

**I. The Enantioselective Synthesis of Chiral Allenyl Carbonyl Compounds and
Their Use as Synthetic Intermediates**

**II. Rhodium-Catalyzed C-H Functionalization: Application to the Synthesis
of 3-Carboxylindoles and Attempted Applications to Allenes**

By

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Dedicated to Keith Fagnou

*“ Tho’ much is taken, much abides; and tho’
We are not now that strength which in old days
Moved earth and heaven, that which we are, we are;
One equal temper of heroic hearts,
Made weak by time and fate, but strong in will
To strive, to seek, to find, and not to yield. ”*

- **Alfred, Lord Tennyson, 1833**

*“ The only guide to a man is his conscience; the only shield to his
memory is the rectitude and sincerity of his actions. It is very imprudent
to walk through life without this shield, because we are so often mocked
by the failure of our hopes and the upsetting of our calculations; but
with this shield, however the fates may play, we march always in the
ranks of honour. ”*

- **Winston Churchill, 1940**

Abstract

Allenes are unique compounds in organic chemistry by virtue of their adjacent, orthogonal π -bonds. While of limited use in and of themselves, some classes of allenes have found use in organic synthesis as building blocks for more complex products. Previous work in the Fagnou group has identified a silver lewis acid-catalyzed enantioselective isomerization protocol for the synthesis of allenyl esters and amides. This protocol has been subject to reproducibility issues, the source of which is explored in this thesis. Initial work into the development of a phase-transfer catalytic process for the isomerization of alkynyl amides is also presented.

The use of allenyl esters in lactonization reactions has become more common in recent years. The scope of the halolactonization of allenyl esters to form halobutenolides is explored here. The lactonization of allenyl carboxylic acids has also been demonstrated in the literature. The attempted synthesis of allenyl carboxylic acids *via* the oxidative deprotection of dimethoxybenzyl esters is also presented.

Indole is an important and biologically and medicinally relevant compound in organic synthesis. Though many classical methods for its synthesis exist, the discovery of new, complex indole-containing compounds necessitates the development of efficient ways to synthesize indoles. Previous work in the Fagnou group has led to the discovery of a rhodium-catalyzed oxidative synthesis of indole with a key C-H functionalization step. This protocol has been applied to alkynyl esters to synthesize an array of 3-carboxylindoles in moderate to good yields.

The competency of allenes as an intra- and intermolecular coupling partner in a similar rhodium-catalyzed hydroarylation reaction has also been explored, leading to the discovery that allenyl compounds are not tolerated in this reaction protocol.

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And finally, thank you Keith. What can I say here about you that hasn't yet been said? My greatest regret in life is having never taken the chance to truly thank you for everything you did for me. You took me as a summer student back when I was an undergrad and gave me my shot, even though I had no scholarship at first. I attribute all my present and future success to the opportunities you gave me, your welcome advice and patient guidance. Not a day goes by that I don't think about you or something I learned as a direct result of being your student. Words cannot express the debt that I owe you, and I will spend the rest of my life hoping that wherever you are, you are proud of me.

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Glossary of Abbreviations

Å – angstrom (10^{-10} m)	R – generic carbon containing group
Ac – acetyl	TBAI – tetrabutylammonium iodide
AcO – acetate	TBAP – tetrabutylammonium phosphate
AcOH – acetic acid	TBS – <i>tert</i> -butyl-di-methylsilyl
<i>t</i> -AmOH – <i>tert</i> -amylalcohol	TCP – tetra(<i>p</i> -chlorophenyl)porphyrin
Ar – generic aryl group	Tf – trifluoromethanesulfonyl
Bn – benzyl	TFA – trifluoroacetic acid
Boc – <i>t</i> -butoxycarbonyl	THF – tetrahydrofuran
<i>n</i> -Bu – <i>n</i> -butyl	TMS – trimethylsilyl or tetramethylsilane
<i>t</i> -Bu – <i>t</i> -butyl	Ts – <i>p</i> -toluenesulfonyl
CDCl ₃ – chloroform- <i>d</i> ₃	X – generic halide
CDK – cyclin dependant kinase	
CMD – concerted metallation-deprotonation	
Cp* – 1,2,3,4,5-pentamethylcyclopentadienyl	
Cy – cyclohexyl	
DCE – 1,2-dichloroethane	
DCM – dichloromethane	
DDQ – 2,3-dichloro-5,6-dicyanobenzoquinone	
DMF – <i>N,N</i> -dimethylformamide	
Et – ethyl	
FTIR – Fourier transform infrared	
Het – generic aromatic heterocycle	
<i>n</i> -Hex – <i>n</i> -hexyl	
HMDS – hexamethyldisilazide	
HPLC – high-performance liquid chromatography	
HRMS – high resolution mass spectrometry	
L – generic ligand	
LDA – lithium diisopropylamide	
LG – generic leaving group	
M – generic metal	
Me – methyl	
MOM – methoxymethyl	
MS – molecular sieves	
NIS – <i>N</i> -iodosuccinimide	
NMM – <i>N</i> -methylmorpholine	
NMR – nuclear magnetic resonance	
NSAID – non-steroidal anti-inflammatory drug	
[O] – generic oxidant	
PGE ₂ – prostaglandin E ₂	
Ph – phenyl group	
Piv – pivaloyl	
PivOH – pivalic acid	
<i>n</i> -Pr – <i>n</i> -propyl	
py – pyridine	

Part 1: The Enantioselective Synthesis of Chiral Allenyl Carbonyl Compounds and Their Use as Synthetic Intermediates

1 Introduction

1.1 Allenes

Since the first prediction of their existence in 1875 by Van't Hoff,¹ allenes have fascinated synthetic and organic chemists. The first attempts to synthesize an allene in 1887 by Burton and von Pechman² were in fact analytically inconclusive since the allene was nearly indistinguishable from the isomeric alkyne. It was not until nearly 70 years later with the advent of IR spectroscopy that the cumulated structure of their compound was confirmed.³ Possibly the most intriguing of the physical properties of allenes is their ability to exhibit axial chirality by virtue of their adjacent, orthogonal π -bonds which form an elongated tetrahedron. As such, allenyl compounds without C_2 -symmetric axes are non-racemic (Figure 1.1).

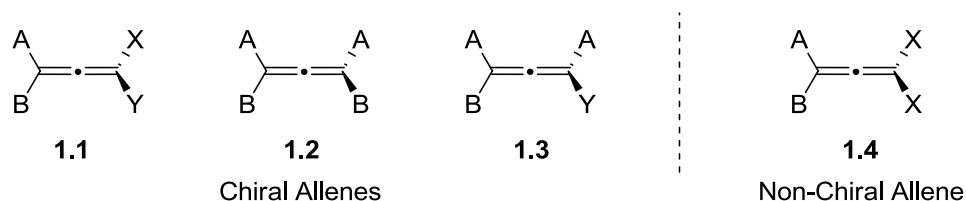


Figure 1.1: Configurations of Chiral and Non-Chiral Allenes

In addition to their aesthetic qualities, allenes are also found in many natural products⁴ (Figure 1.2), the most famous of which is Grasshopper Ketone (**1.5**) a simple sesquiterpene which was isolated from the defensive secretion of the grasshopper species *romalea microptera*.⁵

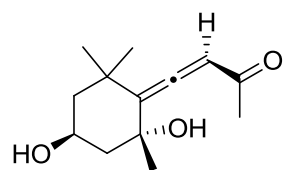
¹ Van't Hoff, J.H. *La Chimie dans L'Espace*, Rotterdam, **1875**.

² Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

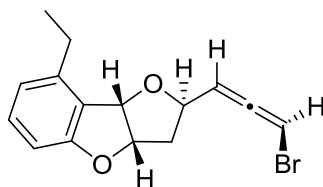
³ Jones, E. R. H.; Mansfield, G. H.; Whiting, M. L. H. *J. Chem. Soc.* **1954**, 3208.

⁴ Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.

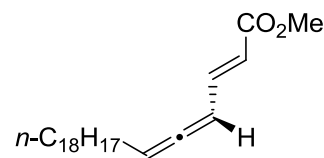
⁵ Meinwald, J.; Erickson, K.; Hartshorn, M.; Meinwald, Y. C.; Eisner, T. *Tetrahedron Lett.* **1968**, 2959.



Grasshopper Ketone
1.5



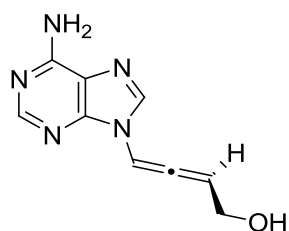
Panacene
1.6



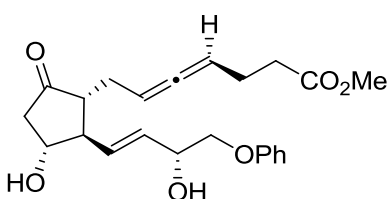
Insect Pheromone
1.7

Figure 1.2: Selected Allenic Natural Products

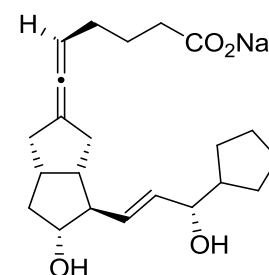
In addition to naturally-occurring allenes, a number of pharmaceutically active allene-containing molecules have been developed (Figure 1.3).⁴



Adenallene 1.8
Nucleoside Analog



Enprostil 1.9
Gastric Acid Secretion Inhibitor



SC-43350 1.10
Antithrombotic Agent

Figure 1.3: Allenic Pharmaceutical Compounds

The anti-ulcer prostaglandin analog drug Enprostil (**1.10**) was the one of the first successfully marketed small molecule drugs containing an allene motif.⁶ It has been found to have gastric acid secretion inhibition over 600 times greater than that of PGE₂.⁷ Enprostil is manufactured as a racemic mixture of diastereomers about the chiral axis of the allene. Allenyl esters and amides have also been recently explored as cysteine protease inhibitors.⁸ The small number of allene-containing pharmaceutically active molecules that exist today is most likely due to challenges in their synthesis.⁹ Furthermore, enantiopure syntheses of useful allene classes have proved to be

⁶ Eglen, R. M.; Whiting, R. L. *Br. J. Pharmacol.* **1989**, *98*, 1335.

⁷ Carpio, H.; Cooper, G.; Edwards, J.; Fried, J.; Garay, G.; Guzman, A.; Mendez, J. A.; Muchowski, J.; Roszkowski, A. P.; Van Horn, A.; Wren, D. *Prostaglandins* **1987**, *33*, 169.

⁸ Takeuchi, Y.; Fujiwara, T.; Shimone, Y.; Miyataka, H.; Satoh, T.; Kirk, K. L.; Hori, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6202.

⁹ Ban, H. S.; Onagi, S.; Uno, M.; Nabeyama, W.; Nakamura, H. *ChemMedChem* **2008**, *3*, 1094.

relatively rare. Therefore, new, effective methods to synthesize allenes, especially stereoselectively, are of great importance to the field of organic and synthetic chemistry.¹⁰

1.2 Synthesis of Acceptor-Substituted Allenes

One class of allene is known as an acceptor-substituted allene. These allenes are characterized by an electron-withdrawing group conjugated to one of the double bonds. These electron-withdrawing groups are typically carbonyl groups or other resonance-stabilizing groups such as sulfones and sulfoxides (Figure 1.4).

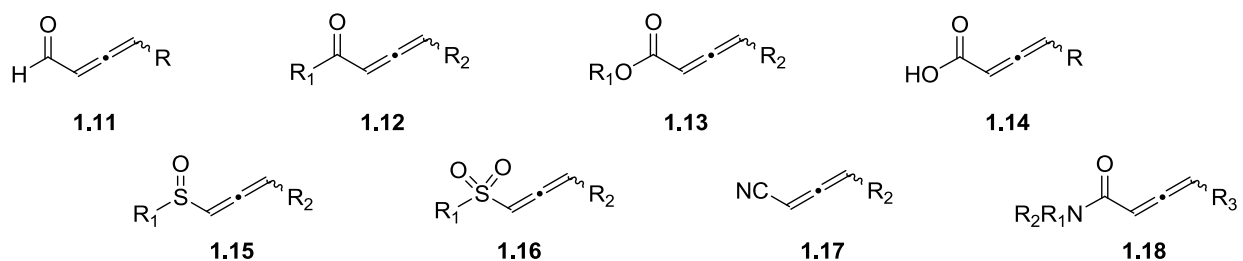


Figure 1.4: Examples of Acceptor-substituted Allenes

These allenes have practical uses due to the fact that one of the two double bonds in the molecule is electron-poor, while the other is, by comparison, more electron-rich. This allows differentiation of the two double bonds based purely on their electronics and this reactivity profile is known as ambiphilicity.¹¹ This summary will be focused predominately on allenyl esters owing to their far greater diversity of research as compared to the other subclasses of acceptor allenes.

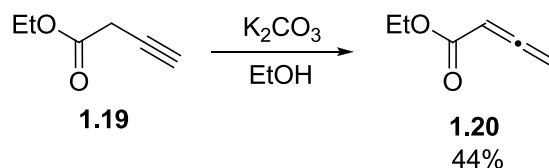
¹⁰ For general reviews on the enantioselective synthesis of allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry vol. 1* **2004**, Wiley-VCH, Weinheim; Hassan, H. H. A. M. *Curr. Org. Synth.* **2007**, *4*, 413; Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933; Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671; Ogasawara, M.; Watanabe, S. *Synthesis* **2009**, 1761; Ogasawara, M. *Tetrahedron: Asym.* **2009**, *20*, 259.

¹¹ For an example of the reactions of ambiphilic allenes, see: Tejedor, D.; Méndez-Abt, G.; González-Platas, J.; Ramírez, M. A.; García-Tellado, F. *Chem. Commun.* **2009**, 2368.

1.2.1 Achiral Synthesis of Acceptor Allenes

A common method to synthesize achiral or racemic acceptor-substituted allenes is by protopic isomerization of a compound containing a propargyl electron-withdrawing group. This is due to the relative acidity of the α -proton and the relative energetic stability of the isomeric allene as compared to the alkyne by virtue of the conjugation of the allene with the electron-withdrawing group. This energetic stability of an allenyl ester over a propargyl alkyne, for example, is in fact the reverse of the stability trend for simple isomeric hydrocarbons where it has been calculated that propyne is approximately 2.1 kcal/mol *more* stable than allene.¹² Whiting *et al.* were the first to publish the isomerization of a acetylenic ester to the corresponding allenic ester in 1954 using dilute ethanolic potassium carbonate solution (Scheme 1.1).¹³

Scheme 1.1: Isomerization of an Alkynyl Ester to its Corresponding Allenyl Ester with Potassium Carbonate

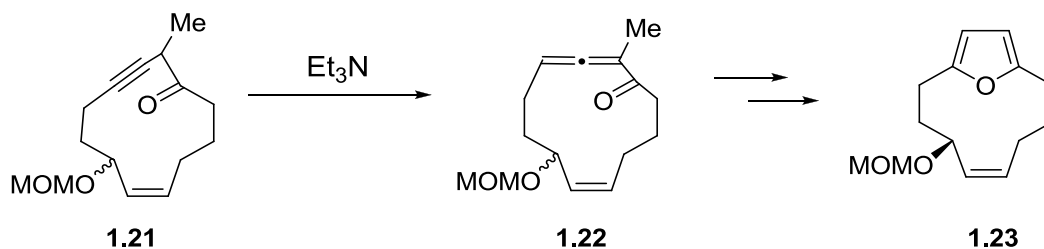


More recently, the Marshall group used a protopic isomerization mediated by triethylamine in their progress towards the total syntheses of 2,5-furanocycles on the way to such natural products as pukalide, lophotoxin and kallolide A and B (Scheme 1.2).

¹² Radom, L.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 5339; Kakkar, R. *Int. J. Quantum Chem.* **2003**, *94*, 93.

¹³ Eglinton, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3197.

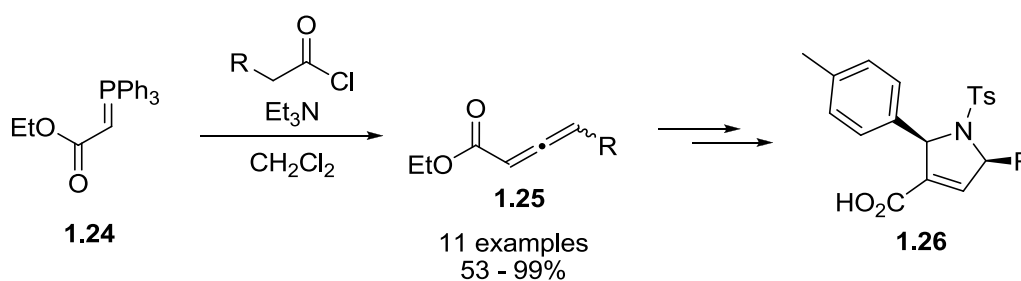
Scheme 1.2: Synthesis of 2,5-furanocycles *via* Prototypic Isomerization of Alkynyl Esters



1.2.2 Racemic Synthesis of Allenyl Esters

Widespread methods of generating racemic allenyl esters include the isomerization method detailed above or by either Wittig or Horner-Wadsworth-Emmons olefinations of ketenes. Indeed, Wadsworth and Emmons themselves were the first to show that this was possible back in 1961.¹⁴ More recently, a series of Wittig reactions of ketenes, (generated *in situ* by the deprotonation of an acyl chloride with triethylamine,) was used to generate an array of disubstituted allenyl esters **1.25** which were derivatized eventually to a library of small-molecule inhibitors of geranylgeranyltransferase type I (GGTase-I) **1.26** (Scheme 1.3).¹⁵

Scheme 1.3: Olefination of an *in situ* Prepared Ketene to Generate Racemic Allenyl Esters



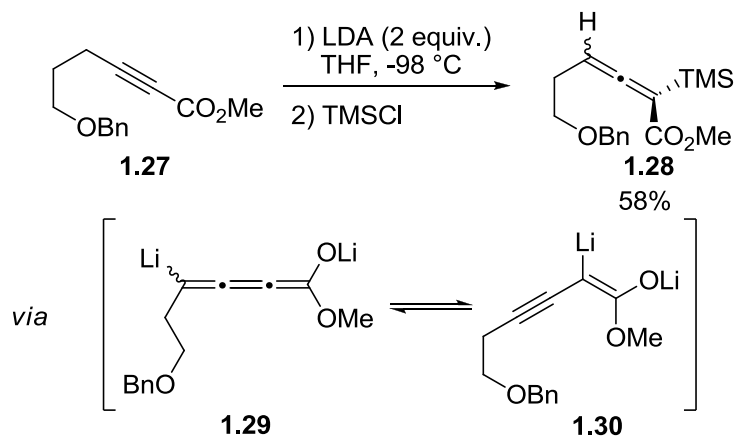
The Lepore group in Florida has taken a somewhat different isomerization approach to the synthesis of allenyl esters. Starting from α -alkynyl esters and using a trimethylsilyl chloride

¹⁴ Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

¹⁵ Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843.

as an alkylating agent, they have been able to report the formation of allenyl esters selectively over the corresponding α,α -disubstituted β -alkynyl esters (Scheme 1.4).¹⁶

Scheme 1.4: Synthesis of Allenyl Esters from α -alkynyl Esters



By using LDA as their base, they propose that they are able to form a dilithiated cumulenoate **1.29** which is in equilibrium with isomeric alkynyl enolate **1.30**, but electrophilic quench leads to allenyl ester **1.28** as the sole isolated product. Interestingly, if the α,α -disubstituted β -alkynyl ester is desired over the allene, 2 equivalents of *n*-butyllithium can be added between the LDA addition and electrophilic quench to force the formation of this product.¹⁷

1.2.3 Enantioselective Synthesis of Acceptor Allenes

Once thought as incredibly difficult to obtain in their enantiopure form, there are now many modern ways to synthesize enantioenriched allenyl esters. Several reviews exist¹⁸ on this topic and below are several key examples of the more important reactions.

¹⁶ Lepore, S. D.; He, Y.; Damisse, P. *J. Org. Chem.* **2004**, *69*, 9171.

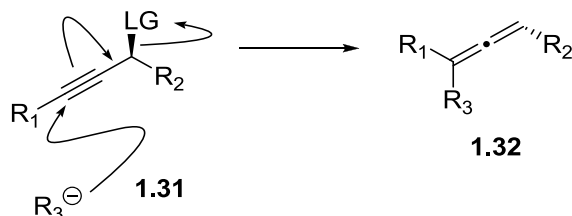
¹⁷ Lepore, S. D.; He, Y. *J. Org. Chem.* **2005**, *70*, 4546.

¹⁸ Rossi, R.; Diversi, P. *Synthesis* **1973**, 25; Miesch, M. *Synthesis* **2004**, 746; Ogasawara, M. *Tetrahedron: Asym.* **2009**, *20*, 259.

1.2.3.1 Chiral Allenes from Enantioenriched Propargyl Leaving Groups

One of the most general methods to synthesize simple chiral allenes is by the S_N2' displacement of a propargyl leaving group by a suitable nucleophile (Scheme 1.5).

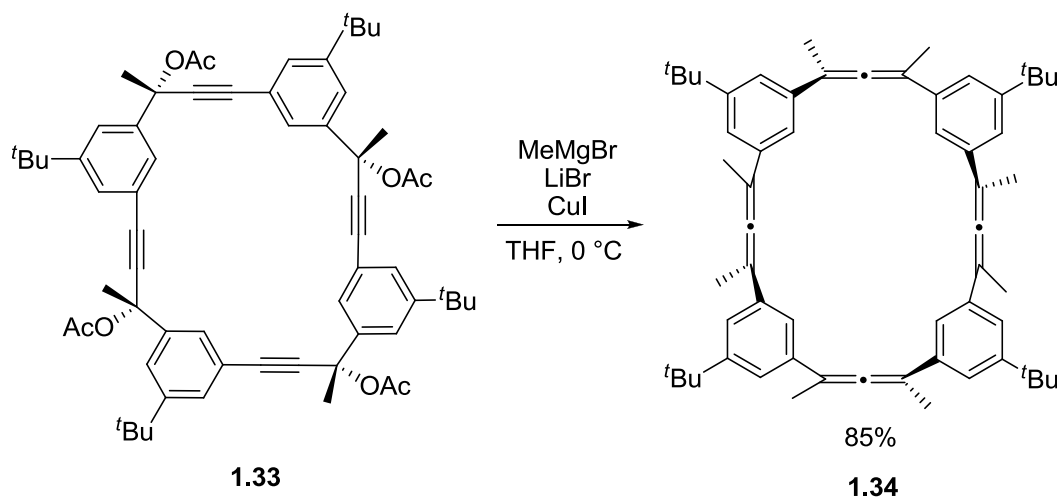
Scheme 1.5: Mechanism of S_N2' Displacement of Propargyl Leaving Groups to form Chiral Allenes



This method was utilized recently by the Fallis group in their synthesis of allenophanes (Scheme 1.6)¹⁹. The nucleophile used in this case was a large excess of a methyl grignard reagent which yielded 85% of the desired allenophane **1.34**. However, the propargyl acetate **1.33** must be synthesized through a lengthy route *via* the chiral epoxidation of an allyl alcohol, oxidation of the alcohol to the aldehyde, reduction of the epoxide, alkylation of the aldehyde and lastly, protection of the alcohol as the acetate.

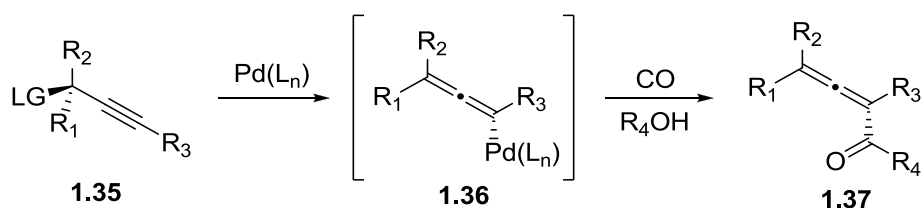
¹⁹ Leclère, M.; Fallis, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 568.

Scheme 1.6: Synthesis of an Allenophane by S_N2' Displacement of a Chiral, Propargyl Leaving Group



This general protocol can be modified to form allenyl esters by the use of palladium. The use of a transition metal allows for the formation of a chiral allenylmetal compound and if the reaction is performed under an atmosphere of carbon monoxide and in the presence of an alcohol, carbonylation and esterification can ensue (Scheme 1.7).

