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SYNTHETIC APPROACHES TO COMPLEX ORGANIC MOLECULES:

DESOGESTREL, ACETYLENIC ALLENOPHANES, AND C_{60}

BY

MATTHEW D. CLAY

B.Sc. (Combined Honours in Chemistry & Psychology), Dalhousie University, 2001

Thesis submitted to the School of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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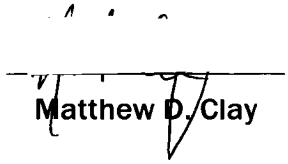

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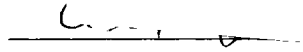

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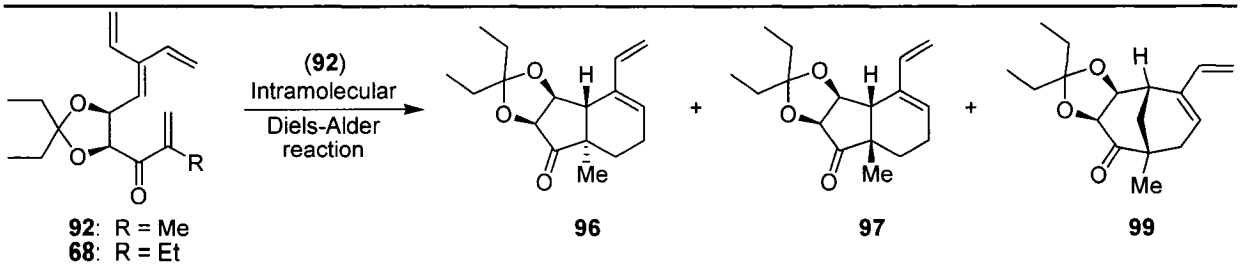
ABSTRACT

This thesis is composed of three sections and describes our work towards the synthesis of three molecules: Desogestrel, the first acetylenic allenophane, and Buckminsterfullerene.

Section **A** details a tether-controlled diene-transmissive intramolecular Diels-Alder reaction approach to the oral contraceptive progestin Desogestrel. Using our indium-mediated γ-pentadienylation chemistry as a key step, we synthesized tetraenes **92** and **68**. Unfortunately, the intramolecular Diels-Alder reaction of these tetraenes resulted in formation of three isomers, bicyclo[4.3.0]nonenes **96** and **97**, and the unusual bicyclo[3.3.1]nonene **99**. Attempts to improve the selectivity were unsuccessful and precluded further pursuit of the synthesis.

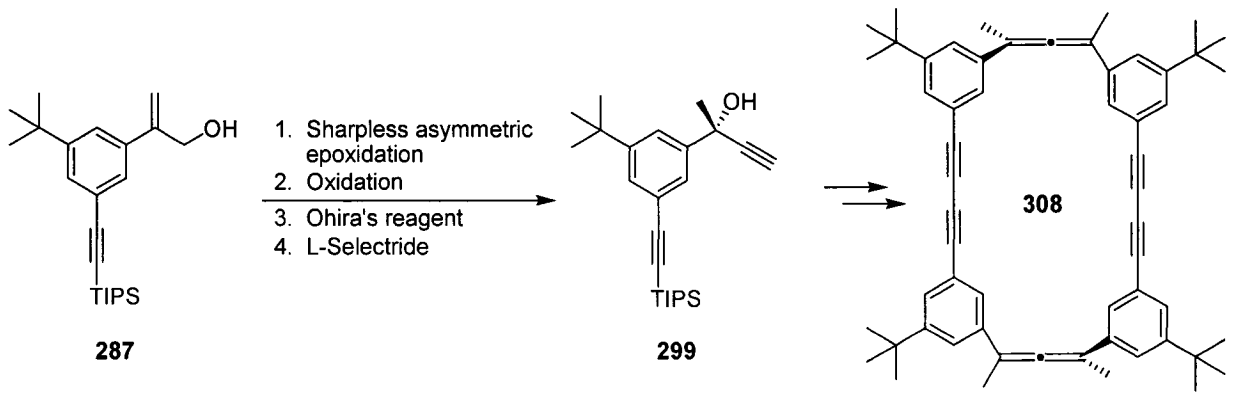
Section **B** of this thesis describes our design and asymmetric synthesis of the first acetylenic allenophane (**308**). This molecule represented a new class of cyclophane, and illustrative of the current interest in this type of molecule, several additional examples have since been reported, as well as an independent highlight in *Angewandte Chemie*. To complete our asymmetric synthesis, we developed a novel method of synthesizing tertiary propargyl alcohols (*e.g.*, **299**) in very good yield and enantioselectivity using a Sharpless asymmetric epoxidation as a key step. In contrast to the few procedures available for the asymmetric synthesis of tertiary propargyl alcohols, our protocol could be completed in roughly half the time, did not require the rigorous exclusion of oxygen or moisture, and did not require particularly specialized equipment.

Section **C** describes our work towards a controlled laboratory synthesis of Buckminsterfullerene (C_{60}) using hexakis[(*Z*)-enynyl]benzenes. We have developed several approaches to these molecules using trisubstituted benzene test substrates and have used these methods to construct hexasubstituted benzenes **417** and **418** from bromoaldehyde **399**. We are presently attempting to convert **418** to our cyclophane precursor to C_{60}.

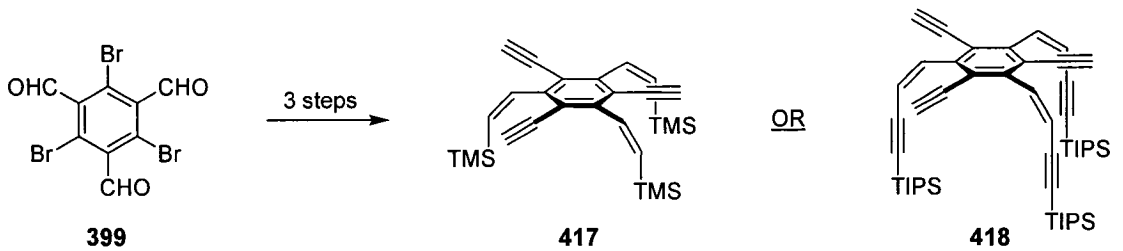


92: R = Me
68: R = Et

96 **97** **99**



287 **299**



399 **417** **418**

ACKNOWLEDGEMENTS

The completion of this thesis would not have been possible without the guidance, support and friendship of several individuals. First and foremost, I owe a debt of gratitude to my supervisor, Alex Fallis. Alex, four years ago you accepted into your lab a somewhat sub-par student fresh out of Dalhousie University and you've since turned him into a confident and capable researcher with the highest of aspirations. I've been infected by your enthusiasm and philosophy towards research and I hope to pass it on to all those who I have the opportunity to teach and work with. The freedom you gave me to pursue my own projects and synthetic strategies was particularly appreciated, as well as your encouragement and support when the routes I chose turned out to occasionally be.....less than ideal!

A number of other individuals have also directly contributed to my growth as a scientist. Matt, when I first arrived you took me under your wing and devoted an enormous amount of time and patience to teaching me the techniques and skills that I needed to excel in chemistry. I owe many successful reactions to your excellent advice! You defined by example that an excellent chemist goes beyond just being a machine, and it's a standard I've tried to match these past few years. Dave and Fabio (the Fallis lab encyclopedias) – you set the gold standard for mechanistic knowledge and helped me to get closer to that standard. Alison – your professional advice and editing of this thesis was most appreciated!

I have also enjoyed the friendship of many individuals during the past four years. Karen – I'll never forget our camping trips to Cape Breton or the unfortunate "frog incident" while fishing. Andrea – it was great to have a kindred spirit from NS around when I arrived in Ottawa! You're one of the kindest people I know. Alison and Ami – thank you for all the talks, advice, and coffee breaks....it goes to show how much I enjoy your company when you consider that I don't even like coffee! Megan and Praew – the Royal Oak just isn't the same with you two! Kelly – I'm already missing skating on the canal and beavertails with you. Christophe – thanks for your...questionable...advice on women! We'll have to wait to see if it pays off! Erica – you've been a truly amazing friend. Thank you for always being there for me whether you realized that's what you were doing or not. You have no idea how much I enjoyed and sometimes needed your company and those getaways to Montreal! I wish I'd had the chance to get to know you better...thank you for being such a great friend. Pam – you made this past year the best year I've had in Ottawa. I never thought I could enjoy rollerblading or mountain biking so much. It was great to finally have someone who could not only keep up with me, but push me to go that extra mile...or two...or ten! I believe I also owe my addiction to Thai food to you. ☺

Thanks are also due to my parents, who endured more than a few rants about life in Ottawa. Mom – thanks for your tolerance and patience with each phone call. Dad – I've thoroughly enjoyed our fishing and hunting trips, and look forward to many more years of them.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2′-azo-bis(isobutyronitrile)
aq.	aqueous
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
cat.	catalytic
CD	circular dichroism
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylidene acetone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
EA	ethyl acetate
EDC·HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
fod	tris-(6,6,7,7,8,8)-Heptafluoro-2,2-dimethyl-3,5-octanedionate
FT-ICR	Fourier transform ion cyclotron resonance
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOBt	*N*-hydroxybenzotriazole monohydrate
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IBX	*ortho*-iodoxybenzoic acid
J	coupling constant
LDA	lithium diisopropylamide

LD-MS	laser desorption mass spectrometry
L-Selectride	$LiBH(CH(CH_3)CH_2CH_3)_3$
LUMO	lowest unoccupied molecular orbital
M^+	molecular ion
*m*CPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
MS (EI)	mass spectrum by electron impact
MS (ES)	mass spectrum by electrospray ionization
MS (MALDI)	mass spectrum by matrix assisted laser desorption ionization
NBS	*N*-bromosuccinimide
NBSH	*ortho*-nitrobenzenesulfonylhydrazine
nOe	nuclear Overhauser effect
ODCB	*ortho*-dichlorobenzene
OLED	organic light emitting diode
PCC	pyridinium chlorochromate
PE	petroleum ether
PMB	*para*-methoxybenzyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
py	pyridine
Red-Al	$NaAlH_2(OCH_2CH_2OCH_3)_2$
rt	room temperature
sat.	saturated
sh	shoulder
sia	isoamyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

SECTION

A TETHER-CONTROLLED INTRAMOLECULAR DIENE-TRANSMISSIVE DIELS-ALDER REACTION APPROACH TO THE ORAL CONTRACEPTIVE DESOGESTREL

1 Introduction

This section of the thesis deals with the application of a tether-controlled intramolecular diene-transmissive Diels-Alder reaction to the synthesis of the third generation oral contraceptive progestin Desogestrel. An overview of oral contraceptives and previous syntheses of Desogestrel will first be presented, followed by an introduction to the Diels-Alder reaction, including the tether-control and diene-transmissive variants. Our approach to Desogestrel and our synthetic work towards this target will then be presented and discussed.

1.1 Oral Contraceptives

The discovery and development of oral contraceptive pills is one of the most significant achievements of the last century. Birth control drugs have revolutionized the mores of society and potentially offer the best method to keep the global population in balance with the finite resources available on Earth. The early discovery that progesterone inhibited ovulation in rabbits paved the way for the relatively swift development of human oral contraceptives.[1] Unfortunately, in humans the rapid elimination by the liver of orally administered progesterone prevented its use as an oral contraceptive. However, within years the systematic chemical modification of progesterone had led to the first orally active steroids. These steroids were initially marketed in 1957 as drugs for the treatment of gynecological disorders.[2] Although those in the pharmaceutical and medical industries were aware of the great potential of these steroids as contraceptives, their development and marketing as such were delayed by perceived political, religious and social implications.

Despite these concerns, their use and acceptance rapidly grew after Enovid was introduced by Searle in 1960 as the first oral contraceptive. These early contraceptive pills, and indeed many of those in use today, used a combination of estrogen and a synthetic progestin to inhibit ovulation. Although revolutionary and highly effective, the first generation oral contraceptives were plagued with side effects ranging from the relatively minor (headache, nausea, dizziness) to the more serious (stroke, venous thromboembolism, cancer).[3] Many of

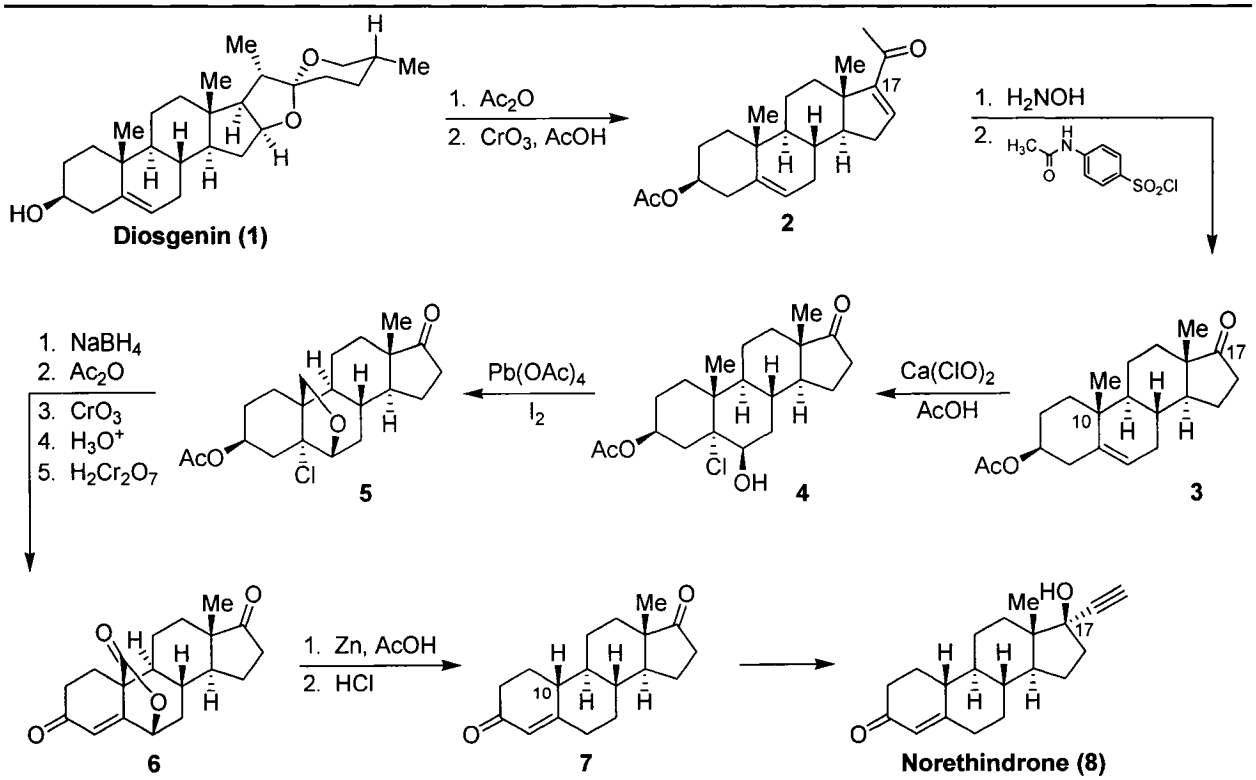
---

[1] Lammers, P.; Blumenthal, P. D.; Huggins, G. R. *Contraception* **1998**, *57*, 1S-27S.
[2] Asbell, B. *The Pill: A Biography of the Drug that Changed the World*; Random House: New York, 1995.
[3] Tyrer, L. *Contraception* **1999**, *59*, 11S-16S.

these side effects were attributed to the high estrogen level in the contraceptives (0.15 mg). In response to this, pharmaceutical companies began lowering the amount of estrogen in oral contraceptives, and by 1974 pills with as little as 0.02 mg of estrogen were available.[4] This advancement was made possible primarily due to the development of more potent progestins, which could now be used as the major component of the pill.

1.1.1 Synthetic development of oral contraceptive progestins

Initial efforts towards synthetic progestins were hindered by the high cost of the steroidal starting materials. The discovery of diosgenin (**1**), a naturally occurring steroid available in large quantities from Mexican yams, offered a solution to this problem and laid the foundation for decades of pharmaceutically relevant steroid research. The synthesis of one of the first oral contraceptive progestins, Norethindrone (**8**), is depicted in Scheme 1.



Scheme 1: Synthesis of Norethindrone (8)

[4] Mishell, D. R. Jr. *Int. J. Fertil.* **1991**, *36S*, 7-18.

The synthesis of Norethindrone (**8**) began with diosgenin (**1**), which was converted to ketone **2** using the first two steps of a process known as the Marker degradation.[5] Removal of the acetyl group at C17 of **2** using a Beckman rearrangement then generated ketone **3**.[6] A lengthy procedure to remove the C10 methyl group ensued (**3** → **7**),[7] followed by an additional step to install the C17 ethynyl group.[8] These two characteristics – the absence of a C10 methyl group and the presence of a C17 ethynyl group – are common to all oral contraceptive progestins and are necessary to ensure contraceptive activity.

The next major synthetic breakthrough in oral contraceptive chemistry came when it was discovered that conversion of the C13 methyl group of Norethindrone (**8**) to an ethyl group produced a progestin, Norgestrel (**9**), that was three times more potent than the parent compound.[9] Further modification of this second generation oral contraceptive progestin rapidly led to the development of three third generation progestins, Norgestimate (**10**), Gestodene (**11**), and Desogestrel (**12**) (Figure 1). These new progestins were substantially more active than their predecessors and offered improved safety profiles, displaying none of the serious side effects of the earlier generations and few minor side effects. Dosages of as little as 0.075 mg[10] (for Gestodene, **11**) gave efficacies of 100% when properly administered.[11]

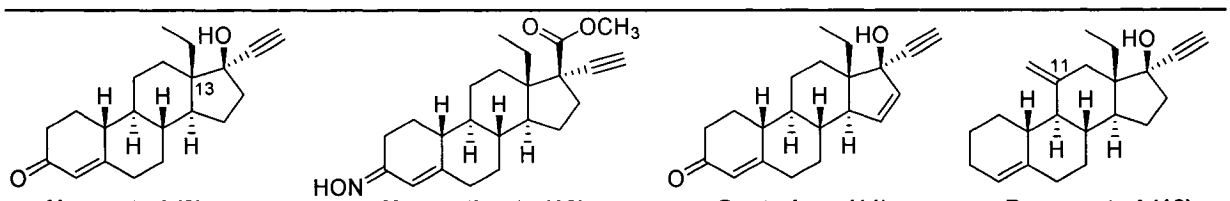


Figure 1: Second and third generation oral contraceptive progestins

The synthesis of the third generation oral contraceptive progestins, however, was somewhat problematic. No naturally occurring steroids contain an ethyl group at C13, so these

[5] The full Marker degradation converts diosgenin to progesterone in 4 steps. See: (a) Marker, R. E.; Rohrman, E. *J. Am. Chem. Soc.* **1939**, *61*, 3592-3593; (b) Marker, R. E.; Tsukamoto, T.; Turner, D. L. *J. Am. Chem. Soc.* **1940**, *62*, 2525-2532.

[6] Rosenkranz, G.; Mancera, O.; Sondheimer, F.; Djerassi, C. *J. Org. Chem.* **1956**, *21*, 520-522.

[7] (a) Jen, T.; Wolff, M. E. *J. Org. Chem.* **1963**, *28*, 1573-1575; (b) Berkoz, B.; Denot, E.; Bowers, A. *Steroids* **1963**, *1*, 251-270.

[8] Schering, A. G. Patent DE 1010963, 1956.

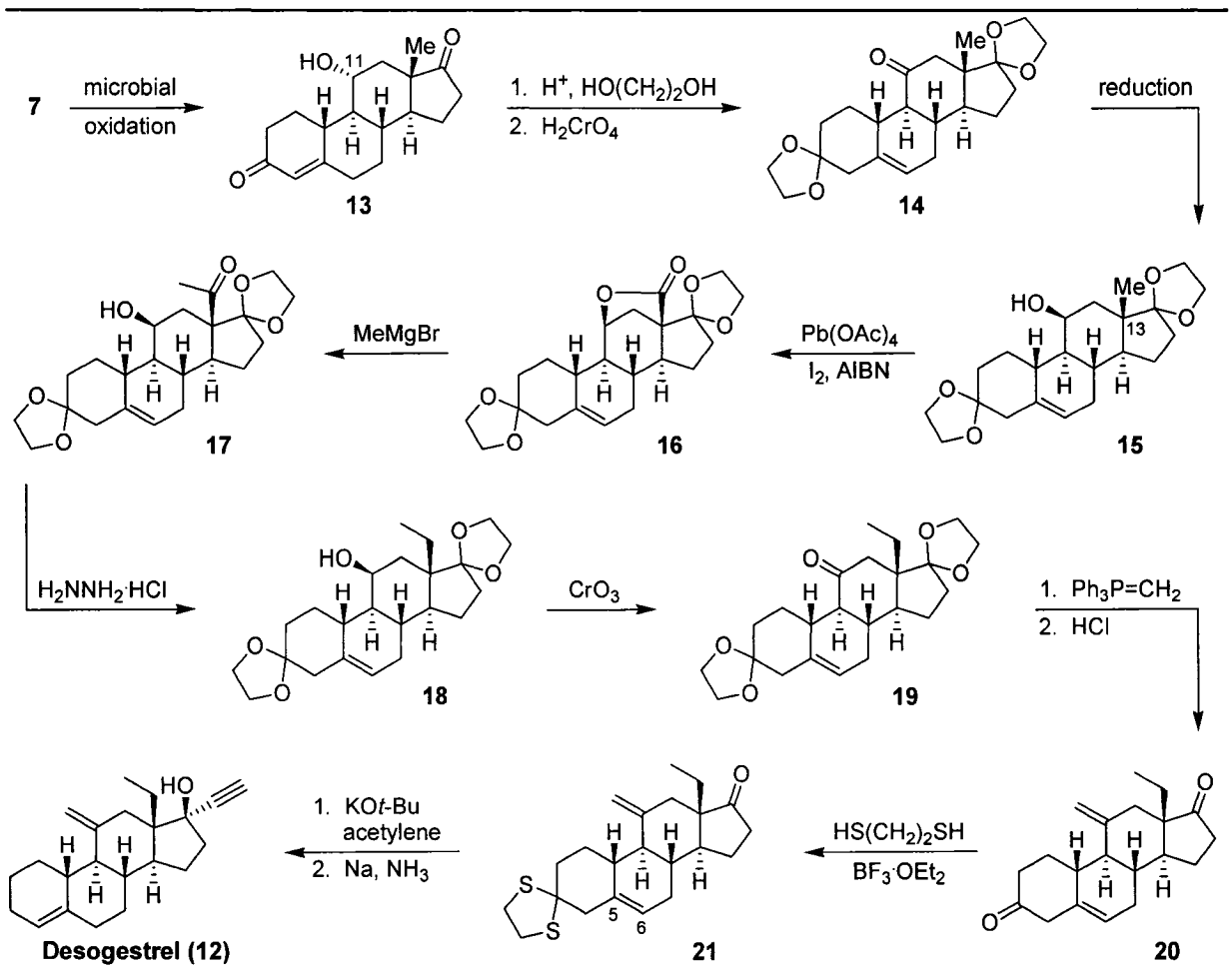
[9] Swyer, G. I. M.; Little, V. *Contraception* **1982**, *26*, 23-27.

[10] The original 1960 formulation contained 9.85 mg of a synthetic progestin.

[11] Bilotta, P.; Favilli, S. *Drug Res.* **1988**, *38*, 932-934.

steroids had to result from either chemical modification of naturally occurring steroids or *via* total synthesis from non-steroidal precursors. A number of syntheses using these approaches have been developed for Norgestimate (**10**) and Gestodene (**11**). However, in addition to the difficulties associated with the introduction of the C13 ethyl group, installation of the C11 methylene group of Desogestrel (**12**) also generated substantial synthetic difficulty.

1.1.2 Initial industrial synthesis of Desogestrel



Scheme 2: Initial industrial synthesis of Desogestrel

Illustrative of these synthetic difficulties, the original industrial synthesis of Desogestrel was 26 steps in length from diosgenin.[12] However, industrial procedures for the synthesis of **7**,

[12] van den Heuvel, M. J.; van Bokhoven, C. W.; de Jongh, H. P.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas.* **1988**, *107*, 331.

which were available from syntheses of previous generations of oral contraceptive progestins, made this procedure more economical than the length of the synthesis may imply. As shown in Scheme 2, the synthesis commenced with a microbial oxidation of **7** to install the C11 hydroxyl group. A three-step procedure to invert the stereochemistry of the C11 hydroxyl group ensued (**13** → **15**), followed by an oxidative lactonization of the hydroxyl group and the C13 methyl group using $Pb(OAc)_4$ and I_2 to generate lactone **16**. Subsequent ring-opening of the lactone using methyl Grignard and reduction of the resulting methyl ketone provided alcohol **18**. Oxidation of the alcohol afforded ketone **19**, which was converted *via* a Wittig reaction to the exocyclic methylene group characteristic of Desogestrel. Hydrolysis of the acetals then provided diketone **20**. Thioacetalization of the more reactive carbonyl group generated **21**, which was reacted with potassium acetylide to generate the characteristic ethynyl moiety. Reductive removal of the thioacetal and migration of the C5,6 alkene then provided Desogestrel (**12**).

1.1.3 Total syntheses of Desogestrel

Several other syntheses of Desogestrel and its active metabolite, 3-ketodesogestrel, from steroidal starting materials are known.[13] However, only two total syntheses of Desogestrel from non-steroidal precursors have been reported and both were completed by E. J. Corey at Harvard. The first, reported in 1999, is illustrated in Scheme 3.[14]

The synthesis began with the ethyl analogue of the Hajos-Parrish ketone (**22**).[15] Sodium borohydride reduction of the more reactive carbonyl group followed by protection as the TBS ether provided **23**.[15b] An efficient cuprate-induced reduction of the α,β-double bond using catalytic *t*-BuCu and stoichiometric DIBALH followed by α-methoxycarbonylation of the ketone then provided the β-keto ester, which existed as its enol tautomer **24**. Sequential double deprotonation of **24** using NaH and *n*-BuLi provided the bis(enolate), which was alkylated with alkyl iodide **25** at the more nucleophilic position to provide tricyclic structure **26**. Cationic cyclization of **26** using CF_3CO_2H then provided the tetracyclic core structure of Desogestrel.

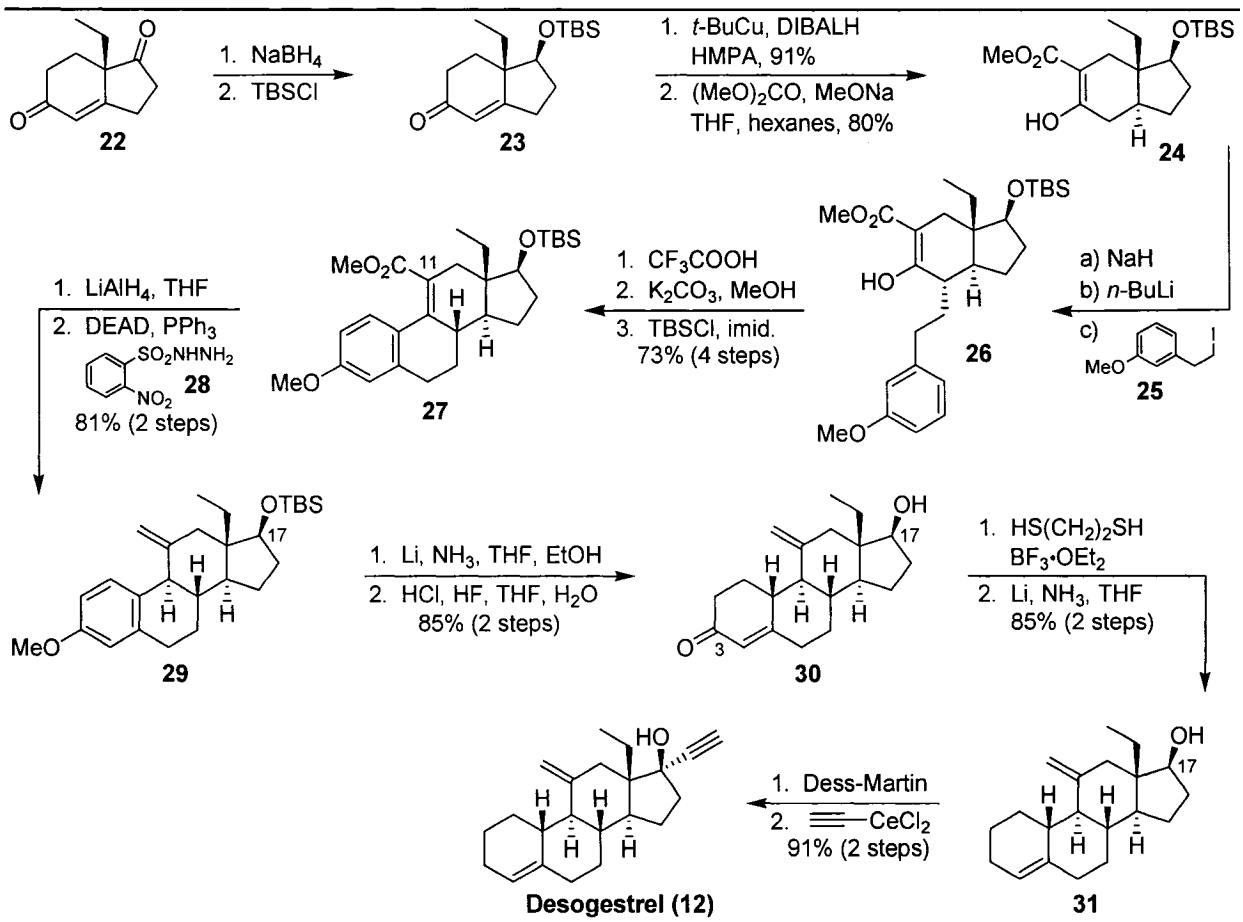
---

[13] (a) Schwarz, S.; Ring, S.; Weber, G.; Teichmuller, G.; Ralme, H.-J.; Pfeiffer, C.; Undeutsch, B.; Erhart, B.; Graive, D. *Tetrahedron* **1994**, *50*, 10709-10720; (b) Gao, H.; Su, X.; Li, Z. *Steroids* **1997**, *62*, 398-402; (c) Groen-Piotrowska, E. M.; Groen, M. B. *Rec. Trav. Chim. Pays-Bas.* **1993**, *112*, 627.

[14] Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710-714.

[15] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612-1615; (b) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675-681.

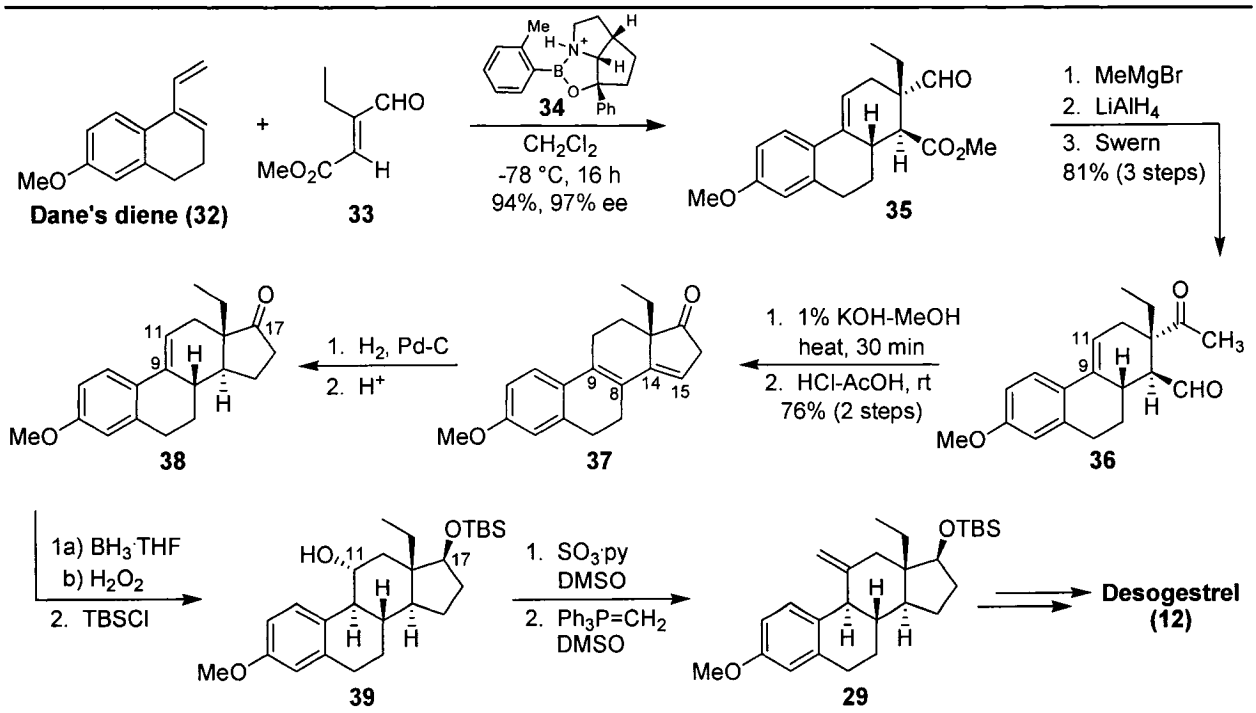
This transformation was unfortunately accompanied by cleavage of the TBS ether and esterification of the resulting alcohol with excess CF_3CO_2H. The TBS group was thus reintroduced *via* sequential treatment with methanolic K_2CO_3 to cleave the ester, followed by silyletherification with TBSCl to give **27**. Reduction of the C11 ester then provided the allylic alcohol, which was then converted to alkene **29** *via* an allylic diazine [3,3]-sigmatropic rearrangement using a clever variation of Myers' procedure for the synthesis of allenes.[16] Thus, exposure of the allylic alcohol to a mixture of PPh_3 and DEAD followed by addition of aryl sulfonylhydrazine **28** generated an alkyl sulfonylhydrazine intermediate, which upon warming and loss of the arylsulfinic acid underwent a [3,3]-sigmatropic rearrangement to give **29**.



Scheme 3: Corey's first synthesis of Desogestrel

[16] Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

A Birch reduction of the aromatic ring then provided the intermediate 1-methoxy-1,4-cyclohexadiene, which provided α,β-unsaturated ketone **30** upon exposure to aqueous acid. The C17 alcohol was also desilylated during this procedure. Removal of the C3 ketone was accomplished *via* the previously described two-step thioacetalization-reduction procedure (Scheme 2) and provided alcohol **31**. Oxidation of the C17 alcohol to the ketone followed by the addition of cerium acetylide concluded the synthesis and provided Desogestrel in 14 linear steps (from **23**) in a reasonably good 28% overall yield.



Scheme 4: Corey's second synthesis of Desogestrel

Corey's second total synthesis of Desogestrel was reported after completion of our synthetic work, but is shown in Scheme 4 for completeness.[17] The key step in this synthesis was an enantioselective Diels-Alder reaction between Dane's diene (**32**)[18] and α,β-unsaturated enal **33** using oxazaborolidine **34** as a chiral catalyst. The reaction afforded adduct **35** in 94% yield and 97% enantiomeric excess, which after one recrystallization yielded enantiomerically pure **35**.

[17] Hu, Q-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984-5986.

[18] Dane, E.; Eder, K. *Liebigs Ann. Chem.* **1939**, *539*, 207-212. Dane's diene has frequently been used in steroid synthesis. For a modern synthesis in this field, see: Quinkert, G.; Grosso, M. D.; Bucher, A.; Bauch, M.; Doring, W.; Bats, J. W.; Durner, G. *Tetrahedron Lett.* **1992**, *33*, 3617-3620.

Continuing the synthesis, reaction of aldehyde **35** with MeMgBr followed by reduction of the ester with $LiAlH_4$ afforded a diol that was oxidized under Swern conditions to yield **36**. A base catalyzed aldol condensation followed by treatment with acid then generated tetracycle **37** in which the C9,11 double bond had isomerized into conjugation with the C14,15 alkene.

The conversion of **37** into Desogestrel was accomplished using a number of known transformations. Thus, hydrogenation of the least-substituted alkene (C14,15) followed by acid-catalyzed isomerization of the C8,9 double bond back to the 9,11-position afforded **38**.[19] Hydroboration-oxidation of the C9,11 alkene and reduction of the C17 carbonyl provided the diol, which was selectively protected as the TBS ether at C17 to provide **39**.[13a] Oxidation of the C11 alcohol under Parikh-Doering conditions followed by a Wittig olefination with $Ph_3P{=}CH_2$ generated **29**,[13a] which could be converted to Desogestrel using a series of transformations from Corey's first synthesis.[14]

1.2 The Diels-Alder Reaction

Our approach to Desogestrel, fully described in Section 1.3, utilizes a Diels-Alder reaction as a key step. An introduction to this reaction is therefore presented in this Section.

[19] Smith, H.; Hughes, G. A.; Douglas, G. H.; Wendt, G. R.; Buzby, G. C., Jr.; Edgren, R. A.; Fisher, J.; Foell, T.; Gadsby, B.; Hartley, D.; Herbst, D.; Jansen, A. B. A.; Ledig, K.; McLoughlin, B. J.; McMenamin, J.; Pattison, T. W.; Phillips, P. C.; Rees, R.; Siddal, J.; Siuda, J.; Smith, L. L.; Tokolics, J.; Watson, D. H. P. *J. Chem. Soc.* **1964**, 4472-4492

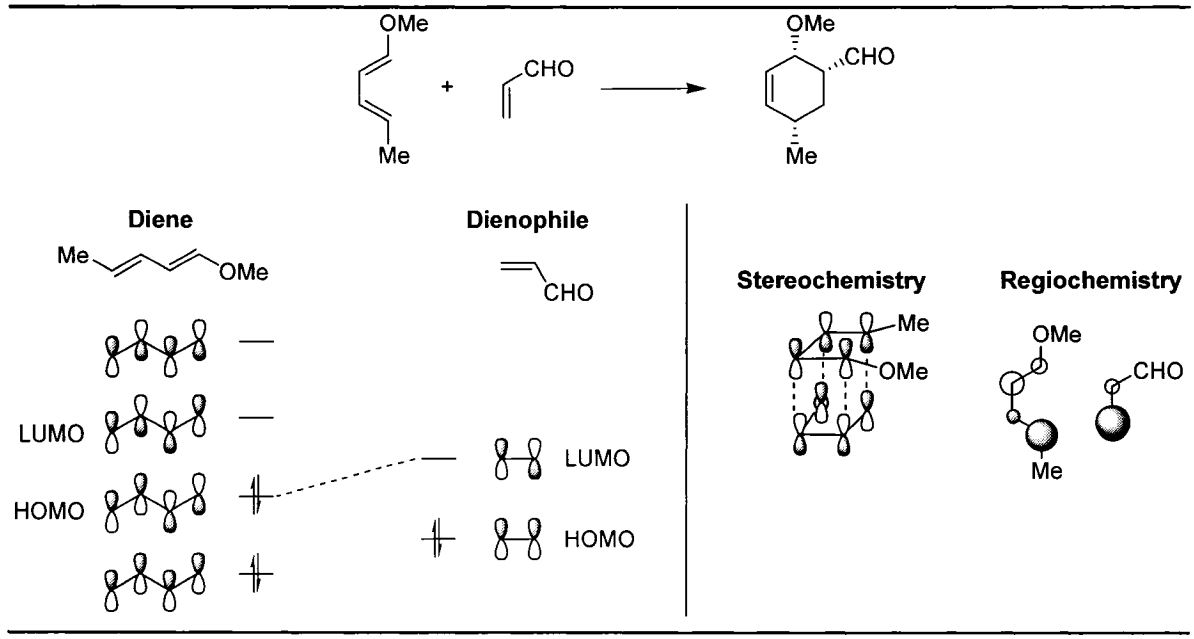


Figure 2: The Diels-Alder reaction

Discovered in 1928 by Otto Diels and Kurt Alder,[20] the Diels-Alder reaction has become one of the most powerful tools available to the synthetic organic chemist.[21] The Diels-Alder reaction is a concerted [4π+2π] cycloaddition reaction between a diene and a dienophile that forms a six-membered ring. Typically the reaction occurs between the HOMO of the diene and the LUMO of the dienophile as these orbitals are closest in energy (Figure 2). The reaction can thus be accelerated by bringing these orbitals closer together in energy. This is most easily accomplished by raising the energy of the diene HOMO *via* the addition of electron-donating groups, or by lowering the energy of the dienophile LUMO *via* the addition of electron-withdrawing groups or complexation to a Lewis acid (usually to a heteroatom substituent present on the dienophile).

The Diels-Alder reaction is often stereoselective. As illustrated in Figure 2, secondary orbital overlap between the electron-withdrawing group of the dienophile and the back portion of the diene causes the dienophile to approach the diene in an *endo* fashion rather than the more sterically favored *exo* approach. The regiochemistry of the Diels-Alder reaction is also

[20] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

[21] For leading reviews, see: (a) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001**, *12*, 597-622; (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741-761; (c) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129-158; (d) Kumar, A. *Chem. Rev.* **2001**, *101*, 1-20.

predictable. The diene and dienophile approach one another so that the orbital coefficients of each species, generalized by Houk's rules,[22] pair up with coefficients of similar size.

1.2.1 Intramolecular Diels-Alder reactions

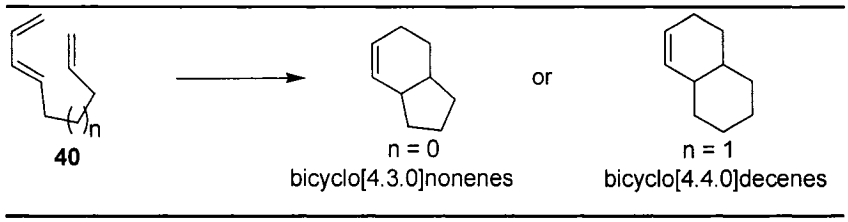


Figure 3: The intramolecular Diels-Alder reaction

The first intramolecular Diels-Alder reaction was reported in 1953 by Alder,[23] but it was not until the 1960's that further examples began to appear in the literature.[24] Interest in this variant of the classic reaction has since increased exponentially and it has been widely investigated and exploited in total synthesis.[25] Generally speaking, an intramolecular Diels-Alder reaction of triene **40** will provide one of two ring systems (Figure 3). When n=0, bicyclo[4.3.0]nonenes (hydrindenes) result, while when n=1 bicyclo[4.4.0]decenes (decalins) are produced. Larger values of n are also possible, although they are substantially less common. The regiochemistry of intramolecular Diels-Alder reactions is nearly always determined by the connectivity of the triene precursor, with only one regioisomer being possible. In comparison to the intermolecular Diels-Alder reaction, the stereochemical outcome of the intramolecular reaction is more strongly influenced by steric interactions in the transition state than by electronic factors, such as secondary orbital interactions.

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[22] (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094; (b) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361-369.

[23] Alder, K.; Schumacher, M. *Fortsch. Chem. Org. Naturst.* **1953**, *10*, 66.

[24] (a) Cram, D. J.; Knox, G. R. *J. Am. Chem. Soc.* **1961**, *83*, 2204-2205; (b) Wasserman, H. H.; Douxaux, R. A. Jr. *J. Am. Chem. Soc.* **1962**, *84*, 4611-4612; (c) Bilovic, D.; Strojanac, Z.; Hahn, V. *Tetrahedron Lett.* **1964**, *5*, 2071-2074.

[25] For reviews on the intramolecular Diels-Alder reaction, see: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183-234; (b) Roush, W. R. In *Comprehensive Organic Synthesis;* Trost, B.; Fleming, I. Pergamon Press: New York, **1991**; Vol. 5; Chapter 4.4; (c) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464-474; (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187-238.

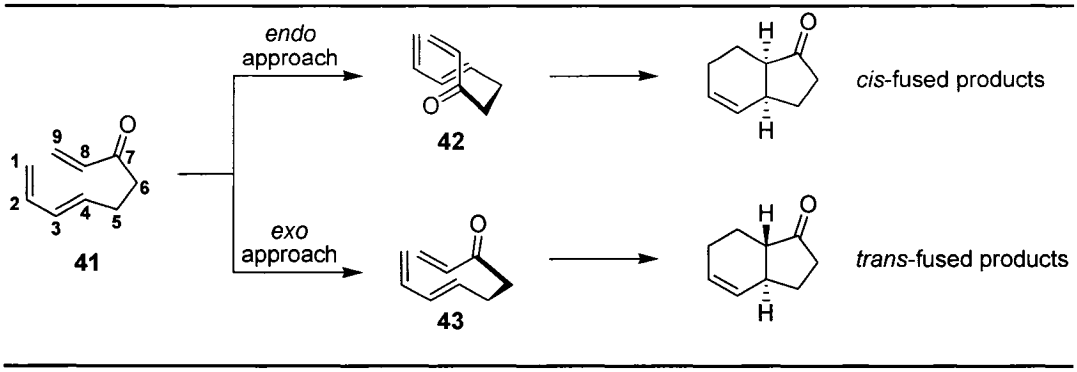
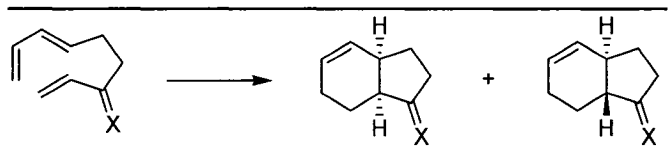


Figure 4: Formation of cis- and trans-fused bicyclo[4.3.0]nonenones

The formation of bicyclo[4.3.0]nonenes is pertinent to this thesis. As illustrated in Figure 4, the intramolecular Diels-Alder reaction of nonatriene **41** results in either *cis*- or *trans*-fused bicyclo[4.3.0]nonenes. An *endo* approach (**42**) of the dienophile to the diene produces *cis*-fused products, while an *exo* approach (**43**) results in *trans*-fused products. The *exo* or *endo* approach of the dienophile from the opposite face of the diene will of course provide the enantiomers. The intramolecular Diels-Alder reaction of **41** can therefore result in four possible products.

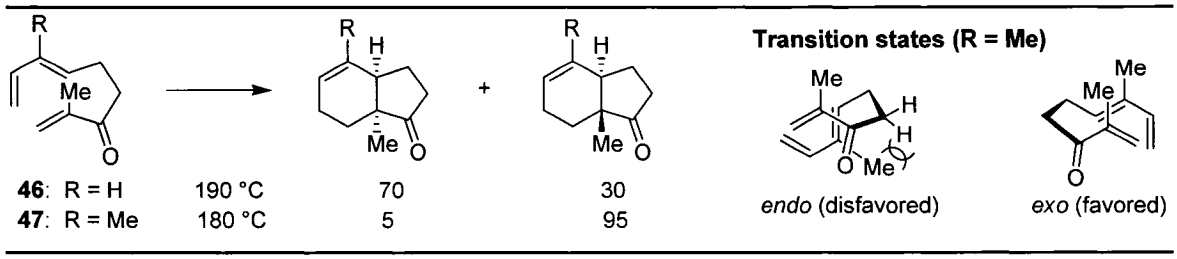


44: X = H_2	250 °C	73	27
45: X = O	180 °C	87	13

Scheme 5: Ratio of cis/trans products for the Diels-Alder reaction of nonatrienes

Considerable research has been directed toward the prediction and control of the stereoselectivity of intramolecular Diels-Alder reactions of systems related to nonatriene **41**. As illustrated in Scheme 5, the simplest nonatriene systems [X = H_2 (**44**) or X = O (**45**)] gave predominately *cis*-fused products,[26] indicating that the reaction was proceeding primarily *via* an *endo* transition state.

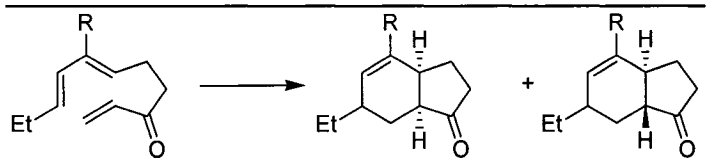
[26] (a) Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269-2272; (b) Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877-4880.



46: R = H	190 °C	70	30
47: R = Me	180 °C	5	95

Figure 5: Intramolecular Diels-Alder reaction and transition states of substituted nonatrienes

The addition of substituents to the nonatriene has also been investigated (Figure 5). It was found that while addition of a methyl group at C8 of the nonatriene (**46**) had little effect on the *cis/trans* product ratio,[27] addition of a methyl group at C3 (**47**) had a substantial effect, reversing the selectivity to strongly favor the *trans*-adduct.[28] This indicated that an *exo* transition state was preferred. As indicated in the transition states shown in Figure 5, steric repulsion between the C3 methyl group and the C6 hydrogen atoms of the connecting chain disfavored an *endo* approach of the dienophile.[25d] These interactions were minimized in the *exo* transition state, and thus *trans*-fused products dominated. This effect was even more pronounced when the size of the C3 substituent was increased (**48**, Scheme 6), as exclusively *trans*-fused adduct was produced.[29]



48: R =	190 °C	0	100

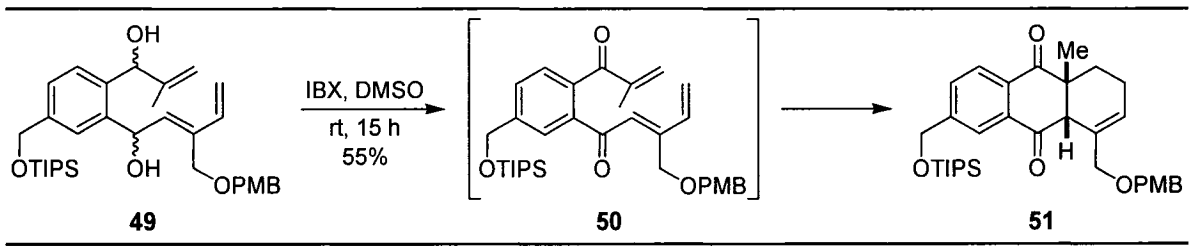
Scheme 6: Intramolecular Diels-Alder reaction of nonatriene 46

Hundreds of other examples of intramolecular Diels-Alder reactions of nonatrienes exist in the literature, and although selectivity trends are apparent in some cases, the stereoselectivity is largely unique for each substrate and is influenced by a complex interplay of steric and electronic factors.[25]

[27] Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929-3932.
[28] Shishido, K.; Airoya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1986**, *27*, 1167-1170.
[29] Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353-6355.

1.2.2 *Tether-controlled intramolecular Diels-Alder reactions*

Multiple strategies have been developed to increase the stereoselectivity of intramolecular Diels-Alder reactions, including the use of chiral Lewis acids,[30] chiral auxiliaries,[31] metal chelation,[32] and cleavable silyl acetal tethers.[33] Another option is through the use of tether-control groups. Tether-control groups are moieties that limit the flexibility of the system. This decreased flexibility facilitates the organization of the diene and dienophile into the desired transition state, thus lowering the activation energy of the reaction and favoring one stereoisomer over the others. Additionally, if chirality is present in the tether-control group, asymmetric induction can be observed in the reaction.



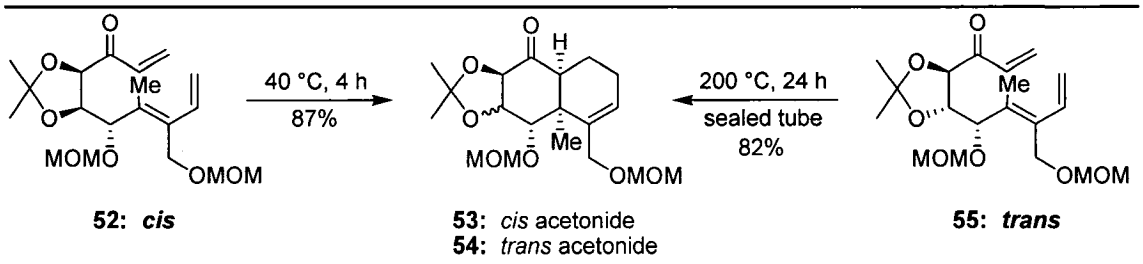
49 **50** **51**

Scheme 7: An aromatic tether-control group

The Fallis research group has extensively explored the use of tether-control groups in the synthesis of decalins as a component of their taxane analogue studies. They discovered that the presence of an aromatic ring tether-control group dramatically accelerated the intramolecular Diels-Alder reaction of triene **49** (Scheme 7).[34] Upon oxidation of **49** with IBX, intermediate diketone **50** spontaneously and diastereoselectively cyclized to provide *cis*-fused hexahydroanthracene dione **51**. The ease with which this cycloaddition occurred is significant as related cycloadditions are often difficult as a result of steric hindrance caused by the methyl group at C2 of the dienophile.[25a] The Fallis group has also investigated the use of isopropylidene acetal tether-control groups (Scheme 8).[35] They found that the *cis*-acetonide (**52**) provided a

[30] Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019.
[31] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263.
[32] Stork, G. *J. Am. Chem. Soc.* **1995**, *117*, 6595-6596.
[33] Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145-1148.
[34] Martin, C.; Macintosh, N.; Lamb, N.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 1021-1023.
[35] (a) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793-2796; (b) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045-7048.

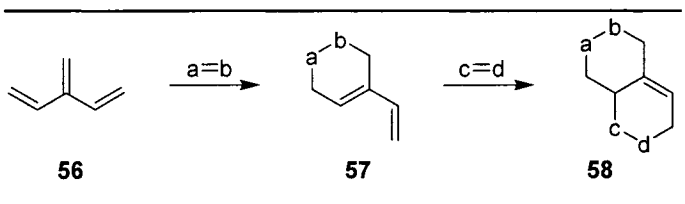
dramatic rate enhancement compared to the analogous *trans*-acetonide (**55**). Additionally, the stereochemistry of the acetonide caused one *endo* transition state to be favored over the other, and thus provided primarily *cis*-fused adduct **53** or **54** (the ratio of enantiomeric *cis*-fused products was solvent dependent and varied from 2.4:1 to 23:1).



Scheme 8: Cycloadditions controlled by cis- and trans-acetonides

1.2.3 Diene-transmissive Diels-Alder reactions

A diene-transmissive Diels-Alder reaction occurs when the reaction of a diene with a dienophile generates a new diene moiety, which can then react with another dienophile. As illustrated in Scheme 9 for cross-conjugated triene **56**, reaction with one equivalent of a dienophile (a=b) generates **57** and places the newly formed double bond in such a position that a new diene is formed. This new diene can then be reacted with a second dienophile (c=d), either *in situ* or in another reaction, to generate two fused six-membered rings (**58**).

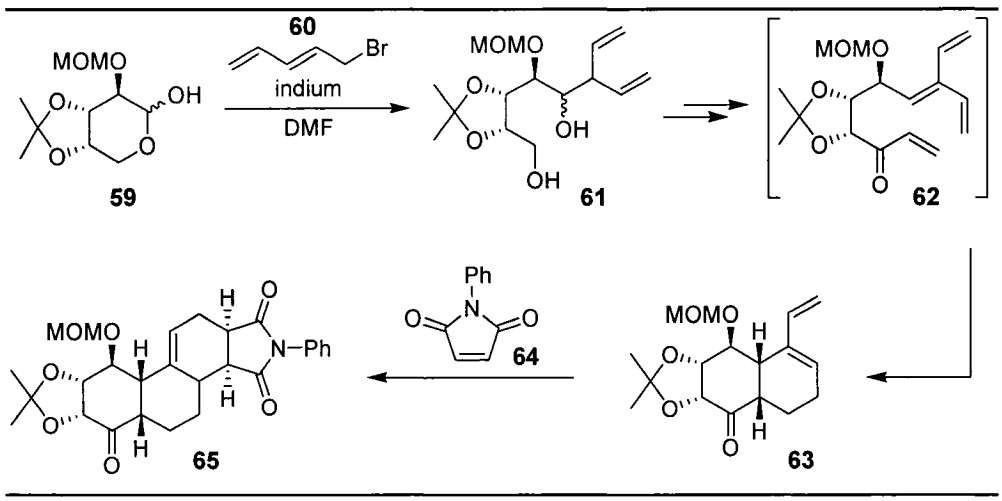


Scheme 9: The diene-transmissive Diels-Alder reaction

Fallis and coworkers have exploited the diene-transmissive Diels-Alder reaction in synthesis. In conjunction with their tether-control group methodology,[35] they synthesized highly oxygenated nor-steroid and nor-triterpenoid skeletons.[36] As depicted in Scheme 10, their

[36] Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013-1016.

synthesis began with an indium-mediated γ-pentadienylation of lactol **59**, which was derived from L-arabinose, to generate diol **61**. Dehydration of the allylic alcohol provided the key triene moiety. Further functional group manipulations added the dienophile component to give **62**, which spontaneously cyclized to stereospecifically generate decalin **63** as a single enantiomer. An intermolecular Diels-Alder reaction with *N*-phenylmaleamide (**64**) then yielded the tetracyclic nor-steroid structure **65**.

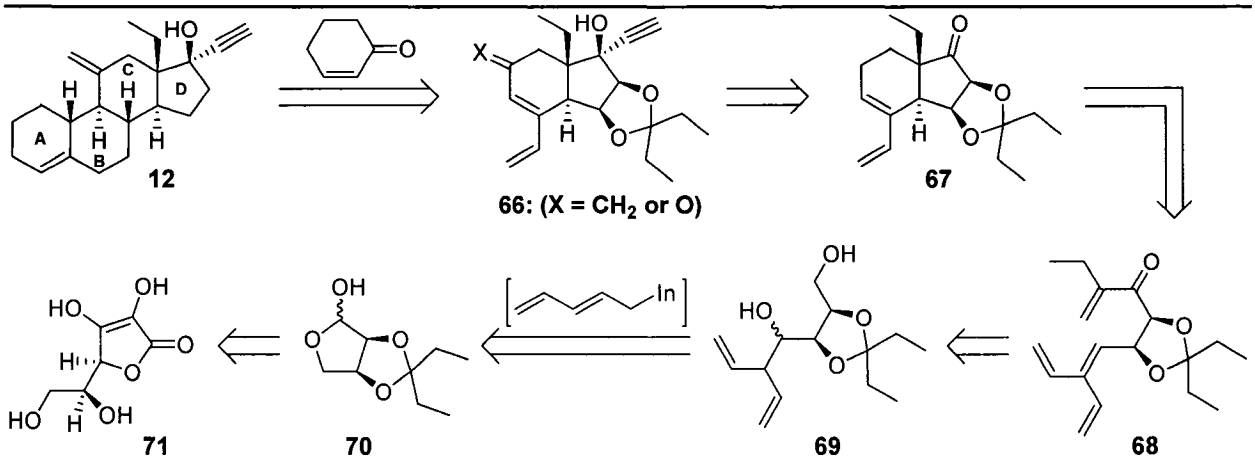


Scheme 10: A tether-controlled diene-transmissive Diels-Alder approach to steroids

1.3 A Tether-Controlled Diene-Transmissive Intramolecular Diels-Alder Reaction Approach to Desogestrel

The success of our tether-controlled diene-transmissive Diels-Alder protocol for the synthesis of nor-steroids prompted us to investigate its utility towards the synthesis of steroids such as Desogestrel (**12**). Our strategy to Desogestrel, outlined in Scheme 11, envisaged sequential Diels-Alder cycloadditions in which the CD ring system would be constructed *via* a tether-controlled intramolecular Diels-Alder reaction. A subsequent intermolecular Diels-Alder reaction with a suitable cyclohexanone derivative would then provide the AB rings. This strategy is essentially the reverse of that previously employed in the Fallis laboratory, where the AB rings of the steroid were assembled *via* the tether-control methodology and the CD rings installed using a subsequent intermolecular Diels-Alder reaction.[36] The primary goal of this project was therefore to evaluate the utility of the tether-controlled intramolecular Diels-Alder

reaction towards the synthesis of the CD rings (hydrindane moiety) of steroids. The ultimate goal was to apply this methodology to the synthesis of Desogestrel.



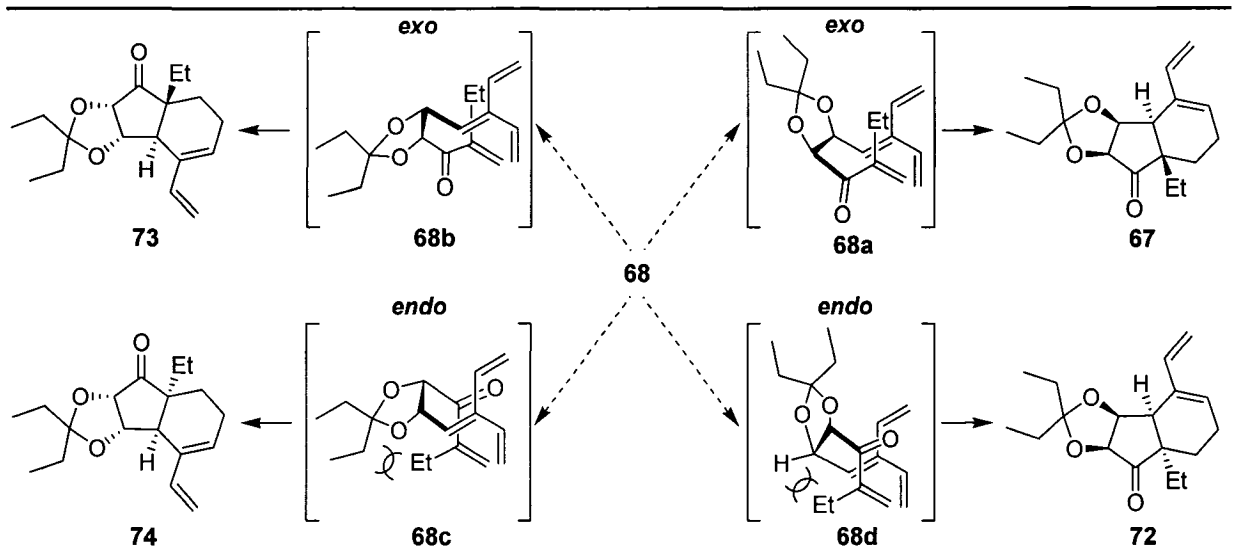
Scheme 11: A tether-controlled diene-transmissive intramolecular Diels-Alder reaction approach to Desogestrel

As illustrated in Scheme 11, the AB rings of Desogestrel (**12**) could arise from a Diels-Alder reaction of **66** with a suitable cyclohexanone derivative using, for example, MacMillan's imine-catalyzed protocol.[37] We believed that the CD rings (**67**) could be generated *via* a tether-controlled intramolecular Diels-Alder reaction of tetraene **68**. This tetraene could be synthesized from diol **69**, which is a product arising from an indium-mediated γ-pentadienylation of lactol **70**. Lactol **70** is available in enantiomerically pure form from D-isoascorbic acid (**71**).

The key step in our retrosynthesis is the tether-controlled intramolecular Diels-Alder reaction of tetraene **68**. A high level of selectivity for the desired isomer (**67**) would be required to justify further pursuit of the synthesis. The possible bicyclo[4.3.0]nonene isomers that could result from the cycloaddition reaction, as well as the transition states that give rise to them, are presented in Scheme 12. The two *endo* transition states **68c** and **68d**, giving rise to *cis*-fused bicyclo[4.3.0]nonenes **74** and **72**, were expected to be disfavored as a result of the steric interactions indicated in Scheme 12. We believed that the isopentylidene acetal tether-control group would help to distinguish between the two *exo* transition states and favor bicyclo[4.3.0]nonene **67** *via* transition state **68a**. If, however, poor selectivities were obtained, the reaction could be conducted using a chiral Lewis acid.[25] This would not only distinguish

[37] (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458-2460; (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

between the two *exo* transition states, but the added steric bulk would further disfavor the *endo* transition states. MacMillan's catalyst[37] could also be employed and would similarly permit the various transition states to be differentiated.



Scheme 12: Possible Diels-Alder products and transition states

2 Results and Discussion

2.1 Synthesis of the Intramolecular Diels-Alder Precursors

Our synthesis commenced with the oxidative degradation of D-isoascorbic acid (**71**) to D-erthyronolactone (**83**) (Scheme 13).[38] Addition of solid Na_2CO_3 to a solution of D-isoascorbic acid in water resulted in the vigorous evolution of CO_2. Subsequent addition of 30% H_2O_2 completed the oxidation, and after acidic workup, isolation and recrystallization, afforded D-erthyronolactone (**83**) in 65% yield. The mechanism proposed by Isbell and Frush for this reaction is quite interesting and complex.[39] A slightly modified version to account for the evolution of CO_2 is presented in Figure 6.

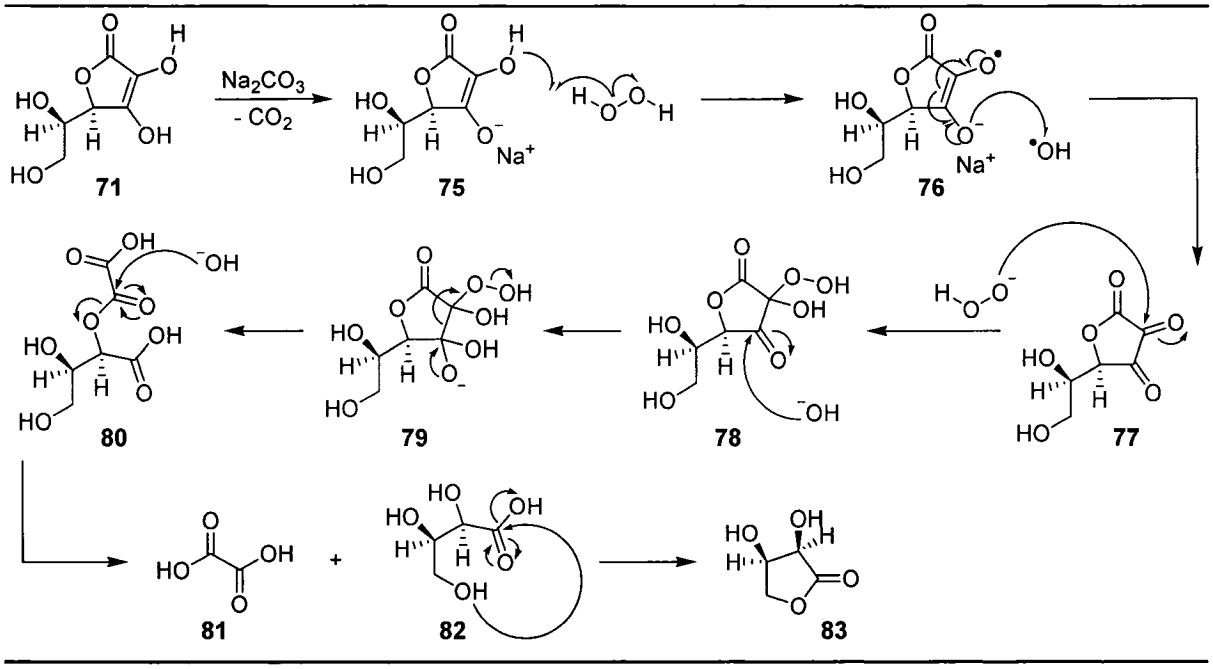
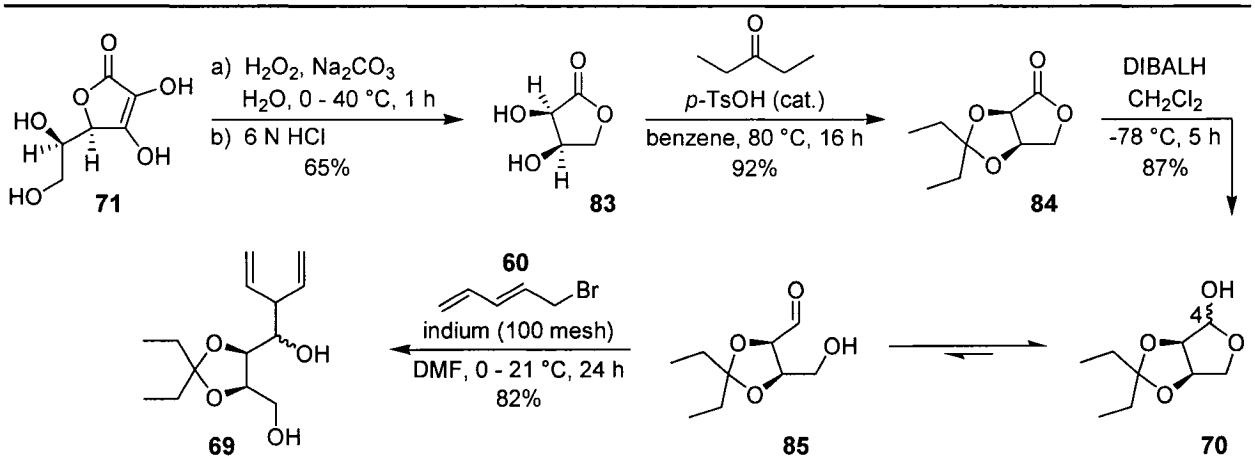


Figure 6: Oxidative degradation of D-isoascorbic acid

The synthesis continued with the acetalization of **83** (Scheme 13). Thus, exposure of diol **83** to 10 equivalents of 3-pentanone and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene using a Dean-Stark apparatus provided *cis*-isopentylidene acetal **84** in 92% yield.

[38] Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Syn.* **1984**, *63*, 127-135.
[39] Isbell, H. S.; Frush, H. L. *Carbohydr. Res.* **1979**, *72*, 301-304.

Reduction of the lactone moiety of **84** with DIBALH then gave lactol **70** in 87% yield as a 5:1 mixture of diastereomers, epimeric at C4. The absence of an aldehyde resonance in the ^{1}H NMR spectrum indicated that the lactol existed nearly entirely in the closed-chain form. A small amount of compound was also obtained where lactol **70** had been further reduced to the corresponding diol. An indium-mediated γ-pentadienylation onto the open-chain aldehyde (**85**) using an excess of the bis(allyl)indium reagent[40] generated from 5-bromo-1,3-pentadiene (**60**) and indium powder then provided diol **69** in 82% yield. Two diastereomers were produced from this addition in ratios ranging from 7:1 to 4:1, depending on the trial. No attempt was made to determine the structure of the major isomer as the stereocenter in question was removed later in the synthesis.

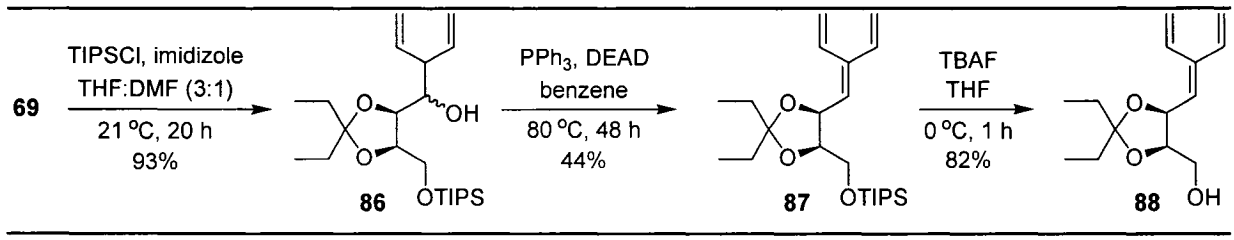


Scheme 13: Synthesis of diol 69

Selective protection of the primary alcohol of **69** using TIPSCl and imidazole in a mixture of THF and DMF then provided alcohol **86** as a mixture of diastereomers in 93% yield (Scheme 14). Mitsunobu-type dehydration of **86** using excess PPh_3 and DEAD in refluxing benzene then gave triene **87** in 44% yield. The low yield of this step was attributed to the instability of triene **87**, which readily decomposed during column chromatography or upon storage in a freezer for short periods. It is interesting to note that the minor isomer of **86** was surprisingly resistant to dehydration. Whereas dehydration of the major isomer (of the mixture)

[40] Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573-575

was complete within one day, dehydration of the minor isomer required up to three days, and often additional reagents (PPh_3 and DEAD) were required.



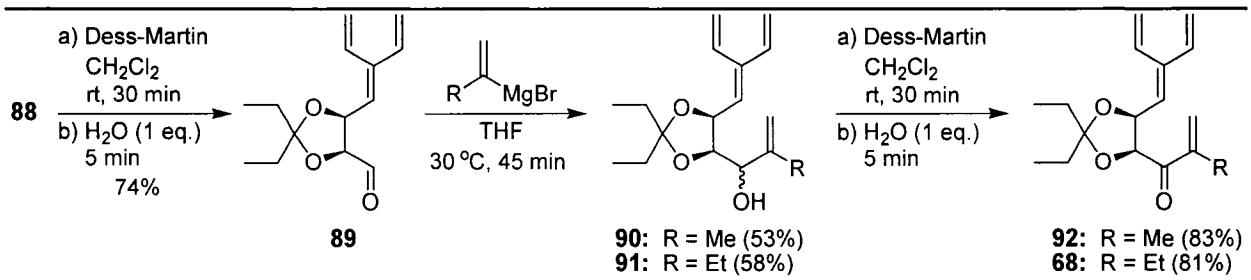
Scheme 14: Synthesis of trienol 88

Desilylation of **87** using TBAF then easily afforded trienol **88** in 82% yield. Trienol **88** was chromatographically stable and could be stored for months in a freezer. In an attempt to increase the yield of the dehydration step, a one-pot reaction sequence, in which alcohol **86** was first dehydrated and then desilylated to **88** without isolation of intermediate **87**, was investigated. We were gratified to achieve a higher yield of crude trienol **88** from the one pot procedure (~71%, compared to 36% over the two separate steps). However, trienol **88** could not be easily separated from several impurities generated during the dehydration phase. In fact, as this reaction had been conducted on large scale, **88** had to be re-protected as the triisopropylsilyl ether and chromatographed to isolate **87**, which was desilylated with TBAF to provide pure **88**! Thus the preferred experimental method to ensure purity was the original two-step sequence.

The oxidation of trienol **88** to aldehyde **89** was also challenging (Scheme 15). Oxidation readily occurred under a variety of conditions (Collins,[41] Corey-Schmidt,[42] IBX,[43] Dess-Martin,[44] Swern[45]), but the product aldehyde slowly decomposed under the reaction conditions, resulting in mixtures of alcohol **88**, aldehyde **89**, and decomposition products. Furthermore, aldehyde **89** could not be separated from the decomposition products. We attributed this instability to the mildly acidic environment of some of the reactions. Thus, to ensure basic conditions we initially tried adding NEt_3 or solid $NaHCO_3$ to the Dess-Martin periodinane oxidation of **88**. Unfortunately, neither of these additives had a positive effect. In frustration, a

[41] Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002.
[42] Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399-402.
[43] (a) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727; (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.
[44] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
[45] Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.

few drops of 10% NaOH were added to a fresh reaction, and within minutes all of alcohol **88** had been converted to aldehyde **89**. A literature search quickly revealed that this rate enhancement was likely the result of the water, which has been shown to dramatically accelerate the oxidation of alcohols using Dess-Martin periodinane.[46] Thus, the oxidation of **88** to **89** using Dess-Martin periodinane was accelerated *via* the addition of water to the point that no appreciable decomposition of the product aldehyde had occurred. This procedure afforded aldehyde **89** in 74% yield (Scheme 15).



Scheme 15: Synthesis of Diels-Alder precursors 68 and 92

Addition of isopropenyllithium or *sec*-butenyllithium (generated from the corresponding bromides *via* lithium-halogen exchange) to aldehyde **89** then provided allyl alcohols **90** and **91**, respectively. It was subsequently discovered that addition of the corresponding Grignard reagents to the aldehyde was more efficient on larger scales and afforded **90** and **91** in 53% and 58% yields, respectively. Oxidation of both compounds was accomplished using the water-accelerated Dess-Martin periodinane procedure described above, and provided intramolecular Diels-Alder reaction precursors **92** and **68** in 83% and 81% yield, respectively.

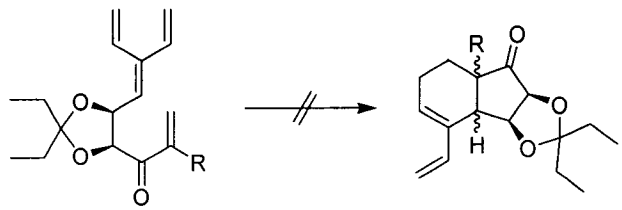
2.2 The Intramolecular Diels-Alder Reaction of Trienes 68 and 92

With trienes **68** and **92** in hand, we turned our attention to the key tether-controlled intramolecular Diels-Alder reaction. We initially attempted the cycloaddition on the slightly simpler model system **92** (R = Me) rather than the ethyl analogue **68**. However, once this material was consumed, subsequent reactions were conducted using **68**. The details of these Diels-Alder reaction studies are presented in Table 1.

[46] Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.

We initially believed that a Lewis acid-mediated cycloaddition at low temperature would provide the best selectivity. Therefore, the Diels-Alder reaction was attempted with either Et_2AlCl or $BF_3{\bullet}OEt_2$ as Lewis acid catalyst. Exposure of **92** to a solution of either Et_2AlCl or $BF_3{\bullet}OEt_2$ in CH_2Cl_2 at –78 °C for two or four hours, respectively, resulted in complete recovery of **92** (entries 1 and 4). The Et_2AlCl-catalyzed reaction was similarly unsuccessful at room temperature (entry 2), while in refluxing CH_2Cl_2 a slow decomposition of **92** to multiple undesired products was observed (entry 3). Warming the $BF_3{\bullet}OEt_2$-catalyzed reaction of **92** to 0 °C led to a rapid change in reaction color (from colorless to deep red) and no identifiable products could be isolated upon workup (entry 5).

Table 1: Tether-controlled intramolecular Diels-Alder reaction of tetraenes 68 and 92



92: R = Me
68: R = Et

93: R = Me
94: R = Et

Entry	Conditions	Temp. (°C)	Time (h)	R	Results
1	Et_2AlCl, CH_2Cl_2	–78	2	Me	Starting material
2	Et_2AlCl, CH_2Cl_2	21	4	Me	Starting material
3	Et_2AlCl, CH_2Cl_2	42	4	Me	Partial decomposition
4	$BF_3{\bullet}OEt_2$, CH_2Cl_2	–78	4	Me	Starting material
5	$BF_3{\bullet}OEt_2$, CH_2Cl_2	0	0.02	Me	Decomposition
6	Toluene, microwave	150	3	Me	76%, 3 isomers (41:20:39)[a]
7	Toluene, microwave	150	3	Et	72%, 3 isomers (53:17:30)[a]
8	Toluene	75	144	Me	61%, 3 isomers (28:24:48)[a]
9	$ZnCl_2$, CH_2Cl_2	42	144	Me	mixture of isomers[b]
10	$Eu(fod)_3$, toluene	100	16	Et	mixture of isomers[b]
11	$HN(i\text{-}Pr)_2$, $HClO_4$, H_2O	0	16	Et	Starting material
12	$HN(i\text{-}Pr)_2$, $HClO_4$, H_2O	21	24	Et	Starting material
13	$HN(i\text{-}Pr)_2$, $HClO_4$, EtOH	21	16	Et	Starting material
14	$HN(i\text{-}Pr)_2$, $HClO_4$, EtOH	65	6	Et	Starting material

(a) Ratio determined by ^1H NMR; ratio of (X:Y:Z) corresponds to isomers A:B:C (see Section 2.3)
(b) Adduct ratio not determined

Given these disappointing results, we decided to focus our attention on the thermally-mediated cycloaddition. Heating a solution of **92** (R = Me) in toluene at 150 °C under

microwave irradiation for three hours resulted in a 41:20:39 mixture of three Diels-Alder adducts in 76% yield (entry 6). The adduct ratio was determined through integration of the ^{1}H NMR resonance arising from the proton at C2 of the diene in each adduct, which occurred without signal overlap (at 500 MHz) between 6.0 and 6.5 ppm, depending on the isomer. When **68** (R = Et) was reacted under identical conditions, an adduct ratio (of the same three adducts) of 53:17:30 resulted (72% yield) (entry 7). Heating a solution of **92** in toluene at 75 °C for six days gave an equally poor adduct ratio of 28:24:48 (61% yield) (entry 8). In an attempt to increase the selectivity, we also tried using Lewis acids at elevated temperature. However, neither the reaction of **92** in refluxing CH_2Cl_2 with $ZnCl_2$ (entry 9) nor the reaction of **68** in toluene at 100 °C with $Eu(fod)_3$ (entry 10) significantly improved the selectivity. Lengthy reaction times were required in each case, suggesting that the effect of the Lewis acid was negligible. It should be noted that it was determined using the NMR spectra of the mixtures that each successful cycloaddition reaction produced the same three adducts. The subtle difference between **93** (R = Me) and **94** (R = Et) did not have an effect on the alkenyl region of the NMR spectra, which was used to distinguish between the isomers.

We next attempted the Diels-Alder cycloaddition using a variation of MacMillan's imine catalyzed procedure.[37] This method offered the advantage that the reaction could likely be conducted at low temperature and thus a more favorable adduct ratio would likely be observed. Additionally, if the selectivity remained poor, a number of related asymmetric catalysts could be employed in an attempt to improve the selectivity. In our studies, diisopropylamine was employed as the amine component in place of the more complex amine used by MacMillan. Unfortunately, in all cases the reaction was unsuccessful (entries 11-14). Using $HClO_4$ as acid catalyst, either H_2O or EtOH as solvent and temperatures ranging from 0 °C to 65 °C, only the tetraene (**68**) was isolated from the reaction. In retrospect, the imine probably never formed due to the steric hindrance caused by the isopropyl groups of the amine.

2.3 Identification of the Diels-Alder Adducts

At this stage we turned our attention to determining the structure of the individual isomers that had formed in the Diels-Alder reaction. As the major isomer differed between 150 °C (Table 1, entry 6) and 75 °C (entry 8), it seemed prudent to determine which reaction had

provided the highest yield of the desired isomer and should thus be further pursued. The isomers obtained from the reaction at 150 °C (R = Me (**92**), entry 6) were therefore separated *via* exhaustive normal-phase preparative HPLC.

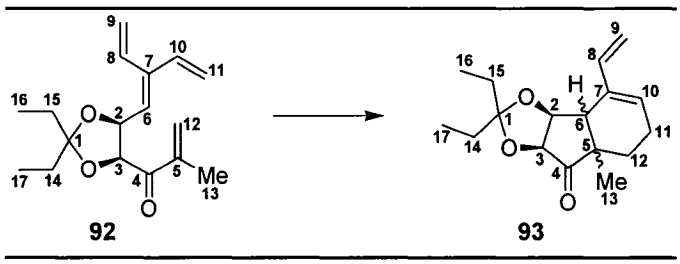


Figure 7: Numbering scheme for NMR analysis

Each isomer was characterized by ^{1}H, ^{13}C, HMQC, COSY, and NOESY NMR experiments. Referring to the numbering scheme in Figure 7 for Diels-Alder adduct **93**, the majority of the protons in each isomer were easily assigned to their respective resonances based on chemical shift and coupling constant data. Protons on carbons 11 and 12 were assigned using the HMQC and COSY data. The HMQC spectrum indicated which protons were on the same carbon atom, while 11 and 12 were distinguished from each other using the COSY spectrum, as only protons on carbon 11 showed coupling to the vinyl proton of carbon 10. The NOESY spectrum was used to distinguish between the diastereotopic ethyl groups (15/16 *vs.* 14/17) of the acetal. For each isomer, reasonably strong nOe's between protons 2 and 3 and the 14/17 ethyl group were found. This ethyl group was therefore assigned to the 'down' position.

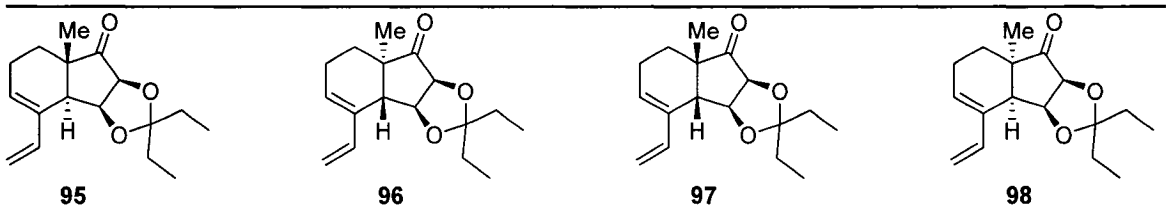
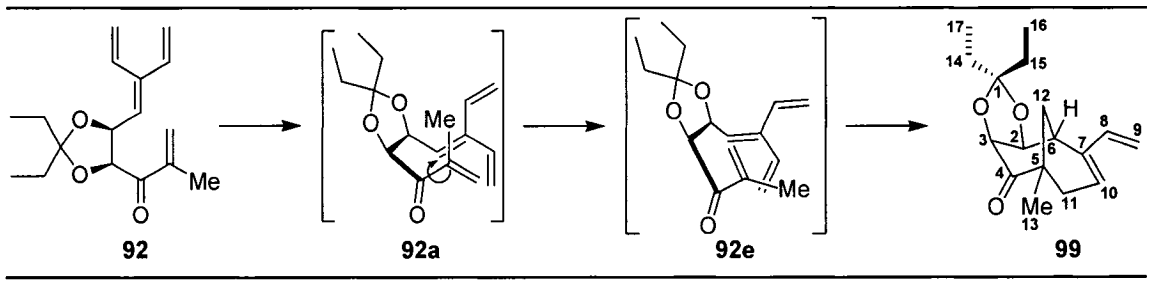


Figure 8: Potential Diels-Alder adducts

We initially only considered the four bicyclo[4.3.0]nonenes shown in Figure 8 as we believed these were the only adducts that could arise from the intramolecular Diels-Alder

reaction of tetraene **93**. Thus, analyzing the NOESY spectrum of isomer **A** (Table 2),[47] the most important information seemed to be the absence of a nOe between methyl group 13 and proton 6, suggesting a *trans* configuration at the ring junction. A relatively strong nOe between protons 6 and 2 and the absence of a nOe between methyl group 13 and protons 2 and 3 suggested that isomer **A** corresponded to bicyclo[4.3.0]nonene **95**. However, a strong nOe between protons 15 and 12a, as well as equally strong nOe's between 6 and both 12a and 12b were inconsistent with this structural assignment. Furthermore, the COSY spectrum indicated strong coupling between proton 6 and both 12a and 12b, as well as a complete lack of coupling between 11 and 12. Isomer **A** was clearly not one of those depicted in Figure 8. A closer examination of the possible transition states indicated that rotation about the indicated bond in **92a** would give rise to a new transition state (**92e**), which would give bicyclo[3.3.1]nonene **99** after reaction (Scheme 16).



