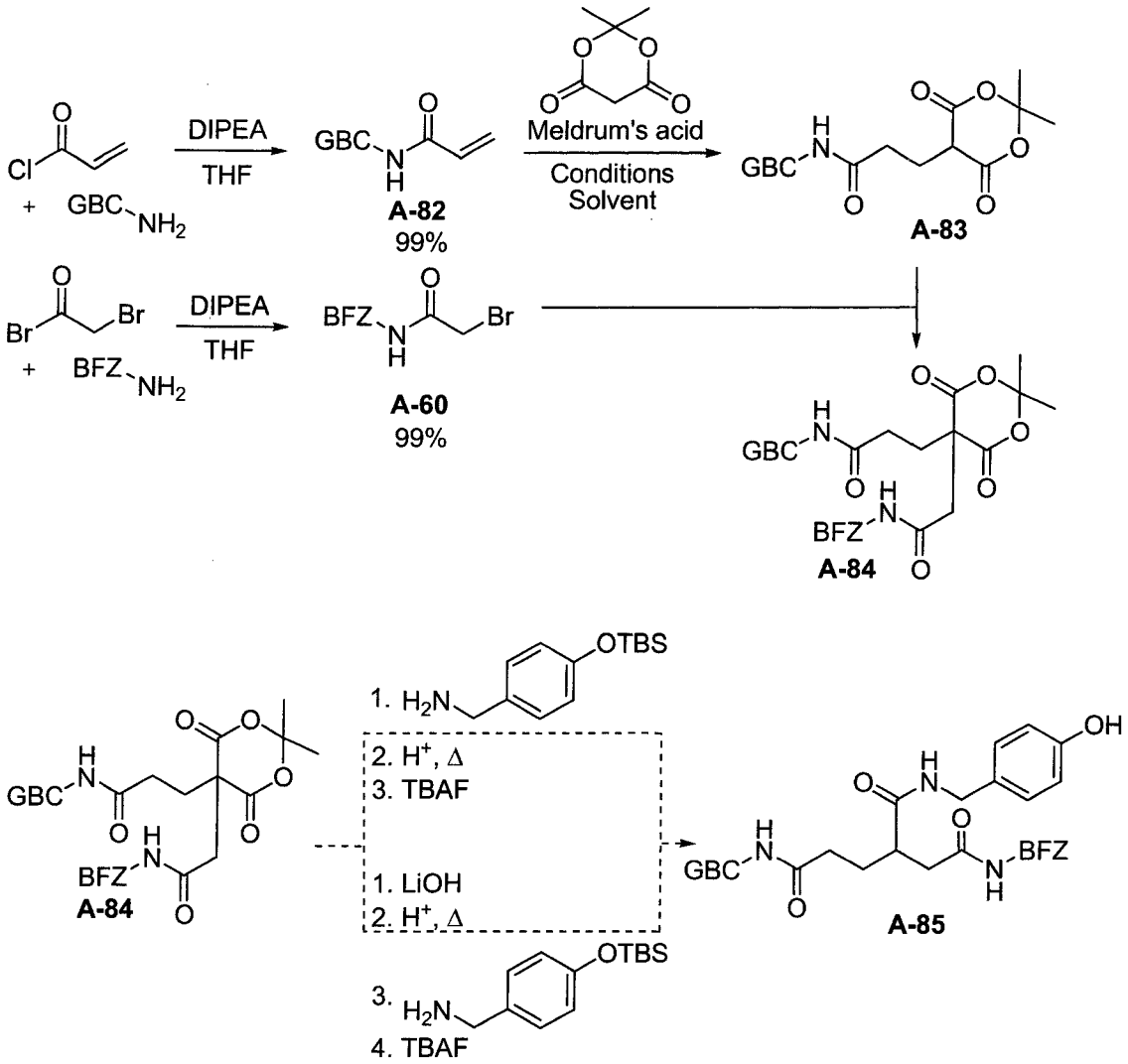
Entry	Conditions	Solvent	Result
1	H_2, Pd/C, 4 atm	EtOH, AcOH	NR
2	Zn, HCl (conc)	EtOH	mixture
3[a]	Zn, HCl (conc)	EtOH	mixture

[a] Upon consumption of the starting material, the reaction was basified, and Boc_2O was added to the mixture.

Even if reduced product **A-81** were successfully isolated, the coupling reaction would be difficult because of the tertiary carbon centre α to the primary amine. In addition, this highly polar product could cyclize with ease to give undesirable lactam products.

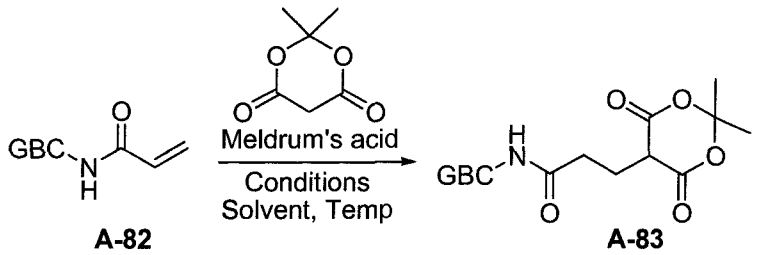
A new route was devised using Meldrum's acid as the starting material that would give phenol **A-85** (Scheme 26). The two acceptors would be linked to the nucleophilic position of the Meldrum's acid to give **A-84**. Ring-opening of this intermediate with a primary amine linked to the phenol would give **A-85**. To begin, amides **A-82** and **A-60** were acylated in quantitative yields using the sequences shown. A few conditions were then investigated in order to produce the required compound **A-83**.

Scheme 26. Derivatization of Meldrum's acid



The reaction of **A-82** with Meldrum's acid was examined using K_2CO_3 as the base and triethylbenzylammonium chloride (TEBA) as a phase-transfer agent (Table 6, entry 1). Unfortunately, only starting material was recovered from the reaction. Similarly, no conversion of the starting material to product was achieved using the same reagents at reflux for two days (entry 2). The use of DIPEA as the base did not give any reactivity (entry 3), but finally, the use of pyrrolidine in CH_2Cl_2 gave a moderate yield (52%) of the desired product **A-83** (entry 4).

Table 6. Michael addition with Meldrum's acid

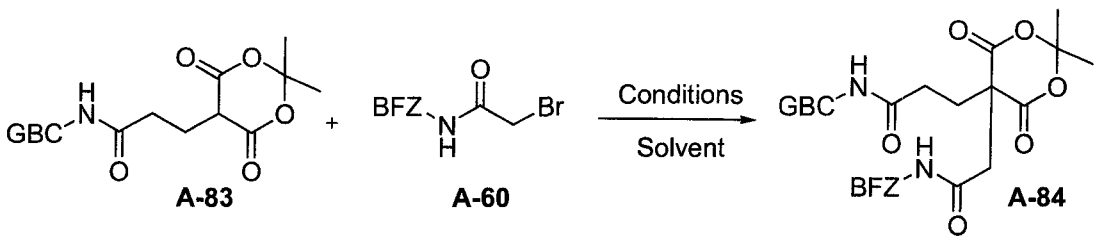


A-82 A-83

Entry	Conditions	Solvent	Temp	Yield (%)
1	TEBA, K_2CO_3	acetonitrile	r.t.	NR
2	TEBA, K_2CO_3	acetonitrile	reflux	NR
3	DIPEA	acetonitrile	r.t.	NR
4	**pyrrolidine**	**CH_2Cl_2**	**r.t.**	**52**

With compound **A-83** in hand, the integration of the BFZ acceptor was attempted. The exposure of **A-83** and **A-60** to TEBA and K_2CO_3 in acetonitrile at room temperature (Table 7, entry 1) or at 60 °C (entry 2) returned only starting material. The use of pyrrolidine in CH_2Cl_2 again gave no reaction (entry 3).

Table 7. Attempted generation of compound A-84



A-83 A-60 A-84

Entry	Conditions	Solvent	Temp	Yield (%)
1	TEBA, K_2CO_3	acetonitrile	r.t.	NR
2	TEBA, K_2CO_3	acetonitrile	60 °C	NR
3	pyrrolidine	CH_2Cl_2	r.t.	NR

The difficulties that were experienced in generating these highly congested centres led us to re-examine the type of design being employed. Fortuitously, an unexpected alternative would soon present itself.

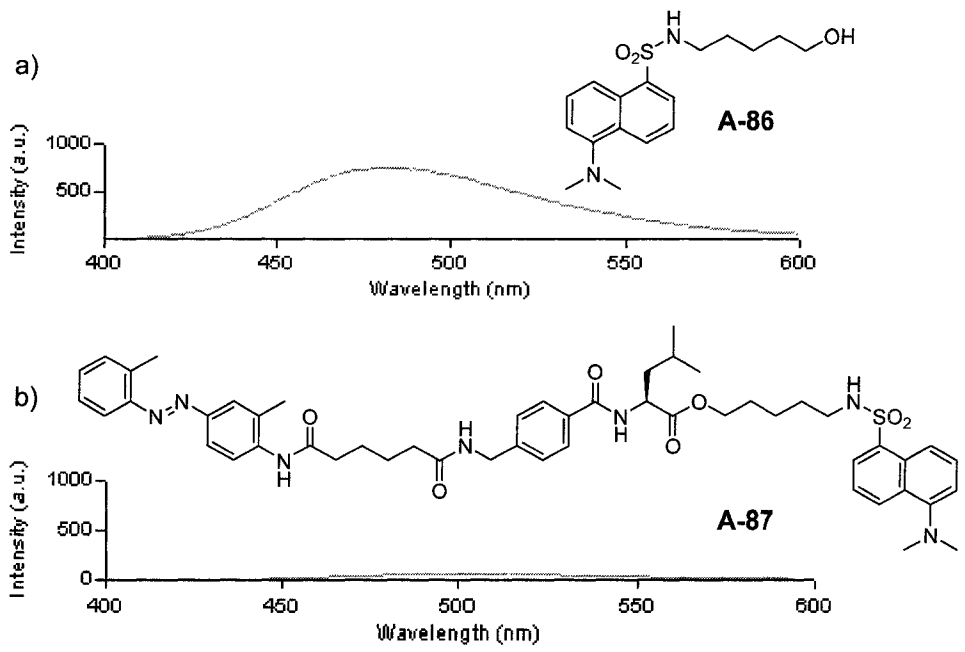
2.2 Identification of GBC as a global acceptor

At the same time as the aforementioned investigations were being performed, a series of donor and acceptor pairs were being analyzed by our research group in order to

identify compatible pairs.[54] The goal was to identify compatible pairs that would operate at distinct wavelengths from each other and that would not interfere with each other. This analysis involved the generation of fluorescence spectra as well as the creation of HPLC calibration curves for the FRET starting materials and products. The HPLC calibration curves would serve to substantiate the results obtained in the FRET analysis in our proof of principle studies.

The fluorescence spectrum of dansyl-bearing compound **A-86** showed a clean spectrum with a maximum emission wavelength at 483 nm (Figure 16). The fluorescence spectrum of molecule **A-87**, which bore a dansyl group tethered to the GBC acceptor through a spacer, showed what we had hoped to see: the fluorescence of the dansyl moiety had disappeared. Advantageously, no extraneous emissions were observed on the spectrum because the GBC is non-fluorescent group. These findings were consistent with reports from the Hartwig group.[45]

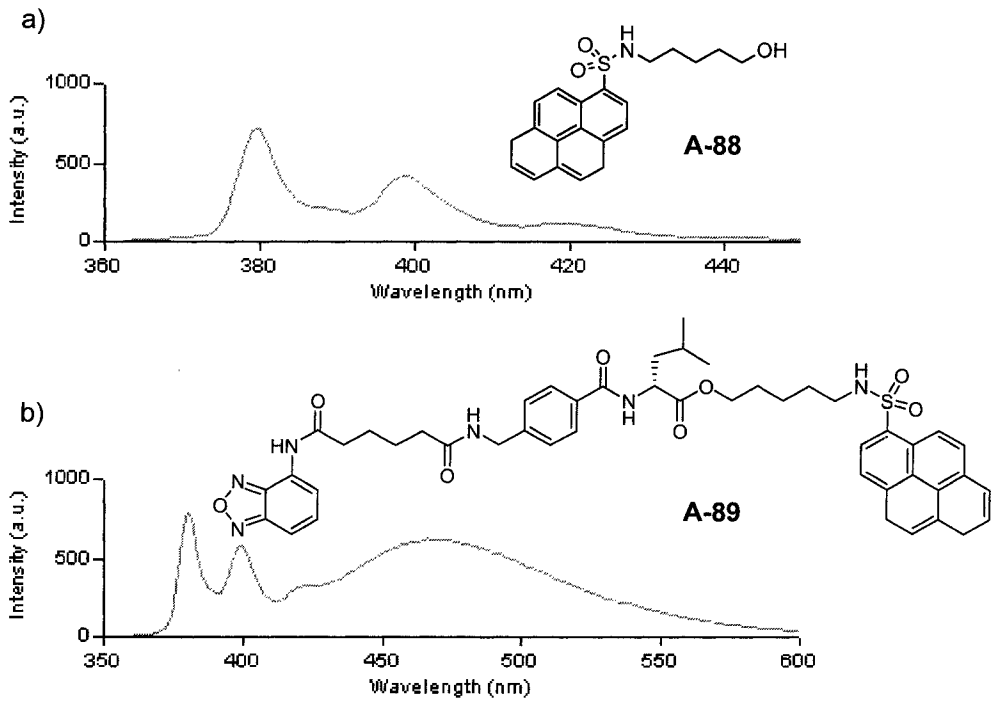
Figure 16. Fluorescence spectrum of DNS (a) and subsequent quenching with GBC (b)



[54] The fluorescence analyses of the donor-acceptor pairs were performed by Josée Cloutier and Ami Chin. HPLC calibration curves of the uncoupled moieties were generated by the author, and HPLC calibration curves of the coupled (donor-acceptor-tethered) moieties were created by Ami Chin. See: Cloutier, J., University of Ottawa, 2004.

Analysis of the fluorescence spectra of the pyrene (PYR) and benzofurazan (BFZ) groups gave less than ideal results. The fluorescence spectrum of pyrene-containing compound **A-88** showed the expected emission bands at 380 nm and 400 nm (Figure 17). A molecule that incorporated both the supposed BFZ acceptor and the pyrene donor (**A-89**) gave an undesirable fluorescence spectrum. The pyrene bands had not been effectively quenched, as evidenced by the characteristic bands at 380 nm and 400 nm. In addition, the BFZ, which is also a fluorophore, showed a complicating strong emission band at 466 nm. To make matters worse, the BFZ emission band overlapped with the dansyl emission (483 nm) and the conclusion that necessarily had to be drawn from all these factors was that the BFZ was an unsuitable acceptor for our purposes.

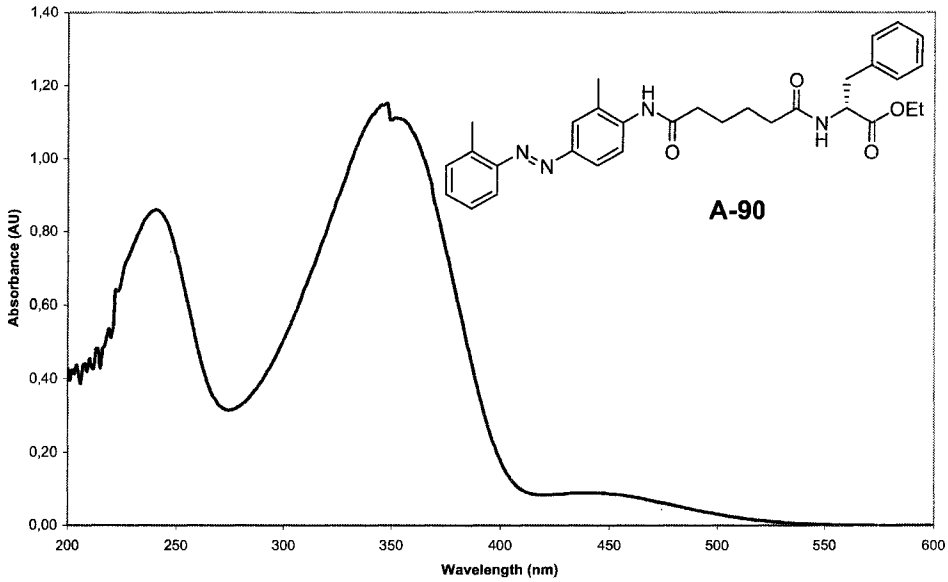
Figure 17. Fluorescence spectra of pyrene (a) and benzofurazan and pyrene (b)



An analysis of the GBC absorption spectrum provided a promising option. The absorption spectrum of the GBC-containing compound **A-90** showed absorption maxima at 239, 348, and 442 nm and the entire absorption spectrum spanned the range from approximately 220–520 nm (Figure 18). This broad absorption spectrum suggested that the PYR might also be quenched by the GBC acceptor as the theoretical emission

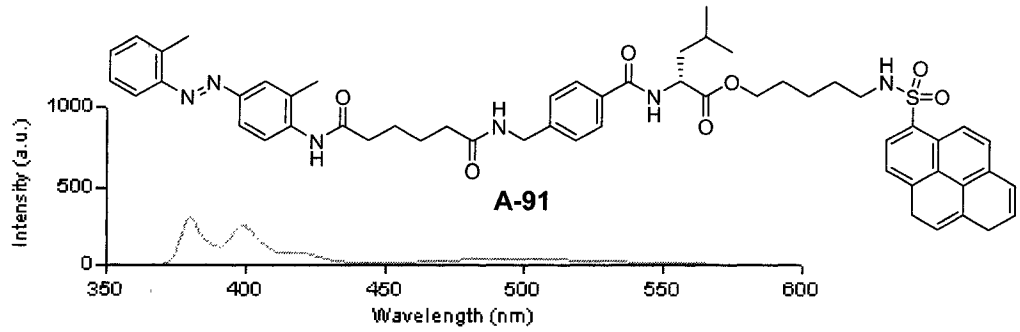
wavelength of PYR was within the range of the broad absorption wavelengths of GBC. One concern was that the PYR, because of its high fluorescence intensity, might overwhelm the spectra and therefore not be a suitable partner, but since this seemed to be the best system identified thus far, we decided to proceed to the testing stage.

Figure 18. Absorption spectrum of a GBC-containing compound



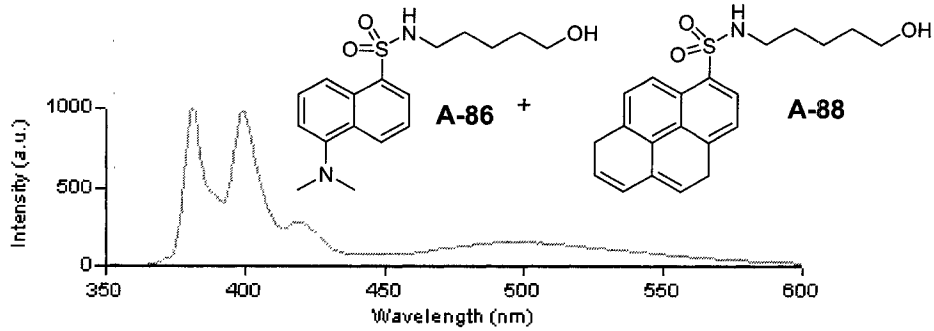
The fluorescence spectrum of a PYR- and GBC-containing molecule (**A-91**) was analyzed to investigate the quenching efficiency of the GBC moiety. As can be seen in Figure 19, the fluorescence of the PYR was not completely quenched in the presence of GBC; however, we felt that the reactions could be calibrated appropriately when required in order to account for this background fluorescence. In addition, other modifications such as exciting the reaction solutions at wavelengths away from the absolute maximum excitation wavelength of the PYR residue would help to decrease the PYR emission intensity sufficiently to enable to use of the PYR moiety as a FRET donor for enantioselective reaction monitoring.

Figure 19. PYR was sufficiently quenched by GBC



A final set of control reactions were performed to ensure that the intense emission of the PYR would not overpower the weaker fluorescence of the DNS. An equimolar mixture of DNS (**A-86**) and PYR (**A-88**) compounds was prepared and tested. Auspiciously, the fluorescence spectrum of the mixture showed that although the PYR emission was very intense, the DNS emission was clearly visible, and the PYR and DNS emission wavelengths were quite distinct (Figure 20). These characteristics would facilitate detection during the testing phase.

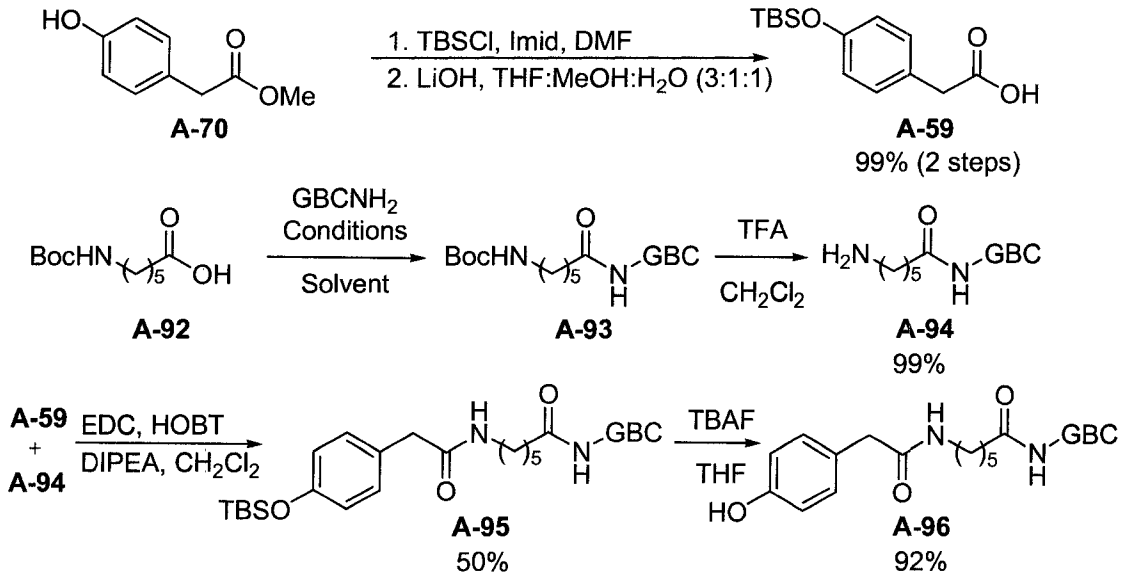
Figure 20. Distinct emission bands were discernable for DNS and PYR



2.3 Re-engineered synthesis of the phenol-acceptor moiety

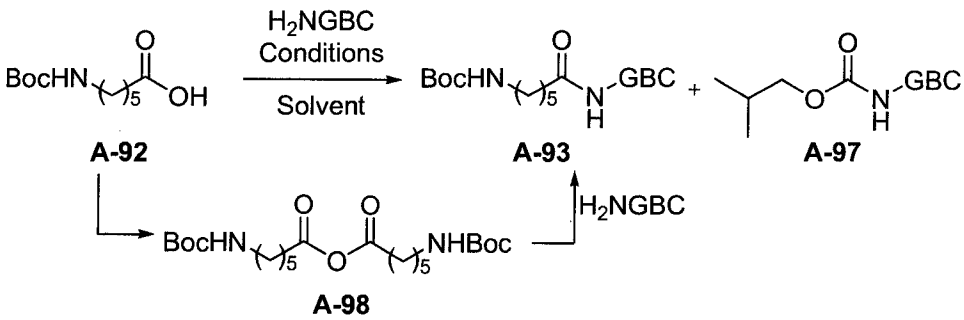
The results described above suggested that only a single acceptor, GBC, needed to be tethered to the phenol moiety. To construct the required fragments, compound **A-70** was protected as the silyl ether and the resulting intermediate was then saponified using LiOH to give carboxylic acid **A-59** (Scheme 27). The preparation of the GBC portion of the molecule began with the coupling of **A-92** to $GBCNH_2$.

Scheme 27. Synthesis of GBC-tethered phenol



A series of conditions were investigated before achieving the desired coupling of the carboxylic acid (**A-92**) with the GBC moiety (Table 8). Using DCC and DIPEA returned only starting material (entry 1). EEDQ, a more potent amide coupling reagent, also gave no reaction at room temperature (entry 2) or at reflux (entry 3). The acid chloride of **A-92** was generated using oxalyl chloride and DMF in CH_2Cl_2, and to this intermediate was added a solution of $GBCNH_2$ in CH_2Cl_2 (entry 4). Unfortunately, no reaction was observed. In a similar reaction, DIPEA was added along with $GBCNH_2$ to the acid chloride of **A-92**; however, no product formation was observed (entry 5). A mixed anhydride was next generated using carboxylic acid **A-92** and isobutylchloroformate. To this was added a solution of $GBCNH_2$ and DIPEA in CH_2Cl_2 (entry 6). From this reaction, a 97% yield of undesired carbamate **A-97** was obtained. Given that some reactivity had at least been observed, this mixed anhydride route was further probed. A mixed anhydride was generated using carboxylic acid **A-92** and pivaloyl chloride. To this was added a solution of $GBCNH_2$ and DIPEA in CH_2Cl_2 (entry 7). The results were encouraging as finally a 20% yield of the desired product **A-93** was obtained. The acid chloride of **A-92** was generated using oxalyl chloride and DMF. The anhydride **A-98** was generated by combining an equivalent of carboxylic acid **A-92** with an equivalent of the acid chloride of **A-92**. To this intermediate was added a solution of $GBCNH_2$ and DIPEA in CH_2Cl_2 (entry 8) and to our delight, a 67% yield of the desired product was obtained.

Table 8. Generation of amide A-93.



Entry	Conditions	Solvent	Temp	Yield (%)
1	DCC, DIPEA	CH_2Cl_2	r.t.	NR
2	EEDQ	CH_2Cl_2	r.t.	NR
3	EEDQ	CH_2Cl_2	reflux	NR
4	$(COCl)_2$, DMF	CH_2Cl_2	r.t.	NR
5[a]	$(COCl)_2$, DMF; DIPEA	CH_2Cl_2	r.t.	NR
6[b]	isobutylchloroformate; DIPEA	CH_2Cl_2	r.t.	97 **A-97**
7[c]	pivaloyl chloride; DIPEA	CH_2Cl_2	r.t.	20
8[d]	**$(COCl)_2$, DMF; DIPEA**	**CH_2Cl_2**	**r.t.**	**67**

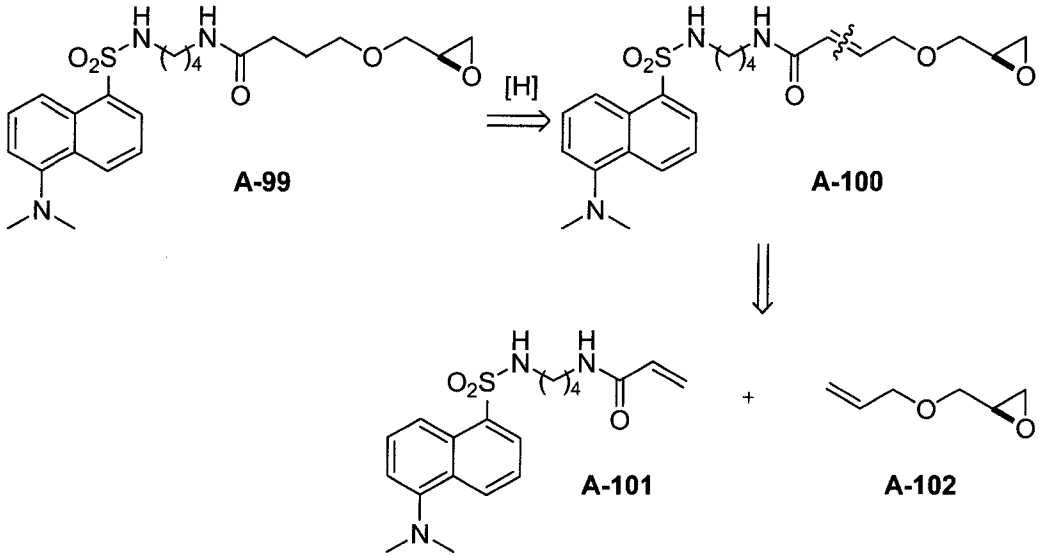
[a] A solution of $GBCNH_2$ and DIPEA in CH_2Cl_2 was added to a solution of the acid chloride in CH_2Cl_2. [b] A mixed anhydride was generated by the reaction **A-92** with isobutylchloroformate. To this was added a solution of $GBCNH_2$ and DIPEA in CH_2Cl_2. [c] A mixed anhydride was generated by the reaction of **A-92** with pivaloyl chloride. To this was added a solution of $GBCNH_2$ and DIPEA in CH_2Cl_2. [d] The acid chloride of **A-92** was generated using $(COCl)_2$ and DMF in CH_2Cl_2. After one hour, the volatives were removed under reduced pressure. To this was added a second equivalent of carboxylic acid **A-92**. After one hour, $GBCNH_2$ and DIPEA in CH_2Cl_2 were added to the reaction.

Deprotection of the BOC-carbamate gave primary amine **A-94** in quantitative yield. Amide bond formation proceeded successfully with the protected phenol **A-59**, albeit in only a 50% yield, to give product **A-95**. Deprotection of the silyl ether with TBAF gave the target phenol **A-96** in 92% yield. With the nucleophilic phenol successfully tethered to the GBC, we turned our attention to the synthesis of the pseudo-enantiomeric epoxides that would bear the fluorescent donors.

2.4 Synthesis of the epoxide-tethered dansyl donor

The preparation of the fluorescent donors tethered to the epoxide enantiomers was envisaged using a cross-metathesis reaction as the key step (Scheme 28). Epoxide **A-99** would result from the hydrogenation of alkene **A-100**. Alkene **A-100** would be generated from a cross metathesis between **A-101** and **A-102**.

Scheme 28. Retrosynthetic analysis of the donor moieties

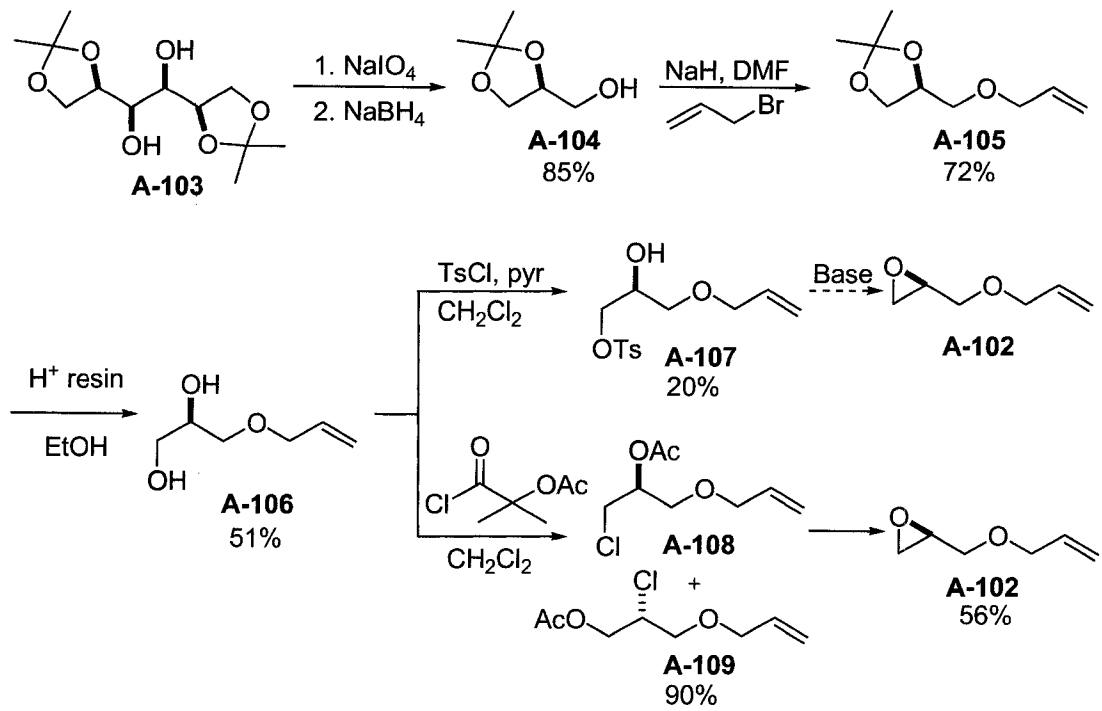


The synthesis of epoxide **A-102** began with protected D-mannitol (**A-103**). The choice of this route ensured that the chiral centre was installed and of known configuration right from the beginning. The oxidative cleavage of diol **A-103** followed by the immediate reduction of the resultant aldehyde gave alcohol **A-104** in 85% yield (Scheme 29).[55] Allyl ether **A-105** was prepared by the S_N2 reaction between the sodium alkoxide of **A-104** and allyl bromide.[56] Acetal deprotection was accomplished using an Amerlyst-120 acidic resin in EtOH to afford diol **A-106** in 51% yield. The selective tosylation of the primary alcohol in the presence of the secondary alcohol was then attempted. The monotosylated product (**A-107**) would then be treated with a base to give the desired epoxide **A-102**.

[55] LeCocq, J.; Ballou, C. E. *Biochemistry* **1964**, *3*, 976. Note: adding solid NaCl to the aqueous layer in the work-up stage greatly facilitated the extraction of the product into $CHCl_3$.
[56] Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005.

Unfortunately, a mixture of ditosylated and alcohols that were monotosylated at either the primary and secondary position were obtained, giving only a 20% yield of **A-107**.[57]

Scheme 29. Preparation of the epoxide moiety



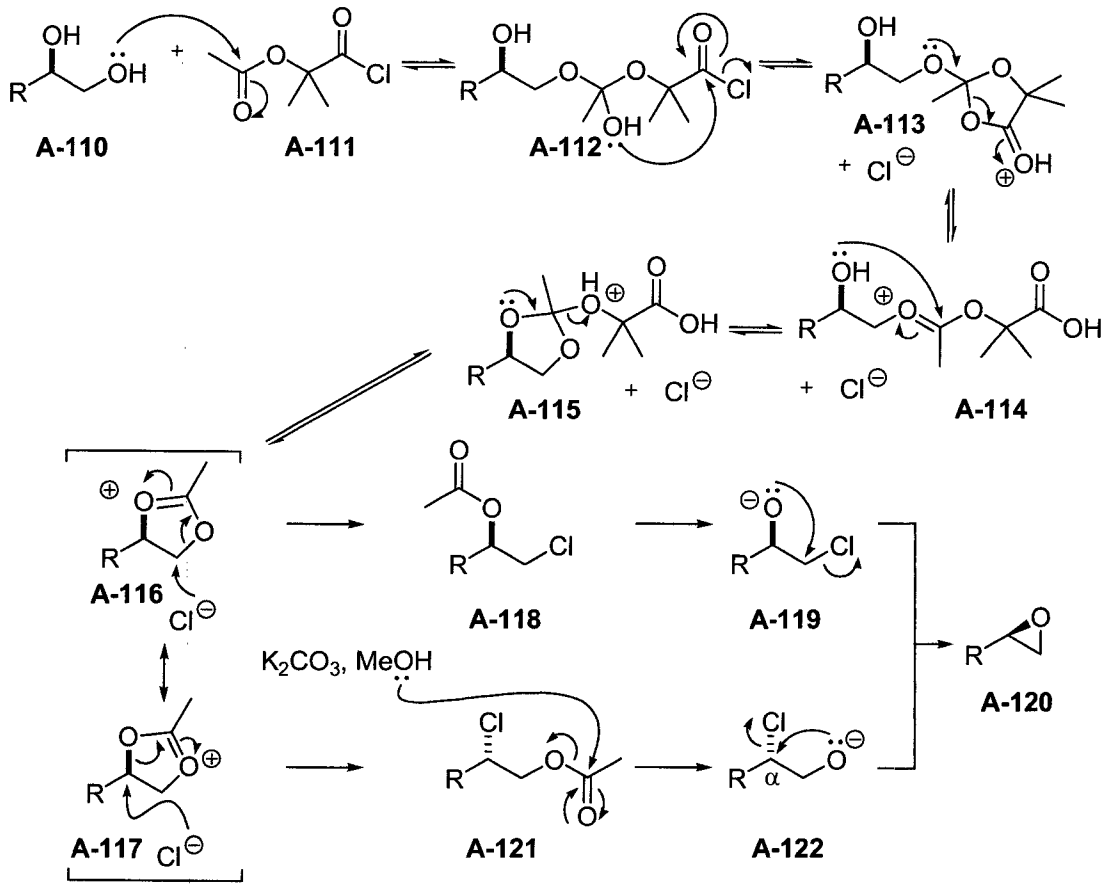
An alternate epoxidation route was explored. Diol **A-106** was exposed to the Moffat reagent,[58] α-acetoxyisobutyryl bromide in CH_2Cl_2, giving the desired products **A-108** and **A-109** in a 90% combined yield.[59] The immediate exposure of the mixture of chlorides **A-108** and **A-109** to sodium methoxide in methanol gave the desired epoxide **A-102** in 56% yield.

The mechanism of the Moffat reaction deserves comment (Scheme 30). Addition of the primary alcohol of **A-110** occurred at the least hindered carbonyl of **A-111** to give product **A-112**. Intramolecular cyclization of **A-112** with concomitant expulsion of the chloride gave 5-membered ring **A-113**. Intramolecular expulsion of the carboxylic acid gave oxonium **A-114**, which underwent another intramolecular cyclization with the

[57] For a preparation *via* an kinetic enzymatic resolution, see: Pederson, R. L.; Liu, K. K. C.; Rutan, J. F.; Chen, L.; Wong, C. H. *J. Org. Chem.* **1990**, *55*, 4897.
[58] Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.
[59] Iranpoor, N.; Zeynizadeh, B. *J. Chem. Res.* **1998**, 582.

secondary alcohol to give 5-membered ring intermediate **A-115**. Expulsion of the tertiary alcohol lead to oxonium resonance structures **A-116** and **A-117**. Attack of the chloride occurred at either the primary or secondary carbons of the ring, giving chlorides **A-118** and **A-121** that possessed opposite configurations at the chiral centre. Upon exposure to K_2CO_3 in MeOH, alkoxides **A-119** and **A-122** were generated and these cyclized with inversion of configuration at the α-carbon, to give the same epoxide **A-120**.

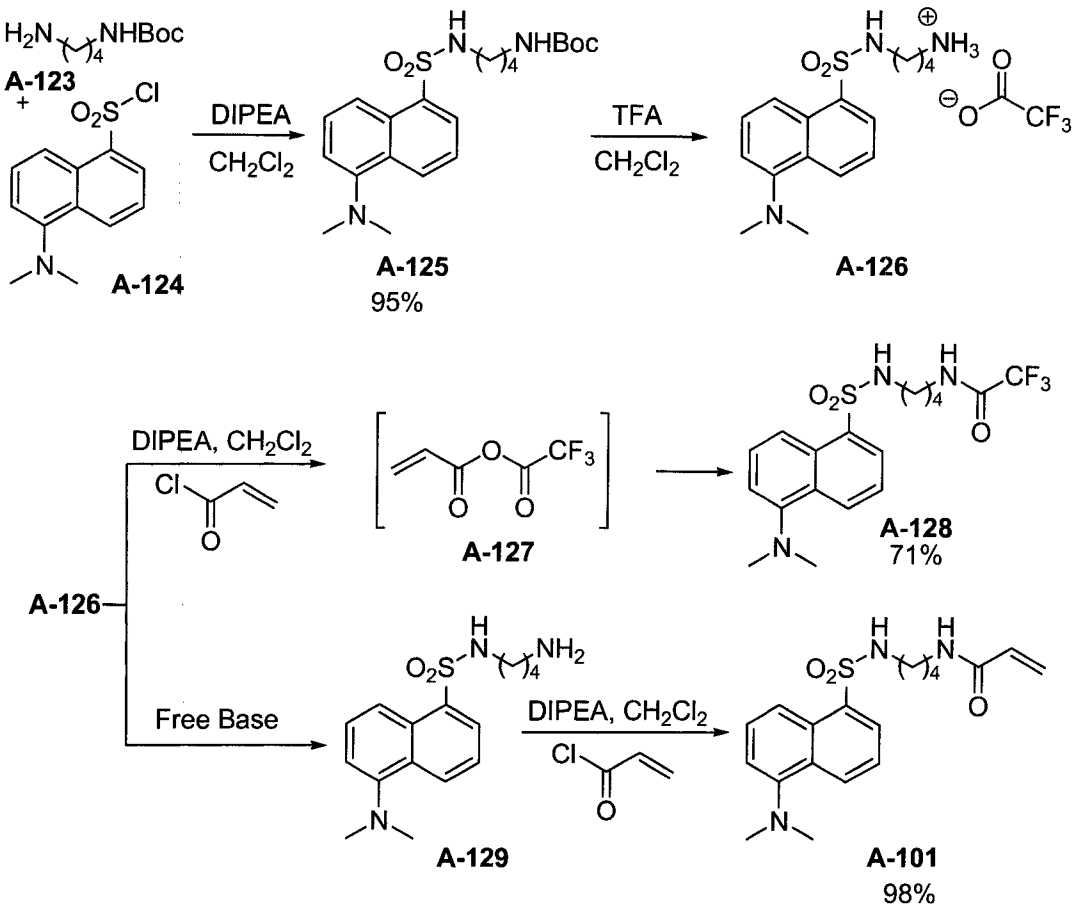
Scheme 30. The mechanism of the Moffat reaction



With this fragment (**A-102**) in hand, the synthesis of the dansyl (DNS) donor moiety began (Scheme 31). The reaction of dansyl chloride (**A-124**) with protected putrescene (**A-123**) gave fluorescent moiety **A-125** in 95% yield. Deprotection of the carbamate gave the primary amine as the TFA salt (**A-126**). The free base of **A-126**, generated by treatment of the salt with a solution of NaOH (1M) and extraction of the amine into EtOAc, was acylated in excellent yield to give acrylamide **A-101**. It was found that if the

TFA salt **A-126** was used directly in the acylation reaction, a side product (**A-128**) resulting from the formation of a mixed anhydride (**A-127**) was obtained in excellent yield.[60]

Scheme 31. Synthesis of the DNS-alkene (A-101)



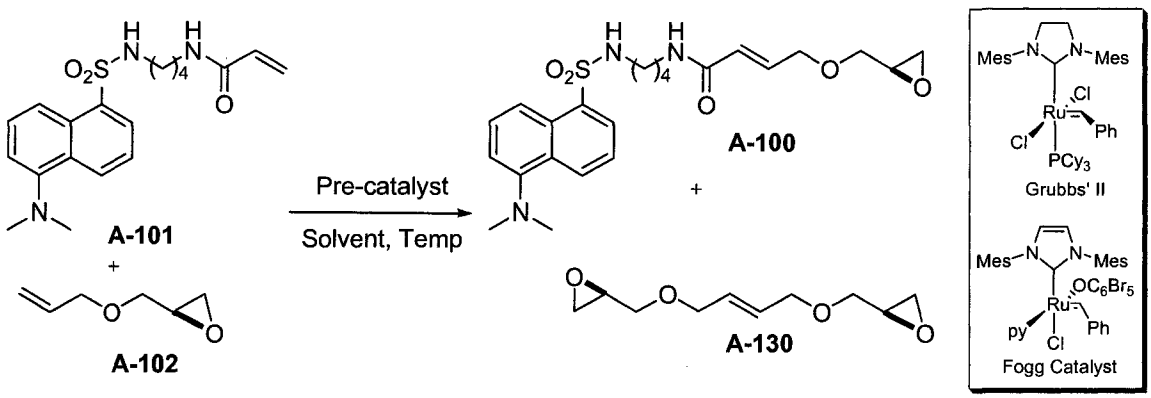
With fluorescent alkene **A-101** and epoxide-tethered alkene **A-102** prepared, the stage was set for the cross metathesis reaction. Olefin metathesis is a powerful method for the formation of substituted double bonds from less-substituted starting olefins. Metathesis processes are commonly used in ring-closing and ring-opening reactions and have achieved broad applications in the synthesis of complex organic molecules.[61] Since the discovery of the cross metathesis reaction almost fifty years ago, extensive research has

[60] The amine was regenerated in 62% yield by the treatment **A-128** with K_2CO_3 in MeOH/H_2O (10:1)
[61] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.

been devoted to the development of metathesis pre-catalysts that show high activity, stability, and functional group tolerance.[62]

Alkenes **A-101** and **A-102** were therefore exposed to Grubbs' second generation pre-catalyst (Grubbs II)[63] in CH_2Cl_2, however only homodimerization product **A-130** was obtained (Table 9, entry 1). A syringe pump addition of the allylic ether **A-102** was performed in an attempt to minimize the homodimerization, however this had no effect on the result (entry 2). A reaction with Grubbs II pre-catalyst was heated to reflux, but again no desired product was observed (entry 3). The Fogg catalyst[64] was then attempted in CH_2Cl_2 at reflux (entry 4) and in $CHCl_3$ at reflux (entry 5), but without success. A higher catalyst loading (10 mol%) was then attempted with both the Grubbs II (entry 6) and Fogg (entry 7) catalysts, but unfortunately, the desired cross metathesis product was never observed.

Table 9. Attempted cross-metathesis of DNS and epoxide moieties



Entry	Pre-catalyst (5 mol%)	Solvent	Temp	Yield (%)
1	Grubbs II	CH_2Cl_2	r.t.	NR[a]
2[b]	Grubbs II	CH_2Cl_2	r.t.	NR[a]
3	Grubbs II	CH_2Cl_2	reflux	NR[a]
4	Fogg Catalyst	CH_2Cl_2	reflux	NR[a]
5	Fogg Catalyst	$CHCl_3$	reflux	NR[a]
6	Grubbs II (10 mol%)	CH_2Cl_2	reflux	NR[a]
7	Fogg Catalyst (10 mol%)	CH_2Cl_2	reflux	NR[a]

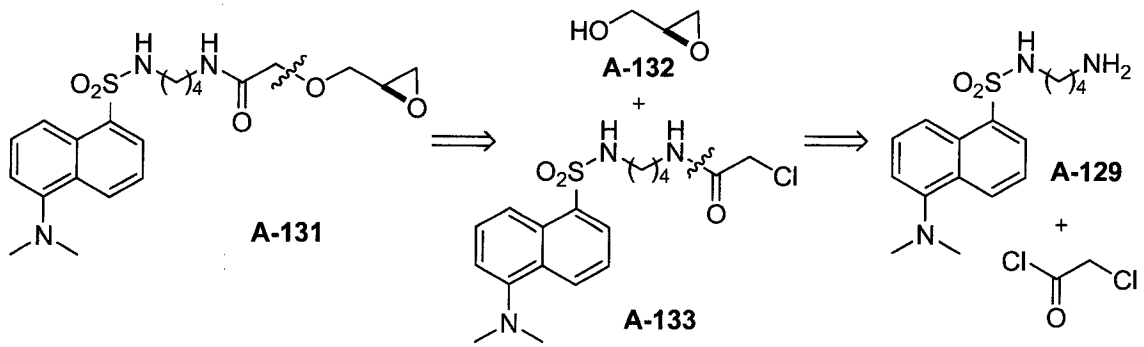
[a] Extensive homodimerization was observed. [b] The epoxide moiety was added via syringe pump.

[62] Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.
[63] Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003.
[64] Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882.

This homodimerization process was clearly favored. This has been reported by Grubbs who noted that terminal alkenes, and in particular allylic ethers, undergo homodimerization very rapidly.[65] Acrylamides homodimerize and react much more slowly, and for our substrate, it seemed that the acrylamide would not react at all. We felt at this point that even if we could force the acrylamide moiety (**A-101**) to react, that at best we would achieve a mixture of cross-coupled products. We therefore decided against this route, and looked to more reliable synthetic strategies for the synthesis of the required substrate.

The modification of the route varied in the manner by which the epoxide was linked to the fluorescent moiety (Scheme 32). Instead of using a cross-metathesis reaction to link the epoxide to the fluorescent donor, an S_N2 reaction between the alkoxide of **A-132** and α-chloroamide **A-133** would be employed. **A-133** would in turn arise from the acylation of **A-129** using chloroacetyl chloride.

Scheme 32. Retrosynthetic analysis of an alternative to the cross-metathesis route

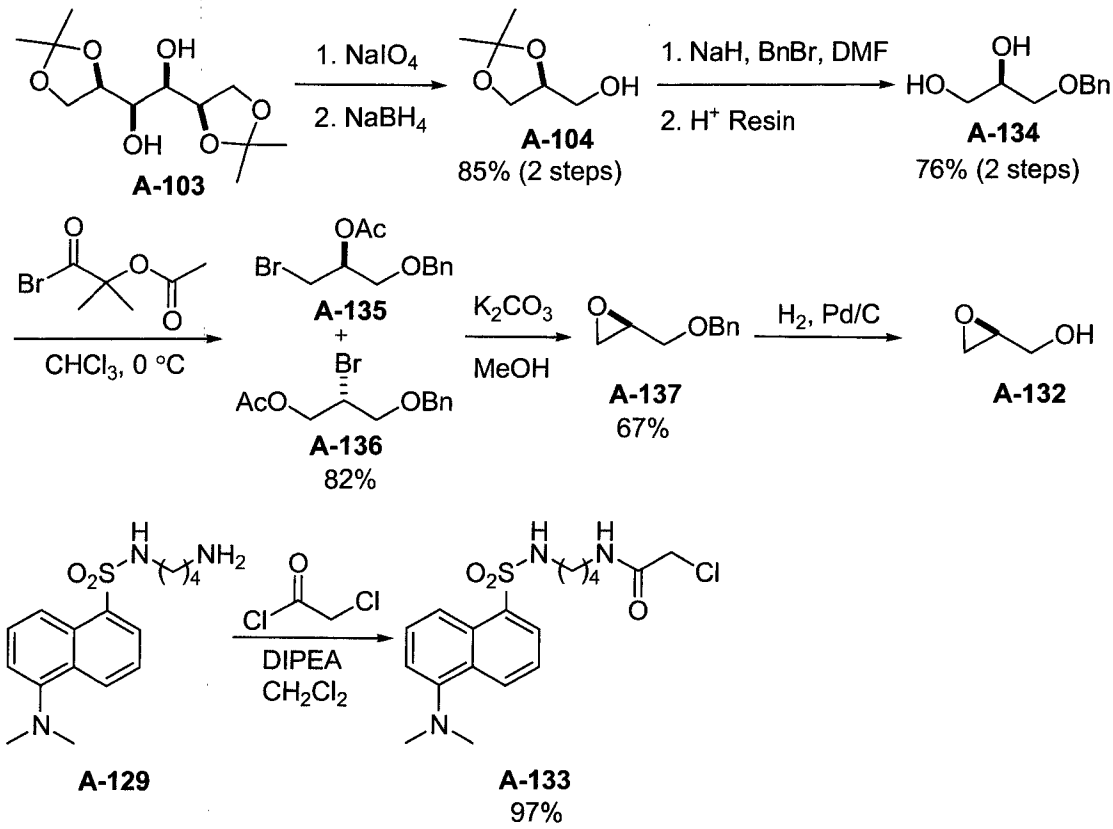


The requisite epoxide (**A-132**) was synthesized starting with protected D-mannitol **A-103** (Scheme 33). Oxidative cleavage of the diol followed by immediate reduction of the resultant aldehyde gave alcohol **A-104** in an 85% yield over two steps. Benzylation of the alcohol[66] and acetal deprotection gave diol **A-134**[67] in a 76% yield over two steps. Diol **A-134** was treated with the Moffat reagent to generate a mixture of bromides **A-135** and

[65] Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
[66] For a similar preparation see: Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M. E. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. *J. Med. Chem.* **1985**, *28*, 926.
[67] For a similar preparation see: Menger, F. M.; Chen, X. Y.; Brocchini, S.; Hopkins, H. P.; Hamilton, D. *J. Am. Chem. Soc.* **1993**, *115*, 6600.

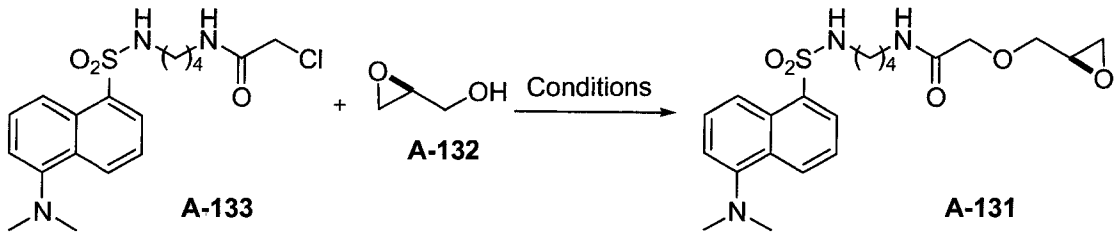
A-136 in 82% yield.[58] Treatment of the mixture with NaOMe in MeOH gave a methoxy-substituted product, however the use of K_2CO_3 in MeOH gave epoxide **A-137** in 67% yield. Debenzylation with H_2 and Pd/C gave alcohol **A-132** cleanly.

Scheme 33. Synthesis of DNS-epoxide A-131



A number of basic conditions were attempted for the generation of epoxide **A-131**. A solution of chloride **A-133** and DIPEA in THF was introduced to a suspension of alcohol **A-132** and NaH in THF, however no product was generated (Table 10, entry 1). The reaction also did not proceed when DMF was used as the solvent (entry 2), or when strong bases such as KH (entry 3) or BuLi (entry 4) were employed.

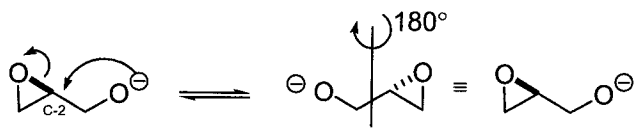
Table 10. Attempted S_N2 reaction to generate epoxide A-131



Entry	Conditions	Result
1	NaH, DIPEA, THF	NR
2	NaH, DIPEA, DMF	NR
3	KH, DIPEA, DMF	NR
4	BuLi, DIPEA, THF	NR

2,3-Epoxy alkoxides such as **A-138** can undergo a Payne rearrangement in which the configuration at C-2 is inverted (Scheme 34).[68] Due to the nature of the substrate, a Payne rearrangement would return the identical compound. The nucleophilicity of alkoxide **A-138** was likely diminished due to this rapid and reversible rearrangement, which would explain the failure of the reaction.

Scheme 34. The Payne rearrangement



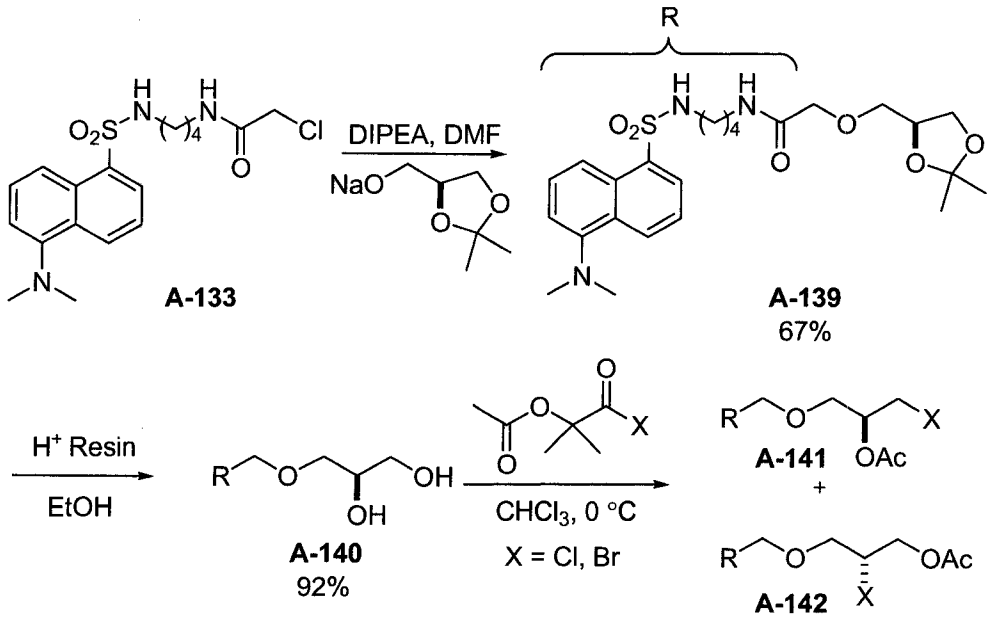
A-138

A slight modification of this route was ultimately successful (Scheme 35). Treatment of chloride **A-133** with the alkoxide derived from the treatment of alcohol **A-104** with NaH gave ether **A-139** in 67% yield. Acetal deprotection proceeded smoothly in 92% yield.[69] Treatment of diol **A-140** with the Moffat reagent[58] gave products **A-141** and **A-142**.

[68] Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

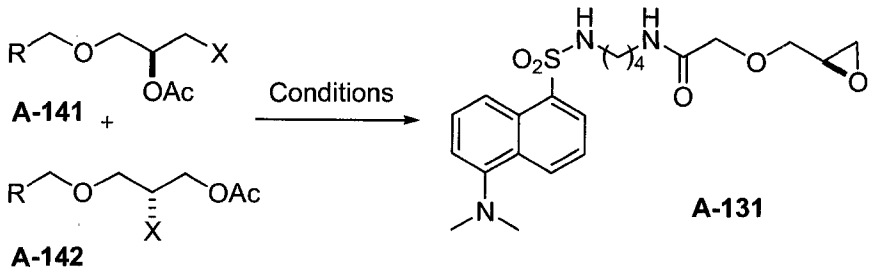
[69] It was found that ethanol was the best solvent for this process, however, lyophilization, or freeze drying, of the product was required to completely removed the ethanol from the material.

Scheme 35. Modification of the synthesis of the DNS-epoxide



A number of conditions were attempted to effect the conversion of chlorides **A-141** and **A-142** to the desired epoxide (Table 11). Exposure of chlorides **A-141** and **A-142** to K_2CO_3 in MeOH and using an EtOAc/H_2O workup gave an intractable mixture of products (entry 1). The use of brine as the aqueous layer in the workup gave 5% of the desired product **A-131** (entry 2). Filtering the reaction mixture directly through a pad of silica gave an intractable mixture of products (entry 3). Exposure of bromides **A-141** and **A-142** to NaOMe in MeOH using an EtOAc/H_2O workup gave a trace of diol **A-140** (entry 4). Exposure of bromides **A-141** and **A-142** to K_2CO_3 in MeOH using an EtOAc/brine workup gave a trace of desired product **A-131** (entry 5). Seemingly, both the starting materials and product were highly sensitive to both the reaction conditions and workup.

Table 11. Generation of epoxide A-131 from the Moffat precursors

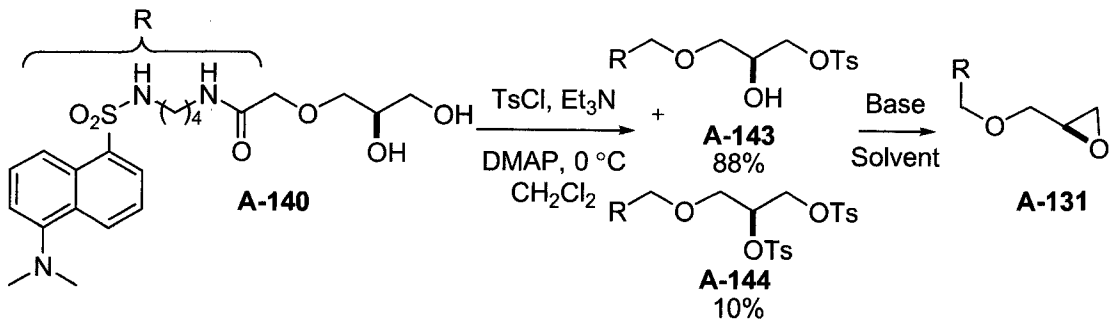


Entry	X	Conditions	Workup[a]	Result
1	Cl	K_2CO_3, MeOH	EtOAc/H_2O	intractable mixture
2	Cl	K_2CO_3, MeOH	EtOAc/Brine	5% **A-131**
3	Cl	K_2CO_3, MeOH	none[b]	intractable mixture
4	Br	NaOMe, MeOH	EtOAc/H_2O	trace diol **A-140**
5	Br	K_2CO_3, MeOH	EtOAc/Brine	trace **A-131**

[a] Upon consumption of the starting material, the reaction mixture was partitioned between EtOAc and the indicated aqueous layer. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. [b] The reaction mixture was filtered through a plug of silica.

A more conventional route was investigated for the generation of the desired epoxide. Tosylation of diol **A-140** generated a mixture of primary tosylate **A-143** (88%) and ditosylated product **A-144** (10%) (Table 12). The conversion of primary tosylate **A-143** to epoxide **A-131** was accomplished in 43% yield using NaOMe in MeOH (entry 1). K_2CO_3 proved to be a superior base for this transformation, providing product **A-131** in a 64% yield (entry 2).

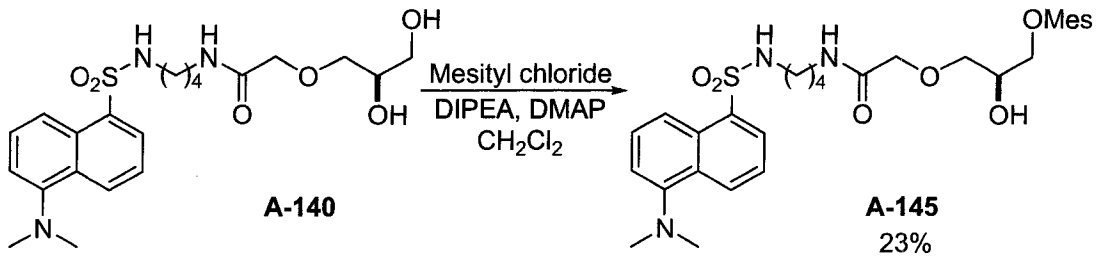
Table 12. Tosylation route to desired epoxide



Entry	Base	Solvent	Yield A-131 (%)
1	NaOMe	MeOH	43
2	**K_2CO_3**	**MeOH**	**64**

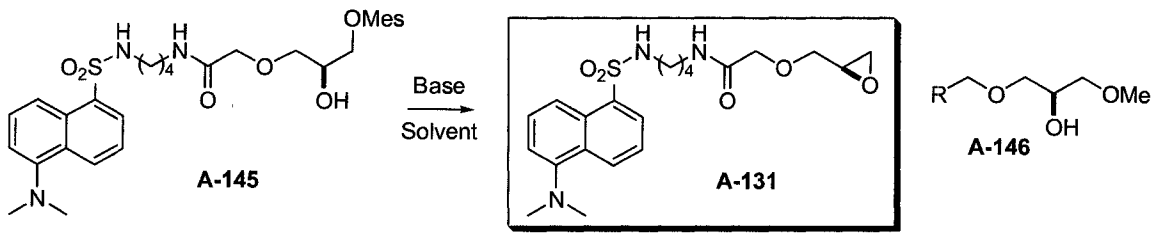
Mesitylation of diol **A-140** was simultaneously investigated (Scheme 36). The exposure of diol **A-140** to mesitylsulfonyl chloride, DIPEA, and DMAP in CH_2Cl_2 gave product **A-145** in 23% yield in addition to a small amount of di-addition product.[70]

Scheme 36. Mesitylation of diol A-140



Exposure of secondary alcohol **A-145** to K_2CO_3 in MeOH resulted in a plethora of unidentifiable products (Table 13, entry 1). The use of sodium methoxide as the base gave undesired intermolecular S_N2 product **A-146** (entry 2). DBU gave a promising result: a trace of product was apparent after a three-day reaction (entry 3). At last, the use of sodium hydride in THF cleanly gave the desired epoxide product (**A-131**) in under one hour in an 81% yield (entry 4).[71]

Table 13. Final step in the synthesis of the DNS-epoxide (A-131)



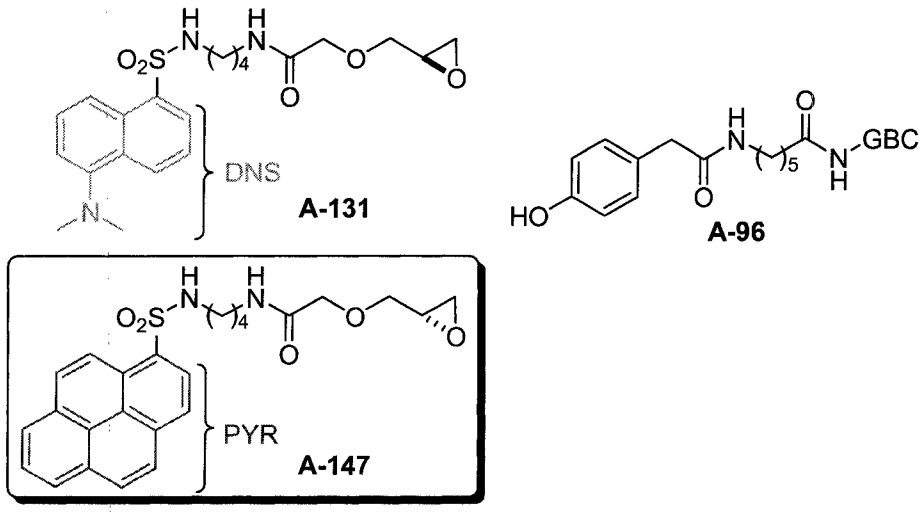
Entry	Conditions	Solvent	Result
1	K_2CO_3	MeOH	mixture
2	NaOMe	MeOH	60% **A-146**
3[a]	DBU	THF	trace
4	**NaH**	**THF**	**81% A-131**

[a] Three-day reaction.

[70] For a mesitylation procedure, see: Xu, Y.-Z.; Zheng, Q.; Swann, P. F. *Tetrahedron* **1992**, *48*, 1729.
[71] The epoxide generated was extremely sensitive to water and acid. The optimal workup consisted of filtration through a plug of silica that was buffered with Et_3N. Purification by column chromatography was successful only if the column was buffered with 1% Et_3N.

We now had two of the three required compounds, and we would apply the principles determined in the synthesis of the dansyl-epoxide to the synthesis of the pseudo-enantiomer that would bear the pyrene-epoxide (Figure 21).

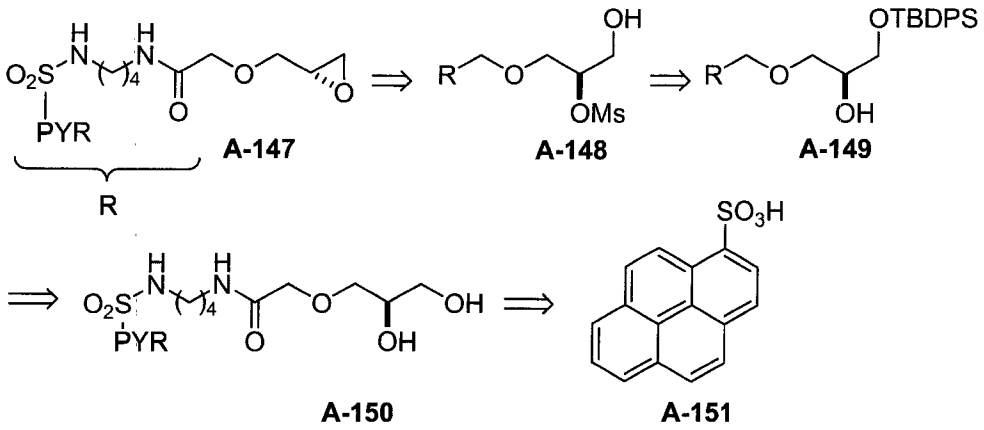
Figure 21. GBC-acceptor moiety and DNS-donor moiety successfully synthesized



2.5 Synthesis of the epoxide-tethered pyrene donor

Our strategy to synthesize the pyrene moiety followed the same general path as the synthesis of the dansyl moiety, however the final steps differed in order to generate the opposite epoxide configuration. The target epoxide **A-147** would arise from cyclization of the primary alcohol **A-148** (Scheme 37). The primary alcohol (**A-148**) would be generated from diol **A-150** by silylation of the primary alcohol to give **A-149**, then mesylation of the secondary alcohol, and finally deprotection of the silyl ether. The pyrene moiety would initially be derived from pyrenesulfonic acid (**A-151**), and diol **A-151** would be generated in a manner analogous to that employed for the synthesis of the dansyl epoxide.

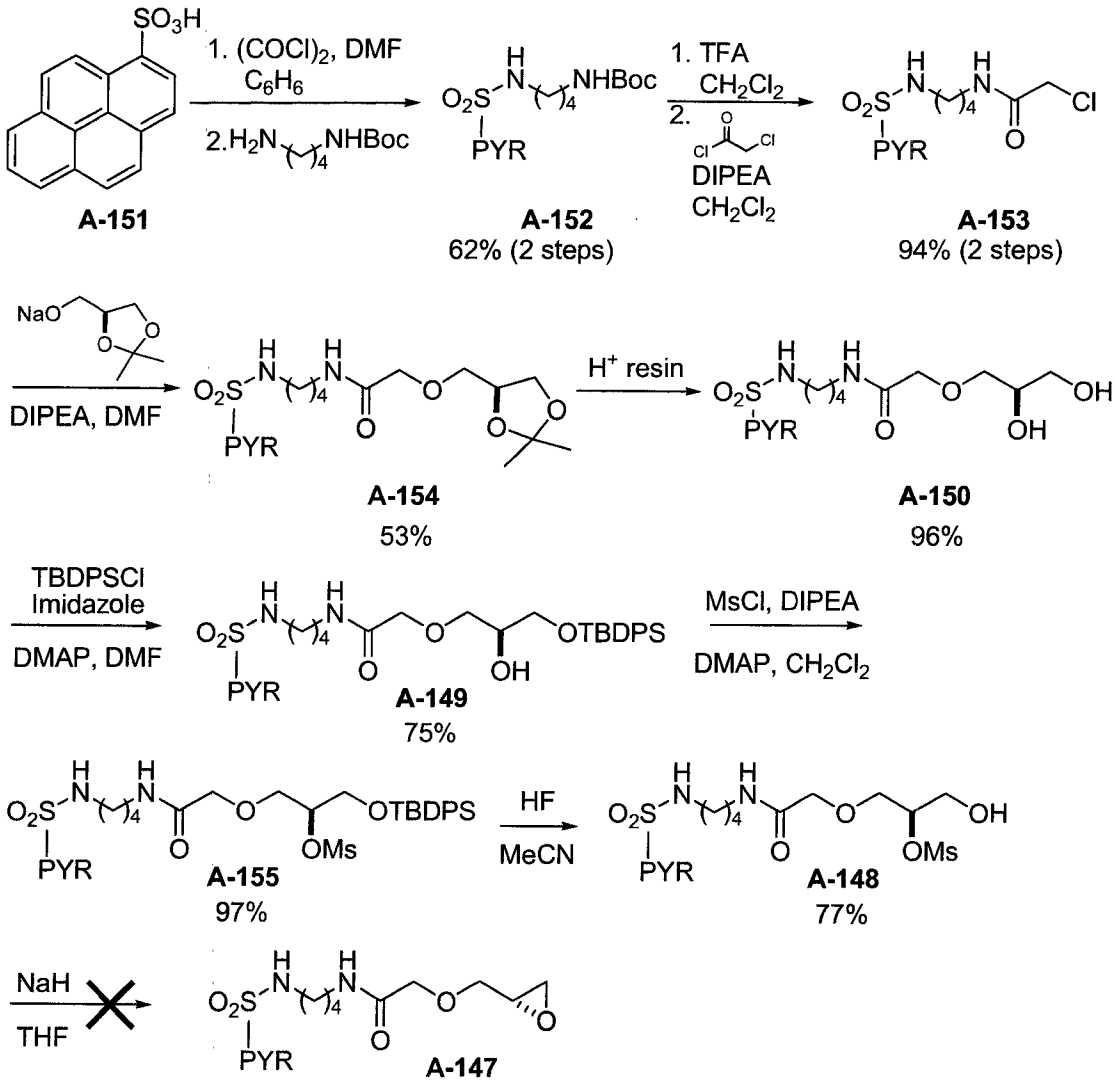
Scheme 37. Retrosynthetic analysis of the fluorescent pyrene epoxide



Pyrenesulfonic acid (**A-151**) was converted to the sulfonyl chloride using oxalyl chloride (Scheme 38). Exposure of the crude product to BOC-protected putrescene (**A-123**) gave carbamate **A-152** in 62% yield over two steps. Deprotection of the amine was accomplished using TFA, and the crude amine was acylated with chloroacetyl chloride to give product **A-153** in a 94% yield over two steps. The sodium alkoxide of acetal **A-104** was generated using NaH in DMF and to this was added a solution of chloride **A-153** and DIPEA in DMF to give ether **A-154** in 53% yield. Deacetylation was done using an acidic resin to give diol **A-150** in 96% yield.[72]

[72] The product was lyophilized to removed the final traces of EtOH.

Scheme 38. Synthesis of the epoxide-tethered pyrene donor



When mono-protection of the primary alcohol was attempted with *tert*-butyldi*methyl*silyl chloride, mixtures of primary and secondary silyl ethers were obtained. The use of the larger *tert*-butyldi*phenyl*silyl chloride,[73] on the other hand, cleanly gave the primary silyl ether **A-149** in 75% yield along with a small amount of double addition product. Mesylation of the secondary alcohol (**A-149**) proceeded smoothly to give compound **A-155** in 97% yield. Deprotection of the silyl ether was performed using HF in acetonitrile to give cyclization precursor **A-148** in 77% yield.

[73] Castagnolo, D.; Armaroli, S.; Corelli, F.; Botta, M. *Tetrahedron Asymm.* **2004**, *15*, 941.

We used the optimized condition for the epoxide generation in the dansyl moiety for the cyclization of primary alcohol **A-148**. Thus, **A-148** was exposed to NaH in THF, however, while gas evolution was observed, only a small amount of a new compound seemed to form as indicated by TLC. Unfortunately, solubility difficulties and likely the instability of the epoxide product prevented isolation of this new product.[74]

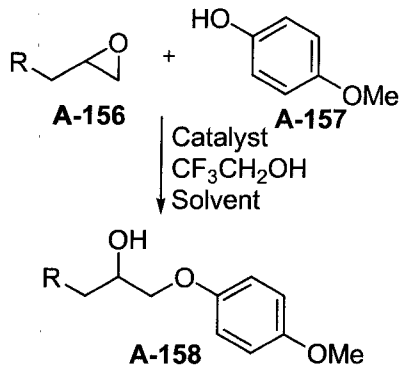
The viability of the epoxide opening between dansyl-epoxide (**A-131**) and GBC-phenol (**A-96**) was investigated before using precious material on the optimization of the cyclization reaction.

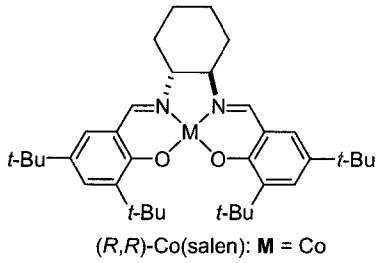
2.6 Testing the DNS-epoxide and the GBC-phenol with the Co(salen) catalyst

Using methodology developed by the Jacobsen group,[48] we identified the ideal reaction conditions for our system and developed HPLC conditions for reaction monitoring. Exposure of (±)-epibromohydrin to *p*-methoxyphenol in the absence of catalyst gave no reaction, confirming that no background reaction would occur in the absence of catalyst (Table 14, entry 1). The same reaction, in the presence of a racemic mixture of Co(salen) catalyst, gave a mediocre yield (entry 2). In contrast, the inclusion of CF_3CH_2OH as an additive gave a much improved yield (entry 3). No reaction was observed when the CH_2O(allyl)-substituted epoxide was subjected to the reaction conditions in CH_2Cl_2 (entry 4), however reactivity returned when TBME was used as the solvent (entry 5), and the maximal yield was achieved when $(CF_3)_3COH$ was employed as an additive (entry 6).

[74] Solubility and isolation of the pyrene-containing compounds were challenges in every step of this synthesis.

Table 14. Testing of the catalyst system





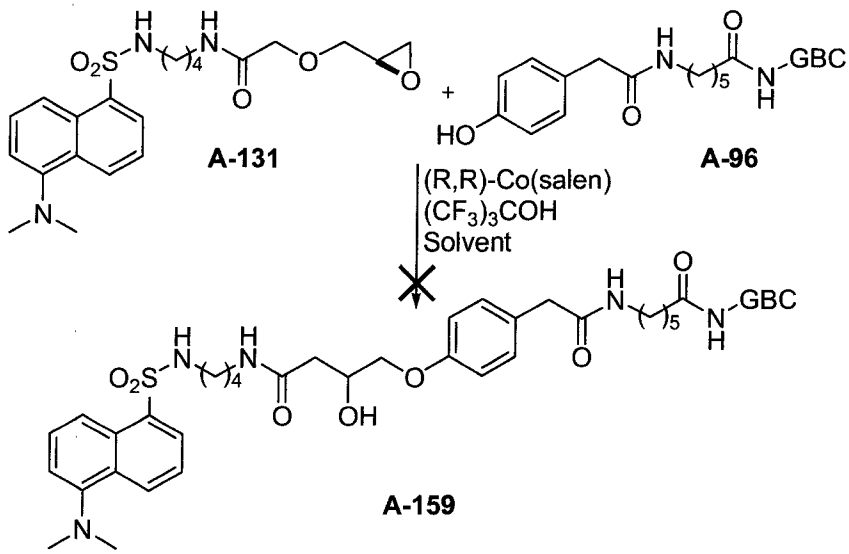
(*R*,*R*)-Co(salen): **M** = Co

Entry	R	Catalyst	Solvent	Yield (%)
1	Br	none	MeCN	NR
2[a]	Br	(±)-Co(salen)	MeCN	40
3	Br	(±)-Co(salen)	MeCN	70
4	OCH_2CHCH_2	(±)-Co(salen)	CH_2Cl_2	NR
5	OCH_2CHCH_2	(±)-Co(salen)	TBME	80
6[b]	**OCH_2CHCH_2**	**(±)-Co(salen)**	**TBME**	**92**

[a] CF_3CH_2OH was excluded. [b] $(CF_3)_3COH$ was used as the additive.

We proceeded to test the donor and acceptor system. Dansyl-epoxide **A-131** was therefore reacted with GBC-phenol **A-96** in the presence of (R,R)-Co(salen) catalyst and $(CF_3)_3COH$ in *tert*-butyl methyl ether (TBME), however, no reaction was observed (Table 15, entry 1). Unfortunately, the use of other solvents such as acetonitrile (entry 2), dichloromethane (entry 3), DMSO (entry 4), ethyl acetate (entry 5), and THF (entry 6) did not give any reaction.

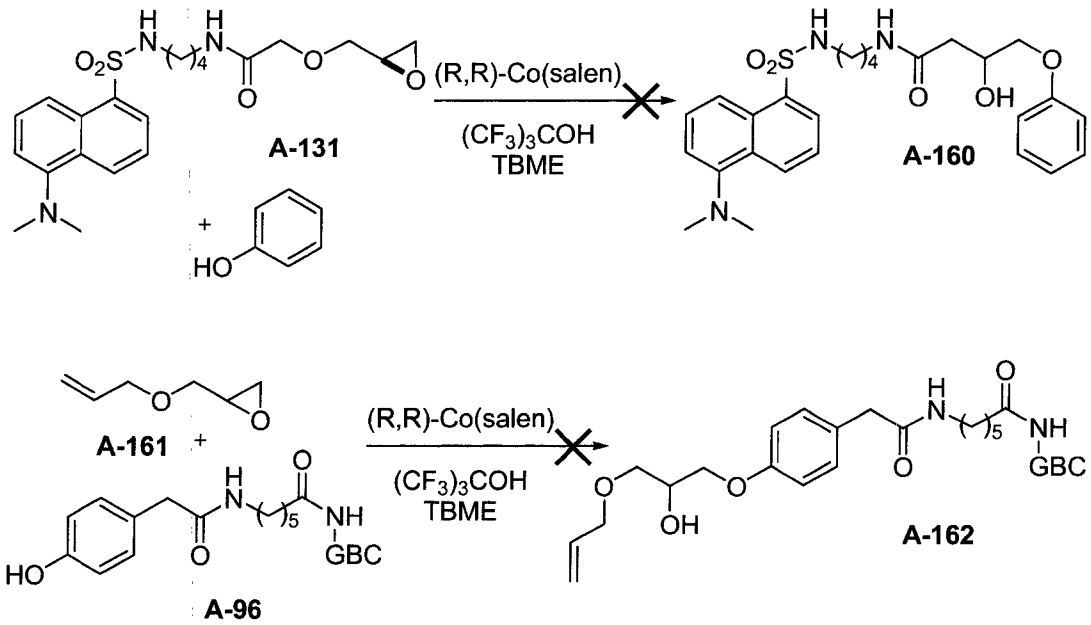
Table 15. The reaction between DNS-epoxide A-131 and GBC-phenol A-96 was unsuccessful



Entry	Solvent	Result
1	TBME	NR
2	MeCN	NR
3	CH_2Cl_2	NR
4	DMSO	NR
5	EtOAc	NR
6	THF	NR

Given the earlier evidence of catalyst activity, we felt that this must be due to substrate interference. To identify the substrate that was the cause of the failure of the reaction, the dansyl-epoxide (**A-131**) and GBC-phenol (**A-96**) were tested individually. Exposure of DNS-epoxide **A-131** to phenol in the presence of the (R,R)-Co(salen) catalyst gave no reaction (Scheme 39). Similarly, no reaction was observed between GBC-phenol **A-96** and epoxide **A-161**.

Scheme 39. No reaction was observed between Dansyl-epoxide A-131 and a simple phenol or between GBC-phenol (A-96) and a simple epoxide

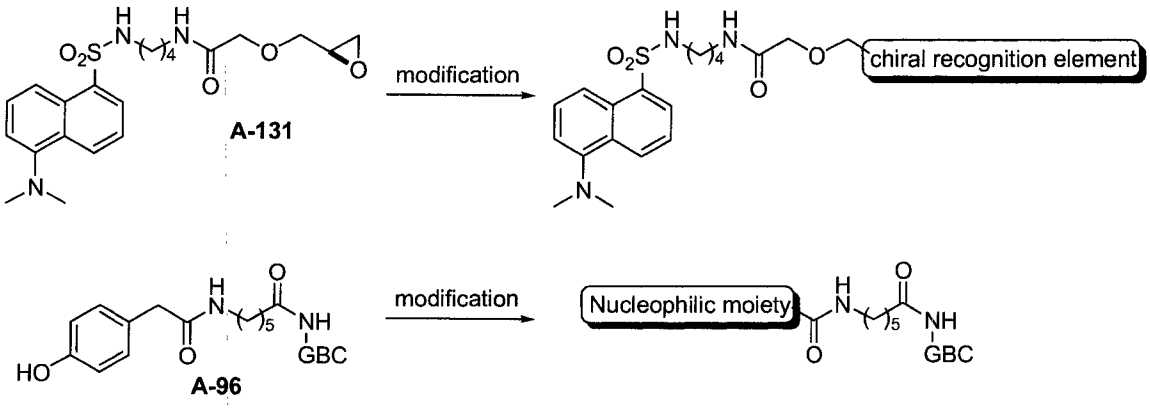


A number of different variables could be examined to promote this reaction such as the solvent, the additive, and catalyst modification. The substrates could also be studied more methodically to determine the source of catalyst inhibition. This would involve the simplification of the substrates and the protection of the acidic residues. This project was set aside, however, in favor of a more promising project in our research group, namely the [3 + 2] dipolar cycloaddition reaction between alkynes as latent dipoles and cyclopropanes.

Chapter 3. Conclusions

While a proof of principle was not successful using Jacobsen's chiral epoxide opening with phenols, the method could yet be successful. A route to enantiomeric epoxides tethered to fluorescent donor moieties was successfully developed. This route could be easily modified to incorporate a different chiral recognition element enabling the application of this methodology to other reactions (Scheme 40).

Scheme 40. Modification of chiral recognition element

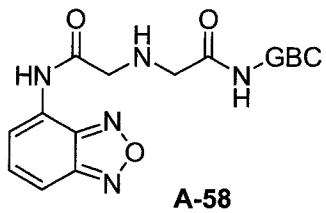


Chapter 4: Experimentals

GENERAL:

Reactions were performed in oven- or flame-dried flasks under N_2 atmosphere and equipped with a magnetic stir bar and a rubber septum, unless otherwise noted. THF was freshly distilled from sodium/benzophenone. Dichloromethane and triethylamine were freshly distilled over calcium hydride. Reagents were purchased from Sigma-Aldrich, Lancaster, and Strem chemical companies. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} pre-coated 0.25 mm thick aluminium plates. TLCs were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or *p*-anisaldehyde stains. When necessary, products were purified using flash column chromatography on silica gel 60 (230–400 mesh) or preparatory TLC glass plates pre-coated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

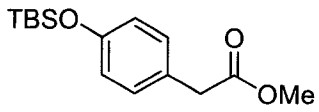
^1H and ^{13}C NMR spectra were acquired using either a Varian Gemini 200 MHz (^1H); a Bruker Avance 500 MHz (^1H) and 125 MHz (^{13}C); or a Bruker Avance 300 MHZ (^1H) and 75 MHz (^{13}C). Infrared spectra were acquired on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques. Melting points were determined using an Electrothermal Meltemp® apparatus and are uncorrected.



A-58

1-(4-Aminobenzofurazan)-2-(2-(2-methyl-4-(*o*-tolyldiazenyl)phenylamino)-2-oxoethylamino)acetamide (A-58). To a solution of 2-amino-*N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)acetamide (**A-63**) (23.0 mg, 0.083 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added DIPEA (0.06 mL, 0.42 mmol, 5.0 equiv) and 1-(4-aminobenzofurazan)-2-bromoacetamide (**A-60**) (16.4 mg, 0.064 mmol, 1.0 equiv). After 18 hours, the reaction

was diluted with EtOAc, and the organic layer was washed sequentially with $NaHCO_3$ (saturated solution) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The pure product was obtained by flash chromatography eluting with 10% EtOAc in hexanes to 40% EtOAc in hexanes to give the title product as a reddish solid that was used immediately (21 mg, 70%).



Methyl 2-(4-(*tert*-butyldimethylsilyloxy)phenyl)acetate.[75] To a solution of methyl 2-(4-hydroxyphenyl)acetate (3.0 g, 18.1 mmol, 1.0 equiv) in DMF (180 mL) was added imidazole (2.46 g, 36.2 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl chloride (4.08 g, 27.1 mmol, 1.5 equiv). After 2 hours the reaction mixture was diluted with H_2O (1000 mL) and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the title product as a colorless oil (5.07 g, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 3.67 (s, 3H), 3.54 (s, 2H), 0.97 (s, 9H), 0.18 (s, 6H).

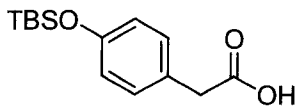
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7 (C), 155.1 (C), 130.6 (C), 127.0 (CH), 120.5 (CH), 52.3 (CH_3), 40.7 (CH_2), 26.1 (CH_3), 18.6 (C), –4.1 (CH_3).

IR (neat) 3050, 1738, 1255 cm^{-1}.

MS (EI) 280 (M^+), 223 (M – ^{t}butyl).

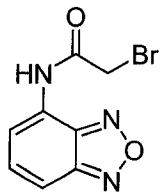
R_f: 0.69 on silica gel (30 % EtOAc in hexanes)

[75] Nakajima, R.; Ono, M.; Aiso, S.; Akita, H. *Chem. Pharm. Bull.* **2005**, *53*, 684.



A-59

2-(4-(*Tert*-butyldimethylsilyloxy)phenyl)acetic acid (A-59).[76] To a solution of methyl 2-(4-(tert-butyldimethylsilyloxy)phenyl)acetate (5.1 g, 18.1 mmol, 1.0 equiv) in THF (90 mL), MeOH (30 mL) and H_2O (30 mL) was added LiOH (2.4 g, 54.0 mmol, 3.0 equiv). After 24 hours, the solution was acidified with HCl (10%) and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the title product as a white solid that was used immediately (4.5 g, 93%).



A-60

1-(4-Aminobenzofurazan)-2-bromoacetamide (A-60). To a solution of 4-aminobenzofurazan (100 mg, 0.74 mmol, 1.0 equiv) in THF (8.0 mL) was added NMM (0.16 mL, 1.48 mmol, 2.0 equiv). To the solution was added bromoacetyl bromide (0.10 mL, 1.12 mmol, 1.5 equiv). After 20 minutes, the reaction was diluted with EtOAc, and the organic layer was washed sequentially with $NaHCO_3$ (saturated solution) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by flash chromatography eluting with 10% EtOAc in hexanes to give the title product as a red oil (175 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.43 (dd, J = 8.8, 8.8 Hz, 1H), 4.11 (s, 2H).

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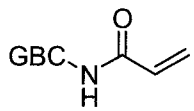
[76] For an alternative preparation see: Brummer, O.; Hoffman, T. Z.; Chen, D.-W.; Janda, K. D. *Chem. Comm.* **2001**, 19.

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (C), 149.2 (C), 144.4 (C), 133.0 (CH), 125.4 (C), 116.6 (CH), 114.4 (CH), 28.8 (CH_2).

IR (neat) 3012, 2985, 1661 cm^{-1}

MS (EI) 255 (M^+), 257 ($M^+ + 2$).

R_f: 0.4 on silica gel (10 % EtOAc in hexanes).



A-82

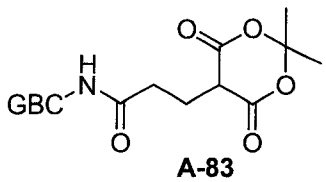
***N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)acrylamide (A-82).** To as solution of $GBCNH_2$ (500 mg, 2.22 mmol, 1.0 equiv) in CH_2Cl_2 (22 mL), was added Hünig's (0.43 mL, 2.44 mmol, 1.1 equiv) and acryloyl chloride (0.21 mL, 3.33 mmol, 1.5 equiv). After 30 minutes the reaction was quenched with NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (saturated solution), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title product as a reddish oil (617 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (br s, 1H), 7.79 (dd, J = 8.4, 2.4 Hz, 1H), 7.75 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 – 7.21 (m, 4H), 6.46 (dd, J = 16.8, 1.2 Hz, 1H), 6.31 (dd, J = 16.8, 9.9 Hz, 1H), 5.80 (dd, J = 9.9, 1.2 Hz, 1H), 2.70 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 150.7 (CH), 138.0 (CH), 131.3 (C), 131.2 (CH), 130.7 (CH), 128.4 (C), 128.35 (C), 128.29 (C), 126.4 (C), 126.4 (CH_2), 124.8 (CH), 122.4 (CH), 122.0 (CH), 115.3 (CH).

MS (EI) 279 (M^+).

R_f: 0.65 on silica gel (50% EtOAc in hexanes).



A-83

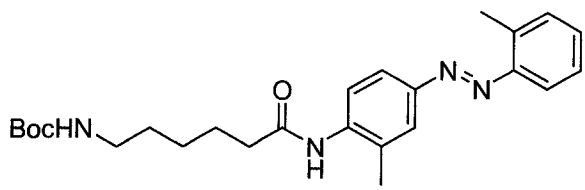
3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-*N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)propanamide (A-83). To a solution of *N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)acrylamide (**A-82**) (60.0 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added pyrrolidine (0.017 mL, 0.22 mmol, 1.0 equiv) and Meldrum's acid (46.5 mg, 0.32 mmol, 1.5 equiv). After 2 hours, the reaction was diluted with EtOAc and the organic layer was washed sequentially with HCl (10%), $NaHCO_3$ (saturated solution), and brine, then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by flash chromatography eluting with 50% EtOAc in hexanes to give the title product as a reddish solid (48.3 mg, 52%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.7 (br s, 1H), 9.33 (d, J = 9.0 Hz, 1H), 8.24 – 8.20 (m, 1H), 8.07 (br s, 2H), 7.21 (br s, 3H), 2.79 (s, 3H), 2.40 – 2.12 (m, 4H), 2.09 – 2.06 (m, 4H), 2.05 (s, 3H), 1.45 – 1.42 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C), 162.9 (C), 150.6 (C), 137.9 (CH), 137.7 (C), 131.3 (CH), 131.2 (CH), 130.7 (CH), 126.4 (CH), 124.8 (CH), 121.8 (C), 121.7 (C), 115.3 (CH), 106.2 (C), 48.2 (CH_2), 46.8 (CH_2), 39.4 (CH), 36.1 (CH_2), 34.8 (CH_2), 27.9 (CH_3), 27.5 (CH_3), 17.9 (CH_3), 17.5 (CH_3).

MS (EI) 423 (M^+).

R_f: 0.72 on silica gel (EtOAc).



A-93

***Tert*-butyl 6-(2-methyl-4-(*o*-tolyldiazenyl)phenylamino)-6-oxohexylcarbamate (A-93).** To a solution of 6-(*tert*-butoxycarbonylamino)hexanoic acid (2.65 g, 11.5 mmol, 1.0

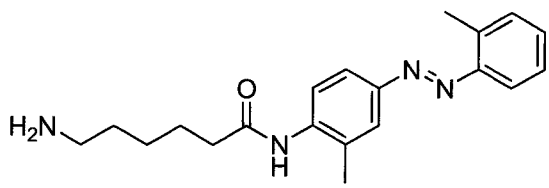
equiv) in CH_2Cl_2 (90 mL) was added oxalyl chloride (4.0 mL, 45.9 mmol, 4.0 equiv) and DMF (0.1 mL). After 2 hours, the volatiles were removed under reduced pressure. The crude reaction mixture was re-dissolved in CH_2Cl_2 (90 mL). To this solution was added sequentially DIPEA (8.0 mL, 45.9 mmol, 4.0 equiv) and 6-(*tert*-butoxycarbonylamino)hexanoic acid (2.65 g, 11.5 mmol, 1.0 equiv). After 1 hour, 4′-Amino-2,3′-dimethylazobenzene (5.2 g, 22.95 mmol, 2.0 equiv), or Fast Garnet GBC base, in CH_2Cl_2 (30 mL) was added. After 24 hours, the reaction was diluted with EtOAc and washed sequentially with H_2O, HCl (10%), then H_2O (Note: the addition of $NaHCO_3$ or brine caused an emulsion). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by flash chromatography eluting with 20% EtOAc in hexanes to 50% EtOAc in hexanes to give the title product as a rusty brown solid (4.19 g, 67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 7.74 – 7.69 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.20 – 7.18 (m, 2H), 4.54 (br s, 1H), 3.05 (s, 2H), 2.64 (s, 3H), 2.36 – 2.34 (m, 2H), 2.29 (s, 3H), 1.73 – 1.69 (m, 2H), 1.47 – 1.45 (m, 2H), 1.37 (s, 11H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0 (C), 156.0 (C), 150.6 (C), 138.1 (C), 131.1 (CH), 130.6 (CH), 126.3 (CH), 124.7 (CH), 122.8 (C), 121.8 (CH), 115.3 (CH), 115.3 (CH), 40.2 (CH_2), 37.4 (CH_2), 33.8 (CH_2), 29.6 (CH_3), 28.3 (CH_3), 27.9 (C), 26.2 (CH_3), 17.9 (CH_2), 17.5 (CH_2).

MS (EI) 438 (M^+), 381 ($M^+ - {}^t$Bu).

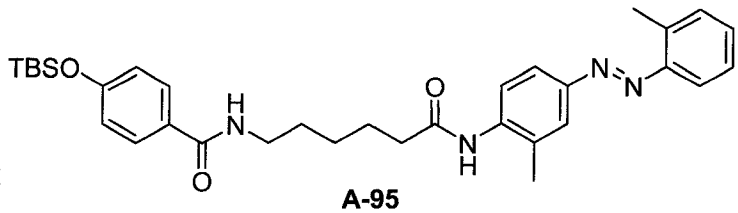
R_f: 0.69 on silica gel (30 % EtOAc in hexanes).



A-94

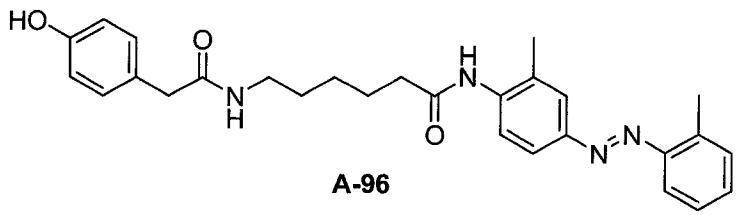
6-Amino-*N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)hexanamide (A-94). To a solution of *tert*-butyl 6-(2-methyl-4-(*o*-tolyldiazenyl)phenylamino)-6-oxohexylcarbamate (**A-93**)

(1.59 g, 3.63 mmol, 1.0 equiv) in CH_2Cl_2 (28 mL) was added TFA (7 mL) and the reaction was stirred for 1 hour. The volatiles were then removed under reduced pressure and the mixture was diluted with NaOH (1M solution in H_2O). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was taken directly to the next step.



A-95

4-(*Tert*-butyldimethylsilyloxy)-*N*-(6-(2-methyl-4-(*o*-tolyldiazenyl)phenylamino)-6-oxohexyl)benzamide (A-95). To a solution of 6-Amino-*N*-(2-methyl-4-(*o*-tolyldiazenyl)phenyl)hexanamide (**A-94**) (554 mg, 1.26 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (10 mL). After 1 hr, the volatiles were removed under reduced pressure. The resulting amine was re-dissolved in CH_2Cl_2 (20 mL) and to this was added DIPEA (1.1 mL, 6.3 mmol, 5.0 equiv), 2-(4-(*tert*-butyldimethylsilyloxy)phenyl)acetic acid (504 mg, 1.89 mmol, 1.5 equiv), *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (362 mg, 1.89 mmol, 1.5 equiv) and 1-hydroxylbenzotriazole hydrate (289 mg, 1.89 mmol, 1.5 equiv). After 24 hours, the reaction was diluted with EtOAc and the organic phase was washed sequentially with HCl (10%), $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography eluting with 30% EtOAc in hexanes to 80% EtOAc in hexanes to give the title product as the unprotected phenol as a rusty brown solid (360 mg, 50%).



A-96

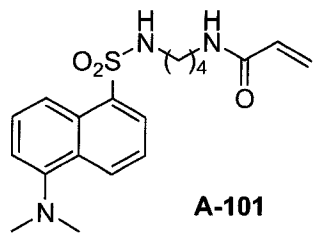
4-Hydroxy-*N*-(6-(2-methyl-4-(*o*-tolyldiazenyl)phenylamino)-6-oxohexyl)benzamide (A-96). To a solution of 4-(*tert*-butyldimethylsilyloxy)-*N*-(6-(2-methyl-4-(o-tolyldiazenyl)phenylamino)-6-oxohexyl)benzamide (**A-95**) (13.4 mg, 0.023 mmol, 1.0 equiv) in THF (5.0 mL) was added TBAF (1.0 M in THF, 0.025 mL, 0.025 mmol, 1.1 equiv). After 2 hours the reaction mixture was poured into a separatory funnel containing $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by flash chromatography eluting with hexanes to EtOAc to give the title product as a brown solid (10 mg, 92%).

^{1}H NMR (300 MHz, acetone-d_6): δ 8.62 (br s, 1H), 8.24 (s, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.78 – 7.74 (m, 2H), 7.61 (d, J = 8.1 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.11 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.18 – 3.14 (m, 2H), 2.69 (s, 3H), 2.47 – 2.36 (m, 2H), 2.39 (s, 3H), 1.72 – 1.10 (m, 6H).

^{13}C NMR (75 MHz, acetone-d_6): δ 162.8 (C), 161.8 (C), 160.7 (C), 147.1 (CH), 141.3 (C), 140.3 (C), 130.9 (C), 128.7 (C), 122.8 (CH), 122.4 (C), 121.2 (CH), 118.0 (CH), 117.9 (CH), 116.02 (C), 115.97 (CH) 111.9 (CH), 106.3 (CH), 106.3 (CH), 33.0 (CH_2), 32.4 (CH_2), 31.0 (CH_2), 20.3 (CH_2), 17.5 (CH), 16.3 (CH_2), 9.4 (CH_3), 8.5 (CH_3).

MS (CI) 459 (M^+ + 1).

R_f: 0.35 on silica gel (EtOAc)



A-101

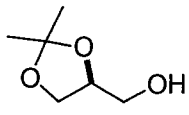
***N*-(4-(5-(Dimethylamino)naphthalene-1-sulfonamido)butyl)acrylamide (A-101).** To a solution of *N*-(4-aminobutyl)-5-(dimethylamino)naphthalene-1-sulfonamide (**A-129**) (305 mg, 0.71 mmol, 1 equiv) in CH_2Cl_2 (7 mL) was added DIPEA (0.25 mL, 1.42 mmol, 2 equiv) followed by acryloyl chloride (0.09 mL, 1.42 mmol, 2 equiv) and the reaction was then stirred for 18 hours. The reaction mixture was diluted with EtOAc and the organic layer was washed sequentially HCl (10%), saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 10% EtOAc in hexanes to 80% EtOAc to give the title compound as a green oil (204 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H). 6.31 (t, J = 5.1 Hz), 6.19 (d, J = 17.1 Hz, 1H), 6.05 (dd, J = 16.8, 9.9 Hz, 1H), 5.84 (t, J = 6.0 Hz, 1H), 5.52 (d, J = 9.9 Hz, 1H), 3.17 – 3.14 (m, 2H), 2.86 (s, 8H), 1.44 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8 (C), 151.7 (C), 134.6 (C), 130.8 (CH), 130.2 (CH), 129.7 (C), 129.4 (C), 129.3 (CH), 128.3 (CH), 126.1 (CH_2), 123.1 (CH), 118.7 (CH), 115.1 (CH), 45.3 (CH_3), 42.7 (CH_2), 38.7 (CH_2), 26.6 (CH_2), 26.2 (CH_2).

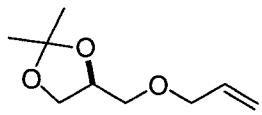
MS (EI) 375 (M^+).

R_f: 0.23 on silica gel (50% EtOAc in hexanes).



A-104

(*S*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (A-104).[55] To a solution of $NaIO_4$ (2.45 g, 11.44 mmol, 1.5 equiv) in H_2O (25 mL) at 0 °C was added 1,2,5,6-di-*O*-isopropylidene-(D)-mannitol (2.0 g, 7.62 mmol, 1.0 equiv). After 5 minutes EtOH (50 mL) was added to precipitate the sodium iodate, which was removed by filtration. A solution of $NaBH_4$ (720.1 mg, 19.05 mmol, 2.5 equiv) in H_2O was added cautiously (foaming) to the reaction mixture. After 2 hours the solution was adjusted to pH 7 with acetic acid and the ethanol was removed under reduced pressure. To the resulting water solution was added NaCl and the aqueous layer was extracted six times with chloroform. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the product as a colourless oil whose NMR data matched the published data (1.99 g, 99%).