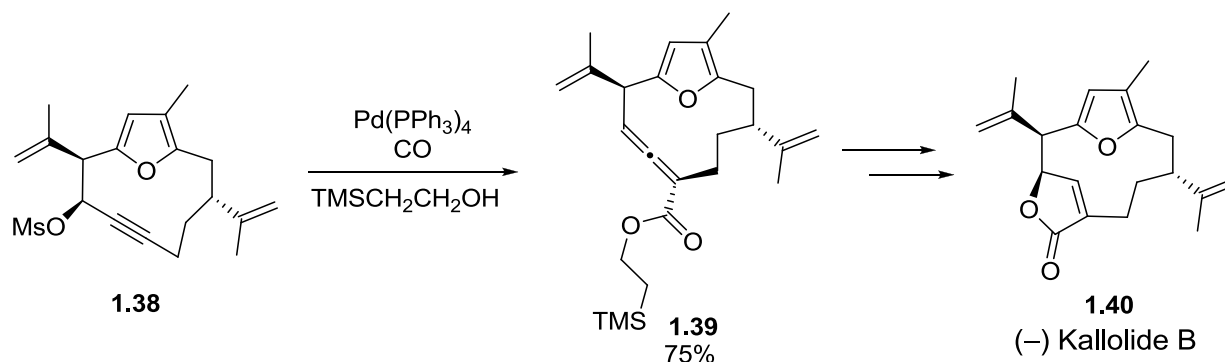
Scheme 1.7: Carboxylation of a Chiral Allenylpalladium Intermediate to form an Allenyl Ester



This method was used by Marshall *et al.* as a step towards the total synthesis of the enantiomer of natural Kallolide B (Scheme 1.8).²⁰ Alkoxy carbonylation of propargyl mesylate **1.38** efficiently gave allenyl ester **1.39** in 75% yield which was transformed into the butenolide incorporated into the macrocycle of (-)-Kallolide B **1.40**.

²⁰ Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729.

Scheme 1.8: Palladium-catalyzed Formation of an Allenyl Ester in Marshall's Synthesis of (-)-Kallolide B



The main drawback of these methods is that the chirality must be set in the starting material before the allene is formed, which, depending on the methods available, may require more synthetic manipulations.

1.2.3.2 Olefination of Ketenes with Chiral Phosphines

With the development of a diverse array of chiral phosphines for various purposes, enantioenriched phosphines have found use in the synthesis of chiral allenes *via* the Wittig and Horner-Wadsworth-Emmons reactions as well.

In 2007, Tang, Shen and co-workers reported the synthesis of a “pseudo- C_2 -symmetric” chiral phosphorus ylide for the expressed purpose of preparing enantioenriched allenyl esters, amides, ketones and nitriles.²¹ Therein, they describe the four-step sequence needed to synthesize an optically active phosphonium salt which could then be deprotonated to form the desired phosphorus ylide **1.41**. This ylide, when reacted with a ketene, led to transfer of chirality and enantioselectively formed chiral allenes in moderate to good yields (Table 1.1). Unfortunately, the fact that the phosphorus ylide must be synthesized beforehand and used in stoichiometric quantities limits the usefulness of this method.

²¹ Li, C.-Y.; Zhu, B.-H.; Ye, L.-W.; Jing, Q.; Sun, X.-L.; Tang, Y.; Shen, Q. *Tetrahedron* **2007**, *63*, 8046.

Table 1.1: Tang and Shen's Synthesis of Acceptor Allenes *via* Olefination of Ketenes with a Chiral Phosphorus Ylid.

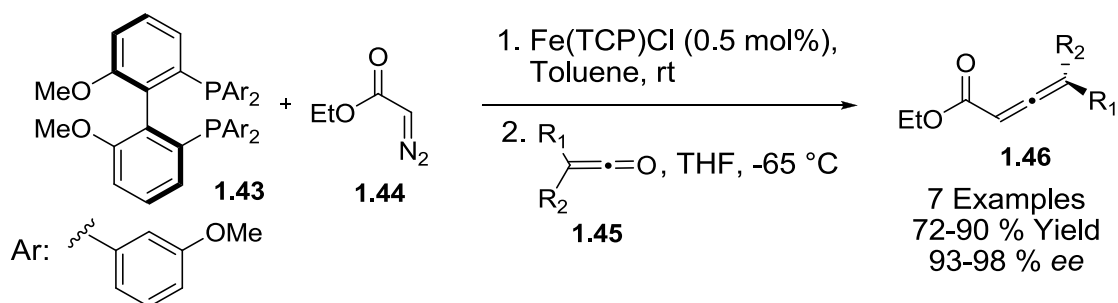
Reaction scheme showing the olefination of a ketene with a chiral phosphorus ylid **1.41** to form an acceptor allene **1.42**. The reaction conditions are THF, -20 °C, 24 h.

Entry	X	Yield ^b (ee)
1		80% (81)
2		69% (32)
3		76% (60)
4		65% (20)
5		65% (40)

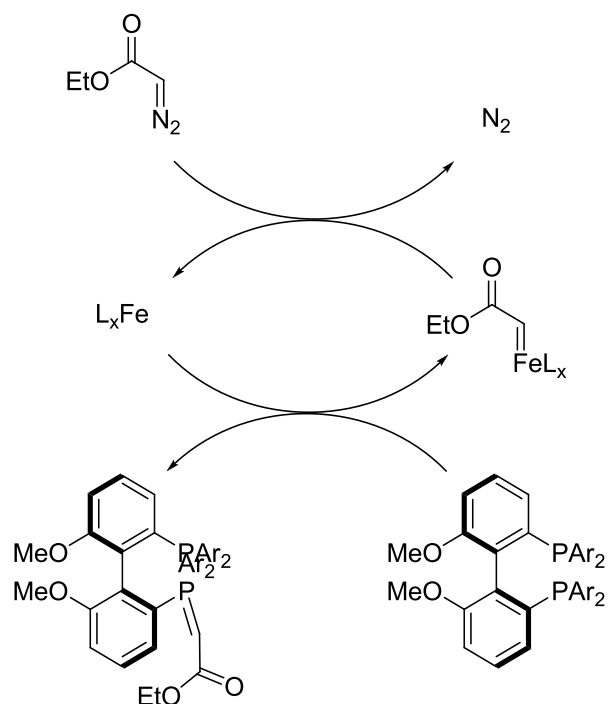
Tang and co-workers, also in 2007, improved upon this methodology by developing an impressive synthesis of chiral allenyl esters *via* the olefination of ketenes with ethyldiazoacetate under iron porphyrin catalysis using a chiral phosphine (Scheme 1.9).²² Excellent yields and enantioselectivities were obtained, and the reaction could take place using the easily accessible phosphine **1.43** whose oxide could be isolated from the reaction mixture. This phosphorus oxide could then be reduced and reused in subsequent reactions without loss of reactivity, though stoichiometric quantities of it were still required. In this case, the necessary phosphorus ylide was made *in situ* using an iron porphyrin catalyst and ethyldiazoacetate (Scheme 1.10).

²² Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494.

Scheme 1.9: Enantioenriched Allenyl Esters from Iron Porphirin-catalyzed Horner-Wadsworth-Emmons with a Chiral Phosphine



Scheme 1.10: Proposed Iron Catalytic Cycle to Generate Phosphorus Ylide

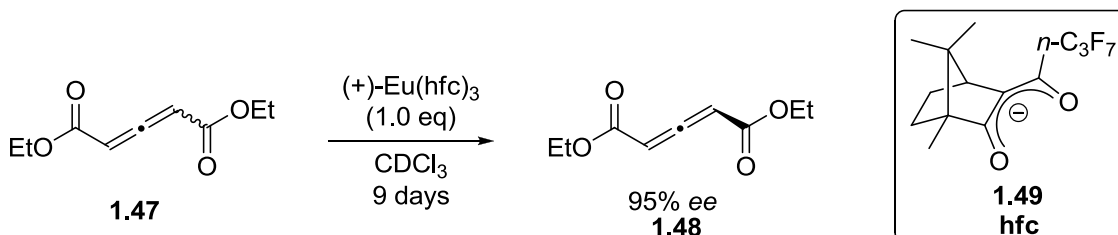


1.2.3.3 Deracemization of Racemic Allenyl Esters

Naruse and co-workers discovered that by reacting racemic allene dicarboxylates with a Lewis-acid, they could effect slow deracemization to give the enantioenriched allene (Scheme

1.11).²³ The Lewis acid of choice in this case was a europium-based complex, (+)-Eu(hfc)₃ **1.49**, commonly used as an NMR shift reagent and in fact these reactions were run in an NMR tube.

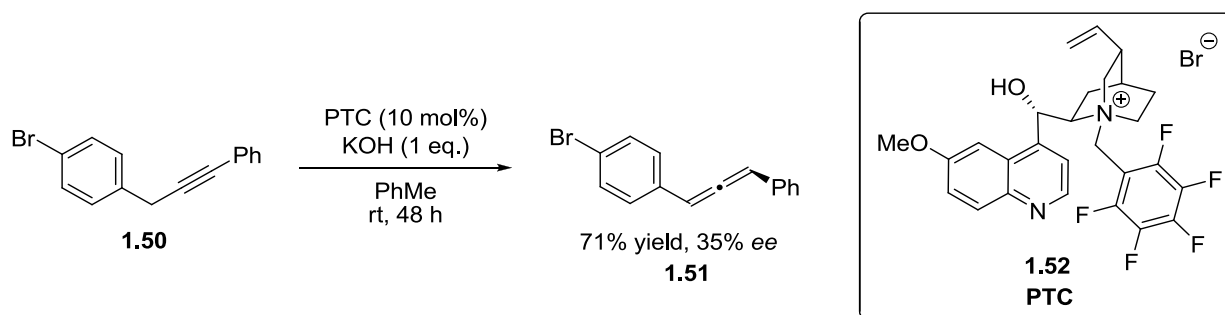
Scheme 1.11: Europium Lewis Acid-catalyzed Deracemization of Allene Dicarboxylates



1.2.3.4 Isomerization

While 1,3-proton shifts of propargyl compounds to allenes are well known (*vide supra*), very few catalytic, enantioselective isomerizations have been reported in the literature. Arai, Shiori and co-workers reported this very transformation under phase-transfer catalysis in 2000 (Scheme 1.12).²⁴ While no allenyl esters are represented in this report, it nonetheless served as a proof of concept that enantioselectivity could be obtained through isomerization.

Scheme 1.12: Catalytic Isomerization of a Propargyl Compound with Enantioenrichment Under Phase-transfer Conditions



During the course of our investigations of a catalytic, enantioselective isomerization of homopropargyl esters to allenic esters, very similar work was being done concurrently by the

²³ Naruse, Y.; Watanabe, H.; Inagaki, S. *Tetrahedron: Asymmetry* **1992**, 3, 603; Naruse, Y.; Watanabe, H.; Ishiyama, Y.; Yoshida, T. *J. Org. Chem.* **1997**, 62, 3862.

²⁴ Oku, M.; Arai, S.; Katayama, K.; Shiori, T. *Synlett* **2000**, 493.

Tan group in Singapore.²⁵ This work culminated in the publication of an article outlining their group's work involving this transformation, employing the chiral guanidine organocatalyst **1.55** as the enantiodiscriminating component. Key examples of this report are summarized in Table 1.2.

This report confirms our findings (*vide supra*) with respect to the feasibility of using a chiral catalyst to effect the transformation of an achiral propargyl ester to an enantioenriched allenyl allene. Unfortunately, they also encountered the problem of allene isolation and chromatographic separation of the allene from the alkynyl starting material has not to date been made possible by any group.

²⁵ Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212.

Table 1.2: The Tan Group's Catalytic, Enantioselective Isomerization of Homopropargyl Esters to Allenic Esters

Reaction scheme showing the isomerization of homopropargyl ester **1.53** to allenic ester **1.54**. Reagents: Guanidine base **1.55** (2 mol%), hexane, $-20\text{ }^{\circ}\text{C}$, 30 h.

Entry	Homopropargyl Ester	Allenic Ester	Yield ^b (ee) ^c
1			70% (91%)
2			62% (95%)
3			70% (91%)
4			80% (93%)
5			39% (89%)
6			60% (93%)
7			76% (79%)

^a Conditions: Guanidine base (2 mol%) dissolved in hexane and cooled to $-20\text{ }^{\circ}\text{C}$. Homopropargyl ester (1 eq.) added and mixture stirred for 30 h. Quenched by filtration through short plug of silica. ^bYields reported as ratio of allene in an inseparable mixture of alkyne and allene. ^cDetermined *via* chiral HPLC.

As can be seen in Table 1.2, the yields for the isomerization are good and the enantioselectivities achieved are excellent in almost all cases. The substrate scope shown above shows only aryl-substituted alkynes, but alkyl-substituted alkynes are also tolerated.

1.3 Practical Uses of Acceptor Allenes in Organic Synthesis

While acceptor-substituted allenes have somewhat limited utility in and of themselves, they have found numerous uses as building blocks in the synthesis of other useful organic compounds, including their obvious roles as Michael acceptors. The following sections address other practical uses for acceptor allenes in organic synthesis.²⁶

1.3.1 Reactions of Racemic Acceptor Allenes

Allenyl esters and acids are the most common acceptor-substituted allenes used as synthetic intermediates in the literature, most likely by virtue of the comparative richness in methods of their synthesis. As such, this summary will focus mainly on the synthetic utility of allenyl esters and acids.

1.3.1.1 Lactonization

One of the most common uses for allenyl esters is intramolecular cyclization, often in the form of a lactonization to form a butenolide. The Ma group in Shanghai have focused much of their research efforts on the conversion of allenyl acids and esters into butenolides (5-membered ring lactones). In these efforts, they and other groups have developed many allenyl acid lactonization protocols involving transition metals such as copper²⁷ and palladium.²⁸

Allenyl esters are somewhat less reactive in lactonization reactions, however recent advances in uncovering their reactivity have been forthcoming. The Marshall group were among the first to explore the iodolactonization of a methyl allenyl ester **1.56** using IBr (Scheme 1.13).²⁹

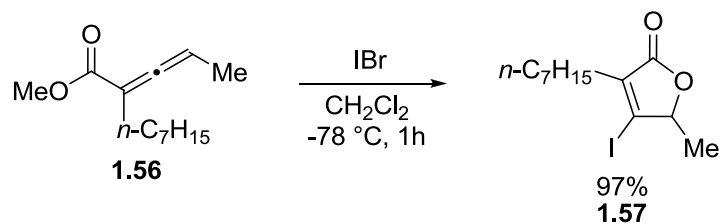
²⁶ For an in-depth review of reactions of allenes, see: Krause, N.; Hashmi, A.S.K. *Modern Allene Chemistry*. **2004**, Wiley-VCH, Weinheim, Vol. 2.

²⁷ Ma, S.; Yu, Z.; Wu, S. *Tetrahedron* **2001**, 57, 1585.

²⁸ Ma, S.; Yu, Z. *Org. Lett.* **2003**, 5, 1507; Gu, Z.; Wang, X.; Shu, W.; Ma, S. *J. Am. Chem. Soc.* **2007**, 129, 10948.

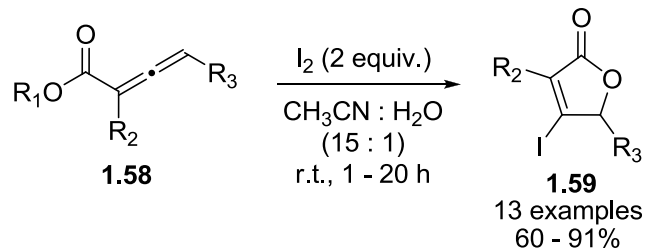
²⁹ Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, 62, 367.

Scheme 1.13: Iodolactonization of a Methyl Allenyl Ester with Iodine monobromide



The Ma group followed up on these results and developed a reaction involving diatomic iodine to provide the iodobutenolide **1.59** in good yields with a much further elaborated substrate scope (Scheme 1.14).³⁰

Scheme 1.14: Iodolactonization of Allenyl Esters with Iodine

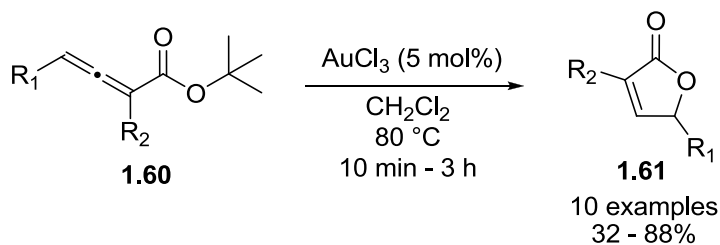


Lastly, Shin *et al.* in 2005 described a gold-catalyzed protocol involving the formation of disubstituted butenolides **1.61** from *tert*-butyl allenyl esters **1.60** in moderate to good yields (Scheme 1.15).³¹

³⁰ Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942.

³¹ Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron* **2005**, *46*, 7431.

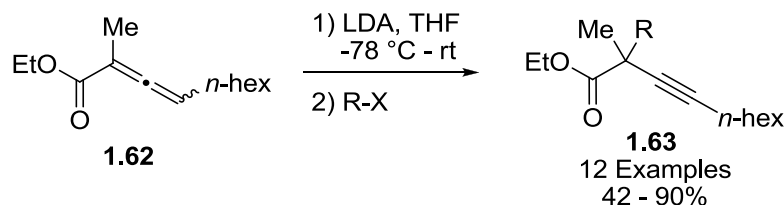
Scheme 1.15: Gold-catalyzed Lactonization of *tert*-butyl Allenyl Esters



1.3.1.2 Alkynyl Esters from Allenyl Esters

The Hammond group has taken an interesting perspective on the uses of allenyl esters and in 2008 developed a procedure for the synthesis of α,α -disubstituted- β -alkynyl esters **1.63** from racemic allenyl esters **1.62** (Scheme 1.16).³² This is particularly intriguing because this reaction is essentially the reverse of the protopic isomerization reaction used to form the allenes in the first place.

Scheme 1.16: Synthesis of α,α -disubstituted- β -alkynyl Esters from Allenyl Esters



By alkylating at the α -carbon, this reaction becomes essentially irreversible and no protopic equilibrium is encountered. Furthermore, the selectivity for alkylation at the α position over the γ position is particularly noteworthy. The Hammond group has since extended this protocol to involve a terminal aldol reaction as opposed to the simple alkylations shown in Scheme 1.16.³³

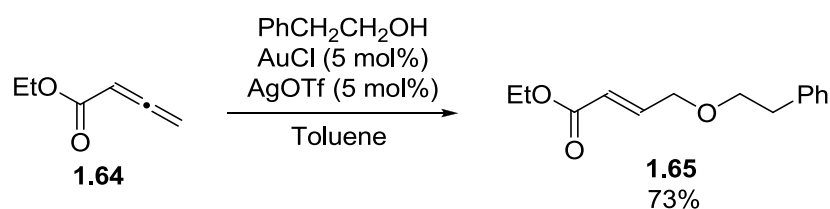
³² Wang, W.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3713.

³³ Liu, L.-P.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3887.

1.3.1.3 Gold-Catalyzed Hydroalkoxylation

In 2007, the Widenhoefer group at Duke University published a gold-catalyzed intramolecular hydroalkoxylation of allenes.³⁴ While none of the entries in that publication involved allenyl esters, in their subsequent extension to this work involving the intermolecular hydroalkoxylation of allenes, they included one entry whereby an allenyl ester **1.64** was successfully hydroalkoxylated in good yield (Scheme 1.17).³⁵

Scheme 1.17: Gold-catalyzed Hydroalkoxylation of Alkynyl Esters.



1.3.2 Reactions of Enantioenriched Acceptor Allenes

Although chemistry involving enantioenriched acceptor allenes is well-represented in the chemical literature, reactions involving the transfer of chirality from the acceptor allene to the desired product are somewhat less prevalent. Below are some of the more common reactions.

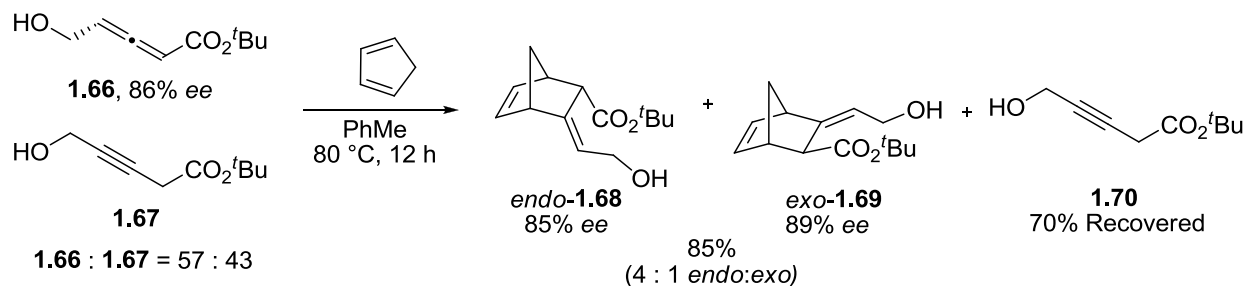
1.3.2.1 Cycloadditions

Cycloadditions are probably the oldest reactions performed with acceptor allenes, of which Diels-Alder additions are among the most common. The Tan group used their inseparable mixture of alkynyl *tert*-butyl ester **1.67** and allenyl *tert*-butyl ester **1.66** to perform a thermal Diels-Alder reaction in good yield, (relative to the allenyl ester,) and moderate diastereoselectivity (Scheme 1.18).²⁵

³⁴ Zhang, Z.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283.

³⁵ Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079.

Scheme 1.18: Diastereoselective Diels-Alder Reaction of an Enantioenriched Allenyl Ester with Cyclopentadiene

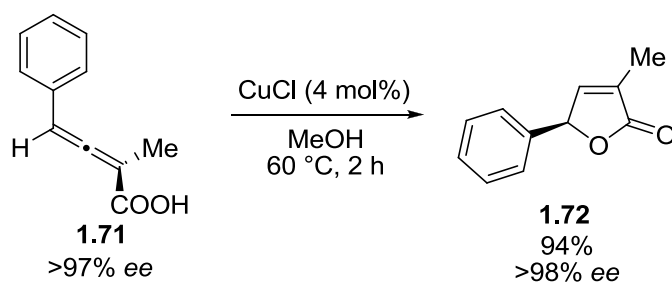


This reaction shows that it is indeed possible to separate the allenyl ester from the isomeric achiral alkyne through derivatization and still obtain reasonable transfer of chirality.

1.3.2.2 Lactonization

Common lactonization reactions of achiral or racemic acceptor allenes have been adapted to include the reaction of enantioenriched allenyl acids and esters. The Ma group has been particularly interested in this reaction set. One example involves the lactonization of optically active allenyl acid **1.71** catalyzed by copper(I) chloride (Scheme 1.19).³⁶

Scheme 1.19: Copper-catalyzed Lactonization of an Enantioenriched Allenyl Acid

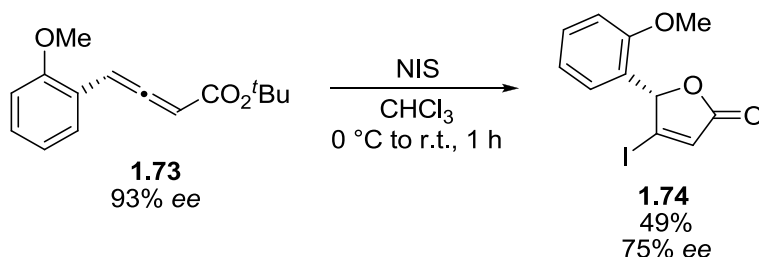


Yet another example of the derivatization of allenyl esters comes from the Tan group whereby a similar halolactonization protocol as developed by the Marshall group (*vide supra*)

³⁶ Ma, S.; Yu, Z. *Synthesis*, **2006**, 3711.

was followed to give the desired iodobutenolide **1.74** in moderate yield, albeit with some erosion of chirality (Scheme 1.20).²⁵

Scheme 1.20: Iodolactonization of an Enantioenriched Allenyl Ester with Some Loss of Chirality

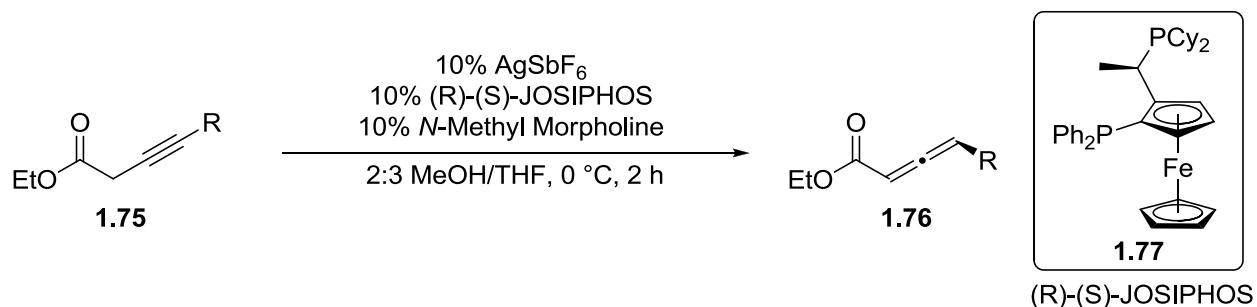


1.4 Efforts Towards the Development of an Asymmetric Acceptor Allene Synthesis in the Fagnou Group

1.4.1 Silver-Catalyzed Enantioselective Synthesis of Chiral Allenyl Esters and Amides

Previous work in the Fagnou group in the field of enantioselective synthesis of chiral allenyl esters **1.75** culminated in the development of a silver-catalyzed isomerization reaction (Scheme 1.21).³⁷

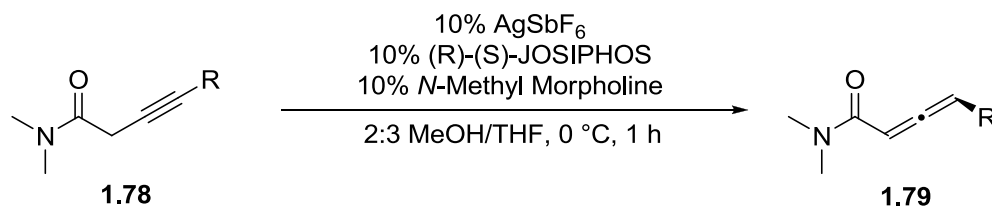
Scheme 1.21: Silver-Catalyzed Enantioselective Synthesis of Allenyl Esters



³⁷ ApSimon, M. *M.Sc. Thesis*, **2008**, University of Ottawa.