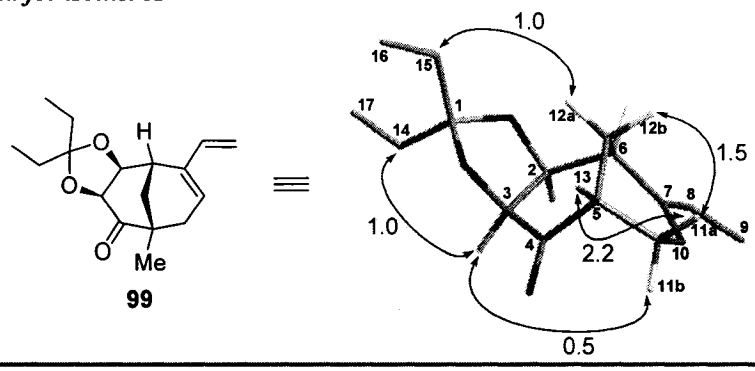
Scheme 16: Formation of bicyclo[3.3.1]nonene 99

The COSY spectrum of isomer **A** was consistent with the structure of bicyclo[3.3.1]nonene **99** and the formerly troublesome couplings were now easily explained. For example, in **99** no coupling would be expected between protons 11 and 12, while coupling would be expected between protons 12 and 6, as was observed. The NOESY spectrum was also consistent with this new structural assignment. All nOe's for isomer **A** are presented in Table 2, while significant values are highlighted in the accompanying figure. As illustrated, relatively strong nOe's existed between protons 12a and 15 and between 12b and 11a, both of which were consistent with the bridged structure of **99**. Additional strong nOe's were found between protons 11b and 3 and between 11a and 13. These are both in excellent agreement with the proposed

[47] The three-dimensional structures for isomers **A**, **B**, and **C** were generated by physically constructing a molecular model, drawing the structure in the Chem3D Ultra program (v. 9.0, CambridgeSoft Inc., 2004) and conducting an energy minimization.

structure. A further examination of the nOe data confirmed that no extraneous correlations existed and that all expected correlations were present.

Table 2 – NOESY data for isomer A

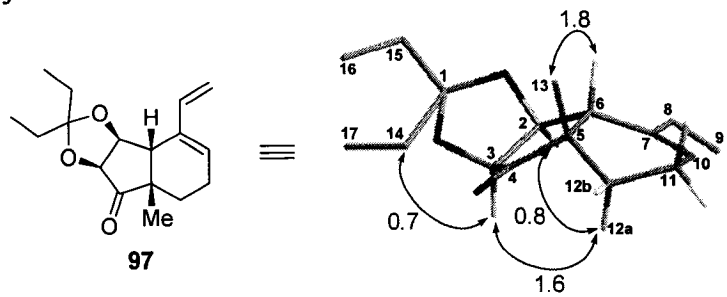


Proton(s) irradiated	2H	3H	6H	8H	9Ha	9Hb	10H	11Ha	11Hb	12Ha	12Hb	13H	14H	15H	16H	17H
2H		2.7	2.0			1.7							2.1			0.6
3H	2.7								0.4				1.1			0.3
6H	2.0			0.2		4.2				1.7	1.8					
8H	0.3		0.3		2.1	1.3	3.0									
9Ha				2.6		12.3										
9Hb	1.9		5.0	1.1	12.8											
10H				3.2				1.3	1.8							
11Ha							1.5		11.5		1.4	2.7				
11Hb		0.5					2.5	12.9				1.2				
12Ha			2.3								19.8	2.0		1.3	1.0	
12Hb			2.1					1.5		17.4						
13H								1.6	0.6	0.9	0.6					
14H	1.5	0.9												0.8	1.1	2.8
15H										0.7			0.6		3.1	1.2
16H										0.3			0.8	1.7		
17H	0.3	0.1											1.7	0.8		

The structure of isomer **B** was determined in a similar manner. A quick check of the COSY spectrum indicated a strong coupling between protons 11 and 12, suggesting the structure corresponded to one of the bicyclo[4.3.0]nonene isomers of Figure 8. The NOESY spectrum was used to determine the exact stereochemistry. The individual nOe correlations are presented in Table 3. Unfortunately, overlap of protons 11 and 15 and of 12b and 16 slightly limited the amount of reliable data that could be obtained. These protons are therefore reported together in Table 3. The most important interaction observed for isomer **B** was between methyl group 13 and proton 6. The relatively strong nOe between the two strongly suggested that isomer **B** corresponded to one of the *cis*-fused isomers (**97** or **98**). The strong nOe's between 12a and both 2 and 3 indicated that isomer **B** corresponded to **97**, as the concave conformation of **97** forces

12a into relative proximity to 2 and 3. This would not be possible with isomer **98**. As with isomer **A**, no extraneous nOe's existed and all those that were expected were present.

Table 3: NOESY data for isomer B

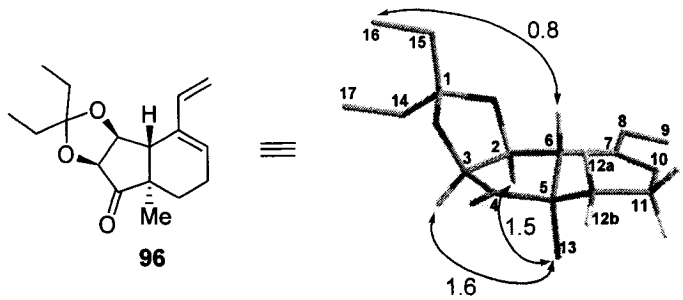


Proton(s) irradiated	2H	3H	6H	8H	9Ha	9Hb	10H	11H, 15H[a]	12Ha	12Hb, 16H[b]	13H	14H	17H
2H		1.6	0.8	0.2		1.0			0.6			1.7	0.6
3H	1.1		0.1						1.5			0.8	
6H	0.9	0.2				3.0					2.4		
8H	0.1				2.2	1.3	3.3						
9Ha				2.5		10.6							
9Hb	1.1		3.5	1.9	11.3								
10H				3.2				2.6					
11H, 15H[a]			0.3				1.9			2.2	0.8	0.6	0.9
12Ha	0.8	1.6						2.5		11.1			
12Hb, 16H[b]			0.2					1.7	2.6		0.3	0.4	
13H			1.3					1.0		0.9			
14H	1.2	0.6											3.0
17H	0.3	0.2										1.7	

(a) Protons 11 and 15 overlap
(b) Protons 12b and 16 overlap

The structure of isomer **C** was also determined using the NOESY and COSY spectra. Again, a strong coupling between protons 11 and 12 in the COSY spectrum indicated isomer **C** corresponded to one of the remaining bicyclo[4.3.0]nonene isomers of Figure 8. The complete nOe data is given in Table 4. Similar to isomer **B**, complete overlap between protons 12a and 14 and partial overlap between 12b and 15 limited the amount of reliable data that could be obtained. In contrast to isomer **B**, only a very weak nOe existed between methyl group 13 and proton 6, strongly suggesting a *trans*-configuration at the ring junction. Strong nOe's between methyl group 13 and both protons 2 and 3 indicated that the methyl group was 'down', while a nOe between protons 6 and 16 indicated proton 6 was 'up'. The structure of isomer **C** was therefore assigned to **96**. All other nOe's in Table 4 were in agreement with this assignment and no inexplicable nOe's were present.

Table 4: NOESY data for isomer C

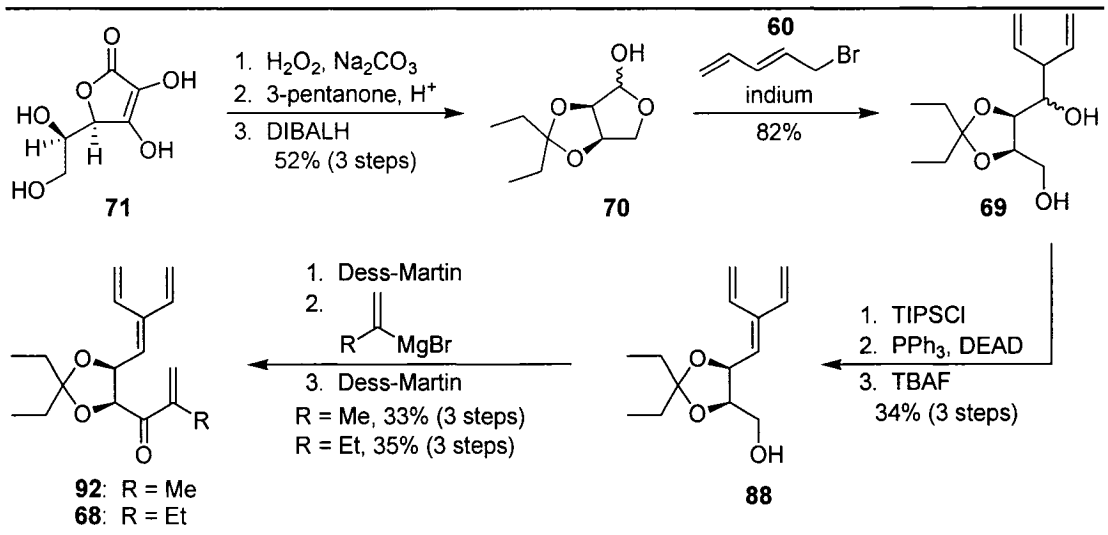


Proton(s) irradiated	2H	3H	6H	8H	9Ha	9Hb	10H	11H	12Ha, 14H[a]	12Hb, 15H[b]	13H	16H	17H
2H		1.8	0.7	0.5		1.3			1.2		2.4		0.4
3H	1.0		0.2						2.0		2.2		0.5
6H	0.6	0.2		0.3		0.4	0.2	0.2	2.3	0.9	0.3	1.1	
8H	0.5		0.3		2.3	2.3	2.8						
9Ha				2.6		10.6							
9Hb	1.4		0.4	2.7	10.9		0.7						
10H			0.2	2.8		0.7		3.2			0.3		
11H			0.1				2.7		1.8	1.9	1.4		
12Ha, 14H[a]	0.6	1.0	1.1					1.0		2.9		0.7	2.1
12Hb, 15H[b]			0.4					2.1	3.5		1.4	0.7	0.8
13H	1.1	1.0	0.2				0.2	1.0		0.9			
16H			0.5						0.5	2.0			1.7
17H	0.2	0.2							2.1	0.9			

(a) 12a and 14 overlap
(b) 12b and 15 overlap

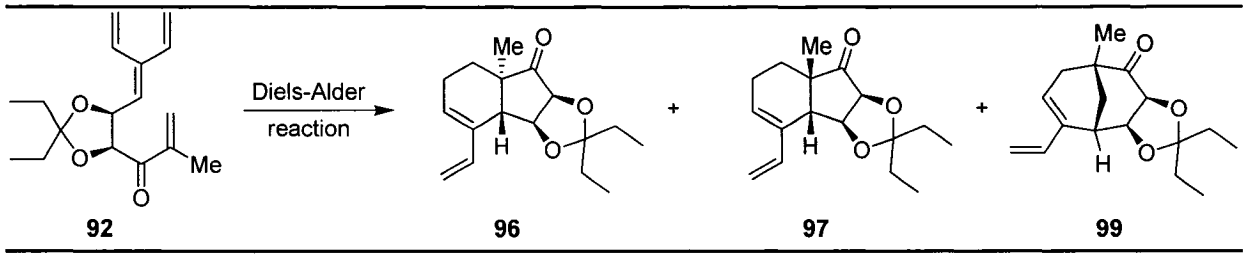
3 Summary and Conclusions

We have successfully synthesized methyl (**92**) and ethyl (**68**) substituted tetraenes in 10 steps from D-isoascorbic acid as precursors to the key tether-controlled intramolecular Diels-Alder reaction (Scheme 17). A key step in our approach was the synthesis of diol **69** from lactol **70** using an indium-mediated γ-pentadienylation, the chemistry of which had previously been developed in the Fallis laboratory. A three step sequence then yielded the crucial triene moiety necessary for the diene-transmissive Diels-Alder reaction, after which an additional three steps provided tetraenes **92** and **68**.



Scheme 17: Summary of synthesis of tetraenes 68 and 92

To our disappointment, the thermally-mediated Diels-Alder reaction of **92** (or **68**) was unselective, producing a mixture of three cycloaddition adducts in relatively equal proportions (Scheme 18). Unfortunately, both the Lewis acid and imine-catalyzed variants of the intramolecular Diels-Alder reaction failed to produce any product, thereby precluding their use as tools to increase the stereoselectivity. Clearly the isopentylidene tether-control group strategy is not useful for the stereospecific synthesis of hydrindanes, in contrast to its significant utility in the synthesis of decalins.



Scheme 18: Diels-Alder reaction of tetraene 92

The absence of the desired isomer **95** in the adduct mixture was also disappointing and surprising. As rationalized in Section 1.3, the intramolecular Diels-Alder reaction had been expected to yield, at worst, a mixture of enantiomeric *trans* bicyclo[4.3.0]nonenes **95** and **96**. The formation of bicyclo[3.3.1]nonene **99** was also highly unexpected. This appears to be the first time such a compound has resulted from an intramolecular Diels-Alder reaction of a nonatriene. Extensive reviews of intramolecular Diels-Alder reactions explicitly state that only fused bicyclo[4.3.0]nonenes result from related cycloadditions.[25]

The formation of such diverse products in similar quantities suggests that the competing transition states were roughly equal in energy. The formation of *cis*-bicyclo[4.3.0]nonene **97** occurred *via endo* transition state **68c** (Scheme 12) and implied that the anticipated unfavorable steric interactions described in Figure 5 were negligible. However, the facts that **97** was always the minor component of the mixture and that the other *cis* isomer (**98**) was never observed suggests that this interaction may have played a minor role in distinguishing between the transition states. An unfavorable interaction may also have existed between the R substituent and the ethyl groups of the acetal as two of the observed products, **96** and **99**, formed *via* transition states (**68b** and **92e**) where this interaction was minimized. However, the formation of *cis*-bicyclo[4.3.0]nonene **97** occurred *via endo* transition state **68c** in which this interaction was present, implying that the interaction was not particularly significant. Clearly no one steric interaction can adequately explain the results.

Evidently, a more complex interplay of steric and electronic factors than we had anticipated is occurring during the intramolecular Diels-Alder reaction of tetraene **68** or **92**. Although the list of Lewis acids and reaction conditions employed for the cycloaddition is far from extensive, the poor selectivities observed and the complete absence of the desired isomer from the reaction mixture precluded further study.

4 Experimental

4.1 General Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. Tetrahydrofuran was distilled from sodium/benzophenone. Dichloromethane, benzene and toluene were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. Starting materials were purchased from Aldrich Chemical Company and used without further purification unless otherwise stated. 2-Bromo-1-butene was purchased from Alfa Aesar Chemical Company and used as received.

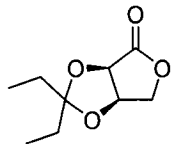
Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254} (E. Merck). TLC spots were developed by heating the plate after treatment with a 5% solution of phosphomolybdic acid in ethanol or a solution of $KMnO_4$ in aqueous potassium hydroxide. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry solutions in organic solvents. Excess solvents were removed (concentrated) *in vacuo* at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with E. Merck Silica Gel 60 (230-400 mesh). Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C.

Melting points were determined with a Thomas-Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were run on a Bruker AVANCE 500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. ^{1}H NMR data are reported as follows: Chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet), coupling constants (Hz), and integration). The multiplicity of each carbon atom in the ^{13}C NMR was determined using the DEPT 135 spectrum. Low resolution mass spectroscopy (MS) using electron impact (EI), was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV. High resolution mass spectroscopy

(HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam energy of 70 eV. The purity of all title compounds was judged to be >95% as determined by a combination of ^{1}H NMR and ^{13}C NMR analyses unless otherwise indicated.

4.2 Experimental Procedures for New Compounds

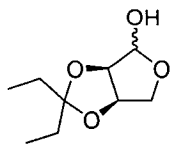
(3a*R*,6a*R*)-2,2-Diethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (84)



$C_9H_{14}O_4$
Mol. Wt.: 186.21

Diol **83** (14.0 g, 0.119 mol), 3-pentanone (125 mL, 1.19 mol), and *p*-TsOH·H_2O (2.00 g, 10.5 mmol) were dissolved in benzene (150 mL) and refluxed overnight using a Dean-Stark apparatus. The solution was then cooled to rt and the majority of solvent and excess 3-pentanone were removed by rotary evaporation at a bath temperature of ~50 °C. The remaining brown oil was distilled under aspirator pressure using a propane burner to provide the title compound as a pale brown oil (20.4 g, 92%) over a fluctuating temperature range of 160-200 °C (the aspirator pressure varied during the distillation). ^{1}H NMR (500 MHz, C_6D_6) δ 4.17-4.19 (m, 1H), 4.02-4.05 (m, 1H), 3.91 (d, J = 10.8 Hz, 1H), 3.54-3.58 (m, 1H), 1.56 (q, J = 7.5 Hz, 2H), 1.41 (q, J = 7.5 Hz, 2H), 0.86 (t, J = 7.5 Hz, 3H), 0.75 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0 (C), 117.7 (C), 75.6 (CH), 74.7 (CH), 70.3 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 7.9 (CH_3), 7.0 (CH_3); IR (neat): ν = 2976, 2946, 2880, 1785, 1465, 1183, 1107, 1069, 921 cm^{-1}; MS (EI) *m/z* 157 ($M^+ - C_2H_5$) (45), 57 (100), 29 (85); HRMS calculated for $C_7H_{11}O_4$ ($M^+ - C_2H_5$) 157.0501, found 157.0492.

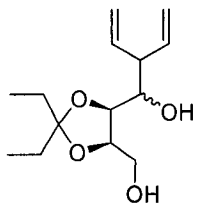
(3a*R*,6a*R*)-2,2-Diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (70)



$C_9H_{16}O_4$
Mol. Wt.: 188.22

Lactone **84** (19.0 g, 0.102 mol) was dissolved in CH_2Cl_2 (285 mL) and cooled to –78 °C. A 1.5 M solution of DIBALH in THF (81.6 mL, 0.122 mol) was added dropwise over a period of 15 min, after which time the solution was stirred for 5 h at –78 °C. The reaction was quenched at –78 °C with MeOH (16.0 mL) and brine (8.0 mL) and allowed to warm to rt. Ether (420 mL) and $MgSO_4$ (121 g) were then added under vigorous stirring and stirring was continued overnight. The mixture was then suction filtered and the filter cake washed generously with ether (~1.0 L) in several portions until the presence of product was no longer detected in the filtrate (use of a soxhlet extractor to extract the product from the filter cake was also effective). The solvent was removed under reduced pressure to yield a colorless oil identified as a 5:1 mixture of diastereomers of the title compound (16.7 g, 87%). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.79 (dd, J = 6.0 and 3.3 Hz, 1H), 4.53 (d, J = 6.0 Hz, 1H), 4.03-3.92 (m, 2H), 3.18 (br s, 1H), 1.65 (q, J = 7.5 Hz, 2H), 1.54 (q, J = 7.5 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.5 (C), 101.9 (CH), 85.3 (CH), 80.2 (CH), 72.1 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 8.3 (CH_3), 7.3 (CH_3); IR (neat): ν = 3425, 2975, 2943, 2883, 1464, 1102, 1075, 929 cm^{-1}; MS (EI) *m/z* 159 ($M^+ - C_2H_5$) (64), 85 (17), 57 (100), 29 (37); HRMS calculated for $C_7H_{11}O_4$ ($M^+ - C_2H_5$) 159.0657, found 159.0659.

1-((4*S*,5*R*)-2,2-Diethyl-5-(hydroxymethyl)-1,3-dioxolan-4-yl)-2-vinylbut-3-en-1-ol (69)

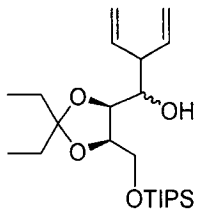


$C_{14}H_{24}O_4$
Mol. Wt.: 256.34

Lactol **70** (5.00 g, 26.6 mmol) was dissolved in DMF (15 mL), the solution was cooled to 0 °C, and 5-bromo-1,3-pentadiene (**60**) (15.6 g, 106 mmol) was added. Indium powder (100 mesh, 6.10 g, 53.1 mmol) was added to the vigorously stirred solution in small portions over a period of 55 min. The dark green mixture was then warmed to rt and stirred overnight. The reaction was poured into a vigorously stirred solution of ether (1000 mL) and water (3.2 mL) and stirred for a further 10 min. The mixture was then dried, filtered and concentrated. Column chromatography (4:1 PE:EA) yielded the title compound as a waxy solid mixture of diastereomers (5.55 g, 82%). Major diastereomer: mp: 42.5 – 44.0 °C. ^{1}H NMR (500 MHz, C_6D_6) δ 6.05-6.14 (m, 2H), 5.06-

5.26 (m, 4H), 4.15-4.23 (m, 2H), 3.92 (m, 1H), 3.69-3.74 (m, 1H), 3.56-3.60 (m, 1H), 3.33-3.37 (m, 2H), 2.73 (br s, 1H), 1.57 (q, J = 7.5 Hz, 2H), 1.51 (q, J = 7.5 Hz, 2H), 0.86 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.6 (CH), 136.1 (CH), 118.4 (CH_2), 116.4 (CH_2), 112.4 (C), 78.0 (CH), 77.7 (CH), 72.7 (CH), 61.9 (CH_2), 51.4 (CH), 30.5 (CH_2), 29.4 (CH_2), 9.2 (CH_3), 8.4 (CH_3); IR (neat): ν = 3323, 3245, 2940, 2916, 2880, 1459, 1173, 1081, 920 cm^{-1}; MS (EI) *m/z* 227 ($M^+ - C_2H_5$) (38), 209 (0.2), 159 (11), 87 (100), 57 (87); HRMS calculated for $C_{12}H_{19}O_4$ ($M^+ - C_2H_5$) 227.1284, found 227.1283.

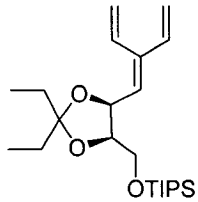
1-((4*S*,5*R*)-2,2-Diethyl-5-((triisopropylsilyloxy)methyl)-1,3-dioxolan-4-yl)-2-vinylbut-3-en-1-ol (86)



$C_{23}H_{44}O_4Si$
Mol. Wt.: 412.68

Diol **69** (19.0 g, 74.2 mmol) was dissolved in a mixture of DMF (65 mL) and THF (200 mL) and cooled to 0 °C. Imidazole (10.1 g, 149 mmol) and TIPSCl (23.8 mL, 111 mmol) were sequentially added and the solution was stirred overnight. Water was then added and the mixture extracted with ether. The ether extracts were washed once with saturated NH_4Cl, dried, filtered, and concentrated. Column chromatography (50:1 PE:EA) yielded the title compound as a colorless oil (28.62 g, 93%). Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6) δ 6.31-6.41 (m, 2H), 5.12-5.32 (m, 4H), 4.37-4.41 (m, 1H), 4.29-4.33 (m, 1H), 4.19 (ddd, J = 5.5, 2.5, and 0.5 Hz, 1H), 4.00 (t, J = 10.2 Hz, 1H), 3.96 (dd, J = 3.3 and 1.3 Hz, 1H), 3.73 (dd, J = 10.3 and 3.4 Hz, 1H), 3.46 (t, J = 7.8 Hz, 1H), 1.64 (dq, J = 7.5 and 1.5 Hz, 2H), 1.58 (q, J = 7.5 Hz, 2H), 0.92-1.00 (m, 21H), 0.93 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.5 (CH), 137.2 (CH), 117.6 (CH_2), 115.6 (CH_2), 112.5 (C), 78.6 (CH), 77.9 (CH), 72.8 (CH), 63.6 (CH), 51.9 (CH), 30.7 (CH_2), 29.4 (CH_2), 18.29 (CH_3), 18.28 (CH_3), 12.7 (CH), 12.4 (CH), 9.3 (CH_3), 8.5 (CH_3); IR (neat): ν = 3467, 2965, 2940, 2867, 1638 cm^{-1}; MS (EI) *m/z* 383 ($M^+ - C_2H_5$) (8), 187 (53), 131 (56), 67 (100); HRMS calculated for $C_{21}H_{39}O_4Si$ ($M^+ - C_2H_5$) 383.2618, found 383.2628

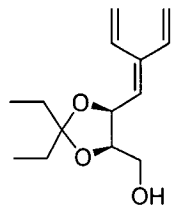
[((4*R*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)methoxy]triisopropylsilane (87)



$C_{23}H_{42}O_3Si$
Mol. Wt.: 394.66

Allylic alcohol **86** (22.0 g, 53.3 mmol) was dissolved in benzene (1.20 L), cooled to 0 °C, and PPh_3 (41.9 g, 160 mmol) and DEAD (25.2 mL, 160 mmol) were successively added. The solution was refluxed for 2 d and the majority of the solvent was removed *in vacuo* to yield a red oil. A slurry of silica gel (30:1 PE:EA) was then added and the mixture was quickly filtered through a thin (~7 cm) plug of silica gel to remove the majority of reaction byproducts. The silica gel plug was washed (30:1 PE:EA) until no additional product was detected in the filtrate. The washes were combined and concentrated, PE was added, and the triphenylphosphine oxide precipitate was filtered off and discarded. Rapid column chromatography (100:1 PE:EA) yielded the title compound as a colorless oil (9.36 g, 44%). Due to the instability of the product in common NMR solvents, clean NMR spectra could not be obtained. IR (neat): ν = 3089, 2867, 2943, 2867, 1464, 1129, 1087, 939, 883 cm^{-1}; MS (EI) *m/z* 394 (M^+) (19), 265 (100), 108 (84); HRMS calculated for $C_{23}H_{42}O_3Si$ (M^+) 394.2903, found 394.2925

((4*R*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)methanol (88)

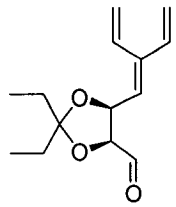


$C_{14}H_{22}O_3$
Mol. Wt.: 238.32

Triene **87** (13.7 g, 34.7 mmol) was dissolved in THF (300 mL), cooled to 0 °C, and a 1.0 M solution of TBAF in THF (41.7 mL, 41.7 mmol) was added dropwise over a period of two min. The reaction was stirred at 0 °C for 1 h. After warming to rt, the reaction was diluted with water and the organics were extracted with ether, dried, filtered and concentrated. Column chromatography (9:1 PE:EA) yielded the title compound as a colorless oil (6.79 g, 82%). ^1H

NMR (500 MHz, C_6D_6) δ 6.27 (dd, J = 17.4 and 10.7 Hz, 1H), 6.23 (dd, J = 17.6 and 11.2 Hz, 1H), 5.25 (dd, J = 17.4 and 1.3 Hz, 1H), 5.16 (d, J = 17.5 Hz, 1H), 5.10 (d, J = 11.2 Hz, 1H), 5.02 (m, 1H), 4.96 (d, J = 10.7 Hz, 1H), 4.13 (dd, J = 11.5 and 7.0 Hz, 1H), 3.47-3.57 (m, 2H), 2.16 (br s, 1H), 1.70 (q, J = 7.5 Hz, 2H), 1.58 (q, J = 7.5 Hz, 2H), 0.97 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 141.2 (C), 138.1 (CH), 132.2 (CH), 128.0 (CH), 119.8 (CH_2), 116.4 (CH_2), 113.1 (C), 79.9 (CH), 74.5 (CH), 62.8 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 9.3 (CH_3), 8.5 (CH_3); IR (neat): ν = 3431, 3090, 2975, 2941, 2882, 1604, 1173, 1077, 1041, 927 cm^{-1}; MS (EI) *m/z* 238 (M^+) (4), 135 (38), 108 (38), 91 (78), 57 (100), 29 (88); HRMS calculated for $C_{14}H_{22}O_3$ (M^+) 238.1569, found 238.1551.

(4*S*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolane-4-carbaldehyde (89)

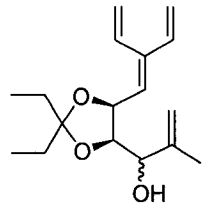


$C_{14}H_{20}O_3$
Mol. Wt.: 236.31

Trienol **88** (1.50 g, 6.29 mmol) was dissolved in CH_2Cl_2 (60 mL) and Dess-Martin reagent (5.45 g, 13.2 mmol) was added. The solution was stirred for 30 min at rt, and then water (0.113 mL, 6.29 mmol) was added. A white precipitate formed within a few min. After a further 15 min of stirring the reaction was quenched with a 1:1 mixture of 2 M $Na_2S_2O_3$ and saturated $NaHCO_3$ and the reaction was extracted with CH_2Cl_2. The organics were then dried, filtered and concentrated. Column chromatography (12:1 PE:EA) yielded the title compound as a colorless oil (1.11 g, 74%). ^{1}H NMR (500 MHz, C_6D_6) δ 9.45 (d, J = 3.5 Hz, 1H), 6.17$_1$ (dd, J = 17.4 and 10.7 Hz, 1H), 6.16$_7$ (dd, J = 17.6 and 11.2 Hz, 1H), 5.51 (d, J = 9.0 Hz, 1H), 5.22 (dd, J = 17.6 and 1.9 Hz, 1H), 5.20 (dd, J = 17.4 and 0.9 Hz, 1H), 5.12 (dd, J = 11.2 and 1.7 Hz, 1H), 5.10 (t, J = 8.5 Hz, 1H), 4.94 (dd, J = 10.7 and 0.9 Hz, 1H), 4.08 (dd, J = 8.0 and 3.5 Hz, 1H), 1.75 (q, J = 7.5 Hz, 2H), 1.48 (q, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.5 (C), 142.7 (C), 137.7 (CH), 132.0 (CH), 125.7 (CH), 120.6 (CH_2), 117.2 (CH_2), 115.7 (C), 83.5 (CH), 76.2 (CH), 30.2 (CH_2), 29.5 (CH_2), 9.1 (CH_3), 8.5 (CH_3); IR (neat): ν = 3093, 2976, 2942, 2884, 2812, 1736, 1464, 1172, 1075, 924 cm^{-1}; MS (EI) *m/z* 207

($M^+ - C_2H_5$) (11), 133 (31), 99 (100), 57 (95), 29 (53); HRMS calculated for $C_{12}H_{15}O_3$ ($M^+ - C_2H_5$) 207.1021, found 207.1016.

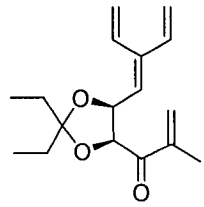
1-((4*R*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol (90)



$C_{17}H_{26}O_3$
Mol. Wt.: 278.39

2-Bromopropene (1.00 mL, 11.3 mmol) was dissolved in THF (10 mL) and added dropwise to a flask containing freshly washed (sequentially with 10% HCl, water, and acetone) and dried magnesium turnings (0.270 g, 11.3 mmol) in THF (10 mL). A small chip of iodine was added to initiate the Grignard reaction. When the Grignard had fully formed (as indicated visually by the complete consumption of Mg), 1.1 eq. of it (13.3 mL, 7.49 mmol) was added dropwise to a solution of aldehyde **89** (1.61 g, 6.83 mmol) in THF (90 mL). The resultant pale yellow solution was stirred for 45 min. The reaction was quenched with saturated NH_4Cl, extracted with ether, dried, filtered and concentrated. Column chromatography (30:1 PE:EA) yielded the title compound as an oily solid mixture of diastereomers (1.10 g, 58%). Major diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 6.36 (dd, J = 17.3 and 10.7 Hz, 1H), 6.29 (dd, J = 17.6 and 11.2 Hz, 1H), 6.13 (d, J = 9.1 Hz, 1H), 5.34 (dd, J = 17.3 and 1.5 Hz, 1H), 5.21 (dd, J = 17.7 and 1.8 Hz, 1H), 5.14 (ddd, J = 11.2, 1.9 and 0.7 Hz, 1H), 5.09 (dd, J = 9.1 and 7.3 Hz, 1H), 5.01 (dd, J = 10.7 and 1.5 Hz, 1H), 5.01 (quintet, J = 0.9 Hz, 1H), 4.87 (t, J = 1.5 Hz, 1H), 4.10 (dd, J = 7.9 and 3.1 Hz, 1H), 2.58 (d, J = 6.9 Hz, 1H), 1.74 (q, J = 7.5 Hz, 2H), 1.73 (s, 3H), 1.58 (q, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H), (OH not detected); ^{13}C NMR (125 MHz, C_6D_6) δ 146.0 (C), 141.0 (C), 138.2 (CH), 132.4 (CH), 129.1 (CH), 119.5 (CH_2), 116.5 (CH_2), 113.2 (CH_2), 112.9 (C), 80.5 (CH), 75.0 (CH), 74.1 (CH), 30.0 (CH_2), 28.8 (CH_2), 19.2 (CH_3), 9.3 (CH_3), 8.6 (CH_3); IR (neat): ν = 3422, 3089, 2973, 2941, 1648, 1460, 1172, 1073 cm^{-1}; MS (EI) *m/z* 278 (M^+) (0.1), 249 (5), 121 (52), 105 (85), 91 (65), 57 (100), 29 (63); HRMS calculated for $C_{15}H_{21}O_3$ ($M^+ - C_2H_5$) 249.1491, found 249.1488.

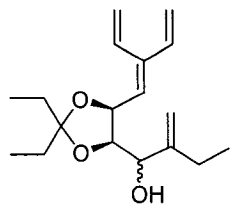
1-((4*S*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-one (92)



$C_{17}H_{24}O_3$
Mol. Wt.: 276.37

Allylic alcohol **90** (1.10 g, 3.96 mmol) was dissolved in CH_2Cl_2 (60 mL) and Dess-Martin reagent (3.35 g, 8.12 mmol) was added. The solution was stirred for 30 min at rt, and then water (0.071 mL, 3.96 mmol) was added. A white precipitate formed within a few min. After a further 15 min of stirring the reaction was quenched with a solution of 2 M $Na_2S_2O_3$ and saturated $NaHCO_3$ (1:1) and the reaction was extracted with CH_2Cl_2. The organics were dried, filtered and concentrated. Column chromatography (30:1 PE:EA) yielded the title compound as a colorless oil (0.85 g, 78%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.20 (dd, J = 17.6 and 11.2 Hz, 1H), 6.12 (dd, J = 17.3 and 10.7 Hz, 1H), 5.58 (d, J = 9.7 Hz, 1H), 5.33 (s, 1H), 5.10-5.23 (m, 6H), 4.88 (d, J = 10.7 Hz, 1H), 2.01 (qd, J = 7.5 and 2.4 Hz, 2H), 1.69 (t, J = 0.6 Hz, 3H), 1.65 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.5 (C), 144.9 (C), 141.3 (C), 137.7 (CH), 132.0 (CH), 127.8 (CH), 124.5 (CH_2), 119.8 (CH_2), 117.0 (CH_2), 115.3 (C), 80.3 (CH), 75.0 (CH), 30.5 (CH_2), 29.6 (CH_2), 18.3 (CH_3), 9.3 (CH_3), 8.9 (CH_3); IR (neat): ν = 3091, 2974, 2942, 2883, 1693, 1463, 1173, 1071, 1056, 930 cm^{-1}; MS (EI) *m/z* 276 (M^+) (0.2), 247 (11), 139 (50), 69 (100), 57 (44), 41 (58), 29 (33); HRMS calculated for $C_{15}H_{19}O_3$ ($M^+ - C_2H_5$) 247.1334, found 247.1334.

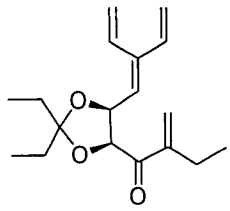
1-((4*R*,5*S*)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)-2-methylenebutan-1-ol (91)



$C_{18}H_{28}O_3$
Mol. Wt.: 292.41

The title compound was prepared analogously to the methyl analogue (**90**) using the following quantities: Aldehyde **89** (1.00 g, 4.23 mmol); 2-bromomagnesium-1-butene (9.30 mL, 0.50 M, 4.66 mmol); THF (60 mL). Column chromatography (30:1 PE:EA) provided the title compound as a colorless oil (0.655 g, 53%). Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6) δ 6.33 (ddd, *J* = 17.3, 10.7 and 0.6 Hz, 1H), 6.26 (dd, *J* = 17.5 and 11.2 Hz, 1H), 6.10 (d, *J* = 9.1 Hz, 1H), 5.32 (dd, *J* = 17.4 and 1.5 Hz, 1H), 5.19 (dd, *J* = 17.3 and 1.9 Hz, 1H), 5.05-5.13 (m, 3H), 4.98 (dd, *J* = 10.7 and 1.5 Hz, 1H), 4.89 (m, 1H), 4.21 (dd, *J* = 7.3 and 3.9 Hz, 1H), 4.10-4.13 (m, 1H), 2.08-2.16 (m, 1H), 1.93-2.01 (m, 1H), 1.72 (q, *J* = 7.5 Hz, 2H), 1.57 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.96_8 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H), (OH group not detected); ^{13}C NMR (125 MHz, C_6D_6) δ 151.2 (C), 140.9 (C), 138.2 (CH), 132.4 (CH), 129.2 (CH), 119.4 (CH_2), 116.4 (CH_2), 112.9 (CH_2), 110.9 (C), 80.6 (CH), 75.0 (CH), 73.7 (CH), 30.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 12.7 (CH_3), 9.3 (CH_3), 8.6 (CH_3); IR (neat): ν = 3475, 3089, 2971, 2940, 2882, 1463, 1172, 1074, 1056, 928 cm^{-1}; MS (EI) *m/z* 263 ($M^+ - C_2H_5$) (3), 149 (34), 121 (54), 105 (74), 91 (61), 57 (100), 29 (79); HRMS calculated for $C_{16}H_{23}O_3$ ($M^+ - C_2H_5$) 263.1647, found 263.1664.

1-((4S,5S)-2,2-Diethyl-5-(2-vinylbuta-1,3-dienyl)-1,3-dioxolan-4-yl)-2-methylenebutan-1-one (68)



$C_{18}H_{26}O_3$
Mol. Wt.: 290.4

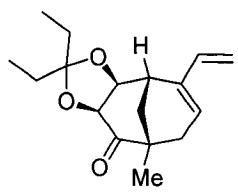
The title compound was prepared analogously to the methyl analogue (**92**) using the following quantities: Allylic alcohol **91** (0.300 g, 1.03 mmol); Dess-Martin periodinane (0.888 g, 2.15 mmol); H_2O (18 μL, 1.03 mmol); CH_2Cl_2 (15 mL). Column chromatography (30:1 PE:EA) provided the title compound as a colorless oil (0.215 g, 72%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.20 (dd, *J* = 17.6 and 11.2 Hz, 1H), 6.12 (ddd, *J* = 17.4, 10.7 and 0.6 Hz, 1H), 5.59 (d, *J* = 9.6 Hz, 1H), 5.40 (s, 1H), 5.10-5.25 (m, 6H), 4.88 (dd, *J* = 10.6 and 1.5 Hz, 1H), 2.19 (qq, *J* = 7.5 and 0.8 Hz, 2H), 2.01 (dq, *J* = 7.5 and 2.4 Hz, 2H), 1.65 (dq, *J* = 7.5 and 1.1 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.2

(C), 150.5 (C), 141.2 (C), 137.8 (CH), 132.1 (CH), 127.9 (CH), 123.2 (CH_2), 119.9 (CH_2), 116.9 (CH_2), 115.2 (C), 80.2 (CH), 75.1 (CH), 30.5 (CH_2), 29.7 (CH_2), 24.9 (CH_2), 13.0 (CH_3), 9.3 (CH_3), 8.9 (CH_3); IR (neat): ν = 3091, 2973, 2940, 2882, 1692, 1463, 1173, 1078, 930 cm^{-1}; MS (EI) *m/z* 290 (M^+) (0.1), 261 (6), 153 (28), 83 (100), 55 (73), 29 (62); HRMS calculated for $C_{16}H_{21}O_3$ ($M^+ - C_2H_5$) 261.1491, found 261.1508.

The intramolecular Diels-Alder reaction of 92:

Tetraene **92** (0.051 g, 0.185 mmol) was dissolved in toluene (20 mL) and the solution was purged with argon for 20 min. The solution was then placed in the microwave reactor (program: 300 W power, ramped temperature to 150 °C in 15 min, then held at 150 °C for 3 h). After allowing the reaction to cool to near rt, the toluene was removed under reduced pressure. Column chromatography (20:1 PE:EA) afforded a 41:20:39 mixture of Diels-Alder adducts (0.039 g, 78%) (Table 1, entry 6). A pure sample of each isomer was obtained by exhaustive preparative HPLC (2% hexanes in ethyl acetate; Waters Nova-Pak 19 x 300 mm silica (6 um) column).

(1*R*,2*S*,6*S*,8*R*)-4,4-Diethyl-8-methyl-11-vinyl-3,5-dioxatricyclo[6.3.1.$0^{2,6}$]dodec-10-en-7-one (99)

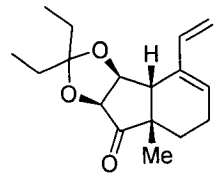


$C_{17}H_{24}O_3$
Mol. Wt.: 276.37

T_r = 64.5 min; ^1H NMR (500 MHz, C_6D_6) δ 6.08 (dd, *J* = 17.7 and 10.9 Hz, 1H), 5.26 (dd, *J* = 4.3 and 4.3 Hz, 1H), 5.16 (d, *J* = 17.7 Hz, 1H), 4.87 (d, *J* = 10.9 Hz, 1H), 4.49 (dt, *J* = 6.3 and 2.2 Hz, 1H), 3.95 (d, *J* = 6.3 Hz, 1H), 3.00 (d, *J* = 2.2 Hz, 1H), 2.37 (dt, *J* = 13.2 and 1.9 Hz, 1H), 1.96 (dd, *J* = 19.6 and 4.6 Hz, 1H), 1.71 (q, *J* = 7.6 Hz, 2H), 1.65 (dd, *J* = 19.6 and 1.1 Hz, 1H), 1.50 (qd, *J* = 7.6 and 2.4 Hz, 1H), 1.22 (ddd, *J* = 13.2, 3.6, and 1.8 Hz, 1H), 1.10 (s, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.8 (C), 137.6 (CH), 136.9 (C), 130.2 (CH), 114.5 (C), 111.3 (CH_2), 78.8 (CH), 77.4 (CH), 43.1 (C), 38.2 (CH_2), 32.6 (CH), 30.7 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 25.0 (CH_3), 8.7 (CH_3), 8.6 (CH_3); MS

(EI) *m/z* 276 (M^+) (1), 247 (77), 191 (19), 145 (38), 119 (54), 105 (27), 91 (15), 57 (100); HRMS calculated for $C_{15}H_{19}O_3$ ($M^+ - C_2H_5$) 247.1334, found 247.1314.

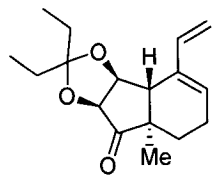
(3a*S*,3b*R*,7a*S*,8a*S*)-2,2-Diethyl-7a-methyl-4-vinyl-7,7a-dihydro-3a*H*-indeno[2,1-*d*][1,3]dioxol-8(3b*H*,6*H*,8a*H*)-one (97)



$C_{17}H_{24}O_3$
Mol. Wt.: 276.37

T_r = 70.0 min; ^{1}H NMR (500 MHz, C_6D_6) δ 6.26 (dd, *J* = 17.7 and 11.1 Hz, 1H), 5.66 (d, *J* = 17.7 Hz, 1H), 5.49 (t, *J* = 4.3 Hz, 1H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.29 (dd, *J* = 6.9 and 2.8 Hz, 1H), 4.23 (dd, *J* = 6.9 and 0.5 Hz, 1H), 2.80 (br s, 1H), 1.65 (q, *J* = 7.5 Hz, 2H), 1.70-1.53 (m, 2H), 1.47 (q, *J* = 7.5 Hz, 2H), 1.22 (ddd, *J* = 13.0, 8.4 and 5.5 Hz, 1H), 1.10 (s, 3H), 0.97-0.93 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 215.6 (C), 138.7 (CH), 136.0 (C), 130.0 (CH), 116.8 (C), 112.8 (CH_2), 80.7 (CH), 79.7 (CH), 48.7 (C), 46.6 (CH), 30.0 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 22.0 (CH_2), 22.0 (CH_3), 8.6 (CH_3), 8.2 (CH_3); MS (EI) *m/z* 276 (M^+) (2), 247 (44), 191 (8), 162 (12), 145 (34), 119 (100), 105 (24), 57 (50), 43 (32); HRMS calculated for $C_{17}H_{24}O_3$ (M^+) 276.1725, found 276.1748.

(3a*S*,3b*R*,7a*R*,8a*S*)-2,2-Diethyl-7a-methyl-4-vinyl-7,7a-dihydro-3a*H*-indeno[2,1-*d*][1,3]dioxol-8(3b*H*,6*H*,8a*H*)-one (96)



$C_{17}H_{24}O_3$
Mol. Wt.: 276.37

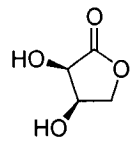
T_r = 72.0 min; ^{1}H NMR (500 MHz, C_6D_6) δ 6.37 (ddd, *J* = 17.8, 11.5 and 0.8 Hz, 1H), 5.93 (d, *J* = 17.8 Hz, 1H), 5.39 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 11.5 Hz, 1H), 4.59 (ddd, *J* = 7.6, 7.6 and 1.4 Hz, 1H), 4.49 (d, *J* = 7.6 Hz, 1H), 2.67 (br dd, *J* = 8.3 and 2.9 Hz, 1H), 1.84-1.74 (m, 2H), 1.63 (qd, *J* = 7.6 and 2.9 Hz, 2H), 1.60-1.57 (m, 1H), 1.51-1.45 (m, 1H), 1.46 (q, *J*= 7.6 Hz, 2H),

0.92 (t, J = 7.6 Hz, 3H), 0.81 (t, J = 7.6 Hz, 3H), 0.58 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.6 (C), 137.5 (CH), 135.4 (C), 127.9 (CH), 118.5 (C), 113.6 (CH_2), 79.9 (CH), 77.4 (CH), 51.8 (C), 50.8 (CH), 29.5 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 23.4 (CH_2), 15.3 (CH_3), 8.7 (CH_3), 7.8 (CH_3); MS (EI) *m/z* 276 (M^+) (0.1), 247 (38), 181 (30), 145 (16), 119 (46), 99 (14), 43 (100); HRMS calculated for $C_{15}H_{19}O_3$ ($M^+ - C_2H_5$) 247.1334, found 247.1342.

4.3 Experimental Procedures for Previously Reported Compounds

Experimental procedures and ^{1}H NMR data for previously reported compounds synthesized in this thesis are presented for convenience in this section. Full characterization data is available in the indicated references.

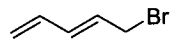
3,4-Dihydroxydihydrofuran-2-one (83)[38]



$C_4H_6O_4$
Mol. Wt.: 118.09

D-Isoascorbic acid (**71**) (35.0 g, 0.200 mol) was dissolved in H_2O (500 mL) and cooled to 0 °C. Sodium carbonate (42.4 g, 0.400 mol) was then added in small portions (CAUTION: gas evolution). Hydrogen peroxide (30% by wt., 46.0 mL, 0.450 mol) was then slowly added over a period of 10 min (CAUTION: exothermic). The reaction was then heated in a water bath at 42 °C for 30 min. Powdered charcoal (8 g) was then carefully added (CAUTION: gas evolution) and the solution was heated over a steam bath (reaction temp 75 – 78 °C) until a starch-iodide test was negative for peroxide. The solution was then filtered through a Celite pad (wash H_2O) and acidified with 6 N HCl (150 mL). The solvent was then removed under reduced pressure and the resultant solid was repeatedly triturated with hot EA. After removal of all solvent, recrystallization from EA afforded colorless needles of the title compound (15.4 g, 65%). ^{1}H NMR (500 MHz, D_2O) δ 4.77 (d, J = 4.9 Hz, 1H), 4.65 (dd, J = 4.9 and 3.0 Hz, 1H), 4.59 (dd, J = 10.8 and 3.0 Hz, 1H), 4.43 (d, J = 10.8 Hz, 1H).

(E)-5-Bromopenta-1,3-diene (60)[48]



C_5H_7Br
Mol. Wt.: 147.01

1,4-Pentadien-3-ol (50.0 g, 0.594 mol) was cooled to 0 °C and an aqueous solution of HBr (48% by wt., 75.0 mL, 0.654 mol) was added dropwise over a period of 10 min. Once the addition was complete, the ice bath was removed and the reaction was stirred for 1 h at rt. The reaction was then poured into a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with ether (3 x 20 mL). The organics were combined, dried and filtered. Vacuum distillation at rt using a water aspirator removed the majority of the ether, and rapid heating (under aspirator pressure) isolated the product as a pale yellow oil (T ~ 75 °C; dependent on aspirator pressure). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37-6.24 (m, 2H), 5.91-5.84 (m, 1H), 5.27-5.24 (m, 1H), 5.15-5.13 (m, 1H), 4.09 (d, J = 8.6 Hz, 2H).

[48] Prevost, C.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim. Fr.* **1964**, *101*, 2485-2492.

SECTION B

THE DESIGN AND ASYMMETRIC SYNTHESIS OF THE FIRST ACETYLENIC ALLENOPHANE

5 Introduction

The design and asymmetric synthesis of the first acetylenic allenophane is presented in the second section of this thesis. An introduction to cyclophanes and the use of palladium- and copper-mediated couplings in the formation of new carbon-carbon bonds will be presented first. These topics are also highly relevant to the third section of this thesis. A discussion of allenophanes and the asymmetric synthesis of allenes will conclude the introduction. Our design of an acetylenic allenophane, our synthetic approaches to such a target, and our successful asymmetric synthesis of the first acetylenic allenophane will then be presented and discussed.

5.1 Cyclophanes

Cyclophanes are defined as "molecules with at least one aromatic ring bridged by at least one aliphatic *n*-membered bridge".[49] The first two cyclophanes, [2.2]metacyclophane[50] (**100**) and [2.2]*para*cyclophane[51] (**101**) were reported in 1899 and 1949 by Pellegrin and Brown, respectively. However, it was not until the work of Cram in 1951 that the term cyclophane, a contraction of the words *cyclo*, *ph*enyl, and alk*ane*, was introduced.[52] A comprehensive nomenclature system was later developed by Vögtle and is still in use today.[53]

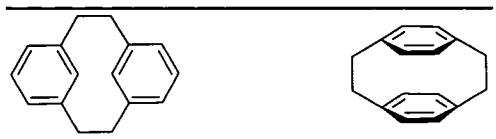


Figure 9: [2.2]metacyclophane (100) and [2.2]paracyclophane (101)

Many different types of cyclophane have been designed and synthesized since these early reports. Several have been developed for specific applications, some examples of which are

[49] Weber, E. *Top. Curr. Chem.* **1994**, *172*, preface.
[50] Pellegrin, M. *Recl. Trav. Pays-Bas* **1899**, *18*, 457.
[51] Brown, C. J.; Farthing, A. C. *Nature* **1949**, *164*, 915.
[52] Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704.
[53] (a) Vögtle, F.; Neumann, P. *Tetrahedron Lett.* **1969**, *10*, 5329-5334; (b) Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847-5873.

illustrated in Figure 10. Acetylenic cyclophane **102** and related structures have been shown to form discoid nematic liquid crystalline phases over a wide temperature range.[54] Water soluble cyclophane **103**, based on the [2.2]paracyclophane moiety, has been developed for use in fluorescent sensor applications.[55] Imino alcohol **104** has been used as a catalyst for the asymmetric addition of phenyl groups to aryl imines,[56] while carboxylic acid **105** has found use as a catalyst for the asymmetric reduction of pyrimidyl aldehydes to the corresponding alcohols.[57] Carbamate **106** is a useful chiral auxiliary in Diels-Alder, Michael, and aldol reactions,[58] while the rhodium complex of phosphonite **107** is a highly selective catalyst for the asymmetric hydrogenation of dehydroamino acids and esters.[59]

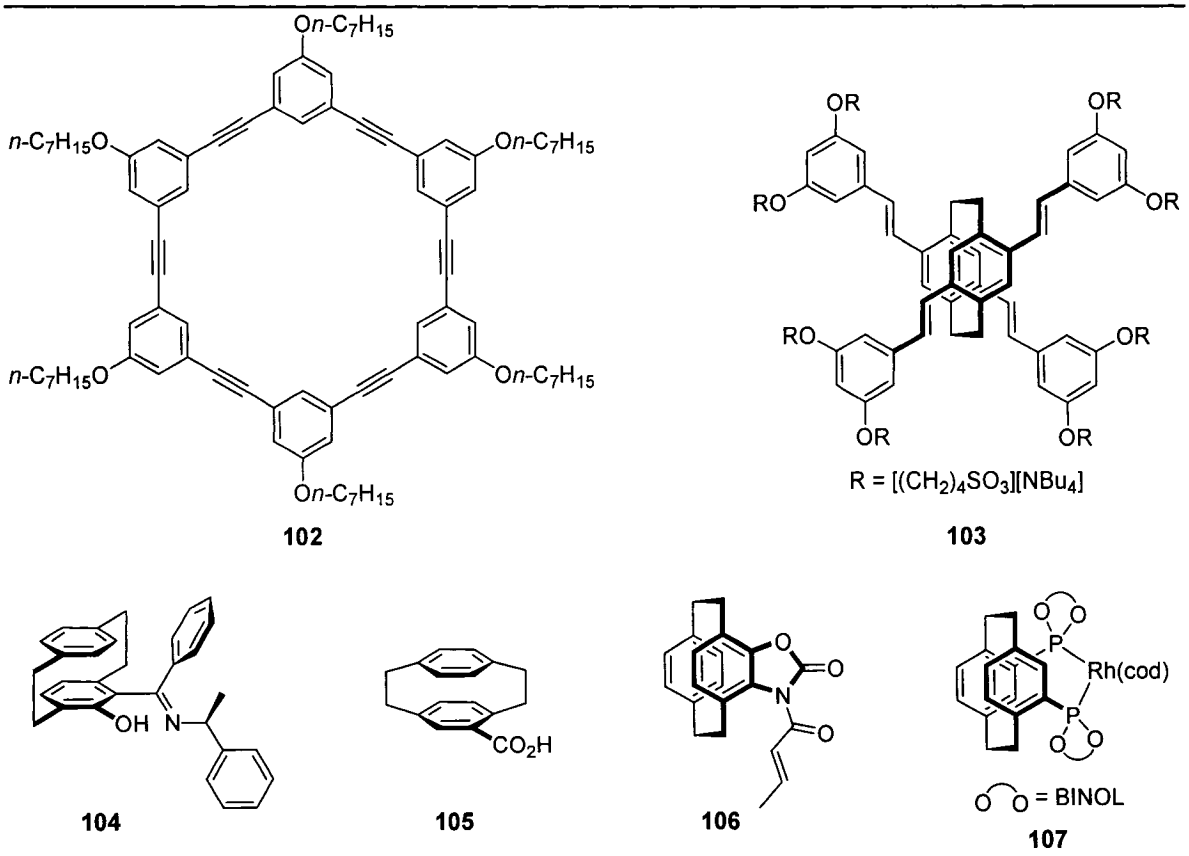


Figure 10: Cyclophanes used in specific chemical applications

[54] Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 2655-2656.
[55] Hong, J. W.; Gaylord, B. S.; Bazan, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 11868-11869.
[56] Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 3692-3694.
[57] Tanji, S.; Ohno, A.; Sato, I.; Soai, K. *Org. Lett.* **2001**, *3*, 287-289.
[58] Cipiciani, A.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **2002**, *67*, 2665-2670.
[59] Zanotti-Gerosa, A.; Malan, C.; Herzberg, D. *Org. Lett.* **2001**, *3*, 3687-3690.

An additional reason for synthesizing many cyclophanes is to develop new methods and strategies for overcoming the challenges associated with their syntheses. The chemical knowledge gained during the synthesis is often applicable to other areas of chemistry. A quick glance at the complex and aesthetically pleasing structures in Figure 11 provides an appreciation for the unique and diverse synthetic problems that may be encountered during synthesis. The difficulty of synthesizing molecules with such high symmetry is an aspect of cyclophane chemistry that is often underappreciated. Furthermore, the complex and rigid structure of these cyclophanes often provides basic information about molecular structure and chemical bonding. The bond strain and molecular structure of cyclophanes **108**[60] (befittingly termed a "superphane")[61] and **109**[62], as well as the conjugation and aromatic properties of strained pyrenophane **110**[63] and **111**[64] (a molecular "bracelet") are of high interest. The latter two (**110** and **111**) are also of interest for the synthesis of aromatic or Vögtle "belts".

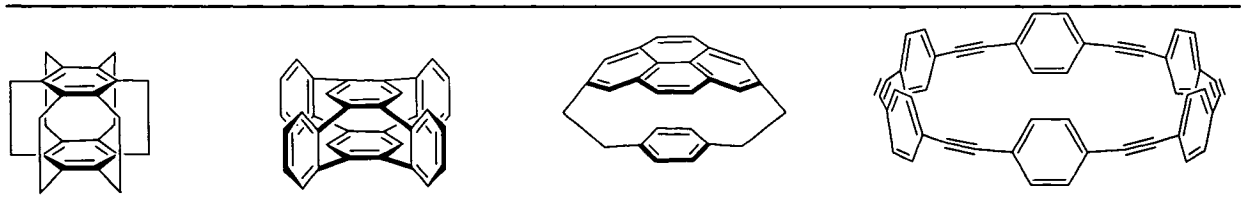


Figure 11: Synthetically challenging and aesthetically pleasing cyclophanes

In recent years, chiral, non-racemic cyclophanes have attracted considerable attention. When appropriately substituted, these cyclophanes may be useful as chiral catalysts or as chiral hosts for metal atoms or small molecules. Studies of their physical, spectroscopic, and optical properties are also of high interest.

Chirality in many chiral cyclophanes is derived from an asymmetrically substituted [2.2]paracyclophane core. A few cyclophanes adopt helical conformations that make them helically chiral, although this chirality is often caused by the presence of a chiral directing group. Multiple examples of chiral [2.2]paracyclophane-based cyclophanes are illustrated in Figure 10,

[60] Sekine, Y.; Boekelheide, V. *J. Am. Chem. Soc.* **1981**, *103*, 1777-1785.
[61] *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, 2004
[62] Brettreich, M.; Bendikov, M.; Chaffins, S.; Perepichka, D. F.; Dautel, O.; Duong, H.; Helgeson, R.; Wudl, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 3688-3691.
[63] Bodwell, G. J.; Miller, D. O.; Vermeij, R. J. *Org. Lett.* **2001**, *3*, 2093-2096.
[64] Kawase, T.; Ueda, N.; Tanaka, K.; Seirai, Y.; Oda, M. *Tetrahedron Lett.* **2001**, *42*, 5509-5511.

while a couple of helically chiral cyclophanes that were isolated as single enantiomers are presented in Figure 12. In cyclophane **112** the helical chirality arises from the two helicene moieties,[65] while in cyclophane **113** the helical chirality is derived from the two binaphthyl moieties.[66]

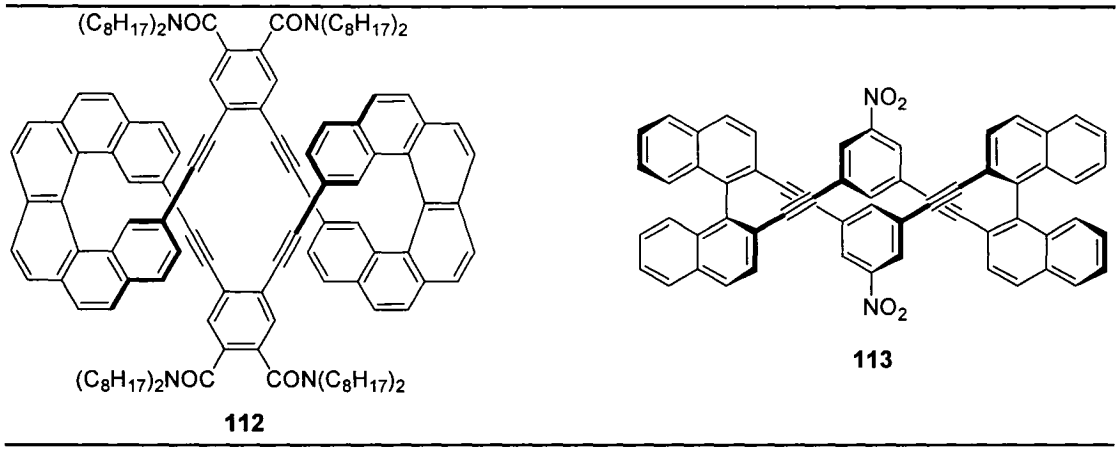


Figure 12: Helically chiral cyclophanes

5.2 Previous Fallis Laboratory Cyclophane Chemistry

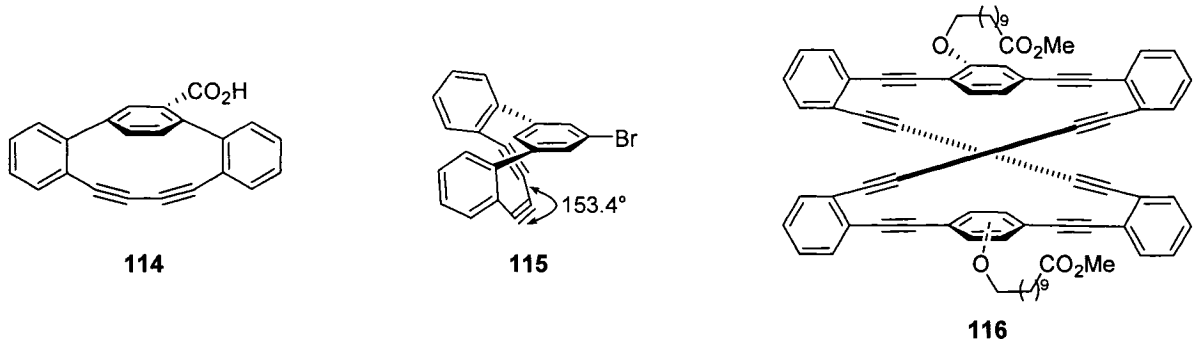


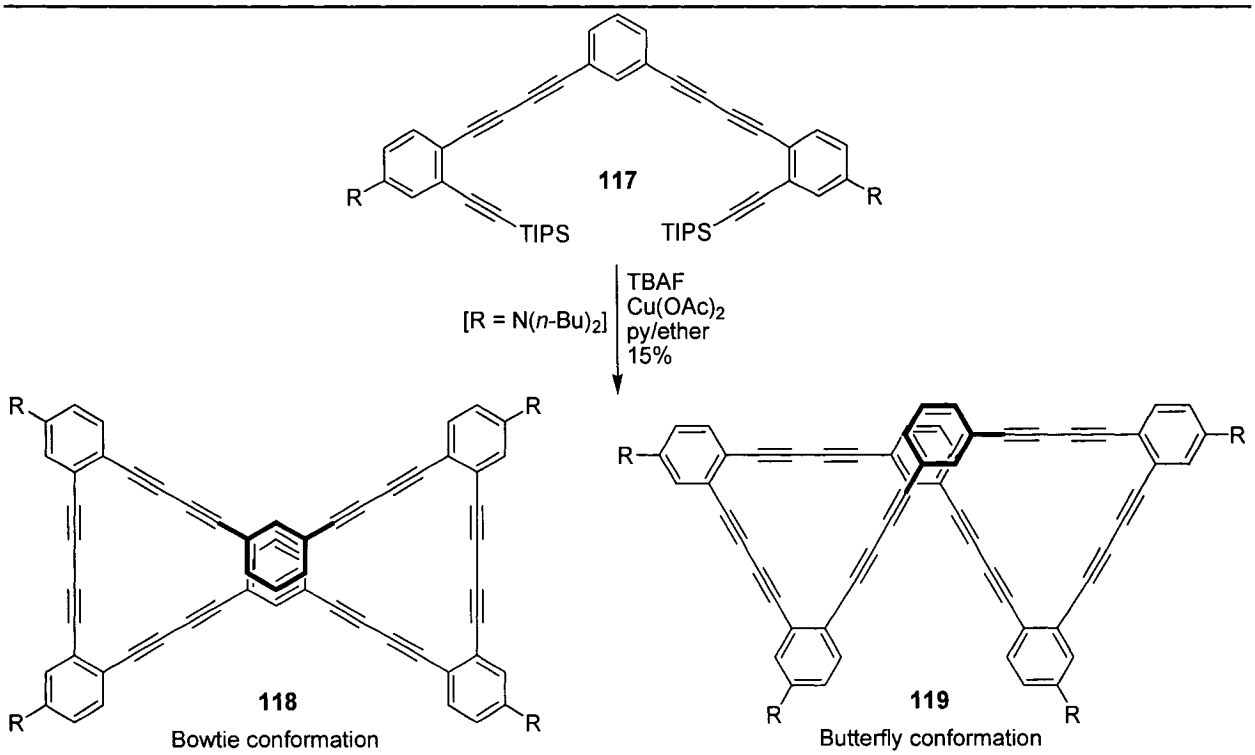
Figure 13: Strained acetylenic cyclophanes (114 and 115) and a potential liquid crystal (116)

The Fallis research group has been investigating cyclophanes for over a decade. Initial efforts focused on the preparation of highly strained acetylenic cyclophanes such as **114**[67] and **115**,[68] and on the synthesis of potential liquid crystals such as **116**[69] (Figure 13). To the best of

[65] Fox, J. M.; Lin, D. *J. Org. Chem.* **1998**, *63*, 2031-2038.
[66] An, D. L.; Nakano, T.; Orita, A.; Otera, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 171-173.
[67] Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem. Int. Ed.* **2000**, 39, 385-388.
[68] Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11-14.

our knowledge, the acetylene bond angle of 153.4° in **115** is the most highly strained stable acetylene reported.

The Fallis research group also reported some acetylenic cyclophanes as an extension of their work toward a rational chemical synthesis of buckminsterfullerene (C_{60}) (Scheme 19).[70] Two non-interconverting isomers, the bowtie (**118**) and the butterfly (**119**), were isolated from the dimerization of monomer **117**. Each isomer arose from a different conformation of the molecule after the first octatetrayne bridge had formed. The desilylation-dimerization protocol[71] used to dimerize the monomer was particularly useful and has been used in many subsequent syntheses.

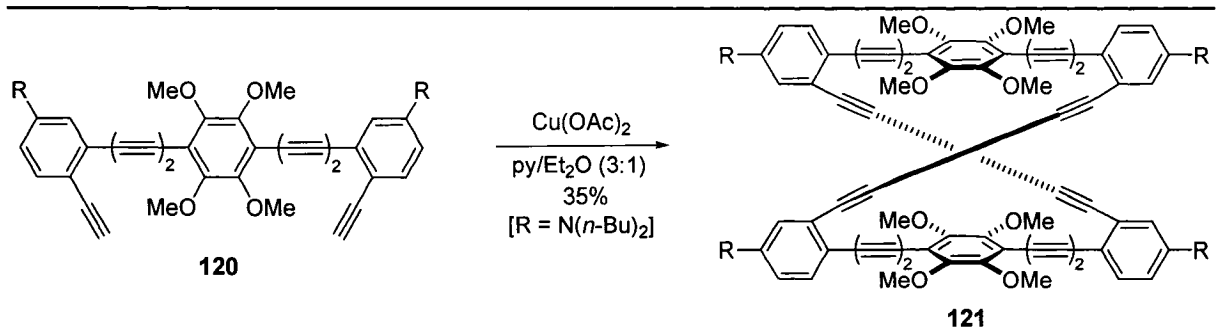


Scheme 19: The bowtie (118) and butterfly (119) conformations of C60 acetylenic cyclophanes

The bowtie conformation (**118**) was helically chiral, but could not be isolated in enantiomerically pure form due to the rapid interconversion of the helical isomers at room temperature. It was postulated that if the helical isomerization could be inhibited by some

[69] Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 3185-3187.
[70] Heuft, M. A.; Collins, S. K.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 1911-1914.
[71] Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883-2886.

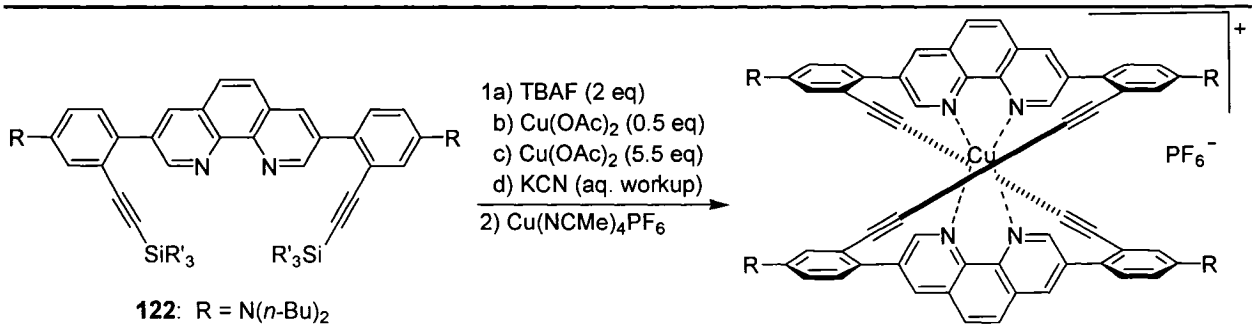
means, enantiopure helical isomers could be separated and characterized. Fallis and co-workers hypothesized that coordination of a metal atom between the central aromatic rings of cyclophanes similar to **118** would inhibit the isomerization, and two cyclophanes based on this approach were designed and synthesized.



Scheme 20: Synthesis of cyclophane 121

The first cyclophane designed based on this concept was cyclophane **121**, which contained tetramethoxybenzene rings as η^6 ligands for metal coordination (Scheme 20).[72] Unfortunately, conditions could not be found to coordinate a suitable metal to the cyclophane. A second cyclophane was therefore designed that contained phenanthroline moieties to coordinate to metal ions (Scheme 21).[73] Copper coordination to phenanthrolinophanes **124** and **125** was found to increase the helical isomerization barrier height of each by over 7.0 kcal/mol relative to the uncomplexed cyclophanes. Unfortunately, this increase was insufficient to inhibit isomerization at room temperature and so enantiopure phenanthrolinophanes could not be isolated.

[72] Heuft, M. A. Ph.D. Thesis, University of Ottawa, Ottawa, 2003.
[73] Heuft, M. A.; Fallis, A. G. *Angew. Chem. Int. Ed.* **2002**, *41*, 4520-4523.



122: R = N(*n*-Bu)$_2$
123: R = *i*-Pr

124: R = N(*n*-Bu)$_2$ (39%)
125: R = *i*-Pr (23%)

Scheme 21: Synthesis of copper-complexed phenanthrolinophanes 124 and 125

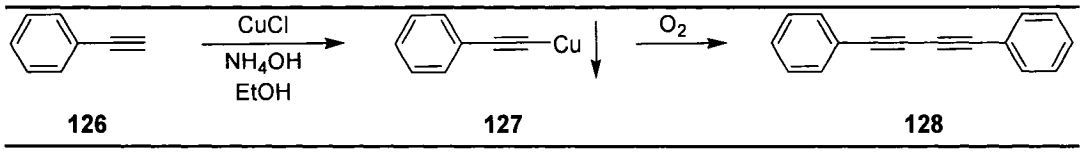
5.3 Palladium and Copper-Mediated Coupling Reactions

Modern cyclophane chemistry makes extensive use of palladium and copper-mediated coupling reactions for the formation of new carbon-carbon bonds. New acetylene-acetylene [C(*sp*)-C(*sp*)] bonds are commonly formed using copper catalysts, although palladium catalysts are also frequently employed. Other couplings involving aryl, alkenyl, and alkynyl species [C(sp^2)-C(sp^2) or C(sp^2)-C(*sp*) bond formation] are nearly always accomplished using palladium catalysis. An introduction to these two coupling methods is therefore provided in this section.

5.3.1 Acetylene-acetylene [C(sp)-C(sp)] bond formation[74]

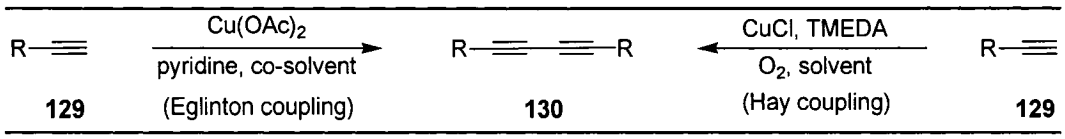
The first report of an acetylene homocoupling reaction was made by Glaser in 1869 who observed that when copper(I) phenylacetylide (**127**) was exposed to oxygen it underwent an oxidative dimerization to form the acetylene dimer (**128**) (Scheme 22).[75] This reaction was subsequently termed the Glaser coupling. Unfortunately, the utility of the process was limited as isolation of the potentially explosive intermediate copper acetylide was required.

[74] For an excellent review, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657.
[75] Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422-424.



Scheme 22: The Glaser coupling

The second significant development in acetylene homocoupling chemistry occurred in 1937 when it was discovered that tertiary alkynols dimerized *in situ* upon exposure to CuCl, essentially eliminating the problematic operation in the Glaser coupling.[76] This process, however, was limited to tertiary alkynols. It was not until 1956 that Eglinton reported a general, *in situ* oxidative homocoupling of acetylenes *via* exposure of terminal acetylenes to $Cu(OAc)_2$ and pyridine (Scheme 23).[77] A co-solvent was often required to increase the solubility of the intermediates. An alternative solution to the solubility problem was developed by Hay in 1962 who found that the addition of a copper-coordinating ligand, TMEDA, significantly increased the solubility of the intermediates.[78] The simplicity and effectiveness of the Eglinton and Hay couplings quickly led to their widespread use in synthesis, and they are still extensively employed in cyclophane chemistry today. Several synthetically appealing variants have also been developed, including those that allow for the *in situ* dimerization of TMS-[79] or TIPS-protected[71] acetylenes.

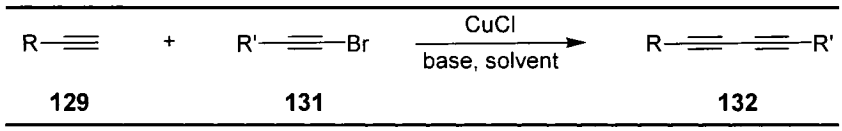


Scheme 23: The Eglinton and Hay couplings

The Glaser, Eglinton, and Hay coupling reactions, however, are only capable of synthesizing symmetric diacetylenes *via* the homocoupling of identical acetylenes. The first example of the heterocoupling of two different acetylenes was reported in 1957 when Cadiot and Chodkiewicz demonstrated that a terminal acetylene (**129**) and a bromoacetylene (**131**) could be

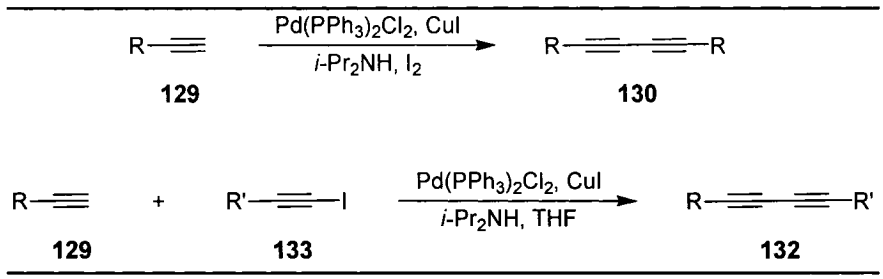
[76] Zalkind, Y. S.; Aizikovich, M. A. *J. Gen. Chem. USSR* **1937**, *7*, 227-233.
[77] Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737-738.
[78] Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320-3321.
[79] Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. *Tetrahedron Lett.* **1997**, *38*, 7483-7486.

successfully coupled under oxidative conditions (Scheme 24).[80] A number of methods similar to the Cadiot-Chodkiewicz coupling have also been developed, including a polymer-supported variant of the reaction[81] and the coupling of alkynylsilanes with chloroalkynes.[82]



Scheme 24: The Cadiot-Chodkiewicz coupling

A number of palladium-catalyzed acetylene coupling reactions have also been reported (Scheme 25). The homocoupling of acetylenes (**129**) can be accomplished using a palladium(II) catalyst and copper co-catalyst, and can be made catalytic in palladium *via* the addition of a suitable oxidant such as iodine.[83] This reaction is often an unwanted side process in the Sonogashira reaction. The heterocoupling of terminal acetylenes (**129**) with haloalkynes (**133**) can also be accomplished using a palladium catalyst and copper co-catalyst; however, in this case the active catalyst is palladium(0) and thus the exclusion of oxidants is required.[84]

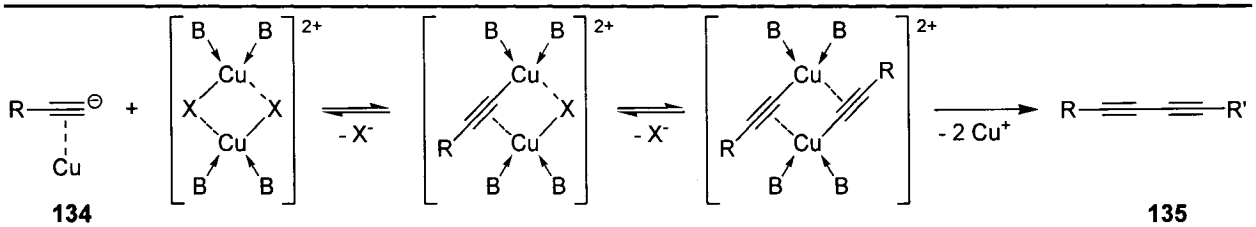


Scheme 25: Palladium-mediated acetylene coupling reactions

The mechanism of the oxidative homocoupling of acetylenes using copper is not well understood. For many years it was believed to proceed *via* a free radical mechanism,[74] but this possibility has largely been discounted based on the observation that mixtures of electronically different acetylenes give predominantly homocoupled product rather than the statistical mixture

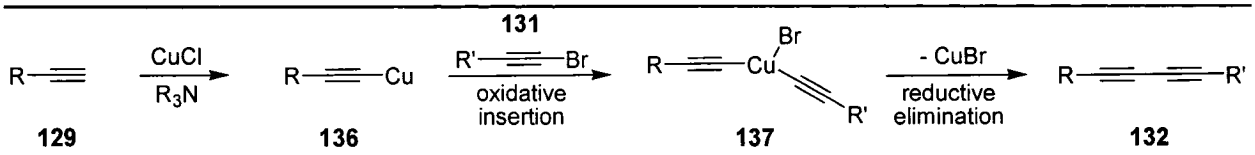
[80] Chodkiewicz, W. *Ann. Chim. (Paris)* **1957**, *2*, 819-869.
[81] Montierth, J. M.; DeMario, D. R.; Kurth, M. J.; Schore, N. E. *Tetrahedron* **1998**, *54*, 11741-11748.
[82] Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075-4078.
[83] Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371-4374.
[84] Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977-979.

that would be expected if free radicals were involved.[85] This observation was explained by the formation of a copper(I) acetylene π-complex, which would assist deprotonation and would depend on the electronics of the acetylene. Currently, the most widely accepted mechanism for the oxidative dimerization using copper, proposed by Bohlmann,[85] involves dimeric copper(II) acetylides (Scheme 26), although multiple variations have since been put forth.[86]



Scheme 26: Proposed mechanism for the copper-catalyzed homocoupling of acetylenes

There have been very few mechanistic investigations of the Cadiot-Chodkiewicz coupling, but it is presumed to proceed *via* the mechanism depicted in Scheme 27.[87] The initial step is believed to be formation of copper(I) acetylide **136**. Oxidative insertion of **136** into the carbon-bromine bond of bromoacetylene **131** would then generate copper(III) species **137**, which upon reductive elimination would generate diacetylene **132** and copper(I).

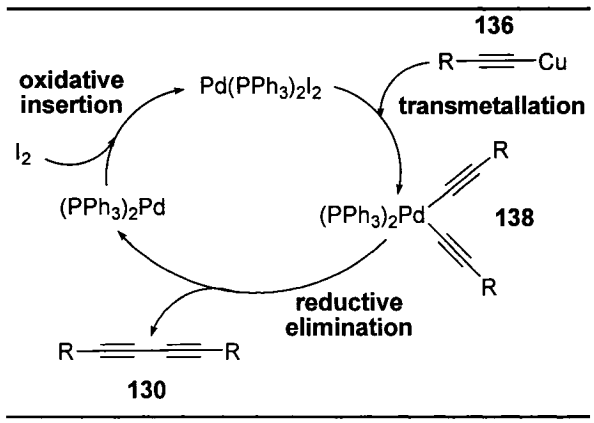


Scheme 27: Proposed mechanism of the Cadiot-Chodkiewicz coupling

There has also been no extensive investigation into the mechanism of the palladium catalyzed oxidative homocoupling process. However, it is believed to occur *via* the mechanism shown in Scheme 28.[83] Transmetallation of two copper acetylides (**136**) to palladium(II) generates palladium(II) dialkyne **138**, which upon reductive elimination produces diacetylene

[85] Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* **1964**, *97*, 794-800.
[86] (a) Challa, G.; Meinders, H. C. *J. Mol. Catal.* **1977**, *3*, 185-190; (b) Federnok, L. G.; Berdnikov, V. M.; Shvartsberg, M. S. *J. Org. Chem. USSR* **1973**, *9*, 1806-1809; (c) Hoan, H. M.; Brailovskii, S. M.; Temkin, O. N. *Kinet. Catal. (Engl. Transl.)* **1994**, *35*, 242-246.
[87] Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Dekker, New York, **1969**, Chapter 9, pp 597-647.

130 and a palladium(0) complex. Palladium(0) is then re-oxidized to palladium(II), which in the case shown in Scheme 28 occurs *via* the oxidative insertion of palladium(0) into iodine. The mechanism for the palladium catalyzed heterocoupling of an acetylene with an alkynylhalide is very similar to that for all other palladium-mediated cross coupling reactions, which are discussed in detail in Section 5.3.2.

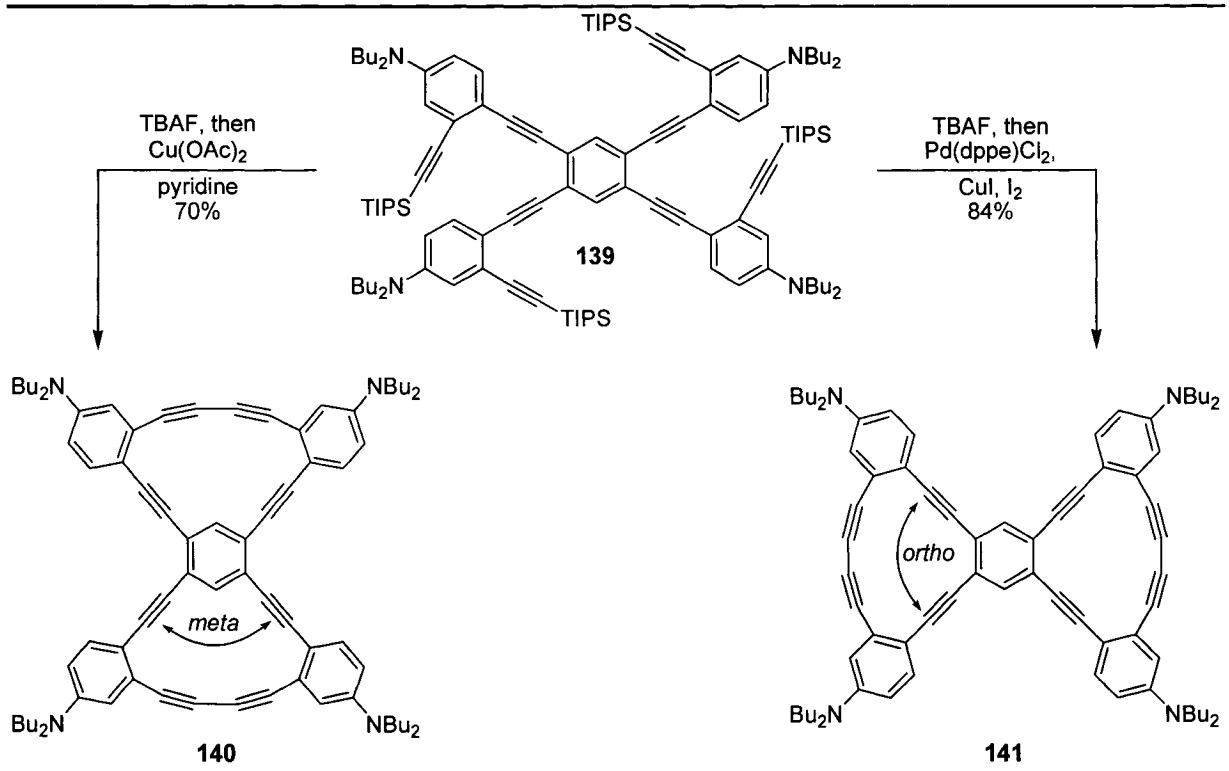


Scheme 28: Proposed mechanism of palladium-catalyzed oxidative coupling reaction

An interesting implication of the different copper and palladium-catalyzed mechanisms was recently realized and investigated by Haley.[88] In the Eglinton or Hay coupling reaction mechanism, the two acetylenes are arranged in a pseudo-*trans* configuration (Scheme 28), while in the palladium-mediated coupling reaction mechanism, they are in a pseudo-*cis* configuration (Scheme 26).[89] Haley realized that this could have a profound effect on the intramolecular dimerization of acetylenes. In a rigid system, the acetylenes may only be able to adopt one configuration and so one method could give superior results over the other. Alternatively, completely different products could be obtained depending on the method chosen to couple the acetylenes. This was demonstrated by Haley, who cyclized polyyne **139** using both copper and palladium catalysis (Scheme 29). Coupling of the pseudo-*meta* acetylenes would occur through a *trans*-orientation of the acetylenes and give annulene **140**, while coupling of the pseudo-*ortho* acetylenes would proceed *via* a *cis*-orientation and give annulene **141**. As hypothesized, an Eglinton coupling reaction using $Cu(OAc)_2$ generated exclusively annulene **140**, while a coupling reaction employing $Pd(dppe)Cl_2$ generated exclusively annulene **141**.

[88] Marsden, J. A.; Miller, J. J.; Haley, M. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1694-1697.