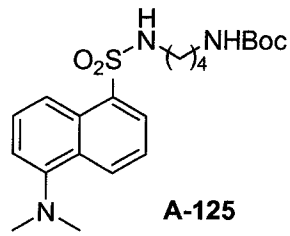
A-105

(*S*)-4-(allyloxymethyl)-2,2-dimethyl-1,3-dioxolane (A-105).[56] To a suspension of NaH (249.6 mg, 10.4 mmol, 2.1 equiv) in DMF (10 mL) was added a solution of (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**A-104**) (653.4 mg, 4.94 mmol, 1.0 equiv) in DMF (20 mL). After ½ hour allyl bromide (0.90 mL, 10.4 mmol, 2.1 equiv) was added dropwise over 10 minutes. The reaction was stirred for 24 hours, upon which time H_2O (400 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated to give a colourless oil (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92 – 5.79 (m, 1H), 5.23 (dd, J = 17.4, 1.2 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 4.28 – 4.20 (m, 1H0, 4.04 – 3.98 (m, 3H), 3.68 (dd, J = 8.1, 6.8 Hz,

1H), 3.48 (dd, J = 9.9, 8.0 Hz, 1H), 3.40 (dd, J = 9.9, 7.2 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ.134.4 (CH), 117.3 (CH_2), 109.3 (C), 74.6 (CH_2), 72.4 (CH), 71.0 (CH_2), 66.7 (CH_2), 26.7 (CH_3), 25.3 (CH_3).



A-125

***Tert*-butyl 4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylcarbamate (A-125).** To a solution of *N*-Boc-1,4-butanediamine (5.04 g, 26.8 mmol, 1.5 equiv) in CH_2Cl_2 (300 mL) was added dansyl chloride (5.0 g, 17.9 mmol, 1 equiv) and the reaction was stirred for 1 hour. The mixture was washed sequentially HCl (10%), saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 10% EtOAc in hexanes to 40% EtOAc to give the title compound as a yellow oil (7.23 g, 96%).

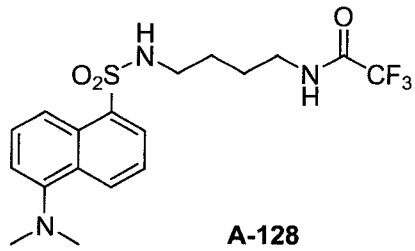
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 8.1 Hz, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 6.9 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.51 (br s, 1H), 4.56 (br s, 1H), 2.87 (s, 10H), 1.39 (s, 13H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9 (C), 151.8 (C), 134.7 (C), 130.2 (CH), 129.7 (C), 129.5 (C), 129.4 (CH), 128.2 (CH), 123.1 (CH), 118.7 (CH), 115.0 (CH), 79.0 (C), 45.3 (CH_3), 42.7 (CH_2), 39.7 (CH_2), 28.3 (CH_3), 26.9 (CH_2), 26.5 (CH_2).

IR (neat) 3383, 2976, 1692 cm^{-1}.

MS calcd for $C_{21}H_{31}N_3O_4S$ (M^+) 421, found 421.

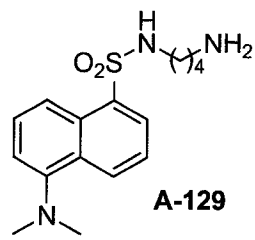
R_f: 0.46 on silica gel (50% EtOAc in Hexanes)



A-128

***N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)-2,2,2-trifluoroacetamide (A-128).** To a solution of 4-(5-(dimethylamino)naphthalene-1-sulfonamido)butan-1-aminium 2,2,2-trifluoroacetate (**A-126**) (1.19 g, 3.45 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was added DIPEA (2.41 mL, 13.8 mmol, 4 equiv) followed by acryloyl chloride (0.44 mL, 6.9 mmol, 2 equiv) and the reaction was then stirred for 18 hours. The reaction mixture was diluted with EtOAc and the organic layer was washed sequentially HCl (10%), saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 10% EtOAc in hexanes to 80% EtOAc to give the title compound as a yellow oil (1.02 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J = 8.5 Hz, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.23 (dd, J = 7.3, 1.2 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.19 (d, J = 7.5 Hz, 1H), 6.62 (br s, 1H), 5.18 (t, J = 6.2 Hz, 1H), 3.22 (q, J = 6.6 Hz, 2H), 2.89 (br s, 8H), 1.55 – 1.46 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (d, J = 152 Hz, C), 140.4 (C), 134.3 (CH), 130.6 (CH), 129.7 (CH), 129.5 (C), 128.5 (CH), 123.2 (CH), 118.5 (C), 115.2 (CH), 129.8 (C), 60.4 (C), 45.4 (CH_3), 42.5 (CH_2), 39.2 (CH_2), 26.5 (CH_2), 25.7 (CH_2).
MS (CI) 418 (M^+ + 1).



A-129

***N*-(4-aminobutyl)-5-(dimethylamino)naphthalene-1-sulfonamide (A-129).** To a solution of *tert*-butyl 4-(5-(dimethylamino)naphthalene-1- sulfonamido)butylcarbamate

(**A-125**) (7.23 g, 17.2 mmol) in CH_2Cl_2 (160 mL) was added TFA (40 mL) and the reaction was stirred for 1 hour. The volatiles were removed under reduced pressure, and a solution of NaOH (1M) was added. The mixture was extracted with EtOAc and the organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title product as a green oil (5.47 g, 99%).

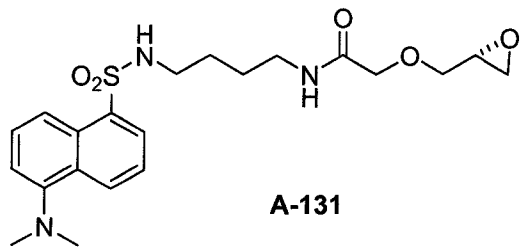
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 10.2 Hz, 1H), 8.21 (d, J = 7.2 Hz, 1H), 7.50 – 7.47 (br s, 2H), 7.15 (d, J = 7.5 Hz, 1H), 5.83 (br s, 1H), 4.05 (br s, 2H), 2.86 (s, 8H), 2.60 (br s, 2H), 1.41 (br s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8 (C), 135.0 (C), 130.1 (CH), 129.8 (C), 129.6 (C), 129.6 (CH), 128.1 (CH), 123.2 (CH), 118.9 (CH), 115.1 (CH), 45.4 (CH_3), 42.9 (CH_2), 40.8 (CH_2), 29.4 (CH_2), 27.2 (CH_2).

IR (neat) 3301, 2939 cm^{-1}

MS calcd for $C_{16}H_{23}N_3O_2S$ (M^+) 321, found 321.

R_f: 0.00 on silica gel (50 % EtOAc in hexanes)



A-131

(*R*)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)-2-(oxiran-2-ylmethoxy)acetamide (A-131).[77] To a solution of (*S*)-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)-2-hydroxypropyl 2,4,6-trimethylbenzenesulfonate (**145**) (50 mg, 0.079 mmol, 1.0 equiv) in THF was added NaH (5.7 mg, 0.095 mmol, 1.2 equiv) and the reaction was stirred for 10 minutes. The

[77] For an epoxidation procedure on a related substrate see: Boydell, A. J.; Jeffery, M. J.; Burkstummer, E.; Linclau, B. *J. Org. Chem.* **2003**, *68*, 8252.

reaction mixture was diluted with EtOAc, washed with H_2O, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The pure product was obtained by column chromatography on silica gel eluting with EtOAc to give the title compound as a green oil (28.0 mg, 81%).

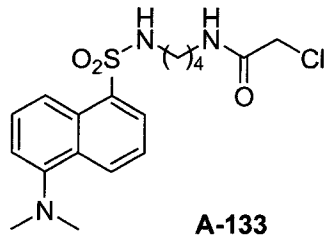
^{1}H NMR (300 MHz, acetone-d_6): δ 8.55 (d, J = 8.5 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H), 8.21 (dd, J = 7.3, 7.3 Hz, 1H), 7.61 (dd, J = 7.4, 7.3 Hz, 1H), 7.56 (dd, J = 7.6, 7.6 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.16 (br s, 1H), 6.78 (t, J = 5.7 Hz, 1H), 3.90 (d, J = 9.0 Hz, 1H), 3.86 (d, J = 9.0 Hz, 1H), 3.82 (dd, J = 11.7, 2.5 Hz, 1H), 3.37 (dd, J = 11.7, 6.2 Hz, 1H), 3.12 – 3.10 (m, 3H), 2.92 – 2.90 (m, 2H), 2.87 (s, 6H), 2.73 (dd, J = 5.1, 4.2 Hz, 1H), 2.58 (dd, J = 5.1, 2.6 Hz, 1H), 1.42 (br s, 1H).

^{13}C NMR (75 MHz, acetone -d_6): δ 170.5 (C), 153.7 (C), 138.3 (C), 131.7 (C), 131.6 (C), 131.5 (CH), 130.7 (CH), 129.6 (CH), 125.2 (CH), 121.4 (CH), 117.0 (CH), 73.9 (CH_2), 72.2 (CH_2), 51.9 (CH), 46.6 (CH_3) 45.1 (CH_2), 44.5 (CH_2), 39.5 (CH_2), 28.6 (CH_2), 28.5 (CH_2).

IR (neat) 3394, 2943, 1658 cm^{-1}.

MS (CI) 436 (M^+ + 1).

R_f: 0.38 on silica gel (EtOAc).

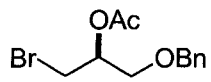


A-133

2-Chloro-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (A-133). To a solution of *N*-(4-aminobutyl)-5-(dimethylamino)naphthalene-1-sulfonamide (**A-129**) (50 mg, 0.15 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added DIPEA (0.031 mL, 1.8 mmol, 1.2 equiv). To this was added a solution of chloroacetyl chloride (0.014 mL, 1.8 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) *via* canula and the reaction was stirred for 15 minutes. The mixture was diluted with EtOAc and the organic layer was washed

sequentially water, saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 10% EtOAc in hexanes to 60% EtOAc to give the title compound as a yellow oil (58 mg, 97%).

^{1}H NMR (300 MHz, benzene-d_6): δ 8.82 (d, J = 8.6 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 7.6 Hz, 1H), 7.49 (dd, J = 8.1, 8.1 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.22 (t, J = 5.1 Hz, 1H), 5.91 (t, J = 6.0 Hz, 1H), 3.65 (s, 2H), 2.88 – 2.82 (m, 2H), 2.68 – 2.65 (m, 2H), 2.47 (s, 6H), 1.10 – 1.08 (m, 4H).
^{13}C NMR (75 MHz, benzene-d_6): δ 165.9 (C), 152.0 (C), 130.4 (C), 130.3 (C), 130.2 (CH), 129.7 (CH), 128.5 (CH), 123.5 (CH), 120.1 (CH), 115.6 (CH), 45.1 (CH_3), 42.9 (CH_2), 42.8 (CH_2), 39.3 (CH_2), 26.9 (CH_2), 26.5 (CH_2).
IR (neat) 3299, 2944, 2869, 1662 cm^{-1}.
MS calcd for $C_{18}H_{24}ClN_3O_3S$ (M^+) 397 found 397.
R_f: 0.22 on silica gel (50 % EtOAc in hexanes).



A-135

(*S*)-1-(Benzyloxy)-3-bromopropan-2-yl acetate (A-135).[78] To a solution of (*R*)-3-(benzyloxy)propane-1,2-diol (**A-134**) (260 mg, 1.43 mmol, 1 equiv) in $CHCl_3$ (15 mL) was added the Moffat reagent[79] (0.27 mL, 1.85 mmol, 1.3 equiv) and the reaction was stirred for ½ hour. The solution was then washed sequentially with $NaHCO_3$, brine, and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 10 % EtOAc in hexanes to give the title compound as a colorless oil (336 mg, 82 %).

[78] This compound has been reported, however, no spectral data was described: Hoff, B. H.; Anthonsen, T. *Chirality* **1999**, *11*, 760.
[79] Greenberg; Moffatt.

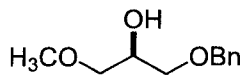
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 5H), 5.06 (m, J = 5.2 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 3.62 – 3.42 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (C), 137.4 (C), 128.2 (CH), 127.6 (CH), 127.4 (CH), 73.2 (CH_2), 71.1 (CH), 68.7 (CH_2), 30.7 (CH_2), 20.7 (CH_3).

IR (neat) 3089, 2867, 1743 cm^{-1}.

MS (EI) 286 (M^+), 179 (M^+ – 0Bn).

R_f: 0.57 on silica gel (20 % EtOAc in hexanes).



(*R*)-1-(benzyloxy)-3-methoxypropan-2-ol.[80] To a solution of (*R*)-2-(benzyloxymethyl)oxirane (336 mg, 1.11 mmol, 1 equiv) in MeOH (10 mL) was added K_2CO_3 (229 mg, 1.66 mmol, 1.5 equiv). After 18 hours, the reaction mixture was diluted with Et_2O and the organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 20% EtOAc in hexanes to 50% EtOAc in hexanes to give the title compound as a colorless oil (43 mg, 22%).

^{1}H NMR (300 MHz, benzene-d_6): δ 7.25 – 7.08 (m, 5H), 4.30 (s, 2H), 4.05 – 3.98 (m, 1H), 3.45 (d, J = 5.5 Hz, 2H), 3.33 (d, J = 5.4 Hz, 2H), 3.05 (s, 3H), 2.59 (br s, 1H).

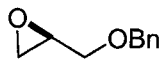
^{13}C NMR (75 MHz, benzene-d_6): δ 138.8 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 74.3 (CH_2), 73.4 (CH_2), 71.9 (CH_2), 69.7 (CH).

IR (neat) 3448, 3066, 2897 cm^{-1}

MS (EI) calcd for $C_{11}H_{16}O_3$ (M^+) 196, found 196.

R_f: 0.33 on silica gel (20% EtOAc in hexanes).

[80] For a preparation via the reductive cleavage of benzylidene acetals, see: Guindon, Y.; Girard, Y.; Berthiaume, S.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990**, *68*, 897.



A-137

(*R*)-2-(benzyloxymethyl)oxirane (A-137). To a solution of (*S*)-1-(benzyloxy)-3-bromopropan-2-yl acetate (**A-135**) (336 mg, 1.11 mmol, 1 equiv) in MeOH (10 mL) was added K_2CO_3 (229 mg, 1.66 mmol, 1.5 equiv). After 18 hours the reaction was diluted with Et_2O and the organic layer was washed with H_2O and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 20% EtOAc in hexanes to 50% EtOAc in hexanes to give the title compound as a colorless oil (122.1 mg, 67%).

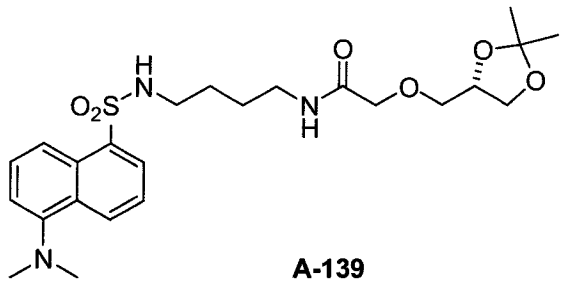
^{1}H NMR (300 MHz, benzene-d_6): δ 7.26 – 7.05 (m, 5H), 4.33 (dd, J = 19.0, 12.0 Hz, 2H), 3.37 (dd, J = 11.4, 2.7 Hz, 1H), 3.07 (dd, J = 11.4, 6.0, 1H), 2.86 – 2.81 (m, 1H), 2.26 (dd, J = 5.1, 4.2 Hz, 1H), 2.13 (dd, J = 2.4, 5.1 Hz, 1H).

^{13}C NMR (75 MHz, benzene-d_6): δ 138.3 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 73.1 (CH_2), 71.1 (CH_2), 50.7 (CH), 43.5 (CH_2).

IR (neat) 3062, 2999 cm^{-1}.

MS (EI) 73 (M^+ – Bn), 91 (Bn).

R_f: 0.44 on silica gel (20 % EtOAc in hexanes).

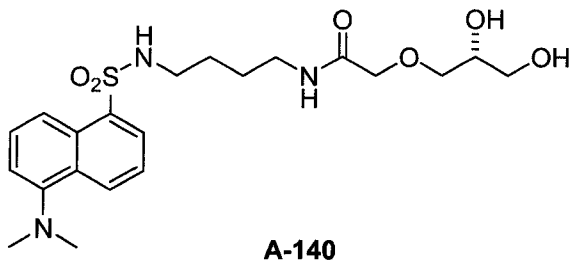


A-139

(S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (A-139). To a suspension of NaH (91 mg, 2.3 mmol, 1.8 equiv) in DMF (20 mL) was added a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (252 mg, 1.9 mmol, 1.5 equiv) in DMF

(10 mL). The reaction was stirred for 1 hour, upon which time a solution of 2-chloro-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (**A-153**) (504 mg, 1.27 mmol, 1 equiv) and DIPEA (0.88 mL, 5.04 mmol, 4 equiv) in DMF (10 mL) was canulated into the first solution. After 18 hours, the reaction was quenched with H_2O (400 mL), and the aqueous layer was extracted with Et_2O (4 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 50% EtOAc in hexanes to EtOAc to give the title compound as a yellow oil (430 mg, 69%).

^{1}H NMR (300 MHz, benzene-d_6): δ 8.85 (d, J = 8.7 Hz, 1H), 8.43 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 6.0 Hz, 1H), 7.46 (dd, J = 7.9, 7.9 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.87 (d, J = 7.5 Hz, 1H), 6.68 (t, J = 5.7 Hz, 1H), 5.92 (t, J = 6.0 Hz, 1H), 3.95 – 3.90 (m, 1H), 3.90 (s, 2H), 3.64 (dd, J = 6.6, 6.6 Hz, 1H), 3.41 (dd, J = 6.9, 6.9 Hz, 1H), 3.08 – 2.95 (m, 4H), 2.72 (q, J = 5.7 Hz, 1H), 2.49 (s, 6H), 1.36 (s, 3H), 1.27 (s, 3H), 1.17 – 1.15 (m, 4H)
^{13}C NMR (75 MHz, benzene-d_6): δ 169.5 (C), 152.0 (C), 136.8 (C), 130.5 (C), 130.4 (C), 129.9 (CH), 129.6 (CH), 128.5 (CH), 123.5 (CH), 120.6 (CH), 115.5 (CH), 109.6 (C), 74.9 (CH), 72.2 (CH_2), 70.9 (CH_2), 65.9 (CH_2), 45.1 (CH_3), 43.0 (CH_2), 38.2 (CH_2), 27.0 (CH_2), 26.9 (CH_3), 25.5 (CH_3).
IR (neat) 3368, 2985, 2870, 1662 cm^{-1}.
MS (ESI) calcd for $C_{24}H_{35}N_3O_6S$ (M^+ + Na) 516, found 516.
R_f: 0.39 on silica gel (EtOAc)



A-140

(*R*)-2-(2,3-dihydroxypropoxy)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (A-140). Amberlyst-120 H^+ acidic resin (1.0 g) was activated by stirring concentrated HCl for ½ hour. The resin was subsequently rinsed well

with H_2O followed by EtOH, and was then added to a solution of (*S*)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (**A-139**) (7.13 g, 14.5 mmol) in EtOH (140 mL) and the reaction was stirred vigorously for 4 days. The reaction was filtered and the product was concentrated under reduced pressure. The pure product was obtained by column chromatography on silica gel eluting with EtOAc to 30% EtOH in EtOAc to give the title compound as a white solid (2.57 g, 40%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 6.29 (br s, 1H), 4.78 (br s, 1H), 4.23 (br s, 1H), 3.96 (br s, 3H), 3.68 – 3.51 (m, 4H), 3.09 (br s, 1H), 2.81 (s, 6H), 2.75 (s, 2H).

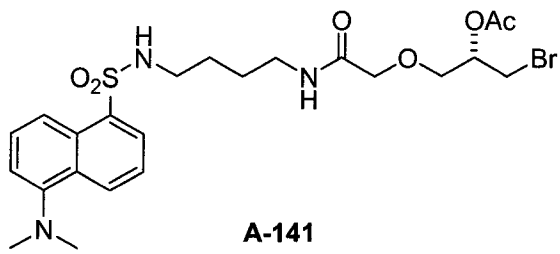
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (C), 151.8 (C), 134.7 (C), 130.2 (CH), 129.7 (C), 129.5 (CH), 129.2 (CH), 128.3 (CH), 123.1 (CH), 118.8 (CH), 115.2 (CH), 125.8 (CH), 72.8 (CH_2), 70.6 (CH), 70.3 (CH_2), 63.4 (CH_2), 45.3 (CH_3), 42.6 (CH_2), 38.4 (CH_2), 26.8 (CH_2), 26.2 (CH_2).

IR (neat) 3392, 2943, 2871, 1656 cm^{-1}.

MP: 40 – 41 °C.

MS (CI) calcd for $C_{21}H_{31}N_3O_6S$ (M^+ + 1) 454, found 454.

R_f: 0.26 on silica gel (EtOAc).



A-141

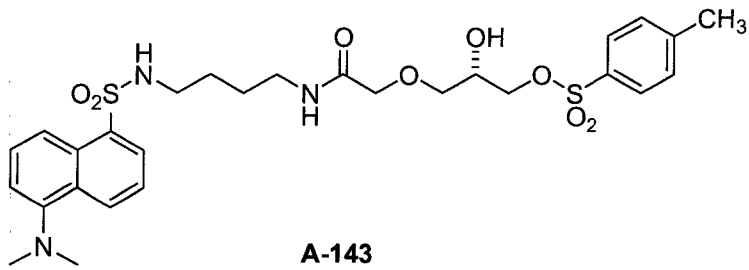
(*S*)-1-bromo-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)propan-2-yl acetate (A-141). To a solution of (*R*)-2-(2,3-dihydroxypropoxy)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (**A-140**) (52.6 mg, 0.117 mmol, 1.0 equiv) in $CHCl_3$ (4.0 mL) and DMF (1.0 mL) at 0 °C

was added the Moffat reagent (0.022 mL, 0.152 mmol, 1.3 equiv) and the reaction was stirred for 10 minutes. To the reaction mixture was added $NaHCO_3$ (saturated solution) and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 7.0 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.38 (br s, 1H), 7.18 (d, J = 7.0 Hz, 1H), 5.92 (br s, 1H), 3.99 – 3.93 (m, 3H), 3.72 – 3.70 (m, 3H), 3.18 – 3.17 (m, 2H), 2.88 – 2.87 (m, 9H), 2.04 (s, 3H), 1.47 – 1.46 (m, 4H).

MS (CI) 558 (M^+ + 1), 560 (M^+ + 2).

R_f: 0.57 on silica gel (70% EtOAc in EtOH)



A-143

(*S*)-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)-2-hydroxypropyl 4-methylbenzenesulfonate (A-143). To a solution of **(*R*)-2-**(2,3-dihydroxypropoxy)-N-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (**A-140**) (31 mg, 0.061 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added triethylamine (0.04 mL, 0.28 mmol, 4 equiv) and DMAP (crystal). To this was added *p*-toluenesulfonyl chloride (13.2 mg, 0.069 mmol, 1 equiv) and the reaction was stirred for 3 hours. The mixture was diluted with EtOAc, washed with H_2O, and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 85% EtOAc in hexanes to 30 % EtOH in EtOAc to give the title compound as a brown foam (32 mg, 88%).

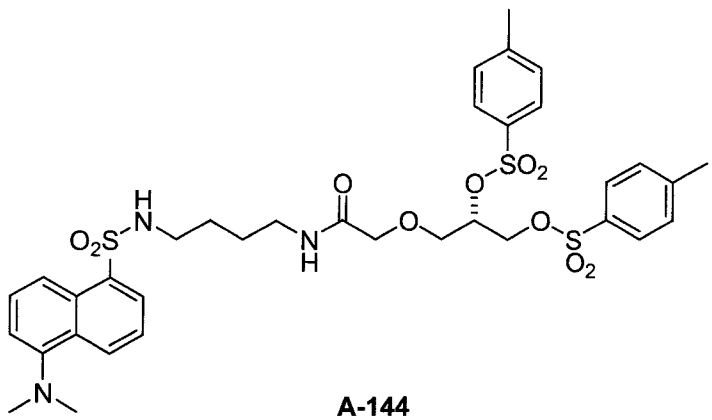
^{1}H NMR (500 MHz, benzene-d_6): δ 8.39 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H). 8.05 (d, J = 7.2 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.02 (d, J = 7.5 Hz, 1H), 6.00 (br s, 1H), 4.44 (br s, 1H), 3.89 (s, 2H), 3.85 (br s, 1H), 3.04 – 3.03 (m, 2H), 2.75 (s, 6H), 2.71 – 2.70 (m, 2H), 1.33 (br s, 4H);

^{13}C NMR (100 MHz, benzene-d_6): δ 170.5 (C), 151.8 (C), 134.7 (CH), 130.3 (C), 130.3 (C), 129.8 (CH), 129.5 (CH), 129.3 (C), 128.3 (CH), 128.2 (CH), 123.2 (C), 123.1 (CH), 118.9 (C), 118.8 (CH), 115.2 (CH), 72.9 (CH_2), 70.7 (CH), 70.4 (CH_2), 63.5 (CH_2), 45.4 (CH_3), 42.71 (CH_3), 42.69 (CH_2), 38.4 (CH_2), 26.8 (CH_2), 26.2 (CH_2);

IR (neat) 3323, 2929, 2873, 1656 cm^{-1}

MS (ESI) calcd for $C_{28}H_{37}N_3O_8S_2$ (M^+ + 1) 608, found 608.

R_f: 0.14 on silica gel (EtOAc)



A-144

(*S*)-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)propane-1,2-diyl bis(4-methylbenzenesulfonate).

^{1}H NMR (500 MHz, benzene-d_6): δ 8.81 (d, J = 14.0 Hz, 1H), 8.41 (d, J = 14.5 Hz, 1H), 8.37 (d, J = 12.0 Hz, 1H), 7.80 (d, J = 13.5 Hz, 2H), 7.64 (d, J = 14.0 Hz, 1H), 7.45 (dd, J = 13.0, 13.0 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.87 – 6.71 (m, 5H), 5.91 – 5.81 (m, 1H), 4.81 – 4.70 (m, 1H), 3.96 – 3.58 (m, 4H), 3.18 – 3.09 (m, 5H), 2.75 – 2.71 (m, 2H), 2.48 (s, 6H), 1.85 (s, 3H), 1.83 (s, 3H), 1.27 – 1.20 (m, 6H);

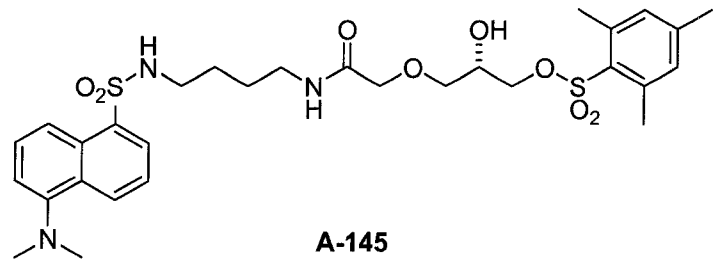
^{13}C NMR (125 MHz, benzene-d_6): δ 168.7 (C), 152.8 (C), 145.2 (C), 145.1 (C), 136.6 (CH), 134.0 (CH), 132.9 (C), 130.4 (CH), 130.3 (CH), 130.14 (CH), 130.09 (CH), 130.05

(C), 129.96 (C), 128.6 (CH), 128.2 (C), 128.1 (C), 127.8 (C), 123.6 (CH), 120.4 (CH), 115.6 (CH), 79.1 (CH), 77.1 (CH_2), 70.8 (CH_2), 70.1 (CH_2), 69.0 (CH_2), 67.5 (CH_2), 45.2 (CH_3), 43.1 (CH_2), 38.4 (CH_2), 26.9 (CH_3), 23.0 (CH), 21.2 (CH_3);

IR (neat) 3381, 2942, 1666 cm^{-1};

MS(ESI) calcd for $C_{35}H_{43}N_3O_{10}S_3$ (M^+ + Na) 784, found 784.

R_f: 0.74 on silica gel (EtOAc)



A-145

(*S*)-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)-2-hydroxypropyl 2,4,6-trimethylbenzenesulfonate (A-145). To a solution of (*R*)-2-(2,3-dihydroxypropoxy)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)acetamide (**A-140**) (600 mg, 1.3 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added DIPEA (0.68 mL, 3.9 mmol, 3 equiv), DMAP (crystal) and 2,4,6-trimethylbenzenesulfonyl chloride (347 mg, 1.6 mmol, 1.2 equiv). After 18 hours, the reaction was diluted with EtOAc and washed sequentially with HCl (10%), saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 85% EtOAc in hexanes to 30% EtOH in EtOAc to give the title compound as a brown oil (190 mg, 23%).

^{1}H NMR (300 MHz, acetone-d_6): δ 8.59 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.21 (d, J = 7.3 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.54 – 7.29 (m, 2H), 7.08 (s, 2H), 6.80 (br s, 1H), 4.01 (br s, 1H), 3.99 – 3.94 (m, 2H), 3.83 (s, 2H), 3.74 – 3.70 (m, 1H), 3.55 – 3.54 (m, 2H), 3.10 – 3.04 (m, 2H), 2.89 (s, 8H), 2.60 (s, 6H), 2.30 (s, 3H), 1.41 (br s, 4H).

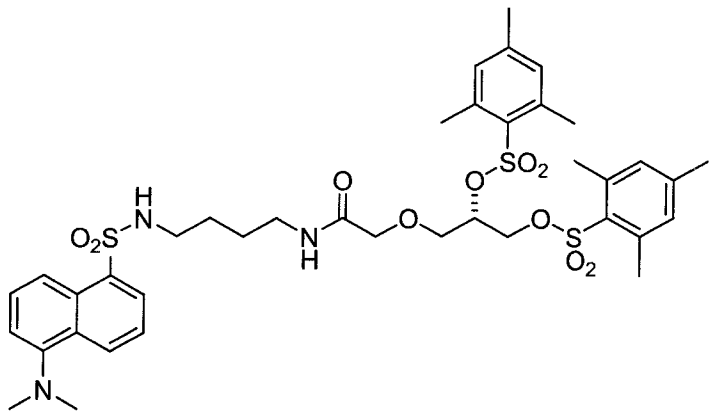
^{13}C NMR (75 MHz, acetone-d_6): δ 169.7 (C), 144.4 (C), 144.3 (C), 140.6 (C), 140.4 (C), 137.2 (C), 132.49 (CH), 132.46 (C), 131.3 (C), 130.5 (CH), 130.4 (CH), 129.7 (CH),

128.6 (CH), 124.3 (CH), 120.7 (CH), 117.3 (C), 116.2 (CH), 72.9 (CH), 70.2 (CH_2), 45.7 (CH_3), 43.4 (CH_2), 38.5 (CH_2), 27.2 (CH_2), 28.8 (CH_2), 22.9 (CH_3), 22.8 (CH_3), 20.8 (CH_2).

IR (neat) 3336, 2941, 2873, 1656 cm^{-1}

MS (ESI) calcd for $C_{30}H_{41}N_3O_8S_2$ (M^+ + 1) 636, found 636.

R_f: 0.55 on silica gel (EtOAc).



(*S*)-3-(2-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butylamino)-2-oxoethoxy)propane-1,2-diyl bis(2,4,6-trimethylbenzenesulfonate).

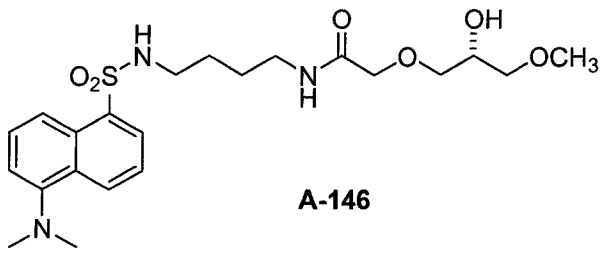
^{1}H NMR (300 MHz, acetone-d_6): δ 8.55 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.61 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.55 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.35 (s, 1H), 7.09 – 7.03 (m, 5H), 6.76 (t, *J* = 6.0 Hz, 1H), 4.86 – 4.80 (m, 1H), 4.30 – 4.04 (m, 4H), 3.54 – 3.53 (m, 2H), 3.10 – 3.03 (m, 2H), 2.91 – 2.88 (m, 2H), 2.61 (s, 6H), 2.54 (s, 6H), 2.50 (s, 6H), 2.31 (s, 6H), 1.42 – 1.43 (m, 4H);

^{13}C NMR (75 MHz, acetone -d_6): δ 169.9 (C), 153.7 (C), 145.7 (C), 145.71 (C), 145.69 (C), 145.2 (C), 141.7 (C), 141.6 (C), 141.5 (C), 138.1 (C), 133.60 (CH), 133.57 (CH), 133.5 (CH), 131.6 (C), 131.5 (CH), 130.7 (CH), 130.1 (CH), 129.6 (CH), 125.1 (CH), 121.3 (CH), 117.0 (CH), 133.0 (C), 132.4 (C), 131.7 (C), 78.2 (CH), 72.6 (CH_2), 72.1 (CH_2), 71.5 (C), 70.7 (CH_2), 68.7 (CH_2), 64.4 (CH_2), 46.6 (CH_3), 44.4 (CH_2), 39.5 (CH_2), 28.5 (CH_3), 28.4 (CH_3), 23.8 (CH_3), 23.63 (CH_3), 23.60 (CH_3);

IR (neat) 3393, 2979, 1698 cm^{-1};

MS (ESI) calcd for $C_{39}H_{51}N_3O_{10}S_3$ (M^+ + Na) 840, found 840.

R_f: 0.89 on silica gel (EtOAc)



A-146

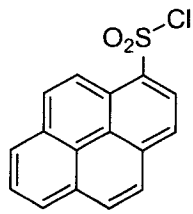
(*R*)-*N*-(4-(5-(dimethylamino)naphthalene-1-sulfonamido)butyl)-2-(2-hydroxy-3-methoxypropoxy)acetamide (A-146).

^{1}H NMR (500 MHz, benzene-d_6): δ 8.70 (d, *J* = 8.7 Hz, 1H), 8.43 (d, *J* = 8.7 Hz, 1H), 8.39 (d, *J* = 7.3 Hz, 1H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.24 (t, *J* = 5.4 Hz, 1H), 7.16 – 7.14 (m, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 5.96 (t, *J* = 6.0 Hz, 1H), 3.94 (s, 2H), 3.94 – 3.88 (m, 1H), 3.32 – 3.02 (m, 6H), 3.06 (s, 3H), 2.74 – 2.68 (m, 2H), 2.49 (s, 6H), 1.25 (br s, 4H).

IR (neat) 3321, 2935, 1653 cm^{-1}.

MS (ESI) 468 (M^+ + 1).

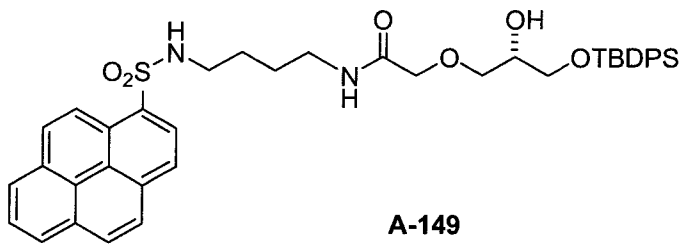
R_f: 0.093 on silica gel (EtOAc).



A-151

Pyrenesulfonyl chloride (A-151). To a solution of pyrenesulfonic acid (10.0 g, 35.5 mmol, 1 equiv) in C_6H_6 (350 mL) was added oxalyl chloride (15.5 mL, 177.3 mmol, 5 equiv) and DMF (2.7 mL). **Caution: evolution of gas.** The reaction was heated at reflux

for 3 hours, upon which time the solvent was removed under reduced pressure to give a brown oil that was used directly in the next step (10.65 g, 100%).



A-149

(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (A-149). To a solution of (*R*)-2-(2,3-dihydroxypropoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (**A-150**) (1.45 g, 3.13 mmol, 1.0 equiv) in DMF (30 mL) were added imidazole (1.07 g, 15.7 mmol. 5.0 equiv), DMAP (crystal), and *tert*-butyl(chloro)diphenylsilane (0.90 mL, 3.45 mmol, 1.1 equiv). After 72 hrs the reaction was quenched with H_2O (300 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by column chromatography on silica gel eluting with 50% EtOAc in hexanes to 80% EtOAc in hexanes to give the title compound as a brown oil (1.70 g, 75%).

^{1}H NMR (300 MHz, benzene-d_6): δ 9.40 (d, J = 9.4 Hz, 1H), 8.82 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 9.5 Hz, 1H), 7.84 – 7.56 (m, 10H), 7.31 (t, J = 6.0 Hz, 1H), 7.22 – 7.19 (m, 6H), 6.61 (t, J = 6.0 Hz, 1H), 3.96 – 3.93 (m, 1H), 3.91 (s, 2H), 3.74 – 3.71 (m, 2H), 3.37 – 3.35 (m, 2H), 3.21 – 3.12 (m, 2H), 2.84 – 2.82 (m,. 2H), 1.33 (br s, 4H), 1.55 (s, 1H), 1.09 (s, 9H).

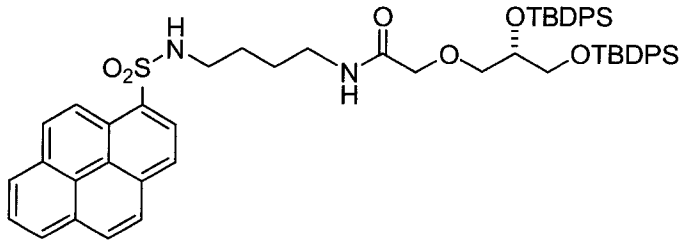
^{13}C NMR (75 MHz, benzene-d_6): δ 170.4 (C), 135.9 (CH), 134.7 (C), 133.6 (C), 133.0 (C), 131.1 (C), 130.6 (C), 130.1 (CH), 130.0 (CH), 129.8 (CH), 128.5 (CH), 128.2 (C), 127.6 (CH), 128.0 (C), 127.2 (CH), 126.8 (CH), 126.6 (CH), 125.5 (CH), 124.4 (C),

124.3 (CH), 124.1 (CH), 73.2 (CH_2), 71.3 (CH), 70.8 (CH_2), 65.2 (CH_2), 43.0 (CH_2), 38.5 (CH_2), 27.03 (CH_3), 27.01 (CH_2), 26.9 (CH_2), 19.4 (C).

IR (neat) 3402, 2931, 1698 cm^{-1}.

HRMS calcd for $C_{41}H_{46}N_2O_6SSi$ (M^+ + Na) 745, found 745.

R_f: 0.42 on silica gel (EtOAc).



(*S*)-2-(2,3-bis(*tert*-butyldiphenylsilyloxy)propoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide.

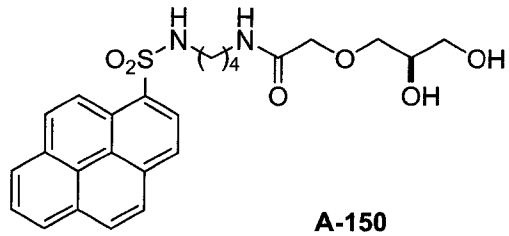
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.97 (d, J = 9.4 Hz, 1H), 8.69 (d, J = 8.2 Hz, 1H), 8.32 – 8.08 (m, 7H), 7.58 – 7.52 (m, 7H), 7.40 – 7.28 (m, 13H), 6.12 (t, J = 6.0 Hz, 1H), 5.13 (t, J = 6.0 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.63 – 3.61 (m, 4H), 3.50 – 3.47 (m, 2H), 2.96 – 2.83 (m, 4H), 1.31 – 1.17 (m, 4H), 0.98 (s, 9H), 0.96 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (C), 135.6 (CH), 135.5 (CH), 135.48 (CH), 135.4 (CH), 133.2 (C), 130.2 (CH), 130.1 (CH), 129.8 (CH), 129.7 (CH), 127.7 (CH), 127.6 (CH), 128.3 (C), 127.5 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 123.8 (CH), 123.0 (CH), 72.7 (CH_2), 72.4 (CH), 70.1 (CH_2), 64.6 (CH_2), 42.82 (CH_2), 42.81 (CH_2), 37.8 (CH_2), 26.8 (CH_3), 26.7 (CH_3), 26.4 (CH_2), 19.3 (C), 19.2 (C).

IR (neat) 3587, 2933, 2888, 1668 cm^{-1}.

HRMS calcd for $C_{57}H_{64}N_2O_6SSi_2$ (M^+ + Na) 983, found 983.

R_f: 0.92 on silica gel (EtOAc).



A-150

(*R*)-2-(2,3-dihydroxypropoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (A-150). Amberlyst-120 H^+ acidic resin (~ 1.0 g) was activated by stirring concentrated HCl for ½ hour. The resin was subsequently rinsed well with H_2O followed by EtOH, and was then added to a solution of (*S*)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (**A-154**) (1.64 g, 3.26 mmol, 1.0 equiv) in EtOH (30 mL). After 48 hours the reaction mixture was filtered and the volatiles were removed under reduced pressure to give a brown foam (1.52 g, 96%).

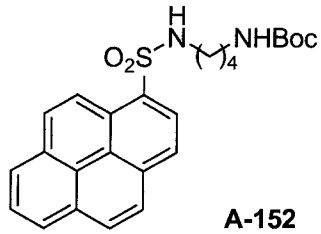
^{1}H NMR (300 MHz, acetone-d_6): δ 9.09 (d, *J* = 9.6 Hz, 1H), 8.69 (d, *J* = 8.1 Hz, 1H), 8.44 – 8.14 (m, 7H), 7.42 (br s, 1H), 7.04 (t, *J* = 6.0 Hz, 1H), 4.17 (d, *J* = 4.8 Hz, 1H), 3.83 – 3.73 (m, 4H), 3.58 – 3.42 (m, 4H), 3.07 (q, *J* = 6.6 Hz, 2H), 2.94 (q, *J* = 6.6 Hz, 2H), 1.45 – 1.32 (m, 4H);

^{13}C NMR (75 MHz, acetone -d_6): δ 171.2 (C), 136.3 (C), 134.8 (C), 132.9 (C), 132.1 (C), 131.8 (CH), 131.3 (CH), 129.6 (C), 129.03 (CH), 129.01 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 125.9 (CH), 125.6 (CH), 126.8 (C), 125.7 (C), 75.0 (CH_2) 72.6 (CH), 65.0 (CH_2), 44.5 (CH_2), 39.5 (CH_2), 28.5 (CH_2), 28.4 (CH_2);

IR (neat) 3363, 2937, 1650 cm^{-1}.

MS (ESI) calcd for $C_{25}H_{28}N_2O_6S$ (M^+ + Na) 507, found 507.

R_f: 0.05 on silica gel (EtOAc).



A-152

***Tert*-butyl 4-(pyrene-1-sulfonamido)butylcarbamate (A-152).** To a solution of *N*-Boc-1,4-butanediamine (6.68 g, 35.5 mmol, 1 equiv) and DIPEA (18.6 mL, 106.5 mmol, 3 equiv) in CH_2Cl_2 (100 mL) was added a solution of pyrenesulfonyl chloride (10.65 g, 35.5 mmol, 1 equiv) in CH_2Cl_2 (200 mL) *via* canula. After 6 hours the reaction was quenched with H_2O and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel eluting with 20% EtOAc in hexanes to EtOAc to give the title compound as a brown oil (9.95 g, 62%).

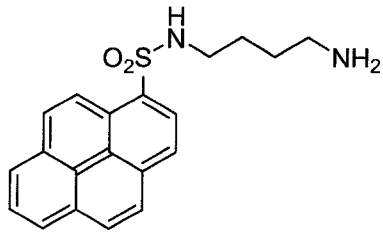
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (d, J = 9.6 Hz, 1H), 8.85 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 9.6 Hz, 1H), 7.89 – 7.61 (m, 6H), 6.60 (t, J = 6.3 Hz, 1H), 6.50 (t, J = 6.0 Hz, 1H), 3.13 – 2.93 (m, 4H), 1.33 – 1.17 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (C), 134.6 (C), 133.3 (C), 131.2 (C), 130.6 (C), 129.9 (CH), 129.8 (CH), 128.5 (C), 127.7 (CH), 127.3 (CH), 126.8 (CH), 126.67 (CH), 126.66 (CH), 125.5 (C), 124.4 (CH), 124.1 (CH), 79.0 (C), 43.2 (CH_2), 41.2 (CH_2), 29.0 (CH_3), 28.2 (CH_2), 27.3 (CH_2).

IR (neat) 3355, 2984, 1665 cm^{-1}.

MS (CI) 453 (M^+ + 1).

R_f: 0.45 on silica gel (EtOAc).



***N*-(4-aminobutyl)pyrene-1-sulfonamide.** To a solution of *tert*-butyl 4-(pyrene-1-sulfonamido)butylcarbamate (**A-152**) (9.95 g, 22.0 mmol, 1 equiv) in CH_2Cl_2 (180 mL) was added TFA (45 mL). After 2 hours the volatiles were removed under reduced pressure and the mixture was diluted with NaOH (1 M). The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to give a brown oil that was used immediately (7.67 g, 99%).

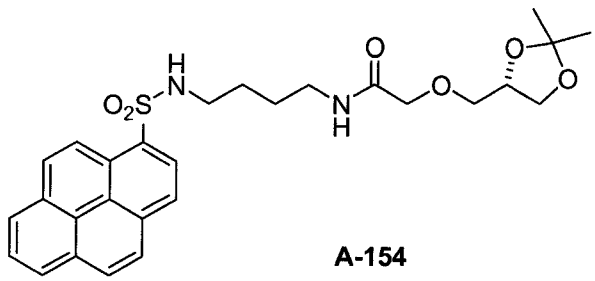
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (d, J = 9.6 Hz, 1H), 8.85 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 9.6 Hz, 1H), 7.89 – 7.61 (m, 6H), 6.60 (t, J = 6.3 Hz, 1H), 5.40 (br s, 2H), 3.23 – 2.90 (m, 4H), 1.30 – 1.20 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 134.5 (C), 133.1 (C), 130.9 (C), 130.6 (C), 129.8 (CH), 129.7 (CH), 128.5 (C), 127.7 (CH), 127.3 (CH), 126.8 (CH), 126.67 (CH), 126.66 (CH), 125.5 (C), 124.4 (CH), 124.1 (CH), 43.0 (CH_2), 41.4 (CH_2), 28.2 (CH_2), 27.3 (CH_2).

IR (neat) 3355, 2984 cm^{-1}.

MS (CI) 353 (M^+ + 1).

R_f: 0.0 on silica gel (EtOAc).



A-154

(*S*)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (A-154). To a suspension of NaH (492 mg, 12.3 mmol, 2.0 equiv) in DMF (30 mL) was added (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (0.77 mL, 9.2 mmol, 1.5 equiv). After ½ hour, a solution of 2-chloro-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (**A-153**) (2.51 g, 6.15 mmol, 1.0 equiv) and DIPEA (3.22 mL, 18.5 mmol, 3.0 equiv) in DMF (30 mL) was added *via* canula and the reaction was stirred for 18 hours. The reaction mixture was diluted with H_2O (600 mL) and the aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by column chromatography on silica gel eluting with EtOAc to give the title compound as a brown oil (1.64 g, 53%).

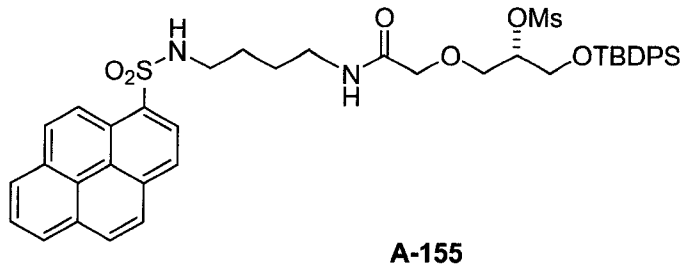
^{1}H NMR (300 MHz, benzene-d_6): δ 9.44 (d, J = 9.6 Hz, 1H), 8.86 (d, J = 8.1 Hz, 1H), 8.08 (d, J = 9.6 Hz, 1H), 7.89 – 7.58 (m, 6H), 6.74 (t, J = 6.3 Hz, 1H), 6.54 (t, J = 6.0 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.83 (s, 2H), 3.59 (dd, J = 8.4, 6.9 Hz, 1H), 3.35 (dd, J = 8.1, 6.6 Hz, 1H), 3.13 – 2.93 (m, 4H), 2.84 (q, J = 6.3 Hz, 2H), 1.33 – 1.17 (m, 4H), 1.30 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (75 MHz, benzene-d_6): δ 169.7 (C), 162.0 (C), 134.6 (C), 133.3 (C), 131.2 (C), 130.6 (C), 129.9 (CH), 129.8 (CH), 128.5 (C), 127.7 (CH), 127.3 (CH), 126.8 (CH), 126.67 (CH), 126.66 (CH), 125.5 (C), 124.4 (CH), 124.1 (CH), 109.6 (C), 74.8 (CH), 72.1 (CH_2), 70.8 (CH_2), 65.8 (CH_2), 43.0 (CH_2), 38.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_3), 25.5 (CH_3).

IR (neat) 3355, 2984, 1662 cm^{-1}.

MS (EI) 524 (M^+).

R_f: 0.48 on silica gel (EtOAc)



A-155

(*S*)-2,2-dimethyl-10-oxo-3,3-diphenyl-15-(pyrene-1-sulfonamido)-4,8-dioxa-11-aza-3-silapentadecan-6-yl methanesulfonate (A-155). To a solution of (*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropoxy)-*N*-(4-(pyrene-1-sulfonamido)butyl)acetamide (**A-149**) (1.44 g, 2.06 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added DIPEA (1.08 mL, 6.18 mmol, 3.0 equiv), DMAP (crystal) and methanesulfonyl chloride (0.32 mL, 4.11 mmol, 2.0 equiv) and the reaction was stirred for 18 hrs. The solution was diluted with EtOAc, and the organic layer was washed sequentially with HCl (10%), $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by column chromatography on silica gel eluting with 50% EtOAc in hexanes to 80% EtOAc in hexanes to give the title compound as a brown foam (1.56 g, 97%).

^{1}H NMR (300 MHz, acetone-d_6): δ 9.09 (d, J = 9.4 Hz, 1H), 8.69 (d, J = 8.2 Hz, 1H), 8.44 – 8.14 (m, 7H), 7.72 – 7.69 (m, 4H), 7.44 – 7.35 (m, 6H), 7.11 (t, J = 2.15, 1H), 6.97 (t, J = 9.0 Hz, 1H), 4.91 – 4.88 (m, 1H), 3.92 – 3.79 (m, 6H), 3.10 – 2.88 (m, 7H), 1.42 – 1.40 (m,. 4H), 1.03 (s, 9H).

^{13}C NMR (75 MHz, acetone-d_6): δ 170.1 (C), 137.3 (CH), 137.2 (CH), 129.0 (CH), 136.3 (C), 134.8 (C), 134.6 (C), 134.5 (C), 132.9 (C), 132.1 (C), 131.3 (CH), 131.83 (CH), 131.80 (CH), 130.1 (CH), 129.7 (CH), 129.6 (C), 129.1 (CH), 128.8 (CH), 128.6 (CH), 126.8 (C), 125.9 (CH), 125.7 (C), 125.6 (CH), 82.7 (CH), 72.2 (CH_2), 71.8 (CH_2), 64.9 (CH_2), 44.4 (CH_2), 39.6 (CH_3), 39.4 (CH_2), 28.41 (CH_2), 28.40 (CH_2), 28.1 (CH_3), 20.7 (C).

IR (neat) 3386, 2935, 1662 cm^{-1}.

MS (ESI) calcd for $C_{42}H_{48}N_2O_8S_2Si$ (M^+ + Na) 823, found 823.

R_f: 0.68 on silica gel (70 % EtOAc in hexanes).

B. Synthesis of Single Isomer Tetrasubstituted Olefins from the Regioselective and Stereospecific Palladium-Catalyzed Coupling Reactions of β-Chloro-α-Iodo-α,β-Unsaturated Esters and Amides

Chapter 1. Introduction

1.1 Introduction

The efficient regio- and stereoselective synthesis of tetrasubstituted olefins bearing four different carbon-linked groups presents a particular challenge in organic synthesis. The congested nature of the double bond can make it difficult for reagents to approach, and the eclipsing interactions in the products destabilize both the products and the transition states leading to them. This eclipsing destabilization can be severe enough to force geometric distortions of the sp^2 centers. These issues are compounded by the modern expectation of forming single isomers on diverse scaffold. Because of these formidable barriers, only recently has serious study been directed towards this synthetic challenge.

The significance of tetrasubstituted olefins is reflected in their presence in drugs such as Tamoxifen **B-1**,[81] or Vioxx **B-2**,[82] natural products such as Nileprost analogs **B-3**[83] or epi-Illudol **B-4**,[84] and in derivatives of these and other biologically active substances

[81] (a) Robertson, D. W.; Katzenellenbogen, J. A.; Hayes, J. R.; Katzenellenbogen, B. S. *J. Med. Chem* **1982**, *25*, 167. (b) Al-Hassan, M. *Synthesis* **1987**, 816. (c) Levenson, A. S.; Jordan, V. C. *Eur. J. Cancer* **1999**, *35*, 1628. (d) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem* **2006**, *71*, 9552. (e) Shimizu, K.; Takimoto, M.; Mori, M.; Sato, Y. *Synlett* **2006**, 3182.

[82] (a) Caturla, F.; Amat, M.; Reinoso, R. F.; Cordoba, M.; Warrellow, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3209. (b) Wadman, M. *Nature* **2006**, *440*, 277. (c) Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.

[83] Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643.

[84] (a) Rychlet Elliott, M.; Dhimane, A. L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427. (b) Arnone, A.; Brambilla, U.; Nasini, G.; de Pava, O. V. *Tetrahedron* **1995**, *51*, 13357.

(Figure 1).[85] Recently, compounds containing tetrasubstituted alkenes have been examined for their potential as dipeptide mimetics[86] and as polymerization substrates or catalysts.[87] Stereodefined tetrasubstituted olefins are also key starting materials for various asymmetric transformations such as hydrogenations,[88] osmylations,[89] epoxidations,[90] and other processes that generate contiguous, stereogenic, sp^3–hybridized centers.[91]

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[86] Oishi, S.; Miyamoto, K.; Niida, A.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Kuroda, Y.; Asai, A.; Fujii, N. *Tetrahedron* **2006**, *62*, 1416.

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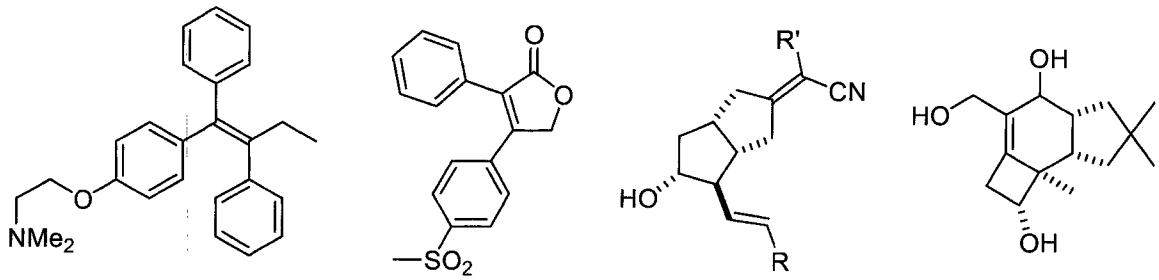
[90] (a) Katsuki, T.; Martin, V. *Org. React.* **1996**, *48*, 1. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (c) Rozen, S.; Golan, E. *Eur. J. Org. Chem.* **2003**, *2003*, 1915. (d) Adam, W.; Blancafort, L. *J. Am. Chem. Soc.* **1996**, *118*, 4778. (d) Thede, K.; Diedrichs, N.; Ragot, J. P. *Org. Lett.* **2004**, *6*, 4595.

[91] (a) *Krause, N., Ed. Modern Organocopper Chemistry; Wiley-VCH: Weinheim, 2002, 224.* (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (e) Varela, J. A.; Peña, D.; Goldfuss, B.; Denisenko, D.; Kulhanek, J.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2004**, *10*, 4252. (f) Bauld, N. L.; Stufflebeme, G. W.; Lorenz, K. T. *J. Phys. Org. Chem.* **1989**, *2*, 585. (g) Meijere, A. d.; Kozhushkov, Sergei I. *Eur. J. Org. Chem.* **2000**, *2000*, 3809. (h) Lhermitte, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2459. (i) de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, *2000*, 3809. (j) Bräse, S.; Meijere, A. d. *Angew. Chem. Int. Ed.* **1995**, *34*, 2545. (k) Gotoh, T.; Padias, A. B.; Hall, H. K. *J. Am. Chem. Soc.* **1986**, *108*, 4920. (l) Varela, J. A.; Pena, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001**, *3*, 2395.

Figure 1. Biologically active compounds containing tetrasubstituted olefins



B-1 **B-2** **B-3** **B-4**

Tetrasubstituted olefins are implicated in materials research because useful physical,[92] structural, and electronic properties are imparted, or arise from the presence of the double bond.[93] A number of helicenes containing fully substituted alkenes have been prepared and studied as potential liquid crystals.[94] The hindered olefins are twisted in these compounds, imparting helical chirality to the structures. In other structures, the tetrasubstituted olefin may be conjugated in such a way to produce chromophores. The rotationally locked nature of the tetrasubstituted olefin can be exploited to produce molecular switches and other devices.[95] These compounds have been explored

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[92] (a) Chiappe, C.; Detert, H.; Lenoir, D.; Pomelli, C. S.; Ruasse, M. F. *J. Am. Chem. Soc.* **2003**, *125*, 2864. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Topics in Curr. Chem.* **2000**, *207*, 89.

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[94] (a) Harada, N.; Saito, A.; Koumura, N.; Uda, H.; de Lange, B.; Jager, W. F.; Wynberg, H.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7241. (b) Harada, N.; Saito, A.; Koumura, N.; Roe, D. C.; Jager, W. F.; Zijlstra, R. W. J.; de Lange, B.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7249. (c) Harada, N.; Koumura, N.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7256. (d) Treitel, N.; Eshdat, L.; Sheradsky, T.; Donovan, P. M.; Tykwinski, R. R.; Scott, L. T.; Hopf, H.; Rabinovitz, M. *J. Am. Chem. Soc.* **2006**, *128*, 4703. (e) Eelkema, R.; Pollard, M. M.; Katsonis, N.; Vicario, J.; Broer, D. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14397.

[95] (a) Browne, W. R.; Pollard, M. M.; deLange, B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 12412. (b) Schreivogel, A.; Maurer, J.; Winter, R.; Baro, A.; Laschat, S. *Eur. J. Org. Chem.* **2006**, *2006*, 3395.

extensively for their potential use in optical data storage devices, among other applications.[96]

Classical double bond-forming methods such as the Wittig and Horner-Wadsworth-Emmons reactions encounter serious problems of generality and stereoselectivity when used to form tetrasubstituted double bonds. For this reason, indirect methods have been developed to synthesize tetrasubstituted olefins in geometrically defined ways.

1.1.1 Structures of Tetrasubstituted Olefins

The construction of tetrasubstituted olefins first requires a consideration of their shape and steric requirements. Fully substituted contiguous sp^2 centers experience eclipsing and steric interactions that can cause severe distortion of the double bonds. The degree of distortion is reflected in twisting along the olefin and depends on the steric demands of the substrates. Tetra-aryl substituted product **B-5** was isolated and crystallized by Daik *et al.* in 1998.[97] The X-ray structure illustrated the twisting about the double bond, showing an 11 to 12° departure from planarity of the olefin system (Figure 2). Similar twisting was also found in cycloalkyl product **B-6**, prepared by Tietze *et al.*, in which the improper torsion was found to be as much as 11°.[98] Smaller substituents on the olefin carbons reduce the steric compression and give flatter structures. The methyl groups in **B-7** experienced less eclipsing than the aryl rings, resulting in an olefin that was closer to planarity.[97] The aryl groups produced more steric strain, resulting in a slightly larger dihedral angle between these moieties than between the methyl groups. Twisted tetrasubstituted olefins have also been demonstrated in several other systems.[85bd,99]

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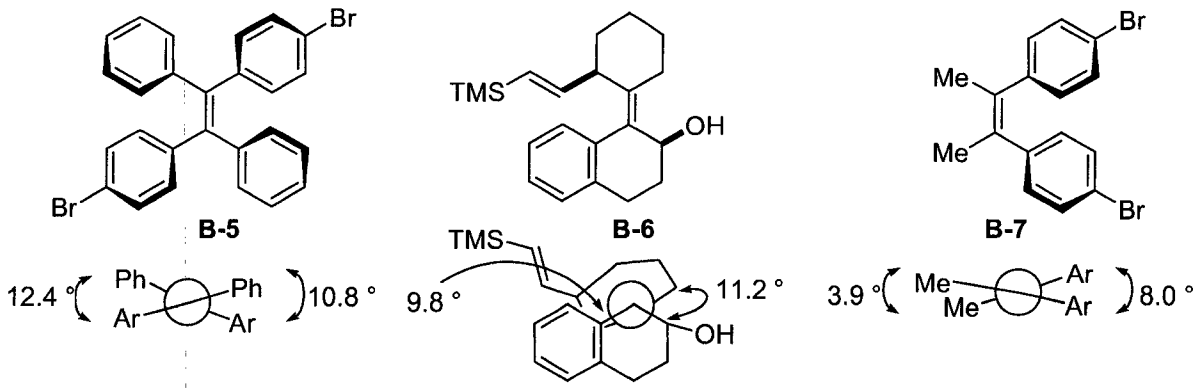
[96] (a) Feringa, B. L.; Jager, W. F.; De Lange, B. *Tetrahedron* **1993**, *49*, 8267. (b) Wolter F. Jager; Jong, J. C. d.; Lange, B. d.; Huck, N. P. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 348. (c) Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127.

[97] Daik, R.; Feast, W. J.; Batsanov, A. S.; Howard, J. A. K. *New J. Chem.* **1998**, 1047.

[98] Tietze, L. F.; Kahle, K.; Raschke, T. *Chem. Eur. J.* **2002**, *8*, 401.

[99] (a) Moonen, N. N. P.; Boudon, C.; Gisselbrecht, J.-P.; Seiler, P.; Gross, M.; Diederich, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 3044. (b) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608. (c) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317.

Figure 2. Selected examples of twisting about double bonds

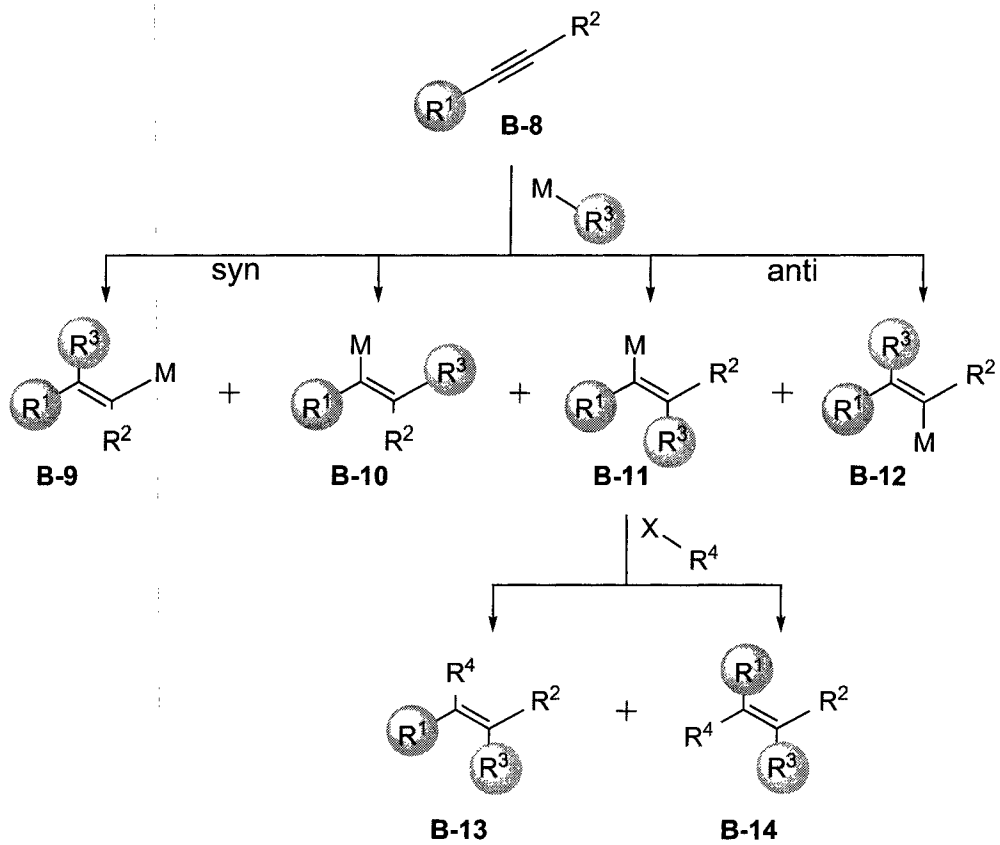


1.2 Carbometallation of Alkynes

The carbometallation of alkynes is the most widely-used method for the formation of tetrasubstituted olefins.[100] In principle, a high degree of control is possible in these processes and significant structural variation is attainable because of the convergent nature of the strategy. Regio- and stereocontrol are two key issues to be addressed in this technology because multiple products are possible (Scheme 1). The problem of regioselectivity has been addressed by the use of directing groups or by employing symmetrical alkynes as substrates. The use of symmetrical alkynes greatly simplifies many of the synthetic issues, however this results in a decrease in structural flexibility. With unsymmetrical alkyne substrates, directing groups are routinely employed to avoid the formation of isomeric mixtures. This directing influence may be steric, electronic, or chelating in nature.

[100] (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Doyle, M. P. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Ed.; Pergamon Press: Oxford, 1995; Vol. 12, 387.

Scheme 1. Regio- and stereoisomeric possibilities from carbometallation processes

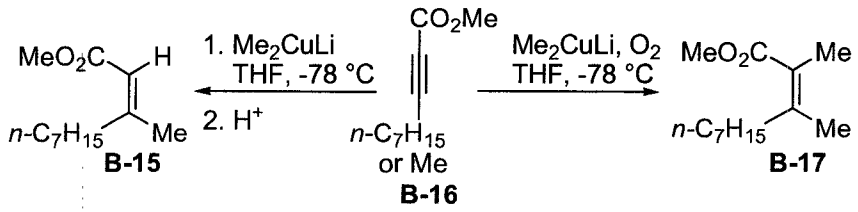


Depending on the nature of the metal or catalyst used, the carbometallation of the alkyne may proceed in a *syn* or *anti* fashion. Although the initial addition across the π bond may be stereoselective or stereospecific, in some cases there is configurational erosion or full inversion during the subsequent coupling reaction (*i.e.* **B-11** can produce **B-13** or **B-14** depending on reaction conditions). This is usually a consequence of the low reactivity of the intermediates; however, some researchers have identified electronic contributions to these occurrences, particularly when the intermediate organometallic species is of low nucleophilicity. Loss of configurational integrity typically occurs through enolization or elimination processes. This can be suppressed by manipulating the ionic character of the metal, by improving substrate design, by carefully selecting the catalyst, or by simply keeping the solution cold. In the following sections, the strategies have been organized according to the metal used to affect the carbometallation.

1.2.1 Copper

Some of the earliest attempted carbometalationions involved the *syn* conjugate addition of copper species to α,β-acetylenic esters **B-16**. Regiochemical control was achieved by directing the addition of the organic substituent to the β-position (Scheme 2).[101] Quenching the reactions at −78 °C gave trisubstituted olefins such as **B-15** in good yield and with excellent stereoselectivity (*E:Z* 92:8 to 99.8:0.2) provided that THF was used as the solvent. It was noted that equilibration of the cuprate intermediates occurred at higher temperatures and so quenching at −78 °C was imperative. Using a large excess of Gilman reagent in the presence of oxygen gave the tetrasubstituted product **B-17** in unspecified yield.[102]

Scheme 2. Carbocupration of alkynoates



Alexakis *et al.* approached the problem of enolization by using acetals as directing groups (Scheme 3).[103] The addition of Gilman reagents to alkynyl acetals proceeded with high selectivity and stereointegrity in THF at low temperatures. Significant effort was invested to elucidate the factors controlling regio- and stereoselectivity in the initial cuprate addition. Copper species derived from organolithiums were required and the reactions had to be performed in THF to prevent the competing elimination pathway to form allenes. The intermediate vinylogous cuprates proved to have low reactivity and tetrasubstituted olefins could only be obtained by using powerful electrophiles such as methyl iodide or allyl bromide. More diversity was achieved using electrophiles such as butyl iodide in the presence of four equivalents of HMPT, and two examples were given of palladium-mediated cross-couplings after *in-situ* conversion of the cuprates to the corresponding zinc species.

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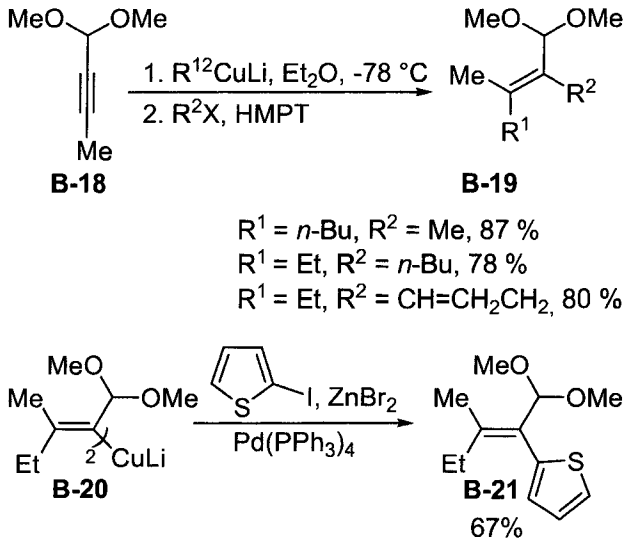
[101] Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
[102] Whitesides, G. M.; San Filippo, J.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.
[103] Alexakis, A.; Commercon, A.; Coulentianos, C.; Normant, J. F. *Tetrahedron* **1984**, *40*, 715.

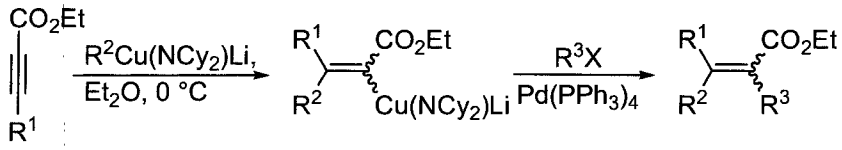
Scheme 3. Tetrasubstituted olefins from alkynyl acetals



The palladium-catalyzed cross-coupling of organocuprates was subsequently used to generate tetrasubstituted olefins from acetylenic esters (Table 1).[104] In this study, cuprates carrying a dicyclohexylamido dummy ligand were employed. The addition of $R^2Cu(NCy_2)Li$ to acetylenic esters at 0 °C gave an intermediate organocuprate species that was efficiently coupled to several vinylogous halides in the presence of $Pd(PPh_3)_4$. This method was useful for the formation of tetrasubstituted olefins that carried identical substituents on the β-carbon of the unsaturated ester **B-22** ($R^1 = R^2 = Me$), because the low reactivity of the intermediate copper species necessitated room temperature treatment during the palladium-catalyzed cross-coupling reaction. This increased temperature resulted in a *ca.* 1:1 mixtures of *E* and *Z* isomers through enolization of the intermediate copper anion when the preparation of differentially substituted products ($R^1 \neq Me$) was attempted (entries 7 to 9). One example was reported of a tetrasubstituted double bond bearing four different groups with an *E* to *Z* ratio of 6 to 4 (entry 7).

[104] Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem* **1988**, *53*, 607.

Table 1. Tetrasubstituted olefins by organocopper addition to acetylenic esters



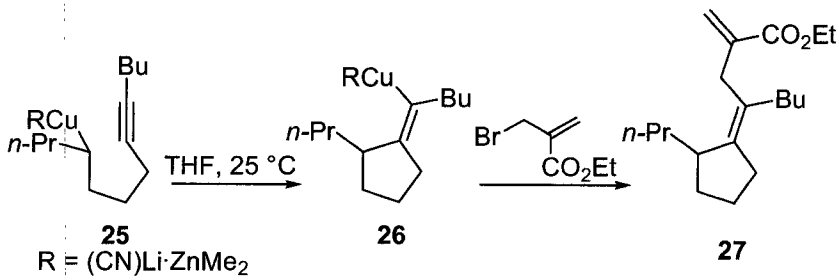
B-22 **B-23** **B-24**

Entry	R^1	R^2	R^3X	% Yield (*E*:*Z*)
1	Me	Me	PhI	89
2	Me	Me	PhBr	60
3	Me	Me	(*E*)-BuCH=CHI	62
4	Me	Me	(*E*)-PhCH=CHBr	59
5	Me	Me		70
6	Me	Me	$PhCH_2I$	53
7	Me	Bu	PhI	61 (40:60)
8	Me	Ph	PhI	77 (44:56)
9	Ph	Me	PhI	52 (38:62)

The difficulties associated with achieving regiochemical control in the addition of alkyl copper onto simple alkynes was addressed by Knochel *et al.* who used an intramolecular delivery of the organo-copper species (Scheme 4).[105] Thus zinc-copper intermediates such as **B-25,** generated from the corresponding alkylzinc halides and CuCN·LiCl underwent an intramolecular carbometallation to produce cyclic intermediates **B-26**. Because the structures of the intermediate vinyl cuprates precluded enolization, the condensations could be done at elevated temperatures without any loss of stereochemical integrity, thus increasing the reactivity of **B-26** towards electrophiles.

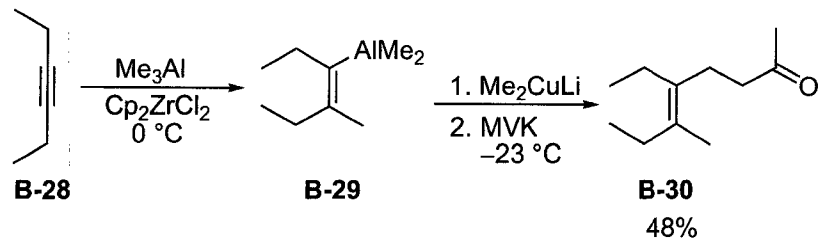
[105] Rao, S. A. K., P. *J. Am. Chem. Soc.* **1991**, *113*, 5735.

Scheme 4. Intramolecular carbocupration



Regiochemical issues have been circumvented by using symmetrically-substituted alkynes. Thus the Wipf group[106] employed Schwartz chemistry,[107] exposing 3-hexyne to Me_3Al in the presence of Cp_2ZrCl_2 to generate vinylic alane **B-29** (Scheme 5). This intermediate could then be transmetallated to the corresponding copper reagent for subsequent condensations with methyl vinyl ketone (MVK). In this manner, derivative **B-30** was made in 48% overall yield.

Scheme 5. Approach to tetrasubstituted alkenes using symmetric alkynes



Deslongchamps and coworkers exploited the reactivity of α-halo ethers to improve the scope of electrophilic additions with vinyl cuprates (Table 2).[108] The high reactivity of the α-halo ethers allowed the temperature of the final alkylation to be lowered to 0 °C, thus improving selectivity. This method delivered more than ten examples of tetrasubstituted products **B-33** and **B-35** in yields greater than 60%, with typical selectivities of greater than 5:1 (**B-33**:**B-35**). In four cases the minor products (**B-35**) were not detected.

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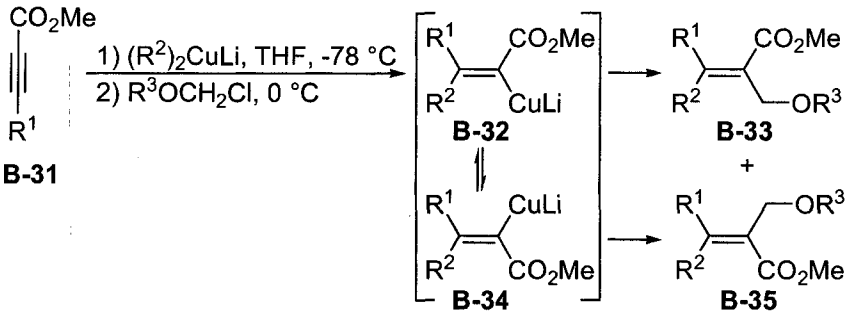
[106] Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem* **1992**, *57*, 3178.
[107] (a) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65. (b) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375. (c) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. (d) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.
[108] Hall, D. G.; Chapdelaine, D.; Préville, P.; Deslongchamps, P. *Synlett* **1994**, 660.

Table 2. Addition of organocuprates and α-halo ethers to acetylenic esters



Entry	R^1	R^2	R^3	Yield (%) (B-33:B-35)
1	$TBDPSO(CH_2)_2$	Me	Bn	59 (24:1)
2	$TBDPSO(CH_2)_2$	Me	$4\text{-}MeOC_6H_4$	66 (6:1)
3	$TBDPSO(CH_2)_2$	Me	$(CH_2)_2Si(CH_3)_3$	68 (>25:1)
4	$TBDPSO(CH_2)_2$	Me	$(CH_2)_2Si(CH_3)_3$	86 (5:1)
5	$TBDPSO(CH_2)_2$	Me	Me	47 (21:1)
6	$TBDPSO(CH_2)_2$	Me	Me	71 (5:1)
7	$TBDPSO(CH_2)_2$	Me	Me	87 (25:1)
8	$TBDPSO(CH_2)_2$	Bu	$(CH_2)_2Si(CH_3)_3$	61 (4.5:1)
9	$TBDPSO(CH_2)_3$	Me	$4\text{-}MeOC_6H_4$	72 (6:1)
10[a]	Et	Me	Bn	70 (10:1)

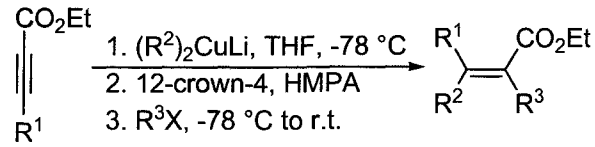
[a] Ethyl ester was used.

This technology was later expanded to improve the substrate scope (Table 3).[109] Excellent regio- and stereoselectivities were achieved by using additives such as HMPA and 12-crown-4 to control the extent of allenoate formation. 12-Crown-4 was added to chelate excess lithium, a species known to degrade stereochemical information in related

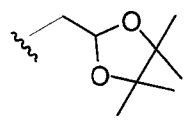
[109] (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898. (b) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066.

substrates.[91a,110] The use of this additive alone gave unsatisfactory yields with the electrophiles attempted, and to overcome this several equivalents of HMPA were included. These conditions were applied to a number of active electrophiles giving excellent selectivity in all cases. This methodology has since been applied to acid-catalyzed allylboration reactions in order to generate stereogenic quaternary centers.[111,112]

Table 3. Addition of organocuprates and α-halo ethers to acetylenic esters



B-36 **B-37**
>19:1 *cis* addition

Entry	R^1	R^2	R^3	Yield (%)
1	Et	Me	$-CH_2SnBu_3$	80
2	Et	Me	$-CH_2SiMe_3$	30
3	Et	Me	$-CH_2Ph$	40
4	Et	Me	$-CH_2CH=CH_2$	76
5	Et	Me	$-CH_2C(Br)=CH_2$	57
6	Et	Me	$-CH_2CH=CMe_2$	78
7	Et	*s*-Bu	$-CH_2CH=CH_2$	72
8	$TBSOCH_2$	Me	$-CH_2CH=CH_2$	85
9	Et	Me		66

[110] (a) Klein, J.; Levene, R. *J. Chem. Soc. Perk. 2* **1973**, 1971. (b) Nilsson, K.; Anderson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051. (c) Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219.
[111] (a) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412. (b) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.
[112] Oishi, S.; Niida, A.; Kamano, T.; Miwa, Y.; Taga, T.; Odagaki, Y.; Hamanak, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Chem. Soc. Perk. 1* **2002**, 1786.

1.2.2 Boron

The use of boron instead of copper for the carbometallation of alkynes offers significant reactivity advantages because the intermediate vinyl boranes make excellent cross-coupling partners for subsequent palladium-mediated processes. Regiochemical issues can be addressed through the use of directing groups, or avoided by making symmetrically substituted products. The loss of stereochemical information occurs less frequently with these types of reactions than with organocuprates because unactivated alkynes can be used as substrates. The initial carbometallations occur with *cis* geometry, although a loss of stereopurity sometimes occurs during the subsequent cross-coupling reaction. Substrate scope can be somewhat limited for these reactions as the couplings are normally done with simple aryl and alkenyl partners.

Early work illustrated a method for the generation of tetrasubstituted alkenes involving a tin-induced alkyl transfer from a boron-ate complex followed by functionalization (Scheme 6).[113] In this method, a lithium acetylide, generated from acetylene **B-38**, was transmetallated with Et_3B to produce -ate complex **B-39**. This material then rearranged and was trapped in the presence of tributyltin chloride to afford tin adduct **B-40** as a single isomer.[114] The intramolecular delivery of the ethyl group from boron ensured that the process was regiospecific. The crude intermediate **40** underwent transmetallation twice, once with *n*-BuLi and then with $CuBr{\cdot}SMe_2$, a process that was necessary to avoid losing stereochemical information. The resulting organocuprate was quenched with allylbromide to give vinyl tin adduct **B-41**. The tin group proved to be remarkably resistant to lithium exchange, allowing for excellent regioselectivity in this process. The low reactivity of the tin moiety necessitated a halogen exchange before subsequent elaboration could be attempted and a further three steps (lithium exchange, copper exchange and quench with MeI) were required to produce adduct **B-42** as single isomer in 54% overall yield from **B-41**. This ten-step sequence was applied in two other cases using cyclohexenone as the terminal electrophile. In each case, single isomers were obtained.

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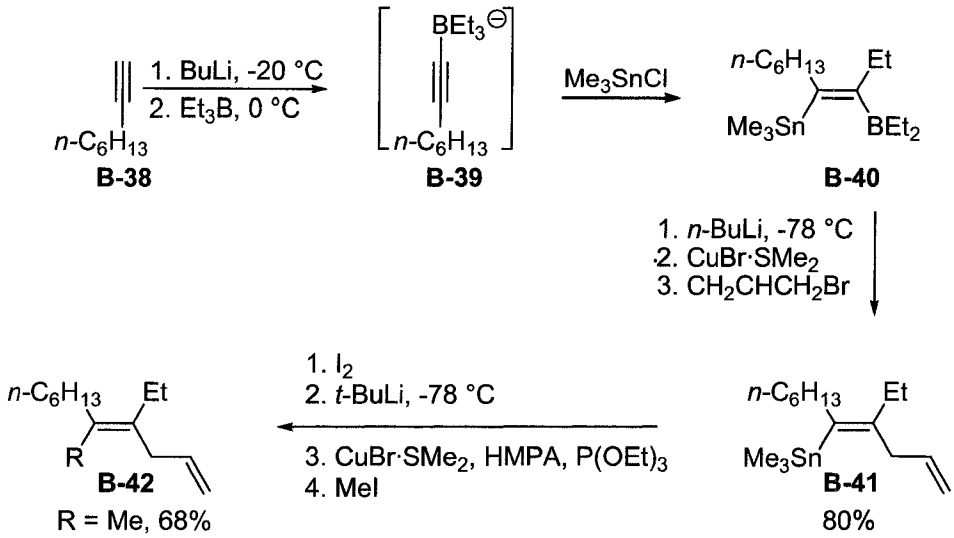
[113] (a) Chu, K.-H.; Wang, K. K. *J. Org. Chem* **1986**, *51*, 767. (b) Wang, K. K.; Chu, K.-H.; Lin, Y.; Chen, J.-H. *Tetrahedron* **1989**, *45*, 1105.
[114] Hooz, J.; Mortimer, R. *Tetrahedron Lett.* **1976**, *17*, 805.

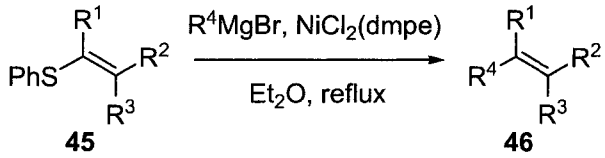
Scheme 6. Rearrangement of boron ate-complexes to give tetrasubstituted olefins

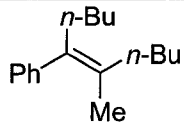
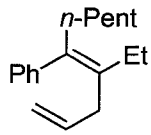
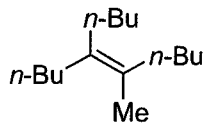
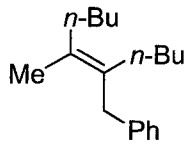


Using a very similar method, Gerard *et al.* demonstrated the rearrangement of a boronate complex in the presence of PhSCl.[115] The preparation of a series of tetraalkyl-substituted olefins was disclosed using this method (Table 4).[116] Commencing with intermediate boranes similar to **B-40** in structure, a lithium-boron exchange was performed using MeLi in the presence of HMPA. The resulting lithio species could be converted to the corresponding cuprates by the addition of CuI, and then alkylation was accomplished as before using reactive electrophiles. Reactions that were performed in the presence of HMPA could be run at slightly elevated temperatures (–33 °C) thus increasing the reactivity of the metal species and delivering corresponding yield improvements. When less active alkylating agents were employed, the presence of $P(OEt)_3$ during the alkylation was necessary in order to realize significant amounts of intermediates analogous to **B-41**. The scope of the final nickel-catalyzed coupling was expanded in this account to include methyl and *n*-butyl Grignard coupling partners. The structures of the final products were inferred based on the preference of the boron to lithium exchange to occur with retention of stereochemistry,[91] and by the results of an NOE experiment that was conducted on one isomer.

[115] Gerard, J.; Bietlot, E.; Hevesi, L. *Tetrahedron Lett.* **1998**, *39*, 8735.
[116] Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367.

Table 4. Tranformation of β-chalcogeno alkenylboranes

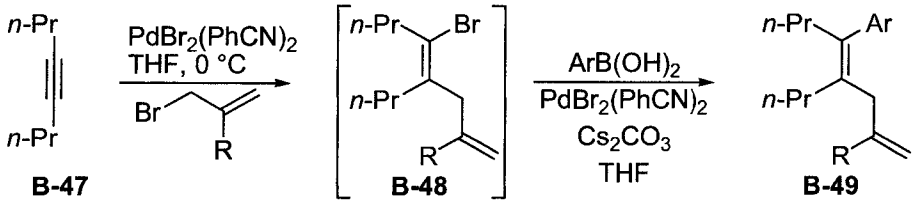


Entry	R^1	R^2	R^3	R^4	Product	*E/Z*	Yield (%)
1	*n*-Bu	*n*-Bu	Me	Ph		>99:1	82
2	*n*-Pent	Et	allyl	Ph		<1:99	38
3	*n*-Bu	*n*-Bu	Me	*n*-Bu		-	70
4	*n*-Bu	*n*-Bu	CH_2Ph	Me		>99:1	24

A related method was recently reported to prepare tetrasubstituted olefins as part of skipped diene systems.[117] A technique developed by Kaneda and coworkers[118] was modified to produce skipped dienes such as **B-49** (Scheme 7). In the original work,[118] it was found that a large excess of allyl bromide was necessary to promote the initial alkyne addition, a constraint that limited the practicality of the process. Rawal's group demonstrated that slow addition of the alkyne reduced polymerizing side reactions and gave the desired bromides **B-48**. Regiochemical issues in these reactions were circumvented by using symmetrical alkynes.[119] The subsequent Suzuki reactions could then be done in the same flask simply by adding the appropriate reagents upon completion of the allyl additions. The stereochemistry of the final products was assumed based on an initial *syn* addition across the alkyne.

[117] Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317.
[118] Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem* **1979**, *44*, 55.
[119] One TBSO-substituted propargylic alcohol gave a single isomer in 81% yield.

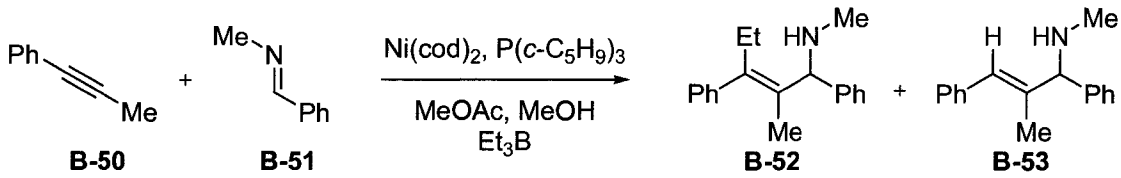
Scheme 7. Tetrasubstituted olefins in a skipped diene system



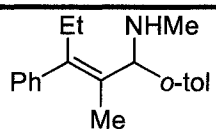
R = H, Ar = 3-$NO_2C_6H_4$, 78 %
R = Me, Ar = *N*-tosyl-3-indoyl, 85 %

Jamison *et al.* developed a multi-component method of tetrasubstituted olefin formation involving a nickel-catalyzed addition of imines to alkynes, followed by an alkylative coupling with an ethyl group from the borane to give **B-52** (Table 5).[120] The reactions were regioselective (9:1) with respect to imine addition, and were accompanied by small amounts of reduction products **B-53** (4 to 10%). Nine different imines, bearing a variety of functional groups, were successfully coupled with two different alkynes (PhC≡CMe and *n*Pr-C≡C-*n*Pr). It was also found that aryl and vinylboronic acids, used in the place of triethylborane, were compatible with the process, resulting in yields of 68 to 72%.

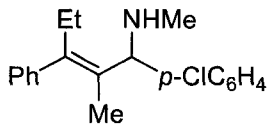
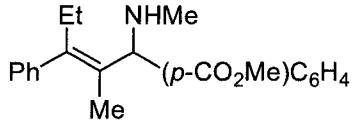
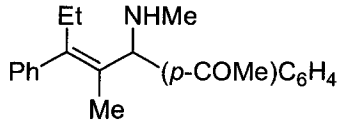
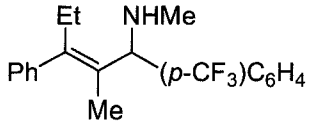
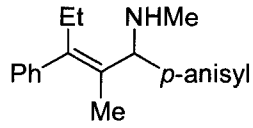
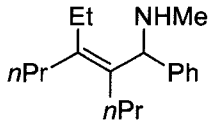
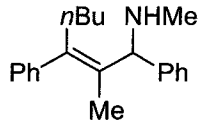
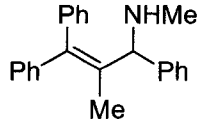
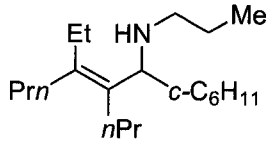
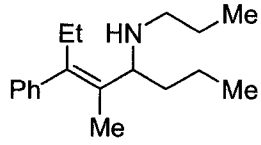
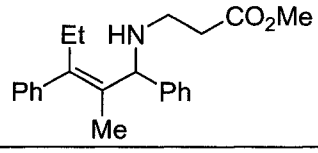
Table 5. Multi-component assembly of alkynes, imines, and organoboron reagents



30-95 % combined yield
>86:14
B-52:B-53

Entry	Product	Yield (%)	B-52:B-53	Regio-selectivity
1		85	94:6	90:10

[120] Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364.

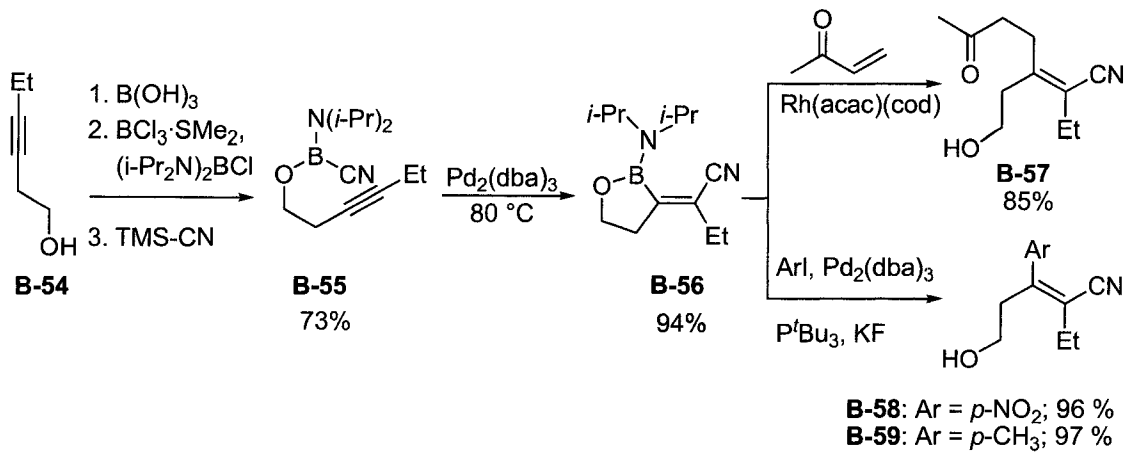
2		95	96:4	90:10
3		82	> 96:4	90:10
4		78	> 96:4	91:9
5		98	96:4	89:11
6		64	86:14	91:9
7		91	94:6	-
8		70	90:10	91:9
9		65	-	93:7
10		52	> 96:4	-
11		30	90:10	91:9
12		75	94:6	91:9

Suginome, Yamamoto, and Murakami used a directing group to control the cyanoboration of homopropargylic alcohols (Scheme 8).[121] Primary homopropargylic alcohols, such as **B-54**, were converted to initial cyanoboryl ethers **B-55** by a three-step

[121] Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358.

procedure.[122] Compound **B-55** smoothly underwent a cyclo-cyanoboration with the alkyne moiety giving intermediate adduct **B-56** as a single stereoisomer in 94% isolated yield. In the examples provided, the products were obtained as single isomers, but slight *E/Z* isomerization was observed in one case (93:7). The intermediate boryl ether **B-56** was converted to tetrasubstituted alkene **B-57** using rhodium catalysis. Two other examples of tetrasubstitued olefins (**B-58** and **B-59**) were given, each obtained by a Suzuki cross-coupling using the appropriate aryl iodide.

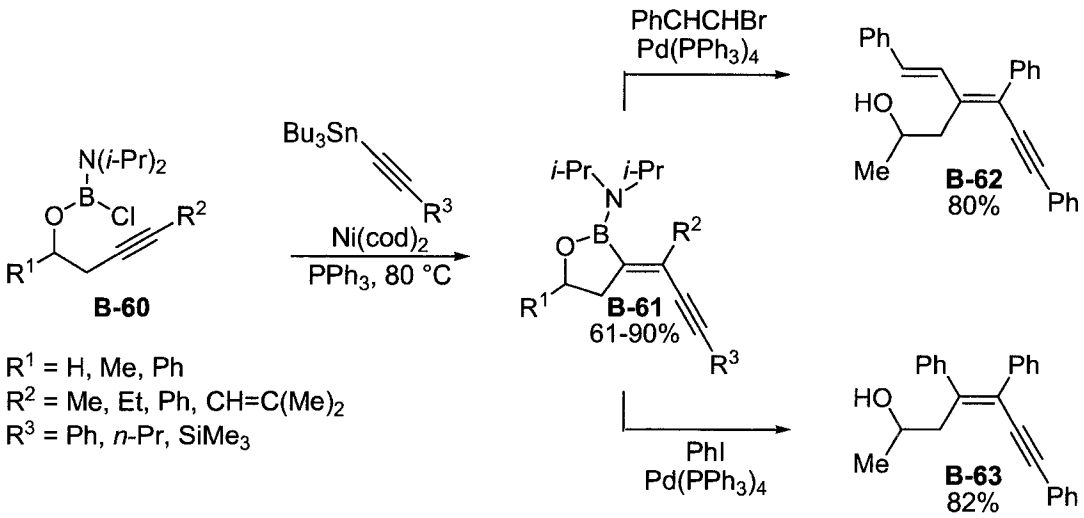
Scheme 8. Intramolecular cyclocyanoboration of alkynes



Subsequently, it was shown that when chloroboryl ethers were treated with alkynyl stannanes in the presence of a nickel catalyst, *trans* addition across the alkyne occurred, to deliver cycloboranes such as **B-61** (Scheme 9).[123] The production of the *trans* product **B-61** was thought to arise from a *cis/trans* isomerization prior to insertion into the alkyne, brought about by unfavorable steric interactions between the nickel complex and the bulky amine group on boron. One of the crude intermediates, **B-61** ($R^2 = R^3 =$ Ph, $R^1 =$ Me), was cross-coupled with an aryl iodide or a vinyl bromide to afford products **B-62** and **B-63** respectively.

[122] Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Comm.* **2002**, 1392.
[123] Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2005**, *127*, 15706.

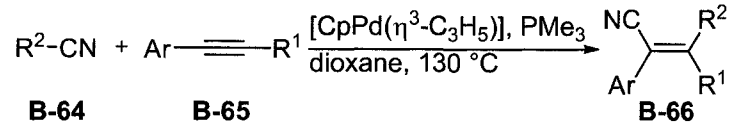
Scheme 9. Tetrasubstituted alcohols from cycloboration of chloroboryl alkynyl ethers



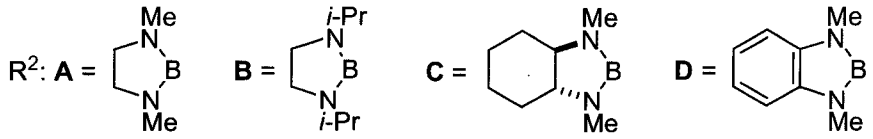
This methodology also worked in an intermolecular sense (Table 6), achieving excellent regioselectivity for differentially-substituted alkynes, provided that a bulky cyanoborane was employed.[124]

[124] Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2380.

Table 6. Intermolecular cyanoborane addition to alkynes



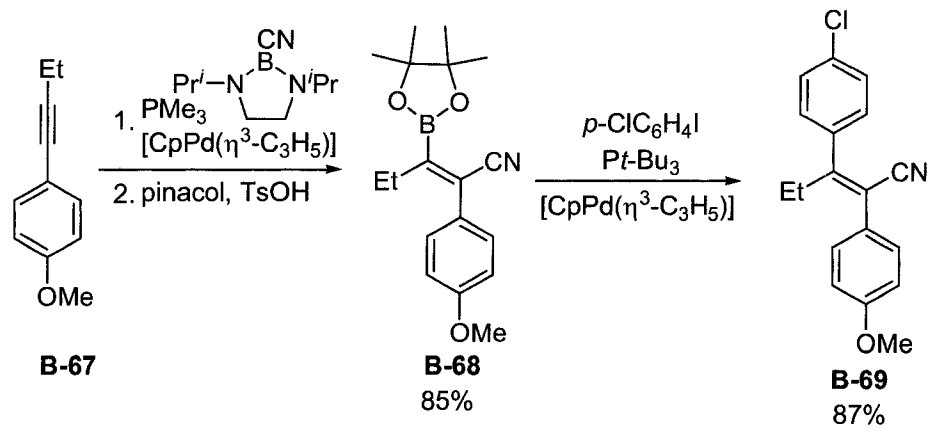
B-64 **B-65** **B-66**



Entry	Ar	R^1	R^2	Regioisomeric Ratio	Yield (%)
1	Ph	Me	**A**	85:15	77
2	Ph	Me	**B**	95:5	94
3	Ph	Me	**C**	83:17	97
4	Ph	Me	**D**	83:17	96
5	Ph	Bu	**B**	95:5	89
6	4-$EtO_2CC_6H_4$	Bu	**B**	88:12	72
7	4-$CF_3C_6H_4$	Bu	**B**	93:7	81
8	2-$CH_3C_6H_4$	Bu	**B**	98:2	59
9	2-$MOMOC_6H_4$	Bu	**B**	99:1	80
10	1-naphthyl	Me	**B**	99:1	72
11	2-naphthyl	Bu	**B**	91:9	61

One demonstration of the conversion of these borylated products into tetrasubstituted olefins using a Suzuki coupling reaction afforded **B-69**, the precursor to a squalene synthetase inhibitor, in 74% overall yield from the starting alkyne **B-67** (Scheme 10). For the Suzuki process to be successful however, the boron moiety first had to be converted to the pinacol boronate ester.

Scheme 10. Generation of tetrasubstituted olefins from intermolecular cyanoboration



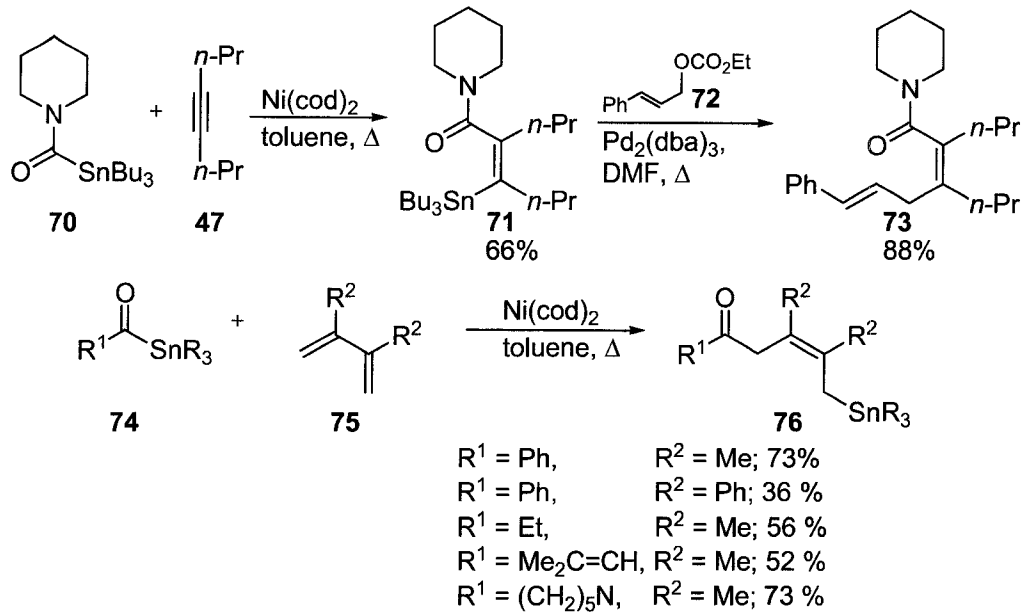
1.2.3 Tin

The use of tin coupling reactions in tetrasubstituted olefin preparation has received somewhat less attention than the use of boron or copper. As with all methods using tin, toxicity and purification problems are encountered, in addition to the wonderful smell. The tin-mediated methods tend to be highly stereoselective but moderately regioselective.