This reaction proved efficient, but the isomeric alkyne and allene were chromatographically inseparable. These isolation difficulties have also been observed historically by several other groups working in this field.³⁸ When these conditions were subjected to alkynyl amides **1.78** however, similar catalytic activity was observed (Scheme 1.22).

Scheme 1.22: Silver-Catalyzed Enantioselective Synthesis of Chiral Allenyl Amides



Even more fortuitously, the chiral allenyl amide was chromatographically separable from the starting material, allowing for the isolation of the enantioenriched material without the alkyne starting material contaminant. These results are summarized in Table 1.3.³⁷

³⁸ Suárez, A.; Fu, G. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3580; Wotiz, J. H. *J. Am. Chem. Soc.* **1950**, *72*, 1639; Wotiz, J. H.; Palchak, J. *J. Am. Chem. Soc.* **1951**, *73*, 1971.

Table 1.3: Scope of Silver-Catalyzed Enantioselective Synthesis of Allenyl Amides^a

Reaction scheme: $\text{1.78} \xrightarrow[\text{MeOH/THF, 0 } ^\circ\text{C, 1 hour}]{\text{AgSbF}_6 (10\%), \text{ (R)-(S)-JOSIPHOS (10\%), \text{ NMM (5\%)}} \text{1.79}$

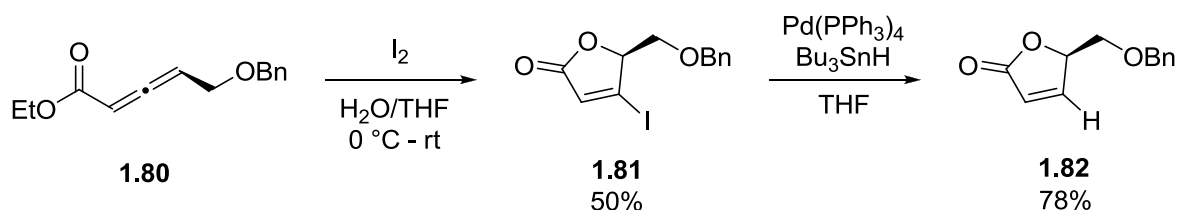
Entry	R	% ee	% yield
1		90	95
2		96 ^c	72
3		96	68
4		91	73
5		80	81
		91 ^c	60
6		83	76
		91 ^c	60
7		90	80
		95 ^c	73
8		>99	27
9		40	60

^aConditions: AgSbF₆ (0.1 equiv.) and (R)-(S)-JOSIPHOS (0.1 equiv.) are stirred in MeOH/THF (0.05 M) for 0.5h. **1.78** (1 equiv.) and *N*-methylmorpholine (0.05 equiv.) are added and stirred for 1h. ^bDetermined by HPLC. ^cReaction performed at -10 °C

1.4.2 Derivatization of Allenes to Halobutenolides

Efforts to derivatize an allene in order to determine the absolute stereochemistry were undertaken, leading to the assignment of the allenyl axis of chirality as S_a . This was achieved by derivatizing the allene to a known compound with a known optical rotation and then tracing back to elucidate the chirality of the axis. This was realized by reacting enantioenriched allenyl ester **1.80** with I_2 to effect iodolactonization in 50% yield with full transfer of chirality from the axis of the allene to a chiral centre, followed by hydrodehalogenation of the vinyl iodide with tributyltinhydride under palladium catalysis to generate the butenolide **1.82** (Scheme 1.23).

Scheme 1.23: Derivatizing an Allenyl ester to a Known Butenolide with Known Absolute Stereochemistry



Butenolide **1.23** had been prepared in a completely different fashion and its optical rotation and absolute stereochemistry was known.³⁹ As such, the allene's stereochemistry was confirmed to be S_a which is the same enantiomer that is predicted when the Lowe-Brewster Rule is applied to assign the stereochemistry of allenes based on optical rotation.⁴⁰

1.5 Project Goals

The synthesis of enantioenriched allenyl esters and amides in the Fagnou group was first described by M. ApSimon in her M.Sc. thesis,³⁷ but these reactions were often subject to significant variability based on scale and reagent sources. The first goal of this project was to identify the source of this variability and develop a reliable protocol for consistent yields and enantioselectivities.

³⁹ Fazio, F.; Schneider, M.P. *Tetrahedron: Asymm.* **2000**, 1869.

⁴⁰ Brewster, J.H. *J. Am. Chem. Soc.* **1959**, 81, 5475; Lowe, G. *Chem. Comm.* **1965**, 17, 411.

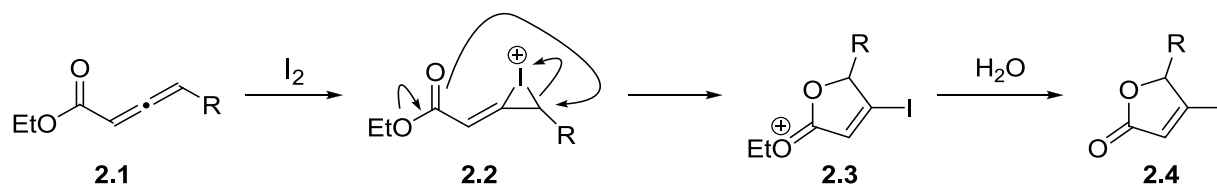
Pursuant to this goal, uses of enantioenriched allenyl esters and amides are limited in the literature, most likely due to the difficulty associated with their synthesis. Halolactonization has been explored in the literature (*vide supra*), but very few examples exist with transfer of chirality from the axis of the allene to the chiral centre of the halobutenolide. A second goal of this thesis is to explore methods to use enantioenriched acceptor allenes under various synthetic protocols to access valuable enantioenriched products. Indeed, these methods of derivatization could be used as a way to separate the products of the isomerization reaction when they are inseparable otherwise, such as in the case of the allenyl esters.

2 Results and Discussion

2.1 Generality of Iodolactonization to Prepare Iodobutenolides

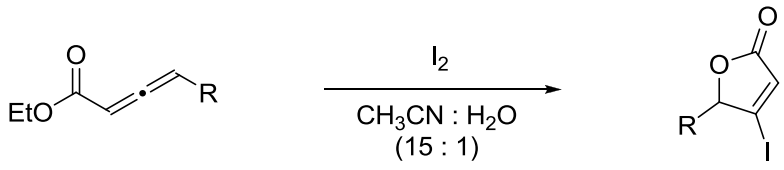
As shown in section 1.4.2, allenyl esters could be derivatized to iodobutenolides by reacting them with electrophilic I_2 . Presumably, the iodolactonization that occurs is precipitated by iodonium ion formation followed by an intramolecular condensation with subsequent release of ethanol. This potential mechanism is summarized in Scheme 2.1.

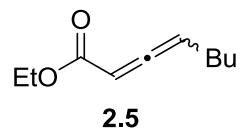
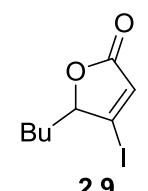
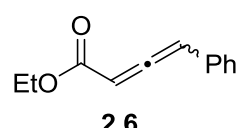
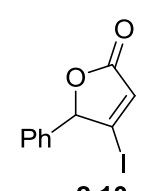
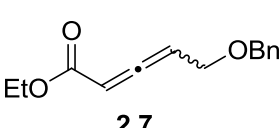
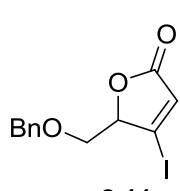
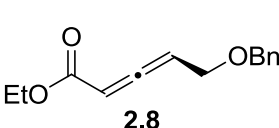
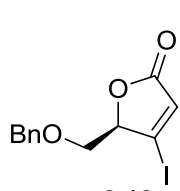
Scheme 2.1: Potential Iodolactonization Mechanism for the Formation of Iodobutenolides from Allenyl Esters



One of our goals for this project was to explore synthetic uses of the chiral allenyl esters that we were forming. As such, this halolactonization reaction was explored in more depth using several substrates. After experimenting with several conditions, we settled on a method adapted from a protocol originally published by Ma *et al.*³⁰ The results of the submission of various allenyl esters to the action of these conditions are summarized in Table 2.1.

Table 2.1: Scope of Iodolactonization of Allenic Esters



Entry	Allenic Ester	Product	Yield ^b
1	 2.5	 2.9	36%
2	 2.6	 2.10	51%
3	 2.7	 2.11	33%
4	 2.8 (86% ee) ^c	 2.12	42% (71% ee) ^c

^aConditions: Allenic ester (1 eq.), (used as an inseparable mixture of allene and isomeric alkyne,) dissolved in CH₃CN:H₂O (15:1) (0.13 M), cooled to 0 °C and I₂ (2.0 eq.) added. Allowed to warm slowly to r.t and stirred for 11 h. Quenched by addition of sat. aq. Na₂S₂O₃. ^bIsolated yields, based on allene. ^cDetermined *via* chiral HPLC.

Though synthetically useful yields are obtained for both alkyl- and aryl-substituted allenyl esters, the yields are somewhat disappointing. Furthermore, there is some erosion of enantiomeric enrichment based on the result shown by Table 2.1, Entry 4 whereby the allenyl ester **2.8** had an

enantiomeric excess of 86% but the resultant iodobutenolide **2.12** has only 71% *ee*. Similar erosion of chirality with a similar substrate has since been observed by Tan *et al.*²⁵

Moreover, it should be noted that utilisation of *N*-bromosuccinimide, bromine or pyridinium tribromide to effect halolactonization with these substrates led predominantly to the formation of intractable mixtures of products, which may be polyhalogenated compounds as has been suggested previously in the literature.⁴¹

2.2 Dimethoxybenzylesters as a Synthetic Handle to Access Butenolides

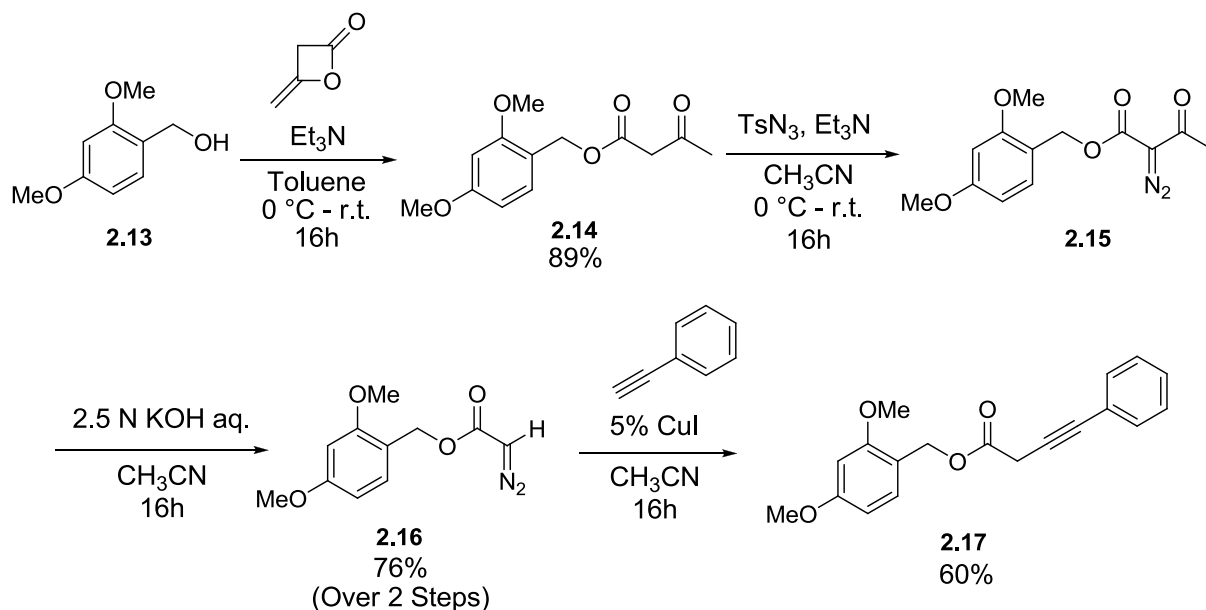
While the synthesis of iodobutenolides from allenyl esters represents a facile way to generate significant molecular complexity in a single step, if halo or aryl substitution at C4 of the butenolide is not desired, the halogen must be reduced off in a discrete step. However, the direct synthesis of enantioenriched butenolides from chiral allenyl acids is a known chemical transformation in the literature,³⁶ but has only been explored with very simple substrates, most likely due to the difficulty associated with accessing the required starting materials. Indeed, efforts conducted in our own laboratory as well as in others⁴² have led to the knowledge that simple hydrolysis of the allenyl ester to the allenyl acid generally leads to erosion of enantiopurity, most likely due to the protopic isomerization equilibrium enabled by the base needed for ester hydrolysis or reduction. A pH neutral way to deprotect an allenyl ester would then in theory allow for the cyclization of the resultant allenyl acid to the butenolide while maintaining the enantiopurity of the starting material.

One such method to deprotect an allenyl ester to an allenyl acid under neutral conditions is the redox process of 2,4-dimethoxybenzyl ester oxidation. Kim and Misco reported such a mild dimethoxybenzyl ester deprotection with DDQ in 1985.⁴³ If we could synthesize a 2,4-dimethoxybenzyl allenyl ester with high enantiopurity, oxidative reduction of an allenyl ester could give the allenyl acid without racemization which could allow us to cyclize to form the butenolide. The synthetic route taken to access the dimethoxybenzyl alkyne starting material is shown below (Scheme 2.2).

⁴¹ Font, J.; Gracia, A.; de March, P. *Tetrahedron* **1990**, *46*, 4407.

⁴² Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

⁴³ Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1985**, *26*, 2027.

Scheme 2.2: Synthetic Route to Access 2,4-Dimethoxybenzyl Alkynyl Esters

2,4-Dimethoxybenzyl alcohol was first treated with diketene and triethylamine to generate 2,4-dimethoxybenzyl acetoacetate **2.14** in 89% yield. This was then converted to diazoacetate **2.16** by treatment with tosyl azide and triethylamine in acetonitrile followed by hydrolysis of the acetyl group with aqueous KOH in acetonitrile in 76% yield over two steps. Lastly, the usual copper-catalyzed alkynyl ester formation³⁸ was performed using phenylacetylene as the terminal alkynyl coupling partner giving the desired 2,4-dimethoxybenzyl alkynyl ester **2.17** in 60% yield. It should be noted that, in contrast to the ethyl alkynyl esters, this alkyne-diazoacetate coupling yielded the alkyne as the exclusive product without formation of the isomeric allene. Racemic samples of the dimethoxybenzyl allenyl ester could be obtained by treating the alkyne with 2.0 equivalents of triethylamine in methanol for 1 h, though generally a 3:1 inseparable mixture of allene to alkyne was obtained in 63% yield after column chromatography. Allowing the reaction to stir under these conditions for longer than 1 h led to lower isolated yields with significant substrate decomposition observed.

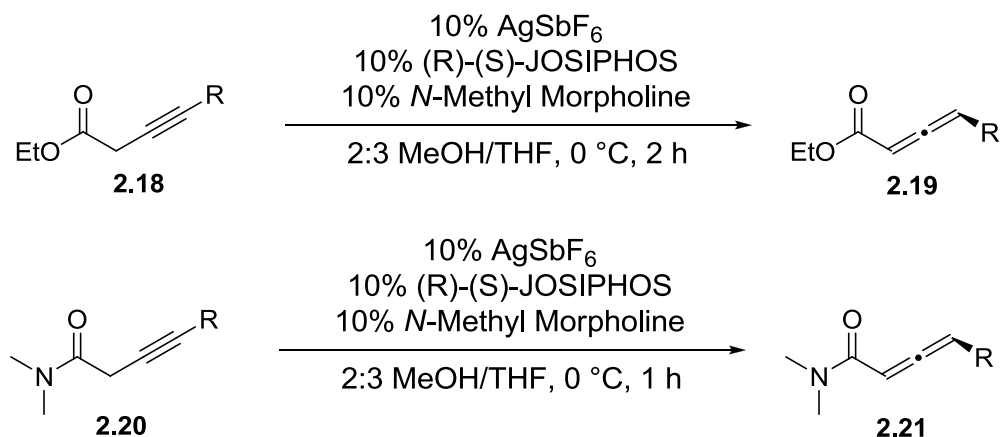
With racemic allene material in hand, dimethoxybenzyl ester oxidation was attempted in order to validate this deprotection method. Unfortunately, treatment of the allenyl ester with DDQ lead only to substrate decomposition with the only isolable compound being 2,4-dimethoxybenzoic acid. This would seem to indicate that oxidation and deprotection is indeed

occurring, but that the allenyl acid is unstable under these reaction conditions. Given that the allenyl esters have proven to be prone to decomposition at room temperature, it is perhaps unsurprising that the acids are also unstable under even mild oxidative conditions. Since few oxidation methods exist that are even milder than DDQ, this approach was abandoned.

2.3 Reproducibility of the Asymmetric Prototypic Isomerization to Access Chiral Allenic Esters and Amides

As mentioned in section 1.4, previous work in the Fagnou Group by Megan ApSimon led to the discovery of a method for the isomerization of homopropargyl esters and amides to enantioenriched allenyl esters **2.19** and amides **2.21** under silver catalysis (Scheme 2.3).

Scheme 2.3: Enantioselective Isomerization of Homopropargyl Esters/Amides to Allenes

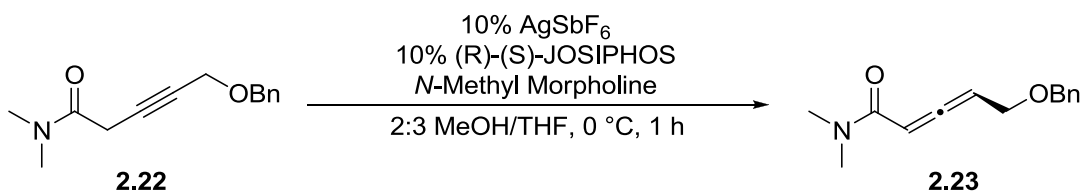


However, unfortunately, this work had been plagued by inconsistency in the results of the reaction based on the quality and source of the silver hexafluoroantimonate salt.⁴⁴ Since reproducibility of this method is crucial to its general utility, a major effort was undertaken to identify the key elements necessary for consistent successful results. Wherever possible, the isomerization reaction used involved alkynyl amides to allow for TLC analysis of reaction mixtures and chromatographic separation of the allenyl product from the isomeric alkyne starting material.

⁴⁴ *Personal Communication*, ApSimon, M.

2.3.1 Source of Silver Lewis Acid

As mentioned above, the source of the silver hexafluoroantimonate salt had a pronounced effect on the success of the reaction. Previous experimentation by M. ApSimon led to the observation that only silver hexafluoroantimonate sourced by Aldrich⁴⁵ was competent in this reaction. However, even newly purchased batches of this salt from the same lot as older bottles showed inconsistencies in activity and even appearance.⁴⁶ Of all the sources of this silver salt used, the one that gave the most consistent results was Aldrich-sourced and had been in our possession for greater than one year. However, when this source was depleted and more recently obtained silver sources had to be used, no appreciable isomerization was obtained under *identical* reaction conditions. While at first it was plausible that when these reactions were run on small test scale, (*circa* 40 mg of substrate,) it was perhaps possible this reaction failure was caused by operator error due to the miniscule amount of *N*-methylmorpholine base required (generally ~1 μ L). This possibility was eventually discounted by repeated reactions using different base equivalents, (up to 0.5 equivalents), with similar undesired results (Figure 2.1).



⁴⁵ Silver hexafluoroantimonate(V); Aldrich Catalog #227730.

⁴⁶ The appearance of silver hexafluoroantimonate varied from a fluffy off-white powder to a granular dark gray powder depending on the source and age of the bottle.

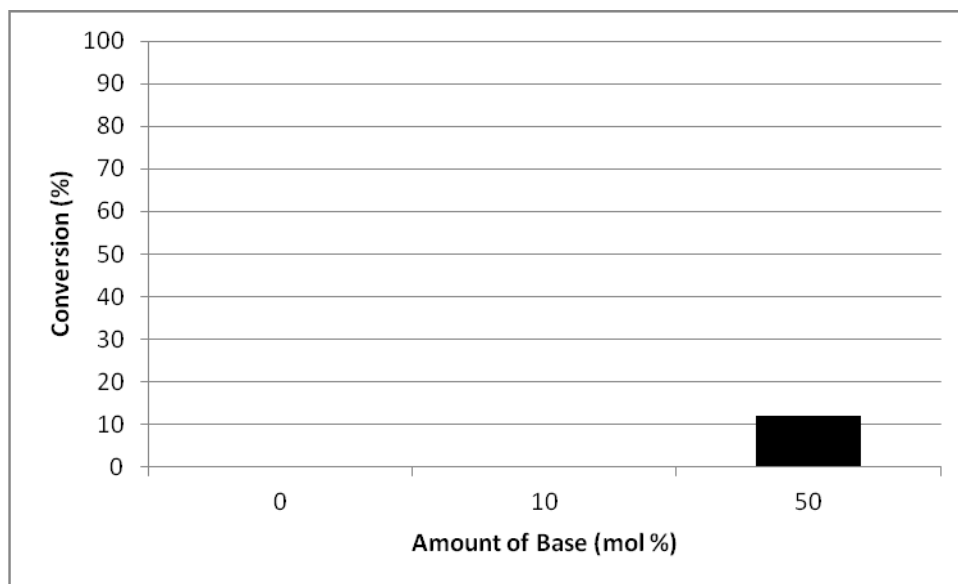


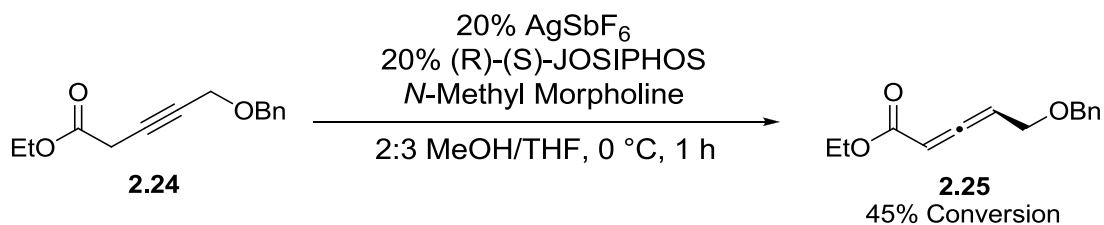
Figure 2.1: Effect of Equivalents of Base on Reaction Conversion (measured by ^1H NMR).

This surprising effect seemingly caused by the new silver salt source led us to believe that this new bottle was contaminated in some way. A new bottle was ordered from Aldrich with the special request that it come from a different lot. Unfortunately, reactions run with this new silver source again led to no conversion.

2.3.2 Catalyst Loading

After months of frustrating experimentation with different substrates and slightly modulated reaction conditions yielding little to no product, we observed an interesting result when we changed the catalyst loading (Scheme 2.4).

Scheme 2.4: Effect of Double Catalyst Loading on Isomerization Conversion

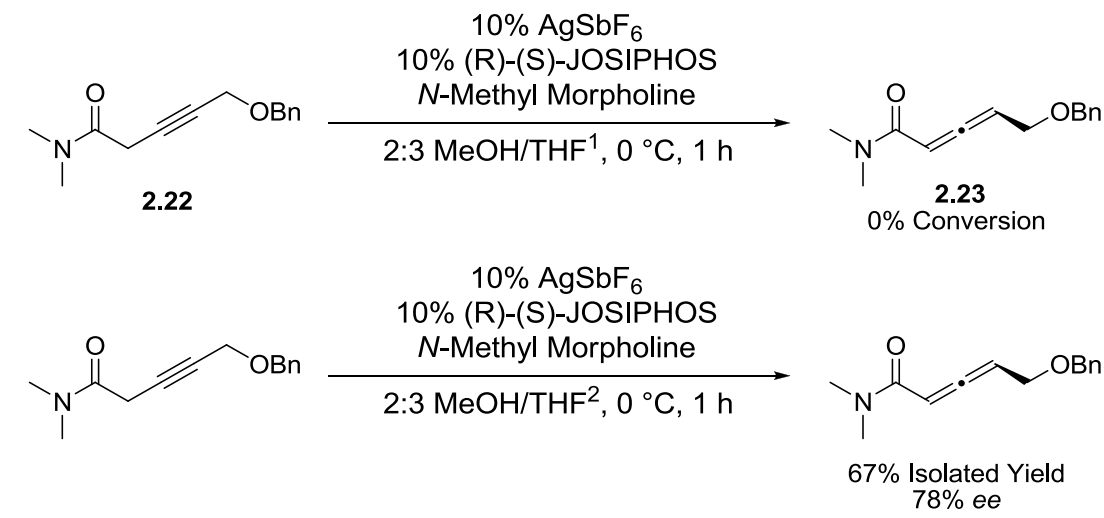


While this result was encouraging and proved that the reaction was still potentially viable, such high loadings of silver and the expensive JOSIPHOS ligand were unacceptable in the interests of a catalytic and atom-economical reaction. Furthermore, this result was not always reproducible depending on the batch of starting material used.