[89] This is especially true when bidentate ligands such as 1,2-bis(diphenylphosphanyl)ethane (DPPE) are employed as the *cis* geometry of the acetylenes is enforced.



Scheme 29: Selective macrocycle formation through palladium- or copper-catalysis

5.3.2 Palladium catalysis: Formation of C(sp^2)-C(sp^2) or C(sp^2)-C(sp) bonds

Over the last 25 years palladium catalysis has revolutionized the way in which new C(sp^2)-C(sp^2) and C(sp^2)-C(sp) bonds are formed in synthesis. Palladium-catalyzed cross-coupling reactions between organometallics and organic electrophiles tolerate a wide variety of functional groups and have been used extensively in synthesis.[90] Palladium-mediated coupling reactions have typically been named after the researcher who discovered the use of a particular organometallic in the cross-coupling reaction, and include the Stille (Sn),[91] Suzuki (B),[92] Kumada (Mg),[93] Negishi (Zn, Zr),[94] Hiyama (Si),[95] and Sonogashira (Cu-acetylide)[96] coupling reactions. Many other metals have also been employed.[97] Three of these coupling reactions –

[90] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.
[91] Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *98*, 504-519.
[92] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
[93] Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.
[94] Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348.
[95] Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845-853.
[96] Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46-49.
[97] Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359-1469.

the Suzuki, Negishi, and Sonogashira – have been used extensively in this research and will be discussed in greater detail later in this section.

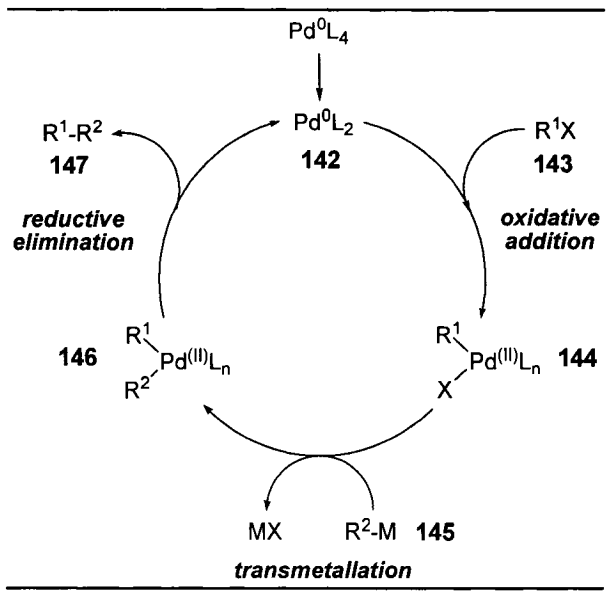


Figure 14: Generalized catalytic cycle for palladium-mediated cross-coupling reactions

The generalized catalytic cycle for palladium-mediated cross-coupling reactions is illustrated in Figure 14. The active catalyst in the reaction is the $14e^-$ Pd^0L_2 species **142**, which is generated from the corresponding $18e^-$ species *via* loss of two ligands, or *via* reduction of a Pd^{II} precatalyst, such as $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$. The reduction of a Pd^{II} precatalyst is the method most frequently employed in our work. The first step in the catalytic cycle is the oxidative addition of the organic electrophile (**143**) to Pd^0L_2 to generate a Pd^{II} species (**144**). The organic electrophile is typically an aryl or vinyl halide, although triflates, sulfonates, carbonyl derivatives, and alkyl halides can also been used. For aryl or vinyl halides, the order of reactivity is approximately: vinyl iodide > vinyl bromide > vinyl chloride ≈ aryl iodide > aryl bromide >> aryl chloride. The next step in the catalytic cycle is the transmetallation of **144** with the organometallic component (**145**) to generate **146**. For vinyl halides and similarly reactive species, this is often the rate-limiting step of the reaction. Reductive elimination then yields the cross-coupled product (**147**) and regenerates the active Pd^0 catalyst (**142**). Each step of the

catalytic cycle has been extensively studied and multiple reaction- or reagent-specific variations have been proposed.[98]

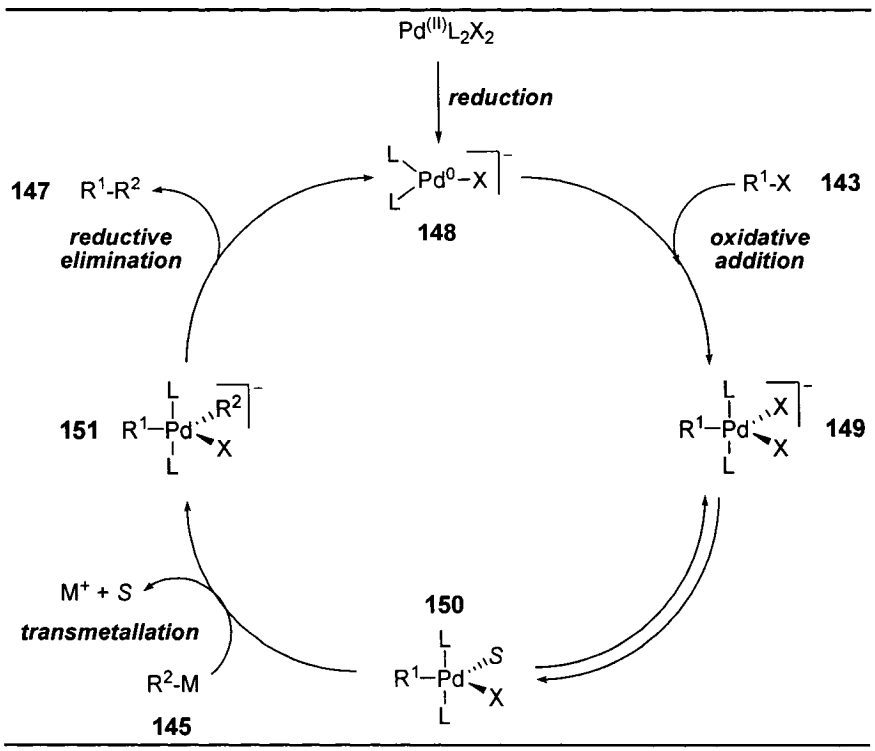
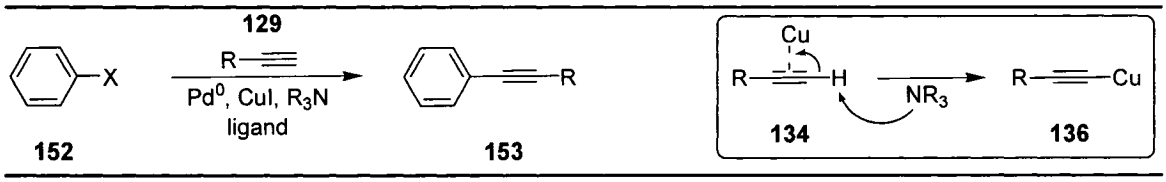


Figure 15: Proposed catalytic cycle involving anionic and pentacoordinate palladium intermediates

Amatore and Jutand have recently proposed a more complex catalytic cycle for palladium mediated cross-coupling reactions (Figure 15).[99] The primary difference between their proposal and the more general mechanism of Figure 14 is the involvement of anionic and pentacoordinate palladium intermediates. As illustrated in Figure 15, reduction of $Pd^{II}L_2X_2$ generates the active catalytic species, $Pd^0L_2X^-$ (**148**) rather than the uncharged catalytic species (**142**) of Figure 14. Oxidative addition of the electrophile then gives anionic pentacoordinate Pd^{II} **149**, which after exchange of an anion for a solvent molecule produces the uncharged pentacoordinate Pd^{II} species **150**. Transmetallation with the organometallic component then produces anionic Pd^{II} species **151**, which after reductive elimination of the cross-coupled product regenerates the active Pd^0 catalyst (**148**). Many reaction parameters affect this catalytic cycle, and are discussed in detail in the account by Amatore and Jutand.[99]

[98] For a review, see: Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704-4734.
[99] Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314-321.

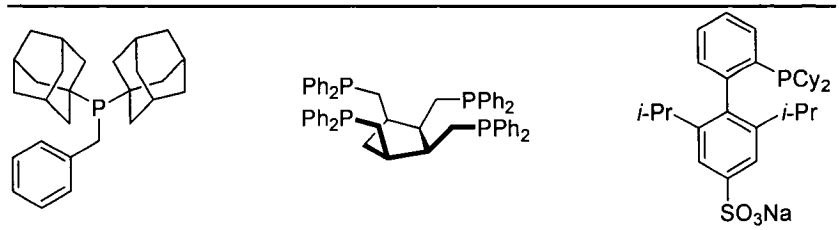
The catalytic cycle for palladium-catalyzed cross coupling reactions put forth by Amatore and Jutand is generally accepted today, although the original more simplified version (Figure 14) is often still used in discussions where detailed mechanistic information is not particularly pertinent. The remainder of this section will provide a brief introduction to the Sonogashira, Suzuki, and Negishi coupling reactions, focusing on synthetic advances made in each area.



Scheme 30: The Sonogashira cross-coupling reaction

The Sonogashira reaction is a palladium-catalyzed cross coupling reaction of a terminal acetylene (**129**) with an organic electrophile (**152**), typically an aryl or vinyl halide (Scheme 30). The reaction is believed to proceed *via* the catalytic cycle presented in Figure 14. The reaction is co-catalyzed by copper, which forms a π-complex with the acetylene (**134**), facilitating deprotonation to form the copper acetylide (**136**). Vinyl halides and aryl iodides react at room temperature using PPh_3 or similar ligands; however, aryl bromides and aryl chlorides typically require elevated temperatures. Specialized ligands to promote the room temperature Sonogashira coupling reaction of both aryl bromides and aryl chlorides have therefore been developed. Fu[100] and Soheili[101] have each reported catalyst systems using P(*t*-Bu)$_3$ as ligand to promote the room temperature Sonogashira coupling reaction of aryl bromides, while Plenio (**154**),[102] Santelli (**155**),[103] and Buchwald (**156**)[104] have each reported ligands for the Sonogashira coupling reactions of aryl chlorides, albeit at elevated temperatures (Figure 16).

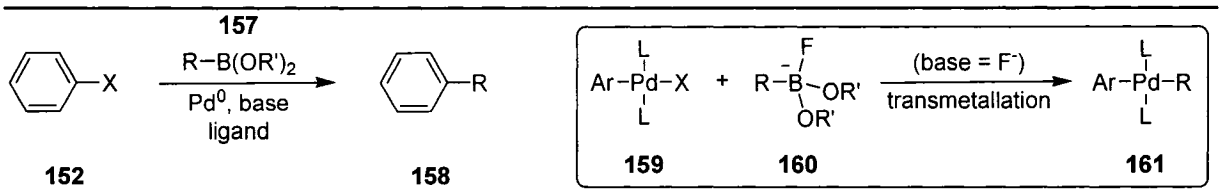
[100] Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729-1731.
[101] Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191-4194.
[102] Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1056-1058.
[103] Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 8443-8446.
[104] Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 6173-6177.



154 **155** **156**

Figure 16: Ligands for the Sonogashira coupling reaction of aryl chlorides

A considerable amount of research has also been devoted to the development of Sonogashira-type reactions that do not require one or more of the typical reagents. These can be particularly useful in situations where one of the reagents may cause undesirable side reactions, or in industry where the exclusion of transition metals may be advantageous. Sonogashira-type coupling reactions have been reported in the absence of copper,[105] without palladium or phosphine ligand,[106] and without palladium, phosphine ligand, or copper.[107]



Scheme 31: The Suzuki cross-coupling reaction

The Suzuki reaction is the palladium-catalyzed cross-coupling of an organoboron compound (**157**) with an organic electrophile (**152**), typically an aryl or vinyl halide (Scheme 31). The reaction is presumed to proceed *via* the catalytic cycle illustrated in Figure 14. However, most organoboron compounds are not sufficiently nucleophilic to undergo transmetallation with palladium (**159**), and so nucleophilic bases, typically fluoride or oxygen-based, are often added to the reaction to facilitate this transformation *via* the more nucleophilic boronate **160**. Thallium(I) hydroxide or ethoxide,[108] fluoride, and Cs_2CO_3 are particularly

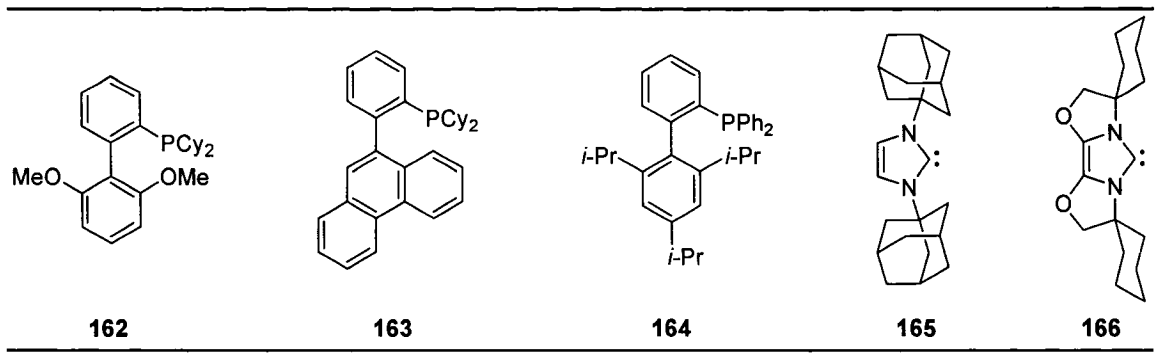
[105] (a) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653-8656; (b) Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, 1934-1935.

[106] (a) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *6*, 215-218; (b) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934-1935.

[107] (a) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713-4716; (b) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919-3922

[108] Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691-2694.

effective bases for this purpose. Considerable progress has also recently been made in the development of ligands to promote the Suzuki coupling of unreactive aryl chlorides and hindered substrates. The Buchwald group has perhaps been most active in this area, producing several biaryl ligands (*e.g.*, **162**, **163**, and **164**) that are capable of effecting Suzuki couplings on hindered and unreactive substrates under relatively mild conditions (Figure 17).[109] *N*-Heterocyclic carbene ligands (*e.g.*, **165** and **166**) have also found considerable use in the Suzuki coupling reaction.[110]



162 **163** **164** **165** **166**

Figure 17: Ligands to promote the Suzuki coupling of poorly reactive substrates

Suzuki coupling reactions were historically restricted to boronic acids and organoboranes and borates. Unfortunately, these substrates are prone to decomposition, are relatively difficult to handle, and sometimes undergo protodeborylation under Suzuki coupling reaction conditions. Potassium trifluoroborate salts, however, are more stable and easier to handle than these other organoboron compounds, and thus are being increasingly used as the organometallic component in the Suzuki coupling reaction. Methodology for the coupling of potassium trifluoroborates with various aryl and vinyl halides using $Pd(dppf)Cl_2$ as catalyst was originally developed by Molander.[111] Buchwald has recently reported an improved protocol using $Pd(OAc)_2$ and S-Phos (**162**) as ligand (Figure 17).[112] It is believed that the reaction proceeds through the boronic acid

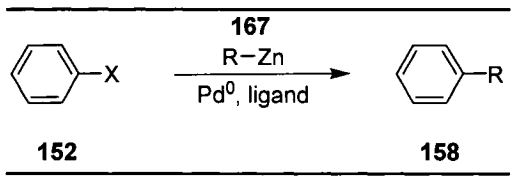
[109] (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696; (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871-1876; (c) Yin, J.; Rainka, M. P.; Zhang, X-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162-1163.

[110] (a) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1363-1365; (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3690-3693.

[111] (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302-4314; (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424-8429; (c) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393-396.

[112] Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649-2652.

(or fluorinated boronic acid) which is formed *in situ* from reaction of the RBF_3K salt with trace water. This hypothesis is supported by the fact that strictly anhydrous conditions afford very little cross-coupled product.[112]



Scheme 32: The Negishi cross-coupling reaction

The Negishi reaction is the palladium-catalyzed cross-coupling of an organic electrophile (**152**) with an organozinc (**167**) or zirconium, although organozincs are usually the organometallic of choice (Scheme 32). The reaction is believed to proceed through the catalytic cycle given in Figure 14. The reactivity of organozincs precludes their isolation, and so they are often formed *in situ* from the aryl or vinyl halide *via* a lithium-halogen exchange – ZnX_2 quench protocol. This is the method used in this thesis. This reactivity has also limited the development of the Negishi reaction, with considerably more effort being directed to the Suzuki and Stille reactions which have relatively stable organometallic components. However, similar to the Sonogashira and Suzuki coupling reactions described earlier, advances in the Negishi coupling reaction have primarily come in the form of new ligands to promote the reaction of typically unreactive substrates. Fu has reported the use of P(*t*-Bu)$_3$ as a ligand in Negishi coupling reactions of aryl chlorides,[113] while Buchwald reported the use of a ligand similar to **162** (Figure 17) where the methoxy groups have been replaced by isopropoxide groups.[114]

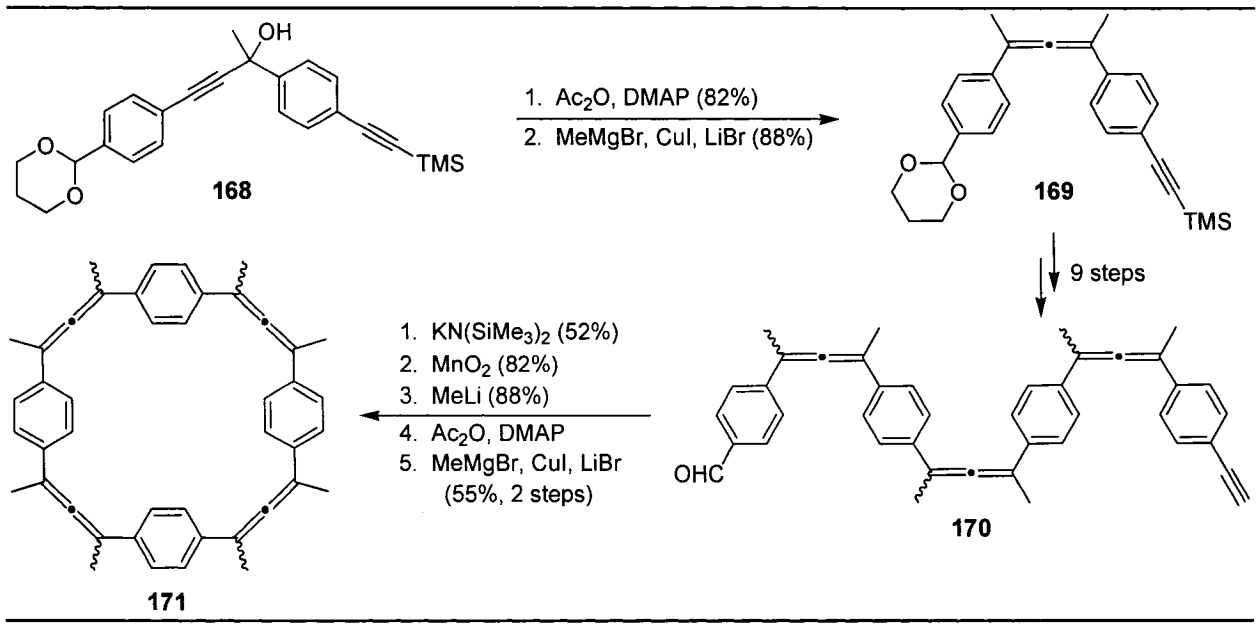
The choice of which palladium coupling reaction to employ in a given reaction is largely substrate-specific. For the formation of C(sp^2)-C(sp) bonds, the Sonogashira reaction is often the method of choice due to the mild and *in situ* formation of the organometallic, although both the Suzuki and Negishi reactions are also capable of forming these bonds. For C(sp^2)-C(sp^2) bond formation, the choice between Negishi or Suzuki coupling conditions is largely dependent upon the stability of the substrates towards the reaction conditions. The higher nucleophilicity of an organozinc compared to an organoboron precludes the use of the Negishi coupling reaction when

[113] Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724.
[114] Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028-13032.

good electrophiles are present in the system. However, the *in situ* formation of an organozinc does make the Negishi coupling reaction preferable for tolerable substrates as this step eliminates the isolation and purification of the organoboron compounds necessary for the Suzuki coupling.

5.4 Allenophanes and Acetylenic Allenophanes

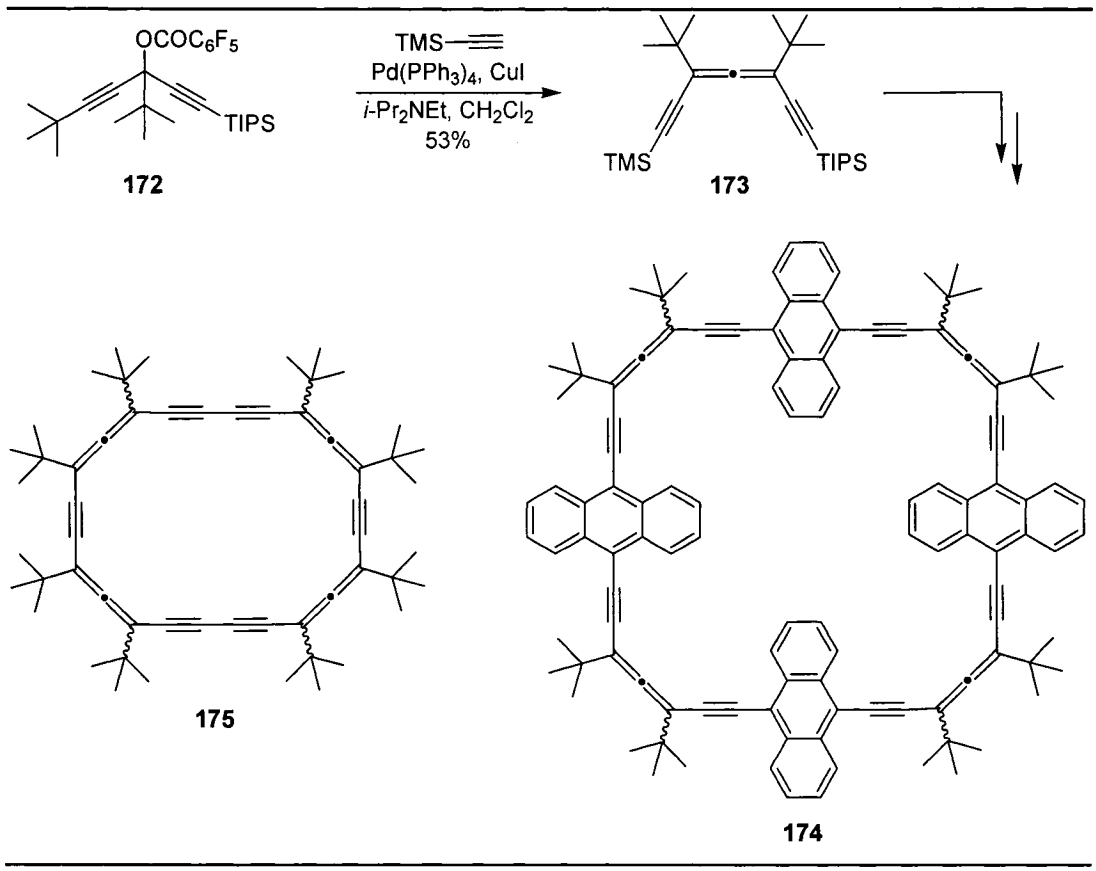
In 1999 a new class of chiral cyclophane was reported by Krause.[115] Comprised exclusively of alternating allene bridges and benzene rings, this cyclophane was chiral due to the allenes and was termed an allenophane. The key steps in the synthesis of this allenophane are illustrated in Scheme 33. Beginning with tertiary propargyl alcohol **168**, a two-step sequence of acetylation and organocuprate addition provided allene **169**, which was converted to tris(allene) **170** *via* a somewhat repetitive series of nine transformations. Cyclization of the acetylene onto the aldehyde followed by oxidation with MnO_2 provided a ketone, which was converted to the tertiary propargyl acetate *via* addition of MeLi and subsequent acetylation. Allenophane **171** was then obtained upon conversion of the acetate to the allene by exposure to the organocuprate.



Scheme 33: Synthesis of the first allenophane

[115] Thorand, S.; Vögtle, F.; Krause, N. *Angew. Chem. Int. Ed.* **1999**, *38*, 3721-3723.

This was the first reported allenophane; however, it was a racemic synthesis that produced a mixture of diastereomers. Attempts to separate and fully characterize the isomers were hindered by the poor solubility of the compounds. Insight into the conformation of each diastereomer was provided through molecular modeling studies and revealed that two pairs of enantiomers and two achiral diastereomers likely formed in the reaction.



Scheme 34: Synthesis of acetylenic allenophanes 174 and 175

A related family of cyclophanes comprise structures containing both allene and acetylene bridges. These molecules are termed acetylenic allenophanes, and at the time of this work none had been reported. However, after completion and publication of our work in this area in 2005,[116] two additional acetylenic allenophanes, **174** and **175**, were reported by Diederich (Scheme 34).[117] The allene corner pieces (**173**) necessary for the synthesis were accessed from

[116] Clay, M. D.; Fallis, A. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4039-4042.
[117] Odermatt, S.; Alonso-Gómez, J. L.; Seiler, P.; Cid, M. M.; Diederich, F. *Angew. Chem. Int. Ed.* **2005**, *44*, 5074-5078.

propargyl acetate **172** using a palladium-mediated coupling they had previously developed.[118] Unfortunately, this synthesis was also racemic and resulted in a 1:1:4:1:1 mixture of five stereoisomers consisting of two pairs of enantiomers and three achiral diastereomers. The presence of the *tert*-butyl groups, however, provided sufficient solubility that the isomers, although not the individual enantiomers, could be separated by exhaustive preparative HPLC and fully characterized.

The fact that the second of these two syntheses was also racemic and was reported six years after the original report clearly indicates a growing need for an asymmetric synthesis of this type of molecule. To achieve this goal, a clear understanding of the chemistry and asymmetric synthesis of allenes will be required. An introduction to these two topics is therefore provided in the following sections.

5.5 Synthesis of Allenes

Allenes are a class of organic compound containing two directly connected double bonds (1,2-dienes). The central carbon of an allene is *sp*-hybridized, and the two remaining *p*-orbitals of this carbon each overlap with a *p*-orbital of an adjacent carbon. The two substituents on each terminal carbon are thus forced into perpendicular planes, and if they are different, the allene is chiral (Figure 18).

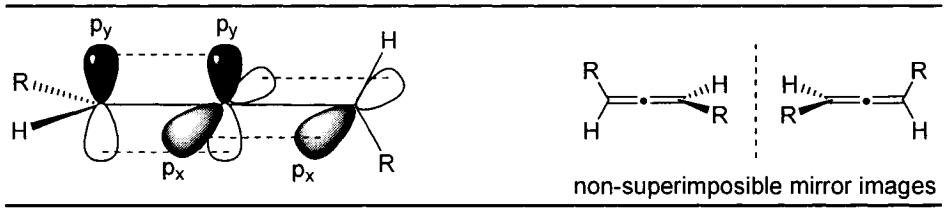


Figure 18: Bonding and chirality of allenes

The synthesis of allenes has been exhaustively explored and thousands of methods are currently available for the synthesis of allenes from a myriad of starting materials. Of relevance to this thesis is the *asymmetric* synthesis of allenes. Syntheses in this area can generally be divided into two categories: Those that begin with chiral, non-racemic starting materials

[118] Livingston, R.; Cox, L. R.; Odermatt, S.; Diederich, F. *Helv. Chim. Acta.* **2002**, *85*, 3052-3077.

(substrate control), and those that introduce the chirality using an external source such as a chiral catalyst (reagent control).

5.5.1 Synthesis of allenes from non-racemic propargylic compounds

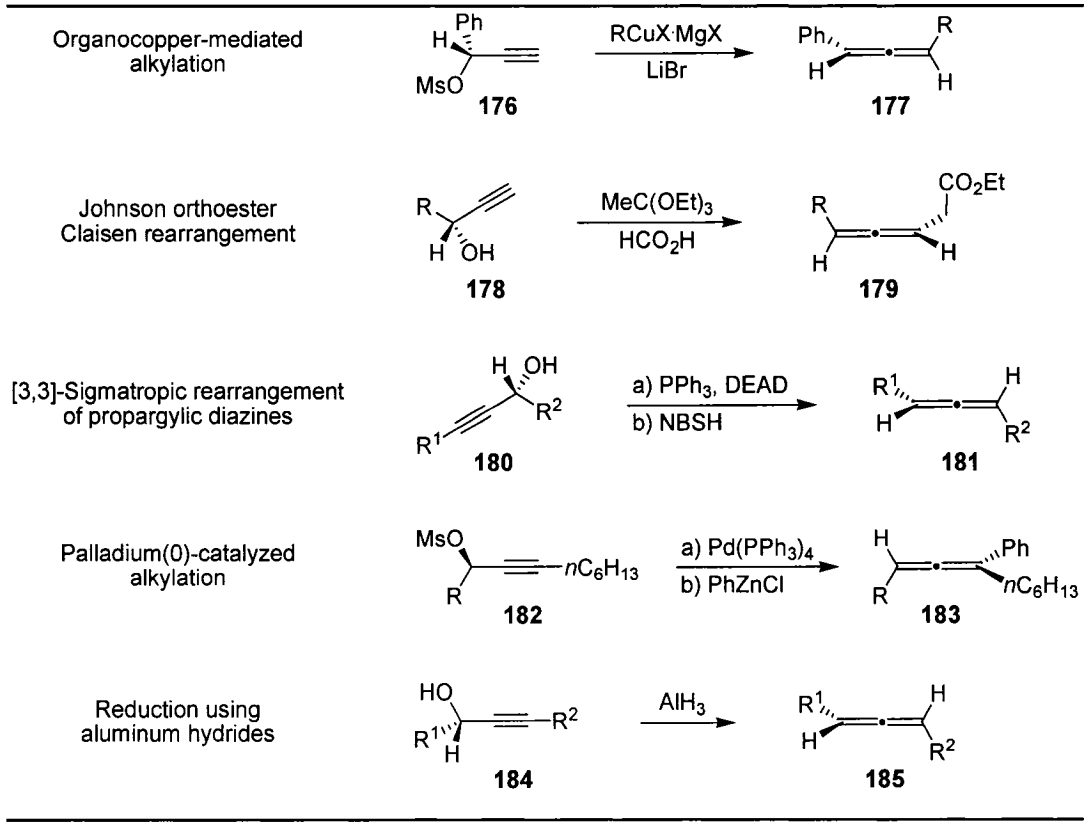


Figure 19: Asymmetric synthesis of allenes from non-racemic propargylic compounds

The most common approach to the asymmetric synthesis of allenes uses non-racemic propargylic compounds as starting material. During the reaction, the tetrahedral chirality of the propargyl substrate is transferred to the axial chirality of the allene. Multiple methods have been developed based on this concept and are summarized in Figure 19. The S_N2' addition of an organocuprate to a propargylic substrate such as mesylate **176** is the most frequently employed method and has been shown to occur with complete tetrahedral to axial chirality transfer.[119] Johnson orthoester Claisen rearrangements of propargyl alcohols (**178**) have also been used in the asymmetric synthesis of allenes, although this method can only provide allenes containing an

[119] Macdonald, T. L.; Reagan, D. R. *J. Org. Chem.* **1980**, *45*, 4740-4747.

ester functionality (**179**).[120] Myers has reported a protocol in which a propargyl alcohol (**180**) was converted *in situ* to the corresponding alkyl sulfonylhydrazine intermediate, which then underwent a [3,3]-sigmatropic rearrangement to generate the allene (**181**).[16] Palladium-catalyzed alkylations of propargyl mesylates (**182**) have also been used to synthesize allenes;[121] however, partial racemization often occurs during the reaction.[122] An older method for the asymmetric synthesis of allenes involves the reduction of a propargyl alcohol (**184**) with an aluminum hydride, although this method also often results in erosion of the enantiomeric excess.[123]

5.5.2 Synthesis of allenes using chiral reagents and catalysts

Allenes can also be synthesized asymmetrically from achiral starting materials using a chiral reagent or catalyst. Several syntheses in this area have been reported in recent years, although only those that have generated good enantioselectivities are discussed below (Figure 20). Tanaka generated allenecarboxylates **188** in good to excellent enantioselectivities using a Horner-Wadsworth-Emmons reaction between ketene **187** and the chiral ylid derived from BINOL **189**.[124] Hayashi has reported two palladium-catalyzed methods for the asymmetric synthesis of allenes. In the first, an asymmetric hydrosilylation of enyne **190** using the palladium complex generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and ferrocene-based ligand **192** provided allenyl(trichloro)silanes **191** in excellent enantioselectivities, although the alkynyl substituent of **190** had to be bulky for acceptable selectivity to be observed.[125] In the second method, a palladium-catalyzed asymmetric alkylation of a vinyl bromide (**193**) using BINAP **195** as chiral ligand generated the desired allenes **194** in up to 89% enantiomeric excess.[126] Unfortunately, these three catalytic methods are all highly limited in scope as they only provide allenes with very specific substitution patterns.

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[120] Cooper, G. F.; Wren, D. L.; Jackson, D. Y.; Beard, C. C.; Galeazzi, E.; Van Horn, A. R.; Li, T. T. *J. Org. Chem.* **1993**, *58*, 4280-4286.
[121] Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360-1361.
[122] Colas, Y.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 845-848.
[123] Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302-7311.
[124] Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669-675.
[125] Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.
[126] Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089-2090.

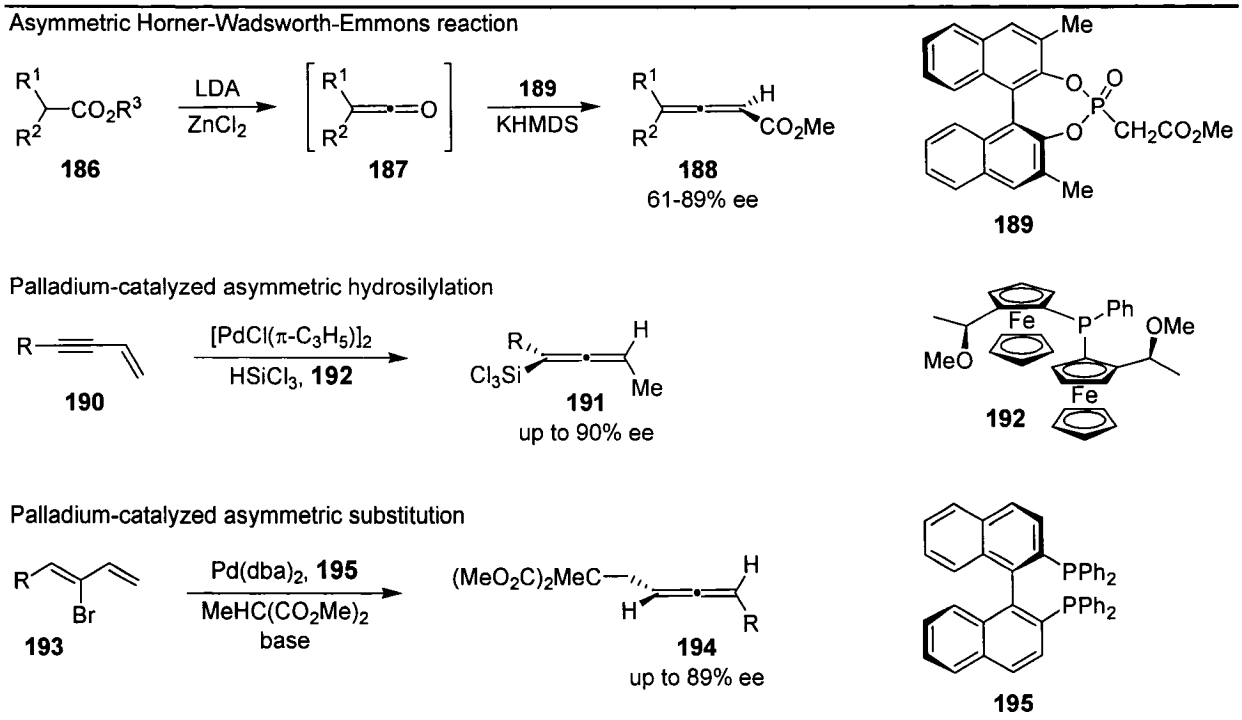
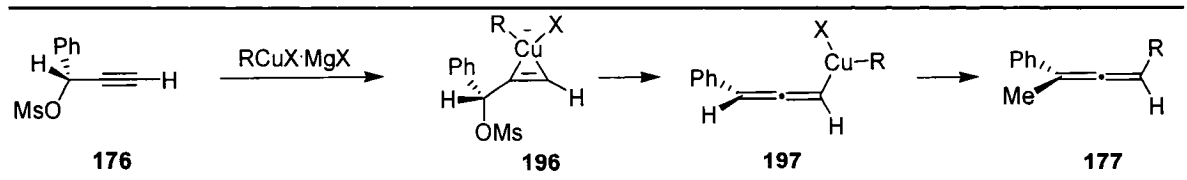


Figure 20: Asymmetric synthesis of allenes from achiral compounds using metal catalysis

5.5.3 Optimal allene syntheses

The termini of the allenes necessary for our synthesis must have identical substituents (see Section 5.7.1). Of the available methods, both the organocopper-mediated alkylation and Myers' propargylic diazine rearrangement are capable of easily synthesizing allenes with this symmetry constraint and are acceptably reliable. These two methods are therefore discussed in greater detail below.



Scheme 35: Organocopper-mediated alkylation of propargylic substrates

The organocopper-mediated alkylation of propargylic substrates has been extensively studied and is believed to proceed *via* the mechanism illustrated in Scheme 35.[127] Initial complexation of the organocuprate with the alkyne (**176**) generates π-complex **196**. Expulsion of the leaving group then provides the allenylcuprate (**197**), which provides the allene (**177**) after reductive elimination of CuX. The observed *anti* selectivity of the reaction is rationalized on stereoelectronic grounds as depicted in Figure 21.[127] As illustrated, copper complexes the acetylene such that there is overlap between the acetylenic π and π* systems and the p and d orbitals of copper, as well as between the $3d_{xz}$ orbital of copper and the σ* antibonding orbital of the leaving group. It is this latter interaction that initiates departure of the leaving group and thus accounts for the high degree of *anti* stereoselectivity.

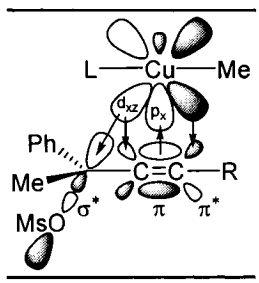
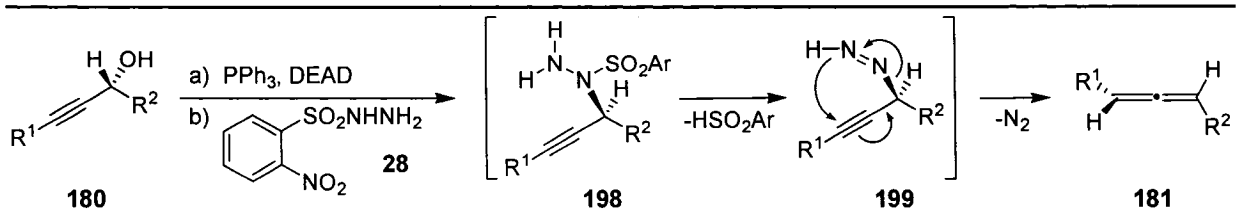


Figure 21: Stereoelectronic rationale for observed anti-selectivity

The mechanism of Myers' propargyl diazine rearrangement is illustrated in Scheme 36. Mitsunobu inversion of propargyl alcohol **180** with *o*-nitrobenzenesulfonylhydrazine (NBSH, **28**) generates the alkylated sulfonylhydrazine **198**, which after loss of the aryl sulfinic acid undergoes a [3,3]-sigmatropic rearrangement with expulsion of nitrogen to generate the allene (**181**). The hydride is delivered to the same face of the acetylene as the diazine due to conformational constraints, so as long as the preceding Mitsunobu reaction occurs with complete inversion of stereochemistry the product allene will exhibit the same enantiomeric excess as the starting propargyl alcohol.

[127] Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726-3730.



Scheme 36: Mechanism of Myers' propargyl diazine rearrangement

5.6 The Asymmetric Synthesis of Propargyl Alcohols

If allenes with identically substituted termini are to be obtained *via* the organocopper-mediated allene synthesis method, the precursor must be a non-racemic tertiary propargyl alcohol or related substrate. Similarly, non-racemic secondary propargyl alcohols are required for the propargyl diazine rearrangement method of synthesizing allenes. Protocols for the synthesis of these substrates are therefore discussed in this section.

5.6.1 Secondary propargyl alcohols

Secondary propargyl alcohols are most commonly synthesized *via* the addition of a terminal acetylene to an aldehyde. Catalysts used to conduct this reaction asymmetrically can be divided into two general categories: Those that are amino alcohol-based and those that are binaphthyl-based (Figure 22). Typically, a zinc acetylide is formed *in situ* by reaction of a terminal acetylene with a dialkylzinc, which is then reacted with an aldehyde at ambient temperature in the presence of an organic catalyst. The first system to exhibit excellent enantioselectivities and yields for a variety of aliphatic and aromatic substrates was reported by Carreira in 2000 and used *N*-methylephedrine (**200**) as chiral ligand.[128] Excellent enantioselectivities (>95%) and yields were consistently obtained, heteroatoms on either reactive species were well tolerated, and the reaction was operationally simple.[129]

[128] (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807; (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.
[129] Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.

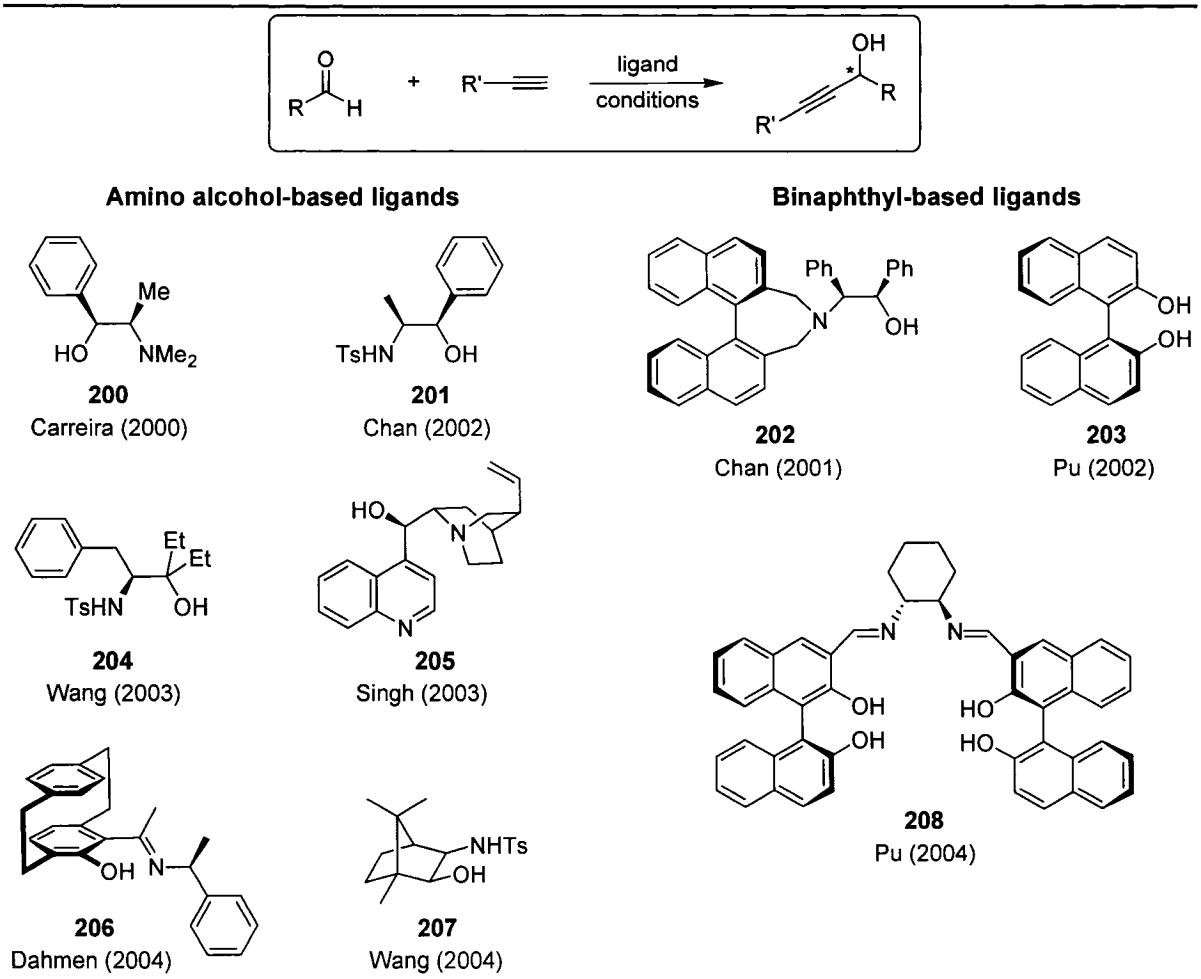


Figure 22: Ligands that catalyze the asymmetric addition of acetylides to aldehydes

The mechanism of the reaction has not been well investigated, but is likely very similar to the reaction in which an alkylzinc is added to an aldehyde.[130] A plausible transition state to account for the observed selectivity when *N*-methylephedrine is used as catalyst is illustrated in Figure 23. Initial complexation of zinc to the amino alcohol moiety of *N*-methylephedrine is followed by coordination of the aldehyde to the least hindered face of the zinc atom. The larger group of the aldehyde is oriented downward to minimize steric interactions with the alkyl ligand on zinc. Coordination of the zinc acetylide to the oxygen of the catalyst completes the transition state and leads to *si* face attack of the acetylide on the aldehyde. In many protocols titanium isopropoxide is used in place of zinc for coordination to the catalyst.

[130] Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2003**, *125*, 5130-5138.

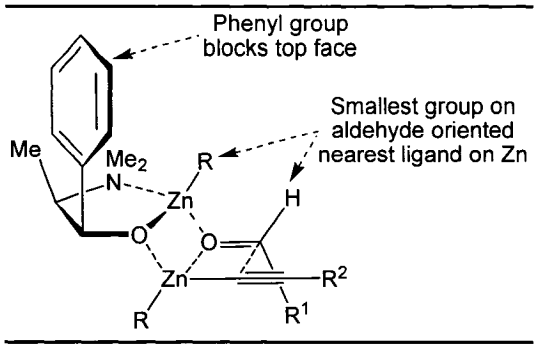


Figure 23: Transition state for the asymmetric addition of a zinc acetylide to an aldehyde using N-methylephedrine as chiral catalyst

Several other catalyst systems have since been developed to catalyze the same transformation. In 2001 Chan reported that amino alcohol binaphthyl **202** catalyzed the asymmetric addition of zinc acetylides to aromatic aldehydes in good yields and enantioselectivities (61-90%).[131] This was followed by a second report in which excellent enantioselectivities (>90%) were obtained for aromatic aldehydes using the catalyst formed from a 3:3:4 mixture of amino alcohol **201**, BINOL (**203**) and Ti(O*i*-Pr)$_4$.[132] Interestingly, Pu later reported that only BINOL (**203**) and Ti(O*i*-Pr)$_4$ were necessary to catalyze the addition of phenylacetylide to aromatic and aliphatic aldehydes in excellent enantioselectivities (>90%).[133] In 2003, Wang reported that the catalyst resulting from mixing amino alcohol **204** and Ti(O*i*-Pr)$_4$ generated enantiomeric excesses greater than 90% for the addition of phenylacetylene to simple aromatic aldehydes.[134] In the same year, Singh reported that a mixture of cinchonidine (**205**) and Ti(O*i*-Pr)$_4$ was successful in promoting the addition of phenylacetylene to both aromatic and aliphatic aldehydes with enantioselectivities of 61-85%.[135] Cyclophane-based amino alcohol **206** has been reported to catalyze the asymmetric addition of a variety of acetylenes to aromatic and aliphatic ketones with enantioselectivities of 77-98%.[136] Camphor-based amino alcohol **207**[137] and BINOL-based **208**[138] have also both been used to catalyze the asymmetric addition of

[131] Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147-2152.
[132] Li, X.; Lu, G.; Kwok, W. H.; Chan. A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636-12637.
[133] (a) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855-1857; (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143-4146.
[134] Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W.-J.; Chen, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5747-5749.
[135] Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5347-5349.
[136] Dahmen, S. *Org. Lett.* **2004**, *6*, 2113-2116.
[137] Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193-1195.
[138] Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065-1068.

acetylides to aldehydes in >80% enantiomeric excess, although **207** was only successful with aromatic acetylenes.

Surprisingly, none of these newer catalyst systems have proven as effective as Carreira's original *N*-methylephedrine-catalyzed protocol. Although some ligands have generated slightly higher enantiomeric excesses for certain substrates, *N*-methylephedrine is clearly the ligand of choice, primarily due to its effectiveness and versatility on a wide variety of aromatic and aliphatic aldehydes and acetylenes.

5.6.2 Tertiary propargyl alcohols

The asymmetric synthesis of tertiary propargyl alcohols is substantially more difficult than that of secondary propargyl alcohols. The increased steric bulk and lower electrophilicity of ketones as compared to aldehydes is primarily responsible for this difficulty. Many catalysts that work well for aldehydes are unreactive toward ketones and reaction times of several days are not unusual for successful protocols. It is also difficult to distinguish between the *re* and *si* faces of a ketone as a result of the often similarly sized groups on either side of the carbonyl. For this reason, good enantioselectivities are usually only observed when a large difference in size exists between the two substituents of the ketone.

Analogously to secondary propargyl alcohols, tertiary propargyl alcohols can be synthesized asymmetrically *via* the addition of a zinc acetylide to a ketone in the presence of a chiral organic catalyst. However, as a result of the low reactivity of ketones, many of the early reports in this field dealt with the asymmetric addition of acetylides to highly activated aryl trifluoromethyl ketones. The addition of cyclopropylacetylide was particularly well investigated[139] as the structural moiety generated from this reaction is present in Efavirenz®, a potent non-nucleosidal HIV reverse transcriptase inhibitor. These methods, however, were unsuccessful when applied to less reactive ketones, necessitating the development of more broadly applicable protocols.

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[139] (a) Tan, L.; Chen, C-y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 771-773; (b) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975-2977; (c) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028-2038.

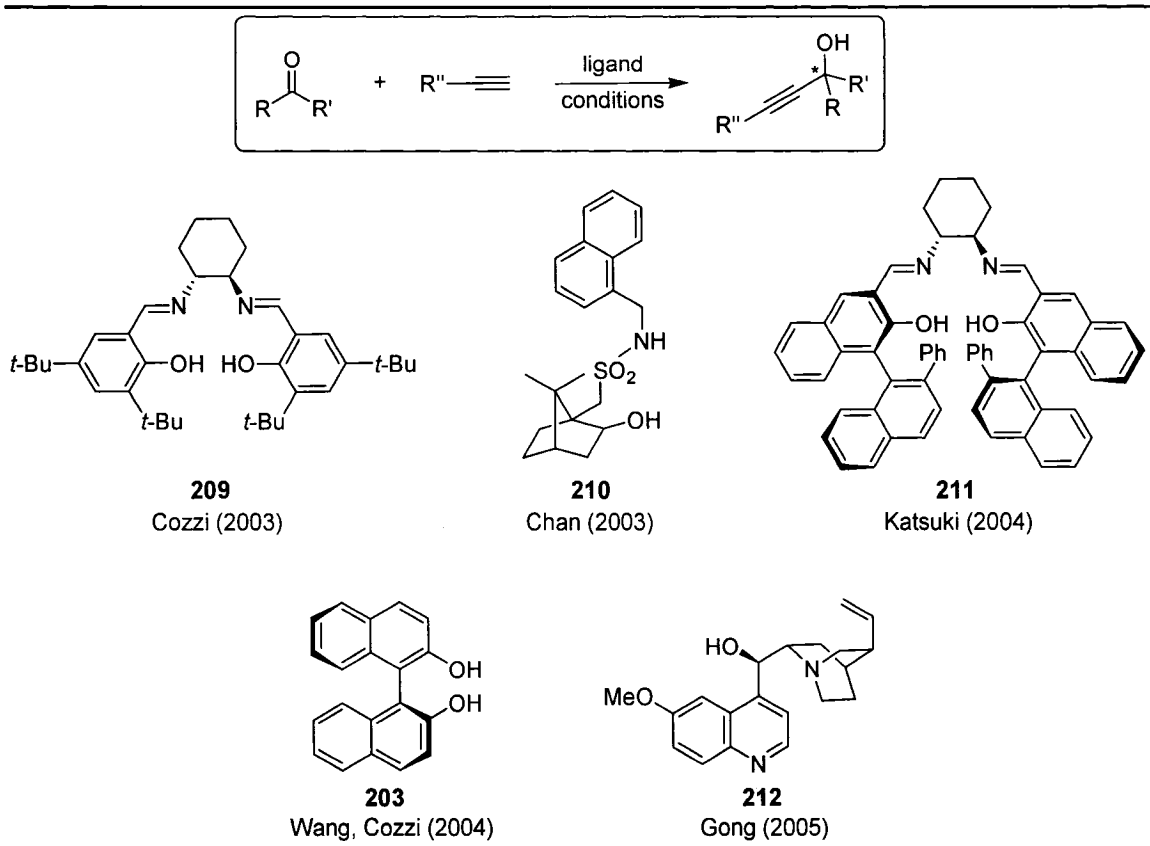


Figure 24: Ligands that promote the asymmetric addition of acetylides to ketones

Six methods for the asymmetric addition of an acetylide to an unactivated ketone using the organic catalysts depicted in Figure 24 have been reported.[140] The first successful catalyst system was reported in 2003 by Cozzi, who demonstrated that salen **209** catalyzed the asymmetric addition of zinc acetylides (primarily phenylacetylide) to a variety of aromatic and aliphatic methyl ketones in moderate yields (40-89%) and enantiomeric excesses (32-80%).[141] Also in 2003, Chan reported a protocol in which camphorsulfonamide **210** catalyzed the asymmetric addition of zinc phenylacetylide to substituted acetophenones in the presence of $Cu(OTf)_2$.[142] Although generally high yields and enantioselectivities were obtained, the procedure was severely limited in scope. In 2004, Katsuki reported a more general method that used BINOL-based salen **211** to promote the asymmetric addition of a variety of zinc acetylides to both aliphatic and aromatic ketones.[143] Good yields (13-98%, median ~70%) and

[140] Four of these were reported after conclusion of our work in this area in early 2004.
[141] Cozzi, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 2895-2898.
[142] Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5057-5058.
[143] Saito, B.; Katsuki, T. *Synlett* **2004**, 1557-1560.

enantiomeric excesses (71-94%) were obtained. Later in 2004, Wang[144] and Cozzi[145] each independently reported that a titanium BINOL (**203**) complex catalyzed the asymmetric addition of phenylacetylide to substituted acetophenones. As with Chan's report in 2003, good yields and enantioselectivities were obtained, but the poor generality of the protocol limited its utility. A sixth report in early 2005 by Wang used a cinchona alkaloid (**212**) to catalyze the asymmetric addition of phenylacetylene to substituted acetophenones in the presence of Et_3Al and Et_2Zn.[146] Again, good yields (61-80%) and enantiomeric excesses (70-89%) were obtained, but the scope of the reaction was highly limited.

In theory, tertiary propargyl alcohols can also arise from the addition of an alkyl or phenyl group to a propargyl ketone, although to date there have been no reported examples of this reaction. However, a few protocols exist that catalyze the asymmetric addition of these groups to similarly reactive ketones that may be useful for our purpose.

The first such example was reported in 1998 by Fu, who described the asymmetric addition of phenyl groups to methyl ketones using diphenylzinc and camphor-based amino alcohol **213** (Figure 25).[147] Good yields (53-91%) and enantioselectivities (60-91%) were observed for both aromatic and aliphatic ketones. In the same year, Yus reported that camphorsulfonamide **210** and titanium tetraisopropoxide catalyzed the asymmetric addition of methyl or ethyl groups to aliphatic and aromatic ketones.[148] Yields averaging near 70% and enantioselectivities of ~60-90% were obtained in most cases, although substantially lower selectivities were observed when the two groups of the ketone were similar in steric bulk (*e.g.*, Ph and *t*-Bu). In 2002, Walsh disclosed that dihydroxy bis(sulfonamide) **214** and $Ti(O\textit{i}\text{-}Pr)_4$ gave good to excellent enantioselectivities in the asymmetric addition of ethyl groups to a variety of aromatic ketones.[149] This has since become the catalyst of choice for this transformation. The scope of the reaction has been expanded to include the addition of phenyl[150] or alkyl groups to

[144] Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147-4149.
[145] Cozzi, P. G.; Alesi, S. *Chem. Commun.* **2004**, 2448-2449.
[146] Liu, L.; Wang, R.; Kang, Y-F.; Chen, C.; Xu, Z-Q.; Zhou, Y-F.; Ni, M.; Cai, H-Q.; Gong, M-Z. *J. Org. Chem.* **2005**, *70*, 1084-1086.
[147] Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445-446.
[148] Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239-1242.
[149] García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970-10971.
[150] García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641-3644.

aromatic, aliphatic,[151] and cyclic ketones,[152] and it has already been used in at least one total synthesis.[153]

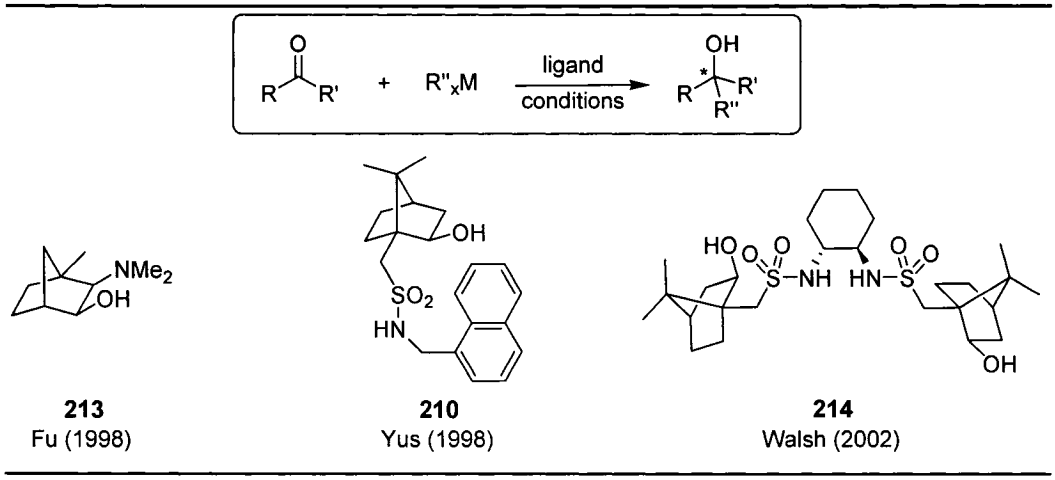


Figure 25: Ligands that promote the asymmetric addition of alkyl groups to ketones

As is evident from the preceding discussion, methods for the asymmetric synthesis of tertiary propargyl alcohols are still in their infancy, with all protocols currently available suffering from serious issues of generality. Although substantial progress has been made in recent years, no one method is particularly attractive. At present it would appear that the most useful protocols for the asymmetric synthesis of tertiary propargyl alcohols are those involving the addition of an acetylide to a ketone, although the addition of an alkyl group to a ketone is becoming an attractive alternative. The chemistry of these transformations will undoubtedly continue to develop.

5.7 The Design of an Acetylenic Allenophane

The goal of this project was to synthesize a chiral, non-racemic cyclophane containing allenes as the source of chirality for the macrocycle. In contrast to the reported allenophane, we envisioned a cyclophane containing both allene and acetylene bridges, which we termed an acetylenic allenophane. The general design of our acetylenic allenophane is depicted in Figure

[151] Jeon, S-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448-455.
[152] Jeon, S-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544-9545.
[153] Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745-2748.

26. We incorporated a considerable amount of flexibility in the design to allow the properties of the cyclophane to be easily altered and controlled. Such flexibility may also be synthetically advantageous by expanding the number of potential synthetic methods and strategies that could be used during the synthesis. As noted, the size of the macrocycle can be varied *via* the introduction of aryl or acetylene spacers between the allene and aryl ring or by changing the number of bridging acetylenes. Substituents (R^2) could be added to the aromatic rings to both increase the solubility and tune the properties of the cyclophane. These groups are necessary as the poor solubility of the reported allenophane[115] prevented a full investigation of its properties. The R^1 groups on the allene may be hydrogen or alkyl, depending on the method selected to synthesize the allene.

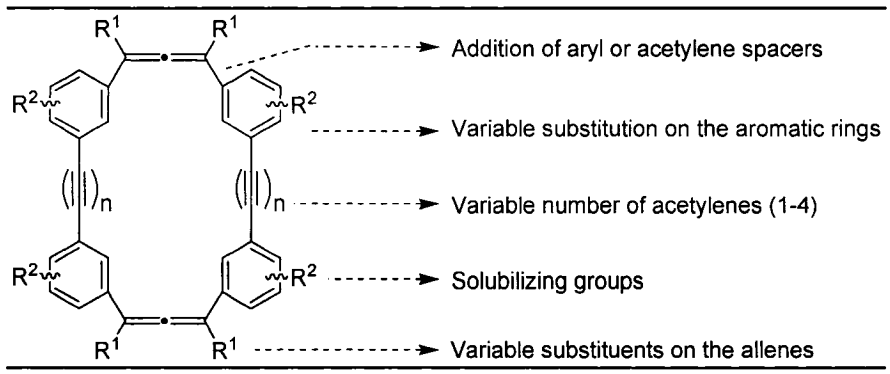
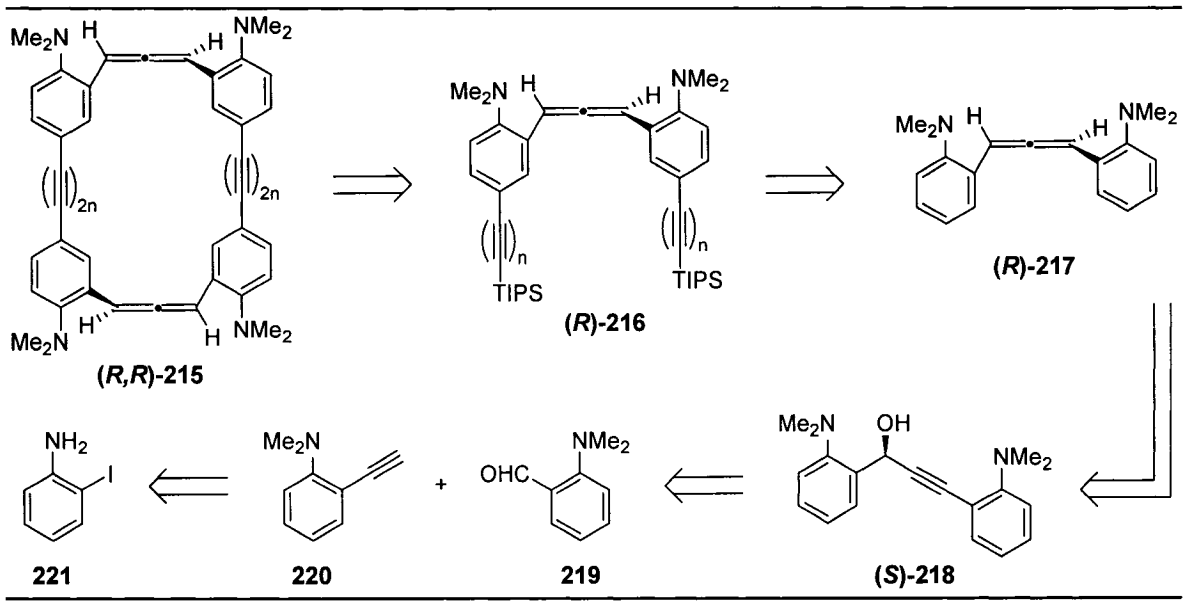


Figure 26: Our design of an acetylenic allenophane

5.7.1 Retrosynthesis

Our retrosynthetic approach to our first acetylenic allenophane (**215**) is shown in Scheme 37. It was anticipated that the dimethylamino groups on the aromatic rings would both increase the solubility of the cyclophane and serve as a handle for selective *para* functionalization of the aromatic ring. We envisioned that the desired acetylenic allenophane **215** could arise from monomer **216** using the desilylation-dimerization protocol developed in our laboratory.[71] The aforementioned requirement (Section 5.5.3) that the allene termini be identically substituted is clearly demonstrated here. If they were differentially substituted, both the symmetric and non-symmetric products would arise from this dimerization. The monomer (**216**) could readily be accessed from allene **217** *via* selective *para*-iodination of the aromatic rings using Kajigaeshi's

reagent[154] followed by a palladium-mediated coupling with an appropriate acetylene. This disubstituted allene (**217**) could be synthesized directly from secondary propargyl alcohol **218** using Myers' propargyl diazine rearrangement.[16] We chose to use this method to synthesize the allenes asymmetrically primarily because the non-racemic secondary propargyl alcohols necessary for this protocol were more readily available than the tertiary propargyl alcohols that would be required for the organocopper-mediated procedure. Thus, propargyl alcohol **218** could be synthesized asymmetrically from aldehyde **219** and acetylene **220** using the procedures mentioned in Section 5.6.1. These two precursors could be readily accessed from commercially available 2-iodoaniline (**221**).



Scheme 37: Our retrosynthetic approach to acetylenic allenophane 215

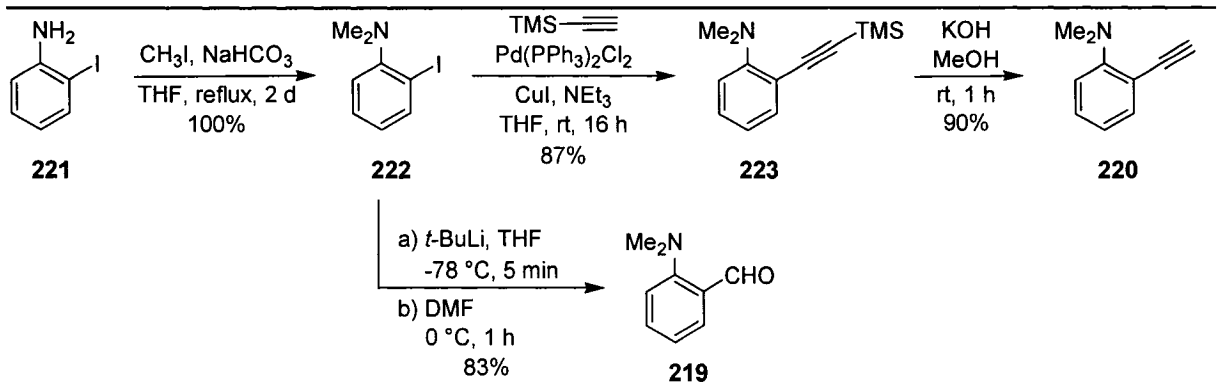
We anticipated that the most difficult aspect of our synthesis would be obtaining propargyl alcohol **218** in an acceptably high enantiomeric excess. For this reason, we chose to first pursue the racemic synthesis to confirm that the subsequent steps of the synthesis were feasible before focusing our efforts on optimizing the asymmetric addition of acetylene **220** to aldehyde **219** to generate propargyl alcohol **218**.

[154] Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600-602.

6 Results and Discussion

6.1 Racemic Synthesis of Propargyl Alcohol 218

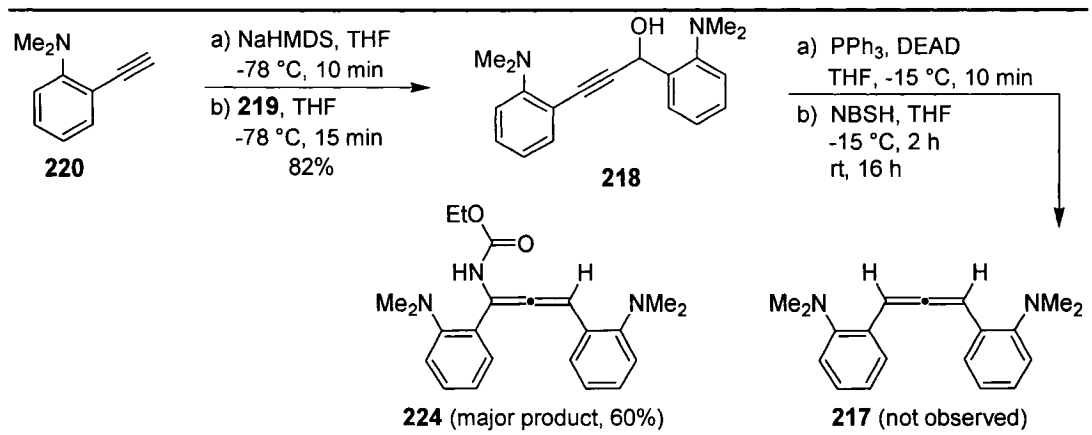
The acetylene (**220**) and aldehyde (**219**) necessary for the synthesis of secondary propargyl alcohol **218** were readily synthesized *via* the short sequences shown in Scheme 38. Beginning with commercially available 2-iodoaniline, *N,N*-dimethylaniline **221** was synthesized in quantitative yield using CH_3I and $NaHCO_3$. A Sonogashira reaction of **222** with TMS-acetylene under standard conditions then provided **223** in 87% yield, which was desilylated using KOH in MeOH to generate terminal acetylene **220** in 90% yield. Aldehyde **219** was isolated in 83% yield after formylation *via* successive treatment of **222** with *t*-BuLi and DMF.



Scheme 38: Syntheses of acetylene 220 and aldehyde 219

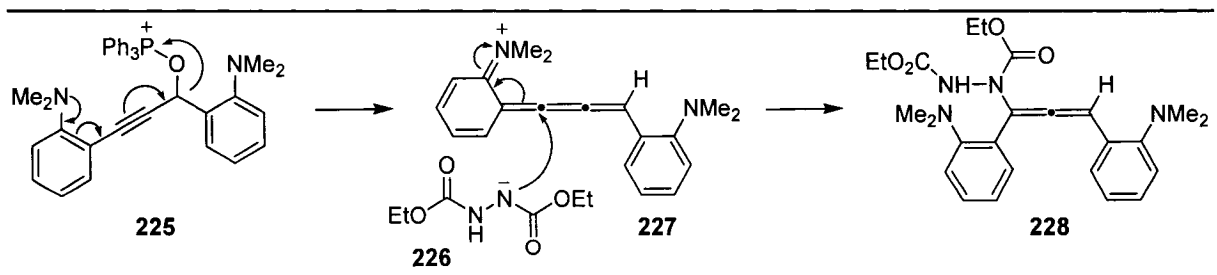
Subsequent deprotonation of acetylene **220** using NaHMDS generated the intermediate sodium acetylide, which was quenched with aldehyde **219** to provide racemic propargyl alcohol **218** in 82% yield (Scheme 39). Conversion of **218** to the allene was then attempted using Myers' protocol.[16] Exposure of propargyl alcohol **218** to a mixture of PPh_3 and DEAD followed by the addition of NBSH (**28**) should have generated allene **217** *via* the previously described propargyl diazine [3,3]-sigmatropic rearrangement. Instead, a compound with a molecular weight of 365 and exhibiting ^1H NMR resonances characteristic of aromatic, dimethylamino, and ethyl ester groups was isolated as the major product in 60% yield. A temperature of 75 °C was necessary to achieve sharp resonances in the ^1H NMR spectrum, suggesting the presence of

rotamers. Careful analysis of the data indicated that the product was the unusual allenylcarbamate **224**. The hypothesized presence of rotamers can likely be explained by hindered rotation about the nitrogen-carbonyl bond of the carbamate moiety of **224**.



Scheme 39: Attempted formation of allene 217

This product could have arisen *via* the mechanism illustrated in Scheme 40. Dimethylamine-assisted expulsion of triphenylphosphine oxide from **225** would generate cumulene **227**, which would be quenched by **226** (formed from reaction of DEAD with PPh_3 and alcohol **218**) to generate allene **228**. A more direct mechanism involving the S_N2' addition of **226** to **225** can largely be discounted due to the success of this protocol in the literature, as well as our results for the substrates in Section 6.2. The exact mechanism to convert allene **228** into the allenylcarbamate we isolated (**224**) is not known; however, participation from PPh_3 is likely.



Scheme 40: Possible mechanism to account for the formation of allene 224

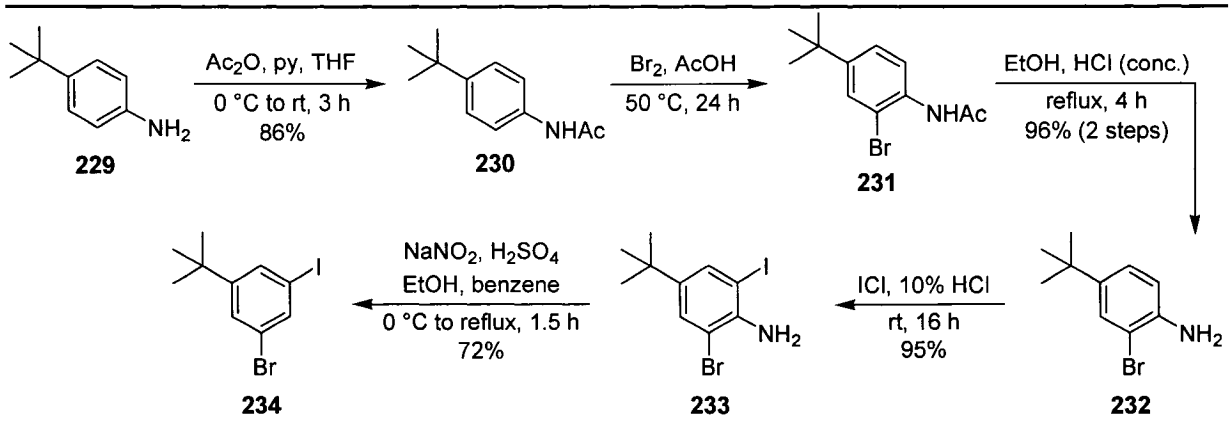
This mechanism was consistent with experimental observations. When monitored by TLC, it was observed that the reaction was complete before the addition of NBSH, and when

quenched before NBSH had been added, an identical product was obtained. In early attempts to circumvent this undesirable reaction, we sought to synthesize the corresponding tosylate or acetate of alcohol **218**, believing that these could be isolated and further reacted with NBSH to generate the alkyl sulfonylhydrazine intermediate necessary for allene formation. In both cases alcohol **218** was completely converted within minutes to the tosylate or acetate (as indicated by TLC); however, this product then decomposed. This decomposition very likely occurred in a manner similar to that shown in Scheme 40. At this point it seemed prudent to abandon the dimethylamino functionality and pursue the synthesis using a different solubilizing group.

6.2 Racemic Synthesis of Allenes with *tert*-Butyl Solubilizing Groups

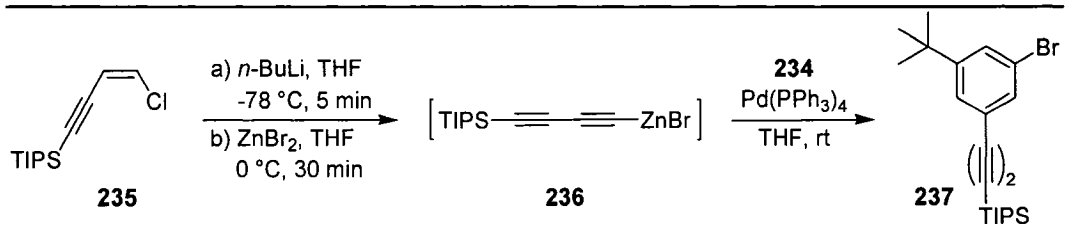
We chose *tert*-butyl groups as our new solubilizing groups because they have previously been shown to improve solubility and are relatively electronically neutral. Additionally, we decided to place the group *meta* to the other ring substituents so that any potential steric or electronic effects would be minimized. A compound matching these criteria, 1-bromo-3-*tert*-butyl-5-iodobenzene (**234**), has previously been reported and was synthesized using the procedure shown in Scheme 41.[155] Beginning with 4-*tert*-butylaniline (**229**), acetylation of the amine using Ac_2O and pyridine provided amide **230**, which was mono-*ortho*-brominated using bromine in AcOH. Hydrolysis of the amide using concentrated HCl in EtOH provided the amine (**232**), which was *ortho*-iodinated with ICl in 10% HCl to give **233**. A Sandmeyer-type reaction of **233** with EtOH then generated the desired starting material, **234**, for our synthesis. The length of the synthesis was offset by the ease at which it could be performed on large scale.

[155] Tobe, Y.; Utsumi, N.; Nagano, A.; Sonoda, M.; Naemura, K. *Tetrahedron* **2001**, *57*, 8075-8083.



Scheme 41: Synthesis of 1-bromo-3-tert-butyl-5-iodobenzene (234)

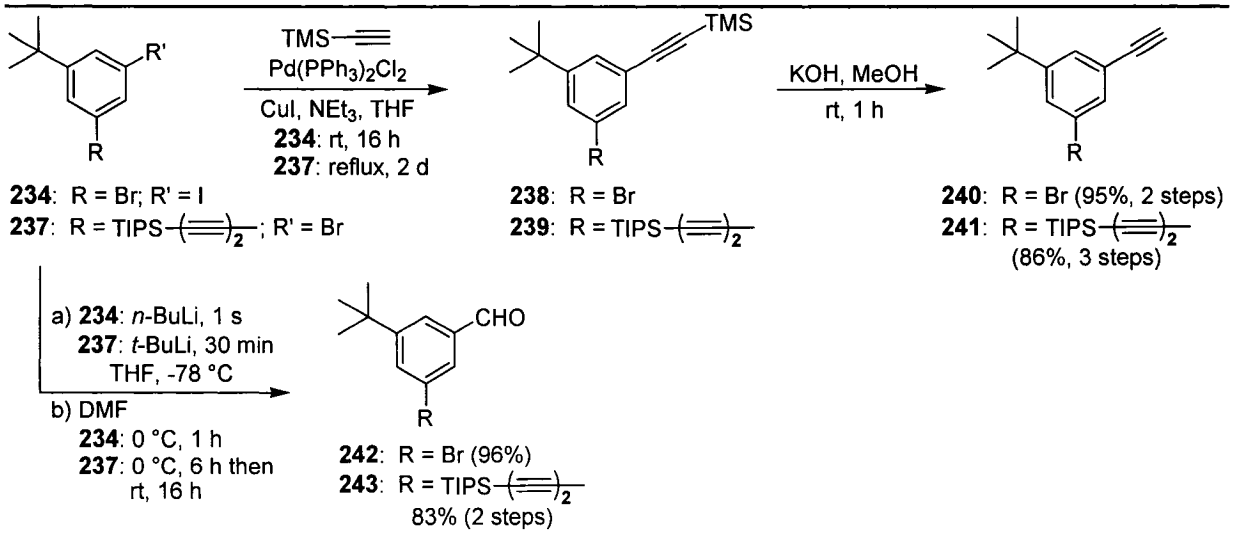
In contrast to amine **221**, this new starting material already contained two halogens and thus the reaction sequence to synthesize the allene could be conducted on two possible substrates. More specifically, the substituent in the 3-position of the benzene ring could be either a bromine or a substituted acetylene (*e.g.*, see Scheme 43). The synthesis of aryl bromide **237**, with a substituted acetylene in the 3-position, is shown in Scheme 42. Chloroenyne **235**, prepared *via* a Sonogashira reaction between TIPS-acetylene and *cis*-1,2-dichloroethene, was converted *in situ* to the zinc acetylide (**236**) by treatment with two equivalents of *n*-BuLi followed by $ZnBr_2$. Zinc acetylide **236** then underwent a Negishi coupling with iodide **234** to generate the desired aryl bromide (**237**). Several minor impurities (~5%) could not be separated from **237** at this stage and were removed later in the synthesis once more polar functionalities were introduced.



Scheme 42: Synthesis of bromide 237

Acetylenes **240** and **241** and aldehydes **242** and **243**, necessary for the synthesis of the required propargyl alcohols (**244** and **245**) were synthesized as shown in Scheme 43. A Sonogashira reaction between TMS-acetylene and iodide **234** was complete within 16 hours at

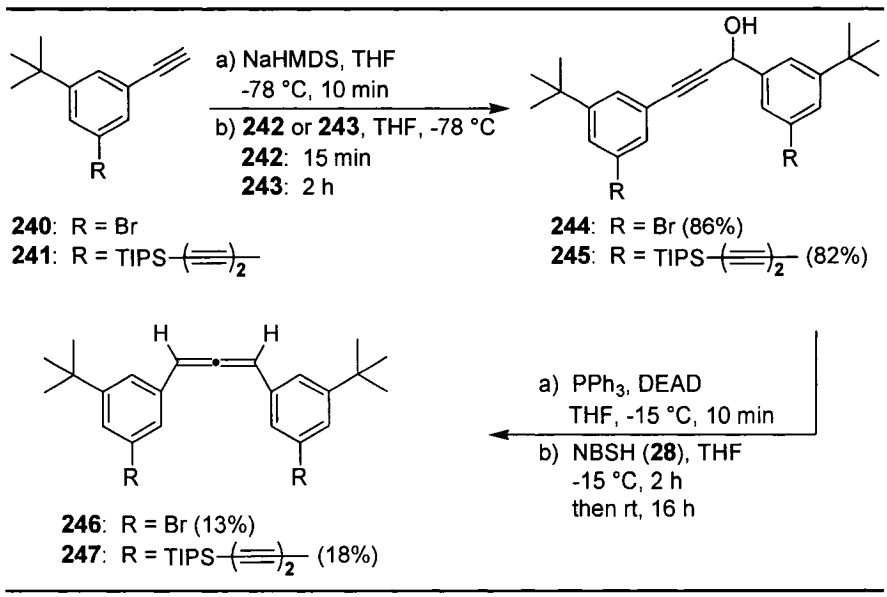
room temperature, while the analogous reaction on the less reactive bromide **237** required two days at reflux to complete. Removal of the trimethylsilyl groups of **238** and **239** using KOH in MeOH then yielded acetylenes **240** and **241** in 95% yield (2 steps) and 86% yield (3 steps), respectively. At this stage, the polarity of the terminal acetylene permitted the product to be separated from the impurities generated in the preceding reactions. Aldehyde **242** was synthesized in 96% yield *via* treatment of **234** with one equivalent of *n*-BuLi followed by the immediate addition of excess DMF. A similar treatment of **237** with two equivalents of *t*-BuLi and excess DMF generated aldehyde **243** in 83% yield (from **234**).



Scheme 43: Synthesis of acetylenes 240 and 241 and aldehydes 242 and 243

The racemic secondary propargyl alcohols were then synthesized. Deprotonation of acetylene **240** using NaHMDS generated the intermediate sodium acetylide, which was reacted with its corresponding aldehyde (**242**) to provide propargyl alcohol **244** in 86% yield (Scheme 44). Alcohol **244** was then subjected to Myers' protocol[16] to form the disubstituted allene. Treatment of **244** with a mixture of PPh_3 and DEAD followed by the addition of NBSH (**28**) generated allene **246** in 13% yield. Similar procedures on **241** and **243** afforded alcohol **245** in 82% yield and allene **247** in 18% yield. The low yield of allene was disappointing, but the problem we had previously observed with this protocol when using dimethylamino solubilizing groups appeared to have been solved, as no products resembling allenylcarbamate **224** were isolated from the reaction. Although this is certainly not sufficient proof, this result does lend

support to our mechanistic proposal for the formation of the allenylcarbamate shown in Scheme 40. We thus turned our attention to optimizing this reaction.

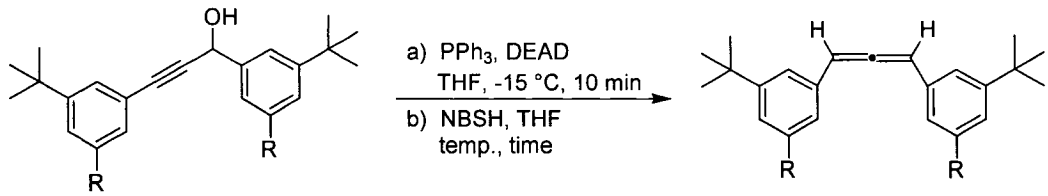


Scheme 44: Synthesis of allenes 246 and 247

Our attempts to optimize the yield of the allene-formation are presented in the following tables. Table 5 describes our modifications to the optimized reaction conditions reported by Myers, while Table 6 details more substantial changes to the reaction, such as the use of different reagents. We initially varied the number of equivalents of each reagent while preserving the 1:1:1 ratio of PPh_3:DEAD:NBSH (Table 5). As reported by Myers, hindered substrates often required a moderate excess of each reagent for the reaction to complete. However, using either 1.3, 1.5 or 3 equivalents of each reagent produced poor yields of allene ranging from 13-18% (entries 1-3), while the use of a stoichiometric amount produced a mixture of allene **246** and alcohol **244** (entry 4). The absence of alcohol (**244** or **245**) from the product mixture when excess reagent was used suggested that the alkyl sulfonylhydrazine was forming and that the problematic step was likely the sigmatropic rearrangement of this intermediate. We therefore attempted the reaction at different temperatures, but observed complete decomposition at 55 °C (entry 5) and achieved only an 8% yield of allene at 0 °C (entry 6). Myers also reported that NBSH can be decomposed by excess PPh_3 and DEAD. However, when the reaction was conducted with excess NBSH (entry 7), or when a solution of NBSH was slowly added *via*

syringe pump to the reaction (entry 2c), similarly poor yields of allene were obtained. These discouraging results prompted us to investigate alternatives to PPh_3, DEAD, and NBSH.