Shirakawa and Hiyama found that $Ni(cod)_2$ catalyzed the addition of an allyl or acyl stannanes such as **B-70** to an alkyne such as **B-47** to give an initial vinylic stannane **B-71** with excellent *cis*-selectivity (> 99:1) (Scheme 11).[125] In the case of unsymmetrical alkynes, the major regioisomers resulted from addition of the tributyltin moiety to the more electron-deficient alkynyl carbon. Two examples of tetrasubstituted alkenes were given in which the substrate was then elaborated using palladium-mediated allylation and carbonylation reactions. While the acylstannylations gave mixtures of regioisomers in ratios as low as 2:1, the allylstannylations were highly selective, with many reactions giving regioselectivities of > 99:1. These authors later reported a variation in which acyl stannanes could be added across disubstituted dienes to afford derivatives such as **B-76**.[126] Yields of 36 to 88% were realized and single isomers were obtained when symmetrically substituted dienes were employed ($R^2 = R^3$).

[125] Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221.
[126] Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 9030.

Scheme 11. Addition of acyl stannanes to alkynes



When differentially-substituted alkynes were used, a radical carbostannylation could be done regioselectively if electron-withdrawing groups were present. This principle was demonstrated by Hosomi *et al.*, who used alkynoate esters such as **B-77** to direct the addition of tin radicals to the triple bond (Scheme 12).[127] Vinyl tin species such as **B-79** were obtained in 27 to 85% yields along with small amounts of stereo- and regioisomeric side products. The resulting vinyl tin compounds (**B-79**) were not converted to tetrasubstituted olefins, but in principle the products could be so utilized.

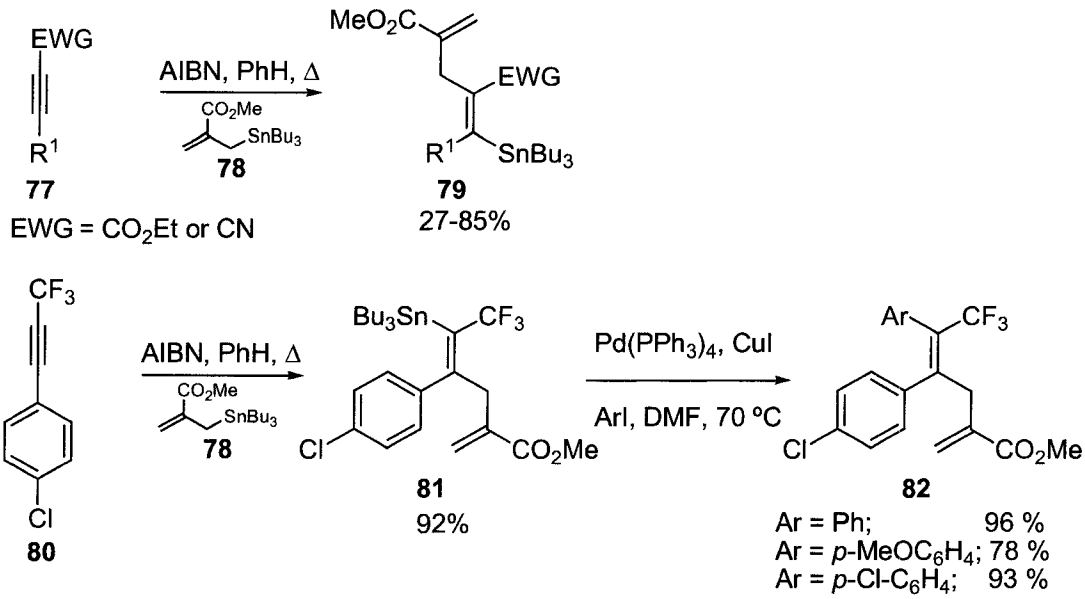
In a similar strategy, CF_3 groups were used, instead of alkynoate esters, to direct the addition of tin radicals (Scheme 12). The CF_3 group exerted powerful regiocontrol, completely reversing the regioselectivity observed for aryl-alkylalkynes. Allyl tin reagent **B-78** was successfully added to a series of CF_3 substituted alkynes **B-80** which gave the corresponding olefins **B-81**, in a *trans* fashion with complete control of regio- and stereochemistry.[128] Eight related alkynes were carbostannylated in 83 to 94% isolated yields. Further Stille couplings of **B-81** with three different aryl iodides gave the corresponding tetrasubstituted olefins **B-82** in 78 to 96% yield.

---

[127] (a) Miura, K.; Itoh, D.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 8539. (b) Miura, K.; Matsuda, T.; Hondo, T.; Ito, H.; Hosomi, A. *Synlett* **1996**, 555.

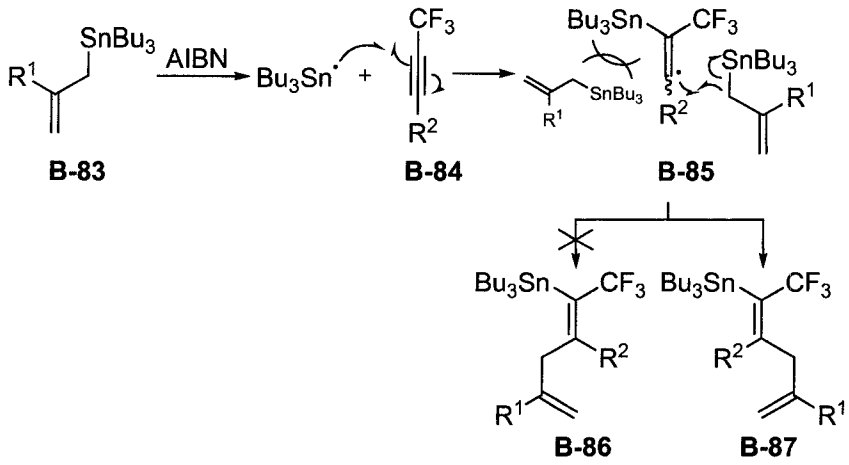
[128] Konno, T.; Takehana, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 2188.

Scheme 12. Carbostannylation of differentially-substituted alkynes



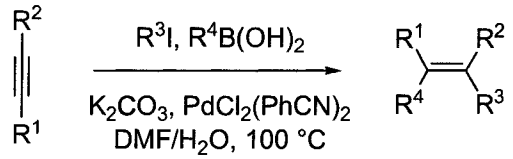
The proposed mechanism for the carbostannylation reaction involved an initial addition of Bu_3Sn radical to the alkyne **B-84**. This resulted in an intermediate radical **B-85** which had indeterminate stereochemistry at the sp^2–hybridized center (Scheme 13). Selective addition of the allyltin moiety was thought to be a consequence of strong steric interactions between the Bu_3Sn group and the incoming allyl reagent, forcing these two groups to become *anti* to one another in the product (**B-87**).

Scheme 13. Proposed mechanism of radical carbostannylation of alkynes



The one-pot synthesis of tetrasubstituted alkenes was subsequently accomplished via the carbopalladation of fluorine-containing acetylene derivatives (Table 7).[129] In this account, the fluorinated substituents did not seem to provide sufficient electronic bias to govern the regioselectivity of the addition. Mixtures of regioisomers were obtained when iodides and boronic acids bearing different aryl substituents were employed (entries 11 to 15).

Table 7. Carbopalladation of fluorine-containing acetylene derivatives



B-88 **B-89**

69 - 93 %

Entry	R^1	R^2	R^3	R^4	Yield (%)	Ratio
1	CF_3	4-ClC_6H_4	Ph	Ph	85	-
2	CF_3	4-ClC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	(86)	-
3	CF_3	4-ClC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	82	-
4	CF_3	4-$MeOC_6H_4$	Ph	Ph	(88)	-
5	CF_3	4-MeC_6H_4	Ph	Ph	81	-
6	CF_3	3-$MeOC_6H_4$	Ph	Ph	71	-
7	CF_3	2-$MeOC_6H_4$	Ph	Ph	(85)	-
8	CF_3	$Ph(CH_2)_3$	Ph	Ph	(83)	-
9	CHF_2	4-ClC_6H_4	Ph	Ph	80	-
10	$(CF_2)_2CHF_2$	4-ClC_6H_4	Ph	Ph	73	-
11	CF_3	4-ClC_6H_4	Ph	4-$MeOC_6H_4$	(76)	40 : 60
12	CF_3	4-ClC_6H_4	4-$MeOC_6H_4$	Ph	(80)	63 : 37
13	CF_3	4-ClC_6H_4	4-MeC_6H_4	Ph	(89)	39 : 61

[129] Konno, T.; Taku, K.-i.; Ishihara, T. *J. Fluorine Chem.* **2006**, *127*, 966.

14	CF_3	4-ClC_6H_4	3-$MeOC_6H_4$	Ph	(84)	57 : 43
15	CF_3	4-ClC_6H_4	2-$MeOC_6H_4$	Ph	(60)	62 : 38

This method was complementary to a technique reported by the Jennings group that involved the radical-mediated addition of fluoroalkyl iodides to alkynes.[130] Although most of the alkynes described were terminal, two internal alkynes were employed, giving vinylic iodide products. These could, in principle, serve as coupling partners to generate tetrasubstituted alkenes. Yields greater than 78% and *E/Z* ratios of more than 91:9 were obtained, although regioisomers resulted from the use of an unsymmetrical alkyne.

1.2.4 Magnesium

The addition of Grignard reagents to alkynes has proven to be highly successful, using directing groups to achieve reliable regioselectivity. The organomagnesium addition to the alkyne often proceeds in a *trans* fashion, resulting in predictable stereochemical outcomes. This *anti* addition is complementary to many transition metal-catalyzed processes, which often occur in a *syn* manner. All the methods shown build on a carbomagnesiation process, developed by Mornet, in which two equivalents of a Grignard reagent were added to propargylic alcohols, in a highly selective fashion, to give intermediates such as **B-91** (Scheme 14).[131]

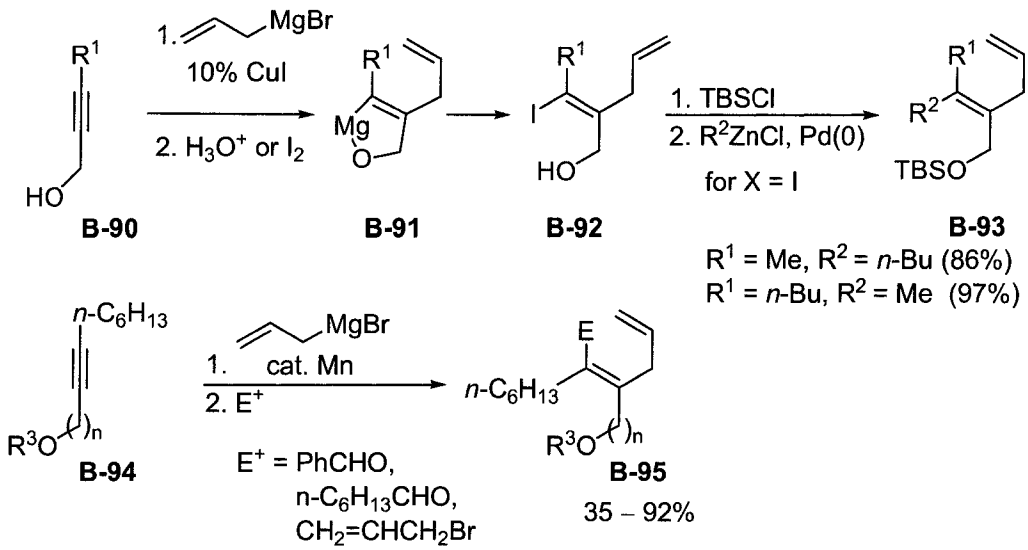
This process was exploited by the Negishi group, who showed that the magnesium species could be converted into iodides **B-92**, intermediates that could be cross-coupled using zinc reagents after protecting the hydroxyl group.[132] The *anti* addition of the Grignard reagent set the initial stereochemistry that was preserved in the subsequent coupling to give tetrasubstituted olefins such as **B-93**.

Similarly, Okada, Oshima, and Utimoto found that the carbomagnesiation could be catalyzed by manganese catalysts such as $Mn(acac)_3$.[133] Propargylic or homopropargylic

[130] Jennings, M. P.; Cork, E. A.; Ramachandran, P. V. *J. Org. Chem.* **2000**, *65*, 8763.
[131] Mornet, R.; Gouin, L. *Tetrahedron Lett.* **1977**, *18*, 167.
[132] (a) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (b) Anastasia, L.; Dumond, Yves R.; Negishi, E.-i. *Eur. J. Org. Chem.* **2001**, *2001*, 3039.
[133] (a) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076. (b) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061.

alcohols (or ethers) **B-94** could be treated with organomanganese species and then trapped with electrophiles such as benzaldehyde or allyl bromide to directly afford tetrasubstituted alkene products such as **B-95** (Scheme 14). This process typically occurred in a *syn* fashion.

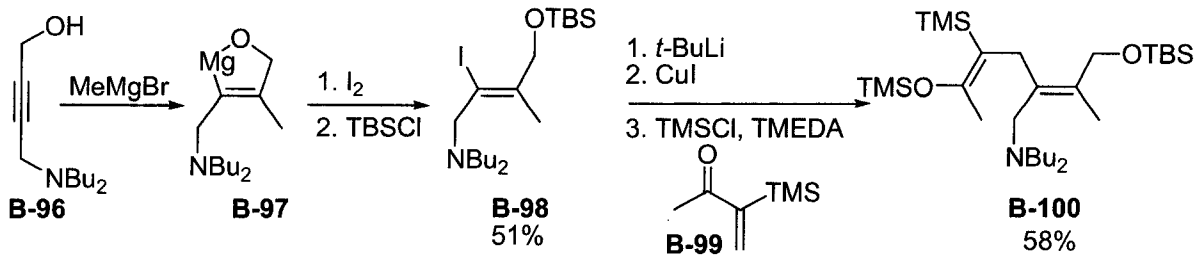
Scheme 14. Carbomagnesiation of propargylic alkynes



Another example of a tetrasubstituted olefin being produced by this type of Grignard addition was disclosed in 1990 (Scheme 15).[134] This method built on the carbomagnesiation process developed earlier[131] in which two equivalents of Grignard reagent were added to propargylic alcohols, giving the cyclic species **B-97**, in a highly selective manner. Quenching this intermediate with I_2 gave the corresponding iodo alcohol that could be protected with a TBS group to afford **B-98** in 51% yield from **B-96**. It was found that compound **B-98** could be rendered nucleophilic by lithium exchange followed by copper exchange, and that the resulting intermediate could be exposed to Michael acceptor **B-99** to afford **B-100** as the sole product.

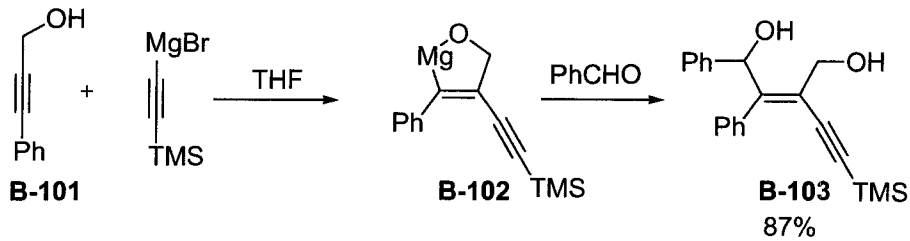
[134] Germanas, J.; Vollhardt, K. P. C. *Synlett* **1990**, 505.

Scheme 15. Carbomagnesiation-iodination-Michael sequence



This methodology was extended and made practical by eliminating the halogenation/double-exchange sequence through direct electrophile displacement (Scheme 16).[135] The cyclomagnesium species were formed directly and could be exposed to aldehydes to give tetrasubstituted olefins such as **B-103**. For successful reactions, the aldehyde addition required reflux temperatures in a mixture of THF and cyclohexane. A variety of propargylic alcohols were converted to olefin products in yields varying from 68 to 87%.

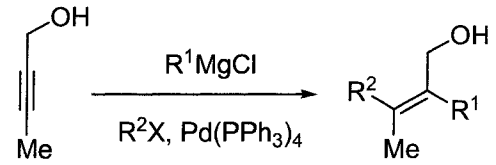
Scheme 16. Carbomagnesiation-carbonyl trapping



Also reported was the condensation of the intermediate cyclomagnesium species **B-102** with CO_2 giving two furanones, including Vioxx®.[135,136] This method was further adapted to include halide electrophiles[137] by using palladium catalysis to cross-couple the intermediate magnesium complexes with a variety of aryl and vinylic halides (Table 8).

[135] (a) Forgione, P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11. (b) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793.
[136] Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17.
[137] Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

Table 8. Three-component coupling of alkenes and dienes

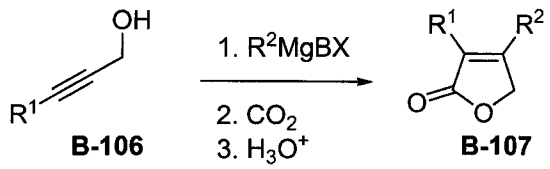


B-104 **B-105**

Entry	R^1	R^2X	Yield
1	Ph	PhI	73
2	Ph	*p*-$MeOC_6H_4I$	71
3	Ph	CH_2=$CHCH_2I$	64
4	CH_2=$CHCH_2$	PhI	60
5	Ph	Me_2C=CMeBr	71
6	CH_2=CH	PhI	41
7	Me	PhI	10

Duboudin and Jousseaume have also described the exposure of propargylic alkynes to Grignard reagents and subsequent trapping with carbon dioxide to give butenolides **B-107** (Table 9).[138]

Table 9. Preparation of butenolides



B-106 **B-107**

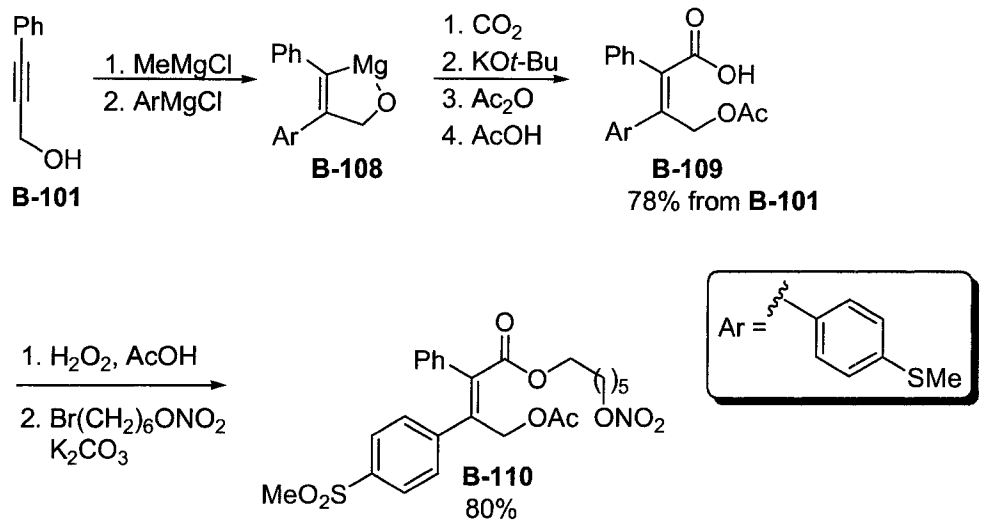
30 - 61%

Entry	R^1	R^2	Yield (%)
1	Me	Et	30
2	Ph	Me	51
3	Ph	Et	45
4	Ph	-CH_2CH=CH_2	61
5	PhCC-	Et	38
6	CH_2=(CH_3)C-	Et	38

[138] (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 233. (b) Duboudin, J. G.; Jousseaume, B.; Saux, A. *J. Organomet. Chem.* **1979**, *168*, 1.

This carbomagnesiation strategy has been used by Merck & Company to synthesize a NO-releasing prodrug of Vioxx® (Scheme 17).[139] Significant effort was devoted to modifying and optimizing the reaction in order to sucessfully acetylate the intermediate magnesium alkoxide and prevent facile cyclization to the corresponding furanone. All steps in the reaction were carefully examined, and a particularly important factor was the sequestering of excess CO_2 with potassium *tert*-butoxide prior to acetylation. Thus, tetrasubstituted alkene **B-109** was obtained after six steps from **B-101** in 78% overall yield. This was impressive because the first sequence attempted gave a 6% yield. As in the aforementioned methods, regio- and stereoselectivity were excellent.

Scheme 17. Application of the hydroxy-directed carbometallation



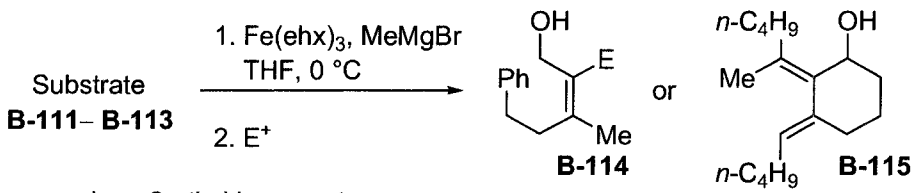
A complementary method was disclosed by Zhang and Ready in which iron catalyzed carbomagnesiation of propargylic and homopropargylic alcohols generated tri- and tetrasubstituted olefins with the opposite regio- and stereoselectivity as had been previously observed (Table 10).[140] In this method, alcohols were treated with a Grignard reagent in the presence of $Fe(ehx)_3$ (ehx = 2-ethyl hexanoate). *Syn*-addition of the Grignard reagent across the triple bond followed by electrophilic trapping gave products **B-114**. Trapping of the vinyl iron or magnesium intermediate species generated from substrate **B-113** with a pendant alkyne gave diene **B-115** in good yield.

---

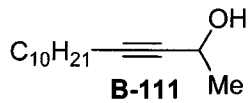
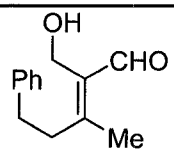
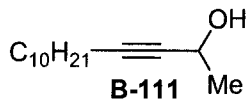
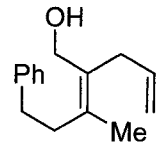
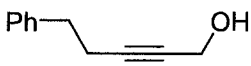
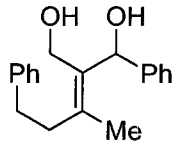
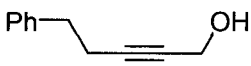
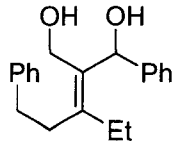
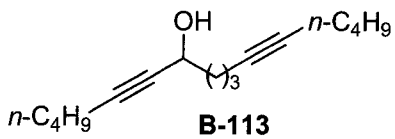
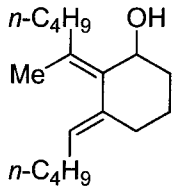
[139] Engelhardt, F. C.; Shi, Y. J.; Cowden, C. J.; Conlon, D. A.; Pipik, B.; Zhou, G.; McNamara, J. M.; Dolling, U. H. *J. Org. Chem* **2006**, *71*, 480.

[140] Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050.

Table 10. Iron-catalyzed carbomagnesiation of propargylic and homopropargylic alcohols



ehx = 2-ethyl hexanoate

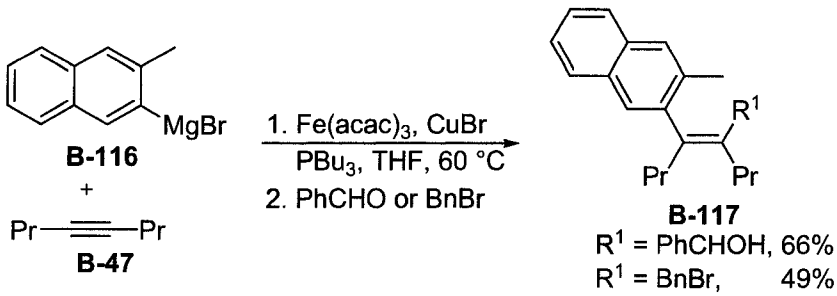
Entry	Substrate	E^+	Product	Yield (%)
1	 B-111	DMF		50
2	 B-111	$CuCN_2$·LiCl, allyl bromide		61
3	 B-112	PhCHO		51
4[a]	 B-112	PhCHO		52
5[b]	 B-113	-		70

[a] EtMgBr was used. [b] $Fe(acac)_3$, CuBr, and Bu_3P were used.

The arylmagnesiation of alkynes using an iron/copper catalyst system was recently described (Scheme 18).[141] This process employed a *syn* addition across the alkyne to give an intermediate magnesium reagent that could be trapped with benzaldehyde or benzyl bromide to give tetrasubstituted olefins.

[141] Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164.

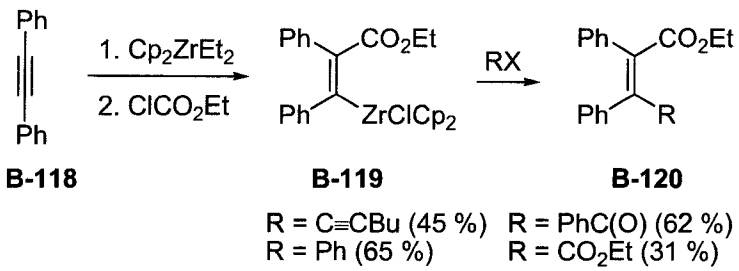
Scheme 18. *Syn* arylmagnesiation of alkynes



1.2.5 Other metals

Carbozirconation is a highly reliable method to functionalize alkynes, proceeding with a high degree of stereoselectivity, and consistently providing *syn* isomers.[107] The regioselectivity of zirconium additions has been extensively studied, and these reagents have significant potential for preparing tetrasubstituted olefins. Takahashi *et al.* described a zirconium-based method to selectively construct functionalized α,β-unsaturated esters (Scheme 19).[142] Thus diphenylacetylene was treated with Cp_2ZrEt_2 in the presence of ethyl chloroformate to produce an intermediate acyl zirconium species that could be cross-coupled with electrophiles in the presence of $Pd(PPh_3)_4$ to give tetrasubstituted olefins **B-120** in 31 to 65% yield. Four examples were illustrated and in each case the addition was found to occur in the expected *syn* fashion.

Scheme 19. Carbozirconation

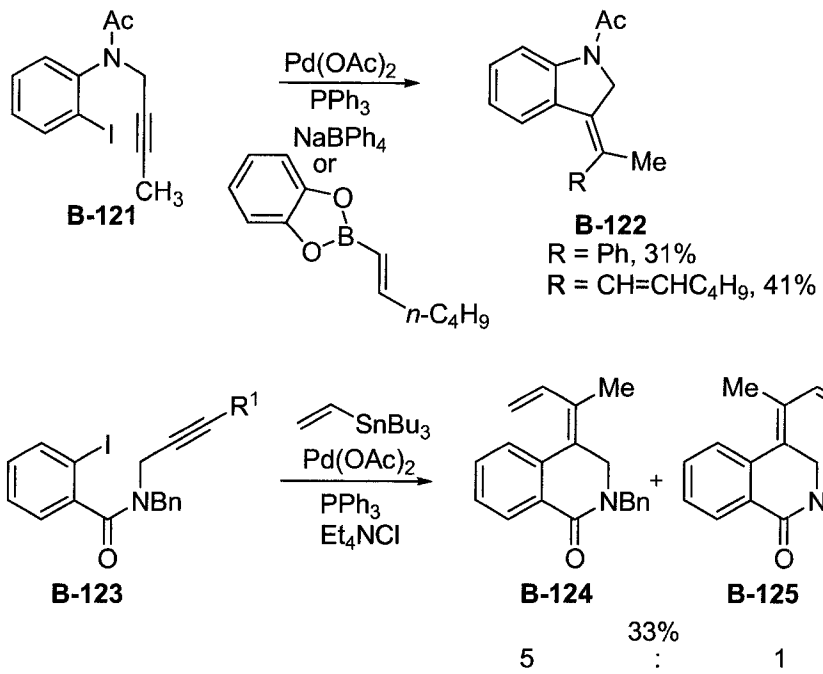


Grigg and coworkers showed that carbopalladations could be carried out intramolecularly to give products such as **B-122**. This compound was isolated as a single isomer in 31% yield after Suzuki-type coupling (Scheme 20).[143] A hexenyl group was

[142] Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228.
[143] Grigg, R.; Sansano, J.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803.

also transferred in slightly higher yield (41%). In this example, regiochemistry was controlled by the intramolecular reaction in which only the formal *exo*-dig pathway was productive. Indolylborate could be used in similar reactions as transfer reagents,[144] and tin coupling partners could be used in place of the boron reagents.[145] These reactions occurred successfully in both the 5-*exo*-dig or 6-*exo*-dig modes in the four examples described. The 5-*exo*-dig processes gave single isomer products whereas one of the 6-*exo*-dig cyclizations gave a 5:1 mixture of *syn* and *anti* isomers **B-124** and **B-125** in a 33% combined yield.

Scheme 20. Intramolecular carbopalladation

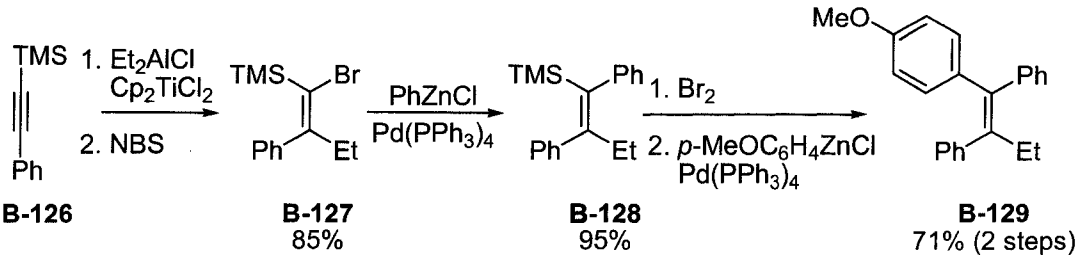


Carboalumination has been used to prepare Tamoxifen through the addition of Tebbe-type reagents to alkynes (Scheme 21). In this case TMS acetylene **B-126** was exposed to Et_2AlCl and Cp_2TiCl_2 to effect carboalumination, and the resulting intermediate was quenched at low temperature with NBS to afford silylbromide **B-127**.[146] This material was subjected to Negishi coupling conditions to introduce a second phenyl group with excellent yield and stereocontrol. After exchanging the silicon group with bromine, a

[144] Ishikura, M.; Takahashi, N.; Yamada, K.; Yanada, R. *Tetrahedron* **2006**, *62*, 11580.
[145] Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525.
[146] Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121.

second Negishi reaction supplied tetrasubstituted product **B-129** in 71% yield over the two steps. This material was then elaborated to Tamoxifen using a four-step sequence. In a subsequent communication, a modification of this route allowed the synthesis of Tamoxifen in 35% yield in a single procedure from diphenyl acetylene.[81b]

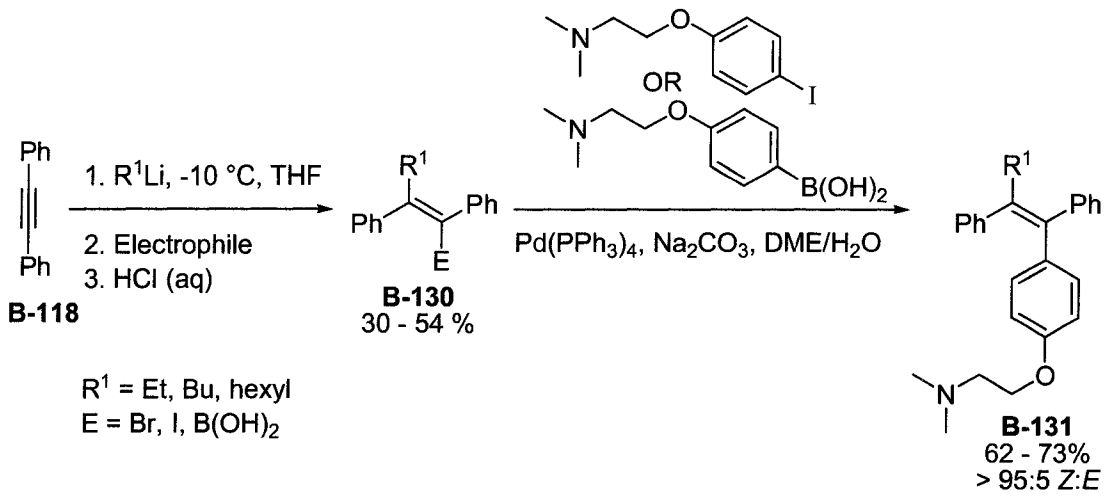
Scheme 21. Carboalumination route to tetrasubstituted alkenes



B-126 → **B-127** 85% → **B-128** 95% → **B-129** 71% (2 steps)

Tamoxifen and related compounds have similarly been prepared by carbolithiation strategies.[81d] The carbolithiation of diphenylacetylene generated a series of (*E*)-1-lithio-1,2-diphenylalkyl-1-enes (Scheme 22). These alkenes were reacted *in situ* with electrophiles such as 1,2-dibromoethane, 1,2-diiodoethane, or triisopropylborate to form tetrasubstituted precursors **B-130**. These materials were either treated with an aryl iodide or an arylboronic acid, as appropriate, in refluxing DME/H_2O using $Pd(PPh_3)_4$ as catalyst and Na_2CO_3 as a base to give tetrasubstitued olefins **B-131** in 62 to 73% yield and with greater than 95:5 selectivity (*E*:*Z*).

Scheme 22. Carbolithiation of diphenylacetylene to form Tamoxifen

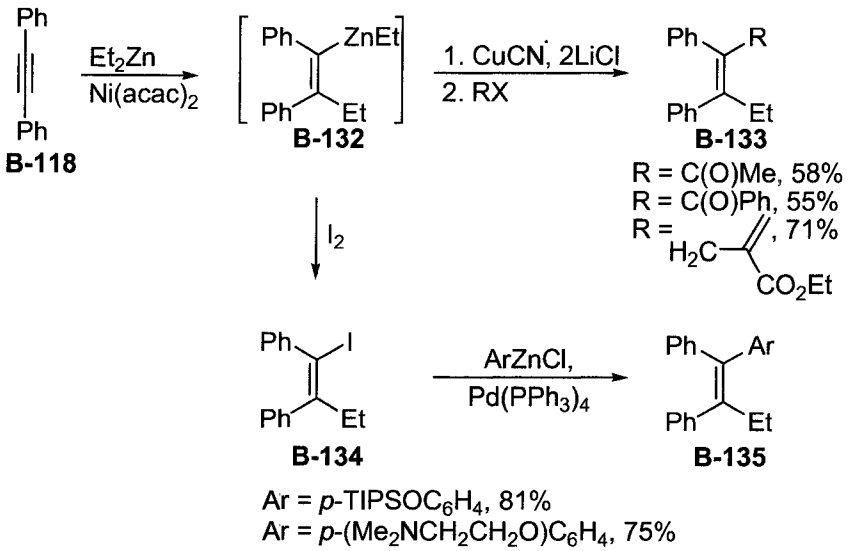


B-118 → **B-130** 30 - 54 % → **B-131** 62 - 73%, > 95:5 *Z*:*E*

R^1 = Et, Bu, hexyl
E = Br, I, $B(OH)_2$

Zinc has been used in several instances to prepare tetrasubstituted olefins, primarily through Negishi coupling reactions, but also in other contexts. For example, a carbozincation of alkynes was described in which nickel catalysis provided smooth *syn* addition to diphenylacetylene affording a vinyl zinc intermediate (**B-132**). This material could be captured with different electrophiles to give tetrasubstituted products (Scheme 23).[147] Although the intermediate zinc species could be directly coupled with electrophiles in the presence of CuCN and LiCl,[148] the authors reported that superior results were obtained when the intermediate zinc species were captured with I_2 and the resulting vinylic iodides cross-coupled with other organozincs under Negishi conditions.[149] Similar results were described using cobalt catalysts to mediate initial allyl zinc couplings.[150]

Scheme 23. Carbozincation of alkynes

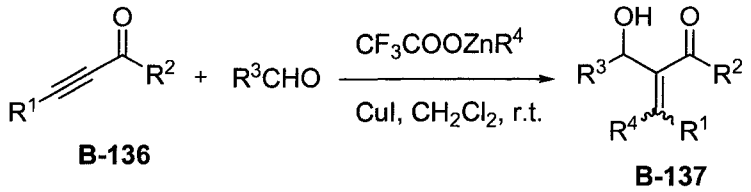


Xue *et al* found that organozinc species reacted with β-substituted α,β-acetylenic ketones, when CuI was used as a catalyst, to give tetrasubstituted olefin products as mixtures of stereoisomers (Table 11).[151]

---

[147] Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299.
[148] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
[149] Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573.
[150] Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* **2004**, 1573.
[151] Xue, S.; He, L.; Liu, Y.-K.; Han, K.-Z.; Guo, Q.-X. *Synthesis* **2006**, 666.

Table 11. Carbozincation of alkynes promoted by CuI

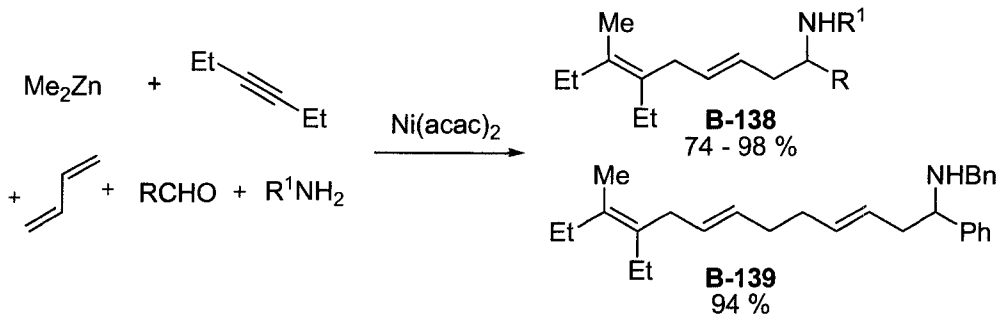


B-136 **B-137**

R^1	R^2	R^3	R^4	Yield (%)	*Z/E*
n-C_3H_7	Ph	Ph	Me	91	4 : 1
n-C_3H_7	Ph	4-MeC_6H_4	Me	88	3 : 1
n-C_3H_7	Ph	Ph	Et	85	1.2 : 1
n-C_3H_7	Ph	4-$MeOC_6H_4$	Et	90	1.3 : 1
Ph	Ph	Ph	Et	85	3 : 1
n-C_3H_7	Me	4-$MeOC_6H_4$	Et	82	1.2 : 1

A nickel-catalyzed five-component reaction utilizing dimethylzinc, symmetric alkynes, 1,3-butadiene, aldehydes, and amines furnished either **B-138** or **B-139** depending on the type of amines employed (Scheme 24).[152] Aromatic amines gave product **B-138**, while aliphatic amines gave product **B-139**.

Scheme 24. Nickel-catalyzed five-component coupling

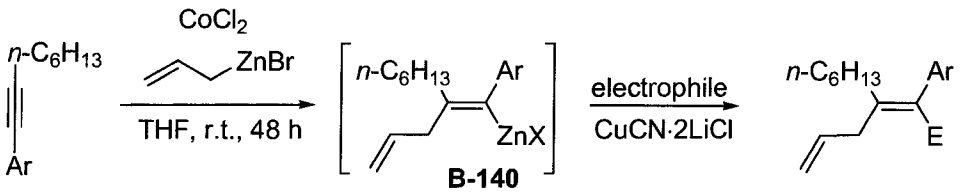


A common limitation of the carbometallation of internal alkynes is the issue of regioselectivity. Nishikawa, Yorimitsu and Oshima reported that the allyzincation of 1-phenyl-1-alkynes took place with high regio- and *syn* stereoselectivity when the reaction was catalyzed by cobalt (Scheme 25).[150] Numerous examples were reported that gave

[152] Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 6332.

trisubstituted products after quenching the intermediate alkenylzinc compound **B-140** with H_3O^+. In addition, two examples were shown in which the alkenylzinc compound was condensed with acetyl chloride or allyl bromide in the presence of CuCN·2LiCl to give tetrasubstituted olefins **B-141** and **B-142,** whose geometry was confirmed by NOE experiments.

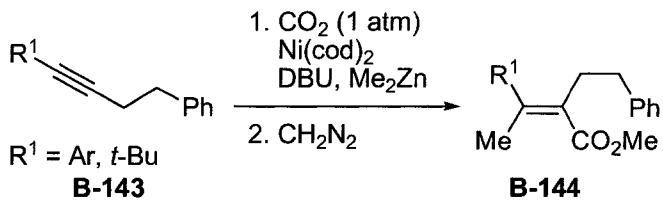
Scheme 25. Cobalt-catalyzed regio- and stereoselective allylzincation of 1-phenyl-1-alkynes



B-141: Ar = 4-ClC_6H_4, E = CH_3COCl; 44 %
B-142: Ar = 3,5-$(CF_3)_2C_6H_3$, E = CH_2=$CHCH_2Br$; 70 %

The Mori group has developed a nickel-catalyzed alkylative carboxylation of alkynes that was used to make four tetrasubstituted olefins with complete stereoselectivity (in one case, a 3:1 mixture was obtained).[153] Regioselectivity was apparently controlled by steric interactions as the initial carbonylation occurred at the less hindered side of the triple bond. The intermediate oxanickel species, that resulted from CO_2 insertion, underwent coupling with Me_2Zn to afford **B-144** after esterification with diazomethane (Scheme 26). This methodology was applied to the synthesis of Tamoxifen, affording the drug in eight steps in 36% overall yield.[81e]

Scheme 26. Alkylative carboxylation of alkynes

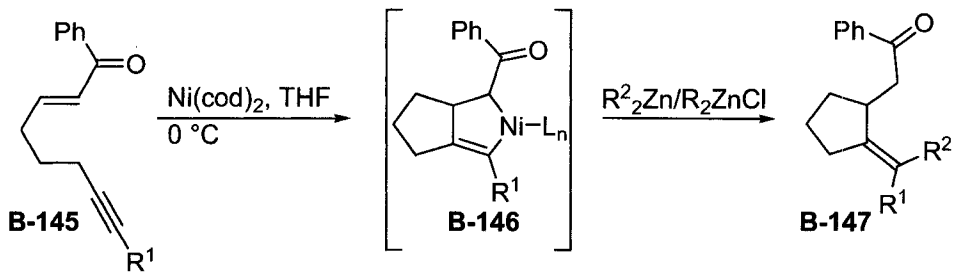


Montgomery's research group has extensively used organozinc reagents, together with nickel-catalyzed reactions, to construct tetrasubstituted olefins by intramolecular alkyne additions. It was initially shown that enones could serve as effective electrophiles for a

[153] Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195.

multicomponent process involving alkynes and alkyl zinc reagents.[154] Earlier work by Ikeda and Sato had demonstrated that, in the presence of TMSCl under nickel catalysis, enones would serve as electrophilic π-allyl partners for alkyne insertions[155] and that tetrasubstituted olefins could be realized from this process (only one example was shown). It was found that $Ni(cod)_2$ would catalyze multicomponent additions of alkynes, enones and alkyl zincs, without the need for TMSCl, if the reaction was run intramolecularly. The reaction was presumed to operate *via* the formation of a nickel(0) π-complex that underwent oxidative cyclization to form metallocycle **B-146** (Scheme 27).[156] This complex could then undergo transmetallation with the organozinc, followed by reductive elimination to produce the tetrasubstituted olefins **B-147**. These compounds were obtained as single isomers, with the regioselectivity of the addition being dictated by the steric constraints of the substrate. A dramatic effect was observed if phosphine ligands were used together with alkyl zincs containing β-hydrogens.[154] Under these conditions, a trisubstituted product was obtained, resulting from a β-hydride elimination that was likely a consequence of the increased electron-density imparted by the phosphine ligands. These ligands presumably displaced the electron-poor alkene spectator ligands that are known to promote reductive elimination. Two examples were given of tetrasubstituted olefins that were produced stereoselectively. The intermolecular variant was also successful using aldehydes and terminal alkynes, giving trisubstituted olefins.

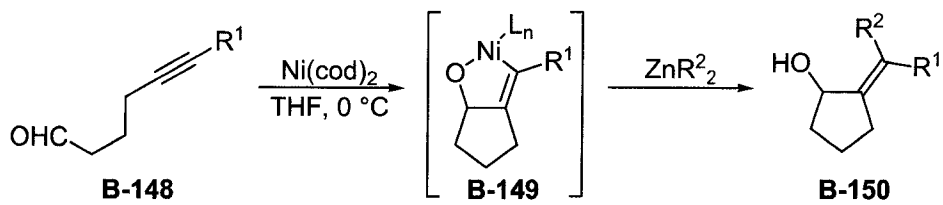
Scheme 27. Intramolecular carbozincation



[154] Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.
[155] (a) Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b)Ikeda, S. i.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248.
[156] (a) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (b)Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. and references therein. (c) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

Other electrophilic partners could participate in this process. Aldehydes gave allylic alcohols through a multicomponent ynal cyclization (Scheme 28).[156a] Treatment of substrates **B-148** with $Ni(cod)_2$ and a suitable alkyl zinc, resulted in smooth conversion to the tetrasubstituted products with complete stereocontrol. This method was extremely flexible because a common intermediate was used. The desired substituted alkynals were prepared simply by a Sonogashira extension or acetylide alkylation to the corresponding terminal alkyne. Four examples were given, with yields ranging from 64 to 76%. The reaction was thought to proceed through oxametallacycle **B-149** which would be produced by the oxidative cyclization of the nickel species, alkyne and aldehyde, or by the carbometallation of the alkyne followed by cyclization with the aldehyde. Once **B-149** had formed, transmetallation and reductive elimination provided the observed products **B-150**. Reductive cyclization was only efficient if PBu_3 was added as a ligand, in conjunction with alkyl zinc reagents.

Scheme 28. Carbozincation-aldehyde trapping

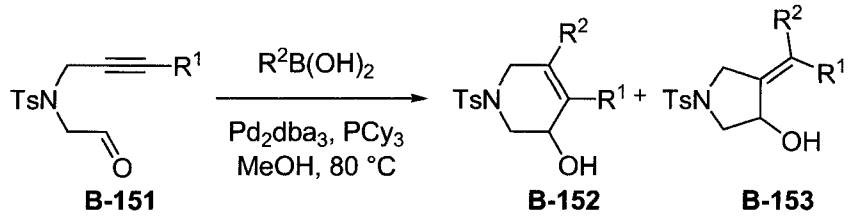


B-148 **B-149** **B-150**

A *trans*-selective variant of the above reaction could be accomplished through the use of a palladium catalyst (Table 12) to give tetrasubstituted alkenes.[157] Employing terminal alkynes as substrates gave products of type **B-152** almost exclusively, while mixtures of **B-152** and **B-153** were observed when an internal alkyne was used.

[157] Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406.

Table 12. *Trans*-selective addition of organoboron reagents



B-151 B-152 B-153

Entry	R^1	R^2	Yield (%)	B-152:B-153
1	Me	Ph	90	61:39
2	Bu	Ph	66	83:17
3	4-MeC_6H_4	4-$MeOC_6H_4$	97	93:7

A four-component extension of the Ikeda group's three-component method[155] was subsequently developed (Scheme 29).[158] By including an alkynylstannane, and performing the reaction intermolecularly, substituted carbocycles bearing exocyclic tetrasubstituted double bonds, were obtained. Several tetrasubstituted examples were given that were isolated as single alkene isomers (Table 13). This process involved a sequence of two nickel-mediated oxidative cyclizations, both of which occurred with complete *syn* selectivity. Thus an initial cyclization between components **B-154**, **B-155**, and **B-156** gave aldehydes **B-157**, which were then exposed to alkyl zincs in the presence of $Ni(cod)_2$, affording the products **158**.

[158] Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106.

Scheme 29. Four-component nickel-catalyzed cyclization

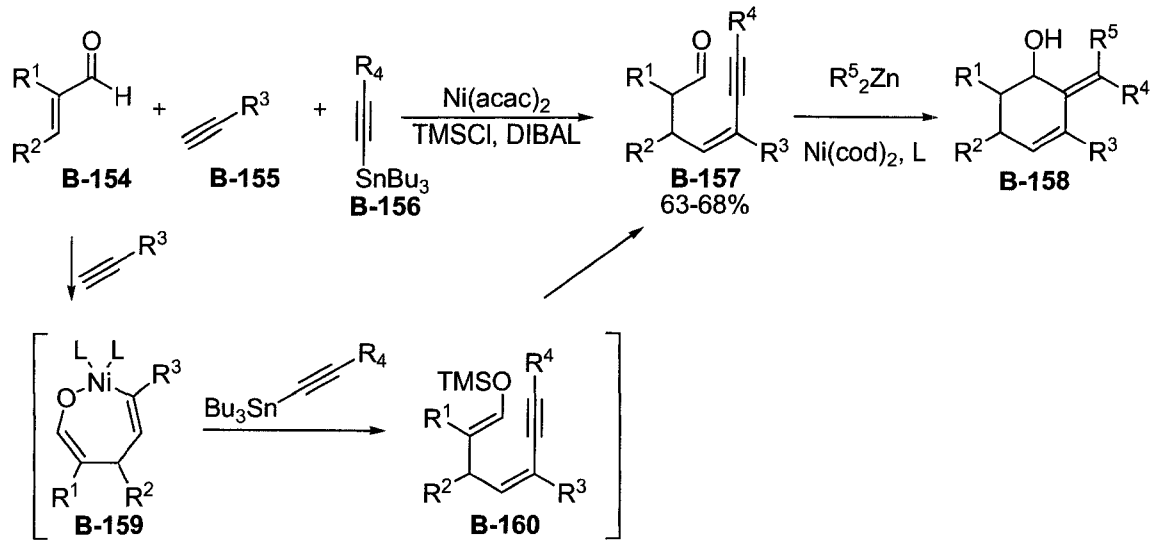


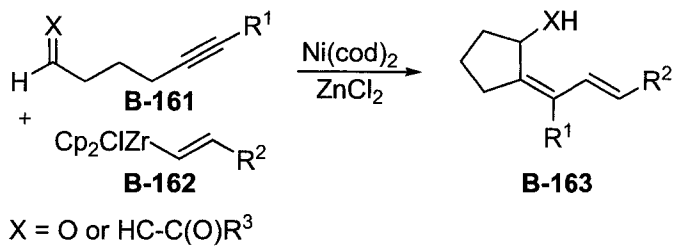
Table 13. Multi-component coupling to give B-158

Entry	R^1	R^2	R^3	R^4	R^5 (reagent)	Yield of B-157 (%)	Yield of B-158 (%) (dr)
1	H	H	H	Ph	Et (Et_2Zn)	68	81
2	CH_3	H	H	Ph	Me (MeLi/$ZnCl_2$)	63	74 (2.7:1)
3	H	H	H	Ph	Me (MeLi/$ZnCl_2$)	68	71
4	H	CH_3	H	Ph	Me (MeLi/$ZnCl_2$)	67	80 (5.3:1)

It has been shown that zirconium can participate in analogous processes (Scheme 30).[159] A catalytic amount of zinc was required for the successful vinylzirconation of alkynes. These reactions were followed by intramolecular additions to a variety of electrophiles. Thus, alkynyl enones were cyclized in the presence of vinyl zirconium reagents using $Ni(cod)_2$ and $ZnCl_2$ as catalysts. The cyclic products contained highly substituted 1,3-dienes, which are potentially valuable synthetic intermediates. Using ynals as precursors, the reaction was found to be capable of producing both 5- and 6-membered rings, and worked well in the presence of amines. When enones were used as electrophiles, the reaction would not function intermolecularly, in contrast to the tin process described above,[158] however an intermolecular version of the alkynal process, producing trisubstituted olefins was provided.

[159] Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743.

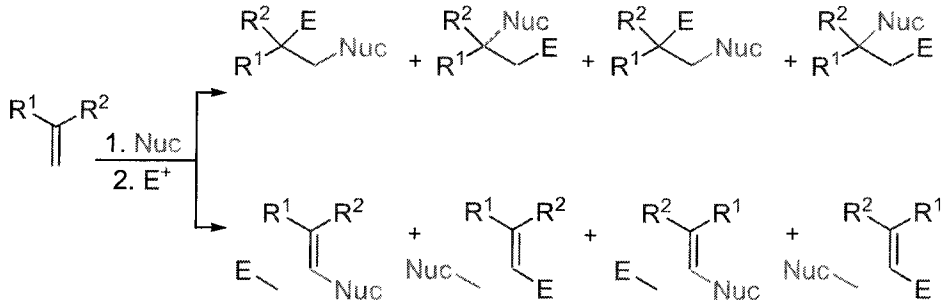
Scheme 30. Nickel-catalyzed cyclizations and couplings with vinyl zirconium reagents



1.2.6 Additions to allenes

Allenes provide an interesting case of tetrasubstituted olefin formation.[160] These functional groups are known to insert rapidly into carbon metal bonds, readily forming π–allyl complexes.[161] Carrying out a carbometallation across one of the π bonds of the allene system creates new sp^2 and sp^3 centers and leaves behind an olefin product. Issues of regioselectivity become more complex here as the reagents must not only select the correct double bond, but must add in the correct direction to that bond (Scheme 31). This raises the possibility of forming four distinct regioisomers from the allene, in addition to the issue of stereocontrol during the addition.

Scheme 31. Possible regioisomers from the addition to allenes

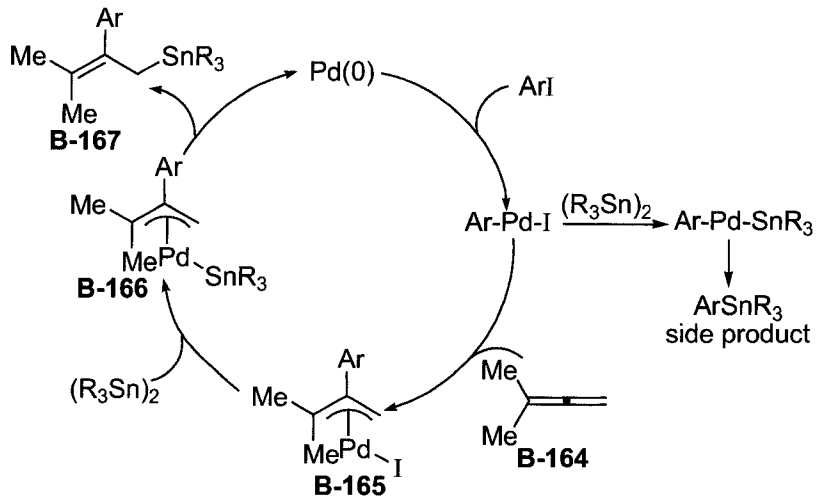


The problem of regioselectivity in the allene insertion process has been extensively studied by the Cheng group. In an early report it was shown that symmetrically substituted allene **B-164**, could be carbostannylated using palladium catalysis to give

[160] Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons Ltd.: Chichester, 2004.
[161] (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853.(c) Vicart, N.; Cazes, B.; Goré, J. *Tetrahedron* **1996**, *52*, 9101. (d) Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154. (e) Larock, R. C.; Tu, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859.

allylstannanes such as **B-167** (Scheme 32).[162] This reaction proceeded in a typical manner, in which carbopalladation of the allene afforded the π-allyl intermediate **B-165**. Transmetallation of **B-165** gave **B-166**, and reductive elimination subsequently occurred, during which the tin added to the less-substituted carbon, thus delivering the major product **B-167**. Aryl, vinyl or heterocyclic iodides could be used as coupling partners and the reactions were highly regioselective, producing a single isomer in each case. Yields varied between 26 and 93%. For an effective reaction, syringe pump addition of the tin component was required. Surprisingly, the less reactive reagent $Bu_3SnSnBu_3$ produced a more effective reaction than $Me_3SnSnMe_3$. This was postulated to be a consequence of a competing two-component coupling between the dialkyl tin reagent and the aryl iodide. As $Me_3SnSnMe_3$ was more reactive, this competing process was more significant and lower yields of the desired three-component coupling product **B-167** were observed.

Scheme 32. Aryl stannylation of allenes



The analogous silicon variation has also been reported.[163] Symmetrically substituted allene **B-164** was coupled with the same iodides as in the above study, but this time $Bu_3SnSiMe_3$ was used as the coupling partner. Efficient overall carbosilylation was realized in yields over 80% giving numerous examples of single isomer allylsilane products bearing tetrasubstituted olefins.

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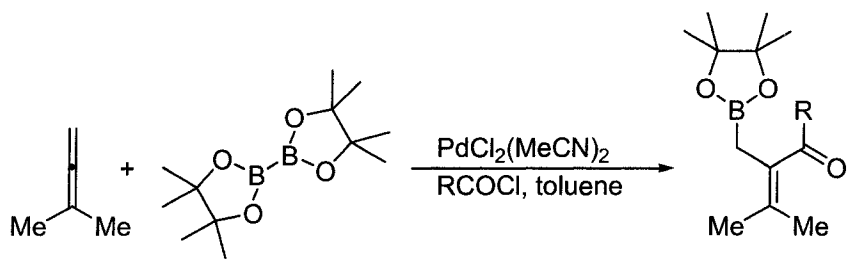
[162] Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *Tetrahedron Lett.* **1999**, *40*, 6055.

[163] (a) Wu, M. Y.; Yang, F. Y.; Cheng, C. H. *J. Org. Chem.* **1999**, *64*, 2471. (b) Yang, F. Y.; Shanmugasundaram, M.; Chuang, S. Y.; Ku, P. J.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12576.

The use of boron was subsequently explored in an acylboration sequence (Scheme 33).[163a,164] Symmetrically substituted allene **B-164** was coupled with a series of acyl chlorides using pinacol borane to give the corresponding allylboranes **B-168**. Fourteen examples of single isomer allylborane products bearing tetrasubstituted olefins were produced, in yields ranging from 57 to 92%.

Scheme 33. Allylic boranes from allenes

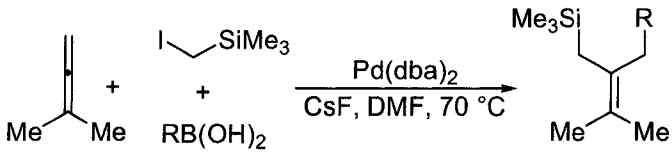


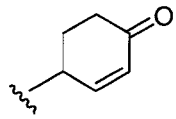
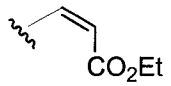
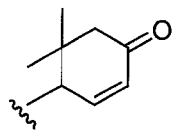
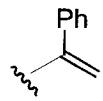
B-164 **B-168**

In the above reaction, the production of an allylboron species represents a valuable synthetic intermediate. The utility of this was demonstrated in a multicomponent variation that introduced further diversity (Table 14).[165] By employing substituted phenylboronic acids and adding CsF, further coupling took place to furnish the tetrasubstituted olefin products (**B-169**) shown. The halide partner could be aryl, vinyl, heterocyclic or even an α-haloester. Iodides and bromides readily underwent the process, and a variety of substituents were tolerated on the arylboronic acid moiety.

[164] (a) Yang, F. Y.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (b) Yang, F. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2001**, *123*, 761.
[165] Huang, T. H.; Chang, H. M.; Wu, M. Y.; Cheng, C. H. *J. Org. Chem.* **2002**, *67*, 99.

Table 14. Three-component coupling incorporating allenes



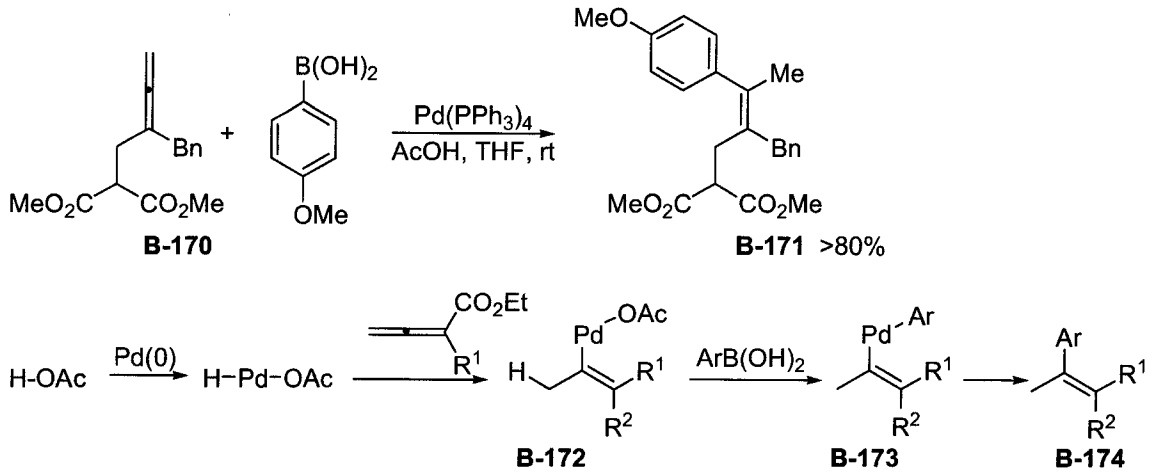
Entry	R	Yield (%)
1	Ph	85
2	4-$NO_2C_6H_4$	88
3	4-$MeOC_6H_4$	86
4	2-$MeOC_6H_4$	83
5	4-$EtO_2CC_6H_4$	82
6	2-thienyl	85
7		82
8		78
9		61
10		83

Ma and co-workers exploited the electronic and steric biases inherent in the allene system to carry out hydropalladations (Scheme 34).[166] They found that aryl substituents could be added across one double bond of the allene, in the presence of acetic acid, using boronic acids together with $Pd(PPh_3)_4$ as a catalyst. Allene **B-170** was converted into tetrasubstituted olefin **B-171** in 81% yield, as a 9:1 mixture of *E/Z* isomers. Four other examples were illustrated giving similar yields and ratios of products. Selectivity was

[166] Ma, S.; Jiao, N.; Ye, L. *Chem. Eur. J.* **2003**, *9*, 6049.

significantly improved when the starting allene bore an ester substituent. Intermediate **B-172** was converted to **B-174** in an 86% yield as a single regioisomer and with excellent control of stereoselectivity (97:3). Four other examples proceeded equally successfully, in most cases providing only one isomer of the product. While hydropalladation processes typically add first to the central carbon of the allene to generate a π-allyl intermediate,[160] in this case a less commonly observed regioselection was observed. The initial hydropalladation gave the intermediate **B-172**, in which the palladium was situated on the central carbon, this precluded the formation of a π-allyl intermediate, as is typically observed in allene chemistry. Subsequent transmetallation and elimination gave the major regioisomer **B-174**.

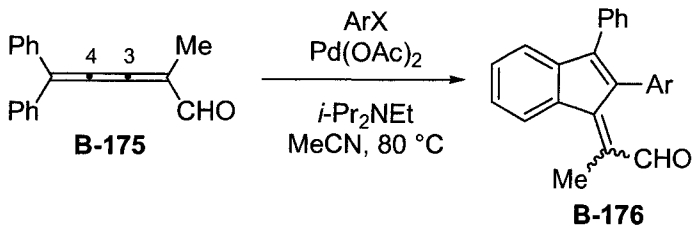
Scheme 34. Hydropalladation-transmetallation of allenes

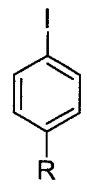
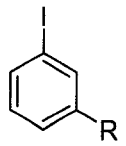


Furata and coworkers explored domino Heck reactions of unsymmetrically substituted [3]cumulenes (Table 15).[167] The aryl palladium species, generated from the oxidative addition of the palladium catalyst with the aryl halide, inserted selectively into the C_{3-4} double bond of cumulene **B-174**. A C-H insertion reaction at the *ortho* position of the neighboring phenyl moiety, followed by reductive elimination, gave the tetrasubstituted alkene products **B-175** as mixtures of *E/Z* isomers in yields of 39 to 66% (combined yields of the mixtures of isomers obtained).

[167] Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Comm.* **2006**, 3648.

Table 15. Domino Heck-C-H activation reaction of unsymmetrically-substituted [3]cumulenes

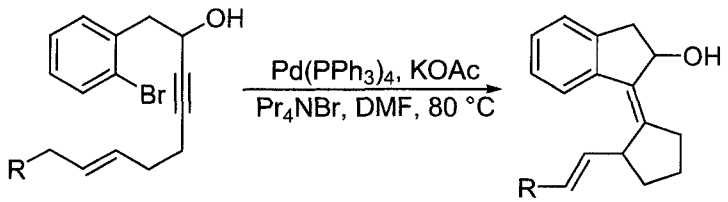


Entry	ArX		Yield (%)	Ratio (*Z* : *E*)
1	PhI		61	3.4 : 1
2		R = OMe	46	3.6 : 1
3		R = OMs	39	2.4 : 1
4		R = NO_2	66	4.3 : 1
5		R = Br	55	2.7 : 1
6		R = OMe	47	2.3 : 1
7		R = OMs	62	2.3 : 1
		R = NO_2		
8			47	2.5 : 1

1.2.7 Direct Alkyne Functionalization

A cascading cyclization process that delivered tetrasubstituted olefins in a specialized ring system was developed in which two successive palladium-mediated cyclizations across unsaturated bonds produced central tetrasubstituted alkenes (Scheme 35).[98] Aryl bromides such as **B-177**, when exposed to the appropriate palladium catalyst, underwent an initial ring closure involving the triple bond, followed by a Heck process with elimination to give the products shown. The process worked well to give 5- to 7-membered rings from the initial ring closure, and 5- to 6-membered rings from the second ring forming process.

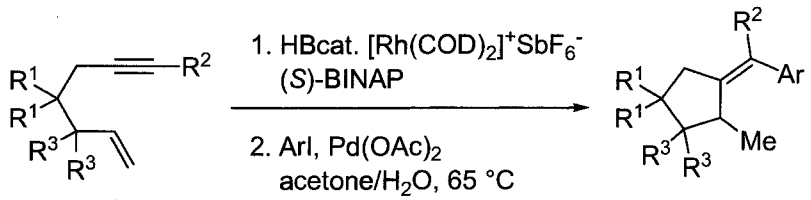
Scheme 35. Allylsilane-terminated domino-Heck double cyclization



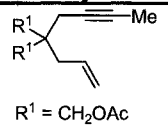
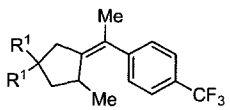
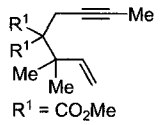
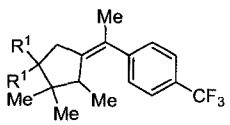
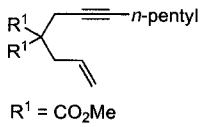
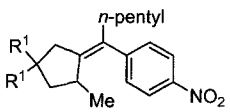
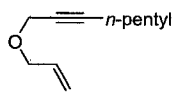
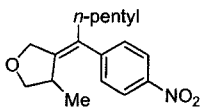
B-177 B-178

A rhodium-catalyzed cyclization/hydroboration of 1,6-enynes (**206**) permitted the simultaneous generation of a chiral center and a tetrasubstituted olefin moiety (Table 16).[168] A ligand scan was performed and (*S*)-BINAP proved to be the best. In this report, four tetrasubstituted olefin examples were reported in addition to other cyclization products.

Table 16. Rhodium-catalyzed asymmetric cyclization/hydroboration of 1,6-enynes



B-179 B-180

Entry	Enyne	Product	Yield (%)	ee (%)
1			61[a]	87
2			70	45
3			68	82
4			40	98

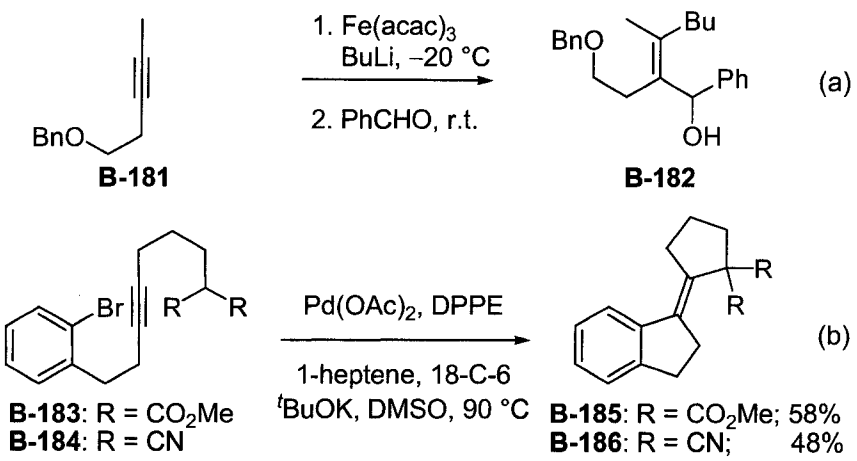
[a] 20:2:1 mixture of isomers

[168] Kinder, R. E.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 1967.

An iron catalyzed carbolithiation process was shown to generate tetrasubstituted olefins when the product of the alkynyl carbolithiation was quenched with aldehydes or ketones (Scheme 36a).[169] Three examples were provided of reactions with benzaldehyde, propionaldehyde, and 1-phenylpropanone. Single isomers were obtained in all reported cases.

This type of cyclization could also be done with the nucleophilic capture of an intermediate palladium π-complex in a Wacker-type process (Scheme 36b).[170] Thus bromides **B-183** or **B-184**, in the presence of $Pd(OAc)_2$ and DPPE, underwent cyclization to the corresponding products **B-185** and **B-186** as single isomers in 58 and 48% yields respectively.[171]

Scheme 36. Carbolithiation-carbonyl trapping

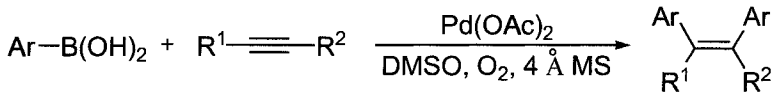


An interesting multicomponent reaction has been developed by the Larock group involving the direct addition of aryl boronic acids to alkynes (Scheme 37).[172] This process featured an unusual twist in which the regiochemical issue was circumvented by adding the same aromatic group to both ends of the alkyne. Stereochemical control was complete and the reaction tolerated a wide variety of functional groups on the substrate (OH, CHO, ketone, ester, TMS, aryl). Unfortunately, the reaction failed for dialkyl-

[169] Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 621.
[170] Bruyère, C.; Monteiro, N.; Bouyssi, D.; Balme, G. *J. Organomet. Chem.* **2003**, *687*, 466.
[171] Bruyère, C.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007.
[172] (a) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259. (b) Zhou, C.; Larock, R. C. *J. Org. Chem* **2006**, *71*, 3184.

substituted alkynes, but a wide variety of tetrasubstituted olefins bearing three or four aryl groups were prepared. Several key experimental modifications made this process possible. Improved yields were observed when molecular sieves were used, either by providing a surface upon which the reactions could take place, or by simply acting as water scavengers.[173] The reaction proceeded much faster if performed under an O_2 atmosphere rather than being simply left open to air and the $Pd(OAc)_2$/DMSO system was found to be superior to others tested.[174] Two possible mechanistic pathways were presented, although investigations to support one over the other are still in progress.[172b]

Scheme 37. Pd-catalyzed addition of arylboronic acids to alkynes



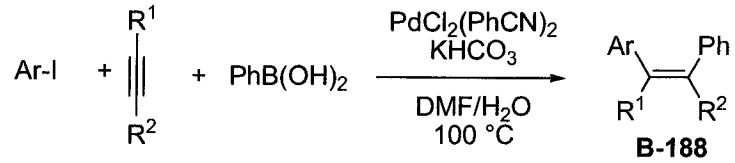
B-187

53-90%

Another multi-component process saw the palladium-catalyzed coupling of iodides and boronic acids with alkynes (Table 17).[175] The reactions required tight control of stoichiometry, solvent, and base. The presence of water was necessary for efficient conversion to products, with optimal results being obtained in 4:1 DMF:H_2O. Using $KHCO_3$ as the base gave significant advantages over other bases such as KF or K_2CO_3, and a 2:1:3 ratio of iodide:alkyne:boronic acid gave the cleanest reactions. Other stoichiometries resulted in oligomer formation after to multiple alkyne insertions.

[173] De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615.
[174] DMSO is known to facilitate the re-oxidation of Pd(0) to Pd(II) by O_2: (a) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766.
[175] Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.

Table 17. One-pot route to tetrasubstituted alkenes from alkynes



B-188

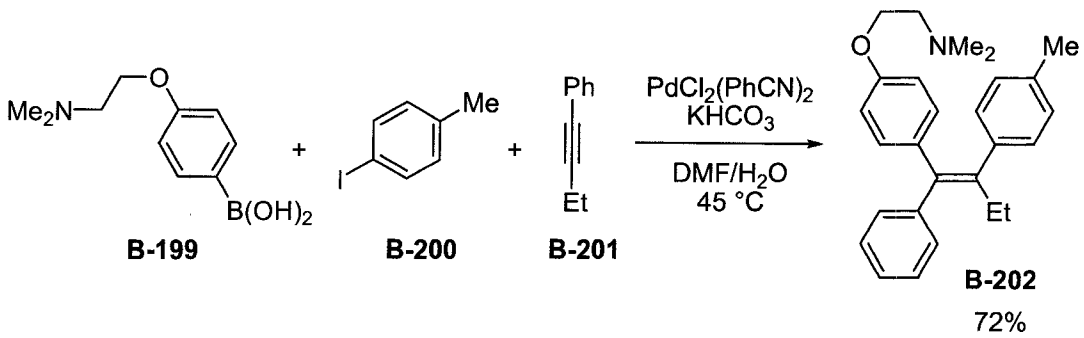
Entry	Ar	R^1	R^2	Yield
1	Ph	Me	Ph	90
2	Ph	*n*-C_4H_9	Ph	86
3	Ph	Ph	Ph	92
4	4-MeC_6H_4	COMe	Ph	80 (1:2)[a]
5	4-MeC_6H_4	CO_2Et	Ph	78 (1:2)[a]
6	Ph	CH_2OH	Ph	77
7	Ph	Me	CO_2Et	82
8	Ph	$CH(OEt)_2$	Ph	85
9	Ph	CO_2Et	CO_2Et	78
10	Ph	*n*-C_3H_7	*n*-C_3H_7	32
11	Ph	Ph	4-$NO_2C_6H_4$	88

[a] Mixture of regioisomers

Regioselectivity was reasonable for this process (mixtures of 2:1 to 15:1 were obtained) and the geometry of the major products was found to be a consequence of steric effects in which the aryl iodide tended to add to the less-hindered carbon. Electronic influences were also seen, as the arylboronic acid was connected to the electron-deficient side of the alkyne. These compounds were well-characterized, and nOe data were presented to support the assignments. The reaction was stereospecific, and no evidence of *trans*-addition was reported. In all, more than 16 tetrasubstituted olefins were prepared, each bearing at least three aryl groups. This method was employed to construct a Tamoxifen derivative (**B-202**) in a highly convergent synthesis in which the product was obtained as a mixture of regioisomers that was presumed to be >20:1 (Scheme 38).

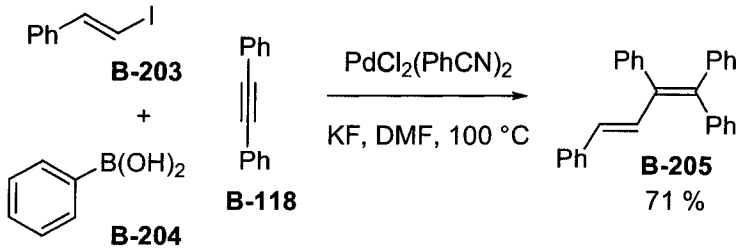
Notably, the target olefin was obtained in 72% yield using the multicomponent, single-step process.[175]

Scheme 38. Three-component coupling of aryl iodides, internal alkynes and arylboronic acids



An extension of this work described the coupling of vinyl iodides and vinyl boronic acids across alkynes to give tetrasubstituted olefins bearing 1,3-diene and 1,3,5-triene units (Scheme 39).[176] The additions were completely stereoselective but regioselectivity was limited in this method. Unsymmetrical alkynes gave low ratios of products (1.5:1 ratio of regioisomers) unless a strong electron withdrawing group was present as one substituent of the alkyne.

Scheme 39. A representative three-component coupling to give 1,3-dienes

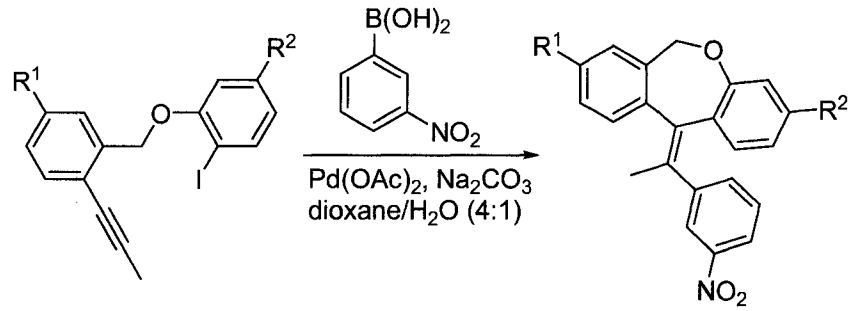


Researchers at Eli Lilly & Company have prepared dibenzoxapines containing tetrasubstituted exocyclic alkenes (as single stereoisomers) through the cyclocarbopalladation of alkynes (Scheme 40).[177] The cyclization precursors (**B-206**) were prepared through Sonogashira couplings of aryl halides followed by either Mitsunobu reactions or a two-step alkylation procedure. Alkynyl halides **B-206** were then

[176] Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993.
[177] Yu, H.; Richey, R. N.; Carson, M. W.; Coghlan, M. J. *Org. Lett.* **2006**, *8*, 1685.

exposed to a variety of boronic acids, in the presence of $Pd(OAc)_2$ and Na_2CO_3 in dioxane/water at 100 °C. The use of water as a co-solvent and ligand-free conditions proved to be critical in order to give the seven-membered rings **B-207**.

Scheme 40. Cyclocarbopalladation of alkynes



B-206

R^1 = H, F, OMe
R^2 = H, F

B-207
59 - 91%

Carbometallation is the most widely used method for the generation of tetrasubstituted alkenes as evidenced by the number of methods which have been developed to address the various challenges in the formation of these substrates. The regioselectivity in most methods has been controlled by electronic differentiation on the alkyne. Steric differentiation of the alkynyl termini can also be effective, but requires a significant size difference between the substituents.

The stereochemistry of the initial attack usually proceeds reliably, with most methods showing a strong preference for *syn* addition. A*nti* carbometallation is sometimes observed, and dominates the carbomagnesiation of propargyl alcohols. Low temperatures during the carbometallation step normally must be maintained to preserve stereochemical information, particularly when lithium and copper serve as the counter ion. This often requires reactive electrophiles to be used, although additives can prevent stereochemical degradation. Metals such as boron and tin can resist stereochemical degradation, and a wide variety of organometallic coupling techniques are available to further elaborate these intermediates.

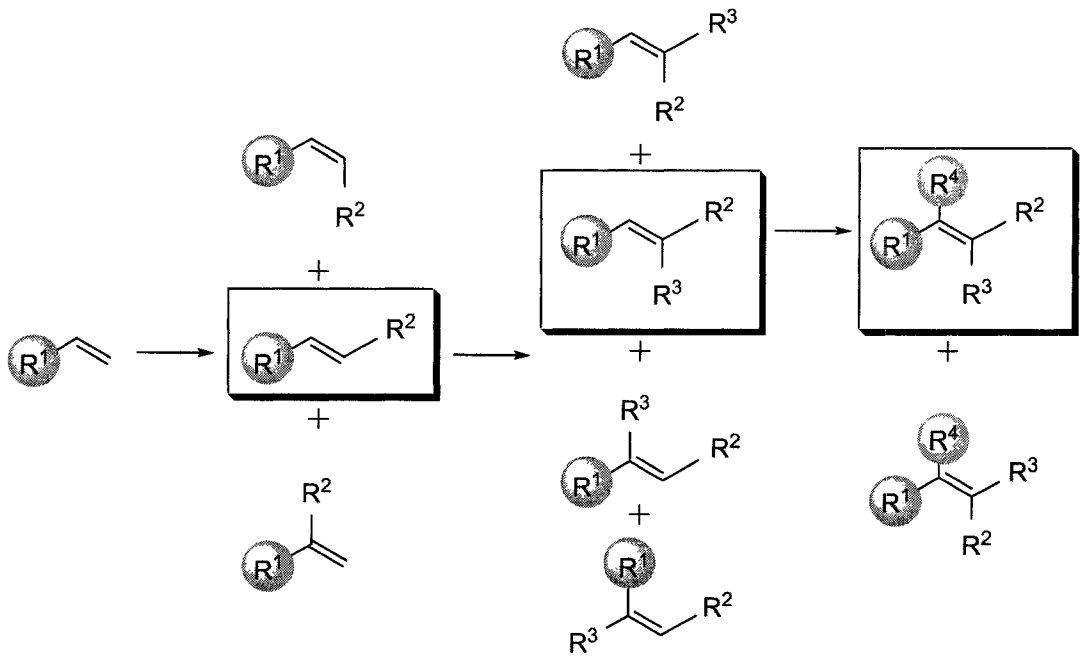
Developing technologies in this field include radical processes, in which the stereochemistry is typically controlled by sterics, as well as allene reactions, which offer

somewhat more regiochemical control as the initial addition usually occurs on the central carbon. Highly efficient multi-component processes offer significant advantages by delivering complex products in a single chemical transformation. Geometric control remains a significant obstacle to overcome in many cases.

1.3 Manipulation of Existing Olefins

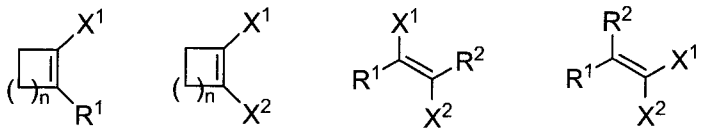
Tetrasubstituted double bonds of distinct geometry can be prepared by manipulating a pre-existing olefin template. The stereocontrolled generation of the template is often the most difficult aspect of this chemistry as mixtures of regio- and stereoisomers are often obtained (Figure 3). Once the template has been generated, the desired substituents should be introduced at a single position, but frequently mixtures of regio- and stereoisomers are obtained. Even if the desired isomer is obtained, occasionally stereochemical information is lost either during the reaction or during subsequent workup and purification, and it remains therefore essential to carefully identify the reaction product(s).

Figure 3. Modification of an alkene template can generate numerous products.



The types of templates that can be synthesized are currently somewhat limited, thus diminishing the scope of attainable olefins. Some examples of common motifs are shown in Figure 4. Cyclic templates such as **B-208** and **B-209** are generally formed from the halogenation or metallation of an existing olefin, although Dieckmann condensations have also been used. A few examples exist in which unsubstituted alkenes are sequentially coupled, thereby directly accessing tetrasubstituted olefins without the need for intermediate template generation.

Figure 4. Common olefin template motifs and general template strategy



B-208 **B-209** **B-210** **B-211**

X=halogen or pseudo halogen

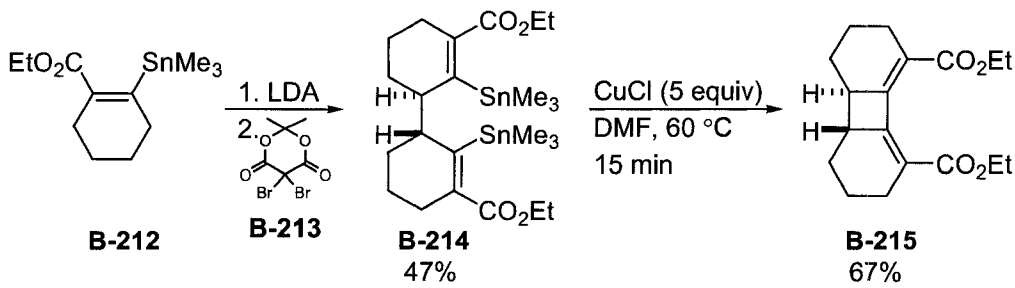
Regioselectivity is the first issue faced during cross-coupling reactions because identical halogens ($X^1 = X^2$) are often employed at both template locations, and the system therefore requires some type of influence that distinguishes the two. The simplest way to avoid regioisomers is to use symmetric substrates, a tactic that limits the types of products that can be synthesized. Other alternatives expand the scope of products by exploiting steric or electronic biases in the substrate, or by the use of directing groups. Over-reaction during the couplings can be problematic, resulting in simultaneous substitution at both of the halo-substituted carbons, producing symmetric products.

Stereoselectivity is the largest hurdle to overcome in any tetrasubstituted olefin synthesis. Cyclic templates circumvent this problem, but generating acyclic molecules in this manner requires built-in functionality such that the ring can be opened once the desired olefin has been installed. The use of an acyclic olefin template will usually give products of defined stereochemistry if the original template was created or isolated as a single isomer. It is always necessary to verify the structure of the products rather than rely on literature precedent, because stereochemical information is occasionally lost, particularly when highly ionic conditions are used or when enolization provides a mechanism for olefin isomerization.

1.3.1 Cyclic, monosubstituted olefin templates

When employing cyclic templates, stereocontrol is not an issue and so researchers using cyclic substrates focus on the challenge of regioselectivity. Piers and Romero generated carbocyclic systems bearing polysubstituted conjugated diene units such as **B-215**, *via* an intramolecular CuCl-mediated stannane coupling of **B-214** (Scheme 41).[178] The required β-trimethylstannyl-α,β-unsaturated ester **B-212**, prepared from 2-ethoxycarbonylcyclohexanone,[179] was deprotonated with LDA and the resulting enolate was exposed to the brominating agent shown (**B-213**) to provide the dimeric stannane **B-214** in 47% yield. A final ring closure using five equivalents of CuCl in DMF at 60 °C gave tetrasubstituted diene **B-215** in 67% yield. This methodology was used in the construction of 4 to 8-membered rings, and tolerated remote substituents such as esters and haloalkyl groups.

Scheme 41. Polysubstituted conjugated dienes



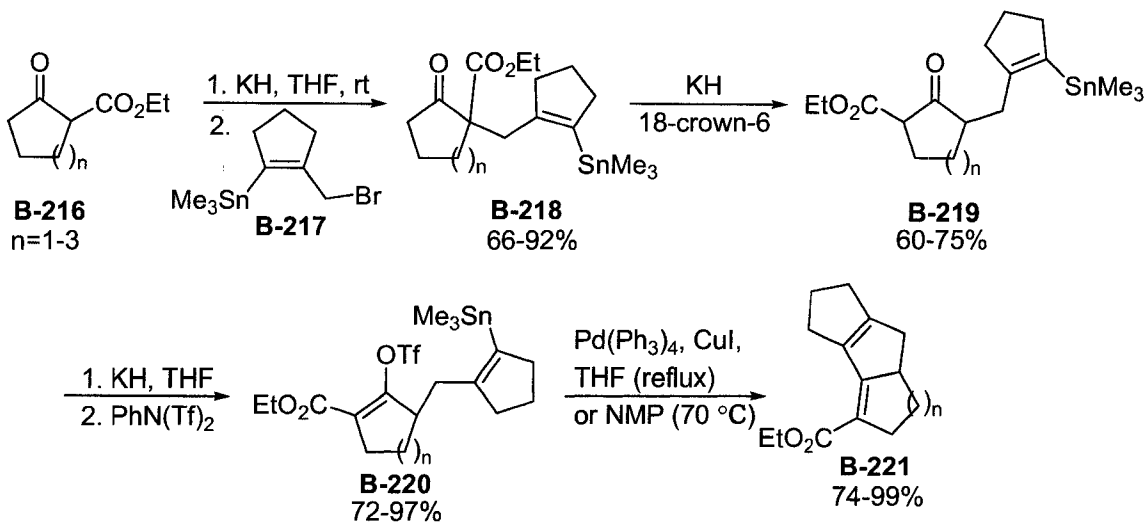
B-212 **B-213** **B-214** 47% **B-215** 67%

The formation of tricyclic compounds such as **B-221** (Scheme 42) has also been explored by the Piers group.[180] The required olefin templates (**B-217**) were generated from the reduction of esters of type **B-212**, followed by treatment of the resulting alcohols with Ph_3PBr_2 in the presence of imidazole. These reagents were used to alkylate 2-ethoxycarbonylcyclopentanone or 2-ethoxycarbonylcyclohexanone, thus providing access to the derivatives **B-218**. A subsequent 1,3-ester shift of **B-218** and functional group manipulations gave the required coupling partners **B-220.** Intramolecular Stille coupling reactions led to tricyclic dienes **B-221**. It was shown using related substrates that many functional groups were tolerated in the Stille process, including ketones,

[178] Piers, E.; Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215.
[179] Piers, E.; Tse, H. L. A. *Can. J. Chem.* **1993**, *71*, 983.
[180] Piers, E.; Romero, M. A.; Walker, S. D. *Synlett* **1999**, 1082.

acetals, and esters. The intramolecular couplings were fast and regiospecific, giving the desired products in excellent yields.

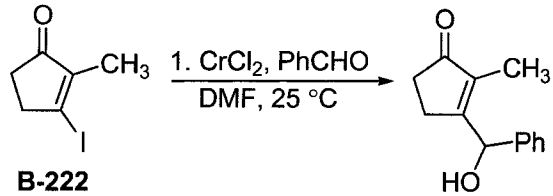
Scheme 42. Polycycles *via* sequential 1,3-ester shift and Stille reaction



Metal insertion into the carbon-halogen bond of β-halogenated enones results in the generation of umpolung reagents, because the typical reactivity of the β-position of an α,β-unsaturated carbonyl is reversed. Knochel and coworkers have used this technique and have described the preparation and reactivity of several types of organozinc, organochromium, and organocopper derivatives (Scheme 43).[181] A wide variety of cyclic, heterocyclic, and acyclic iodo-enones have been coupled with vinyl, aryl, stannyl, and acyl electrophiles, forming tetrasubstituted olefins. One tetrasubstituted olefin was formed through the insertion of $CrCl_2$ into β-iodoenone **B-222**, followed by condensation with benzaldehyde, to give **B-223** in 57% yield.

[181] Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, *49*, 29.

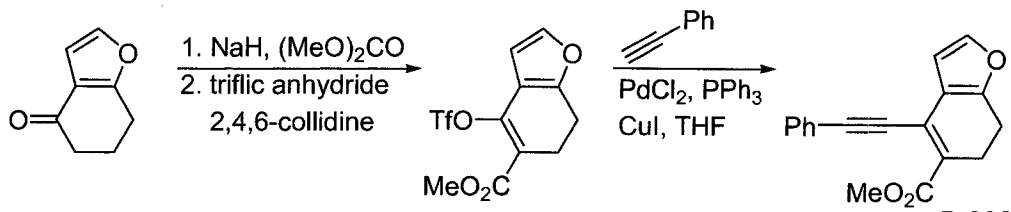
Scheme 43. Generation of nucleophilic β-enone



B-222 **B-223** 57%

Hesse and Kirsch recently used a β-vinyl triflate (**B-225**), in a Sonogashira coupling to generate the corresponding tetrasubstituted olefin **B-226** in 42% overall yield (Scheme 44).[182] This method enabled the generation of a compound **B-225** by carbonylation of a cyclic ketone (**B-224**), provided the starting ketone was symmetrical or bore a single enolizable proton.

Scheme 44. Sonogashira coupling with a vinyl triflate

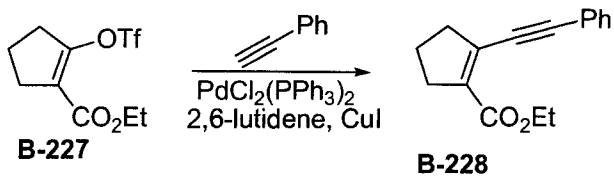


B-224 **B-225** 53% **B-226** 79%

Substrates of type **B-227** could also be generated by a Dieckmann condensation followed by enolate trapping to give β-triflate esters (Scheme 45). Nakatani and Saito showed that a subsequent Sonogashira coupling reaction with phenylacetylene gave tetrasubstituted alkene **B-228** in 88% yield.[183] The presence of the highly activated triflate in both of these substrates could potentially allow many alternatives to the Sonogashira coupling reaction to proceed under mild conditions.

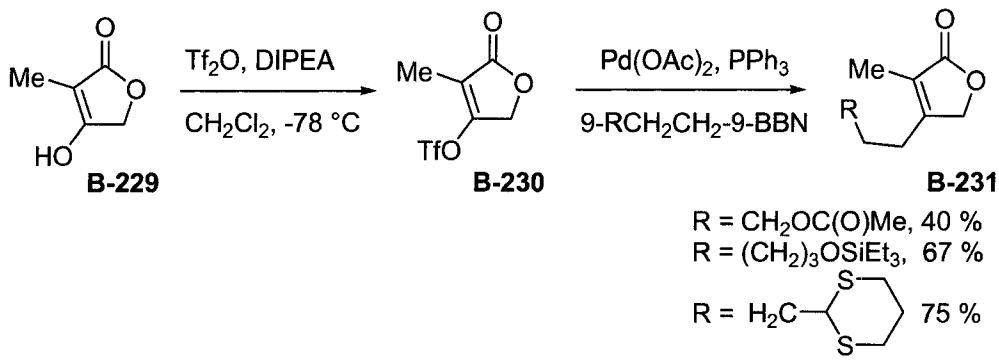
[182] Hesse, S.; Kirsch, G. *Tetrahedron Lett.* **2003**, *44*, 97.
[183] Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.

Scheme 45. Sonogashira coupling with vinyl triflate template generated from a Dieckmann condensation



Butenolides have been functionalized at the 3-position to provide an insertion point for palladium-catalyzed cross-coupling with 9-alkyl-9-borobicyclo[3.3.1]nonanes (Scheme 46).[184] In this method, β-ketolactones were converted to the corresponding enol triflates **B-230** and these compounds underwent alkyl Suzuki coupling to deliver tetrasubstituted olefins **B-231**. Three examples were provided of fully substituted alkenes that were prepared in 40 to 75% yield.

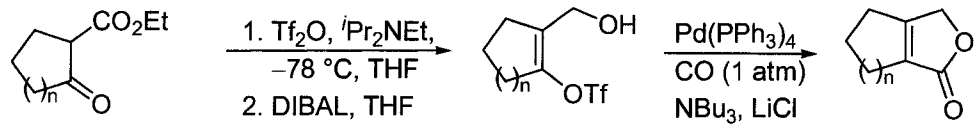
Scheme 46. Suzuki coupling of an enol triflate



Bicyclic rings could be generated by analogous reactions, using carbon monoxide as the coupling partner, in a process developed by Crisp and coworkers (Scheme 47).[185] Treatment of β-ketoester **B-232** with triflic anhydride, followed by exposure to DIBAL, generated the olefin template **B-233**. The vinyl triflate **B-233** was then extended with carbon monoxide in the presence of a palladium catalyst, base, and lithium chloride, to afford a variety of tetrasubstituted bicyclic rings **B-234** (n = 1 to 4) in 36 to 65% overall yields.

[184] Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489.
[185] Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

Scheme 47. Olefin templates applied to the synthesis of bicyclic molecules.



B-232 n=1-4 | **B-233** | **B-234** 36 – 65% overall yields

In most cases, the coupling of α-halo enones requires more forcing conditions than the corresponding β-halo counterparts due to the reduced reactivity of the α-position.

The palladium-catalyzed cross-coupling of alkenyl zincs with cyclic α-iodoenones[186] has been described by Negishi and coworkers (Scheme 48).[187] The increased reactivity of iodide over bromide allowed the cross-coupling reactions to proceed without carbonyl protection. Three examples were shown, in which the α-iodide or triflate (**B-235**[188] or **B-237**) was first treated with *n*-BuLi to effect lithium-iodine exchange. The resulting organolithiums were then coupled to alkenyl zinc partners using palladium catalysis.

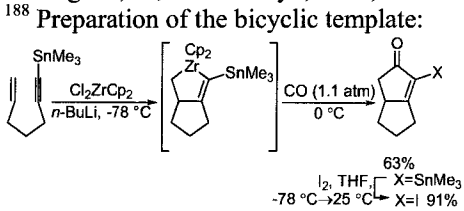
Later studies expanded the scope of these reactions, that had initially been limited to α-alkenylation and α-arylation. In 2000, the palladium-catalyzed α-alkynylation of cyclic iodoenones to give trisubstituted alkenes was reported, and impressively, the α-alkylation of cyclic iodoenones such as **B-239** with organozincs to give tri- and tetrasubstituted alkenes.[189] Although stringent reaction conditions were required for this process, the use of organozincs expanded the scope of the reaction significantly beyond simple Sonogashira substrates.

---

[186] (a) Preparation of cyclic α-iodoenones: McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045. (b) Preparation of bicyclic α-iodoenones: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

[187] Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453.

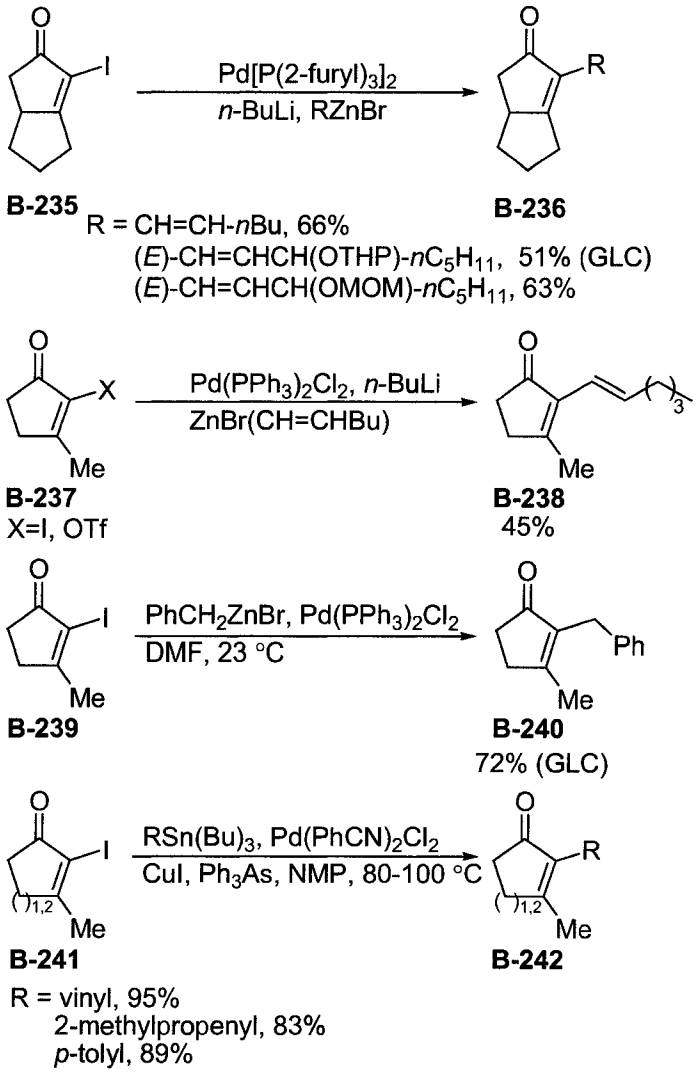
[188] Preparation of the bicyclic template:



[189] Negishi, E. T., Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.

Stille reaction conditions were also employed to generate tetrasubstituted olefins from similar templates. Thus, α-iodo enones **B-241** were coupled with a variety of alkenyl, alkynyl, and aryl stannanes to give tetrasubstituted alkenes **B-242** (Scheme 48).[190] High temperatures were required to effect the sterically hindered couplings; however, the reactions were complete in under seven hours.

Scheme 48. Negishi and Stille coupling of α-iodides and triflates



[190] (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919. (b) Margaretha, P.; Agosta, W. C.; Reichow, S. *J. Org. Chem.* **1994**, *59*, 5393.

Recently a Suzuki-Miyaura coupling of related α-iodocycloenones with arylboronic acids was disclosed.[191] The catalyst used was simply 10% Pd/C, and could be recycled after minimal workups. This represented the first time that metallic palladium had been used for α-halo-cyclo-enone coupling reactions with arylboronic acids. The reactions typically proceeded in air and at room temperature, in a mixture of DME and H_2O. Though only two examples of tetrasubstituted olefin products were given, this method was extremely practical, cost-effective, and highly amenable to extension.

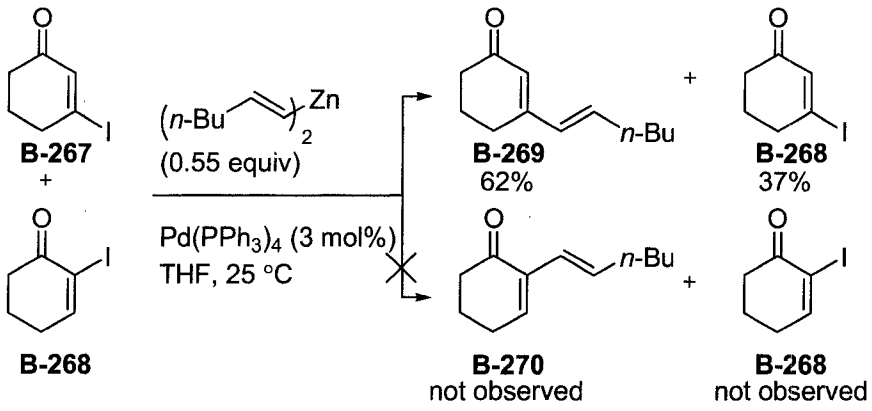
1.3.2 Cyclic di-halosubstituted enones and lactones

Cyclic dichloro-, dibromo-, or diiodosubstituted enones and lactones can undergo controlled, sequential organometallic coupling reactions to give fully substituted products with more structural diversity. Regioselectivity is the only issue to address as the cyclic structures preclude the formation of stereoisomers. This regiocontrol normally arises from the presence of a carbonyl group that provides electronic differentiation between the reaction sites. The more activated, electron-poor β-site reacts significantly faster than the α-positions, although over-addition at the α-site is a common side reaction in these processes.

The elevated reactivity of β-haloenones over the α-halo variants was illustrated by the Negishi group in a competition experiment.[187] An equimolar mixture of β– and α–iodoenones (**B-267** and **B-268**) was subjected to an organozinc reagent using conditions under which coupling was known to occur on both substrates (Scheme 49). The results showed that coupling occurred exclusively at the β-position of enone **B-267** to give alkene **B-269**. An instability of the α-haloenone **B-268** was also demonstrated, as neither the coupled α-product **B-270** nor the starting material **B-268** were detected after the reaction. This instability mandated that conditions be controlled such that cross-coupling reactions occurred faster than the competing decomposition pathway.

[191] Felpin, F. X. *J. Org. Chem.* **2005**, *70*, 8575.