2.3.3 The Effect of Solvent and Additives on the Reaction

A breakthrough towards learning the cause of this isomerization's irreproducibility came when the reaction was run identically as before, but instead of using THF that had been freshly purified by our group's mBraun Solvent Purifier, (as was generally the protocol,) solvent that had been sitting in the collection flask for greater than 24 hours was used. Fortuitously, this was the first reaction in many months that showed a conversion and enantiomeric excess approaching those originally reported by M. ApSimon (Scheme 2.5).

Scheme 2.5: Effect of Aged THF on the Allene Isomerization Reaction



¹ Freshly purified THF by MBRAUN MB AUTO-SPS Solvent Purification System

² THF aged in collection flask for 24 hours

This surprising result led to our questioning why these subtly different isomerization conditions had yielded isomerized (and enantioenriched) allene when so many similar reactions had failed. On close inspection of the THF collection flask of the solvent purification system, it appeared that the septum was compromised and could have potentially allowed ambient

atmosphere to contaminate the contents of the flask. As such, it was hypothesized that perhaps trace water is beneficial to the reaction. To test this notion, several reaction conditions were explored whereby: 1) Freshly purified THF from the solvent system was used as a control and little to no conversion was expected; 2) Freshly distilled THF from a still and dried over sodium metal was used as a negative control; 3) The same THF as in 2) was used but the reaction was spiked with 5 equivalents of water; 4) The same conditions as 1) were used but with added oven-dried 4Å molecular sieves to sequester any water that may have been present and act as a further negative control. The results of these experiments are summarized in Figure 2.2.

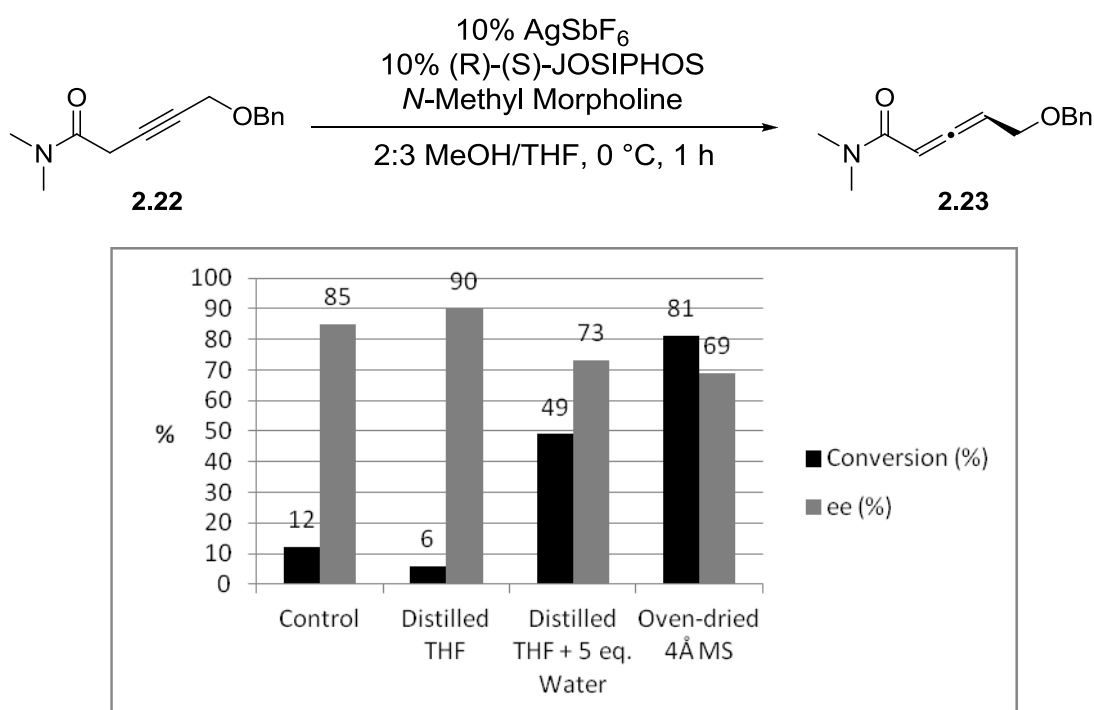


Figure 2.2: The Effect of Water and Molecular Sieves on the Isomerization Reaction

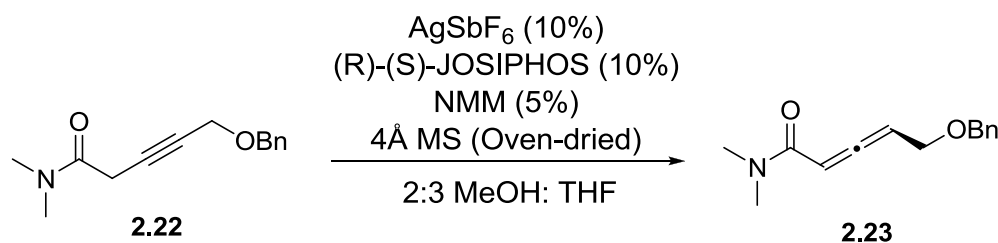
The results of this experiment were surprising and opened the door to further experimentation. Firstly, it is clear that only trace isomerization occurred under the anhydrous conditions provided by using freshly purified THF from the solvent purifier and from a THF still. Furthermore, there is evidence that water may be beneficial to the isomerization reaction as shown by the much higher conversion (49%), observed when water was deliberately added to otherwise anhydrous conditions compared to the anhydrous conditions themselves. Lastly, and most surprisingly, when 4Å molecular sieves were added to the already anhydrous conditions,

81% conversion was obtained, while keeping nearly the same enantiomeric excess as the reaction with added water. This result would seem to run contrary to the other observations in this experiment.

To identify the source of these unexpected results, it was necessary to prepare a new batch of this homopropargyl ester **2.26** starting material since the starting material used in the previous experiments was nearly depleted and had likely begun to decompose. This was inferred by the appearance of many small unidentified peaks in the proton NMR spectrum of this old starting material and its progressive darkening colour over time, despite being stored in a freezer when not in use. As such, a new batch of starting material was prepared in the standard manner³⁷ which was deemed to be pure by proton NMR.

With a new supply of the homopropargyl ester in hand, kinetic experiments were performed in order to determine the time necessary for full isomerization and whether higher enantioselectivities could be obtained by performing the reaction over a shorter time period (Scheme 2.6).

Scheme 2.6: Reaction Monitored During Kinetic Experiments



These experiments were run at both 0 °C and -78 °C and aliquots were taken after 10, 20, 30, 45 and 60 minutes. Unfortunately however, *none* of these aliquots showed that any isomerization had occurred, despite being performed under identical reaction conditions as the molecular sieve example shown in Figure 2.2. These discouraging results were echoed in further studies using these reaction conditions involving the effects of the number of equivalents of water and the source of molecular sieves which both showed only trace isomerization to allene under all conditions examined, much as had been seen before.

It was clear that this new batch of starting material, though >95% pure by proton NMR, was not identical to the previous batch and was perhaps contaminated by some unknown NMR silent impurity which interfered with the substrate's isomerization. Therefore, a new study of the effect of molecular sieves was performed on starting material which had been freshly filtered through a short pad of silica. The sieves examined were 4Å molecular sieves (pellets) both from the bottle and flame-dried, 4Å molecular sieves (powdered), 3Å molecular sieves (balls) and powdered Na-Y zeolites, commonly used as a catalyst support. It should be noted that all of these molecular sieves were "unactivated" in that they had been used directly out of the bottle and had not been oven- or flame-dried before use. This was because previous studies had shown that "activated" molecular sieves had actually caused *less* isomerization than "unactivated" molecular sieves for as yet unknown reasons. A standard control reaction was also run. The results of this study are summarized in Figure 2.3.

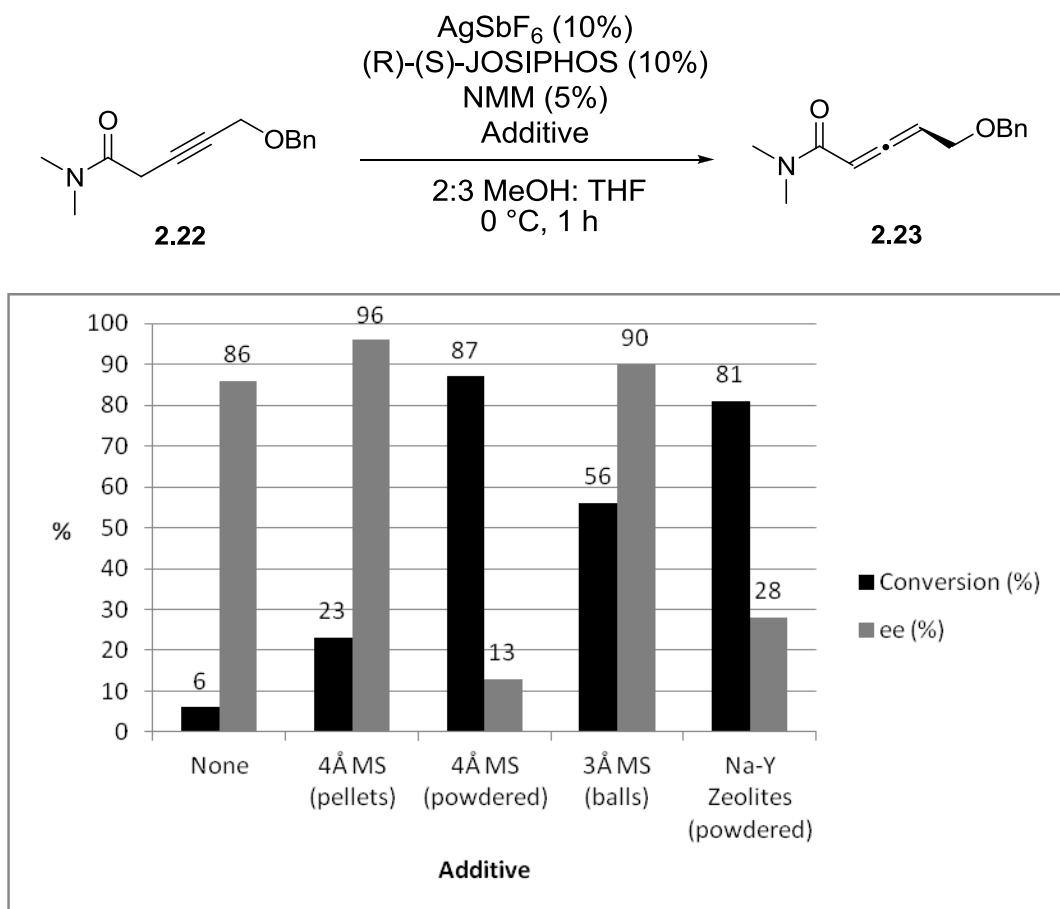


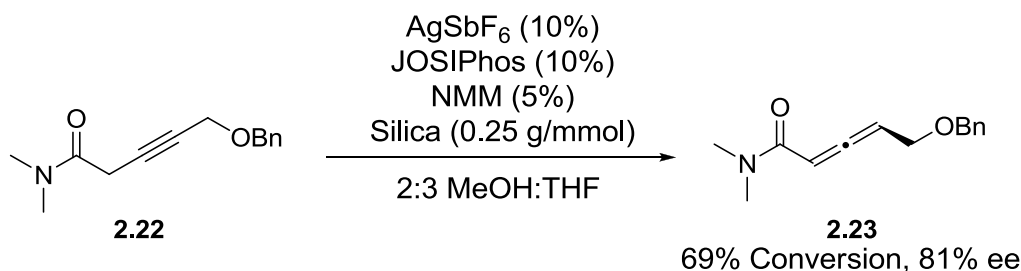
Figure 2.3: Effect of Various Molecular Sieve and Solid Additives on Isomerization Conversion and Enantioselectivity.

The results of this study are again surprising. The first observation is that higher conversions than the control experiment were obtained for all samples, something that could not be said of the preceding reactions using this starting material. This would seem to indicate that it was *necessary* to purify the starting material by filtering it through a pad of silica *immediately* before using it in an isomerization reaction. Next, 3Å balls seem to be more competent at enabling the enantioselective isomerization than 4Å pellets while maintaining roughly the same conversion overall. Most strikingly however, the use of a powdered additive, be it 4Å MS or Na-Y Zeolites, enables very high conversions to the desired isomerized allene product, albeit with significantly less enantioselectivities.

The results obtained with powdered molecular sieves or zeolites were quite surprising considering the observed beneficial effect of water on the reaction. That said, the sieves used were presumably not “dry” in that they had been used directly from the bottle without oven- or flame-drying. It is perhaps possible that these sieves had been saturated with water and some of this water had leached into the solution, enabling the isomerization. There is also perhaps the catalytic activity of the sieves themselves, possibly by virtue of their Lewis acidity.⁴⁷

To test the hypothesis that the powdered sieves are acting merely as Lewis acids, a test reaction was conducted in the usual manner but in the presence of silica, a known weak Lewis acid (Scheme 2.7).

Scheme 2.7: The Effect of Silica on the Isomerization of a Homopropargyl Amide to the Isomeric Allene



⁴⁷ For general reviews on the catalytic activity of molecular sieves, see: Davis, M. E. *Ind. Eng. Chem. Res.* **1991**, *30*, 1675; Davis, M. E. Lobo, R. F. *Chem. Mater.* **1992**, *4*, 156; Corma, A. *Chem. Rev.* **1997**, *97*, 2373

When 0.25 g of silica per mmol of substrate was present in the reaction vial during an isomerization reaction, impressive enantiomeric excess was obtained with moderate conversion observed. This result was very encouraging as it was the best combination of conversion and enantiomeric excess that had been obtained for this reaction in months since the reproducibility issues had become significant.

The origin of the beneficial effect of silica on this reaction is puzzling to say the least. If indeed the silica is merely acting as a Lewis acid, we would expect significantly diminished enantioselectivity as seen with the powdered molecular sieves. However, enhanced isomerization conversion and the maintenance of enantioselectivity seems to indicate that our proposed silver-chiral phosphine catalyst is still playing a catalytic role in the reaction so the role that the silica is playing is indistinct.

Although the role of silica was still unclear, efforts to optimize the silica loading and temperature were undertaken. For this task, yet another batch of starting material was synthesized but frustratingly, this batch was again not active under the isomerization conditions, though, much as before, the ^1H NMR spectrum confirmed substrate purity as >95%. This lack of competency in the isomerization reaction was observed even after purification immediately before use by passing the allenyl alkyne through a short silica plug. Clearly, an allenyl alkyne purification method which yielded active and consistently reproducible isomerization starting material was required.

2.3.4 Purification of Allenyl Alkynes

It was obvious throughout the course of these studies that substrate homogeneity between experiments and starting material batches was significantly hampering our ability to optimize and troubleshoot the isomerization reaction. If ultra-pure starting material was necessary for the reaction to proceed, we needed to develop a protocol to obtain this material every time, with every new batch of starting material. As such, a study of the standard isomerization protocol was performed using alkyne **2.22** that had been subjected to activated carbon, (to adsorb trace organic impurities,) or a metal scavenger,⁴⁸ (to adsorb trace metal impurities). Identical parallel reactions using each of these “purified” starting materials as well as a control reaction using “unpurified”

⁴⁸ The metal scavenger used was MesoPure™ Thiol, a thiol linked to mesoporous silica.

starting material were performed in duplicate. The results of this study are summarized in Figure 2.4.

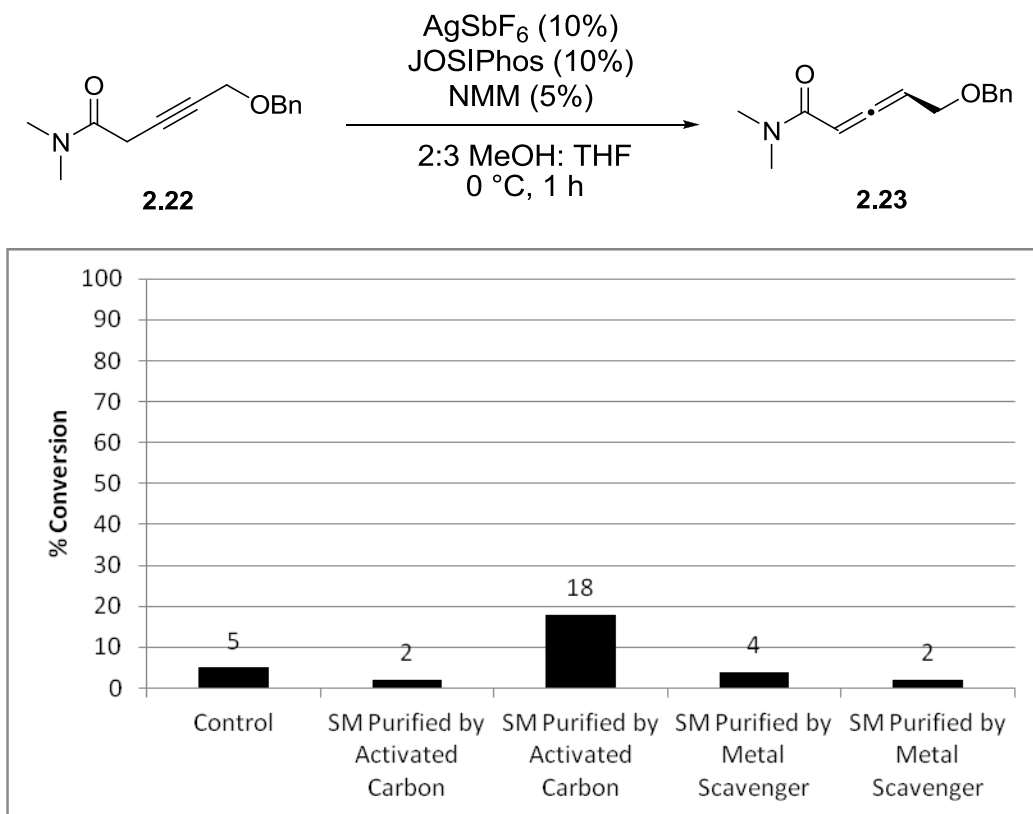


Figure 2.4: Effect of Starting Material Purification on Isomerization Conversion

As can be seen in the figure above, none of the trials yielded isomerization conversions approaching what is possible. More worryingly is the lack of consistency that is occasionally observed between reactions from the same batch of starting material.

The inconsistency between identical reactions is very worrisome since it again hampers our efforts to elucidate the mechanisms which hamper reactivity. Efforts to compare the reactivity between starting material purified through vacuum distillation at high temperature and by washing with saturated aqueous ammonium chloride solution to remove traces of base again led to inconsistent results.

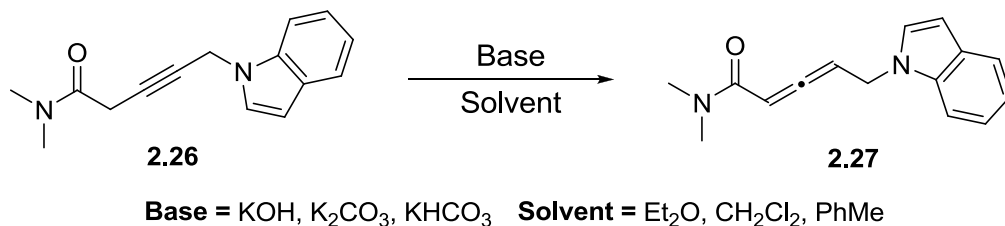
2.4 Initial Forays into Phase-Transfer Allenyl Amide Isomerization Conditions

While it was clear that the silver Lewis acid-catalyzed protocol for the isomerization of allenyl esters and amides studied in the previous section was possible, the irreproducibility observed severely limited its applicability and relevance. Furthermore, with the concurrent publication of this same reaction²⁵ with an organocatalyst with very similar, (and presumably reproducible,) results as the original protocol developed by M. ApSimon, the impact of this method was lost. Furthermore, the source or sources of the irreproducibility of the isomerization reaction remained elusive after considerable experimentation. As such, a new isomerization approach was investigated for its applicability to form allenyl amides.

Since the prototypic isomerization to form allenes was known to occur, it was determined that this was an opportunity to perform the reaction under phase transfer conditions. To date, the only phase-transfer mediated allene isomerization known in the literature continues to be from Shiori *et al.* published in 2000.²⁴ We proposed that it might be feasible to perform the isomerization reaction of our allenyl amides enantioselectively under phase-transfer conditions following this proof-of-concept. Amides were chosen to be the initial substrate class examined due to the relative ease of chromatographic separation of the allene product from the isomeric alkyne starting material which would facilitate reaction monitoring and optimization.

To begin to establish whether this phase-transfer isomerization was possible, we began by screening different ionic bases and solvents to determine a set of conditions which would, in the absence of a phase-transfer catalyst, effect very slow isomerization that could potentially be accelerated by the inclusion of a phase-transfer catalyst (Scheme 2.8).

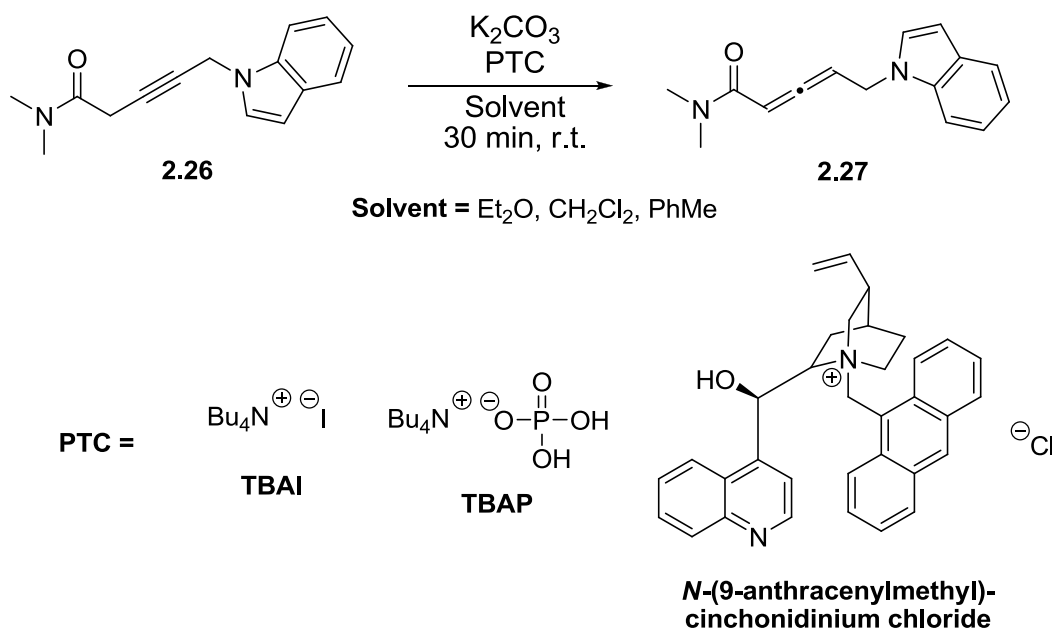
Scheme 2.8: Control Reaction for Determining Optimal Base and Solvent Conditions



This reaction was monitored by TLC over time and after 1 hour, KOH had effected isomerization to the allene in all solvents. This was clearly too fast to allow for enantioselection with a chiral phase-transfer catalyst. The reactions with KHCO_3 did not yield any allene product by TLC even after 72 hours and so it is likely that this base is insufficiently basic to bring about the initial deprotonation required for the isomerization to occur. Lastly, potassium carbonate yielded no allene product by TLC after 1 hour, but had caused nearly complete isomerization after 72 hours in all solvents. As such, this base was chosen to go forward.

Next, a series of phase-transfer catalysts were screened to see if a rate-enhancement was observed (Scheme 2.9). The phase transfer catalysts tetrabutylammonium iodide, tetrabutylammonium phosphate and *N*-(9-anthracenylmethyl)-cinchonidinium chloride were selected for the initial screen, the latter of these being non-racemic and with the potential to effect enantioselective reprotonation. The results of this study are summarized in Figure 2.5.