Table 5: Attempted optimization of Myers' reported conditions



244: R = Br
245: R = TIPS-(≡)$_2$-

246: R = Br
247: R = TIPS-(≡)$_2$-

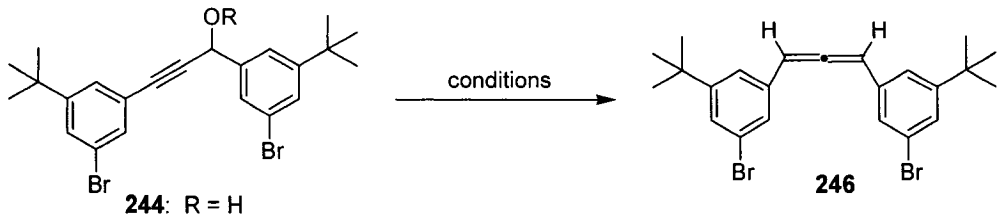
Entry	Alcohol	Equivalents of PPh_3, DEAD and NBSH	Conditions (after addition of NBSH)	Result
1	**245**	1.3	-15 °C (15 min) to rt (16 h)	14% **247**
2	**245**	3	-15 °C (2 h) to rt (16 h)[c]	18% **247**
3	**244**	1.5	-15 °C (1 h) to rt (16 h)	13% **246**
4	**244**	1	-15 °C (1 h) to rt (16 h)	mixture[b]
5	**244**	3	-15 °C (30 min) to 55 °C (3 h)	decomposition
6	**244**	3	-15 °C (30 min) to 0 °C (10 h	8% **246**
7	**244**	6[a]	-15 °C (30 min) to rt (16 h)	mixture[b]

a) Four equivalents of PPh_3 and DEAD were used
b) The mixture contained some of the desired allene
c) A similar result was obtained when NBSH was added slowly *via* syringe pump.

We next tried changing the various reagents present in the reaction to find more optimal conditions (Table 6). Changing the phosphine and dicarboxylate sources to PBu_3 and DIAD was detrimental, generating a complex mixture of products (entry 1). Similarly, employing $TsNHNH_2$ as the hydrazine source failed to provide any allene product (entry 2). This procedure had also been investigated by Myers and was found to be inferior to using NBSH.[16] We also tried converting the hydroxyl group of **244** into a leaving group other than triphenylphosphine oxide. Thus, *in situ* mesylation of the alcohol provided the mesylate (as suggested by TLC), which was consumed upon addition of NBSH. Unfortunately, a complex mixture of products resulted from the reaction (entry 3). Alcohol **244** was similarly converted *in situ* to the corresponding triflate (as suggested by TLC); however, unlike the mesylate the triflate was not consumed by NBSH (entry 4). Attempts to isolate the triflate yielded only alcohol **244**, presumably *via* hydrolysis of the triflate. In a final attempt we synthesized the corresponding

trifluoroacetate (**248**) of alcohol **244** and reacted it with the lithium anion of NBSH (entry 5) or $TsNHNH_2$ (entry 6). Unfortunately, alcohol **244** resulted from each reaction (by TLC, and isolated), indicating the nucleophile had preferentially attacked the acetate carbonyl rather than the propargylic position.

Table 6: Significant changes to Myers' reported protocol



244: R = H
248: R = $COCF_3$

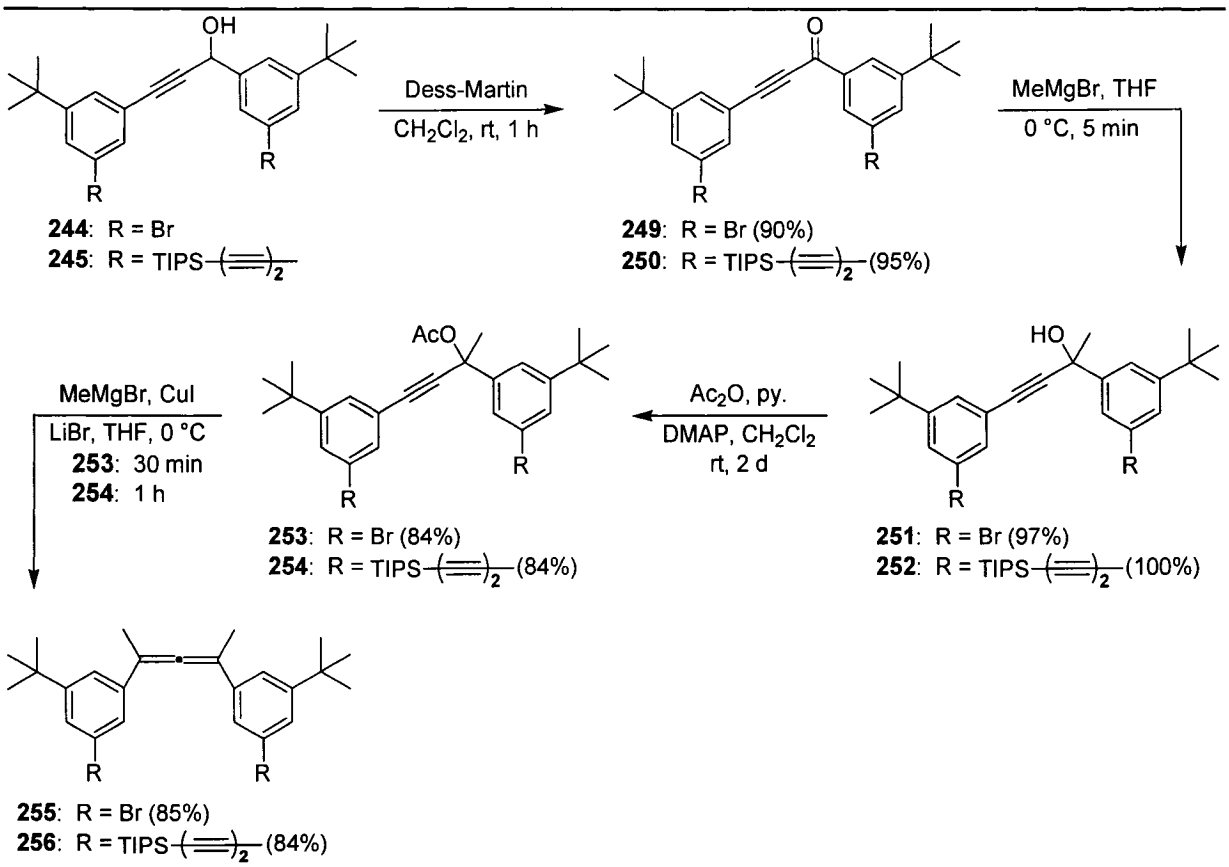
246

Entry	Substrate	Conditions	Result
1	**244**	a) Bu_3P, DIAD, -15 °C (15 min) b) NBSH, -15 °C (10 min) to rt (16 h)	complex mixture
2	**244**	a) PPh_3, DEAD, -15 °C (15 min) b) $TsNHNH_2$, -15 °C (10 min) to rt (1 h) c) Remove solvent, add MeOH, stir at rt (16 h)	complex mixture
3	**244**	a) MsCl, NEt_3, 0 °C (15 min) then cool to -15 °C b) NBSH, -15 °C (1 h) to rt (16 h)	complex mixture
4	**244**	a) Tf_2O, py., DMAP, 0 °C (25 min) b) NBSH, -15 °C (2 h) to rt (16 h)	Triflate (R = Tf)
5	**248**	NBSH + *n*-BuLi, -15 °C, 1 min then add **248** and stir at -15 °C (2 h), then at rt (16 h)	**244** (R = H)
6	**248**	$TsNHNH_2$ + *n*-BuLi, -15 °C, 1 min then add **248** and stir at -15 °C (2 h), then remove solvent, add MeOH, and stir at rt (16 h)	**244** (R = H)

The reason for the low yield of allene remains elusive. Although Myers and other authors employing his procedure have not reported any examples of diphenylsubstituted allenes, we do not believe this should not have adversely affected the reaction. It could be that a subtle combination of steric and electronic factors may have favored attack at the β-position of the acetylene (S_N2') rather than direct displacement of the leaving group. Regardless of the cause however, an alternative and higher yielding method of synthesizing the allene was clearly necessary.

6.3 Racemic Synthesis of Allenes Using Organocuprates

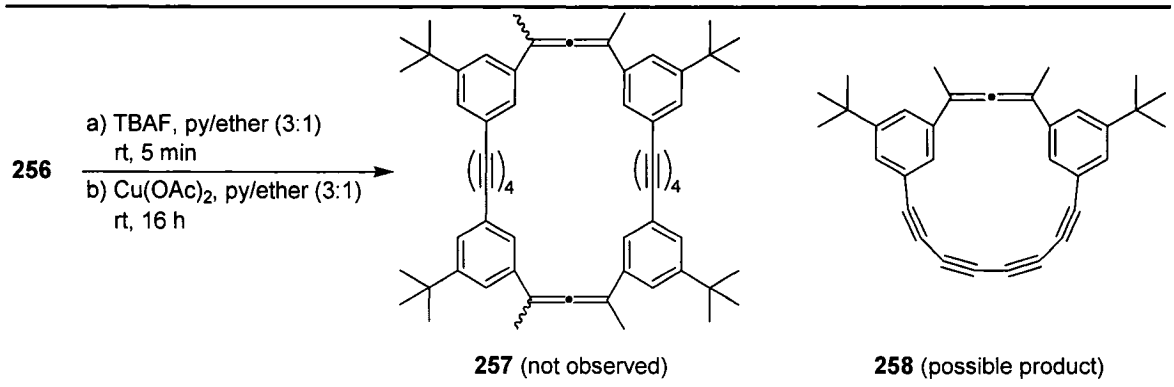
The S_N2' addition of an organocuprate to a propargylic substrate described in Section 5.5.3 was the method of synthesizing allenes we chose to pursue next. As previously described, this method has been successfully employed for decades and thus should be tolerant of the functionalities present in our system. This protocol, however, had the major disadvantage that enantiomerically enriched tertiary propargyl alcohols would now be required, which are substantially more difficult to synthesize than the secondary propargyl alcohols that had previously been required. As we had done previously, we initially pursued the racemic synthesis to verify that the other synthetic steps were feasible before attempting an asymmetric synthesis.



Scheme 45: Racemic synthesis of allenes 255 and 256

The required propargyl acetates **253** and **254** were rapidly accessed from secondary propargyl alcohols **244** and **245** following the procedures in Scheme 45. Both acetates **253** and

254 were investigated in order to determine whether there was a difference in reactivity between them. Oxidation of alcohols **244** and **245** using Dess-Martin periodinane provided ketones **249** and **250** in 90% and 95% yield, respectively. Addition of MeMgBr then gave racemic tertiary alcohols **251** and **252** in 97% and 100% yield and acetylation of each using Ac_2O provided the corresponding tertiary propargyl acetates **253** and **254**, each in 84% yield. Gratifyingly, addition of **253** to a mixture of MeMgBr, CuI, and LiBr in THF at 0 °C smoothly generated allene **255** in 85% yield. Acetate **254** was subjected to an identical procedure and produced allene **256** in 84% yield.

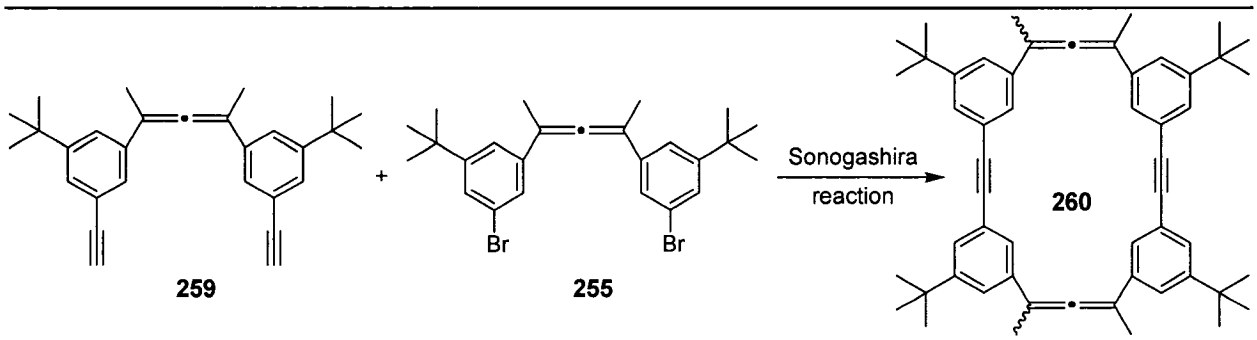


Scheme 46: Attempted formation of racemic acetylenic allenophane 257

With allene **256** in hand, we attempted the critical dimerization to form acetylenic allenophane **257** (Scheme 46) using an Eglinton coupling. Thus, allene **256** was dissolved in a 3:1 mixture of pyridine and ether, TBAF was added, and then this solution was slowly added over a period of six hours to a solution of $Cu(OAc)_2$ in pyridine and ether to affect the dimerization. Within hours an intensely yellow-colored product had formed (as indicated by TLC). After workup and filtration through silica, a brilliant yellow oil was isolated together with an insoluble white solid. The ^1H NMR of the yellow oil contained three broad singlets in the aromatic region as well as resonances belonging to the methyl and *tert*-butyl groups, suggesting the desired acetylenic allenophane (**257**) had formed. Unfortunately, the yellow oil completely decomposed into the insoluble white powder within hours of isolation. Repetition of the experiment provided additional material for mass spectral analysis; however, neither the monomer (**258**) or dimer (**257**) molecular ions or any obvious fragments of either were observed. As we had fully expected acetylenic allenophane **257** to be stable, we hypothesized that

intramolecular dimerization of the terminal acetylenes had occurred to generate the unusual allenophane **258**.

This theory was strongly supported by precedent in our lab[72] and the literature,[156] as well as molecular modeling studies, which have shown that an acetylene termini separation distance of <7 Å leads to intramolecular acetylene dimerization, while a separation distance of >10 Å gives intermolecular dimerization product in the Eglinton coupling. Separations between 7 and 10 Å typically give mixtures of both products. Our initial calculation of the acetylene termini separation of allene **256** was erroneous[157] and suggested that exclusively intermolecular dimerization would occur. In actuality the acetylene termini of **256** are in close contact with one another, which would very likely produce intramolecularly coupled product, as we suspect occurred. The instability of our compound, however, prevented a definitive structural assignment.



259 **255** **260**

Scheme 47: Modified racemic synthesis of an acetylenic allenophane

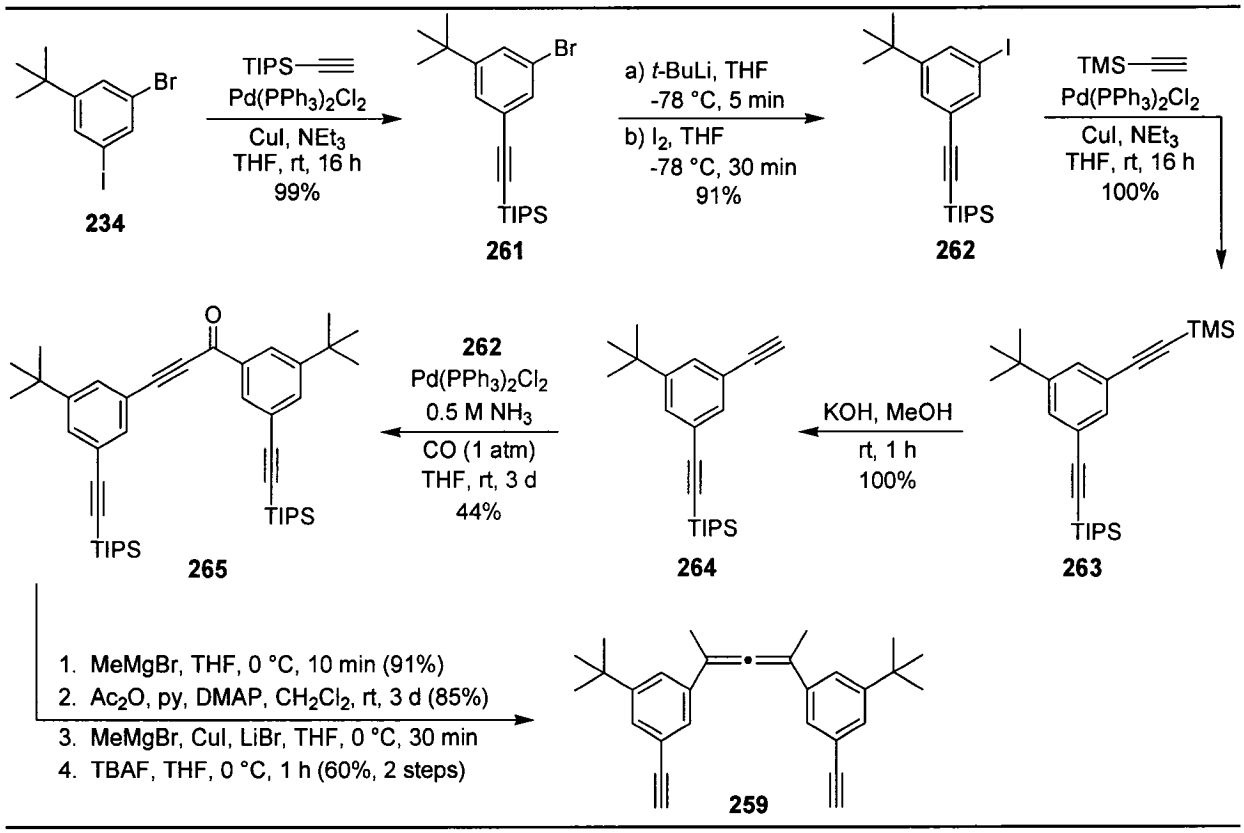
The distance between the acetylene termini in our precursor was decreased by using an ethyne spacer rather than a butadiyne moiety (Scheme 47). However, the calculated acetylene termini separation of 8.87 Å[158] in this molecule suggested that a mixture of intra- and intermolecular dimerization products would result from an Eglinton coupling. To resolve this

[156] Tobe, Y.; Kishi, J-y.; Ohki, I.; Sonoda, M. *J. Org. Chem.* **2003**, *68*, 3330-3332.

[157] The most stable conformer of related molecules has the terminal acetylenes oriented on opposite sides of the bridge (in our case, the allene). To calculate the minimum distance between the acetylene termini in previous examples (*i.e.*, the most reactive conformer for intramolecular dimerization), the free rotation about the bridge-aryl bonds was restricted. This method, however, did not account for the geometry of the allene present in our molecule and led to the erroneous value for the acetylene termini separation. For a full description of this method, see reference 72.

[158] Semiempirical AM1 calculations were performed by using the Cerius^2-Dmol^3 Molecular Modeling Suite from Molecular Simulations Inc. of San Diego, CA (1999) and by using the methods in: Dewar, M.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4499-4500.

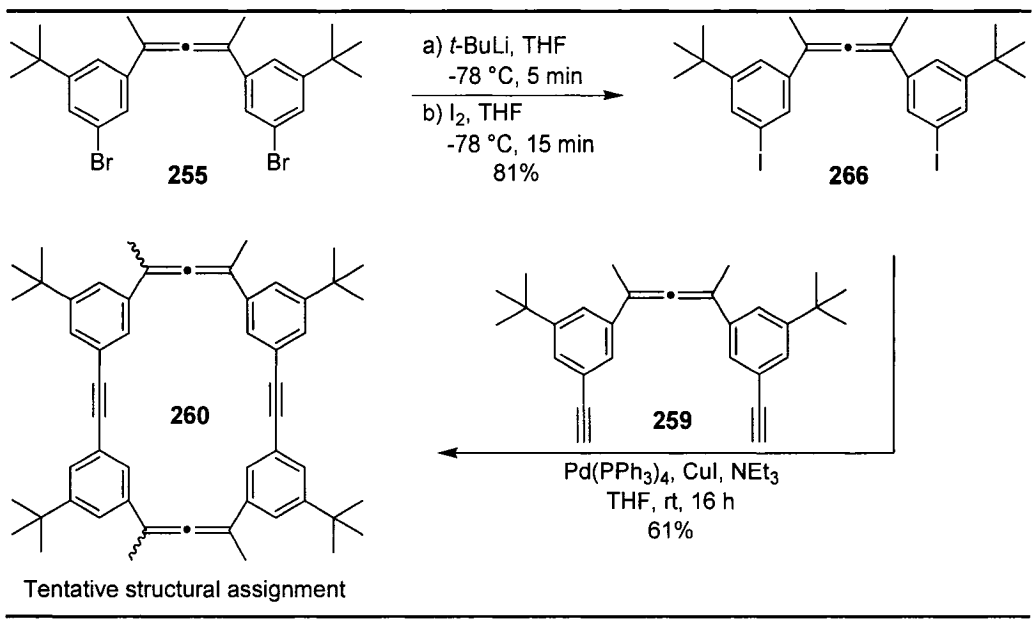
potential problem, we chose to use a Sonogashira coupling to synthesize the acetylenic allenophane, as intramolecular dimerization of the acetylenes of **259** would be much less likely using this method. The related Sonogashira reaction between desilylated **256** and bromide **255** was not feasible due to the instability of the unprotected aryl butadiyne moieties.



Scheme 48: Racemic synthesis of allene 259

The synthesis of acetylene **259** closely paralleled the synthesis of **256**, commencing with a Sonogashira reaction between iodide **234** and TIPS-acetylene to provide bromide **261** in 99% yield (Scheme 48). Lithium-halogen exchange of bromide **261** with *t*-BuLi followed by an iodine quench then provided iodide **262** in 91% yield, which smoothly underwent a Sonogashira reaction with TMS-acetylene to provide **263** in quantitative yield. The analogous Sonogashira reaction on bromide **261** had been unsuccessful, necessitating its conversion to iodide **262**. Cleavage of the trimethylsilyl group of **263** then quantitatively provided the terminal alkyne (**264**), which then underwent a carbonylative Sonogashira coupling with iodide **262** to provide

ketone **265**.[159] This procedure eliminated three steps from the analogous route to ketone **250** (Schemes 44 and 45), which compensated for the low yield of the coupling reaction. The conversion of ketone **265** to allene **259** was accomplished using previously described conditions. Thus, methyl Grignard addition to ketone **265** followed by acetylation provided the propargyl acetate, which was converted to the allene using the cuprate generated from a mixture of MeMgBr, CuI and LiBr. Desilylation then provided allene **259** in an overall yield of 46% from ketone **265**.[160]



Scheme 49: Synthesis of acetylenic allenophane 260

The stage was now set for the key Sonogashira reaction to assemble racemic acetylenic allenophane **260**. To ensure the reaction would proceed under sufficiently mild conditions, bromide **255** was converted in 81% yield to iodide **266** *via* the previously described lithium-halogen exchange – iodine quench procedure (Scheme 49). The Sonogashira reaction between acetylene **259** and iodide **266** then provided a colorless and stable product in 61% yield. The ^{1}H NMR exhibited the expected methyl, *tert*-butyl, and aromatic resonances, although the three resonances in the aromatic region each appeared as a broad singlet. The mass spectrum (EI) was

[159] Ahmed, M. S. M.; Mori, A. *Org. Lett.* **2003**, *5*, 3057-3060.

[160] In retrospect, a substantially shorter route to **259** could have been a Sonogashira reaction between bromide **255** and TMS-acetylene, followed by desilylation. Our route, however, allowed us to investigate the carbonylative Sonogashira reaction as well as confirm the critical allene-forming step was also possible on this substrate.

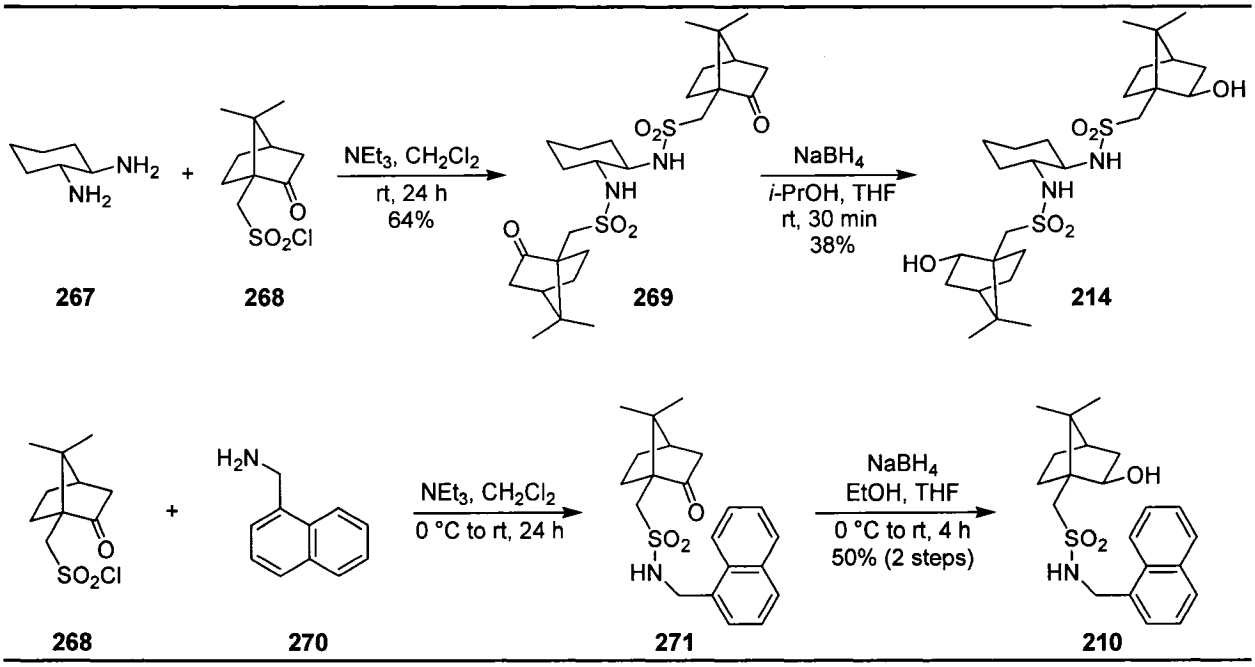
very clean, exhibiting only the M^+ (708) and M^+-57 (651) peaks above molecular weight 380. High resolution mass-spectrometry confirmed the molecular formula was $C_{54}H_{60}$. However, the ^{13}C NMR was complex, exhibiting approximately 25 resonances tightly clustered in the aromatic, allenyl, and alkyl regions. We believed this resulted from the diastereomeric acetylenic allenophanes that would have resulted from the coupling of racemic **266** and **259**. It would be expected that the ^1H NMR resonances of the diastereomers would be less well resolved than the ^{13}C NMR signals due to the narrower frequency range of ^1H NMR, which would explain the broadening of the aromatic signals. We were therefore satisfied that we had successfully synthesized the desired acetylenic allenophane and thus turned our attention to developing an *asymmetric* synthesis.

6.4 The Asymmetric Synthesis of Tertiary Propargyl Alcohols

6.4.1 Literature methods for the asymmetric synthesis of propargyl alcohols

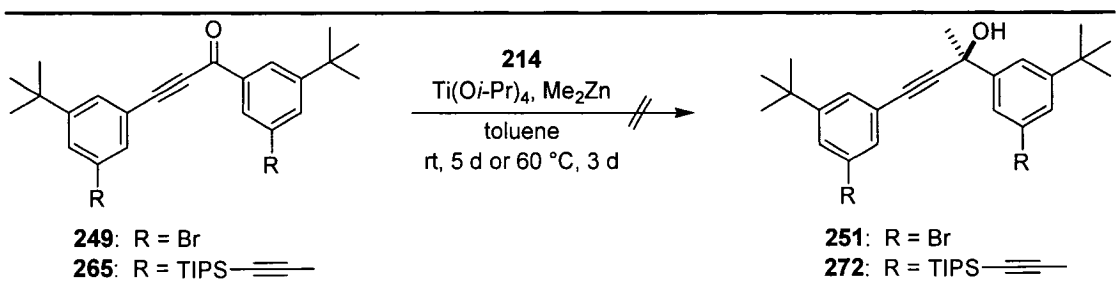
As previously discussed, an asymmetric synthesis of our acetylenic allenophane required a non-racemic tertiary propargyl alcohol. The asymmetric synthesis of this species was initially attempted using the methods available in the literature (Section 5.6.2). At the time of this work, ligands **209** and **210** had been reported to promote the asymmetric addition of an acetylide to a ketone (Figure 24), while ligands **210**, **213**, and **214** had been shown to catalyze the asymmetric addition of an alkyl group to a ketone (Figure 25). Salen **209** was commercially available, while dihydroxy bis(sulfonamide) **214** and camphorsulfonamide **210** were synthesized *via* the short procedures shown in Scheme 50. Consistent with the literature procedure,[149] reaction of 1,2-diaminocyclohexane **267** with camphorsulfonyl chloride **268** in the presence of NEt_3 generated diketone **269** in 64% yield. Reduction of the diketone with $NaBH_4$ then furnished dihydroxy bis(sulfonamide) **214** in 38% yield. We used a similar procedure to synthesize **210** rather than the substantially more complicated literature preparation.[161] Thus, reaction of camphorsulfonyl chloride **268** with 1-naphthylmethylamine **270** provided ketone **271**, which was reduced with $NaBH_4$ to provide camphorsulfonamide **210** in 50% yield over two steps.

[161] Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651-5666.



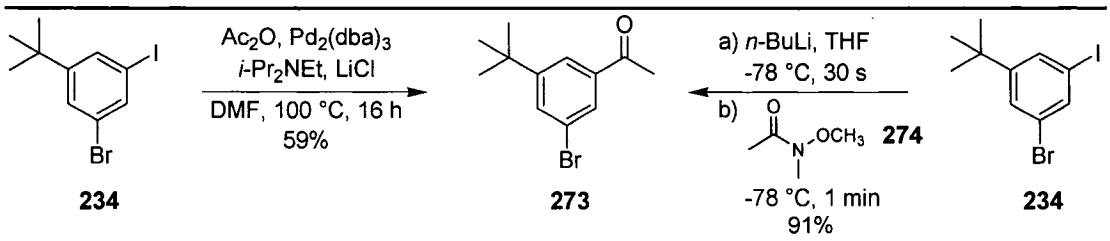
Scheme 50: Synthesis of catalysts 210 and 214

Our first attempt at the synthesis of a non-racemic tertiary propargyl alcohol was the unprecedented asymmetric addition of a methyl group to a propargyl ketone (Scheme 51). We attempted this reaction using only ligand **214** as it has been successfully used on the widest variety of substrates. Unfortunately, the reaction of ketone **249** or **265** with Me_2Zn in the presence of ligand **214** and $Ti(O\textit{i}\text{-}Pr)_4$ at either room temperature or 60 °C resulted in complete recovery of the ketone. We attributed this result to the inherent poor electrophilicity of the ketones. It is also somewhat likely that the bulkiness of the *tert*-butyl groups may have prevented the correct organization of the reactive species in the transition state.



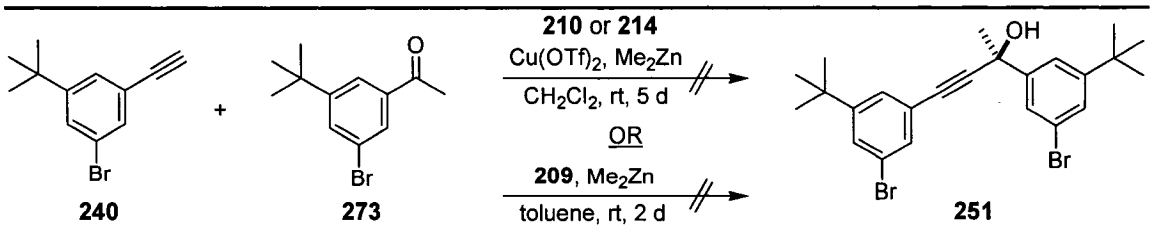
Scheme 51: Attempted asymmetric addition of methyl groups to propargyl ketones

We thus decided to focus our efforts on the asymmetric addition of an acetylide to a ketone because this reaction did have literature precedent, suggesting it would be more likely to succeed. Two routes to the ketone (**273**) necessary for this procedure were investigated (Scheme 52). A palladium-mediated acetylation[162] of iodide **234** using $Pd_2(dba)_3$ and Ac_2O provided the desired ketone in 59% yield. However, it was later found that selective lithium-halogen exchange of the iodide of **234** with *n*-BuLi followed by quenching of the anion with Weinreb-type amide **274** provided the ketone in a much higher and cleaner yield of 91%.



Scheme 52: Syntheses of ketone 273

Unfortunately, the attempted addition of acetylene **240** to ketone **273** using either ligand **210** or **214** and the conditions of Chan[142] [$Cu(OTf)_2$, Me_2Zn, and CH_2Cl_2] did not provide any of the desired product. The same result was observed using ligand **209** and the conditions of Cozzi[141] (Me_2Zn, toluene). In all cases, the starting acetylene (**240**) and ketone (**273**) were recovered nearly quantitatively. In addition, a small amount of product resulting from the addition of a methyl group to ketone **273** was also isolated from each trial. This latter result suggested to us that the required zinc acetylide may not have properly formed, leaving Me_2Zn available to react with the ketone.

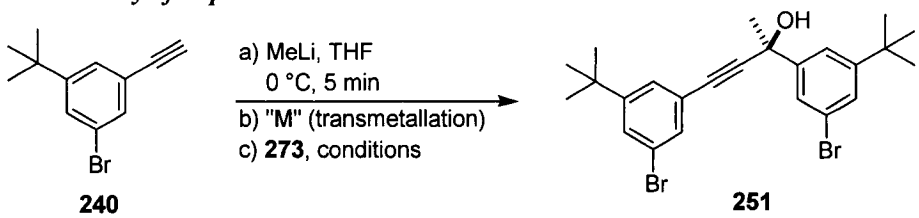


Scheme 53: Attempted synthesis of 251 via the asymmetric addition of acetylene 240 to ketone 273

[162] Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 289-291.

To solve this potential problem and ensure that the zinc acetylide was formed, we chose to conduct the reaction stepwise, pre-forming the acetylide using standard conditions and then reacting it with ketone **273**. These results are summarized in Table 7. After deprotonation of **240** with MeLi, the lithium acetylide was transmetallated with either 1 (entries 1, 2) or 0.5 (entries 4, 5) equivalents of zinc bromide to provide the zinc mono- or di-acetylide, respectively. Unfortunately, reaction of either of these species with ketone **273** using ligand **210** or **214** under the appropriate reaction conditions resulted in near quantitative recovery of the starting material. Quenching the lithium acetylide with $ClTi(O\textit{i}\text{-}Pr)_3$ to generate the titanium acetylide and reacting it with ketone **273** using ligand **209** also failed to provide any trace of product (entry 3). We hypothesized that the failure of these reactions could be due to steric crowding between the *tert*-butyl groups and the bulky ligands, which may have prevented the reactive species from organizing properly in the transition state. Although the reaction of phenylacetylide with mono-substituted acetophenones has been reported, no examples existed which approached the complexity of our substrates.

Table 7: Summary of stepwise reaction conditions

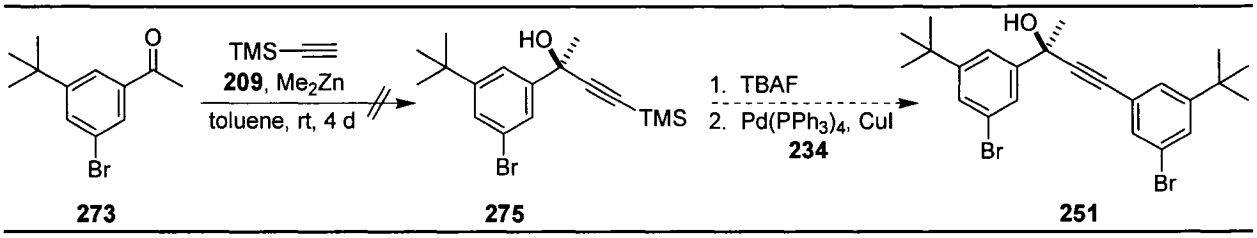


240 **251**

Entry	"M"	eq. "M"	Catalyst	Conditions	Result
1	$ZnBr_2$	1	**209**	toluene, rt, 4 d	Starting materials
2	$ZnBr_2$	1	**210**	$Cu(OTf)_2$, CH_2Cl_2, rt, 4 d	Starting materials
3	$ClTi(O\textit{i}\text{-}Pr)_3$	1	**214**	toluene, rt, 4 d	Starting materials
4	$ZnBr_2$	0.5	**210**	$Cu(OTf)_2$, CH_2Cl_2, rt, 3 d	Starting materials
5	$ZnBr_2$	0.5	**209**	toluene, rt, 3 d	Starting materials

One possible solution to the problem of steric crowding was to use a smaller reactive species. Cozzi has shown that the addition of TMS-acetylene to bulky aliphatic methyl ketones proceeds in good yield and reasonable enantioselectivity using salen **209** as ligand.[141] If applied to our substrate, the product of the reaction (**275**) could easily be converted to the desired tertiary propargyl alcohol (**251**) *via* desilylation and a subsequent Sonogashira coupling with iodide **234**

(Scheme 54). Unfortunately, when ketone **273** was exposed to the reported reaction conditions, no reaction was observed.



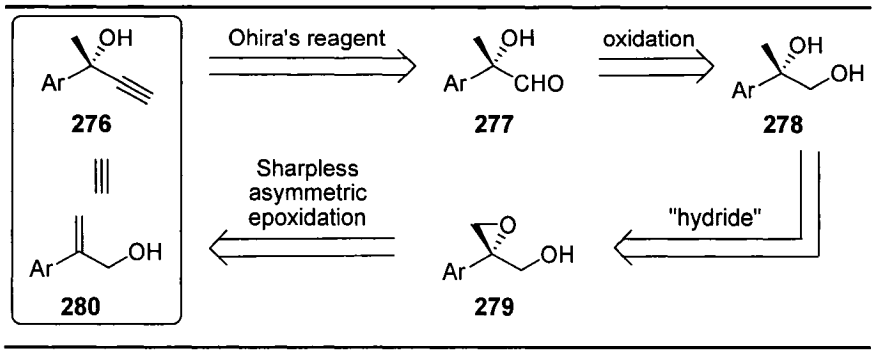
Scheme 54: Attempted asymmetric addition of TMS-acetylene to ketone 273

The failure of the literature procedures to produce the desired tertiary propargyl alcohols asymmetrically left us with three possible solutions. The literature methods could potentially be optimized to provide the tertiary propargyl alcohols in high yield and enantioselectivity; however, our preliminary results suggested that this course of action would be fruitless. The racemic propargyl alcohols could also be formed using the methods outlined in Scheme 48 and the individual enantiomers separated *via* formation of intermediate diastereomers; however, this method would be rather inelegant. Alternatively, a completely new approach for the asymmetric synthesis of tertiary propargyl alcohols could be developed. The potential utility of a conceptually new asymmetric protocol to these substrates motivated us to pursue this third option.

6.4.2 A Sharpless asymmetric epoxidation-based route to tertiary propargyl alcohols

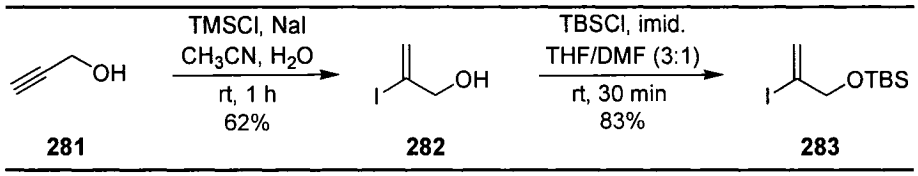
The novel retrosynthetic approach we envisioned to tertiary propargyl alcohols is shown in Scheme 55. What we realized was that the desired tertiary propargyl alcohol (**276**) could arise from an allylic alcohol (**280**). Focussing on a more detailed retrosynthesis, the terminal acetylene of tertiary propargyl alcohol **276**, which could be elaborated *via* a Sonogashira coupling, could arise from aldehyde **277** using Ohira's reagent or the Corey-Fuchs procedure. Aldehyde **277** is accessible from the oxidation of diol **278**, which itself could arise from ring-opening of epoxide **279** with a suitable hydride reagent. Epoxide **279** is the product of a Sharpless asymmetric epoxidation of allylic alcohol **280**. The use of a Sharpless asymmetric

epoxidation to set the chirality of a tertiary propargyl alcohol was unprecedented at the time. The wide functional group tolerance of the method and relative simplicity of the subsequent transformations in our retrosynthesis should easily allow for the synthesis of a large variety of substrates.



Scheme 55: Our novel asymmetric approach to tertiary propargyl alcohols

The synthesis of the allylic alcohol would require a suitable coupling partner for a palladium-mediated reaction with the aromatic moiety (*e.g.*, **234**). The synthesis of this species is depicted in Scheme 56. Hydroiodination of propargyl alcohol (**281**) using TMSCl and NaI in CH_3CN and H_2O proceeded with complete regiocontrol to provide geminally substituted vinyl iodide **282** in 62% yield.[163] Protection of the primary alcohol as the TBS ether then generated the desired vinyl iodide coupling partner **283** in 83% yield.

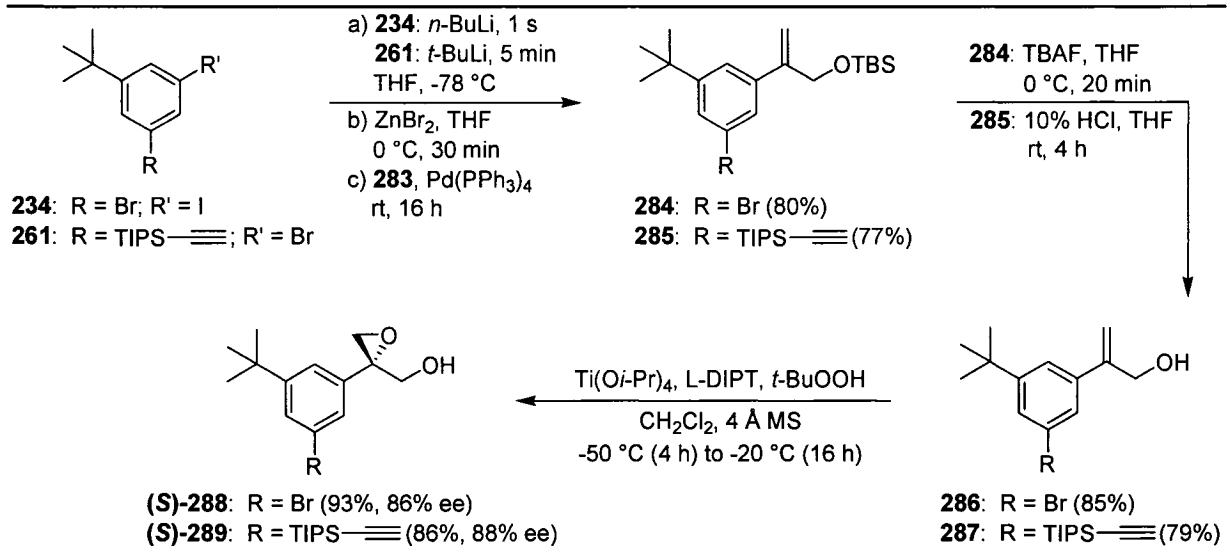


Scheme 56: Synthesis of vinyl iodide 283

The syntheses of epoxides **288** and **289** from aryl halides **234** and **261** is depicted in Scheme 57. Selective lithium-halogen exchange of the iodide of **234** using *n*-BuLi followed by the immediate addition of a solution of $ZnBr_2$ in THF generated an intermediate arylzincate which underwent a Negishi coupling with vinyl iodide **283** to provide styrene **284** in 80% yield. A similar sequence on **261** using *t*-BuLi provided styrene **285** in 77% yield. Interestingly, the

[163] Irifune, S.; Kibayahsi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366-369.

analogous reaction between the zincate of **283** and aryl halide **234** or **261** failed completely. Preliminary results suggested that the problematic step in the sequence was the lithium-halogen exchange on **283**.[164] Regardless, removal of the silyl group of **284** with TBAF then yielded allylic alcohol **286** in 85% yield. Likewise, a solution of 10% HCl in THF selectively cleaved the TBS ether of **285** while leaving the TIPS-acetylene moiety intact to provide allylic alcohol **287** in 79% yield. Exposure of **286** to standard Sharpless asymmetric epoxidation conditions ($Ti(O\textit{i}\text{-}Pr)_4$, L-DIPT, *t*-BuOOH, CH_2Cl_2, 4 Å MS) then yielded key (*S*)-epoxide **288** in 93% yield and 86% enantiomeric excess.[165] Similarly, (*S*)-epoxide **289** was formed in 86% yield and 88% enantiomeric excess.[166] The enantioselectivity of both reactions was consistently in the range of 86-88%, regardless of changes to the temperature or catalyst concentration aimed at increasing the selectivity.



Scheme 57: Asymmetric synthesis of epoxides 288 and 289

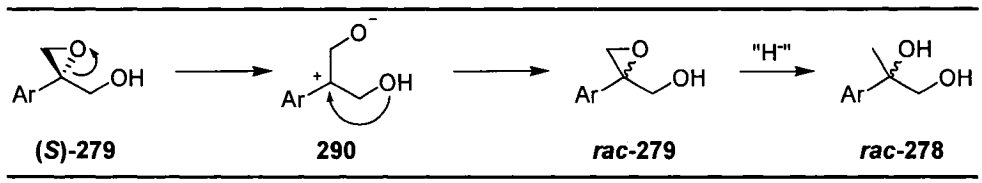
We were now ready to open the epoxides to generate the diols. One potentially frustrating problem we faced is that the epoxide could open at the benzylic center to generate a symmetric diol and relatively stable carbocation (**290**) (Scheme 58). Recyclization from either

[164] The chloride analogue of **283** was similarly problematic.

[165] All enantiomeric excesses reported in this thesis were determined using chiral HPLC by comparing racemic samples prepared *via* epoxidation of **284** or **285** using *m*CPBA to the asymmetric samples. Details are provided in the experimental section.

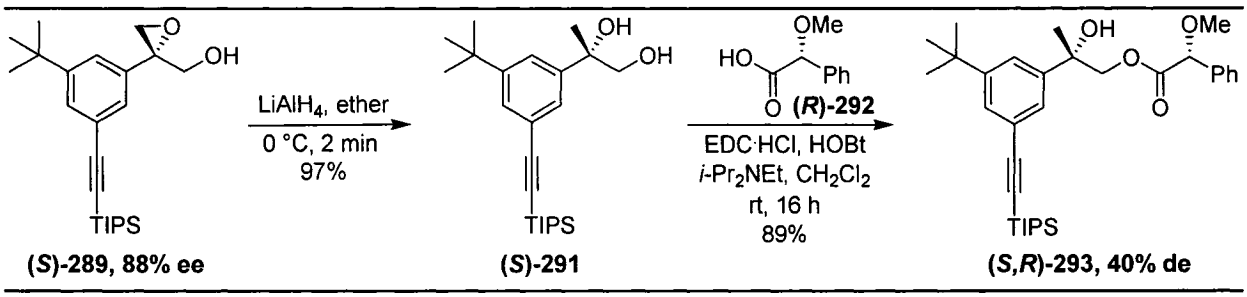
[166] The absolute configuration of epoxides **288** and **289** was inferred from literature precedent, see: Jørgensen, K. A.; Wheeler, R. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1987**, *109*, 3240-3246.

side of the cation would then generate racemic α-hydroxy epoxide **279**, which after ring opening of the epoxide at the desired position would provide racemized diol **278**.



Scheme 58: Potential racemization of α-hydroxy epoxide 279

Fortunately, literature precedent on similarly substituted substrates suggested that ring opening of the epoxide could be easily accomplished without loss of the enantiomeric excess using $LiAlH_4$.[167] As expected, the epoxide of **289** was rapidly opened to provide tertiary alcohol **291** upon exposure to $LiAlH_4$ in cold ether (Scheme 59). The enantiomeric excess of this compound could not be easily measured, and so **291** was esterified with carboxylic acid **292** (similar to Mosher's acid) to generate a mixture of diastereomeric esters (**293**). A diastereomeric excess of 40% was determined through integration of the ^1H NMR resonance resulting from the tertiary methyl group of **293** on each diastereomer. Clearly α-hydroxy epoxide **289** had partially racemized, in stark contrast to the literature reports.



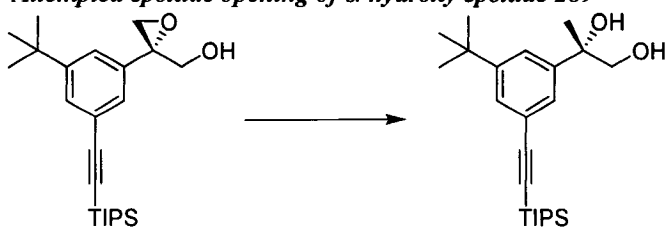
Scheme 59: Epoxide opening of 289 using $LiAlH_4$

Several other reagents have been reported to selectively ring open α-hydroxy epoxides to provide the diol, although only $LiAlH_4$ has been used on enantiomerically enriched substrates. Unfortunately, all reagents that cleanly opened the epoxide of **289** also partially racemized the material, while other reagents gave complex mixtures of products (Table 8). Exposure of **289** to

[167] (a) Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203-212; (b) Capriati, V.; Florio, S.; Luisi, R.; Salomone, R. *Org. Lett.* **2002**, *4*, 2445-2448; (c) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985-5990.

a solution of Red-Al® [$NaAlH_2(OCH_2CH_2OCH_3)_2$][168] (entry 2) or $LiAl(O\textit{t}\text{-}Bu)_3H$ (entry 3) in THF easily provided the desired diol, but as in the case of $LiAlH_4$ substantial racemization occurred. A modified procedure[169] using the reducing agent resulting from a 1:1 mixture of Red-Al® and MeOH in THF provided a complex mixture of products (entry 4). Likewise, the attempted ring opening of **289** using either Pd/C and HCO_2NH_4 in EtOH[170] (entry 5) or DIBALH in THF[171] (entry 6) also failed to generate the desired diol.

Table 8: Attempted epoxide opening of α-hydroxy epoxide 289



(S)-289 **(S)-291**

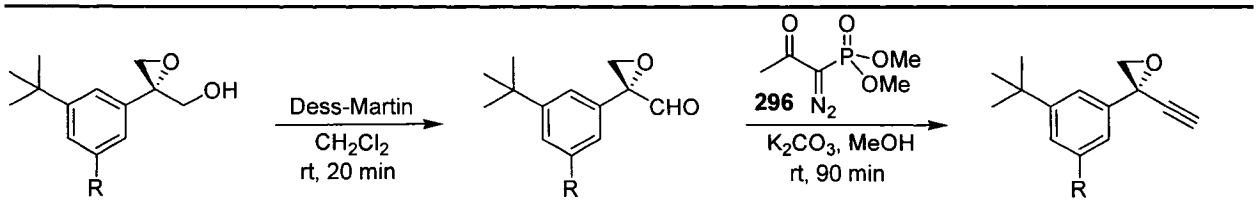
Entry	Conditions	Result
1	$LiAlH_4$, ether, 0 °C	97%, partial racemization[a]
2	Red-Al®, THF, 0 °C	100%, partial racemization[a]
3	$LiAl(O\textit{t}\text{-}Bu)_3H$, THF, 0 °C	50%, partial racemization[a]
4	Red-Al®, MeOH, THF, 0 °C	mixture of products
5	5% Pd/C, HCO_2NH_4, EtOH, rt	mixture of products
6	DIBALH, THF, 0 °C	mixture of products

a) Determined through NMR analysis of the Mosher-type ester described previously

The failure to successfully open the epoxide of **289** with preservation of the enantiomeric excess was not particularly troubling as we anticipated that the epoxide could likely be opened at another stage in the synthesis. The synthesis therefore continued with the Dess-Martin oxidation of **288** and **289** to give aldehydes **294** and **295** in 83% and 89% yield, respectively (Scheme 60). Exposure of aldehyde **294** or **295** to a solution of Ohira's reagent and K_2CO_3 in MeOH then generated the corresponding terminal acetylenes **297** and **298** in 86% and 93% yield,

[168] Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722;
[169] (a) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081-4084; (b) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535-3538.
[170] (a) Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922-4924; (b) Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781-2783.
[171] (a) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135-137; (b) Jung, M.; Lee, K.; Jung, H. *Tetrahedron Lett.* **2001**, *42*, 3997-4000.

respectively. The enantiomeric excess of 83% measured for **297** indicated that only minimal racemization had occurred in the preceding two steps.[172]



(*S*)-**288**: R = Br
(*S*)-**289**: R = TIPS—≡

(*S*)-**294**: R = Br (83%)
(*S*)-**295**: R = TIPS—≡ (89%)

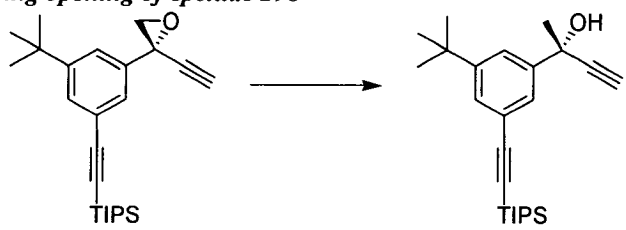
(*S*)-**297**: R = Br (86%, 83% ee)
(*S*)-**298**: R = TIPS—≡ (93%)

Scheme 60: Synthesis of epoxy alkynes 297 and 298

The ring opening of epoxy acetylene **298** was now attempted (Table 9). Although we anticipated that $LiAlH_4$ would also reduce the acetylene to the alkene, a methodology paper by Nussbaumer indicated that similar epoxy acetylenes could be cleanly ring-opened without reaction of the acetylene.[173] However, as we had originally expected, ring opening of epoxy acetylene **298** with $LiAlH_4$ was accompanied by complete reduction of the acetylene to the alkene (entry 1). When $NaBH_4$ was employed, no reaction was observed at room temperature, and only decomposition occurred in refluxing *i*-PrOH/THF (entry 2). The attempted epoxide ring opening of **298** with either $LiEt_3BH$[174] (entry 3) or MeMgBr (entry 4) in THF also each gave multiple products. Finally, exposure of a solution of **298** in THF to L-Selectride® [$LiBH(CH(CH_3)CH_2CH_3)_3$] led to rapid opening of the epoxide and provided the desired tertiary propargyl alcohol **299** in 88% yield. An identical procedure on alcohol **297** afforded tertiary propargyl alcohol **300** in 80% yield and 87% enantiomeric excess.

[172] The enantiomeric excess of all compounds could not be easily measured, but at all stages when it could be, no racemization was observed.
[173] Nussbaumer, P.; Stiltz, A. *Tetrahedron Lett.* **1992**, *33*, 7507-7508.
[174] Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486-8487.

Table 9: Epoxide ring opening of epoxide 298

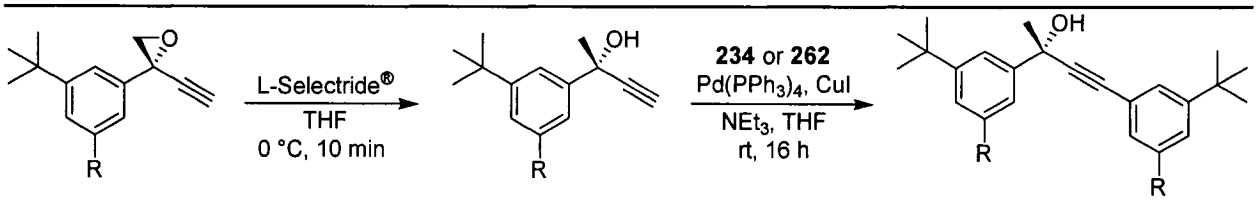


(*S*)-298 **(*S*)-299**

Entry	Conditions	Result
1	$LiAlH_4$, ether, 0 °C	3° alcohol, alkyne reduced to alkene
2	$NaBH_4$, *i*-PrOH, THF, rt or reflux	no reaction at rt; decomposition at reflux
3	$LiEt_3BH$, THF, 0 °C	multiple products
4	MeMgBr, THF, 0 °C	multiple products
5	L-Selectride®, THF, 0 °C	tertiary propargyl alcohol **299**, 88% yield

The desired tertiary propargyl alcohols **299** and **300** had thus been synthesized in very good enantioselectivity and yield. The four step sequence to convert the allylic alcohol into the tertiary propargyl alcohol was operationally simple and could easily be completed in two days without the need for specialized laboratory equipment. It is worth noting that although the protocol was four steps in length, the overall reaction time of two days was significantly less than that required for the more direct methods previously described (Section 5.6). The rigorous exclusion of oxygen and moisture was also unnecessary with our protocol.

6.5 Completion of the Synthesis



(*S*)-297: R = Br
(*S*)-298: R = TIPS—≡

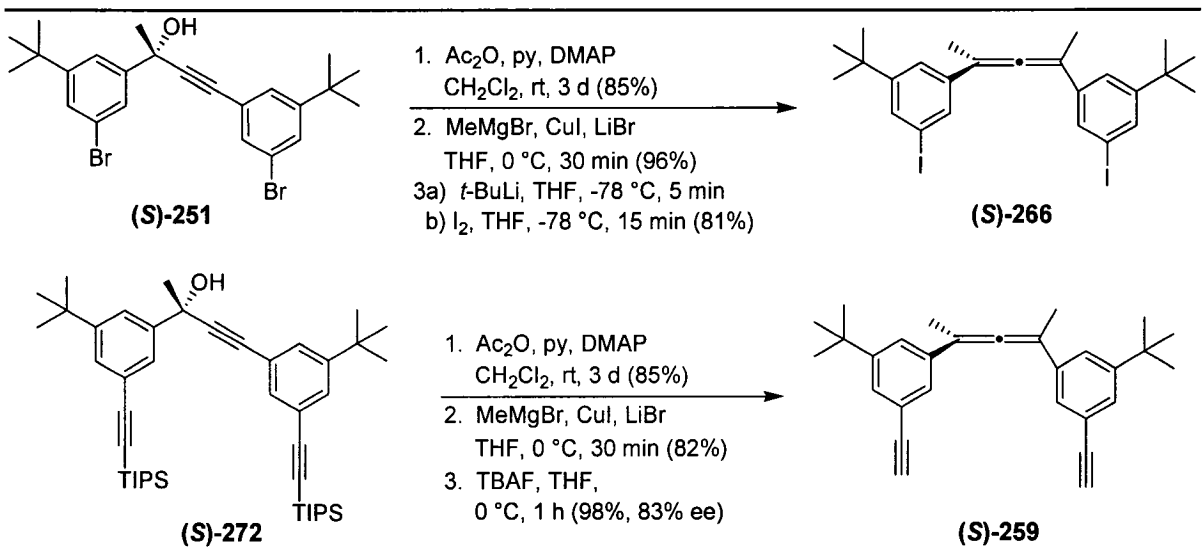
(*S*)-300: R = Br (80%)
(*S*)-299: R = TIPS—≡ (88%, 87% ee)

(*S*)-251: R = Br (75%)
(*S*)-272: R = TIPS—≡ (75%)

Scheme 61: Asymmetric synthesis of alcohols 251 and 272

With the desired tertiary propargyl alcohols **299** and **300** in hand and in good enantiopurity, we continued the synthesis (Scheme 61). Thus, tertiary propargyl alcohol **300** underwent a Sonogashira coupling with aryl iodide **234** to provide alcohol **251** in 75% yield.

Likewise, a Sonogashira coupling between **299** and **262** gave alcohol **272**, also in 75% yield. These couplings, however, were substantially more difficult than other Sonogashira couplings presented in this thesis. Initial experiments under standard conditions gave very poor yields of the product alcohols and large quantities of homocoupled acetylene. The amount of homocoupling could be decreased *via extremely* vigorous degassing of the reaction with argon; however, the yield of desired alcohol rarely exceeded 70% with homocoupled acetylene (and unreacted aryl iodide) accounting for the remaining mass balance. Attempts to limit the amount of homocoupling using polymethylhydrosiloxane (PMHS) as an additive[175] or by conducting the reaction under a hydrogen atmosphere[176] did not have a beneficial effect.

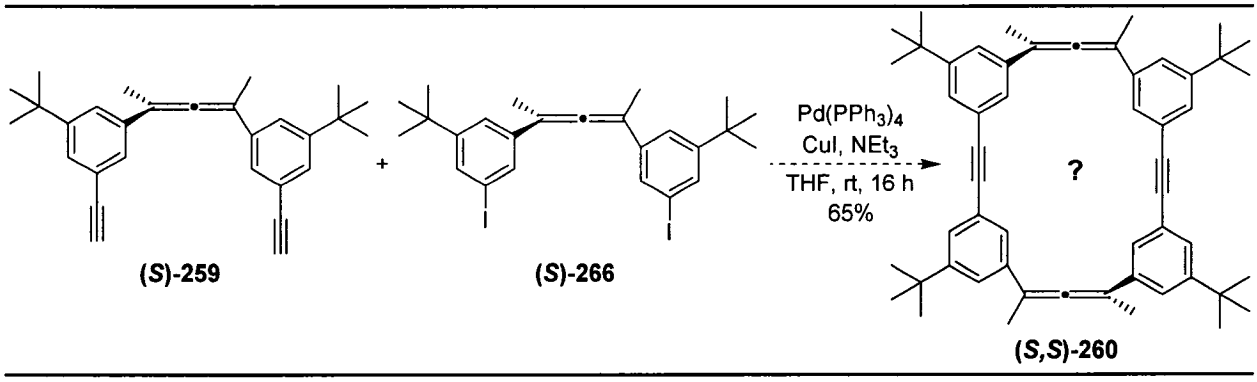


Scheme 62: Asymmetric synthesis of allenes 266 and 259

Alcohols **251** and **272** were then converted to allenes **266** and **259** using the procedures previously employed on the racemic substrates (Scheme 62). The enantiomeric excess of 83% for acetylene **259** indicated that no significant racemization had occurred during the process. A Sonogashira coupling between iodide **266** and acetylene **259** then produced a white solid in 65% yield (Scheme 63). The major component exhibited a retention factor (TLC), ^{1}H NMR and mass spectrum identical to the racemate and corresponding to the desired acetylenic allenophane **260**. However, as was the case with the racemate, the ^{13}C NMR was complex. Our previous "multiple diastereomers" interpretation of the complex ^{13}C NMR spectrum for the racemate appeared to be

[175] Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2003**, *68*, 6775-6779.
[176] Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841-1844.

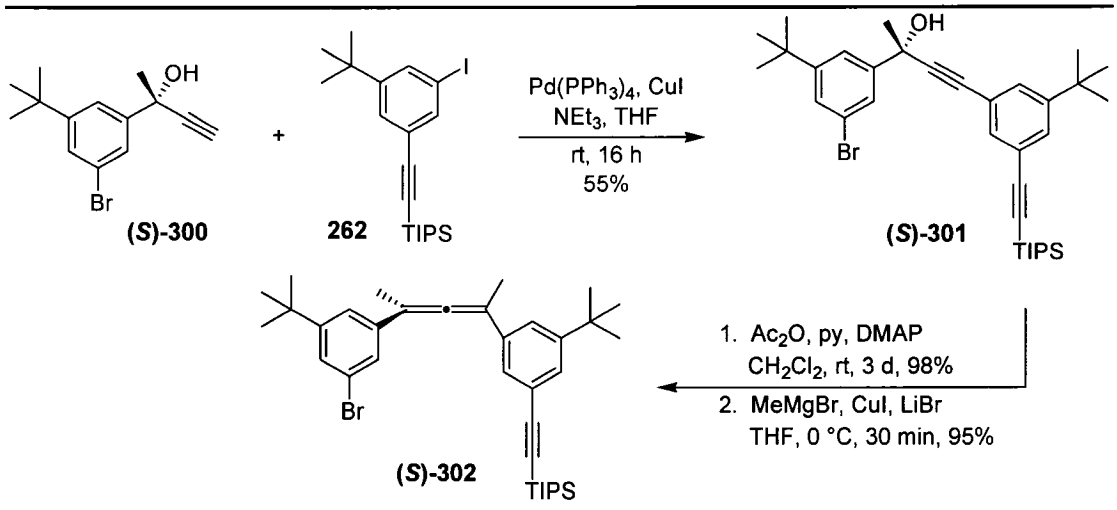
incorrect as only one diastereomer should have formed from reaction of non-racemic **259** and **266**. Although only one product was apparent on TLC using multiple solvent systems, repeated slow elution on preparative TLC revealed a remarkably complex mixture of at least six overlapping products which were distinguishable largely by their different colors under the UV lamp. Similar results were obtained using chiral and achiral HPLC. Numerous attempts to separate these compounds using either TLC or HPLC (normal and reverse phase) were completely unsuccessful.



Scheme 63: Attempted asymmetric synthesis of acetylenic allenophane 260

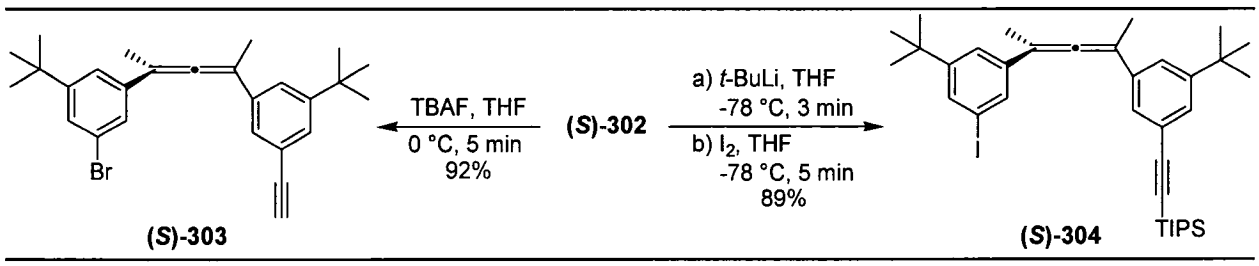
In an attempt to prevent and perhaps explain this perplexing result we decided to conduct the key dimerization reaction in two steps, connecting one side of the molecules first followed by a separate reaction to complete the macrocycle. This approach required precursors in which the aryl ring substituents were different on each end of the allene.

The synthesis of these precursors commenced with a Sonogashira reaction between acetylene **300** and iodide **262** to generate alcohol **301** in 55% yield (Scheme 64). Similarly to our previous syntheses, acetylation of the alcohol with Ac_2O provided the acetate in 98% yield, which was subsequently converted to allene **302** in 95% yield upon exposure to a mixture of MeMgBr, CuI and LiBr in THF.



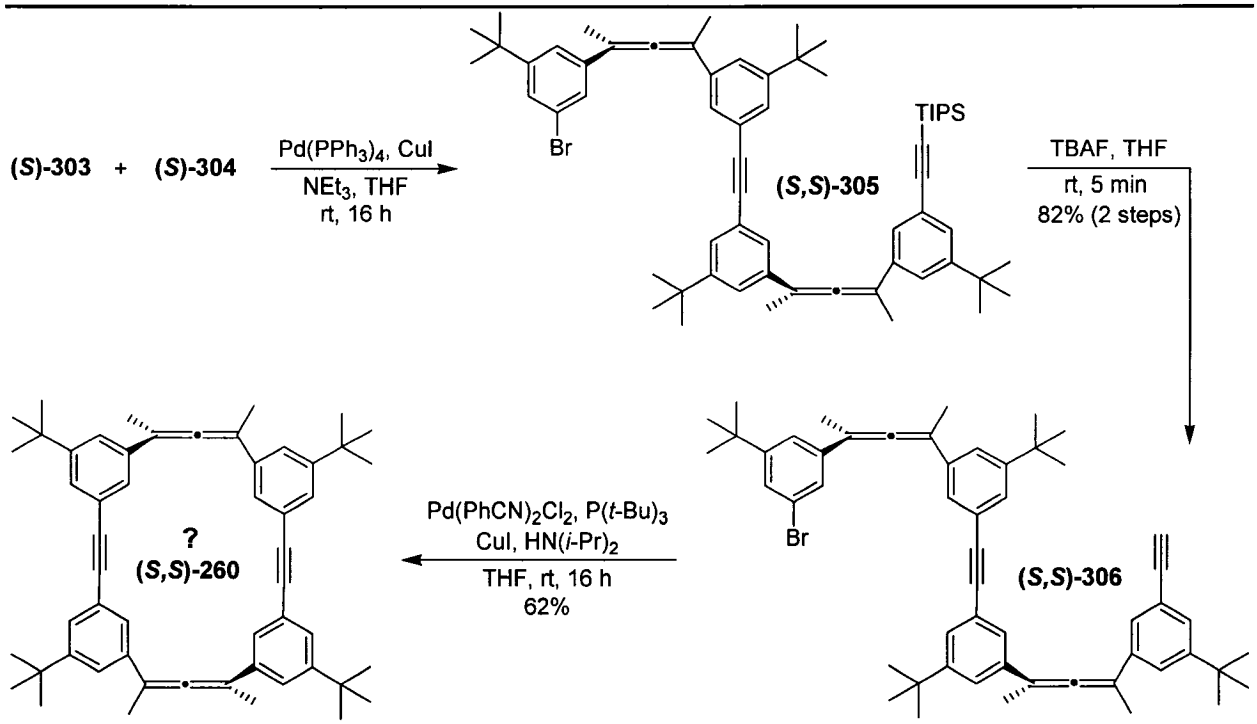
Scheme 64: Synthesis of allene 302

The coupling partners necessary for the stepwise synthesis of acetylenic allenophane **260** were derived from allene **302** as depicted in Scheme 65. Acetylene **303** was synthesized in 92% yield *via* desilylation of **302** using TBAF. Aryl iodide **304** was synthesized in 89% yield *via* successive treatment of allene **302** with *t*-BuLi and I_2.



Scheme 65: Synthesis of acetylene 303 and iodide 304

A Sonogashira coupling between acetylene **303** and iodide **304** then provided bis(allene) **305**. A subsequent desilylation with TBAF then generated terminal acetylene **306** in 68% yield over two steps (Scheme 66). The key Sonogashira reaction to complete the macrocyclization was accomplished at room temperature using P(*t*-Bu)$_3$ and Pd(PhCN)$_2$Cl$_2$ as catalyst[100] and provided a white solid in 62% yield. To our dismay, this white solid was identical in all respects to that which resulted from the original one-step asymmetric synthesis.

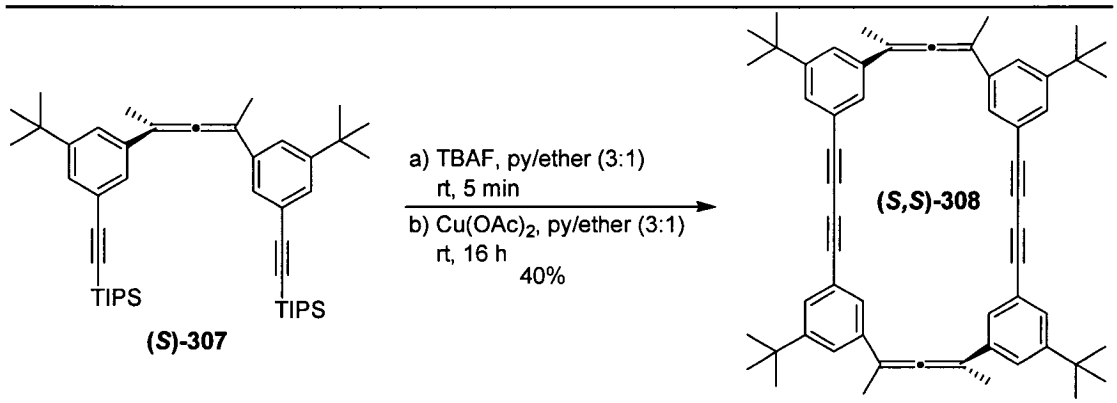


Scheme 66: Stepwise synthesis of acetylenic allenophane 260

The identities of the compounds in this mixture remain unknown. It is somewhat conceivable that acetylenic allenophane **260** could exist as a mixture of non-interconverting conformers, which would explain the simplicity of the mass spectrum as well as the complicated ^{13}C NMR (the simplicity of the ^{1}H NMR is a consequence of its narrower frequency range). However, no change was observed in the ^{13}C NMR spectrum at higher temperatures. It also seems quite unlikely that the subtle conformational changes that are possible in **260** could produce conformers that exhibited such different behavior on preparative TLC. It may also be possible that the allenes racemized upon exposure to the Sonogashira coupling conditions. However, even if complete racemization had taken place, only three acetylenic allenophanes would be expected, and two of these would be enantiomers (*i.e.*, indistinguishable by preparative TLC). Perhaps the most likely explanation is the formation of trimers, tetramers, and higher cyclic oligomers of the allene monomers rather than the desired dimer. This explanation would be most consistent with the spectral results, but it seems surprising that differences between these would not be observed on TLC. In any event, we clearly required an alternate approach in our asymmetric synthesis of an acetylenic allenophane.

6.5.1 An Eglinton coupling approach to an acetylenic allenophane

We had chosen to synthesize the acetylenic allenophane (**260**) containing only one bridging acetylene *via* a Sonogashira coupling in order to ensure that only the dimer formed. Molecular modeling studies had suggested that an Eglinton coupling (dimerization) of allene **259** to give the acetylenic allenophane with two bridging acetylenes would give a mixture of both intra and intermolecular dimerization products. However, given the difficulty we encountered in the synthesis of acetylenic allenophane **260**, we decided to pursue this seemingly riskier route. If necessary, a stepwise approach could be devised to prevent the undesired intramolecular dimerization.



Scheme 67: An Eglinton coupling approach to acetylenic allenophane 308

To our delight, when allene **307** was desilylated *in situ* with TBAF and slowly added *via* syringe pump to a solution of $Cu(OAc)_2$ in pyridine and ether, acetylenic allenophane **308** was formed in 40% yield (Scheme 67). No product resulting from the anticipated and undesired intramolecular dimerization was detected. However, in light of the instability of our previous intramolecular dimerization product **258**, this product would likely have been very unstable and probably would have decomposed during the reaction or isolation, if it had formed at all.

6.5.2 Properties of acetylenic allenophane 308

Acetylenic allenophane **308** was a pale yellow glassy solid that was stable under standard laboratory conditions. Sharp resonances for the aromatic, methyl, and *tert*-butyl groups were

observed in the ^{1}H NMR and all expected ^{13}C resonances were present. The mass spectrum was very clean, containing only the molecular ion (756) and M^{+}-(*t*-Bu) (699) peaks above mass 200. An optical rotation of +87.1° was observed in $CHCl_3$ solution. Exhaustive attempts to grow X-ray quality crystals were unsuccessful; however, molecular modeling studies predicted the most stable conformation of our acetylenic allenophane (Figure 27).[177] Two perspectives of this conformation are illustrated to provide a more complete picture of its shape. Figure 27b also reveals that the molecule possesses helical chirality. However, construction of a model revealed that the two helical isomers would likely readily interconvert at room temperature.

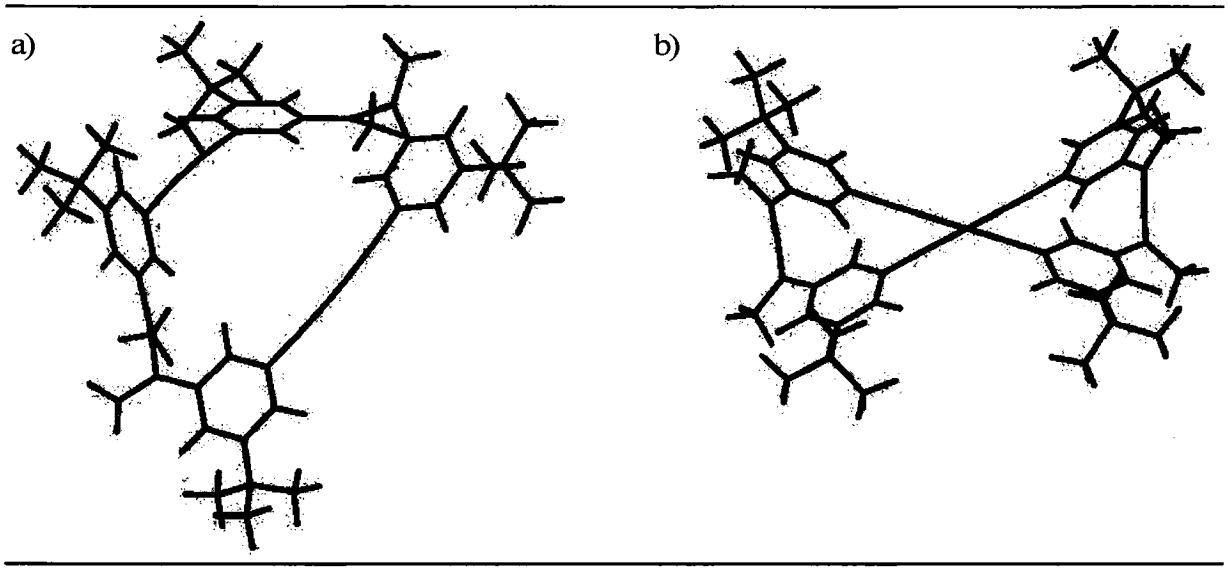


Figure 27: Molecular models of acetylenic allenophane 308

The UV/Vis absorption and circular dichroism (CD) spectra of acetylenic allenophane **308** were recorded in $CHCl_3$ solution and are illustrated in Figures 2 and 3, respectively. Unfortunately, there are very few literature examples of cyclic allene UV/Vis and CD spectra to compare with our acetylenic allenophane. The only experimental CD spectra for cyclic allenes appear to be a report by Krause in 2004 where 9 and 10 membered rings containing allenes were compared.[178] No similarities to the CD spectrum of acetylenic allenophane **308** were apparent, and no UV/Vis spectra were reported. Nevertheless, the typical 'finger-type' acetylene pattern at

[177] Semiempirical AM1 calculations were performed by using a PC Spartan Pro (v. 1.03) program from Wavefunction, Inc. of Irvine, CA (2000).
[178] Zelder, C.; Krause, N. *Eur. J. Org. Chem.* **2004**, 3968-3971.

295, 313, and 335 nm is apparent in the UV/Vis spectrum. In the CD spectrum, we suspect that the major signals at 263 and 270(sh) arose from the juxtaposed phenyl rings.

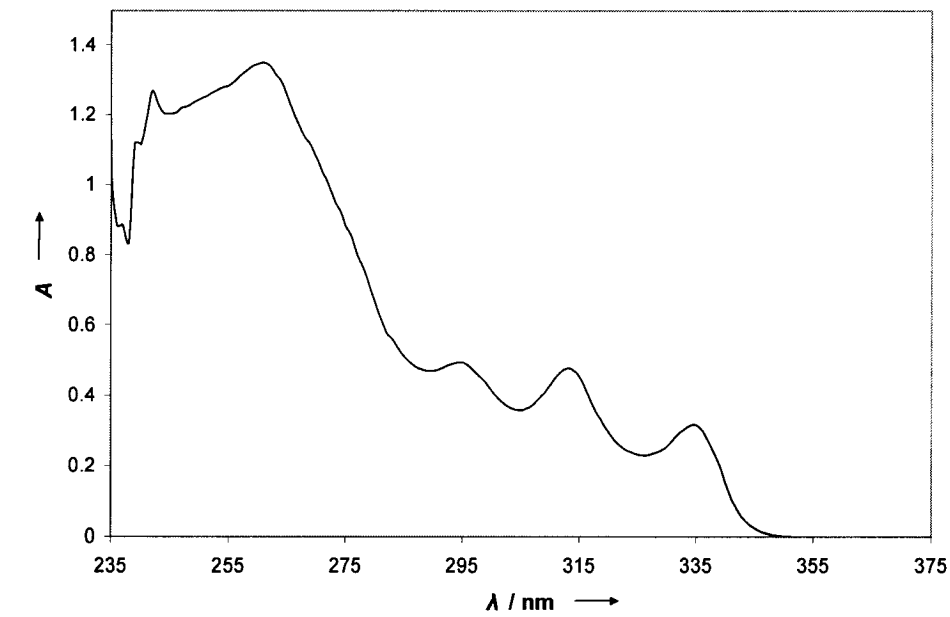


Figure 28: UV-Vis spectrum of acetylenic allenophane 308

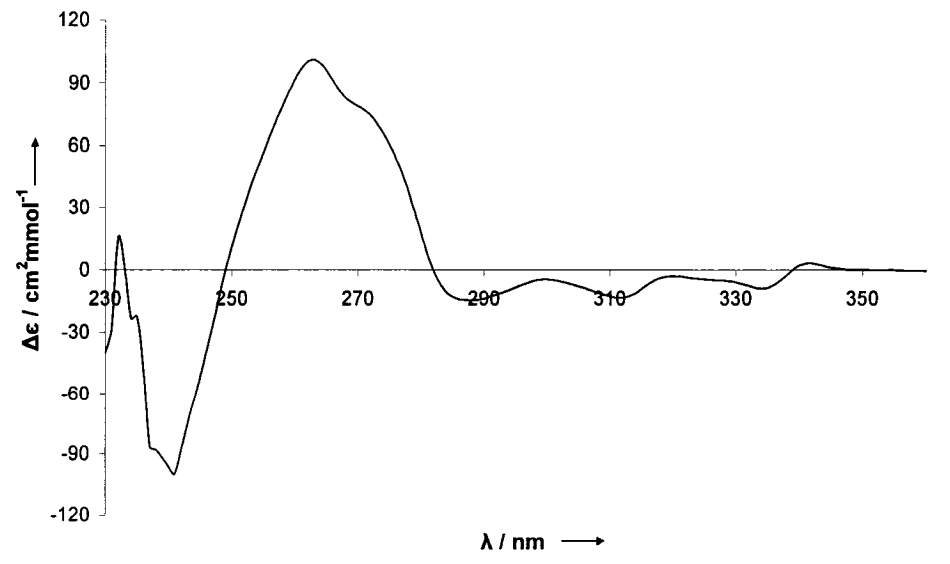
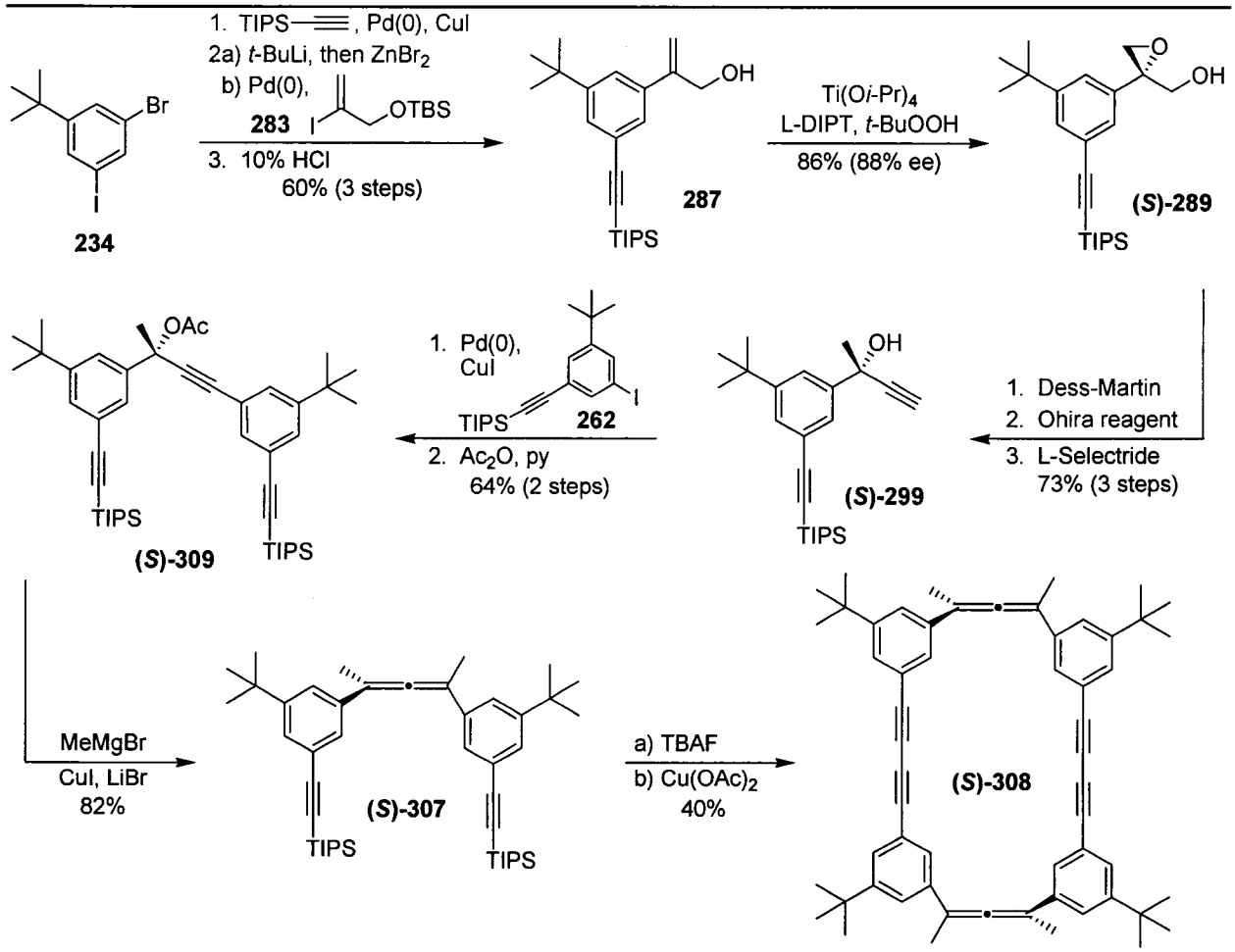


Figure 29: Circular dichroism of acetylenic allenophane 308

7 Conclusions and Future Work

We have successfully designed and completed the first asymmetric synthesis of an acetylenic allenophane. Beginning with dihalogenated benzene **234**, we synthesized acetylenic allenophane **308** asymmetrically in 11 linear steps (Scheme 68). A key step in our synthesis was a Sharpless asymmetric epoxidation of allylic alcohol **287** to yield epoxide **289** in 88% enantiomeric excess, which was subsequently converted to tertiary propargyl alcohol **299** using a high yielding and operationally simple three-step protocol. The allene moiety was introduced *via* the stereospecific addition of an organocuprate to propargyl acetate **309**. An *in situ* desilylation-dimerization protocol developed in the Fallis laboratory was then used to synthesize the acetylenic allenophane.