Scheme 49. Competition experiment between α- and β-iodo enones

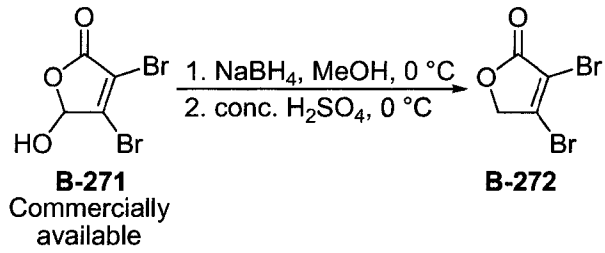


Bellina and coworkers have explored the Sonogashira, Stille, and Suzuki coupling reactions of 3,4-dibromo and 3,4-dichloro furanones such as **B-272** (Scheme 50),[192] that were readily prepared from the reduction of mucobromic or mucochloric acid **B-271**.[193] Aryl substituents were selectively coupled to the β-position of di-bromofuranone **B-272** *via* the Stille reaction (Table 18, entries 1 – 4).[192b] A number of side-products were observed however, including addition of the undesired alkyl tin substituents (*i.e.* CH_3 when $ArSn(CH_3)_3$ was employed as the coupling partner) rather than the targeted aryl moiety. Attempts to couple alkyl substituents with substrates **B-272** using the Stille process gave poor results, although unbranched alkyl groups could be introduced using alkyl boronic acids (entries 6 – 8). It was not possible to couple hindered alkyl substituents using either Suzuki (iPrB(OH)$_2$) or Kumada protocols (iPrMgBr). To circumvent this, an indirect route was employed to access the β-isopropyl derivative of **B-273**. Thus, a Stille coupling reaction was carried out using (2-methylvinyl)tributyltin and the resulting terminal olefin was reduced by hydrogenation with Wilkinson's catalyst to furnish the corresponding β-isopropyl furanone in 78% yield (entry 5).[192b] Alkynyl substituents could be coupled to **B-272** using tin derivatives.[192c] Sonogashira reactions of furanone **B-272** with a variety of acetylenes proceeded using electron-donating acetylenes (entries 9 to 14). [192a]

---

[192] (a) Bellina, F.; Falchi, E.; Rossi, R. *Tetrahedron* **2003**, *59*, 9091. (b) Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749. (c) Bellina, R.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 3851. (d) Bellina, F.; Rossi, R. *Synthesis* **2002**, 2729. (e) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017.
[193] Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997.

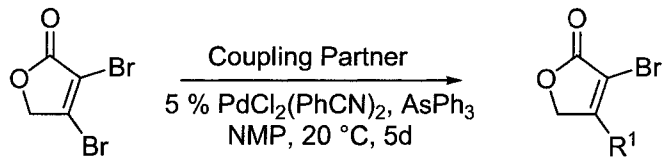
Scheme 50. Preparation of dibromo olefin template B-272.



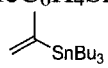
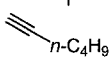
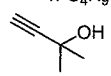
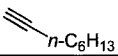
B-271 Commercially available

B-272

Table 18. Coupling of dibromofuranone B-272 with a variety of coupling partners



B-272 **B-273**

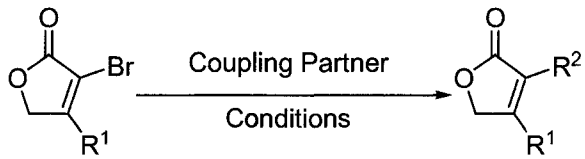
Entry	Coupling Partner	Yield (%)
1	$PhSnBu_3$	67
2	$4\text{-}MeOC_6H_4SnBu_3$	68
3	$3\text{-}FC_6H_4SnBu_3$	58
4	$4\text{-}MeC_6H_4SnBu_3$	73
5		78
6[a]	$n\text{-}C_8H_{17}B(OH)_2$	71
7[a]	$t\text{-}BuO(CH_2)_6B(OH)_2$	70
8[a]	$n\text{-}C_4H_9B(OH)_2$	78
9[b]		85
10[b]		84
11[c]		91
12[c]		40
13[c]		30
14[c]		75

[a] 3 equiv of Ag_2O were added, THF was used instead of NMP, reflux, 24 h. [b] $P(2\text{-furyl})_3$ was used in place of $AsPh_3$ and 10% CuI was added, toluene:water (1:1) was used in place of NMP, 40 °C. [c] $P(2\text{-furyl})_3$ was used in place of $AsPh_3$ and 10% CuI was added, toluene was used in place of NMP, 60 °C.

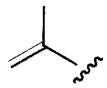
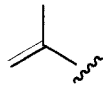
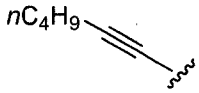
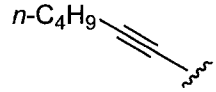
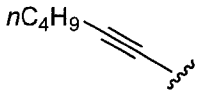
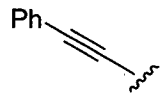
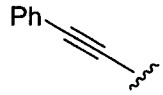
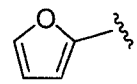
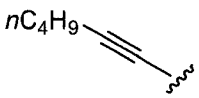
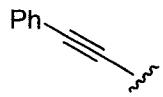
The compounds of type **B-273** were converted to tetrasubstituted structures using various coupling reactions (Table 19). Using the Stille reaction, α-aryl substituents were introduced onto the enone carrying a phenyl substituent at position 3 (entries 1 and 2).

Simple methyl transfers could also be done using Me_4Sn.[192b] Other products were obtained through Stille couplings using tetramethyltin in the presence of both phenyl and long-chain alkyl groups at position 3 (entries 3, 4). A more complex side chain at position 3 of the enone was also tolerated (entry 5). The introduction of a benzyl moiety in the presence of the isopropenyl substituent was possible, using either Stille or Negishi conditions (entries 6, 7).[192d] A Sonogashira reaction was demonstrated in one case at the α-position, giving the desired product in 31% yield.[192a] In this account, the authors also described a series of Stille-type couplings with enones bearing alkynyl groups at the β-position (entries 9 to 11). The Suzuki reaction proved to be the most successful when alkynyl groups were present in the β-position, and two electron-donating arylboronic acids were employed, to give products in 59 and 69% yields respectively (entries 12, 13). Single regioisomers were obtained in all cases, as coupling occurred selectively at the β-position of the dibromides, followed by coupling at the α-position.

Table 19. Coupling of α-bromoenone B-273 with various coupling partners to form tetrasubstituted olefins



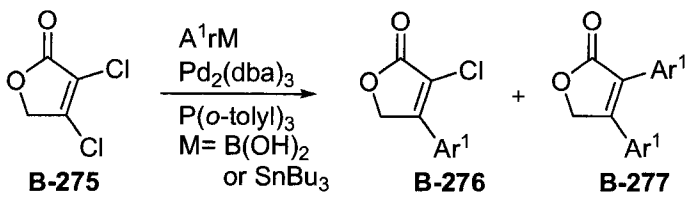
B-273 B-274

Entry	R^1	Coupling Partner	R^2	Cond.[a]	Yield (%)
1	Ph	3,5-Cl_2-$C_6H_3SnBu_3$	3,5-Cl_2-C_6H_3	A	26
2	Ph	4-$MeSC_6H_4SnMe_3$	4-$MeSC_6H_4$	A	23
3	Ph	$SnMe_4$	Me	B	58
4	nC_8H_{17}	$SnMe_4$	Me	C	90
5	$^tC_4H_9O(CH_2)_6$	$SnMe_4$	Me	C	88
6		$PhCH_2SnBu_3$	$PhCH_2$	D	36
7		$PhCH_2ZnBr$	$PhCH_2$	E	22
8				F	31
9		4-$MeOC_6H_4SnBu_3$	4-$MeOC_6H_4$	C	50
10		2-$MOMOC_6H_4SnBu_3$	2-$MOMOC_6H_4$	C	36
11		(2-furyl)$SnBu_3$		C	15
12		4-$MeOC_6H_4B(OH)_2$	4-$MeOC_6H_4$	G	59
13		3,4,5-$(MeO)_3C_6H_2B(OH)_2$	3,4,5-$(MeO)_3C_6H_2$	G	69

[a]Conditions: **A**: 5% $PdCl_2(PhCN)_2$, 10% $AsPh_3$, 10% CuI, NMP, 80 °C, 3 d. **B**: 5% $Pd_2(dba)_3$, 10% $AsPh_3$, 10% CuI, NMP, 80 °C, 3 d. **C**: 5% $PdCl_2([(o\text{-tolyl})_3P]_2$, 10% CuI, NMP, 85 °C, 3 d. **D**: 5% $PdCl_2([(o\text{-tolyl})_3P]_2$, 10% DMF/THF (1:1), 60 °C. **E**: 2.5% $Pd_2(dba)_3$, 10% P(2-furyl)$_3$, 10% CuI, NMP, 80 °C. **F**: 5% $PdCl_2(PhCN)_2$, 10% $AsPh_3$, 10% CuI, 4 equiv. of KF, toluene, 90 °C. **G**: 5% $PdCl_2(PPh_3)_2$, toluene/water (1:1).

The analogous dichlorofuranones were of interest not only for their utility in tetrasubstituted olefin formation, but also for their anti-cancer properties.[194] Initially the coupling of dichloroenones had suffered from poor yields, but, optimization quickly improved the results.[195] Suzuki coupling reactions of **B-275** with aryl boronic acids, bearing electron-donating or electron-withdrawing groups, gave 33 to 61% isolated yields of the mono-coupled products **B-276** (Scheme 51). In the case of phenylboronic acid, double coupling to give product **B-277** ($Ar^1 = Ar^2 = Ph$) was a significant side reaction. The analogous Stille process produced slightly improved yields, but mixtures of mono- and double-coupled products **B-276** and **B-277** were realized. Efforts towards the deliberate generation of **B-277** from **B-275** using large excesses of arylboronic acids were successful, giving yields of 63 to 67%. Paradoxically, attempts to generate **B-277** from **B-276** *via* the Stille or Suzuki processes resulted in lower yields of 26 to 58%. The best results were achieved using Suzuki-type conditions with *t*-Bu_3P as the ligand. With these conditions, yields ranged from 39 to 58% (Table 20, entries 1 – 4). The use of tin reagents as coupling partners resulted in slightly lower yields. The reason for the lower yields when using the differential-substitution sequence, in light of the facile conversions of **B-275** to **B-277**, was not clear.

Scheme 51. Coupling of dichloro enones



Ar = Ph, 53%
4-$MeOC_6H_4$, 78 %
3,4-$(MeO)_2C_6H_4$, 75 %
2-naphthyl, 67 %

[194] Ortega, M. J.; Zubia, E.; Ocaña, J. M.; Naranjo, S.; Salvà, J. *Tetrahedron* **2000**, *56*, 3963.
[195] Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290.

Table 20. Preparation of tetrasubstituted lactones

B-276 B-277

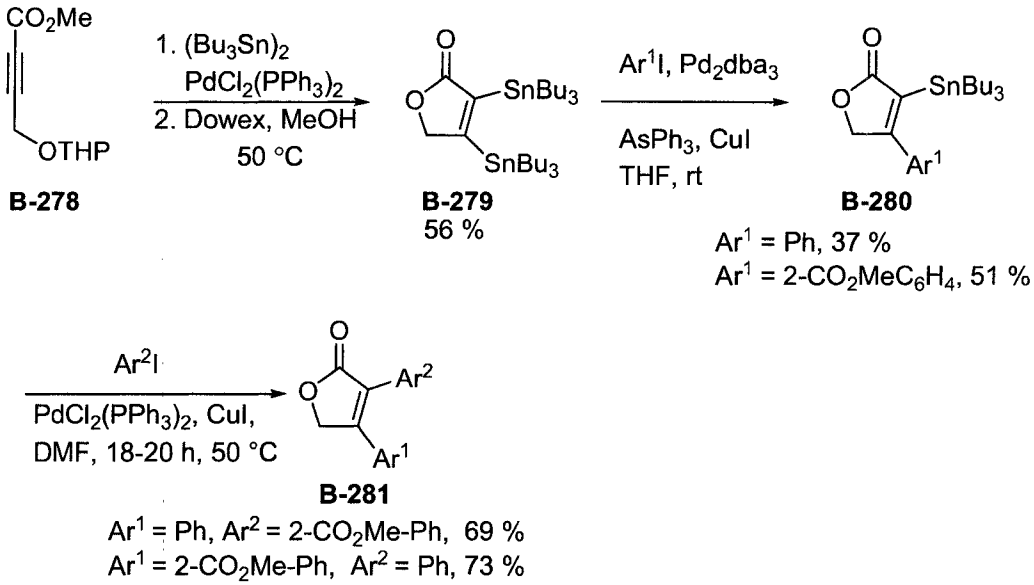
Entry	Ar^1	Ar^2	Conditions[a]	Yield (%)
1	Ph	3,4,5-$(MeO)_3C_6H_2$	A	42
2	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	A	58
3	3,4-$(MeO)_2C_6H_3$	3,4,5-$(MeO)_3C_6H_2$	A	58
4	2-naphthyl	3,4,5-$(MeO)_3C_6H_2$	A	39
5	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	B	46
6	4-$MeOC_6H_4$	Ph	B	26

[a]A: Ar^2-$B(OH)_2$, $Pd_2(dba)_3$, *t*-Bu_3P, toluene. B: Ar^2-$SnBu_3$, $Pd(OAc)_2$, Cy_3P, toluene

Olefin templates can also serve as the nucleophilic component in cross-coupling methods to obtain tetrasubstituted alkenes. Mabon, Richecoeur, and Sweeney[196] generated a number of cyclic olefin templates **B-279** by bis-stannylation of alkyne **B-278**[197] followed by an acid-catalyzed cyclization (Scheme 52), and subsequent Stille coupling reactions provided trisubstituted furanones as single regioisomers in yields of 22 to 51%. It is likely that steric hindrance from the remaining tributyltin substituent was a major factor that inhibited the initial coupling. Two examples illustrated the viability of a second Stille process to form tetrasubstituted olefins. Two aryl iodides were introduced onto β-stannyl enones **B-280** to produce the corresponding tetrasubstituted olefin products **B-281**. Higher temperatures were required to force these reactions at the less activated α-position, but conversions were significantly better than for the initial coupling reactions.

[196] Mabon, R.; Richecour, A. M. E.; Sweeney, J. B. *J. Org. Chem.* **1999**, *64*, 328.
[197] This initial stannylation used a procedure developed by the Piers research group: (a) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1602. (b) Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421. (c) Piers, E.; Skerlj, R. T. *J. Chem. Soc. Chem. Commun.* **1986**, 626.

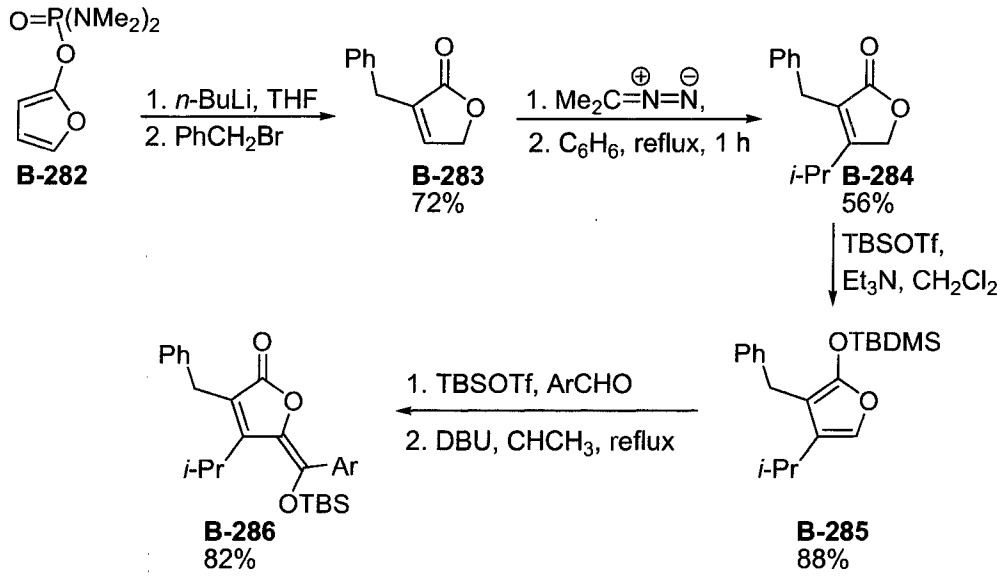
Scheme 52. Stannyl-olefin templates



A previous approach to substituted furanones, Nostoclides I and II, employed furanolate chemistry.[198] Using straightforward reactions, the desired product was obtained in 30% overall yield (Scheme 53). Tetramethyldiamidophosphate **B-282** was *ortho*-lithiated, and the resulting anion trapped with benzyl bromide to provide butenolide **B-283** in 72% yield. The isopropyl group was introduced regioselectively in 56% yield *via* a 1,3-dipolar cycloaddition, followed by thermolysis to release gaseous nitrogen. Aromatization was accomplished by treatment of the tetrasubstituted butenolide with triethylamine and *tert*-butyldimethylsilyl triflate providing furan **B-285** in 88% yield. The desired target (**B-286**) was obtained as a mixture of diastereomers (4.3:1) after *tert*-butyldimethylsilyl triflate-induced aldolization and dehydration.

[198] Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897.

Scheme 53. Nostoclides *via* furanoate chemistry



Barluenga *et al.* accessed cyclic olefin templates *via* the electrophilic iodoarylation of alkynes.[199] A wide variety of trisubstituted vinyl iodides were produced using this method, and while these were not transformed to tetrasubstituted alkenes, in principle they could have been. Three examples were shown in which the cyclic bromo-iodo intermediates **B-289** were converted to tetrasubstituted olefins **B-290** (Scheme 54). In all cases, the first coupling occurred selectively at the iodide position. The subsequent coupling occurred at the bromide position, and the substituents were introduced in a selective manner. High temperatures were required to effect the coupling reactions, and in many cases heating in sealed tubes was necessary.

[199] Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; González, J. M. *Chem. Comm.* **2005**, 2008.

Scheme 54. Cyclic olefin templates

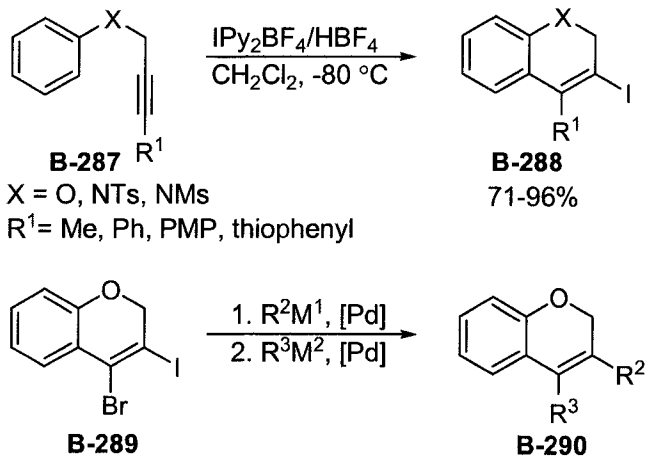


Table 21. Conversion of bromoiodo derivatives B-289 into tetrasubstituted olefins B-290

Entry	R^2	R^3	Yield (%)
1	4-$MeOC_6H_4$	4-MeC_6H_4CHCH	72
2	Ph	4-$MeOC_6H_4$	54
3	2-thienyl	4-MeC_6H_4CC	67

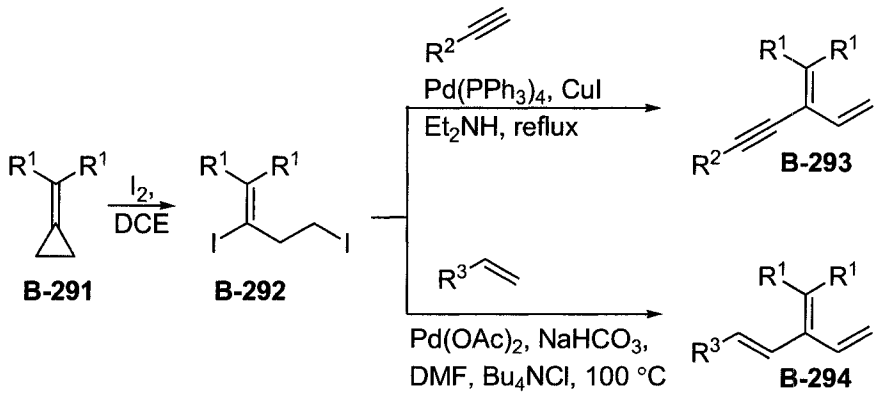
1.3.3 Geminally Symmetric Olefin Templates

There are significantly fewer methods available for the formation of acyclic, tetrasubstituted double bonds than for the formation of cyclic olefins. Yields can erode dramatically when mixtures of isomers are formed in the process, and so methods often employ geminally symmetric double bonds as templates. This facilitates the discovery of new methodology to access molecules of intriguing architecture before the issue of asymmetrically substituting the double bonds must be addressed. Some of the successful techniques for the generation of acyclic, tetrasubstituted double bonds are described below.

Shao and Shi reported methodology for the formation of acyclic 2-alkynylbuta-1,3-dienes **B-293** from diiodide precursors **B-292** (Table 22), that were prepared from an

electrophilic ring-opening of methylene cyclopropanes.[200] The reaction worked with a wide variety of aryl alkynes, although significantly lower yields were observed when coupling reactions were attempted with alkyl alkynes. In each case, elimination of the alkyl iodide was observed, giving an extended conjugated system. This was unfortunate, as the alkyl iodides would have provided a handle for further elaboration. The effectiveness of the method could only be demonstrated with symmetric cyclopropanes because mixtures of isomers were obtained when R^1 and R^2 were different.[201] The analogous Heck reactions were then examined, that produced conjugated trienes, such as **B-294**, in yields of 30 to 99%.[201b] Again, elimination of the alkyl iodide occurred under the reaction conditions, producing triene products.

Table 22. Tetrasubstituted alkenes *via* iodide templates



Entry	R^1	R^2	Yield (%)
1	4-$MeOC_6H_4$	Ph	91
2	4-MeC_6H_4	Ph	87
3	4-ClC_6H_4	Ph	97
4	Ph	4-$MeOC_6H_4$	99
5	4-ClC_6H_4	4-$MeOC_6H_4$	99
6	4-$MeOC_6H_4$	CH_2OH	30
7	4-MeC_6H_4	CH_2OH	49

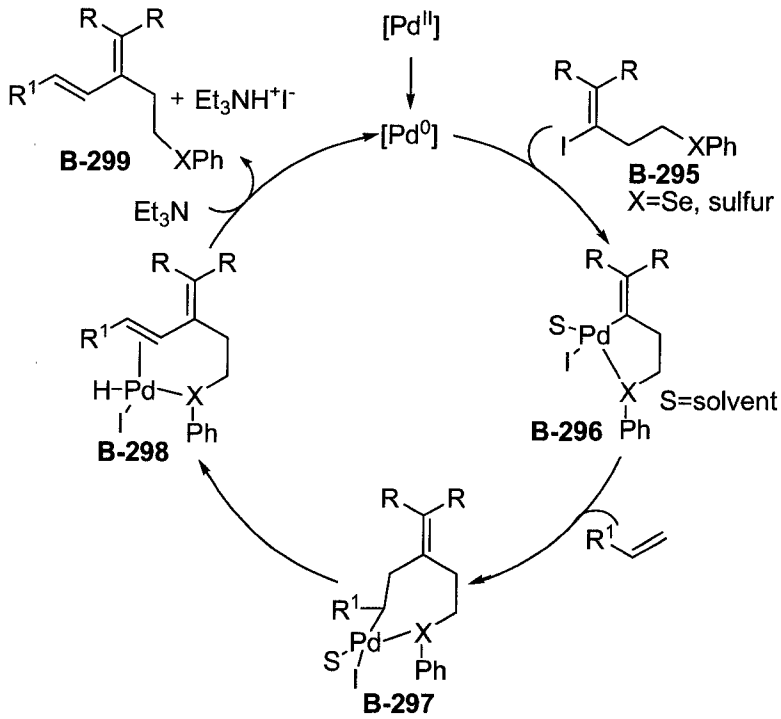
[200] (a) Shao, L. X.; Shi, M. *J. Org. Chem.* **2005**, *70*, 8635. (b) Shi, M.; Liu, L. P.; Tang, J. *Org. Lett.* **2005**, *7*, 3085.
[201] (a) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415. (b) Shi, M.; Shao, L. X. *Synlett* **2004**, 807.

8	Ph	CH_2OH	28
9	4-$MeOC_6H_4$	CH_2OBn	92
10	4-MeC_6H_4	CH_2OBn	78
11	4-$MeOC_6H_4$	*n*-C_4H_9	51
12	4-MeC_6H_4	*n*-C_4H_9	47

This method was later improved and expanded by replacing the iodine on the side chain of **B-292** with a selenium or sulfur substituent.[202] This avoided the elimination process during the coupling reaction, and allowed for subsequent alkyl transformations at the selenium of sulfur position. Heck reactions were achieved with a wide variety of substrates, in yields of 82 to 94%. Kumada couplings were also successful, although lower yields were reported for substrates bearing electron-withdrawing aryl moieties. Suzuki and Negishi couplings were effective, and notably, the Negishi reaction made possible the introduction of an alkyl substituent to the tetrasubstituted alkene. Most reactions proceeded at room temperature and in many cases without using ligands or additives. This was explained by a mechanism that involved the participation of the selenium or sulfur atom as a ligand to the palladium, thus activating and directing the catalyst to the desired site (Scheme 55). These reactions did not proceed with substrates lacking the selenium or sulfur atom (*i.e.* Se replaced with CH_3).

[202] Shi, M.; Liu, L. P.; Tang, J. *J. Org. Chem.* **2005**, *70*, 10420.

Scheme 55. Catalytic cycle describing the role of a S or Se substituent



This methodology was recently extended by Chen and coworkers in their synthesis of pyrrolotriazoles (Scheme 56).[203] The olefin templates were prepared as before through the CuI-mediated dihalogenation of methylene cyclopropanes **B-300**, to give olefin templates **B-301**. These were treated with sodium azide in refluxing ethanol, and a variety of acetylenes were subsequently introduced to give 1,3-dipolar cycloaddition products **B-303** in yields of 51 to 70%. Intramolecular Heck reactions were then carried out to provide the final products **B-304**, that each contained a tetrasubstituted olefin moiety (Table 23). In one case, three different R groups on the methylene cyclopropane were employed (R^1 = Me, R^2 = Ph, R^3 = C_5H_{11}).

[203] Chen, W.-L.; Su, C.-l.; Huang, X. *Synlett* **2006**, 1446.

Scheme 56. Synthesis of pyrrolotriazoles

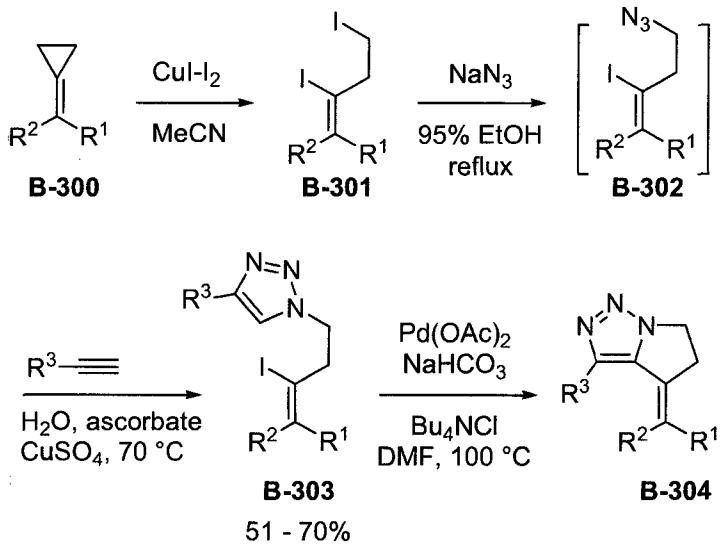


Table 23. Conversion of template B-303 to B-304.

Entry	R^1	R^2	R^3	Yield (%)[a]
1	Ph	Ph	*n*-C_4H_9	82
2	Ph	Ph	*n*-C_5H_{11}	85
3	Ph	Ph	$MeOCH_2$	52
4	4-ClC_6H_4	4-ClC_6H_4	*n*-C_4H_9	82
5	4-ClC_6H_4	4-ClC_6H_4	*n*-C_5H_{11}	58
6	4-FC_6H_4	4-FC_6H_4	*n*-C_4H_9	68
7	Me	Ph	*n*-C_5H_{11}	71

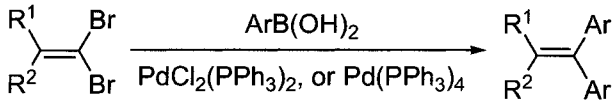
[a]Yields are based on recovered **317**

Geminal halide substitution provides more opportunities for elaboration,[204] but the control of stereoselectively poses a serious challenge. Methodology was disclosed forming geminally symmetric tetrasubstituted olefins (Table 24) using Corey-Fuchs[205] templates (**B-305**) that were generated from various ketones.[206] Suzuki coupling reactions with four to six equivalents of various arylboronic acids furnished the olefins **B-306** in

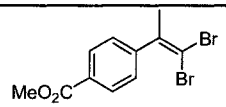
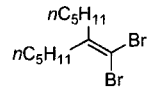
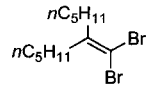
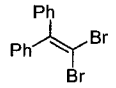
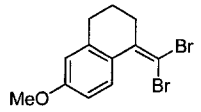
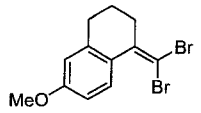
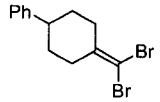
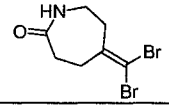
[204] (a) Neidlein, R.; Winter, M. *Synthesis* **1998**, 1362. (b) Reiser, O. *Angew. Chem. Int. Ed.* **2006**, *45*, 2838.
[205] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
[206] Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254.

yields of 75 to 97%. A wide variety of functionalities were tolerated, including esters, acetals, ketones, oximes, and amides, but yields were reduced when *ortho*-substituted aryls were employed, presumably due to the steric crowding in these already congested centers. Higher reaction temperatures were necessary to couple acyclic olefins, and it was found that large excesses of the boronic acids were required to force the reactions to completion. Interestingly, the mono-arylated products were never isolated, likely indicating that these substrates were more activated toward coupling than the dibromo starting materials. It was not possible to couple two different arylboronic acids using this method.

Table 24. Coupling of geminal dibromo olefins



B-305 **B-306**

Entry	Alkene B-305	Ar	Yield (%)
1		3-MeOC$_6$H$_4$	97
2		Ph	26
3[a]		4-pyridyl	46
4[a]		4-MeOC$_6$H$_4$	87
5		Ph	77
6		4-MeOC$_6$H$_4$	79
7		Ph	69
8		Ph	92

[a] $Pd(PPh_3)_4$ and DME/H_2O (4:1) were employed at 90 °C.

In order to achieve differentiation at the geminally-substituted carbon, an extra step was added by Shimizu and colleagues to the sequence described above. This gave the *gem*-diboryl alkenes **B-308** shown in Scheme 57.[207,208] Treatment of the 1,1-dibromoalkene **B-307** with butyllithium at −110 °C, followed by slow addition of the solution at −110 °C to bis(pinacolato)diboron in THF, gave the 1,1-diborylalkenes **B-308** in 48 to 93% yield. These materials were then cross-coupled, and impressively, single isomers (**B-309**) were formed, a fact that was confirmed by both NOE and X-ray analysis. Yields ranged from 39 to 87% for a wide variety of alkyl groups, including sterically crowded *i*-Pr and *t*-Bu moieties, although small drops in yields were observed when *tert*-butyl groups were present (39 to 54%). A wide range of functionality was tolerated on the aryl moiety, including a free aniline. Yields of 59 to 89% were achieved for the second, more difficult, coupling reaction to give final product **B-310** (Table 25). Often steric hindrance is the factor that determines the regioselectivity in such couplings. However, it appeared that this was not the case in this example, as the Ar^1 moiety was delivered *cis* to the alkyl (R) group in every example, even when R was a *tert*-butyl group. Naturally, this incurred limitations, requiring at least one aryl and one alkyl group to be on the distal carbon, and only aryl couplings were described. The exceptional regioselectivity observed provided a distinct advantage over many other methods and makes an impressive contribution to the formation of tetrasubstituted olefins.

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[207] (a) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (b) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 790.

[208] This is an improvement of a known method to generate 1,1-diborylalkenes: Matteson, D. S. *Synthesis* **1975**, 147.

Scheme 57. Differentiation of dibromo substituents

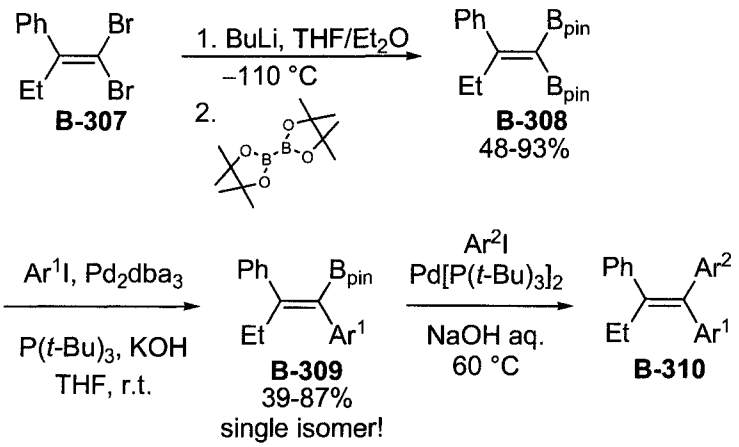


Table 25. Conversion of B-309 to tetrasubstituted olefin B-310

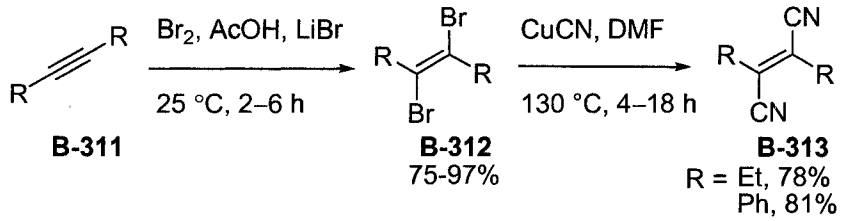
Entry	Ar^1	Ar^2	Yield (%)
1	Ph	4-$Me_2N(CH_2)_2OC_6H_4$	59
2	4-FC_6H_4	4-$MeOC_6H_4$	75
3	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	78
4	4-$MeOC_6H_4$	4-MeC_6H_4	89
5	4-$EtOC_6H_4$	Ph	75
6	4-MeC_6H_4	Ph	89

1.3.4 Acyclic, Vicinally Symmetric Olefin Templates

Methodology outside the domain of geminally substituted olefins requires controlling elements, either at the coupling stage or, more often, during the construction of the template. An early example by Fitzgerald and colleagues, utilized symmetrical, 1,2-dibromo olefins for the generation of tetraazaporphyrins (Scheme 58).[209] Bromination of 3-hexyne or diphenylacetylene **B-311** gave the dibromo alkenes **B-312**. These alkenes were converted, *via* the Rosenmund-von Braun reaction, to dinitriles **B-313** that were further transformed to tetraazaporphoryns.

[209] Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686.

Scheme 58. 1,2-Dibromo olefin precursors to tetraazaporphoryns



B-311

B-312
75-97%

B-313
R = Et, 78%
Ph, 81%

It has been shown that *E*-dibromo olefin templates **B-315** could be generated, in greater than 98% stereochemical purity, by the exposure of 2-alkynyl esters **B-314** to pyridinium bromide perbromide (Scheme 59).[210] Mixtures of *E* and *Z* isomers were obtained if Br_2 was used alone at temperatures above −78 °C, or if the reaction was contaminated with traces of HBr.[211] Various palladium-catalyzed reactions of the 1,2-dibromo olefins gave the corresponding trisubstituted olefins in 18 to 61% yields (Table 26).[210] Several side products were obtained in these reactions, including doubly-coupled products (2 to 5%), alkynes resulting from eliminations of the dibromide substrates (8 to 15%), and significant amounts of homocoupled biaryl materials. Mixtures of stereoisomers were observed when phenyl or ester substituents were present at R^1 (entries 7 to 10).

[210] Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095.
[211] Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

Scheme 59. Generation of *E*-dibromo alkenes for the production of tetrasubstituted olefins

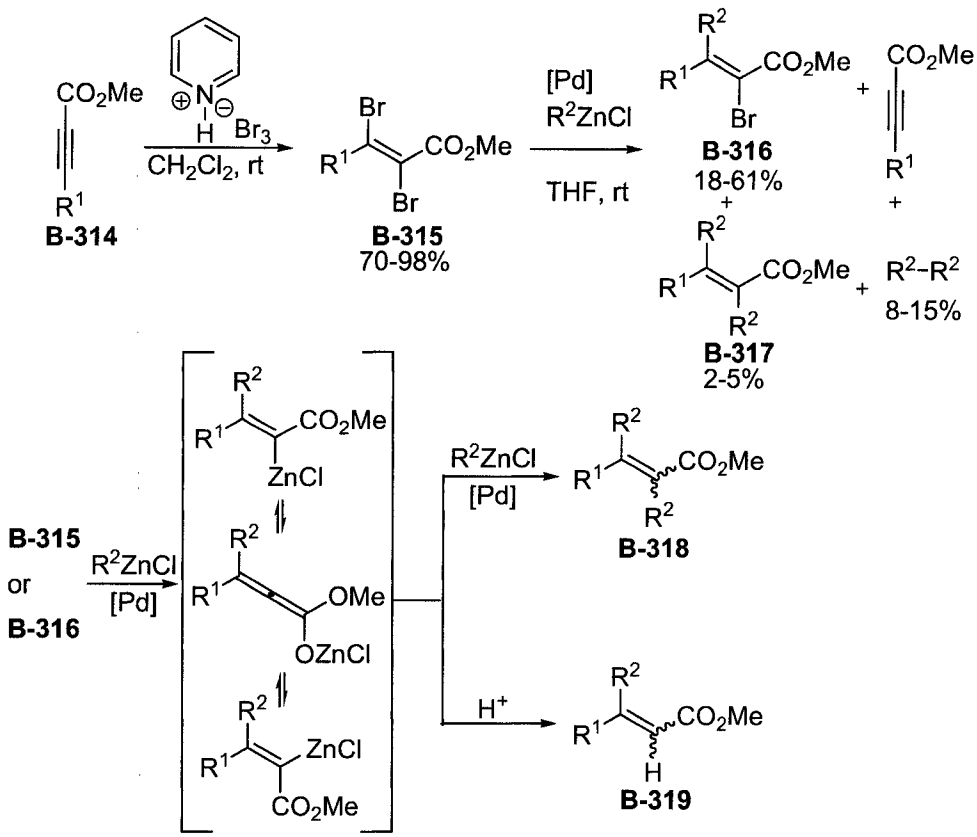
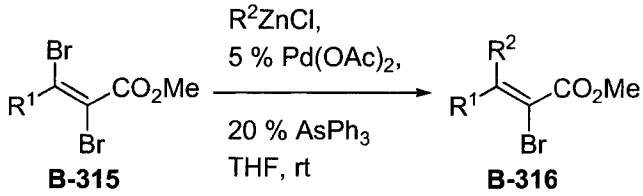


Table 26. Generation of trisubstituted alkenes from 2,3-dibromoalkenoates

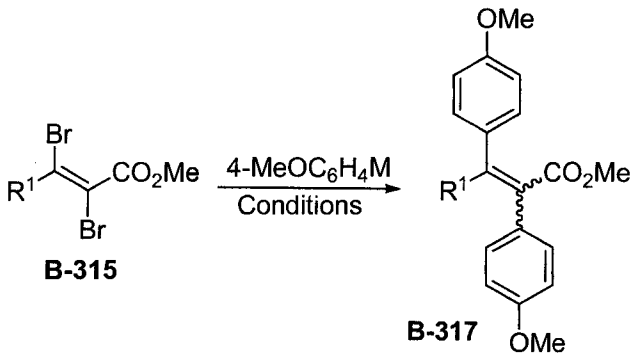


Entry	R^1	R^2	Yield (%)
1	C_5H_{11}	4-$MeOC_6H_4$	61
2	C_5H_{11}	2-$MOMOC_6H_4$	43[a]
3	C_5H_{11}	4-FC_6H_4	56
4[b]	Me	2-$MOMOC_6H_4$	24
5	C_5H_{11}	$C_6H_{13}C{\equiv}C$	57
6[b]	Me	4-$MeOC_6H_4$	49
7[b]	Ph	4-FC_6H_4	27
8[b]	Ph	4-$MeOC_6H_4$	18
9[b]	Ph	2-$MOMOC_6H_4$	38
10[b]	CO_2Et	4-$MeOC_6H_4$	43

[a]5% $Pd(PPh_3)_4$ was used as catalyst. [b] The ethyl ester was employed.

Tetrasubstituted olefins were subsequently obtained from these products, as mixtures of isomers, by Negishi or Stille coupling reactions (Table 27). The loss of stereochemical integrity in these transformations was likely due to the formation of zinc allenoate intermediates. A single isomer was achieved in only one example by using the Stille reaction, in 27% yield (entry 3). Isomeric side products, **B-319**, were obtained in the Negishi couplings, and were probably derived from halogen-zinc exchange and isomerization through the zinc allenoates, followed by protonation in the workup stage.

Table 27. Generation of tetrasubstituted alkenes



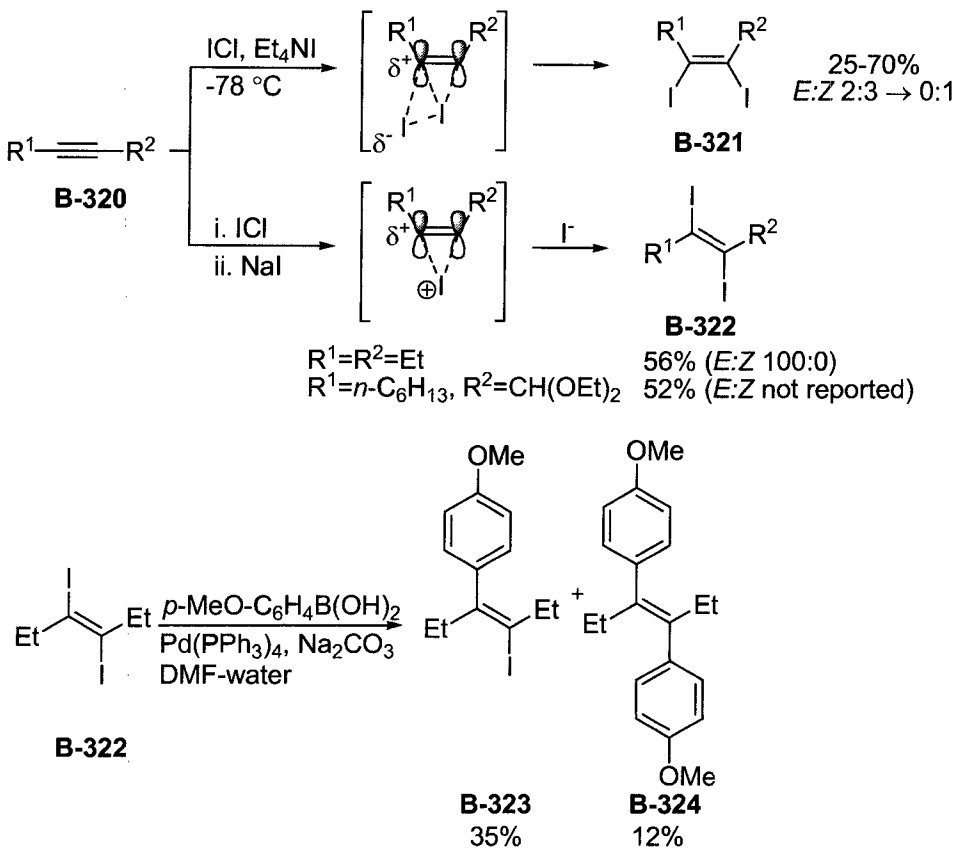
Entry	R^1	M	Conditions[a]	Yield (*E*:*Z*)
1	C_5H_{11}	ZnCl	A	13% (1:1)
2[b]	C_5H_{11}	ZnCl	B	13% (1:9)
3	C_5H_{11}	$SnBu_3$	C	27% (*E*)
4	CO_2Et	ZnCl	B	[c]
5	CO_2Et	$SnBu_3$	C	60% (55:45)[d]

[a] Catalyst A: $Pd(PPh_3)_4$, THF, r.t., 48 h. Catalyst B: $Pd(OAc)_2$, $AsPh_3$, THF, r.t., ~50 h. Catalyst C: $PdCl_2(PhCN)_2$, CuI, $AsPh_3$, NMP, r.t. [b] Starting material was (*E*)-**271**; R^2 = 4-$MeOC_6H_4$. [c] An *E*/*Z* mixture was obtained but the ratio was not determined. The *E*-isomer was isolated in 39% yield. The ethyl ester was employed [d] Yield and *E*/*Z* ratio were determined indirectly. The ethyl ester was employed

Hénaff and Whiting described a method for the selective formation of either *E*- or *Z*-diiodo templates.[212] By carefully controlling the reaction conditions, they could access either the *E* or *Z* isomers (Scheme 60). Unfortunately, isomeric mixtures were obtained during the generation of most *Z*-iodo alkenes (**B-321**), and it was only possible to obtain pure *E* tetrasubstituted precursors in two cases. Suzuki or Stille coupling reactions of the *E*-diiodo templates **B-322** were described to give trisubstituted alkenes **B-323**, and one tetrasubstituted olefin (**B-324**) was reported, a result of over addition to the *E*-diiodo substrate **B-322**, in 12% yield. The attempted generation of *Z*-tetrasubstituted products from the corresponding *Z*-iodides (**B-321**) was not described.

[212] Hénaff, N.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, 395.

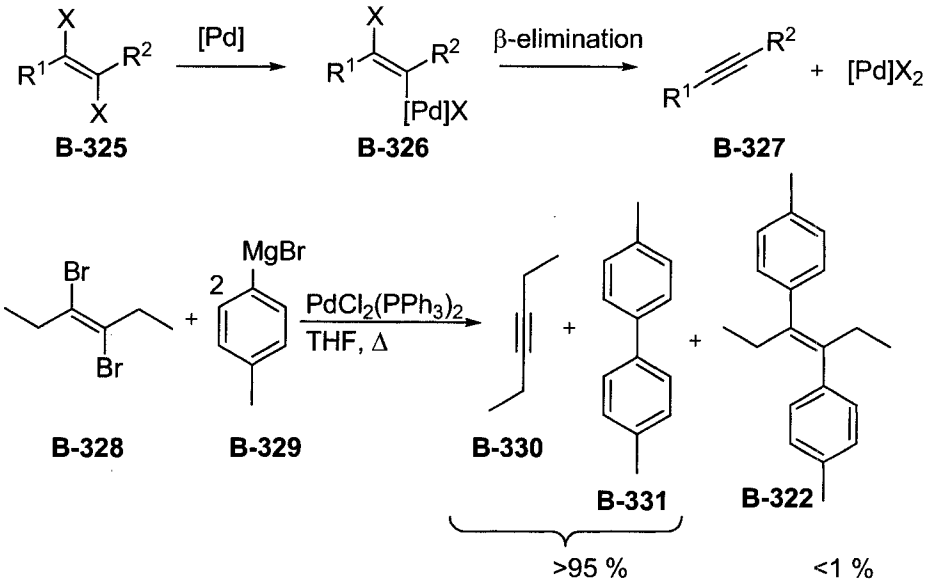
Scheme 60. Attempted generation of tetrasubstituted olefins *via* di-halo olefin templates



A potential explanation for the extremely low yield of tetrasubstituted olefin **B-324** was the competitive palladium-catalyzed elimination of the vicinal dihalides (Scheme 61).[210,213] Oxidative addition of palladium into the first carbon-halogen bond of template **B-325** would form the organopalladium intermediate **B-326** that could then undergo β-halogen elimination to produce alkyne **B-327**. A reaction performed by Rathore[214] using *p*-tolyl-magnesium bromide **B-329** and dibrominated alkene **B-328** produced less than 1% of the desired tetrasubstituted isomer **B-322** and instead gave the eliminated alkyne product **B-330** and biaryl **B-331**, consistent with the above hypothesis.

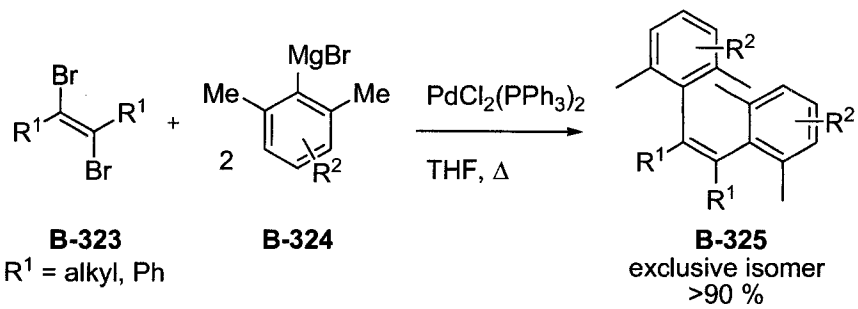
[213] Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453.
[214] Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832.

Scheme 61. Palladium-catalyzed elimination of vicinal dihalogens



An interesting effect was demonstrated by the Rathore research group (Scheme 62).[214] Six different *trans*-dibromoalkenes (**B-323**) were coupled with *ortho*-substituted aryl magnesium bromides (**B-324**) in yields greater than 90%. Complete inversion of stereochemistry was noted in all cases to give exclusively the *Z*-alkene products (**B-325**). The stereochemistry was confirmed in one case by X-ray crystallographic analysis and the remaining structures were assigned through the correlation of NMR chemical shifts. This method allowed access to highly hindered *Z*-tetrasubstituted alkenes (**B-325**) that are typically very difficult to prepare, but was only effective for di-*ortho*-substituted aryl Grignard reagents.

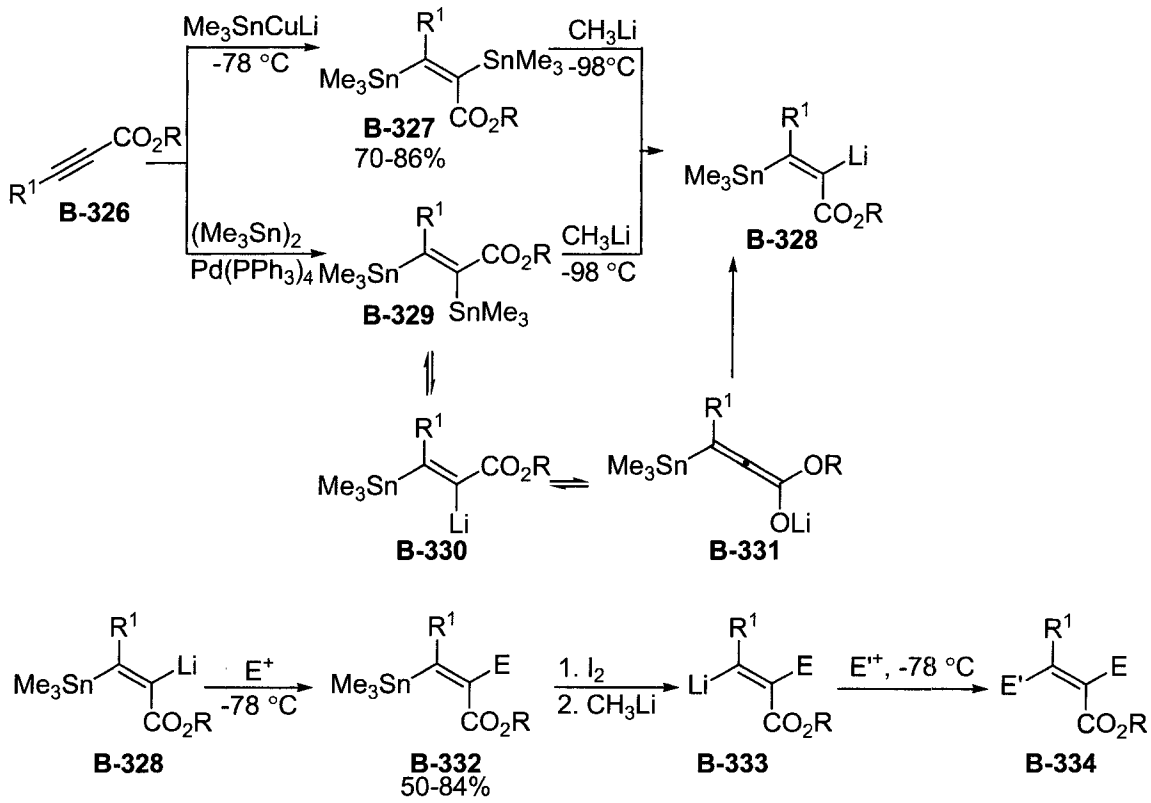
Scheme 62. The formation of sterically congested tetrasubstituted alkenes with simultaneous full inversion of configuration



The elimination product was not observed when stannanes were used instead of halides, as illustrated by the Piers research group (Scheme 63).[215] Double stannylation of alkynylesters **B-326**, gave *E*- and *Z*-stannanes **B-327** or **B-329**. Tin-lithium exchange on *trans*-distannane **B-327** provided the α-lithiated alkene **B-328** that captured strong electrophiles regioselectively (MeI, 84%; CH_2=$CHCH_2Br$, 79%; BnBr, 76%; C_4H_9I, 50%; cyclohexanone, 71%). Exposure of the *cis*-stannane **B-329** to methyllithium caused a rapid isomerization, after lithium exchange, to give **B-328** exclusively, presumably through allenoate **B-331**. Direct tin-lithium exchange was not possible at the β-position of **B-332**. Instead, the β-stannane **B-332** was treated with iodine, and the resulting iodide was lithiated with methyl or butyllithium to afford **B-333**. Finally, an electrophile was introduced giving the tetrasubstituted products **B-334** (MeI, 93%; *n*-BuI, 65%; ICH_2CH=CMe_2, 67%; $I(CH_2)_5Cl$, 72%). Multiple steps were required, under strictly controlled conditions, and only highly activated electrophiles could be employed. Single isomers were produced, as shown by careful NOE analysis.

[215] (a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263. (b) Piers; Chong. (c) Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265.

Scheme 63.



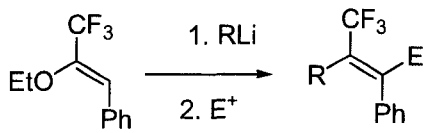
1.3.5 Differentially-Substituted Olefin Templates

Additional control must be introduced when utilizing fully asymmetric templates. Reactivity is controlled primarily by electronic effects in these compounds, and additional control elements such as directing groups must therefore be present. The distinct advantage of these templates lies in their potential use to generate tetrasubstituted olefins bearing four different carbon substituents.

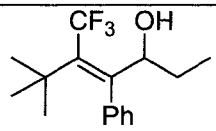
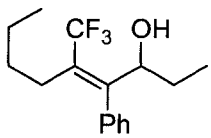
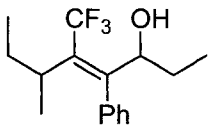
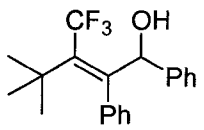
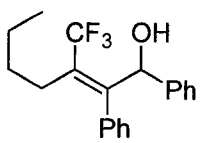
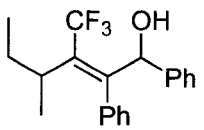
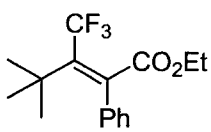
Bonnet-Delpon *et al.* demonstrated that carbolithiation of alkenes such as **B-335** using various alkyl lithium reagents (*t*-BuLi, *n*-BuLi, *s*-BuLi), followed by trapping with electrophiles, generated tetrasubstituted alkenes stereoselectively in yields of 75 to 95% (Table 28).[216]

[216] (a) Bégué, J. P.; Bonnet-Delpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111. (b) Bouvet, D.; Sdassi, H.; Ourévitch, M.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 2104.

Table 28. Carbolithiation of trifluoromethyl enolethers to generate tetrasubstituted alkenes



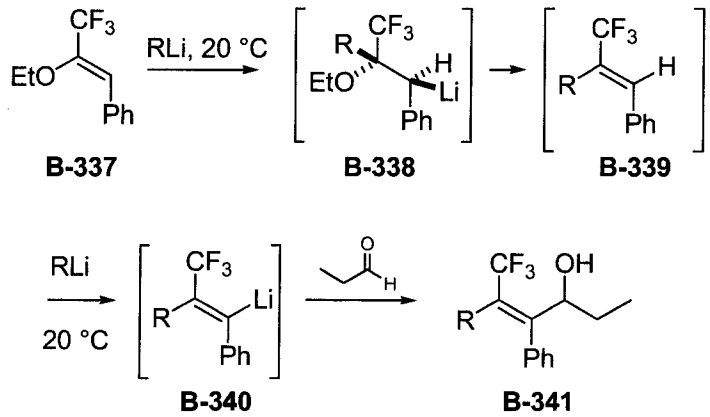
B-335 **B-336**

Entry	RLi	Electrophile (E^+)	Product	Yield (%)
1	^{t}BuLi	C_2H_5CHO		75
2	^{n}BuLi	C_2H_5CHO		83
3	^{s}BuLi	C_2H_5CHO		82
4	^{t}BuLi	PhCHO		95
5	^{n}BuLi	PhCHO		85
6	^{s}BuLi	PhCHO		88
7	^{t}BuLi	$ClCO_2Et$		79

The mechanism of this transformation apparently involved an unusual pseudosubstitution of the ethoxy group. Similar processes implicating fluoride as the

leaving group are known in reactions of *gem*-difluoroalkenes and perfluoroalkenes.[217] In the present case, the reaction was thought to involve a *cis* addition of alkyllithium across the double bond, a process encouraged by the electron-poor nature of the initial olefin (Scheme 64). Regioselectivity was controlled by the stabilizing influence of the β–aryl ring, and was responsible for the reaction following a pseudosubstitution pathway. As the reactions were performed at room temperature, *anti*-elimination of the intermediate species (**B-338**) occurred rapidly to produce trisubstituted olefins **B-339**. These compounds were deprotonaned *in-situ* by a second equivalent of alkyllithium affording the reactive species **B-340**. Intermediate **B-340** was trapped with electrophiles such as propanal to give the tetrasubstituted olefin products (**B-341**).

Scheme 64. Carbolithiation to generate alkenes



An innovative approach, developed by Itami and colleagues, efficiently elaborated very simple alkene templates to tetrasubstituted olefins by using vinyl-2-pyrimidylsulfide precursors **B-342** (Scheme 65).[218] Beginning with the vinyl sulfide **B-342**, two successive Heck reactions gave product **B-343** with defined stereochemistry. Exposure of **B-343** to two equivalents of *t*-BuLi introduced a *t*-butyl substituent onto the pyrimidine ring, and the resulting lithio species underwent directed metallation at the α-position[219] to generate

[217] (a) Kooyman, J. G. A.; Hendricks, H. P. G.; Montijin, P. P.; Brandsma, L.; Arens, J. F. *Rec. Trav. Chim.* **1968**, *87*, 69. (b) Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045. (c) Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 415. (d) Ishikawa, N.; Nakai, T.; Hayashi, S. *Chem. Lett.* **1980**, 935.

[218] Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778.

[219] α-Lithiation of vinyl sulfides: Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.

intermediate **B-344**. A cross-coupling reaction of intermediate **B-344** in the presence of an aryl iodide gave the corresponding trisubstituted derivative **B-345**. Subsequent re-aromatization of the pyrimidine gave the vinyl pyrimidyl sulfide that was subjected to a final palladium-catalyzed cross-coupling reaction with aryl Grignard reagents (Table 29). Low yields were obtained when Ar^3 was particularly bulky (2-naphthyl for example), although the palladium-catalyzed coupling reaction tolerated Grignard reagents bearing electron-withdrawing and electron-donating substituents.

Scheme 65. Pyrimidyl sulfide-templated alkenes

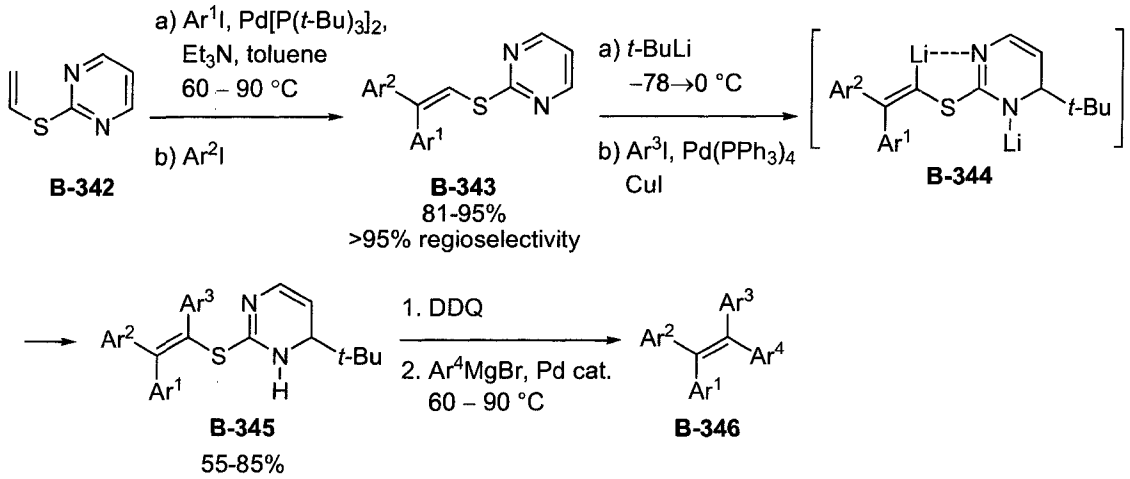
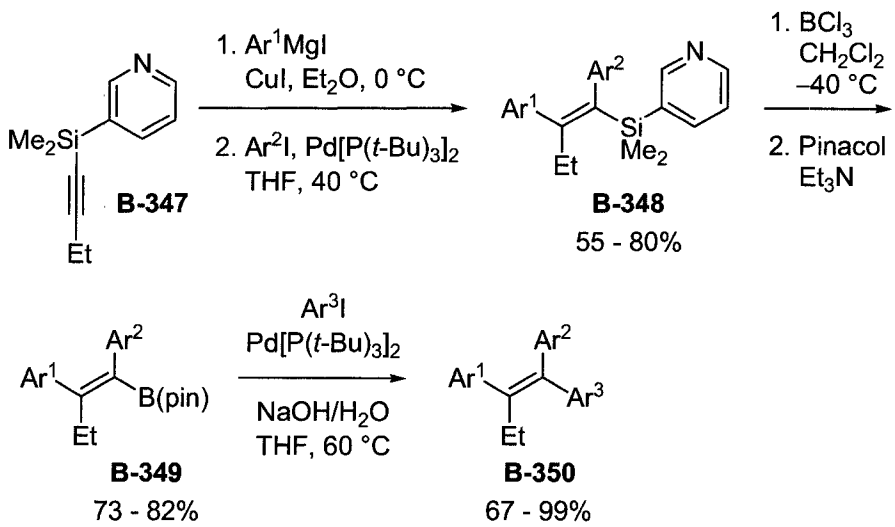


Table 29. Generation of tetrasubstituted olefin B-346

Entry	Ar^1	Ar^2	Ar^3	Ar^4	Yield (%)
1	Ph	Ph	4-$MeOC_6H_4$	Ph	72
2	Ph	Ph	4-$MeOC_6H_4$	2-naphthyl	46
3	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	4-MeC_6H_4	40
4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	4-FC_6H_4	52
5	4-$MeOC_6H_4$	4-MeC_6H_4	Ph	4-FC_6H_4	42
6	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	Ph	22
7	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	2-naphthyl	14
8	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	2-thienyl	21
9	1-naphthyl	1-naphthyl	4-MeC_6H_4	Ph	31

Itami and coworkers also developed a copper-catalyzed carbomagnesation across alkynyl(2-pyridyl)silanes **B-347** to give products such as **B-348** (Scheme 66).[220] Borodesilylation occurred stereoselectively at low temperature and subsequent treatment of this reaction intermediates with pinacol in the presence of triethylamine gave products **B-349** with retention of stereochemistry. Interestingly, it was found that the isomeric purities of **B-349** were greater than those of the starting alkenylsilanes. The authors felt this may have been due to reactivity differences between the isomeric alkenylsilanes during the borodesilylation. A final palladium-catalyzed cross-coupling reaction, with a wide variety of aryl iodides, gave tetrasubstituted olefins **B-350**.

Scheme 66. Regio- and stereoselectivity achieved in the pyridylsilane-directed carbometallation of alkynes



Overall, olefin templates are emerging as a reliable method of forming tetrasubstituted alkenes, however, there is still significant room to improve the generality and practicality of the methods. The selective production of the template is a limiting factor for much of this chemistry, and for reasons of convenience, symmetrical templates have often been used. Symmetrical carbon substitution often limits diversity whereas symmetry in the construction handles (halogens) presents obstacles of regio- and stereocontrol. The most successful templates utilize electronic differences and/or directing groups to generate stereodefined products. While cyclic templates are quite practical and generally give the

[220] Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670.

highest control, their structural variety is limited. Much greater structural variety is possible in acyclic templates, but only a few of the acyclic methods are practical.

1.4 Summary

The stereoselective synthesis of tetrasubstituted olefins has become the subject of investigation in research groups around the world. Preparing these products as single isomers with four different carbon-linked groups was traditionally so difficult that the majority of the literature on this topic has been published in the last decade. Many of the methods which have been developed involve multiple steps and can involve challenging manipulations to accomplish. The most successful methods employ short, indirect routes to the targets, and use robust transformations.

The majority of the explored routes have used alkynyl carbometallation strategies, methods that have a great deal of potential in terms of product diversity. The main difficulties associated with these transformations are the regioselectivity of the initial carbometallation and the reactivity of the penultimate organometallic coupling partner. The latter issue often limits the final coupling to the use of strong electrophiles, or results in a loss of stereochemical integrity. This area has seen the greatest evolution of reactivity, from the first applications of organocuprate technology to the development of complex, multicomponent reactions.

The transformation of existing olefins has also been widely used and this area has enjoyed the development of many of the more practical and general methods. Unfortunately, processes in which the olefin template is used as the electrophilc component are frequently low yielding, particularly when vicinal halides are present. The majority of these methods have drawbacks including limitations in coupling partners, isomerization, regioisomeric mixtures, complex, multistep sequences, and necessitate low temperatures and additives.

Olefin formation methods such as the Wittig and Horner-Wadsworth-Emmons reactions are less useful for the production of single isomer tetrasubstituted olefins

because these processes are inefficient in sterically demanding environments.[221] The McMurry coupling has been extremely successful in producing highly congested products, although stereochemistry can only be controlled in cyclic cases. Strategies such as olefin metathesis, radical processes, and ynolate chemistry are just beginning to emerge as viable techniques for the formation of tetrasubstituted olefins and offer potential in this area. This rapidly growing area of research will undoubtedly provide a wealth of new synthetic tools in the near future.

1.5 Objective

The goal of this project was the stereodefined synthesis of single-isomer, tetrasubstituted olefins bearing four distinct carbon substituents. We sought to design a practical approach that minimized the number of chemical transformations required, that would incorporate great flexibility in substituents, and that would generate single isomers. To accomplish this, we chose to use an olefin template approach (Scheme 67). Our template design would ensure that the following five requirements were met during subsequent organometallic coupling reactions:

(1) Regioselectivity: The halogens X^1 and X^2 would be differentiated in order to effect site-selective reactions

(2) Stereospecificity: Reaction conditions would be chosen to avoid alkene isomerization

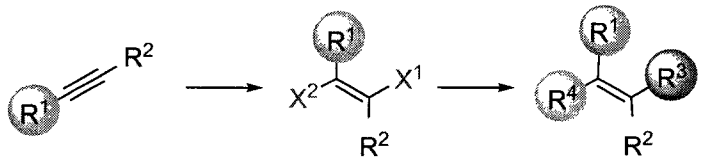
(3) Efficiency: Dihalide elimination to give undesired alkyne products would be avoided

(4) Practicality: The number of chemical transformations required would be minimized

(5) Flexibility: The template would allow great diversity in substituents and design options

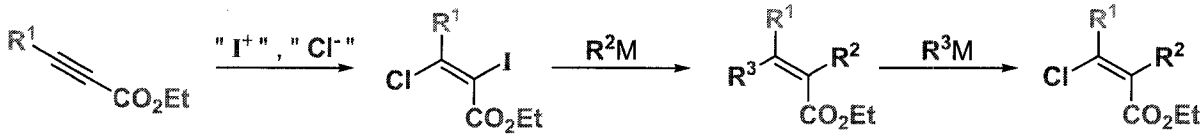
[221] Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *submitted.*

Scheme 67. Tetrasubstituted olefins *via* olefin templates



To meet these requirements, β-chloro-α-iodo-a,β-unsaturated esters and amides would be generated as single isomers via the iodochlorination of alkynes (Scheme 68). The ester or amide functionality would provide an electronic bias, permitting regiocontrol during the halogenation process. Stereocontrol during the halogenation reaction would be achieved through careful selection of cross-coupling reaction conditions. The use of two different halogens would provide a means of site differentiation during the coupling reactions and the reaction conditions would be chosen such that stereochemical integrity would be preserved.

Scheme 68. Design of olefin template



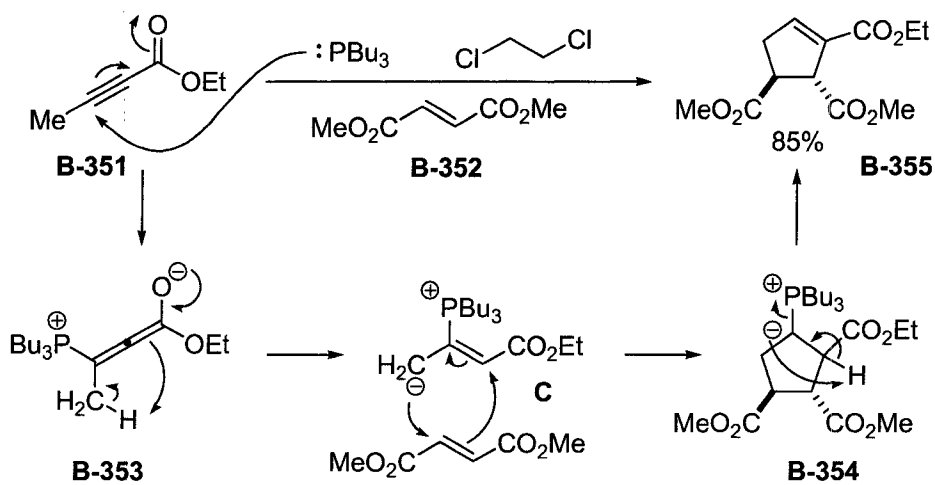
Chapter 2. Results and Discussion

2.1 Single Isomer Chloroiodination of Alkynes and Chlorination of Alkenes Using Tetrabutylammonium Iodide and Dichloroethane

2.1.1 Discovery of a new process for the halogenation of alkynes

A [3 + 2] cycloaddition reaction has recently been disclosed that employed alkynoates, potent dipolarophiles, such as dimethyl fumarate, and using Bu_3P as the catalyst.[222] In this process, the alkynoate served as a latent 1,3-dipole that was generated in solution upon addition of Bu_3P (Scheme 69). The dipolarophile then underwent a [3 + 2] cycloaddition to provide highly substituted cyclopentenes such as **B-355**.

Scheme 69. [3 + 2] dipolar cycloaddition reaction



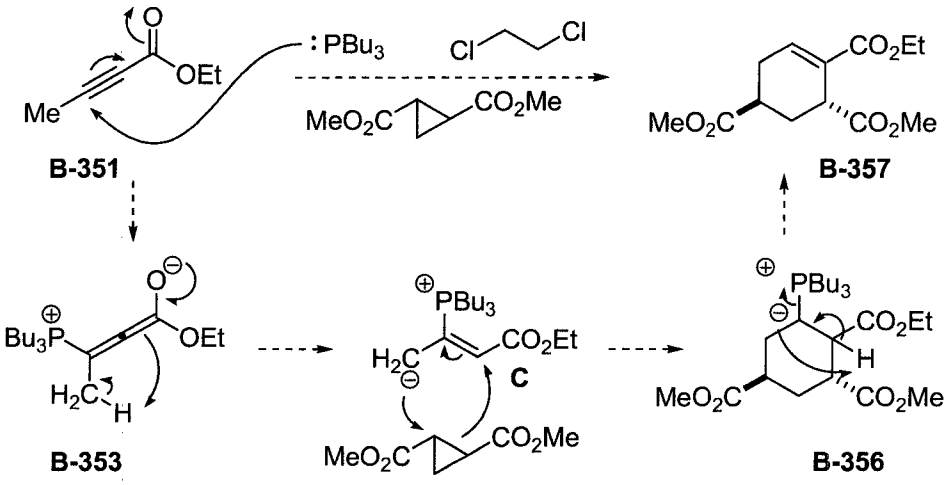
The use of cyclopropanes to serve as dipolarophiles in this process was investigated because of the potential of such a process in asymmetric synthesis (Scheme 70).[223] The use of cyclopropanes would provide access to six-membered rings with substitution patterns that differed from those obtained by a typical Diels–Alder reaction.

---

[222] Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549.

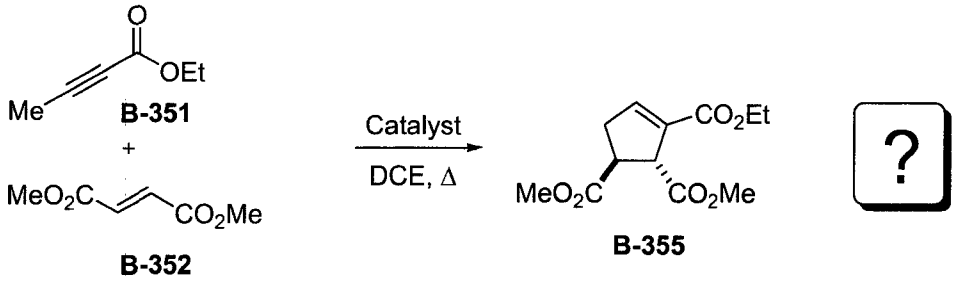
[223] The Kerr group has investigated the [3 + 2] cycloaddition of nitrones with cyclopropanes. See Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953.

Scheme 70. Cyclopropane dipolarophile in the [3 + 2] dipolar cycloaddition reaction



Knowing that the reaction shown in Scheme 69 was limited to phosphine-catalysis (Table 30, entry 1), a variety of other reagents were tested that could potentially serve as catalysts for this reaction. Cyanide proved ineffective regardless of whether potassium cyanide or 2-hydroxy-2-methylpropanenitrile were used as the cyanide source (entries 2 and 3). Employing NaI, KI, or CuI as alternate nucleophilic sources similarly gave no reaction (Table 30, entries 4–6). Much to our surprise, the exposure of alkyne **B-351** and alkene **B-352** to Bu_4NI in refluxing DCE for twenty-four hours gave quantitative conversion to an unanticipated product (entry 7). Focus quickly turned to the identification of this compound.

Table 30. Analysis of potential nucleophilic sources for halogenation reaction



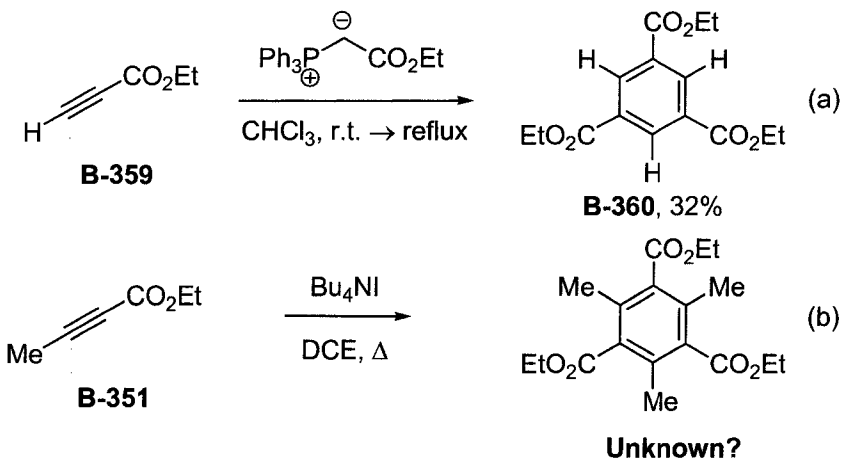
Entry	Catalyst	Yield (Product)
1	Bu_3P	85% (**B-355**)
2	Cyanohydrin	NR
3	KCN	NR
4	NaI	NR
5	KI	NR
6	CuI	NR
7	**Bu_4NI**	**100% conversion to unknown product**

2.1.2 Structure determination of the alkene templates

The pattern of the proton spectrum of this colorless compound was very similar to that of the starting ethyl alkynoate with significant differences in chemical shifts. The phosphonium ylide-catalyzed cyclotrimerization of an alkynoate had been reported with ethyl propiolate to give trisubstituted benzene rings (**B-360**) (Scheme 71, equation a).[224] It was therefore plausible that the same reaction had been catalyzed by Bu_4NI to give the analogous hexasubstituted aromatic compound (Scheme 71, equation b).

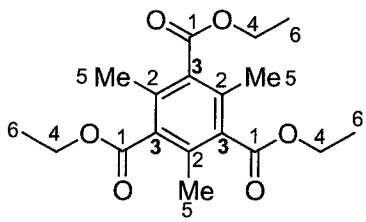
[224] Labuschagne, A. J.; Malherbe, J.; Meyer, C.; Schneider, D. *Syn. Comm.* **2002**, *32*, 297.

Scheme 71. Potential structure of unknown product



The NMR data of the unknown was almost consistent with the formation of a symmetrically hexasubstituted benzene **B-361** (Table 31). However, one anomaly was apparent when the observed ^{13}C chemical shifts were compared with predicted chemical shifts for the same molecule. We would have expected the resonance of the carbon alpha to the carbonyl to appear at approximately 130 ppm (Table 31, entry 3, carbon 3), however the chemical shift observed for this atom was approximately 81 ppm, out of the range of a typical alkene or aromatic carbon chemical shift.

Table 31. Comparison of the observed ^{13}C chemical shifts for the unknown compound with the predicted ^{13}C chemical shifts of B-361[a]



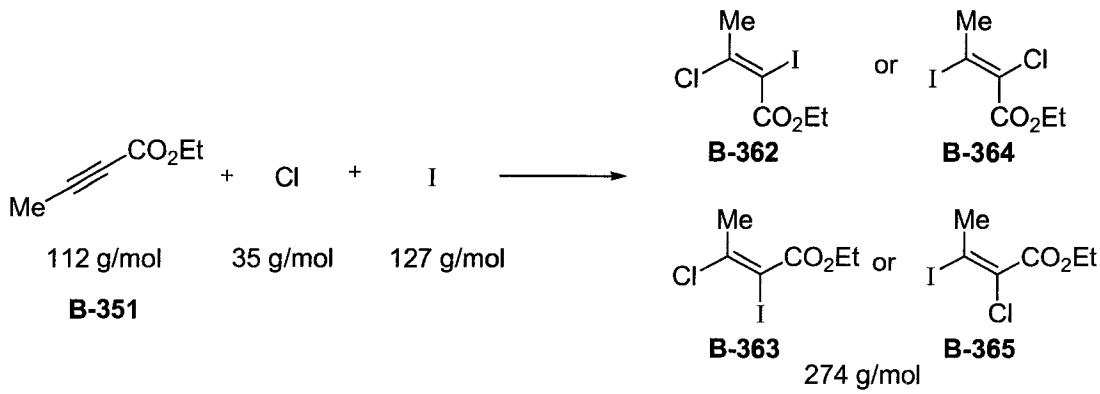
B-361
Molecular weight = 336 g/mol

Entry	Carbon #	^{13}C predicted	^{13}C observed
1	1	166	165
2	2	148	135
3	**3**	**130**	**81**
4	4	61	62
5	5	19	30
6	6	14	14

[a] ^{13}C chemical shifts were rounded to the nearest whole number.

Mass spectral analysis (GC–MS) confirmed the presence of a single compound with a molecular weight of 274 g/mol. The electron impact (EI) spectrum showed the 3:1 isotope pattern (M^+ : $M^+ + 2$) characteristic of the presence of a single chlorine atom.[225] Given the mass of the starting material of 112 g/mol and the mass of the chlorine (35 g/mol), the remaining mass was 127 g/mol—consistent with iodine incorporation into the molecule (Scheme 72). This mass was consistent with one of four possible structures.

Scheme 72. Mass spectroscopy provided insight as to the possible structures of the unknown

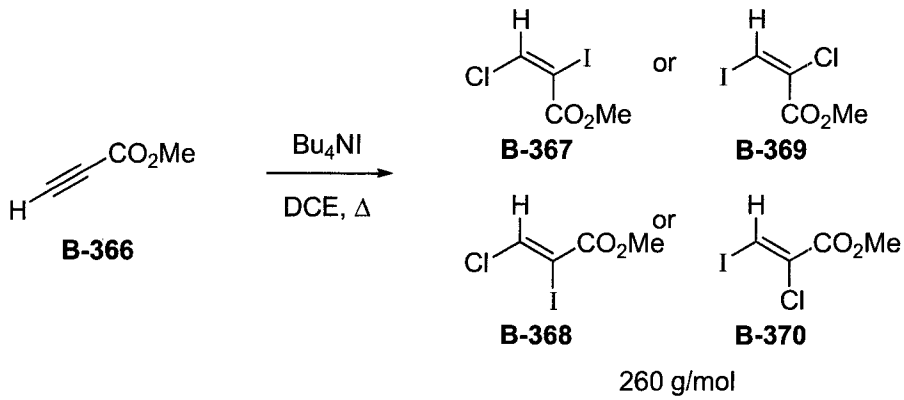


In order to identify the regioisomer formed, the reaction was repeated using methyl propiolate (**B-366**) as the substrate (Scheme 73). The exposure of the methyl propiolate to Bu_4NI in refluxing DCE gave complete conversion to a *single* product. GC–MS analysis of the crude reaction mixture confirmed the formation of a single isomer,[226] the presence of chlorine in the molecule, and a molar mass of 260 g/mol. These data were consistent with compounds **B-367** and **B-369** or their stereoisomers, **B-368** and **B-370**.

[225] The natural abundance of chlorine is: ^{35}Cl:^{37}Cl; 75.78%:24.22%. See: *Pure and Applied Chemistry* **1998**, *70*, 217.

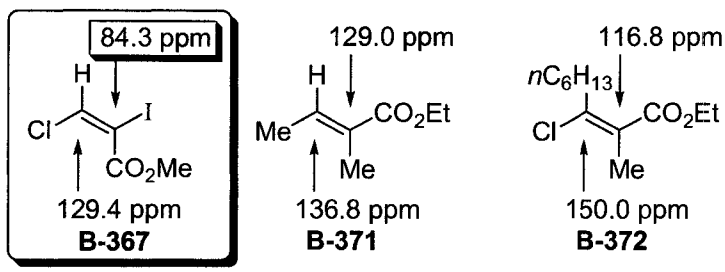
[226] In a control experiment, a solution of the unknown product in CH_2Cl_2 was exposed to UV light (350 nm) for two hours. This generated a mixture of *E*/*Z* isomers that were easily distinguishable by GC.

Scheme 73. Methyl propiolate was converted to an analogous product using Bu_4NI/DCE



The structure of the product was subsequently confirmed as being **B-367**. The regiochemistry of the product of the **B-367** reaction was established by ^{13}C and DEPT NMR[227] analysis. The quaternary α-carbon showed a prominent upfield shift consistent with iodine substitution. An anomalous upfield shift of an iodine-bearing carbon is well documented and is referred to as the heavy atom effect (Figure 5).[228] The methine (CH) carbon of **B-367** displayed a chemical shift of 129.4 ppm, consistent with chlorine substitution at the β-position of an α,β-unsaturated ester. The regiochemistry of all the other products obtained by this Bu_4NI/ DCE method was established by similar chemical shift correlations (see below).[229]

Figure 5. Regiochemistry was determined by ^{13}C NMR chemical shift data

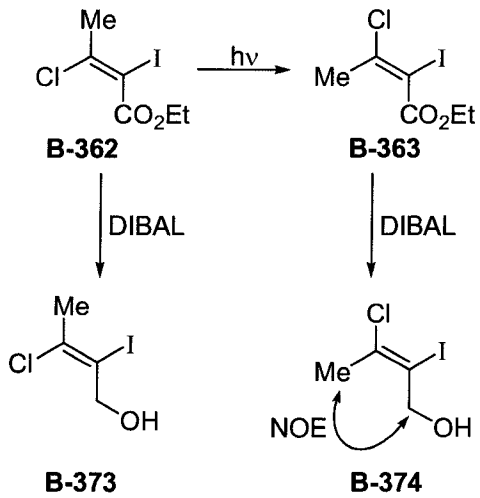


The stereochemistry of the chloroiodinated alkene products was deduced by compound derivatization followed by NOE analysis. In a representative example, *E*-ester

[227] Lemay (Flynn), A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615.
[228] The carbon-13 chemical shifts of carbons bearing heavy atoms such as iodine are frequently shifted upfield by a significant degree. See: Wilson, E. K. *Chem. Eng. News.* **1998**, *76*, 25.
[229] Hua, R.; Onozawa, S.-Y.; Tanaka, M. *Chem. Eur. J.* **2005**, *11*, 3621.

B-362 was briefly photolyzed to generate the corresponding *Z*-isomer **B-363** (Scheme 74).[230] The mixture of esters was immediately reduced with DIBAL to give the corresponding alcohols **B-373** and **B-374** that were separated and analyzed by NMR. A sample of ester **B-362** was directly reduced to **B-373** in a separate experiment to establish the identity of the original isomer.

Scheme 74. NOE network used to established olefin stereochemistry



Consistent with the structural assignments shown, NOE enhancements were observed between the methyl and methylene groups of compound **B-374**, whereas these interactions were lacking in isomer **B-373**. This Bu_4NI/DCE process, in which single isomers were cleanly formed from alkynes using a simple procedure, unquestionably merited investigation.

2.1.3 Optimization of reaction conditions

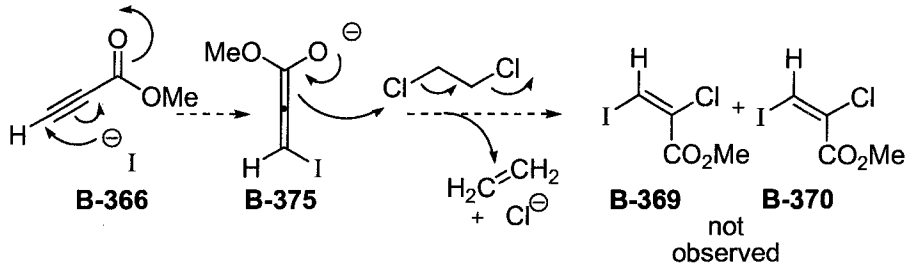
Two plausible mechanisms could be proposed for the combination of tetrabutylammonium iodide with an alkynyl ester such as **B-366** and DCE (Scheme 75). The first involved conjugate addition of iodide to the β-position of the α,β-unsaturated ester **B-366**. The resulting allenoate **B-375** would then react with dichloroethane, thereby generating ethene and producing stereoisomeric α-chloro-β-iodo-α,β-unsaturated esters **B-369** and **B-370**. The second possible mechanism involved initial reaction of the iodide

[230] The product was generated as an inseparable mixture of stereoisomers.

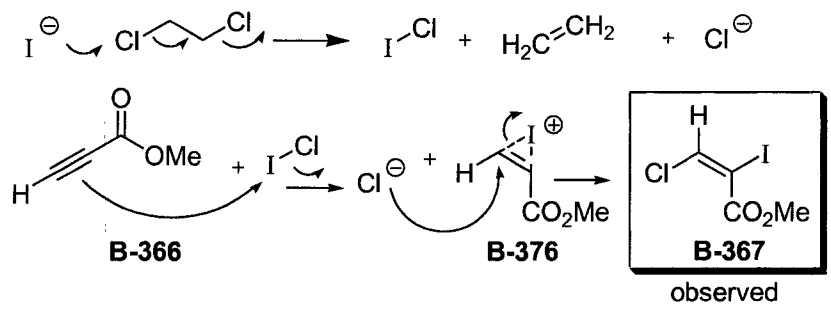
with dichloroethane, which would generate iodine monochloride and ethene. Alkyne **B-366** could then react with the electrophilic iodine to generate cyclic iodonium **B-376**.[231] This intermediate would undergo displacement by the chloride at the more electropositive β-position to generate the *E*-β-chloro-α-iodo-α,β-unsaturated ester **B-367**.

Scheme 75. Plausible mechanisms for the iodochlorination of B-366 with Bu_4NI and DCE

Conjugate addition mechanism:



Electrophilic addition mechanism:

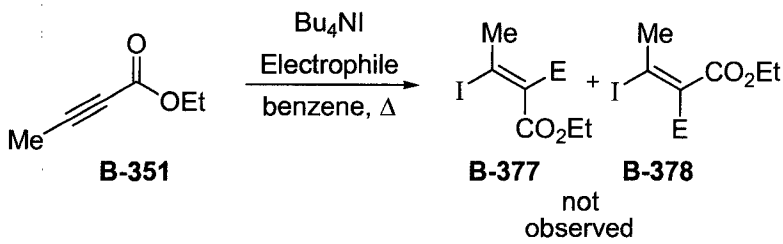


Based on the structure of the product, we felt that a conjugate addition mechanism was highly unlikely, because this would give rise to the opposite regiochemistry to that observed. If the reaction were proceeding through a conjugate addition mechanism, we postulated that the allenoate intermediates would be easily trapped with a variety of electrophiles. Ethyl 2-butynoate (**B-351**) was exposed to Bu_4NI and an electrophile in refluxing benzene (Table 32). Product **B-362** was obtained when DCE was used as the electrophile (entry 1). The regioisomer obtained clearly did not result from a conjugate addition of the iodide. No reaction occurred when benzaldehyde (entry 3), *p*-nitrobenzaldehyde (entry 4), methyl iodide (entry 5), or benzyl bromide (entry 6) was

[231] (a) Bellina, F.; Colzi, F.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2003**, *68*, 10175. (b) Tendil, J.; Verney, M.; Vessiere, R. *Tetrahedron* **1974**, *30*, 579. (c) Voorhees, V.; Skinner, G. S. *J. Am. Chem. Soc.* **1925**, *47*, 1124.

used as the electrophile. If allenoate intermediate **B-375** was in fact forming, we would have expected it to react readily with these strong electrophiles. Because we observed no reaction in the presence of these electrophiles, it seemed less likely that the reaction was proceeding through a conjugate addition mechanism. This conclusion was supported by the regiochemistry of the products that could not have resulted from a conjugate addition process. An electrophilic addition mechanism was far more plausible.

Table 32. Analysis of potential electrophiles for conjugate addition mechanism



Entry	Electrophile	Result
1	**DCE**	**89% B-362**
2	PhCHO	NR
3	*p*-$NO_2C_6H_4CHO$	NR
4	MeI	NR
5	BnBr	NR

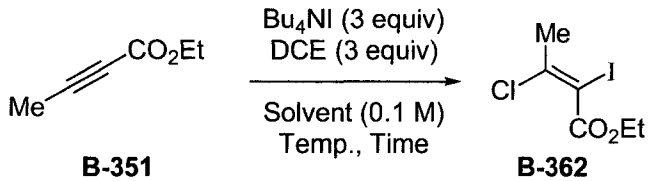
Control reactions were performed to determine the extent to which the reagents were required in the process. Potassium iodide was investigated as a possible iodide source in conjunction with 10 mol% Bu_4NI that could serve as a phase-transfer agent. The reaction, performed in refluxing DCE for 24 hours, gave only a trace of the desired product.

A solvent scan was conducted in which alkyne **B-351** and Bu_4NI were refluxed with three equivalents of DCE in various solvents (Table 33).[232] No obvious correlation was apparent between the solvent polarity and the results of the reactions. Little or no product formation was observed using 1,4-dioxane (entry 1), nitromethane (entry 15), or water (entry 18). A three-day reaction at 60 °C in chloroform produced only a 20% yield (entry 2). Increasing the reaction temperature to 90 °C in a sealed system gave only a moderate increase in yield (entry 3). Ethyl acetate fared no better as a solvent at 90 °C, affording a

[232] Selected experiments were performed by Katarina Vulic, an undergraduate student in the Ogilvie research group.

22% yield (entry 4). A moderate improvement in yield was observed with THF (entry 5) and dichloromethane (entry 7) at 90 °C. This is in contrast to the same reaction in dichloromethane at reflux (40 °C) in which no product formation was observed after three days (entry 6). Increasing the amount of DCE from three to ten equivalents resulted in a noticeable enhancement–an 80% yield was observed for this reaction (entry 8). Only mediocre yields were obtained at high temperature with trifluorotoluene (entry 9), isopropanol (entry 11), acetone (entry 12), ethanol (entry 13), acetonitrile (entry 14), and DMSO (entry 17). The use of DCE at reflux, which provided an enormous excess of the chlorine source, gave the best result (entry 10). DCE was therefore retained as the solvent for future investigations.

Table 33. Solvent scan for the chloroiodination of alkynes with Bu_4NI and DCE



B-351 **B-362**

Entry	Dielectric constant	Solvent (0.1M)	Time	Temp (°C)	Yield (%)
1	2.2	1,4-Dioxane	24 h	90	trace
2	4.8	$CHCl_3$	72 h	60	20
3	4.8	$CHCl_3$	24 h	90	30
4	6.1	EtOAc	24 h	90	22
5	7.5	THF	24 h	90	50
6	8.9	CH_2Cl_2	72 h	40	NR
7	8.9	CH_2Cl_2	24 h	90	50
8[a]	8.9	CH_2Cl_2	24 h	90	80
9	9.2	Trifluorotoluene	24 h	90	10
10	**10.4**	**DCE**	**72 h**	**84**	**91**
11	20.2	*i*PrOH	24h	90	22
12	21.0	Acetone	24 h	90	30
13	25.3	EtOH	24h	90	20
14	36.6	CH_3CN	24 h	90	20
15	37.3	CH_3NO_2	24 h	90	trace
16	38.2	DMF	72 h	90	NR
17	47.2	DMSO	24 h	100	25
18	80.1	H_2O	24h	100	trace

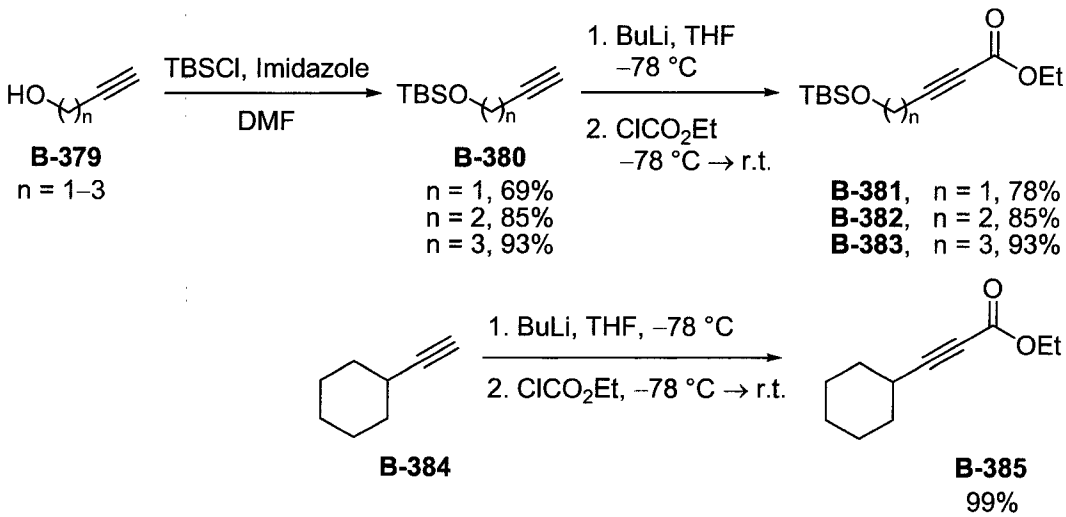
[a] 10 equivalents of DCE were used.

With this remarkable selectivity and generality, we saw great potential for the application of these halogenated substrates as olefin templates for the generation of tetrasubstituted olefins. To be significantly useful, this reaction would have to be general and a series of alkynes were accordingly prepared and evaluated.

2.1.4 Substrate preparation

The required substrates were prepared, typically via the carboxylation of terminal alkynes, or were purchased. Alkynes **B-381, B-382**, and **B-383** were prepared from the corresponding alkynyl alcohols (Scheme 76). Alcohol **B-379** was first protected as silyl ether **B-380**. BuLi was then added via syringe pump to a solution of terminal alkyne **B-380** at −78 °C. After one hour, a solution of ethyl chloroformate in THF was introduced to the reaction mixture and the solution was allowed to warm to room temperature. Ethyl 3-cyclohexylpropiolate (**B-385**) was prepared in a similar fashion in 99% yield.[233]

Scheme 76. Preparation of alkynyl esters

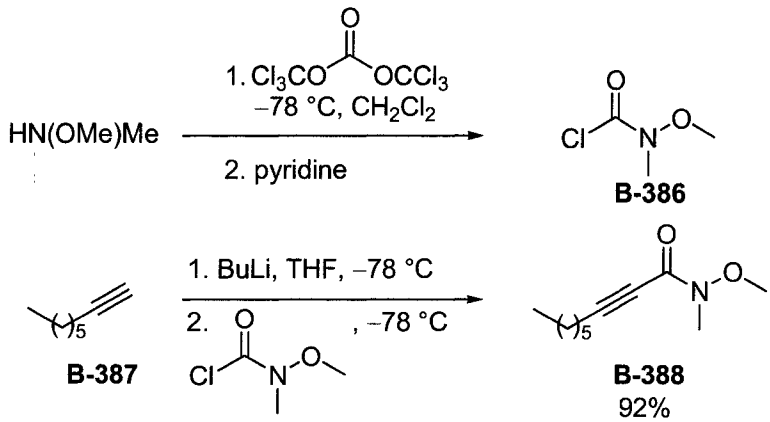


The synthesis of the Weinreb amide (**B-388**) began with the preparation of *N*-methoxy-*N*-methylcarbamoyl chloride (Scheme 77).[234] *N,O*-dimethylhydroxylamine hydrochloride was added in three portions to a solution of triphosgene[235] in CH_2Cl_2 at −78 °C. To this was added a solution of pyridine in CH_2Cl_2 using a syringe pump over 30

[233] For an alternative preparation using the Corey-Fuchs reaction, see: Liu, P.; Jordan, R. W.; Kibbee, S. P.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2006**, *71*, 3793.
[234] Amos B. Smith, I.; Beiger, J. J.; Davulcu, A. H.; Cox, J. M. *Org. Syn.* **2005**, *82*, 147.
[235] This compound is a solid and is frequently employed as a substitute for phosgene gas (ClC(O)Cl).

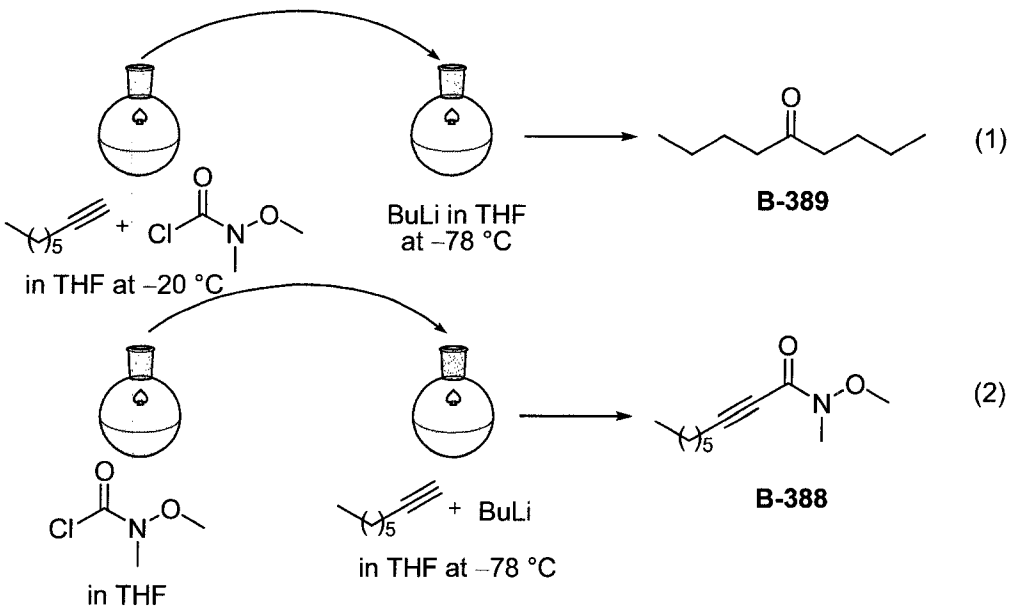
minutes. The alkynyl amide was prepared by a slight modification of the published procedure.[234] To a solution of octyne in THF at −78 °C was added butyllithium over ½ hour. A solution of *N*-methoxy-*N*-methylcarbamoyl chloride in THF was then added and the solution was stirred at −78 °C for four hours.

Scheme 77. Preparation of the Weinreb amide substrate



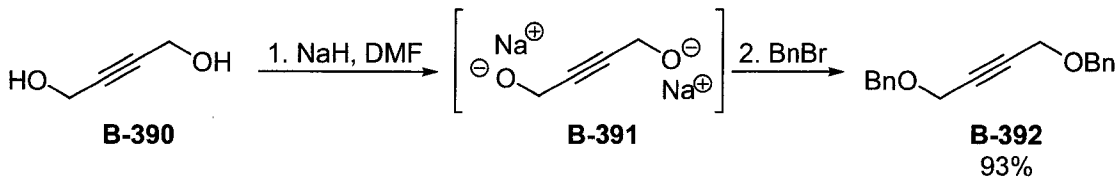
A specific order of addition was essential for the success of the reaction. The published procedure described the addition of the solution of alkyne and acid chloride in THF *to* a solution of BuLi (Figure 6, equation 1). In our hands, these conditions gave only the formation of 5-nonanone (**B-389**). After experimenting with different conditions, we found it necessary to premix the terminal alkyne and butyllithium and add to this mixture a solution of the acid chloride in THF (equation 2).

Figure 6. A specific order of addition was required for the formation of the Weinreb amide



The benzylation of 2-butyn-1,4-diol **B-390** required the deprotonation of the two hydroxy moieties, which resulted in the generation of dianion **B-391** in solution (Scheme 78). Because of this, DMF was required as the solvent, and NaH was used as the base. Subsequent treatment of the dianion intermediate with benzyl bromide gave the desired product **B-392** in 93% yield.

Scheme 78. Benzylation of 2-butyn-1,4-diol



With the required substrates in hand, the generality of the chloroiodination of alkynes in DCE was probed.