Scheme 2.9: Screen of Phase-transfer Catalysts



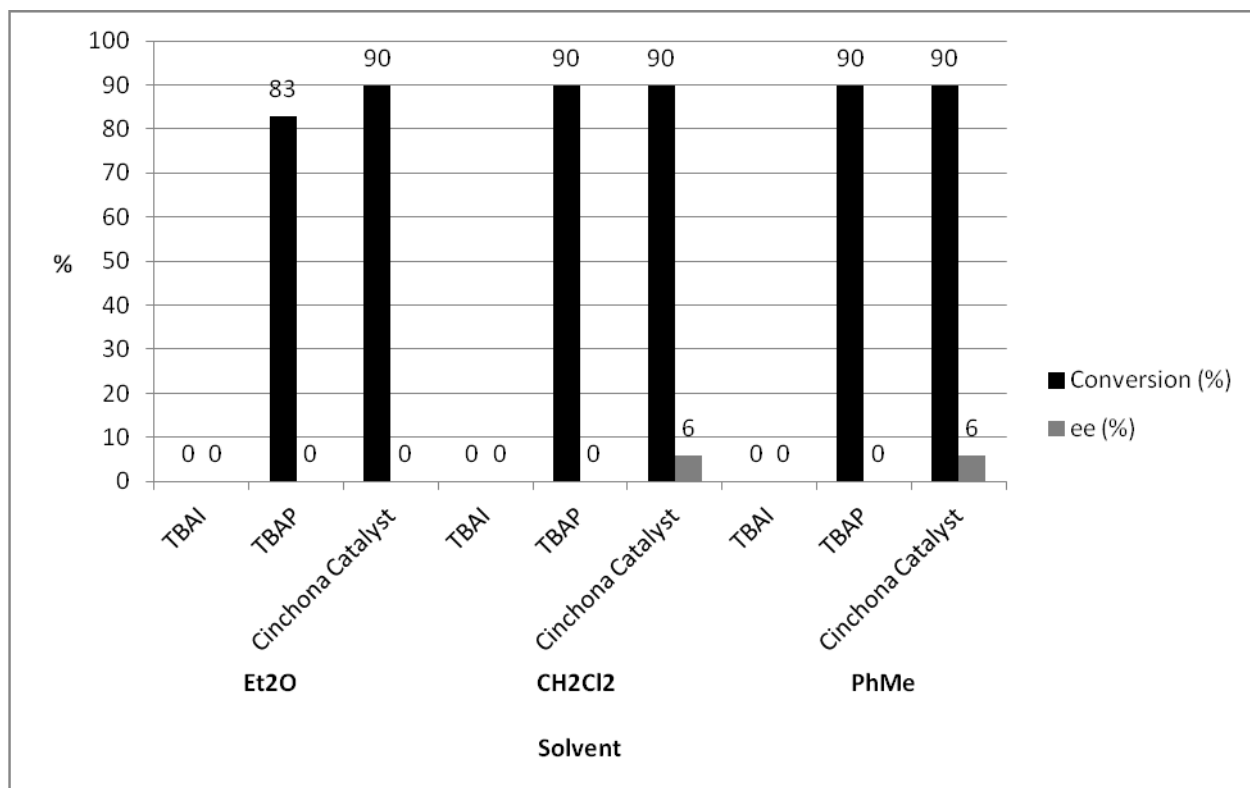


Figure 2.5: Conversions and Enantioselectivities of Various Phase-transfer Catalysts in Different Organic Solvents (Conversions Determined *via* ¹H NMR and *ee* Determined *via* Chiral HPLC)

As can be seen above, it is obvious that the rate of the prototypic isomerization can be greatly enhanced when performed in the presence of an appropriate phase-transfer catalyst. While TBAI proved to be unable to act as a competent catalyst in this regard, TBAP and the cinchonidine-based catalyst enabled the isomerization to proceed to near completion. Unfortunately in the case of the non-racemic cinchonidine-based catalyst, only very minimal amount of enantioselectivity was observed. While disappointing that only a small amount of enantiodiscrimination is obtained with this particular catalyst, it does show that it is possible to induce chirality from a chiral phase-transfer catalyst.

2.5 Conclusions

While it is clear that the silver-catalyzed asymmetric isomerization of alkynyl esters and amides developed in the Fagnou group is a viable reaction to form valuable acceptor allenes asymmetrically, it is unfortunately plagued by as yet unresolved reproducibility issues. While

the addition of small amounts of water, silica and/or molecular sieves to the reaction may have beneficial effects, the true benefits are difficult to discern due to the variability in the reaction outcomes which hampers rational evaluation. Most importantly, starting material compounds with consistent reactivity from batch to batch have been thus far elusive. Indeed, in order to be able to fully characterize this reaction, determining the source of this starting material variability would be necessary as well.

With the publication of a similar process by the Tan group in Singapore,²⁵ the novelty and impact of this method to form allenyl esters is diminished. While the Tan group forms *tert*-butyl allenyl esters exclusively, the method we have developed can be used to prepare ethyl allenyl esters as well as dimethyl allenyl amides, currently an under-represented substrate class in organic chemistry. As viable uses for these amides come to the forefront of synthetic chemistry, this method may yet prove valuable as another tool for the modern synthetic chemist.

Part 2: Oxidative Rhodium-Catalyzed C-H Functionalization: Application to the Synthesis of 3-Carboxylindoles and Attempted Applications to Allenes

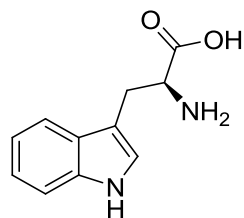
3 Introduction

3.1 Indole as a Privileged Motif in Synthetic and Medicinal Chemistry

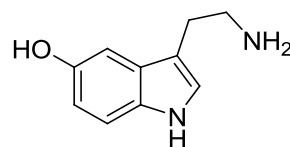
Indole is without doubt one of the most important heterocycles known to the scientific community.⁴⁹ Indeed, its structure permeates nearly all branches of the biologically-related sciences. It can be found in such elementary compounds as the natural amino acid tryptophan **3.1** and the neurotransmitter serotonin **3.2**. Indole can also be found in hundreds of natural products including the famous ergot alkaloids **3.3** and the more recently synthesized hapalindoles **3.4**⁵⁰ (Figure 3.1).

⁴⁹ Sundberg, R. J. *Indoles* (1996), Academic Press, San Diego.

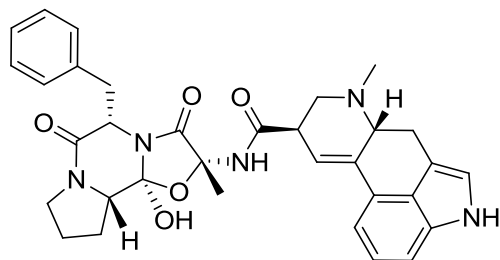
⁵⁰ Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.



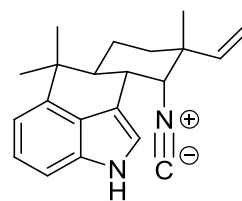
L-Tryptophan 3.1
Natural Amino Acid



Serotonin 3.2
Neurotransmitter



Ergotamine 3.3
Neurotransmitter
Receptor Agonist



(-)-Hapalindole 3.4
Marine Natural Product

Figure 3.1: Natural Compounds Incorporating the Indole Motif

Finally, its biological activity makes it an attractive scaffold for medicinal compounds as can be evidenced by the multitude of drugs incorporating its structure including the anti-inflammatory Indomethacin **3.7** from Merck,⁵¹ Glaxo-SmithKline's Sumatriptan **3.5**,⁵² for migraine relief, Fluvastatin **3.8** from Novartis for the treatment of hypercholesterolemia⁵³ and the cyclin-dependent kinase inhibitors known as the Paullones **3.6**⁵⁴ (Figure 3.2).

⁵¹ Hart, F.; Boardman, P. *Br. Med. J.* **1963**, 5363, 965.

⁵² Humphrey, P. P. A. *Headache*, **2007**, 47, S10.

⁵³ Kathawala, F. G. U.S. Patent 5,354,772, 1994; Kathawala, F. G. U.S. Patent 4,739,073, 1988; Repič, O.; Prasad, K.; Lee, G. T. *Org. Process Res. Dev.* **2001**, 5, 519.

⁵⁴ Meijer, L.; Leost, M.; Lozach, O.; Schmitt, S.; Kunick, C. *Handbook of Experimental Pharmacology* **2005**, 167, 47.

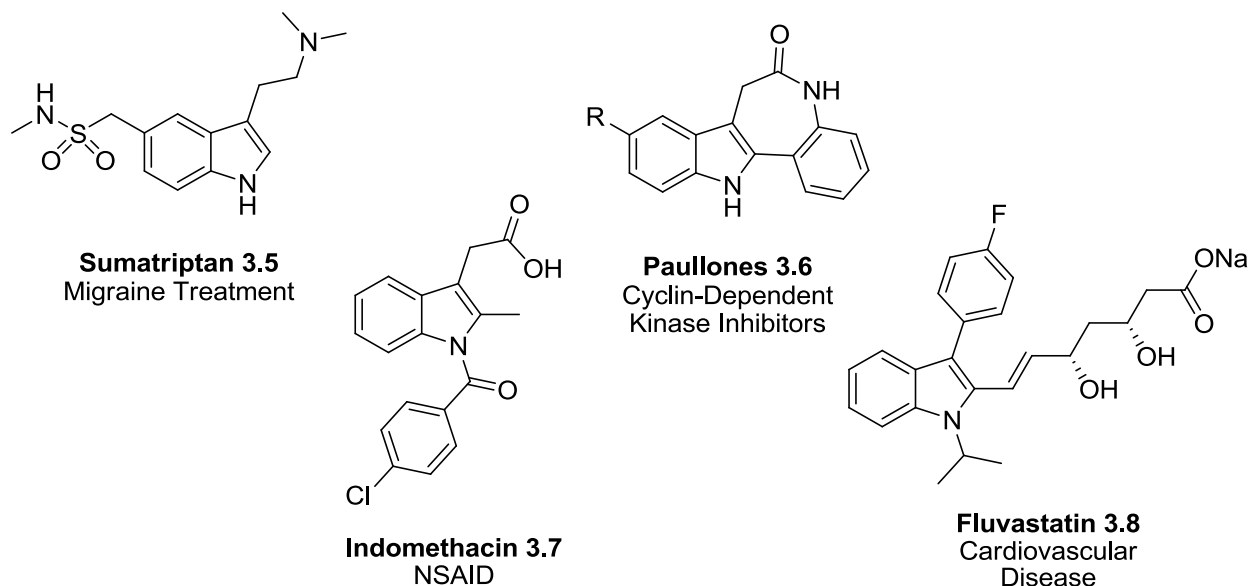


Figure 3.2: Indoles in Medicinal Chemistry

3.2 Synthesis of Indoles

3.2.1 Classic Indole Syntheses

Due to their prevalence throughout organic chemistry, the synthetic chemist has numerous methods to synthesize indole in his arsenal.⁵⁵ So-called “classic” indole syntheses such as the Fischer⁵⁶, Bartoli⁵⁷ or Reissert⁵⁸ Indole Syntheses are still very important methods to access the indole motif, but suffer from limitations such as starting material availability, indole substitution restrictions and functional group tolerance.

3.2.2 Transition Metal-Mediated Indole Syntheses

3.2.2.1 Larock Indole Synthesis

Due to the ever-increasing complexity of synthetic targets incorporating indoles, new, more efficient methods for their synthesis are necessary. Catalytic transition metal-mediated

⁵⁵ For a review on practical indole syntheses, see: Humphrey, G. R.; Kuethe, J. T. *Chem Rev.* **2006**, *106*, 2875.

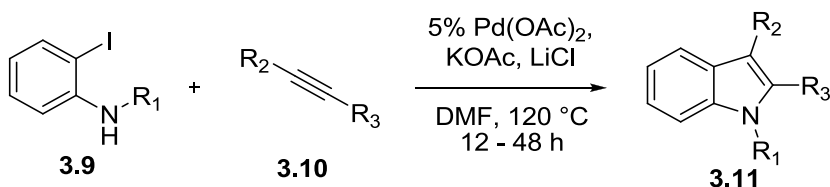
⁵⁶ Robinson, B. *Chem. Rev.* **1963**, *63*, 373.

⁵⁷ Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163.

⁵⁸ Reissert, A. *Chem. Ber.* **1897**, *30*, 1030.

methods for the synthesis of indole represent a relatively new class of indole-forming reactions.⁵⁹ Arguably, one of the first of these to gain widespread popularity was what is now termed the Larock Indole Synthesis (Scheme 3.1).⁶⁰

Scheme 3.1: Larock Indole Synthesis



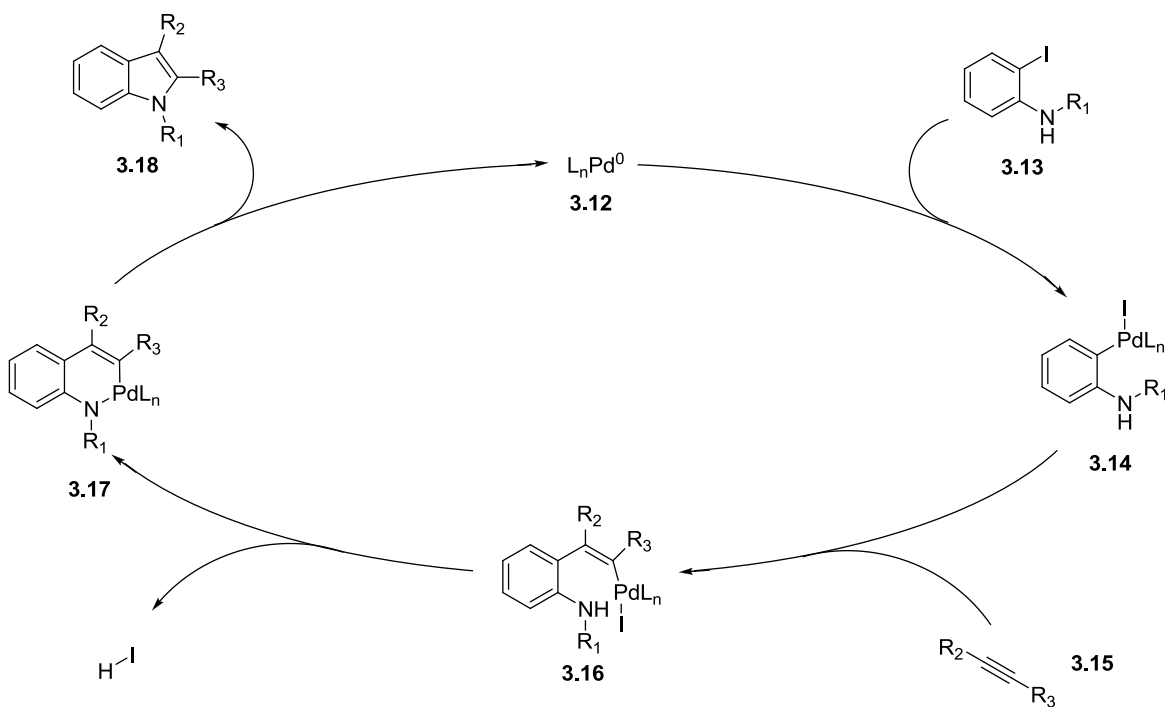
This reaction involved reaction of an *o*-iodoaniline with an alkyne under palladium catalysis (Scheme 3.2). The generally accepted mechanism for this transformation involves the oxidative addition of an activated Pd(0) species **3.12** into the C-I bond of the iodoaniline **3.13**. This is followed by the coordination of the alkyne **3.15** to the Pd species and subsequent *syn*-insertion into the aryl-Pd bond. Attack of the nitrogen atom on the vinyl palladium species **3.16** releases HI and generates a 6-membered palladacycle **3.17** which subsequently reductively eliminates to form the indole **3.18** and regenerates the Pd(0) species, closing the catalytic cycle.⁶¹

Scheme 3.2: Catalytic Cycle for the Larock Indole Synthesis

⁵⁹ For a review, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285

⁶⁰ Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689

⁶¹ Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652



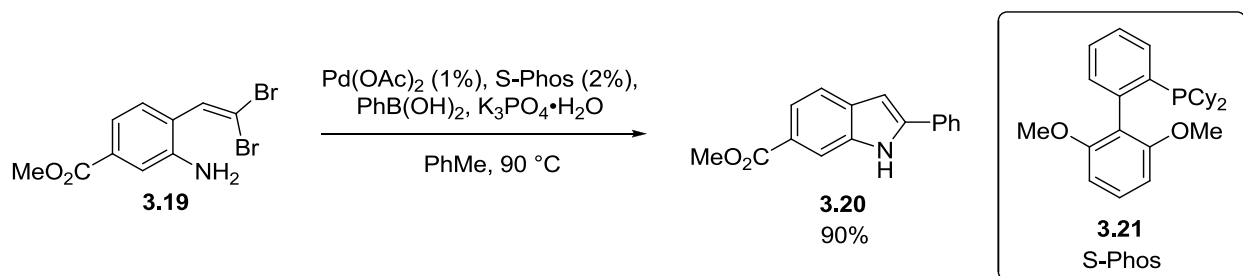
The Larock Indole Synthesis represents a convenient alternative to traditional indole syntheses primarily due to its functional group tolerance. The limitations of this method included the relatively high cost or synthetic inaccessibility of the *o*-iodoaniline as well as the lack of broadly applicable general conditions that could be used for new substrates without the need for optimization. Still, this transformation has been the inspiration behind the discovery of even more efficient transition metal-mediated methods for preparing indoles.

3.2.2.2 Modern Transition-Metal Catalyzed Indole Syntheses

Since the introduction of the Larock indole synthesis conditions, many new transition metal-mediated reactions have been developed. Among them include Lautens' synthesis of indoles **3.20** from *ortho-gem*-dibromovinylanilines **3.19** (Scheme 3.3).⁶²

⁶² Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, 7, 3549; Fang, Y.-Q.; Lautens *J. Org. Chem.* **2008**, 73, 538.

Scheme 3.3: Lautens' Indole Synthesis *via* Tandem Intramolecular Buchwald/Intermolecular Suzuki



The reaction mechanism involved a tandem palladium-catalyzed process whereby an intramolecular Buchwald-Hartwig C-N coupling was followed by a terminal Suzuki-Miyaura reaction with an aryl boronic acid. The starting *ortho-gem*-dibromovinylaniline materials were synthesized according to standard Corey-Ramirez olefination conditions from the appropriate benzaldehyde. This reaction has wide scope, though is limited by the synthesis of the dibromovinylaniline. The initial indole formation protocol by C-N coupling can also be successfully united with a terminal Heck reaction⁶³ or a Sonogashira coupling.⁶⁴

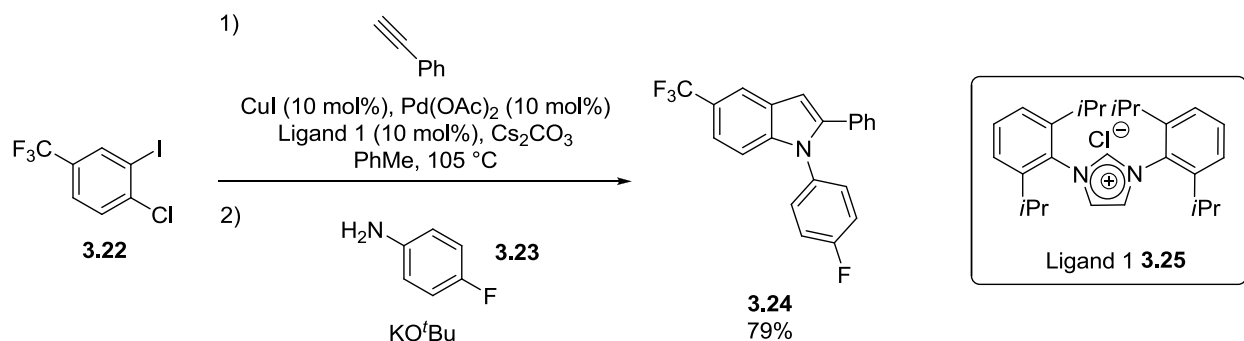
Another example comes from the Ackermann group who published an indole formation reaction *via* a palladium-catalyzed three-component coupling between an *ortho*-iodochlorobenzene **3.22**, a terminal aryl acetylene and an aniline **3.23** to give 1,2-diarylindoles **3.24** (Scheme 3.4).⁶⁵

⁶³ Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203.

⁶⁴ Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.

⁶⁵ Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311.

Scheme 3.4: Palladium-catalyzed Three-component Coupling to form 1,2-diarylindoles



This reaction presumably proceeds *via* a one-pot protocol involving a Sonogashira reaction followed by a Buchwald-Hartwig C-N coupling and ending with an intramolecular hydroamination, with these last two steps similar to a Cacchi indole synthesis⁶⁶ reaction. While this reaction is quite novel, it is unfortunately limited in scope with respect to the availability of suitable *ortho*-dihalobenzene substrates.

The common thread between most of these transition metal-mediated indole formation reactions is the need for a carbon-halogen bond to effect the initial oxidative insertion. The next section will focus on C-H functionalization-involving indole formation reactions that obviate the need for this carbon-halogen bond that often causes this aryl-halide component to be scope-limiting due to poor availability.

3.2.2.3 Transition Metal-Mediated Syntheses of Indole with C-H Functionalization

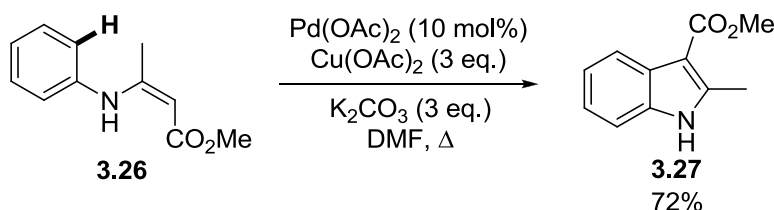
Recent advances in transition metal-catalyzed processes have led to the discovery of analogous indole syntheses to the Larock Indole Synthesis, (*vide supra*), incorporating an element of C-H functionalization instead of a carbon-halogen bond insertion. A notable example includes the oxidative palladium-catalyzed synthesis of 3-carboxylindoles **3.27** from *N*-arylenamines **3.26** reported by Glorius *et al.* in 2008 (Scheme 3.5).⁶⁷ This approach was tolerant of an array of arylenamines on both the ester and aryl portions of the substrate. Furthermore, the enamine could be synthesized from the aniline under Lewis acidic conditions and then used

⁶⁶ For a review see: Battistuzzi, B.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.

⁶⁷ Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230.

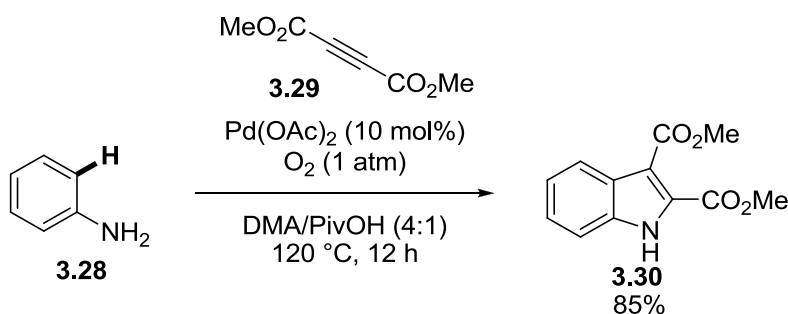
directly in the in the palladium-catalyzed reaction conditions in one-pot to obtain similar yields as were obtained when the enamine was synthesized beforehand.

Scheme 3.5: Palladium-catalyzed Synthesis of 3-Carboxylindoles with C-H Functionalization



A more recent example comes from the Jiao group in China who describe the discovery of a palladium-catalyzed process whereby simple anilines **3.28** could be reacted with symmetrical, electron-poor alkynes **3.29** to obtain the free N-H indole product **3.30** under oxidative conditions (Scheme 3.6).⁶⁸ This process is presumed to go through a similar enamine intermediate as the Glorius conditions (*vide supra*) based on mechanistic studies. These conditions are notable particularly due to the use of diatomic oxygen as the terminal oxidant which holds industrial and economic advantages over the stoichiometric use of the more common organic or metal-based oxidants. The main drawback of this approach is that generally only considerably electron poor alkynes are competent reaction partners and removal of one of the electron-withdrawing groups from the alkyne led to severely diminished conversions.

Scheme 3.6: Oxidative Palladium-catalyzed Indole Synthesis from Alkynes and Simple Anilines



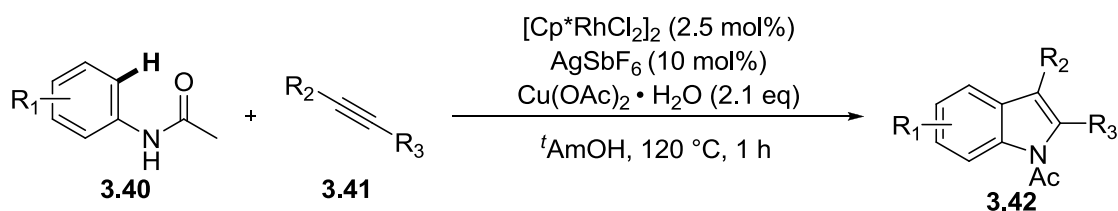
⁶⁸ Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.

3.3 Previous Work in the Fagnou Group Towards an Oxidative Rhodium-Catalyzed Synthesis of Indole with C-H Functionalization

3.3.1 First Generation Conditions

In the Fagnou group, much effort was dedicated towards using the ability of *N*-acetylanilines to orthometallate to discover new reaction pathways involving this directed C-H functionalization. Attempts to use palladium to perform this function were not met with success. Fortuitously however, a metal catalyst screen yielded a hit in the form of the rhodium dimer $[\text{Cp}^*\text{RhCl}_2]_2$. Optimization of these conditions yielded the discovery of a fairly general oxidative, rhodium-catalyzed indole synthesis (Scheme 3.7).⁶⁹

Scheme 3.7: Initially Disclosed Conditions for the Rhodium-Catalyzed Indole Synthesis with C-H Functionalization



These conditions were found to be amenable to a variety of substrates, with both electron-rich and electron-deficient arenes. Most importantly however, they often yielded a single indole regioisomer.