Scheme 68: Asymmetric synthesis of the first acetylenic allenophane (308)

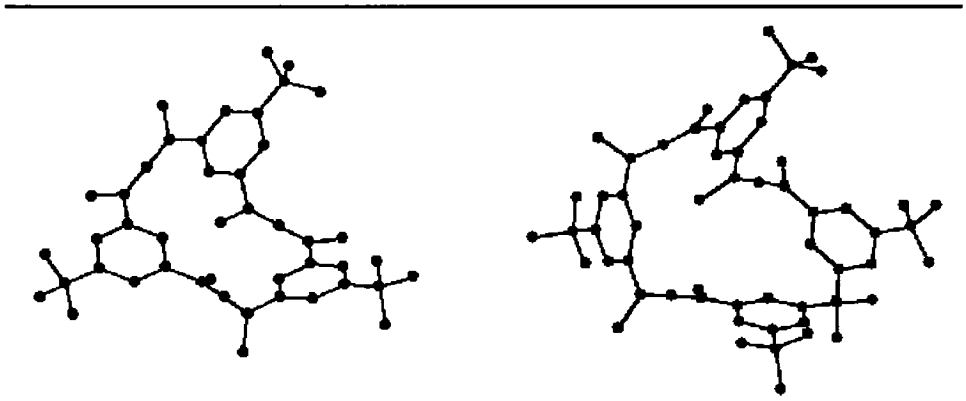
This acetylenic allenophane (**308**) represented a new class of cyclophane, and, illustrative of the current interest in these macrocycles, additional examples[117] of this class of molecule emerged within months of our publication. These syntheses, however, were racemic, leaving our synthesis to stand alone as the only asymmetric version. The significance of our work, as well as the emerging importance of this new class of compounds, was recently highlighted in an independent highlight in *Angewandte Chemie*.[179]

Our novel method of synthesizing tertiary propargyl alcohols asymmetrically using a Sharpless asymmetric epoxidation as the chiral inducing step also represented a conceptually new approach to tertiary propargyl alcohols and was superior to the reported methods in several respects. In contrast to the literature procedures, our protocol could be completed in roughly half the time, did not require the rigorous exclusion of moisture or oxygen, and did not require specialized equipment. Perhaps most importantly, our protocol succeeded where the others had failed.

7.1 Future Work

Two strong areas of research may result from this work. The first involves the asymmetric synthesis of true allenophanes (defined[115] as those containing only allenes and benzene rings in the macrocycle) using the methods we developed for our acetylenic allenophane. The adaptation of our methods to such a synthesis should be relatively simple, requiring only a new method of closing the final macrocycle. Two attractive targets for such an asymmetric synthesis are allenophane **310**, containing three alternating allenes and three aryl rings, and related allenophane **171**, which has been previously synthesized as a mixture of isomers (Figure 30).[115] This particular project is currently being investigated by a post-doctoral researcher in the Fallis laboratory. Allenophanes or acetylenic allenophanes capable of binding metal atoms or encapsulating small molecules would also be attractive synthetic targets.

[179] Kawase, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 7334-7336.



310 171

Figure 30: Potential synthetic targets: [3$_3$] (310) and [3$_4$] (171) allenophanes

The second potential avenue of research resulting from this work would be the further development of our method of synthesizing tertiary propargyl alcohols asymmetrically. The method was highly effective on the two substrates used in this work, but the scope and utility of the reaction can be significantly expanded. Furthermore, tertiary propargyl alcohols are present in several natural products and pharmaceuticals. The development of an asymmetric synthesis of such a target would be a particularly attractive use of our chemistry.

8 Experimental

8.1 General Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. All reactions involving palladium were performed under argon. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Dichloromethane, toluene, acetonitrile, diisopropylamine and triethylamine were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. *n*-Butyllithium and *t*-BuLi solutions in hexanes or pentanes from Aldrich Chemical Company were titrated prior to use against diphenylacetic acid and used directly. Starting materials were purchased from Aldrich Chemical Company or Strem and used without further purification unless otherwise stated.

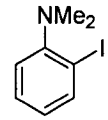
Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254} (E. Merck). TLC spots were developed by heating the plate after treatment with a 5% solution of phosphomolybdic acid in ethanol or a solution of $KMnO_4$ in aqueous potassium hydroxide. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry solutions in organic solvents. Excess solvents were removed (concentrated) *in vacuo* at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Degassed refers to bubbling a stream of argon through a solution for 20 minutes. Product purification by flash chromatography was performed with E. Merck Silica Gel 60 (230-400 mesh). Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C.

Melting points were determined with a Thomas-Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were run on a Bruker AVANCE 500 or a Varian INOVA 500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. ^{1}H NMR data are reported as follows: Chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet), coupling constants (Hz), and

integration). The multiplicity of each carbon atom in the ^{13}C NMR was determined using the DEPT 135 spectrum. Low resolution mass spectroscopy (MS) using electron impact (EI) was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV. High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam energy of 70 eV. Electrospray mass spectra ES (MS) were determined on a Micromass Quattro LC with a pump rate of 20 μL/min. The purity of all title compounds was judged to be >95% as determined by a combination of ^{1}H NMR and ^{13}C NMR analyses unless otherwise indicated.

8.2 Experimental Procedures for New Compounds

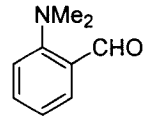
(2-Iodophenyl)dimethylamine (222)



$C_8H_{10}IN$
Mol. Wt.: 247.08

2-Iodoaniline (**221**) (25.0 g, 0.114 mol) was dissolved in a mixture of THF (400 mL) and DMF (80 mL) and solid $NaHCO_3$ (28.8 g, 0.342 mol) and MeI (17.8 mL, 0.285 mol) were sequentially added. The mixture was heated at reflux overnight, at which time a further 5 mL of MeI was added. After refluxing for a further 24 h, the reaction was diluted with water and extracted with ether. The combined organic layers were washed with water (2X), dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using 10:1 PE:EA as eluent afforded the title compound as a pale yellow oil (28.1 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.8 and 1.5 Hz, 1H), 7.32 (ddd, J = 8.0, 7.3 and 1.5 Hz, 1H), 7.11 (dd, J = 8.0 and 1.0 Hz, 1H), 6.78 (ddd, J = 7.8, 7.3 and 1.5 Hz, 1H), 2.78 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (C), 140.4 (CH), 129.3 (CH), 125.2 (CH), 120.7 (CH), 97.3 (C), 45.2 (CH_3); IR (neat): ν = 3054, 2981, 2941, 2860, 2827, 2779, 1580, 1470, 1452, 1316, 1185, 1158, 1046, 1013, 945, 759, 721 cm^{-1}; MS (EI) *m/z* 247 (M^+) (100), 162 (14), 105 (16), 91 (13), 77 (18); HRMS calculated for $C_8H_{10}NI$ (M^+) 246.9858, found 246.9865.

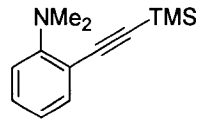
2-(Dimethylamino)benzaldehyde (219)



$C_9H_{11}NO$
Mol. Wt.: 149.19

Dimethylaniline **222** (10.0 g, 0.0405 mol) was dissolved in THF (200 mL) and cooled to –78 °C. A solution of *t*-BuLi in pentane [0.0850 mol from two bottles: 1.30 M (40.0 mL) and 1.54 M (21.4 mL)] was then rapidly added and the solution was stirred for 5 min. Dimethylformamide (12.8 mL, 0.166 mol) was then added, and the solution was stirred for 5 min at –78 °C, and then at 0 °C for 1 h. The reaction was quenched with sat. NH_4Cl, diluted with water, and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (30:1 PE:EA) afforded the title compound as a brilliantly yellow oil (5.01 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (d, J = 0.4 Hz, 1H), 7.75 (dd, J = 7.7 and 1.8 Hz, 1H), 7.44 (ddd, J = 8.3, 7.2 and 1.8 Hz, 1H), 7.03 (dd, J = 8.3 and 0.6 Hz, 1H), 6.96-7.00 (m, 1H), 2.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2 (CH), 155.9 (C), 134.7 (CH), 131.0 (CH), 127.2 (C), 120.7 (CH), 117.8 (CH), 45.6 (CH_3); IR (neat): ν = 3067, 2987, 2947, 2868, 2839, 2795, 1684, 1598, 1488, 1455, 1434, 1280, 1188, 1152, 1138, 1101, 949, 832, 764 cm^{-1}; MS (EI) *m/z* 149 (M^+) (73), 120 (71), 117 (25), 91 (36), 77 (66), 44 (100); HRMS calculated for $C_9H_{11}NO$ (M^+) 149.0841, found 149.0833.

Dimethyl-(2-(trimethylsilanylethynyl)phenyl)amine (223)

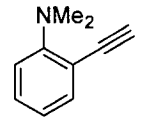


$C_{13}H_{19}NSi$
Mol. Wt.: 217.38

Dimethylaniline **222** (10.0 g, 40.5 mmol), $Pd(PPh)_3Cl_2$ (1.42 g, 2.02 mmol), and CuI (0.392 g, 2.02 mmol) were dissolved in a mixture of THF (200 mL) and NEt_3 (10 mL) and the solution was degassed. Trimethylsilylacetylene (8.58 mL, 60.7 mmol) was then added and the solution was stirred at rt overnight. Silica gel was then added and the solvent was removed *in vacuo*. Column chromatography (dry pack, 75:1 PE:EA) yielded the title compound as a yellow oil (7.63 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.6 and 1.7 Hz, 1H), 7.24 (ddd, J = 8.4, 7.3 and 1.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.85 (ddd, J = 7.5, 7.5 and 0.9 Hz, 1H), 2.99

(s, 6H), 0.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3 (C), 135.1 (CH), 129.6 (CH), 120.2 (CH), 116.9 (CH), 114.9 (C), 105.0 (C), 99.6 (C), 43.5 (CH_3), 0.2 (CH_3); IR (neat): ν = 3065, 2957, 2898, 2834, 2786, 2150, 1594, 1493, 1431, 1249, 950, 866, 842, 757 cm^{-1}; MS (EI) *m/z* 217 (M^+) (29), 202 (5), 144 (100); HRMS calculated for $C_{13}H_{19}NSi$ (M^+) 217.1287, found 217.1280.

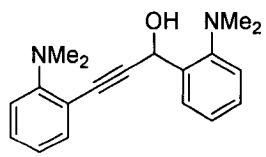
(2-Ethynylphenyl)dimethylamine (220)



$C_{10}H_{11}N$
Mol. Wt.: 145.2

Potassium hydroxide (3.61 g, 0.0644 mol) was dissolved in MeOH (100 mL) and a solution of aryl TMS-acetylene **223** (7.00 g, 0.0322 mol) in MeOH (~20 mL) was added. The solution was stirred for 1 h and diluted with water. The organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (50:1 PE:EA) afforded the title compound as a pale orange oil (3.91 g, 84 %). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.28 (ddd, *J* = 8.3, 7.3 and 1.7 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.90 (ddd, *J* = 7.5, 7.5 and 1.1 Hz, 1H), 3.43 (s, 1H), 2.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 (C), 135.2 (CH), 129.9 (CH), 120.9 (CH), 117.3 (CH), 114.6 (C), 83.2 (C), 82.5 (CH), 43.8 (CH_3); IR (neat): ν = 3065, 2980, 2945, 2835, 2786, 2100, 1593, 1490, 1431, 1329, 1159, 1046, 949, 757, 746 cm^{-1}; MS (EI) *m/z* 145 (M^+) (72), 144 (100), 129 (18), 103 (16), 91 (7), 77 (19); HRMS calculated for $C_{10}H_{11}N$ (M^+) 145.0892, found 145.0876.

1,3-Bis(2-(dimethylamino)phenyl)prop-2-yn-1-ol (218)

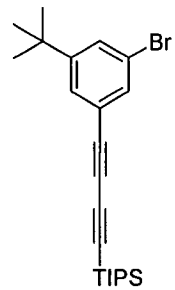


$C_{19}H_{22}N_2O$
Mol. Wt.: 294.39

Acetylene **220** (0.500 g, 3.44 mmol) was dissolved in THF (25 mL) and cooled to –78 °C. A solution of NaHMDS in THF (1.0 M, 4.13 mL, 4.13 mmol) was added and the green solution was stirred for 5 min. A solution of aldehyde **219** (0.514 g, 3.44 mmol) in THF (5 mL) was then

added and the yellow solution was stirred at –78 °C for 10 min. The solution was quenched with sat. NH_4Cl and made basic by addition of sat. $NaHCO_3$. The organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (5:1 PE:EA) yielded the title compound as a pale yellow oil (0.830 g, 82%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.49 (m, 1H), 7.39 (dd, J = 7.6 and 1.7 Hz, 1H), 7.31-7.32 (m, 2H), 7.22 (ddd, J = 8.2, 7.4 and 1.7 Hz, 1H), 7.17-7.19 (m, 1H), 6.88 (dd, J = 8.3, 0.7 Hz, 1H), 6.84 (ddd, J = 7.5, 7.5 and 1.1 Hz, 1H), 5.95 (s, 1H), 2.86 (s, 6H), 2.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (C), 151.8 (C), 136.1 (C), 134.5 (CH), 129.4 (CH), 128.9 (CH), 128.5 (CH), 125.6 (CH), 121.8 (CH), 120.5 (CH), 117.0 (CH), 115.1 (C), 95.4 (C), 85.8 (C), 65.2 (CH), 45.8 (CH_3), 43.5 (CH_3); IR (neat): ν = 3062, 2977, 2942, 2864, 2832, 2787, 1657, 1489, 1452, 1323, 1190, 1156, 947, 759 cm^{-1}; MS (EI) *m/z* 294 (M^+) (0.6), 277 (10), 261 (14), 172 (10), 160 (24), 148 (69), 132 (100), 91 (19); HRMS calculated for $C_{19}H_{21}N_2$ (M^+ – OH) 277.1705, found 277.1704.

[4-(3-Bromo-5-*tert*-butylphenyl)buta-1,3-diynyl]triisopropylsilane (237)

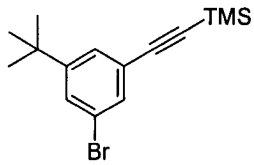


$C_{23}H_{33}BrSi$
Mol. Wt.: 417.50

Chloroenyne **235** (3.94 g, 16.2 mmol) was dissolved in THF (125 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.7 M, 19.1 mL, 32.5 mmol) was added and the solution was stirred for 5 min. A solution of $ZnBr_2$ (3.82 g, 17.0 mmol) in THF (80 mL) was then added and the solution was stirred for 5 min at –78 °C, and then warmed to 0 °C. After 30 min, a solution of aryl iodide **234** (5.00 g, 14.8 mmol) and $Pd(PPh_3)_4$ (0.853 g, 0.737 mmol) in THF (125 mL) was added and the reaction was stirred at rt overnight. Silica gel was then added and the solvent removed *in vacuo*. Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a pale yellow oil (6.19 g, ~100%). A minor impurity (~5%) could not be separated from the product. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 1.8 and 1.8 Hz, 1H), 7.47 (d, J = 1.8 Hz, 2H), 1.30 (s, 9H), 1.11-1.13 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8

(C), 132.5 (CH), 130.1 (CH), 128.9 (CH), 123.3 (C), 122.3 (C), 89.5 (C), 89.0 (C), 75.5 (C), 74.7 (C), 35.1 (C), 31.2 (CH_3), 18.9 (CH_3), 11.6 (CH); IR (neat): ν = 2961, 2866, 2809, 2101, 1591, 1561, 1463, 1366, 1242, 996, 883, 866, 795, 759 cm^{-1}; MS (EI) *m/z* 418 (6, ^{81}Br), 416 (M^+, 6, ^{79}Br), 375 (100, ^{81}Br), 373 (96, ^{79}Br), 347 (30, ^{81}Br), 345 (27, ^{79}Br), 319 (30, ^{81}Br), 317 (25, ^{79}Br); HRMS calculated for $C_{23}H_{33}Si^{79}Br$ (M^+) 416.1535, found 416.1516.

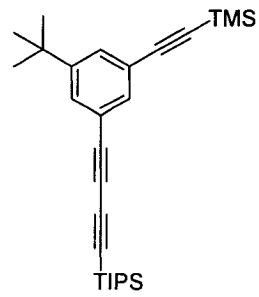
(3-Bromo-5-*tert*-butylphenylethynyl)trimethylsilane (238)



$C_{15}H_{21}BrSi$
Mol. Wt.: 309.32

Aryl iodide **234** (12.0 g, 0.0352 mol), $Pd(PPh_3)_2Cl_2$ (0.493 g, 0.704 mmol) and CuI (0.132 g, 0.704 mmol) were dissolved in a mixture of NEt_3 (10 mL) and THF (200 mL) and degassed. Trimethylsilylacetylene (5.17 mL, 0.0366 mol) was added and the solution was stirred at rt overnight. The mixture was then filtered through a silica gel pad (10 cm high) using ether as eluent, and concentrated. The resultant orange oil was filtered through a second silica gel pad (10 cm) using PE as eluent. Removal of the solvent afforded a pale yellow oil identified as the title compound (10.8 g, 99%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 1.8 and 1.8 Hz, 1H), 7.45 (dd, J = 1.8 and 1.4 Hz, 1H), 7.41 (dd, J = 1.8 and 1.4 Hz, 1H), 1.30 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C), 132.0 (CH), 129.3 (CH), 128.0 (CH), 124.8 (C), 122.2 (C), 104.2 (C), 95.2 (C), 35.1 (C), 31.3 (CH_3), 0.1 (CH_3); IR (neat): ν = 3068, 2964, 2903, 2871, 2165, 1590, 1557, 1430, 1406, 1365, 1274, 1250, 936, 857, 844, 759 cm^{-1}; MS (EI) *m/z* 310 (22, ^{81}Br), 308 (M^+, 22, ^{79}Br), 295 (100, ^{81}Br), 293 (93, ^{79}Br), 179 (6), 126 (11); HRMS calculated for $C_{15}H_{21}{}^{79}BrSi$ (M^+) 308.0596, found 308.0583.

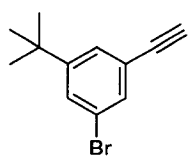
1-*tert*-Butyl-3-(4-(triisopropylsilanyl)buta-1,3-diynyl)-5-(trimethylsilanylethynyl)benzene (239)



$C_{28}H_{42}Si_2$
Mol. Wt.: 434.8

The title compound was prepared analogously to aryl TMS-acetylene **238** using the following reagent quantities: Aryl bromide **237** (2.80 g, 6.71 mmol); $Pd(PPh_3)_4$ (0.094 g, 0.134 mmol); CuI (0.026 g, 0.134 mmol); THF (40 mL); NEt_3 (2 mL); TMS-acetylene (1.42 mL, 10.1 mmol). Additional CuI (0.050 g), $Pd(PPh_3)_4$ (0.18 g) and TMS-acetylene (1.42 mL) were added the following day and refluxing was continued for another night. The title compound was isolated as a pale orange oil (3.05 g, ~100%). Minor impurities (~5%) could not be separated from the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 1.6 and 1.6 Hz, 1H), 7.47 (dd, J = 1.6 and 1.6 Hz, 1H), 7.45 (dd, J = 1.6 and 1.6 Hz, 1H), 1.30 (s, 9H), 1.13-1.14 (m, 21H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C), 133.4 (CH), 130.2 (CH), 130.1 (CH), 123.5 (C), 121.6 (C), 104.6 (C), 94.8 (C), 89.7 (C), 88.3 (C), 75.5 (C), 74.8 (C), 34.9 (C), 31.2 (CH_3), 18.9 (CH_3), 11.6 (CH), 0.1 (CH_3); IR (neat): ν = 2960, 2866, 2209, 2161, 2097, 1582, 1463, 1250, 941, 880, 843, 759 cm^{-1}; MS (EI) *m/z* 434 (M^+) (7), 391 (66), 363 (16), 345 (31), 319 (53), 311 (36), 271 (40), 179 (45), 73 (100); HRMS calculated for $C_{28}H_{42}Si_2$ (M^+) 434.2825, found 434.2822.

1-Bromo-3-*tert*-butyl-5-ethynylbenzene (240)

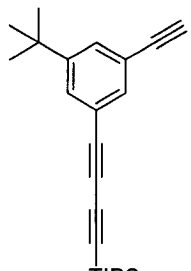


$C_{12}H_{13}Br$
Mol. Wt.: 237.14

Potassium hydroxide (3.85 g, 0.0685 mol) was dissolved in MeOH (110 mL) and a solution of aryl TMS-acetylene **238** (10.6 g, 0.0343 mol) in MeOH (~20 mL) was added. The solution was stirred for 1 h and then neutralized by the addition of sat. NH_4Cl. The organics were extracted

with ether, dried, filtered, and concentrated. Filtration through a silica gel pad (10 cm) using PE as eluent, followed by removal of the solvent, provided the title compound as a pale yellow oil (7.83 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 1.7 and 1.7 Hz, 1H), 7.47 (dd, J = 1.7 and 1.7 Hz, 1H), 7.45 (dd, J = 1.7 and 1.7 Hz, 1H), 3.10 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 132.1 (CH), 129.7 (CH), 128.2 (CH), 123.8 (C), 122.2 (C), 82.9 (CH), 78.0 (C), 35.1 (C), 31.2 (CH_3); IR (neat): ν = 3295, 2966, 2905, 2871, 1589, 1557, 1478, 1428, 1405, 1365, 1273, 1193, 867, 824, 759 cm^{-1}; MS (EI) *m/z* 238 (30, ^{81}Br), 236 (M^+, 31, ^{79}Br), 223 (99, ^{81}Br), 221 (100, ^{79}Br), 142 (30), 115 (11), 69 (15); HRMS calculated for $C_{12}H_{13}{}^{79}Br$ (M^+) 236.0201, found 236.0176.

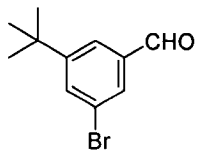
[4-(3-*tert*-Butyl-5-(ethynylphenyl))buta-1,3-diynyl]triisopropylsilane (241)



$C_{25}H_{34}Si$
Mol. Wt.: 362.62

The title compound was prepared analogously to acetylene **240** using the following reagent quantities: KOH (0.77 g, 13.7 mmol); aryl TMS-acetylene **239** (2.92 g, 6.72 mmol); MeOH (35 mL). Ether was used to solubilize aryl TMS-acetylene **239**. The title compound was isolated as a yellow oil (2.09 g, 86%). Minor impurities (<5%) could not be separated from the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.7 and 1.7 Hz, 1H), 7.51 (dd, J = 1.7 and 1.7 Hz, 1H), 7.46 (dd, J = 1.7 and 1.7 Hz, 1H), 3.07 (s, 1H), 1.30 (s, 9H), 1.12-1.13 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C), 133.4 (CH), 130.6 (CH), 130.4 (CH), 122.5 (C), 121.8 (C), 89.6 (C), 88.4 (C), 83.2 (CH), 77.6 (C), 75.3 (C), 74.9 (C), 34.9 (C), 31.2 (CH_3), 18.8 (CH_3), 11.6 (CH); IR (neat): ν = 3300, 2961, 2944, 2866, 2362, 2332, 2211, 2095, 1585, 1463, 1366, 1245, 1072, 996, 880, 856 cm^{-1}; MS (EI) *m/z* 362 (M^+) (10), 319 (100), 291 (35), 249 (61), 124 (20); HRMS calculated for $C_{25}H_{34}Si$ (M^+) 362.2430, found 362.2418.

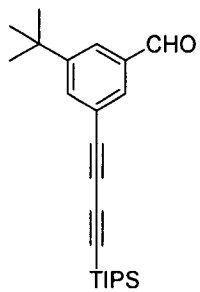
3-Bromo-5-*tert*-butylbenzaldehyde (242)



$C_{11}H_{13}BrO$
Mol. Wt.: 241.12

Aryl iodide **234** (6.00 g, 0.0177 mol) was dissolved in THF (100 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.70 M, 10.4 mL, 0.0177 mol) was then added, followed immediately by DMF (6.47 mL, 0.0885 mol). The solution was stirred for 20 min at –78 °C and then quenched with water. The mixture was then diluted with water and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (50:1 PE:EA) afforded the title compound as a yellow oil (3.75 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.83 (dd, J = 1.8 and 1.4 Hz, 1H), 7.82 (dd, J = 1.8 and 1.4 Hz, 1H), 7.77 (dd, J = 1.8 and 1.8 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3 (CH), 154.9 (C), 138.1 (C), 134.9 (CH), 130.1 (CH), 125.6 (CH), 123.4 (C), 35.3 (C), 31.3 (CH_3); IR (neat): ν = 3067, 2964, 2870, 2721, 1705, 1593, 1566, 1480, 1365, 1274, 1261, 1190, 871, 850, 782, 695 cm^{-1}; MS (EI) *m/z* 242 (10, ^{81}Br), 240 (M^+, 10, ^{79}Br), 227 (27, ^{81}Br), 225 (29, ^{79}Br), 214 (27, ^{81}Br), 212 (30, ^{79}Br), 199 (96, ^{81}Br), 197 (100, ^{79}Br), 171 (16), 118 (24); HRMS calculated for $C_{11}H_{13}{}^{79}BrO$ (M^+) 240.0150, found 240.0129.

3-*tert*-Butyl-5-(4-(triisopropylsilanyl)buta-1,3-diynyl)benzaldehyde (243)

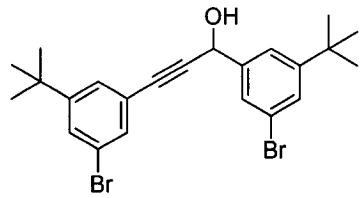


$C_{24}H_{34}OSi$
Mol. Wt.: 366.61

Aryl bromide **237** (2.80 g, 6.71 mmol) was dissolved in THF (100 mL) and cooled to –78 °C. A solution of *t*-BuLi in pentane (1.2 M, 12.3 mL, 14.8 mmol) was then added and the solution stirred for 30 min at –78 °C. Dimethylformamide (2.60 mL, 33.5 mmol) was then added and the solution was warmed and stirred at 0 °C for 6 h, and then at rt overnight. The reaction was

quenched with water and diluted with brine, and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (30:1 PE:EA) afforded the title compound as a pale orange oil (1.98 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.90 (dd, J = 1.9 and 1.5 Hz, 1H), 7.81 (dd, J = 1.5 and 1.5 Hz, 1H), 7.79 (dd, J = 1.9 and 1.5 Hz, 1H), 1.35 (s, 9H), 1.12-1.13 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6 (CH), 153.0 (C), 136.8 (C), 135.7 (CH), 131.9 (CH), 126.9 (CH), 122.7 (C), 89.4 (C), 89.1 (C), 75.7 (C), 74.7 (C), 35.1 (C), 31.2 (CH_3), 18.8 (CH_3), 11.5 (CH); IR (neat): ν = 2967, 2867, 2809, 2727, 2208, 2096, 1708, 1463, 1383, 1367, 1245, 1169, 882, 735 cm^{-1}; MS (EI) *m/z* 366 (M^+) (10), 323 (100), 295 (22), 281 (23), 267 (28), 253 (63), 203 (17), 126 (16), 69 (48); HRMS calculated for $C_{24}H_{34}OSi$ (M^+) 366.2386, found 366.2358.

1,3-Bis(3-bromo-5-*tert*-butylphenyl)prop-2-yn-1-ol (244)

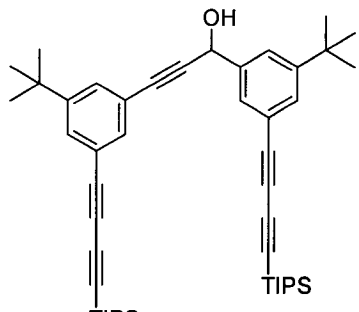


$C_{23}H_{26}Br_2O$
Mol. Wt.: 478.26

Acetylene **240** (1.00 g, 4.22 mmol) was dissolved in THF (50 mL), cooled to –78 °C, and a solution of NaHMDS in THF (1.0 M, 5.06 mL, 5.06 mmol) was added. The solution was stirred for 5 min, and then a solution of aldehyde **242** (1.02 g, 4.22 mmol) in THF (10 mL) was added dropwise. After stirring at –78 °C for 20 min, the reaction was quenched with water, diluted with ether, and washed with 1 M HCl (2X). The organics were dried, filtered, and concentrated. Column chromatography (20:1 PE:EA) provided the title compound as a colorless foam (1.71 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.7 and 1.7 Hz, 1H), 7.55 (dd, J = 1.7 and 1.7 Hz, 1H), 7.51 (dd, J = 1.7 and 1.7 Hz, 1H), 7.50 (dd, J = 1.7 and 1.7 Hz, 1H), 7.44 (dd, J = 1.7 and 1.7 Hz, 1H), 7.43 (dd, J = 1.7 and 1.7 Hz, 1H), 5.65 (s, 1H), 1.34 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3 (C), 153.8 (C), 142.4 (C), 131.7 (CH), 129.6 (CH), 129.1 (CH), 127.9 (CH), 127.1 (CH), 123.9 (C), 122.9 (C), 122.8 (CH), 122.3 (C), 89.1 (C), 86.2 (C), 64.9 (CH), 35.3 (C), 35.1 (C), 31.4 (CH_3), 31.3 (CH_3); IR (neat): ν = 3319, 2963, 2907, 2869, 2198, 1635, 1559, 1439, 1365, 1301, 1247, 1197, 1062, 878, 863, 741 cm^{-1}; MS (EI) *m/z* 480 (7, $^{81}Br_2$), 478 (15, $^{81}Br^{79}Br$), 476 (M^+, 9, $^{79}Br_2$), 423 (11, $^{81}Br_2$), 421 (22, $^{81}Br^{79}Br$), 419 (11, $^{79}Br_2$),

225 (28, $^{81}Br_2$), 223 (32, $^{81}Br^{79}Br$), 221 (25, $^{79}Br_2$), 57 (100); HRMS calculated for $C_{23}H_{26}{}^{79}Br_2O$ (M^+) 476.0350, found 476.0316.

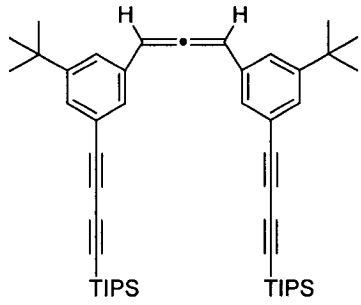
1,3-Bis[3-*tert*-butyl-5-(4-(triisopropylsilanyl)buta-1,3-diynyl)phenyl]prop-2-yn-1-ol (245)



$C_{49}H_{68}OSi_2$
Mol. Wt.: 729.23

Acetylene **241** (0.94 g, 2.59 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (2.4 M, 1.13 mL, 2.72 mmol) was added and the red solution was stirred for 5 min. A solution of aldehyde **243** (0.95 g, 2.59 mmol) in THF (10 mL) was added and the yellow solution was stirred at –78 °C for 20 min. The reaction was then quenched with sat. NH_4Cl, and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (30:1 PE:EA) yielded the title compound as an orange solid (1.14 g, 60%). mp: 92 – 95 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 1.7 and 1.7 Hz, 1H), 7.60 (dd, J = 1.5 and 1.5 Hz, 1H), 7.55 (dd, J = 1.5 and 1.5 Hz, 1H), 7.53 (dd, J = 1.7 and 1.6 Hz, 1H), 7.50 (dd, J = 1.7 and 1.6 Hz, 1H), 7.44 (dd, J = 1.5 and 1.5 Hz, 1H), 5.66 (s, 1H), 2.32 (br s, 1H), 1.34 (s, 9H), 1.31 (s, 9H), 1.11-1.13 (m, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 152.0 (C), 140.8 (C), 132.9 (CH), 130.5 (CH), 130.2 (CH), 130.1 (CH), 128.3 (CH), 125.2 (CH), 122.6 (C), 121.9 (C), 121.8 (C), 89.8 (C), 89.7 (C), 88.8 (C), 88.4 (C), 88.1 (C), 86.6 (C), 76.1 (C), 75.3 (C), 75.0 (C), 74.7 (C), 65.1 (CH), 35.1 (C), 34.9 (C), 31.4 (CH_3), 31.2 (CH_3), 18.8 (CH_3), 11.6 (CH) (Carbon signals for both TIPS groups overlap at 11.6 and 18.8 ppm); IR (neat): ν = 3399, 2960, 2945, 2892, 2866, 2207, 2097, 1588, 1463, 1365, 1244, 1073, 1039, 1018, 996, 880, 780 cm^{-1}; MS (ES) *m/z* 767.3 ($M^+ + K^+$).

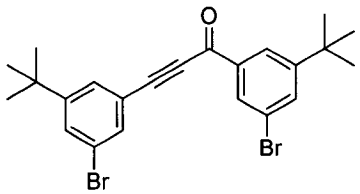
1,3-Bis(3-*tert*-butyl-5-(4-(triisopropylsilyl)buta-1,3-diynyl)phenyl)propa-1,2-diene (247)



$C_{49}H_{68}Si_2$
Mol. Wt.: 713.24

Triphenylphosphine (0.162 g, 0.617 mmol) was dissolved in THF (3 mL) and cooled to –15 °C. Diethylazodicarboxylate (0.097 mL, 0.617 mmol) was then added and the solution was stirred for 10 min at –15 °C. A solution of propargyl alcohol **245** (0.150 g, 0.206 mmol) in THF (2 mL) was then added and the solution was stirred for 10 min, at which time a solution of NBSH (0.134 g, 0.617 mmol) in THF (3 mL) was added. The reaction was stirred at –15 °C for 2 h and then allowed to warm to rt. The reaction was then diluted with sat. $NaHCO_3$, and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (PE) yielded the title compound as a yellow solid (0.026 g, 18%). mp: dec. 70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 1.6 and 1.6 Hz, 1H), 7.34 (dd, J = 1.6 and 1.6 Hz, 1H), 7.32 (dd, J = 1.6 and 1.6 Hz, 1H), 6.56 (s, 1H), 1.31 (s, 9H), 1.11-1.12 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2 (C), 152.3 (C), 133.7 (C), 129.2 (CH), 128.4 (CH), 125.7 (CH), 121.9 (C), 98.6 (CH), 89.8 (C), 88.0 (C), 76.2 (C), 74.5 (C), 35.0 (C), 31.3 (CH_3), 18.8 (CH_3), 11.6 (CH); IR (neat): ν = 2959, 2945, 2866, 2206, 2096, 1585, 1462, 1365, 1245, 1072, 1018, 996, 881, 782 cm^{-1}; MS (EI) *m/z* 712 (M^+) (25), 669 (13), 627 (9), 157 (100), 115 (51).

1,3-Bis(3-bromo-5-*tert*-butylphenyl)propynone (249)

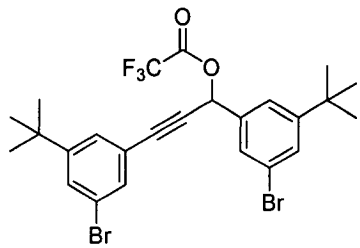


$C_{23}H_{24}Br_2O$
Mol. Wt.: 476.24

Propargyl alcohol **244** (0.170 g, 0.356 mmol) was dissolved in CH_2Cl_2 (5 mL, not dried), Dess-Martin periodinane (0.181 g, 0.427 mmol) was added, and the solution was stirred at rt for 30

min. A 1:1 mixture of 1 M $Na_2S_2O_3$ and sat. $NaHCO_3$ was then added and the mixture was stirred until both layers were clear. The reaction was diluted with ether, washed with $NaHCO_3$ and brine, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using CH_2Cl_2 as eluent followed by removal of the solvent afforded the product as a white powder (90%). mp: 154 – 156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 1.7 and 1.7 Hz, 1H), 8.15 (dd, J = 1.7 and 1.7 Hz, 1H), 7.79 (dd, J = 1.7 and 1.7 Hz, 1H), 7.65 (dd, J = 1.7 and 1.7 Hz, 1H), 7.64 (dd, J = 1.7 and 1.7 Hz, 1H), 7.63 (dd, J = 1.7 and 1.7 Hz, 1H), 1.38 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8 (C), 154.4 (C), 154.3 (C), 138.4 (C), 134.7 (CH), 132.8 (CH), 131.9 (CH), 130.1 (CH), 129.3 (CH), 125.2 (CH), 123.0 (C), 122.6 (C), 121.6 (C), 92.5 (C), 87.0 (C), 35.3 (C), 35.2 (C), 31.3 (CH_3), 31.2 (CH_3); IR (neat): ν = 2963, 2906, 2869, 2198, 1635, 1559, 1438, 1364, 1300, 1247, 1197, 1060, 863, 741 cm^{-1}; MS (EI) *m/z* 478 (16, $^{81}Br_2$), 476 (30, $^{81}Br^{79}Br$), 474 (M^+, 15, $^{79}Br_2$), 463 (48, $^{81}Br_2$), 461 (100, $^{81}Br^{79}Br$), 459 (51, $^{79}Br_2$), 223 (16), 162 (10), 57 (26); HRMS calculated for $C_{23}H_{24}{}^{79}Br_2O$ (M^+) 474.0194, found 474.0181.

Trifluoroacetic acid 1,3-bis(3-bromo-5-*tert*-butylphenyl)prop-2-ynyl ester (248)

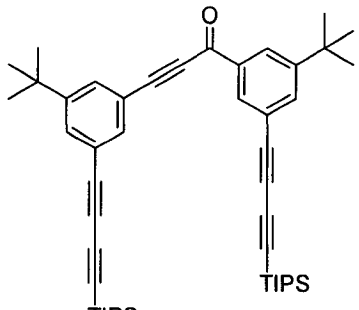


$C_{25}H_{25}Br_2F_3O_2$
Mol. Wt.: 574.27

Alcohol **244** (0.50 g, 1.05 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C and NEt_3 (0.29 mL, 2.09 mmol), DMAP (catalytic), and $(CF_3CO_2)O$ were sequentially added. After 10 min the reaction was diluted with sat. NH_4Cl, and the organic layer was washed with water and brine, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using ether as eluent afforded a colorless oil identified as the title compound (0.60 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60_2 (dd, J = 1.7 and 1.7 Hz, 1H), 7.59_7 (dd, J = 1.7 and 1.7 Hz, 1H), 7.55 (dd, J = 1.7 and 1.7 Hz, 1H), 7.53 (dd, J = 1.7 and 1.7 Hz, 1H), 7.47 (dd, J = 1.7 and 1.7 Hz, 1H), 7.44 (dd, J = 1.7 and 1.7 Hz, 1H), 6.70 (s, 1H), 1.35 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (q, J = 44 Hz, C), 154.7 (C), 154.0 (C), 136.5 (C), 132.0 (CH), 130.6 (CH),

130.4 (CH), 128.3 (CH), 128.1 (CH), 124.0 (CH), 123.1 (C), 122.8 (C), 122.4 (C), 114.6 (q, J = 284 Hz, CF_3), 89.0 (C), 83.3 (C), 69.9 (CH), 35.3 (C), 35.2 (C), 31.3 (CH_3), 31.2 (CH_3); IR (neat): ν = 2966, 2910, 2871, 2231, 1789, 1559, 1477, 1366, 1224, 1174, 1142, 1049, 865 cm^{-1}; MS (EI) *m/z* 576/574/572 (M^+) (4/10/4), 561/559/557 (5/10/5), 423/421/419 (15/29/16), 57 (100); HRMS calculated for $C_{25}H_{25}{}^{79}Br_2F_3O_2$ (M^+) 572.0173, found 572.0166.

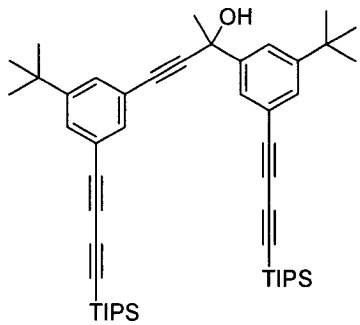
1,3-Bis[3-*tert*-butyl-5-(4-(triisopropylsilanyl)buta-1,3-diynyl)phenyl]propynone (250)



$C_{49}H_{66}OSi_2$
Mol. Wt.: 727.22

The title compound was prepared analogously to propargyl ketone **249** using the following reagent quantities: Propargyl alcohol **245** (0.60 g, 0.823 mmol); CH_2Cl_2 (30 mL); (0.45 g, 1.07 mmol). Filtration through a silica gel plug (10 cm) using 10:1 PE:EA as eluent afforded the title compound as a yellow powder (0.57 g, 95%). mp: 99.0 – 100.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 1.6 and 1.6 Hz, 1H), 8.18 (dd, *J* = 1.4 and 1.4 Hz, 1H), 7.82 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.70 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.67 (dd, *J* = 1.4 and 1.4 Hz, 1H), 7.65 (dd, *J* = 1.4 and 1.4 Hz, 1H), 1.38 (s, 9H), 1.34 (s, 9H), 1.13 (m, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3 (C), 152.6 (C), 137.1 (C), 135.6 (CH), 133.9 (CH), 132.6 (CH), 131.7 (CH), 131.3 (CH), 126.9 (CH), 122.4 (C), 122.3 (C), 120.4 (C), 92.9 (C), 89.44 (C), 89.41 (C), 89.03 (C), 89.00 (C), 86.9 (C), 75.6 (C), 75.5 (C), 75.0 (C), 74.6 (C), 35.2 (C), 35.1 (C), 31.3 (CH_3), 31.2 (CH_3), 18.8 (CH_3), 11.5 (CH) (Carbon signals for TIPS groups overlap at 11.5 and 18.8 ppm; one aromatic quaternary carbon not visible); IR (neat): ν = 2960, 2866, 2204, 2097, 1649, 1582, 1463, 1366, 1341, 1234, 1175, 996, 881, 744, 677 cm^{-1}; MS (ES) *m/z* 765.5 ($M^+ + K^+$).

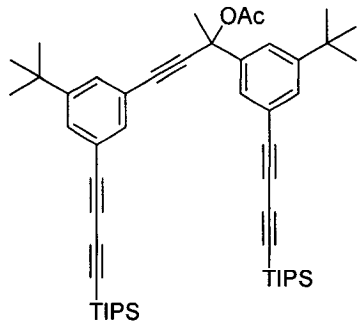
2,4-Bis[3-*tert*-butyl-5-(4-(triisopropylsilanyl)buta-1,3-diynyl)phenyl]but-3-yn-2-ol (252)



$C_{50}H_{70}OSi_2$
Mol. Wt.: 743.26

Propargyl ketone **250** (0.15 g, 0.206 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of MeMgBr in THF (3.0 M, 0.076 mL, 0.227 mmol) was then added and the solution stirred for 30 min. The reaction was then diluted with 1 M HCl, extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (5 cm) using 10:1 PE:EA as eluent afforded the title compound as a yellow powder (0.15 g, 100%). mp: 98.0 – 99.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 1.7 and 1.7 Hz, 1H), 7.69 (dd, J = 1.7 and 1.7 Hz, 1H), 7.53 (dd, J = 1.7 and 1.7 Hz, 1H), 7.52 (dd, J = 1.7 and 1.7 Hz, 1H), 7.50 (dd, J = 1.7 and 1.7 Hz, 1H), 7.46 (dd, J = 1.7 and 1.7 Hz, 1H), 2.52 (br s, 1H), 1.85 (s, 3H), 1.35 (s, 9H), 1.31 (s, 9H), 1.13-1.14 (m, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C), 151.9 (C), 145.8 (C), 132.9 (CH), 130.4 (CH), 130.1 (CH), 129.5 (CH), 126.9 (CH), 123.4 (CH), 122.7 (C), 121.8 (C), 121.3 (C), 92.5 (C), 89.8 (C), 89.6 (C), 88.4 (C), 87.9 (C), 84.8 (C), 76.3 (C), 75.3 (C), 75.0 (C), 74.4 (C), 70.5 (C), 35.1 (C), 34.9 (C), 33.5 (CH_3), 31.4 (CH_3), 31.2 (CH_3), 18.8 (CH_3), 11.5 (CH) (Carbon signals for both TIPS groups overlap at 11.5 and 18.8 ppm); IR (neat): ν = 3360, 2960, 2944, 2866, 2206, 2097, 1585, 1463, 1366, 1245, 881 cm^{-1}; MS (ES) *m/z* 781.5 ($M^+ + K^+$).

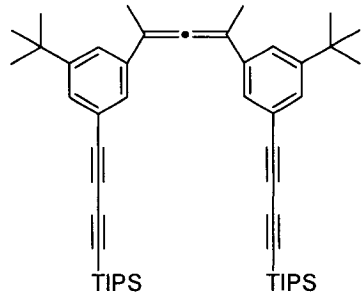
2,4-Bis(3-*tert*-butyl-5-(4-(triisopropylsilyl)buta-1,3-diynyl)phenyl)but-3-yn-2-yl acetate (254)



$C_{52}H_{72}O_2Si_2$
Mol. Wt.: 785.30

Propargyl alcohol **252** (0.58 g, 0.775 mmol) was dissolved in CH_2Cl_2 (20 mL) and DMAP (catalytic), pyridine (0.32 mL, 3.88 mmol), and Ac_2O (0.37 mL, 3.88 mmol) were sequentially added. After stirring at rt for 3 d, the reaction was diluted with ether and washed with 1 M HCl (2X). The organics were combined, dried, filtered, and concentrated. Column chromatography (50:1 PE:EA) afforded the title compound as a yellow powder (0.50 g, 82%). mp: 96.0 – 99.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 1.6 and 1.6 Hz, 1H), 7.56 (dd, J = 1.6 and 1.6 Hz, 1H), 7.53 (dd, J = 1.6 and 1.6 Hz, 1H), 7.52 (dd, J = 1.6 and 1.6 Hz, 1H), 7.50_4 (dd, J = 1.6 and 1.6 Hz, 1H), 7.49_6 (dd, J = 1.6 and 1.6 Hz, 1H), 2.12 (s, 3H), 1.95 (s, 3H), 1.34 (s, 9H), 1.31 (s, 9H), 1.11-1.13 (m, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C), 151.9 (C), 151.8 (C), 143.0 (C), 133.3 (CH), 130.4 (CH), 130.1 (CH), 129.7 (CH), 126.6 (CH), 123.7 (CH), 122.7 (C), 121.7 (C), 121.4 (C), 89.8 (C), 89.7 (C), 88.7 (C), 88.3 (C), 88.0 (C), 87.0 (C), 76.3 (C), 75.9 (C), 75.4 (C), 74.9 (C), 74.4 (C), 35.1 (C), 34.9 (C), 32.1 (CH_3), 31.4 (CH_3), 31.2 (CH_3), 22.0 (CH_3), 18.8 (CH_3), 11.5 (CH) (Carbon signals for both TIPS groups overlap at 11.5 and 18.8 ppm); IR (neat): ν = 2960, 2941, 2892, 2866, 2207, 2096, 1756, 1586, 1366, 1229, 1068, 1013, 996, 880, 678 cm^{-1}; MS (EI) *m/z* 785 (M^+) (5), 725 (38), 681 (15), 639 (6), 533 (12), 157 (100), 115 (48).

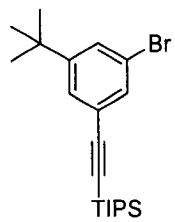
2,4-Bis(3-*tert*-butyl-5-(4-(triisopropylsilyl)buta-1,3-diynyl)phenyl)penta-2,3-diene (256)



$C_{51}H_{72}Si_2$
Mol. Wt.: 741.29

Lithium bromide (0.055 g, 0.629 mmol) and CuI (0.120 g, 0.629 mmol) were added to THF (4 mL) and cooled to 0 °C. A solution of MeMgBr in THF (2.0 M, 0.314 mL, 0.629 mmol) was added and the solution was stirred for 15 min at 0 °C, after which a solution of acetate **254** (0.056 g, 0.105 mmol) in THF (1 mL) was added dropwise. The yellow mixture was stirred at 0 °C for 30 min and then quenched *via* the slow addition of sat. NH_4Cl. The organics were extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using PE afforded the title compound as a pale yellow solid (0.040 g, 78%). mp: 106.5 – 108.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.8 and 1.8 Hz, 1H), 7.44 (dd, J = 1.8 and 1.8 Hz, 1H), 7.40 (dd, J = 1.8 and 1.8 Hz, 1H), 2.20 (s, 3H), 1.30 (s, 9H), 1.12-1.13 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2 (C), 151.7 (C), 137.3 (C), 128.7 (CH), 127.6 (CH), 124.2 (CH), 121.4 (C), 102.6 (C), 89.9 (C), 87.8 (C), 76.5 (C), 74.2 (C), 35.0 (C), 31.4 (CH_3), 18.8 (CH_3), 17.1 (CH_3), 11.5 (CH); IR (neat): ν = 2958, 2944, 2865, 2206, 2098, 1584, 1462, 1365, 1244, 1068, 1018, 996, 876, 848, 791, 695, 677 cm^{-1}; MS (EI) *m/z* 741 (M^+) (100), 683 (7), 631 (5), 592 (6), 327 (6), 157 (40), 115 (36).

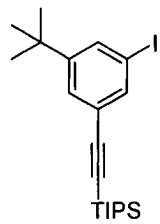
(2-(3-Bromo-5-*tert*-butylphenyl)ethynyl)triisopropylsilane (261)



$C_{21}H_{33}BrSi$
Mol. Wt.: 393.48

Aryl iodide **234** (12.0 g, 35.4 mmol), $Pd(PPh_3)_2Cl_2$ (0.50 g, 0.71 mmol) and CuI (0.27 g, 1.42 mmol) were added to a mixture of NEt_3 (20 mL) and THF (200 mL) and degassed. Triisopropylsilylacetylene (8.34 mL, 37.2 mmol) was then added. After stirring at rt overnight, the mixture was concentrated. The resultant oily solid was repeatedly washed with PE and the PE extracts were filtered through a silica gel plug (10 cm). Removal of the solvent afforded the title compound as a clear oil (14.0 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 1.7 and 1.7 Hz, 1H), 7.46 (dd, J = 1.7 and 1.7 Hz, 1H), 7.40 (dd, J = 1.7 and 1.7 Hz, 1H), 1.32 (s, 9H), 1.16 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C), 132.2 (CH), 129.2 (CH), 127.8 (CH), 125.2 (C), 122.2 (C), 106.2 (C), 91.7 (C), 35.1 (C), 31.3 (CH_3), 18.9 (CH_3), 11.5 (CH); IR (neat): ν = 2960, 2941, 2865, 2165, 1558, 1275, 996, 933, 882, 866, 840, 759 cm^{-1}; MS (EI) *m/z* 394 (6, ^{81}Br), 392 (M^+, 6, ^{79}Br), 351 (99, ^{81}Br), 349 (100, ^{79}Br), 309 (28, ^{81}Br), 307 (27, ^{79}Br), 295 (37, ^{81}Br), 293 (35, ^{79}Br), 281 (58, ^{81}Br), 279 (59, ^{79}Br), 57 (13); HRMS calculated for $C_{21}H_{33}BrSi$ (M^+) 392.1535, found 392.1510.

(2-(3-*tert*-Butyl-5-iodophenyl)ethynyl)triisopropylsilane (262)

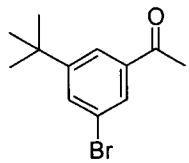


$C_{21}H_{33}ISi$
Mol. Wt.: 440.48

Aryl bromide **261** (7.50 g, 19.1 mmol) was dissolved in THF (250 mL) and cooled to –78 °C. A solution of *t*-BuLi in pentane (1.5 M, 28.0 mL, 41.9 mmol) was then added all at once and the solution was stirred for 5 min at –78 °C. A solution of I_2 (9.68 g, 38.1 mmol) in THF (50 mL) was then added dropwise. After stirring for 25 min, the reaction was quenched with water and allowed to warm to rt. Excess I_2 was reduced with 1 M $Na_2S_2O_3$ and the organics were extracted with ether. The organics were combined, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a pale yellow oil (7.75 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, J = 1.6 and 1.6 Hz, 1H), 7.65 (dd, J = 1.6 and 1.6 Hz, 1H), 7.42 (dd, J = 1.6 and 1.6 Hz, 1H), 1.30 (s, 9H), 1.14 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5 (C), 138.0 (CH), 135.1 (CH), 128.5 (CH), 125.3 (C), 106.0 (C), 94.0 (C), 91.7

(C), 34.9 (C), 31.3 (CH_3), 18.9 (CH_3), 11.5 (CH); IR (neat): ν = 2964, 2945, 2865, 2160, 1585, 1550, 1463, 1420, 1272, 995, 930, 883, 865, 832, 746 cm^{-1}; MS (EI) *m/z* 440 (M^+) (10), 397 (100), 367 (23), 327 (35), 271 (63), 201 (27), 57 (11); HRMS calculated for $C_{21}H_{33}ISi$ (M^+) 440.1396, found 440.1387.

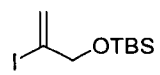
1-(3-Bromo-5-*tert*-butylphenyl)ethanone (273)



$C_{12}H_{15}BrO$
Mol. Wt.: 255.15

Aryl iodide **234** (3.00 g, 8.85 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (2.46 M, 3.60 mL, 8.85 mmol) was then added, followed immediately by *N*-methoxy-*N*-methylacetamide (1.03 mL, 9.73 mmol). The solution was stirred for 1 min, quenched with water and diluted with 1 M HCl. The organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (30:1 PE:EA) afforded the title compound as a pale yellow waxy solid (1.66 g, 74%). mp: 53.5 – 54.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.88 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.71 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.59 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1 (C), 154.3 (C), 138.9 (C), 133.4 (CH), 128.9 (CH), 124.0 (CH), 122.9 (C), 35.3 (C), 31.3 (CH_3), 26.8 (CH_3); IR (neat): ν = 2963, 2870, 1684, 1559, 1281, 1233, 874, 752, 690, 600 cm^{-1}; MS (EI) *m/z* 256 (23, ^{81}Br), 254 (M^+, 23, ^{79}Br), 241 (93, ^{81}Br), 239 (100, ^{79}Br), 213 (14, ^{81}Br), 211 (13, ^{79}Br), 132 (8), 117 (10, ^{81}Br), 115 (17, ^{79}Br); HRMS calculated for $C_{12}H_{15}{}^{79}BrO$ (M^+) 254.0306, found 254.0290.

***tert*-Butyl(2-iodoallyloxy)dimethylsilane (283)**

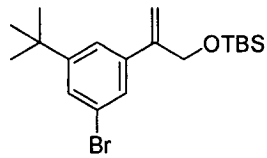


$C_9H_{19}IOSi$
Mol. Wt.: 298.24

Imidazole (1.14 g, 16.8 mmol) was dissolved in a mixture of THF (20 mL) and DMF (7 mL), cooled to 0 °C, and TBSCl (2.03 g, 13.4 mmol) and 2-iodoprop-2-en-1-ol (**282**) (2.06 g, 11.2 mmol) were successively added. After stirring at 0 °C for 30 min, the reaction was diluted with

water and 1 M HCl (~1:1) and extracted with ether. The organic extracts were combined and concentrated, re-dissolved in ether and washed with water (2X). The organics were then dried, filtered, and concentrated. Filtration through a silica gel plug (5 cm) using PE as eluent afforded the title compound as a red oil (2.47 g, 74%). The product slowly turned dark red over time (days), but NMR analysis indicated the product remained pure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, J = 3.4 and 1.8 Hz, 1H), 5.82 (dd, J = 3.4 and 1.8 Hz, 1H), 4.18 (t, J = 1.8 Hz, 2H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.2 (CH_2), 110.0 (C), 71.3 (CH_2), 26.0 (CH_3), 18.6 (C), –5.1 (CH_3); IR (neat): ν = 2952, 2929, 2884, 2856, 1559, 1541, 1507, 1472, 1256, 1083, 838, 779 cm^{-1}; MS (EI) *m/z* 241 ($M^+ - C_4H_9$), (76), 184 (77), 44 (38), 29 (100); HRMS calculated for $C_5H_{10}IOSi$ ($M^+ - C_4H_9$) 240.9546, found 240.9576.

(2-(3-Bromo-5-*tert*-butylphenyl)allyloxy)(*tert*-butyl)dimethylsilane (284)

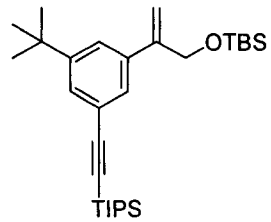


$C_{19}H_{31}BrOSi$
Mol. Wt.: 383.44

Aryl iodide **234** (0.188 g, 0.553 mmol) was dissolved in THF (5 mL) and cooled to –78 °C. A solution of *n*-BuLi in pentane (2.50 M, 0.22 mL, 0.553 mmol) was then added all at once, followed immediately by a solution of $ZnBr_2$ (0.136 g, 0.604 mmol) in THF (3 mL). The solution was stirred at –78 °C for 30 min and then warmed to 0 °C. After a further 5 min, a solution of vinyl iodide **283** (0.150 g, 0.503 mmol) and $Pd(PPh_3)_4$ (0.058 g, 0.050 mmol) in THF (5 mL) was added *via* canula. After stirring at rt overnight, the reaction was quenched by the addition of sat. NH_4Cl and extracted with ether. The organics were combined, dried, filtered, and concentrated. Column chromatography (PE) afforded the title compound as a colorless oil (0.116 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.7 and 1.7 Hz, 1H), 7.37 (dd, J = 1.7 and 1.7 Hz, 1H), 7.36 (dd, J = 1.7 and 1.7 Hz, 1H), 5.41 (dd, J = 1.8 and 1.5 Hz, 2H), 4.49 (t, J = 1.5 Hz, 2H), 1.33 (s, 9H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5 (C), 146.8 (C), 141.2 (C), 128.1 (CH), 126.6 (CH), 122.5 (C), 122.3 (CH), 112.9 (CH_2), 65.1 (CH_2), 35.1 (C), 31.4 (CH_3), 26.1 (CH_3), 18.6 (C), –5.1 (CH_3); IR (neat): ν = 2957, 2929, 2857, 1559, 1507, 1472, 1363, 1255, 1140, 1094, 906, 835, 776 cm^{-1}; MS (EI) *m/z* 369 (15, ^{81}Br), 367

($M^+ - CH_3$, 14, ^{79}Br), 329 (24, ^{81}Br), 327 (86, ^{79}Br), 328 (66, ^{81}Br), 326 (66, ^{79}Br), 75 (55), 57 (100); HRMS calculated for $C_{18}H_{28}{}^{79}BrOSi$ ($M^+ - CH_3$) 367.1093, found 367.1107.

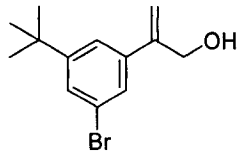
1-*tert*-Butyl-3-(1-(*tert*-butyldimethylsilyloxy)prop-2-en-2-yl)-5-(2-(triisopropylsilyl)ethynyl)benzene (285)



$C_{30}H_{52}OSi_2$
Mol. Wt.: 484.9

Aryl bromide **261** (2.08 g, 5.28 mmol) was dissolved in THF (40 mL) and cooled to –78 °C. A solution of *t*-BuLi in pentane (1.7 M, 6.51 mL, 11.1 mmol) was then added, and after stirring for 5 min, a solution of $ZnBr_2$ (2.61 g, 11.6 mmol) in THF (20 mL) was added. After stirring for a further 5 min, the reaction was warmed to 0 °C and stirred for 30 min, at which time a solution of vinyl iodide **283** (1.50 g, 5.03 mmol) and $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) in THF (30 mL) was added. After stirring at rt overnight, the reaction was quenched with sat. NH_4Cl and extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a colorless oil (2.47 g, 100%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.7 and 1.7 Hz, 1H), 7.40 (dd, J = 1.7 and 1.7 Hz, 1H), 7.34 (dd, J = 1.7 and 1.7 Hz, 1H), 5.41 (dd, J = 3.0 and 1.5 Hz, 1H), 5.39 (dd, J = 3.0 and 1.5 Hz, 1H), 4.50 (dd, J = 1.5 and 1.5 Hz, 2H), 1.34 (s, 9H), 1.16 (s, 21H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3 (C), 147.4 (C), 139.4 (C), 128.4 (CH), 127.4 (CH), 124.0 (CH), 123.3 (C), 112.5 (CH_2), 107.9 (C), 89.8 (C), 65.3 (CH_2), 34.9 (C), 31.5 (CH_3), 26.1 (CH_3), 18.8 (CH_3), 18.6 (C), 11.6 (CH), –5.1 (CH_3); IR (neat): ν = 2956, 2895, 2869, 2150, 1694, 1591, 1462, 1363, 1253, 1200, 1109, 995, 881, 835, 778 cm^{-1}; MS (EI) *m/z* 484 (M^+), (0.4), 441 (31), 427 (100), 164 (19), 129 (10), 57 (32); HRMS calculated for $C_{26}H_{43}OSi_2$ ($M^+ - C_4H_9$) 428.2848, found 428.2834.

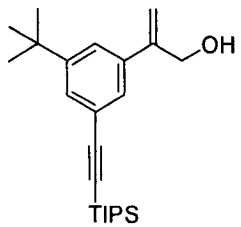
2-(3-Bromo-5-*tert*-butylphenyl)prop-2-en-1-ol (286)



$C_{13}H_{17}BrO$
Mol. Wt.: 269.18

Allylic silyl ether **284** (0.082 g, 0.214 mmol) was dissolved in THF (5 mL), cooled to 0 °C, and a solution of TBAF in THF (1.0 M, 0.24 mL, 0.235 mmol) was added. After stirring at 0 °C for 20 min, H_2O and sat. $NaHCO_3$ (~5:1) were added and the organics were extracted with ether. The combined organics were dried, filtered, and concentrated. Column chromatography (10:1 PE:EA) afforded the title compound as a colorless oil (0.046 g, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 1.7 and 1.7 Hz, 1H), 7.40 (dd, J = 1.7 and 1.7 Hz, 1H), 7.38 (dd, J = 1.7 and 1.7 Hz, 1H), 5.46 (dd, J = 0.8 and 0.8 Hz, 1H), 5.38 (dd, J = 2.5 and 1.3 Hz, 1H), 4.51 (dd, J = 1.3 and 0.8 Hz, 2H), 1.75 (br s, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 146.9 (C), 140.6 (C), 128.4 (CH), 126.6 (CH), 122.8 (C), 122.2 (CH), 113.9 (CH_2), 65.2 (CH_2), 35.1 (C), 31.4 (CH_3); IR (neat): ν = 3326, 2964, 2903, 2873, 1594, 1559, 1474, 1364, 1253, 1049, 906, 865 cm^{-1}; MS (EI) *m/z* 270 (42, ^{81}Br), 268 (M^+, 44, ^{79}Br), 255 (100, ^{81}Br), 253 (99, ^{79}Br), 156 (18), 115 (12), 57 (23); HRMS calculated for $C_{13}H_{17}O^{79}Br$ (M^+) 268.0463, found 268.0478.

2-(3-*tert*-Butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)prop-2-en-1-ol (287)

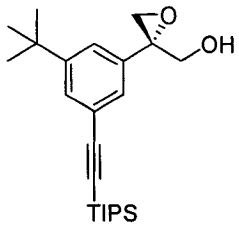


$C_{24}H_{38}OSi$
Mol. Wt.: 370.64

Allylic silyl ether **285** (0.120 g, 0.248 mmol) was dissolved in THF (5 mL) and HCl (10% aq., 1.8 mL) was added. After stirring for 4 h at rt, the reaction was carefully quenched with sat. $NaHCO_3$ and extracted with ether. The organics were dried, filtered, and concentrated. Column chromatography (35:65 CH_2Cl_2:PE) provided the title compound as a colorless oil (0.072 g, 79%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.7 and 1.7 Hz, 1H), 7.42 (dd, J = 1.7 and 1.7

Hz, 1H), 7.36 (dd, J = 1.7 and 1.7 Hz, 1H), 5.46 (d, J = 1.0 Hz, 1H), 5.38 (d, J = 1.0 Hz, 1H), 4.54 (s, 2H), 1.80 (br s, 1H), 1.35 (s, 9H), 1.16 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (C), 147.6 (C), 138.8 (C), 128.7 (CH), 127.3 (CH), 123.8 (CH), 123.6 (C), 113.2 (CH_2), 107.7 (C), 90.1 (C), 65.3 (CH_2), 34.9 (C), 31.4 (CH_3), 18.9 (CH_3), 11.6 (CH); IR (neat): ν = 3412, 2964, 2941, 2869, 2150, 1588, 1462, 1078, 1059, 877, 793 cm^{-1}; MS (EI) *m/z* 370 (M^+), (7), 327 (100), 255 (7), 183 (7), 128 (11), 57 (36); HRMS calculated for $C_{24}H_{38}O^{79}Br$ (M^+) 370.2692, found 370.2701.

(*S*)-(2-(3-*tert*-Butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)oxiran-2-yl)methanol (289)

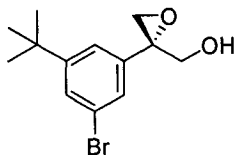


$C_{24}H_{38}O_2Si$
Mol. Wt.: 386.64

A solution of allylic alcohol **287** (0.600 g, 1.619 mmol) in CH_2Cl_2 (15 mL) was added to a flask containing activated 4 Å molecular sieves (1.10 g). L-Diisopropyl tartrate (0.136 mL, 0.648 mmol) was then added. The mixture was stirred at rt for 30 min, then cooled to –50 °C and Ti(O*i*-Pr)$_4$ (0.143 mL, 0.486 mmol) was added. After stirring at –50 °C for 15 min, *t*-BuOOH (0.589 mL, 3.24 mmol) was added dropwise. After stirring for 3 h at –50 °C, the reaction was placed in a –20 °C freezer overnight (no stirring). The next day, sat. Na_2SO_4 (0.87 mL) was added and the mixture was vigorously stirred for 35 min, and then $MgSO_4$ was added to dry the mixture. After filtration through a celite pad and removal of the solvent, column chromatography (10:1 PE:EA) provided the title compound as a white solid (0.442 g, 78%, 89% ee). Enantiomeric excess determined using a ChiralCel OD-H column, eluent: 99.0:1.0 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 12.00 min, T_r(minor): 12.75 min. mp: 61.0 – 62.5 °C; $[\alpha]^{20}_D$ = –10.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 1.7 and 1.7 Hz, 1H), 7.33 (dd, J = 1.7 and 1.7 Hz, 1H), 7.29 (dd, J = 1.7 and 1.7 Hz, 1H), 4.05 (dd, J_{AB} = 12.6 Hz, J_{AX} = 4.1 Hz, 1H), 3.97 (dd, J_{AB} = 12.6 Hz, J_{BX} = 9.2 Hz, 1H), 3.24 (d, J = 5.4 Hz, 1H), 2.79 (d, J = 5.4 Hz, 1H), 1.94 (dd, J_{AX} = 4.1 Hz, J_{BX} = 9.2 Hz, 1H), 1.29 (s, 9H), 1.12 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (C), 137.2 (C), 128.8 (CH), 126.9 (CH), 123.4 (C), 123.1 (CH), 107.1 (C),

90.3 (C), 63.1 (CH_2), 60.5 (C), 52.2 (CH_2), 34.7 (C), 31.2 (CH_3), 18.7 (CH_3), 11.3 (CH); IR (neat): ν = 3420, 2944, 2865, 2154, 1591, 1462, 1363, 1200, 1055, 942, 881 cm^{-1}; MS (EI) *m/z* 386 (M^+), (5), 343 (100), 325 (28), 313 (82), 257 (23), 243 (38), 162 (20), 57 (52); HRMS calculated for $C_{24}H_{38}O_2Si$ (M^+) 386.2641, found 386.2626.

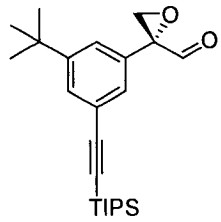
(*S*)-(2-(3-Bromo-5-*tert*-butylphenyl)oxiran-2-yl)methanol (288)



$C_{13}H_{17}BrO_2$
Mol. Wt.: 285.18

The title compound was prepared analogously to epoxide **289** using the following quantities: Allylic alcohol **286** (0.403 g, 1.50 mmol); CH_2Cl_2 (12 mL); activated 4 Å molecular sieves (0.90 g); L-DIPT (0.126 mL, 0.60 mmol); Ti(O*i*-Pr)$_4$ (0.133 mL, 0.45 mmol); *t*-BuOOH (0.544 mL, 2.99 mmol); sat. Na_2SO_4 (0.80 mL). Column chromatography (7:1 PE:EA) provided the title compound as a colorless oil (0.398 g, 93%, 86% ee). Enantiomeric excess determined using a ChiralCel OD-H column, eluent: 99.0:1.0 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 18.32 min, T_r(minor): 20.45 min. $[\alpha]^{20}_D$ = –10.3 (*c* 0.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.36 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.32 (dd, *J* = 1.7 and 1.7 Hz, 1H), 4.08 (dd, J_{AB} = 12.6 Hz, J_{AX} = 3.4 Hz, 1H), 3.98 (dd, J_{AB} = 12.6 Hz, J_{BX} = 8.6 Hz, 1H), 3.26 (d, *J* = 5.3 Hz, 1H), 2.80 (d, *J* = 5.3 Hz, 1H), 1.99 (br s, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2 (C), 139.5 (C), 128.8 (CH), 126.5 (CH), 122.8 (C), 121.8 (CH), 63.3 (CH_2), 60.4 (C), 52.7 (CH_2), 35.2 (C), 31.4 (CH_3); IR (neat): ν = 3421, 2965, 2911, 2869, 1595, 1567, 1363, 1196, 1053, 862, 751, 702 cm^{-1}; MS (EI) *m/z* 286 (6, ^{81}Br), 284 (M^+, 6, ^{79}Br), 256 (36, ^{81}Br), 254 (37, ^{79}Br), 241 (69, ^{81}Br), 239 (68, ^{79}Br), 227 (12, ^{81}Br), 225 (17, ^{79}Br), 160 (10), 57 (59), 43 (100); HRMS calculated for $C_{13}H_{17}{}^{79}BrO_2$ (M^+) 284.0412, found 284.0395.

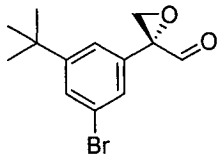
(*R*)-2-(3-*tert*-Butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)oxirane-2-carbaldehyde (295)



$C_{24}H_{36}O_2Si$
Mol. Wt.: 384.63

Epoxy alcohol **289** (0.39 g, 0.996 mmol) was dissolved in CH_2Cl_2 (10 mL) and Dess-Martin reagent (0.55 g, 1.29 mmol) was added. After stirring at rt for 30 min, a mixture of 1 M $Na_2S_2O_3$ (5 mL) and sat. $NaHCO_3$ (5 mL) was added and the mixture was stirred until both layers were clear. The reaction was diluted with ether, washed with $NaHCO_3$ and brine, and the organics were dried, filtered, and concentrated. Column chromatography (15:1 PE:EA) afforded the title compound as a white solid (0.34 g, 89%). mp: 51.0 – 52.5 °C; $[\alpha]^{20}_D$ = +40.1 (*c* 0.84, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.46 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.43 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.37 (dd, *J* = 1.7 and 1.7 Hz, 1H), 3.36 (d, *J* = 5.5 Hz, 1H), 3.15 (d, *J* = 5.5 Hz, 1H), 1.30 (s, 9H), 1.12 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4 (CH), 151.6 (C), 131.6 (C), 129.4 (CH), 128.0 (CH), 124.4 (CH), 123.4 (C), 106.9 (C), 90.5 (C), 61.3 (C), 52.8 (CH_2), 34.8 (C), 31.1 (CH_3), 18.7 (CH_3), 11.3 (CH); IR (neat): ν = 2960, 2945, 2866, 2146, 1732, 1592, 1463, 1382, 1246, 996, 951, 883, 703, 682 cm^{-1}; MS (EI) *m/z* 384 (M^+), (2), 341 (100), 271 (33), 57 (30); HRMS calculated for $C_{24}H_{36}O_2Si$ (M^+) 384.2485, found 384.2484.

(*R*)-2-(3-Bromo-5-*tert*-butylphenyl)oxirane-2-carbaldehyde (294)

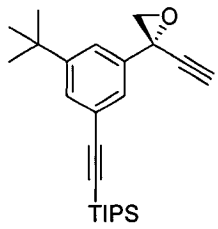


$C_{13}H_{15}BrO_2$
Mol. Wt.: 283.16

The title compound was prepared analogously to aldehyde **295** using the following quantities: Epoxy alcohol **288** (0.310 g, 1.09 mmol); CH_2Cl_2 (15 mL); Dess-Martin reagent (0.555 g, 1.30 mmol). Column chromatography (PE:EA 10:1) afforded the title compound as a colorless oil (0.256 g, 83%). $[\alpha]^{20}_D$ = +55.6 (*c* 0.91, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.53 (dd, *J* = 1.8 and 1.8 Hz, 1H), 7.45 (dd, *J* = 1.8 and 1.8 Hz, 1H), 7.44 (dd, *J* = 1.8 and 1.8 Hz,

1H), 3.39 (d, J = 5.4 Hz, 1H), 3.16 (d, J = 5.4 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2 (CH), 154.0 (C), 133.7 (C), 129.4 (CH), 127.5 (CH), 123.2 (CH), 122.6 (C), 61.0 (C), 53.2 (CH_2), 35.2 (C), 31.3 (CH_3); IR (neat): ν = 3070, 2965, 2903, 2869, 2819, 1735, 1603, 1569, 1367, 1249, 1113, 1006, 930, 871, 754, 701 cm^{-1}; MS (EI) *m/z* 284 (94, ^{81}Br), 282 (M^+, 100, ^{79}Br), 267 (45), 253 (95), 241 (21, ^{81}Br), 239 (24, ^{79}Br), 227 (68, ^{81}Br), 225 (69, ^{79}Br), 158 (11), 115 (21), 57 (36); HRMS calculated for $C_{13}H_{15}{}^{79}BrO_2$ (M^+) 282.0256, found 282.0238.

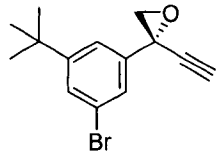
(*S*)-(2-(3-*tert*-Butyl-5-(2-ethynyloxiran-2-yl)phenyl)ethynyl)triisopropylsilane (298)



$C_{25}H_{36}OSi$
Mol. Wt.: 380.64

A solution of epoxy aldehyde **295** (0.288 g, 0.749 mmol) in MeOH (10 mL) was added to a flask containing K_2CO_3 (0.155 g, 1.12 mmol) and cooled to 0 °C. A solution of Ohira's reagent (**296**) (0.232 g, 1.12 mmol) in MeOH (2 mL) was then added dropwise and the reaction was stirred at 0 °C for 5 min, and then at rt for 90 min. After quenching the reaction with sat. NH_4Cl, the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (40:1 PE:EA) provided the title compound as a colorless oil (0.264 g, 93%). $[\alpha]^{20}_D$ = +33.0 (*c* 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 1.7 and 1.7 Hz, 1H), 7.42 (dd, J = 1.7 and 1.7 Hz, 1H), 7.38 (dd, J = 1.7 and 1.7 Hz, 1H), 3.40 (d, J = 6.2 Hz, 1H), 2.97 (d, J = 6.2 Hz, 1H), 2.52 (s, 1H), 1.31 (s, 9H), 1.13 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6 (C), 136.4 (C), 129.1 (CH), 126.2 (CH), 123.5 (C), 122.8 (CH), 107.1 (C), 90.3 (C), 81.2 (C), 72.7 (C), 58.7 (CH_2), 50.6 (C), 34.8 (C), 31.2 (CH_3), 18.7 (CH_3), 11.3 (CH); IR (neat): ν = 3310, 2960, 2941, 2865, 1591, 1462, 1363, 1238, 949, 881, 679 cm^{-1}; MS (EI) *m/z* 380 (M^+), (3), 337 (100), 267 (39), 126 (22), 57 (48); HRMS calculated for $C_{25}H_{36}OSi$ (M^+) 380.2535, found 380.2517.

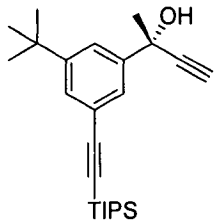
(*S*)-2-(3-Bromo-5-*tert*-butylphenyl)-2-ethynyloxirane (297)



$C_{14}H_{15}BrO$
Mol. Wt.: 279.17

The title compound was prepared analogously to epoxy acetylene **298** using the following quantities: Epoxy aldehyde **294** (0.150 g, 0.530 mmol); MeOH (7 mL); K_2CO_3 (0.110 g, 0.795 mmol); Ohira's reagent (**296**) (0.164 g, 0.795 mmol). Filtration through a silica gel plug (5 cm) using 30:1 PE:EA provided the title compound as a colorless oil (0.127 g, 86%, 83% ee). Enantiomeric excess determined using a ChiralCel OJ-H column, eluent: 99.8:0.2 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 8.33 min, T_r(minor): 7.70 min. $[\alpha]^{20}_D$ = +39.8 (*c* 0.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.43 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.42 (dd, *J* = 1.6 and 1.6 Hz, 1H), 3.40 (d, *J* = 6.1 Hz, 1H), 2.94 (d, *J* = 6.1 Hz, 1H), 2.52 (s, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (C), 138.4 (C), 128.9 (CH), 125.8 (CH), 122.5 (C), 121.2 (CH), 80.9 (CH), 73.0 (C), 58.8 (CH_2), 50.3 (C), 35.0 (C), 31.2 (CH_3); IR (neat): ν = 3295, 3063, 2966, 2907, 2873, 2124, 1603, 1569, 1474, 1420, 1280, 1242, 926, 865, 736, 699 cm^{-1}; MS (EI) *m/z* 280 (26, ^{81}Br), 278 (M^+, 28, ^{79}Br), 265 (41), 250 (100, ^{81}Br), 248 (84, ^{79}Br), 235 (27), 171 (15, ^{81}Br), 169 (20, ^{79}Br), 155 (23, ^{81}Br), 153 (27, ^{79}Br), 115 (19), 57 (42); HRMS calculated for $C_{14}H_{15}O^{79}Br$ (M^+) 278.0306, found 278.0299.

(*S*)-2-(3-*tert*-Butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)but-3-yn-2-ol (299)

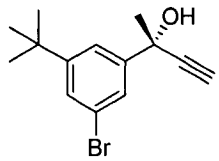


$C_{25}H_{38}OSi$
Mol. Wt.: 382.65

Propargyl alcohol **298** (0.528 g, 1.39 mmol) was dissolved in THF (25 mL) and cooled to 0 °C. A solution of L-Selectride® in THF (1.0 M, 2.91 mL, 2.91 mmol) was then added and the reaction was stirred at 0 °C for 10 min. After quenching the reaction with water, the organics were extracted with ether, dried, and filtered. Silica gel was then added and the solvent removed

in vacuo. Column chromatography (dry pack, 30:1 PE:EA) provided the title compound as a colorless oil (0.465 g, 88%, 87% ee). Enantiomeric excess determined using a ChiralCel OD-H column, eluent: 99.0:1.0 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 8.61 min, T_r(minor): 7.62 min. $[\alpha]^{20}_D$ = +4.2 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.57 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.41 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.68 (s, 1H), 2.48 (br s, 1H), 1.77 (s, 3H), 1.32 (s, 9H), 1.13 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C), 144.8 (C), 128.4 (CH), 125.8 (CH), 123.1 (C), 122.2 (CH), 107.5 (C), 89.8 (C), 87.0 (C), 73.3 (C), 69.8 (C), 34.8 (C), 33.1 (CH), 31.2 (CH_3), 18.7 (CH_3), 11.3 (CH); IR (neat): ν = 3408, 3313, 2960, 2941, 2866, 2154, 1591, 1458, 1436, 1363, 1227, 1097, 995, 923, 882, 820, 683 cm^{-1}; MS (EI) *m/z* 382 (M^+) (7), 339 (100), 311 (15), 269 (18), 134 (18), 57 (14); HRMS calculated for $C_{25}H_{38}OSi$ (M^+) 382.2692, found 382.2679.

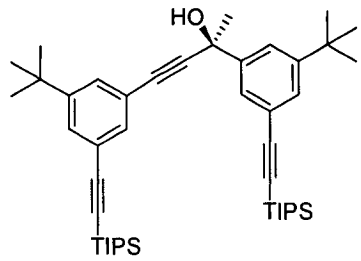
(*S*)-2-(3-Bromo-5-*tert*-butylphenyl)but-3-yn-2-ol (300)



$C_{14}H_{17}BrO$
Mol. Wt.: 281.19

The title compound was prepared analogously to propargyl alcohol **299** using the following quantities: Epoxy acetylene **297** (9.70 g, 34.7 mmol); THF (350 mL); L-Selectride® in THF (1.0 M, 45.0 mL, 45.0 mmol). Filtration through a silica gel plug (10 cm) using 5:1 PE:EA as eluent followed by column chromatography (20:1 PE:EA) provided the title compound as a colorless oil (7.78 g, 80%). $[\alpha]^{20}_D$ = +4.8 (*c* 1.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.8 Hz, 2H), 7.43 (dd, *J* = 1.8 and 1.8 Hz, 1H), 2.67 (s, 1H), 2.56 (br s, 1H), 1.74 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C), 146.8 (C), 128.1 (CH), 125.3 (CH), 122.2 (C), 120.6 (CH), 86.7 (CH), 73.5 (C), 69.5 (C), 35.0 (C), 33.2 (CH_3), 31.2 (CH_3); IR (neat): ν = 3370, 3297, 2907, 2869, 2116, 1598, 1569, 1364, 1271, 1215, 1158, 1097, 1056, 869, 750, 703 cm^{-1}; MS (EI) *m/z* 282 (45, ^{81}Br), 280 (M^+, 45, ^{79}Br), 267 (100, ^{81}Br), 265 (100, ^{79}Br), 115 (36), 69 (64), 57 (92); HRMS calculated for $C_{14}H_{17}O^{79}Br$ (M^+) 280.0463, found 280.0460.

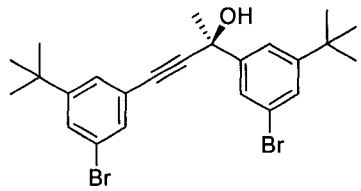
(*S*)-2,4-Bis(3-*tert*-butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)but-3-yn-2-ol (272)



$C_{46}H_{70}OSi_2$
Mol. Wt.: 695.22

Proparyl alcohol **299** (2.00 g, 5.23 mmol), aryl iodide **262** (2.30 g, 5.23 mmol) and CuI (0.100 g, 0.523 mmol) were dissolved in a mixture of NEt_3 (30 mL) and THF (80 mL). The solution was then *vigorously* degassed with argon for 75 min. A *vigorously* degassed solution of $Pd(PPh_3)_4$ (0.302 g, 0.261 mmol) in THF (10 mL) was then added *via* canula. (**CAUTION**: This reaction is substantially more O_2-sensitive than other Sonogashira couplings. Failure to adequately degas either solution results in significantly reduced yields). After stirring at rt overnight, the reaction was diluted with sat. NH_4Cl. The organics were extracted with ether, combined, dried, filtered, and concentrated. Column chromatography (30:1 PE:EA) yielded the title compound as a solid white foam (2.71 g, 75%). mp: 68.5 – 71.0 °C; $[\alpha]^{20}_D$ = +1.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 1.9 and 1.9 Hz, 1H), 7.66 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.45-7.47 (m, 3H), 7.44 (dd, *J* = 1.6 and 1.6 Hz, 1H), 2.48 (br s, 1H), 1.88 (s, 3H), 1.37 (s, 9H), 1.33 (s, 9H), 1.16_3 (s, 21H), 1.15_8 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (C), 151.6 (C), 145.7 (C), 132.7 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 126.2 (CH), 123.7 (C), 123.4 (C), 122.7 (CH), 122.5 (C), 107.9 (C), 106.9 (C), 92.4 (C), 90.9 (C), 90.1 (C), 85.1 (C), 70.6 (C), 35.1 (C), 34.9 (C), 33.4 (CH_3), 31.5 (CH_3), 31.3 (CH_3), 18.93 (CH_3), 18.91 (CH_3), 11.60 (CH), 11.57 (CH); IR (neat): ν = 3048, 2960, 2944, 2865, 2154, 1586, 1463, 1365, 1228, 996, 921, 881, 681 cm^{-1}; MS (EI) *m/z* 694 (M^+) (1), 651 (6), 591 (3), 519 (7), 477 (12), 379 (10), 313 (100), 243 (63), 181 (21), 157 (36), 57 (46), 43 (33).

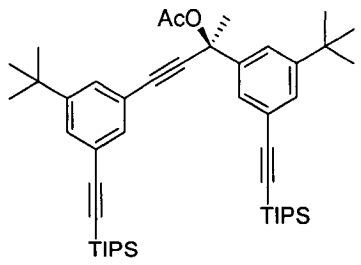
(*S*)-2,4-Bis(3-bromo-5-*tert*-butylphenyl)but-3-yn-2-ol (251)



$C_{24}H_{28}Br_2O$
Mol. Wt.: 492.29

The title compound was prepared analogously to propargyl alcohol **272** using the following quantities: Propargyl alcohol **300** (0.314 g, 1.12 mmol); aryl iodide **234** (0.379 g, 1.12 mmol); CuI (0.021 g, 0.112 mmol); NEt_3 (5 mL); THF (25 mL); $Pd(PPh_3)_4$ (0.065 g, 0.0559 mmol). Column chromatography (20:1 PE:EA) yielded the title compound as a colorless oil (0.414 g, 75%). $[\alpha]^{20}_D$ = –0.3 (*c* 0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.67 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.51 (dd, *J* = 1.9 and 1.8 Hz, 1H), 7.48 (dd, *J* = 1.8 and 1.8 Hz, 1H), 7.45 (dd, *J* = 1.9 and 1.8 Hz, 1H), 7.43 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.50 (br s, 1H), 1.86 (s, 3H), 1.35 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 153.8 (C), 147.5 (C), 131.7 (CH), 129.5 (CH), 128.3 (CH), 127.8 (CH), 125.7 (CH), 124.0 (C), 122.6 (C), 122.3 (C), 121.0 (CH), 92.8 (C), 84.5 (C), 70.3 (C), 35.3 (C), 35.1 (C), 33.5 (CH_3), 31.4 (CH_3), 31.3 (CH_3); IR (neat): ν = 3359, 2964, 2902, 2869, 1596, 1559, 1475, 1432, 1364, 1201, 1149, 866 cm^{-1}; MS (EI) *m/z* 494 (6, $^{81}Br_2$), 492 (10, $^{81}Br^{79}Br$), 490 (M^+, 5, $^{79}Br_2$), 477/475 (54/31), 435/433 (23/11), 241/239 (12/13), 57 (100); HRMS calculated for $C_{24}H_{28}{}^{79}Br_2O$ (M^+) 490.0507, found 490.0534.