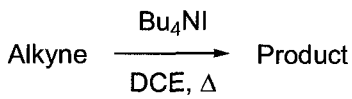
2.1.5 Chloroiodination of alkynes: reaction scope

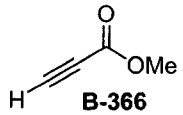
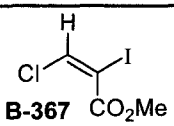
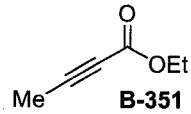
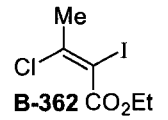
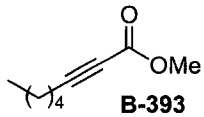
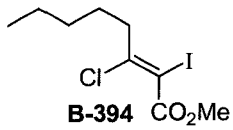
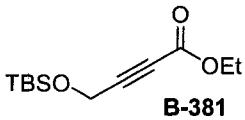
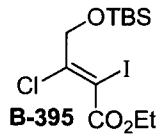
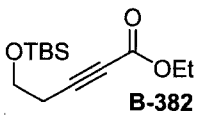
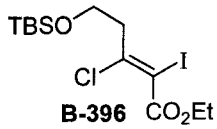
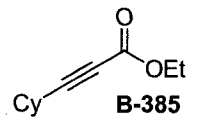
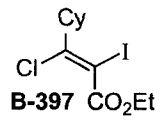
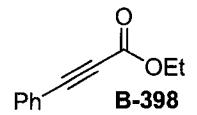
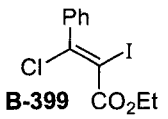
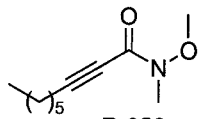
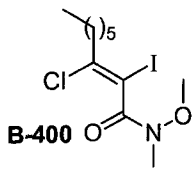
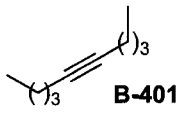
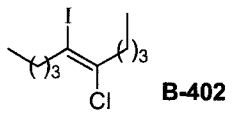
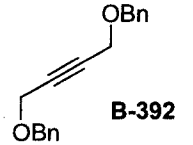
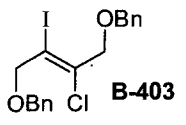
This completely regio- and stereoselective Bu_4NI/DCE reaction tolerated a variety of substituents on the alkyne terminus including a hydrogen (Table 34, entry 1) and simple alkyl groups (entries 2–3). The Bu_4NI/DCE reaction was very successful if the

substituent was a functionalized alkyl chain (entries 4–5) or a branched alkyl group (entry 6). A single isomer was obtained in each case. The Bu_4NI/DCE reaction of an alkyne bearing a phenyl substituent followed the same trend, producing a single isomer (**B-399**) in good yield (entry 7).

The Bu_4NI/DCE reaction could be extended to other carbonyl derivatives such as alkynyl amides (entry 8) with perfect control of selectivity. The exposure of unconjugated alkyne **B-401** to Bu_4NI in DCE gave a single isomer product in excellent yield (entry 9). Functionalized alkyne **B-392** was cleanly converted to *E*-isomer **B-403** by using Bu_4NI in DCE (entry 10). The reliability, selectivity, and effectiveness of the Bu_4NI/DCE reactions were remarkable, and this method enabled the efficient generation of single isomer chloroiodinated alkenes, a class of compounds whose utility has until now been limited by preparative challenges.

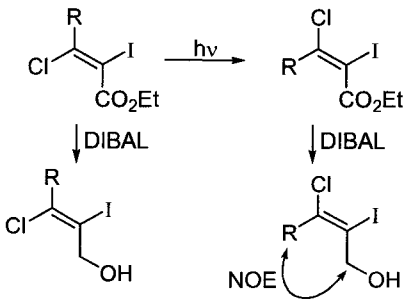
Table 34. Conversion of alkynes to single isomer products with Bu_4NI in DCE

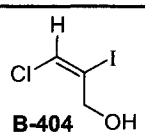
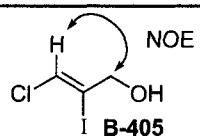
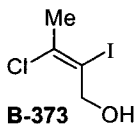
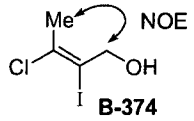
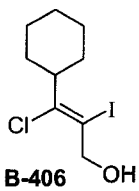
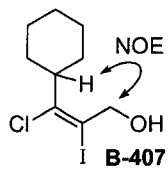
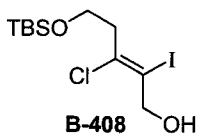
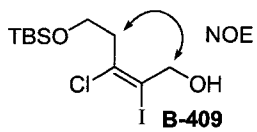


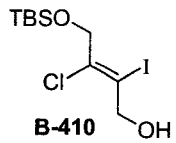
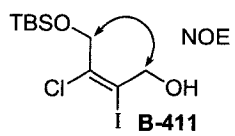
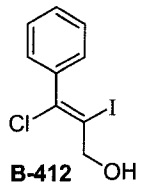
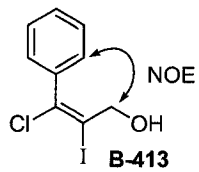
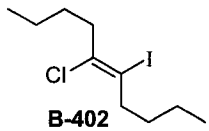
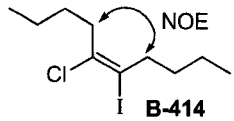
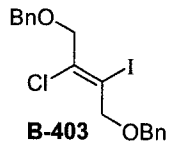
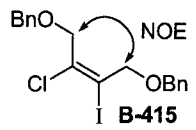
Entry	Alkyne	Product	Isolated yield (%)
1	 **B-366**	 **B-367**	89
2	 **B-351**	 **B-362**	91
3	 **B-393**	 **B-394**	92
4	 **B-381**	 **B-395**	92
5	 **B-382**	 **B-396**	67
6	 **B-385**	 **B-397**	75
7	 **B-398**	 **B-399**	76
8	 **B-388**	 **B-400**	92
9	 **B-401**	 **B-402**	97
10	 **B-392**	 **B-403**	93

The regio- and stereochemistry of the products were determined using the same methods as previously described. The *E*-ester was briefly photolyzed to generate the corresponding *Z*-isomer (Table 35), and then the esters were immediately reduced with DIBAL to give the corresponding alcohols. In all cases, the stereochemistry of the original product was confirmed to be as shown. It was essential to establish the identity of the stereoisomer of each compound as the absence of an NOE enhancement in the original compounds in and of itself did not constitute a proof of stereochemistry.

Table 35. Proof of stereochemistry *via* NOE analysis of alcohols



Entry	(*E*)-Isomer	(*Z*)-Isomer
1	 **B-404**	 **B-405**
2	 **B-373**	 **B-374**
3	 **B-406**	 **B-407**
4	 **B-408**	 **B-409**

5	 **B-410**	 **B-411**
6	 **B-412**	 **B-413**
7[a]	 **B-402**	 **B-414**
8[a]	 **B-403**	 **B-415**

[a] The *Z*-isomer was generated by the treatment of the starting alkyne with ICl.

Having prepared a series of olefin templates from *alkynes* as single isomers, the Bu_4NI/DCE reaction was further investigated using *alkenes* as substrates.

2.1.6 Chlorination of alkenes

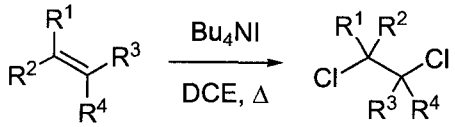
The use of Bu_4NI in refluxing DCE with related alkene substrates such as **B-416** did not give the anticipated iodochlorinated products.[236] Instead, single isomer, *dichlorinated* alkyl products such as **B-417** were obtained (Table 36, entry 1).[237] A control reaction performed by refluxing allyloxybenzene in DCE gave no reaction. This illustrated that the tetrabutylammonium iodide was an essential component of this process. The clean production of dichlorinated products using the Bu_4NI/DCE method was a surprising and useful result.

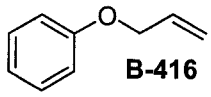
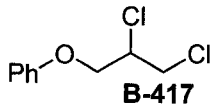
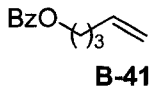
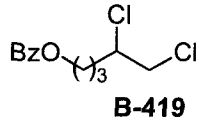
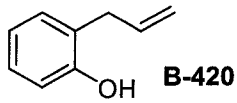
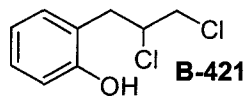
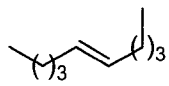
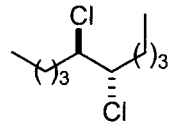
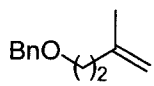
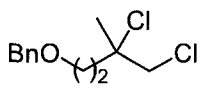
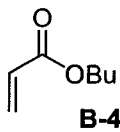
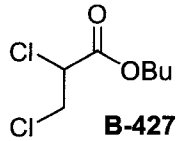
The remarkable selectivity of halogenations of alkenes using Bu_4NI in refluxing DCE was further investigated. An alkene bearing a substituted alkyl chain (**B-418**, entry 2) gave single isomer dichlorinated product **B-419** using Bu_4NI/DCE. An allylic alkene

[236] Ho, M. L.; Flynn, A. B.; Ogilvie, W. W. *J. Org. Chem.* **2007**, *72*, 977.
[237] Selected experiments were performed by Michael Ho, an undergraduate student in our group.

ortho to an unprotected phenol moiety reacted smoothly with Bu_4NI/DCE to give compound **B-421** exclusively and in high yield (entry 3). Internal *trans* alkene **B-422** reacted very well under the Bu_4NI/DCE conditions to give a single isomer **B-423**, confirmed by both ^1H and ^{13}C NMR spectra (entry 4). A 2,2-disubstituted alkene proved to be completely unreactive towards Bu_4NI/DCE (entry 5). An electron-deficient alkene reacted sluggishly under refluxing conditions with Bu_4NI in DCE but nevertheless produced only a single product, **B-427** (entry 6).

Table 36. Alkenes reacted with Bu_4NI/DCE to give dichlorides



Entry	Substrate	Product	Yield[a] (%)
1	 **B-416**	 **B-417**	99
2	 **B-418**	 **B-419**	99
3	 **B-420**	 **B-421**	89
4	 **B-422**	 **B-423**	78
5	 **B-424**	 **B-425**	NR[b]
6	 **B-426**	 **B-427**	20[c]

[a] Isolated yield. [b] NR = no reaction. [c] Reaction time was 4 days.

The dichlorination process observed under Bu_4NI/DCE conditions was unexpected, however the single products that were cleanly obtained in this process would undoubtedly be useful synthetic substrates.

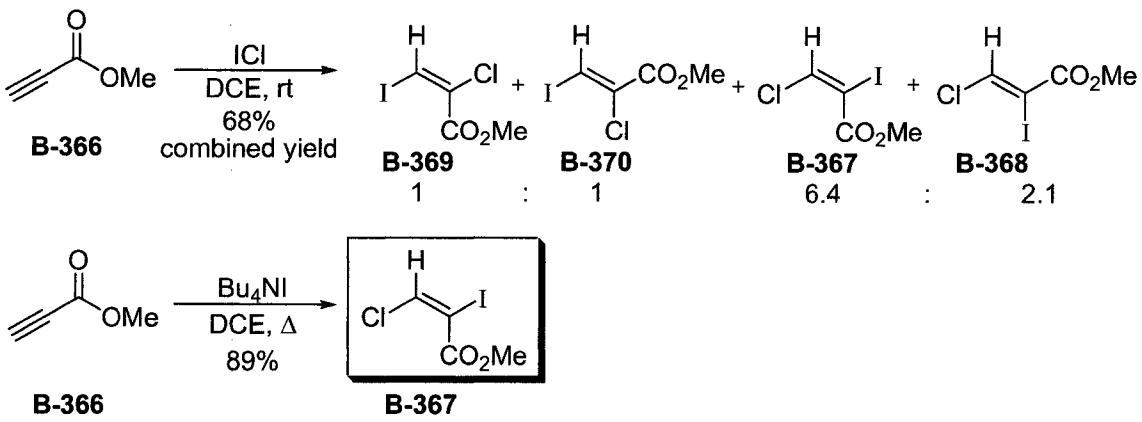
2.1.7 Mechanistic studies

2.1.7.1 Identification of the mechanism for the chloroiodination of alkynes

The exceptional selectivity observed with alkynes and alkenes using the Bu_4NI/DCE system merited further investigation. The source of the remarkable formation of single isomer products was investigated via a series of control reactions.

As preliminary experiments had shown, it was far more plausible that the products obtained from the Bu_4NI/DCE process occurred via an electrophilic addition mechanism. This hypothesis was confirmed by means of parallel experiments performed using ICl.[236] Exposure of **B-366** to ICl in DCE gave a mixture of alkenes **B-369**, **B-370**, **B-367**, and **B-368** (Scheme 79).[238] This reaction using ICl was completely non-selective as the products were formed as a mixture of regioisomers as well as mixtures of *E* and *Z* isomers **B-369**, **B-370**, **B-367**, and **B-368**. In contrast, exposure of alkyne **B-366** to Bu_4NI in refluxing DCE gave *E*-alkene **B-367** as the only product.

Scheme 79. Comparison of methyl propiolate reaction with ICl and Bu_4NI/DCE

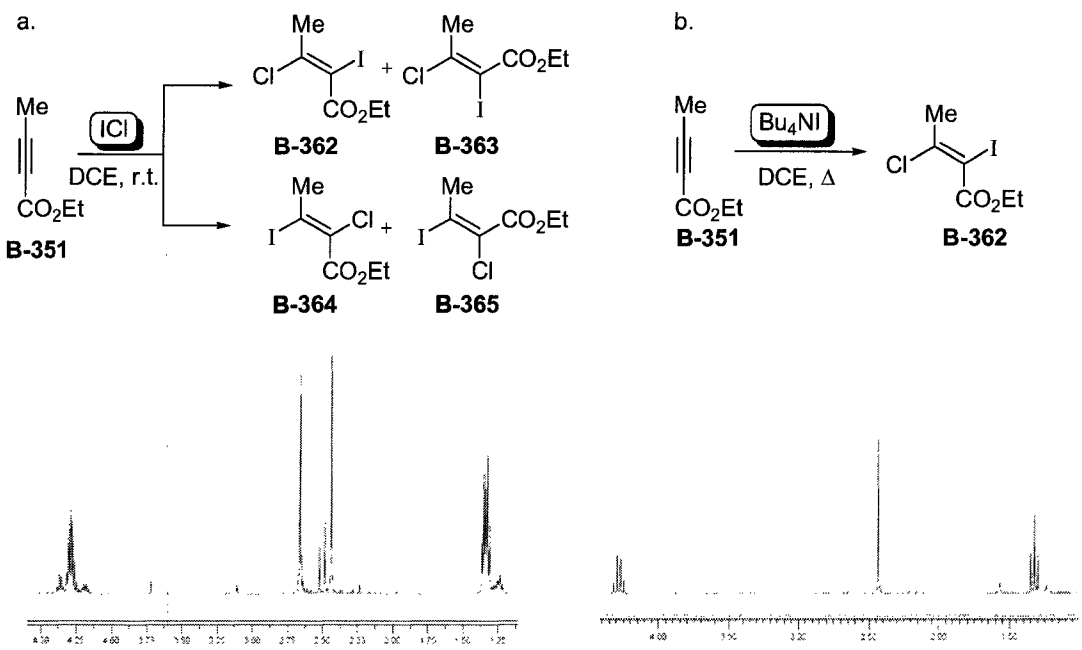


A dramatic demonstration of the selectivity of the Bu_4NI process is shown in Figure 7. Exposure of alkyne **B-351** to ICl gave a mixture of at least four products as shown by the complex ^1H NMR spectrum of the crude reaction isolate (Figure 7a). Conversely, the reaction of alkyne **B-351** with Bu_4NI in DCE was remarkably clean, as exemplified by

[238] Four peaks with a mass consistent with the compounds shown were observed by GC-MS. Diiodinated products were also detected by mass spectroscopy (EI).

the ^{1}H NMR spectrum of the crude reaction product from Bu_4NI (Figure 7b) which showed the presence of compound **B-362** only.

Figure 7. Comparison of the NMR spectra of the crude products obtained from the reaction of B-351 with ICl (1a) and with Bu_4NI/DCE (1b)

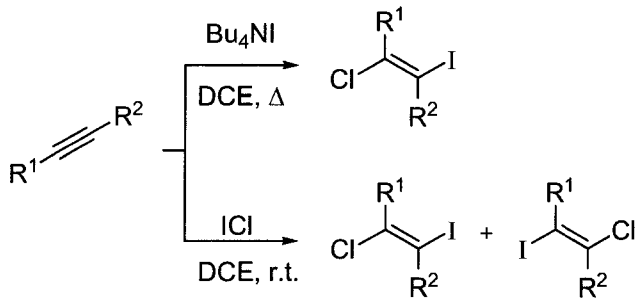


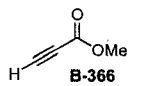
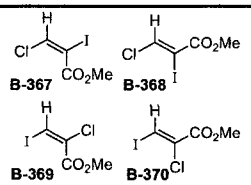
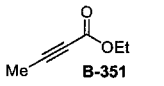
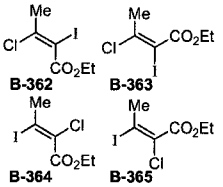
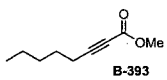
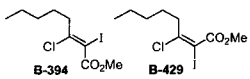
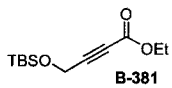
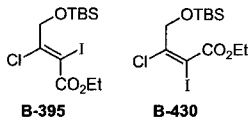
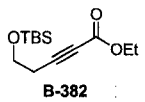
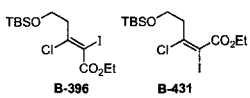
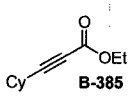
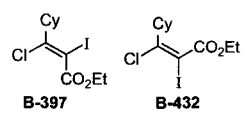
This trend was observed for all of the subsequent substrates investigated (Table 37). The Bu_4NI/DCE always gave single isomer products in good yields. Conversely, the ICl method consistently gave mixtures of isomers. The spectral data of the *Z*-stereoisomers isomers (i.e. **B-365**) generated through use of ICl were consistent with those generated upon exposure of the corresponding *E*-isomer (i.e. **B-364**) to ultraviolet light. Treatment of **B-366** with ICl in DCE gave a mixture of alkenes **B-369**, **B-370**, **B-367**, and **B-368**.[239] In contrast, exposure of alkyne **B-366** to Bu_4NI in refluxing DCE gave *E*-alkene **B-367** as the only product. Subsequent control reactions employing ICl directly gave mixtures in almost every case. Inseparable mixtures were obtained upon exposure of the alkyl and substituted alkyl substrates to ICl (entries 2–6). The ICl reaction of an alkyne bearing a phenyl substituent (entry 7) afforded an inseparable mixture of products. The ICl reaction could be extended to other carbonyl derivatives, such as alkynyl amides (entry 8). Exposure of unconjugated alkyne **B-401** to ICl gave a single isomer in this case in which

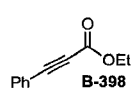
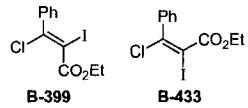
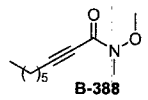
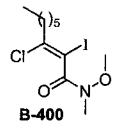
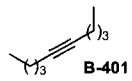
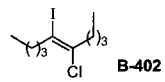
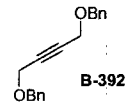
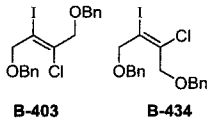
[239] Diiodinated products were also observed by mass spectroscopy.

symmetry in the substrate most likely controlled the outcome of the process (entry 9). Functionalized alkyne **B-392** was cleanly converted to *E*-isomer **B-403** using Bu_4NI in DCE, whereas this same compound gave a mixture of *E* and *Z* products, **B-403** and **B-434**, when ICl was used (entry 10).

Table 37. Conversion of alkynes to single isomer products with Bu_4NI in DCE and comparison to analogous reaction with ICl alone



Entry	Substrate	Products	Bu_4NI/DCE Product	Bu_4NI/DCE Yield[a] (%)	ICl Products (Ratio)	ICl Yield[b] (%)
1	 B-366	 B-367 B-368 B-369 B-370	**B-367**	89	**B-369, B-370, B-367, B-368**[c] (6:2:1:1)	68
2	 B-351	 B-362 B-363 B-364 B-365	**B-352**	91	**B-369, B-370, B-362, B-363**[c] (5:6:1.5:1)	90
3	 B-393	 B-394 B-429	**B-394**	92	**ND**[d]	
4	 B-381	 B-395 B-430	**B-395**	92	**B-395, B-430**[c] (2:1)	67
5	 B-382	 B-396 B-431	**B-396**	67	**B-396, B-431**[c] **(1:1)**	66
6	 B-385	 B-397 B-432	**B-397**	75	**B-397, B-432**[c] (1:1)	99

7	 B-398	 B-399 B-433	**B-399**	76	**B-399, B-433**[c] (3:1)	93
8	 B-388	 B-400	**B-400**	92	**B-400**	99
9	 B-401	 B-402	**B-402**	97	**B-402**	92
10	 B-392	 B-403 B-434	**B-403**	93	**B-403, B-434** (1:1)	99

[a] Isolated yield. [b] Combined isolated yield. [c] Mass spectrum showed traces of diiodinated compounds. [d] ND = Not determined.

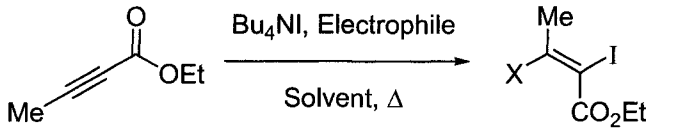
As noted above, the regioselectivity in the ICl reaction with alkynyl substrates such as **B-351**, which produced products such as **B-362**, was consistent with the regioselectivity observed in the Bu_4NI/DCE process. This supported the presumption of an ICl intermediate in the latter method. As this intermediate must be formed by the reaction between Bu_4NI and DCE, it was reasonable to assume that similar reactivity could be realized with other electropositive halide sources.

The treatment of alkyne **B-351** with Bu_4NI and *N*-chlorosuccinimide (NCS) in refluxing benzene successfully gave product **B-362** as a single isomer in 90% yield (Table 38, entry 1). This reaction could be performed in a variety of solvents such as DCE (entry 2), DCM (entry 3), ethanol (entry 4), and *iso*-propanol (entry 5). DCE proved to be the superior solvent for the transformation and using this solvent, NCS could be utilized with substrates bearing longer alkyl chains (entry 6) and substituted alkyl chains (entry 7) to give single isomer products in good yields.

Bromine could be incorporated into the olefin template using *N*-bromosuccinimide in refluxing trifluorotoluene, giving a 68% yield of the product as a mixture of isomers (entry 8). Dibromoethane proved to be a more effective source of Br^+ as the treatment of alkyne **B-351** with Bu_4NI and dibromoethane (DBE) in refluxing benzene gave product **B-435** in 85% yield as a mixture of isomers (entry 9). Moderate yields were observed when the reaction was performed in EtOH (entry 10) or *iso*-propanol (entry 11). The use

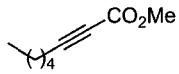
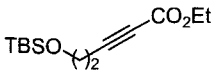
of bromine directly generated a mixture of isomers (entry 12), while the use of bromine in the presence of imidazole gave no reaction (entry 13). These results supported the supposition that IX (X = Cl or Br) was being formed slowly *in situ* by the reaction between Bu_4NI and electrophilic halide sources such as DCE, NCS, or DBE.

Table 38. Exposure of ethyl 2-butynoate to electrophilic sources of chlorine and bromine sources



B-351

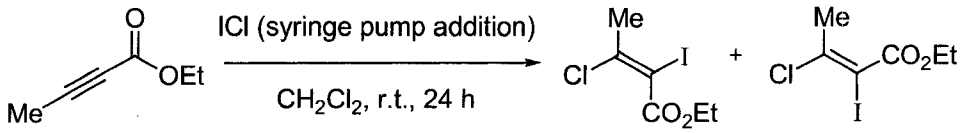
B-362: X = Cl
B-435 : X = Br

Entry	Substrate	Electrophile	Solvent	Yield (%)
1	**B-351**	NCS	C_6H_6	90
2	**B-351**	**NCS**	**DCE**	**91**
3	**B-351**	NCS	CH_2Cl_2	51
4	**B-351**	NCS	EtOH	47
5	**B-351**	NCS	^{i}PrOH	40
6		NCS	DCE	81
7		NCS	DCE	61
8	**B-351**	NBS	trifluorotoluene	68[a]
9	**B-351**	DBE	C_6H_6	85[a]
10	**B-351**	DBE	EtOH	60[a]
11	**B-351**	DBE	^{i}PrOH	64[a]
12	**B-351**	Br_2	CH_2Cl_2	95[a]
13	**B-351**	Br_2/Imidazole	CH_2Cl_2	NR

[a] Obtained as an equimolar mixture of isomers.

This *in situ* generation of IX could not by itself explain the remarkable selectivity observed in every case when using Bu_4NI in DCE. If the effect was due to the slow generation of ICl, then presumably the selectivity of the Bu_4NI/DCE system was simply the result of a low concentration of ICl. This was examined by adding ICl *via* syringe-pump to a solution of alkyne **B-351** in CH_2Cl_2 over twenty-four hours (Scheme 80). The reaction resulted in full conversion to products **B-362** and **B-363** but virtually no selectivity was observed, thus ruling out a possible concentration effect.

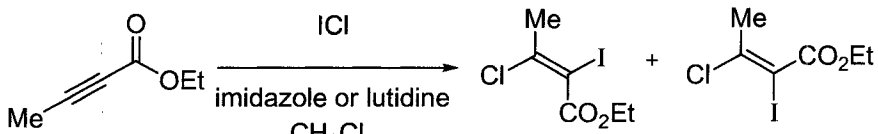
Scheme 80. Syringe pump addition of ICl gave a mixture of isomers



B-351 **B-362** **B-363**

Another possible explanation for the Bu_4NI selectivity could be a buffering effect. The ICl reactions may have given poor selectivity because of an acid-catalyzed isomerization of the alkenes. To test this hypothesis, compound **B-351** was exposed, in separate reactions, to ICl in the presence of an excess of the bases imidazole and lutidine. Despite this precaution, these reactions gave mixtures of isomeric products **B-362** and **B-363** as before.

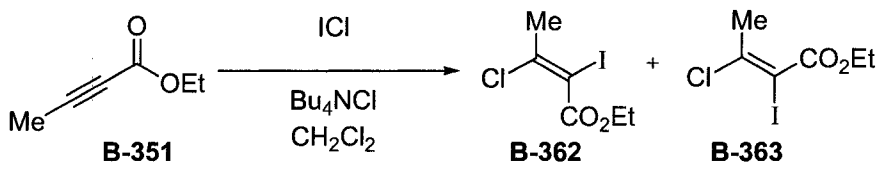
Scheme 81. The use of a base gives a mixture of isomers



B-351 **B-362** **B-363**

If the Bu_4NI was reacting with the DCE to generate ICl, it was possible that the Bu_4NCl generated as a byproduct was somehow modulating the reactivity of the ICl. To test this hypothesis, alkyne **B-351** was treated with ICl in the presence of excess Bu_4NCl (Scheme 82). Once again the outcome of the reaction was indistinguishable from results obtained using ICl alone.

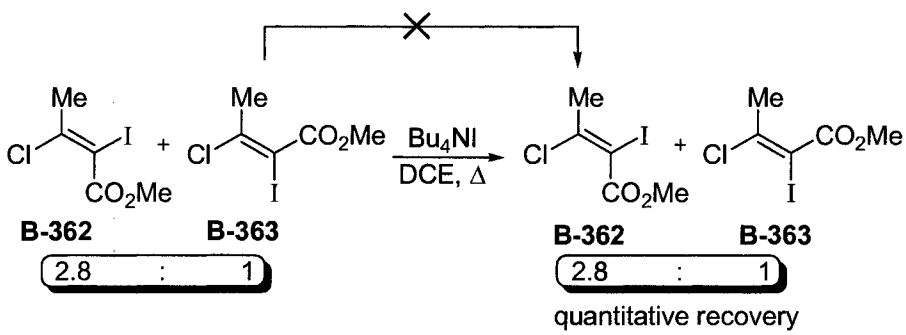
Scheme 82. The introduction of Bu_4NCl did not improve the selectivity of the ICl process



B-351 B-362 B-363

It was possible that the *Z*-alkene (**B-363**) was the kinetic product of the reaction and that the *E*-alkene (**B-362**) was the thermodynamic product of the reaction. This could explain the fact that a mixture of *E*/*Z* isomers were obtained at room temperature with ICl and a single product, perhaps the most stable product, was obtained at reflux with Bu_4NI. If this were the case, one would expect the *Z*-isomer to convert into the *E*-isomer over time.[240] Subjecting an *E*/*Z* (2.8:1) mixture of compounds **B-362** and **B-363** to Bu_4NI in DCE at reflux for 18 hours returned the original mixture quantitatively (Scheme 83).[241] This illustrated that this particular explanation could not describe the observed reactivity differences between the two methods.

Scheme 83. The *Z*-isomer did not convert to the *E*-isomer in Bu_4NI/DCE at reflux



B-362 B-363 2.8 : 1

B-362 B-363 2.8 : 1 quantitative recovery

Nevertheless, given the high stereo- and regioselectivity of the Bu_4NI/DCE process for the halogenation of alkynes, the possibility of a regioselective Bu_4NI reaction with aromatic rings was investigated. It was anticipated that an analysis of the reactivity with aromatic substrates would provide additional mechanistic insight.

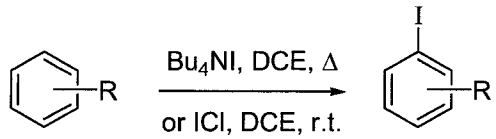
[240] Eighteen hours was the typical reaction time required for complete conversion of substrates using the Bu_4NI/DCE process.

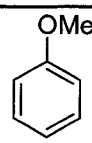
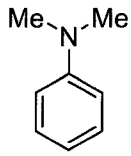
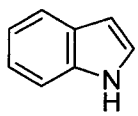
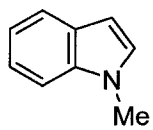
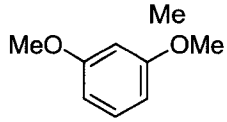
[241] A mixture of isomers was employed because the stereoisomers were inseparable.

2.1.7.2 Halogenation of aromatic rings

While the Bu_4NI/DCE system was highly selective for the iodochlorination of *alkynes* with a wide variety of substitution patterns and for the chlorination of monosubstituted *alkenes*, *aromatic rings* proved to be completely unreactive. Anisole did not react upon exposure to Bu_4NI in DCE even after several days at reflux (Table 39, entry 1). However, anisole reacted readily upon exposure to ICl at room temperature, giving a mixture of multiple addition products. *N,N*-dimethylaniline was completely unreactive upon exposure to Bu_4NI in refluxing DCE, but rapidly gave a mixture of multiple addition products in the related ICl reaction (entry 2). Indole and *N*-methylindole were similarly unreactive with the Bu_4NI/DCE system (entries 3 and 4). Even the electron-rich 1,3-dimethoxybenzene was unreactive in the presence of Bu_4NI/DCE although this substrate readily gave a mixture of products in the presence of ICl alone (entry 5).

Table 39. Comparison of reactivity of aromatic rings with Bu_4NI/DCE and ICl

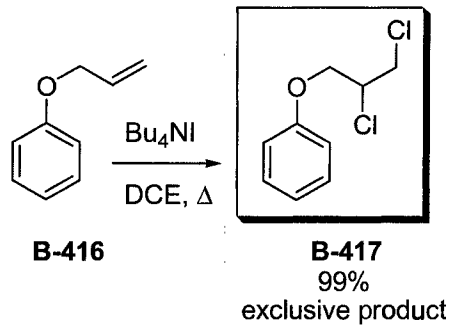


Entry	Substrate	Bu_4NI Result	ICl Result
1		NR	Multiple iodine addition products
2		NR	Multiple iodine addition products
3		NR	Multiple iodine addition products
4		NR	Multiple iodine addition products
5		NR	Multiple iodine addition products

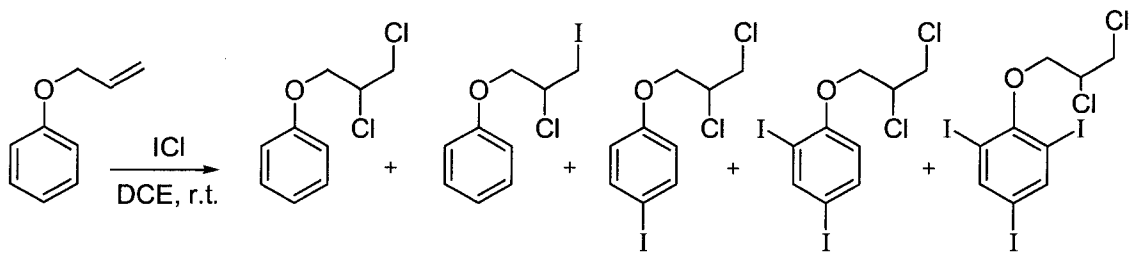
The reactivity of the Bu_4NI/DCE system allowed for selective reaction at alkenyl or alkynyl functional groups in the presence of electron-rich aromatic systems, while leaving the aromatic moieties untouched. This was demonstrated in the reaction of allyloxybenzene **B-416** with Bu_4NI/DCE, which was cleanly converted to dichloride **B-417**, leaving the aromatic group undisturbed (Scheme 85). This is in contrast to the treatment of the same substrate (**B-416**) with ICl which gave inseparable mixtures of products bearing mono-, di-, and trisubstitution of the aromatic ring even if only a slight excess of ICl was employed (Scheme 84). Many conditions have been developed for the halogenation of aromatic compounds,[242] but the current Bu_4NI method is remarkable for the chemoselectivity demonstrated towards the electrophilic addition to alkenes and alkynes rather than electrophilic aromatic substitution. As anticipated, the analysis of the reactivity of the Bu_4NI/DCE system with aromatic substrates provided mechanistic insight—a new mechanistic hypothesis was formed, one that invoked a Bu_4NI–ICl complex.

[242] (a) Mohan, K. K. V. V.; Narender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45*, 8015. (b) Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 6051. (c) Baird, W. C.; Surridge, J. H. *J. Org. Chem.* **1970**, *35*, 3436. (d) Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synlett* **1980**, 486. (e) Garden, S. J.; Torres, J. C.; de Souza Melo, S. C.; Lima, A. S.; Pinto, A. C.; Lima, E. L. S. *Tetrahedron Lett.* **2001**, *42*, 2089. (f) Kosynkin, D. V.; Tour, J. M. *Org. Lett.* **2001**, *3*, 991. (g) Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc. Perkin 1* **1976**, 1161.

Scheme 84. The Bu_4NI/DCE system enabled a chemoselective reaction at the olefin



B-416 **B-417** 99% exclusive product



B-416 **B-417** **B-436** **B-437** **B-438** **B-439**

2.1.7.3 Source of selectivity: a Bu_4NI–ICl complex

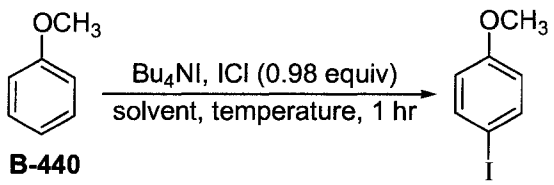
Two significant observations led us to suspect that a Bu_4NI–ICl complex was forming and that this complex was responsible for the remarkable selectivity achieved with the Bu_4NI/DCE system. The first was the low reactivity of the Bu_4NI/DCE system towards electrophilic aromatic substitution when all other experimental results clearly showed that ICl was implicated in the transformations. ICl alone was highly reactive towards electrophilic aromatic substitution with electron-rich substrates such as anisole.

Why was iodine addition to the aromatic rings not observed in the Bu_4NI/DCE system? If ICl was being slowly generated, an attenuating factor must have been operative. This would account for the decreased reactivity when Bu_4NI was used and could be explained if a Bu_4NI–ICl complex had formed. The second observation was the fact that the slow introduction of ICl into a solution of alkene **B-416** did not result in a selective reaction.

Control reactions were performed using anisole to investigate the possibility of complexation. Exposure of anisole (**B-440**) to 0.98 equivalents of ICl in DCE gave *p*-iodoanisole **B-441** in 90% yield after one hour at room temperature (Table 40, entry 1).

Adding small amounts of Bu_4NI to the mixture suppressed the reactivity of ICl resulting in yield decreases that were dependant on the amount of Bu_4NI present. The addition of 0.25 equivalents of Bu_4NI gave a drop in yield from 90% to 56% (entry 2). The yield of **B-441** was reduced to 14% when 0.5 equivalents of Bu_4NI was present (entry 3) and the reaction was effectively suppressed when one or more equivalents of Bu_4NI were introduced (entry 4–5). Increasing the temperature of the reaction did not restore the reactivity of ICl when Bu_4NI was present, regardless of the solvent used (entries 6–7). These results suggested that complexation between ICl and Bu_4NI was responsible for the reactivity control observed when Bu_4NI was used in DCE.

Table 40. Decreased reactivity was observed upon introduction of Bu_4NI to reactions of ICl with anisole



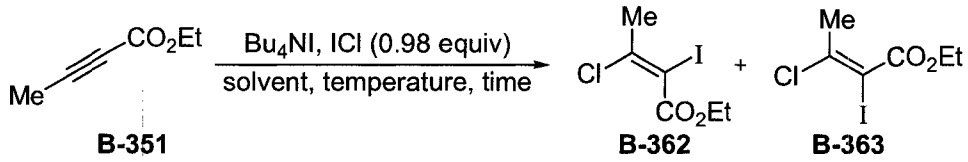
B-440 **B-441**

Entry	Equiv Bu_4NI	Solvent	Temperature (°C)	Yield (%)
1	0	DCE	22	90
2	0.25	DCE	22	56
3	0.5	DCE	22	14
4	1.05	DCE	22	3
5	3.0	DCE	22	trace
6	3.0	DCE	83	trace
7	3.0	benzene	80	trace

Control reactions performed with alkyne **B-351** further confirmed that a complex was involved in the stereocontrol of the reaction. Adding increasing amounts of Bu_4NI to a reaction mixture at room temperature containing alkyne **B-351** and ICl suppressed the reactivity of ICl (Table 41). A 91% combined yield of isomers **B-362** and **B-363** was obtained in the absence of Bu_4NI (entry 1). Decreases in yield were observed upon introduction of Bu_4NI and these yields were strongly dependent on the amount of Bu_4NI present. Interestingly, a sharp increase in the ratio of **B-362**:**B-363** was observed upon addition of 0.25 equivalents of Bu_4NI (entry 2). The reaction was completely suppressed when alkyne **B-351** was treated with 3.0 equivalents of Bu_4NI at room temperature in

DCE in the presence of ICl (entry 5). In contrast to the reaction with anisole, the reactivity returned when the reaction was heated to reflux, giving a 30% yield of single isomer product **B-362** (entry 6). A reaction in benzene gave only 2% of the product (entry 7). These results indicated that the Bu_4NI exerted strong stereocontrol over the reaction, presumably through complexation with the ICl present. The analogous reactions of ICl with alkenes were next studied to probe the existence of a Bu_4NI–ICl complex in that process.

Table 41. Decreased reactivity and improvement in selectivity were observed upon introduction of Bu_4NI to reactions of ICl with alkyne B-351.



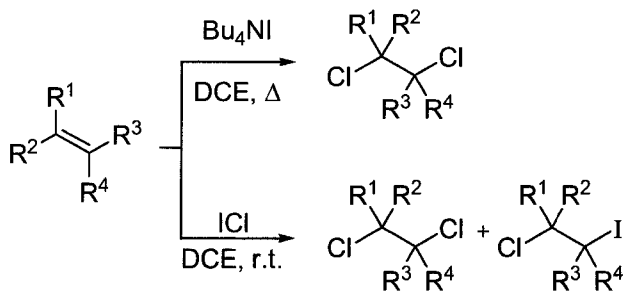
B-351 **B-362** **B-363**

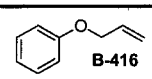
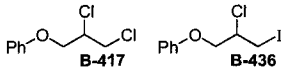
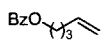
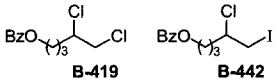
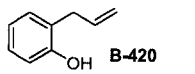
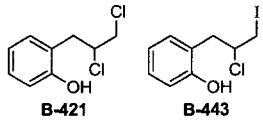
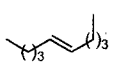
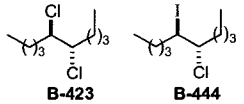
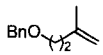
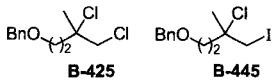
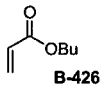
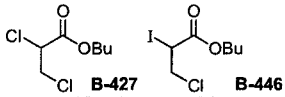
Entry	Equiv Bu_4NI	Temp	Time	Solvent	Yield (%)	B-362:B-363
1	0	r.t.	2 h	DCE	91	5:6
2	0.25	r.t.	2 h	DCE	23	19:1
3	0.50	r.t.	2 h	DCE	6	19:1
4	1.05	r.t.	2 h	DCE	trace	-
5	3.00	r.t.	2 h	DCE	NR	-
6	3.00	reflux	18 h	DCE	30	**B-362** exclusively
7	3.00	reflux	18 h	benzene	2	**B-362** exclusively

The Bu_4NI/DCE process with alkenes had given dichlorides as the exclusive products. To determine whether this was common to the treatment of alkenes with ICl, each alkene that was examined under the Bu_4NI/DCE conditions was also tested with ICl. This time, mixtures of dichlorides and chloro*iodinated* alkyl products were observed (Table 42). Allyloxybenzene (**B-416**) had given a single-isomer dichlorinated product using Bu_4NI/DCE, however the same substrate afforded a mixture of products when exposed to ICl (entry 1). An alkene bearing a substituted alkyl chain (**B-418**, entry 2) gave single-isomer dichlorinated product **B-419** using Bu_4NI/DCE. In contrast, treatment of the same alkene with ICl gave an inseparable mixture of dichlorinated and iodochlorinated products (**B-419** and **B-442**). The reaction of an alkene tethered to an unprotected phenol (entry 3) gave a mixture of products (**B-421**, **B-443**) when exposed to ICl. Internal *trans*

alkene **B-422** reacted very quickly under the ICl conditions to give the iodochlorinated compound **B-444** (entry 4). A 2,2-disubstituted alkene reacted slowly with ICl under forcing conditions to give a mixture of products **B-425** and **B-445** (entry 5). An electron-deficient alkene (entry 6) reacted sluggishly under refluxing conditions with Bu_4NI in DCE but nevertheless produced a single product **B-427**. Treatment of the same Michael acceptor with ICl produced a mixture of products **B-427** and **B-446** in moderate yield. There was a stark contrast between the Bu_4NI/DCE process, in which single isomers were obtained, and the ICl process that consistently gave mixtures.

Table 42. Comparison of alkene reactivity with Bu_4NI/DCE and ICl

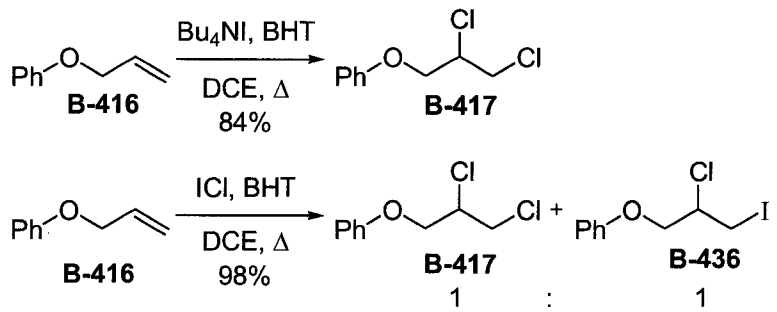


Entry	Substrate	Products	Bu_4NI/DCE		ICl[a]	
			Product	Yield[b] (%)	Product(s) (Ratio)	Yield[c] (%)
1	 B-416	 B-417 B-436	**B-417**	99	**B-417, B-436** (1:1)	99
2	 B-418	 B-419 B-442	**B-419**	99	**B-419, B-442** (1:1)	92
3	 B-420	 B-421 B-443	**B-421**	89	**B-421, B-443** (1:1)	99
4	 B-422	 B-423 B-444	**B-423**	78	**B-423**	66
5	 B-424	 B-425 B-445	-	NR[d]	**B-425, B-445** (1:1)	14[e]
6	 B-426	 B-427 B-446	**B-427**	20[f]	**B-427, B-446** (5.3:1)	61

[a] All reactions performed with 0.98 equiv of ICl. [b] Isolated yield. [c] Combined isolated yield. [d] NR = no reaction. [e] Reaction performed in DCE at reflux. [f] Reaction time was 4 days.

These significant improvements in selectivity obtained with the use of the Bu_4NI/DCE system merited an explanation. Disproportionation and radical mechanisms are the typical means by which the chlorination of alkenes is thought to occur in the presence of ICl.[246] In the case of Bu_4NI/DCE, the radical mechanism was ruled out by adding the radical inhibitor 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) to a reaction of alkene **B-416** and Bu_4NI in DCE (Scheme 85).[243] The results of this reaction were comparable to those obtained without BHT as dichloride **B-417** was obtained in 84% yield. Similarly, the use of BHT had no effect on the reaction of alkene **B-416** with ICl, as a mixture of products **B-417** and **B-436** was obtained when this radical inhibitor was used. As this radical scavenger did not inhibit the reactions, the process was most likely proceeding *via* the disproportionation of complexed ICl rather than by the intermediacy of free radicals.

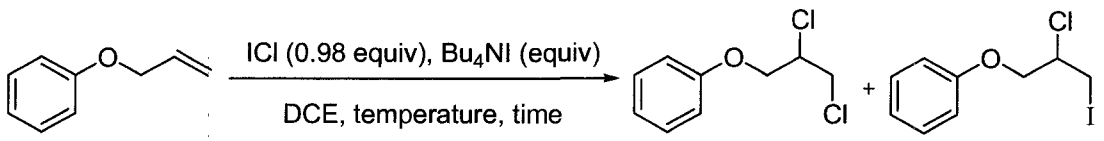
Scheme 85. The radical inhibitor BHT had no effect on the chloroiodination of alkenes



A series of reactions were performed to investigate the feasibility of the disproportionation of ICl as the operative mechanism. ICl was added to reaction mixtures of alkene **B-416** containing increasing amounts of Bu_4NI (Table 43). The yield of the room temperature reactions dropped significantly with each increase in Bu_4NI (entries 1–4). Using three equivalents of Bu_4NI and one equivalent of ICl in DCE at room temperature gave only traces of products **B-417** and **B-436** (entry 4).

[243] BHT (20 mol%) was added to a mixture of alkene **B-416** (1 equiv) and Bu_4NI (3 equiv) in DCE. The solution was heated at reflux until consumption of starting material was complete as indicated by TLC.

Table 43. Reduced reactivity and improvement in selectivity were observed upon introduction of Bu_4NI to reactions of ICl with alkene B-416



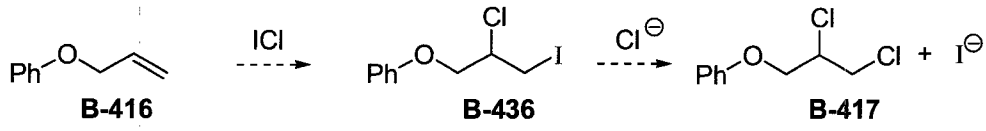
B-416 B-417 B-436

Entry	Equiv Bu_4NI	Temperature	Time	Solvent	Yield (%)	B-417:B-B-436
1	0	r.t.	5 h	DCE	99	1:1
2	0.25	r.t.	5 h	DCE	62	1:1
3	0.50	r.t.	5 h	DCE	11	1.2:1
4	1.05	r.t.	5 h	DCE	6	1:1
5	3.00	r.t.	5 h	DCE	trace	1:1
6	3.00	reflux	18 h	DCE	32	**B-417** exclusively
7	3.00	reflux	18 h	benzene	9	**B-417** exclusively

In all cases examined at *room temperature*, even when Bu_4NI was employed, mixtures of isomers were observed (entries 1–4). The same reagents, using three equivalents of Bu_4NI relative to starting alkene (1 equiv), gave dichlorinated compound **B-417** as the exclusive product when the reactions were heated to *reflux* in DCE (entry 6) or in benzene (entry 7). This surprising observation lead us to question whether the chloroiodinated product **B-436** was simply being converted to product **B-417** under the reaction conditions via S_N2 attack (Scheme 86, equation a), or whether a disproportionation reaction was occurring (Scheme 86, equation b). If a disproportionation reaction were indeed taking place, then in order for chloroiodinated compound **B-436** to be converted into dichloride **B-417**, compound **B-436** might first be converted back to alkene **B-416**. If this were, in fact taking place, exposure of compound **B-436** to the reaction conditions should result in the observation of alkene intermediate **B-416** and eventually an increase in the amount of product **B-417**.

Scheme 86. Two possible pathways for the generation of dichlorinated compound B-417

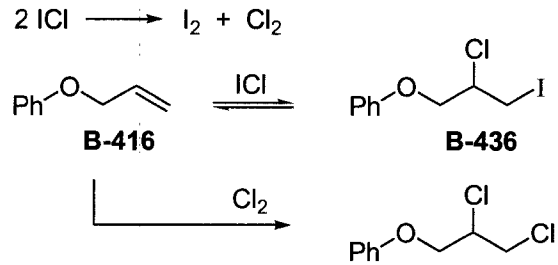
(a) Diplacement of iodide with chloride



B-416 **B-436** **B-417**

VERSUS

(b) Disproportionation of ICl generates Cl_2 that directly chlorinates the alkene

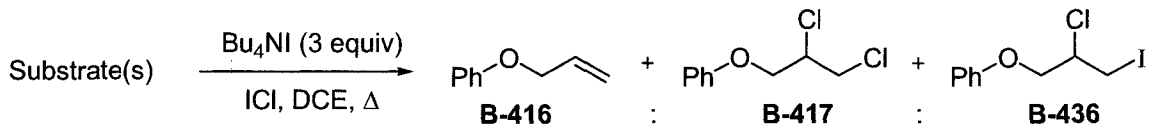


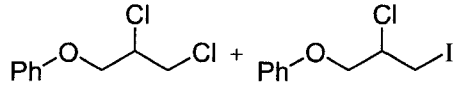
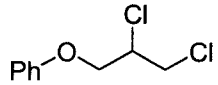
B-416 **B-436** **B-417**

Exposure of an equimolar mixture of dichlorinated ether **B-417** and chloroiodinated ether **B-436** to Bu_4NI in refluxing dichloroethane gave essentially quantitative recovery of dichlorinated ether **B-417** (Table 44, entry 1). No chloroiodinated compound **B-436** was recovered; however, alkene **B-416** was now present in the mixture. This supported our hypothesis that the chloroiodinated compound **B-436** underwent an elimination to give alkene **B-416** which was then chlorinated (Scheme 86).[244] The formation of dichloride **B-417** was consistent with a disproportionation mechanism. Support for this was obtained by refluxing dichlorinated ether **33** with Bu_4NI in DCE (entry 2). After three days at reflux, dichloride **B-417** was recovered in quantitative yield and no side products were observed, showing that **B-417** was stable under the reaction conditions. These experiments did not conclusively prove, however, that an S_N2 reaction was not occurring with **B-436** to give **B-417** directly.

[244] The chloroiodinated alkane was generated by the halogenation of alkene **B-416** using ICl. This product could not be separated from the dichlorinated alkane.

Table 44. Disproportionation mechanism was supported by control experiments



Entry	Substrate(s)	B-416 : B-417 : B-436 (%)
1	 1 : 1.2	19 : 43 : 0
2		0 : 99 : 0

The mechanistic experiments led to the same conclusion: ICl was being formed *in situ* upon reaction of Bu_4NI with DCE. A Bu_4NI–ICl complex would explain the extreme selectivity of the addition reactions to alkynes, which gave single isomer products. This complex could explain the moderation of the reactivity of the ICl observed during addition to alkenes such that dichlorinated products were obtained exclusively rather than the expected chloroiodinated derivatives. The reactions proceeded chemoselectively, as evidenced by the fact that aromatic rings were unaffected by the reaction conditions.

An alternative process could potentially explain the selectivity observed in the Bu_4NI/DCE reactions, namely that the Bu_4NI was reacting with the ICl (generated *in situ* as previously described) to form I_2 and Bu_4NCl. The I_2 would not be reactive enough to halogenate aromatic rings, but could form an iodonium with alkynyl or alkenyl substrates. The remarkable stereoselectivity observed in the formation of the olefin templates could be due to a $Bu_4N^+Cl^-$ ion pair that diminshed the reactivity of the Cl^- such that only anti-attack onto the iodonium intermediate, to give the *E*-isomer, was kinetically feasible. A control reaction using ethyl 2-butynoate, I_2, and Bu_4NCl in a refluxing, polar solvent could serve to either support or negate this possibility.

Halogenation reactions feature prominently in the toolbox of the organic chemist. Bromination and chlorination are straightforward processes, but iodination is frequently more difficult because the reaction proceeds very slowly and is often reversible under

standard conditions.[245] Because of these reactivity challenges, additives are typically required to promote the iodination of alkenes and alkynes. Halogenation using iodine monochloride is more facile because a permanent dipole exists in the reagent that greatly facilitates electrophilic attack.[246] Unfortunately, this process usually produces regio- and stereoisomers that are difficult to separate and purify. The use of iodine monochloride for the iodination of aromatic compounds frequently gives mixtures of mono-, di- and triiodinated arene products.[246] To overcome these selectivity and reactivity difficulties, a variety of conditions have been developed for the more efficient and selective iodination of alkenes[247] and aromatic compounds,[242] and many of these involve the generation of ICl *in situ*. For example, the halogenation of alkenes can be done using iodine and copper (II) chloride, but the method tends to give mixtures of iodochlorinated regioisomers and dichlorinated products.[247a,b] Thallium(I) azide has been employed as an additive in combination with iodine and gives predominantly *anti* addition products.[247c] As in the case of other methods, the control of regioselectivity and stereoselectivity are significant issues associated with this transformation.

The iodination of silyl enol ethers has been accomplished using a combination of NaI and $FeCl_3$.[245a] Aromatic compounds have been iodinated with moderate selectivity for the *para* position using combinations of ammonium iodide and oxone,[242a] tetrabutylammonium peroxydisulfate and iodine,[242b] iodine and copper (II) chloride,[242c] and hypervalent iodine.[242d] The iodination of aromatic heterocycles has been reported using aqueous potassium dichloroiodate.[242e] Anilines have been iodinated with high *para* selectivity using benzyltriethylammonium dichloroiodate and sodium bicarbonate.[242f] The iodination of phenols is selective for the *ortho*-position when thallium acetate is used in combination with iodine.[242g]

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[245] (a) Mohanakrishnan, A. K.; Prakash, C.; Ramesh, N. *Tetrahedron* **2006**, *62*, 3242. (b) Sumrell, G.; Wyman, B. M.; .Howell, R. G.; Harvey, M. C. *Can. J. Chem.* **1964**, *42*, 2710. (c) Zanger, M.; Rabinowitz, J. L. *J. Org. Chem.* **1975**, *40*, 248.

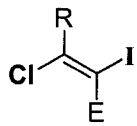
[246] McCleland, C. W. *Synthetic Reagents*; Pizey, J. S., Ed.; Ellis Horwood Limited: Chichester, 1983; Vol. 5, 85.

[247] (a) Bortolini, O.; Bottai, M.; Chiappe, C.; Conte, V.; Pieraccini, D. *Green Chem.* **2002**, *4*, 621. (b) Baird, W. C.; Surridge, J. H.; Buza, M. *J. Org. Chem.* **1971**, *36*, 2088. (c) Baird, W. C.; Surridge, J. H.; Buza, M. *J. Org. Chem.* **1971**, *36*, 3324. (d) Cambie, R. C.; Hayward, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc. Perkin I* **1976**, 840. (e) Cambie, R. C.; Hayward, R. C.; Lindsay, B. G.; Phan, A. I. T.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc. Perkin I* **1962**, 1961.

The iodochlorination of alkynes also remains problematic. The addition of ICl to alkynes provides the desired iodochlorinated alkenes, unfortunately mixtures of regio- and stereoisomers are normally observed.[231] This is inefficient since the products can be extremely difficult to separate and purify. Because of their use in the production of asymmetrically substituted olefins,[214,213] methods to prepare single isomer iodochlorinated products are highly desirable. Our group has provided a simple and effective solution for the iodochlorination of alkynes and for the chlorination of alkenes.[227,236]

The generation of single isomer β-chloro-α-iodo-α,β-unsaturated esters and amides was of great value to our group as olefin templates (Figure 8). The uses of these templates will be discussed in the following section.

Figure 8. β-chloro-α-iodo-α,β-unsaturated esters and amides serve as olefin templates



E = ester or amide

2.2 The Synthesis of Trisubstituted Olefins

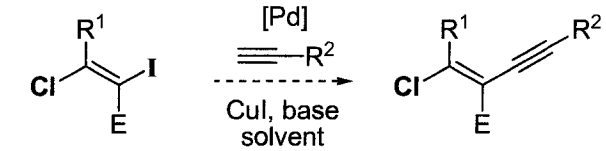
2.2.1 The Sonogashira Coupling Reaction

The halogens on the olefin template should provide effective handles for the transformation of the olefin templates to highly congested tetrasubstituted olefins. It was expected that the selectivity of the organometallic coupling reactions would have to be controlled and it was anticipated that forcing conditions would have to be employed to generate the sterically encumbered products.

The Sonogashira reaction was initially selected for the coupling reaction of the alkene template because of the small steric demand of the incumbent acetylene substituent

(Scheme 87). We felt confident that we could achieve regioselectivity in the coupling reaction because of the greater reactivity of vinylic iodides over vinylic chlorides.[248]

Scheme 87. Regioselective Sonogashira reaction will deliver trisubstituted olefins



E = ester or amide

2.2.1.1 Background: the Sonogashira reaction

The Sonogashira reaction[249,250] is the palladium-catalyzed cross-coupling reaction of aryl or alkenyl halides with terminal alkynes in the presence of CuI and a base.[251] Palladium(0) complexes serve as the active catalytic species. When a palladium(II) precursor is used, reduction to the active palladium(0) catalyst must first take place.[160] This can occur in a number of ways. The first transformation may occur via two successive transmetallations of the R-M coupling agent with the X-ligand on the palladium(II) centre (Scheme 88, equation a). This Pd(II) complex can then undergo reductive elimination to give the active Pd(0) catalyst. This process occurs commonly in all types of coupling reactions.

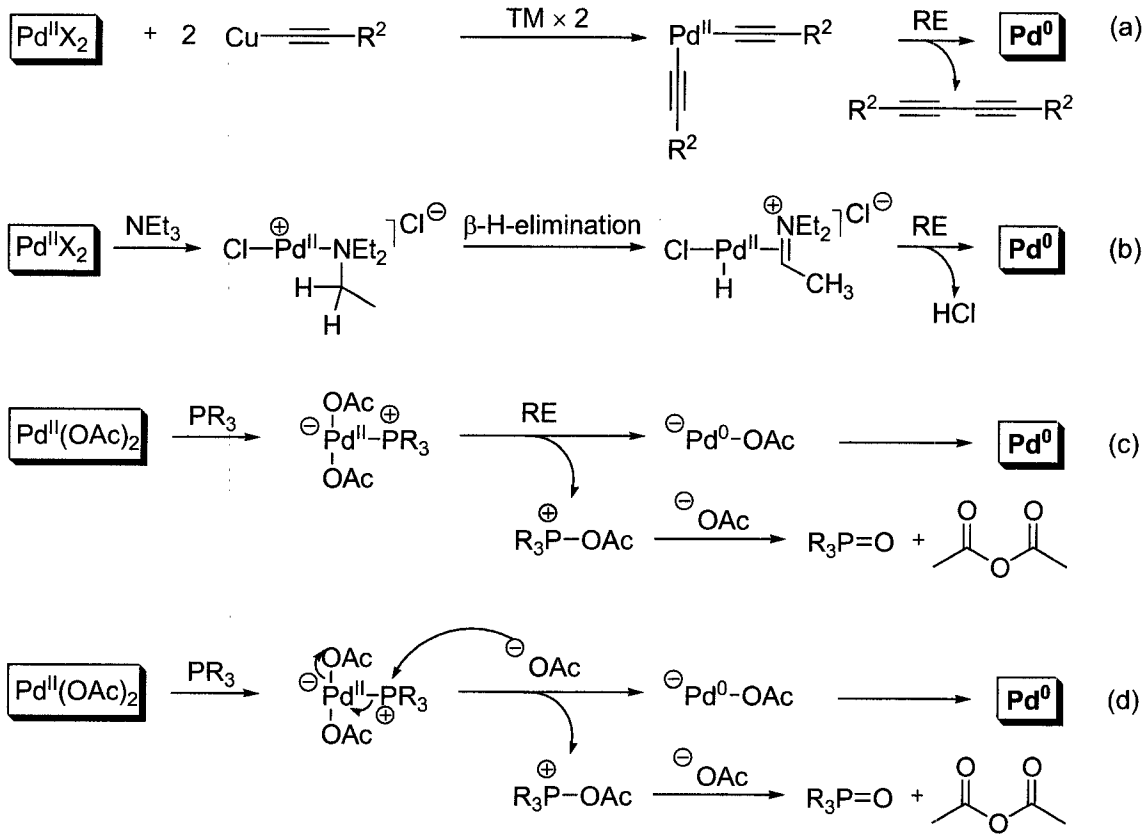
[248] The reactivity of C-X bonds tends to decrease in the order of C-I > C-Br > C-Cl >>>C-F. See reference 160.

[249] (a) The original report by Kenkichi Sonogashira: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Review of Pd-catalyzed alkynylation reactions: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

[250] Review of the Sonogashira reaction: Sonogashira, K. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Ed.; Wiley-VCH: New York, 1998, 203.

[251] The direct reaction of aryl and alkenyl halides with copper acetylides is known as the Castro reaction: Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

Scheme 88. Generation of the active Pd(0) catalyst from Pd(II) precursors[160]



Alternatively, an amine base, such as triethylamine, can also be implicated in the Pd(II) to Pd(0) transformation (Scheme 88, equation b). The amine can complex to the palladium (II) species, which typically occurs with concomitant displacement of the X-ligand to give a cationic Pd(II) centre. This species undergoes β-hydride elimination followed by reductive elimination of HX to give the active Pd(0) catalyst.

A third palladium reduction mechanism can take place when $Pd(OAc)_2$ is used in conjunction with phosphine ligands (Scheme 88, equation c). Complexation of the phosphine ligand with the palladium occurs first, generating an ylide. The oxophilic phosphine reductively eliminates with one of the acetates, leaving an anionic Pd(0) complex. The remaining acetate departs from the palladium(0) and reacts with the phosphine species to generate phosphine oxide and acetic anhydride. An alternative mechanism for this reduction has been proposed by Alper, in which the PR_3-OAc complex initially formed via an intermolecular S_N2 reaction at the phosphine center

(Scheme 88, equation d).[252] This mechanism was supported by experiments that employed a chiral phosphine ligand in which inversion of stereochemistry of the phosphorous was observed.[253]

The general catalytic cycle of the Sonogashira reaction is depicted in Scheme 89. Oxidative addition (OA) occurs readily onto the Pd(0) complex **A** to give the Pd(II) intermediate **B**.[254] Typically electron-rich phosphines are used as ligands because their σ-donor ability increases the electron density on the palladium and oxidative addition is consequently facilitated. Pd(II) complex **B** undergoes transmetallation with the copper acetylide generated *in situ*. The generation of the copper acetylide involves copper iodide, the terminal acetylene and a base—usually a tertiary amine base.[255] The terminal alkyne is activated through complexation with the CuI. Electron density is withdrawn from the triple bond and the acidity of the terminal proton is thereby increased, enough that deprotonation by the amine base becomes feasible. This deprotonation would not occur in the absence of CuI because the pK_a of a terminal acetylene is approximately 29 in DMSO,[256] while that of a protonated amine is approximately 9 in DMSO.[257]

The copper acetylide generated from this deprotonation event provides intermediate **C** that can undergo reductive elimination to give the cross-coupled product and regenerate the Pd(0) catalyst (**A**).

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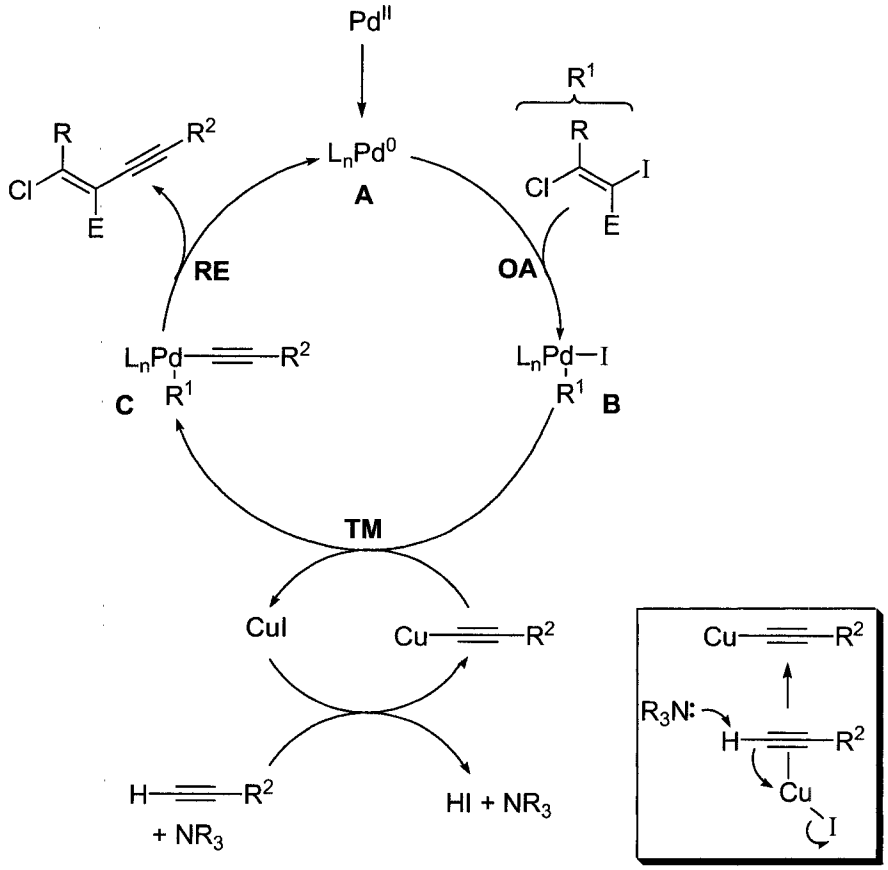
[252] Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890.
[253] Retention of configuration is observed in reductive elimination processes.
[254] While few facile reactions with aryl chlorides have been reported (see Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1056.), alkenyl halides, and even alkenyl chlorides, usually react smoothly (see reference 248).
[255] The use of a sterically hindered base prevents undesired amination reactions.
[256] Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.
[257] Kolthoff, I. M.; Chantooni, M. K.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.

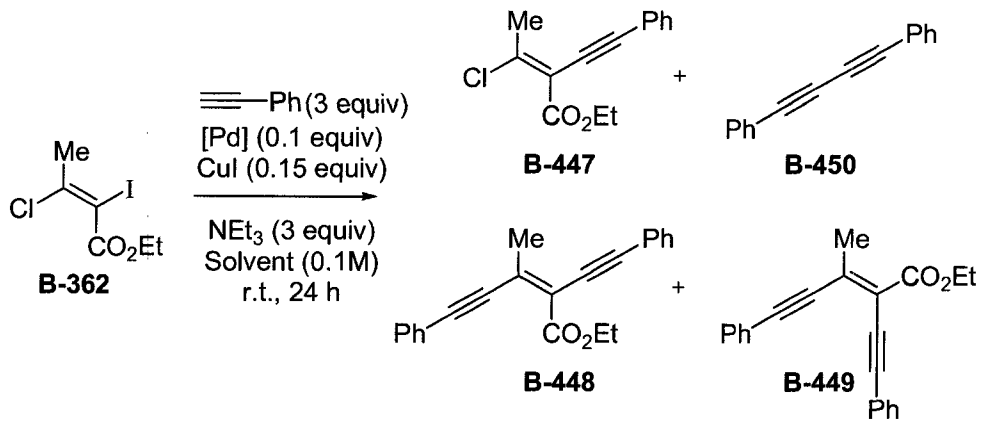
Scheme 89. General catalytic cycle of the Sonogashira coupling reaction



2.2.1.2 Double-addition and isomerization observed initially in the Sonogashira reaction

Our initial attempts to promote a site-selective Sonogashira reaction were met with mixed results. As shown in Table 45, the reaction did indeed take place under most reaction conditions, however double-addition dominated, isomers were observed, and an alkyne dimer was a significant side-product. Catalysts generated from $Pd(PPh_3)_4$ (entry 1) or $Pd(OAc)_2$ (entry 2) were not reactive enough in acetonitrile; starting material remained in each case after 24 hours. Complete conversion to double-addition products was observed using $Pd(PPh_3)_2Cl_2$ (entry 3) or $Pd_2(dba)_3$ (entry 4) in acetonitrile, however, mixtures of isomers **B-448** and **B-449** were obtained. No reaction was observed in THF when the previously active $Pd(PPh_3)_2Cl_2$ was tested (entry 5). The use of DCM (entry 6) or CH_3CN as the solvent gave a mixture of double-addition products **B-448** and **B-449**.

Table 45. Initial Sonogashira results

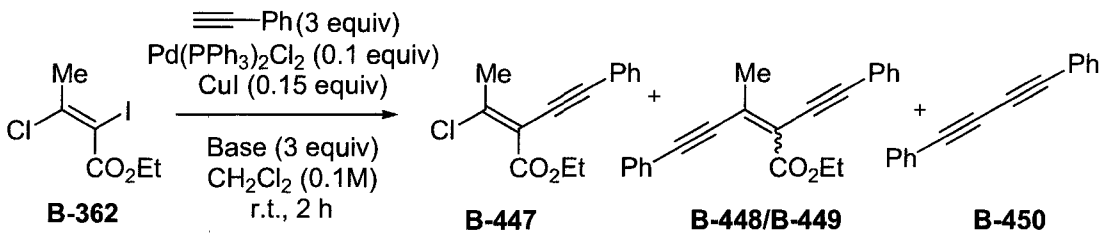


Entry	Catalyst	Solvent	% Conversion (B-448:B-449)
1	$Pd(PPh_3)_4$	MeCN	Incomplete
2[a]	$Pd(OAc)_2$	MeCN	Incomplete
3	$Pd(PPh_3)_2Cl_2$	MeCN	100% (3:1)
4[a]	$Pd_2(dba)_3$[b]	MeCN	100% (2:1)
5	$Pd(PPh_3)_2Cl_2$	THF	NR
6	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	100% (3:1)

[a] PPh_3 (2 equiv relative to the palladium loading) was added. [b] 0.05 equiv of the catalyst was added.

A base screen was next conducted using $Pd(PPh_3)_2Cl_2$ in CH_2Cl_2 (Table 46). The use of triethylamine gave conversion to isomers **B-448** and **B-449** and 38% of homocoupled product **B-450** (entry 1). The use of DIPEA was slightly more effective, as a modest percentage of compound **B-447** was observed, in addition to double-addition and homocoupled products (entry 2). DABCO proved ineffective for this reaction, as a significant amount of starting material was recovered, and low yields of products were obtained (entry 3). Carbonate bases were completely ineffective. The presence of Cs_2CO_3 in the reaction returned starting material in almost quantitative yield (entry 4), and K_2CO_3 faired even worse, giving back only 24% of the starting material and delivering almost no product (entry 5). In this last reaction, a very large proportion of homocoupled product **B-450** was observed.

Table 46. Base scan for the regioselective Sonogashira reaction



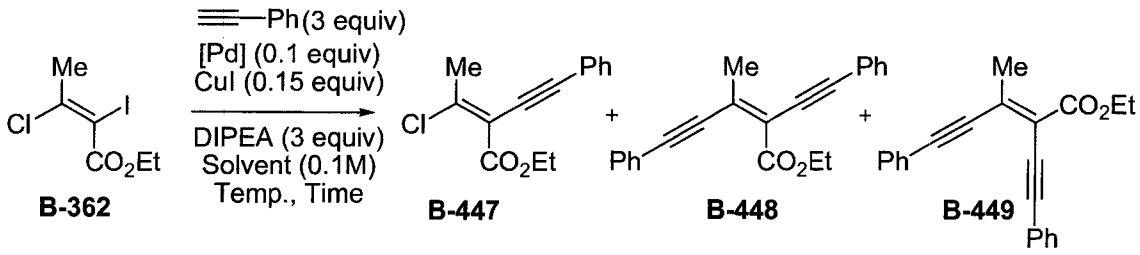
Entry	Base	Yield B-362:B-447:B-448/B-449:B-450 (%)
1	Et_3N	0:0:68:38
2	**DIPEA**	**0:21:10:44**
3	DABCO	40:5:25:41
4	Cs_2CO_3	90:3:0:22
5	K_2CO_3	24:1:0:43

These results were nevertheless encouraging as the reactivity of the system simply had to be *decreased* and isomerization avoided. Attempts would be made to minimize the homocoupling of the alkyne side reaction that was consistently observed. Starting from the result from $Pd(PPh_3)_2Cl_2$ in CH_2Cl_2 (Table 46, entry 2) and using DIPEA as the base, the reaction time was decreased to only 3 hours. These conditions gave a mixture of desired product **B-447**, as well as double-addition isomers **B-448** and **B-449** (Table 47, entry 1). The use of $Pd(dppf)Cl_2$ gave similar results: a mixture of **B-448** and **B-449** was obtained with a 24 hour reaction (entry 2) and a mixture of the desired product **B-447** together with double-addition isomers **B-448** and **B-449** were observed from a two hour reaction (entry 3). This reaction could be halted after one half hour to give exclusively product **B-447** in 99% yield (entry 4). Because these conditions required very careful monitoring of the reaction, a less active and more selective system was sought that would leave the β-position untouched even after prolonged reaction times. A switch to $Pd(PPh_3)_4$ successfully reduced the activity of the catalyst. A reaction at room temperature in DCM for 1 hour gave an excellent yield of product **B-447** exclusively (entry 5). Conducting the reaction at 0 °C still produced exclusively product **B-447**, but in only a 45% yield (entry 6). Decreasing the reaction temperature to −20 °C inhibited the reaction completely and no product was observed (entry 7).

The use of $Pd(PPh_3)_4$ was not satisfactory as a catalyst because this catalyst decomposes at room temperature and upon exposure to air.[258] The use of a more stable catalyst source that could be handled on the bench would be more practical and would give results that would be more reliable. Two ligands must dissociate from $Pd(0)(PPh_3)_4$ before the active catalytic species, $Pd(0)(PPh_3)_2$, is formed. Because $Pd(0)(PPh_3)_2$ is often only present at trace levels, and in unpredictable amounts depending on the reaction conditions, a more reliable alternative was sought. The $Pd(PPh_3)_2Cl_2$ catalyst was re-examined and a one hour reaction was attempted. The initial result showed the generation of only product **B-447** in excellent yield as the exclusive product (entry 8), however it was found with repeated trials that occasionally the second addition to **B-447** occurred before the starting material had been consumed. Lowering the temperature had the desired effect: at 0 °C, the coupling reaction proceeded smoothly at the α-position, but no subsequent reaction at the β-position was observed (entry 9). The use of dioxane at the same temperature gave a slightly lower yield of the product (entry 10).

[258] Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

Table 47. Optimization of the Sonogashira reaction conditions



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (B-448:B-449)
1	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	r.t.	3	Mixture of **B-362**:**B-447**:**B-448**
2	$Pd(dppf)Cl_2$	CH_2Cl_2	r.t.	24	90% **B-448**:**B-449** (2:1)
3	$Pd(dppf)Cl_2$	CH_2Cl_2	r.t.	2	Mixture of **B-362**:**B-447**:**B-448**
4	$Pd(dppf)Cl_2$	CH_2Cl_2	r.t.	0.5	99% **B-447**
5	$Pd(PPh_3)_4$	CH_2Cl_2	r.t.	1	99% **B-447**
6	$Pd(PPh_3)_4$	CH_2Cl_2	0	3	45% **B-447**
7	$Pd(PPh_3)_4$	CH_2Cl_2	−20	18	NR
8	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	r.t.	1	99% **B-447**
9	**$Pd(PPh_3)_2Cl_2$**	**CH_2Cl_2**	**0**	**3**	**91% B-447**
10	$Pd(PPh_3)_2Cl_2$	Dioxane	0	3	78% **B-447**

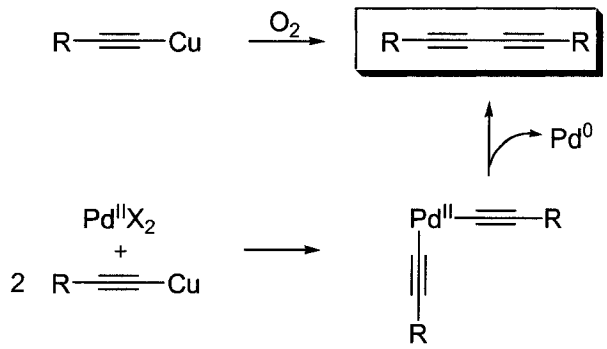
2.2.1.3 Minimizing the formation of homocoupled acetylenes

Having achieved selectivity, the next goal was to limit the formation of homocoupled alkyne products, which had been observed in a significant amount in every reaction studied thus far. This is a well-known competitive reaction in the Sonogashira process, and can proceed by different mechanisms. A common route to homocoupled alkynes is through a Glaser coupling, catalyzed by CuI in the presence of O_2 (Scheme 90).[259,260] Careful sparging of the reaction mixtures to eliminate traces of oxygen only slightly decreased the amounts homocoupled product. Homocoupling can also result from transmetallation of $Pd^{II}X_2$ with two equivalents of copper acetylide followed by reductive

[259] Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
[260] I_2 can act as an oxidant for this process, and ICl may play the same role if present in our system. See Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371.

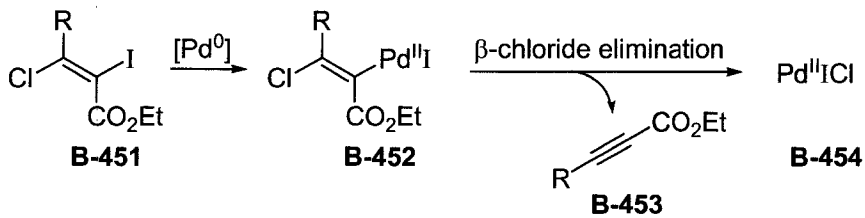
elimination.[160] In this case, one would therefore expect to observe an equivalent amount of homocoupled product to the palladium loading in the reaction (i.e. if 0.1 equiv Pd was used in the reaction, we would expect up to 0.1 equiv of diacetylene to be generated). In most cases, more than an equivalent of the homocoupled product relative to the catalyst loading was observed.

Scheme 90. Mechanisms for the homocoupling of 1-alkynes



In the olefin template, it was possible that $Pd^{II}ICl$ was being formed from the elimination of ICl from the alkene substrate (Scheme 91). This would provide a means for the formation of additional homocoupled alkyne via the route described above.

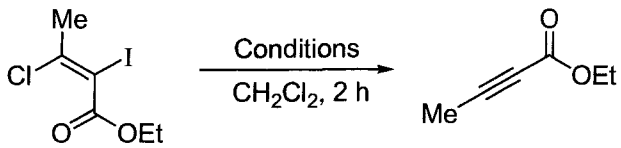
Scheme 91.



A series of control reactions were performed to determine whether the olefin templates were in fact being converted to alkynyl esters (Table 48). No reaction was observed when **B-362** was subjected to phenylacetylene alone (entry 1). Exposure of alkene **B-362** to $Pd(PPh_3)_4$ (20 mol%) at room temperature gave a trace of product **B-351** (entry 2). Heating the reaction to reflux gave a 20% yield of product **B-351** (entry 3). This yield was equivalent to the catalyst loading, and presumably generated a matching amount of Pd(II)ICl. The introduction of CuI to a solution of **B-362** in CH_2Cl_2 caused no disappearance of **B-362** (entry 4). The use of DIPEA alone with alkene **B-362** similarly

gave no reaction (entry 5). These results illustrated that the palladium complex was essential for the conversion of **B-362** into **B-351**, and that the formation of **B-351** was sluggish at room temperature, but more facile at reflux.

Table 48. Control reactions identified Pd as a requisite element for alkynyl ester formation



B-362 **B-351**

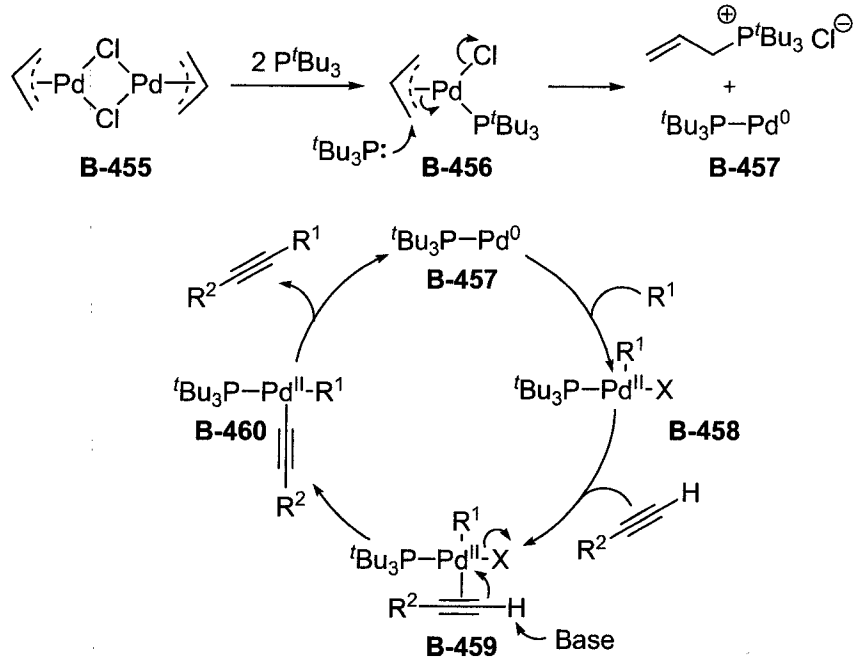
Entry	≡—Ph (equiv)	Catalyst (0.2 equiv)	CuI (equiv)	DIPEA (equiv)	Temp	Result
1	3	-	-	-	r.t.	NR
2	-	$Pd(PPh_3)_4$	-	-	r.t.	trace
3	-	$Pd(PPh_3)_4$			reflux	20%
4	-	-	0.15	-	r.t.	NR
5	-	-	-	4	r.t.	NR

Based on the mechanisms shown in Scheme 90, the exclusion of copper was the first modification to attempt to minimize alkyne homocoupling. While a number of reports have been disclosed that do not utilize co-catalysts such as CuI, researchers at Merck have advanced this methodology and have disclosed an efficient protocol for a copper-free Sonogashira reaction.[261] They found that the use of allylpalladium chloride dimer with DABCO and acetonitrile at room temperature promoted the Sonogashira coupling reaction between aryl bromides and acetylenes (Scheme 92). Only 1.1 equivalents of the acetylene were required for excellent conversion. Investigation into the reaction mechanism implicated a highly active Pd-L catalyst. Addition of two equivalents of P^tBu_3 to allyl palladium chloride dimer **B-455** gave the monophosphine Pd(II) species. Upon attack of P^tBu_3, allylphosphonium chloride and the virtually naked Pd(0)-L catalyst **B-457** were generated. Oxidative addition proceeds as usual to give Pd(II) complex **B-458**. At this point, a transmetallation step is not possible, however, the alkyne can complex

[261] Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191.

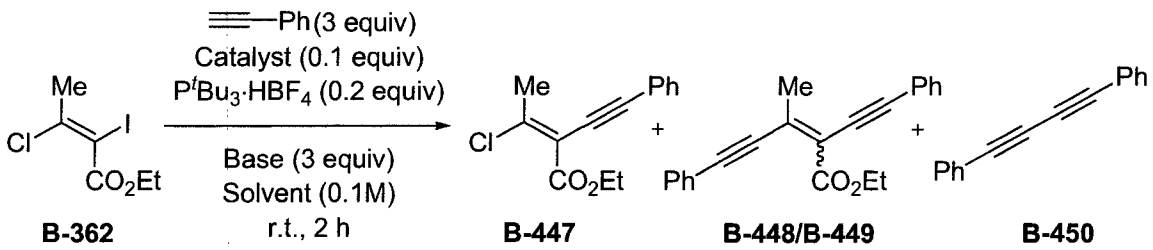
with the coordinatively unsaturated palladium. Consequently, the pKa of the terminal proton increases sufficiently as to allow deprotonation by the base. Complex **B-460** can undergo reductive elimination to simultaneously regenerate the highly active catalyst **B-457** and produce the coupled product.

Scheme 92. Mechanism for the copper-free Sonogashira coupling reaction



Copper-free Sonogashira coupling reactions of alkene **B-362** with phenylacetylene were attempted under a number of different conditions (Table 49). Triethylamine was ineffective when used as the solvent. Regardless of the palladium source used, the reaction was sluggish and significant amounts of homocoupled product were obtained (entries 1–4). The use of DABCO in acetonitrile with $(allylPdCl)_2$, the optimal conditions developed by Soheili *et al.*,[261] gave rapid over-reaction to products **B-448/B-449** (a mixture of isomers), and still gave a significant amount of homocoupled product **B-450** (entry 5). The results were not improved using other palladium sources: $Pd(OAc)_2$ (entry 6), $Pd(PPh_3)_2Cl_2$ (entry 7), $Pd_2(dba)_3$ (entry 8), and $Pd(PPh_3)_4$ (entry 9) all gave rapid conversion to products **B-448/B-449** and even larger amounts of diacetylene **B-450**. Clearly copper-free conditions would not eliminate homo-coupling in this system.

Table 49. Copper-Free Sonogashira Coupling



B-362 **B-447** **B-448/B-449** **B-450**

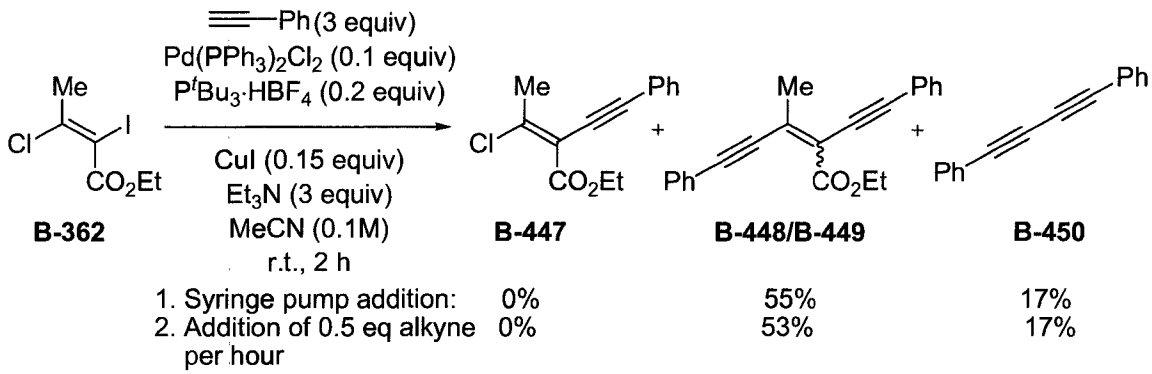
Entry	Catalyst	Base	Solvent	% Conversion to B-448/B-449[a]	B-450 (%)
1	$Pd(OAc)_2$	Et_3N	Et_3N	trace	34
2	$Pd(PPh_3)_2Cl_2$	Et_3N	Et_3N	trace	32
3	$Pd_2(dba)_3$	Et_3N	Et_3N	trace	25
4	$Pd(PPh_3)_4$	Et_3N	Et_3N	trace	38
5	$(AllylPdCl)_2$	DABCO	CH_3CN	100	54
6	$Pd(OAc)_2$	DABCO	CH_3CN	100	71
7	$Pd(PPh_3)_2Cl_2$	DABCO	CH_3CN	100	65
8	$Pd_2(dba)_3$	DABCO	CH_3CN	100	63
9	$Pd(PPh_3)_4$	DABCO	CH_3CN	100	65

[a] **B-447** was not observed under these conditions.

Herrmann has observed that slow addition of the acetylene component to the reaction can minimize homocoupling and decomposition of the alkyne in solution and thereby promote the desired coupling reaction.[262] The slow addition of the acetylene component, either by syringe pump or by staggered addition of the alkyne component gave no product and resulted in the formation of extensive amounts of the homocoupled alkyne (Scheme 93). Decreasing the amount of acetylene used in the reaction simply decreased the conversion to product, to the point that the use of 0.8 equivalents of phenylacetylene gave no product.

[262] Böhm, V. P. W.; Herrmann, Wolfgang A. *Eur. J. Org. Chem.* **2000**, *2000*, 3679.

Scheme 93. Slow addition of the acetylene component



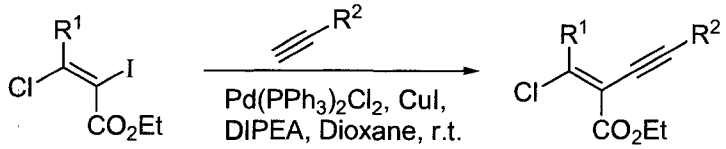
Early mechanistic investigations into the Glaser-type coupling of acetylenes had postulated radical intermediates in the process.[259] Therefore, in a final attempt 20 mol% BHT was added to a typical reaction. This has absolutely no effect on the reaction, and attempts to minimize homocoupling of the alkyne were finally abandoned, and focus turned instead to the generation of trisubstituted alkenes.

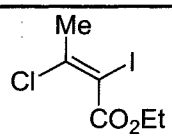
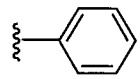
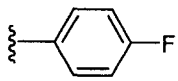
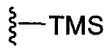
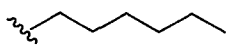
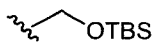
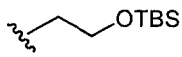
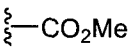
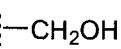
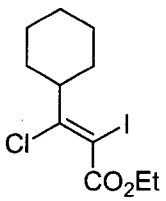
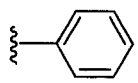
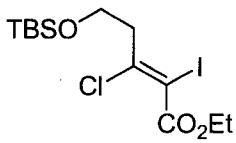
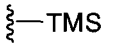
2.2.1.4 Success!

Using our optimized conditions from Table 47, complete conversion and good yields were achieved for the coupling of methyl-substituted olefin **B-362** with a wide range of acetylenes (Table 50). The reaction tolerated a variety of substituent functionalities, including aryl (entries 1 and 2), silyl (entry 3), and alkyl groups (entry 4), as well as tethered silyl ethers of varying chain lengths (entries 5 and 6). These reactions all gave single isomer products as evidenced by GC-MS, ^{1}H, and ^{13}C NMR analysis. Methyl propiolate proved unreactive, despite a number of conditions attempted (entry 7).[263] Propargyl alcohol was also unreactive (entry 8). The R^1 substituent could be varied to a branched alkyl substituent, as evidenced by the smooth coupling of the cyclohexyl-substituted alkene with phenylacetylene (entry 9). A functionalized alkyl chain was also coupled with ease, giving the desired trisubstituted product in 79% yield (entry 10).

[263] Alkynes bearing electron-withdrawing groups are less effective coupling partners for the Sonogashira coupling reaction. Masked electron-withdrawing groups have been employed as alternatives: Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746.

Table 50. Sonogashira reactions delivered a range of trisubstituted alkenes[264]



Entry	Substrate	R^2	Product	Yield (%)[b]
1[c]	 **B-362**		**B-447**	78
2	**B-362**		**B-461**	77
3	**B-362**		**B-462**	68
4	**B-362**		**B-463**	74
5	**B-362**		**B-464**	76
6	**B-362**		**B-465**	72
7	**B-362**		**B-466**	NR
8	**B-362**		**B-467**	NR
9			**B-468**	68
10			**B-469**	79

[a] Reaction conditions: vinyl iodide (1 equiv), alkyne (3 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (15 mol %), DIPEA (3 equiv), dioxane (0.1 M), 2 h. [b] Isolated yield [c] Reaction was performed at 0 °C.

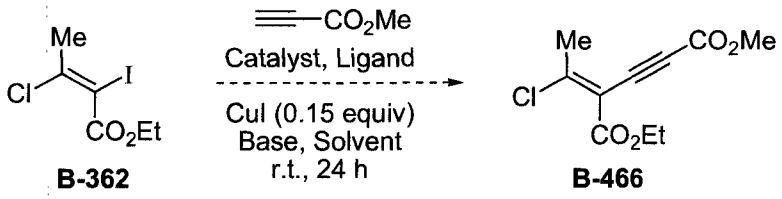
Notably, Sonogashira coupling was observed exclusively at the α-position in all cases, a fact readily identified by NMR and GC–MS.[265] In no case was a product coupled only

[264] CH_2Cl_2 was found to be the optimal solvent when the coupling partner was phenylacetylene, however trimethylsilylacetylene did not react in this solvent. A solvent scan using TMS-acetylene as the substrate identified dioxane as a satisfactory solvent, and it was therefore used for subsequent reactions.

at the β-position observed. This result was in stark contrast to those reported for related substrates incorporating the same halogen at both the α- and β-positions.[266] In those substrates, the β-position was far more activated toward oxidative addition than the α-position and gave regioselective coupling at the former. In our substrates, the enhanced reactivity of the iodide over the chloride overrode the inherent reactivity of the system. To our knowledge, this was the first time that selective coupling has been observed at the α-position of α,β-dihalo-α,β-unsaturated esters.

Attempts to achieve coupling using methyl propiolate as the substrate were unsuccessful. The reaction with $Pd(PPh_3)_2$ in CH_2Cl_2 was attempted using DIPEA as the base with no success (Table 51, entry 1). Changing the catalyst to $PdCl_2$(dppf) likewise gave no reaction (entry 2). The use of $Pd(PPh_3)_4$ with P^tBu_3 as the ligand in THF using Et_3N as the base was unsuccessful (entry 3), and no better was the same system in dioxane (entry 4).

Table 51. Attempted Sonogashira coupling reaction with methyl propiolate



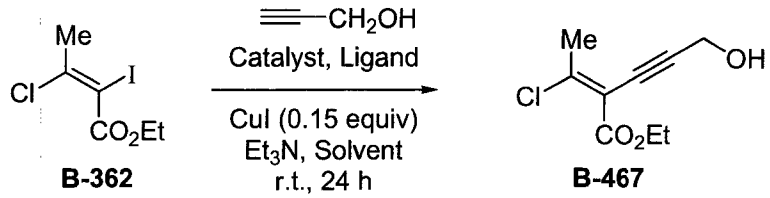
Entry	Catalyst (0.1 equiv)	Ligand (0.2 equiv)	Base (3 equiv)	Solvent (0.1 M)	Result
1	$Pd(PPh_3)_2Cl_2$	-	DIPEA	CH_2Cl_2	NR
2	$PdCl_2$dppf	-	DIPEA	CH_2Cl_2	NR
3	$Pd(PPh_3)_4$	$P^tBu_3 \cdot HBF_4$	Et_3N	THF	NR
4	$Pd(PPh_3)_4$	$P^tBu_3 \cdot HBF_4$	Et_3N	dioxane	NR

Attempts to promote the Sonogashira coupling reaction with propargyl alcohol were more extensive but equally fruitless. The reaction of alkene **B-362** with propargyl alcohol in the presence of $Pd(PPh_3)_2$ and P^tBu_3 in THF did not produce the desired product (Table

[265] ^{13}C chemical shift and MS data showed iodine replacement and not chlorine replacement. The stereochemistry was established by NOE (see below).
[266] (a) Ref. 210. (b) **Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

52, entry 1). Copper-free conditions were similarly unproductive (entry 2), as was a reaction without P^tBu_3 (entry 3), and a reaction in dioxane (entry 4). Analogous tests with $Pd(OAc)_2$ (entries 5–7) and $Pd(PPh_3)_4$ (entries 8–12) gave no trace of the desired product.

Table 52. Attempted Sonogashira coupling reaction with propargyl alcohol



Entry	Catalyst (0.5 equiv)	Ligand (0.1 equiv)	Solvent	Result
1	$Pd(PPh_3)_2Cl_2$	$P^tBu_3 \cdot HBF_4$	THF	NR
2[a]	$Pd(PPh_3)_2Cl_2$	$P^tBu_3 \cdot HBF_4$	THF	NR
3	$Pd(PPh_3)_2Cl_2$	-	THF	NR
4	$Pd(PPh_3)_2Cl_2$	$P^tBu_3 \cdot HBF_4$	dioxane	NR
5	$Pd(OAc)_2$	$P^tBu_3 \cdot HBF_4$	THF	NR
6	$Pd(OAc)_2$	-	THF	NR
7[a]	$Pd(OAc)_2$	$P^tBu_3 \cdot HBF_4$	dioxane	NR
8[b]	$Pd(PPh_3)_4$	$P^tBu_3 \cdot HBF_4$	THF	NR
9[a,b]	$Pd(PPh_3)_4$	$P^tBu_3 \cdot HBF_4$	THF	NR
10[b]	$Pd(PPh_3)_4$	-	THF	NR
11[b]	$Pd(PPh_3)_4$	$P^tBu_3 \cdot HBF_4$	dioxane	NR
12[b,c]	$Pd(PPh_3)_4$	-	CH_2Cl_2	NR

[a] Copper-free conditions were used. [b] 0.1 equivalents of the catalysts were employed. [c] DIPEA was used as the base.

We were pleased with our success with the Sonogashira reaction at the α-position, despite the two unreactive substrates mentioned above. The relatively high stability and tuneable reactivity of the β-chloro-α-iodo-α,β-unsaturated esters was extremely promising for the generation of tetrasubstituted olefins. First, however, we wanted to incorporate greater diversity of substituents at the α-position and the Suzuki coupling reaction was exploited for that purpose.

2.2.2 The Suzuki Coupling Reaction

2.2.2.1 Background: the Suzuki reaction

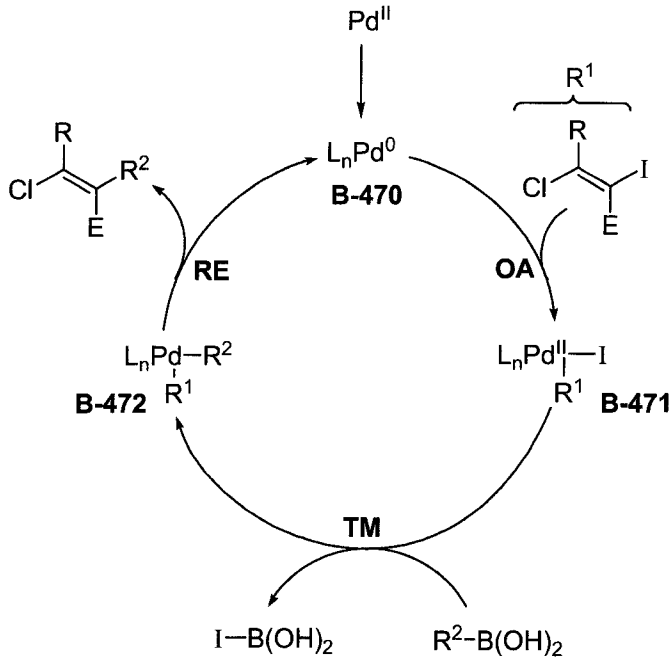
The Suzuki, or Suzuki-Miyaura,[267] reaction is the cross-coupling reaction between sp or sp^2 halides or sulfonates with organoboron compounds in the presence of a base.[268] This reaction is extremely popular because of the mild reactions and tolerance to a wide range of functional groups. The organoboranes are frequently commercially available or are at least easily prepared.[160] They generally have a high stability to heat, air, and moisture, and have low toxicity. The general reaction mechanism is shown in Scheme 94. A number of palladium precursors can be used, including $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$ and $PdCl_2(dppf)$.[269] If a palladium(II) precursor is used, it is first reduced to palladium(0) (See: 2.2.1 The Sonogashira Coupling Reaction). Oxidative addition occurs to give Pd(II) complex **B-471**, and transmetallation followed by reductive elimination regenerates the Pd(0) catalyst and delivers the desired product.

[267] For reviews of the Suzuki reaction, see (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Reference 250.

[268] Isolated examples of alkyl halides have been coupled with boronic acids and esters. One report described substrates in which the alkyl halides bore β-hydrogens: Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

[269] $PdCl_2(dppf)$ is primarily used for sp^3-sp^2 couplings and will be discussed in a later section.

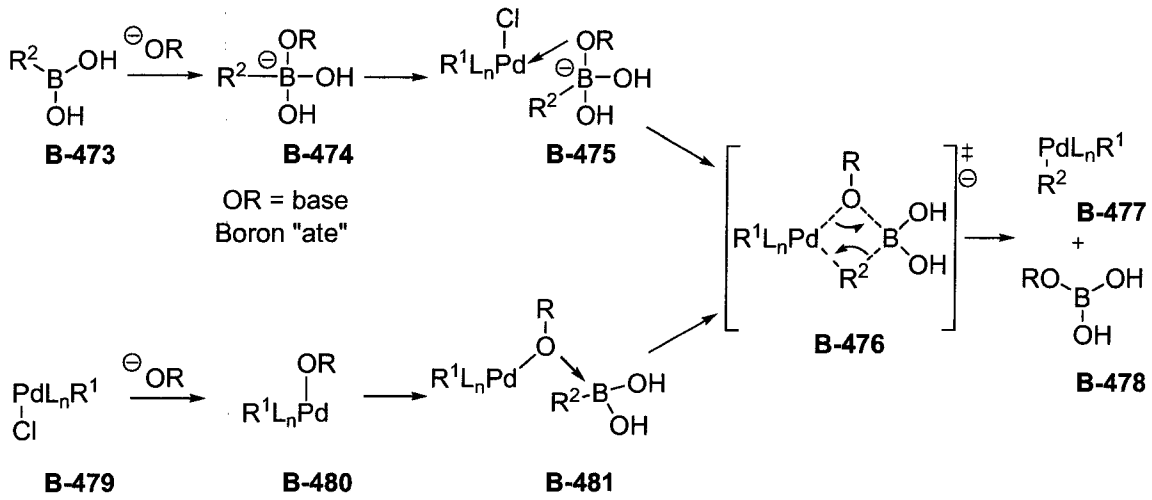
Scheme 94. General catalytic cycle of the Suzuki coupling reaction



The transmetallation step occasionally proceeds sluggishly because of the low nucleophilicity of the R^2 group on the boron. Transmetallation is more facile with more electropositive metals such as Mg and Zn, however when boron is used, carbonate or hydroxide bases are essential.[270] The base is thought to promote the formation of a boron "ate" complex (**B-474**), formed by the quaternization of the oxophilic boron (Scheme 95).[271] This would increase the nucleophilicity of the R^2 substituent and a four-centered transition state (**B-476**) would facilitate R^2 group transfer. Another possibility arises from the coordination of the base to the palladium centre with concomitant departure of the halide to give intermediate **B-480**. Oxygen is better able to donate its lone pairs to the Lewis-acidic boron than the more electronegative chlorine and the initial approach of the borane (**B-481**) is thereby promoted. This mechanism would pass through the same four-centered transition state **B-476** to give transmetallation products **B-477** and **B-478**.