3.3.2 Second Generation Conditions

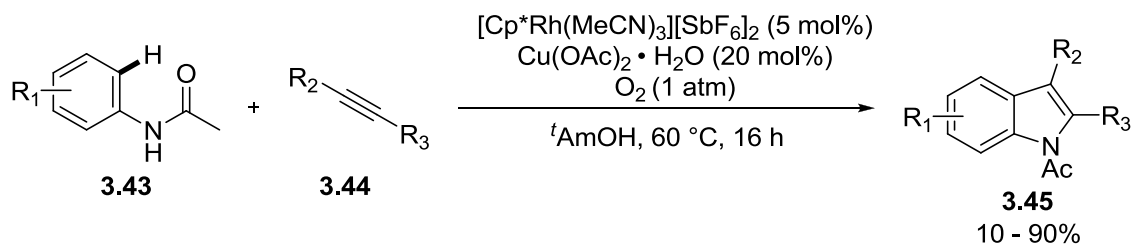
Since the discovery and publishing of the first-generation rhodium-catalyzed indole synthesis from the Fagnou group, attention was immediately turned towards the development of milder second-generation conditions which were hoped to be more tolerant of complex substrates. Through various mechanistic investigations, it was found that the presence of chloride ions in the reaction medium was detrimental to the yield of the reaction, hence the need for a stoichiometric amount, (with respect to catalyst,) of a silver salt in the original reaction

⁶⁹ Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

conditions to generate the active catalyst and cause the precipitation of silver (I) chloride.⁷⁰ It was then found that if the (pre-made) cationic rhodium source $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ was used as catalyst that the use of the silver salt in the reaction was obviated.

Another goal that was sought in the development of the second-generation conditions was the reduction of the amount of the superstoichiometric copper (II) oxidant with a catalytic amount and the use of diatomic oxygen as the terminal oxidant. This goal was obtained by employing the pre-formed cationic rhodium catalyst described above, but moreover, under these conditions, the reaction temperature could be lowered to 60 °C if the reaction was allowed to react over a longer period. These newly optimized reaction conditions are summarized in Scheme 3.8.

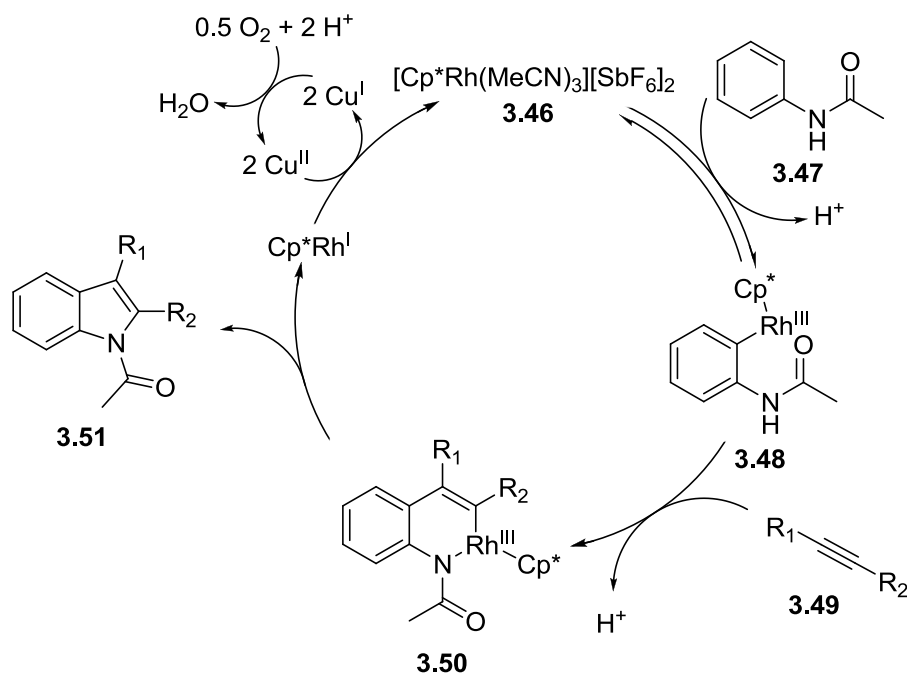
Scheme 3.8: Improved Conditions for the Rhodium-Catalyzed Indole Synthesis with C-H Functionalization



Mechanistic studies of the reaction pathway were undertaken involving the kinetic isotope effect and Hammett Plot studies and led to the generation of a catalytic cycle proposal, (Scheme 3.9). In our proposed cycle, our active catalyst **3.46**, having been pre-formed before the reaction can directly metallate *ortho* to the acetanilide directing group to generate a carbon-rhodium bond. Insertion of this intermediate **3.48** into the alkyne **3.49** with loss of the nitrogen proton can generate a rhodacycle **3.50** which can reductively eliminate to give the indole product **3.51**. The newly-formed rhodium(I) species is then oxidized back to rhodium(III) by two equivalents of copper which are turned over by molecular oxygen, consuming the two equivalents of protons generated by the reaction to give a pH-neutral reaction and closing the catalytic cycle.

⁷⁰ Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.

Scheme 3.9: Proposed Catalytic Cycle for the Rhodium-Catalyzed Indole Synthesis



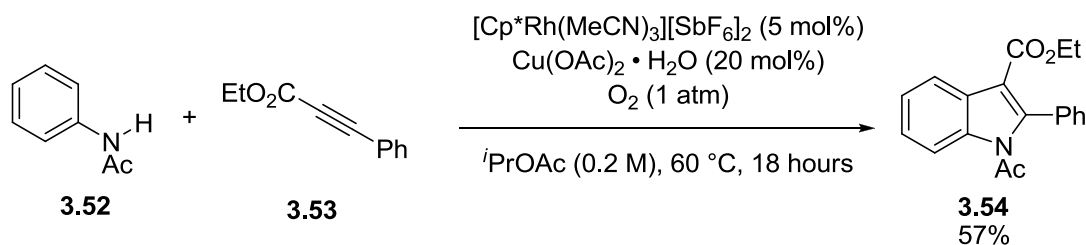
3.4 Synthesis of 3-Carboxylindoles

The discovery of these exciting conditions led to a re-screen of reaction partners to see if incompatible substrates under the first-generation conditions could be coaxed into reaction under these milder conditions. One such class of incompatible alkynes under the first-generation conditions were alkynyl esters. These substrates were viewed to be valuable due to the possibility of their ester hydrolysis followed by their reaction under decarboxylative cross-coupling conditions⁷¹ or even simple decarboxylation to give monosubstituted indoles, which are directly inaccessible under the rhodium-catalyzed protocol.

The efficient reaction of the alkynyl ester **3.53** with acetanilide **3.52** to give the indole product **3.54** showed the potential of these substrates (Scheme 3.10). Furthermore, it is notable that indole **3.54** is formed as a single regioisomer whose regiochemistry was determined *via* derivatization and comparison with literature spectral data. The elaboration of the scope of this reaction scheme was thus explored in this thesis.

⁷¹ Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Eur. J.* **2009**, *15*, 3674.

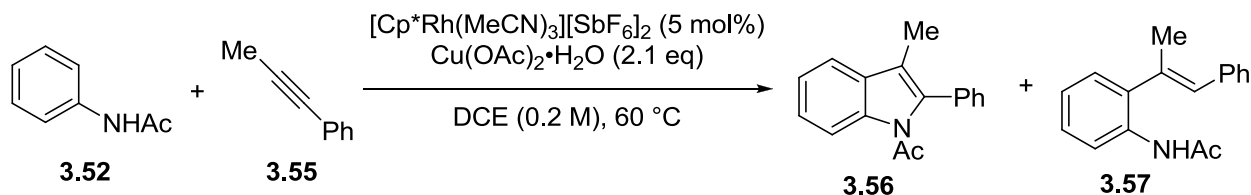
Scheme 3.10: Reaction of an Alkynyl Ester with Acetanilide Under Slightly Modified Second-generation Conditions



3.5 Rhodium-catalyzed Hydroarylation of Acetanilides

During the course of optimization of this rhodium-catalyzed, oxidative cyclization reaction, it was noticed that occasionally a byproduct **3.57** was formed in a high enough yield to be isolated, in addition to the desired indole product in this thesis (Scheme 3.11).⁷²

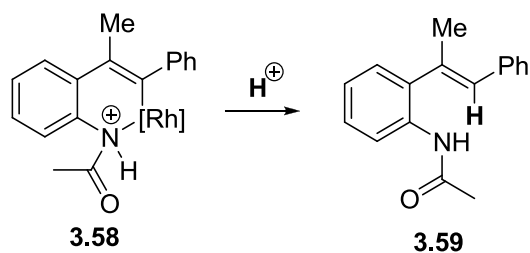
Scheme 3.11: Observation of a Hydroarylated Side Product



After analysis through a variety of NMR methods, it was determined that this side product arose from the decomposition of the post-alkyne insertion, pre-cyclization Rh^{III} intermediate **3.58** and it was postulated that this side product **3.59** may have come from a protonation of this intermediate by residual acid formed by the decomposition of the chlorinated solvent (Scheme 3.12).

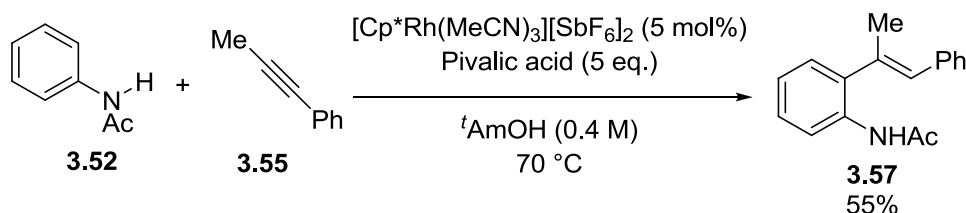
⁷² The optimized hydroarylation has since been published: Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910.

Scheme 3.12: Proposed Formation of a Hydroarylated Side Product *via* Proto-demetalation



Concurrently with this work, efforts were being made to optimize this reaction pathway and these eventually led to the discovery of optimized conditions (Scheme 3.13). The generation of an aryl-vinyl C-C bond and the formation of a single geometric isomer was seen as useful reactivity and so this reaction was further explored with allenyl substrates in this work.

Scheme 3.13: Optimized Conditions for the Rhodium-catalyzed Hydroarylation of Alkynes with Acetanilides



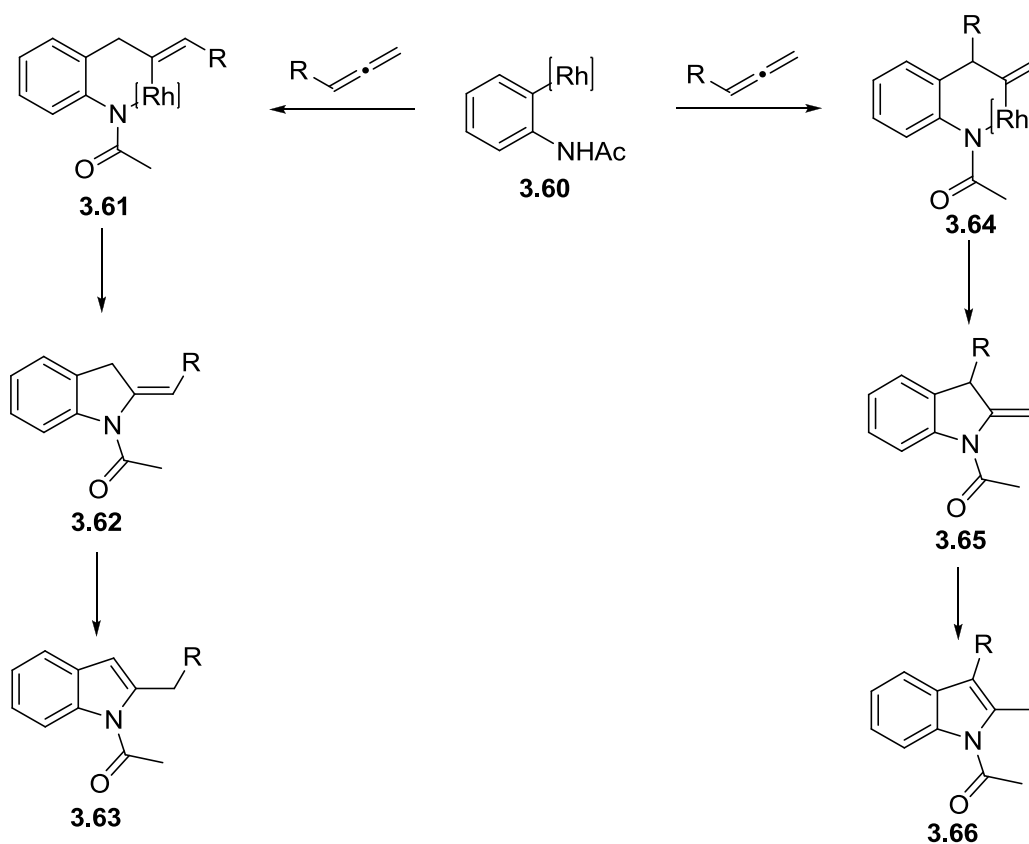
3.6 Project Goals

Though the rhodium-catalyzed protocols developed in the Fagnou group and described above have been proven to be productive with acetylenic substrates, the use of allenes as substrates in this class of chemistry had not yet been attempted and the use of alkynyl esters had not yet been fully explored. As such, the goals of this project were two-fold: 1) to evaluate the use of allenes as potential components in this rhodium-catalyzed process; 2) to evaluate the scope of the rhodium-catalyzed formation of 3-carboxylindole substrates with respect to the alkyne component.

With respect to the first goal, a considerable limitation of the rhodium-catalyzed process developed in the Fagnou lab was a lack of reactivity towards terminal alkynes, for reasons that

have not yet been fully elucidated, but possibly due to copper-catalyzed dimerization. The use of terminal allenes could possibly allow for the synthesis of C3-unsubstituted indoles **3.63** if the aryl rhodium inserted into the terminal olefin, leading eventually to the indole product, presumably after aromatization/isomerization (Scheme 3.14).

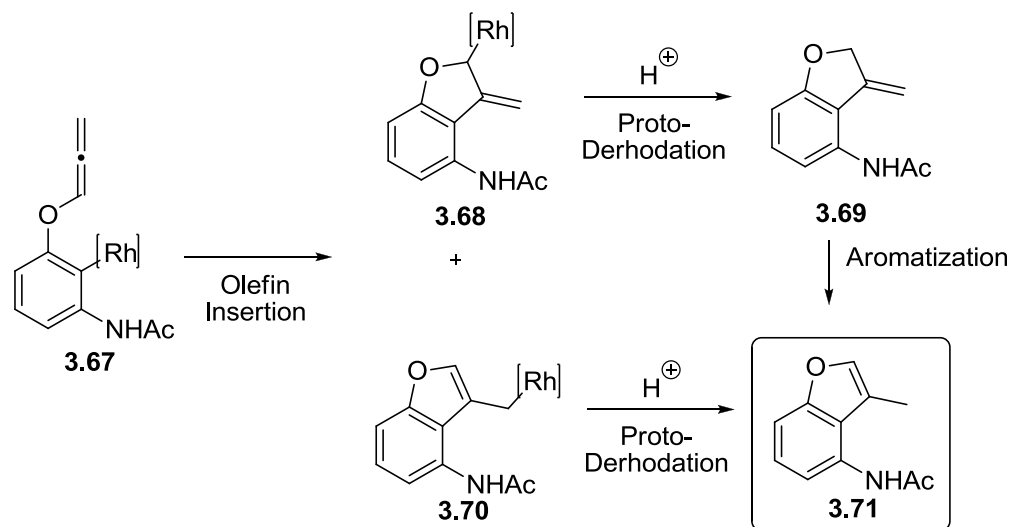
Scheme 3.14: Potential Synthetic Outcomes upon Reaction of Acetanilides with Terminal Allenes Using the Rhodium-catalyzed Indole Formation Protocol



Furthermore, the hydroarylation protocol⁷³ could potentially form a new intramolecular carbon-carbon bond where the reaction of the isomeric terminal alkyne could not, possibly yielding new syntheses of bicyclic unsaturated heterocycles using the acetylamide moiety as a simple directing group (Scheme 3.15). To this end, both intramolecular and the analogous intermolecular reactions were investigated.

⁷³ Stuart, D. *Ph.D Thesis* University of Ottawa, 2009.

Scheme 3.15: Potential Synthetic Pathway of Intramolecular Hydroarylation of Allenes



With respect to the second goal, the reactivity and regioselectivity of the rhodium-catalyzed indole formation reaction with 3-phenyl ethylpropiolate opened the door to functionalized indole products. By probing this reaction, we could determine substrate compatibility and the scope of this reaction that could potentially lead to interesting indole molecules (*vide supra*).

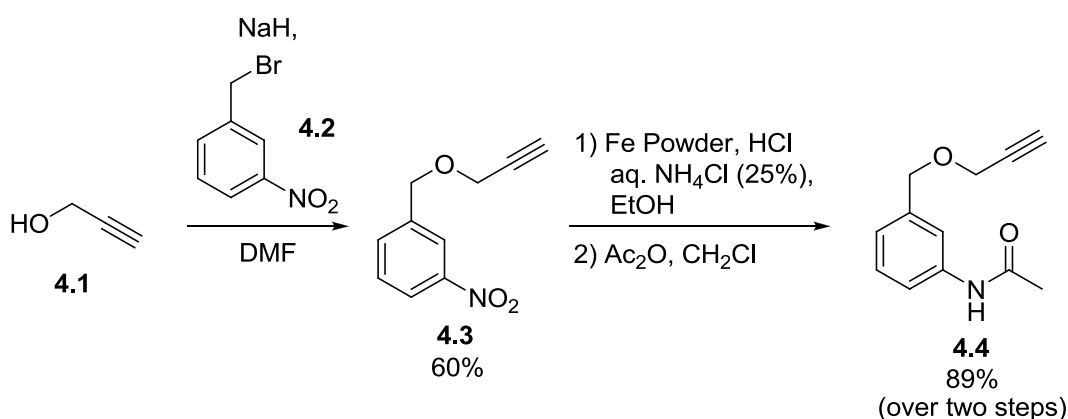
4 Results and Discussion

4.1 Efforts Towards Intramolecular Reactions with Allenes

4.1.1 Synthesis of Starting Materials

Synthesis of alkyne precursor **4.4** was effected starting from **4.1** as shown below (Scheme 4.1). Propargyl alcohol was deprotonated at 0 °C followed by alkylation with *m*-nitrobenzyl bromide **4.2** to give the desired propargyl ether **4.3** in 60% yield. The nitro group was then reduced under mild conditions using iron powder and a 25% aqueous ammonium chloride solution in ethanol with a catalytic amount of hydrochloric acid.⁷⁴ The aniline product **4.4** was obtained in near quantitative yield and was used crude in the subsequent acetylation with acetic anhydride in dichloromethane to give the alkyne precursor in 89% yield over the reduction and acetylation steps. It should be noted here that compound **4.3** is incompatible with palladium on carbon hydrogen reduction conditions due to competitive hydrogenation of the alkyne. Also, alkyne precursor **4.3** is incompatible with the rhodium-catalyzed indole formation conditions as expected due to its terminal alkyne. Furthermore, attempts to effect cyclization with an internal alkyne at the same position were unsuccessful.

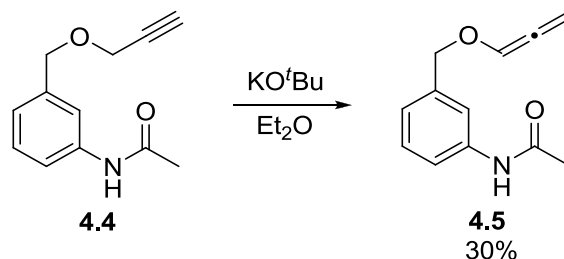
Scheme 4.1: Synthesis of Alkyne Precursor



⁷⁴ Liu, Y.; Lu, Y.; Prashad, M.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, 347, 217.

Terminal acetylene **4.4** was then isomerized to the terminal allene **4.5** under equilibrium conditions by stirring in diethylether with potassium *tert*-butoxide at room temperature (Scheme 4.2) using conditions developed by Trost and Xie.⁷⁵

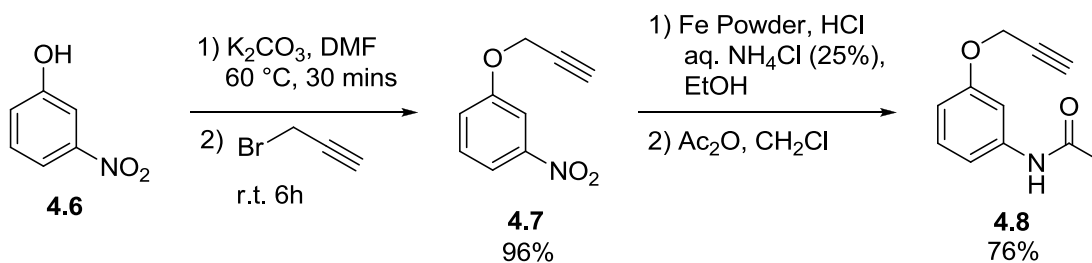
Scheme 4.2: Isomerization of Terminal Alkyne **4.4** to Terminal Allene **4.5**



Concurrent with the synthesis of this terminal allenic acetanilide, the analogous phenolic compound **4.9** was also synthesized to investigate the hydroarylation protocol with this class of substrates. The attractiveness of this compound came from the possibility of the formation of a benzofuran if reaction occurred at either olefin of the allene (*vide supra*).

Synthesis began with the alkylation 3-nitrophenol with propargyl bromide **4.6** to give propargyl ether **4.7** in 96% yield (Scheme 4.3). The nitro group was then reduced and the resulting aniline acetylated using the similar methods as used for the synthesis of **4.4** (*vide supra*) to give the acetanilide **4.8** in 76% yield over two steps.

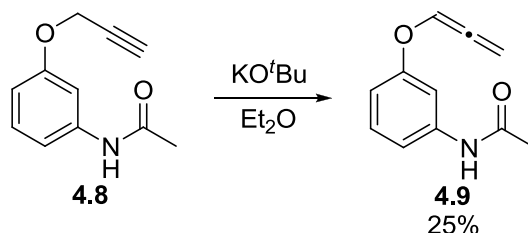
Scheme 4.3: Synthesis of Acetanilide **4.8**



⁷⁵ Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

This alkynyl acetanilide **4.8** was then isomerized to the terminal allene using the same conditions as above, allowing the isolation of desired starting material **4.9** in a synthetically useful 25% yield (Scheme 4.4). It should be noted here that the only other tractable compound from this reaction is the isomeric terminal alkyne starting material.

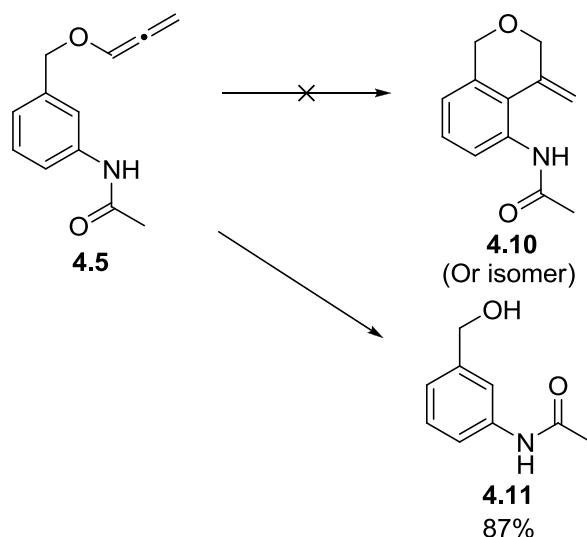
Scheme 4.4: Isomerization of Terminal Alkyne **4.8** to Terminal Allene **4.9**



4.1.2 Reaction Results

With terminal allenes **4.5** and **4.9** in hand, attempts were made to effect intramolecular cyclization using the rhodium-catalyzed hydroarylation conditions developed previously in the Fagnou group.⁷³ When substrate **4.5** was submitted to these conditions, the hydroarylated product **4.10** (or isomer) was not obtained. However, the allenyl acetanilide starting material had been consumed and after flash column chromatography, a much more polar byproduct was isolated in high quantity and purity. After ¹H and ¹³C NMR spectroscopy and mass spectrometric analysis, this byproduct was identified as 3-(hydroxymethyl)acetanilide, **4.11**.

Scheme 4.5: Reaction of Allenic Acetanilide **4.5** led to the Formation of the Benzylic Alcohol Derivative **4.11** Instead of the Desired Hydroarylated Product^a

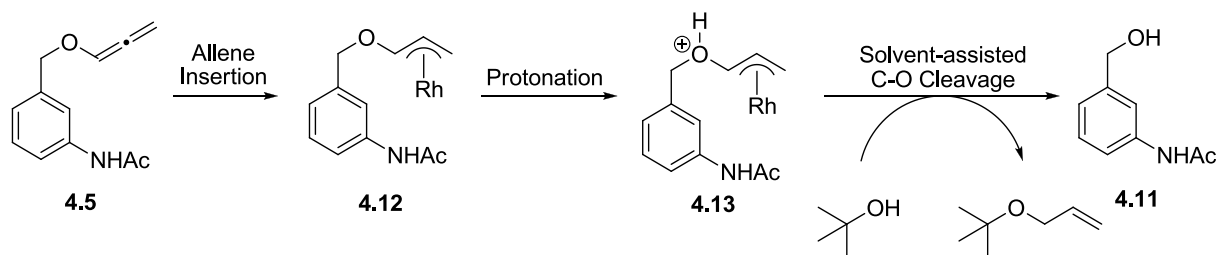


^a Conditions: Acetanilide, (1.0 eq.) [Cp*Rh(MeCN)₃][SbF₆]₂, (5 mol%), pivalic acid, (5.0 eq.) were added to a screw-capped vial. *t*-AmOH (0.2 M) was added, the vial was capped and heated to 60 °C for 16 h.