(*S*)-2,4-Bis(3-*tert*-butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)but-3-yn-2-yl acetate (309)

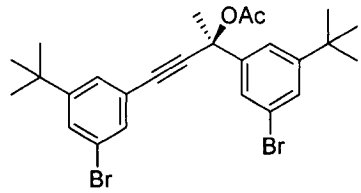


$C_{48}H_{72}O_2Si_2$
Mol. Wt.: 737.26

Propargyl alcohol **272** (2.60 g, 3.74 mmol) was dissolved in CH_2Cl_2 (80 mL) and DMAP (catalytic), pyridine (1.51 mL, 18.7 mmol) and Ac_2O (1.77 mL, 18.7 mmol) were sequentially added. After stirring at rt overnight (longer reaction times were often required) the reaction was

diluted with ether and successively washed with 1 M HCl (2X), sat. $NaHCO_3$, and brine. The organics were then dried, filtered, and concentrated. Column chromatography (50:1 PE:EA) provided the title compound as a solid white foam (2.70 g, 98%). mp: 59.0 – 62.0 °C; $[\alpha]^{20}_D$ = +13.6 (*c* 1.30, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.53 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.49 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.47 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.46 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.44 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.13 (s, 3H), 1.99 (s, 3H), 1.36 (s, 9H), 1.33 (s, 9H), 1.160 (s, 21H), 1.159 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C), 151.6 (C), 151.5 (C), 142.8 (C), 132.8 (CH), 129.5 (CH), 129.3 (CH), 128.8 (CH), 126.0 (CH), 123.7 (C), 123.5 (C), 122.8 (CH), 122.5 (C), 107.9 (C), 106.9 (C), 90.7 (C), 90.1 (C), 88.5 (C), 87.3 (C), 76.2 (C), 35.0 (C), 34.8 (C), 32.1 (CH_3), 31.4 (CH_3), 31.3 (CH_3), 22.0 (CH_3), 18.9 (CH_3), 11.60 (CH), 11.57 (CH) (Carbon signal for both TIPS CH_3 groups overlap at 18.9 ppm); IR (neat): ν = 2960, 2944, 2865, 2154, 1758, 1585, 1463, 1366, 1226, 1064, 996, 881, 680 cm^{-1}; MS (EI) *m/z* 736 (M^+) (2), 676 (5), 633 (21), 591 (12), 549 (12), 232 (22), 157 (100), 115 (46), 57 (22), 43 (17).

(*S*)-2,4-Bis(3-bromo-5-*tert*-butylphenyl)but-3-yn-2-yl acetate (312)

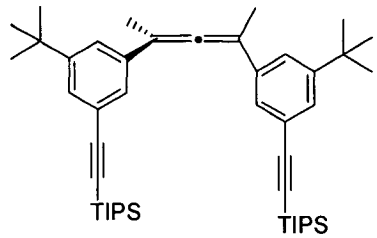


$C_{26}H_{30}Br_2O_2$
Mol. Wt.: 534.32

The title compound was prepared analogously to acetate **309** using the following quantities: Propargyl alcohol **251** (2.64 g, 5.36 mmol); CH_2Cl_2 (70 mL); DMAP (catalytic); pyridine (2.17 mL, 26.8 mmol); Ac_2O (2.53 mL, 26.8 mmol). Column chromatography (30:1 PE:EA) provided the title compound as a colorless oily foam (2.47 g, 84%, 84% ee). Enantiomeric excess determined using a ChiralCel OD-H column, eluent: 99.8:0.2 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 6.27 min, T_r(minor): 5.47 min. $[\alpha]^{20}_D$ = +14.2 (*c* 0.72, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.55 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.51 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.49 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.47 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.45 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.13 (s, 3H), 1.96 (s, 1H), 1.34 (9H), 1.32 (9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C), 153.72 (C), 153.67 (C), 144.6 (C), 131.9 (CH), 129.5 (CH), 128.5 (CH),

127.9 (CH), 125.4 (CH), 123.9 (C), 122.6 (C), 122.2 (C), 121.1 (CH), 88.9 (C), 86.7 (C), 75.7 (C), 35.2 (C), 35.1 (C), 32.1 (CH_3), 31.4 (CH_3), 31.3 (CH_3), 21.9 (CH_3); IR (neat): ν = 2965, 2907, 2870, 1754, 1598, 1559, 1432, 1365, 1230, 1207, 1157, 1064, 1012, 866, 757 cm^{-1}; MS (EI) *m/z* 536 (9, $^{81}Br_2$), 534 (15, $^{81}Br^{79}Br$), 532 (M^+, 8, $^{79}Br_2$), 494 (17, $^{81}Br_2$), 492 (30, $^{81}Br^{79}Br$), 490 (17, $^{79}Br_2$), 476 (49, $^{81}Br_2$), 474 (81, $^{81}Br^{79}Br$), 472 (40, $^{79}Br_2$), 461 (23, $^{81}Br_2$), 459 (37, $^{81}Br^{79}Br$), 457 (20, $^{79}Br_2$), 436 (18), 222 (21), 57 (100); HRMS calculated for $C_{26}H_{30}{}^{79}Br_2O_2$ (M^+) 532.0613, found 532.0608.

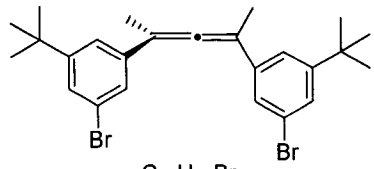
(*R*)-2,4-Bis(3-*tert*-butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)penta-2,3-diene (307)



$C_{47}H_{72}Si_2$
Mol. Wt.: 693.25

Lithium bromide (0.460 g, 5.29 mmol), CuI (1.01 g, 5.29 mmol) and THF (45 mL) were combined, cooled to 0 °C, and a solution of MeMgBr in ether (2.0 M, 2.64 mL, 5.29 mmol) was added. After stirring for 15 min, a solution of acetate **309** (0.650 g, 0.882 mmol) in THF (15 mL) was added dropwise. The yellow mixture was stirred at 0 °C for 2 h and then quenched *via* the slow addition of H_2O and diluted with sat. NH_4Cl. The organics were extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as an oily white foam (0.501 g, 82%). $[\alpha]^{20}{}_D$ = +198.9 (*c* 0.60, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.67 (dd, *J* = 1.4 and 1.4 Hz, 1H), 7.62-7.63 (m, 2H), 1.93 (s, 3H), 1.17-1.21 (m, 21H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.3 (C), 151.6 (C), 137.9 (C), 128.3 (CH), 127.1 (CH), 124.0 (C), 123.9 (CH), 108.9 (C), 103.0 (C), 90.0 (C), 34.6 (C), 31.1 (CH_3), 18.9 (CH_3), 16.8 (CH_3), 11.7 (CH); IR (neat): ν = 2960, 2892, 2865, 2158, 1584, 1462, 1363, 1236, 995, 945, 876 cm^{-1}; MS (EI) *m/z* 692 (M^+) (100), 635 (8), 565 (8), 421 (6), 157 (54), 115 (55), 57 (45).

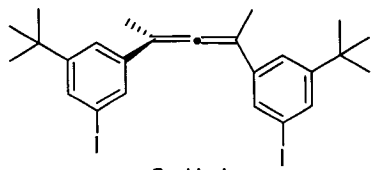
(*R*)-2,4-Bis(3-bromo-5-*tert*-butylphenyl)penta-2,3-diene (255)



$C_{25}H_{30}Br_2$
Mol. Wt.: 490.31

The title compound was prepared analogously to allene **307** using the following quantities: LiBr (2.35 g, 27.1 mmol); CuI (5.15 g, 27.1 mmol); THF (165 mL); MeMgBr in ether (2.0 M, 13.5 mL, 27.1 mmol); acetate **312** (2.41 g, 4.51 mmol). Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a colorless oil (96%). $[\alpha]^{20}_D$ = +270.2 (*c* 0.51, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.8 and 1.8 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 2H), 2.20 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1 (C), 153.7 (C), 139.1 (C), 127.4 (CH), 126.3 (CH), 122.9 (C), 121.7 (CH), 102.5 (C), 35.1 (C), 31.4 (CH_3), 17.2 (CH_3); IR (neat): ν = 2964, 2903, 2869, 1593, 1561, 1476, 1365, 1275, 1229, 862, 814, 756 cm^{-1}; MS (EI) *m/z* 492 (2, $^{81}Br_2$), 490 (4, $^{81}Br^{79}Br$), 488 (M^+, 2, $^{79}Br_2$), 477 (1, $^{81}Br_2$), 475 (2, $^{81}Br^{79}Br$), 473 (1, $^{79}Br_2$), 241/239 (6/6), 78 (21), 57 (41), 43 (100); HRMS calculated for $C_{25}H_{30}{}^{79}Br_2$ (M^+) 488.0714, found 488.0704.

(*S*)-2,4-Bis(3-*tert*-butyl-5-iodophenyl)penta-2,3-diene (266)

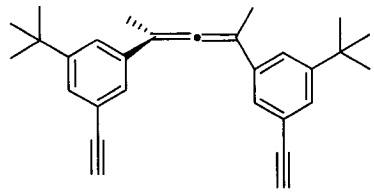


$C_{25}H_{30}I_2$
Mol. Wt.: 584.31

Allene **255** (0.095 g, 0.194 mmol) was dissolved in THF (5 mL), cooled to –78 °C, and a solution of *t*-BuLi in pentane (1.6 M, 0.54 mL, 0.872 mmol) was added. After stirring for 5 min, a solution of I_2 (0.20 g, 0.775 mmol) in THF (2 mL) was added dropwise. During the addition, the initial bright red solution changed to orange, then pale yellow, and then to brown (color of I_2 in solution). After stirring for 2 min, the reaction was quenched by the addition of 2 M $Na_2S_2O_3$, extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (5 cm) using PE as eluent provided the title compound as a colorless oil (0.092 g, 81%). $[\alpha]^{20}_D$ = +239.4 (*c* 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.56 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.40 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.18 (s, 3H), 1.30 (s, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 206.0 (C), 153.7 (C), 139.3 (C), 133.4 (CH), 132.3 (CH), 122.5 (CH), 102.3 (C), 95.2 (C), 35.0 (C), 31.4 (CH_3), 17.2 (CH_3); IR (neat): ν = 2962, 2902, 2869, 1588, 1555, 1471, 1423, 1364, 1271, 1229, 1117, 1024, 861, 740 cm^{-1}; MS (EI) *m/z* 584 (M^+) (51), 527 (10), 458 (10), 401 (10), 277 (9), 57 (100); HRMS calculated for $C_{25}H_{30}I_2$ (M^+) 584.0437, found 584.0410.

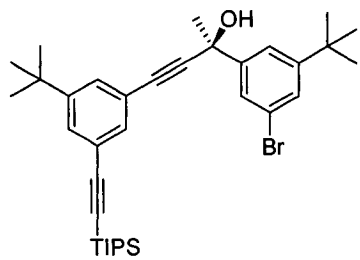
(*S*)-2,4-Bis(3-*tert*-butyl-5-ethynylphenyl)penta-2,3-diene (259)



$C_{29}H_{32}$
Mol. Wt.: 380.56

Allene **307** (0.070 g, 0.101 mmol) was dissolved in THF (5 mL), cooled to 0 °C and a solution of TBAF in THF (1.0 M, 0.25 mL, 0.25 mmol) was added. After stirring for 10 min at 0 °C the reaction was diluted with water and sat. $NaHCO_3$ (~5:1) and extracted with ether. The organics were combined, dried and concentrated. Column chromatography (100:1 PE:EA) provided the title compound as a colorless oil (0.0378 g, 98%, 83% ee). Enantiomeric excess determined using a ChiralCel OD-H column, eluent: 98.0:2.0 hexane:*i*-PrOH, 0.8 mL/min, T_r(major): 5.08 min, T_r(minor): 6.51 min. $[\alpha]^{20}_D$ = +278.1 (*c* 0.31, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.63 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.58 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.54 (dd, *J* = 1.6 and 1.6 Hz, 1H), 2.72 (s, 1H), 1.94 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.2 (C), 151.7 (C), 137.7 (C), 128.6 (CH), 127.2 (CH), 123.9 (CH), 122.9 (C), 102.9 (C), 84.5 (CH), 77.3 (C), 34.6 (C), 31.1 (CH_3), 16.8 (CH_3); IR (neat): ν = 3292, 2964, 2902, 2873, 1586, 1363, 1235, 1033, 878 cm^{-1}; MS (EI) *m/z* 380 (M^+) (55), 365 (32), 323 (36), 267 (14), 181 (17), 131 (25), 57 (100); HRMS calculated for $C_{29}H_{32}$ (M^+) 380.2504, found 380.2512.

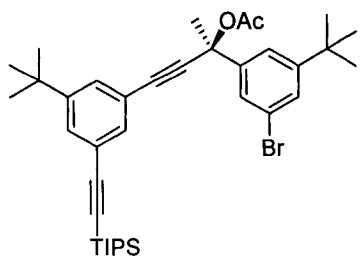
(*S*)-2-(3-Bromo-5-*tert*-butylphenyl)-4-(3-*tert*-butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)but-3-yn-2-ol (301)



$C_{35}H_{49}BrOSi$
Mol. Wt.: 593.75

The title compound was prepared analogously to propargyl alcohol **251** using the following quantities: Acetylene **300** (1.50 g, 5.33 mmol); aryl iodide **262** (2.35 g, 5.33 mmol); CuI (0.102 g, 0.533 mmol); NEt_3 (30 mL); THF (100 mL); $Pd(PPh_3)_4$ (0.308 g, 0.267 mmol). Column chromatography (30:1 PE:EA) yielded the title compound as a solid white foam (1.75 g, 55%). mp: 48.5 – 50.0 °C; $[\alpha]^{20}_D$ = –2.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.88 (dd, *J* = 1.5 and 1.5 Hz, 1H), 7.84 (dd, *J* = 1.5 and 1.5 Hz, 1H), 7.76 (dd, *J* = 1.5 and 1.5 Hz, 1H), 7.63 (dd, *J* = 1.5 and 1.5 Hz, 1H), 7.56 (dd, *J* = 1.5 and 1.5 Hz, 1H), 7.51 (dd, *J* = 1.5 and 1.5 Hz, 1H), 1.98 (s, 1H), 1.68 (s, 3H), 1.20-1.19 (m, 21H), 1.11 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.7 (C), 152.0 (C), 148.5 (C), 133.1 (CH), 129.5 (CH), 129.3 (CH), 128.2 (CH), 126.0 (CH), 124.2 (C), 123.2 (C), 123.0 (C), 121.3 (CH), 107.6 (C), 93.3 (C), 91.2 (C), 84.9 (C), 70.0 (C), 34.9 (C), 34.5 (C), 33.5 (CH_3), 31.1 (CH_3), 30.8 (CH_3), 18.9 (CH_3), 11.7 (CH); IR (neat): ν = 3355, 2963, 2865, 2154, 1584, 1420, 1364, 1209, 996, 931, 880, 684 cm^{-1}; MS (EI) *m/z* 594 (2, ^{81}Br), 592 (M^+, 2, ^{79}Br), 579 (2, ^{81}Br), 577 (2, ^{79}Br), 551 (99, ^{81}Br), 549 (95, ^{79}Br), 419 (10, ^{81}Br), 417 (9, ^{79}Br), 295 (8), 240 (18), 57 (98), 43 (100).

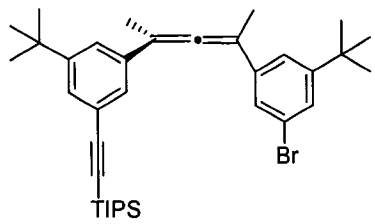
(*S*)-2-(3-Bromo-5-*tert*-butylphenyl)-4-(3-*tert*-butyl-5-(2-(triisopropylsilyl)ethynyl)phenyl)but-3-yn-2-yl acetate (313)



$C_{37}H_{51}BrO_2Si$
Mol. Wt.: 635.79

The title compound was prepared analogously to acetate **309** using the following quantities: Propargyl alcohol **301** (1.65 g, 2.78 mmol); CH_2Cl_2 (35 mL); DMAP (catalytic); pyridine (1.12 mL, 13.9 mmol); Ac_2O (1.31 mL, 13.9 mmol). Column chromatography (30:1 PE:EA) provided the title compound as a white paste (1.73 g, 98%). $[\alpha]^{20}_D$ = +10.2 (*c* 0.62, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.96 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.83 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.82 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.63 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.61 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.52 (dd, *J* = 1.7 and 1.7 Hz, 1H), 1.88 (s, 3H), 1.58 (s, 3H), 1.19-1.18 (m, 21H), 1.10 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.8 (C), 153.8 (C), 152.0 (C), 145.5 (C), 133.2 (CH), 129.7 (CH), 129.5 (CH), 128.6 (CH), 125.6 (CH), 124.2 (C), 123.1 (C), 123.0 (C), 122.0 (CH), 107.5 (C), 91.0 (C), 89.3 (C), 87.7 (C), 75.6 (C), 34.9 (C), 34.4 (C), 31.7 (CH_3), 31.0 (CH_3), 30.7 (CH_3), 21.1 (CH_3), 18.9 (CH_3), 11.7 (CH); IR (neat): ν = 2963, 2865, 2156, 1756, 1584, 1420, 1365, 1229, 1187, 1064, 1012, 997, 937, 881, 756, 684 cm^{-1}; MS (EI) *m/z* 636 (9, ^{81}Br), 634 (M^+, 9, ^{79}Br), 533 (68, ^{81}Br), 531 (56, ^{79}Br), 223 (12), 162 (36), 57 (100); HRMS calculated for $C_{37}H_{51}O_2Si^{79}Br$ (M^+) 634.2842, found 634.2851.

S-(2-(3-(4-(3-Bromo-5-*tert*-butylphenyl)penta-2,3-dien-2-yl)-5-*tert*-butylphenyl)ethynyl)triisopropylsilane (302)

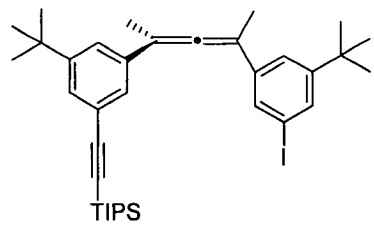


$C_{36}H_{51}BrSi$
Mol. Wt.: 591.78

The title compound was prepared analogously to allene **307** using the following quantities: LiBr (1.34 g, 15.4 mmol); CuI (2.93 g, 15.4 mmol); THF (105 mL); MeMgBr in ether (2.0 M, 7.69 mL, 15.4 mmol); acetate **313** (1.63 g, 2.56 mmol). Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a pale yellow oil (1.45 g, 95%). $[\alpha]^{20}_D$ = +192.4 (*c* 2.50, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.69 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.65 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.60 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.56 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.50 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.46 (dd, *J* = 1.7 and 1.7 Hz, 1H), 1.92 (s, 3H), 1.89 (s, 3H), 1.21-1.20 (m, 21H), 1.09 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.3 (C),

153.7 (C), 151.7 (C), 139.7 (C), 128.3 (CH), 127.6 (CH), 127.2 (CH), 126.4 (CH), 124.1 (C), 123.8 (CH), 123.5 (C), 122.0 (CH), 108.8 (C), 103.2 (C), 102.6 (C), 90.2 (C), 34.8 (C), 34.6 (C), 31.1 (CH_3), 31.0 (CH_3), 18.9 (CH_3), 16.79 (CH_3), 16.75 (CH_3), 11.7 (CH) (missing one aromatic quaternary carbon); IR (neat): ν = 2962, 2865, 2157, 1587, 1561, 1464, 1365, 1235, 996, 931, 862, 682 cm^{-1}; MS (EI) *m/z* 592 (3, ^{81}Br), 590 (M^+, 3, ^{79}Br), 549 (10, ^{81}Br), 547 (9, ^{79}Br), 69 (100), 57 (15); HRMS calculated for $C_{36}H_{51}Si^{79}Br$ (M^+) 590.2943, found 590.2937.

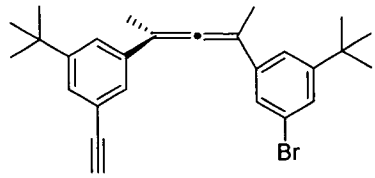
(*S*)-(2-(3-*tert*-Butyl-5-(4-(3-*tert*-butyl-5-iodophenyl)penta-2,3-dien-2-yl)phenyl)ethynyl)triisopropylsilane (304)



$C_{36}H_{51}ISi$
Mol. Wt.: 638.78

The title compound was prepared analogously to allene **266** using the following quantities: Aryl bromide **302** (0.636 g, 1.08 mmol); THF (25 mL); *t*-BuLi in pentane (1.5 M, 1.58 mL, 2.36 mmol); I_2 (0.600 g, 2.36 mmol). Filtration through a silica gel plug (10 cm) using PE as eluent provided the title compound as a colorless oil (0.614 g, 91%). A minor impurity could not be separated from the product. $[\alpha]^{20}_D$ = +117.0 (*c* 0.83, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.74 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.66 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.65 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.61 (dd, J = 1.6 and 1.6 Hz, 1H), 7.58 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.51 (dd, *J* = 1.6 and 1.6 Hz, 1H), 1.93 (s, 3H), 1.88 (s, 3H), 1.10 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.2 (C), 153.7 (C), 151.7 (C), 139.8 (C), 137.6 (C), 133.6 (CH), 132.4 (CH), 128.3 (CH), 127.2 (CH), 124.1 (C), 123.8 (CH), 122.7 (CH), 108.8 (C), 103.1 (C), 102.4 (C), 95.6 (C), 90.1 (C), 34.62 (C), 34.58 (C), 31.12 (CH_3), 31.05 (CH_3), 19.0 (CH_3), 16.9 (CH_3), 16.8 (CH_3), 11.8 (CH); IR (neat): ν = 2962, 2865, 2157, 1586, 1556, 1463, 1365, 1235, 994, 958, 929, 876, 682 cm^{-1}; MS (EI) *m/z* 638 (M^+) (44), 595 (100), 553 (8), 469 (6), 262 (16), 57 (33); HRMS calculated for $C_{36}H_{51}ISi$ (M^+) 638.2805, found 638.2790.

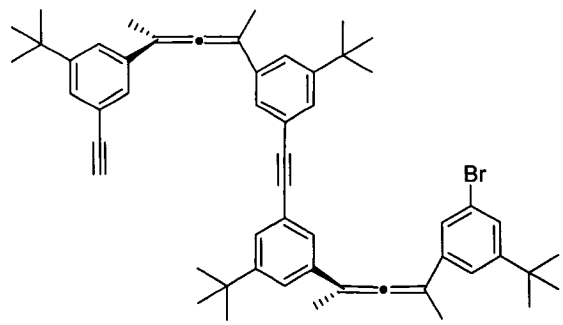
(*S*)-1-(4-(3-Bromo-5-*tert*-butylphenyl)penta-2,3-dien-2-yl)-3-*tert*-butyl-5-ethynylbenzene (303)



$C_{27}H_{31}Br$
Mol. Wt.: 435.44

The title compound was prepared analogously to allene **259** using the following quantities: Aryl TIPS-acetylene **302** (0.810 g, 1.37 mmol); THF (20 mL); TBAF in THF (1.0 M, 1.64 mL, 1.64 mmol). Column chromatography (PE) afforded the title compound as a colorless oil (0.546 g, 91%). $[\alpha]^{20}_{D}$ = +186.9 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.55 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.54 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.52 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.46 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.44 (dd, *J* = 1.6 and 1.6 Hz, 1H), 2.74 (s, 1H), 1.96 (s, 3H), 1.92 (s, 3H), 1.10 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.2 (C), 153.7 (C), 151.7 (C), 139.6 (C), 137.5 (C), 128.4 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH), 123.8 (CH), 123.5 (C), 122.9 (C), 121.9 (CH), 103.1 (C), 102.6 (C), 84.5 (CH), 77.4 (C), 34.8 (C), 34.6 (C), 31.11 (CH_3), 31.07 (CH_3), 16.8 (CH_3) (allenyl CH_3 groups overlap); IR (neat): ν = 3295, 2964, 2880, 1589, 1563, 1477, 1365, 1276, 1234, 1030, 877, 863, 757, 695 cm^{-1}; MS (EI) *m/z* 436 (80, ^{81}Br), 434 (M^+, 76, ^{79}Br), 421 (35, ^{81}Br), 418 (35, ^{79}Br), 379 (23, ^{81}Br), 377 (22, ^{79}Br), 355 (10), 299 (7), 202 (12), 162 (9), 57 (100); HRMS calculated for $C_{27}H_{31}{}^{79}Br$ (M^+) 434.1609, found 434.1652.

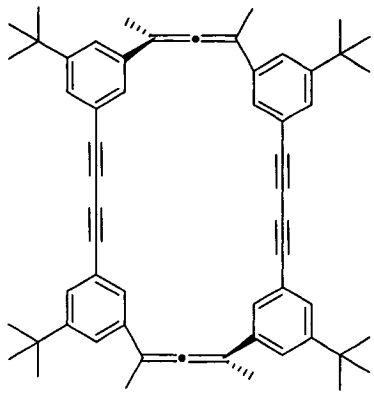
(*S*)-1-(4-(3-Bromo-5-*tert*-butylphenyl)penta-2,3-dien-2-yl)-3-*tert*-butyl-5-(*S*)-(2-(3-*tert*-butyl-5-(4-(3-*tert*-butyl-5-ethynylphenyl)penta-2,3-dien-2-yl)phenyl)ethynyl)benzene (305)



$C_{54}H_{61}Br$
Mol. Wt.: 789.97

Tri(2-furyl)phosphine (3.9 mg, 0.0169 mmol), $Pd(OAc)_2$ trimer (1.9 mg, 0.00847 mmol), CuI (3.2 mg, 0.0169 mmol), NEt_3 (1 mL) and THF (4 mL) were added to a flask and degassed. A solution of aryl iodide **304** (54.1 mg, 0.0847 mmol) and acetylene **303** (36.9 mg, 0.0847 mmol) in THF (1 mL) was then added. After stirring overnight at rt, the reaction was diluted with sat. NH_4Cl, and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (100:1 PE:EA) provided TIPS-protected acetylene **305** along with an impurity that could not be separated. This mixture (0.030 g, max. 0.0317 mmol of **305**) was then dissolved in THF (2 mL) and a solution of TBAF in THF (1.0 M, 0.038 mL, 0.0380 mmol) was added. After stirring for 5 min at rt, the reaction was quenched with H_2O and a little sat. $NaHCO_3$, and the organics were extracted with ether, dried, filtered, and concentrated. Preparative TLC (50:1 PE:EA) yielded the title compound as a colorless oil (0.0174 g, 51%, 2 steps). $[\alpha]^{20}_D$ = +97.1 (*c* 3.01, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.79 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.78 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.700 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.697 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.65 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.63 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.613 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.609 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.57 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.55 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.51 (dd, *J* = 1.7 and 1.7 Hz, 1H), 7.47 (dd, *J* = 1.7 and 1.7 Hz, 1H), 2.72 (s, 1H), 1.99 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H), 1.134 (s, 9H), 1.131 (s, 9H), 1.09 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.24 (C), 206.22 (C), 153.65 (C), 151.80 (C), 151.75 (C), 151.65 (C), 139.70 (C), 137.77 (C), 137.75 (C), 137.57 (C), 128.34 (CH), 128.25 (C), 128.15 (C), 127.59 (CH), 127.20 (CH), 126.74 (CH), 126.72 (CH), 126.48 (CH), 124.12 (C), 124.01 (CH), 123.59 (CH), 123.51 (CH), 123.47 (C), 122.88 (C), 122.04 (CH), 103.29 (C), 103.12 (C), 102.94 (C), 102.63 (C), 90.46 (C), 90.31 (C), 84.55 (CH), 77.28 (C), 34.75 (C), 34.67 (C), 34.56 (C), 31.13 (CH_3), 31.06 (CH_3), 31.01 (CH_3), 16.88 (CH_3), 16.85 (CH_3), 16.79 (CH_3), 16.76 (CH_3) (missing one quaternary carbon and one CH_3: Appear to occur at 34.67 and 31.13 ppm based on peak intensity); IR (neat): ν = 3294, 2964, 2869, 1559, 1457, 1364, 1230, 1094, 876, 697 cm^{-1}; MS (ES) *m/z* 748.3 ($M^+ + K^+ - Br$).

7,16,26,35-Tetra(*tert*-butyl)-11,13,30,32-tetramethyl[4.4.3.3]metacyclophan-11,12,30,31-tetraen-1,3,20,22-tetrayne (380)



$C_{58}H_{60}$
Mol. Wt.: 757.10

Copper(II) acetate (0.556 g, 3.06 mmol) was dissolved in pyridine (75 mL) and ether (25 mL). A solution of allene **307** (0.097 g, 0.255 mmol) in pyridine (7.5 mL) and ether (2.5 mL) was then added *via* syringe pump over a period of 6 h and the reaction was allowed to stir overnight. The original royal blue solution was a deep forest green by morning. The reaction was then diluted with ether and washed repeatedly (~10X) with 1 M citric acid to remove all pyridine, followed by a single wash with sat. $NaHCO_3$ to remove any citric acid. The organics were dried, filtered, and concentrated. Dry pack column chromatography (100:1 PE:EA) yielded the title compound contaminated with small quantities of intensely pink and yellow colored products. Preparative TLC (50:1 PE:EA) yielded the pure title compound as a colorless solid (0.0387 g, 40%). mp: dec. ~160 °C; $[\alpha]^{20}_{D}$ = +87.1 (*c* 2.68, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (dd, *J* = 1.6 and 1.6 Hz, 1H), 7.39-7.38 (m, 2H), 1.99 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.0 (C), 151.8 (C), 138.6 (C), 129.6 (CH), 127.4 (CH), 124.1 (CH), 122.4 (C), 102.9 (C), 83.4 (C), 75.1 (C), 34.6 (C), 31.1 (CH_3), 17.3 (CH_3); IR (neat): ν = 2964, 2903, 2869, 2226, 2186, 1583, 1366, 875, 758, 696 cm^{-1}; MS (EI) *m/z* 756 (M^+) (48), 699 (16), 57 (97), 43 (100).

8.3 Experimental Procedures for Previously Reported Compounds

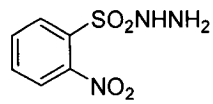
Experimental procedures and ^{1}H NMR data for previously reported compounds synthesized for this thesis are presented for convenience in this section. Full characterization data is available in the indicated references.

(*Z*)-(4-Chlorobut-3-en-1-ynyl)triisopropylsilane (235)[180]

$C_{13}H_{23}ClSi$
Mol. Wt.: 242.86

cis-1,2-Dichloroethene (10.0 g, 103 mmol), $Pd(PPh_3)_2Cl_2$ (1.03 g, 1.47 mmol), CuI (0.28 g, 1.47 mmol), *n*-$BuNH_2$ (10 mL) and ether (200 mL) were added to a flask and degassed. Triisopropylsilylacetylene (11.0 mL, 49.1 mmol) was added and the reaction was protected from light by aluminum foil and stirred overnight at rt. The next day the reaction was filtered through silica (PE) and concentrated. Filtration of the resultant yellow oil through a second silica gel plug (10 cm) using PE as eluent provided the title compound (11.7 g, 98%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.37 (d, J = 7.4 Hz, 1H), 5.88 (d, J = 7.4 Hz, 1H), 1.07 (s, 21H).

2-Nitrobenzenesulfonylhydrazide (28)[181]

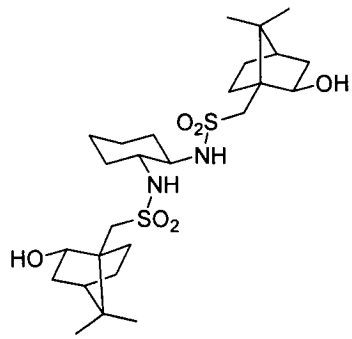


$C_6H_7N_3O_4S$
Mol. Wt.: 217.20

2-Nitrobenzenesulfonyl chloride (10.0 g, 45.1 mmol) was dissolved in THF (50 mL) and cooled to –30 °C. Hydrazine monohydrate (5.47 mL, 113 mmol) was added dropwise and the reaction was stirred at –30 °C for 30 min. The reaction was then diluted with EA and quickly washed with ice cold brine (5 x 75 mL). The organics were dried (Na_2SO_4) and poured into hexanes (500 mL). The precipitated solid was collected by filtration and identified as the title compound (7.75 g, 79%). ^{1}H NMR (300 MHz, CD_3CN) δ 8.03-8.16 (m, 1H), 7.77-7.91 (m, 3H), 5.95 (br s, 1H), 3.93 (br s, 2H).

[180] Lu, Y-F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 4202-4204.
[181] Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

***N,N'*-(Cyclohexane-1,2-diyl)bis((2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methanesulfonamide) (214)[149,182]**

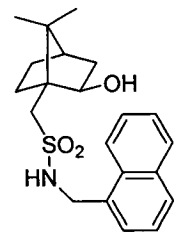


$C_{26}H_{46}N_2O_6S_2$
Mol. Wt.: 546.78

(*R,R*)-Diaminocyclohexane (**267**) (1.11 g, 9.72 mmol) was dissolved in CH_2Cl_2 (90 mL) and Et_3N (3.00 mL, 21.4 mmol) was added. A solution of (*S*)-camphorsulfonyl chloride (**268**) (5.36 g, 21.4 mmol) in CH_2Cl_2 (40 mL) was then slowly added over 10 min. After stirring for 24 h at rt the reaction was sequentially washed with 2 N HCl and water. The organics were dried (Na_2SO_4) and concentrated. Recrystallization from hexane/CH_2Cl_2 then provided the diketone (3.40 g, 64%). The diketone (3.40 g, 6.26 mmol) was added to a mixture of THF (65 mL) and *i*-PrOH (65 mL) (does not fully dissolve) and $NaBH_4$ (1.66 g, 43.9 mmol) was added in small portions over 5 min. Stirring was continued until all foaming had subsided (30 min), at which time the reaction was quenched VERY slowly with sat. NH_4Cl. After removal of the THF and *i*-PrOH *in vacuo*, the organics were extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (70:30 hexane:EA) provided the title compound as a white solid (1.31 g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, J = 7.3 Hz, 2H), 4.01-4.12 (m, 2H), 3.50 (d, J = 13.6 Hz, 2H), 3.32 (d, J = 3.5 Hz, 2H), 3.05-3.12 (m, 2H), 2.92 (d, J = 13.6 Hz, 2H), 2.09-2.21 (m, 2H), 1.66-1.88 (m, 12H), 1.43-1.56 (m, 2H), 1.26-1.43 (m, 4H), 1.08-1.20 (m, 2H), 1.07 (s, 6H), 0.84 (s, 6H).

[182] Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250-3251.

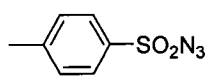
(1*S*,2*R*,4*S*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)-*N*-(naphthalen-2-ylmethyl) methanesulfonamide (210)[161]



$C_{21}H_{27}NO_3S$
Mol. Wt.: 373.51

A modified literature procedure was used: 1-Naphthalenemethylamine (**270**) (0.93 mL, 6.36 mmol) was dissolved in CH_2Cl_2 (40 mL), Et_3N (1.07 mL, 7.63 mmol) was added and the reaction was cooled to 0 °C. A solution of (*S*)-camphorsulfonyl chloride (**268**) (1.75 g, 7.00 mmol) in CH_2Cl_2 (15 mL) was then slowly added over 10 min. After stirring for 24 h at rt the reaction was sequentially washed with 2 N HCl and water. The organics were dried (Na_2SO_4), filtered and concentrated. The impure ketone was then dissolved in a mixture of THF (30 mL) and 99% EtOH (30 mL), cooled to 0 °C, and $NaBH_4$ (0.84 g, 22.3 mmol) was slowly added in portions. After stirring for 4 h at 0 °C, the reaction was carefully quenched with sat. NH_4Cl and concentrated. Ether and 1 M HCl were added and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (75:25 PE:EA) yielded the title compound as a white solid (1.18 g, 50% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-8.10 (m, 1H), 7.75-7.90 (m, 2H), 7.20-7.60 (m, 4H), 5.12 (t, J = 5.8 Hz, 1H), 4.63-4.79 (m, 2H), 3.96-4.03 (m, 1H), 3.13 (s, 1H), 3.22 (d, J = 13.7 Hz, 1H), 2.62 (d, J = 13.7 Hz, 1H), 1.20-1.70 (m, 6H), 0.94-1.06 (m, 1H), 0.86 (s, 3H), 0.59 (s, 3H).

***p*-Toluenesulfonylazide (314)[183]**



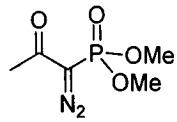
$C_7H_7N_3O_2S$
Mol. Wt.: 197.21

Sodium azide (2.73 g, 42.0 mmol) was dissolved in a mixture of H_2O (120 mL) and acetone (120 mL) and cooled to 0 °C. A solution of TsCl (8.00 g, 42.0 mmol) in acetone (20 mL) was added and the reaction was stirred at 0 °C for 2 h. The acetone was then removed under reduced

[183] Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Syn. CV5*, 179.

pressure and the organics were extracted with ether, dried, and concentrated to yield the title compound as a colorless oil that solidified upon refrigeration. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 2.47 (s, 3H).

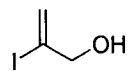
Dimethyl-1-diazo-2-oxopropylphosphonate (296)[184]



$C_5H_9N_2O_4P$
Mol. Wt.: 192.11

A modified literature procedure was used: A solution of dimethyl (2-oxopropyl)phosphonate (12.0 g, 72.3 mmol) in THF (150 mL) was added dropwise to a slurry of NaH (60% dispersion in mineral oil, 3.18 g, 79.5 mmol) in THF (160 mL) at 0 °C. The resultant thick mixture was stirred at 0 °C for 1 h and then a solution of TsN_3 (**314**) (15.7 g, 79.5 mmol) in THF (50 mL) was added dropwise. After stirring at 0 °C for 15 min, the reaction was filtered on a Buchner funnel (EA wash), followed by filtration through a silica gel plug (5 cm) using EA as eluent. Column chromatography (1:1 PE:EA) afforded the title compound as a pale yellow oil (11.3 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.85 (s, 3H), 2.28 (s, 3H).

2-Iodoprop-2-en-1-ol (282)[163]



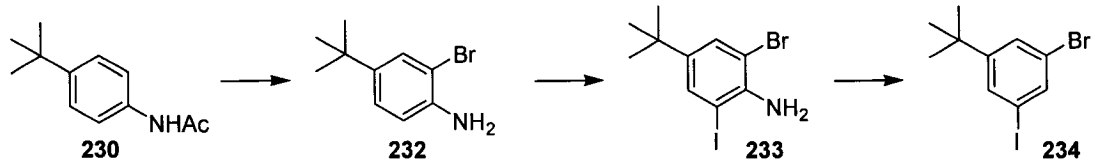
C_3H_5IO
Mol. Wt.: 183.98

Sodium iodide (13.6 g, 91.0 mmol) was dissolved in CH_3CN (70 mL), TMSCl (9.88 g, 91.0 mmol) and H_2O (0.96 g, 53.5 mmol) were sequentially added, and the reaction was stirred for 10 min at rt. A solution of propargyl alcohol (3.00 g, 53.5 mmol) in CH_3CN (12 mL) was then added and the reaction was stirred for 1 h at rt. The reaction was then diluted with water and the organics were extracted with ether and washed with 1 M $Na_2S_2O_3$. The organics were then dried, filtered, and concentrated to yield the title compound as a colorless oil (6.10 g, 62%). ^{1}H NMR

[184] (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522; (b) Xu, Z.; Peng, Y.; Ye, T. *Org. Lett.* **2003**, *5*, 2821-2824.

(400 MHz, $CDCl_3$) δ 6.36 (q, J = 1.8 Hz, 1H), 5.83 (dt, J = 1.8 and 1.2 Hz, 1H), 5.17 (dd, J = 1.8 and 1.2 Hz, 2H), 2.67 (br s, 1H)

1-Bromo-3-*tert*-butyl-5-iodobenzene (234)[155]



230 $C_{12}H_{17}NO$ Mol. Wt.: 191.27

232 $C_{10}H_{14}BrN$ Mol. Wt.: 228.13

233 $C_{10}H_{13}BrIN$ Mol. Wt.: 354.03

234 $C_{10}H_{12}BrI$ Mol. Wt.: 339.01

N-(4-tert-Butylphenyl)acetamide (230)

A modified literature procedure was used: 4-*tert*-Butylaniline (**229**) (50.0 g, 0.335 mol) was dissolved in a mixture of THF (35 mL) and pyridine (70 mL) and cooled to 0 °C. Acetic anhydride (79.2 mL, 0.838 mol) was then added dropwise at 0 °C and the mixture was warmed to rt and stirred overnight. Water and ether were added, the layers were separated, and the ether layer was washed with 1 M HCl and concentrated. Methanol (~120 mL) was added to the resultant pink crystals and the mixture was cooled on ice. The white crystals were collected by filtration and washed with a small amount of cold MeOH. The filtrate was then concentrated, MeOH was added, and the collection procedure repeated (5 times). The combined crystals were identified as the title compound (54.6 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dt, J = 8.7 and 2.0 Hz, 2H), 7.32 (dt, J = 8.7 and 2.0 Hz, 2H), 2.15 (s, 3H), 1.30 (s, 9H).

2-Bromo-4-tert-butylphenylamine (232)

A modified literature procedure was used: Amide **230** (54.6 g, 0.285 mol) was added to glacial AcOH (200 mL) and warmed to 45 °C. The starting material does not fully dissolve. A solution of Br_2 (19.0 mL, 0.371 mol) in glacial AcOH (20 mL) was then added dropwise to the reaction. During the addition and subsequent stirring, large quantities of precipitate appeared and disappeared. After stirring for 24 h at 50 °C, excess bromine was neutralized by the addition of 2 M $Na_2S_2O_3$. Water was then added and the organics were extracted with ether, dried, filtered, and concentrated to yield crude *N*-(2-bromo-4-*tert*-butylphenyl)acetamide (**231**) as white crystals (~80 g). The crude acetate was then dissolved in a mixture of EtOH (180 mL) and concentrated HCl (80 mL) and heated at reflux for 4 h. Once cooled to rt, the solution was neutralized by the addition of 50% NaOH and the organics were extracted with ether, dried, filtered, and

concentrated to yield an orange oil identified as the title compound [61.6 g, 94% (2 steps)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 2.2 Hz, 1H), 7.15 (dd, J = 8.4 and 2.2 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 4.01 (br s, 2H), 1.29 (s, 9H).

2-Bromo-4-tert-butyl-6-iodophenylamine (233)

A modified literature procedure was used: Amine **232** (61.6 g, 0.269 mol) was added to 10% HCl (300 mL). A large amount of precipitate immediately formed. A solution of ICl (43.1 mL, 0.861 mol) in 10% HCl (200 mL) was then added dropwise to the reaction. During the addition, a purple crystalline precipitate formed in the dropping funnel and could not be added to the reaction. A large amount of thick black tar also formed in the reaction flask, quickly settling to the bottom and preventing stirring. The mixture was allowed to sit and quiver overnight, after which time it was cooled to 0 °C and neutralized by the cautious addition of 10% NaOH (exothermic). The mixture was extracted with ether and the combined extracts were washed with 1 M $Na_2S_2O_3$, dried, filtered, and concentrated to yield a black tar identified as the title compound (95.0 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 2.1 Hz, 2H), 7.42 (d, J = 2.1 Hz, 2H), 4.39 (br s, 2H), 1.26 (s, 9H).

1-Bromo-3-tert-butyl-5-iodobenzene (234)

Amine **233** (103 g, 0.289 mol) was dissolved in a mixture of EtOH (460 mL) and benzene (150 mL), cooled to 0 °C and concentrated H_2SO_4 (42 mL) was added. Sodium nitrite (43.9 g, 0.636 mol) was then added in small portions. Once the addition was complete the reaction was heated at reflux until the vigorous evolution of gas ceased (~90 min). The reaction was then cooled and diluted with water. The organics were extracted with ether, washed with 1 M $Na_2S_2O_3$, dried, filtered, and concentrated to yield a black oil. Distillation under high vacuum (0.5 mmHg) yielded a red oil which distilled at 160 °C. This oil was dissolved in ether, washed with 1 M $Na_2S_2O_3$, dried, filtered, and concentrated to yield the title compound as a pale yellow oil (70.5 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 1.7 and 1.6 Hz, 1H), 7.64 (dd, J = 1.7 and 1.6 Hz, 1H), 7.48 (dd, J = 1.7 and 1.7 Hz, 1H), 1.29 (s, 9H).

SECTION C

A SYNTHETIC APPROACH TO BUCKMINSTERFULLERENE (C_{60})

9 Introduction

The third section of this thesis involves our work towards a controlled chemical synthesis of Buckminsterfullerene (C_{60}). Buckminsterfullerene and previous synthetic approaches to it will be introduced first, followed by a discussion of our synthetic strategy to C_{60}. The chemistry of palladium- and copper-mediated couplings is also relevant to this project, and was presented in Section 5.3. Our studies on model compounds as well as our synthetic work towards C_{60} will then be presented and discussed.

9.1 Buckminsterfullerene

In 1984 Rohlfing, Cox, and Kaldor vaporized graphite with a laser beam under helium at high pressure.[185] Time of flight mass spectral analysis detected carbon clusters up to 190 carbon atoms in size, and it was observed that for carbon clusters greater than 40 atoms, exclusively even sized clusters were detected. They theorized that these clusters represented the hypothesized "carbyne phase"[186] of carbon and were composed of cross-linked acetylene moieties, which would explain the observance of only even number carbon clusters.

We now know that this theory was incorrect. In 1985 Kroto, Heath, O'Brien, Curl, and Smalley conducted a very similar experiment aimed at understanding the mechanisms by which long-chain carbon molecules are formed in interstellar space.[187] Using an apparatus similar to that used by Rohlfing *et al.*, they found conditions that resulted in nearly exclusive formation of a C_{60} cluster, with a smaller C_{70} cluster also present. Kroto *et al.* quickly recognized that the structure of this C_{60} cluster could not logically be derived from the known forms of carbon, namely diamond and graphite, and thus searched for another plausible structure. Realizing that a spherical structure would satisfy all valence requirements, they consulted the papers of architect Buckminster Fuller and hypothesized that the structure of the C_{60} molecule was a truncated icosahedron, identical to a standard soccerball (Figure 31). Illustrative of their thought process

[185] Rohlfing, E. A.; Cox, D. M.; Kaldor, A. *J. Chem. Phys.* **1984**, *81*, 3322-3330.
[186] Goresy, A. E.; Donnay, G. *Science* **1968**, *161*, 363-364.
[187] Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162-163.

as well as in honour of Fuller, they named this new allotrope of carbon Buckminsterfullerene. Kroto, Smalley, and Curl were awarded the 1996 Nobel Prize in Chemistry for this discovery.

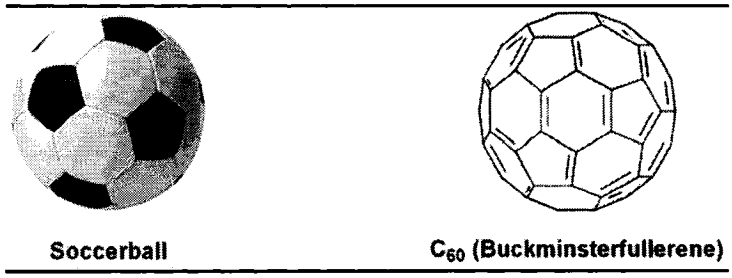


Figure 31: The structure of C_{60} (Buckminsterfullerene)

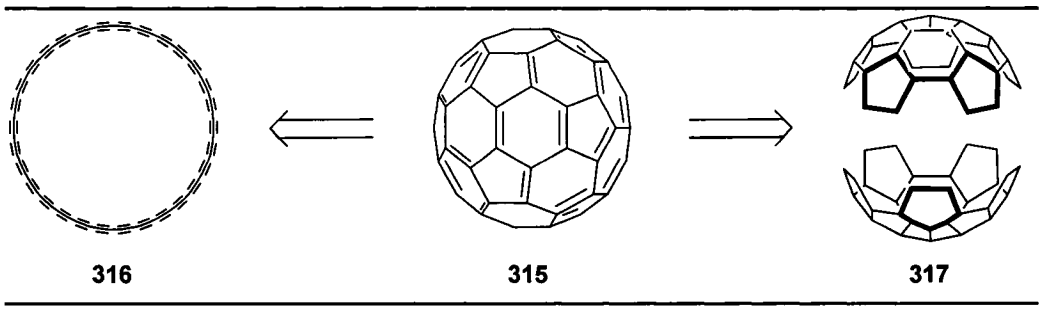
Synthetically speaking, from its discovery in 1985 until 1990, C_{60} was produced in miniscule and unisolable amounts using methods similar to those employed by Rohlfing and Kroto in their pioneering studies. However, in 1990 Krätschmer reported a substantially more efficient method of synthesizing C_{60}.[188] By vaporizing graphite electrodes in an atmosphere of helium and extracting the resultant black soot with benzene, C_{60} was isolated in gram quantities, as well as smaller quantities of C_{70}. They also confirmed by X-ray diffraction studies that C_{60} had the hypothesized fullerene structure put forth five years earlier by Kroto.[187] Currently, C_{60} and higher fullerenes are produced industrially on the multi-ton scale *via* the combustion of simple hydrocarbons in fuel rich flames.[189]

9.1.1 Laboratory Syntheses of C_{60}

The need for a milligram-scale laboratory synthesis of C_{60} is often questioned given the fact that large quantities of C_{60} are industrially available relatively inexpensively (~$200/kg).[190] The reasons for the development of new strategies to C_{60}, however, lie with the higher fullerenes.[191] It has been theorized based on the isolated pentagon rule[192] that more than 1000 stable fullerenes could be assembled using 100 carbon atoms or less.[193] For example, 24 isomers

[188] Krätschmer, W.; Lamb, L. D.; Fostiropoulos, K.; Huffman, D. R. *Nature* **1990**, *347*, 354-358.
[189] Howard, J. B.; McKinnon, J. T.; Makarovsky, Y.; Lafleur, A. L.; Johnson, M. E. *Nature* **1991**, *352*, 139-141.
[190] Scott, L. T. *Angew. Chem. Int. Ed.* **2004**, *43*, 4994-5007.
[191] Additional reasons for pursuing such a synthesis are remarkably similar to those used to justify the lengthy total syntheses of readily available natural products such as Taxol.
[192] Smalley, R. E. *Acc. Chem. Res.* **1992**, *25*, 98-105.
[193] Fowler, P. W.; Manolopoulos, D. E. *Atlas of Fullerenes*; Oxford University, Oxford, **1995**.

are possible for C_{84} while 450 are possible for C_{100}. Only a few of these have been isolated and studied, and given the remarkable properties that C_{60} has exhibited, it seems reasonable to assume that some of these other fullerenes could exhibit even more fascinating properties. The logical way to access these fullerenes is of course through chemical synthesis. A synthesis of C_{60} is a rational starting point as it has been extensively characterized and studied, thereby providing a standard with which to compare the results of a laboratory synthesis.



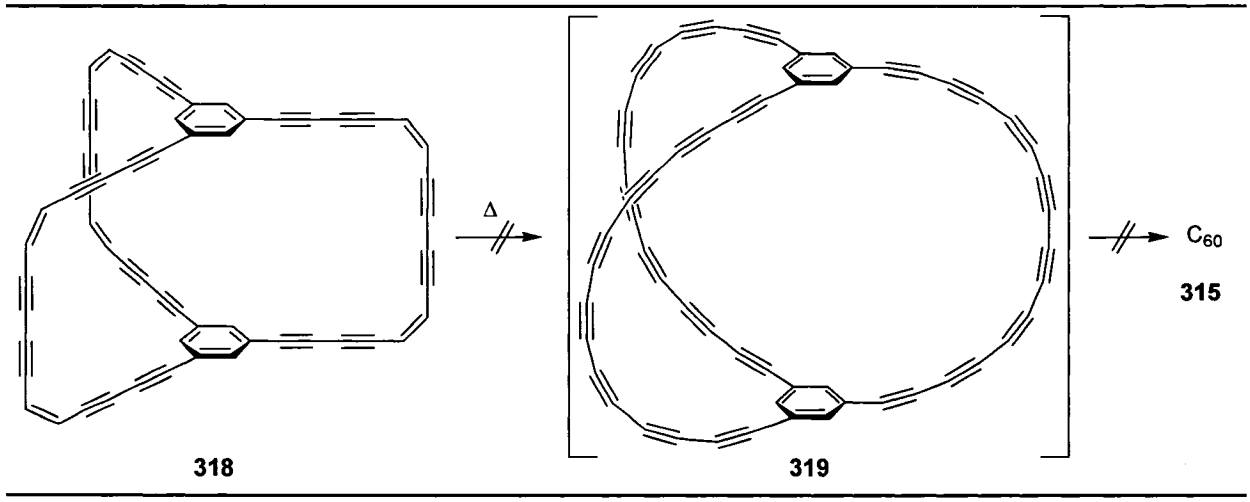
Scheme 69: Previous synthetic approaches to C_{60}

Two general approaches to C_{60} (and other fullerenes) have been reported in the literature (Scheme 69).[194] In the first, it was theorized that C_{60} (**315**) could result from the thermal rearrangement of a strained polyyne (**316**) containing 60 carbon atoms, while in the second C_{60} could arise from the fusion of two C_{30} buckybowl precursors (**317**). A few successful detections of C_{60} and other fullerenes have been reported based on the polyyne approach.[195] These experiments, however, were conducted in high energy environments such as mass spectrometers and no C_{60} could be isolated. Syntheses of C_{60} based on the buckybowl approach have thus far been unsuccessful, failing primarily due to the absence of suitable methods to fuse the two portions together.[196]

[194] Goroff, N. S. *Acc. Chem. Res.* **1996**, *29*, 77-83.

[195] (a) von Helden, G.; Gotts, N. G.; Bowers, M. T. *Nature* **1993**, *363*, 60-63; (b) McElvany, S. W.; Ross, M. M.; Goroff, N. S.; Diederich, F. *Science* **1993**, *259*, 1594-1596; (c) Hunter, J.; Fye, J.; Jarrold, M. F. *Science* **1993**, *260*, 784–786.

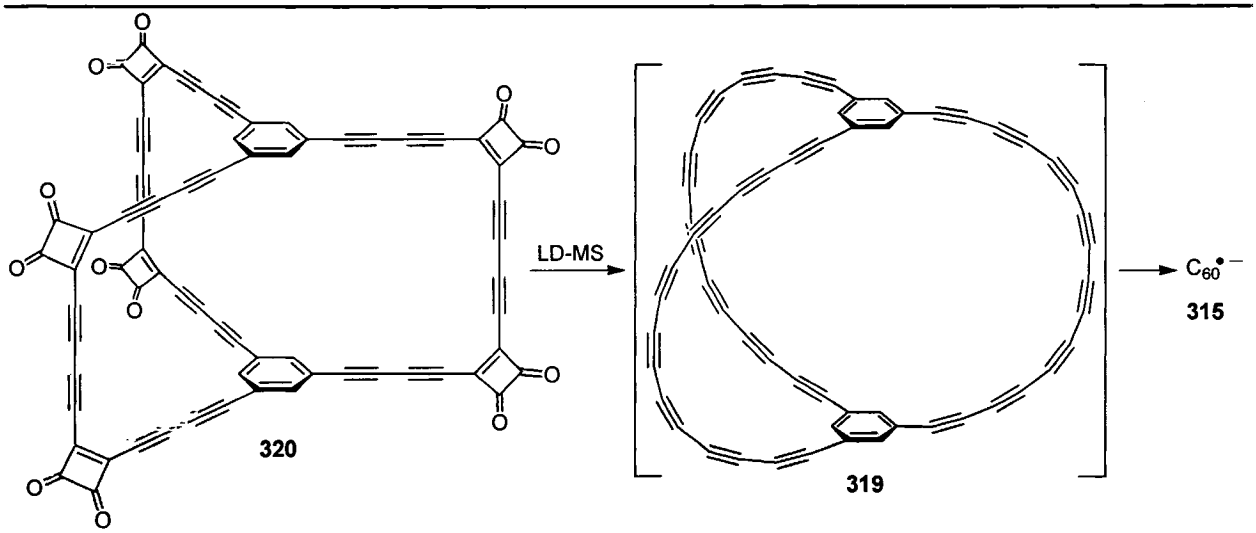
[196] (a) Abdourazak, A. H.; Marcinow, Z.; Sygula, A.; Sygula, R.; Rabideau, P. W. *J. Am. Chem. Soc.* **1995**, *117*, 6410-6411; (b) Rabideau, P. W.; Sygula, G. *Acc. Chem. Res.* **1996**, *29*, 235-242.



Scheme 70: Rubin's approach to C_{60}

In 1996 Rubin reported a potential route to C_{60} that was based on the rearrangement of a strained cyclophane and was similar in concept to the polyyne approach (Scheme 70).[197] Rubin hypothesized that dehydrogenation of the alkenyl bonds in $C_{60}H_{18}$ cyclophane **318** would produce the strained $C_{60}H_6$ cyclophane **319**, which would further rearrange to C_{60} with the loss of six hydrogen atoms. Unfortunately, using several high energy mass spectrometry techniques, they were unable to produce ions corresponding to C_{60}. Several ions corresponding to the loss of individual hydrogen atoms from **318** down to $C_{60}H_{14}$ were detected, however, which led to them to hypothesize that dehydrogenation of the alkenyl bonds was the problematic step in the synthesis.

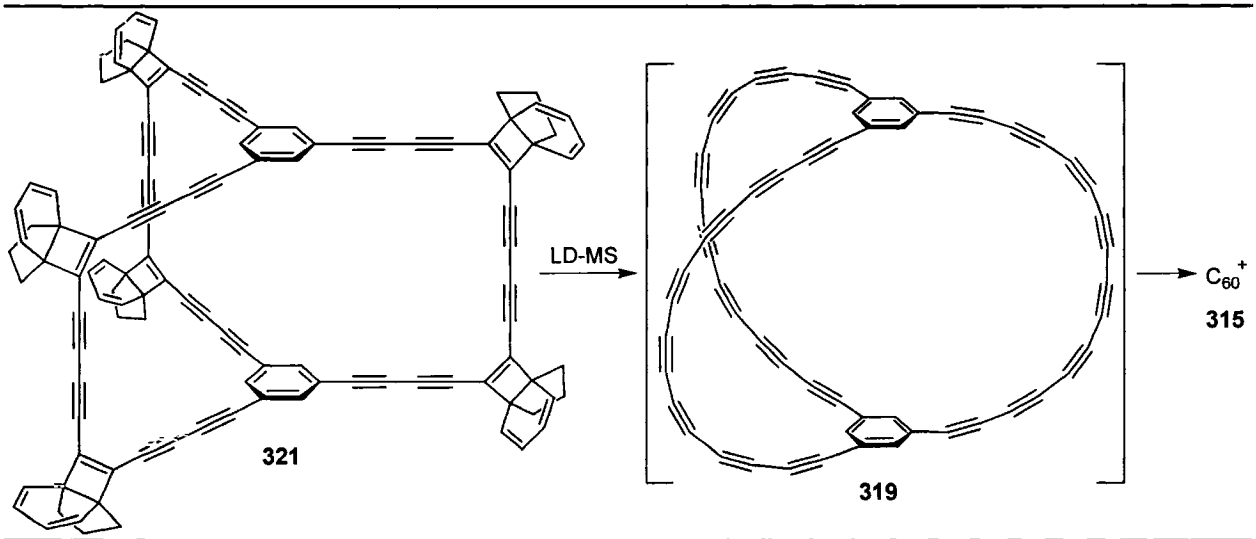
[197] Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 5308-5309.



Scheme 71: Rubin's modified approach to C_{60}

The failure of the alkenyl bonds of cyclophane **318** to fully dehydrogenate meant that the key concept of the synthesis – that is, the collapse of cyclophane **319** to C_{60} – remained untested. Rubin therefore designed an alternative precursor (**320**) to cyclophane **319** containing cyclobutenedione moieties in place of the alkenes of **318** (Scheme 71).[198] These species had been previously shown to produce the desired acetylene bonds upon liberation of carbon monoxide in either a mass spectrometer or under flash vacuum pyrolysis conditions.[195b,199] They were gratified to discover that upon exposure of cyclophane **320** to Fourier transform ion cyclotron resonance laser desorption mass spectrometry (FT-ICR LD-MS), prominent ions corresponding to $C_{60}H_6$ and C_{60} were observed, as well as several smaller ions corresponding to the sequential loss of carbon monoxide molecules from **320**. It was assumed that $C_{60}H_6$ corresponded to cyclophane **319** and arose from the expulsion of 12 carbon monoxide molecules from cyclophane **320**, and that C_{60} resulted from further rearrangement of this strained intermediate with the loss of six hydrogen atoms. Tobe also reported a successful detection of C_{60} using Rubin's approach (Scheme 72).[200] However, in his case indane substituents were extruded from the cyclophane **321** to produce cyclophane **319**.

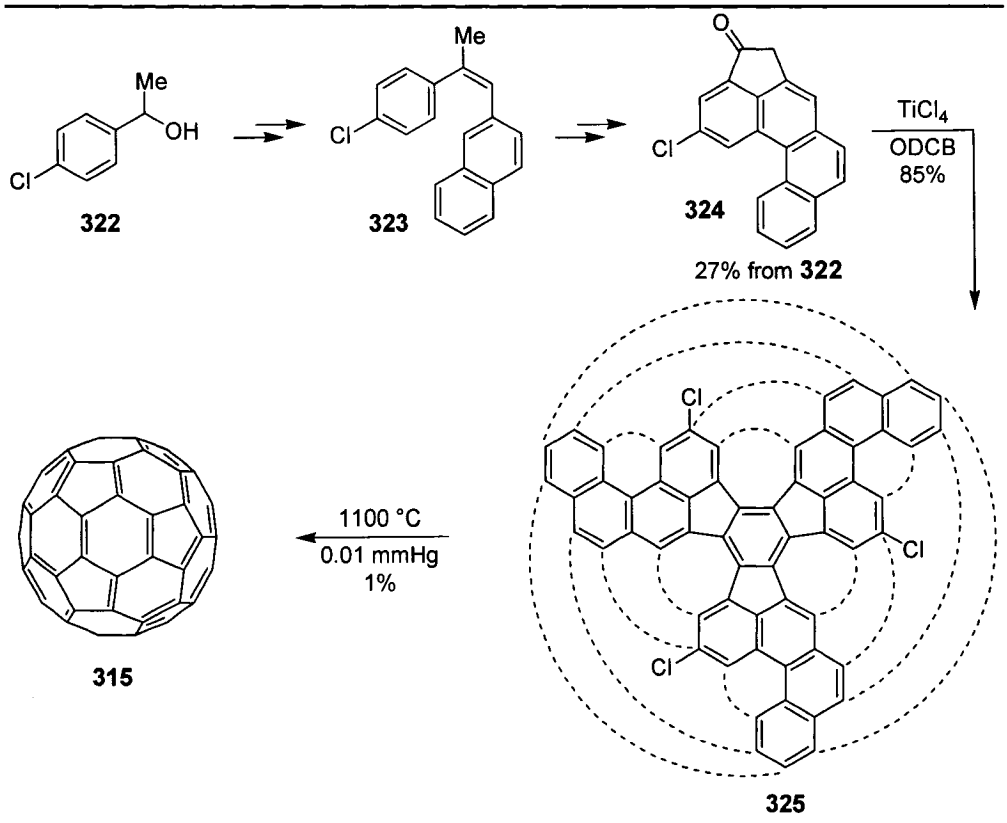
[198] Rubin, Y.; Parker, T. C.; Pastor, S. J.; Jalisatgi, S.; Boulle, C.; Wilkins, C. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 1226-1229.
[199] Rubin, Y.; Kahr, M.; Knobler, C. B.; Diederich, F.; Wilkins, C. L. *J. Am. Chem. Soc.* **1991**, *113*, 495-500.
[200] Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4544-4545.



Scheme 72: Tobe's approach to C_{60}

The approaches reported by Rubin and Tobe did not produce appreciable quantities of C_{60}, and that which was produced was destroyed in the mass spectrometer. The first and only chemical synthesis to produce isolable quantities of C_{60} thus far was reported by Scott in 2002 and was loosely based on the previously described buckybowl approach (Scheme 73).[201] Beginning with alcohol **322**, Scott synthesized pentacycle **324** in nine steps and 27% overall yield. A titanium-catalyzed aldol cyclotrimerization of **324** then yielded the large precursor (**325**) to C_{60} in 85% yield. Flash vacuum pyrolysis of **325** at 1100 °C and 0.01 mmHg then yielded a black soot from which pure C_{60} was isolated in ~1% yield. The dotted lines surrounding **325** in Scheme 73 represent the bonds that formed during its conversion to C_{60}. Careful mass spectral and HPLC analysis of the reaction soot indicated that the only fullerene present was C_{60}, which was taken as evidence that **325** did indeed "zip-up" to provide C_{60} rather than simply fragment and recombine at the high temperature. Had this process occurred, fullerenes other than C_{60} (*e.g.*, C_{70}) would also be expected to result from the reaction. This synthesis thus represented a landmark in fullerene synthesis, albeit in very low yield and under harsh conditions. However, it does not seem practical to adapt such an inefficient synthesis towards the ultimate goal of synthesizing previously unknown fullerenes. The development of new methods and strategies to C_{60} are therefore desirable.

[201] Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295*, 1500-1503.



Scheme 73: Scott's chemical synthesis of C_{60}

9.2 Hexasubstituted Benzenes

Our approach to C_{60}, fully described in Section 1.3, uses hexakis(enynyl)benzenes as precursors to the fullerene. Hexasubstituted benzenes have also attracted considerable attention over the past two decades due to their interesting properties and potential use in such diverse applications as light-harvesting materials, discotic liquid crystals, and non-linear optical materials. They are also challenging to synthesize. The properties of, and synthetic approaches to, this type of molecule are therefore presented in this section.

For the purposes of this discussion, hexasubstituted benzenes are defined as those that have six carbon substituents bonded to a central benzene ring, with the exception of polycyclic aromatic hydrocarbons. In part due to synthetic difficulties, all six substituents are usually identical, and in cases where they do differ, the difference is usually remote from the central benzene ring. Hexasubstituted benzenes can therefore be loosely divided into four categories

based on the type of substituent (alkynyl, phenyl, alkenyl, or alkyl) bonded to the benzene ring. Those with alkynyl or phenyl substituents are by far the most common.

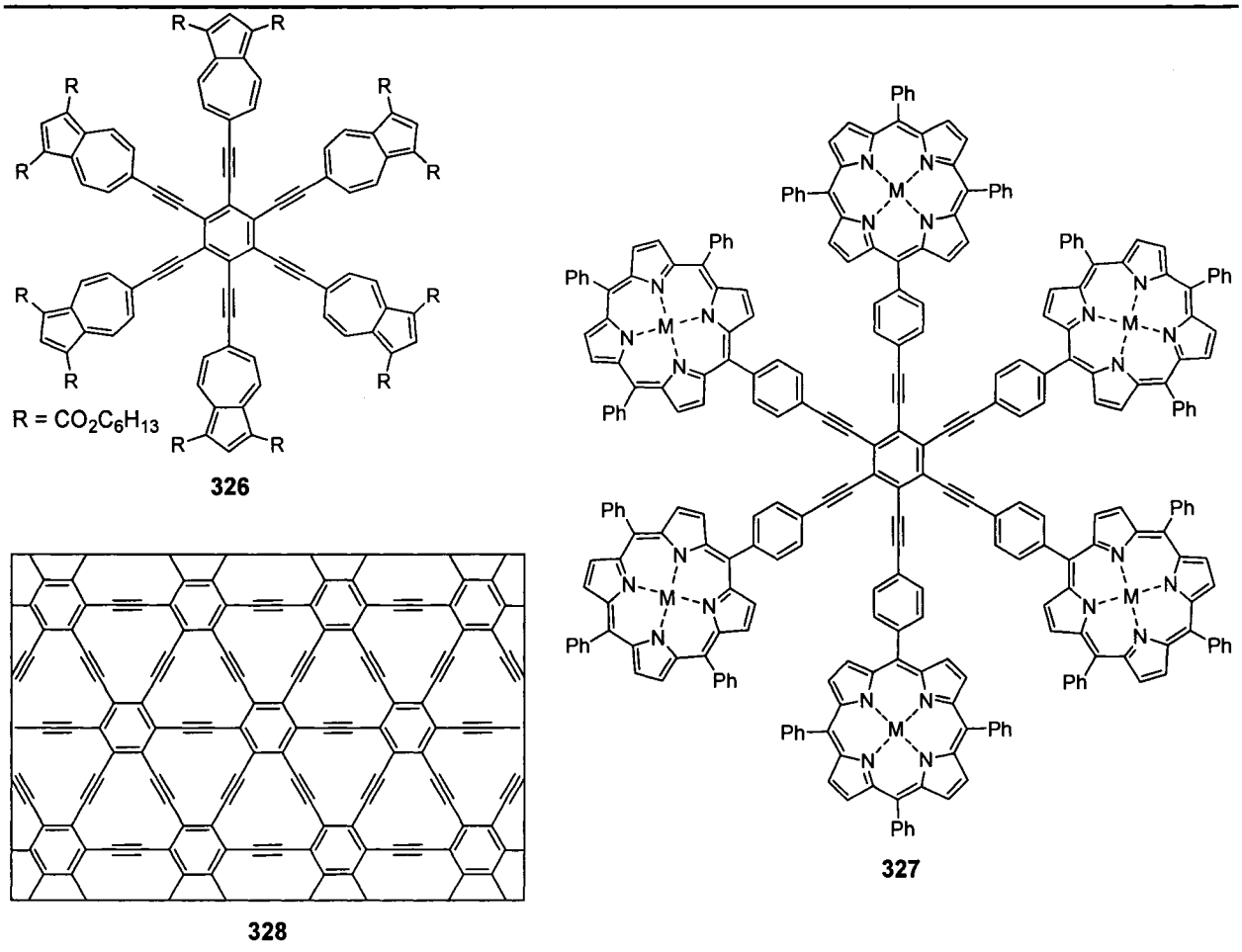


Figure 32: Representative hexa(ethynyl)benzenes

Considerable effort has been directed towards the synthesis and study of hexa(ethynyl)benzenes (Figure 32). Such compounds have exhibited fascinating properties and have several potential applications. Hexa(azulenylethynyl)benzene **326** displays unusual electrochemical and liquid crystalline behavior,[202] while the hexa(arylethynyl)benzene terminating in porphyrin moieties (**327**) mimics the "antenna complex" of chlorophyll as a light-harvesting material.[203] A substantial amount of work has also focused on the synthesis of

[202] Ito, S.; Inabe, H.; Morita, N.; Ohta, K.; Kitamura, T.; Imafuku, K. *J. Am. Chem. Soc.* **2003**, *125*, 1669-1680.
[203] Mongin, O.; Hoyler, N.; Gossauer, A. *Eur. J. Org. Chem.* **2000**, 1193-1197.

portions of graphyne (**328**), a theoretical form of carbon[204] comprised of a cross-linked network of acetylenes and benzenes.[205]

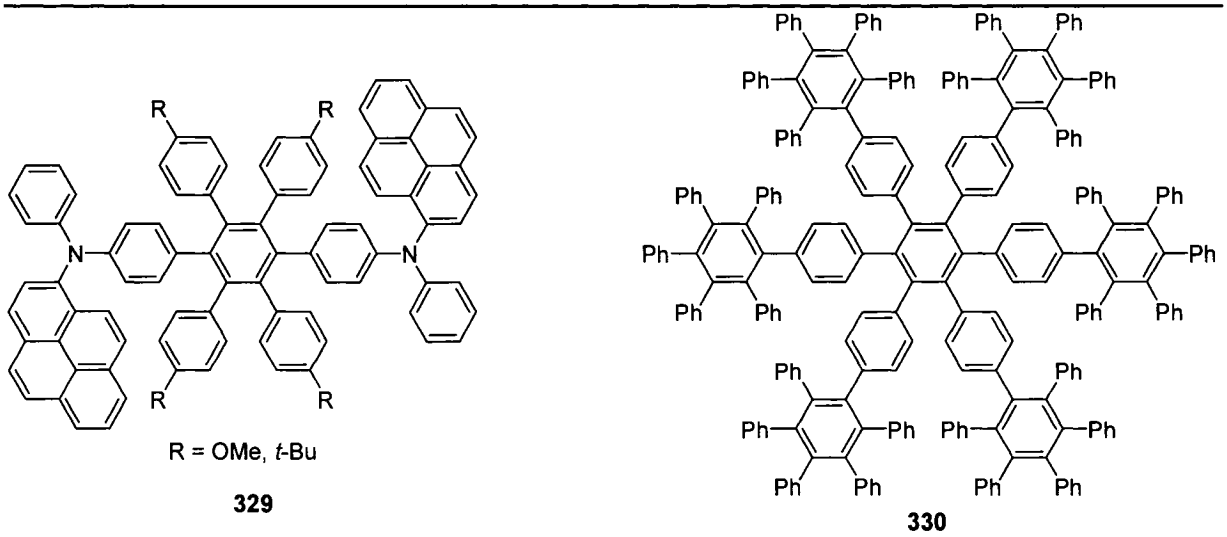


Figure 33: Representative hexa(phenyl)benzenes

Many hexa(phenyl)benzenes have also been synthesized and studied (Figure 33). Hexa(phenyl)benzene **329** containing pyrenylamine moieties has been used as the hole transporting layer in an efficient electroluminescent device and may have use in the organic light-emitting diode (OLED) industry.[206] Polyphenylene dendrimers such as **330** have been synthesized as potential precursors to "cubic graphite", a hypothetical allotrope of carbon[207] where each benzene ring is bonded to six different benzene rings.[208] Other hexa(phenyl)benzenes have found use as the anode material of lithium batteries[209] and as discotic liquid crystals.[210]

Hexa(alkenyl)- and hexa(alkyl)benzenes are substantially less common than the less saturated variants. Only two reports of hexa(alkenyl)benzenes exist and no specific properties of

[204] Baughmann, R. H.; Eckhardt, H.; Kertesz, M. *J. Chem. Phys.* **1987**, *87*, 6687-6699.
[205] (a) Haley, M. M. *Synlett* **1997**, 557-565; (b) Bunz, U. H. F.; Rubin, Y.; Tobe, Y. *Chem. Soc. Rev.* **1999**, *28*, 107-119; (c) Kehoe, J. M.; Kiley, J. H.; English, J. J.; Johnson, C. A.; Petersen, R. C.; Haley, M. M. *Org. Lett.* **2000**, *2*, 969-972; (d) Wan, W. B.; Haley, M. M. *J. Org. Chem.* **2001**, *66*, 3893-3901.
[206] Thomas, K. R. J.; Velusamy, M.; Lin, J. T.; Chuen, C. H.; Tao, Y-T. *J. Mater. Chem.* **2005**, *15*, 4453-4459.
[207] Gibson, J.; Holohan, M.; Riley, H. L. *J. Chem. Soc.* **1946**, 456-461.
[208] Shen, X.; Ho, D. M.; Pascal, R. A. Jr. *J. Am. Chem. Soc.* **2004**, *126*, 5798-5805.
[209] Bonino, F.; Brutti, S.; Piana, M.; Scrosati, B.; Brambilla, L.; Fustella, G.; Castiglioni, C.; Zerbi, G.; Zane, D.; Renouard, T.; Mathis, C. *J. Electrochem. Soc.* **2005**, *152*, A2023-A2029.
[210] Wu, J.; Watson, M. D.; Zhang, L.; Wang, Z.; Müllen, K. *J. Am. Chem. Soc.* **2004**, *126*, 177-186.

them have been investigated,[211] although it is hypothesized that they should exhibit properties similar to the hexa(alkynyl)- and hexa(phenyl)benzenes. Hexa(alkyl)benzenes are primarily synthesized as a test for new synthetic methods (discussed below) and are generally regarded as less suitable for most applications due to the greater flexibility of the substituents and the absence of extended π-systems.[212] The synthesis of all types of hexasubstituted benzenes, however, is particularly challenging and is discussed in the following paragraph.

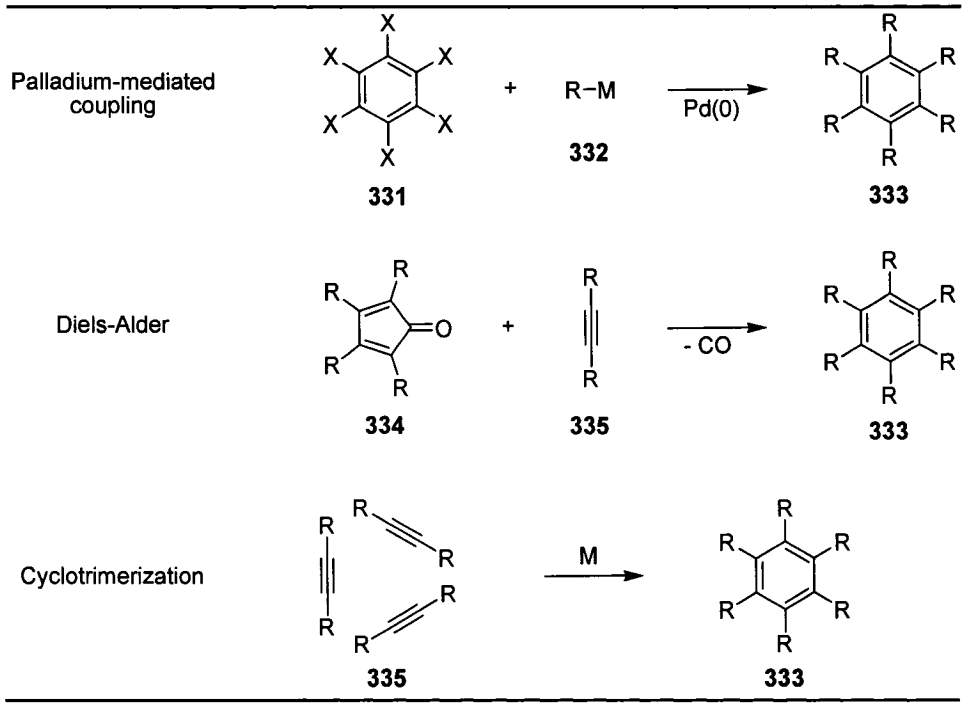


Figure 34: Primary methods for the synthesis of hexasubstituted benzenes

Three primary methods are currently available for the synthesis of hexasubstituted benzenes (Figure 34). The method most commonly employed is the palladium-mediated coupling of an organometallic (**332**) with a perhalogenated benzene (**331**). If the halogens on the benzene ring are nonequivalent, different substitution patterns can be obtained in the final product (**333**) in a controlled manner. However, due to difficulties in the synthesis of the starting perhalogenated benzene, this method usually only produces benzenes with equivalent

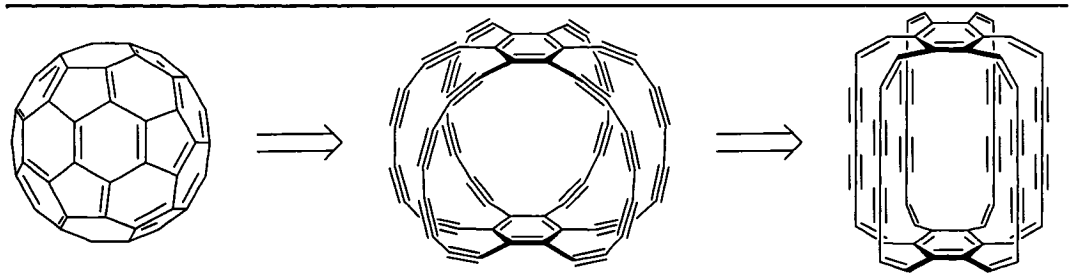
[211] (a) Stulgies, B.; Prinz, P.; Magull, J.; Rauch, K.; Meindl, K.; Rühl, S.; de Meijere, A. *Chem. Eur. J.* **2005**, *11*, 308-320; (b) Meier, H.; Hanold, N.; Kalbitz, H. *Synthesis* **1997**, 276-278.

[212] (a) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474-1475; (b) Taber, D. F.; Rahimizadeh, M. *Tetrahedron Lett.* **1994**, *35*, 9139-9140; (c) Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, *66*, 3627-3629.

substituents[202,211a] or those with a 1,3,5-tri(X)-2,4,6-tri(Y) substitution pattern.[203,213] A second common method of synthesizing hexasubstituted benzenes involves a Diels-Alder reaction between a fully substituted cyclopentadienone (**334**) with a disubstituted acetylene (**335**).[206,214] This method typically produces benzenes with a 1,2,3,4-tetra(X)-5,6-di(Y) substitution pattern, although with careful (and lengthy) assembly of the starting cyclopentadienone many other substitution patterns are also possible. The third method of synthesizing hexasubstituted benzenes involves a metal catalyzed cyclotrimerization reaction between three disubstituted acetylenes (**335**). This method is most commonly used to assemble hexa(alkyl)benzenes,[212] which are difficult to assemble *via* other methods, although is has also been used to synthesize hexa(phenyl)benzenes.[208,210] However, regioisomers are always obtained if the R groups on the acetylenes are different. A few other methods are also available for the synthesis of hexasubstituted benzenes, but are specific to the particular synthesis in which they are employed.

These three methods are highly limited and cannot produce many substitution patterns, or more importantly, benzenes with certain substituents. For example, no hexa[(*Z*)-alkenyl]benzenes have been reported, and no available method is capable of synthesizing such a species. Alternate methods for the synthesis of hexasubstituted benzenes are thus desirable. Our approach to these substrates is discussed in Section 9.3.1.

9.3 Fallis Approach to C_{60}

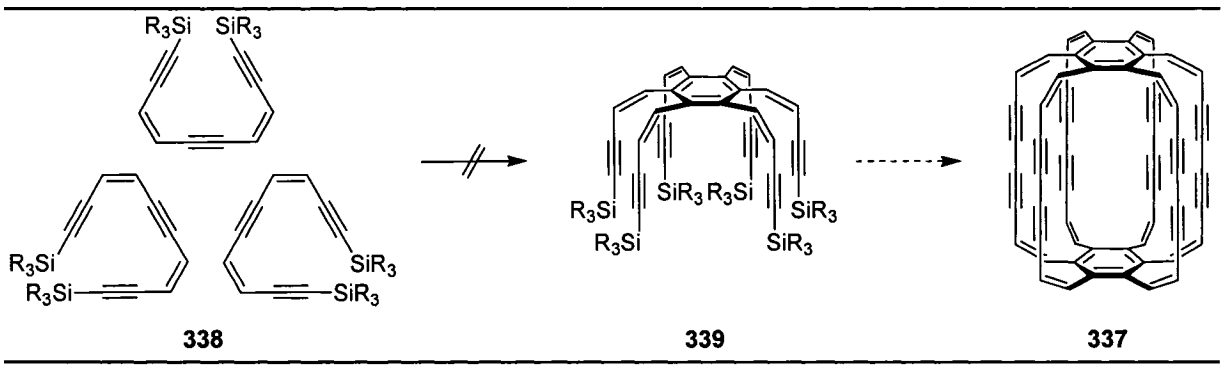


315 **336** **337**

Scheme 74: Fallis approach to C_{60}

[213] Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2001**, *3*, 2419-2421.
[214] (a) Tobe, Y.; Kubota, K.; Naemura, K. *J. Org. Chem.* **1997**, *62*, 3430-3431; (b) Tovar, J. D.; Jux, N.; Jarrosson, T.; Khan, S. I.; Rubin, Y. *J. Org. Chem.* **1997**, *62*, 3432-3433;

The Fallis approach to C_{60} is similar in concept to that used by Rubin and Tobe (Scheme 74). We believe that dehydrogenation of the styrenyl bonds in $C_{60}H_{24}$ cyclophane **337**[215] will lead to strained C_{60} cyclophane **336**, which should rearrange to the more thermodynamically stable fullerene. The absence of hydrogen on **336** and its relative similarity to C_{60} should allow it to rearrange to the fullerene under substantially more mild conditions than have been required in previous syntheses. This should permit the rearrangement to occur under normal laboratory conditions and be successful on a preparatively useful scale. The styrenyl bonds in **337** could be dehydrogenated using several methods, although we believe that the most synthetically useful protocol would be bromination of each alkene followed by the mass elimination of HBr. It is also worth noting that the addition of two additional acetylenes to each of the bridges in **337** would give $C_{84}H_{24}$, which could potentially be used to synthesize a C_{84} fullerene. Other modifications to provide larger fullerenes are also theoretically possible. The ultimate goal of this project is to demonstrate the potential of producing C_{60} on the preparative scale *via* rearrangement of a cyclophane precursor.



338 **339** **337**

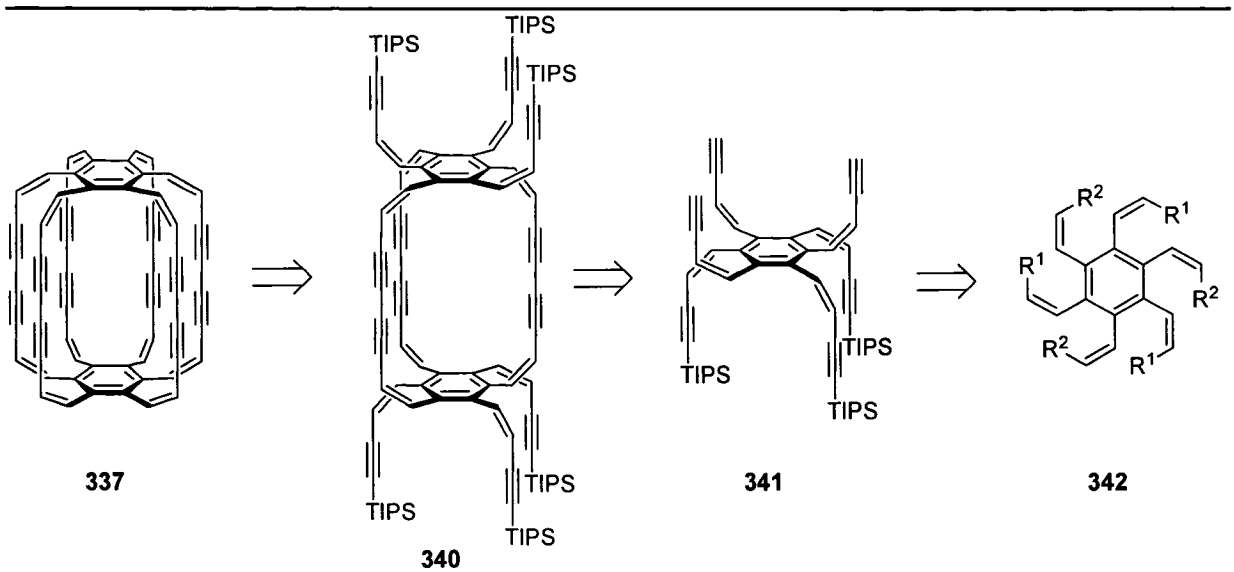
Scheme 75: Initial approach to cyclophane 337

This project had been previously investigated in the Fallis laboratory.[216] The retrosynthetic approach to cyclophane **337** used in these early studies is illustrated in Scheme 75. It was believed that cyclophane **337** would arise from a six-fold intermolecular oxidative coupling of the terminal acetylenes in the monomeric precursor **339**. However, all attempts to

[215] Cyclophane **337** does not exist as drawn in Scheme 74. Rather, the alkene bond angles of the most stable conformer of **337** are all 120°. This results in a twisted structure where the capping benzene rings are offset from one another, which in turn imparts helical chirality to the molecule. The two helical isomers interconvert through the strained conformer (**337**) shown in Scheme 74.