[270] CsF and CsCl are occasionally employed.
[271] Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

Scheme 95. The role of the base in the transmetallation step

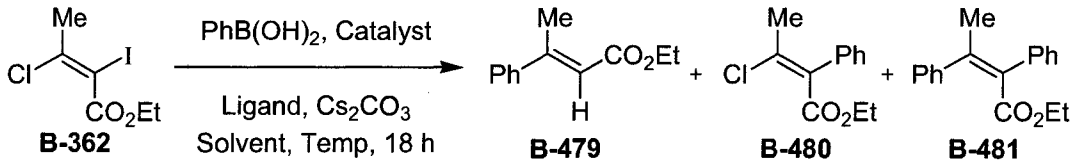


Keeping these requirements in mind, the Suzuki coupling reaction was investigated at the α-position of the β-chloro-α-iodo-α,β-unsaturated esters and amides.

2.2.2.2 Development of the Suzuki coupling reaction at the α-position

The initial conditions tested showed that $Pd(PPh_3)_4$ was not appropriate as a catalyst for the desired transformation (Table 53, entry 1). A reaction using $Pd_2(dba)_3$ as the palladium source together with P^tBu_3 as the ligand in dioxane gave a trace of double-addition product **B-481** (entry 2). This was encouraging as this was the first time evidence had been observed of coupling at the α-position. The use of the more polar acetonitrile as the solvent showed no product formation (entry 3). A pronounced difference was observed when the conditions of entry 2 were employed again, but this time at reflux using a large excess of phenylboronic acid. This gave a 94% yield of product **B-479**. While this was not the desired product, we would nevertheless investigate this interesting result (see below). Exposure of the substrate (**B-362**) to similar reaction conditions using four equivalents of phenylboronic acid in refluxing acetonitrile delivered only 35% of product **B-479**. No trace of products **B-480** or **B-481** were seen by GC–MS of the crude reaction mixture.

Table 53. Suzuki coupling of phenyboronic acid at the α-position of B-362

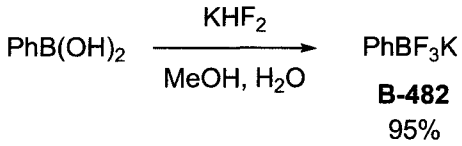


Entry	Catalyst (0.1 equiv)	Ligand (0.2 equiv)	Solvent	Additive	Temp.	Result
1[a]	$Pd(PPh_3)_4$	-	THF	-	r.t.	NR
2	**$Pd_2(dba)_3$**	**$P^tBu_3 \cdot HBF_4$**	**dioxane**	**-**	**r.t.**	**trace B-481**
3	$Pd_2(dba)_3$	$P^tBu_3 \cdot HBF_4$	MeCN	4Å MS	r.t.	NR
4[b]	$Pd_2(dba)_3$	$P^tBu_3 \cdot HBF_4$	dioxane	-	reflux	**B-479** (94%)
5	$Pd_2(dba)_3$	$P^tBu_3 \cdot HBF_4$	MeCN	4Å MS	reflux	**B-479** (35%)

[a] K_2CO_3 was used as the base. [b] 40 equivalents of $PhB(OH)_2$ were used.

Organotrifluoroborate salts can be more reactive than their boronic acid or ester counterparts. In addition, trifluoroborate salts are more air and moisture stable and resist decomposition.[272] $PhBF_3K$ was easily prepared in an excellent yield by the treatment of the corresponding boronic acid with KHF_2 in a mixture of $MeOH/H_2O$ (Scheme 96).[273]

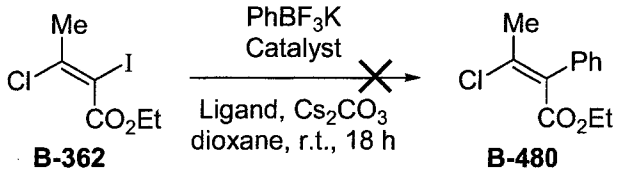
Scheme 96. Preparation of trifluoroborate salts



The resulting potassium phenyltrifluoroborate salt was then tested in a series of cross-coupling reactions (Table 54). Treatment of alkene **B-362** with $PhBF_3K$, $Pd_2(dba)_3$, P^tBu_3, and Cs_2CO_3 in dioxane returned only starting material (entry 1). The use of $PdCl_2(dppf)$ or $PdCl_2(PPh_3)_2$ proved no better (entries 2 and 3). Employing P^tBu_3 with $PdCl_2(PPh_3)_2$ gave no reaction (entry 4), nor did the use of S-PHOS with the same catalyst (entry 5).

[272] These advantages of organotrifluoroborates and others have been described: (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (b) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
[273] Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

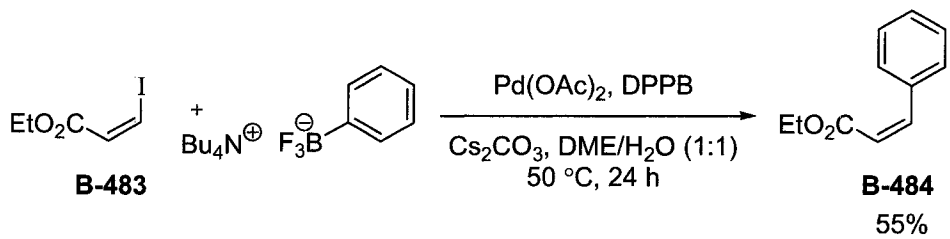
Table 54. The use of $PhBF_3K$ did not give the desired product



Entry	Catalyst	Ligand	Result
1	$Pd_2(dba)_3$	$P^tBu_3 \cdot HBF_4$	NR
2	$PdCl_2(dppf)$	-	NR
3	$PdCl_2(PPh_3)_2$	-	NR
4	$PdCl_2(PPh_3)_2$	$P^tBu_3 \cdot HBF_4$	NR
5	$PdCl_2(PPh_3)_2$	S-PHOS	NR

A number of potential solutions exist for this lack of reactivity. Water is often found to be required for this reaction, in part to improve the solubility of the trifluoroborate salt and to promote the transmetallation step.[274] Reduced reactivity due to the use of less soluble potassium salts can be improved by using a different counter ion such as tetrabutylammonium or by adding a phase-transfer catalyst such as Bu_4NOH.[274] This has been shown by the reaction of alkenyl iodide **B-483** with tetrabutylammonium phenyltrifluoroborate salt, which proceeded smoothly to give product **B-484** (Scheme 97).

Scheme 97. The combination of Bu_4N^+ salt and aqueous reaction mixture gave the desired product in one example

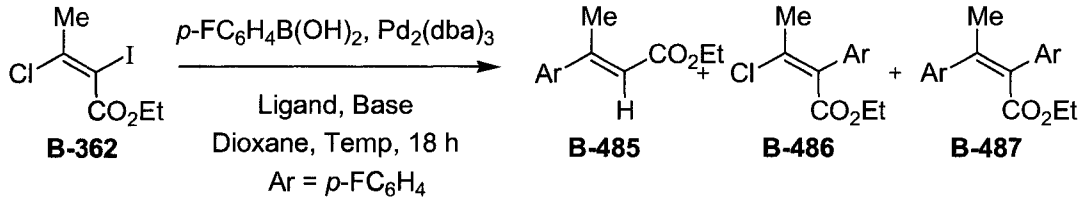


These modifications were not tested because other conditions discovered at the same time, described in the following paragraph, gave the desired products. However, in the event of difficulties in reactivity of boronic acid substrates, trifluoroborate salts should be examined as potential coupling partners.

[274] Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099.

Alkene **B-362** did not react when exposed to the more electron-poor *p*-fluorophenylboronic acid, using $Pd_2(dba)_3$, S-PHOS, and K_3PO_4 in dioxane at room temperature (Table 55, entry 1). The replacement of S-PHOS with P^tBu_3 as the ligand and the use of Cs_2CO_3 as the base gave an inseparable mixture of product **B-485** and **B-486**, as well as a trace amount of double-addition product **B-487** (entry 2). We were nevertheless encouraged by this result, as the production of **B-487** indicated that sp^2 coupling was occurring at the α-position of **B-362**. Increasing the amount of arylboronic acid to 40 equivalents resulted in an inseparable mixture of compound **B-485** and its *Z*-isomer (entry 3). Heating the same composition of components to reflux gave an inseparable, unidentifiable mixture of products (entry 4). Undaunted, we returned to a more reasonable loading of the boronic acid (four equivalents) and again heated the reaction to reflux. The reaction gave 20% of product **B-485** as well as an isolable amount of double-addition product **B-487** (entry 5).

Table 55. Suzuki coupling of *p*-fluorophenyboronic acid at the α-position of B-362



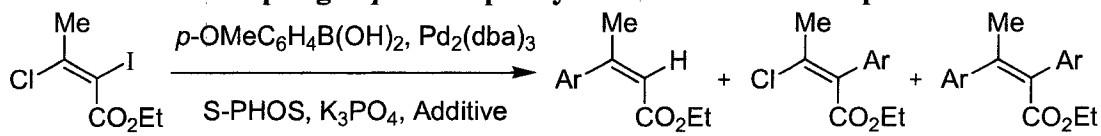
Entry	Ligand (0.2 equiv)	Base (3 equiv)	Temp	Result (% B-485 : B-486 : B-487)
1	S-PHOS	K_3PO_4	r.t.	NR
2	**P^tBu_3·HBF$_4$**	**Cs_2CO_3**	**r.t.**	**18 : 6 : trace**
3[a]	P^tBu_3·HBF$_4$	Cs_2CO_3	r.t.	8 : 0 : 0[b]
4[a]	P^tBu_3·HBF$_4$	Cs_2CO_3	reflux	mixture
5	P^tBu_3·HBF$_4$	Cs_2CO_3	reflux	20 : 0 : 12

[a] 40 equivalents of $PhB(OH)_2$ were used. [b] Product **B-485** was generation as a 2.5:1 mixture of isomers.

In an effort to promote this rather difficult coupling at the α-position, we turned to the more nucleophilic *p*-methoxyphenylboronic acid. Subjecting alkene **B-362** to *p*-methoxyphenylboronic acid, $Pd_2(dba)_3$, S-PHOS, and K_3PO_4 in dioxane at room temperature immediately delivered 20% of the desired product **B-489** (Table 56, entry 1).

The poor reactivity observed might be due to the accumulation of iodide anions in the reaction mixture, which could poison the palladium catalyst. The iodide could be sequestered by precipitation with a silver salt. Accordingly, Ag_2CO_3 (1 equiv) was tested as an additive, however, no improvement in yield was observed (entry 2).

Table 56. Suzuki coupling of *p*-fluorophenyboronic acid at the α-position of B-362



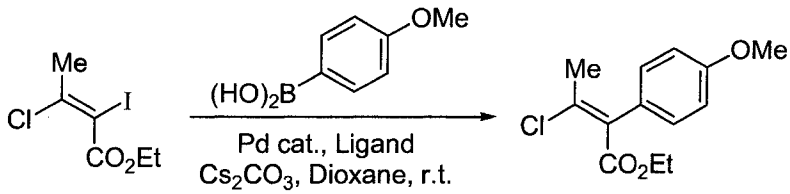
B-362 **B-488** **B-489** **B-490**

Entry	Additive	Yield (%)
1	-	**B-489**: 20%
2	Ag_2CO_3	**B-489**: 20%
3	H_2O	trace **B-489**

Water is frequently used as an additive, a solvent, or a co-solvent to promote Suzuki coupling reactions because the resulting hydroxide anion formed can complex with the boron to form a more reactive boron "ate" complex as described in Scheme 95 above. The use of a dioxane:H_2O (5:1) mixture resulted in only trace amounts of the desired product being formed (entry 3). Clearly, the presence of water did not promote the reaction in our system.

Investigation of a variety of catalyst precursors illustrated the importance of the source of palladium to the success of the reaction (Table 57). The combination of $Pd_2(dba)_3$, P^tBu_3 as the ligand, and Cs_2CO_3 as the base (Table E, entry 1) gave no improvement over the original conditions (Table C, entry 1). The yield of **B-489** dropped to only 10% when $PdCl_2$(dppf) was employed (entry 2). $PdCl_2(PPh_3)_2$ was a somewhat better palladium source, giving a 35% yield of the product (entry 3). The combination of palladium acetate and P^tBu_3 as the ligand was the most successful, giving a yield of 45% (entry 4).

Table 57. Screening of palladium sources



B-362 **B-489**

Entry	Catalyst	Ligand	Result [a]
1	$Pd_2(dba)_3$	$P^tBu_3 \cdot HBF_4$	17
2	$PdCl_2dppf$	-	10
3	$PdCl_2(PPh_3)_2$	$P^tBu_3 \cdot HBF_4$	35
4	**$Pd(OAc)_2$**	**$P^tBu_3 \cdot HBF_4$**	**45**

[a] 15–25% of double-addition product was also observed.

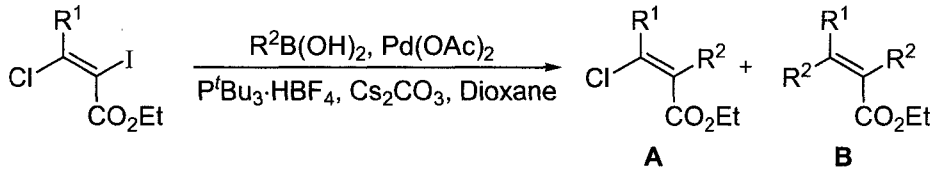
Presently satisfied that a regioselective reaction could be achieved at the α-position of the α,β-unsaturated esters, the most successful conditions (Table 57, entry 4) were utilized for a series of substrates.

2.2.2.3 Scope of trisubstituted olefin generation

The scope of this process was evaluated using the optimized conditions developed in the previous section. Phenylboronic acid, a previously unreactive substrate, could now be coupled with relative ease to give product **B-491** in 67% yield (Table 58, entry 1). Over-reaction also occurred at the β-position, giving product **B-492** in 15% yield. *p*-Methylphenylboronic acid coupled with a slightly better yield of 61% of the desired product **B-493** together with 22% of the double-addition product **B-494** (entry 2). The use of an alkenylboronic acid led to a mixture of products (entry 3), and utilizing styrenylboronic acid gave an inseparable mixture of the starting material, mono-, and di-addition products (entry 4). The use of *p*-methoxyphenyboronic acid gave a 50% yield of product **B-489** and another 30% of double-addition product **B-490** (entry 5). The reaction with *p*-fluorophenyboronic acid proceeded well, giving 57% of the desired product along with 20% of the over addition product (entry 6). The yield of the major product of this

reaction based on unrecovered starting material was 74%. The yield of the reaction dropped slightly when a branched alkyl group was used at R^1 (entry 7). A very low yield was obtained when a more sensitive silyl ether side chain was employed at the R^1 position, probably due to starting material decomposition (entry 8).

Table 58. Trisubstituted olefins generated from the Suzuki coupling reaction



Entry	R^1	R^2	Products (A:B)	Yield A:B[a] (%)
1	Me	C_6H_5	**B-491:B-492**	67:15
2	Me	*p*-MeC_6H_4	**B-493:B-494**	61:22
3	Me		**B-495:B-496**	mixture
4	Me	styrenyl	**B-497:B-498**	mixture
5	Me	*p*-$OMeC_6H_4$	**B-489:B-490**	50:30
6	Me	*p*-FC_6H_4	**B-499:B-500**	57:20 (74)
7	Cy	*p*-$OMeC_6H_4$	**B-501**	43
8	$TBSOCH_2$	*p*-$OMeC_6H_4$	**B-502**	15

[a] Yield in parenthesis is the yield of **B-499** based on unrecovered starting material.

Combined yields from these reactions illustrated that the reaction proceeded well in most cases at the α-position. A major cause for the moderate yields in some cases was because the reaction was stalling, perhaps due to precipitation of Pd black[275] or because of catalyst poisoning by the iodide anions generated in the reaction. Over-reaction was a key source of the lower observed yields, and we would seek to reduce this for future reactions. In addition, the problematic reactions of alkenylboronic acids required

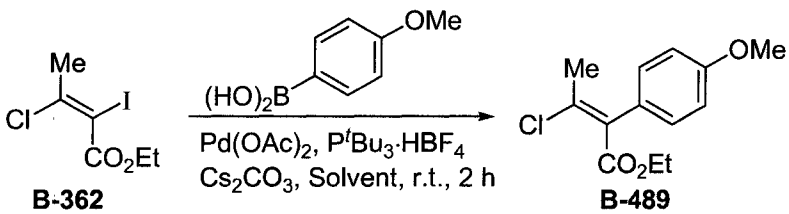
[275] The loss of ligands from the palladium(0) catalyst will result in the formation of palladium black metal, which precipitates out of solution.

resolution and the reactivity of substrates bearing branched alkyl and substituted alkyl moieties had to be increased.

2.2.2.3 Reaction optimization

Seeking to solve the issues discovered in our initial investigations, a solvent screen was performed (Table 59). Surprisingly, the reaction did not proceed in the most polar solvents: acetonitrile (entry 1), DMSO (entry 2), and DMF (entry 3). Only a trace of product was observed from a reaction performed in dichloromethane (entry 4). Mediocre solvents were THF, benzene, $CHCl_3$, trifluorotoluene, and *tert*-butyl methyl ether (entries 5–9). The use of dioxane (entry 10) and ethyl acetate (entry 11) gave above average results, while toluene proved to be the best solvent for this conversion, giving a 60% yield of product **B-489** (entry 12).

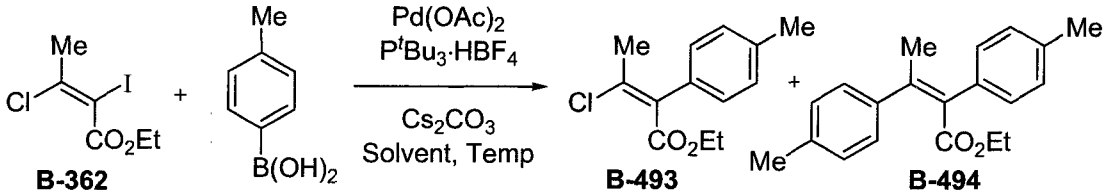
Table 59. Solvent scan for the Suzuki coupling at the α-position



Entry	Solvent	Result
1	CH_3CN	NR
2	DMSO	NR
3	DMF	NR
4	CH_2Cl_2	trace
5	THF	26
6	Benzene	17
7	$CHCl_3$	34
8	Trifluorotoluene	38
9	^{t}BuOMe	35
10	Dioxane	45
11	EtOAc	50
12	**Toluene**	**60**

A temperature scan was performed in an attempt to decrease the reactivity of the system.[276] The reaction of **B-362** with *p*-methylphenylboronic acid in dioxane at room temperature gave a 61% yield of **B-493**, but with an additional 22% of over-addition product **B-494** (Table 60, entry 1). Decreasing the reaction temperature decreased the yield dramatically, and the reaction seemed to stall after approximately one hour (entry 2). Over-addition product **B-494** was also observed in 9% yield. The use of toluene as the solvent at 45 °C gave a low yield of 18% in addition to 23% of product **B-494** (entry 3). A reaction at room temperature in toluene gave only a 21% yield of the desired product, but this time only a small amount of over-addition product was obtained (entry 4). The product distribution was very similar in the 0 °C reaction (entry 5), and therefore the more practical room temperature reaction in toluene were employed for the next set of experiments.

Table 60. Temperature and solvent study



Entry	Solvent	Temp (°C)	Yield[a] B-493 (%)	Yield B-494 (%)
1	Dioxane	23	61	22
2	Dioxane	12	32 (53)	9
3	Toluene	45	18 (51)	13
4	**Toluene**	**23**	**21 (35)**	**3**
5	Toluene	0	23 (34)	2

[a] Yield in parenthesis is based on unrecovered starting material.

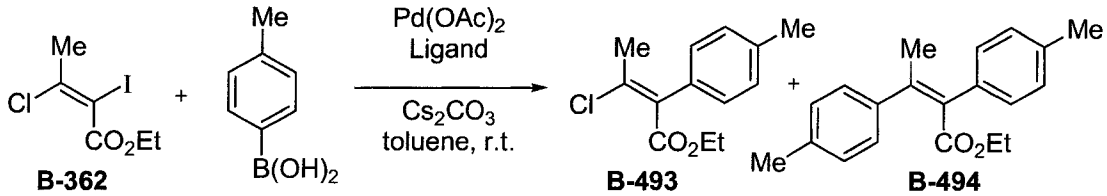
A ligand scan was performed on substrate **B-362** using *p*-methylphenylboronic acid, $Pd(OAc)_2$, and Cs_2CO_3 (Table 61).[276] The smaller phosphine ligands PMe_3 and PEt_3 gave poor yields and high levels of over-addition products (entries 1 and 2). Triphenylphosphine was even worse as a ligand, giving only a 10% yield of the desired product (entry 2). The bulkier phosphines, P^tBuMe_2 and PCy_3 were no better, giving low yields of the desired product **B-493**, and relatively high amount of double-addition

[276] Study performed by Julie Mercier, a graduate student in the Ogilvie research group.

product **B-494** (entries 4 and 5). S-PHOS proved to be a fantastic ligand, giving an 81% yield of the desired product, or 99% based on un-recovered starting material, and only a trace of **B-494** was observed (entry 6). This indicated that at some point the reaction had stalled. A reaction using S-PHOS was conducted at 40 °C, however this caused more over-addition to tetrasubstituted olefin **B-494** (entry 7). The same reaction performed at room temperature for three days gave a lower yield of the product, although only a trace of over-addition product **B-494** was obtained (entry 8). The use of Dave-PHOS gave only a moderate yield of the product (entry 9), and the use of the bidentate DPPF ligand gave a measly yield of 7% (entry 10).

A few ligand-free conditions were attempted, as these are occasionally quite successful in Suzuki reactions.[177] The use of a toluene/H_2O mixture (4:1) gave a trace of product and 15% of **B-494** (entry 11). A change in solvent system to a dioxane/H_2O (10:1) gave only a trace reaction (entry 12). Increasing the amount of water to a 4:1 dioxane/H_2O mixture resulted in only a trace of product (entry 13). Finally, an attempt to sequester the iodide using Ag_2CO_3 and S-PHOS as the ligand gave a moderate 64% yield of the product. The results obtained with S-PHOS were more than satisfactory even though complete conversion of the starting material had not been observed.

Table 61. Ligand scan identified S-PHOS as the optimal ligand



Entry	Ligand	Yield B-493[a] (%)	Yield B-494 (%)
1	$PMe_3 \cdot HBF_4$	20 (28)	27
2	$PEt_3 \cdot HBF_4$	23	20
3	PPh_3	10 (23)	12
4	$P^tBuMe_2 \cdot HBF_4$	16 (22)	30
5	$PCy_3 \cdot HBF_4$	21	43
6	**S-PHOS**	**81 (99)**	**trace**
7[b]	S-PHOS	75 (85)	15
8[c]	S-PHOS	62 (99)	trace
9	Dave-PHOS	45 (65)	15
10	dppf	7 (14)	19
11[d]	None	trace	15
12[e]	None	trace	25
13[f]	None	trace	20
14	$S\text{-PHOS}/Ag_2CO_3$	64 (68)	13

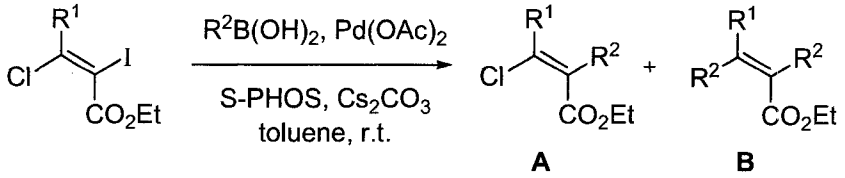
[a] Yield in parenthesis is based on unrecovered starting material. [b] Reaction performed at 40 °C. [c] Reaction run for 3 days. [d] Conducted in 4:1 toluene:H_2O. [e] Conducted in 10:1 dioxane:H_2O. [f] Conducted in 4:1 dioxane:H_2O.

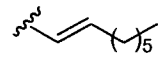
These optimization studies identified toluene as the optimal solvent $Pd(OAc)_2$ as the ideal catalyst precursor, and S-PHOS as the optimal ligand. The temperature scan had also indicated that room temperature provided the best results in which maximal conversion starting material was achieved while minimizing over addition.

The use of these optimal conditions gave a significant improvement in the yield of the desired products and little or no over-addition product (Table 62).[276] The use of *p*-$MeC_6H_4B(OH)_2$ gave an 81% yield of the desired product (**B-493**) or 99% based on un-recovered starting material and only a trace of over-addition was observed (entry 1). The use of *p*-$OMeC_6H_4B(OH)_2$ gave an 84% yield of the desired product (**B-489**) and no over-addition product could be detected (entry 2). The use of the slightly more hindered *o*-$OMeC_6H_4B(OH)_2$ gave a 50% yield of olefin (**B-503**) or an 82% yield based on un-recovered starting material (entry 3). Again, no trace of over-addition product could be detected. Phenylboronic acid could be employed at room temperature to give a 50% yield

of alkene **B-491** (entry 4), however the reaction was more efficient at 0 °C, giving a 63% yield of the product (entry 5). The electron-poor *p*-fluorophenylboronic acid gave only a moderate yield of product when the optimized conditions were employed (entry 6), however the reaction proceeded more efficiently using $^{t}Bu_3P$ as the ligand and dioxane as the solvent, giving the desired product in 57% yield (entry 7). The use of *p*-chlorostyrenylboronic acid gave an unisolable mixture of products (entry 8), however the use of an alkenylboronic acid proceeded more smoothly to give the desired olefin in a 40% yield (entry 9). Thiophenylboronic acid could be employed as a substrate, thereby giving access to heterocycle-substituted olefins (entry 10). The bulky aromatic substrate 2-naphthylboronic acid reacted smoothly to give product **B-509** (entry 11). Variation of the R^1 substituent was also possible, as shown by the coupling of CH_2OTBS-substituted substrate (**B-502**) with *p*-$MeC_6H_4B(OH)_2$ to give the desired trisubstituted olefin in 75% yield (entry 12).

Table 62. Generation of trisubstituted olefins under optimized conditions



Entry	R^1	R^2	Product (A,B)	Yield A (%)[a]	Yield B (%)
1	Me	*p*-MeC_6H_4	**B-493, B-494**	81 (99)	trace
2	Me	*p*-$OMeC_6H_4$	**B-489, B-490**	84 (86)	0
3	Me	*o*-$OMeC_6H_4$	**B-503, B-504**	50 (82)	0
4	Me	C_6H_5	**B-491, B-492**	50 (70)	0
5[b]	Me	C_6H_5	**B-491, B-492**	63 (73)	0
6	Me	*p*-FC_6H_4	**B-499, B-500**	36 (83)	0
7[c]	Me	*p*-FC_6H_4	**B-499, B-500**	57 (75)	20
8	Me	*p*-chlorostyrenyl	**B-505, B-506**	mixture	0
9	Me		**B-495, B-496**	40 (50)	0
10	Me	thiophenyl	**B-507, B-508**	30 (85)	0
11	Me	2-naphthyl	**B-509, B-510**	95 (99)	0
12	$TBSOCH_2$	*p*-$OMeC_6H_4$	**B-502, B-511**	74 (87)	0

[a] Yield is brackets is based on un-recovered starting material. [b] The reaction was conducted at 0 °C. [c] P^tBu_3 was used as the ligand and dioxane was employed as the solvent.

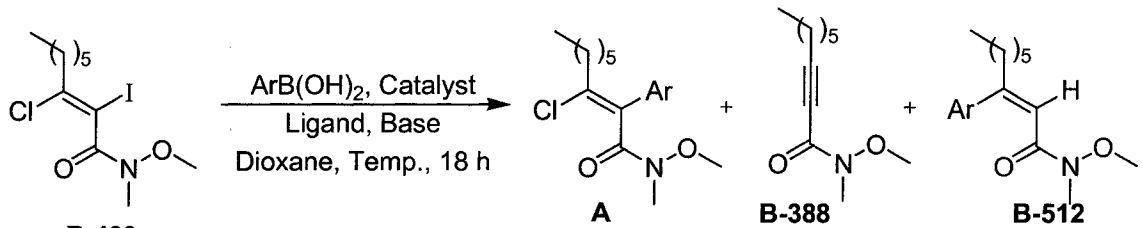
2.2.2.4 Studies of a Weinreb amide-substituted alkene template

Our success in the generation of trisubstituted olefins from β-chloro-α-iodo-α,β-unsaturated ester templates gave us reason to believe that our methodology could be extended to other types of olefin templates. A Weinreb amide template would give a handle for further functionalization, and its potential for derivatization was therefore explored. Olefin **B-400** was exposed to *p*-methoxyphenylboronic acid, $Pd_2(dba)_3$, S-PHOS, and K_3PO_4 in dioxane. After 18 hours, alkyne **B-388** was recovered in 80% yield from the reaction (Table 63,entry 1). Performing the reaction with the careful exclusion of water, in the presence of molecular sieves had no effect (entry 2). The starting material

was recovered quantitatively when water was used as an additive (entry 3). The use of $PdCl_2(dppf)$ with Cs_2CO_3 as the base gave no reaction (entry 4). A change in the catalyst to $Pd(OAc)_2$ and the ligand to P^tBu_3 gave an 87% yield of the undesired alkyne **B-388** (entry 5).

Clearly, room temperature was not sufficient to effect the desired transformation. Using the same condition as in entry 4, a reaction was heated to reflux (entry 6). This time 91% of trisubstituted olefin **B-512** was obtained, in addition to 8% of alkyne **B-388**. The source of this product was unknown at the time, but will be subject to further investigations. Unfortunately, the analogous products were not obtained when phenylboronic acid (entry 7) or *p*-fluorophenylboronic acid (entry 8) were employed under refluxing conditions. Instead, only product **B-388** was observed in these cases.

Table 63. Attempted derivatization of a Weinreb amide olefin template



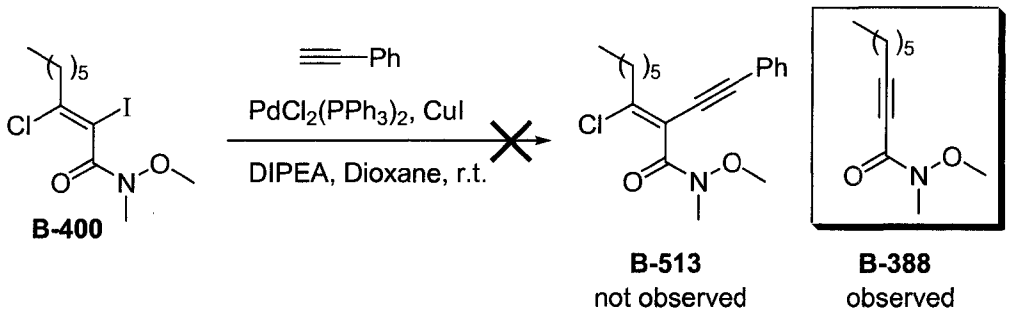
Entry	$ArB(OH)_2$	Catalyst	Ligand	Base	Temp	Yield A : B-388 : C (%)
1	*p*-$MeOC_6H_4$	$Pd_2(dba)_3$	S-Phos	K_3PO_4	r.t.	0:80:0
2[a]	*p*-$MeOC_6H_4$	$Pd_2(dba)_3$	S-Phos	K_3PO_4	r.t.	0:84:0
3[b]	*p*-$MeOC_6H_4$	$Pd_2(dba)_3$	S-Phos	K_3PO_4	r.t.	NR
4	*p*-$MeOC_6H_4$	$PdCl_2(dppf)$	-	Cs_2CO_3	r.t.	NR
5	*p*-$MeOC_6H_4$	$Pd(OAc)_2$	P^tBu_3[c]	Cs_2CO_3	r.t.	0:87:0
6	*p*-$MeOC_6H_4$	$Pd(OAc)_2$	P^tBu_3[c]	Cs_2CO_3	reflux	0:8:91[d,e]
7	C_6H_5	$Pd_2(dba)_3$	P^tBu_3[c]	Cs_2CO_3	reflux	0:95:0
8	*p*-FC_6H_4	$Pd_2(dba)_3$	P^tBu_3[c]	Cs_2CO_3	reflux	0:93:0

[a] 4Å MS were added. [b] H_2O (5 equiv) was added. [c] Added as the HBF_4 salt. [d] Based on unrecovered starting material. [e] Compound # **B-512**.

Because of the evident reactivity problems with the sp^2-Suzuki reactions, the Sonogashira reaction was subsequently examined as an alternative (Scheme 98).

Unfortunately, the degradation of amide **B-400** to product **B-388** under previously effective Sonogashira coupling conditions was observed as the sole product.

Scheme 98. Attempted Sonogashira coupling reaction with Weinreb amide template



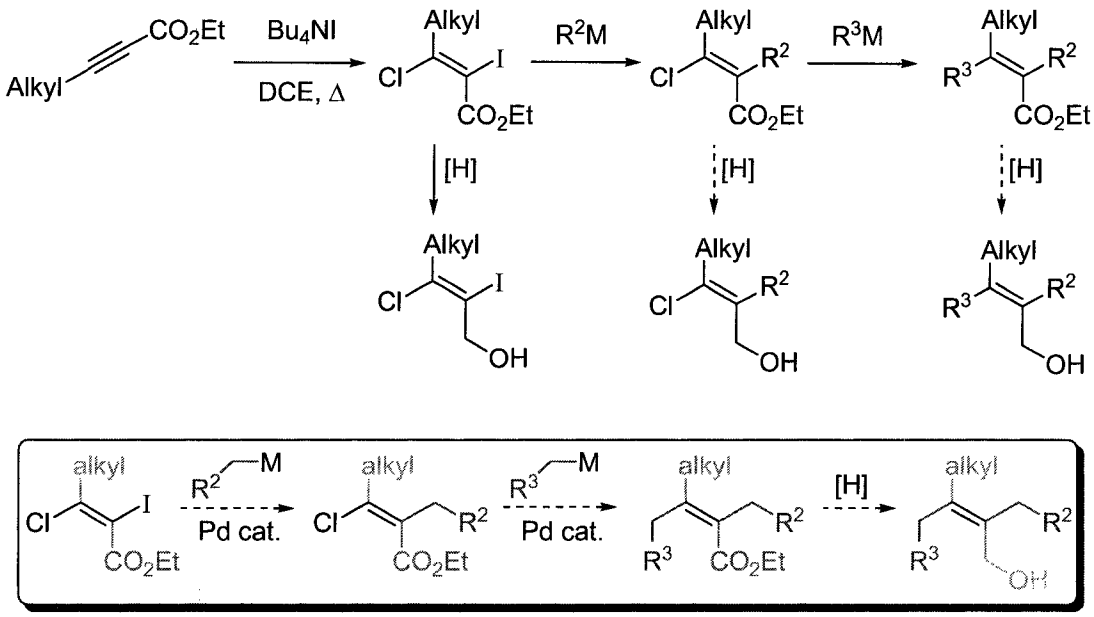
Studies towards the generation of tetrasubstituted alkenyl amides were set aside for the time being, and our focus shifted instead to the generation of tetra-alkyl-substituted alkenes.

2.2.2.5 The alkyl-Suzuki coupling reactions with β-chloro-α-iodo-alkene templates

The facile generation of alkyl substituents at two positions had already been accomplished from the β-chloro-α-iodo-α,β-unsaturated ester templates (Scheme 99). Alkynes bearing alkyl substituents had been the best substrates for the chloroiodination process. The ester could also be readily reduced with DIBAL to generate allylic alcohols.[277] All that remained was the substitution of two additional alkyl moieties for the iodide and chloride, and this had to be done regio- and stereoselectively.

[277] It will be later demonstrated that the ester can be reduced at any of the coupling stages, either from the alkene template, from the trisubstituted olefin, or from the tetrasubstituted olefins.

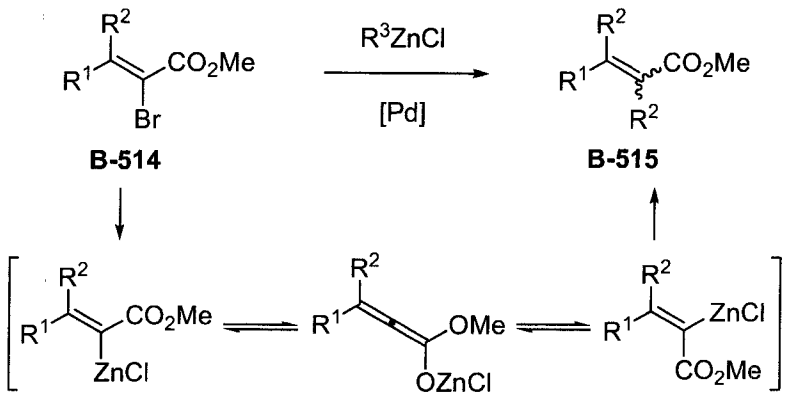
Scheme 99. Development of tetra-alkyl substituted olefins



The Negishi coupling reaction[278,279] was avoided at this stage. Although this reaction is capable of installing alkyl substituents, previous research groups had reported olefin isomerization during coupling at the α-position.[210] This isomerization was thought to proceed via an allenoate intermediate as shown in Scheme 100. Stille reactions[280] were an option, however they were avoided at this point due to the toxicity of the tin reagents and the potential purification difficulties that are often associated with the removal of tin byproducts.[281]

[278] Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
[279] *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Ed.; Wiley-VCH: New York, 1998.
[280] Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1.
[281] A few unsuccessful attempts were made to generate α-alkyl-substituted products via the Stille reaction.

Scheme 100. The Negishi reaction was avoided due to probable isomerization of the alkene substrate

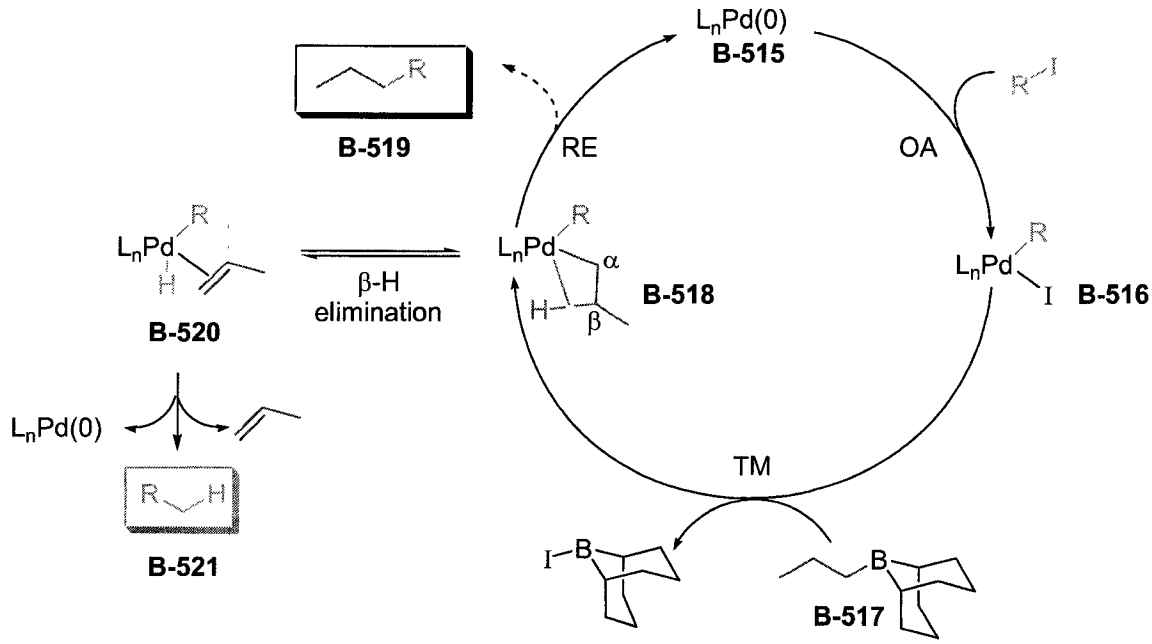


It appeared that the Suzuki coupling reaction would be most suitable for alkyl coupling reactions.[160,279,282] The mechanism for the alkyl-Suzuki reaction is the same as that described previously (Section 2.2.2.1 Background: the Suzuki reaction), however there were a few fine points to be heeded to ensure success. The alkyl groups being transferred are less nucleophilic than their sp^2- or sp-hybridized counterparts and the use of carbonate or hydroxide bases is therefore essential. Water is frequently used to promote this reaction.

The alkyl-Suzuki reaction often suffers from decreased yields or side products due to β-hydride elimination (Scheme 101). If the palladium possesed a vacant coordination site after the transmetallation step, coordination can occur with a β-C-H bond (**B-518**) that is *cis* to the metal. The β-H-elimination, or dehydropalladation, of the hydride from the original organic moiety results in a palladium hydride and an alkene (**B-520**). Dissociation of the alkene and reductive elimination of RH regenerates the palladium(0) catalyst and generates the undesired product **B-521**. The β-hydride elimination process is in competition with the desired reductive elimination process that would give product **B-519**.

[282] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

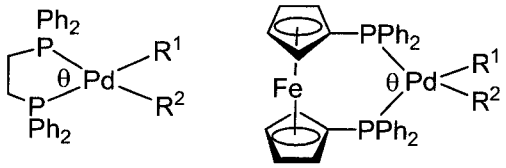
Scheme 101. β-hydride elimination is competitive with reductive elimination



The desired reductive elimination process can be promoted by using bulky, bidentate ligands with large bite angles. Bulky, bidentate ligands occupy coordination sites on the metal; this hinders the coordination of the β-CH bond. Bidentate ligands also enforce *cis* geometry between the coupling partners. Reductive elimination is consequently favored because the coupling partners are held in close proximity to each other and there is no longer a need for a *trans-cis* isomerization before reductive elimination can take place. The large bite angle of the ligands forces the coupling partners even closer together, increasing the steric bulk around the metal, and favoring reductive elimination (Figure 9). Bidentate ligands such as DPPE[283] are occasionally employed; however, DPPF is frequently reported to be the superior ligand for alkyl-Suzuki reactions.[160,282]

[283] Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, *120*, 8527.

Figure 9. A large bite angle of the ligand favors reductive elimination



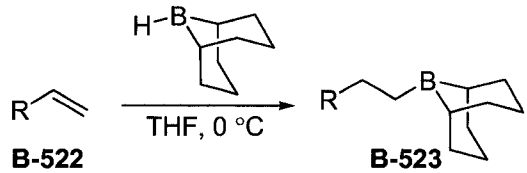
θ = 85°
DPPE

θ = 99°
DPPF

Bite angle = θ

Considering these factors, the alkyl-Suzuki reaction was investigated on the olefin templates. The requisite 9-alkyl-BBN reagents (**B-523**) were generated via the hydroboration of terminal alkenes (**B-522**) with 9-BBN (Scheme 102) and used immediately.

Scheme 102. Preparation of 9-alkyl-BBN reagents



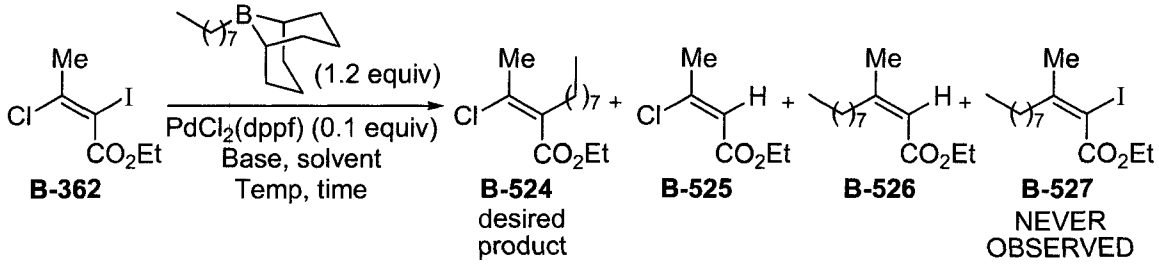
B-522 **B-523**

R = $CH_3(CH_2)_5$, $AcO(CH_2)_5$, $BzO(CH_2)_5$, $BnO(CH_2)_5$

The alkyl-Suzuki coupling reaction between olefin **B-362** and 9-octyl-BBN was first attempted using $PdCl_2$(dppf) as the catalyst and K_3PO_4 as the base in THF at room temperature (Table 64, entry 1). This returned primarily starting material **B-362**, however the GC–MS results also showed a trace of compound **B-525**. This product would result from β-hydride elimination at the α-position of the olefin as shown in the catalytic cycle in Scheme 101. A trace of the desired product **B-524** was observed by GC–MS when a reaction using identical reagents was heated to reflux (entry 2). Unfortunately, the separation of the product from the starting material was not possible. Extensive efforts were made to identify a solvent system that could purify the products. Techniques such as multiple TLC developments, 2D TLC, and HPLC separation were unsuccessfully attempted. No reaction was observed when the incorporation of water into the reaction was investigated at room temperature (entry 3). Reactivity was only slightly restored when this reaction was heated to reflux, generating a trace of compound **B-524,** which

could only be observed by GC–MS (entry 4). The reaction of **B-362** with three equivalents of 9-alkyl-BBN reagent using $K_3PO_4 \cdot H_2O$ as the base in THF at reflux gave 27% of compound **B-526** as a mixture of isomers (entry 5). This was the highest yield obtained thus far, and although it was of the undesired product, an alkyl-Suzuki reaction had nevertheless taken place at the β-position.

Table 64. Initial studies toward the alkyl-Suzuki coupling reaction of an olefin template



Entry	Base (3 equiv)	Solvent (0.1M)	Temp	Time	GC–MS Result
1	K_3PO_4	THF	r.t.	3 h	**B-362**, trace **B-525**
2	K_3PO_4	THF	reflux	3 h	trace **B-524**
3	K_3PO_4/H_2O (3M)[a]	THF	r.t.	48 h	NR
4	K_3PO_4/H_2O (3M)[a]	THF	reflux	3 h	trace **B-524**
5[c]	$K_3PO_4 \cdot H_2O$	THF	reflux	48 h	27% **B-526**[b]
6	K_3PO_4	DMF	r.t.	48 h	trace **B-525**, **B-526** and unidentified products
7	$NaOH/H_2O$ (3M)[a]	THF	r.t.	24 h	10% **B-526**

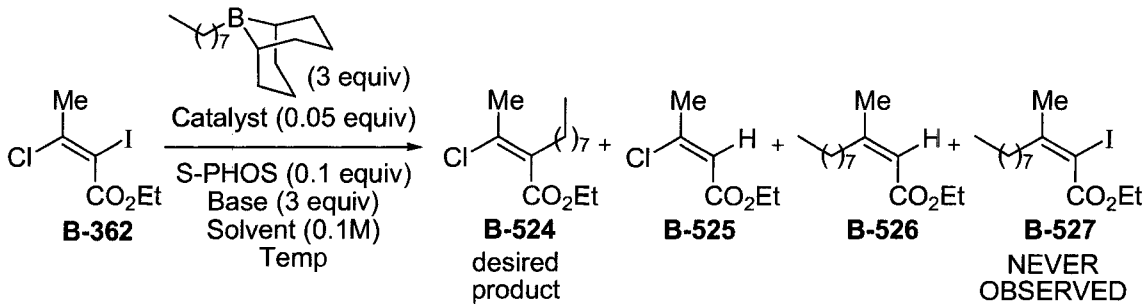
[a] A 3M K_3PO_4 solution was prepared in H_2O and was sparged for 1 hour with N_2. The solution was added to the reaction mixture via syringe such that 3 equivalents of the base were employed. The 9-octyl-BBN solution was added last. [b] Obtained as a 4:1 mixture of isomers [c] 3 equiv 9-octyl-BBN were employed

Since the DPPF ligand seemed to be ineffective at preventing β-hydride elimination for the substrate in question, S-PHOS was examined. This bulky and strongly electron-donating ligand has been highly successful for many difficult cross-coupling reactions.[284] The first experiment used $Pd(OAc)_2$ and K_3PO_4 in THF at reflux; rigorously excluding

[284] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

water from the reaction (Table 65, entry 1). This returned 50% of the starting material, but GC–MC analysis did indicate trace levels of products **B-524** and **B-526**. The use of $K_3PO_4 \cdot H_2O$ gave a 30% yield of **B-526** as a mixture of isomers (entry 2). The same reaction, conducted at room temperature, gave a marginally higher yield of **B-526**, again as a mixture of isomers (entry 3). A decrease in the amount of borane used returned 80% of the starting material and gave only a trace of product **B-526** (entry 4). A return to the first conditions with a change in solvent to DMF at 85 °C gave a 30% yield of **B-526** as a mixture of isomers (entry 5). The yield was slightly improved when $K_3PO_4 \cdot H_2O$ was employed in DMF at 85 °C, however a detectable amount of the minor isomer was still present (entry 6). The use of $PdCl_2(PPh_3)_2$ as the palladium source in refluxing THF gave a 36% yield of **B-526** as a nearly equimolar mixture of isomers (entry 7). Lastly, using $PdCl_2$ as the palladium source in THF at reflux gave **B-526** as a single isomer, albeit in only 21% yield.

Table 65. Analysis of S-PHOS as a ligand for the alkyl-Suzuki reaction



Entry	Catalyst	Base	Solvent	Temp	Result (*Z*:*E*)
1	$Pd(OAc)_2$	K_3PO_4	THF	reflux	50% **B-362**, trace **B-524**, trace **B-526**
2	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	THF	reflux	30% **B-526** (2:1)
3	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	THF	r.t.	38% **B-526** (3:1)
4[a]	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	THF	r.t.	80% **B-362**; trace **B-526**
5	$Pd(OAc)_2$	K_3PO_4	DMF	85 °C	30% **B-526** (6:1)
6	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	DMF	85 °C	47% **B-526** (13:1)
7	$PdCl_2(PPh_3)_2$	$K_3PO_4 \cdot H_2O$	THF	reflux	36% **B-526** (1.7:1)
8	$PdCl_2$	$K_3PO_4 \cdot H_2O$	THF	reflux	21% **B-526** (single isomer)

[a] One equiv 9-octyl-BBN was employed.

The fact that product **B-525** *had* been observed, but that compound **B-527** was *never* observed in the reaction mixtures suggested that coupling at the β-position occurred after β-hydride elimination/reductive elimination at the α-position. Employing the initial conditions but using DMF as the solvent resulted in the detection of a trace of **B-524**, **B-525**, along with a number of unidentified, inseparable products (entry 6). A change in base to NaOH (3M solution in H_2O) at room temperature gave a 10% yield of product **B-526**, but no other identifiable compounds were evident. It was highly probable that the starting material had decomposed under the reaction conditions. From these encouraging results, coupling at the β-position of trisubstituted alkenes was expected to proceed smoothly.

Because of the difficulties encountered with the separation of the product from the non-polar substrate when 9-octyl-BBN was used as the coupling partner, the reaction of alkyl reagents bearing protected alcohol functionalities was investigated. Initially, $PdCl_2$(dppf) was attempted in a 5:1 mixture of THF:H_2O, however no reaction was observed (Table 66, entry 1). Similarly, a reaction conducted in a 5:1 mixture of CH_2Cl_2:H_2O gave no reaction (entry 2). A number of products were obtained upon reaction in dioxane:H_2O, however, none of these were isolable (entry 3). The same reaction, run for 12 hours instead of 2 hours, gave another inseparable mixture of products (entry 4). No improvement was observed when the reaction was performed in DMF:H_2O (5:1) (entry 5).

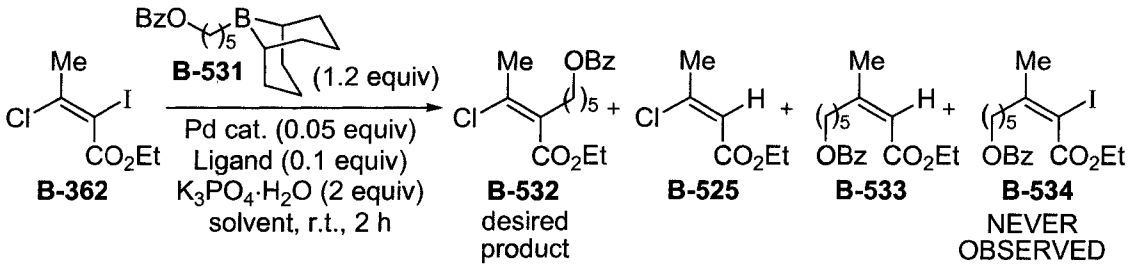
Due to the undesirable results obtained using $PdCl_2$(dppf), $Pd(OAc)_2$ was used as the palladium source and a variety of ligands were analyzed. None of the bidentate ligands tested, DPPM, DPPE, DPPP, and XANTPHOS, (structures are shown in Figure 10) showed any reaction (entries 5–9). Two very bulky, monodentate *N*-heterocyclic carbene (NHC) ligands were investigated next (Structures are shown in Figure 10). These ligands are excellent σ-donors, and are robust under many reaction conditions.[285] Neither the use of **B-528** or **B-529** resulted in the conversion to any product, however (entries 10–11).

[285] (a) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046. (b) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

Both XANTPHOS and **B-528** were tested using $Pd_2(dba)_3$ as the pre-catalyst; again, no product was observed in either case (entries 12–13).

A number of monodentate phosphine ligands were then screened (Table 66). These varied in size from the much smaller PMe_3 ligand to the much larger P^tBu_2Me and PCy_3 ligands (entries 14–21). Unfortunately, none of these ligands showed any reactivity and only starting material was recovered in each case.

Table 66. Alkyl-Suzuki reaction using more polar substrates

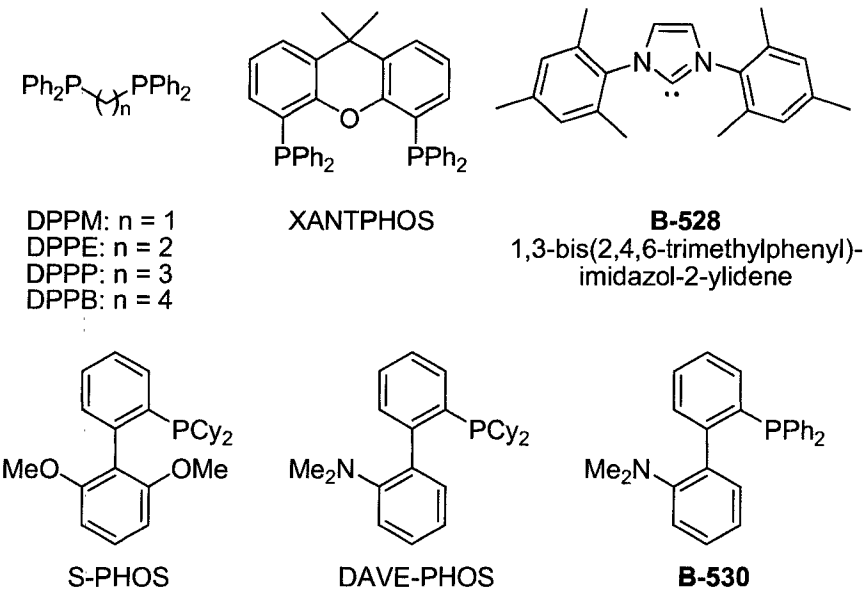


Entry	Catalyst, Ligand	Solvent	Result (% conversion)
1	$PdCl_2(dppf)$	THF:H_2O (5:1)	NR
2	$PdCl_2(dppf)$	CH_2Cl_2:H_2O (5:1)	NR
3	$PdCl_2(dppf)$	Dioxane:H_2O (5:1)	mixture
4[a]	$PdCl_2(dppf)$	Dioxane:H_2O (5:1)	mixture
5	$PdCl_2(dppf)$	DMF:H_2O (5:1)	mixture
6	$Pd(OAc)_2$, DPPM	Dioxane:H_2O (5:1)	NR
7	$Pd(OAc)_2$, DPPE	Dioxane:H_2O (5:1)	NR
8	$Pd(OAc)_2$, DPPP	Dioxane:H_2O (5:1)	NR
9	$Pd(OAc)_2$, XANTPHOS	Dioxane:H_2O (5:1)	NR
10	$Pd(OAc)_2$ **B-528**	Dioxane	NR
11	$Pd(OAc)_2$, **B-529**	Dioxane	NR
12	$Pd_2(dba)_3$ XANTPHOS	Dioxane	NR
13	$Pd_2(dba)_3$, **B-528**	Dioxane	NR
14	$Pd(OAc)_2$, PMe_3·HBF_4	Dioxane	NR
15	$Pd(OAc)_2$, PEt_3·HBF_4	Dioxane	NR
16	$Pd(OAc)_2$, **B-530**	Dioxane	NR

17[b]	$Pd(OAc)_2$, **B-530**	Dioxane	NR
18	$Pd(OAc)_2$, Dave-Phos	Dioxane	NR
19[b]	$Pd(OAc)_2$, Dave-Phos	Dioxane	NR
20	$Pd(OAc)_2$, $PCy_3 \cdot HBF_4$	Dioxane	NR
21	$Pd(OAc)_2$, $P^tBu_2Me \cdot HBF_4$	Dioxane	NR

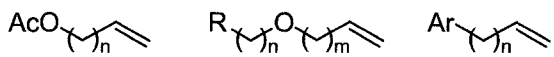
[a] The reaction was run for 12 h. [b] The reaction was conducted at reflux.

Figure 10. Structures of ligands used in ligand scan



The results obtained using the benzoate ester substrate **B-362** seemed inferior to those obtained using the 9-hexenyl-BBN substrate, even though product separation was possible using the more polar substrate. Alternative substrates, such as acetates or ethers will be investigated in future studies (Figure 11).

Figure 11. Alternative substrates for the alkyl-Suzuki reaction

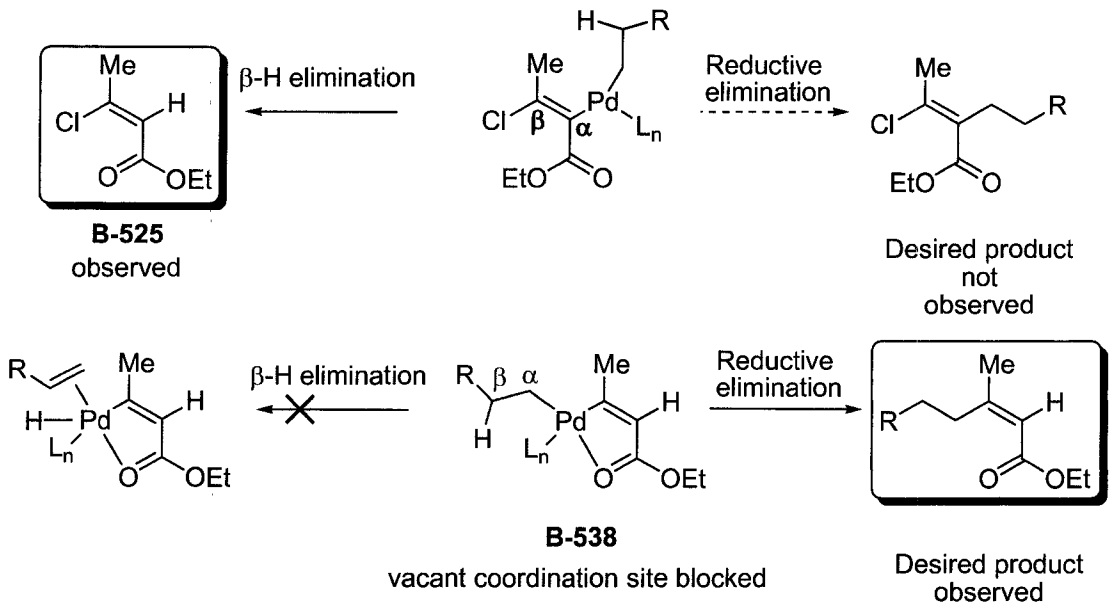


B-535 **B-536** **B-537**

The question remained as to why β-hydride elimination was observed at the α-position to give products such as **B-525**, but the alkyl-Suzuki reaction proceeded smoothly at the β-position to give products such as **B-526** (Scheme 103). One plausible explanation was

the formation of a five-membered palladacycle (**B-538**) with the carbonyl oxygen during coupling at the β-position.[286] As shown in Scheme 103, the carbonyl oxygen would occupy a vacant coordination site on the palladium. This would hinder the coordination of the β-CH bond, thereby hindering or preventing β-hydride elimination altogether. In addition to *cis* geometry being mandated by the bidentate ligand, the addition presence of the carbonyl ligand would force the coupling partners into even closer proximity to each other.

Scheme 103. Coupling at the β-position was promoted by palladacycle formation

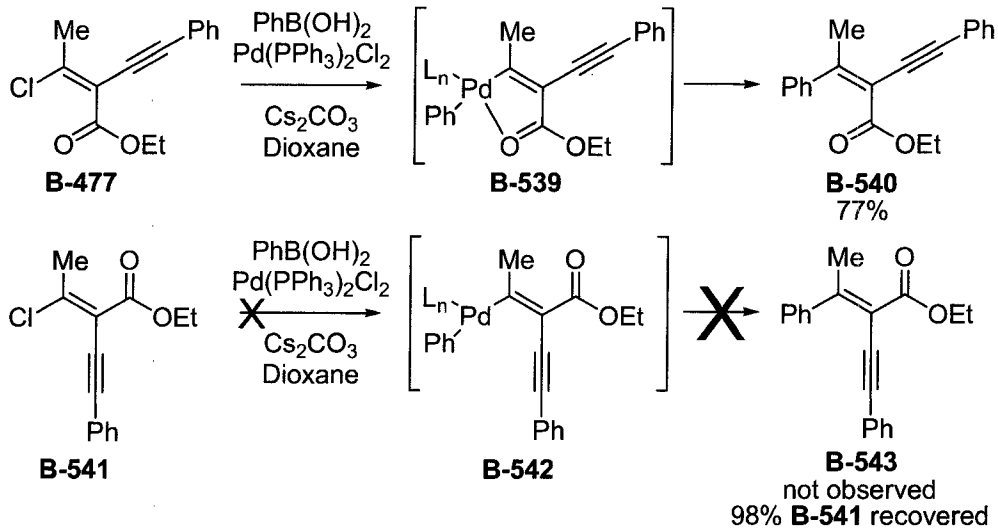


This palladacycle hypothesis was supported by two parallel Suzuki experiments (Scheme 104).[287] First, substrate **B-477** was subjected to phenylboronic acid, $Pd(PPh_3)_2Cl_2$, and Cs_2CO_3 in dioxane.[288] This gave a 77% yield of tetrasubstituted alkene **B-540** as a single isomer.[227] Conversely, no reaction was observed with trisubstituted alkene **B-541**, the stereoisomer of **B-477**, and the starting material was recovered almost quantitatively. Given that there is relatively little steric difference between compounds **B-477** and **B-541**, the reaction with **B-477** was likely facilitated by the formation of

[286] Review of palladacycle formation and chemistry: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.
[287] Reaction performed by Philippa Robyn Payne.
[288] The development of the β-Suzuki coupling conditions are described in 2.3 The Synthesis of Tetrasubstituted Olefins.

palladacycle **B-539**. The formation of a palladacycle was not possible in compound **B-542** due to the geometry of the molecule.

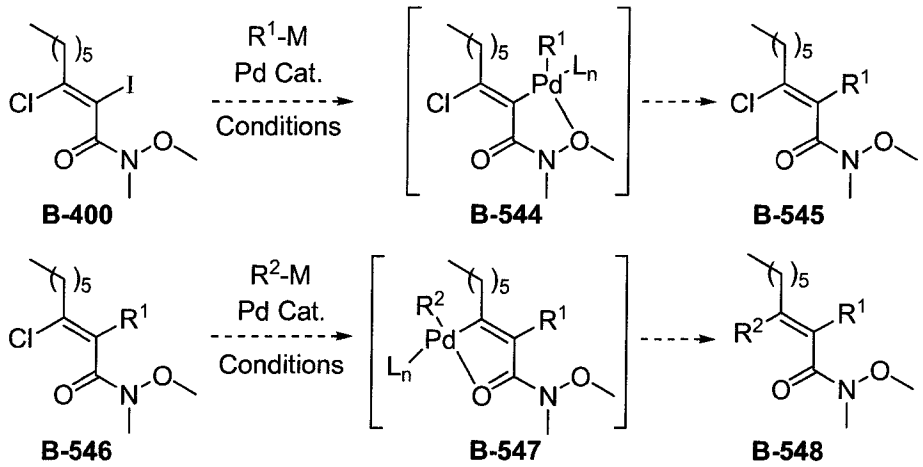
Scheme 104. Palladacycle formation supported by parallel Suzuki experiments



Our investigations turned to substrates in which palladacycle formation would be possible at the α-position. Two substrates types were examined: the first was a Weinreb amide and the second was a derivative of the original alkenyl ester templates.

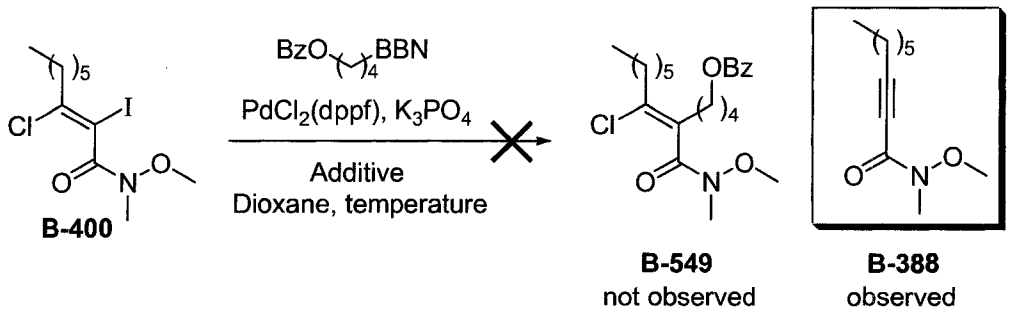
The use of a Weinreb amide should be particularly advantageous, because not only would palladacycle formation be possible at the α-position, but also the carbonyl would also still be in place for the formation of a palladacycle at the β-position (Scheme 105). The Weinreb amide substrate **B-400** was therefore subjected to alkyl-Suzuki coupling conditions.

Scheme 105. The Weinreb amide should enable palladacycle formation at both the α- and β-positions



The attempted alkyl-Suzuki reaction gave only alkyne **B-388** under the three reaction conditions investigated (Table 67). Typical alkyl-Suzuki reaction conditions were attempted first: $PdCl_2(dppf)$ and K_3PO_4 in dioxane (entry 1). In addition, a room temperature reaction was investigated with two equivalents of water (entry 2), and another reaction was examined with two equivalents of water at reflux (entry 3). In all cases, only alkyne **B-388** was obtained and not a trace of product **B-549** was detected by GC–MS or by NMR.

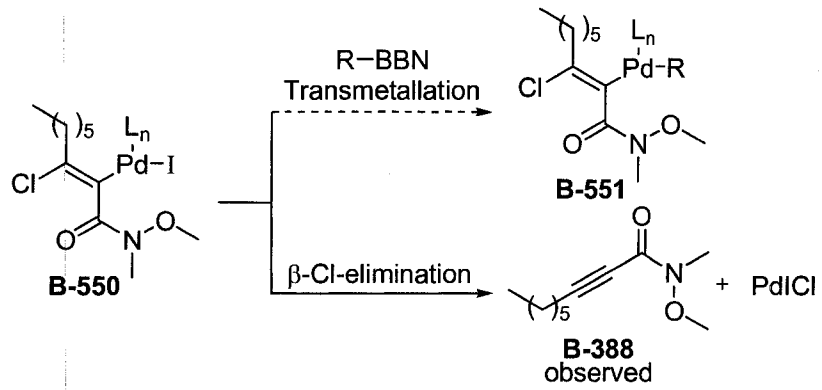
Table 67. Attempted alkyl-Suzuki coupling reaction with Weinreb amide template



Entry	Additive	Temperature	Result
1	none	r.t.	**B-388** only
2	H_2O	r.t.	**B-388** only
3	H_2O	reflux	**B-388** only

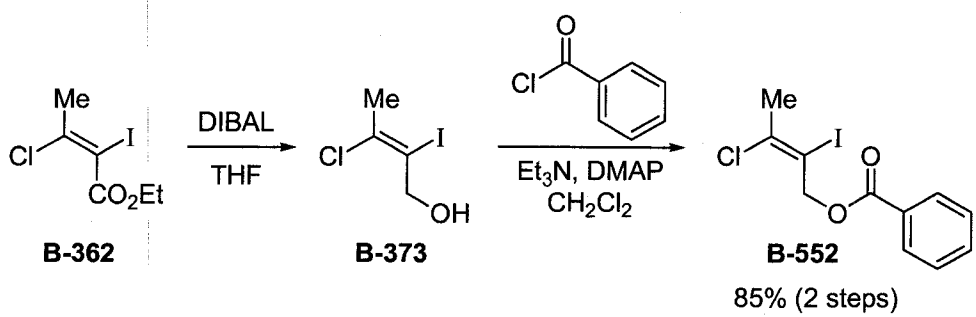
It seemed that the transmetallation step had not taken place at all (Scheme 106). If the transmetallation step been successful for this process, we should have seen evidence of the desired product **B-549** or at least evidence of the product resulting from β-hydride elimination. In order to promote the transmetallation and subsequent reductive elimination processes, different borane substrates would have to be investigated,[289] the effect of H_2O would have to be studied in greater depth, as would the effects on the reaction of different bases, ligands, and solvents.

Scheme 106. Competitive steps: transmetallation and β-chloride elimination



Given the failure of the Weinreb amide to effect alkyl-Suzuki reactions at either the α- or β-positions, the next substrate type was investigated. The presence of an ester moiety was intended to enable palladacycle formation and thereby facilitate the alkyl-Suzuki process. The required substrate (**B-552**) was obtained by reduction of ester **B-362** followed by esterification of alcohol **B-373** (Scheme 107).

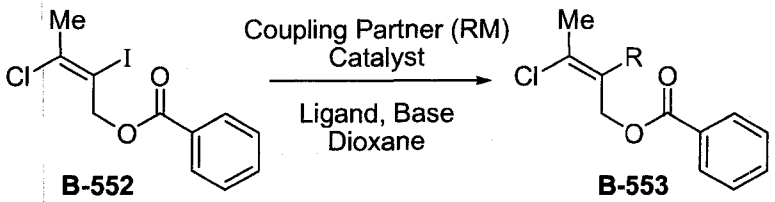
Scheme 107. Substrate designed to enable palladacycle formation at the α-position



[289] The 4-(9-bora-bicyclo[3.3.1]nonan-9-yl)butyl benzoate seemed to be an unsuitable substrate in previous investigations.

To ensure that this substrate would be reactive under coupling conditions that had previously given desired coupling products at the α-position, two sp^2-Suzuki reactions were attempted on substrate **B-552** as controls. Exposure of substrate **B-552** to phenylboronic acid to $Pd_2(dba)_3$, $P^tBu_3 \cdot HBF_4$, and Cs_2CO_3 in dioxane gave no reaction (Table 68, entry 1). Using the same reaction conditions with the more nucleophilic *p*-methoxyphenylboronic acid had no effect (entry 2). In spite of these results, we attempted two room temperature alkyl-Suzuki reactions on substrate **B-552**. Exposure of the substrate (**B-552**) to the 9-alkyl-BBN reagent (**B-531**) and using $PdCl_2(dppf)$ and $K_3PO_4 \cdot H_2O$ in dioxane as the solvent gave no reaction (entry 3). Similarly, a dioxane:H_2O (10:1) solvent system showed no product (entry 4). Evidently, this change in substrate changed the reactivity of the system too drastically for the previously successful reaction conditions to be effective. Surely, reaction optimization would be possible and many factors could be examined and improved, however this would be left for future work.

Table 68. Investigating the reactivity of substrate B-552



B-552 **B-553**

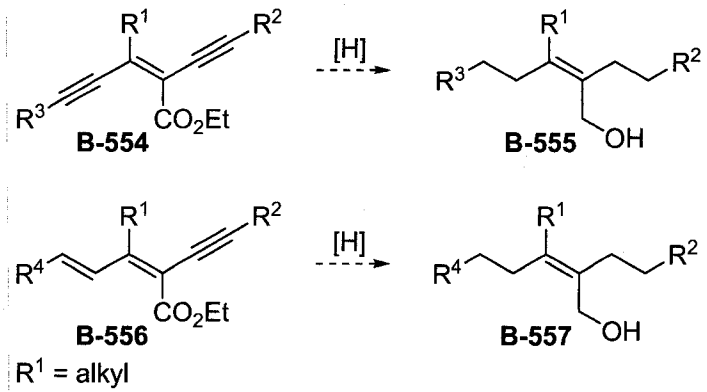
Entry	Coupling Partner	Catalyst system	Base	Result
1	$PhB(OH)_2$	$Pd_2(dba)_3$, P^tBu_3[a]	Cs_2CO_3	NR
2	*p*-$MeOPhB(OH)_2$	$Pd_2(dba)_3$, P^tBu_3[a]	Cs_2CO_3	NR
3	$BzO(CH_2)_5BBN$	$PdCl_2(dppf)$	$K_3PO_4 \cdot H_2O$	NR
4[b]	$BzO(CH_2)_5BBN$	$PdCl_2(dppf)$	$K_3PO_4 \cdot H_2O$	NR

[a] As the HBF_4 salt. [b] Dioxane:H_2O (10:1)

Refusing to be thwarted by the inertness of these substrates, alternative, indirect routes to the generation of the desired tetra-alkyl-substituted olefins were sought. The tetra-alkylsubstituted olefins would be synthesized via the selective reduction of tetrasubstituted olefins such as **B-554** and **B-556** that bear unsaturated substituents such as alkyne and alkene functionalities (Scheme 108). The generation of single isomer olefins bearing four distinct alkyl substituents would thus be realized. The development

of the methodology for the synthesis of the required tetrasubstituted olefins is described below.

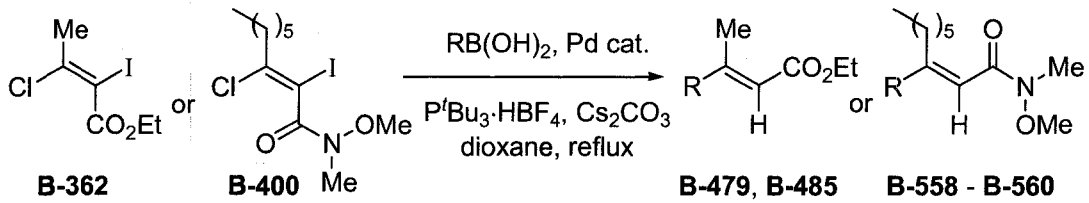
Scheme 108. Selective reduction of olefins B-554 and B-556 would generation tetra-alkyl-substituted olefins



2.2.2.6 Suzuki cross-coupling reactions with β-chloro-α-iodo-α,β-unsaturated ester and amide templates at elevated temperatures

At this point, we examined some surprising products that had been obtained during our optimization studies of trisubstituted olefins (Table 69). The attempted coupling of substrate **B-362** to phenylboronic acid in refluxing dioxane provided trisubstituted olefin **B-479** as a single isomer (entry 1). Similarly, the attempted coupling with *p*-fluorophenylboronic acid gave analogous product **B-485** (entry 2). The use of Weinreb amide-substituted olefin **B-400** produced similar results, regardless of whether phenylboronic acid was used (entry 3), or whether an electron-donating (entry 4) or electron-withdrawing (entry 5) boronic acid was employed.

Table 69. Summary of trisubstituted olefin products generated at high temperatures



B-362 **B-400** **B-479, B-485** **B-558 - B-560**

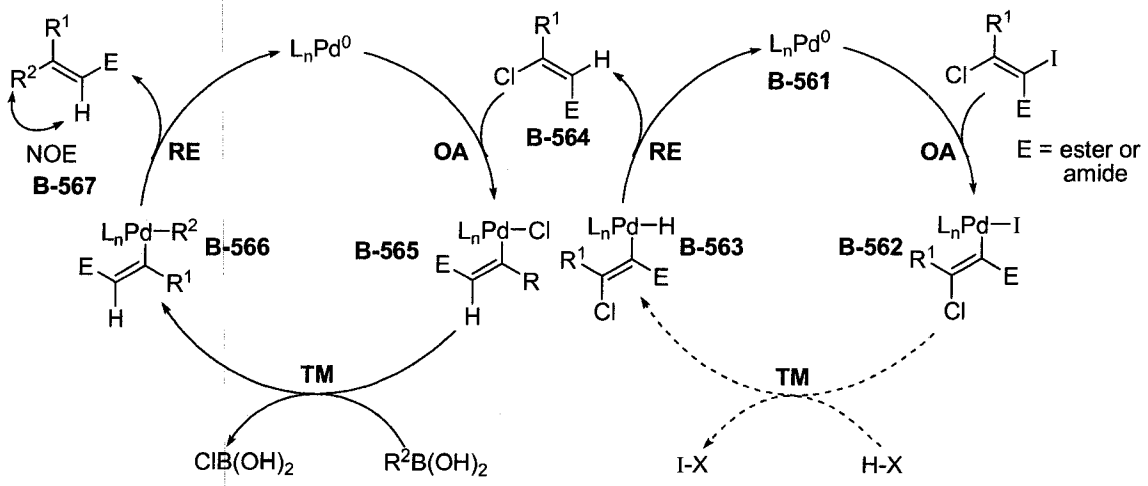
Entry	Substrate	$RB(OH)_2$	Pd cat.	Product	Yield (%)
1	**B-362**	$C_6H_5B(OH)_2$	$Pd_2(dba)_3$	**B-479**	94
2	**B-362**	*p*-$FC_6H_4B(OH)_2$	$Pd_2(dba)_3$	**B-485**	20
3	**B-400**	$C_6H_5B(OH)_2$	$Pd(OAc)_2$	**B-558**	54
4	**B-400**	*p*-$MeOC_6H_4B(OH)_2$	$Pd(OAc)_2$	**B-559**	91
5	**B-400**	*p*-$FC_6H_4B(OH)_2$	$Pd(OAc)_2$	**B-560**	80

The formation of trisubstituted products such as **B-479** was surprising for two reasons. One, the production of such materials under cross-coupling conditions would seemingly require a hydride source and none were evident in the medium.[290] Second, the selective production of the *E*-isomer, or *cis*-addition of the introduced substituents, involved a complete inversion of the original configuration to give single isomer products.[291]

The initial hypothesis postulated to explain these results was that the reaction mechanism might be analogous to the β-hydride elimination process observed during alkyl-Suzuki reactions (Scheme 109). After oxidative addition of the substrate to give **B-562**, a hydride would be incorporated from either a ligand or an external source, giving intermediate **B-563**. Reductive elimination would give olefin **B-564** and this product would undergo a second oxidative insertion to give intermediate **B-565**. Transmetallation with the boronic acid would give **B-566** and this intermediate would reductively eliminate. This mechanism would additionally require the *complete* isomerization of the double bond at some point during the catalytic cycle to give the observed product **B-567**.

[290] The need for a hydride source was based on the assumption that the mechanism was analogous to the β-hydride elimination process in the alkyl-Suzuki reaction, discussed below.
[291] The stereochemistry was proven by NOE analysis.

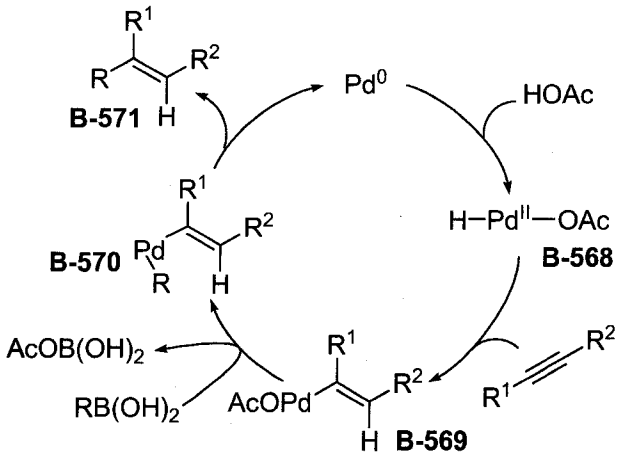
Scheme 109. Hypothetical mechanism for the generation of trisubstituted olefins



This mechanism however, was improbable, as it was difficult to conceive of the origin of the hydride and the inversion of olefin stereochemistry had yet to be rationalized. An alternative mechanism, one that had more precedence, was therefore postulated. The palladium-catalyzed addition of organoboronic acids to alkynes is a known process (Scheme 110).[292] To explain these reactions, it was proposed that oxidative addition of acetic acid occurred with a palladium(0) catalyst (**B-568**), thereby providing a hydride source. A *syn* hydropalladation then gave intermediate **B-569** and transmetallation with the phenylboronic acid, followed by reductive elimination, generated the trisubstituted product **B-571** while regenerating the palladium(0) catalyst.

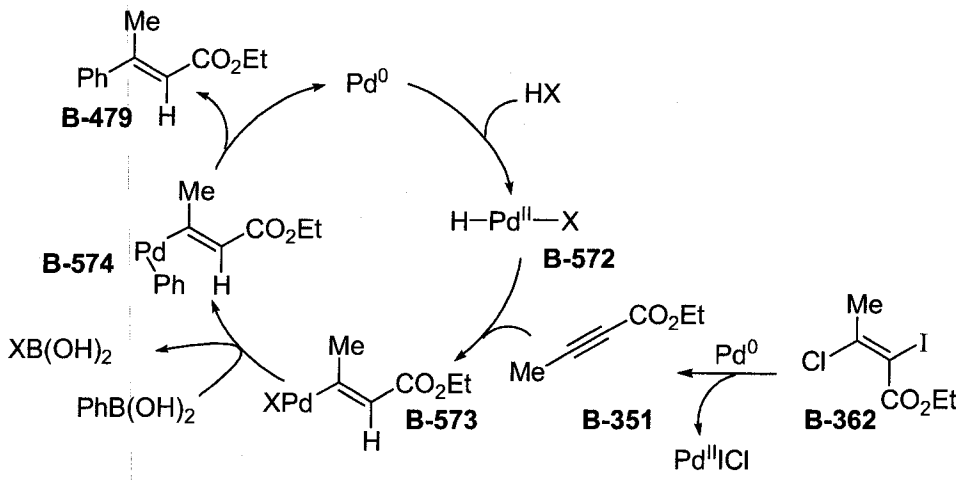
[292] (a) Oh, C. H.; Hoon, H.; Seong, J. K.; Kim, K. N. *Angew. Chem. Int. Ed.* **2003**, *42*, 805. (b) Gupta, A. K.; Kim, K. S.; Oh, C. H. *Synlett* **2005**, 457. (c) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

Scheme 110. HOAc as a hydride source for the hydropalladation of alkynes



α,β-Dihalogenated alkenes have the propensity to undergo halogen elimination in the presence of a palladium catalyst. In fact, this is a significant side process in many attempted coupling reactions on highly substituted substrates when dibromide and diiodide olefin templates are employed. The chloroiodo templates seemed particularly resistant to this elimination, presumably due to the lesser leaving group ability of the chloride at the β-position. However, the higher temperatures of these reactions may have facilitated this process. As shown in a representative example below, compound **B-362** could undergo a palladium-catalyzed dihalide elimination to give compound **B-351** (Scheme 111). The alkyne (**B-351**) could then enter into the catalytic cycle as described above. The major difference would therefore be the identity of HX, analogous to the acetic acid employed in previous examples.

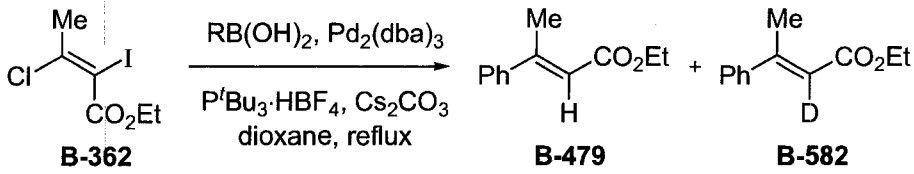
Scheme 111. Hypothetical mechanism for the generation of trisubstituted olefins from olefin precursors



This mechanistic possibility was probed using a series of deuteration experiments.[293] The reference reaction, performed in dioxane and using a large excess of $PhB(OH)_2$, is shown in Table 70, entry 1. CD_3CN was chosen as the solvent for this labeling study because it was significantly less expensive than d^8-dioxane.[294] A control study was performed to ensure that the reaction would proceed in this new solvent, giving a lower but still reasonable yield of 35% (entry 2). The reaction was then conducted in CD_3CN. The reaction produced only product **B-479** with no evidence of deuterium incorporation (entry 3). This result was further verified using benzene as the solvent. The use of both benzene (entry 4) and benzene-d_6 (entry 5) gave very low yields of product **B-479** but no trace of **B-582** in the product was apparent using either NMR or MS. These results suggested that the solvent was not the hydride source in the process.

[293] Deuteration experiments were performed by Michael Ho.
[294] www.sigmaaldrich.com, 2007: $C_4D_8O_2$ was $204 for 5 g, while CD_3CN was $36 for 5 g.

Table 70. Labeling experiments discounted the solvent as the hydrogen source

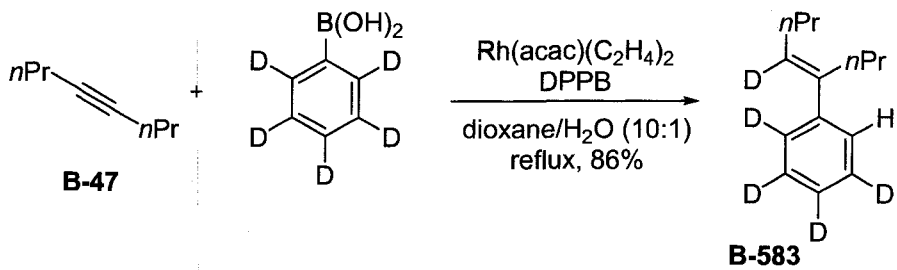


Entry	Boronic acid	Solvent	Additive	Product (Yield)
1	$PhB(OH)_2$[a]	dioxane	-	**B-479** (94%)
2	$PhB(OH)_2$	CH_3CN	4 ÅMS	**B-479** (35%)
3	$PhB(OH)_2$	CD_3CN	-	**B-479** (32%)
4	$PhB(OH)_2$	C_6H_6	-	**B-479** (5%)
5	$PhB(OH)_2$	C_6D_6	-	**B-479** (5%)
6	$C_6D_5(OH)_2$	dioxane	-	**B-479** (65%)[b]

[a] A large excess of boronic acid was employed (40 equiv boronic acid: 1 equiv **B-362**). [b] R = C_6D_5.

Hayashi has reported that hydroarylation reactions of alkynes under rhodium catalysis gave trisubstituted alkene products (Scheme 112).[295] In this process, the hydrogens from phenyl ring of the boronic acid served as the hydride source. To determine whether the hydride had come from the aromatic ring in our reaction, compound **B-362** was subjected to the reaction conditions in the presence of $C_6D_5B(OH)_2$, however no deuterium incorporation was observed (Table 70, entry 6). The aromatic ring was therefore eliminated as the source of hydride.

Scheme 112. Phenyl ring supplied the hydrogen in the rhodium-catalyzed hydroarylation of alkynes

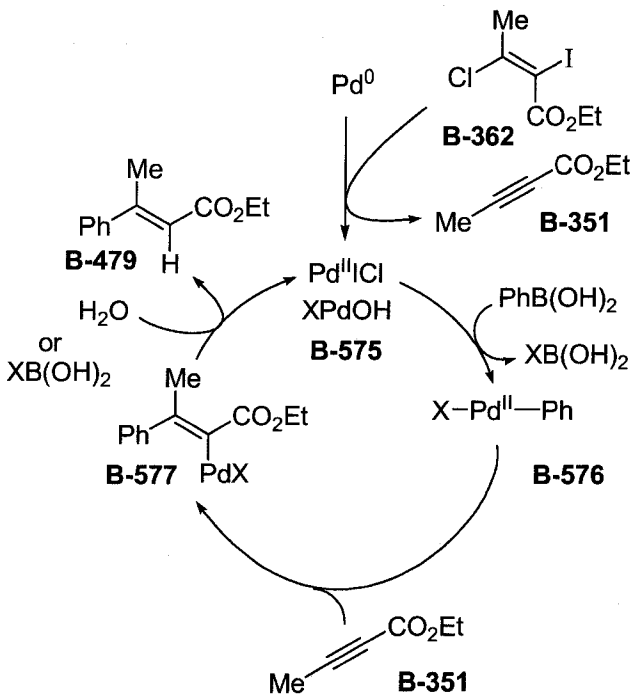


[295] Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

These deuteration experiments indicated that neither the solvent nor the aromatic ring of the boronic acid provided a hydride source for the reaction. The boronic acid itself may have been the source of the hydride, however if this were the case, another mechanistic possibility would have to be considered.

The Pd(II) (**B-575**), generated from the reduction of olefin **B-362**, could undergo transmetallation with phenylboronic acid to give intermediate **B-576** (Scheme 113). Carbopalladation of alkyne **B-351** would provide the alkenylpalladium complex **B-577**. The hydrolysis of complex **B-577** with water or with the boronic acid could give the observed product and regenerate palladium complex **B-575** The oxidation state of the palladium(II) would remain constant throughout this hypothetical catalytic cycle.

Scheme 113. Alternative, hypothetical mechanism for the generation of trisubstituted olefins

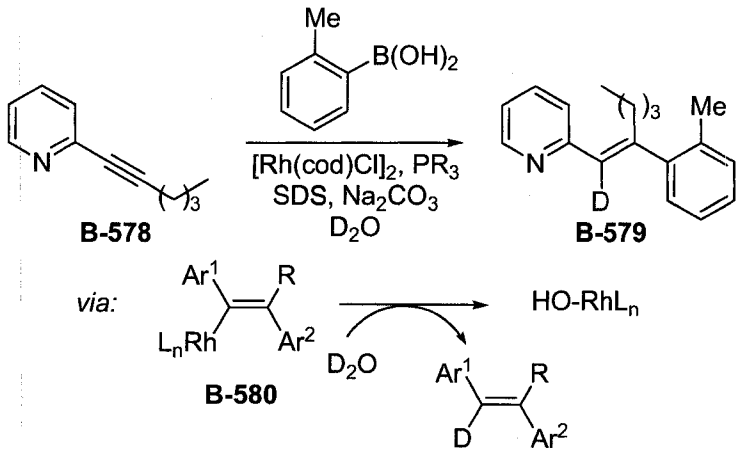


This last proposal is consistent with work by Lautens and Yoshida in which a plausible mechanism was reported for a related reaction involving the pyridine-directed hydroarylation of alkynes under rhodium catalysis.[296] In their study, it was found that deuterium was incorporated at the alkenyl position when the reaction was run in D_2O

[296] Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123.

(Scheme 114). It was postulated that this product was obtained via the hydrolysis of intermediate **B-580**.

Scheme 114. D_2O solvent supplied the hydrogen in the pyridine-directed rhodium-catalyzed hydroarylation of alkynes

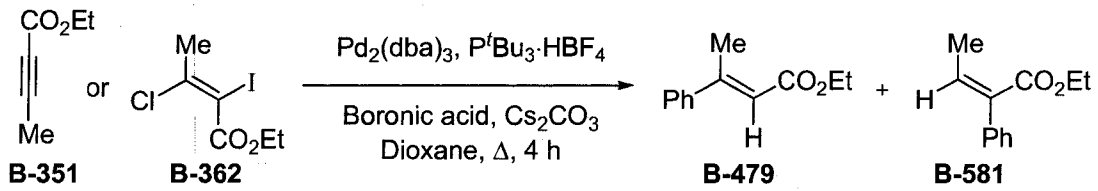


A control reaction was performed to investigate this proposed mechanism in which ethyl 2-butynoate **B-351** was subjected to the reaction conditions. The trisubstituted product **B-479** was produced, however the yield was very low, only 10%, and a mixture of regioisomers **B-479** and **B-581** was obtained (Table 71, entry 1). These results were consistent with the work of Oh and coworkers in which mixtures of regioisomers were typically observed and only a trace of product was obtained when HOAc was excluded from the carbopalladation reaction.[292]

The use of $PhB(OD)_2$, recrystallized from D_2O, gave a similar yield and showed deuterium incorporation at the olefinic position (Table 71, entry 2). To ensure that the deuterium had not come from residual D_2O from the recrystallization step, in a separate experiment the boronic acid was dried over P_2O_5 prior to use. Deuterium incorporation into the product regioisomers was again observed (entry 3).

A reaction employing substrate **B-362** was conducted in a mixture of dioxane:D_2O (10:1) and gave the deuterated product as a single isomer (Table 71, entry 4). Similarly, employing $PhB(OD)_2$ with the olefin substrate (**B-362**), gave the deuterated product as a single isomer (entry 5). These results suggested that the path shown in Scheme 113 might be operative.

Table 71. The use of the alkyne substrate gave mixtures of regioisomers



B-351 **B-362** **B-479** **B-581**

Entry	Substrate	Boronic acid	Ratio (B-479:B-581)	Yield B-479 (%)	D incorporation
1	**B-351**	$PhB(OH)_2$	3:1	10	-
2	**B-351**	$PhB(OD)_2$	2:1	10	46%
3[a]	**B-351**	$PhB(OD)_2$	2:1	16	37%
4[b]	**B-362**	$PhB(OH)_2$	1:0	88	57%
5	**B-362**	$PhB(OD)_2$	1:0	60	57%

[a] The boronic acid was dried for 18 h over P_2O_5 prior to use. [b] The reaction was performed in dioxane/D_2O (10:1).

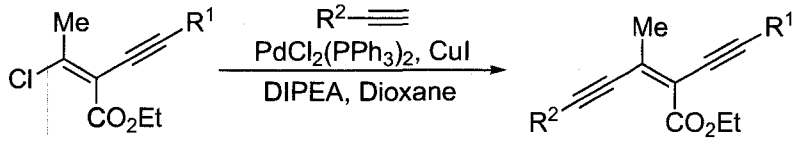
The mixture of regioisomers and the low yields produced when an alkyne was employed as the starting material was in stark contrast to the generation of single products in good yields when the β-chloro-α-iodo-α,β-unsaturated ester or amide served as the starting material. Research is currently ongoing in our laboratory to analyze the mechanism and the scope of this promising process.

2.3 The Synthesis of Tetrasubstituted Olefins

2.3.1 The Sonogashira coupling reaction

With a wide variety of trisubstituted olefins in hand bearing a chloride at the β-position, we faced the challenge of forming all-carbon tetrasubstituted olefins. α-Alkynyl substrates were first subjected to the optimized coupling conditions developed for the Sonogashira reaction. While no reaction was observed when the coupling of 1-octyne was attempted (Table 72, entry 1), phenylacetylene was successfully coupled to two different trisubstituted olefins (entries 2 and 3).

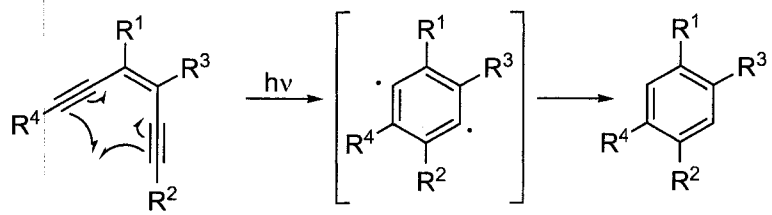
Table 72. Preparation of tetrasubstituted alkenes via the Sonogashira reaction



Entry	R^1	R^2	Product	Yield (%)
1	TMS	$(CH_2)_5CH_3$	**B-584**	NR
2	TMS	Ph	**B-585**	55
3	Ph	Ph	**B-448**	42

The enediyne compounds have great potential applications in Bergmann cyclization reactions (Scheme 115).[297] These reactions have attracted increasing interest as antibiotics, particularly because the benzene diradical intermediates generated upon cycloaromatization are implicated in DNA cleavage.[298] A minimum separation, or critical distance, of the alkyne termini is required for spontaneous cyclization to occur. Various techniques have been reported to generate structures in the lab and *in situ* that enable access to the critical distance of 3.1 Å. Frequently an activation reaction, such as a ring-opening reaction, is induced in a distal part of the molecule. This causes a conformation change in the molecule, which brings the alkynyl termini within the critical distance.

Scheme 115. General mechanism for the Bergmann cyclization reaction



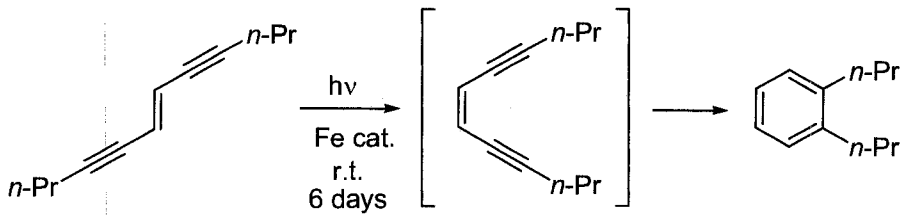
B-587 **B-588** **B-589**

O'Connor and coworkers have recently described a transition-metal-catalyzed Bergmann cycloaromatization of a ***trans***-disubstituted enediyne (Scheme 116).[299] This

[297] Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.
[298] (a) Nicolaou, K. C.; Smith, A. L. *Pure & Appl. Chem.* **1993**, *65*, 1271. (b) Fallis, A. G. *Can. J. Chem.* **1999**, *77*, 159. (c) Schreiner, P. R.; Navarro-Vazquez, A.; Prall, M. *Acc. Chem. Res.* **2005**, *38*, 29.
[299] O'Connor, J. M.; Friese, S. J.; Rodgers, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 16342.

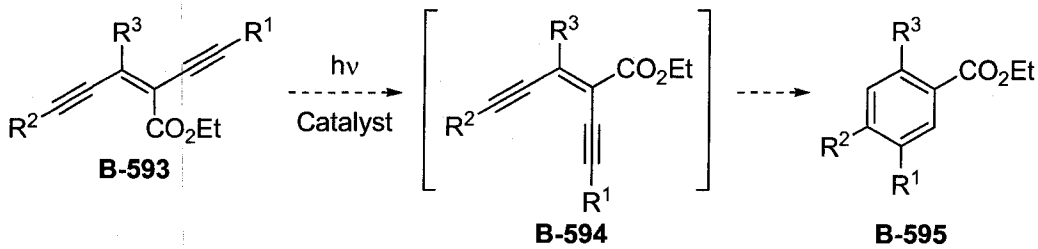
chemistry took advantage of the well-established interconversion of *cis*- and *trans*-enediynes.[300] The one example reported used 4.2 mg of the enediyne and proceeded in an 83% NMR yield, however the reaction took six days. The related photochemical cycloaromatization of 1,2-dialkynyl-substituted benzene rings has also bee reported.[301]

Scheme 116. Iron-catalyzed cycloaromatization of a *trans*-enediyne



Our group will use the substrates generated in the Sonogashira coupling reactions of alkene templates in Bergmann cyclization reactions (Scheme 117). The cycloaromatization of a **tetrasubstituted *trans*-enediyne** would be the first of its kind. The large substituents on the alkene will promote the cyclization event by enforcing the critical distance required for spontaneous cyclization. In addition, the use of a *trans*-enediyne precludes cyclization until the reaction is selectively activated. This could be accomplished simply by the application of UV light. Such a structure would be highly desirable in potential drugs that require site-specific activity. This work is currently under investigation in our laboratory.

Scheme 117. Proposed cycloaromatization of tetrasubstituted *trans*-enediynes



2.3.2 Sp^2-substituted olefins generated via the Suzuki coupling reaction

[300] (a) Koenig, B.; Schofield, E.; Bubenitschek, P.; Jones, P. G. *J. Org. Chem.* **1994**, *59*, 7142. (b) Miki, Y.; Mornotake, A.; Arai, T. *Org. Biomol. Chem* **2003**, *1*, 2655. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.
[301] Evenzahav, A.; Turro, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 1835.

Seeking structural variety in the coupling partners, the Suzuki coupling reaction was explored.[160,279] The introduction of trisubstituted olefin **B-462** to phenylboronic acid, $Pd_2(dba)_3$, $P^tBu_3 \cdot HBF_4$, and Cs_2CO_3 in dioxane for 3 hours at room temperature cleanly gave compound **B-396** as a *single isomer* in 77% yield (Table 73, entry 1).[302] The generation of tetrasubstituted olefins was very successful with other substrates after some optimization. The twenty-four hour reaction of *p*-methylphenylboronic acid gave a 38% yield of the desired product **B-597**, however a mixture of isomers was obtained (entry 2). Twenty-four hour reactions using K_2CO_3 as the base (entry 3) or THF as the solvent (entry 4) gave better yields of the product but still as mixtures of isomers. A return to the original conditions from entry 2, but stopping the reaction after one hour gave a 40% yield of the product as a single isomer. The low yield was primarily due to incomplete conversion of the starting material (entry 5). This last result was promising, so the following reaction was run for two hours and resulted in a 75% of the product as a single isomer (entry 6). Satisfied with this result, we proceeded to examine a more electron-deficient substrate.

Exposure of trisubstituted olefin **B-462** to *p*-fluorophenylboronic acid, $Pd_2(dba)_3$, $P^tBu_3 \cdot HBF_4$, and Cs_2CO_3 in dioxane for 24 hours at room temperature gave compound **B-598** as a mixture of isomers (entry 7). The use of THF as the solvent resulted in an intractable mixture (entry 8). Employing $Pd(OAc)_2$ gave the lowest yield obtained thus far, in addition to a mixture of isomers (entry 9). Mimicking the conditions that had provided single isomers with the *p*-methylphenylboronic acid substrate, a one-hour reaction with the *p*-fluorophenylboronic acid was examined (entry 10). This gave the desired product (**B-598**) as a *single isomer*,[302] however, because the reaction did not go to completion—only a 52% yield was obtained. Lengthening the reaction time to three hours provided compound **B-498** in 71% as a *single isomer* (entry 11).

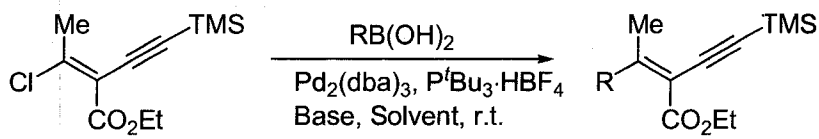
The substrate scope was then extended to alkenyl substituents. The electron-deficient *p*-chlorophenylboronic acid was unreactive under all the reaction conditions attempted. Standard Suzuki coupling conditions at room temperature were unsuccessful (entry 12),

[302] GC–MS analysis of the crude mixture was performed after each reaction and was compared to GC–MS results of a mixture of isomers that either had been generated under the reaction conditions or by the photolysis of a pure isomer.