The formation of this product is fascinating and curious as *O*-benzyl-protected substrates are generally relatively competent partners in the rhodium-catalyzed oxidative cyclization reaction. They had not however been explored under the hydroarylation conditions. It is postulated that while reversible dehydrometallation may be occurring, the more productive reaction involves insertion of the rhodium into the allene itself⁷⁶ followed by protonation of the ether oxygen and cleavage of the carbon-oxygen bond, possibly with participation of solvent (Scheme 4.6).

⁷⁶ For a review of transition-metal insertion into allenyl substrates, see: Bai, T.; Ma, S.; Jia, G. *Coord. Chem Rev.* **2009**, *253*, 423.

Scheme 4.6: Proposed Mechanism of Benzyl Alcohol Formation



With these results in hand, it was clear that the allenic starting material was incompatible with the acidic reaction conditions. Though these conditions were also employed using the phenolic substrate **4.9** synthesized above, interestingly, while no desired product was obtained, no phenol byproduct was able to be isolated either, and though complete consumption of the allene was observed by TLC, no productive compound could ever be isolated from the reaction mixture. As such, an intermolecular variant of this reaction was explored using non- α -allenyl ethers.

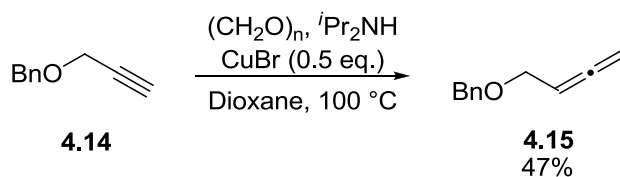
4.2 Efforts Towards an Intermolecular Reaction with Allenes

4.2.1 Synthesis and Reaction of Terminal Allenes

In order to probe the potential reactivity of terminal allenenes under these oxidative rhodium-catalyzed conditions, it was necessary to synthesize a series of practical allenyl substrates since very few are commercially available. Furthermore, to allow for the monitoring of the reaction by TLC or GCMS, it was practical to use an allene with both a chromophore and a substantial enough molecular weight so as to be simple to work with as well as the ability to be synthesized easily and in practical quantities. As such, benzyl-protected propargyl alcohol **4.14** was investigated as a model test substrate. This known compound was synthesized according to a literature precedent whereby easily synthesized benzyl-protected propargyl alcohol was homologated with paraformaldehyde using copper(I) bromide and a secondary amine (Scheme 4.7).⁷⁷

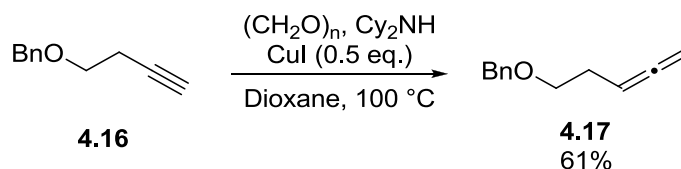
⁷⁷ Nakamura, H.; Sugiishi, T; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49*, 7230.

Scheme 4.7: Representative Synthesis of Terminal Allenyl Test Substrate



A similar, more optimized process⁷⁸ was used to access terminal allene **4.17** (Scheme 4.8).

Scheme 4.8: Synthesis of Terminal Allene **4.17**



With these two substrates in hand, it was sought to determine if any reaction could be observed under either the hydroarylation or second-generation alkyne cyclization protocols developed previously in the Fagnou group. Unfortunately, no productive reaction was ever observed under either of these reaction conditions. It is likely that the benzyl protecting group of these substrates is unstable under the hydroarylation conditions possibly due to the similar reasons that were eventually discovered for substrate **4.5**, (*vide supra*), and benzyl alcohol is released during the reaction, though it was never specifically isolated. This is also suggested by the fact that the allene substrate was never able to be recovered from the reaction mixture, while the acetanilide starting material was always present by TLC analysis.

With respect to the rhodium-catalyzed oxidative cyclization conditions, similar unproductive results as with the hydroarylation procedure were obtained when using terminal allenes in the place of alkynes. Furthermore, again, while the allenyl substrate was always consumed, the acetanilide was always recovered unreacted, suggesting that it is the allene itself that is not tolerated by these reaction conditions. In light of these unsuccessful results, efforts were turned instead to the reaction of more functionalized alkynes and their reaction under previously discovered conditions.

⁷⁸ Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763.

4.3 Synthesis of 3-carboxylindoles

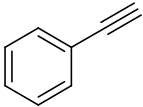
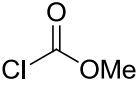
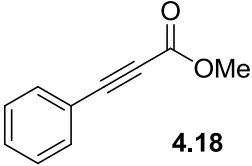
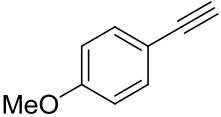
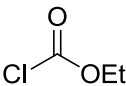
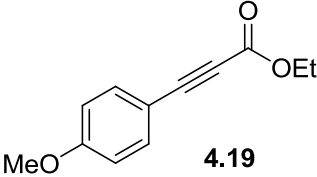
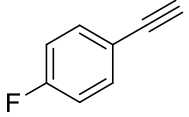
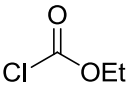
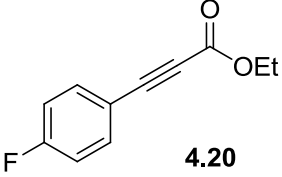
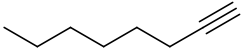
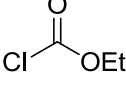
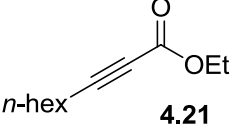
4.3.1 Synthesis of Alkyne Starting Materials

Various non-commercially available ynoates were prepared by a method adapted by Woodgate *et al.*⁷⁹ The terminal acetylene is dissolved in diethylether and deprotonated at low temperature by *n*-butyllithium and quenched with the desired chloroformate.⁸⁰ It is important to note here that higher yields were obtained when the lithiated acetylene is cannulated into a solution of the chloroformate in diethylether as opposed to addition of the chloroformate directly to the deprotonated alkyne as this suppresses reaction of the acetylide with the desired ester product. Using this method, an assortment of ynoate substrates were prepared (Table 4.1).

⁷⁹ Woodgate, P. D.; Sutherland, H. S.; Rickard, C. E. F. *J. Organomet. Chem.* **2001**, 627, 206.

⁸⁰ See supporting information for more details.

Table 4.1: Synthesis of Ynoates from Terminal Acetylenes and Chloroformates

Entry	Terminal Acetylene	Chloroformate	Product	Yield ^b
1			 4.18	77%
2			 4.19	63%
3			 4.20	69%
4			 <i>n</i> -hex 4.21	91%

^aConditions: *n*-BuLi (0.99 eq.) added dropwise to a solution of terminal acetylene (1 eq., 1.2 M) in Et₂O at -78 °C. Stirred for 20 mins at -78 °C. Cannulated into flask containing chloroformate (2.0 eq. 14.0 M) in Et₂O at -20 °C. Stirred for 40 mins and quenched by addition of sat. aq. NH₄Cl.

^bIsolated yields are reported above.

4.3.2 Rhodium-Catalyzed Synthesis of 3-Carboxyindoles

With an array of easily prepared or commercially available carboxyalkynyl compounds in hand, these substrates were subjected to the 2nd generation rhodium-catalyzed indole formation conditions. The results of these studies are summarized in Table 4.2.

Table 4.2: Scope of Rhodium-catalyzed Indole Formation with Alkynoates

Entry	Alkyne	Product	Yield ^b
1	 4.18	 4.24	37%
2	 4.22	 4.25	50%
3	 4.19	 4.26	25%
4	 4.20	 4.27	39%
5	 4.21	 4.28	0%
6	 4.23	 4.29	0%

^a Conditions: Acetanilide (1.1 eq.), the appropriate alkyne (1.0 eq.), copper (II) acetate monohydrate (0.20 eq.) and rhodium complex $[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3][\text{SbF}_6]$ (0.05 eq.). The reaction vessel was purged with O_2 and *t*AmOH was added (0.2 M). The tube was then inserted into an oil bath pre-heated to 60 °C and stirred for 16 h. ^bIsolated yields are reported above.

The results of this substrate screen showed that the reaction conditions were relatively versatile with synthetically useful amounts of indole obtained for most substrates. It would seem that a larger ester (entry 2) is preferred over a smaller ester (entry 1) on the alkyne. Electron-rich (entry 3) and electron-poor (entry 4) aryl groups on the alkyne are both tolerated with a slight preference for electron-poor aryls. It should be noted that all the 3-carboxyindole products were obtained as a single regioisomer, in line with previous observations.⁸¹

However, it seems that at this time, only aryl-substituted alkynoates are competent substrates for this reaction. As can be seen in Table 4.2, Entry 5, no desired product is obtained when alkyl-substituted alkyoates are used. The fact that no *n*-hexyl-substituted alkyne could be recovered from the reaction mixture but a considerable amount of acetanilide starting material remained would seem to suggest that the alkyne is unstable to the reaction conditions. Likewise can be said for entry 6 which is unfortunate since it appears that masking of a carboxylic acid as an ester is required for the reaction to proceed. This is in line with the observation that unprotected alcohols present on the alkyne are not tolerated by these reaction conditions.⁸²

4.4 Conclusions

Though the 2nd generation rhodium-catalyzed indole formation reaction conditions developed in the Fagnou laboratory have broad functional group tolerance and applicability towards the efficient formation of synthetically useful indole substrates, limitations do exist. As presented in sections 4.1 and 4.2, allenes are not tolerated as reaction partners under these conditions. Furthermore, only 2,3-disubstituted indoles are accessible directly, though the methodology could potentially be used to obtain 2-hydro-3-arylindoles *via* ester hydrolysis followed by decarboxylation. Lastly, though 3-carboxyindoles could be obtained in low to moderate yields using the presented protocol, more optimization is required to potentially give the desired product indoles in higher yields.⁸³

⁸¹ Stuart, D. *Ph.D.Thesis* University of Ottawa, **2009**, Chapter 4.

⁸² *Ibid.*

⁸³ This chemistry has since been further optimized by an undergraduate student, Kevin Burgess.

Part 3: Supporting Information

5.1 General Methods

All reagents and solvents were purchased from commercial sources and used without further purification, unless otherwise stated. HPLC grade THF, Et₂O, toluene, and DCM were purified *via* MBraun SP Series solvent purification system. THF used in reactions with *n*-BuLi or NaH was freshly distilled from Na/benzophenone before every use. Triethylamine was freshly distilled from NaOH before every use. All other reaction solvents used were HPLC grade (minimum). [Cp*Rh(MeCN)₃]₂[SbF₆] was synthesized by literature methods.⁸⁴ All oxidative reactions (Chapter 4) were set up without regard for exclusion of ambient air or moisture, and when stated were run under an atmosphere of oxygen. Room temperature in the laboratory was 21 ± 2 °C, reactions heated above this temperature were done so in an oil bath heated externally by a Heidolph MR Hei-Standard heating/stirring mantle equipped with a Heidolph EKT HeiCON temperature control, unless otherwise stated. All reactions were stirred by a magnetic stir bar, unless otherwise stated. Analysis of crude reaction mixtures was done by thin-layer chromatography (TLC) on Merck TLC plates (silica gel 60Å F₂₅₄) and visualized by UV or KMnO₄ stain or by ¹H NMR. Reactions were purified by flash chromatography on Silicycle Ultra Pure silica gel (60 Å). NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ solutions on a Bruker AVANCE 300 MHz or Bruker AVANCE 400 MHz spectrometer at ambient temperature and chemical shifts are reported relative to tetramethylsilane (TMS) or the solvent's residual signal. The following notation is used: br – broad, s – singlet, d – doublet, t – triplet, q – quartet, quin – quintet, m – multiplet, dd – doublet of doublets. Fourier-transform infrared (FTIR) spectra were obtained as thin films on sodium chloride plates. High resolution mass spectra were obtained with a Kratos Concept IIIH mass spectrometer. Chiral HPLC data was obtained on a Waters 2695 Solvent Delivery System equipped with a Waters 2996 PDA detector. Melting points were recorded using a Gallenkamp Melting Point apparatus and are reported uncorrected. All ¹H, and ¹³C NMR spectra of compounds completely characterized in this thesis are provided in section 5.3. All other compounds that have been previously

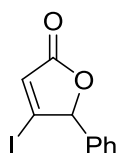
⁸⁴ White, C.; Thompson, S. J.; Maitlis, P.M. *J. Chem. Soc., Dalton Trans.* **1977**, 1654.

synthesized or are commercially available have been appropriately referenced and their NMR spectra are not presented here.

5.2 Experimental Procedures and Characterization of Novel Compounds

5.2.1 Compounds from Part 1

3-Alkynoate **2.24** and 3-alkynamides **2.22** and **2.26** were synthesized as previously reported by Suárez and Fu³⁸ or ApSimon.³⁷ Allenyl esters **2.5**, **2.6**, **2.7**, **2.8**, **2.23**, **2.25** and **2.27** were synthesized as previously reported.³⁷ Butenolides **2.9**³⁰, **2.11**³⁷, and **2.12**³⁷ were synthesized as previously reported.



4-Iodo-5-phenylfuran-2(5H)-one (**2.9**)

Synthesized according to a modified literature procedure.³⁰

An inseparable mixture comprised of 84% ethyl 4-phenylbuta-2,3-dienoate and 16% isomeric ethyl 4-phenylbut-3-ynoate (0.192 g, 1.01 mmol, 1.00 eq.) was dissolved in 8 mL of CH₃CN:H₂O, (15:1) and cooled to 0 °C. Iodine (0.512 g, 2.02 mmol, 2.00 eq.) was then added and the mixture was allowed to warm slowly to r.t. After 11 h, the reaction was quenched by the addition of a sat. aq. solution of sodium thiosulfate and this mixture was extracted with Et₂O, (3 x 30 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified *via* column chromatography over silica gel (5% EtOAc/Pet. Ether) to yield the product as white needles in 51% yield, based on allene starting material.

R_f: 0.16 on silica gel (5% EtOAc/Pet. Ether);

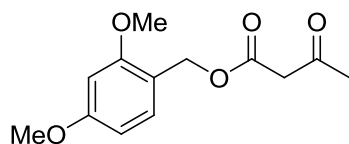
mp: 118 – 120 °C (CH₂Cl₂);

¹H NMR (300MHz, CDCl₃, 293K): 7.46-7.38 (m, 3H), 7.29-7.22 (m, 2H), 6.65 (d, *J* = 1.8Hz, 1H), 5.83 (d, *J* = 1.8Hz, 1H);

¹³C NMR (75MHz, CDCl₃, 293K): 171.1 (CH), 132.9 (C), 130.0 (CH), 129.5 (CH), 129.0 (CH), 127.5 (CH), 125.9 (C), 90.1 (CH);

IR (ν_{max}, cm⁻¹): 3115, 2921, 1792, 1758, 1579, 1453, 1239, 1157, 987;

HRMS calculated for C₁₀H₇IO₂ (M⁺): 285.9491; Found: 285.9466.



2,4-Dimethoxybenzyl 3-oxobutanoate (2.14)

To a solution of 2,4-dimethoxybenzyl alcohol (**2.13**) (1.00 g, 5.95 mmol, 1.00 eq.) in toluene (30 mL) under Ar was added triethylamine (0.870 mL, 6.25 mmol, 1.05 eq.). The mixture was cooled to 0 °C and diketene (0.480 mL, 6.25 mmol, 1.05 eq.) was added dropwise. The mixture was stirred and allowed to warm slowly to r.t. After 16 h, the reaction was diluted with 30 mL of EtOAc and poured into a separatory funnel. The organic layer was washed with a sat. aq. solution of NH₄Cl separated and the aqueous layer was extracted with EtOAc, (2 x 30 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified *via* column chromatography over silica gel (40% Et₂O/Pet. Ether) to yield the product as a pale yellow oil in 89% yield.

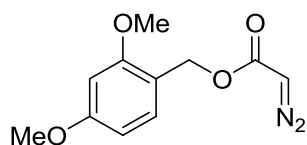
R_f: 0.39 on silica gel (50% Et₂O/Pet. Ether);

¹H NMR (300MHz, CDCl₃, 293K): 7.26-7.20 (m, 1H), 6.50-6.42 (m, 2H), 5.16 (s, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 3.45 (s, 2H), 2.24 (d, 3H);

¹³C NMR (75MHz, CDCl₃, 293K): 200.5 (C), 167.0 (C), 161.4 (C), 159.0 (C), 131.5 (CH), 115.8 (C), 103.9 (CH), 98.4 (CH), 62.5 (CH₂), 55.3 (CH₃), 55.2 (CH₃), 50.0 (CH₂), 29.8 (CH₃);

IR (ν_{max}, cm⁻¹): 3427, 2947, 2838, 1740, 1715, 1617, 1512, 1210, 1159, 1034, 957;

HRMS calculated for C₁₃H₁₆O₅ (M⁺): 252.0998; Found: 252.1004.



2,4-Dimethoxybenzyl 2-diazoacetate (2.16)

Synthesized according to a modified literature procedure.⁸⁵

To a solution of 2,4-dimethoxybenzyl 3-oxobutanoate (**2.14**) (1.00 g, 3.96 mmol, 1.00 eq.) in acetonitrile (5 mL) under Ar was added triethylamine (0.72 mL, 5.17 mmol, 1.30 eq.). The mixture was cooled to 0 °C and a solution of tosyl azide (0.67 mL, 4.37 mmol, 1.10 eq.) in 5 mL of acetonitrile was added dropwise. The mixture was stirred and allowed to warm slowly to r.t. After 16 h, the solvent was removed under diminished pressure and the crude residue was diluted with 20 mL Et₂O and poured into a separatory funnel. The organic layer was washed with a 2M

⁸⁵ Qi, X.; Ready, J. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3242.

solution of $\text{KOH}_{(\text{aq})}$ and the organic layer concentrated *in vacuo*. The mixture was dissolved in a 1:1 mixture of CH_3CN : 2M $\text{KOH}_{(\text{aq})}$ (40 mL) and stirred vigorously for 2 h. The mixture was then poured into a separatory funnel and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified *via* column chromatography over silica gel (30% Et_2O /Pet. Ether) to yield the product as a yellow solid in 76% yield.

R_f: 0.24 on silica gel (30% Et_2O /Pet. Ether);

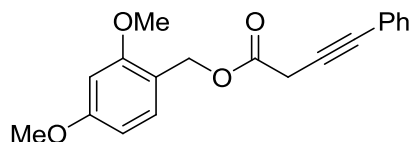
mp: 53 – 54 °C (CH_2Cl_2);

¹H NMR (400MHz, CDCl_3 , 293K): 7.26-7.22 (m, 1H), 6.49-6.44 (m, 2H), 5.18 (s, 2H), 4.77 (br s, 1H) 3.81 (s, 3H), 3.80 (s, 3H);

¹³C NMR (100MHz, CDCl_3 , 293K): 166.9 (C), 161.3 (C), 158.9 (C), 131.3 (CH), 116.5 (C), 104.0 (CH), 98.5 (CH), 61.9 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 46.2 (CH);

IR (ν_{max} , cm^{-1}): 3433, 3120, 2967, 2841, 2111, 1701, 1689. 1616, 1511, 1390, 1210, 1159, 1133, 1036, 996.3;

HRMS calculated for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4$ (M⁺): 236.0797; Found: 236.0785.



2,4-Dimethoxybenzyl 4-phenylbut-3-ynoate (2.17)

To a round-bottomed flask containing copper (I) iodide (0.023 g, 0.12 mmol, 0.05 eq.) under Ar was added acetonitrile (2 mL) followed by phenylacetylene (0.30 mL, 2.70 mmol, 1.10 eq.). A solution of 2,4-dimethoxybenzyl 4-phenylbut-3-ynoate (0.579 g, 2.45 mmol, 1.00 eq.) in acetonitrile (1 mL) was then added and the mixture was stirred at r.t. After 16 h, the solvent was removed under diminished pressure and the crude residue was diluted with Et_2O and filtered through celite using Et_2O as eluent. The filtrate was concentrated *in vacuo* and the crude residue was purified *via* column chromatography over silica gel (20% Et_2O /Pet. Ether) to yield the product as an orange oil in 60% yield containing < 5% isomeric allene.

R_f: 0.41 on silica gel (25% Et_2O /Pet. Ether);

¹H NMR (400MHz, CDCl_3 , 293K): 7.46-7.40 (m, 2H), 7.31-7.27 (m, 4H), 6.49-6.44 (m, 2H), 5.19 (s, 2H) 3.82 (s, 3H), 3.81 (s, 3H), 3.52 (s, 2H);

¹³C NMR (100MHz, CDCl_3 , 293K): 168.3 (C), 161.4 (C), 159.0 (C), 131.7 (CH), 131.5 (CH), 128.2 (CH), 128.1 (CH), 123.1 (C), 116.3 (C), 104.1 (CH), 98.6 (CH), 83.4 (C), 81.4 (C), 62.8 (CH_2), 55.5 (CH_3), 55.4 (CH_3), 26.8 (CH_2);

IR (ν_{max} , cm^{-1}): 3430, 2940, 2836, 1953, 1717, 1616, 1511, 1209, 1159, 1035;

HRMS calculated for $\text{C}_{19}\text{H}_{18}\text{O}_4$ (M⁺): 310.1205; Found: 310.1210.

Representative Procedure for the Enantioselective Isomerization of Alkynyl Esters and Amides

To a vial was added (R)-(S)-JOSIPhos (0.10 eq.) in a glovebox. The vial was capped with a septum cap and removed from the glovebox. Degassed THF was added (0.37 M relative to alkyne) followed by AgSbF₆ (0.10 eq.) in degassed MeOH (1.1 M relative to alkyne). This catalyst mixture was stirred for 30 min at room temperature then the appropriate alkyne (1.0 eq.) was added as a solution in degassed MeOH (1.1 M relative to alkyne). The solution was then cooled to 0 °C for 20 min followed by addition of *N*-methylmorpholine (0.05 eq.). The reaction mixture was stirred for 2 h in the case of alkynyl esters or 1 h in the case of alkynyl amides then quenched by the addition of hexanes until precipitation of the catalyst occurred. The mixture was then filtered through a short pad of silica, rinsing once with EtOAc and the filtrate was concentrated *in vacuo*. The reaction mixture was then analyzed by TLC and/or ¹H NMR and if desired, the product was isolated *via* column chromatography on silica gel, eluting with EtOAc/hexane mixtures.

Representative Procedure for the Isomerization of Alkynyl Amides under Phase-Transfer Conditions (Figure 2.5)

To a vial was added alkyne (1.0 eq.), the phase transfer catalyst (0.1 eq.) and the appropriate base (1.0 eq.). The vial was capped with a septum cap and the appropriate solvent was added (0.1 M). The reaction mixture was stirred at room temp for 30 min then diluted with water. The layers were separated and the organic layer was washed with water (2x), dried over MgSO₄, filtered and concentrated *in vacuo*. The reaction mixture was then analyzed by TLC, ¹H NMR and Chiral HPLC.

Compounds from Part 2

Compounds **4.15**,⁸⁶ **4.18**,⁸⁷ **4.19**,⁹⁶ **4.20**,⁹⁶ and **4.21**⁹⁶ were synthesized as previously reported.

General Procedure A for Rhodium-catalyzed Hydroarylation

To a vial was added the appropriate acetanilide (1.0 eq.), rhodium complex [Cp*Rh(CH₃CN)₃]₂[SbF₆] (0.05 eq.) and pivalic acid. The reaction vessel was capped with a

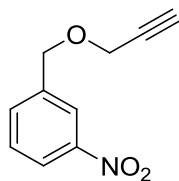
⁸⁶ Nakamura, H.; Sugiishi, T; Tanaka, Y. *Tetrahedron Lett.* **2008**, 49, 7230.

⁸⁷ Woodgate, P. D.; Sutherland, H. S.; Rickard, C. E. F. *J. Organomet. Chem.* **2001**, 627, 206.

septum cap and t AmOH was added (0.2 M) and the appropriate allene (1.1 eq.) (if applicable). The tube was then inserted into an oil bath pre-heated to 60 °C and stirred for 16 h. At this point, the reaction mixture was filtered through celite (CH_2Cl_2 as eluent) and concentrated *in vacuo*. The crude residue was then purified by flash chromatography with the appropriate solvent system.