[216] Collins, S. K. Ph.D. Thesis, University of Ottawa, Ottawa, Canada, 2002.

synthesize hexakis[(*Z*)-enynyl]benzene **339** *via* the metal catalyzed cyclotrimerization of three bis(enynyl)alkynes (**338**) failed due to the thermal instability of the starting materials. The failure of the synthesis at such an early stage and before the key steps in the approach had been attempted was disappointing and necessitated the development of an alternative route to cyclophane **337**.

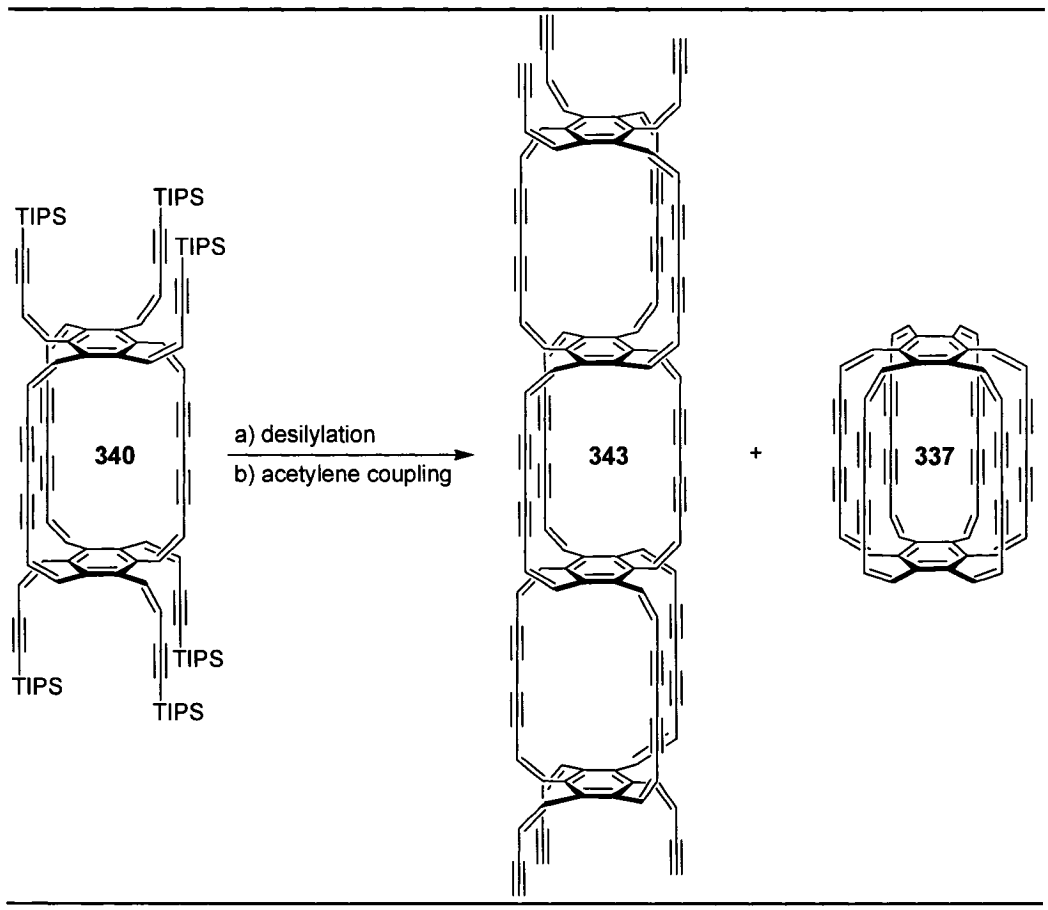


Scheme 76: Modified approach to cyclophane 337

Our modified route to cyclophane **337** made two primary improvements over the initial approach (Scheme 76). First, more reliable methods such as palladium-mediated coupling reactions would be used to synthesize the hexakis[(*Z*)-enynyl]benzene monomer (**341**) from hexasubstituted benzene **342**. As previously mentioned, there are no reports of hexa[(*Z*)-alkenyl]benzenes upon which to base our synthesis, and thus we will be required to develop a new protocol for their construction. We believe, however, that these substrates can be synthesized using known methods for the synthesis of (*Z*)-alkenes in conjunction with the palladium-mediated coupling approach previously described (Section 9.2) for the synthesis of hexasubstituted benzenes.

Second, as the key dimerization to form cyclophane **337** was anticipated to be particularly difficult, we would conduct this transformation in two steps. To accomplish this, benzenes substituted at the 1,3,5-positions with one substituent and at the 2,4,6-positions with a different substituent would be required (**342**). As illustrated in Scheme 76, intermolecular

oxidative coupling of the three terminal acetylenes of **341** would generate cyclophane **340**, which after desilylation of the remaining acetylenes could undergo a second oxidative coupling of the acetylenes to produce the desired cyclophane **337**.



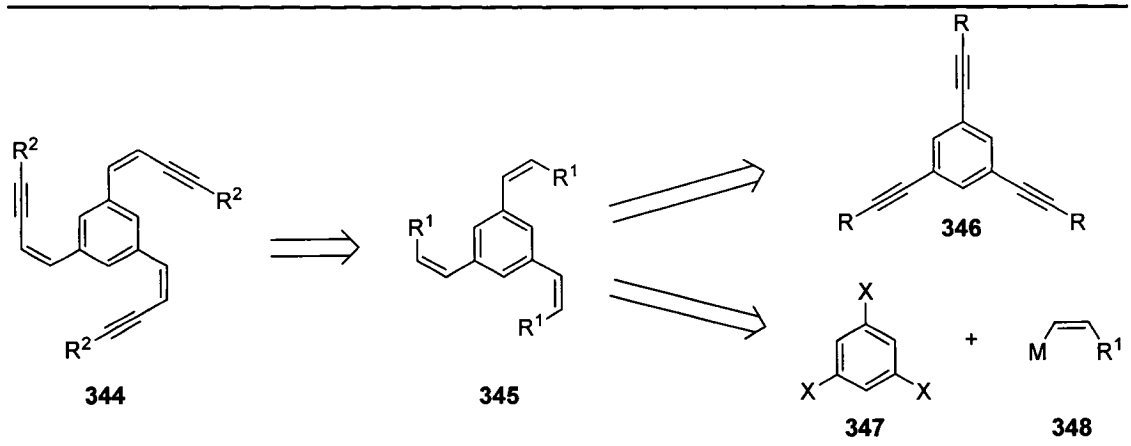
Scheme 77: Potential formation of nano-"Christmas cracker" structure 343

A potential side product may result from the final closure of cyclophane **340** (Scheme 77). If intermolecular oxidative coupling of the terminal acetylenes were to occur rather than the desired intramolecular oxidative coupling, structure **343**, resembling a nano-ladder or nano-"Christmas cracker", could result. Longer analogues could also be possible. We believe, however, that intramolecular coupling of the acetylenes to give desired cyclophane **337** will dominate, despite the rotational barriers that will be encountered as the enyne moieties of **340** organize into the correct conformation for intramolecular coupling. On the other hand, should this hypothesis prove incorrect, the "Christmas cracker" structure **343** would be highly interesting in its own respect.

9.3.1 Synthetic Strategy

Hexasubstituted benzenes with a 1,3,5-tri(X)-2,4,6-tri(Y) substitution pattern are most easily prepared *via* palladium-mediated coupling reactions, as described in Section 9.2. This method, however, would require three identical reactions (*e.g.*, those at the 1,3,5-positions) to be conducted on the same molecule. Practically, this must be conducted in one reaction flask. We anticipated that this would be a particularly challenging aspect of this synthesis. For example, a single reaction that yields 80% would yield only 51% of the desired product when conducted three times on the same molecule. As well, the substrates used in our synthesis would primarily be hydrocarbons with no polar functionalities, and so separation of the product from the byproducts would be extremely difficult on a preparative scale.

We therefore chose to conduct several test reactions on 1,3,5-trisubstituted benzenes to identify those reactions that would provide acceptable selectivity for our synthesis. As well, we wished to distinguish between those reactions that generally gave poor selectivity and those that were only problematic when conducted on hexasubstituted benzenes. In other words, we did not want to expend considerable effort on a particular reaction involving a hexasubstituted benzene when the reaction does not even work on simpler substrates. Reactions that failed on trisubstituted benzenes would not be expected to succeed on hexasubstituted benzenes, while those that were successful on trisubstituted benzenes could likely be adapted to work on the hexasubstituted variant. Additionally, we considered the selectivity of the reaction (*e.g.*, *trans vs. cis* isomers) to be more important than yield in these test reactions, as the yield could likely be optimized on our actual substrates. We also chose not to test the intermolecular dimerization of the acetylenes to yield the 1,3,5-trisubstituted variation of cyclophane **337** as the dynamics of this particular reaction would change considerably when six substituents were present.



Scheme 78: Retrosynthetic approach to 1,3,5-tris(enynyl)benzene 344

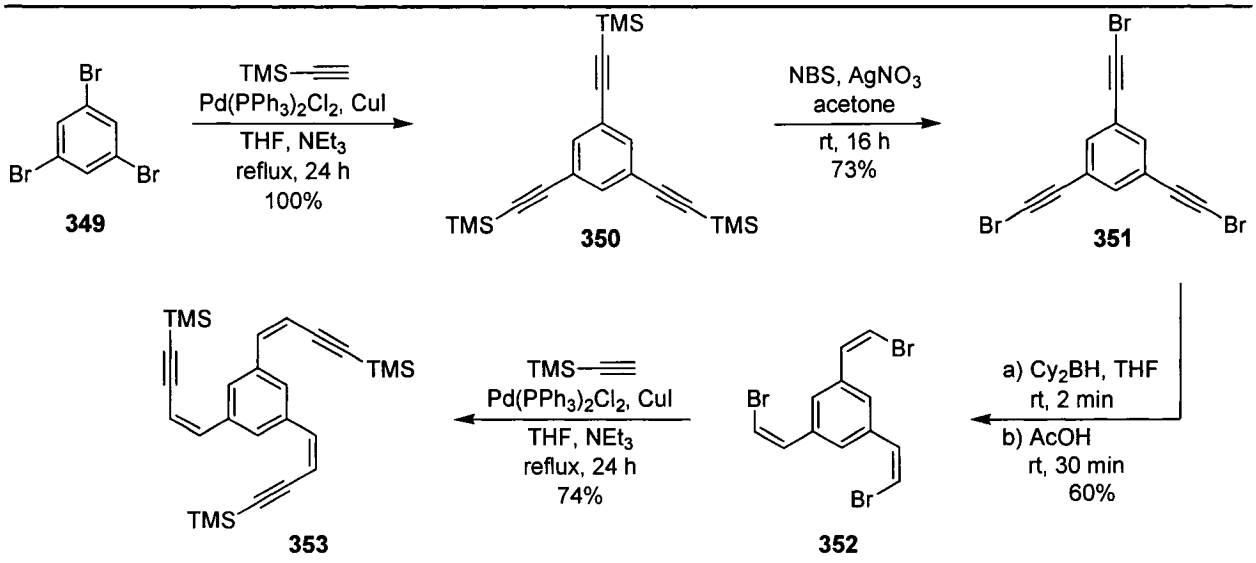
Our retrosynthetic approach to 1,3,5-tris(enynyl)benzenes, which could easily be adapted for use with the hexasubstituted variants, is shown in Scheme 78. The aryl enyne moieties of **344** could be accessed from tri[(*Z*)-alkenyl]benzene **345** *via* a cross coupling reaction with a suitable acetylene derivative. This transformation would require the R^1 substituents of **345** to be either halogen or metal atoms. We envisioned two general approaches to tri[(*Z*)-alkenyl]benzene **345**. In the first, the (*Z*)-alkene moiety would arise from the reduction of an acetylene derivative. The required R^1 substituent could either be present before the reduction (*i.e.*, $R = R^1$) or be added during the reduction reaction. The second route to **345** involves the coupling of an aryl halide (**347**) with a suitably substituted (*Z*)-alkene (**348**). A few other routes to the (*Z*)-alkenes that do not fit into these general categories are also available, as well as a few more direct routes to the aryl enyne moieties, and these will be discussed as they arise. For clarity, the results of our work on 1,3,5-trisubstituted benzenes are organized based on the synthetic target rather than on the synthetic method used.

10 Results and Discussion

Chronologically speaking, our confidence and ambition led us to begin our studies on hexasubstituted benzenes before we had conducted any model studies on trisubstituted benzenes. However, after encountering significant difficulty in the synthesis we realized a series of model studies would be an appropriate course of action. For clarity and organizational purposes, our results are not presented in chronological order. Rather, our work with model compounds will be presented first, followed by our work on hexasubstituted benzenes, which will include a discussion of our initial, pre-model studies, results.

10.1 Model Studies on 1,3,5-Trisubstituted Benzenes

10.1.1 Syntheses of 1,3,5-tris[(Z)-2-halovinyl]benzenes

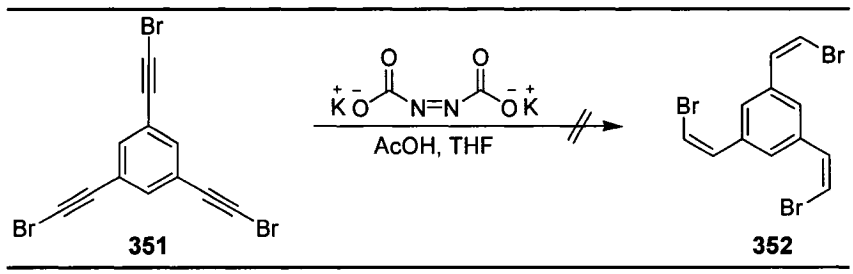


Scheme 79: Synthesis of 1,3,5-tris(enynyl)benzene 353

We initially sought to synthesize tris[(*Z*)-bromovinyl]benzene **352** *via* the reduction of the corresponding aryl bromoacetylenes (**351**) (Scheme 79). Thus, a Sonogashira reaction of 1,3,5-tribromobenzene (**349**) with TMS-acetylene under standard conditions yielded the protected aryl acetylenes in quantitative yield, which were converted to the aryl bromoacetylenes

(**350**) in 73% yield upon exposure to NBS and $AgNO_3$. Reduction of the triple bond *via* hydroboration with dicyclohexylborane (Cy_2BH) followed by protonolysis with AcOH then gave the desired (*Z*)-vinylbromides (**352**) in 60% yield.[217] A Sonogashira reaction of **353** with TMS-acetylene then generated the protected aryl enynes in 74% yield.

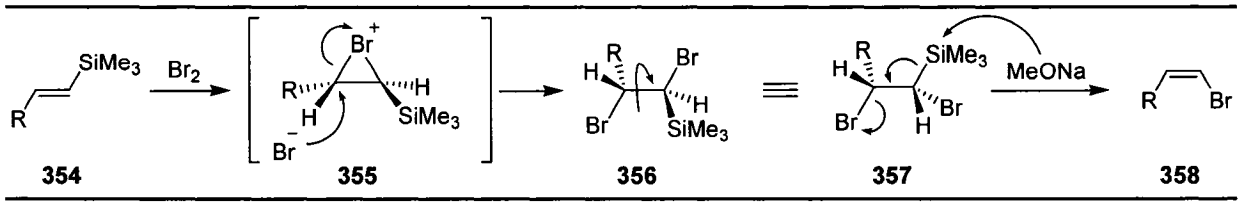
Unfortunately, when the synthesis was repeated to provide additional material, the hydroboration-protonolysis sequence to produce **352** failed. Attempts to recreate the initial result using fresh Cy_2BH, changing the temperature or quantity of AcOH, and using $(sia)_2BH$ in place of Cy_2BH were all unsuccessful. In many cases the desired product (**352**) was present in the reaction, but could not be separated from multiple unidentified byproducts. It appeared that the cleanliness of the initial reaction was largely serendipitous, and so we searched for an alternate and more reliable synthesis.



Scheme 80: Diimide reduction of bromoacetylenes to (Z)-vinylbromides

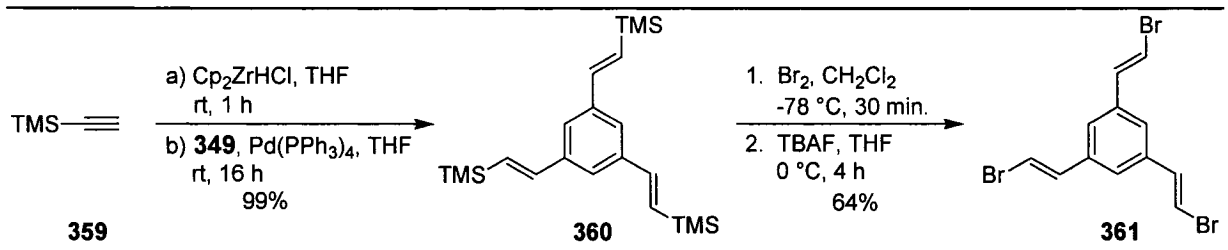
The only other reported method for the reduction of bromoacetylenes to (*Z*)-vinylbromides is that using diimide generated *in situ* from dipotassium azodicarboxylate (Scheme 80).[218] However, this method provided inseparable product mixtures containing unreduced bromoacetylenes, the desired (*Z*)-vinylbromides, as well as the corresponding alkyl bromides. The failure of this reaction and the reproducibility problems of the hydroboration procedure meant that we required an alternate approach to synthesizing the (*Z*)-vinylbromides.

[217] (a) Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064-6067; (b) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068-4071.
[218] Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985-3988.



Scheme 81: Conversion of (E)-vinylsilanes to (Z)-vinylbromides

It has been reported that bromination of a vinylsilane followed by formal elimination of TMS-Br will produce the vinylbromide with overall inversion of the alkene geometry (Scheme 81).[219] As illustrated, *trans*-bromination of (*E*)-vinylsilane **354** proceeds through the standard bromonium ion intermediate (**355**) to provide dibromide **356**. Elimination of TMS-Br then occurs through the *anti* conformation (**357**) to provide the (*Z*)-vinylbromide (**358**). We therefore sought to synthesize aryl (*E*)-vinylsilanes as precursors to the desired aryl (*Z*)-vinylbromides.

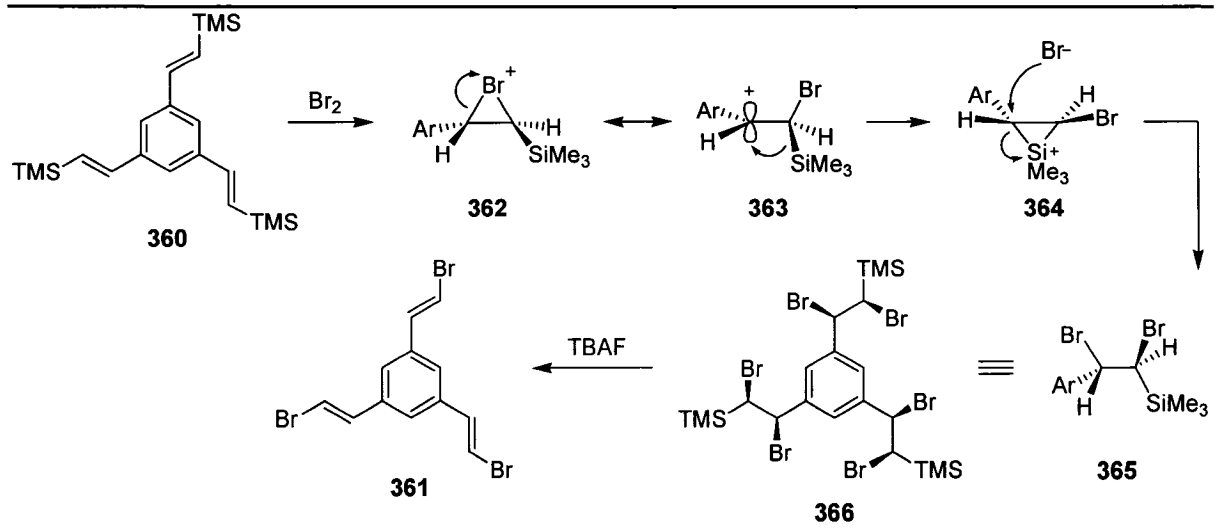


Scheme 82: Attempted synthesis of aryl (Z)-vinylbromides

The aryl (*E*)-vinylsilanes were efficiently synthesized as shown in Scheme 82. A hydrozirconation of TMS-acetylene with Cp_2ZrHCl provided the (*Z*)-vinylzirconium, which smoothly underwent a palladium-mediated coupling with 1,3,5-tribromobenzene (**349**) to provide the (*E*)-vinylsilanes (**360**) in nearly quantitative yield. To our surprise, bromination of the alkenes followed by formal elimination of TMS-Br with TBAF yielded exclusively (*E*)-vinylbromides instead of the expected (*Z*)-vinylbromides. An extensive literature search subsequently revealed that when a cation-stabilizing substituent, such as a phenyl ring, is attached to the vinylsilane the bromination-elimination sequence proceeds with overall retention of the alkene geometry, as we had observed.[220]

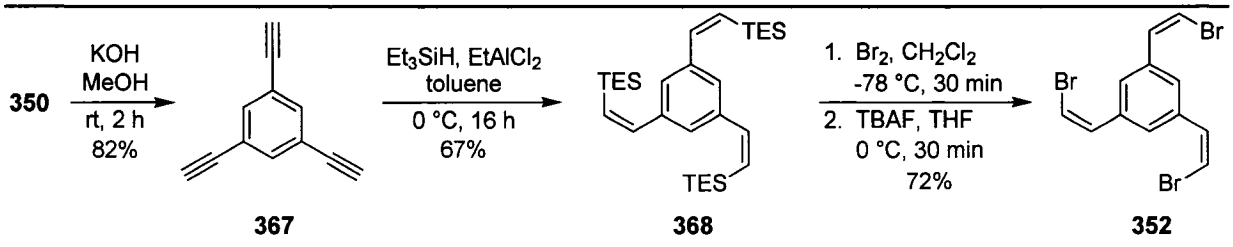
[219] (a) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100-1106; (b) Ashe, A. J. III; Fang, X.; Kampf, J. W. *Organometallics* **1999**, *18*, 466-473; (c) Takayama, Y.; Hanazawa, H.; Andou, T.; Muraoka, K.; Ohtani, H.; Takahashi, M.; Sato, F. *Org. Lett.* **2004**, *6*, 4253-4256; (d) Brook, M. A.; Neuy, A. *J. Org. Chem.* **1990**, *55*, 3609-3616.

[220] Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424-4431.



Scheme 83: Mechanism to explain the conversion of (E)-vinylsilanes to (E)-vinylbromides

A potential explanation for this observation is given in Scheme 83. Bromination of an alkene of **360** will likely generate a bromonium ion (**362**).[221] However, the presence of a β-silyl group and α-phenyl group renders the benzylic carbocation (**363**) more stable than the bromonium ion. Slight rotation of the carbon-carbon bond in **363** then generates a silicon-stabilized cationic species (**364**), which upon attack by bromide affords dibromide **365**, formally the product of *cis*-bromination. Elimination of TMS-Br with TBAF then yields the observed (*E*)-vinylbromides (**361**). If this was indeed the case, (*Z*)-vinylsilanes should provide (*Z*)-vinylbromides. We therefore turned our attention to synthesizing the all-(*Z*) analogue of **360**.

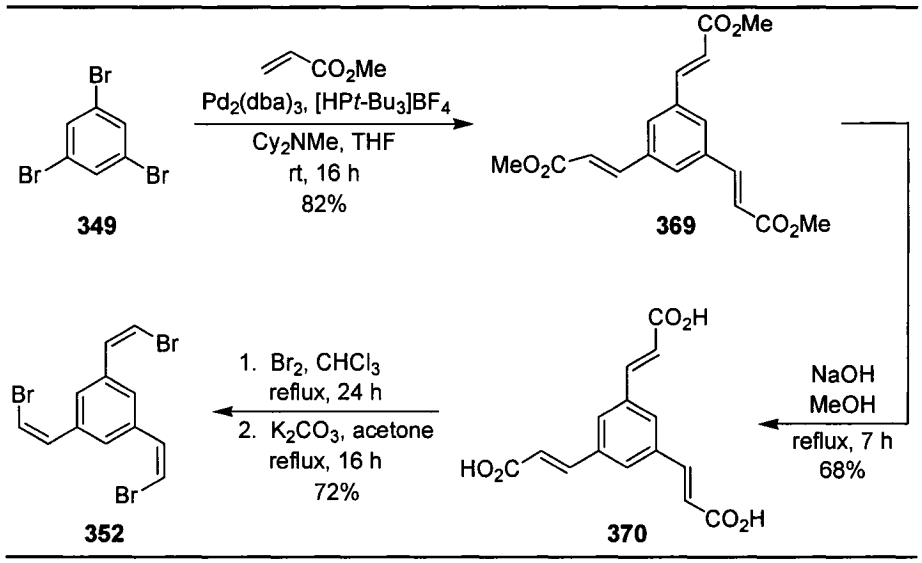


Scheme 84: Synthesis of (Z)-vinylbromides from (Z)-vinylsilanes

Our route to aryl (*Z*)-vinylsilanes is shown in Scheme 84. Removal of the trimethylsilyl protecting groups of **350** in basic methanol yielded the terminal acetylenes (**367**) in 82% yield.

[221] The mechanism may not proceed through a bromonium ion, but rather produce the benzylic carbocation directly.

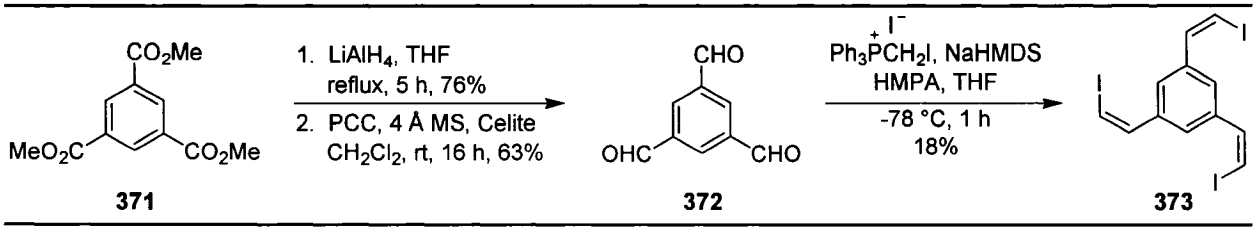
A *trans*-hydrosilylation[222] of the acetylenes using Et_3SiH and catalytic $EtAlCl_2$ then provided exclusively (*Z*)-vinylsilane (**368**). Bromination of the alkenes followed by formal elimination of TMS-Br with TBAF then provided the expected (*Z*)-vinylbromides in 72% yield and 100% in the (*Z*)-configuration.



Scheme 85: An alternative synthesis of (Z)-vinylbromide 352

We also predicted that if the benzylic carbocation could be destabilized relative to the bromonium ion that the expected inversion of alkene geometry would occur in the bromination-elimination sequence. A literature search suggested that this hypothesis was true, in that bromination of (*E*)-cinnamic acid followed by decarboxylative elimination of bromide provided exclusively (*Z*)-vinylbromide.[223] We therefore chose to synthesize tricarboxylic acid **370** (Scheme 85). A three-fold Heck reaction[224] between 1,3,5-tribromobenzene (**349**) and methyl acrylate generated triester **369** in 82% yield, which upon hydrolysis with NaOH yielded tricarboxylic acid **370**. Bromination of the alkenes followed by decarboxylative elimination of bromide with K_2CO_3 then yielded (*Z*)-vinylbromide **352** in 72% yield. With this success we now had in hand two reliable methods for the synthesis of (*Z*)-vinylbromides.

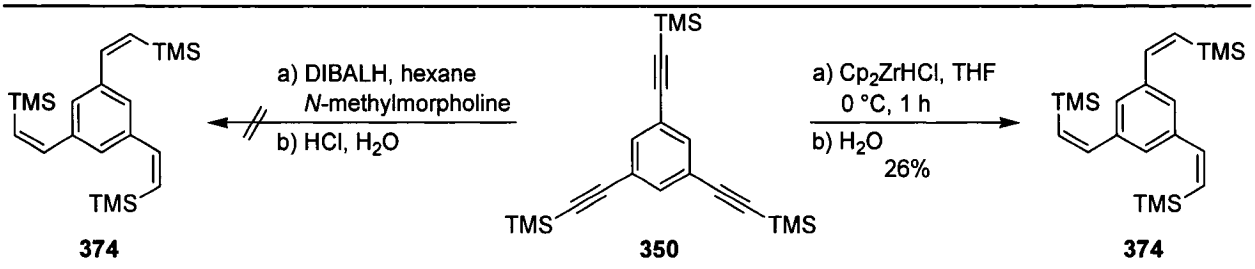
[222] Sudo, T.; Asao, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2494-2499.
[223] (a) Galamb, V.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 2965-2968; (b) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 4043-4052.
[224] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000.



Scheme 86: Synthesis of aryl (Z)-vinyliodide 373

A potential alternate route to aryl (*Z*)-vinylhalogens is a Wittig reaction between an appropriate ylide and trialdehyde **372** (Scheme 86). The required trialdehyde **372** was synthesized from triester **371** *via* reduction with $LiAlH_4$ and subsequent oxidation with PCC. Fortunately, exposure of trialdehyde **372** to Ph_3PCHI generated the desired aryl (*Z*)-vinyliodide in 18% yield and approximately 95:5 selectivity for the (*Z*)-isomer. We were delighted with the high selectivity of the reaction as considerably lower selectivities are usually reported,[225] and anticipated that the unusually low yield could be optimized during our work with hexasubstituted benzenes.

10.1.2 Syntheses of 1,3,5-tris[(Z)-2-silylvinyl]benzenes

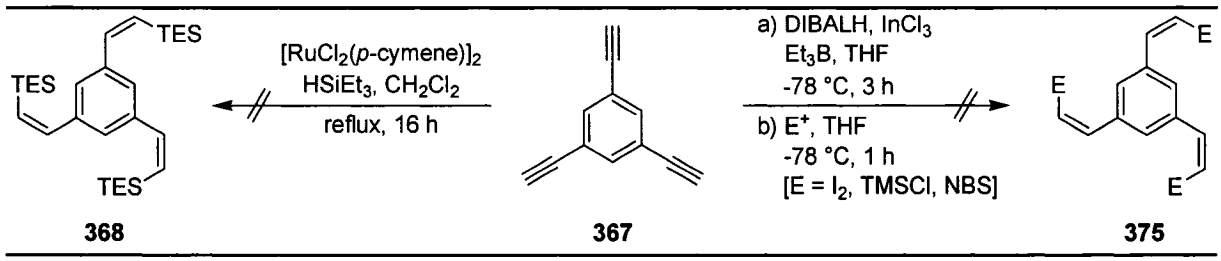


Scheme 87: Reduction of TMS-acetylenes to (Z)-vinylsilanes

The bromination of vinylsilane **368** was remarkably facile compared to that of the corresponding vinyl carboxylic acid (**370**), or other alkenes in general, which was likely due to the greater electron density of the double bond of the vinylsilane. This rate difference suggested that we could selectively brominate vinylsilanes in the presence of several other alkenes, thereby making this procedure highly useful in the synthesis of heavily functionalized hexasubstituted benzenes. We therefore searched for additional methods for the synthesis of (*Z*)-vinylsilanes.

[225] (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174; (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021-4024.

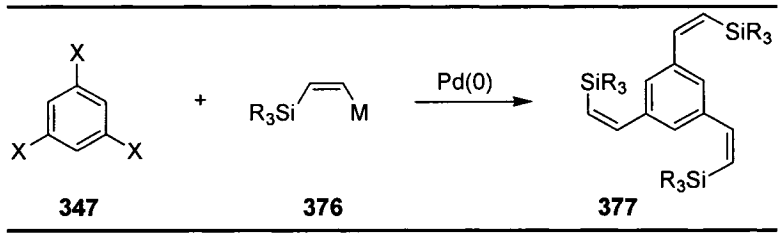
One potential route to aryl (*Z*)-vinylsilanes involves the reduction of aryl TMS-acetylene **350** (Scheme 87). Unfortunately, a hydroalumination-protonolysis protocol[220,226] yielded only complicated mixtures in which the desired product (**374**) could not be detected. A hydrozirconation-protonolysis of the acetylenes of **350**, however, did produce the (*Z*)-vinylsilanes in 26% yield, with the majority of the remaining mass balance being accounted for by products in which only one or two of the acetylenes had been reduced. Repeated attempts to force the reaction to completion were met with little success.



Scheme 88: Reduction of aryl acetylenes to (Z)-vinylsilanes or (Z)-vinylhalides

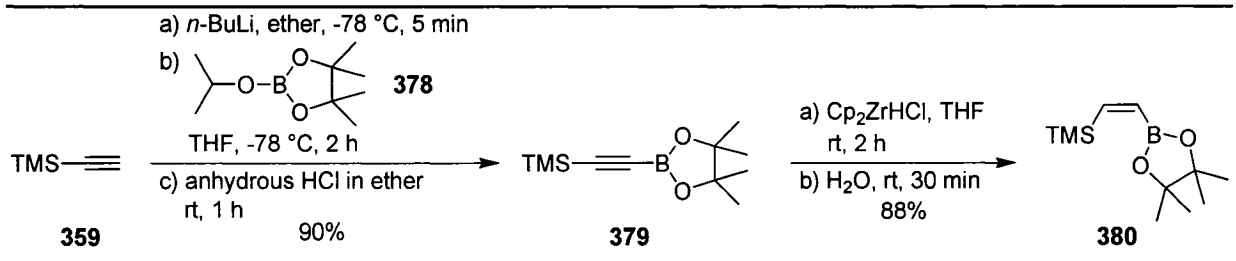
We also attempted to synthesize aryl (*Z*)-vinylsilanes *via* a ruthenium-catalyzed hydrosilylation protocol (Scheme 88).[227] Oddly, in contrast to the literature report, the only product isolated from the reaction was the terminal aryl alkene resulting from formal addition of H_2 across the acetylene. A hydroindanation was similarly unsuccessful. Despite literature reports of selectivities greater than 95:5 favoring the (*Z*)-alkene for hydroindanations of aryl acetylenes,[228] we consistently obtained a 90:10 mixture of *E*:*Z* alkenes using the same procedure. The *E*:*Z* ratio was independent of the electrophile used (I_2, NBS, TMSCl) and of several other reaction parameters that were varied. The reason for this reversal of selectivity is not clear as the presence of the additional acetylenes on our molecule should not have had such a dramatic effect (no electronic effect of aryl substitution was found in the original report).

[226] (a) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214-2215; (b) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623-4628; (c) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520-3526.
[227] Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887-1889.
[228] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993-2995.



Scheme 89: A palladium-mediated coupling approach to aryl (Z)-vinylsilanes

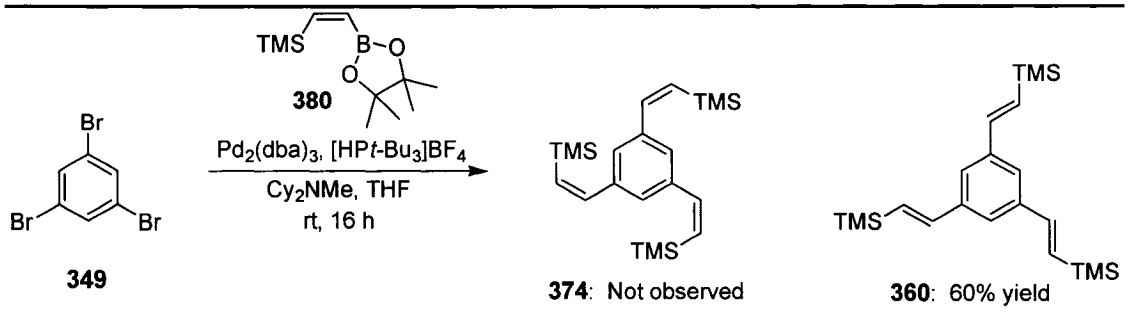
A conceptually different approach to aryl (*Z*)-vinylsilanes involves a palladium-mediated coupling of a 1,3,5-trihalobenzene (**347**) with a suitably substituted (*Z*)-vinylsilane (**376**) (Scheme 89). Although in theory we could use a 1,3,5-trimetallobenzene and a vinylhalogen as the coupling partners, the presence of three metals around an aromatic ring did not seem practical, particularly on hexasubstituted benzenes. A literature search revealed vinylboronate **380** as the only suitable coupling partner for a palladium-mediated coupling with an aryl halide, which we synthesized using literature procedures (Scheme 90).[229] Thus, deprotonation of TMS-acetylene followed by the sequential addition of isopropylpinacol boronate **378** and anhydrous HCl afforded the desired alkynylboronate **379** in 90% yield, which was reduced to the desired alkene (**380**) using a hydrozirconation-protonolysis protocol. Interestingly, the alkene of **380** exhibited a coupling constant of 18.9 Hz, strongly suggesting a *trans*-configuration about the alkene. However, the *trans* analogue[230] of **380** exhibits a coupling constant of 21.8 Hz, indicating that we had indeed synthesized the desired *cis* isomer.



Scheme 90: Synthesis of vinylboronate 380

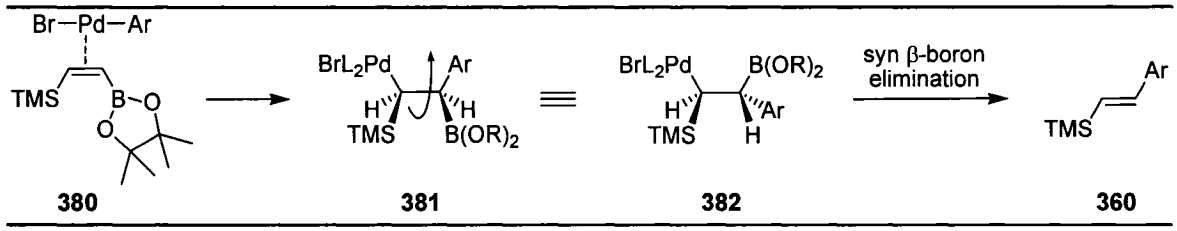
[229] (a) Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871-6873; (b) Deloux, L.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Srebnik, M. *J. Am. Chem. Soc.* **1994**, *116*, 10302-10303; (c) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631-2634.

[230] Pereira, S.; Srebnik, M. *Organomet.* **1995**, *14*, 3127-3128.



Scheme 91: Suzuki coupling reaction of 380 using Fu's conditions

We then turned our attention to the Suzuki coupling of **380** with 1,3,5-tribromobenzene (Scheme 91). Remarkably, using the modern conditions of Fu,[231] the major product of the reaction was aryl (*E*)-vinylsilane **360** and not the expected aryl (*Z*)-vinylsilane **374**. No trace of the (*Z*) isomer was present in the crude reaction mixture. To the best of our knowledge, the clean isomerization of an alkene during a Suzuki coupling has never been observed, although Buchwald has reported that the Suzuki coupling of vinylboronic acids at high temperature (60 – 100 °C) produced mixtures of (*E*) and (*Z*) isomers.[232] He solved this problem by conducting the reaction at 40 °C. The low temperature of our reaction and the complete absence of (*Z*)-isomer suggested that an alternative process was occurring in our case.



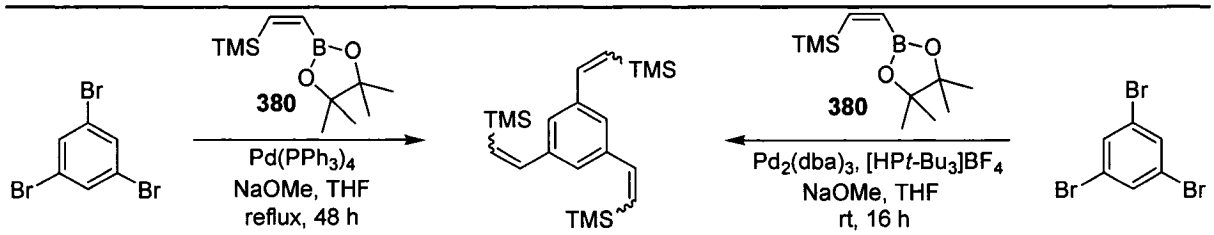
Scheme 92: Heck reaction explanation for formation of exclusively (E)-vinylsilane

To explain our results, we do not believe that a Suzuki coupling is occurring in our reaction. Rather, we believe that the alkene of **380** is undergoing Heck reaction with tribromobenzene **349**. As illustrated in Scheme 92, after oxidative insertion of palladium into the aryl-bromide bond, carbopalladation with the alkene of **380** would generate **381**, which after simple rotation of the carbon-carbon bond would give **382**. An unusual *syn* β-boron elimination would then generate the observed (*E*)-vinylsilane. The absence of any product resulting from

[231] Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295-4298.
[232] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

syn β-hydride elimination can be rationalized on the grounds that this would require the TMS and aryl groups to be co-planar, which is an arguably disfavorable arrangement.

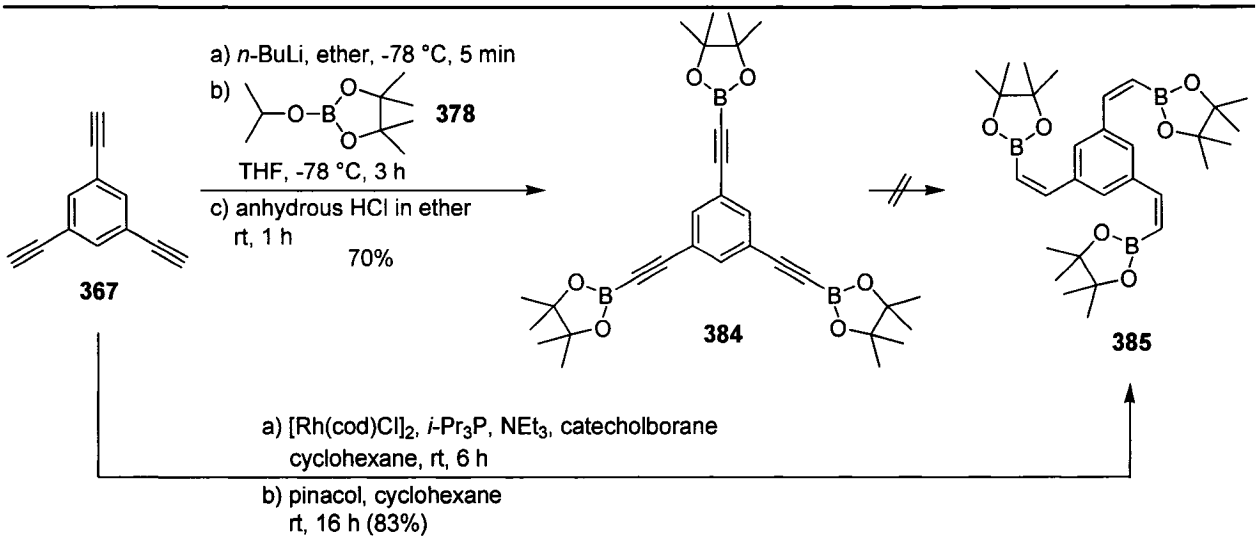
If a Heck reaction was indeed occurring instead of a Suzuki coupling, sufficiently increasing the nucleophilicity of the carbon-boron bond should favor the Suzuki reaction. This is usually accomplished in the Suzuki reaction *via* the addition of a fluoride or oxygen-based nucleophilic base. As the presence of silicon precluded the addition of fluoride ion to our reaction, we chose to use NaOMe. Gratifyingly, the Suzuki coupling of **349** and **380** in refluxing THF using NaOMe as base and $Pd(PPh_3)_4$ produced exclusively (*Z*)-vinylsilane with no trace of (*E*) isomer (Scheme 93). However, some aryl bromide always remained unreacted, likely as a result of the rather unsophisticated reaction conditions. We therefore chose to substitute NaOMe for Cy_2NMe in Fu's protocol, but to our disappointment this resulted in a mixture of both (*Z*) and (*E*)-vinylsilanes! At this point in time our frustration with this reaction led us to pursue other syntheses; however, a solution to this troublesome coupling reaction was eventually found and is presented in Section 10.2.



Scheme 93: Suzuki reactions using NaOMe as base

10.1.3 Syntheses of 1,3,5-tris[(Z)-2-metallovinyl]benzenes

Palladium-mediated coupling reactions usually require aryl or vinyl halide and organometallic components. Aryl (*Z*)-vinylmetals would therefore also be highly useful in our synthesis. These species could in theory arise *via* formation of a Grignard reagent or lithium-halogen exchange of (*Z*)-vinylbromide **352**, but it would also be useful to have more direct routes to these species. The reactivity of many organometallics limits their utility; however, organoboron compounds are relatively stable and are highly useful in palladium-mediated coupling reactions. Our synthesis of aryl (*Z*)-vinylboron **385** is presented in Scheme 94.



Scheme 94: Synthesis of aryl (Z)-vinylboron 385

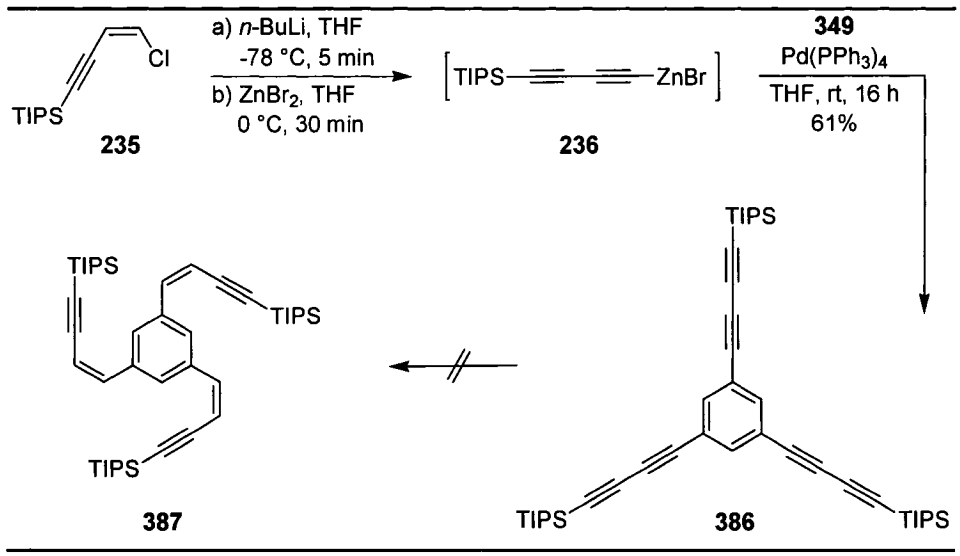
We initially attempted to synthesize aryl (*Z*)-vinylboron **385** *via* reduction of the acetylenes of alkynylboronate **384**, which was synthesized from triacetylene **367** using the same procedure we had employed in the synthesis alkynylboronate **379**. Unfortunately, conditions could not be found to reduce the alkynylboronates to (*Z*)-vinylboronates (**385**). An attempted hydrogenation[233] produced multiple products, while a hydrozirconation-protonolysis procedure[229a,b] resulted primarily in deborylation to produce the terminal acetylene, in stark contrast to the analogous reduction of TMS-substituted alkynylboronate **379**. However, we soon discovered that a rhodium-catalyzed *trans*-hydroboration[234] of triacetylene **367** provided the desired aryl (*Z*)-vinylboronate (**385**) in 83% yield. This highly efficient procedure streamlined our synthesis of **385** and is the only known *trans*-hydroboration protocol.

10.1.4 Direct routes to aryl enynes

A few more direct routes to aryl (*Z*)-enynes were also investigated. The first, an ambitious selective hydrogenation of a diacetylene, is shown in Scheme 95. The required TIPS-protected aryl diacetylene **386** was synthesized in 61% yield *via* a three-fold Negishi coupling between zinc acetylide **236** and 1,3,5-tribromobenzene (**349**). We optimistically believed that the TIPS groups would sterically shield the acetylenes bonded to silicon and allow those adjacent

[233] Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635-2638.
[234] Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990-4991.

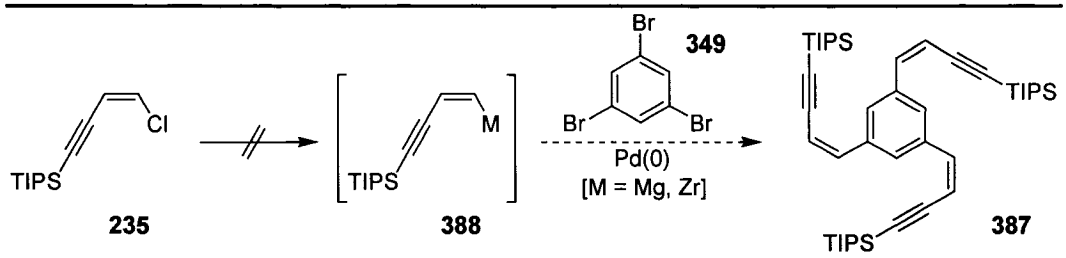
to the aromatic ring to be selectively hydrogenated to (*Z*)-alkenes. However, all attempts at this reaction led to complex mixtures of products in which the desired product **387** could not be detected.



Scheme 95: Attempted hydrogenation of diacetylenes to provide aryl enynes

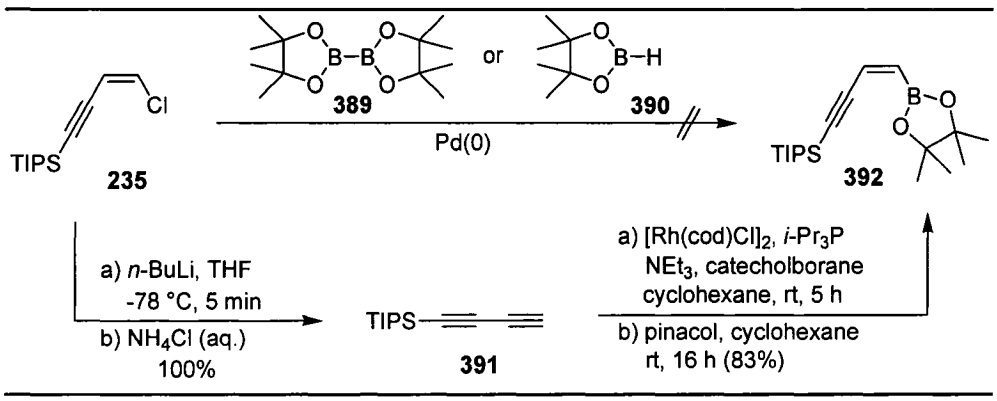
A more promising direct route to aryl (*Z*)-enynes is depicted in Scheme 96. If chloroenyne **235** could be converted to metalloenyne **388** it could undergo a palladium-mediated coupling with 1,3,5-tribromobenzene (**349**) to provide the aryl (*Z*)-enyne (**387**). Typically we synthesize such organometallics *via* a lithium-halogen exchange – metal quench procedure; however, this results in elimination of HCl from chloroenyne **235** to generate the terminal acetylene (*e.g.*, Scheme 95). We therefore attempted to form the organomagnesium (Grignard) or zirconium species directly *via* an oxidative insertion mechanism. An *in situ* palladium-mediated coupling reaction with **349** would then provide aryl enyne **387**. Unfortunately, neither organometallic was successfully formed. The attempted formation of Grignard reagent using Rieke magnesium resulted in elimination of HCl from chloroenyne **235** to generate the terminal acetylene, while the attempted formation of the organozirconium using Cp_2Zr provided only chloroenyne **235** upon workup.[235]

[235] Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039-11040.



Scheme 96: Attempted synthesis of metalloenyne 388

An alternative metalloenyne could be borylenyne **392** (Scheme 97). We initially attempted to synthesize this species *via* a palladium-mediated coupling between chloroenyne **235** and bis(pinacol)diborane (**389**)[236] or pinacolborane (**390**),[237] but in all cases only starting material was isolated from the reaction. Instead, chloroenyne **235** was converted to the terminal acetylene (**391**) *via* elimination of HCl with *n*-BuLi. Terminal acetylene **391** then underwent a rhodium-catalyzed *trans*-hydroboration[234] to provide the desired borylenyne **392** in 83% yield. Unfortunately, preliminary Suzuki couplings between 1,3,5-tribromobenzene and borylenyne **392** were unsuccessful. A more efficient coupling partner was found while this chemistry was in progress and is discussed in Section 10.2.



Scheme 97: Synthesis of borylenyne 392

We now had in hand several methods of synthesizing (*Z*)-vinylbromides from (*Z*)-vinylsilanes, as well as a useful approach to (*Z*)-vinylboronates. Perhaps more importantly, we had determined that several seemingly appealing reactions were unsuitable on our substrates,

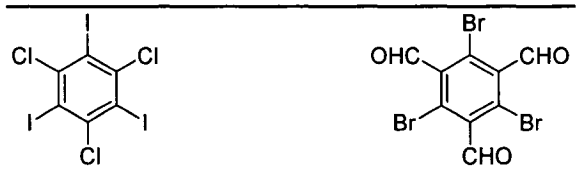
[236] (a) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541-543; (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510; (c) Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729-3732.

[237] (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458-6459; (b) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268-9271.

thereby eliminating numerous potential synthetic routes and their associated frustrations from our work on hexasubstituted benzenes. We therefore felt well prepared to begin our work on hexasubstituted benzenes.

10.2 Hexasubstituted Benzenes

The hexasubstituted benzenes in our synthesis would primarily be prepared using palladium-mediated coupling reactions, as described earlier in Section 9.2, as well as those reactions detailed in Section 10.1. Two potentially useful starting materials for this route have been reported (Figure 35). 1,3,5-Trichloro-2,4,6-triiodobenzene (**393**) has been used by Tobe to synthesize hexa(ethynyl)benzenes *via* Sonogashira and Negishi reactions with substituted acetylenes.[238] However, the yield of desired product was often low, and with some substituted acetylenes the iodide and chloride substituents of **393** exhibited similar reactivity, thereby making it difficult to reliably attain the desired substitution pattern. A more suitable starting material appeared to be 1,3,5-tribromobenzene-2,4,6-tricarbaldehyde (**394**), which has been used in the synthesis of several hexa(ethynyl)benzenes.[239] It is a particularly useful starting material as the bromides can be utilized in palladium-mediated coupling reactions, while the aldehydes can be employed in Wittig reactions or converted to terminal acetylenes, which can subsequently be converted to useful alkenes.



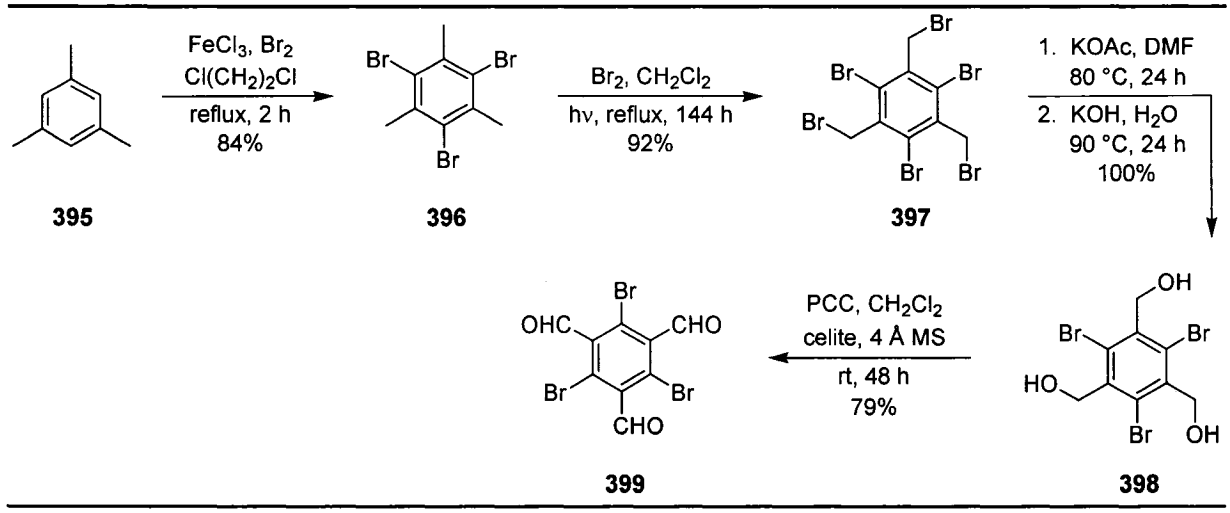
393 **394**

Figure 35: Potential starting materials

We synthesized 1,3,5-tribromobenzene-2,4,6-tricarbaldehyde using a modified literature procedure (Scheme 98).[239b] Beginning with 1,3,5-trimethylbenzene (**395**), bromination of all

[238] Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2001**, *3*, 2419-2421.
[239] (a) Anthony, J. E.; Khan, S. I.; Rubin, Y. *Tetrahedron Lett.* **1997**, *38*, 3499-3502; (b) Bruns, D.; Miura, H.; Vollhardt, K. P. C. *Org. Lett.* **2003**, *5*, 549-552.

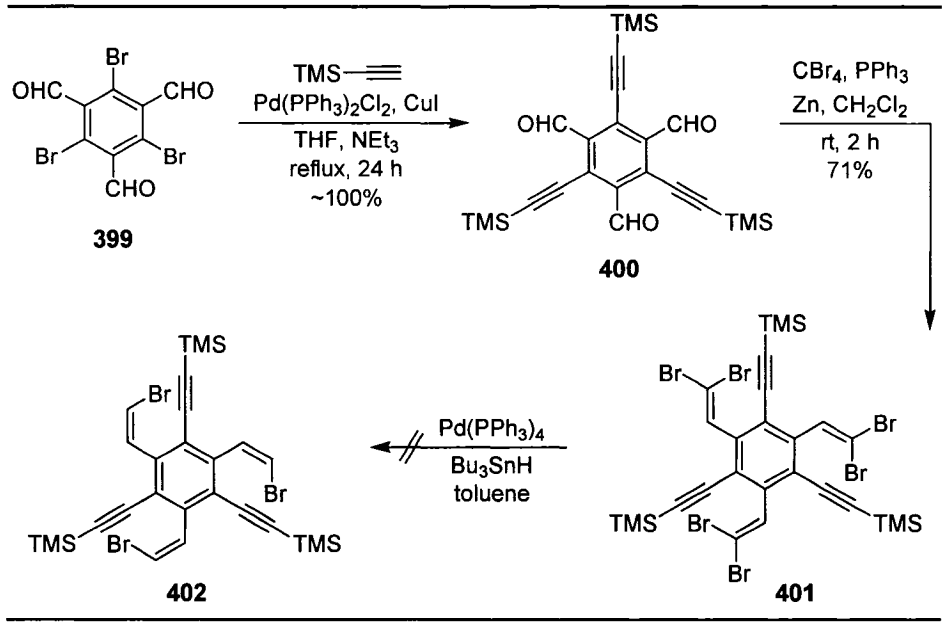
free aromatic positions using bromine and $FeCl_3$ yielded tribromobenzene **396** in 84% yield.[240] Bromination of the benzylic positions then generated hexabrominated **397**. Displacement of the benzylic bromines of **397** with acetate followed by hydrolysis of the esters then gave triol **398**, which upon oxidation with PCC produced the desired bromoaldehyde starting material (**399**) for our synthesis.



Scheme 98: Synthesis of 1,3,5-tribromobenzene-2,4,6-tricarbaldehyde 399

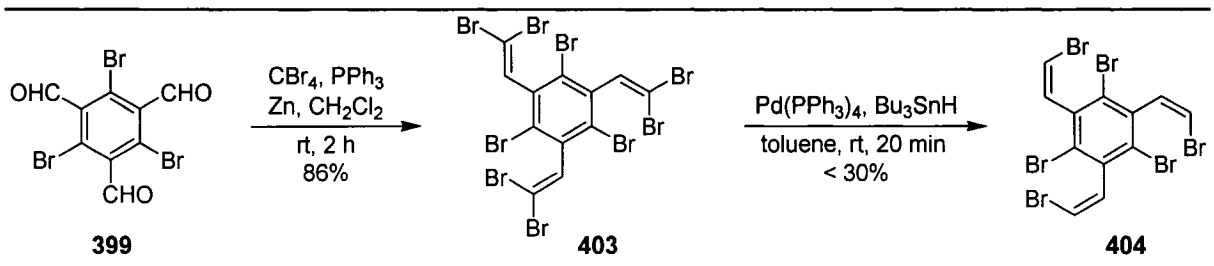
As mentioned at the beginning of Section 10, we ambitiously began our work on hexasubstituted benzenes before we had conducted any model studies. We believed that aryl (*Z*)-vinylbromide **402** could be synthesized *via* a palladium-mediated coupling of *gem*-dibromide **401** with Bu_3SnH (Scheme 99).[241] Towards this goal, an initial Sonogashira coupling of bromoaldehyde **399** with TMS-acetylene yielded trialdehyde **400** in near quantitative yield. This compound decomposed on silica and could not be purified, but was >95% pure by ^1H NMR and was easily converted to *gem*-dibromide **401** in 71% yield upon exposure to CBr_4 and PPh_3. Unfortunately, the (*E*)-bromide could not be cleanly removed upon exposure to $Pd(PPh_3)_4$ and Bu_3SnH, with all attempts producing complex mixtures of product.

[240] Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357-366.
[241] (a) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 6759-6762; (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965-8975.



Scheme 99: Attempted synthesis of (Z)-vinylbromide 402

The failure of this reaction could potentially have been due to two factors. The reaction relies on the more sterically hindered (*Z*)-bromide to be less reactive than the (*E*)-bromide. However, if the reaction rates are comparable it could be that when three substituents are present, some (*Z*)-bromide reacts before all three (*E*)-bromides have reacted, thereby producing complex mixtures. Alternatively, oxidative insertion of palladium into the (*Z*)-bromide carbon-bromine bond would produce a species well suited to form a palladacycle with the adjacent TMS-acetylene, which could lead to many undesired products.

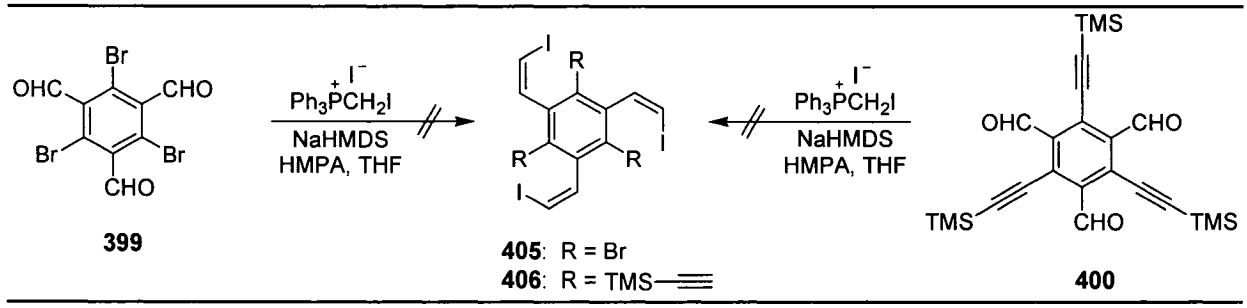


Scheme 100: Attempted synthesis of (Z)-vinylbromide 404

We also attempted to synthesize (*Z*)-vinylbromide **404** *via* the same strategy, delaying the Sonogashira reaction with the aryl bromides until later in the synthesis (Scheme 100). Bromoaldehyde **399** was therefore directly converted to *gem*-dibromide **403** in 86% yield using CBr_4 and PPh_3. Exposure of the *gem*-dibromide to $Pd(PPh_3)_4$ and Bu_3SnH then gave a small

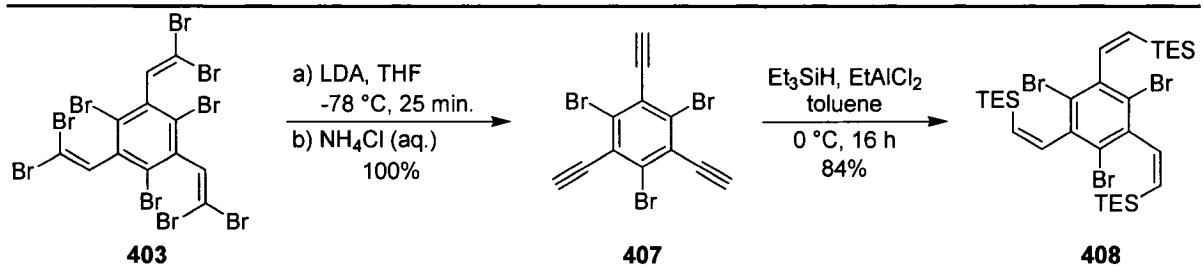
amount of the desired (*Z*)-vinylbromide. However, difficulties were encountered in reproducing this result, and attempts to react the vinylbromides of **404** in a Sonogashira reaction with TMS-acetylene produced multiple unidentified products. At this time these failures, as well as several other one-step difficulties, prompted us to pursue the trisubstituted benzene model studies previously described in Section 10.1. Our work following these studies is presented from this point onward.

One interesting challenge we faced at this point was selecting an appropriate route to the desired aryl (*Z*)-enyne moieties starting with bromoaldehyde **399**. Innumerable possibilities existed and many appeared to be equally feasible. For example, should the bromides or aldehydes of **399** be reacted first, and at what stage should the remaining functional group be reacted? Rather than expend considerable effort on one particular route, especially at an early stage in the synthesis, we chose to investigate many potential synthetic pathways. Those routes that showed promise would then be more extensively explored.



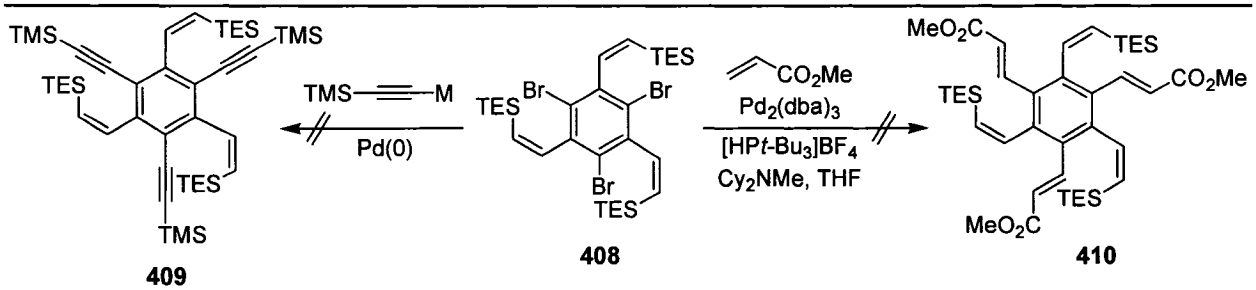
Scheme 101: Attempted Wittig reactions on trialdehydes 399 and 400

We initially attempted a Wittig reaction on both bromoaldehyde **399** and TMS-acetylene aldehyde **400**. Unfortunately, several trials of both reactions resulted in complex mixtures of product from which no identifiable product containing alkenes could be isolated. The complete failure of these reactions, as well as the previously observed instability of TMS-acetylene aldehyde **400**, suggested to us that the aldehyde moieties were relatively unstable. We therefore chose to convert the aldehydes to theoretically more stable and potentially more useful substituents before continuing the synthesis.



Scheme 102: Synthesis of (Z)-vinylsilane 408

We believed that (*Z*)-vinylsilanes met these requirements, and synthesized them from *gem*-dibromide **403** (Scheme 102). Thus, the *gem*-dibromide moieties were first converted to terminal acetylenes (**407**) in quantitative yield using excess LDA, and then reduced to (*Z*)-vinylsilane **408** *via* exposure to Et_3SiH and $EtAlCl_2$. This latter reaction required considerably more forcing conditions (5.0 eq. of $EtAlCl_2$ *vs.* 0.2 eq.) than had been required for the trisubstituted substrate (**367**), indicating the substantial decrease in reactivity caused by the additional substituents present on the benzene ring.

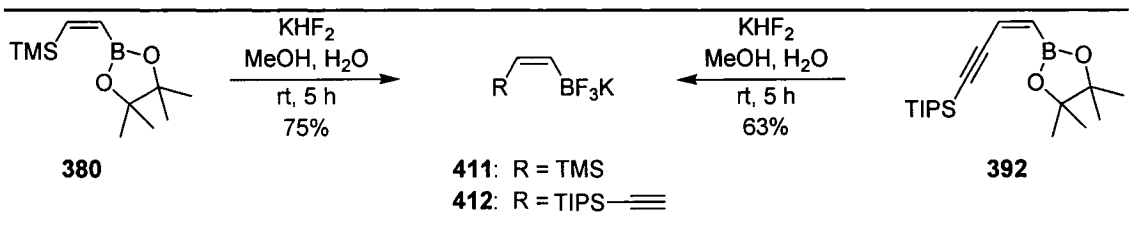


Scheme 103: Attempted elaboration of 410

We initially attempted to further functionalize (*Z*)-vinylsilane **408** *via* a Heck reaction with methyl acrylate (Scheme 103). However, no reaction was observed at room temperature and multiple, unidentifiable products were observed at higher temperatures. In retrospect, the vinylsilane moieties of **408** may also have undergone Heck reactions, thereby leading to the observed complex mixture of products. Numerous attempts to react the aryl bromides of **408** with metal acetylides also failed. Under either standard Sonogashira coupling conditions [$Pd(PPh_3)_2Cl_2$, CuI, NEt_3] or Buchwald and Fu's room temperature Sonogashira conditions [$Pd(PhCN)_2Cl_2$, (HPt-Bu_3)BF_4, CuI, HNi-Pr_2][100] no reaction was observed with TMS-acetylene. In contrast to reactions with bromoaldehyde **399**, however, the starting (*Z*)-vinylsilane could be

isolated from the reaction in near quantitative yield, suggesting that our hypothesis regarding the instability of the aldehydes was correct. A Negishi coupling of **408** with zinc TMS-acetylide generated a small amount of product where one bromide had reacted, but despite using up to 20 equivalents of acetylide, this reaction could not be improved.

At this point in time our results were presented at the Canadian Society for Chemistry conference in Saskatoon, Saskatchewan. Professor Dennis Hall of the University of Alberta took an interest in our work, and in particular those reactions involving boron, as this is his area of expertise. He made the suggestion that an excellent coupling partner in our palladium-mediated coupling reactions would be a potassium trifluoroborate salt rather than the pinacol boronate esters (**380** and **392**) we had unsuccessfully employed in our model studies (Schemes 90 and 97). In agreement with his assessment, we turned our attention to the synthesis of the potassium trifluoroborate analogues of pinacol boronate esters **380** and **392**.



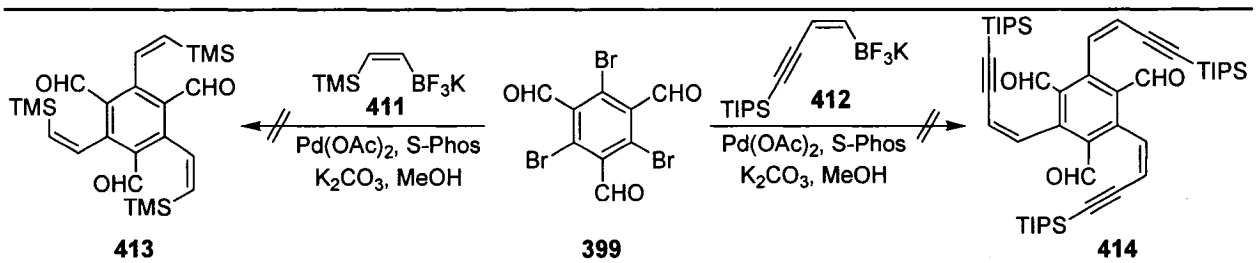
Scheme 104: Synthesis of potassium trifluoroborate salts 411 and 412

The conversion of a pinacol boronate ester to a potassium trifluoroborate salt is nearly always accomplished through an intermediate boronic acid. However, the conversion of a pinacol boronate ester to the boronic acid is often problematic.[242] Our preliminary attempts to synthesize the boronic acid of vinylsilane **380** under oxidative conditions[243] or *via* hydrolysis of an intermediate diethanolamine 'ate' complex[244] resulted only in a low yield of cyclic trimerized boronic acid (a boroxine). We therefore chose to convert the pinacol boronate esters to the potassium trifluoroborate salts directly using a modified version of Mattesons' procedure (Scheme 104).[245] Gratifyingly, addition of vinylsilane **380** to a solution of KHF_2 in MeOH and H_2O afforded pure potassium trifluoroborate **411** in 75% yield as a powdery white solid. An

[242] Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899-7903
[243] Falck, J. R.; Bondlela, M.; Venkataraman, S. K.; Srinivas, D. *J. Org. Chem.* **2001**, *66*, 7148-7150.
[244] Song, Y.-L.; Morin, C. *Synlett* **2001**, 266-268.
[245] Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153-2155.

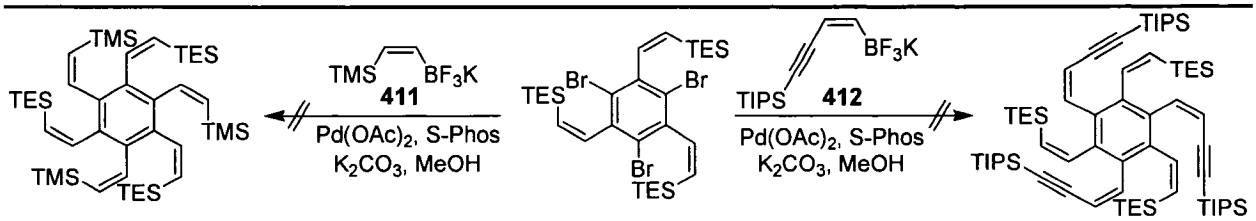
identical procedure afforded potassium trifluoroborate salt **412** in 63% yield from pinacol boronate ester **392**. The purification of **392**, however, was somewhat challenging as the salt was soluble in very polar solvents (*e.g.*, CH_3CN) and extremely non-polar solvents (*e.g.*, hexane), the latter effect likely being caused by the bulky TIPS group.

We expected the potassium trifluoroborate salts (**411** and **412**) to be superior in palladium-mediated coupling reactions due to their greater nucleophilicity and stability as compared to the pinacol boronate esters (**380** and **392**). The poor nucleophilicity of **380** had previously led to difficulties in its Suzuki coupling with 1,3,5-tribromobenzene (Scheme 91), while the attempted cross-coupling of **392** with **349** simply did not produce any product. We chose to attempt the palladium-mediated coupling reactions of the potassium trifluoroborate salts using the optimized conditions of Buchwald, as they have been successful on sterically hindered substrates somewhat similar to ours. [112]



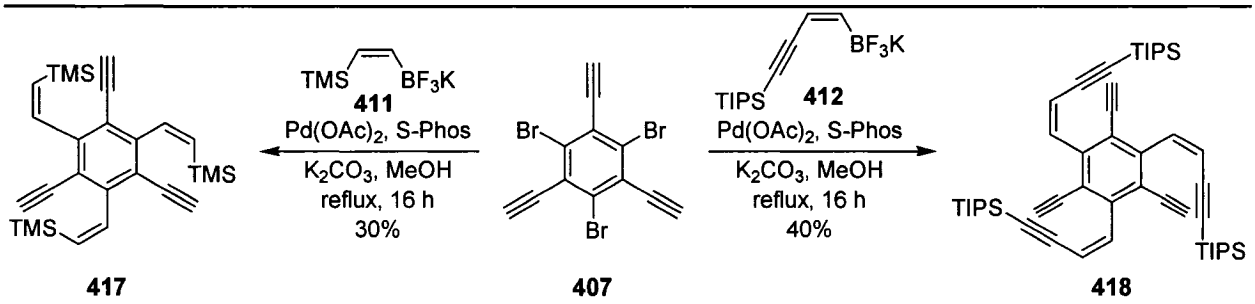
Scheme 105: Attempted Suzuki couplings of potassium trifluoroborates with bromoaldehyde 399

We initially attempted the Suzuki coupling of bromoaldehyde **399** with both potassium trifluoroborate salts (**411** and **412**) (Scheme 105). Unfortunately, neither reaction produced product or partially reacted product. Furthermore, bromoaldehyde **399** could also not be isolated from the reaction, supporting our earlier hypothesis that the aldehydes of **399** could be unstable and were decomposing during the reaction. We therefore attempted the same Suzuki reactions on the more stable (*Z*)-vinylsilane substrate **408** (Scheme 106). Regrettably, neither reaction produced any of the desired products. However, unlike the couplings with bromoaldehyde **399**, the starting (*Z*)-vinylsilane could be isolated from the reaction in near quantitative yield. This suggested to us that the triethylsilyl moieties of **408** were sterically hindering the coupling reaction, and thus we chose to attempt the same coupling reactions on a less sterically hindered substrate.



Scheme 106: Attempted Suzuki couplings of potassium trifluoroborates with (Z)-vinylsilane 408

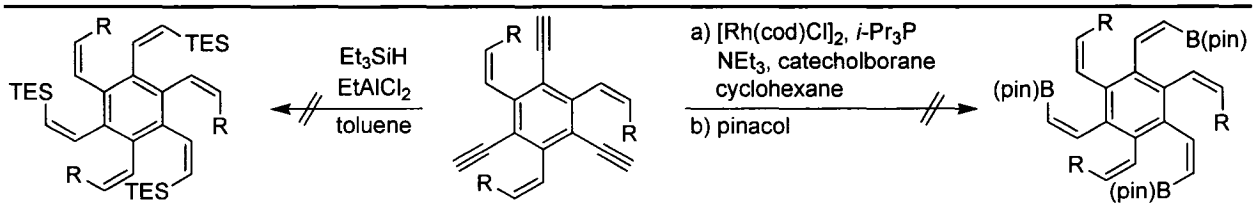
The obvious choice for our new aryl bromide coupling partner was triacetylene **407**, which was in fact the synthetic precursor to (*Z*)-vinylsilane **408** (Scheme 107). To our delight, the Suzuki coupling of triacetylene **407** with potassium trifluoroborate salt **411** produced the desired hexasubstituted benzene (**417**) in 30% yield. A similar reaction employing potassium trifluoroborate salt **412** was also successful and produced hexasubstituted benzene **418** in 40% yield. Although these yields may seem low, the reaction environment is fairly sterically hindered, and as the reaction is occurring three times on the same molecule the actual yield of each individual coupling is around 70%. These two substrates, in particular tris(enynyl)benzene **418**, were synthetically very close to the hexakis(enynyl)benzene required for the key dimerization to cyclophane **337**. We therefore attempted a *trans*-hydroboration or *trans*-hydrosilylation of the terminal acetylenes of **417** and **418**.



Scheme 107: Successful Suzuki couplings of potassium trifluoroborate salts with triacetylene 407

Unfortunately, we have been unable to find conditions to effect either the *trans*-hydrosilylation or *trans*-hydroboration on either hexasubstituted benzene **417** or **418** (Scheme 108). In nearly all cases, the starting material is isolated from the reaction in pure form and near quantitative yield. This is clearly caused by steric crowding about the reaction site as these

transformations worked very well on the trisubstituted test substrates. We hope to be able to find sufficiently forcing conditions to complete these reactions in the future.



415: R = TMS
416: R = TIPS—≡

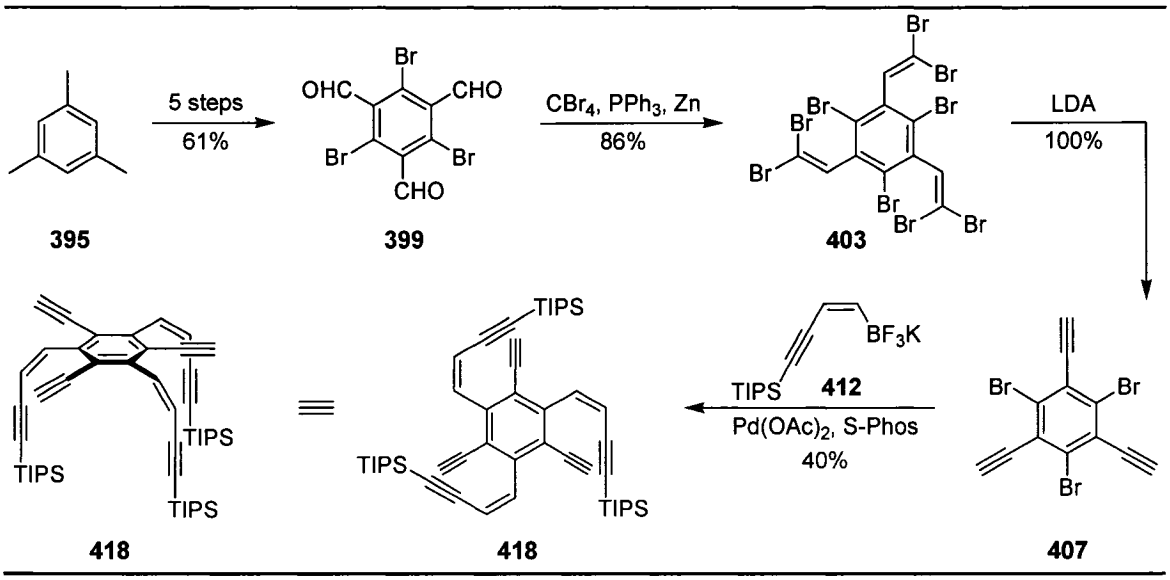
417: R = TMS
418: R = TIPS—≡

419: R = TMS
420: R = TIPS—≡

Scheme 108: Attempted hydroboration or hydrosilylation of hexasubstituted benzene 417 or 418

11 Conclusions and Future Work

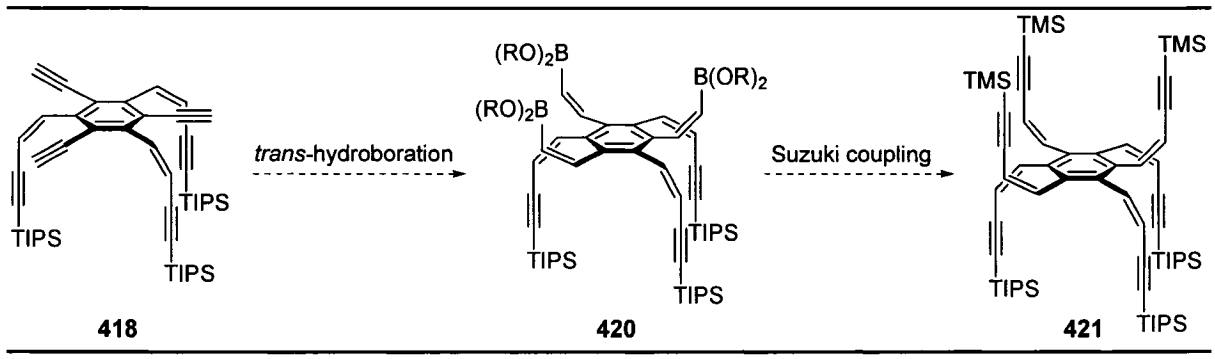
We have identified multiple methods of synthesizing tri[(*Z*)-alkenyl]benzenes suitably substituted for further conversion to tris[(*Z*)-enynyl]benzenes. We anticipate these procedures will be successful in synthesizing the hexakis[(*Z*)-enynyl]benzenes required for our synthesis of Buckminsterfullerene. To date we have used these methods to synthesize several hexasubstituted benzene intermediates *en route* to the key dimerization precursor (**341**) to cyclophane **337** (Scheme 76). The synthesis of the most advanced intermediate, **418**, is shown in Scheme 109. The starting material for our synthesis, bromoaldehyde **399**, was easily accessed from 1,3,5-trimethylbenzene (**395**) using a high yielding five step procedure. The aldehydes of **399** were then converted to terminal acetylenes in high yield using the Corey-Fuchs procedure. A subsequent Suzuki coupling reaction between the aryl bromides of **407** and potassium trifluoroborate salt **412** then provided hexasubstituted benzene **418**.



Scheme 109: Synthesis of hexasubstituted benzene 418

Hexasubstituted benzene **418** is tantalizingly close to the desired dimerization precursor **341** (Scheme 110). A *trans*-hydroboration of the terminal acetylenes, which worked beautifully on our test substrates, followed by a Suzuki coupling reaction between the resultant pinacol boronate esters (**420**) and a suitable acetylene derivative will provide the TMS-protected dimerization precursor (**421**). Should the first of these transformations fail, several other options

are also available, such as a *trans*-hydrosilylation of the terminal acetylenes of **418**, or beginning with a different hexasubstituted benzene such as **417** (Scheme 107).



Scheme 110: Potential conversion of hexasubstituted benzene 418 to hexakis(enynyl)benzene 421

In the longer-term, we plan to attempt the dimerization of **341** to provide **340**, and ultimately cyclophane **337** (Scheme 76). The development of mild conditions to convert cyclophane **337** to C_{60} would be a landmark discovery and potentially open the door to multiple avenues of research into the synthesis of other fullerenes.

12 Experimental

12.1 General Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. All reactions involving palladium were performed under argon. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Dichloromethane, toluene, acetonitrile, diisopropylamine and triethylamine were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. *n*-Butyllithium and *t*-BuLi solutions in hexanes or pentanes from Aldrich Chemical Company were titrated prior to use against diphenylacetic acid and used directly. Starting materials were purchased from Aldrich Chemical Company or Strem and used without further purification unless otherwise stated.