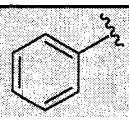
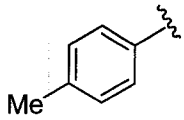
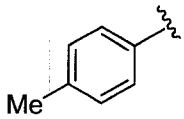
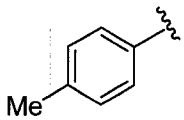
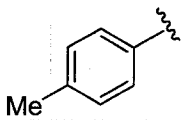
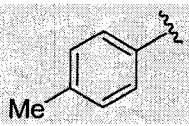
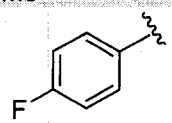
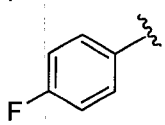
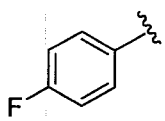
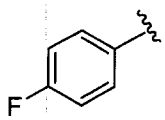
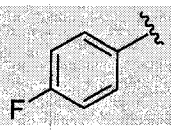
and heating the reaction did not aid the process (entry 13). The use of S-PHOS as the ligand and K_3PO_4 as the base in THF gave no product but no starting material was recovered either (entry 14). Since the starting material was decomposing under these reaction conditions, the syringe pump addition of alkenyl chloride **B-462** to the reaction mixture was attempted, without success (entry 15). The reaction was repeated in dioxane, but still no conversion was observed (entry 16). This substrate was abandoned in favor of analogous styrenylboronic acid substrate.

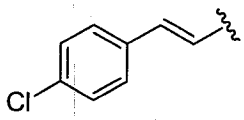
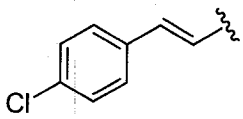
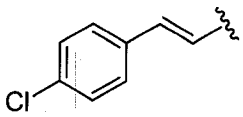
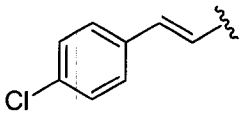
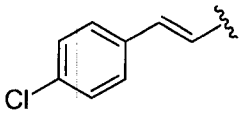
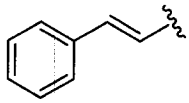
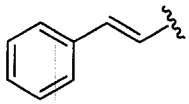
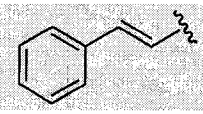
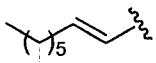
The initial conditions attempted with styrenylboronic acid, $Pd_2(dba)_3$, $^tBu_3P$, and Cs_2CO_3, in dioxane, were ineffective (entry 17). A change of reaction conditions to S-PHOS as the ligand and K_2CO_3 as the base in dioxane immediately gave a mixture of products (entry 18). Encouraged, the base was changed to K_3PO_4 and the reaction time was restricted to four hours. A 67% yield of **B-600** as a *single isomer* was obtained (entry 19).[302] The use of the same conditions with 9-octenylboronic acid gave a 64% yield of **B-601** as a single isomer (entry 20).[302]

Table 73. Optimization of Suzuki reaction conditions for the generation of tetrasubstituted olefins



B-462

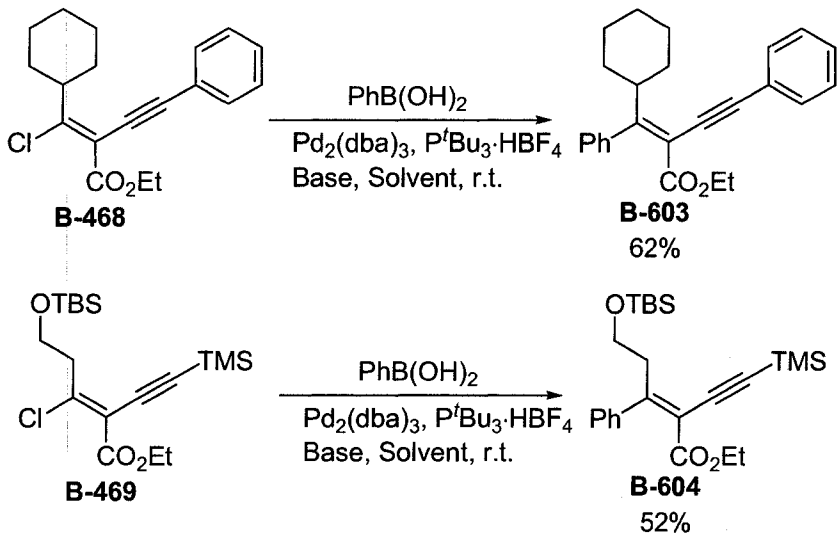
Entry	R	Base	Solvent	Time	Product	% Yield
1		**Cs_2CO_3**	**Dioxane**	**3 h**	**B-596**	**77**
2		Cs_2CO_3	Dioxane	24 h	**B-597**	38[a]
3		K_2CO_3	Dioxane	24 h	**B-597**	75[a]
4		Cs_2CO_3	THF	24 h	**B-597**	85[a]
5		Cs_2CO_3	Dioxane	1 h	**B-597**	40[b]
6		**Cs_2CO_3**	**Dioxane**	**2 h**	**B-597**	**75**
7		Cs_2CO_3	Dioxane	24 h	**B-598**	58[a]
8		Cs_2CO_3	THF	24 h	**B-598**	mixture
9[c]		Cs_2CO_3	Dioxane	24 h	**B-598**	45[a]
10		Cs_2CO_3	Dioxane	1 h	**B-598**	52[b]
11		**Cs_2CO_3**	**Dioxane**	**3 h**	**B-598**	**71**

12		K_2CO_3	Dioxane	18 h	**B-599**	NR
13[d]		K_2CO_3	Dioxane	18 h	**B-599**	NR
14[e]		K_3PO_4	THF	18 h	**B-599**	NR
15[e,f]		K_3PO_4	THF	18 h	**B-599**	NR
16[e]		K_2CO_3	Dioxane	18 h	**B-599**	NR
17		Cs_2CO_3	Dioxane	18 h	**B-600**	NR
18[e]		K_2CO_3	Dioxane	18 h	**B-600**	Mixture
19[e]		**K_3PO_4**	**THF**	**4 h**	**B-600**	**67**
20[e]		K_3PO_4	THF	4 h	**B-601**	64

[a] Approximately equimolar mixture of isomers was obtained. [b] The reaction did not go to completion. [c] $Pd(OAc)_2$ was employed. [d] The reaction was conducted at 90 °C. [e] S-PHOS was employed as the ligand. [f] The starting material was added via syringe pump.

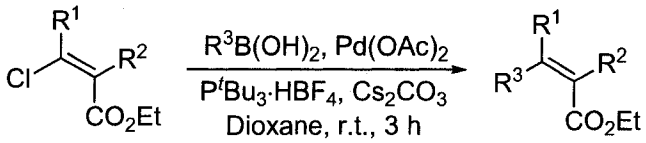
Reactions of up to one gram were successfully performed, giving yields consistent with those shown above and proving that the reaction was scalable. The methyl substituent could be replaced without problem. Tetrasubstituted alkenes were prepared bearing a cyclohexyl group and a functionalized alkyl chain. In both cases, *single isomers* were obtained from the process,[302] thereby overcoming one of the most difficult obstacles in the formation of tetrasubstituted olefins (Scheme 118).

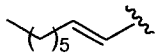
Scheme 118. Branched alkyl and functionalized alkyl moieties employed at the β-position



The next challenge was to increase the steric bulk surrounding the olefin. This was accomplished by generating tetrasubstituted olefins in which the aryl substituent replaced the alkynyl substituent at the α-position. As shown in Table 74, a variety of substituents was tolerated at both the α- and β-positions and a single isomer was obtained in each case.[302] The coupling at the β-position proceeded smoothly with *p*-methoxyphenylboronic acid (entry 1). The use of 1-octenylboronic acid gave an 87% yield of product **B-606** (entry 2). Employing the simple phenylboronic acid gave an 85% yield (entry 3) and the electron-deficient *p*-fluorophenylboronic acid gave a slightly lower yield of 62% (entry 4). Styrenylboronic acid gave an excellent result of 79%, and in contrast to the coupling reaction at the α-position, S-PHOS was not required for the coupling of this reagent at the β-position (entry 5). The R^1 substituent could also be varied. The use of CH_2OTBS as the R^1 substituent and *p*-$FC_6H_4B(OH)_2$ as the coupling partner gave the desired tetrasubstituted olefin in 42% yield (entry 6). Work is ongoing in our research laboratory to expand the substrate scope for the generation of all-carbon tetrasubstituted alkenes.

Table 74. Generation of tetrasubstituted olefins with increased steric bulk



Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	Me	*p*-OMe-Ph	*p*-$OMeC_6H_4$	**B-490**	85 (64)
2	Me	*p*-OMe-Ph		**B-606**	87 (60)
3	Me	*p*-OMe-Ph	Ph	**B-607**	84 (64)
4	Me	*p*-OMe-Ph	*p*-FC_6H_4	**B-608**	97 (82)
5	Me	*p*-OMe-Ph	styrenyl	**B-609**	79 (54)
6	$TBSOCH_2$	*p*-OMe-Ph	C_6H_5	**B-610**	42 (27)

[a] Yield based on un-recovered starting material. Yield in parenthesis is based on starting material employed.

We were delighted with the speed and high conversion of the coupling reactions as the formation of these congested centres is often quite difficult and frequently leads to olefin isomerization. In all the cases investigated using the optimized conditions, the tetrasubstituted olefins were cleanly obtained as single isomers. Importantly, four different carbon substituents could be installed with complete regiocontrol.

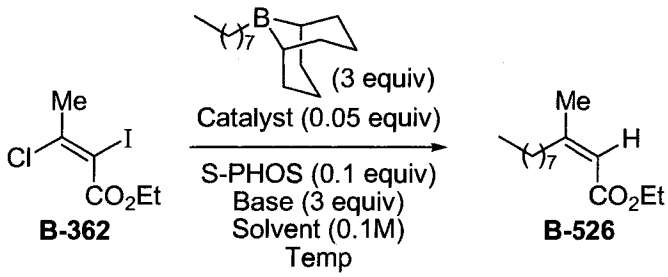
Very few reports exist for the stereoselective generation of tetra-alkyl-substituted olefins. Successful methods tend to incorporate very simple substituents such as methyl groups, and frequently use the Stille reactions,[160] which require the use of toxic tin reagents, reactive reagents, or use Negishi reactions, which often results in *E/Z* isomerization.

2.3.3 The alkyl-Suzuki coupling reaction

In our previously described attempts to install alkyl substituents at the α-position of the olefin templates, we had noted that alkyl-Suzuki coupling proceeded successfully at the β-position (Scheme 119). We would now investigate this reaction on trisubstituted

substituents. The requisite alkyl boranes were generated by the treatment of the corresponding alkene with 9-BBN, and were used immediately.

Scheme 119. Alkyl-Suzuki process proceeded smoothly at the β-position

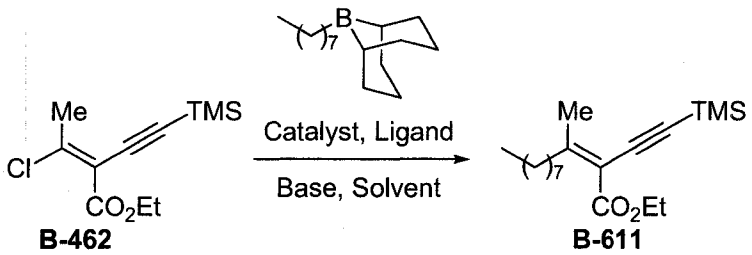


A simple 9-octyl-BBN was initially used in order to optimize the reaction. Thus, exposure of alkene **B-462** to 9-octyl-BBN, $PdCl_2(dppf)$, and anhydrous K_3PO_4 in THF at room temperature gave no reaction (Table 75, entry 1). At this point, a ligand scan was performed. Bidentate ligands with smaller bite angles were completely ineffective, as was XANTPHOS (entries 2–6).

The base, $K_3PO_4 \cdot H_2O$ was examined in its hydrate form and a small but encouraging yield of 19% was obtained (entry 7). Importantly, product **B-611** was obtained as a single isomer. The use of K_3PO_4 in a THF:H_2O (5:1) solvent mixture gave a lower yield of 12% (entry 8). No starting material was recovered in either case—it was likely that the TMS moiety was unstable to the reaction conditions.[303] Still seeking to better the yield, it was found that the solvent had a significant effect; the use of dioxane:H_2O (5:1) gave 64% of product **B-611** as a single isomer (entry 9).[302]

[303] In some reaction, traces of terminal alkynes were isolated during chromatography.

Table 75. Optimization of the alkyl-Suzuki reaction at the β-position

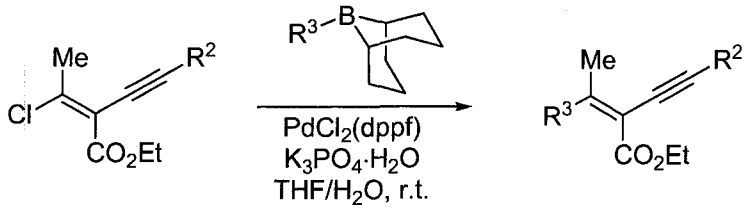


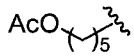
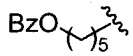
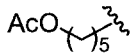
B-462 **B-611**

Entry	Catalyst (0.05 equiv)	Ligand (0.1 equiv)	Base (2 equiv)	Solvent	Yield (%)
1	$PdCl_2(dppf)$		K_3PO_4	THF	NR
2	$Pd(OAc)_2$	dppm	K_3PO_4	THF	NR
3	$Pd(OAc)_2$	dppe	K_3PO_4	THF	NR
4	$Pd(OAc)_2$	dppp	K_3PO_4	THF	NR
5	$Pd(OAc)_2$	dppb	K_3PO_4	THF	NR
6	$Pd(OAc)_2$	XANTPHOS	K_3PO_4	THF	NR
7	$PdCl_2(dppf)$		$K_3PO_4 \cdot H_2O$	THF	19
8	$PdCl_2(dppf)$		K_3PO_4	THF/H_2O	12
9	**$PdCl_2(dppf)$**		**K_3PO_4**	**Dioxane/H_2O**	**64**

A number of trisubstituted alkenyl chlorides were subjected to the previously developed alkyl-Suzuki coupling conditions (Table 76, entry 1) and to our delight, the reactions proceeded smoothly in all cases investigated. The coupling reaction of a simple alkyl chain onto a substrate bearing a phenylacetylene substituent at the α-position gave the tetrasubstituted olefin product **B-612** as a single isomer in 48% yield (entry 2). The use of a more polar substrate bearing an acetate substituent gave a 75% yield of product **B-613** (entry 3). The 9-alkyl-BBN reagent that bore a benzoate ester coupled well, giving an 82% yield of product **B-614** (entry 4). Silyl ethers were tolerated under these reaction conditions as shown by the generation of product **B-615** in 74% yield (entry 5).

Table 76. Alkyl substituents incorporated via the alkyl Suzuki reaction



Entry	R^2	R^3	Product	Yield (%)
1	TMS		**B-611**	64
2	Ph		**B-612**	48
3	Ph		**B-613**	75
4	$(CH_2)_5CH_3$		**B-614**	82
5	CH_2OTBS		**B-615**	74

This reaction was shown to be scalable, as reactions of up to one gram were performed with consistent yields. Each of these products was generated cleanly as a *single isomer* as determined by GC–MS and NMR techniques. Significantly, we had now shown that it was possible to couple alkyl substituents to these highly congested olefin centres. This contribution will undoubtedly facilitate the construction of complex molecules.

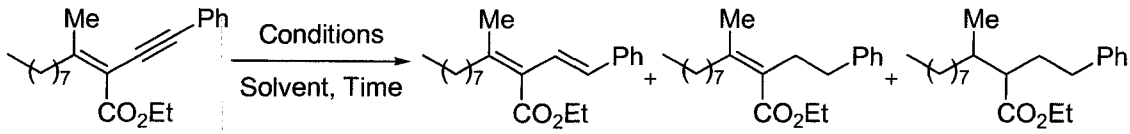
2.3.4 Attempted generation of tetra-alkyl-substituted olefins via the reduction of tetrasubstituted olefins

One major goal remained: the generation of tetra-alkyl substituted olefins. Obstacles had been encountered in the attempted generation of these structures directly from the olefin templates, and so a new strategy was devised. The alkyne in substrate **B-612** would be reduced in the presence of the much more congested tetrasubstituted olefin (Table 77). The initial conditions examined employed Pd/C (5%) in EtOH under a hydrogen atmosphere gave an 8:1 mixture of **B-612**:**B-616** by GC–MS and NMR analysis (entry 1). The use of 10% Pd/C gave a higher ratio of diene **B-616** (entry 2). Running the reaction for eight hours instead of three generated an 8:1 mixture of **B-616**:**B-617** (entry 3). Employing a higher catalyst loading and running the reaction for eighteen hours gave

over-reduction and a mixture of **B-617**:**B-618** was observed (entry 4). The use of ammonium formate returned starting material and a mixture of unidentified products (entry 5). $Pd(OH)_2$ under a hydrogen atmosphere gave a 2:1 mixture of **B-612**: **B-616** by GC–MS and NMR (entry 6).

Wilkinson's catalyst is typically selective for less-substituted olefins in the presence of more substituted olefins.[304] No reaction was observed when Wilkinson's catalyst was utilized (entry 7). A reaction with rhodium on carbon under a hydrogen atmosphere gave full reduction of every unsaturated bond in the molecule, including the phenyl ring (entry 8).

Table 77. Selective reductive of the alkyne in the presence of a tetrasubstituted alkene



B-612 **B-616** **B-617** **B-618**

Entry	Conditions	Solvent	Time	Ratio of B-612 : B-616 : B-617 : B-618
1	H_2, 5% Pd/C	EtOH	3 h	8:1:0:0
2	10% Pd/C	EtOH	3 h	2:1:0:0
3	10% Pd/C	EtOH	8 h	0:8:1:0
4[b]	10% Pd/C	EtOH	18 h	0:0:3:1
5	NH_4HCO_2	EtOH	3 h	mixture[a]
6	H_2, $Pd(OH)_2$	EtOH	5 h	2:1:0:0
7	H_2, $RhCl(PPh_3)_3$	C_6H_6	5 h	NR
8	H_2, Rh/C	EtOH	2 h	full reduction

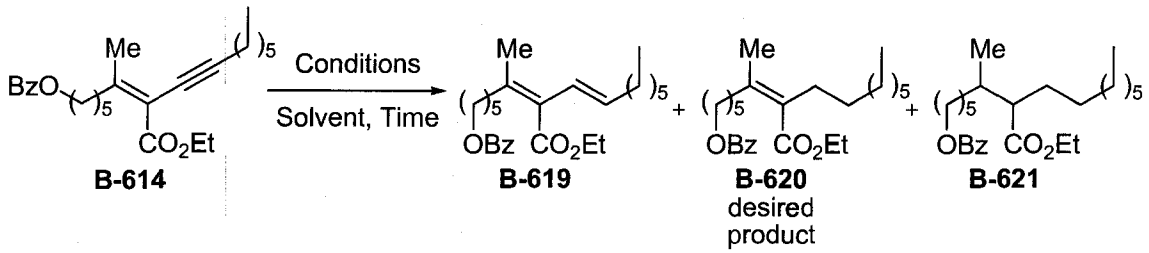
[a] Starting material and an unidentified mixture of compounds was observed. [b] 30% catalyst was used (by wt)

While these results were promising, the reaction was difficult to monitor by TLC due to the non-polar nature of the starting material and products. In addition, it was impossible to separate the various products from each other, and thus far, we had observed only mixtures of products. Attention therefore turned to a more polar substrate (**B-614**).

[304] (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1711. (b) Blay, G.; Cardona, L.; Garcia, B.; Pedro, J. R.; Sanchez, J. J. *J. Org. Chem.* **1996**, *61*, 3815.

The treatment of eneyne **B-614** with Wilkinson's catalyst under a hydrogen atmosphere returned only starting material (Table 78, entry 1). The use of tosylhydrazine and sodium acetate similarly gave no reaction (entry 2). Ammonium formation in the presence of Pd/C gave no reaction. Similarly, exposure of eneyne **B-614** to Pd/C under a hydrogen atmosphere in EtOAc (entry 4) and in EtOH (entry 5) gave no reaction. The use of $Pd(OH)_2$ on carbon under a hydrogen atmosphere in EtOH gave a mixture of products (entry 6). Desired product **B-620** was observed along with over-reduced product **B-621** when the same catalyst was employed in THF (entry 7) and in EtOAc (entry 8).

Table 78. Investigation of conditions for the selective reduction of B-614



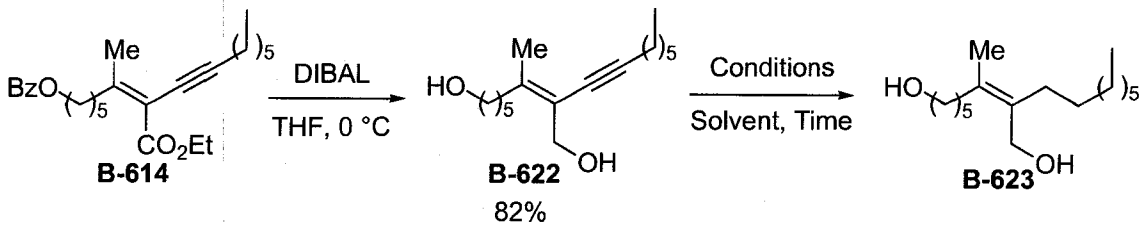
B-614 **B-619** **B-620** desired product **B-621**

Entry	Conditions	Solvent	Time	Result
1	H_2, $RhCl(PPh_3)_3$	benzene	18 h	NR
2	$TsNHNH_2$, NaOAc, reflux	THF/H_2O	18 h	NR
3	$NH_4OC(O)H$, Pd/C	EtOH	18 h	NR[a]
4	H_2, Pd/C	EtOAc	18 h	NR[a]
5[b]	H_2, Pd/C	EtOH	18 h	NR[a]
6	H_2, $Pd(OH)_2/C$	EtOH	18 h	mixture
7	H_2, $Pd(OH)_2/C$	THF	18 h	**B-620 & B-621**
8	H_2, $Pd(OH)_2/C$	EtOAc	18 h	**B-620 & B-621**

[a] Decomposition of the starting material observed. [b] **B-614** was added via syringe pump.

We postulated that the double bond of the α,β-unsaturated ester **B-614** might be too reactive in this particular system. Diol **B-622** was generated by the reduction of diester **B-614** with DIBAL (Table 79). The treatment of diol **B-622** with Lindlar's catalyst under a hydrogen atmosphere gave a mixture of products (Table Y, entry 1). The use of the same system at 0 °C gave another intractable mixture of products (entry 2). Tosylhydrazine and NaOAc in a THF/H_2O mixture at reflux gave no reaction (entry 3), and the use of rhodium on carbon under a hydrogen atmosphere gave a mixture of the fully reduced product together with unidentified products (entry 4).

Table 79. Investigation of conditions for the selective reduction of B-622.

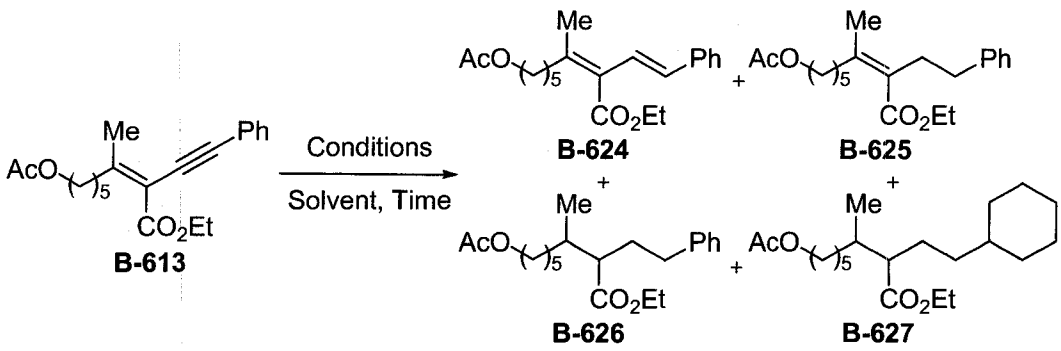


Entry	Conditions	Solvent	Time	Result
1	H_2, $Pd/CaCO_3$	EtOH	18 h	mixture[a]
2	H_2, $Pd/CaCO_3$	EtOH, 0 °C	18 h	mixture[b]
3	$TsNHNH_2$, NaOAc, reflux	THF/H_2O	18 h	NR
4	H_2, Rh/C	EtOH	18 h	mixture[c]

[a] Primarily fully reduced product was mainly observed. [b] Primarily fully reduced product with traces of disubstituted alkene. [c] Fully reduced product with traces of unidentified, intractable products.

Although the generation of the desired motifs using the aforementioned starting materials had not yet been successful, compound **B-613** was subjected to a number of different reducing conditions (Table 80). Exposure of eneyne **B-613** to rhodium on carbon under a hydrogen atmosphere gave full reduction to diester **B-627** in only one hour (entry 1). The use of Pd/C under a hydrogen atmosphere gave compound **B-626** in under an hour (entry 2) as did $Pd(OH)_2$ on carbon (entry 3).

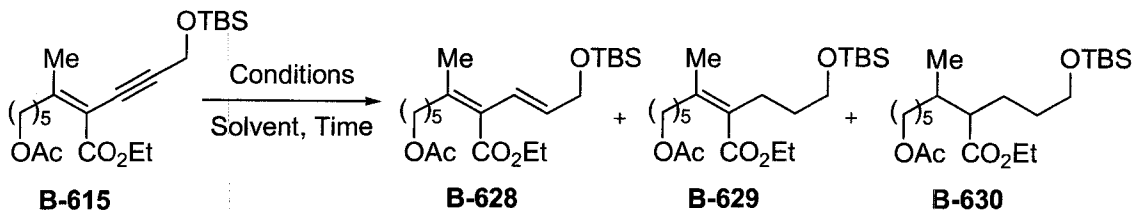
Table 80. Investigation of conditions for the selective reduction of B-613



Entry	Conditions	Solvent	Time	Result
1	H_2, Rh/C (10%)	EtOH	1 h	**B-627**
2	H_2, Pd/C (10%)	EtOH	1 h	**B-626**
3	H_2, $Pd(OH)_2$/C (20%)	EtOH	1 h	**B-626**

A slight modification in substrate did not give any improved results. The exposure of eneyne **B-615** to Pd/C in ethanol gave saturated product **B-630** (Table 81, entry 1). The use of ethyl acetate (entry 2) or THF (entry 3) as the solvent did not reduce the reactivity of the system. Reactions conducted in these solvents gave only compound **B-630**.

Table 81. Investigation of conditions for the selective reduction of B-615



Entry	Conditions	Solvent	Time	Result
1	H_2, Pd/C (10%)	EtOH	12 h	**B-630**
2	H_2, Pd/C (10%)	EtOAc	12 h	**B-630**
3	H_2, Pd/C (10%)	THF	12 h	**B-630**

Clearly, the reduction process proceeded successfully, and the objective became to find less reactive conditions in order to avoid the over-reduction of the tetrasubstituted olefin. This task had been anticipated to be straightforward, but had been complicated by issues of product separation due to compound polarity and by decomposition of the

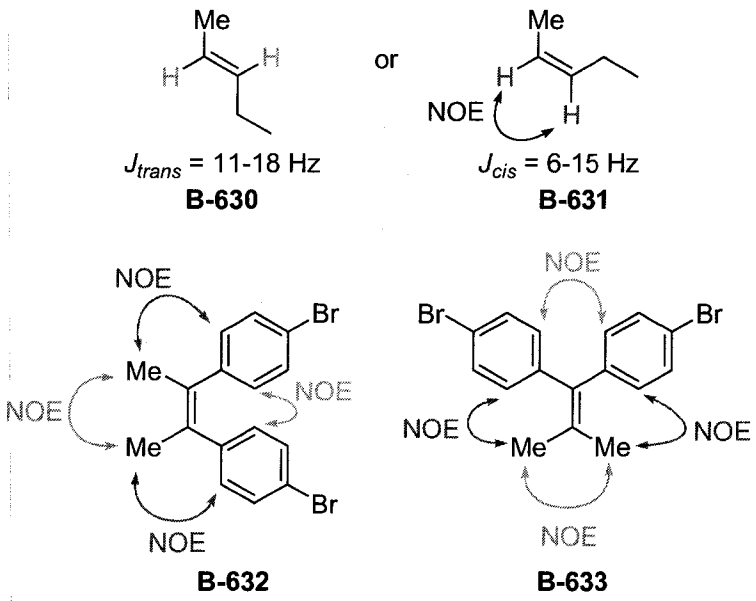
starting material in the case of some substrates. Currently, the more direct route of directly coupling alkyl substituents to the α-position is being investigated in our lab.

2.4 Structure Determination

It is generally not straightforward to determine the structures of tetrasubstituted products obtained from various synthetic strategies and the low polarity of many of the compounds can impair resolution during chromatographic separation. In a surprising number of reports in the literature, researchers have assigned the stereochemistry of their products based only on the *syn* or *anti* preferences of the chosen reaction processes, an assumption that has been false in some cases.[221]

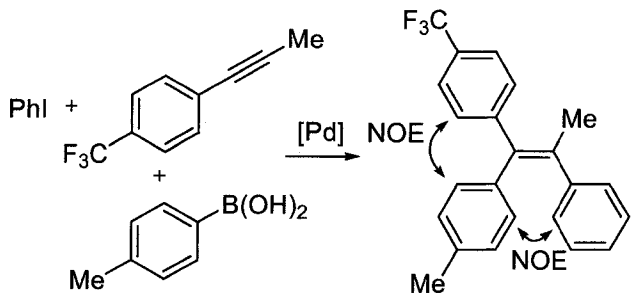
Establishing the regiochemistry and stereochemistry of *di-* or even *tri*substituted olefins such as **B-630** and **B-631** is typically straightforward because one can use coupling constants and NOE networks directly to determine the structures of products (Figure 12). Establishing the structure of tetrasubstituted olefins such as **B-632** and **B-633** in the absence of X-ray results requires particular attention to detail because no direct NMR couplings to olefinic protons are available. NOE measurements can be complicated with these compounds as each substituent can experience interactions with two of the other groups. For example, it would be next to impossible to distinguish between compounds **B-632** and **B-633** using only ^{1}H data such as NOE. In both compounds, enhancements would be observed between the methyl groups (shown in red) and between the two aryl groups (shown in green). Two additional enhancements between a methyl and an aryl moiety would be observed in each compound (shown in blue).

Figure 12. Determining the structure is more straightforward with disubstituted olefins compared to tetrasubstituted olefins



An exemplary method of structure determination has been illustrated by the Larock group, in which the structures of tetrasubstituted olefin products were proven through NOESY experiments performed on every single product of the study (Scheme 120).[305] The first key result elucidated the regiochemistry of addition, showing an NOE enhancement between the geminally substituted aryl moieties of the product. The second key observation showed that addition of the two components across the alkyne had proceeded in a *syn* fashion, made evident by the NOE interaction found between the substituents.

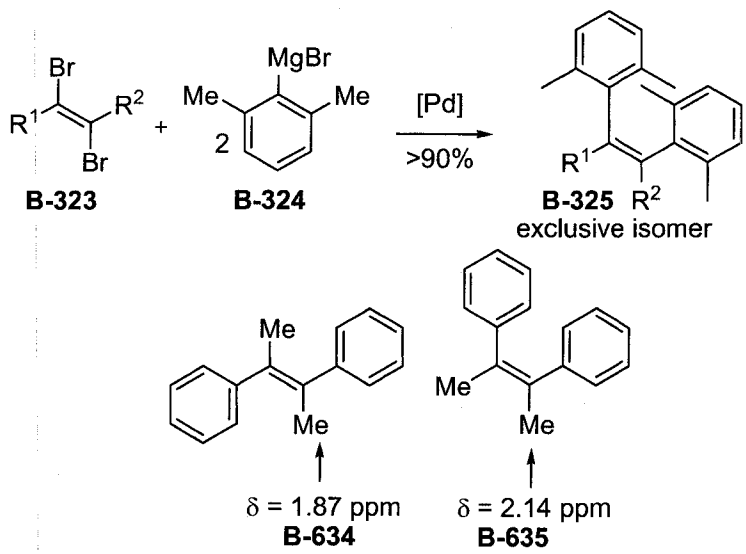
Scheme 120. Representative use of an NOE network to determine regio- and stereochemistry.



[305] Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

In much of the tetrasubstituted olefin literature, the structures of products are assumed rather than rigorously confirmed. For example, the bromination of alkynes is known to proceed in an *anti* fashion; therefore, it is often assumed that subsequent organometallic couplings, for example, will produce products that retain a *trans* relationship between the newly introduced substituents. The implications of this are that some methods may actually produce different products from those reported. A case in point are coupling reactions of (*Z*)-dihaloalkenes, which frequently result in stereochemical changes, and therefore product geometry issues. In a report by Rathore *et al.*,[214] (*E*)-dibromoolefins **B-323** underwent double Kumada coupling with congested Grignard reagent **B-324**, affording the (*Z*)-product **B-325** exclusively, a fact clearly established by X-ray (Scheme 121). This result could not have been anticipated by a simple assumption of the retention of configuration during coupling, especially given the size of the Grignard reagent transferred.

Scheme 121. A surprising result requiring careful product identification



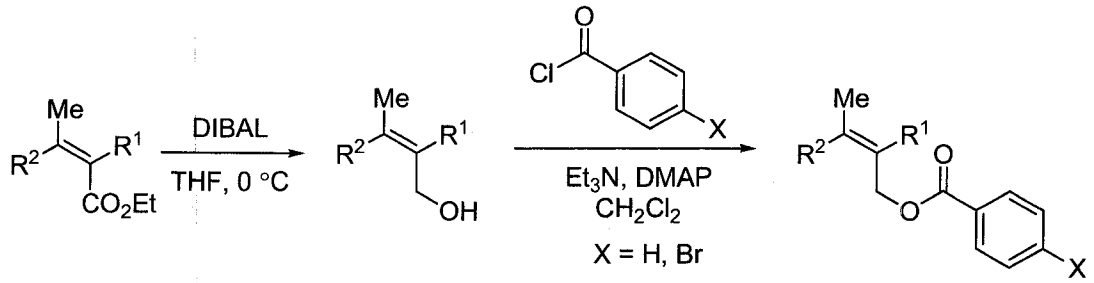
The analysis of chemical shift patterns has been employed to establish stereochemistry. For example, the methylene protons of (*Z*)-stillbene-type hydrocarbons (**B-635**) are reported to resonate downfield of the signals of the corresponding protons of

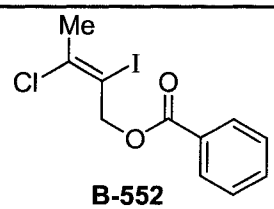
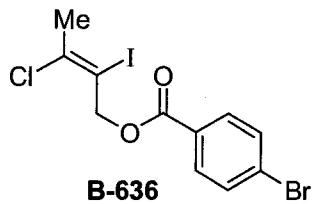
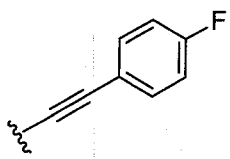
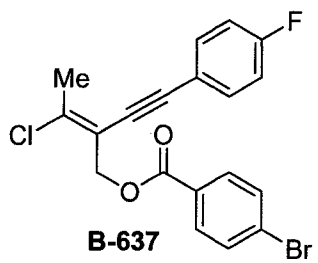
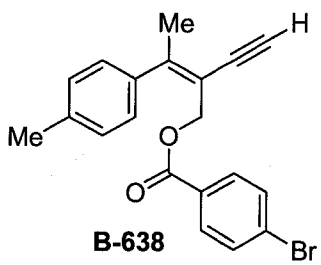
the (*E*)-isomer **B-634**.[306] This has been supported conclusively in at least one case by using X-ray crystallography to correlate the NMR assignments.[306]

The structure determination of the tetrasubstituted olefins synthesized in our studies was not straightforward. Undeniable proof of stereo- and regiochemistry could come from a crystal structure. Toward that end, a few oily ester products were reduced with DIBAL and then converted to the corresponding benzoate esters[307] and the pure products were crystallized (Table 82, entries 1–4). Unfortunately, the crystals obtained were not suitable for X-ray analysis and so an alternative strategy was required for the proof of stereochemistry.

[306] Leimner, H.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 3679.
[307] The generation of *p*-bromo- benzoate esters were generated as *p*-bromo and *p*-nitro benzoate esters often to crystallize well. In addition, X-ray structures can usually be obtained more easily with compounds that bear halogens.

Table 82. Generation of benzoate esters

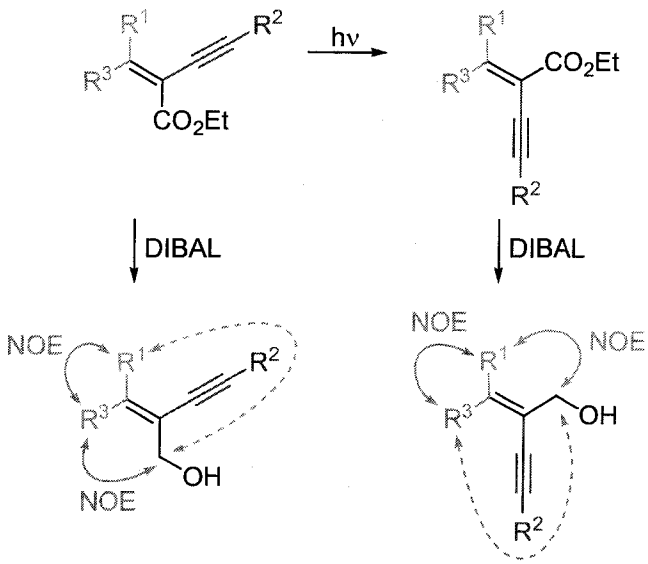


Entry	R^1	R^2	Product	Yield (%)
1	I	Cl	 **B-552**	97
2	I	Cl	 **B-636**	97
3		Cl	 **B-637**	98
4		*p*-MeC_6H_4	 **B-638**	98

The stereochemistry of the olefin templates had been previously established using NOE analysis (See section 2.1.2 Structure determination of the alkene templates). In a similar fashion, the stereochemistry of the olefin templates was confirmed based on the NOE network generated from the original products together with their isomers. Each tetrasubstituted olefin was photolyzed to generate the corresponding isomer (Scheme 122). The esters that bore alkynyl functionalities at the α-position were immediately

reduced with DIBAL, giving the corresponding alcohols. In every case, the structure of the original isomer was consistent with the compound shown in the table below. In both isomers, an NOE interaction was observed between the R^1 and R^3 groups (red arrows), consistent with geminal substitution. In the original isomers, an enhancement was observed between R^3 and the CH_2 (brown arrow). This NOE effect was absent in the photolyzed, reduced isomers (brown dashed arrow) and an additional NOE correlation was now observed between the R^1 substituent and the CH_2 group (green arrow).

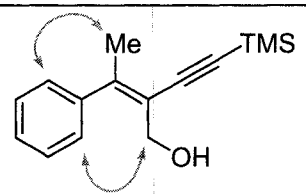
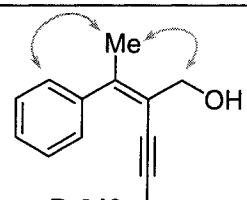
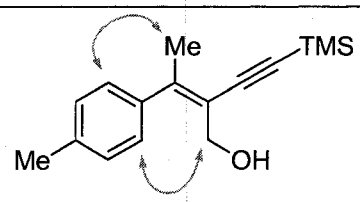
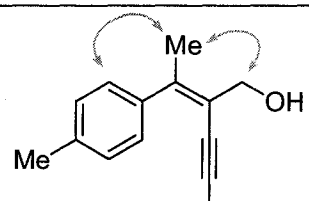
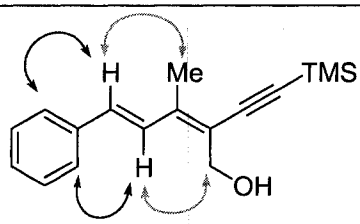
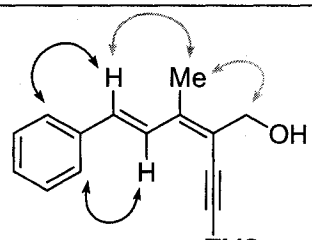
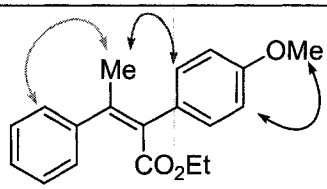
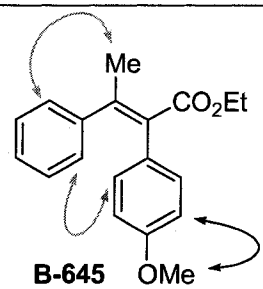
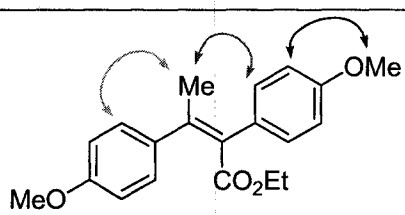
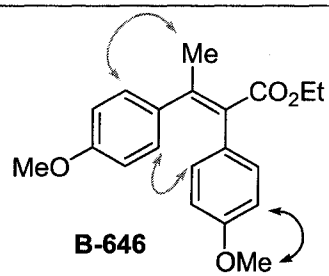
Scheme 122. NOE networks confirmed olefin stereochemistry



This procedure was performed on each tetrasubstituted olefin product and unequivocally proved the stereo- and regiochemistry of the molecules (representative examples are shown in Table 83). The identification of tetrasubstituted olefins bearing aryl substituents at the α-position did not require reduction prior to analysis, and NOE analysis was employed directly on each isomer[308] and unequivocally proved the structures of the products.

[308] The isomeric product was generated by the photolysis of the olefin (350 nm).

Table 83. NOE networks identified in original products and stereoisomers

Original product	Stereoisomeric product
 **B-639**	 **B-640**
 **B-641**	 **B-642**
 **B-643**	 **B-644**
 **B-607**	 **B-645**
 **B-490**	 **B-646**

Chapter 3. Conclusions

A method for the selective chloroiodination of internal alkynes by exposure to Bu_4NI in refluxing dichloroethane was developed. These products were produced regio- and stereoselectively in high yields. The treatment of the same substrates with ICl produced mixtures of isomers. Detailed mechanistic studies indicated that ICl was implicated in the process and that a Bu_4NI-ICl complex was likely responsible for the high selectivity observed in the Bu_4NI/DCE system.

The Bu_4NI/DCE system was shown to be selective for the chlorination of alkenes. The treatment of the same alkenes with ICl returned a mixture of chlorinated and iodochlorinated products. In addition, the Bu_4NI/DCE system was chemoselective in substrates bearing both aromatic and olefinic moieties, reacting at the alkenyl functionality exclusively. Exposure of these substrates to ICl produced a mixture of products.

The halogenated olefins produced by the Bu_4NI/DCE method served as olefin templates for the formation of tetrasubstituted olefins.

Tetrasubstituted *E*-enediynes were generated via sequential Sonogashira reactions and are currently under investigation for their potential as substrates for cycloaromatization reactions.

The cross-coupling reactions proceeded regioselectively and stereospecifically, producing tetrasubstituted olefins bearing four different substituents. Notably, this direct and efficient process produced single isomer tetrasubstituted olefin products in good yields.

Chapter 4. Experimentals

Experimentals - Table of Contents[309]

Compound List:

[309] Compounds are sorted by category and are then arranged in numerical order.

GENERAL:

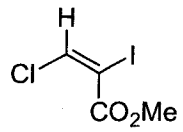
Reactions were performed in oven- or flame-dried flasks under N_2 atmosphere and equipped with a magnetic stir bar and a rubber septum, unless otherwise noted. THF was freshly distilled from sodium/benzophenone. Dichloromethane, benzene, dioxane, toluene, DMF, and triethylamine were freshly distilled over calcium hydride. Acetonitrile was dried over 4Å molecular sieves. Reagents were purchased from Sigma-Aldrich, Lancaster, and Strem chemical companies. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} pre-coated 0.25 mm thick aluminium

plates. TLCs were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or *p*-anisaldehyde stains. When necessary, products were purified using flash column chromatography on silica gel 60 (230–400 mesh) or preparatory TLC glass plates pre-coated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

^{1}H and ^{13}C NMR spectra were acquired using either a Varian Gemini 200 MHz (^{1}H); a Bruker Avance 500 MHz (^{1}H) and 125 MHz (^{13}C); a Bruker Avance 400 MHz (^{1}H) and 100 MHz (^{13}C); or a Bruker Avance 300 MHZ (^{1}H) and 75 MHz (^{13}C). Infrared spectra were acquired on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques. Melting points were determined using an Electrothermal Meltemp® apparatus and are uncorrected.

Chloroiodination of Alkynes

General procedure for the halogenation alkynes using Bu_4NI/DCE



(*E*)-Methyl 3-chloro-2-iodoacrylate (B-367).[227] A solution of methyl-2-propiolate (250 mg, 2.98 mmol, 1.0 equiv) and tetrabutylammonium iodide (3.25 g, 8.95 mmol, 3.0 equiv) in dichloroethane (25 mL) was heated at reflux for 18 h. The reaction mixture was cooled, diluted with Et_2O and washed with $NaHSO_3$ (20% wt solution), saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by flash chromatography eluting with hexanes then 5% EtOAc in hexanes to give the title product as a colorless oil (528 mg, 72%).

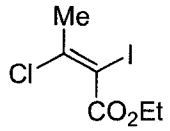
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 3.79 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (C), 129.4 (CH), 84.3 (C), 53.2 (CH_3);

IR (neat) 1728, 1567cm^{-1}; MS (EI) 246 (M^+);

HRMS Calcd for $C_4H_4ClIO_2$ (M^+) 245.8945, found 245.8926.

R_f: 0.45 on silica gel (5% EtOAc in hexanes)



(*E*)-Ethyl 3-chloro-2-iodobut-2-enoate (B-362). Prepared from ethyl-2-butynoate (1.0 g, 8.93 mmol) using a procedure similar to that described above for compound **B-367** that provided the title product as a colorless oil (2.23 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, J = 3.6 Hz, 2H), 1.95 (s, 3H), 1.26 (t, J = 6.9 Hz, 3H);

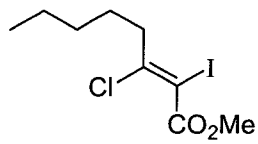
^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 134.8 (C), 80.8 (C), 62.4 (CH), 29.5 (CH_3), 13.8 (CH_3);

IR (neat) 1727, 1627 cm^{-1};

MS (EI) 274 (M+);

HRMS calcd for $C_6H_8ClIO_2$ (M^+) 273.9258, found 273.9294.

R_f: 0.3 on silica gel (5% EtOAc in hexanes)



(*E*)-methyl 3-chloro-2-iodooct-2-enoate (B-394). Prepared from methyl 2-octynoate (1.0 g, 6.49 mmol) using a procedure similar to that described above for compound **B-367** that provided the title compound as a colorless oil (1.89 g, 92%).

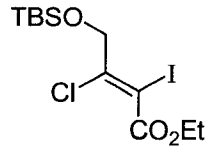
^{1}H NMR (400 MHz, benzene-d_6): δ 3.23 (s, 3H), 2.36 (dd, J = 7.6, 7.6 Hz, 2H), 1.42 – 1.34 (m, 2H), 1.13 – 1.04 (m, 4H), 0.76 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, benzene-d_6): δ 165.3 (C), 138.9 (C), 80.7 (C), 52.6 (CH_3), 41.3 (CH_2), 30.8 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

IR (neat) 2955, 1735 cm^{-1}.

HRMS calcd for $C_9H_{14}ClIO_2$ (M^+) 315.9727, found 315.9737.

R_f: 0.44 on silica gel (5% EtOAc in hexanes)



(*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-3-chloro-2-iodobut-2-enoate (B-395). Prepared from ethyl 4-(tert-butyldimethylsilyloxy)but-2-ynoate (100 mg, 0.41 mmol) using a procedure similar to that described above for compound **B-367** that provided the title compound as a colorless oil (152 mg, 92 %).

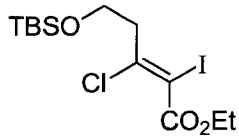
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C), 137.1 (C), 80.1 (C), 68.6 (CH_2), 62.6 (CH_2), 25.8 (CH_3), 18.3 (C), 13.9 (CH_3);

IR (neat) 2956, 1733, 1472 cm^{-1};

HRMS Calcd for $C_8H_{13}ClIO_3Si$ (M^+ – *t*-Bu) 346.9367, found 346.9352; Calcd for $C_{11}H_{19}ClIO_3Si$ ($M^+ - CH_3$) 388.9837, found 388.9830.

R_f: 0.75 on silica gel (10% EtOAc in hexanes)



(*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-chloro-2-iodopent-2-enoate (B-396). Prepared from ethyl 5-(*tert*-butyldimethylsilyloxy)pent-2-ynoate (500 mg, 2.07 mmol) using a procedure similar to that described above for compound **B-367** that provided the title product as a colorless oil (537 mg, 67%).

^{1}H NMR (300 MHz, C_6D_6) δ 3.95 (q, J = 7.2 Hz, 2H), 3.58 (t, J = 6.3 Hz, 2H), 2.59 (t, J = 6.3 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.01 (s, 6H);

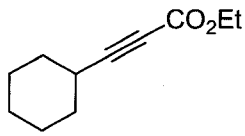
^{13}C NMR (75 MHz, C_6D_6) δ 164.8 (C), 135.0 (C), 83.3 (C), 62.1 (CH_2), 59.8 (CH_2), 44.4 (CH_2), 26.1 (CH_3), 18.4 (C), 13.8 (CH_3), -5.3 (CH_3);

IR (neat) 1734, 1622 cm^{-1};

MS (EI) 360 (M^+-^{t}Bu);

HRMS Calcd for $C_9H_{15}ClIO_3Si$ (M^+-57) 360.9524, found 360.9528.

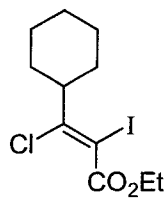
R_f: 0.69 on silica gel (10% EtOAc in hexanes)



Ethyl 3-cyclohexylpropiolate (B-385).[310] To a solution of cyclohexylacetylene (1.0 g, 9.26 mmol, 1.0 equiv) in THF (90 mL) at −78 °C was added butyllithium (2.13 M, 4.79 mL, 10.2 mmol, 1.1 equiv) dropwise. After 1 hour, a solution of ethyl chloroformate (1.36 mL, 13.89 mmol, 1.5 equiv) in THF (5.0 mL) was added dropwise over 10 minutes. After 1 hour, the reaction was quenched carefully with H_2O. The mixture was diluted with Et_2O and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained by flash chromatography eluting with hexanes then 2% EtOAc in hexanes to give the title product as a colorless oil (1.0 g, 60%).

^{1}H NMR (400 MHz, benzene-d_6): δ 3.91 (q, J = 7.2 Hz, 2H), 2.12 – 2.06 (m, 1H), 1.50 – 1.47 (m, 4H), 1.38 – 1.01 (m, 3H), 0.88 – 0.85 (m, 3H), 0.87 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, benzene-d_6): δ 153.9 (C), 92.1 (C), 74.4 (C), 61.4 (CH_2), 31.5 (CH_2), 28.9 (CH), 25.7 (CH_2), 24.6 (CH_2), 13.9 (CH_3);



(*E*)-Ethyl 3-chloro-3-cyclohexyl-2-iodoacrylate (B-397). Prepared from ethyl 3-cyclohexylpropiolate (200 mg, 1.11 mmol) using a procedure similar to that described above for compound **B-367** that provided the title product as a colourless oil (256 mg, 62%).

^{1}H NMR (400 MHz, C_6D_6) δ 3.99 (q, J = 7.2 Hz, 2H), 2.93 (tt, J = 11.2, 3.6 Hz, 1H), 1.31 – 1.52 (m, 6H), 0.85-1.08 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 165.1 (C), 142.0 (C), 79.7 (C), 62.2 (CH_2), 48.3 (CH), 29.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 13.8 (CH_3);

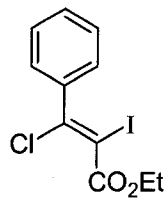
[310] For an alternative preparation via Corey-Fuchs reaction, see: 233.

IR (neat) 1730, 1611, cm^{-1};

MS (EI) 342 (M+);

HRMS calcd for $C_{11}H_{16}O_2ClI$ (M+) 341.9884, found 341.9897.

R_f: 0.43 on silica gel (5% EtOAc in hexanes)



***(E)*-Ethyl 3-chloro-2-iodo-3-phenylacrylate (B-399).** Prepared from ethyl phenylpropiolate (500 mg, 2.87 mmol) using a procedure similar to that described above for compound **B-367** that provided the title product as a colorless oil (647 mg, 67%).

^1H NMR (400 MHz, C_6D_6) δ 7.06 (d, J = 7.6 Hz, 1H), 6.90-6.93 (m, 4H), 4.02 (q, J = 7.2 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H);

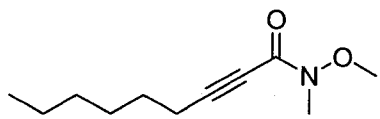
^{13}C NMR (100 MHz, C_6D_6) δ 163.7 (C), 141.3 (C), 129.7 (CH), 129.0 (CH), 129.0 (CH), 128.4 (C), 122.3 (C), 62.6 (CH_2), 13.8 (CH_3);

IR (neat) 1729, 1628, cm^{-1};

MS (EI) 336 (M^+);

HRMS Calcd for $C_{11}H_{10}ClIO_2$ (M^+) 335.9414, found 335.9435.

R_f: 0.5 on silica gel (5% EtOAc in hexanes)



***N*-Methoxy-*N*-methylnon-2-ynamide (B-388).** To a solution of 1-hexyne (2.6 mL, 17.7 mmol, 1.0 equiv) in hexanes (150 mL) at –78 °C was added a solution of butyllithium (2.26 M in THF, 8.63 mL, 19.5 mmol, 1.1 equiv). After 1 hour a solution of *N*-methoxy-*N*-methylcarbamoyl chloride[234] (2.40 g, 19.4 mmol, 1.1 equiv) in THF (20 mL) was slowly added *via* canula. The reaction was stirred for 1 hour at –78 °C and then the reaction was quenched by the dropwise addition of 10 % HCl. The mixture was allowed to warm to room temperature for 1 hour and was then diluted with ether. The organic

layer was washed sequentially with a saturated solution of sodium bicarbonate and brine, then dried over anhydrous $MgSO_4$, filtered and concentrated. The pure product was obtained by chromatography eluting with 5% EtOAc in hexanes then 20% EtOAc in hexanes to give the title product as a pale yellow oil (3.02 g, 92%).

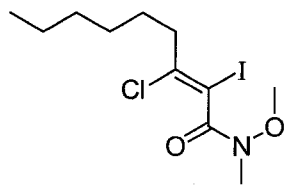
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 2.94 (s, 3H), 2.03 (t, J = 6.4 Hz, 2H), 1.36 – 1.14 (m, 8H), 0.93 (t, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 73.0 (CH_3), 61.8 (CH_3), 31.1 (CH_2), 30.8 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 22.4 (CH_2), 18.8 (CH_2), 13.6 (CH_3);

IR (neat) 2237, 1644 cm^{-1};

HRMS Calcd for $C_{11}H_{19}NO_2$ (M^+) 197.1416, found 197.1405.

R_f: 0.15 on silica gel (5% EtOAc in hexanes)



(*E*)-3-Chloro-2-iodo-*N*-methoxy-*N*-methylnon-2-enamide (B-400). Prepared from *N*-methoxy-*N*-methylnon-2-ynamide (3.02 g, 15.3 mmol) using a procedure similar to that described above for compound **B-367** that provided the title compound as a colorless oil (5.05 g, 92%).

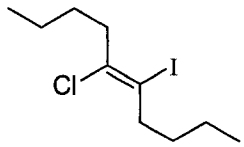
^{1}H NMR (400 MHz, C_6D_6) δ 3.22 (s, 3H), 2.82 (s, 3H), 2.46 (br s, 2H), 1.48 – 1.45 (m, 2H), 1.19 – 1.14 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 166.3 (C), 135.1 (C), 82.7 (C), 60.8 (CH_3), 40.4 (CH_2), 32.4 (CH_3), 31.8 (CH_2), 28.3 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 14.1 (CH_3);

IR (neat) 2954, 2930, 2858, 1654, 1459 cm^{-1};

HRMS Calcd for $C_{11}H_{10}ClIO_2$ (M^+) 359.0149, found 359.0201.

R_f: 0.60 on silica gel (5% EtOAc in hexanes)



(*E*)-5-Chloro-6-iododec-5-ene (B-402). Prepared from 5-decyne (0.13 mL, 0.76 mmol) using a procedure similar to that described above for compound **B-367** that provided the title compound as a colorless oil (210 mg, 92%).

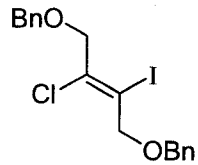
^{1}H NMR (400 MHz, acetone-d_6) δ 2.68 (t, J = 7.2 Hz, 4H), 1.60 – 1.48 (m, 4H), 1.39 – 1.32 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6) δ 133.0 (C), 100.6 (C), 44.3 (CH_2), 43.2 (CH_2), 32.2 (CH_2), 30.9 (CH_2), 23.3 (CH_2), 23.0 (CH_2), 15.2 (CH_3),

IR (neat) 2957, 2860, 1623, 1464 cm^{-1}; MS (EI) 300 (M^+);

HRMS Calcd for $C_{10}H_{18}ClI$ (M^+) 300.0142, found 300.0132.

R_f: 0.62 on silica gel (5% EtOAc in hexanes)



(*E*)-(2-Chloro-3-iodobut-2-ene-1,4-diyl)bis(oxy)bis(methylene)dibenzene (B-403). Prepared from 1,4-bis(benzyloxy)but-2-yne[311] (50 mg, 0.19 mmol) using a procedure similar to that described above for compound **B-367** that provided the title compound as a colorless oil (75 mg, 93%).

^{1}H NMR (400 MHz, acetone-d_6) δ 7.42 – 7.29 (m, 10 H), 4.57 (s, 2H), 4.55 (s, 2H), 4.51 (s, 2H), 4.44 (s, 2H);

^{13}C NMR (100 MHz, acetone-d_6) δ 139.9 (C), 139.8 (C), 132.7 (C), 130.03 (CH), 130.01 (CH), 129.63 (CH), 129.56 (CH), 129.41 (CH), 129.38 (CH), 102.6 (C), 77.9 (CH_2), 74.8 (CH_2), 73.5 (CH_2), 73.2 (CH_2);

IR (nujol) 2957, 1640, 1458 cm^{-1}; MS (EI) 428 (M^+);

HRMS Calcd for $C_{18}H_{18}ClIO_2$ (M^+) 428.0040, found 428.0043.

R_f: 0.35 on silica gel (5% EtOAc in hexanes).

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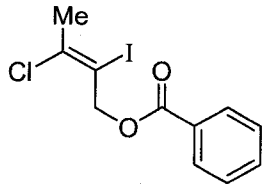
[311] Hecht, S.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 4084.

Proof of Stereochemistry of Olefin Templates



(*E*)-3-Chloro-2-iodobut-2-enyl benzoate (B-552). To a solution of (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) (135 mg, 0.54 mmol, 1.0 equiv) in THF (7.0 mL) was added NaH (19.4 mg, 0.81 mmol, 1.5 equiv). After ½ hour, benzoyl chloride was added (0.09 mL, 0.81 mmol, 1.5 equiv). After 18 hours, the solution was carefully quenched by addition of HCl (10%) and was diluted with Et_2O. The organic layer was washed sequentially with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with hexanes then 2% Et_2O in hexanes afforded the desired compound as a colourless oil (175.9 mg, 97%).

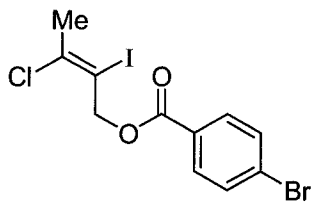
^{1}H NMR (400 MHz, acetone-d_6): δ 8.02 (dd, J = 8.4, 1.2 Hz, 2H), 7.67 – 7.64 (m, 1H), 7.53 (dd, J = 8.0, 8.0 Hz, 2H), 4.91 (q, J = 2.4 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ 167.1 (C), 135.1 (CH), 131.7 (C), 131.2 (CH), 130.5 (CH), 84.6 (C), 75.3 (C), 54.6 (CH_2), 4.26 (CH_3);

IR (neat) 2946, 1723 cm^{-1};

HRMS calcd for $C_{11}H_{10}ClO_2$ (M^+ – I) 209.0369, found 209.0325.

R_f: 0.42 on silica gel (5% EtOAc in hexanes)



(*E*)-3-Chloro-2-iodobut-2-enyl 4-bromobenzoate (B-636). To a solution of (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) (135 mg, 0.54 mmol, 1.0 equiv) in THF (7.0 mL) was added NaH (19.4 mg, 0.81 mmol, 1.5 equiv). After ½ hour, *p*-bromobenzoyl chloride was added (0.09 mL, 0.81 mmol, 1.5 equiv). After 18 hours, the solution was carefully quenched by addition of HCl (10%) and was diluted with Et_2O. The organic layer was

washed sequentially with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with hexanes then 2% Et_2O in hexanes afforded the desired compound as a white solid (216.8 mg, 97%).

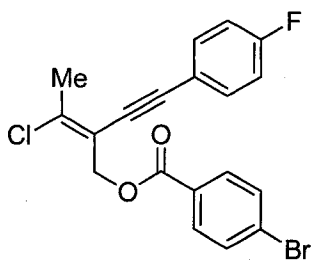
^{1}H NMR (400 MHz, acetone-d_6): δ 7.98 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 5.20 (s, 2H), 2.46 (s, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ 166.2 (C), 133.8 (CH), 133.1 (CH), 130.7 (C), 129.7 (C), 93.4 (C), 70.1 (CH_2), 31.7 (CH_2);

IR (neat)

HRMS calcd for $C_{11}H_9BrClIO_2$ (M^+) 413.8519, found 413.8520.

R_f: 0.31 on silica gel (5% EtOAc in hexanes)



(*Z*)-3-Chloro-2-((4-fluorophenyl)ethynyl)but-2-enyl 4-bromobenzoate (B-637). To a solution of (Z)-3-chloro-2-((4-fluorophenyl)ethynyl)but-2-en-1-ol (26 mg, 0.12 mmol, 1.0 equiv) in DCM (1 mL) was added Et_3N (0.03 mL, 0.24 mmol, 2.0 equiv), 4-bromobenzoyl chloride (39 mg, 0.18 mmol, 1.5 equiv) and DMAP (3 mg, 0.024 mmol, 0.2 equiv). After 20 minutes, the reaction was quenched with HCl (10%) and the mixture was extracted into EtOAc. The organic phase was washed sequentially with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel, eluting with hexanes to 5% EtOAc in hexanes affording the product as a white solid (23 mg, 48%).

MP: 76 – 77 °C

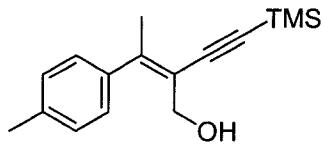
^{1}H NMR (500 MHz, benzene-d_6): δ 7.80 (d, J = 14.2 Hz, 2H), 7.09 (d, J = 14.2 Hz, 2H), 6.99 (dd, J = 14.5, 9.0 Hz, 2H), 6.52 (dd, J = 14.5, 14.5 Hz, 2H), 5.09 (s, 2H), 2.11 (s, 3H);

^{13}C NMR (125 MHz, benzene-d_6): δ 165.2 (C), 163.9 (C), 161.90 (C), 161.91 (C), 141.4 (C), 133.5 (CH), 133.4 (CH), 131.9 (CH), 131.5 (CH), 129.3 (C), 128.5 (CH), 119.1 (C), 116.8 (C), 116.0 (CH), 115.8 (CH), 95.2 (C), 85.2 (C), 63.6 (CH_2), 24.9 (CH_3);

IR (neat) 2952, 1727 cm^{-1};

HRMS calcd for $C_{19}H_{13}BrClFO_2$ (M^+) 405.9771, found 405.9743.

R_f: 0.52 on silica gel (5% EtOAc in hexanes)



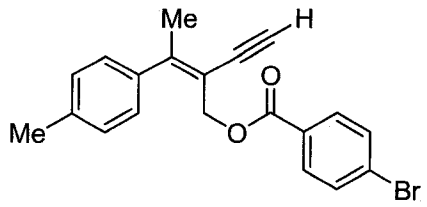
(Z)-3-*p*-Tolyl-2-((trimethylsilyl)ethynyl)but-2-en-1-ol. To a solution of ester **B-597** (100 mg, 0.33 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at 0 °C was added diisobutylaluminum hydride as a 1M solution in hexanes (0.80 mL, 0.80 mmol). The reaction was warmed to room temperature, and stirred for 2 h. Methanol (1 mL) was carefully added drop-wise to quench the reaction. Ether (5 mL) and a saturated solution of Rochelle's salt (3 mL) were then introduced, and the resulting mixture was stirred until both layers became clear. The layers were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel eluting with 10% EtOAc in hexanes gave the desired compound as a colorless oil (68.1 mg, 80%).

^{1}H NMR (400 MHz, benzene-d_6): δ 6.98 (d, J = 8.07 Hz, 2H), 6.88 (d, J = 7.83, 2H), 4.10 (s, 2H), 2.29 (s, 3H), 2.05 (s, 3H), 1.62 (br s, 1H), 0.24 (s, 9H);

^{13}C NMR (100 MHz, benzene-d_6): δ 147.8 (C), 138.2 (C), 137.4 (C), 129.1 (CH), 127.9 (CH), 120.6 (C), 105.5 (C), 100.2 (C), 99.9 (C), 62.6 (CH_2), 24.1 (CH_3), 21.0 (CH_3), 0.19 (CH_3);

HRMS calcd for $C_{15}H_{19}OSi$ (M^+ – Me) 243.1205, found 243.1338.

R_f: 0.26 on silica gel (10% EtOAc in hexanes)



(*Z*)-2-Ethynyl-3-p-tolylbut-2-enyl 4-bromobenzoate (B-638). To a solution of (*Z*)-3-*p*-tolyl-2-(2-(trimethylsilyl)ethynyl)but-2-en-1-ol (28 mg, 0.11 mmol, 1.0 equiv) in DCM (1.0 mL) was added Et_3N (0.03 mL, 0.22 mmol, 2.0 equiv), 4-bromobenzoyl chloride (36 mg, 0.17 mmol, 1.5 equiv) and DMAP (3 mg, 0.022 mmol, 0.2 equiv). After 5 minutes, the reaction was quenched with HCl (10%) and the mixture was extracted into EtOAc. The organic phase was washed sequentially with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel, eluting with hexanes to 5% EtOAc in hexanes affording the product as a white solid (40.0 mg, 99%).

MP: 85 – 87 °C

^{1}H NMR (500 MHz, benzene-d_6): δ 7.80 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 4.92 (s, 2H), 2.87 (s, 1H), 2.25 (s, 3H), 2.02 (s, 3H);

^{13}C NMR (125 MHz, benzene-d_6): δ 165.2 (C), 151.2 (C), 137.8 (C), 137.6 (C), 131.8 (CH), 131.5 (CH), 129.6 (C), 129.3 (CH), 127.9 (C), 127.6 (CH), 114.7 (C), 82.8 (CH), 82.4 (C), 64.8 (CH_2), 24.1 (CH_3), 21.0 (CH_3);

IR (neat) 3287, 2921, 1720 cm^{-1};

HRMS calcd for $C_{20}H_{17}BrO_2$ (M^+) 368.0412, found 368.0468.

R_f: 0.69 on silica gel (10% EtOAc in hexanes)

General procedure for the reduction of (E)-β-chloro-α-iodo-α,β-unsaturated esters to the corresponding (E)-alcohols

(*E*)-3-Chloro-2-iodobut-2-en-1-ol (B-373). To a solution of ester **B-362** (100 mg, 0.36 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at 0 °C was added diisobutylaluminum hydride as a 1M solution in hexanes (0.80 mL, 0.80 mmol). The reaction was warmed to room temperature, and stirred for 2 h. Methanol (1 mL) was carefully added dropwise to quench the reaction. Ether (5 mL) and a saturated solution of Rochelle's salt (3 mL) were then introduced, and the resulting mixture was stirred until both layers became clear. The layers were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel eluting with 10 % EtOAc in hexanes gave the desired compound as a colourless oil (68 mg, 81 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 2H), 2.37 (s, 3H), 2.16 (s, 1H);

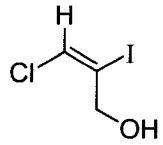
^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6 (C), 99.4 (C), 67.6 (CH_2), 30.6 (CH_3);

IR (neat) 3341, 1626 cm^{-1}; MS (EI) 232 (M^+);

MS (EI) 232) (M^+);

HRMS calcd for C_4H_6ClIO (M+) 231.9152; found 231.9169.

R_f: 0.35 on silica gel (20% EtOAc in hexanes).



(*E*)-3-Chloro-2-iodoprop-2-en-1-ol (B-404). Prepared from ester **B-367** (50 mg, 0.20 mmol) using a procedure similar to that described above for (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) which gave the title compound as a colorless oil (32.7 mg, 75 %).

^{1}H NMR (500 MHz, C_6D_6): δ 5.96 (s, 1H), 3.81 (d, J = 1.0 Hz, 2H), 1.12 (br s, 1H);

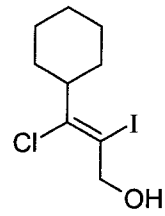
^{13}C NMR (125 MHz, C_6D_6): δ 119.5 (CH), 104.2 (C), 63.3 (CH_2);

IR (neat) 3338, 1603 cm^{-1};

MS (EI) 218 (M^+);

HRMS calcd for C_3H_4ClIO (M^+) 217.8995; found 217.9019.

R_f: 0.50 on silica gel (20% EtOAc in hexanes).



(*E*)-3-Chloro-3-cyclohexyl-2-iodoprop-2-en-1-ol (B-406). Prepared from ester **B-397** (50 mg, 0.28) using a procedure similar to that described above for (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) that gave the title compound as a colorless oil (49 mg, 64%).

^{1}H NMR (400 MHz, C_6D_6): δ 3.99 (q, J = 7.2 Hz, 2H), 2.93 (tt, J = 11.2, 4.5 Hz, 1H), 1.30-1.52 (m, 6H), 0.89-1.09 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H);

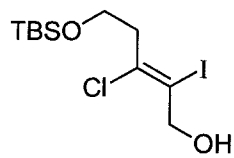
^{13}C NMR (100 MHz, C_6D_6): δ 165.1 (C), 142.0 (C), 79.7 (C), 62.2 (CH_2), 48.3 (CH), 29.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 13.8 (CH_3);

IR (neat) 3342, 1607, 1449 cm^{-1};

MS (EI) 300 (M^+);

HRMS calcd for $C_9H_{14}ClIO$ (M^+) 299.9778, found 299.9765.

R_f: 0.25 on silica gel (10% EtOAc in hexanes).



(*E*)-5-(*Tert*-butyldimethylsilyloxy)-3-chloro-2-iodopent-2-en-1-ol (B-410). Prepared from ester **B-396** (103 mg, 0.25 mmol) using a procedure similar to that described above for (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) which gave the title compound as a colorless oil (86 mg, 92%).

^{1}H NMR (500 MHz, C_6D_6): δ 4.11 (d, J = 7.0 Hz, 2H), 3.67 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 1H), 0.95 (s, 9H), 0.04 (s, 6H);

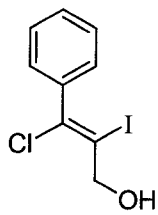
^{13}C NMR (125 MHz, C_6D_6): δ 130.0 (C), 103.2 (C), 67.3 (CH_2), 60.0 (CH_2), 46.3 (CH_2), 26.1 (CH_3), 18.4 (C), -5.2 (CH_3);

IR (neat) 3360, 1618 cm^{-1};

MS (EI) 319 (M^+-^{t}Bu);

HRMS calcd for $C_7H_{13}ClIO_2Si$ (M^+ – ^{t}Bu) 318.9420, found 318.9413.

R_f: 0.15 on silica gel (10% EtOAc in hexanes).



(*E*)-3-Chloro-2-iodo-3-phenylprop-2-en-1-ol (B-412). Prepared from ester **B-399** (10 mg, 0.030 mmol) using a procedure similar to that described above for (*E*)-3-chloro-2-iodobut-2-en-1-ol (**B-373**) which gave the title compound as a colorless oil (7 mg, 79%).

^{1}H NMR (400 MHz, C_6D_6): δ 7.31 (dd, J = 8.4, 1.6 Hz, 2H), 6.91-7.03 (m, 3H), 4.22 (d, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 1H);

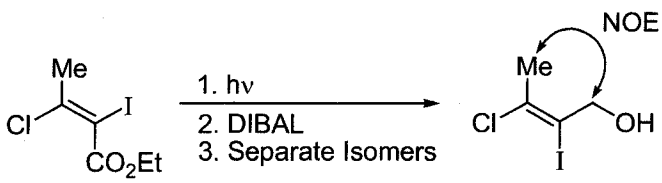
^{13}C NMR (100 MHz, C_6D_6): δ 136.7 (C), 129.1 (C), 129.0 (CH), 129.0 (CH), 128.9 (CH), 67.2 (C), 63.4 (CH_2);

IR (neat) 3362, 1662 cm^{-1};

MS (EI) 294 (M^+).

R_f: 0.25 on silica gel (10% EtOAc in hexanes).

General procedure for the reduction of (Z)-β-chloro-α-iodo-α,β-unsaturated esters to the corresponding (Z)-alcohols



(*Z*)-3-Chloro-2-iodobut-2-en-1-ol (B-374). A solution of ester **B-362** (85 mg, 0.31 mmol) was subjected to UV light (350 nm) for 1 hour, thereby isomerizing to the (*Z*)-β-chloro-α-iodo-α,β-unsaturated ester (**B-363**). To a solution of the crude product (85 mg, 0.31 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at 0 °C was added diisobutylaluminum hydride as a 1M solution in hexanes (0.77 mL, 2.5 equiv). The reaction was stirred for 2 h. Methanol (1 mL) was carefully added dropwise to quench the reaction. Ether (5 mL) and a

saturated solution of Rochelle's salt (3 mL) were then introduced, and the resulting mixture was stirred until both layers became clear. The layers were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel eluting with 10% EtOAc in hexanes gave the desired compound as a colorless oil (15 mg, 21%)

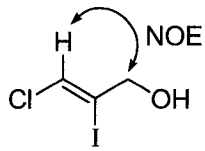
^{1}H NMR (500 MHz, C_6D_6): δ 3.72 (s, 2H), 1.62 (s, 3H), 1.16 (br s, 1H);

^{13}C NMR (125 MHz, C_6D_6): δ 138.4 (C), 103.7 (C), 67.6 (CH_2), 21.9 (CH_3); **IR** (neat) 3382, 1627 cm^{-1};

MS (EI) 232 (M^+);

HRMS calcd for C_4H_6ClIO (M^+) 231.9152; found 231.9147.

R_f: 0.14 on silica gel (20% EtOAc in hexanes).



(*Z*)-3-Chloro-2-iodoprop-2-en-1-ol (B-405). Prepared from ester **B-367** (113 mg, 0.46 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-iodobut-2-en-1-ol (**B-374**) which gave the title compound as a colorless oil (13 mg, 13%).

^{1}H NMR (500 MHz, C_6D_6): δ 6.05 (t, J = 1.5 Hz, 1H), 3.58 (dd, J = 5.0, 1.5 Hz, 2H), 1.20 (br s, 1H);

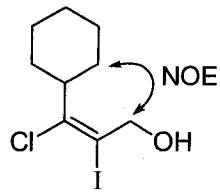
^{13}C NMR (125 MHz, C_6D_6): δ 124.5 (CH), 110.1 (C), 69.7 (CH_2);

IR (neat) 3338, 1590 cm^{-1};

MS (EI) 218 (M^+);

HRMS calcd for C_3H_4ClIO (M^+) 217.8995, found 217.8923.

R_f: 0.36 on silica gel (20% EtOAc in hexanes).



(*Z*)-3-Chloro-3-cyclohexyl-2-iodoprop-2-en-1-ol (B-307). Prepared from ester **B-397** (25 mg, 0.073 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-iodobut-2-en-1-ol (**B-374**) which gave the title compound as a colorless oil (5.1 mg, 23%).

^{1}H NMR (400 MHz, C_6D_6): δ 4.12 (d, J = 6.9 Hz, 2H), 2.63 (m, 1H), 0.91-1.96 (m, 10H);

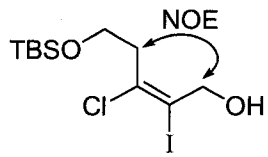
^{13}C NMR (100 MHz, C_6D_6): δ 149.1 (C), 103.8 (C), 67.7 (CH_2), 43.6 (CH), 31.6 (CH_2), 26.1 (CH_2), 25.6 (CH_2);

IR (neat) 3354, 1595 cm^{-1};

MS (EI) 300 (M^+);

HRMS Calcd for $C_9H_{14}ClIO$ (M+) 299.9778, found 299.9773.

R_f: 0.13 on silica gel (10% EtOAc in hexanes).



(*Z*)-5-(*Tert*-butyldimethylsilyloxy)-3-chloro-2-iodopent-2-en-1-ol (B-408). Prepared from ester **B-396** (115 mg, 0.28 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-iodobut-2-en-1-ol (**B-374**) which gave the title compound as a colorless oil (51 mg, 51%).

^{1}H NMR (500 MHz, C_6D_6): δ 4.21 (d, J = 6.5 Hz, 2H), 3.37 (t, J = 5.5 Hz, 2H), 2.59 (t, J = 6.5 Hz, 1H), 2.30 (t, J = 5.5 Hz, 2H), 0.85 (s, 9H), -0.04 (s, 6H);

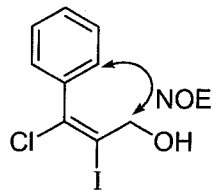
^{13}C NMR (125 MHz, C_6D_6): δ 130.0 (C), 103.2 (C), 69.2 (CH_2), 56.0 (CH_2), 38.8 (CH_2), 26.0 (CH_3 x 3), 18.4 (C), -5.5 (CH_3 x 2);

IR (neat): 3360, 1471 cm^{-1};

MS (EI) 319 ($M^+ - {}^t$Bu).

HRMS calcd for $C_7H_{13}ClIO_2Si$ ($M^+ - {}^t$Bu) 318.9420, found 318.9413.

R_f: 0.40 on silica gel (20% EtOAc in hexanes).



(*Z*)-3-Chloro-2-iodo-3-phenylprop-2-en-1-ol (B-412). Prepared from ester **B-399** (50 mg, 0.15 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-iodobut-2-en-1-ol (**B-374**) which gave the title compound as a colorless oil (19 mg, 45%).

^{1}H NMR (400 MHz, C_6D_6): δ 7.20 (dd, J =8.4, 1.6 Hz, 2H), 6.90-7.03 (m, 3H), 3.76 (d, J = 6.8 Hz, 2H), 1.27 (t, J = 6.8 Hz, 1H);

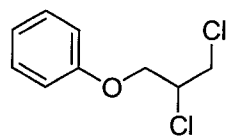
^{13}C NMR (100 MHz, C_6D_6): δ 136.7 (C), 129.2 (C), 129.0 (CH), 129.0 (CH), 128.8 (CH), 67.2 (C), 63.5 (CH_2);

IR (neat) 3356, 1444 cm^{-1};

MS (EI) 294 (M^+).

R_f: 0.25 on silica gel (10% EtOAc in hexanes).

Halogenation of alkenes using Bu_4NI/DCE



(2,3-Dichloropropoxy)benzene (B-417).[312] Prepared from allyloxybenzene (100 mg, 0.75 mmol) using a procedure similar to that described above for compound **B-362** that provided the title compound as a colorless oil (151 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.05 – 6.94 (m, 3H), 4.41 – 4.35 (m, 1H), 4.30 (dd, J = 6.4, 1.2 Hz, 2H), 4.02 – 3.89 (m, 2H);

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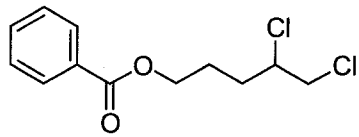
[312] (a) Firouzabadi, H.; Shiriny, F. *Tetrahedron* **1996**, *52*, 14929. (b) Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Nahid, A. *Bull. Chem. Soc. Jap.* **2004**, *77*, 1885. (c) Iranpoor, N.; Firouzabadi, H.; Azadi, R.; Ebrahimzadeh, F. *Can. J. Chem.* **2006**, *84*, 69.

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (C), 129.6 (CH), 121.6 (CH), 114.7 (CH), 68.1 (CH_2), 57.3 (CH), 45.0 (CH_2);

IR (neat) 2959, 2933, 1599, 1496 cm^{-1};

MS (EI) 204 (M^+);

HRMS Calcd for $C_9H_{10}Cl_2O$ (M^+) 204.0109, found 204.0105.



4,5-Dichloropentyl benzoate (B-419). Prepared from pent-4-enyl benzoate[313] (100 mg, 0.53 mmol) using a procedure similar to that described above for compound **B-362** that provided the title compound as a colorless oil (118 mg, 99%).

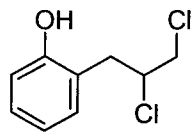
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 6.4, 1.2 Hz, 2H), 7.55 – 7.54 (m, 1H), 7.44 (dd, J = 8.0, 1.6 Hz, 2H), 4.38 – 4.35 (m, 2H), 4.13 – 4.10 (m, 1H), 3.79 (dd, J = 11.0, 5.0 Hz, 1H), 3.66 (dd, J = 11.4, 7.8 Hz, 1H), 2.22 – 1.84 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 132.9 (CH), 130.0 (C), 129.5 (CH), 128.3 (CH), 63.9 (CH_2), 60.4 (CH), 47.9 (CH_2), 31.7 (CH_2), 25.2 (CH_2);

IR (neat) 2956, 2849, 1718, 1451 cm^{-1};

MS (EI) 260 (M^+);

HRMS Calcd for $C_{12}H_{14}ClO_2$ (M^+ – Cl) 225.0682, found 225.0700.



2-(2,3-Dichloropropyl)phenol (B-421). Prepared from 2-allylphenol[314] (100 mg, 0.74 mmol) using a procedure similar to that described above for compound **B-362** that provided the title compound as a colorless oil (135 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 6.94 (dd, J = 7.4, 7.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.42 (br s, 1H), 4.53 – 4.66 (m, 1H), 3.78 (dd, J = 11.7, 5.5 Hz, 1H),

[313] Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1980**, *45*, 3578.
[314] Nguyen Van, T.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199.

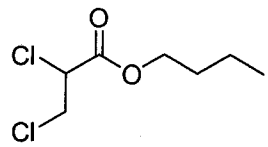
3.76 (dd, *J*= 11.7, 5.36 Hz, 1H), 3.35 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.09 (dd, *J* = 14.0, 7.6 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (C), 131.8 (CH), 128.6 (CH), 123.1 (C), 120.9 (CH), 115.5 (CH), 60.3 (CH), 48.4 (CH_2), 36.5 (CH_2);

IR (neat) 3540, 2951, 1609, 1502 cm^{-1};

MS (EI) 204 (M^+);

HRMS Calcd for $C_9H_{10}Cl_2O$ (M^+) 204.0109, found 204.0121.



Butyl 2,3-dichloropropanoate (B-427).[315] Prepared from *n*-butyl acrylate (50 mg, 0.39 mmol) using a procedure similar to that described above for compound **B-362** that provided the title compound as a colorless oil (15.5 mg, 20%).

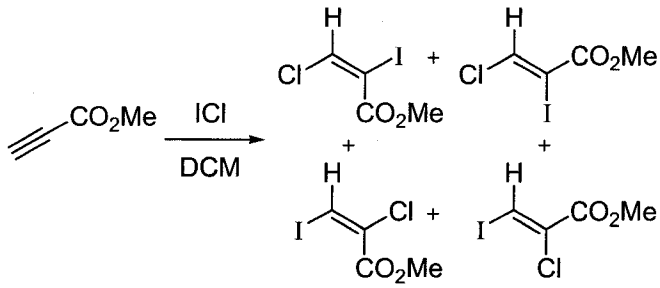
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 8.7, 5.2 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.96 (dd, *J* = 11.1, 8.7 Hz, 1H), 3.80 (dd, *J* = 11.1, 5.2 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.44 – 1.39 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 66.5 (CH_2), 55.1 (CH), 43.9 (CH_2), 30.4 (CH_2), 18.9 (CH_2), 13.6 (CH_3);

IR (neat) 2936, 1750 cm^{-1}.

[315] Horna, A.; Taborsky, J.; Churacek, J.; Dufka, O. *J. Chromatography* **1985**, *348*, 141.

General procedure for the halogenation of alkenes and alkynes using ICl.



Reaction of methyl-2-propiolate with ICl. To a solution of methyl 2-propiolate (50 mg, 0.60 mmol, 1.0 equiv) in dichloroethane (25 mL) was added iodine monochloride (1.0 M solution in DCM, 0.60 mL, 0.60 mmol, 1.0 equiv) and the resulting mixture was stirred for 2 h. The reaction was diluted with Et_2O and washed sequentially with $NaHSO_3$ (20% wt solution), saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was obtained by flash chromatography eluting with hexanes then 5% EtOAc in hexanes to give an inseparable mixture of compounds **B-367**, **B-368**, **B-369**, **B-370** as a pale yellow oil (100 mg, 68%).

B-368:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 3.85 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (C), 142.6 (CH), 87.7 (C), 53.9 (CH_3).

B-369/B-370:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 3.849 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (C), 128.3 (C), 85.5 (CH), 53.4 (CH_3);

B-369/B-370:

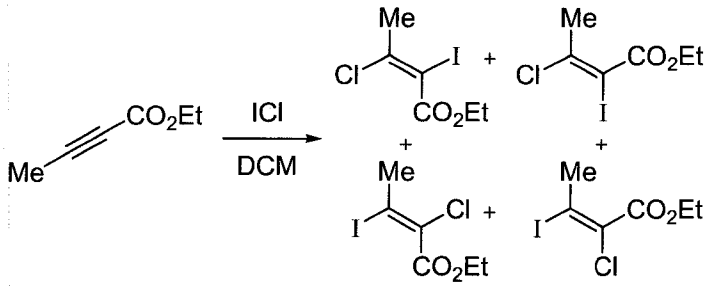
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 3.85 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (C), 97.5 (C), 87.4 (CH), 53.4 (CH_3);

IR (neat) 1725, 1563 cm^{-1};

MS (EI) 246 (M^+).

R_f: 0.45 on silica gel (5% EtOAc in hexanes)



Reaction of ethyl 2-butynoate with ICl. Prepared from ethyl 2-butynoate (50 mg, 0.45 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of **B-362**, **B-363**, **B-364**, **B-365** as a yellow oil (110 mg, 90%).

B-363:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 128.3 (C), 84.9 (C), 62.6 (CH_2), 38.3 (CH_3), 13.9 (CH_3).

B-364/B-365:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J = 7.2 Hz, 2H), 2.66 (s, 3H), 1.35, (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C), 96.9 (C), 64.6 (C), 60.9 (CH_2), 25.2 (CH_3), 13.7 (CH_3).

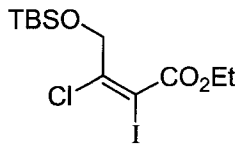
B-364/B-365:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (t, J = 7.2 Hz, 2H), 2.48, (s, 3H), 1.24 (t, J = 7.2 Hz, 3H);

IR (neat) 1728, 1627 cm^{-1};

MS (EI) 274 (M^+).

R_f: 0.3 on silica gel (5% EtOAc in hexanes)



(*Z*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-3-chloro-2-iodobut-2-enoate (B-430). Prepared from ethyl 4-(*tert*-butyldimethylsilyloxy)but-2-ynoate (50 mg, 0.21 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of **B-395** and **B-430** as a yellow oil (56.8 mg, 67%).

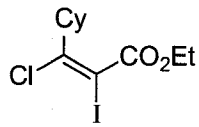
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.39 – 1.25 m, 3H), 0.87 (s, 9H), 0.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C), 107.5 (C), 81.8 (C), 72.9 (CH_2), 62.7 (CH_2), 25.9 (CH_3), 18.4 (C), 14.0 (CH_3), -4.9 (CH_3).

IR (neat) 2929, 1731 cm^{-1}.

MS (EI) 404 (M^+)

R_f: 0.75 on silica gel (10% EtOAc in hexanes)



(*Z*)-Ethyl 3-chloro-3-cyclohexyl-2-iodoacrylate (B-432). Prepared from ethyl 3-cyclohexylpropiolate (50 mg, 0.28 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of **B-397** and **B-432** as a yellow oil (95 mg, 99%).

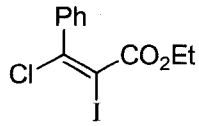
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (q, J = 7.2 Hz, 2H), 2.96 (tt, J = 11.1, 3.3 Hz, 1H), 2.20 – 1.16 (m, 10H), 1.33 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 143.0 (C), 68.5 (C), 62.9 (CH_2), 52.0 (CH), 32.8 (CH_2), 26.4 (CH_2), 23.2 (CH_2), 14.3 (CH_3);

IR (neat) 1732, 1611 cm^{-1};

MS (EI) 342 (M^+).

R_f: 0.43 on silica gel (5% EtOAc in hexanes)



(*Z*)-Ethyl 3-chloro-2-iodo-3-phenylacrylate (B-433). Prepared from ethyl phenylpropiolate (50 mg, 0.29 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of **B-399** and **B-433** as a yellow oil (89 mg, 93%).

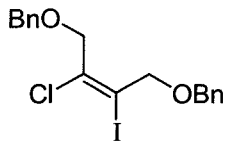
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 5H), 3.99 (q, J = 7.0 Hz, 2H), 0.94 (t, J = 7.0 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (C), 149.0 (C), 138.6 (C), 134.7 (CH), 129.8 (CH), 127.9 (CH), 81.2 (C), 62.5 (CH_2), 13.4 (CH_3);

IR (neat) 1728, 1615 cm^{-1};

MS (EI) 336 (M^+).

R_f: 0.5 on silica gel (5% EtOAc in hexane).



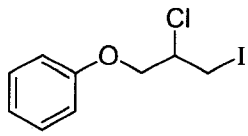
(*Z*)-(2-Chloro-3-iodobut-2-ene-1,4-diyl)bis(oxy)bis(methylene)dibenzene (B-434). Prepared from 1,4-bis(benzyloxy)but-2-yne (50 mg, 0.19 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of compounds **B-403** and **B-434** as a yellow oil (81 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 10H), 4.57 (s, 2H), 4.54 (s, 2H), 4.51 (s, 2H), 4.47 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3 (C), 128.6 (C), 128.5 (C), 128.4 (CH), 127.92 (CH), 127.88 (CH), 100.8 (C), 81.5 (CH_2), 76.3 (CH_2), 73.1 (CH_2), 71.9 (CH_2);

IR (neat) 1461, 1376 cm^{-1};

MS (EI) 393 (M^+ – Cl), 301 (M^+ – I).



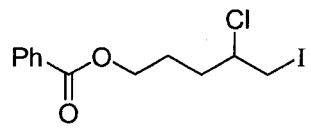
(2-Chloro-3-iodopropoxy)benzene (B-436). Prepared from allyloxybenzene (50 mg, 0.37 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of compounds **B-417** and **B-436** as a yellow oil (89.8 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.06 – 7.02 (m, 1H), 6.99 – 6.96 (m, 2H), 4.54 – 4.29 (m, 1H), 4.07 (d, J = 6.8 Hz, 2H), 3.74 (dd, J = 10.7, 6.4 Hz, 1H), 3.67 (dd, J = 10.7, 4.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8 (C), 129.3 (CH), 121.6 (CH), 114.7 (CH), 70.2 (CH_2), 54.1 (CH), 6.7 (CH_2);

IR (neat) 1594, 1500 cm^{-1};

MS (EI) 296 (M^+).



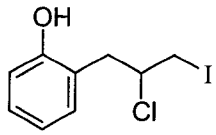
4-Chloro-5-iodopentyl benzoate (B-442). Prepared from pent-4-enyl benzoate[313] (50 mg, 0.26 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of compounds **B-419** and **B-442** as a colorless oil (85 mg, 92%).

^{1}H NMR (400 MHz, acetone-d_6) δ 8.06 (d, J = 10.4 Hz, 2H), 7.57 (dd, J = 10.0, 10.0 Hz), 7.44 (dd, J = 10.4, 10.4 Hz), 4.37 (t, J = 8.0 Hz, 2H), 4.35 – 4.23 (m, 1H), 4.09 – 3.86 (dd, J = 17.2, 5.6 Hz, 1H), 3.83 (dd, J = 14.4, 14.4 Hz, 1H), 2.33 – 1.86 (m, 4H);

^{13}C NMR (100 MHz, acetone-d_6) δ 166.5 (C), 133.0 (CH), 130.1 (C), 129.5 (CH), 128.4 (CH), 63.7 (CH_2), 33.9 (CH), 33.1 (CH_2), 28.2 (CH_2), 10.3 (CH_2);

IR (neat) 1718, 1615 cm^{-1};

MS (EI) 225 (M^+ – I), 317 (M^+ – Cl).



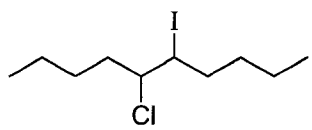
2-(2-Chloro-3-iodopropyl)phenol (B-443). Prepared from 2-allylphenol[314] (50 mg, 0.37 mmol) using a procedure similar to that described above for compound **B-368** that provided the title compound as a yellow oil (109 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 2H), 6.87 (ddd, J = 8.0, 7.6, 0.8 Hz, 1H), 6.78 (d, J = 8.0 Hz), 4.92 – 4.85 (m, 1H), 3.45 (dd, J_{AB} = 8.8, J_{AX} = 6.4 Hz, 1H), 3.34 (dd, J_{AB} = 8.8, J_{BX} = 6.1 Hz, 1H), 3.40 (dd, J = 15.7, 8.9 Hz, 1H), 3.05 (dd, J = 15.7, 6.4 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 128.2 (CH), 125.7 (C), 125.0 (CH), 120.8 (CH), 109.6 (CH), 81.6 (CH), 36.1 (CH_2), 8.9 (CH_2);

IR (neat) 1506, 1479 cm^{-1};

HRMS calc'd for $C_9H_{10}ClIO$ (M^+) 295.9465, found 295.9467.



B-444

5-Chloro-6-iododecane (B-444).[316] Prepared from 5-decene (0.135 mL, 0.71 mmol) using a procedure similar to that described above for compound **B-368** that provided the title compound as an inseparable mixture of **B-423** and **B-444** as a colorless oil (142 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.21 (m, 1H), 3.93 – 3.88 (m, 1H), 2.11 – 2.03 (m, 1H), 1.98 – 1.80 (m, 3H), 1.62 – 1.52 (m, 2H), 1.46 – 1.27 (m, 6H), 0.93 (t, J = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6) δ 66.9 (CH), 42.5 (CH), 37.5 (CH_2), 36.8 (CH), 31.3 (CH_2), 28.2 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 13.9 (CH_3);

IR (neat) 2957, 2931, 1465 cm^{-1};

MS (EI) 302 (M^+);

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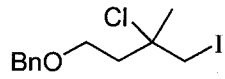
[316] Zavada, J.; Kruipicka, J.; Kocian, O.; Pankova, M. *Collection of Czechoslovak Chemical Communications* **1983**, *48*, 3552.

HRMS calc'd for $C_{10}H_{20}ClI$ (M+) 302.0298, found 302.0218.



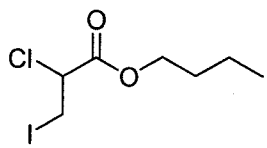
((3-Chloro-4-iodo-3-methylbutoxy)methyl)benzene (B-445). Prepared from ((3-methylbut-3-enyloxy)methyl)benzene[317] (50 mg, 0.28 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of compounds **B-425** and **B-445** as a colorless oil (12 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.36 (m, 5H), 4.51 (s, 2H), 3.81 – 3.60 (m, 4H), 2.29 – 2.15 (m, 2H), 1.66 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 73.1 (CH_2), 70.2 (C), 66.7 (CH_2), 41.2 (CH_2), 28.6 (CH_3), 18.9 (CH_2);

IR (neat) 2925, 1273 cm^{-1};

MS (EI) 338 (M^+).



***n*-Butyl 2-chloro-3-iodopropanoate (B-446).** Prepared from *n*-butyl acrylate (50 mg, 0.39 mmol) using a procedure similar to that described above for compound **B-368** that provided an inseparable mixture of compounds **B-427** and **B-426** as a yellow oil (67 mg, 61%).[315]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (dd, J = 11.5, 4.4 Hz, 1H), 4.23 – 4.18 (m, 2H), 4.10 (dd, J = 10.8, 10.8 Hz, 1H), 3.83 (dd, J = 10.9, 4.4 Hz), 1.70 – 1.63 (m, 2H), 1.47 – 1.37 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 66.4 (CH_2), 44.8 (CH_2), 30.4 (CH_2), 19.0 (CH_2), 16.7 (CH_3), 13.6 (CH);

IR (neat) 2925, 1735 cm^{-1};

MS (EI) 290 (M^+).

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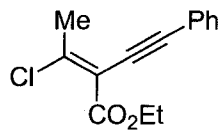
[317] Bondar, D.; Liu, J.; Muller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813.

Synthesis of Trisubstituted Olefins

General procedure for the Sonogashira coupling of (E)-β-chloro-α-iodo-α,β-unsaturated esters:



(*Z*)-Ethyl 3-chloro-2-(2-phenylethynyl)but-2-enoate (B-447). A flask was charged with $Pd(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol, 0.10 equiv) and copper iodide (5.1 mg, 0.027 mmol, 0.15 equiv). To this was added dichloromethane (2 mL) and diisopropylethylamine (0.13 mL, 0.72 mmol, 4 equiv) *via* syringe. (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**B-362**) (50 mg, 0.18 mmol, 1 equiv) was then introduced, and the resulting yellow solution was carefully sparged with nitrogen for 10 minutes. Phenyl acetylene (0.06 mL, 0.55 mmol, 3 equiv) was then added *via* syringe and the resulting black solution was stirred for 2 h. The mixture was partitioned between water and EtOAc and the organic layer collected then dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by column chromatography on silica gel eluting with hexanes then 5% EtOAc in hexanes to afford the title product (35 mg, 78%) as a clear, tan oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H), 7.35 – 7.34 (m, 3H), 4.33 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H);

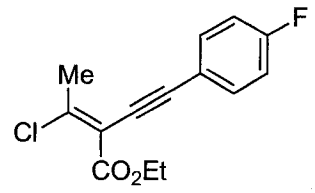
^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C), 146.6 (C), 131.4 (CH), 128.8 (CH), 128.3 (CH), 122.5 (C), 115.3 (C), 96.8 (C), 83.0 (C), 61.7 (CH_2), 26.2 (CH_3), 14.0 (CH_3);

IR (neat) 2201, 1734, 1612 cm^{-1};

MS (EI) 248 (M+);

HRMS calcd for $C_{14}H_{13}ClO_2$ (M^+) 248.0604, found 248.0617.

R_f: 0.22 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-enoate (B-461). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a pale yellow oil (37 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, J = 5.5, 9.0 Hz, 2H), 6.67 (dd, J = 9.0, 9.0 Hz, 2H), 4.17 (q, J = 7.5 Hz, 2H), 2.18 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H);

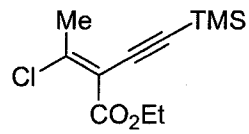
^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0 (C), 163.3 (C), 162.0 (C), 146.2 (C), 133.7 (CH), 133.6 (CH), 119.0 (C), 115.9 (CH), 115.7 (CH), 96.0 (C), 83.6 (C), 61.7 (CH_2), 25.5 (CH_3), 14.0 (CH_3);

IR (neat) 2140, 1733, 1600 cm^{-1};

MS (EI) 266 (M^+);

HRMS calcd for $C_{14}H_{12}ClFO_2$ (M^+) 266.0510, found 266.0490.

R_f: 0.18 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 3-chloro-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (B-462). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a pale yellow oil (30 mg, 68 %).

^{1}H NMR (300 MHz, C_6D_6) δ 3.96 (q, J = 7.2 Hz, 2H), 2.04 (s, 3H), 0.93 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H);

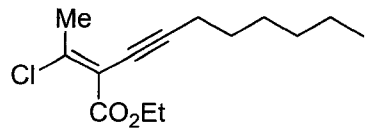
^{13}C NMR (75 MHz, C_6D_6) δ 163.0 (C), 147.6 (C), 116.5 (C), 102.8 (C), 99.0 (C), 61.6 (CH_2), 25.5 (CH_3), 13.9 (CH_3), -0.3 (CH_3);

IR (neat) 2147, 1736, 1586 cm^{-1};

MS (EI) 244 (M^+);

HRMS calcd for $C_{11}H_{17}ClO_2Si$ (M^+) 244.0686, found 244.0668.

R_f: 0.29 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 2-(1-chloroethylidene)hex-3-ynoate (B-463). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a pale yellow oil (34 mg, 74%).

^{1}H NMR (500 MHz, C_6D_6) δ 4.15 (q, J = 7.5 Hz, 2H), 2.20 (s, 3H), 2.19 (t, J = 7.0 Hz, 2H), 1.45 – 1.40 (m, 2H), 1.36 – 1.32 (m, 2H), 1.31 – 1.26 (m, 2H), 1.23 – 1.19 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H);

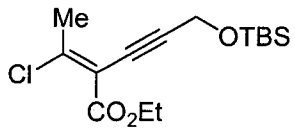
^{13}C NMR (125 MHz, C_6D_6) δ 163.9 (C), 144.0 (C), 116.9 (C), 98.6 (C), 75.5 (C), 61.4 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 25.2 (CH_3), 22.8 (CH_2), 19.8 (CH_2), 14.2 (CH_3), 14.0 (CH_3);

IR (neat) 2223, 1735, 1587 cm^{-1};

MS (EI) 256 (M^+);

HRMS calcd for $C_{14}H_{21}ClO_2$ (M^+) 256.1231, found 256.1232.

R_f: 0.50 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2-(1-chloroethylidene)pent-3-ynoate (B-464). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a pale yellow oil (43 mg, 76%).

^{1}H NMR (500 MHz, C_6D_6) δ 4.22 (s, 2H), 4.02 (q, J = 7.0 Hz, 2H), 2.03 (s, 3H), 0.97 (t, J = 7.0 Hz, 3H), 0.94 (s, 9H), 0.06 (s, 6H);

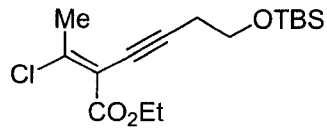
^{13}C NMR (125 MHz, C_6D_6) δ 163.2 (C), 146.6 (C), 100.2 (C), 96.1 (C), 79.1 (C), 61.5 (CH_2), 52.1 (CH_2), 25.9 (CH_3), 25.4 (CH_3), 18.3 (C), 14.0 (CH_3), -5.1 (CH_3);

IR (neat) 1737, 1586 cm^{-1};

MS (EI) 301 (M^+ – Me);

HRMS calcd for $C_{11}H_{16}ClO_3Si$ (M^+ – 57) 259.0557, found 259.0553.