General Procedure B for Rhodium-catalyzed Indole Synthesis

To a test tube equipped with a magnetic stir bar was added the appropriate acetanilide (1.0 eq.), the appropriate alkyne (1.1 eq.), copper (II) acetate monohydrate (0.20 eq.) and rhodium complex $[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3]_2[\text{SbF}_6]$ (0.05 eq.). The reaction vessel was purged with O_2 and t AmOH was added (0.2 M). The tube was then inserted into an oil bath pre-heated to 60 °C and stirred for 16 h. At this point, the reaction mixture was filtered through celite (CH_2Cl_2 as eluent) and concentrated *in vacuo*. The crude residue was then purified by flash chromatography with the appropriate solvent system.

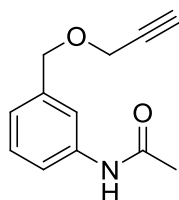


1-Nitro-3-((prop-2-yn-1-yloxy)methyl)benzene (4.3)

To a solution of propargyl alcohol (1.0 mL, 17.6 mmol, 1.0 eq.) in DMF (50 mL) at 0 °C was slowly added NaH (60% w/w dispersion in mineral oil) (0.741 g, 18.5 mmol, 1.05 eq.). The mixture was stirred for 5 mins then 3-nitrobenzylbromide (4.00 g, 18.5 mmol, 1.05 eq.) was added dropwise as a solution in 10 mL DMF. The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched by the addition of 100 mL of a saturated aqueous solution of NH_4Cl . The solution was extracted with Et_2O (3 x 100 mL), the organic extracts were washed with brine (100 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified *via* gradient column chromatography over silica gel (8-12% Et_2O /Pet. Ether) to yield the product (1.96 g) as a yellow oil in 60% yield.

R_f: 0.21 on silica gel (7% Et_2O /Pet. Ether);

¹H NMR (300MHz, CDCl₃, 293K): δ 8.18 – 8.12 (m, 1H), 8.11 – 8.04 (m, 1H), 7.67 – 7.60 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 4.64 (s, 2H), 4.20 (d, *J* = 2.4 Hz, 2H), 2.49 (t, *J* = 2.4 Hz, 1H);
¹³C NMR (75MHz, CDCl₃, 293K): δ 148.2 (C), 139.7 (C), 133.6 (CH), 129.4 (CH), 122.7 (CH), 122.4 (CH), 79.0 (C), 75.3 (CH), 70.1 (CH₂), 57.7 (CH₂);
IR (ν_{max}, cm⁻¹): 3294, 3092, 2860, 2450, 2118, 1618, 1585, 1533, 1353, 1082;
HRMS calculated for C₁₀H₉NO₃ (M⁺): 191.0582; Found: 191.0530.



***N*-(3-((Prop-2-ynoxy)methyl)phenyl)acetamide (4.4)**

Synthesized according to a modified literature procedure.⁸⁸

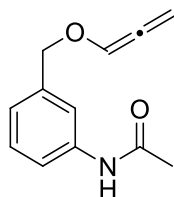
To a slurry of Fe powder (0.584 g, 10.5 mmol, 5.0 eq.) in EtOH (7 mL) was added concentrated HCl (0.09 mL, 1.05 mmol, 0.5 eq.) dropwise. The mixture was heated to 65 °C for 2 h then 25% NH₄Cl_(aq) (3.5 mL) was added followed by nitroarene **4.3** (0.400 g, 2.1 mmol, 1.0 eq.) dropwise as a solution in EtOH (1 mL) over 5 mins and stirred for 1 h (TLC analysis showed complete conversion of starting material). The reaction was cooled to room temperature and filtered through celite, eluting with EtOAc. The filtrate was concentrated *in vacuo* and the crude residue was taken up in EtOAc (10 mL) and washed with sat. aq. NaHCO₃ (1 x 15 mL), brine (1 x 15 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to yield the crude aniline product. The crude aniline product was added to a round-bottomed flask and dissolved in CH₂Cl₂ (17 mL). Acetic anhydride (0.22 mL, 2.37 mmol, 1.13 eq.) was added and the reaction mixture was stirred overnight at room temperature. Upon reaction completion, the reaction was quenched by pouring into sat. aq. NaHCO₃ (20 mL) and the organic layer was separated and washed with sat. aq. NaHCO₃ (3 x 20 mL), brine (1 x 20 mL) dried over MgSO₄, filtered and concentrated *in vacuo* to give the title compound (0.379 g) as a brown oil in 90% yield. The product was used without further purification.

R_f: 0.10 on silica gel (30% EtOAc/Pet. Ether);

¹H NMR (300MHz, CDCl₃, 293K): δ 7.85 (br s, 1H), 7.49 – 7.40 (m, 2H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.53 (s, 2H), 4.13 (d, *J* = 2.4 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.12 (s, 3H).

⁸⁸ Liu, Y.; Lu, Y.; Prashad, M.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217.

¹³C NMR (75MHz, CDCl₃, 293K): δ 168.8 (C), 138.2 (C), 129.0 (CH), 123.8 (CH), 119.5 (CH), 119.4 (CH), 79.5 (C), 77.5 (C), 74.8 (CH), 71.3 (CH₂), 57.2 (CH₂), 24.4 (CH₃);
IR (ν_{max}, cm⁻¹): 3289, 3157, 3089, 2927, 2856, 2121, 1669, 1557, 1490, 1442, 1079;
HRMS calculated for C₁₂H₁₃NO₂ (M⁺): 203.0946; Found: 203.0933.



***N*-(3-((Propa-1,2-dienyloxy)methyl)phenyl)acetamide (4.5)**

Synthesized according to a modified literature procedure.⁸⁹

To a slurry of potassium *tert*-butoxide (0.497 g, 4.44 mmol, 3.5 eq.) in diethyl ether (15 mL) was added alkyne **4.4** (0.257 g, 1.26 mmol, 1.0 eq.). The reaction mixture was stirred for 18 h. The reaction mixture was diluted with diethyl ether (50 mL) and quenched by the addition of H₂O (20 mL). The layers were separated and the organic phase was washed with H₂O (2 x 30 mL), brine (1 x 30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography over silica gel (50% EtOAc/Pet. Ether) to give the product (0.078 g) as a yellow oil in 30% yield.

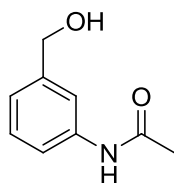
R_f: 0.25 on silica gel (50% EtOAc/Pet. Ether);

¹H NMR (400MHz, CDCl₃, 293K): δ 7.48 (br s, 1H), 7.45 – 7.39 (m, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 5.9 Hz, 1H), 5.46 (d, *J* = 5.9 Hz, 2H), 4.57 (s, 2H), 2.15 (s, 3H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 201.2 (C), 168.3 (C), 138.4 (C), 138.0 (C), 129.1 (CH), 123.5 (CH), 121.6 (CH), 119.2 (CH), 119.0 (CH), 91.3 (CH₂), 70.3 (CH₂), 24.7 (CH₃);

IR (ν_{max}, cm⁻¹): 3297, 2926, 2852, 2350, 1669, 1614, 1595, 1556, 1486, 1431, 1366;

HRMS calculated for C₁₂H₁₃NO₂ (M⁺): 203.0946; Found: 203.0903.



***N*-(3-(Hydroxymethyl)phenyl)acetamide (4.11)**

General procedure **A** was followed using allene **4.5** (0.050 g, 0.25 mmol, 1.0 eq.),

[Cp*Rh(CH₃CN)₃]₂[SbF₆] (0.0102 g, 0.012 mmol, 0.05 eq.), pivalic acid (0.1256 g, 1.23 mmol,

⁸⁹ Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

5.0 eq.) and ^tAmOH (1.2 mL). Gradient chromatography on silica gel (60 – 80% EtOAc in Pet. Ether) afforded the product as an orange solid in 87% yield.

R_f: 0.10 on silica gel (60% EtOAc/Pet. Ether);

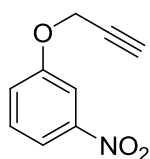
mp: 102 – 104 °C (CH₂Cl₂);

¹H NMR (400MHz, DMSO-*d*₆, 293K): δ 9.85 (br s, 1H), 7.50 (br s, 1H), 7.44 – 7.39 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.14 (t, *J* = 5.7 Hz, 1H), 4.41 (d, *J* = 5.7 Hz, 2H), 1.99 (s, 3H);

¹³C NMR (100MHz, DMSO-*d*₆, 293K): δ 173.4 (C), 148.3 (C), 144.4 (C), 133.5 (CH), 126.2 (CH), 122.6 (CH), 122.3 (CH), 68.1 (CH₂), 29.2 (CH₃);

IR (ν_{max}, cm⁻¹): 3296, 2957, 2926, 2851, 2334, 1655, 1615, 1557, 1434, 1375, 1312, 1004;

HRMS calculated for C₉H₁₁NO₂ (M⁺): 165.0790; Found: 165.0797.



1-Nitro-3-(prop-2-ynyloxy)benzene (4.7)

Synthesized according to a modified literature procedure.⁹⁰

To a round-bottomed flask containing 3-nitrophenol (0.800 g, 5.75 mmol, 1.0 eq.) and potassium carbonate (2.38 g, 17.2 mmol, 3.0 eq.) under Ar was added DMF (12 mL). The solution was heated to 60 °C for 30 mins then cooled to room temperature. Propargyl bromide (0.62 mL, 6.9 mmol, 1.2 eq.) was added dropwise *via* syringe and the solution was stirred at room temperature. After 6 h, TLC analysis showed complete consumption of starting material. The reaction was quenched by the addition of 100 mL ice water and stirred for 20 mins (when all the ice had melted). The solid precipitate was filtered off, washed with cold water and dried under vacuum to yield the product (0.981 g) as a beige solid in 96% yield.

R_f: 0.23 on silica gel (7% Et₂O/Pet. Ether);

mp: 61 – 63 °C (CH₂Cl₂);

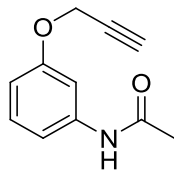
¹H NMR (300MHz, CDCl₃, 293K): δ 7.89 – 7.83 (m, 1H), 7.81 (t, *J* = 2.3 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.37 – 7.25 (m, 1H), 4.76 (d, *J* = 2.4 Hz, 2H), 2.56 (t, *J* = 2.4 Hz, 1H);

¹³C NMR (75MHz, CDCl₃, 293K): δ 157.9 (C), 149.1 (C), 130.0 (CH), 121.9 (CH), 116.6 (CH), 109.5 (CH), 77.3 (C), 76.6 (CH), 56.3 (CH₂);

IR (ν_{max}, cm⁻¹): 3287, 3109, 2922, 2867, 2481, 2449, 2131, 1622, 1586, 1524, 1350, 1022;

HRMS calculated for C₉H₇NO₃ (M⁺): 177.0426; Found: 177.0418.

⁹⁰ Pal, M.; Parasuraman, K.; Yeleswarapu, K, R. *Org. Lett.* **2003**, *5*, 349.



***N*-(3-(Prop-2-ynoxy)phenyl)acetamide (4.8)**

Synthesized according to a modified literature procedure.⁹¹

To a slurry of Fe powder (1.42 g, 25.5 mmol, 5.0 eq.) in EtOH (17 mL) was added concentrated HCl (0.21 mL, 2.55 mmol, 0.5 eq.) dropwise. The mixture was heated to 65 °C for 2 h then 25% NH₄Cl_(aq) (9 mL) was added followed by nitroarene **4.7** (0.90 g, 5.1 mmol, 1.0 eq.) dropwise as a slurry in EtOH (10 mL) over 5 mins and stirred for 1 h (TLC analysis showed complete conversion of starting material). The reaction was cooled to room temperature and filtered through celite, eluting with EtOH. The filtrate was concentrated *in vacuo* and the crude residue was taken up in EtOAc (10 mL) and washed with sat. aq. NaHCO₃ (1 x 15 mL), brine (1 x 15 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to yield the crude aniline product. The crude aniline product was added to a round-bottomed flask and dissolved in CH₂Cl₂ (40 mL). Acetic anhydride (0.50 mL, 5.36 mmol, 1.05 eq.) was added and the reaction mixture was stirred overnight at room temperature. Upon reaction completion, the reaction was quenched by pouring into sat. aq. NaHCO₃ (40 mL) and the organic layer was separated and washed with sat. aq. NaHCO₃ (3 x 40 mL), brine (1 x 40 mL) dried over MgSO₄, filtered and concentrated *in vacuo* to give the title compound (0.783 g) as a beige in 76% yield. The product was used without further purification.

R_f: 0.16 on silica gel (20% EtOAc/Pet. Ether);

mp: 88 – 90 °C (CH₂Cl₂);

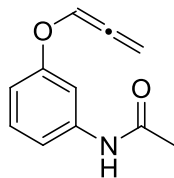
¹H NMR (300MHz, CDCl₃, 293K): δ 7.48 (br s, 1H), 7.32 – 7.27 (m, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.70 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.65 (d, *J* = 2.4 Hz, 2H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.14 (s, 3H);

¹³C NMR (75MHz, CDCl₃, 293K): δ 168.5 (C), 158.0 (C), 139.1 (C), 129.7 (CH), 112.9 (CH), 110.8 (CH), 106.7 (CH), 78.4 (C), 75.5 (CH), 55.8 (CH₂), 24.6 (CH₃);

IR (ν_{max}, cm⁻¹): 3402, 3292, 2122, 1653, 1617, 1600, 1560, 1491, 1442, 1374, 1260, 1157, 1043;

HRMS calculated for C₁₁H₁₁NO₂ (M⁺): 189.0790; Found: 189.0774.

⁹¹ Liu, Y.; Lu, Y.; Prashad, M.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217.



***N*-(3-(Propa-1,2-dienyloxy)phenyl)acetamide (4.9)**

Synthesized according to a modified literature procedure.⁹²

To a slurry of potassium *tert*-butoxide (0.890 g, 7.80 mmol, 3.00 eq.) in THF (26 mL) was added alkyne **4.8** (0.500 g, 2.60 mmol, 1.00 eq.). The reaction mixture was stirred for 16 h. The reaction mixture was diluted with diethyl ether (50 mL) and quenched by the addition of H₂O (20 mL). The layers were separated and the organic phase was washed with H₂O (2 x 30 mL), brine (1 x 30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography over silica gel (5% Acetone/CH₂Cl₂) to give the product (0.127 g) as a pale yellow solid in 25% yield.

R_f: 0.17 on silica gel (5% Acetone/CH₂Cl₂);

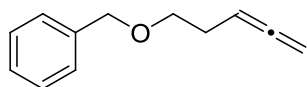
mp: 46 – 48 °C (CH₂Cl₂);

¹H NMR (400MHz, CDCl₃, 293K): δ 7.41 – 7.33 (m, 2H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.83 – 6.76 (m, 2H), 5.43 (d, *J* = 5.9 Hz, 2H), 2.15 (s, 3H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 202.8 (C), 168.4 (C), 157.7 (C), 139.1 (C), 129.8 (CH), 117.6 (CH), 113.9 (CH), 112.6 (CH), 108.4 (CH), 89.6 (CH₂), 24.7 (CH₃);

IR (ν_{max}, cm⁻¹): 3314, 3198, 2935, 2861, 1962, 1669, 1601, 1552, 1489, 1442, 1259, 1183, 1027;

HRMS calculated for C₁₁H₁₁NO₂ (M⁺): 189.0790; Found: 189.0761.



((Penta-3,4-dienyloxy)methyl)benzene (4.17)

Synthesized according to a modified literature procedure.⁹³

To a round-bottomed flask was added CuI (0.597 g, 3.13 mmol, 0.500 eq.), paraformaldehyde, (0.471 g, 15.7 mmol, 2.50 eq.) and *p*-dioxane (31 mL). (Benzylmethyl)propargyl ether (1.00 g, 6.30 mmol, 1.00 eq.) was then added followed by dicyclohexylamine (2.3 mL, 11.6 mmol, 1.8 eq.). A condenser was attached and the solution was heated to 105 °C for 2 h when TLC analysis showed full consumption of starting material. The reaction was quenched by pouring into 10% HCl_(aq) (40 mL), the layers were separated and the organic layer was washed with 10%

⁹² Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

⁹³ Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763.

HCl_(aq) (3 x 40 mL). The combined aqueous layers were back-extracted with CH₂Cl₂ (1 x 40 mL) and the combined organics were then washed with sat. aq NaHCO₃ (1 x 40 mL) and brine (1 x 40 mL). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to give a crude residue which was purified *via* column chromatography over silica gel (2% Et₂O/Pet. Ether) to give the product (0.127 g) as a pale yellow oil in 61% yield.

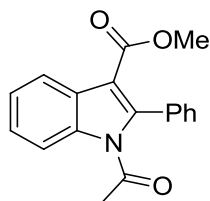
R_f: 0.30 on silica gel (2% Et₂O/Pet. Ether);

¹H NMR (400MHz, CDCl₃, 293K): δ 7.35 – 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 5.14 (quin, *J* = 6.8 Hz, 1H), 4.67 (dt, *J* = 6.5, 3.1 Hz, 2H), 4.51 (s, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.37 – 2.26 (m, 2H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 208.9 (C), 138.4 (C), 128.4 (CH), 127.7 (CH), 128.6 (CH), 86.8 (CH), 75.0 (CH₂), 73.0 (CH₂), 69.6 (CH₂), 28.8 (CH₂);

IR (ν_{max}, cm⁻¹): 3062, 3033, 2914, 2858, 1957, 1722, 1501, 1454, 1363, 1271, 1212, 1100;

HRMS calculated for C₁₂H₁₄O₁ (M⁺): 174.1045; Found: 174.1045.



Methyl 1-acetyl-2-phenyl-1H-indole-3-carboxylate (4.24)

General procedure **B** was followed using acetanilide (0.0676 g, 0.50 mmol, 1.0 eq.), methyl 3-phenylpropionate **4.18** (0.0888 g, 0.55 mmol, 1.1 eq.), copper(II) acetate monohydrate (0.020 g, 0.10 mmol, 0.20 eq.), [Cp^{*}Rh(CH₃CN)₃]₂[SbF₆] (0.0208 g, 0.025 mmol, 0.05 eq.), and ^tAmOH (2.5 mL). Gradient chromatography on silica gel (15 – 20% Et₂O/Pet. Ether) afforded the product as a pale yellow oil in 37% yield.

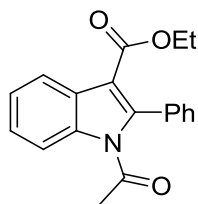
R_f: 0.29 on silica gel (15% Et₂O/Pet. Ether);

¹H NMR (400MHz, CDCl₃, 293K): δ 8.32 – 8.27 (m, 1H), 8.19 – 8.14 (m, 1H), 7.52 – 7.43 (m, 5H), 7.41 – 7.36 (m, 2H), 3.74 (s, 3H), 1.89 (s, 3H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 171.8 (C), 164.7 (C), 143.9 (C), 136.3 (C), 132.4 (C), 130.4 (CH), 129.6 (CH), 128.4 (CH), 126.7 (C), 125.8 (CH), 124.6 (CH), 121.8 (CH), 115.6 (CH), 112.2 (C), 51.3 (CH₃), 27.8 (CH₃);

IR (ν_{max}, cm⁻¹): 2953, 2921, 2849, 2026, 1717, 1702, 1556, 1452, 1387, 1369, 1322, 1297, 1179;

HRMS calculated for C₁₈H₁₅NO₃ (M⁺): 293.1052; Found: 293.1040.



Ethyl 1-acetyl-2-phenyl-1H-indole-3-carboxylate (4.19)

General procedure **B** was followed using acetanilide (0.0405 g, 0.30 mmol, 1.00 eq.), ethyl 3-phenylpropionate (0.054 g, 0.33 mmol, 1.10 eq.), copper(II) acetate monohydrate (0.012 g, 0.06 mmol, 0.20 eq.), [Cp*Rh(CH₃CN)₃]₂[SbF₆] (0.0125 g, 0.015 mmol, 0.05 eq.), and ^tAmOH (1.5 mL). Chromatography on silica gel (15% Et₂O/Pet. Ether) afforded the product as a pale yellow solid in 50% yield.

R_f: 0.31 on silica gel (15% Et₂O/Pet. Ether);

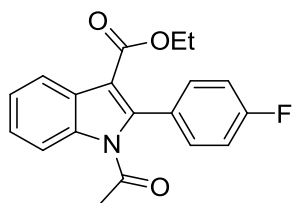
mp: 100 – 102 °C (CH₂Cl₂);

¹H NMR (300MHz, CDCl₃, 293K): δ 8.34 – 8.26 (m, 1H), 8.23 – 8.16 (m, 1H), 7.53 – 7.42 (m, 5H), 7.42 – 7.34 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.90 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);

¹³C NMR (75MHz, CDCl₃, 293K): δ 171.7 (C), 164.2 (C), 143.6 (C), 136.2 (C), 132.6 (C), 130.4 (CH), 129.5 (CH), 128.3 (CH), 126.9 (C), 125.7 (CH), 124.5 (CH), 121.7 (CH), 115.6 (CH), 112.4 (C), 60.1 (CH₂), 27.8 (CH₃), 13.9 (CH₃);

IR (ν_{max}, cm⁻¹): 2985, 2933, 2908, 2880, 1720, 1708, 1692, 1554, 1449, 1363, 1290, 1173;

HRMS calculated for C₁₉H₁₇NO₃ (M⁺): 307.1208; Found: 307.1188.



Ethyl 1-acetyl-2-(4-fluorophenyl)-1H-indole-3-carboxylate (4.27)

General procedure **B** was followed using acetanilide (0.0405 g, 0.30 mmol, 1.0 eq.), ethyl 3-(4-fluorophenyl)propionate **4.20** (0.0626 g, 0.33 mmol, 1.1 eq.), copper(II) acetate monohydrate (0.012 g, 0.06 mmol, 0.20 eq.), [Cp*Rh(CH₃CN)₃]₂[SbF₆] (0.0125 g, 0.015 mmol, 0.05 eq.), and ^tAmOH (1.5 mL). Chromatography on silica gel (15% Et₂O/Pet. Ether) afforded the product as a pale yellow solid in 39% yield.

R_f: 0.34 on silica gel (15% Et₂O/Pet. Ether);

mp: 88 – 90 °C (CH₂Cl₂);

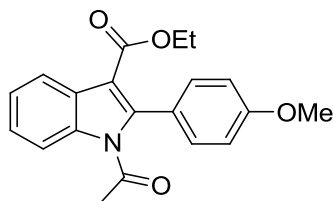
¹H NMR (400MHz, CDCl₃, 293K): δ 8.30 – 8.25 (m, 1H), 8.21 – 8.16 (m, 1H), 7.50 – 7.34 (m, 4H), 7.23 – 7.14 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.94 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 171.4 (C), 164.7 (C), 163.2 (d, *J* = 195.2 Hz) (C), 142.4

(C), 136.3 (C), 132.4 (d, $J = 8.3$ Hz) (CH), 128.6 (d, $J = 3.8$ Hz) (C), 126.8 (C), 125.9 (CH), 124.7 (CH), 121.8 (CH), 115.7 (d, $J = 8.9$ Hz) (CH), 115.5 (CH), 112.8 (C), 60.3 (CH₂), 28.0 (CH₃), 14.1 (CH₃);

IR (ν_{max} , cm⁻¹): 3083, 2990, 2936, 2909, 1900, 1716, 1698, 1561, 1503, 1450, 1294, 1180, 1057;

HRMS calculated for C₁₉H₁₆NO₃F (M⁺): 325.1114; Found: 325.1110.



Ethyl 1-acetyl-2-(4-methoxyphenyl)-1H-indole-3-carboxylate (4.26)

General procedure **B** was followed using acetanilide (0.0405 g, 0.30 mmol, 1.0 eq.), ethyl 3-(4-methoxyphenyl)propionate **4.19** (0.0665 g, 0.33 mmol, 1.1 eq.), copper(II) acetate monohydrate (0.012 g, 0.06 mmol, 0.20 eq.), [Cp*Rh(CH₃CN)₃]₂[SbF₆] (0.0125 g, 0.015 mmol, 0.05 eq.), and ^tAmOH (1.5 mL). Chromatography on silica gel (25% Et₂O/Pet. Ether) afforded the product as a pale yellow solid in 25% yield.

R_f: 0.26 on silica gel (25% Et₂O/Pet. Ether);

mp: 94 – 96 °C (CH₂Cl₂);

¹H NMR (400MHz, CDCl₃, 293K): δ 8.31 – 8.25 (m, 1H), 8.20 – 8.14 (m, 1H), 7.41 – 7.34 (m, 4H), 7.03 – 6.97 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.87 (s, 3H), 1.92 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H);

¹³C NMR (100MHz, CDCl₃, 293K): δ 172.0 (C), 164.4 (C), 160.6 (C), 143.9 (C), 136.2 (C), 131.8 (CH), 126.9 (C), 125.6 (CH), 124.5 (CH), 124.5 (C), 121.7 (CH), 115.5 (CH), 113.8 (CH), 112.2 (C), 60.2 (CH₂), 55.4 (CH₃), 27.9 (CH₃), 14.2 (CH₃);

IR (ν_{max} , cm⁻¹): 2981, 2939, 2909, 2837, 2206, 1712, 1505, 1451, 1288, 1249, 1179, 1058;

HRMS calculated for C₂₀H₁₉NO₄ (M⁺): 337.1314; Found: 337.1312.

5.3 NMR Spectra of Novel Compounds