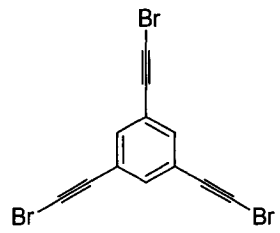
Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254} (E. Merck). TLC spots were developed by heating the plate after treatment with a 5% solution of phosphomolybdic acid in ethanol or a solution of $KMnO_4$ in aqueous potassium hydroxide. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry solutions in organic solvents. Excess solvents were removed (concentrated) *in vacuo* at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Degassed refers to bubbling a stream of argon through a solution for 20 minutes. Product purification by flash chromatography was performed with E. Merck Silica Gel 60 (230-400 mesh). Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C.

Melting points were determined with a Thomas-Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were run on a Bruker AVANCE 500 or a Varian INOVA 500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. ^1H NMR data are reported as follows: Chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet), coupling constants (Hz), and

integration). The multiplicity of each carbon atom in the ^{13}C NMR was determined using the DEPT 135 spectrum. Low resolution mass spectroscopy (MS) using electron impact (EI) was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV. High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam energy of 70 eV. MALDI-MS analysis was performed on a Bruker Daltonics® OmniFlex MALDI-TOF mass spectrometer equipped with a nitrogen laser (337 nm), and interfaced to an MBraun LabMaster® 130 glovebox. Data were collected in positive reflection mode, with an accelerating voltage held at 20 kV for all experiments. Matrix and analyte solutions were prepared in CH_2Cl_2 at concentrations of 25 mg/mL and 1 mg/mL, respectively; samples were mixed in a matrix:analyte ratio of 20:1. The purity of all title compounds was judged to be >95% as determined by a combination of ^1H NMR and ^{13}C NMR analyses unless otherwise indicated.

12.2 Experimental Procedures for New Compounds

1,3,5-Tris(2-bromoethynyl)benzene (351)

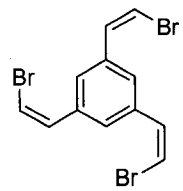


$C_{12}H_3Br_3$
Mol. Wt.: 386.86

Triacetylene **350** (12.0 g, 32.7 mmol) was dissolved in acetone (500 mL) and NBS (26.2 g, 147 mmol) and $AgNO_3$ (1.67 g, 9.82 mmol) were sequentially added. The reaction was protected from light by wrapping the flask in aluminum foil. After stirring overnight at rt, the mixture was concentrated (~100 mL) and diluted with H_2O. The organics were extracted with CH_2Cl_2, dried and filtered. Silica gel was then added and the solvent was removed. Filtration through a silica gel plug (5 cm) using PE as eluent provided the title compound as an off-white solid (10.4 g, 82%). mp: 119.5 – 121.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2 (CH), 123.5 (C), 78.1 (C), 52.1 (C); IR (neat): ν = 2918, 2850, 2203, 1580, 1462, 869 cm^{-1}; MS (EI) *m/z* 390 (33, $^{81}Br_3$), 388 (100, $^{79}Br^{81}Br_2$), 386 (96, $^{79}Br_2^{81}Br$), 384 (M^+,

31, $^{79}Br_3$), 305 (3), 226 (30), 147 (15); HRMS calculated for $C_{12}H_3{}^{79}Br_3$ (M^+) 383.7785, found 383.7792.

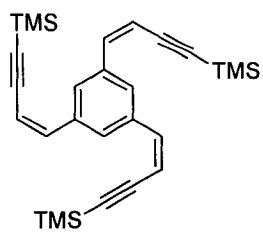
1,3,5-Tris((*Z*)-2-bromovinyl)benzene (352)



$C_{12}H_9Br_3$
Mol. Wt.: 392.91

(*Z*)-Vinylsilane **368** (2.13 g, 4.28 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to –78 °C. A solution of Br_2 (0.703 mL, 13.7 mmol) in CH_2Cl_2 (10 mL) was then added at such a rate that the color of Br_2 disappeared between drops. Once the addition was complete the reaction was stirred at –78 °C for 30 minutes, quenched *via* the addition of 1 M $Na_2S_2O_3$ and warmed to rt. The organics were extracted with ether, dried, filtered, and concentrated. The crude product was then dissolved in THF, cooled to 0 °C and a solution of TBAF in THF (1.0 M, 13.7 mL, 13.7 mmol) was added. The reaction was stirred at 0 °C for 15 minutes and then diluted with water. The organics were extracted with ether, dried, filtered and concentrated. Dry pack column chromatography (PE) afforded the title compound as a pale yellow oil (1.21 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8 (C), 131.6 (CH), 129.0 (CH), 107.4 (CH); IR (neat): ν = 3074, 2923, 2850, 1614, 1587, 1447, 1420, 1336, 1207, 938, 885, 776, 711, 671 cm^{-1}; MS (EI) *m/z* 396 (27, $^{81}Br_3$), 394 (87, $^{79}Br^{81}Br_2$), 392 (75, $^{79}Br_2{}^{81}Br$), 390 (M^+, 21, $^{79}Br_3$), 315 (12), 314 (57), 313 (17), 312 (82), 311 (10), 310 (55), 152 (100), 126 (28), 76 (68); HRMS calculated for $C_{12}H_9{}^{79}Br_3$ (M^+) 389.8255, found 389.8262.

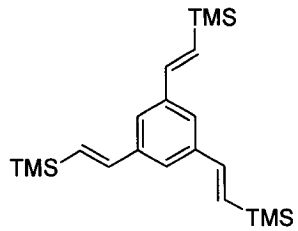
1,3,5-Tris((*Z*)-4-(trimethylsilyl)but-1-en-3-ynyl)benzene (353)



$C_{27}H_{36}Si_3$
Mol. Wt.: 444.83

(*Z*)-Vinylbromide **352** (0.240 g, 0.611 mmol), $Pd(PPh_3)_2Cl_2$ (0.021 g, 0.0305 mmol), CuI (0.012 g, 0.0611 mmol), NEt_3 (2 mL) and THF (10 mL) were added to a flask and degassed. Trimethylsilylacetylene (0.345 mL, 2.44 mmol) was then added and the reaction was refluxed overnight. Silica gel was then added and the solvent removed. Dry-pack column chromatography (100:1 PE:EA) then yielded the title compound as a colorless oil (0.202 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 6.65 (d, J = 12.0 Hz, 1H), 5.74 (d, J = 12.0 Hz, 1H), 0.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (CH), 136.2 (C), 129.1 (CH), 108.2 (CH), 103.2 (C), 102.1 (C), –0.2 (CH_3); IR (neat): ν = 3021, 2959, 2899, 2853, 2142, 1592, 1407, 1250, 1163, 1083, 1036, 759, 684 cm^{-1}; MS (EI) *m/z* 444 (M^+) (1), 341 (7), 283 (5), 73 (100); HRMS calculated for $C_{27}H_{36}Si_3$ (M^+) 444.2125, found 444.2148.

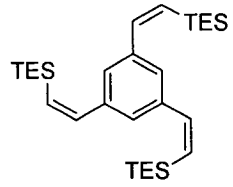
1,3,5-Tris((*E*)-2-(trimethylsilyl)vinyl)benzene (360)



$C_{21}H_{36}Si_3$
Mol. Wt.: 372.77

Schwartz's reagent (Cp_2ZrHCl) (9.83 g, 38.1 mmol) and THF (100 mL) were added to a foil-wrapped flask and cooled to 0 °C. A solution of TMS-acetylene (5.39 mL, 38.1 mmol) in THF (10 mL) was then added and the reaction was warmed to rt and stirred for 1 h, at which time all material was in solution. A solution of 1,3,5-tribromobenzene (**349**) (2.00 g, 6.35 mmol) and $Pd(PPh_3)_4$ (1.10 g, 0.953 mmol) in THF (50 mL) was then added and the reaction was heated at reflux for 2 d. After cooling to rt, silica gel was added and the reaction was concentrated. Filtration through a silica gel plug (5 cm) using PE as eluent afforded a gooey white solid that was further purified *via* column chromatography (PE) to afford the title compound as a white solid (2.36 g, 100%). mp: 156.6 – 158.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.89 (d, J = 19.0 Hz, 1H), 6.54 (d, J = 19.0 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4 (CH), 138.8 (C), 129.9 (CH), 124.1 (CH), –1.2 (CH_3); IR (neat): ν = 2988, 2955, 2899, 1609, 1580, 1418, 1246, 1199, 981, 909, 735, 691 cm^{-1}; MS (EI) *m/z* 372 (M^+) (25), 357 (17), 73 (100), 59 (21); HRMS calculated for $C_{21}H_{36}Si_3$ (M^+) 372.2125, found 372.2133.

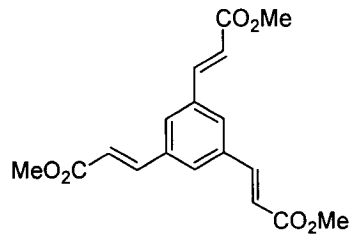
1,3,5-Tris((*Z*)-2-(triethylsilyl)vinyl)benzene (368)



$C_{30}H_{54}Si_3$
Mol. Wt.: 499.01

Toluene (25 mL) and a solution of $EtAlCl_2$ in hexane (1.0 M, 1.33 mL, 1.33 mmol) were added to a flask and cooled to 0 °C. A hot solution of 1,3,5-triethynylbenzene (**367**) (1.00 g, 6.66 mmol) in toluene (15 mL) was then slowly added and the reaction was stirred for 9 h at 0 °C. The reaction was then quenched *via* the sequential addition of excess NEt_3 and sat. $NaHCO_3$. The organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (PE) afforded the title compound as a colorless oil (2.23 g, 67%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 15.1 Hz, 1H), 7.08 (s, 1H), 5.77 (d, J = 15.1 Hz, 1H), 0.86 (t, J = 8.0 Hz, 3H), 0.55 (q, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (CH), 139.8 (C), 129.9 (CH), 126.3 (CH), 7.5 (CH_3), 4.7 (CH_2); IR (neat): ν = 2953, 2909, 2874, 1575, 1457, 1416, 1236, 1015, 1002, 889, 760, 728 cm^{-1}; MS (EI) *m/z* 498 (M^+) (1), 469 (71), 355 (45), 115 (76), 87 (100), 59 (44); HRMS calculated for $C_{30}H_{54}Si_3$ (M^+) 498.3533, found 498.3529.

(*E*)-3-[3,5-Bis((*E*)-2-methoxycarbonylvinyl)phenyl]acrylic acid methyl ester (369)

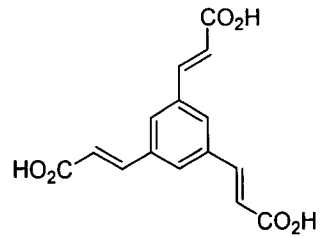


$C_{18}H_{18}O_6$
Mol. Wt.: 330.33

1,3,5-Tribromobenzene (**349**) (0.100 g, 0.318 mmol), $Pd_2(dba)_3$ (0.0145 g, 0.0159 mmol) and [HP*t*-Bu_3]BF_4 (0.0092 g, 0.0318 mmol) were added to a flask and purged with argon. Dioxane (2 mL), methyl acrylate (0.114 mL, 1.27 mmol) and Cy_2NMe (0.286 mL, 1.33 mmol) were then sequentially added and the reaction was stirred at rt overnight. The next day the reaction was diluted with water and the organics were extracted with CH_2Cl_2, dried, filtered and concentrated. Dry-pack column chromatography (2:1 PE:EA) afforded the title compound as a white solid (0.086 g, 82%). mp: 209.0 – 210.0 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.67 (d, J

= 16.1 Hz, 1H), 6.86 (d, J = 16.1 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2 (C), 142.8 (CH), 135.3 (C), 129.2 (CH), 119.5 (CH), 51.2 (CH_3); IR (neat): ν = 2950, 1703, 1638, 1281, 1252, 1167, 1087, 989, 857 cm^{-1}; MS (EI) *m/z* 330 (M^+) (60), 315 (100), 299 (45), 267 (18), 239 (28), 207 (16), 162 (22), 59 (36); HRMS calculated for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1097.

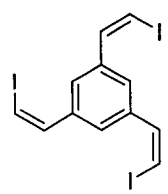
(*E*)-3-[3,5-Bis((*E*)-2-carboxyvinyl)phenyl]acrylic acid (370)



$C_{15}H_{12}O_6$
Mol. Wt.: 288.25

Triester **369** (0.100 g, 0.303 mmol) and NaOH (0.0424 g, 1.06 mmol) were added to MeOH (3 mL) and the reaction was heated at reflux for 7 h (all material dissolved after ~4 h). The reaction was then concentrated to afford a beige solid that was dissolved in a minimal amount of water and acidified *via* the dropwise addition of conc. HCl. The precipitate was filtered and washed with cold water to afford the title compound as a white solid (0.0621 g, 68%). mp: dec. 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 8.08 (s, 1H), 7.61 (d, J = 16.1 Hz, 1H), 6.78 (d, J = 16.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.9 (C), 143.1 (CH), 135.9 (C), 129.5 (CH), 121.3 (CH); IR (neat): ν = 2962, 2842, 1723, 1692, 1634, 1442, 1296, 1166, 984, 856 cm^{-1}; MS (EI) *m/z* 288 (M^+) (53), 224 (100), 162 (64), 69 (70); HRMS calculated for $C_{15}H_{12}O_6$ (M^+) 288.0634, found 288.0607.

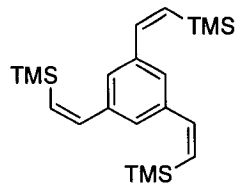
1,3,5-Tris((*Z*)-2-iodovinyl)benzene (373)



$C_{12}H_9I_3$
Mol. Wt.: 533.91

Tetrahydrofuran (10 mL) and $Ph_3PCH_2I_2$ (0.572 g, 1.08 mmol) were added to a flask and a solution of NaHMDS in THF (1.0 M, 1.08 mL, 1.08 mmol) was added dropwise. The yellow solution was stirred at rt for 2 minutes and then cooled to –78 °C and HMPA (0.10 mL) was added. After stirring for 5 minutes, a solution of trialdehyde **372** (0.050 g, 0.308 mmol) in THF (2 mL) was added. After stirring at –78 °C for 1 h, the reaction was quenched with water and diluted with ether. The organics were washed twice with water and then dried, filtered and concentrated. Dry-pack column chromatography (PE) yielded the title compound as a colorless oil (0.030 g, 18%). ^{1}H NMR indicated an approximate ratio of 95:5 *cis:trans* alkenes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (CH), 136.8 (C), 127.9 (CH), 80.6 (CH); IR (neat): ν = 3058, 2920, 2850, 1575, 1291, 1087, 880, 668, 648 cm^{-1}; MS (EI) *m/z* 534 (M^+) (100), 152 (32); HRMS calculated for $C_{12}H_9I_3$ (M^+) 533.7838, found 533.7843.

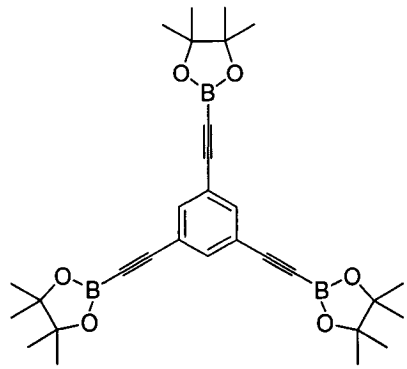
1,3,5-Tris((*Z*)-2-(trimethylsilyl)vinyl)benzene (374)



$C_{21}H_{36}Si_3$
Mol. Wt.: 372.77

Schwartz's reagent (Cp_2ZrHCl) (0.422 g, 1.64 mmol) and THF (5 mL) were added to a flask and protected from light by wrapping the flask in aluminum foil. A solution of aryl TMS-acetylene **350** (0.150 g, 0.409 mmol) in THF (2 mL) was then added dropwise and the reaction was refluxed overnight. After cooling to rt, H_2O (0.147 mL, 8.18 mmol) was added and the reaction was stirred for 30 minutes. Silica gel was added, the solvent was removed, and the reaction was filtered through a silica gel plug (5 cm) using PE as eluent. Removal of the solvent afforded a yellow oil that was further purified by column chromatography (PE) to yield the title compound as a colorless oil (0.039 g, 26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 15.0 Hz, 1H), 7.06 (s, 1H), 5.84 (d, J = 15.0 Hz, 1H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1 (CH), 139.5 (C), 133.5 (CH), 126.8 (CH), 0.3 (CH_3); IR (neat): ν = 2957, 2898, 1574, 1247, 985, 838, 766, 691 cm^{-1}; MS (EI) *m/z* 372 (M^+) (16), 357 (11), 162 (10), 73 (100); HRMS calculated for $C_{21}H_{36}Si_3$ (M^+) 372.2125, found 372.2124.

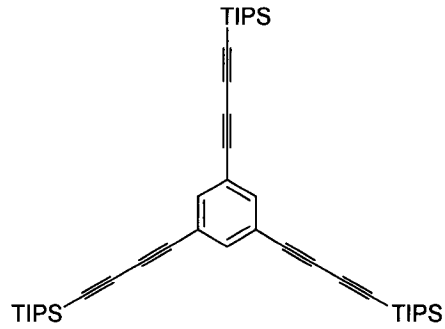
2-(2-(3,5-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl)phenyl)ethynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (384)



$C_{30}H_{39}B_3O_6$
Mol. Wt.: 528.06

Triethynylbenzene **367** (0.500 g, 3.33 mmol) was dissolved in THF (25 mL) and cooled to -78 °C. A solution of *n*-BuLi in hexanes (2.32 M, 4.45 mL, 10.3 mmol) was then added (a very thick slurry formed during the addition) and the reaction was stirred for 5 minutes. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.11 mL, 10.3 mmol) was dissolved in THF (25 mL), cooled to –78 °C, and the acetylide solution was added by canula (note: because of the thick slurry, a wide bore canula should be used). The reaction was stirred (thick slurry) for a further 3 h at –78 °C and then a solution of anhydrous HCl in ether (3.43 M, 3.11 mL, 10.7 mmol) was added. The reaction was then warmed to rt and stirred for 1 h. Hexane (25 mL) was added and the reaction was filtered through a silica gel plug (10 cm) using ether as eluent. After removal of the solvent, hexanes were added and the white crystalline product was filtered and washed with a small amount of cold hexane (1.24 g, 70%). mp: dec. 210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 1.27 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3 (CH), 122.8 (C), 98.9 (C), 84.6 (C), 24.6 (CH_3) (carbon atom bonded to boron not observed); IR (neat): ν = 2977, 2935, 2207, 1586, 1421, 1332, 1268, 1135, 957, 882, 852, 824, 658 cm^{-1}; MS (EI) *m/z* 528 (M^+) (78), 513 (40), 443 (100), 317 (11), 162 (25), 83 (54), 59 (42); HRMS calculated for $C_{30}H_{39}{}^{11}B_3O_6$ (M^+) 528.3026, found 528.2990.

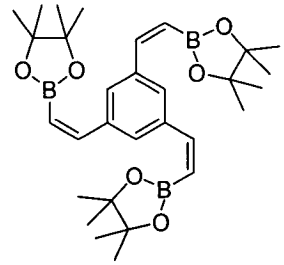
1,3,5-Tris(4-(triisopropylsilyl)buta-1,3-diynyl)benzene (386)



$C_{45}H_{66}Si_3$
Mol. Wt.: 691.26

Chloroenyne **235** (0.771 g, 3.18 mmol) was dissolved in THF (12 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (2.29 M, 3.12 mL, 7.15 mmol) was added and the reaction was stirred for 5 minutes. A solution of $ZnBr_2$ (0.894 g, 3.97 mmol) in THF (7 mL) was then added and the reaction was stirred at –78 °C for 5 minutes, then at 0 °C for 30 minutes. A solution of 1,3,5-tribromobenzene (**349**) (0.250 g, 0.794 mmol) and $Pd(PPh_3)_4$ (0.0918 g, 0.0794 mmol) in THF (10 mL) was then added and the reaction was stirred at rt overnight. The next day the reaction was diluted with water and the organics were extracted with ether, dried, filtered, and concentrated. Filtration through a silica gel plug (5 cm) using PE as eluent afforded an orange oily solid. Addition of hot hexanes followed by careful cooling precipitated a white solid identified as the title compound (0.334 g, 61%). mp: dec. 260 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6 (CH), 122.8 (C), 89.6 (C), 88.9 (C), 76.2 (C), 73.0 (C), 18.5 (C), 11.3 (C); IR (neat): ν = 2947, 2866, 2101, 1576, 1458, 1230, 1075, 991, 883, 828 cm^{-1}; MS (EI) *m/z* 691 (M^+) (8), 647 (100), 605 (13), 162 (54), 28 (69); HRMS calculated for $C_{45}H_{66}Si_3$ ($M^+ - C_3H_7$) 647.3925, found 647.3945.

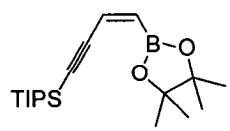
2-((1*Z*,6*Z*,8*Z*)-3,5-Bis((*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)styryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (385)



$C_{30}H_{45}B_3O_6$
Mol. Wt.: 534.11

Chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.0131 g, 0.0266 mmol) was added to a flask and purged with argon. Cyclohexane (5 mL), *i*-Pr_3P (0.0203 mL, 0.107 mmol), NEt_3 (0.269 mL, 1.93 mmol) and catecholborane (0.206 mL, 1.93 mmol) were then successively added and the reaction was stirred for 30 minutes at rt. A solution of triacetylene **367** (0.100 g, 0.666 mmol) in cyclohexane (1 mL) was then added and stirring was continued for 6 h, at which time a solution of pinacol (0.315 g, 2.66 mmol) in cyclohexane (1 mL) was added and the reaction was stirred overnight. The reaction was then diluted with ether, washed with sat. $NaHCO_3$ (3X), and the organics were dried, filtered, and concentrated. Dry-pack column chromatography (15:1 PE:EA) afforded the title compound as a colorless oil (0.073 g, 21%). A large amount of product remained on the column, and was isolated (90% pure) by flushing the column with EA. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.17 (d, J = 14.7 Hz, 1H), 5.56 (d, J = 14.7 Hz, 1H), 1.23 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9 (CH), 137.9 (C), 128.5 (CH), 119.4 (CH), 83.4 (C), 24.8 (CH_3); IR (neat): ν = 2978, 2929, 1620, 1583, 1257, 1142, 968, 846, 691 cm^{-1}; MS (EI) *m/z* 534 (M^+) (100), 191 (12), 101 (20), 84 (18); HRMS calculated for $C_{30}H_{45}{}^{11}B_3O_6$ (M^+) 534.3495, found 534.3511.

(*Z*)-Triisopropyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-ynyl)silane (392)

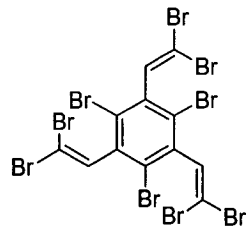


$C_{19}H_{35}BO_2Si$
Mol. Wt.: 334.38

Chloro(1,5-cyclooctadiene)rhodium (I) dimer (0.107 g, 0.217 mmol) was added to a flask, the flask was purged with argon, and cyclohexane (40 mL), *i*-Pr_3P (0.166 mL, 0.868 mmol), NEt_3

(0.907 mL, 6.51 mmol) and catecholborane (0.694 mL, 6.51 mmol) were successively added. After stirring for 30 minutes at rt, a solution of acetylene **391** (1.50 g, 7.23 mmol) in cyclohexane (10 mL) was added and the reaction was stirred for 5 h. A solution of pinacol (1.28 g, 10.9 mmol) in cyclohexane (10 mL) was then added and the reaction was stirred overnight. The reaction was diluted with water and sat. $NaHCO_3$ and the organics were extracted with ether, dried, filtered, and concentrated. Gradient column chromatography (30:1 – 10:1 PE:EA) afforded the title compound as a colorless oil (2.00 g, 83%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 14.7 Hz, 1H), 5.81 (d, J = 14.7 Hz, 1H), 1.25 (s, 12H), 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.1 (CH), 105.5 (C), 97.4 (C), 83.4 (C), 24.8 (CH_3), 18.7 (CH_3), 11.3 (CH) (carbon atom bonded to boron not observed); IR (neat): ν = 2943, 2890, 2865, 2144, 1590, 1463, 1414, 1337, 1259, 1144, 1008, 882, 849, 772, 676, 661 cm^{-1}; MS (EI) *m/z* 334 (M^+) (1), 317 (8), 291 (100), 212 (10), 191 (31), 162 (34), 143 (22), 101 (11), 70 (11); HRMS calculated for $C_{19}H_{35}{}^{11}BO_2Si$ (M^+) 334.2499, found 334.2510.

1,3,5-Tribromo-2,4,6-tris(2,2-dibromovinyl)benzene (403)

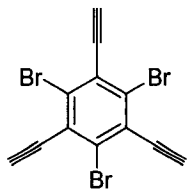


$C_{12}H_3Br_9$
Mol. Wt.: 866.29

Zinc (7.87 g, 120 mmol) and PPh_3 (31.6 g, 120 mmol) were added to CH_2Cl_2 (450 mL), cooled to 0 °C and a solution of CBr_4 (39.9 g, 120 mmol) in CH_2Cl_2 (150 mL) was added dropwise. After stirring the reaction overnight at rt, a solution of bromoaldehyde **399** (6.00 g, 15.0 mmol) in CH_2Cl_2 (200 mL) was added dropwise. The mixture was stirred for 4 h at rt and then filtered through silica using CH_2Cl_2 as eluent. Removal of the solvent afforded a colorless oil that was further purified by column chromatography (80:1 PE:EA) to yield the title compound as a white solid (11.2 g, 86%). [Each resonance in the ^1H and ^{13}C NMR was split into 3 signals as a result of hindered rotation about the aryl-alkene bond]. mp: 164.5 – 166.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27, 7.24, 7.19 (3 s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (138.73, 138.70, 138.5) (C), (136.29, 136.26, 136.2) (CH), (124.7, 124.5, 124.2) (C), (98.4, 98.2, 97.9) (C); IR (neat): ν =

3017, 1604, 1531, 1348, 1087, 843, 801, 727, 635 cm^{-1}; MS (MALDI-TOF, pyrene matrix) *m/z* (M^+ – Br + pyrene) 982.6 (4, $^{81}Br^{79}Br_7$), 984.6 (12, $^{81}Br_2{}^{79}Br_6$), 986.6 (24, $^{81}Br_3{}^{79}Br_5$), 988.6 (28, $^{81}Br_4{}^{79}Br_4$), 990.6 (20, $^{81}Br_5{}^{79}Br_3$), 992.6 (10, $^{81}Br_6{}^{79}Br_2$), 994.6 (2, $^{81}Br_7{}^{79}Br$); (M^+ - Br) 780.4 (1, $^{81}Br^{79}Br_7$), 782.4 (4, $^{81}Br_2{}^{79}Br_6$), 784.4 (10, $^{81}Br_3{}^{79}Br_5$), 786.4 (11, $^{81}Br_4{}^{79}Br_4$), 788.4 (9, $^{81}Br_5{}^{79}Br_3$), 790.4 (3, $^{81}Br_6{}^{79}Br_2$), 792.4 (1, $^{81}Br_7{}^{79}Br$).

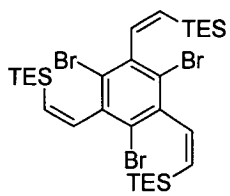
1,3,5-Tribromo-2,4,6-triethynylbenzene (407)



$C_{12}H_3Br_3$
Mol. Wt.: 386.86

gem-Dibromide **403** (10.0 g, 11.5 mmol) was dissolved in THF (100 mL) and cooled to –78 °C. A freshly prepared solution of LDA in THF (0.923 M, 150 mL, 139 mmol) at –78 °C was then added dropwise. After stirring for 10 minutes, the dark solution was quenched *via* the addition of sat. NH_4Cl and warmed to rt. The organics were extracted with ether, dried, filtered and concentrated to afford a brown solid. A small amount (~8 mL) of cold ether was then added and the pale brown solid was collected by suction filtration. The filtrate was concentrated and filtered again to provide a combined 3.31 g of pure product (74%) as well as 1.09 g of slightly impure material from the filtrate. mp: dec. 160 °C; ^1H NMR (500 MHz, THF-d_8) δ 2.67 (s, 1H); ^{13}C NMR (125 MHz, THF-d_8) δ 130.5 (C), 128.1 (C), 90.8 (CH), 81.6 (C); IR (neat): ν = 3276, 2112, 1338, 1087, 685, 635 cm^{-1}; MS (EI) *m/z* 390 (32, $^{81}Br_3$), 388 (100, $^{79}Br^{81}Br_2$), 386 (99, $^{79}Br_2{}^{81}Br$), 384 (M^+, 34, $^{79}Br_3$), 228 (28), 226 (27), 147 (37); HRMS calculated for $C_{12}H_3Br_3$ (M^+) 383.7785, found 383.7787.

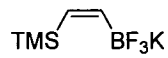
1,3,5-Tribromo-2,4,6-tris((*Z*)-2-(triethylsilyl)vinyl)benzene (408)



$C_{30}H_{51}Si_3Br_3$
Mol. Wt.: 735.70

Toluene (60 mL) and a solution of $EtAlCl_2$ in hexane (1.0 M, 19.4 mL, 19.4 mmol) were added to a flask and cooled to 0 °C. Triethylsilane (3.72 mL, 23.3 mmol) was added and the reaction was stirred for 5 minutes. A solution of triacetylene **407** (1.50 g, 3.88 mmol) in hot toluene (40 mL) was then added and the reaction was stirred at 0 °C for 1 h, then warmed to rt and stirred overnight. Once complete, excess NEt_3, sat. $NaHCO_3$ and water were sequentially added and the organics were extracted with ether, dried, filtered, and concentrated. Column chromatography (PE) yielded the title compound as a white solid (2.40 g, 84%). mp: 50.5 – 52.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (br s, 1H), 6.05 (d, J = 15.7 Hz, 1H), 0.88 (br s, 9H), 0.46 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3 (br, CH), 141.2 (br, C), 134.0 (br, CH), 122.9 (br, C), 7.5 (CH_3), 3.5 (CH_2); IR (neat): ν = 2953, 2909, 2874, 1605, 1414, 1329, 1236, 1015, 967, 739 cm^{-1}; MS (EI) *m/z* 709 (44, $^{81}Br_3$), 707 (100, $^{79}Br^{81}Br_2$), 705 (89, $^{79}Br_2^{81}Br$), 703 ($M^+ - C_2H_5$, 28, $^{79}Br_3$), 115 (28), 87 (40).

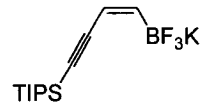
Potassium (*Z*)-2-(trimethylsilyl)vinyl trifluoroborate (411)



$C_5H_{11}BF_3KSi$
Mol. Wt.: 206.13

Pinacol boronate ester **380** (2.00 g, 8.84 mmol) was dissolved in MeOH (50 mL) and a solution of KHF_2 (4.14 g, 53.1 mmol) in H_2O (10 mL) was added. After stirring for 5 h at rt, all solvent was removed under reduced pressure. Acetonitrile was then added, and excess KHF_2 was filtered off and washed with CH_3CN. The filtrate was concentrated and hexane was added to precipitate the product and dissolve pinacol. The product was collected and washed with hexane. Residual impurities were removed by dissolving the product in CH_3CN and filtering. Concentration of the filtrate provided the title compound as a white solid (1.36 g, 75%). mp: 220.0 – 221.5 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 6.51 (dq, J = 18.7 and 5.8 Hz, 1H), 5.97 (br d, J = 16.6 Hz, 1H), 0.04 (s, 10H); ^{13}C NMR (125 MHz, CD_3CN) δ 159.9 (br, CH), 138.3 (q, J = 4.4 Hz, CH), 0.4 (CH_3); ^{11}B NMR (160 MHz, CD_3CN) δ –15.9 (q, J = 56.0 Hz); IR (neat): ν = 2953, 2918, 1612, 1366, 1242, 1196, 1063, 946, 926, 837, 764 cm^{-1}; MS (ES) *m/z* 167 (M^-).

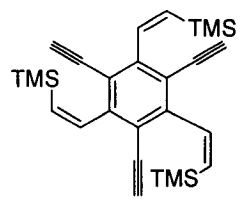
Potassium (*Z*)-4-(triisopropylsilyl)but-1-en-3-ynyl trifluoroborate (412)



$C_{13}H_{23}BF_3KSi$
Mol. Wt.: 314.31

Pinacol boronate ester **392** (2.00 g, 5.98 mmol) was dissolved in MeOH (40 mL) and a solution of KHF_2 (2.80 g, 35.9 mmol) in H_2O (17 mL) was added. After stirring for 5 h at rt, all solvent was removed under reduced pressure. Acetonitrile was then added, and excess KHF_2 was filtered off and washed with CH_3CN. The filtrate was concentrated and hexane was added to precipitate the product and dissolve pinacol. The product was collected and washed with hexane. (Considerable difficulty was encountered in crystallizing the product. The best method appears to be repeatedly scratching the flask while slowly (4 h) evaporating some of the solvent under a stream of nitrogen). Residual impurities were removed by dissolving the product in CH_3CN and filtering. Concentration of the filtrate provided the title compound as a light brown solid (0.400 g, 23%). mp: 197.0 – 199.0 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 5.93 (dq, J = 14.7 and 5.0 Hz, 1H), 5.74 (br d, J = 14.2 Hz, 1H), 1.07-1.09 (m, 21H); ^{13}C NMR (125 MHz, CD_3CN) δ 155.0 (br s, CH), 114.9 (q, J = 4.8 Hz, CH), 110.1 (C), 90.0 (C), 19.1 (CH_3), 12.3 (CH); ^{11}B NMR (160 MHz, CD_3CN) δ –16.4 (q, J = 53.0 Hz); IR (neat): ν = 2943, 2890, 2865, 2137, 1594, 1463, 1389, 1089, 994, 882, 751, 676 cm^{-1}; MS (ES) *m/z* 275 (M^-).

1,3,5-Triethynyl-2,4,6-tris((*Z*)-2-(trimethylsilyl)vinyl)benzene (417)

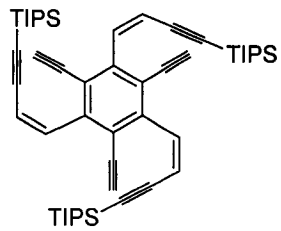


$C_{27}H_{36}Si_3$
Mol. Wt.: 444.83

Tribromobenzene **407** (0.400 g, 1.03 mmol), potassium trifluoroborate **417** (0.853 g, 4.14 mmol), $Pd(OAc)_2$ (0.0232 g, 0.134 mmol), S-Phos (0.0848 g, 0.206 mmol) and K_2CO_3 (1.43 g, 10.3 mmol) were added to a flask, purged with argon, and MeOH (30 mL) was added. After refluxing overnight, the reaction was diluted with ether and filtered through a silica gel plug (5 cm), eluting with ether. After concentration of the organics, hexane was added and the organics that dissolved were purified *via* column chromatography (PE) to yield the title compound as a yellow

solid (0.140 g, 30%). mp: 86.5 – 88.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 15.7 Hz, 1H), 6.09 (d, J = 15.7 Hz, 1H), 3.31 (s, 1H), –0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7 (C), 141.7 (CH), 136.6 (CH), 119.8 (C), 86.1 (CH), 81.2 (C), –0.8 (CH_3); IR (neat): ν = 3283, 2956, 2897, 2104, 1603, 1528, 1395, 1246, 1034, 840, 777, 762, 691, 654 cm^{-1}; MS (EI) *m/z* 444 (M^+) (1), 341 (8), 283 (38), 73 (100); HRMS calculated for $C_{27}H_{36}Si_3$ (M^+) 444.2125, found 444.2164.

1,3,5-Triethynyl-2,4,6-tris((*Z*)-4-(triisopropylsilyl)but-1-en-3-ynyl)benzene (418)



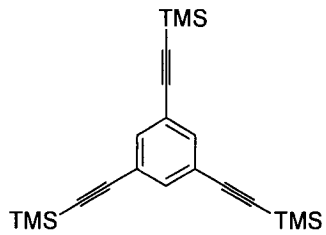
$C_{51}H_{72}Si_3$
Mol. Wt.: 769.37

Tribromobenzene **407** (0.300 g, 0.776 mmol), potassium trifluoroborate **412** (0.804 g, 2.56 mmol), $Pd(OAc)_2$ (0.0174 g, 0.0776 mmol), S-Phos (0.0637 g, 0.155 mmol) and K_2CO_3 (1.07 g, 7.76 mmol) were added to a flask, purged with argon, and MeOH (25 mL) was added. After refluxing overnight, the reaction was diluted with ether and filtered through a silica gel pad (5 cm), eluting with ether. After concentration of the organics, further purification *via* dry pack column chromatography (100:1 PE:EA) afforded the title compound as an orange solid (0.240 g, 40%). mp: 87.0 – 89.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, J = 11.8 Hz, 1H), 5.98 (d, J = 11.8 Hz, 1H), 3.39 (s, 1H), 0.95 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6 (C), 137.1 (CH), 120.5 (C), 114.8 (CH), 104.0 (C), 98.9 (C), 86.9 (CH), 80.6 (C), 18.5 (CH_3), 11.2 (CH); IR (neat): ν = 3306, 3024, 2942, 2890, 2865, 2147, 1605, 1463, 1412, 1366, 1071, 998, 882, 677, 660, 643, 612 cm^{-1}; MS (EI) *m/z* 725 ($M^+ - C_3H_7$) (1), 683 (3), 592 (8), 157 (12), 115 (57), 87 (56), 73 (73), 59 (100).

12.3 Experimental Procedures for Previously Reported Compounds

Experimental procedures and ^{1}H NMR data for previously reported compounds synthesized for this thesis are presented for convenience in this section. Full characterization data is available in the indicated references.

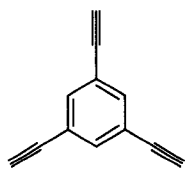
1,3,5-Tris(2-(trimethylsilyl)ethynyl)benzene (350)[246]



$C_{21}H_{30}Si_3$
Mol. Wt.: 366.72

A slightly modified literature procedure was used: 1,3,5-Tribromobenzene (**349**) (7.00 g, 22.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.780 g, 1.11 mmol), CuI (0.420 g, 2.22 mmol), Et_3N (20 mL) and THF (90 mL) were added to a flask and degassed. Trimethylsilylacetylene (12.6 mL, 88.9 mmol) was then added and the reaction was refluxed overnight. The next day the reaction was cooled to rt and concentrated. Petroleum ether was added and the mixture was filtered through a silica gel plug (10 cm) eluting with PE. A substantial quantity of material that did not dissolve was discarded. Removal of the solvent provided the title compound as a pale yellow solid (8.15 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 0.21 (s, 9 H).

1,3,5-Triethynylbenzene (367)[246]



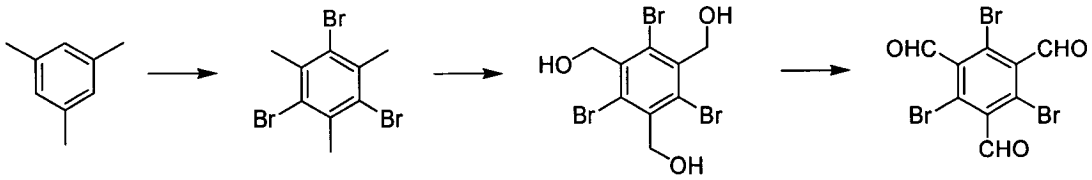
$C_{12}H_6$
Mol. Wt.: 150.18

A slightly modified literature procedure was used: Potassium hydroxide (2.75 g, 49.1 mmol) was dissolved in MeOH (40 mL) and a solution of aryl TMS-acetylene **350** (3.00 g, 8.18 mmol)

[246] Weber, E.; Hecker, M.; Koepp, E.; Orlia, W.; Czugler, M.; Csöregh, I. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1251-1257.

in THF (5 mL) and MeOH (5 mL) was added. After stirring at rt for 1 h, the reaction was neutralized *via* the addition of sat. NH_4Cl. The majority of MeOH and THF was removed under reduced pressure and the organics were extracted with CH_2Cl_2, dried, filtered and concentrated. Column chromatography (PE) afforded the title compound as a white solid (1.00 g, 82%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 3.09 (s, 1H).

2,4,6-Tribromobenzene-1,3,5-tricarbaldehyde (399)[239]



395 C_9H_{12} Mol. Wt.: 120.19

396 $C_9H_9Br_3$ Mol. Wt.: 356.88

398 $C_9H_9Br_3O_3$ Mol. Wt.: 404.88

399 $C_9H_3Br_3O_3$ Mol. Wt.: 398.83

*1,3,5-Tribromo-2,4,6-trimethylbenzene (**396**)*[247]

1,3,5-Trimethylbenzene (**395**) (25.0 g, 0.208 mol) was dissolved in $Cl(CH_2)_2Cl$ (250 mL), and $FeCl_3$ (3.37 g, 0.0208 mol) was added. The reaction was heated to reflux and equipped with a KOH (aq.) trap to neutralize HBr gas generated during the reaction. A solution of Br_2 (32.0 mL, 0.624 mol) in $Cl(CH_2)_2Cl$ (50 mL) was then carefully added over 1 h (CAUTION: Extremely exothermic with vigorous gas evolution). After refluxing for a further 2 h, the mixture was cooled to 0 °C and filtered. The solid was recrystallized from hot $CHCl_3$ to yield beige crystals of the title compound (62.5 g, 84%). ^1H NMR (200 MHz, $CDCl_3$) δ 2.63 (s).

*1,3,5-Tribromo-2,4,6-tris(hydroxymethyl)benzene (**398**)*

A modified literature procedure was used: 1,3,5-Tribromo-2,4,6-trimethylbenzene (**396**) (65.0 g, 0.182 mol) was dissolved in CH_2Cl_2 (1 L) and Br_2 (34.5 mL, 0.674 mol) was added dropwise over 30 minutes while irradiating with a sunlamp. The reaction was equipped with a KOH (aq.) trap to neutralize HBr gas generated during the reaction and heated at reflux while irradiating with the sunlamp. After 6 d the reaction was complete. The majority of CH_2Cl_2 was then removed by distillation and hexane was added to the remaining gooey solid. The resultant solid was filtered and washed with hexanes to provide hexabromo **397** as an off-white solid [^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (s)]. The crude hexabromo substrate (**397**) (99.0 g, 0.167 mol) and

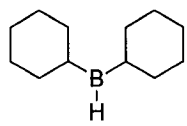
[247] Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357-366.

KOAc (81.8 g, 0.834 mol) were then added to DMF (400 mL) and heated at 80 °C for 20 h. The reaction was then poured into CH_2Cl_2 (1.5 L) and washed with water (5 x 500 mL) to remove DMF. The organics were dried, filtered, and concentrated to yield the crude triacetate. Water (650 mL) and KOH (74.9 g, 1.33 mol) were then added to the crude triacetate and the mixture was heated at 90 °C for 24 h (note: triacetate and product do not dissolve). The reaction was cooled, neutralized with sat. NH_4Cl, and filtered. The solid was sequentially washed with a small amount of MeOH and then ether to yield the title compound as a white solid (67.5 g, 92%, 3 steps). ^1H NMR (500 MHz, DMSO-d_6) δ 5.33 (s).

*2,4,6-Tribromobenzene-1,3,5-tricarbaldehyde (**399**)*

Celite (20 g), PCC (109 g, 504 mmol), activated 4 Å MS (20 g) and CH_2Cl_2 were added to a flask, followed by 1,3,5-tribromo-2,4,6-tris(hydroxymethyl)benzene (**398**) (12.0 g, 29.6 mmol). The reaction was vigorously stirred for 2 d and then the solids were filtered off using a Buchner funnel (CH_2Cl_2 wash). The filtrate was then filtered through a silica gel pad (10 cm high) eluting with CH_2Cl_2 (Note: filtration was stopped before colored fractions began to elute). Removal of the solvent provided the title compound as fluffy white crystals (9.28 g, 79%). ^1H NMR (500 MHz, THF-d_8) δ 10.12 (s).

Dicyclohexylborane (422)[248]

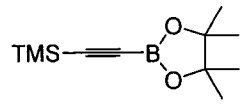


$C_{12}H_{23}B$
Mol. Wt.: 178.12

Cyclohexene (3.70 mL, 36.5 mmol) was dissolved in ether (10 mL) and cooled to 0 °C. A solution of $BH_3{\cdot}SMe_2$ in ether (5.0 M, 3.65 mL, 18.3 mmol) was then added dropwise over 10 minutes. After stirring at 0 °C for 3 h the solid was allowed to settle and as much liquid as possible was removed by syringe (quench by squirting into MeOH). The remaining fluffy white solid was dried under reduced pressure. **Caution: Reacts very readily with air. Use ONLY in glove box!

[248] Abiko, A. *Org. Syn. CV10*, 273.

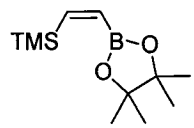
Trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl)silane (379)[249]



$C_{11}H_{21}BO_2Si$
Mol. Wt.: 224.18

Trimethylsilylacetylene (4.32 mL, 30.5 mmol) was dissolved in ether (18 mL), cooled to –78 °C and a solution of *n*-BuLi in hexanes (2.35 M, 13.0 mL, 30.5 mmol) was added dropwise and the reaction was stirred for 5 minutes. This solution was then added *via* canula to a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**378**) (6.23 mL, 30.5 mmol) in ether (18 mL) at –78 °C. After stirring for 2 h at –78 °C, a solution of anhydrous HCl in ether (3.43 M, 9.79 mL, 33.6 mmol) was added and the reaction was warmed to rt and stirred for 1 h. The reaction was then concentrated and a 1:1 mixture of ether:hexane (15 mL) was added. Filtration though a silica gel plug (5 cm) using ether as eluent followed by removal of the solvent provided a white solid. Cold hexane (-20 °C) was added to the residue and the precipitated white crystals were filtered and washed with additional cold hexane. The filtrate was concentrated, cooled (–20 °C), and filtered again to yield a combined 5.63 g (82%) of pure product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 12H), 0.14 (s, 9H).

(*Z*)-Trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (380)[229]



$C_{11}H_{23}BO_2Si$
Mol. Wt.: 226.2

Schwartz's reagent (Cp_2ZrHCl) (5.98 g, 23.2 mmol) and THF (100 mL) were added to a flask and protected from light by wrapping the flask in aluminum foil. A solution of alkynylboronate **379** (4.00 g, 17.8 mmol) in THF (20 mL) was then added and the reaction was stirred for 2 h at rt. Water (3.21 mL, 178 mmol) was then added. After stirring for 30 minutes, the reaction was diluted with sat. NH_4Cl and the organics were extracted with ether, dried, filtered and concentrated. Dry-pack column chromatography (30:1 PE:EA) as eluent afforded the title compound as a colorless oil (3.23 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (br d, J = 18.9 Hz, 1H), 6.38 (d, J = 18.9 Hz, 1H), 1.24 (s, 12H), 0.11 (s, 9H).

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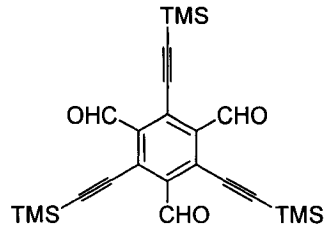
[249] Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* **2004**, *6*, 3405-3407.

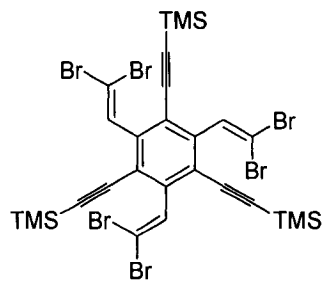
2,4,6-Tris(2-(trimethylsilyl)ethynyl)benzene-1,3,5-tricarbaldehyde (400)[239]



$C_{24}H_{30}O_3Si_3$
Mol. Wt.: 450.75

Improvements from the literature procedure were made: Bromoaldehyde **399** (1.00 g, 2.51 mmol), $Pd(PPh_3)Cl_2$ (0.088 g, 0.125 mmol), CuI (0.048 g, 0.251 mmol), THF (40 mL) and NEt_3 (10 mL) were added to a flask and degassed. Trimethylsilylacetylene (1.42 mL, 10.0 mmol) was then added and the reaction was heated at 40 °C for 3 h. The reaction was cooled and diluted with H_2O and the organics were extracted with CH_2Cl_2, dried, filtered and concentrated to afford a brown solid. The solid was >95% pure product (1.13 g, 100%) by ^1H NMR. Attempts to further purify the title compound by column chromatography resulted in decomposition. ^1H NMR (500 MHz, $CDCl_3$) δ 10.63 (s, 1H), 0.27 (s, 9H).

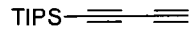
1,3,5-Tris(2,2-dibromovinyl)-2,4,6-tris(2-(trimethylsilyl)ethynyl)benzene (401)[239]



$C_{27}H_{30}Br_6Si_3$
Mol. Wt.: 918.21

Zinc (1.45 g, 22.2 mmol) and PPh_3 (5.82 g, 22.2 mmol) were added to CH_2Cl_2 (80 mL), cooled to 0 °C and a solution of CBr_4 (7.36 g, 22.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After stirring the reaction overnight at rt, a solution of trialdehyde **400** (1.00 g, 2.22 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The mixture was stirred for 2 h at rt and then filtered through silica using CH_2Cl_2 as eluent. Removal of the solvent afforded a brown solid that was further purified by column chromatography (75:1 PE:EA) to yield the title compound as a white solid (1.51 g, 71%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 0.27 (s, 9H).

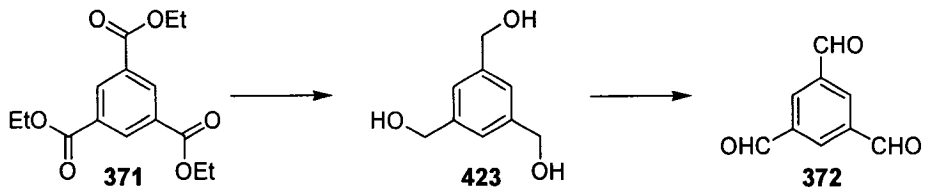
Buta-1,3-diynyltriisopropylsilane (391)[250]



$C_{13}H_{22}Si$
Mol. Wt.: 206.4

Significant improvements from the literature procedure have been made in our lab: Chloroenyne **235** (0.500 g, 2.06 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. A solution of *n*-BuLi in hexanes (2.32 M, 1.96 mL, 4.54 mmol) was added and the reaction was stirred at –78 °C for 1 h and then warmed to rt and stirred for 30 minutes. The reaction was quenched *via* the addition of sat. NH_4Cl and the organics were extracted with ether, dried, filtered, and concentrated to afford a red oil identified as the title compound (0.430 g, 100%). ^1H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 1H), 1.09 (s, 21H).

Benzene-1,3,5-tricarbaldehyde (372)[251]



371 $C_{15}H_{18}O_6$ Mol. Wt.: 294.30

423 $C_9H_{12}O_3$ Mol. Wt.: 168.19

372 $C_9H_6O_3$ Mol. Wt.: 162.14

1,3,5-Tris(hydroxymethyl)benzene (423)

An improved literature procedure was used: Lithium aluminum hydride (4.97 g, 131 mmol) and THF (50 mL) were added to a flask and heated to reflux. A solution of triethyl benzene-1,3,5-tricarboxylate (**371**) (10.0 g, 39.7 mmol) in THF (100 mL) was then carefully added (CAUTION: HIGHLY EXOTHERMIC). After refluxing for 5 h, the solution was cooled to 0 °C and excess $LiAlH_4$ was quenched *via* the dropwise addition of H_2O (5 mL), followed by 1 M NaOH (10 mL). The majority of THF and water (~5 mL remains) was then removed under reduced pressure, and the remaining oily solution was neutralized *via* the dropwise addition of 1 M HCl. Further removal of solvent afforded a white solid. Recrystallization from EtOAc afforded the title compound as fine colorless needles (4.95 g, 76%). ^1H NMR (500 MHz, CD_3OD) δ 7.26 (s, 1H), 4.60 (s, 2H).

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[250] Lange, T.; Loon, J-D.; Tykwinski, R. R.; Schreiber, M.; Diederich, F. *Synthesis* **1996**, 537-550.
[251] Fourmigue, M.; Johannsen, I.; Boubekeur, K.; Nelson, C.; Batail, P. *J. Am. Chem. Soc.* **1993**, *115*, 3752-3759.

Benzene-1,3,5-tricarbaldehyde (372):

A modified literature procedure was used: Celite (7 g), PCC (31.3 g, 145 mmol), 4 A MS (7 g) and CH_2Cl_2 (120 mL) were added to a flask, followed by 1,3,5-tris(hydroxymethyl)benzene (**423**) (2.00 g, 12.1 mmol). After stirring overnight at rt, the majority of solids were removed through filtration on a Buchner funnel (CH_2Cl_2 wash). Further filtration of the filtrate through a silica gel plug (10 cm) using CH_2Cl_2 as eluent afforded a white solid that was recrystallized from EtOAc to provide the title compound as a white powder (1.24 g, 63%). ^1H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.64 (s, 1H).

CLAIMS TO ORIGINAL RESEARCH

1. Synthesized Diels-Alder precursors **68** and **92** and tested the feasibility of the tether-control group methodology in the stereospecific synthesis of hydrindanes.

2. Designed a new class of chiral cyclophane (an acetylenic allenophane) and developed and completed the first asymmetric synthesis of an acetylenic allenophane (**308**).

3. Developed a novel method of synthesizing tertiary propargyl alcohols asymmetrically using a Sharpless asymmetric epoxidation as a key step (Scheme 55).

4. Developed several methods of synthesizing previously unknown hexakis[(*Z*)-enynyl]benzenes, including *via* the use of palladium-mediated couplings of potassium trifluoroborate salts.

5. Synthesized several hexasubstituted benzenes (*e.g.*, **417** and **418**) *en route* to a synthesis of buckminsterfullerene.

PUBLICATIONS

1. Matthew D. Clay and Alex G. Fallis. "Acetylenic Allenophanes: An Asymmetric Synthesis of a bis-Alleno-bis-butadiynyl-*meta*-cyclophane." *Angew. Chem. Int. Ed.* **2005**, *44*, 4039-4042.

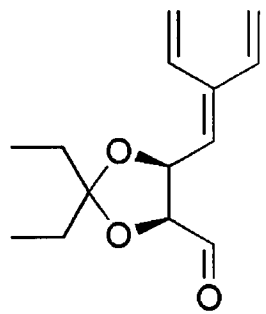
2. Matthew D. Clay, Ditte Riber and Alex G. Fallis. "Competing Diels-Alder Intramolecular Pathways from Cross Conjugated Trienes: Fused Hydrindenones (Bicyclo[4.3.0]nonenones) versus Bridged Ring (Bicyclo[3.3.1]nonenones) Adducts from a Diene-Transmissive Precursor." *Can. J. Chem.* **2005**, *83*, 559-568.

3. Pierre E. Tessier, Natalie Nguyen, Matthew D. Clay and Alex G. Fallis. "Aryl Annulation of Cyclic Ketones *via* a Magnesium Carbometalation-6-π Electrocyclization Protocol." *Org. Lett.* **2005**, *7*, 767-770.

APPENDIX

A

SELECTED ^{1}H AND ^{13}C SPECTRA



89

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
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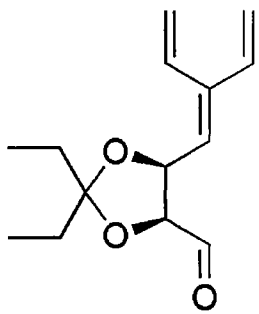
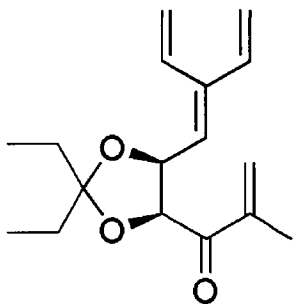
30
20
ppm



89



92

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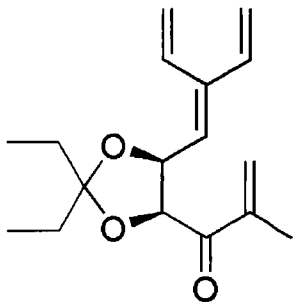

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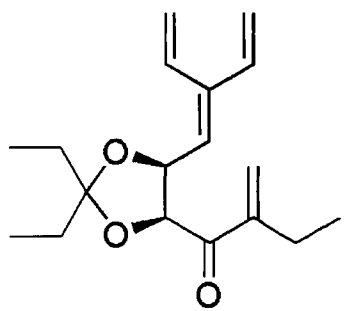

68

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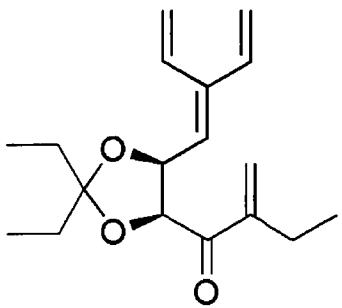

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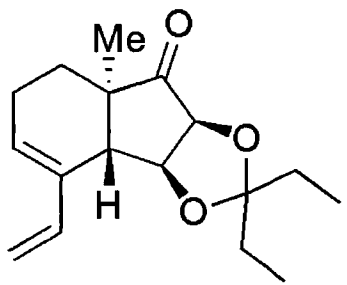

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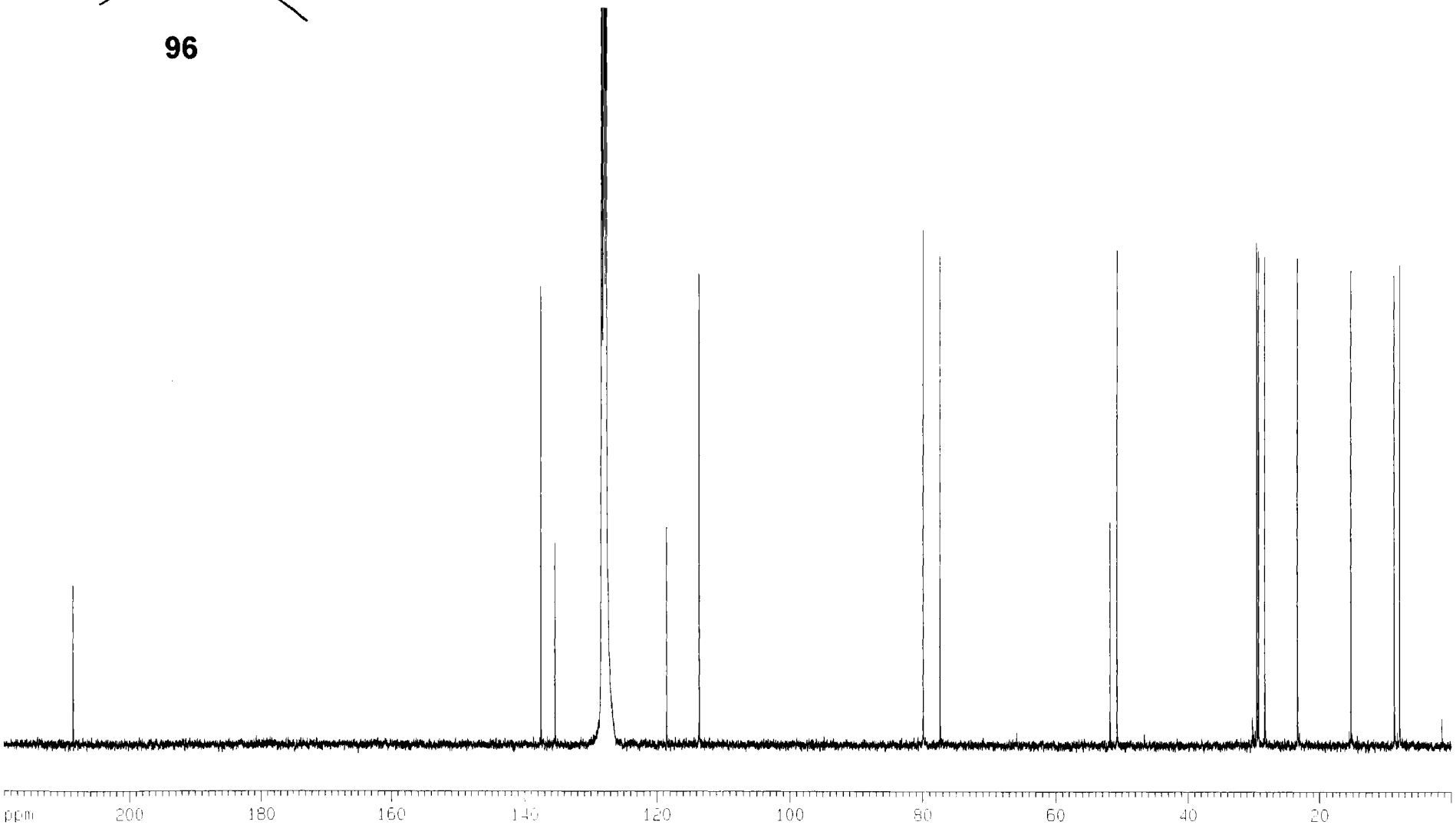

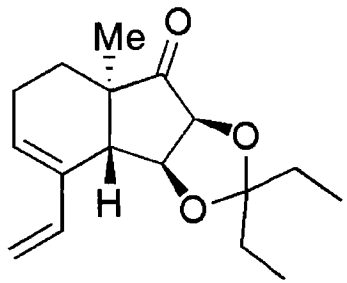

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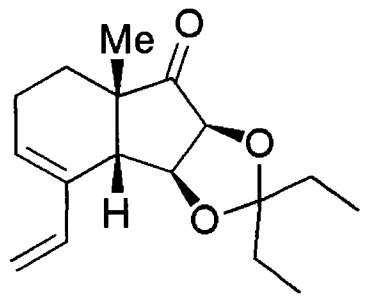

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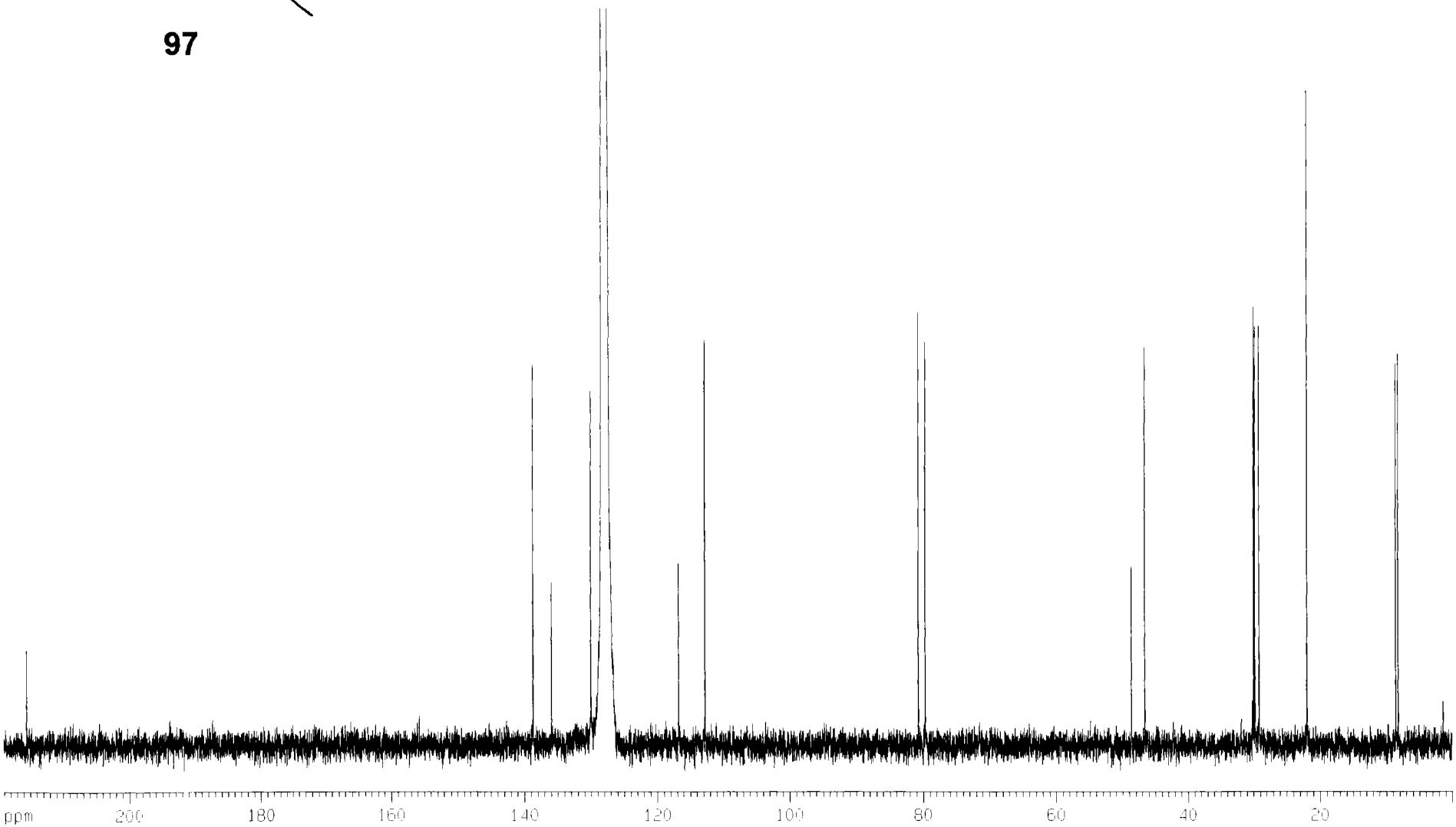

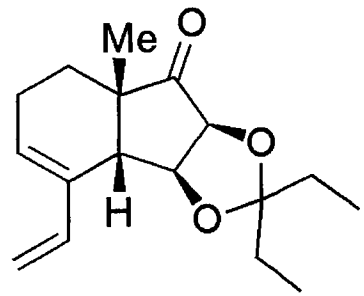

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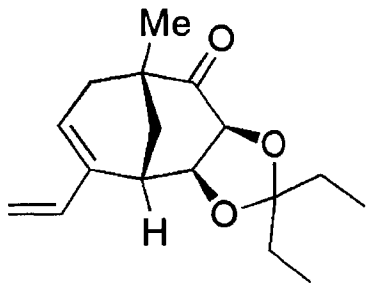

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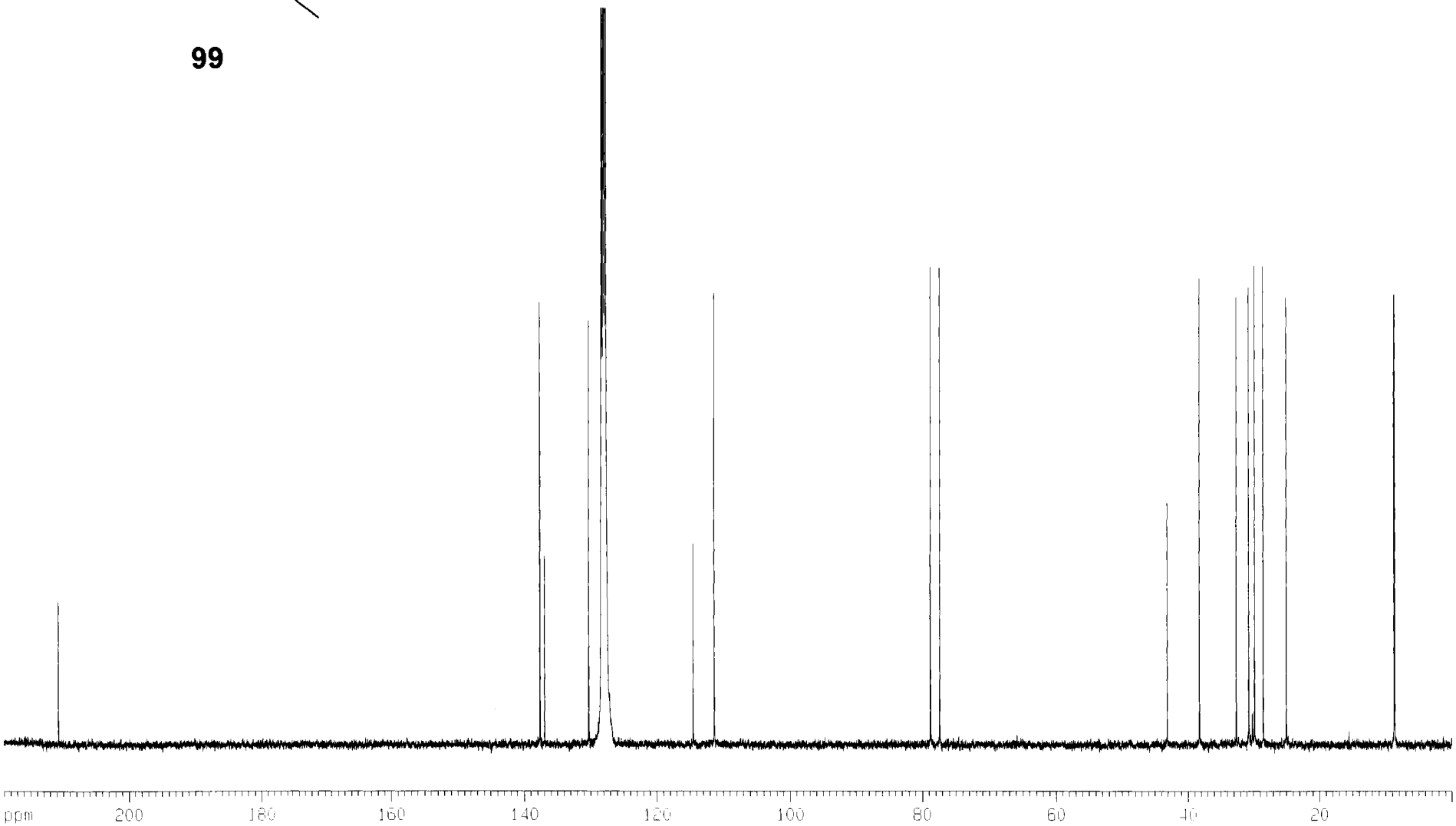

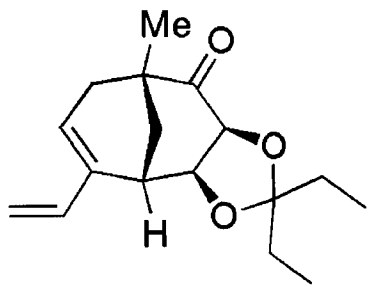

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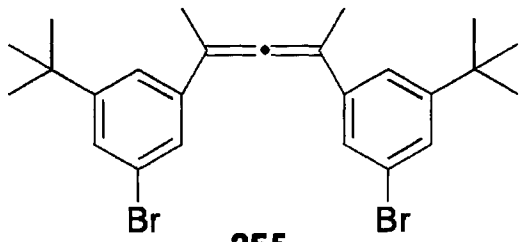
Br
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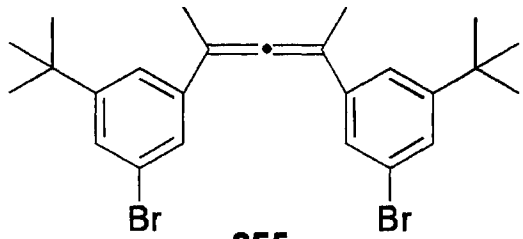

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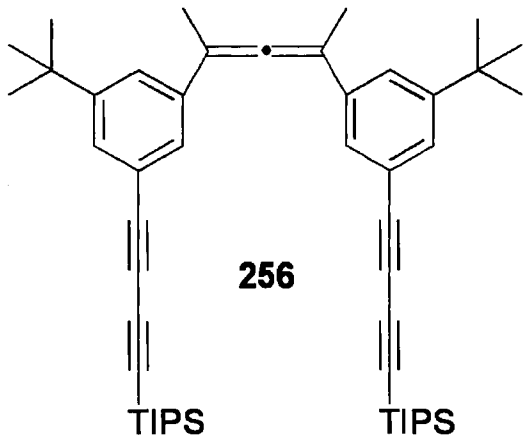
TIPS
TIPS

256

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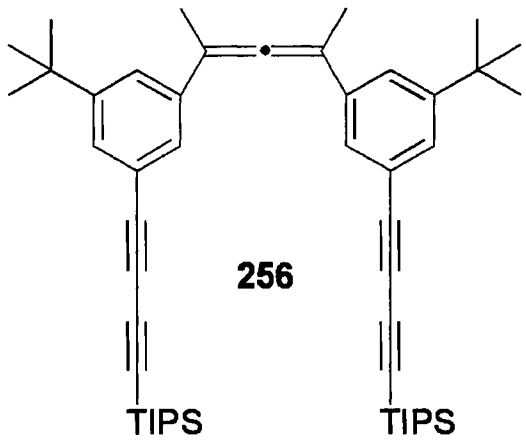

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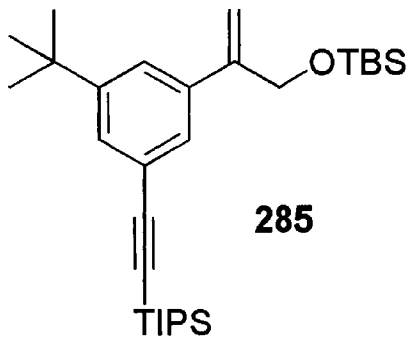
OTBS
TIPS

285

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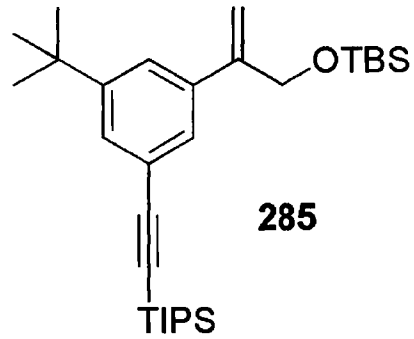

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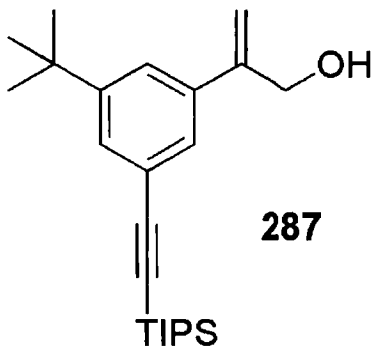
OH
TIPS

287

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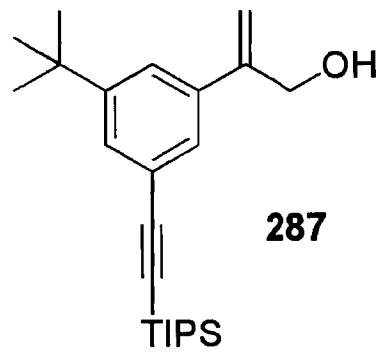

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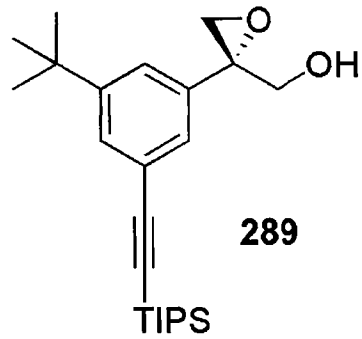
O
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TIPS

289

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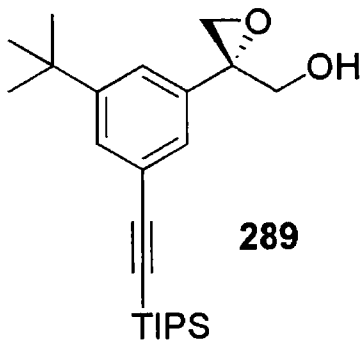

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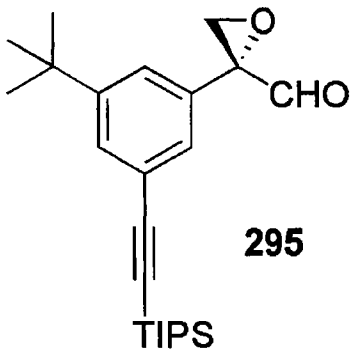
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TIPS

295

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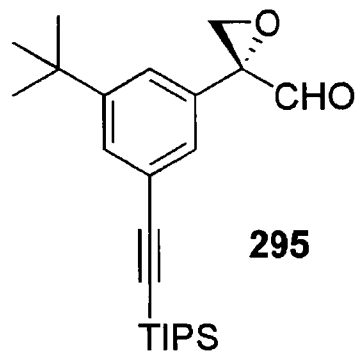

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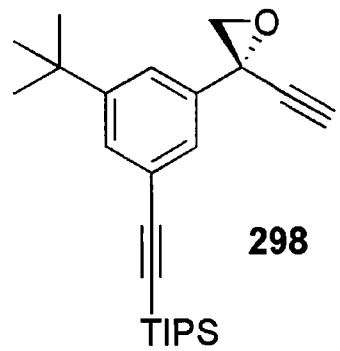
O
TIPS

298

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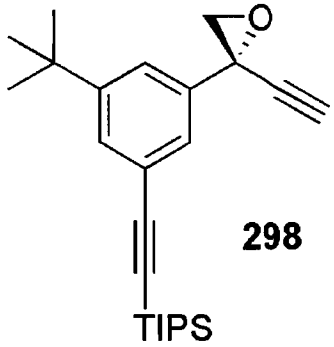

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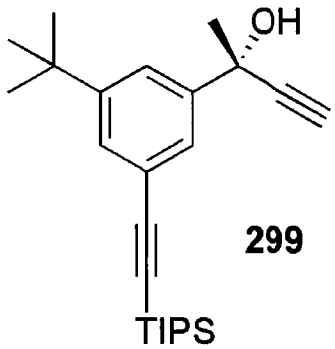
OH
TIPS

299

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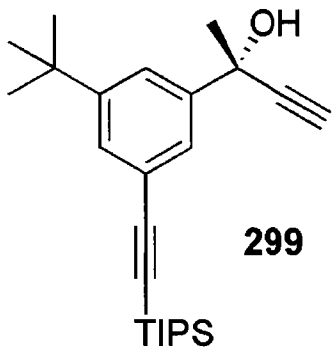

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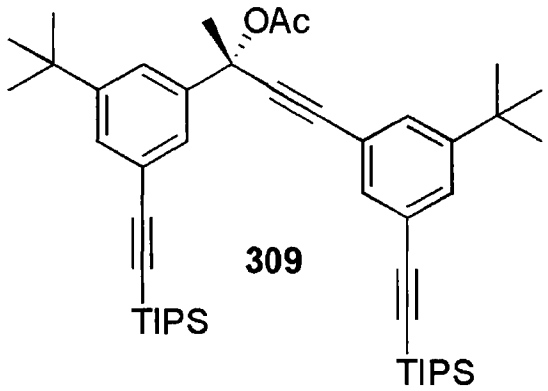
OAc
TIPS
TIPS

309

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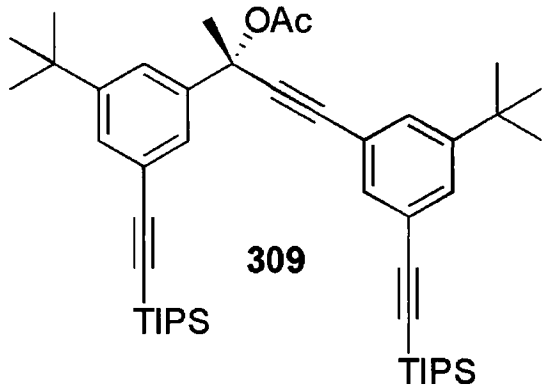

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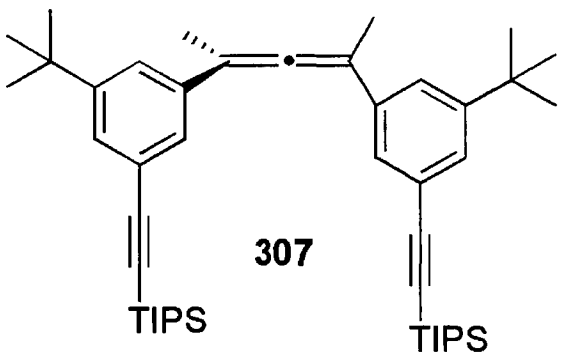
TIPS
TIPS

307

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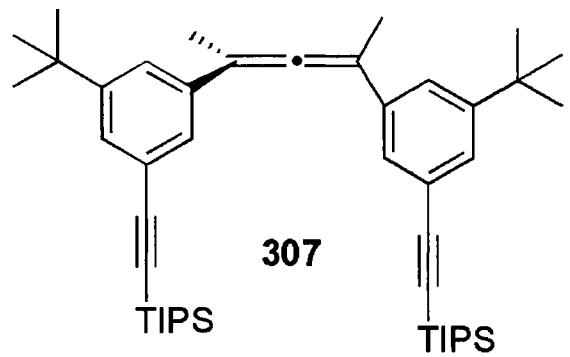

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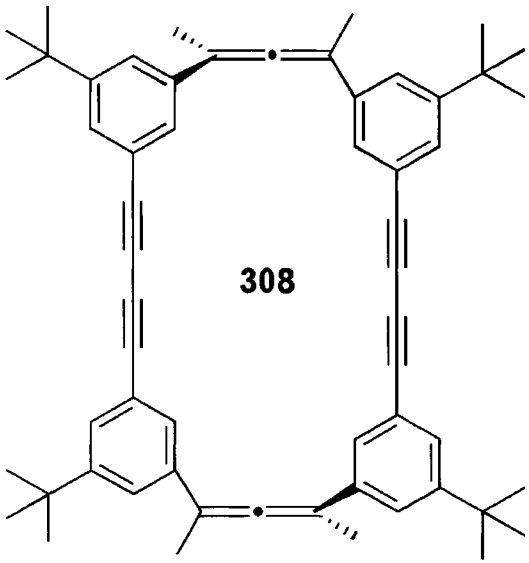
308

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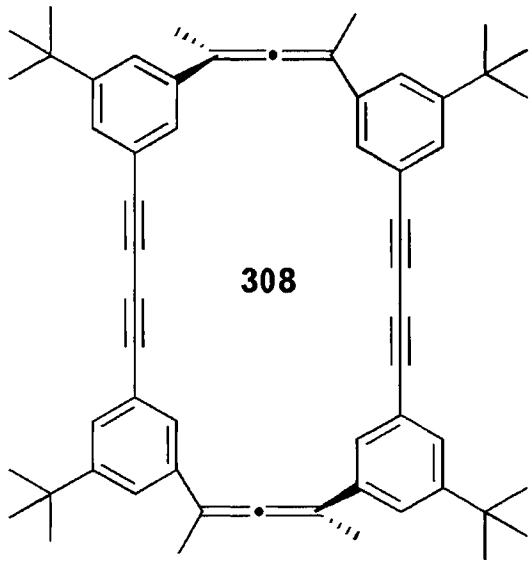
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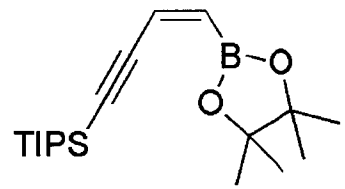
B
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TIPS

392

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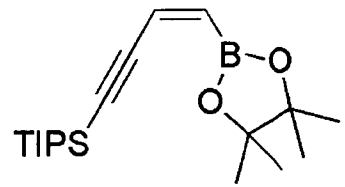

392


TMS
BF3K

411

190
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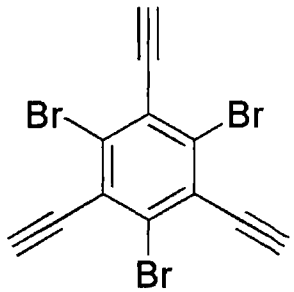
411


Br
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Br

407

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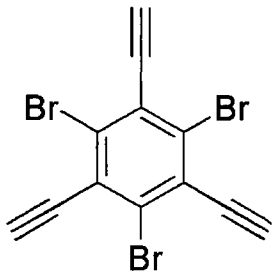

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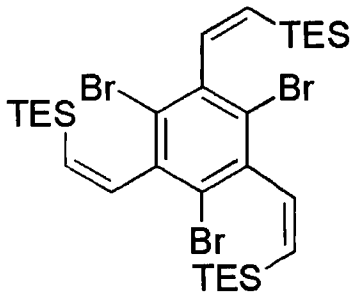
TES
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408

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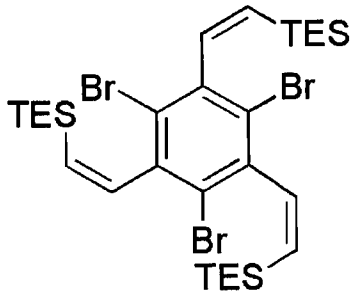
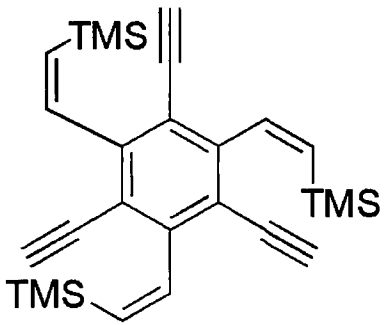


408


TMS
TMS
TMS

417

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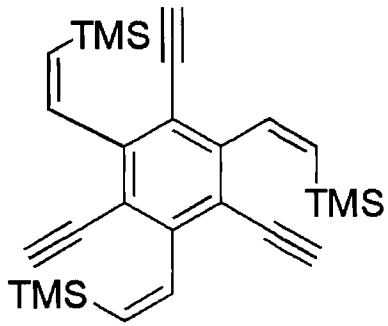
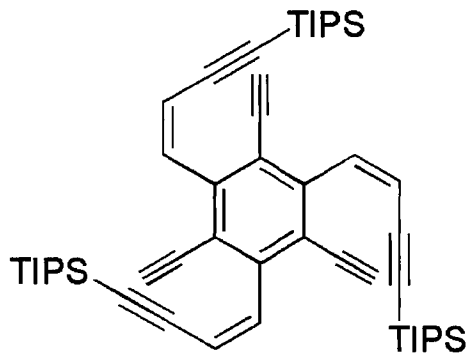


417


TIPS
TIPS
TIPS

418

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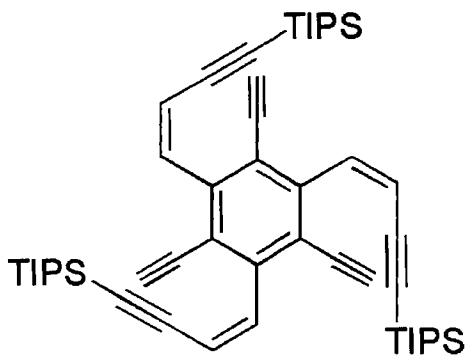
ppm



418