R_f: 0.41 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-2-(1-chloroethylidene)hex-3-ynoate (B-465). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a pale yellow oil (42.8 mg, 72%).

^{1}H NMR (500 MHz, C_6D_6) δ 4.04 (q, J = 7.0 Hz, 2H), 3.5 (t, J = 7.0 Hz, 2H), 2.32 (t, J = 7.0 Hz, 2H), 2.93 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), – 0.02 (s, 6H);

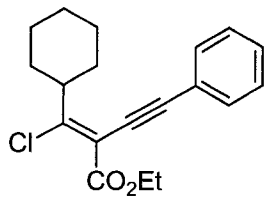
^{13}C NMR (125 MHz, C_6D_6) δ 163.7 (C), 144.6 (C), 116.7 (C), 95.7 (C), 76.2 (C), 61.7 (CH_2), 61.5 (CH_2), 26.0 (CH_3), 25.2 (CH_3), 24.3 (CH_2), 18.4 (C), 14.0 (CH_3), -5.3 (CH_3);

IR (neat) 2224, 1736, 1587 cm^{-1};

MS (EI) 315 (M^+ – Me);

HRMS calcd for $C_{12}H_{18}ClO_3Si$ (M^+ – 57) 273.0714, found 273.0752.

R_f: 0.61 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 2-(chloro(cyclohexyl)methylene)-4-phenylbut-3-ynoate (B-468). Prepared from compound **B-397** (100 mg, 0.305 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a yellow oil (74 mg, 68%).

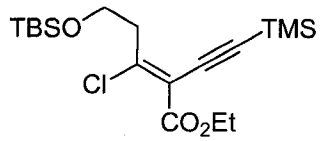
^{1}H NMR (400 MHz, C_6D_6) δ 7.39 – 7.30 (m, 2H), 6.94 – 6.92 (m, 3H), 4.07 (q, J = 7.2 Hz, 2H), 3.38 – 3.32 (m, 1H), 1.67 – 1.22 (m, 10H), 0.98 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 163.7 (C), 153.9 (C), 131.7 (CH), 128.9 (CH), 128.6 (CH), 123.1 (CH), 123.1 (C), 115.0 (C), 97.3 (C), 92.1 (C), 61.7 (CH_2), 45.7 (CH), 30.3 (CH_2), 26.0 (CH_2), 24.6 (CH_2), 14.0 (CH_3);

IR (neat) 2237, 1710 cm^{-1};

HRMS calcd for $C_{19}H_{21}ClO_2$ (M^+) 316.1230, found 316.1241.

R_f: 0..49 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-chloro-2-(2-(trimethylsilyl)ethynyl)pent-2-enoate (B-469). Prepared from compound **B-396** (30 mg, 0.072 mmol) using a procedure similar to that described above for compound **B-447** that provided the title product as a colorless oil (22 mg, 79%).

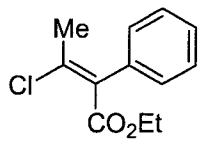
^{1}H NMR (400 MHz, C_6D_6) δ 3.96 (q, J = 7.2 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 0.97 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H), 0.15 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (100 MHz, C_6D_6) δ 163.2 (C), 148.4 (C), 118.2 (C), 102.6 (C), 99.0 (C), 61.6 (CH_2), 60.1 (CH_2), 41.9 (CH_2), 26.0 (CH_3), 18.3 (C), – 0.3 (CH_3), – 5.3 (CH_3);

IR (neat) 2148, 1738 cm^{-1};

HRMS calcd for $C_{14}H_{24}ClO_3Si_2$ (M^+ – *t*-Bu) 331.0950, found 331.0977.

General procedure for the Suzuki coupling reaction of β-chloro-α-iodo-α,β-unsaturated esters and amides.



(*Z*)-Ethyl 3-chloro-2-phenylbut-2-enoate (B-480). A flask was charged with $Pd(OAc)_2$ (12.0 mg, 0.018 mmol, 0.1 equiv), $P^tBu_3{\cdot}HBF_4$ (10.0 mg, 0.036 mmol, 0.2 equiv), Cs_2CO_3 (176 mg, 0.54 mmol, 3.0 equiv), phenylboronic acid (44.0 mg, 0.36 mmol, 2.0 equiv) and was subsequently purged for 10 min with N_2. To this was added dioxane (2.0 mL) and the solution was sparged for 10 min with N_2. To the solution was added (*E*)-ethyl 3-chloro-2-iodobut-2-enoate **B-362** (50.0 mg, 0.18 mmol, 1.0 equiv) and the reaction was stirred for 3 hours. The mixture was partitioned between water and Et_2O and the organic layer was collected, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel eluting with 1% Et_2O in hexanes to 3% Et_2O in hexanes to give the title product as a yellow oil (27.1 mg, 67%).

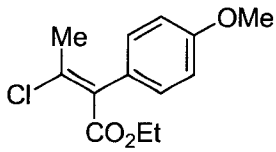
^{1}H NMR (400 MHz, acetone-d_6): δ 7.45 – 7.33 (m, 5H), 4.22 (q, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.25 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, acetone -d_6): δ 168.2 (C), 136.5 (C), 135.3 (C), 134.3 (C), 130.5 (CH), 130.4 (CH), 130.2 (CH), 62.8 (CH_2), 24.5 (CH_3), 15.3 (CH_3).

IR (neat) 3060, 2983, 1727 cm^{-1}.

HRMS calcd for $C_{12}H_{13}ClO_2$ (M^+) 224.0604, found 224.0587.

R_f: 0.33 on silica gel (4% Et_2O in hexanes)



(*Z*)-Ethyl 3-chloro-2-(4-methoxyphenyl)but-2-enoate (B-489). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (15 mg, 33%).

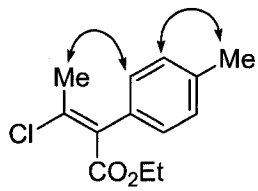
^{1}H NMR (400 MHz, benzene-d_6): δ 7.26 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.15 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, benzene-d_6): δ 167.1 (C), 160.0 (C), 133.6 (C), 132.2 (C), 130.2 (CH), 114.3 (CH), 61.2 (CH_2), 54.7 (CH_3), 23.1 (CH_3), 14.0 (CH_3).

IR (neat) 1637 cm^{-1}

HRMS calcd for $C_{13}H_{15}ClO_3$ (M^+) 254.0710, found 254.0702.

R_f: 0.23 on silica gel (5 % EtOAc in hexanes).



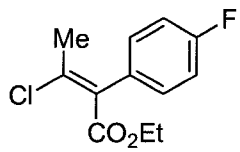
(*Z*)-Ethyl 3-chloro-2-*p*-tolylbut-2-enoate (B-493). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (26 mg, 61%).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.25 – 7.20 (m, 4H), 4.21 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 2.15 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ 168.3 (C), 140.1 (C), 135.3 (C), 133.6 (C), 131.1 (CH), 130.3 (CH), 62.7 (CH_2), 24.4 (CH_3), 22.2 (CH_3), 15.3 (CH_3);

HRMS calcd for $C_{13}H_{15}ClO_2$ (M^+) 238.0761, found 238.0753;

R_f: 0.63 on silica gel (5 % EtOAc in hexanes)



(*Z*)-Ethyl 3-chloro-2-(4-fluorophenyl)but-2-enoate (B-499). Prepared from compound **B-362** (50 mg, 0.18 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (25 mg, 57%).

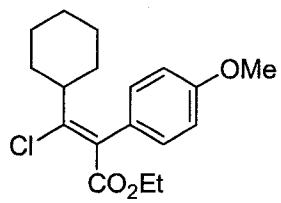
^{1}H NMR (400 MHz, acetone-d_6): δ 7.40 (dd, J = 8.8, 5.6 Hz, 2H), 7.21 (dd, J = 8.8, 8.8 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 169.4 (C), 161.2 (d, J = 244.3 Hz, C), 146.3 (d, J = 3.3 Hz, C), 135.0 (C), 134.1 (C), 132.6 (d, J = 8.3 Hz, CH), 117.4 (d, J = 21.8 Hz, CH), 62.9 (CH_2), 24.6 (CH_3), 15.3 (CH_3).

IR (neat) 2990, 1727 cm^{-1}.

HRMS calcd for $C_{12}H_{12}ClFO_2$ (M^+) 242.0510, found 242.0507.

R_f: 0.41 on silica gel (5% Et_2O in hexanes).



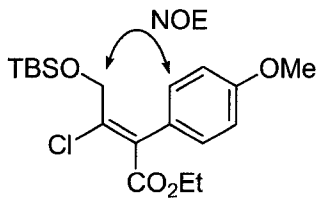
(*Z*)-Ethyl 3-chloro-3-cyclohexyl-2-(4-methoxyphenyl)acrylate (B-501). Prepared from compound **B-397** (25 mg, 0.073 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (10 mg, 43%).

^{1}H NMR (500 MHz, acetone-d_6): δ 7.23 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.19 (q, J = 7.5 Hz, 2H), 3.82 (s, 3H), 2.63 – 2.55 (m, 1H), 1.73 – 1.57 (m, 2H), 1.62 – 1.57 (m, 4H), 1.24 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6): δ 168.6 (C), 161.7 (C), 142.6 (C), 134.0 (C), 131.4 (CH), 128.5 (C), 116.0 (CH), 62.2 (CH_2), 56.6 (CH), 43.6 (CH_3), 32.1 (CH_2), 27.2 (CH_2), 15.4 (CH_3).

IR (neat) 2952, 2855, 1727, 1607 cm^{-1}.

HRMS calcd for $C_{18}H_{23}ClO_3$ (M^+) 322.1336, found 322.1344.



(*Z*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-3-chloro-2-(4-methoxyphenyl)but-2-enoate (B-502). Prepared from compound **B-395** (200 mg, 0.50 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (29 mg, 15%)

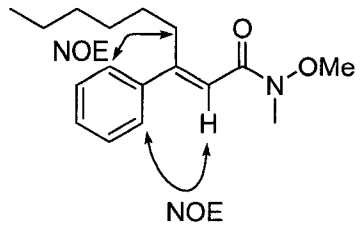
^{1}H NMR (400 MHz, acetone -d_6): δ 7.31 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.34 (s, 2H), 4.26 (q, J = 6.8 Hz, 2H), 3.83 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, acetone-d_6): δ 168.2 (C), 162.1 (C), 137.0 (C), 135.1 (C), 131.6 (CH), 127.6 (C), 115.9 (CH), 65.2 (CH_2), 62.9 (CH_2), 56.7 (CH_3), 27.1 (CH_3), 19.8 (C), 15.3 (CH_3), – 4.2 (CH_3).

IR (neat) 2956, 1720 cm^{-1}.

HRMS calcd for $C_{15}H_{20}ClO_4Si$ (M^+ – ^{t}Bu) 327.0819, found 327.0837.

R_f: 0.41 on silica gel (5% EtOAc in hexanes)

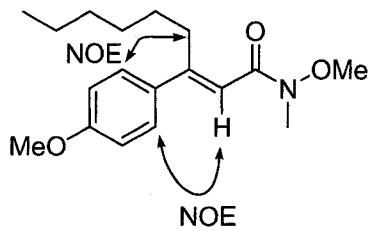


(*E*)-*N*-methoxy-*N*-methyl-3-phenylnon-2-enamide (B-558).

^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (dd, *J* = 6.6, 1.6 Hz, 2H), 7.15 – 7.08 (m, 3H), 6.65 (s, 1H), 3.34 (dd, *J* = 7.7, 7.7 Hz, 2H), 3.06 (s, 3H), 2.97 (s, 3H), 1.65 – 1.57 (m, 2H), 1.45 – 1.38 (m, 2H), 1.24 – 1.19 (m, 4H), 0.83 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ 167.1 (C), 158.0 (C), 143.1 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 117.0 (CH), 60.9 (CH_3), 54.8 (CH_3), 31.9 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 23.0 (CH_2), 14.2 (CH_3).

HRMS: calcd for $C_{17}H_{25}NO_2$ (M^+) 275.1185; found 275.1183.

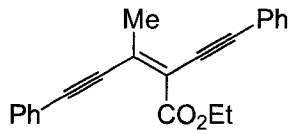


(*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylnon-2-enamide (B-559).

^{1}H NMR (400 MHz, C_6D_6) δ 7.37 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 3.39 (dd, *J* = 7.6, 7.6 Hz, 2H), 3.27 (s, 3H), 3.10 (s, 3H), 3.00 (s, 3H), 1.73 – 1.69 (m, 2H), 1.49 – 1.44 (m, 2H), 1.27 – 1.24 (m, 4H), 0.84 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ 168.0 (C), 160.6 (C), 157.6 (C), 135.1 (C), 128.3 (CH), 115.3 (CH), 114.2 (CH), 60.9 (CH_3), 54.8 (CH_3), 32.0 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 23.0 (CH_2), 14.3 (CH_3).

HRMS: calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1991; found 305.1988.



(*Z*)-Ethyl 3-methyl-5-phenyl-2-(2-phenylethynyl)pent-2-en-4-ynoate (B-448). A flame-dried round bottom flask under nitrogen was charged with $Pd(PPh_3)_2Cl_2$ (51 mg, 0.073 mmol, 0.1 equiv) and CuI (28 mg, 0.146 mmol, 0.15 equiv). Dichloromethane (7.3 mL), DIPEA (0.51 mL, 2.92 mmol, 4.0 equiv), and (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**B-362**) (200 mg, 0.73 mmol, 1 equiv) were then introduced sequentially. The solution was sparged for 5 minutes with N_2 before the addition of phenylacetylene (0.24 mL, 2.19 mmol, 3.0 equiv). The reaction was stirred for 18 h and then was partitioned between water and EtOAc. The layers were separated and the combinded organic phases were washed with HCl (10 %), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography eluting with hexanes then 5 % EtOAc in hexanes affording the title product as a yellow oil (130 mg, 55%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (dd, J = 8.0, 2.0 Hz, 2H), 7.43 (dd, J = 8.0, 1.5 Hz, 2H), 6.96-6.97 (m, 6H), 4.12 (q, J = 7.0 Hz, 2H), 2.27 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H);

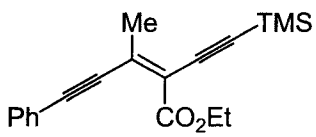
^{13}C NMR (125 MHz, C_6D_6) δ 163.7 (C), 136.7 (C), 132.3 (CH), 131.7 (CH), 129.2 (CH), 128.7 (C), 128.6 (CH), 128.6 (CH), 128.3 (CH), 123.7 (C), 121.5 (C), 104.9 (C), 101.5 (C), 91.0 (C), 86.5 (C), 61.1 (CH_2), 24.0 (CH_3), 14.2 (CH_3);

IR (neat) 2209, 2186, 1723, 1597 cm^{-1};

MS (EI) 314 (M^+);

HRMS calcd for $C_{22}H_{18}O_2$ (M^+) 314.1307, found 314.1276.

R_f: 0.13 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 3-methyl-5-phenyl-2-(2-(trimethylsilyl)ethynyl)pent-2-en-4-ynoate (B-585). A flame-dried round bottom flask was charged with $Pd(PPh_3)_2Cl_2$ (23 mg, 0.033 mmol,

0.1 equiv) and CuI (9.4 mg, 0.050 mmol, 0.15 equiv). Dioxane (3.0 mL), (*Z*)-ethyl 3-chloro-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (**B-464**) (80 mg, 0.33 mmol, 1.0 equiv) and DIPEA (0.17 mL, 0.99 mmol, 3.0 equiv) were added sequentially and the solution was sparged for 10 min with N_2. Phenylacetylene (0.10 mL, 0.99 mmol, 3.0 equiv) was then added and the resulting black reaction mixture was stirred for 1 hour at which time an addition portion of phenylacetylene (0.10 mL, 0.99 mmol, 3.0 equiv) was introduced. The reaction mixture was stirred for an additional 12 h, after which it was partitioned between water and EtOAc. The layers were separated and the organic phase washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica gel eluting with hexanes then 2% Et_2O in hexanes to give the desired product (43 mg, 42%) as a yellow oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.55-7.53 (m, 2H), 6.98-6.93 (m, 3H), 4.05 (q, J = 7.0 Hz, 2H), 2.24 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H), 0.19 (s, 9H);

^{13}C NMR (125 MHz, C_6D_6) δ 163.6 (C), 138.0 (C), 132.3 (CH), 129.2 (CH), 128.6 (CH), 123.5 (C), 121.5 (C), 107.1 (C), 105.3 (C), 101.4 (C), 90.6 (C), 61.1 (CH_2), 24.0 (CH_3), 14.1 (CH_3), -0.1 (CH_3);

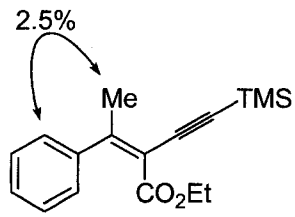
IR (neat) 2196, 2140, 1727, 1598 cm^{-1};

MS (EI) 310 (M^+);

HRMS calcd for $C_{19}H_{22}O_2Si$ (M^+) 310.1389, found 310.1389.

R_f: 0.13 on silica gel (5% EtOAc in hexanes)

General procedure for the Suzuki coupling of β-chloro-α-alkynyl-α,β-unsaturated esters



(*Z*)-Ethyl 3-phenyl-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (B-596). A flame-dried round bottom flask was charged with a solution of (*Z*)-ethyl 3-chloro-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (**B-462**) (50 mg, 0.20 mmol, 1.0 equiv) in 1,4-dioxane (2 mL) and the solution was sparged for 10 minutes with N_2. $Pd_2(dba)_3$ (9.2 m, 0.010 mmol, 0.05 equiv), phenyl boronic acid (49 mg, 0.40 mmol, 2 equiv), and tri-*tert*-

butylphosphine tetrafluoroborate (11.6 mg, 0.040 mmol, 0.20 equiv) were then added. The solution was sparged for an additional 5 minutes with N_2 before the addition of Cs_2CO_3 (130 mg, 0.40 mmol, 2 equiv). The resulting black solution was stirred for 2 h after which water was added. The mixture was extracted with EtOAc and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by column chromatography on silica gel, eluting with hexanes then 5% EtOAc in hexanes affording the product as a pale yellow oil (44 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H), 7.29-7.16 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2,39 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H);

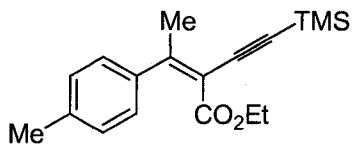
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 156.4 (C), 141.3 (C), 128.1 (CH), 128.0 (CH), 126.6 (CH), 115.0 (C), 101.5 (C), 100.5 (C), 61.0 (CH_2), 24.5 (CH_3), 13.5 (CH_3), -0.1 (CH_3);

IR (neat) 2146, 1728, 1592 cm^{-1};

MS (EI) 286 (M^+);

HRMS calcd for $C_{17}H_{22}O_2Si$ (M^+) 286.1389, found 286.1366.

R_f: 0.14 on silica gel (1 % EtOAc in hexanes)



(*Z*)-Ethyl 3-p-tolyl-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (B-597). Prepared from compound **B-462** (50 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-596** using *p*-tolyl boronic acid (109 mg, 0.80 mmol, 4.0 equiv), which provided the title product as a pale yellow oil (45 mg, 75%).

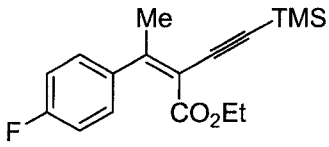
^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 3.80 (q, J = 7.0 Hz, 2H), 2.26 (s, 3H), 2.02 (s, 3H), 0.70 (t, J = 7.0 Hz, 3H), 0.21 (s, 9H);

^{13}C NMR (75 MHz, C_6D_6) δ 165.8 (C), 154.9 (C), 138.8 (C), 137.9 (C), 128.9 (CH), 127.2 (CH), 116.0 (C), 102.1 (C), 101.3 (C), 60.8 (CH_2), 24.0 (CH_3), 21.1 (CH_3), 13.7 (CH_3), – 0.03 (CH_3);

IR (neat) 2145, 1728, 1594 cm^{-1};

MS (EI) 300 (M^+);

HRMS calcd for $C_{18}H_{24}O_2Si$ (M^+) 300.1546; found 300.1547.



(*Z*)-Ethyl 3-(4-fluorophenyl)-2-(2-(trimethylsilyl)ethynyl)but-2-enoate (B-598). Prepared from compound **B-462** (50 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-596**, using *p*-fluorophenyl boronic acid (112 mg, 0.80 mmol, 4 equiv), which provided the title product as a pale yellow oil (43 mg, 72%).

^{1}H NMR (500 MHz, C_6D_6) δ 6.82 (dd, J = 5.5, 9.0 Hz, 2H), 6.66 (dd, J = 8.5, 8.5 Hz, 2H), 3.74 (q, J = 7.0 Hz, 2H), 2.15 (s, 3H), 0.66 (t, J = 7.0 Hz, 3H), 0.20 (s, 9H);

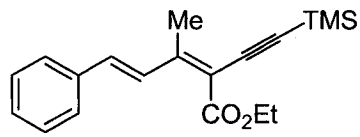
^{13}C NMR (125 MHz, C_6D_6) δ 165.4 (C), 164.5 (C), 161.2 (C), 153.9 (C), 137.5 (C), 129.1 (CH), 128.9 (CH), 115.3 (CH), 115.0 (CH), 101.8 (C), 101.7 (C), 60.9 (CH_2), 24.1 (CH_3), 13.6 (CH_3), – 0.1 (CH_3);

IR (neat) 2147, 1728, 1601 cm^{-1};

MS (EI) 304 (M^+);

HRMS calcd for $C_{17}H_{21}FO_2Si$ (M^+) 304.1295, found 304.1279.

R_f: 0.37 on silica gel (5% EtOAc in hexanes).



(2*Z*,4*E*)-Ethyl 3-methyl-5-phenyl-2-(2-(trimethylsilyl)ethynyl)penta-2,4-dienoate (B-600). Prepared from compound **B-462** (50 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-596**, using S-Phos (16.4 mg, 0.04 mmol, 0.20 equiv) instead of P(*t*-Bu)$_3$·HBF$_4$ and K_2CO_3 (55.3 mg, 0.40 mmol, 2 equiv) as base, which provided the title product as a pale yellow oil (41.5 mg, 67%).

^{1}H NMR (500 MHz, C_6D_6) δ 8.62 (d, J = 16.0 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.06-7.00 (m, 3H), 6.74 (d, J = 16 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 2.34 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H); 0.24 (s, 9H);

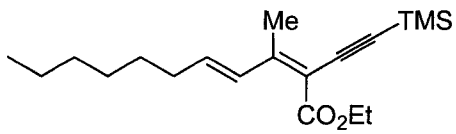
^{13}C NMR (125 MHz, C_6D_6) δ 165.1 (C), 153.6 (C), 137.2 (C), 136.2 (CH), 128.9 (CH), 128.9 (CH), 128.3 (CH), 127.0 (CH), 114.8 (C), 103.9 (C), 103.7 (C), 61.0 (CH_2), 18.3 (CH_3), 14.1 (CH_3), 0.04 (CH_3);

IR (neat) 2138, 1713, 1610, 1575 cm^{-1};

MS (EI) 312 (M^+);

HRMS calcd for $C_{19}H_{24}O_2Si$ (M^+) 312.1546, found 312.1562.

R_f: 0.52 on silica gel (5% EtOAc in hexanes).



(2*Z*,4*E*)-Ethyl 3-methyl-2-(2-(trimethylsilyl)ethynyl)undeca-2,4-dienoate (B-601). Prepared from compound **B-462** (50 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-596**, using S-Phos (16.4 mg, 0.04 mmol, 0.20 equiv) as ligand and K_2CO_3 (55.3 mg, 0.40 mmol, 2 equiv) as base, which provided the title product as a pale yellow oil (41 mg, 64%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.77 (dt, J = 16.0, 1.6 Hz, 1H), 5.93 (dt, J = 15.0, 6.8 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 2.20 (s, 3H), 2.00 (q, J = 6.8 Hz, 2H), 1.14-1.26 (m, 10H), 0.98 (t, J = 7.2, 3H), 0.86 (t, J = 7.2, 3H); 0.23 (s, 9H);

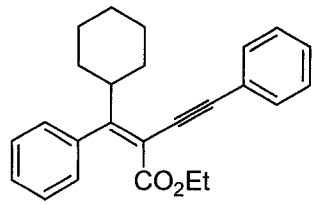
^{13}C NMR (100 MHz, C_6D_6) δ 165.2 (C), 153.7 (C), 139.7 (CH), 129.0 (CH), 113.3 (C), 103.5 (C), 102.6 (C), 60.8 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 22.9 (CH_2), 18.5 (CH_3), 14.3 (CH_3), 14.1 (CH_3), 0.1 (CH_3);

IR (neat) 2140, 1716, 1625, 1426 cm^{-1};

MS (EI) 320 (M^+);

HRMS calcd for $C_{19}H_{32}O_2Si$ (M+) 320.2172, found 320.2185.

R_f: 0.51 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 2-(cyclohexyl(phenyl)methylene)-4-phenylbut-3-ynoate (B-603). Prepared from compound **B-468** (28 mg, 0.078 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow solid (21 mg, 62%).

MP 79-80 °C;

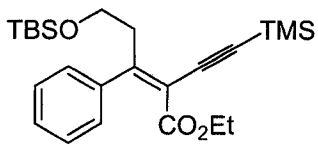
^{1}H NMR (400 MHz, C_6D_6) δ 7.53-7.51 (m, 2H), 7.12-7.06 (m, 5H), 6.98-6.94 (m, 3H), 3.76 (q, J = 7.2 Hz, 2H), 3.40 (tt, J = 3.2, 12.0 Hz, 1H), 1.78 (dd, J = 1.6, 13.2 Hz, 2H), 1.59 (dt, J = 2.8, 12.8 Hz, 2H), 1.47-1.10 (m, 6H), 0.65 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 165.4 (C), 163.2 (C), 139.2 (C), 131.8 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 123.8 (C), 116.3 (C), 100.2 (C), 96.5 (C), 85.8 (C), 60.7 (CH_2), 45.6 (CH), 31.1 (CH_2), 26.7 (CH_2);

IR (neat) 1725 cm^{-1};

HRMS calcd for $C_{25}H_{26}O_2$ (M^+) 258.1933, found 358.1946.

R_f: 0.22 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-phenyl-2-(2-(trimethylsilyl)ethynyl)pent-2-enoate (B-604). Prepared from compound **B-469** (7 mg, 0.018 mmol) using a procedure similar to that described above for compound **B-480** that provided the title product as a yellow oil (4.1 mg, 52%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.18 (d, J = 1.6 Hz, 1H), 7.05-6.98 (m, 4H), 3.73 (q, J = 7.2 Hz, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H), 0.96 (s, 9H), 0.62 (t, J = 7.2 Hz, 3H), 0.23 (s, 9H), 0.02 (s, 6H);

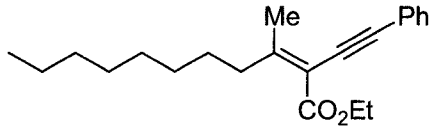
^{13}C NMR (100 MHz, C_6D_6) δ 165.6 (C), 155.8 (C), 140.5 (C), 128.2 (CH), 128.1 (CH), 127.7 (CH), 117.9 (C), 101.6 (C), 101.4 (C), 60.9 (CH_2), 60.8 (CH_2), 41.0 (CH_2), 26.1 (CH_3), 18.4 (C), 13.5 (CH_3), -0.07 (CH_3), –5.2 (CH_3);

IR (neat) 2146, 1725 cm^{-1};

HRMS calcd for $C_{20}H_{29}O_3Si_2$ ($M^+ - t$-Bu) 373.1655, found 373.1665.

R_f: 0.31 on silica gel (5% EtOAc in hexanes).

General procedure for the alkyl-Suzuki coupling reaction of β-chloro-α,β-unsaturated olefins.



(Z)-Ethyl 3-methyl-2-(phenylethynyl)undec-2-enoate (B-612). To a solution of 1-octene (0.05 mL, 0.30 mmol, 3.0 equiv) in THF (1.0 mL) was added 9-borabicyclo[3.3.1]nonane (0.6 mL, 0.30 mmol, 3.0 equiv, 0.5M in THF) and the mixture was stirred for ½ hour. A separate flask was charged with $PdCl_2$(dppf) (3.7 mg, 0.005 mmol, 0.05 equiv) and K_3PO_4 (42.4 mg, 0.20 mmol, 2.0 equiv). To this was added sequentially dioxane (1.0 mL) and (Z)-ethyl 3-chloro-2-(2-phenylethynyl)but-2-enoate (**B-447**) (25.0 mg, 0.10 mmol, 1.0 equiv). The 9-octyl-9-bora-bicyclo[3.3.1]nonane solution was introduced *via* canula, H_2O (0.3 mL) was added, and the reaction mixture was stirred for 18 hours. The mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica gel, eluting with hexanes to 5% EtOAc in hexanes to afford the product as a colorless oil (60.0 mg, 64%).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.49 – 7.37 (m, 5H), 4.22 (q, J = 7.2 Hz, 2H), 2.61 (dd, J = 9.6, 7.6 Hz, 2H), 2.19 (s, 3H), 1.55 – 1.50 (m, 2H), 1.33 – 1.29 (m, 10H), 1.31 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H).

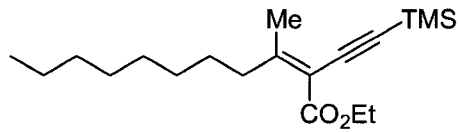
^{13}C NMR (100 MHz, acetone-d_6): δ 166.5 (C), 163.6 (C), 132.9 (CH), 130.4 (CH), 130.1 (CH), 125.4 (C), 114.6 (C), 95.8 (C), 87.8 (C), 62.3 (CH_2), 36.9 (CH_2), 33.6 (CH_2), 31.44

(CH_2), 31.41 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 24.4 (CH_3), 24.3 (CH_2), 15.5 (CH_3), 15.3 (CH_3).

IR (neat) 2926, 2855, 1719 cm^{-1}.

HRMS calcd for $C_{22}H_{30}O_2$ (M^+) 326.2246, found 326.2232.

R_f: 0.45 on silica gel (5 % EtOAc in hexanes)



(*Z*)-Ethyl 3-methyl-2-((trimethylsilyl)ethynyl)undec-2-enoate (B-611). Prepared from compound **B-462** (50.0 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-612** that provided the title product as a colorless oil (12.1 mg, 64%).

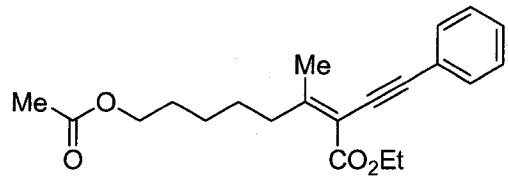
^{1}H NMR (400 MHz, benzene-d_6): δ 4.00 (q, J = 7.2 Hz, 2H), 2.58 (dd, J = 9.6, 8.0 Hz, 2H), 2.02 (s, 3H), 1.46 – 1.22 (m, 12H), 0.99 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, benzene-d_6): δ 165.0 (C), 163.7 (C), 113.9 (C), 102.5 (C), 99.4 (C), 60.6 (CH_2), 35.6 (CH_2), 32.2 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 28.7 (CH_2), 23.5 (CH_3), 23.0 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 0.1 (CH_3).

IR (neat) 2959, 2929, 2861, 2150, 1721 cm^{-1}.

HRMS calcd for $C_{19}H_{34}SiO_2$ (M^+) 322.2328, found 322.2347.

R_f: 0.23 on silica gel (5 % Et_2O in hexanes).



(*Z*)-Ethyl 8-acetoxy-3-methyl-2-(phenylethynyl)oct-2-enoate (B-613). Prepared from compound **B-463** (800.0 mg, 2.53 mmol) using a procedure similar to that described above for compound **B-612** that provided the title product as a colorless oil (648.9 mg, 82%).

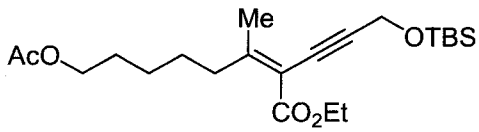
^{1}H NMR (400 MHz, acetone-d_6): δ 7.48 – 7.46 (m, 2H), 7.39 – 7.37 (m, 3H), 4.23 (q, J = 7.2 Hz, 2H), 4.04 (t, J = 6.8 Hz, 2H), 2.63 (dd, J = 9.6, 7.6 Hz, 2H), 2.20 (s, 3H), 1.99 (s, 3H), 1.69 – 1.54 (m, 4H), 1.46 – 1.38 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 171.9 (C), 166.5 (C), 163.4 (C), 132.9 (CH), 130.4 (CH), 130.1 (CH), 125.4 (C), 114.7 (C), 95.9 (C), 87.7 (C), 65.6 (CH_2), 62.3 (CH_2), 36.8 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 24.4 (CH_3), 21.8 (CH_3), 15.5 (CH_3).

IR (neat) 2937, 1738, 1718 cm^{-1}.

HRMS calcd for $C_{21}H_{26}O_4$ (M^+) 342.1831, found 342.1841.

R_f: 0.05 on silica gel (5 % EtOAc in hexanes).



(*Z*)-Ethyl 8-acetoxy-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)-3-methyloct-2-enoate (B-615). Prepared from compound **B-465** (800.0 mg, 2.53 mmol) using a procedure similar to that described above for compound **B-612** that provided the title product as a colorless oil (763.0 mg, 74%).

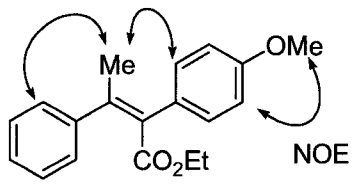
^{1}H NMR (400 MHz, benzene-d_6): δ 4.40 (s, 2H), 4.06 – 3.87 (m, 4H), 2.49 (dd, J = 7.6 Hz, 2H), 1.69 (s, 3H), 1.94 (s, 3H), 1.68 (s, 6H), 1.43 – 1.13 (m, 6H), 1.03 (t, J = 6.8 Hz, 3H), 0.97 (s, 9H).

^{13}C NMR (100 MHz, benzene-d_6): δ 170.1 (C), 165.1 (C), 162.5 (C), 159.4 (C), 113.2 (C), 93.5 (C), 81.7 (C), 64.2 (CH_2), 60.7 (CH_2), 52.5 (CH_2), 35.4 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 26.2 (CH_2), 26.0 (CH_3), 23.4 (CH_3), 14.3 (CH_3), – 5.0 (CH_3).

MS (EI) 410 (M^+).

R_f: 0.19 on silica gel (5 % EtOAc in hexanes).

General procedure for the generation of tetrasubstituted olefins via Suzuki coupling reaction.



(*Z*)-Ethyl 2-(4-methoxyphenyl)-3-phenylbut-2-enoate (B-607). A flask was charged with $Pd(OAc)_2$ (1.1 mg, 0.0016 mmol, 0.1 equiv), $P^tBu_3{\cdot}HBF_4$ (0.93 mg, 0.0032 mmol, 0.2 equiv), Cs_2CO_3 (8.4 mg, 0.048 mmol, 3.0 equiv) and phenylboronic acid (5.9 mg,

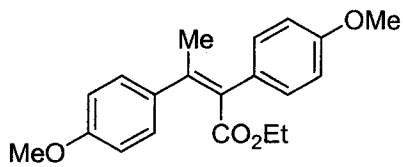
0.048 mmol, 3.0 equiv) and the flask was purged with N_2 for 10 minutes. Dioxane (0.3 mL) was added, the mixture was sparged with N_2 for 10 minutes and (*Z*)-ethyl 3-chloro-2-(4-methoxyphenyl)but-2-enoate (4.0 mg, 0.016 mmol, 1.0 equiv) (**B-489**) was added in dioxane (0.5 mL). After 3 hours, the reaction mixture was partitioned between Et_2O and H_2O. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica gel eluting with 2 % Et_2O in hexanes to 4 % Et_2O in hexanes to give the title product as a yellow oil (3.0 mg, 64%).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.38 – 7.18 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 3.82 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.05 (s, 3H), 0.82 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 170.9 (C), 161.1 (C), 145.1 (C), 143.0 (C), 134.7 (C), 132.2 (CH), 131.3 (C), 129.9 (CH), 129.1 (CH), 129.0 (CH), 115.5 (CH), 61.7 (CH_2), 56.5 (CH_3), 23.1 (CH_3), 14.9 (CH_3).

IR (neat) 3057, 2976, 1709, 1602 cm^{-1}.

HRMS calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1405.



(*Z*)-Ethyl 2,3-bis(4-methoxyphenyl)but-2-enoate (B-490).

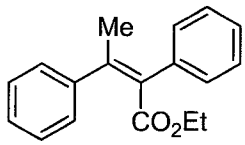
^{1}H NMR (400 MHz, acetone-d_6): δ 7.29 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.87 (q, J = 6.8 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.03 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 171.2 (C), 161.1 (C), 151.0 (C), 142.3 (C), 137.2 (C), 134.2 (C), 132.2 (CH), 131.6 (C), 130.3 (CH), 115.5 (CH), 115.3 (CH), 61.7 (CH_2), 56.54 (CH_3), 56.53 (CH_3), 23.0 (CH_3), 15.1 (CH_3).

IR (neat) 2978, 2956, 2838, 1739, 1736, 1608 cm^{-1}.

HRMS calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1498.

R_f: 0.04 on silica gel (4% Et_2O in hexanes).



(*Z*)-Ethyl 2,3-diphenylbut-2-enoate (B-492).

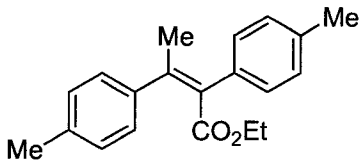
^{1}H NMR (400 MHz, acetone-d_6): δ 7.20 – 7.00 (m, 10H), 4.24 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, acetone -d_6): δ 169.0 (C), 144.2 (C), 141.6 (C), 131.6 (CH), 130.3 (CH), 129.8 (CH), 129.6 (CH), 128.9 (CH), 128.6 (CH), 62.2 (CH_2), 24.3 (CH_3), 15.5 (CH_3).

IR (neat) 3089, 2987, 1718 cm^{-1}

HRMS calcd for $C_{18}H_{18}O_2$ (M^+) 266.1307, found 266.1296.

R_f: 0.14 on silica gel (4% Et_2O in hexanes).



(*Z*)-Ethyl 2,3-di-*p*-tolylbut-2-enoate (B-494).

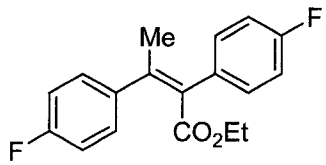
^{1}H NMR (400 MHz, acetone-d_6): δ 7.01 – 6.88 (m, 8H), 4.22 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ 171.0 (C), 143.2 (C), 140.9 (C), 138.4 (C), 138.1 (C), 136.4 (C), 133.8 (C), 131.4 (CH), 130.5 (CH), 130.3 (CH), 62.1 (CH_2), 24.3 (CH_3), 22.1 (CH_3), 15.5 (CH_3);

IR (neat) 2970, 1716 cm^{-1}.

HRMS calcd for $C_{20}H_{22}O_2$ (M^+) 294.1620, found 294.1633.

R_f: 0.15 on silica gel (5% EtOAc in hexanes).



(*Z*)-Ethyl 2,3-bis(4-fluorophenyl)but-2-enoate (B-500).

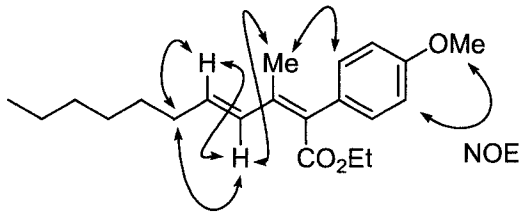
^{1}H NMR (500 MHz, acetone-d_6): δ 7.17 – 6.99 (m, 8H), 2.24 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.25 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6): δ 170.6 (C), 144.4 (C), 143.8 (C), 139.3 (C), 134.1 (C), 131.6 (CH), 130.3 (CH), 129.8 (d, J = 31.0 Hz, CH), 128.7 (d, J = 35.9 Hz, CH), 62.2 (CH_2), 24.3 (CH_3), 15.5 (CH_3).

IR (neat) 2979, 1717 cm^{-1}.

MS (EI) 302 (M^+).

R_f: 0.16 on silica gel (5% EtOAc in hexanes).



(2*Z*,4*E*)-Ethyl 2-(4-methoxyphenyl)-3-methylundeca-2,4-dienoate (B-606). Prepared from compound **B-489** (50.0 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-607** that provided the title product as a yellow oil (20.0 mg, 30%).

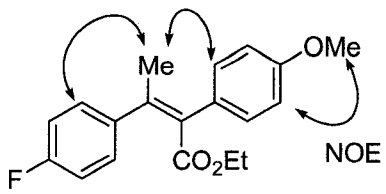
^{1}H NMR (400 MHz, acetone-d_6): δ 7.16 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.70 (dt, J = 15.6, 1.6 Hz, 1H), 6.04 (dt, J = 15.6, 7.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 2.19 (ddd, J = 7.2, 7.2, 1.6 Hz, 2H), 1.81 (s, 3H), 1.47 – 1.29 (m, 8H), 1.21 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 170.5 (C), 160.9 (C), 139.1 (C), 136.4 (CH), 133.4 (C), 132.3 (CH), 131.56 (C), 131.52 (CH), 115.4 (CH), 62.0 (CH_2), 56.5 (CH_3), 34.9 (CH_2), 33.5 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 24.3 (CH_2), 17.1 (CH_3), 15.5 (CH_3), 15.3 (CH_3).

IR (neat) 2956, 2926, 2859, 1713, 1608 cm^{-1}.

HRMS calcd for $C_{21}H_{30}O_3$ (M^+) 330.2195, found 330.2196.

R_f: 0.58 on silica gel (10 % EtOAc in hexanes)



(*Z*)-Ethyl 3-(4-fluorophenyl)-2-(4-methoxyphenyl)but-2-enoate (B-608). Prepared from compound **B-489** (50.0 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-607** that provided the title product as a yellow oil (30.0 mg, 48%).

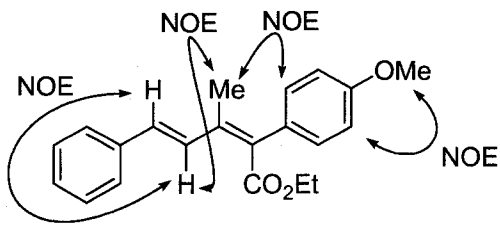
^{1}H NMR (400 MHz, acetone-d_6): δ 7.37 (dd, J = 8.9, 5.4 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H), 7.14 (dd, J = 8.9, 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 3.86 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.05 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 170.8 (C), 164.0 (d, J = 244.3 Hz, C), 161.1 (C), 142.0 (C), 141.3 (d, J = 3.3 Hz, C), 135.1 (C), 132.2 (CH), 131.2 (C), 130.9 (d, J = 8.1 Hz, CH), 116.5 (d, J = 21.5 Hz, CH), 115.3 (CH), 61.8 (CH_2), 56.5 (CH_3), 23.2 (CH_3), 15.0 (CH_3).

IR (neat) 3072, 3042, 3986, 2960, 1715, 1606 cm^{-1}.

HRMS calcd for $C_{19}H_{19}FO_3$ (M^+) 314.1318, found 314.1318.

R_f: 0.49 on silica gel (10 % EtOAc in hexanes)



(2*Z*,4*E*)-Ethyl 2-(4-methoxyphenyl)-3-methyl-5-phenylpenta-2,4-dienoate (B-609). Prepared from compound **B-489** (50.0 mg, 0.20 mmol) using a procedure similar to that described above for compound **B-607** that provided the title product as a yellow oil (35.0 mg, 54 %).

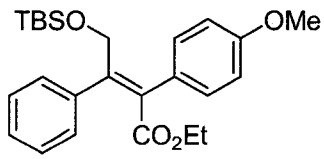
^{1}H NMR (400 MHz, acetone-d_6): δ 7.56 (d, J = 16.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.38 (dd, J = 7.2, 7.2 Hz, 2H), 7.29 (tt, J = 6.8, 1.2 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 16.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 1.97 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, acetone -d_6): δ 170.3 (C), 161.0 (C), 139.5 (C), 139.2 (C), 135.6 (C), 133.8 (CH), 132.3 (CH), 131.5 (C), 130.6 (CH), 130.0 (CH), 129.9 (CH), 128.6 (CH), 115.4 (CH), 62.2 (CH_2), 56.5 (CH_3), 17.2 (CH_3), 15.6 (CH_3).

IR (neat) 3029, 2930, 1712 cm^{-1}.

HRMS calcd for $C_{21}H_{22}O_3$ (M^+) 322.1569, found 322.1587.

R_f: 0.27 on silica gel (5% EtOAc in hexanes).



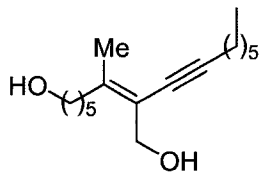
(*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (B-610). Prepared from compound **B-489** (20.0 mg, 0.052 mmol) using a procedure similar to that described above for compound **B-607** that provided the title product as a yellow oil (5.0 mg, 27%).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.41 (d, J = 8.8 Hz, 2H), 7.37 – 7.30 (m, 5H), 6.99 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.85 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.77 (s, 9H), -0.15 (s, 6H).

^{13}C NMR (100 MHz, acetone-d_6): δ 170.7 (C), 161.6 (C), 144.0 (C), 144.2 (C), 136.9 (C), 132.2 (CH), 130.3 (CH), 130.0 (C), 129.5 (CH), 129.2 (CH), 115.5 (CH), 65.3 (CH_2), 61.9 (CH_2), 56.6 (CH_3), 27.1 (CH_3), 19.7 (C), 14.9 (CH_3), -4.4 (CH_3).

IR (neat) 2954, 2929, 2855, 1720, 1607, 1511 cm^{-1}.

HRMS calcd for $C_{25}H_{34}O_4Si$ (M^+) 426.2226, found 426.2232



(*Z*)-3-Methyl-2-(oct-1-ynyl)oct-2-ene-1,8-diol (B-622). To a solution of **B-614** (100.0 mg, 0.23 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added diisobutylaluminum hydride (0.97 mL, 0.97 mmol, 4.2 equiv, 1.0 M solution in hexanes). The reaction was stirred for two hours, upon which time the reaction mixture was quenched via dropwise addition of

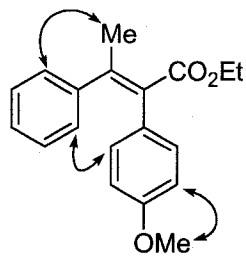
a saturated solution of Rochelle's salt (~2 mL). Ether (~3 mL) was added, and the mixture was stirred until two clear layers were apparent. The layers were separated, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel, eluting with 5% EtOAc in hexanes then 10% EtOAc in hexanes affording the title product (50.0 mg, 82%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 2H), 3.58 (t, J = 6.44 Hz, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.17 (br s, 2H), 2.13 (t, J = 7.2 Hz, 2H), 1.91 (s, 3H), 1.56 – 1.48 (m, 4H), 1.44 – 1.21 (m, 10H), 0.86 (t, J = 5.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (C), 118.1 (C), 94.5 (C), 79.0 (C), 62.6 (CH_2), 61.1 (CH_2), 33.2 (CH_2), 32.4 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 19.5 (CH_2), 14.0 (CH_3);

IR (neat) 3399, 2133, 1492 cm^{-1};

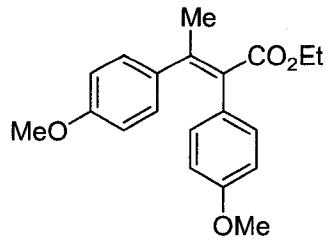
MS (EI) 266 (M^+);



(*E*)-Ethyl 2-(4-methoxyphenyl)-3-phenylbut-2-enoate (B-645).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.20 – 7.07 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 9.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 2.25 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ 171.0 (C), 144.0 (C), 142.9 (C), 134.7 (C), 132.7 (CH), 131.3 (C), 131.3 (C), 130.3 (CH), 129.9 (CH), 129.1 (CH), 115.0 (CH), 62.1 (CH_2), 56.3 (CH_3), 24.2 (CH_3), 15.5 (CH_3);

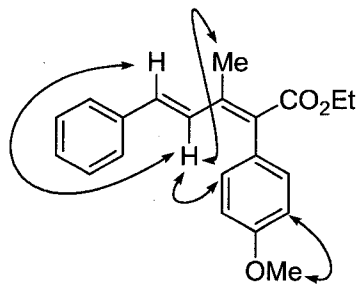


(*E*)-ethyl 2,3-bis(4-methoxyphenyl)but-2-enoate (B-646).

^{1}H NMR (400 MHz, benzene-d_6): δ 7.02 (d, J = 9.2 Hz, 2H), 6.99 – 6.97 (m, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 4.22 (q, J = 6.8 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 2.23 (s, 3H), 1.25 (t, J = 7.2 Hz);

^{13}C NMR (100 MHz, benzene-d_6): δ 171.2 (C), 160.6 (C), 160.4 (C), 142.4 (C), 135.9 (C), 133.2 (C), 132.7 (CH), 132.2 (C), 131.7 (CH), 115.2 (CH), 115.1 (CH), 62.1 (CH_2), 56.4 (CH_3), 56.3 (CH_3), 24.2 (CH_3), 15.5 (CH_3);

R_f: 0.05 on silica gel (4% Et_2O in hexanes).



(2*E*,4*E*)-Ethyl 2-(4-methoxyphenyl)-3-methyl-5-phenylpenta-2,4-dienoate (B-647).

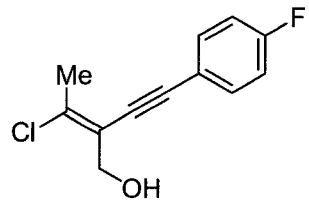
^{1}H NMR (400 MHz, benzene-d_6): δ 7.40 – 7.20 (m, 7H), 7.00 – 6.93 (m, 4H), 4.20 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.22 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, benzene-d_6): δ 170.6 (C), 161.2 (C), 139.1 (C), 138.9 (C), 135.9 (C), 135.7 (C), 135.6 (C), 134.1 (CH), 133.0 (CH), 131.5 (CH), 130.6 (CH), 129.84 (CH), 129.82 (CH), 128.5 (CH), 115.4 (CH);

R_f: 0.25 on silica gel (5% EtOAc in hexanes).

Proof of Stereochemistry of Tetrasubstituted Olefins:

General procedure for the reduction of polysubstituted-α,β-unsaturated esters:



(*Z*)-3-Chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol (B-648). To a solution of (*Z*)-ethyl 3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-enoate **B-461** (20 mg, 0.08 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added diisobutylaluminum hydride (0.16 mL, 0.16 mmol, 2.2 equiv, 1.0 M solution in hexanes). After 2 hours, and additional portion of diisobutylaluminum hydride (0.16 mL, 0.16 mmol, 2.2 equiv) was introduced. The reaction was stirred for an additional 15 minutes, upon which time the reaction mixture was quenched via dropwise addition of a saturated solution of Rochelle's salt (~2 mL). Ether (~3 mL) was added, and the mixture was stirred until two clear layers were apparent. The layers were separated, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel, eluting with 5% EtOAc in hexanes then 10% EtOAc in hexanes affording the title product (26 mg, 99%) as a clear, colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.06 (dd, J = 5.5, 9.0 Hz, 2H), 6.58 (dd, J = 9.0, 9.0 Hz, 2H), 4.25 (s, 2H), 2.12 (s, 3H);

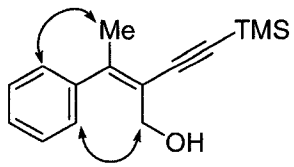
^{13}C NMR (125 MHz, C_6D_6) δ 163.9 (C), 161.9 (C), 138.8 (C), 133.6 (CH), 133.5 (CH), 121.3 (C), 115.9 (CH), 115.7 (CH), 95.2 (C), 85.8 (C), 62.2 (CH_2), 24.9 (CH_3);

IR (neat) 3357, 1598 cm^{-1};

MS (EI) 224 (M^+);

HRMS calcd for $C_{12}H_{10}ClFO$ (M^+) 224.0404, found 224.0397.

R_f: 0.30 on silica gel (20% EtOAc in hexanes).



(*Z*)-3-Phenyl-2-(2-(trimethylsilyl)ethynyl)but-2-en-1-ol (B-649). Prepared from compound **B-596** (123 mg, 0.43 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol that provided the title product as a clear colorless oil (100 mg, 95%).

^{1}H NMR (500 MHz, C_6D_6) δ 6.99 – 7.05 (m, 5H), 4.03 (d, J = 6.0 Hz, 2H), 2.26 (s, 3H), 1.51 (t, J = 6.0 Hz, 1H), 0.23 (s, 9H);

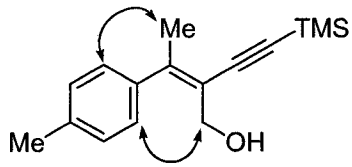
^{13}C NMR (125 MHz, C_6D_6) δ 147.6 (C), 141.1 (C), 128.4 (CH), 127.9 (CH), 127.7 (CH), 120.9 (C), 105.3 (C), 100.0 (C), 62.4 (CH_2), 24.0 (CH_3), 0.2 (CH_3);

IR (neat) 3399, 1492 cm^{-1};

MS (EI) 244 (M^+);

HRMS calcd for $C_{15}H_{20}OSi$ (M+) 244.1283; found 244.1288.

R_f: 0.47 on silica gel (20% EtOAc in hexanes).



(*Z*)-3-*p*-Tolyl-2-(2-(trimethylsilyl)ethynyl)but-2-en-1-ol (B-641). Prepared from compound **B-597** (30 mg, 0.11 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol that provided the title product as a clear colorless oil (29 mg, 99%).

^{1}H NMR (500 MHz, C_6D_6) δ 6.98 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.10 (s, 2H), 2.29 (s, 3H), 2.05 (s, 3H), 0.24 (s, 9H);

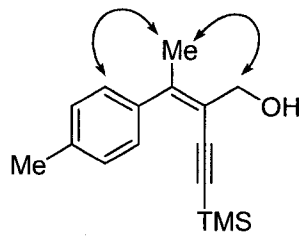
^{13}C NMR (125 MHz, C_6D_6) δ 147.8 (C), 138.2 (C), 137.4 (C), 129.1 (CH), 127.9 (CH), 120.6 (C), 105.5 (C), 99.9 (C), 62.5 (CH_2), 24.1 (CH_3), 21.0 (CH_3), 0.2 (CH_3);

IR (neat) 3399, 2140, 1513 cm^{-1};

MS (EI) 258 (M^+);

HRMS calcd for $C_{16}H_{22}OSi$ (M^+) 258.1440, found 258.1430.

R_f: 0.26 on silica gel (10% EtOAc in hexanes).



(*E*)-3-Phenyl-2-(2-(trimethylsilyl)ethynyl)but-2-en-1-ol (B-642). A solution of ester **B-597** (60 mg, 0.21 mmol) in dichloromethane (2.0 mL) was exposed to UV light (350 nm). After one hour, the solution was reduced using a procedure similar to that described above for (*Z*)-3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol that provided the title product as a clear, colorless oil (16 mg, 31%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.43 (d, J = 7.0 Hz, 2H), 7.0 – 7.72 (m, 3H), 4.23 (d, J = 6.5 Hz, 2H), 1.76 (s, 3H), 0.88 (t, J = 6.5 Hz, 1H), 0.06 (s, 9H);

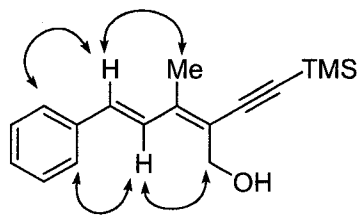
^{13}C NMR (100 MHz, C_6D_6) δ 146.4 (C), 143.1 (C), 128.4 (CH), 127.9 (CH), 127.7 (CH), 120.2 (C), 105.7 (C), 97.9 (C), 62.0 (CH_2), 19.6 (CH_3), –0.2 (CH_3);

IR (neat) 3373, 2134, 1248 cm^{-1};

MS (EI) 244 (M^+);

HRMS calcd for $C_{15}H_{20}OSi$ (M+) 244.1283, found 244.1275.

R_f: 0.26 on silica gel (5% EtOAc in hexanes).



(2*Z*,4*E*)-3-Methyl-5-phenyl-2-(2-(trimethylsilyl)ethynyl)penta-2,4-dien-1-ol (B-643). Prepared from compound **B-600** (50 mg, 0.16 mmol) using a procedure similar to that described above for (*Z*)-3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol that provided the title product as a clear, colorless oil (37 mg, 86%).

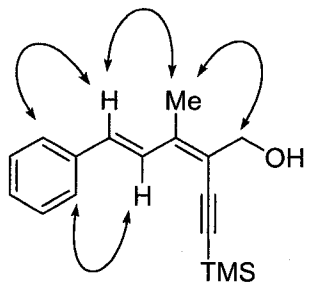
^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (d, J = 14.8, 1H), 7.23 (d, J = 6.0 Hz, 1H), 7.03 – 7.11 (m, 4H), 6.58 (d, J = 16 Hz, 1H), 4.29 (s, 2H), 2.21 (s, 3H), 0.23 (s, 9H);

^{13}C NMR (100 MHz, C_6D_6) δ 142.6 (C), 137.5 (D), 132.3 (CH), 128.9 (CH), 127.2 (CH), 125.7 (CH), 122.4 (C), 106.5 (C), 102.7 (C), 61.0 (CH_2), 19.0 (CH_3), 0.1 (CH_3); IR (neat) 3366, 2129, 1492, 1447 cm^{-1};

MS (EI) 270 (M^+);

HRMS calcd for $C_{17}H_{22}OSi$ (M+) 270.1440, found 270.1431.

R_f: 0.30 on silica gel (5% EtOAc in hexanes).



(2*E*,4*E*)-3-Methyl-5-phenyl-2-(2-(trimethylsilyl)ethynyl)penta-2,4-dien-1-ol (B-644). A solution of ester **B-600** (70 mg, 0.22 mmol) in dichloromethane (2.0 mL) was exposed to UV light (350 nm). After one hour, the solution was reduced using a procedure similar to that described above for (*Z*)-3-chloro-2-(2-(4-fluorophenyl)ethynyl)but-2-en-1-ol that provided the title product as a white solid (15 mg, 25%).

MP 75 – 76 °C;

^{1}H NMR (500 MHz, C_6D_6) δ 8.03 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.13 – 7.16 (m, 2H), 7.03 (m, 1H), 6.63 (d, J = 16.0 Hz, 1H), 4.14 (d, J = 6.0 Hz, 2H), 1.65 (s, 3H), 1.38 (t, J = 6.0 Hz, 1H), 0.23 (s, 9H);

^{13}C NMR (125 MHz, C_6D_6) δ 142.9 (C), 137.9 (C), 131.5 (CH), 130.5 (CH), 129.0 (CH), 127.9 (CH), 122.8 (C), 104.9 (C), 61.8 (CH_2), 13.4 (CH_3), 0.1 (CH_3);

IR (neat) 3327, 2132, 1732 cm^{-1};

MS (EI) 255 (M^+ – Me);

HRMS calcd for $C_{16}H_{19}OSi$ (M^+ – Me) 255.1205, found 255.1142.

R_f: 0.32 on silica gel (5% EtOAc in hexanes).

Claims to Original Research

1. Investigated the potential for enantioselective reaction discovery using Fluorescence Resonance Energy Transfer.

2. Developed the selective Bu_4NI/DCE process with alkynes and olefins.

3. Studied in depth the scope of the technique and contrasted with the unselective ICl method.

4. Investigated in detail the mechanism of the Bu_4NI/DCE process.

5. Studies the source of generation of trisubstituted olefins cross-coupling reactions of β-chloro-α-iodo-α,β-unsaturated esters and amides at elevated temperatures.

6. Investigated the potential of the alkyl-Suzuki cross-coupling reaction for the generation of tetra-alkyl-substituted olefins.

7. Developed the regioselective and stereospecific synthesis of tetrasubstituted olefins as single isomers whose stereo- and regiochemistry was proven by rigorous NMR analysis.

Publications and Presentations

1. Michael L. Ho, Alison B. Flynn and William W. Ogilvie. "Single Isomer Iodochlorination of Alkynes and Chlorination of Alkenes Using Tetrabutylammonium Iodide and Dichloroethane." *J. Org. Chem.* **2007**, *72*, 977–983.

2. Alison B. Flynn and William W. Ogilvie. "Stereodefined Synthesis of Tetrasubstituted Olefins." *Chem. Rev. submitted.*

3. Alison B. Lemay (Flynn), Katarina S. Vulic, William W. Ogilvie. "Single Isomer Tetrasubstituted Olefins from Regioselective and Stereospecific Palladium-Catalyzed Coupling of β-Chloro-α-Iodo-α,β-Unsaturated Esters." *J. Org. Chem.* **2006**, *71,* 3615–3618.

4. "Synthesis of single isomer tetrasubstituted olefins." Seminar presented at the 89th Canadian Chemistry Conference and Exhibition, Halifax, NS, May 2006.

5. "Stereodefined synthesis of tetrasubstituted olefins." Seminar presented at the Ottawa-Carleton Chemistry Institute Day, Ottawa, ON, 2006. **Winner of the CSC local section award for an outstanding seminar**

6. "Regio- and stereoselective synthesis of tetrasubstituted olefins." Poster presented at the Québec/Ontario Minisymposium in Synthetic and Bioorganic Chemistry, St. Adèle, QC, Nov 2005.

7. "Studies toward the regio- and stereoselective synthesis of tetrasubstituted olefins." Poster presented at Synthesis Day, Ottawa, ON, 2005.

8. "Improving Accessibility to tetrasubstituted olefins." Poster presented at the Ottawa-Carleton Chemistry Institute Day, Ottawa, ON, 2005.

9. "Studies towards the Phosphine-Catalyzed Dipolar [3+2] Cycloaddition between alkynes as latent dipoles and cyclopropanes." Poster presented at Synthesis Day, Ottawa, ON, 2004.

10. "Development of a Fluorescence Based Methodology for Enantioselective Reaction Monitoring." Poster presented at the Québec/Ontario Minisymposium in Synthetic and Bioorganic Chemistry, Gatineau, QC, 2004.

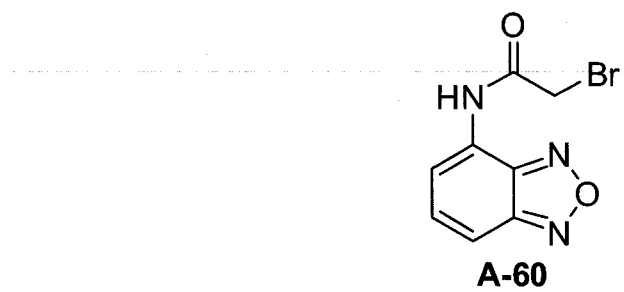
11. "Application of Fluorescence Resonance Energy Transfer (FRET) to the discovery of enantioselective reactions." Poster presented at the 87th Canadian Chemistry Conference and Exhibition, London, ON, 2004.

12. "Development of methodology for reaction monitoring through application of Fluorescence Resonance Energy Transfer (FRET)." Poster presented at the Ottawa-Carleton Chemistry Institute Day, Ottawa, ON, 2004.

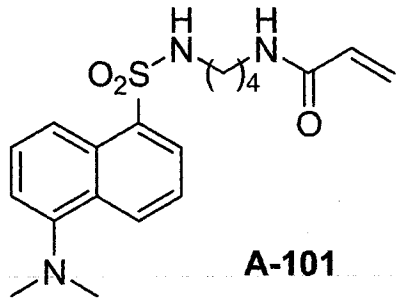
13. "The Aldol: New Developments in an Old Reaction." Seminar presented at the University of Ottawa, Ottawa, ON, 2003.

14. "Coordination chemistry of C_{60} with transition metal carbonyl complexes." Presented at Queen's University, Kingston, ON, 2001.

15. "Coordination chemistry of C_{60} with transition metal complexes." Poster presented at Queen's University, Kingston, ON, 2001.



A-60



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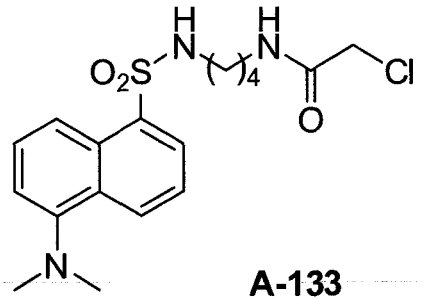

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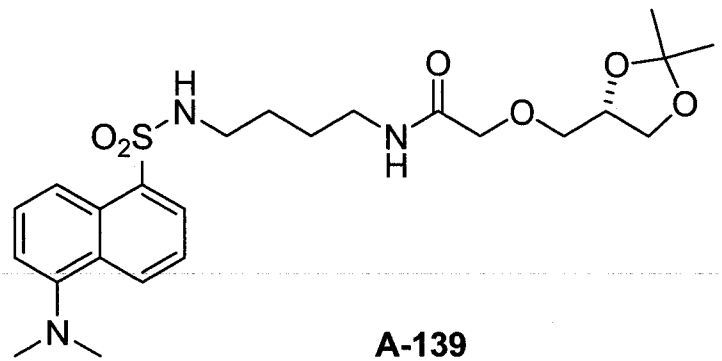

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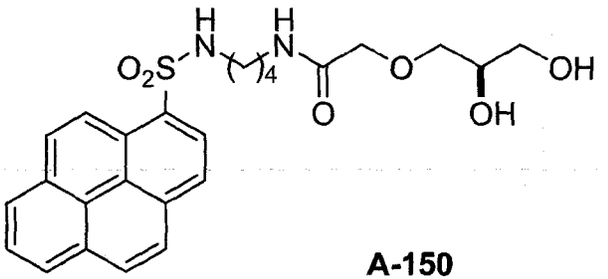

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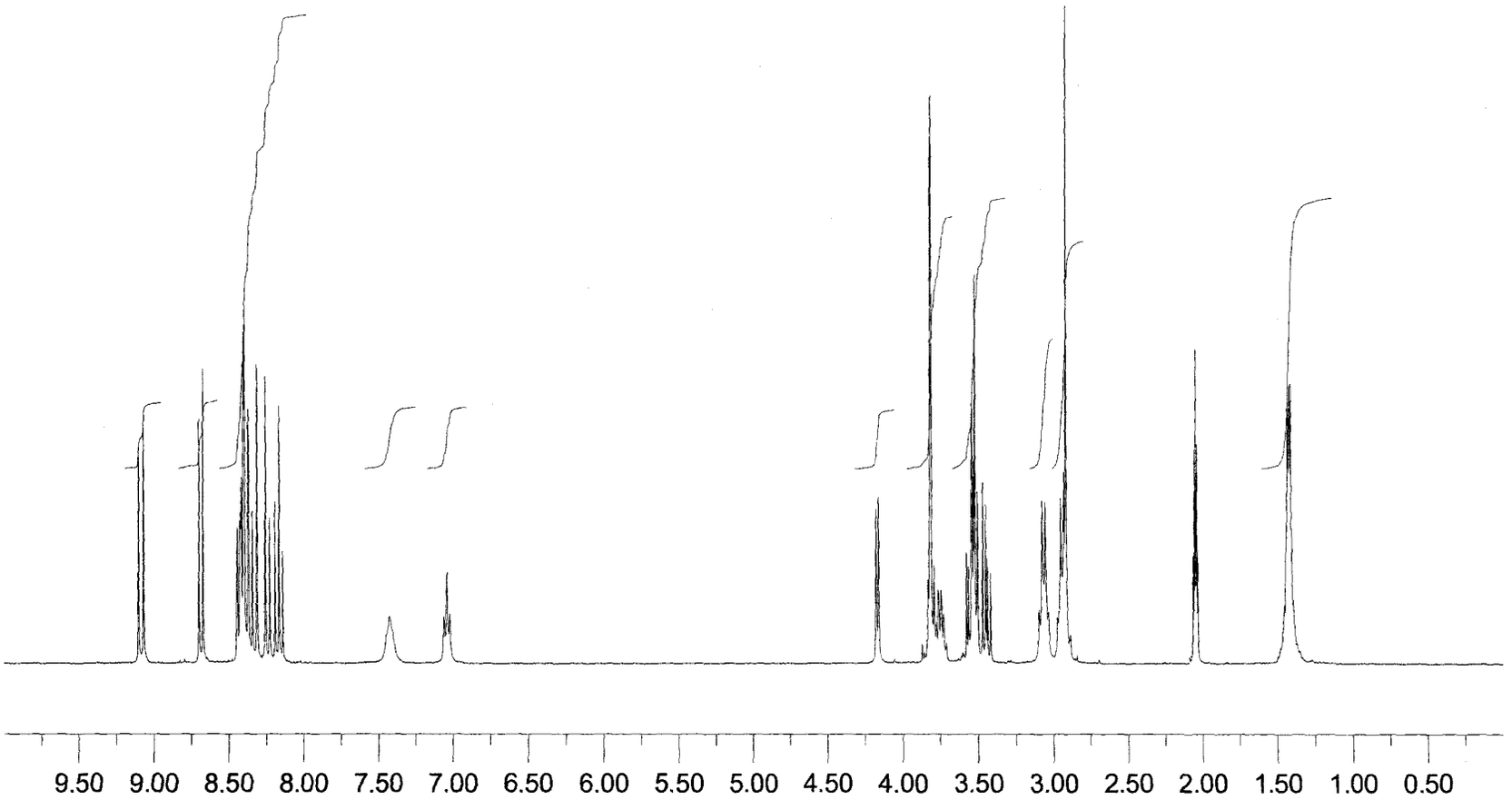
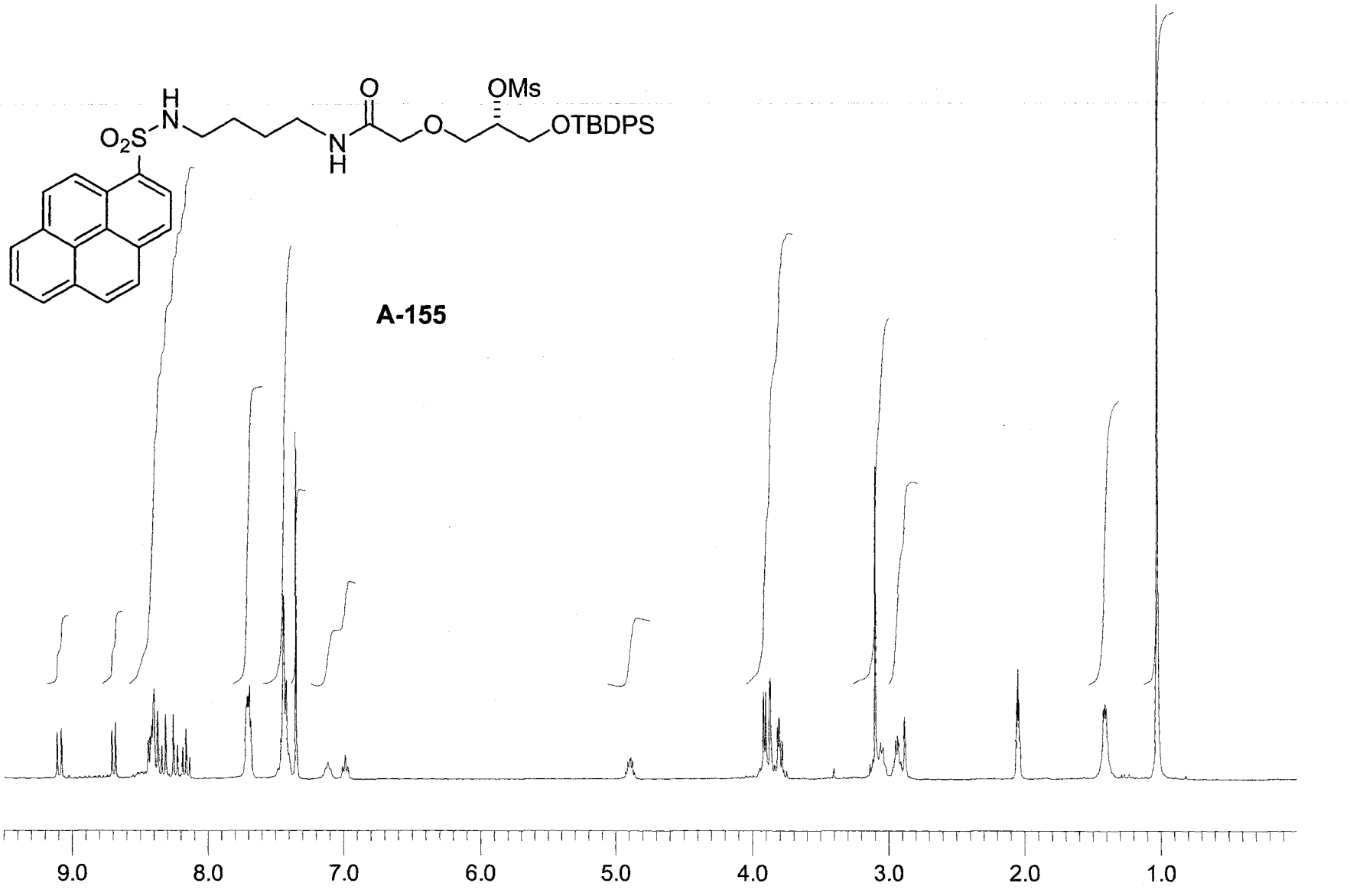
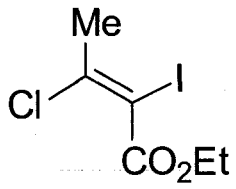
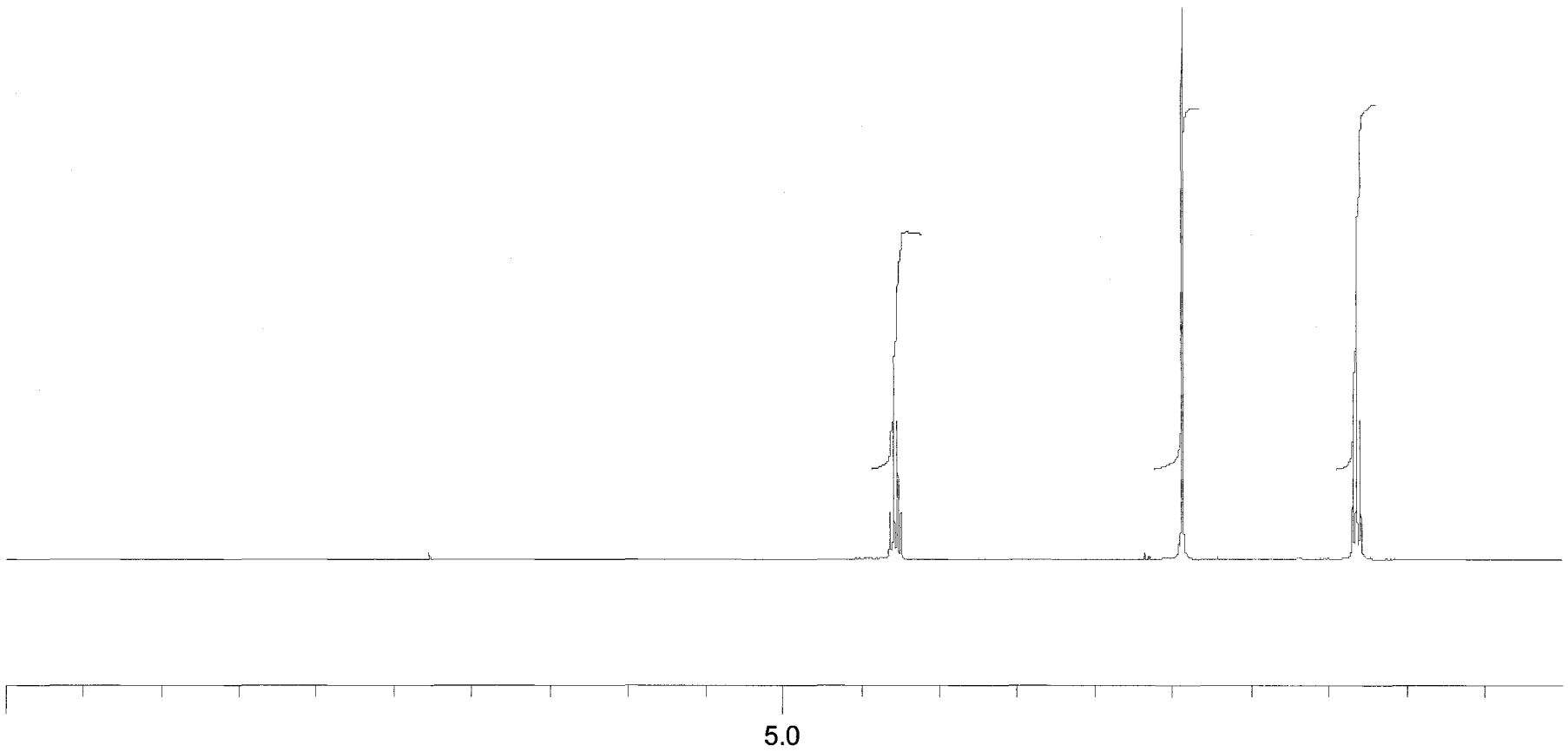
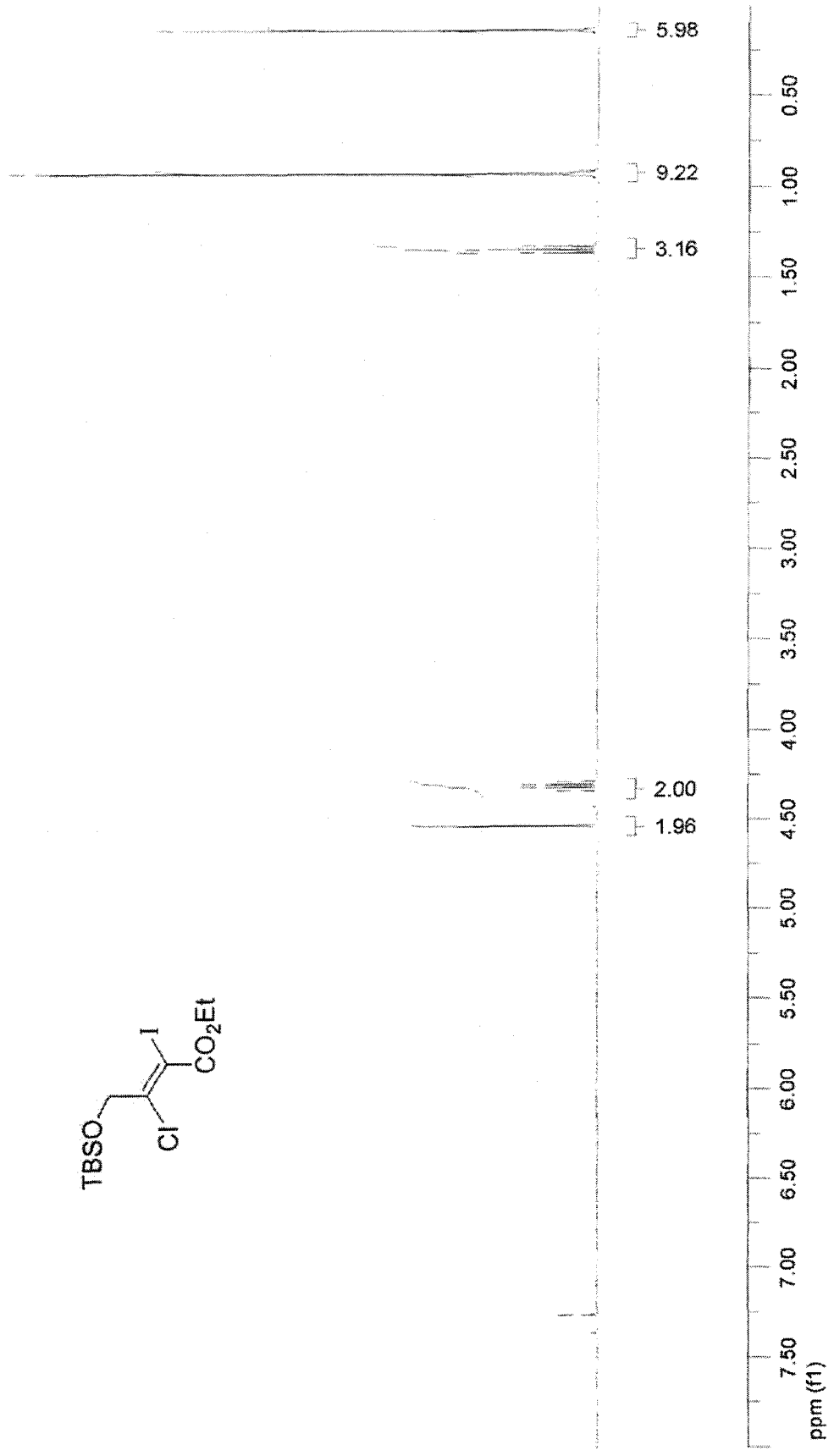


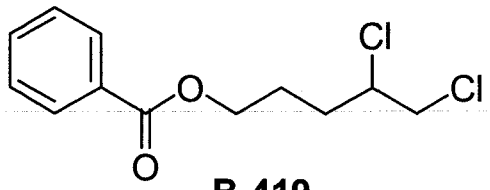




B-362







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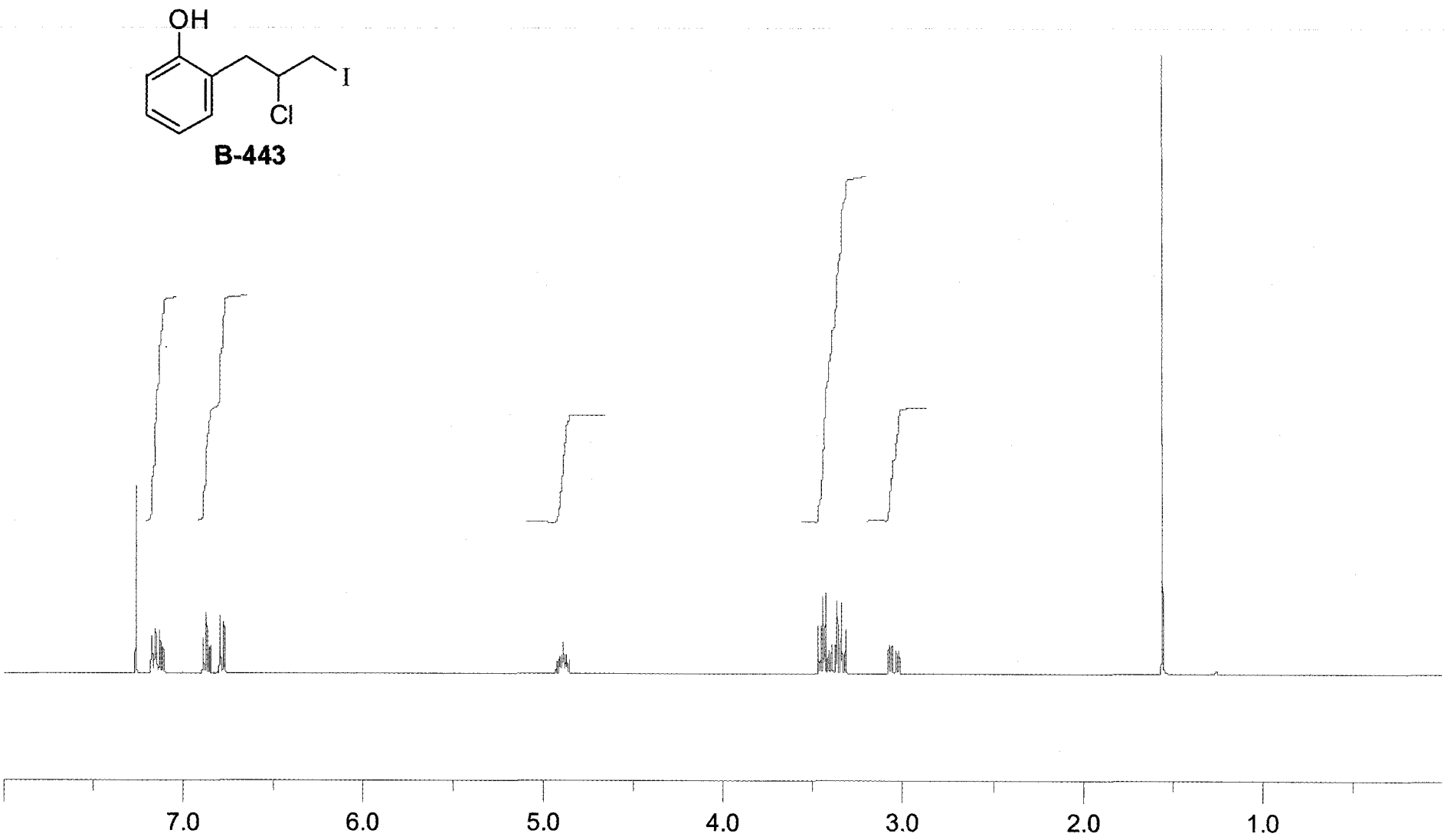

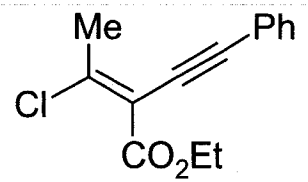

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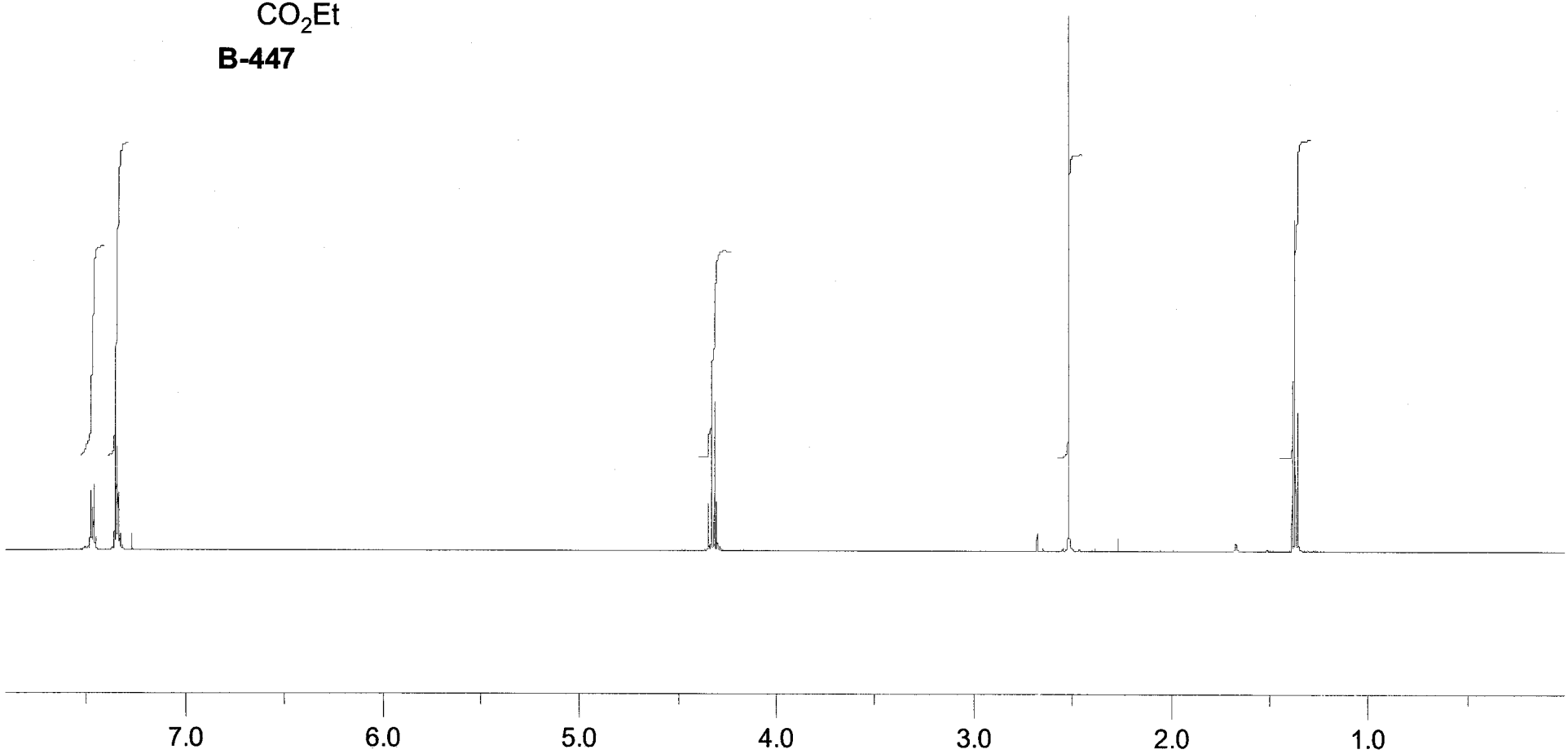

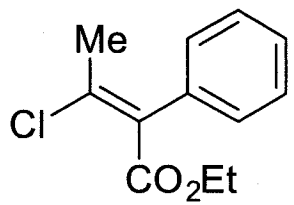

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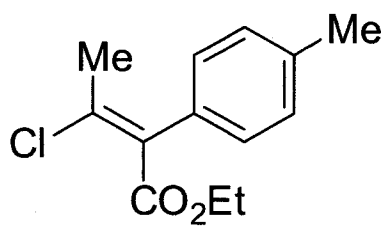

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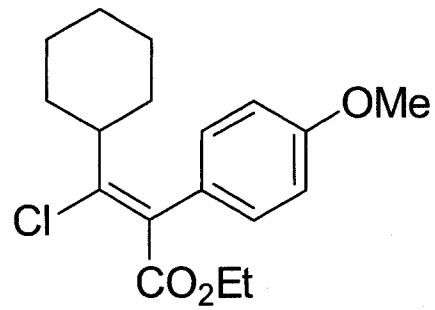

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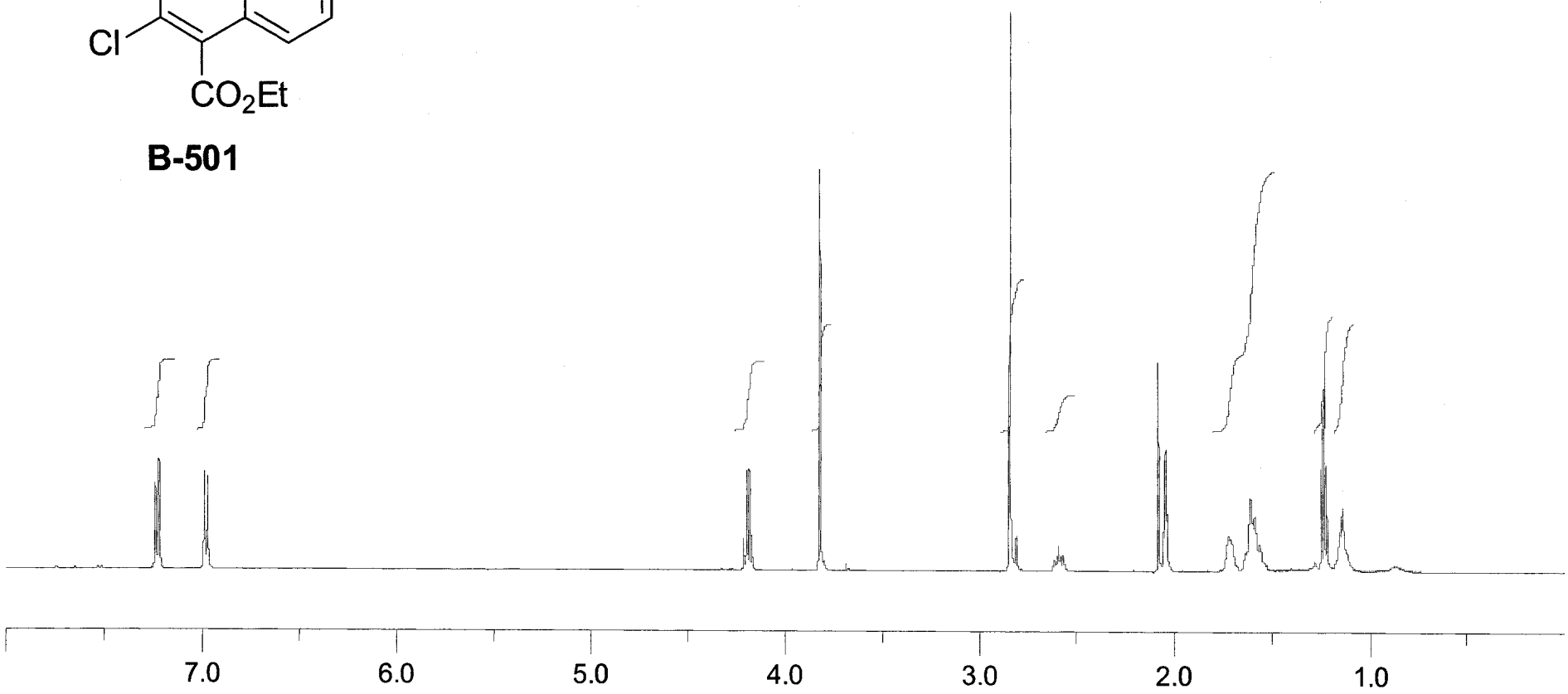
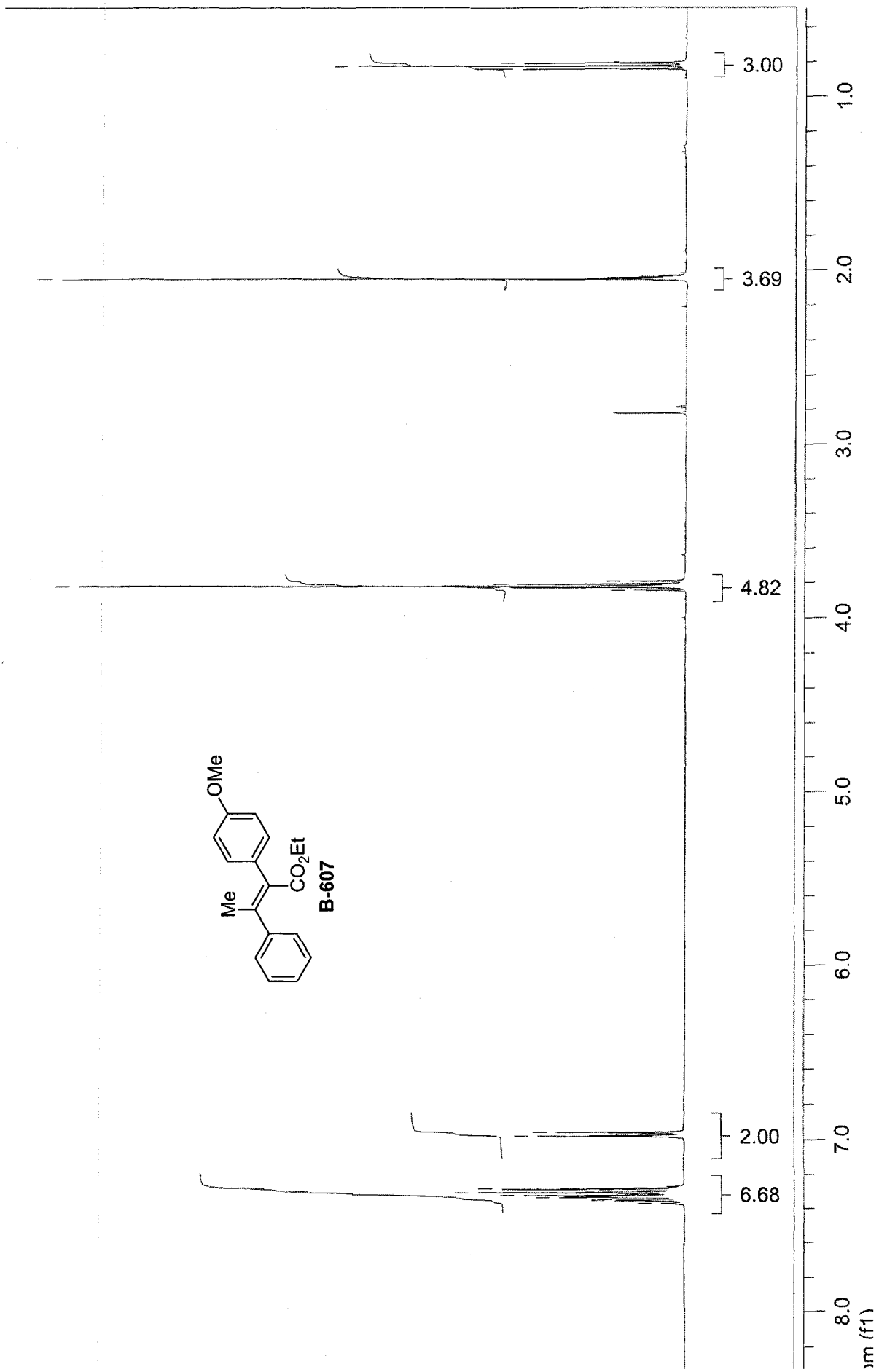
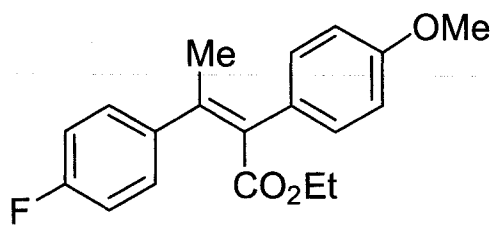
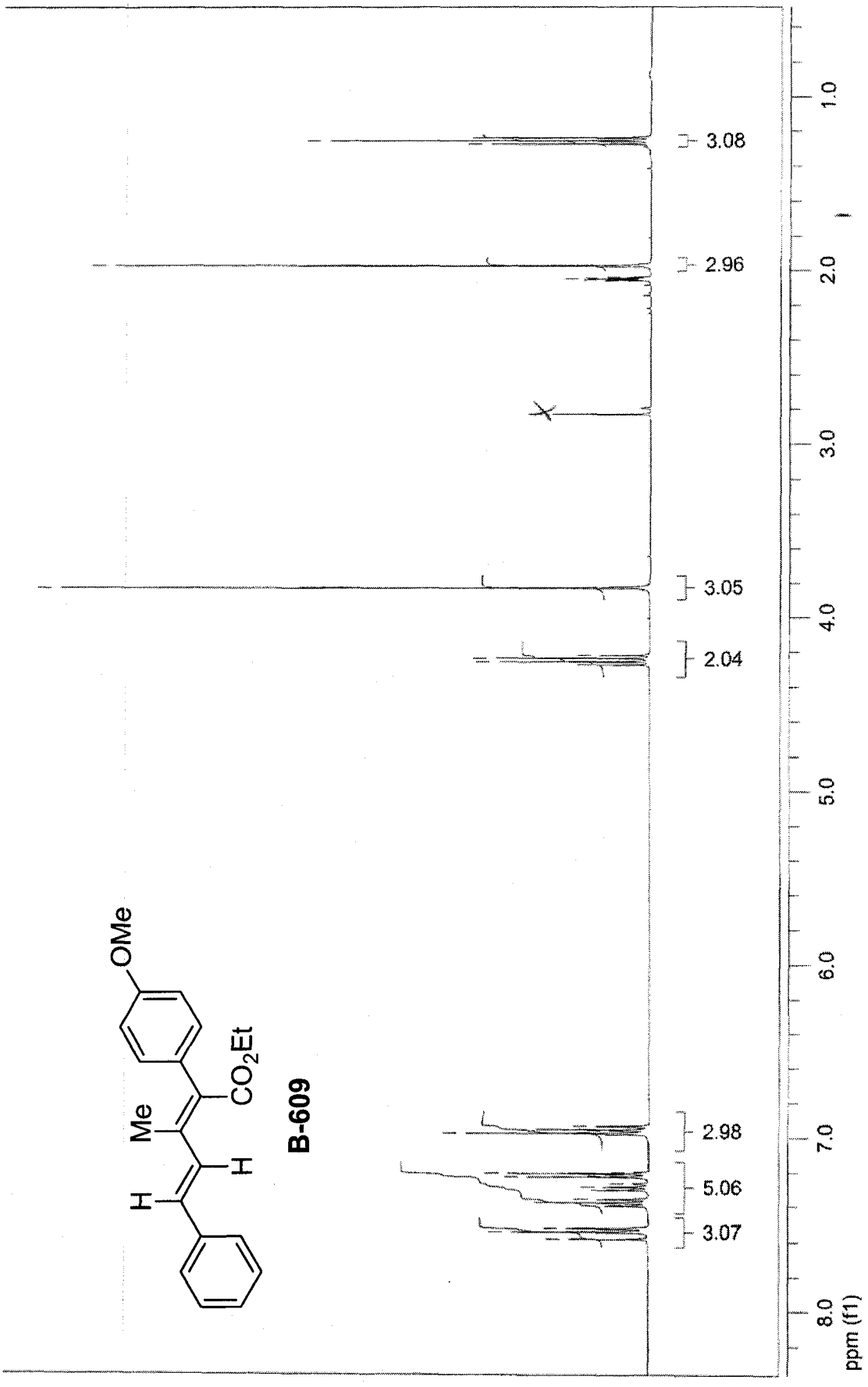
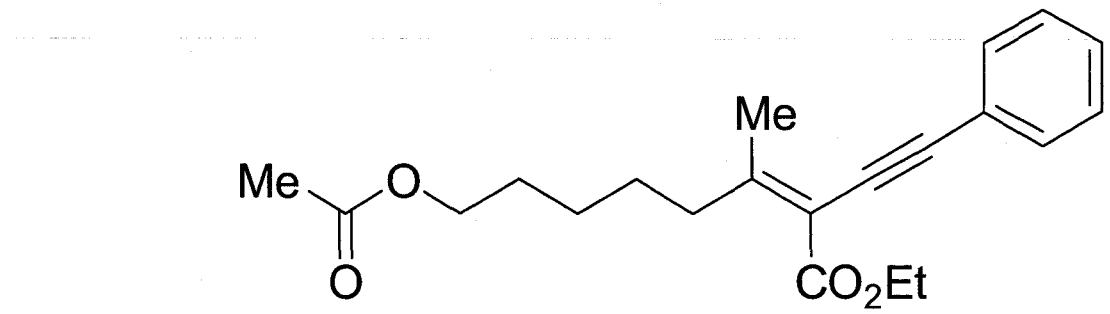






B-608





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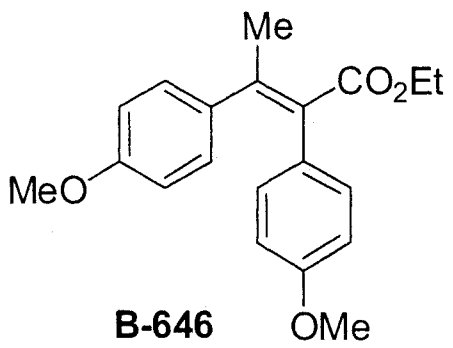

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