COPPER AND ZINC CATALYZED ADDITIONS OF ALKYNES AND YNAMIDES TO CARBONYL ELECTROPHILES

A Dissertation
submitted to the Faculty of the
Graduate School of Arts and Sciences
of Georgetown University
in partial fulfillment of the requirements for the
degree of Doctor of Philosophy
in Chemistry

By

Andrea Moreho Cook, M.S.

Washington, DC
September 4, 2017
COPPER AND ZINC CATALYZED ADDITIONS OF ALKynes AND YnAMIDES TO CARBONYL ELECTROPHILES

Andrea Moreho Cook, M.S.

Thesis Advisor: Christian Wolf, Ph.D.

ABSTRACT

Fluorine-containing pharmaceuticals are of increasing interest which is at least partly due to the favorable stability to biodegradation, increasing bioavailability and lipophilicity and other desirable pharmacological and physicochemical effects. The catalytic enantioselective alkynylation of trifluoromethyl ketones is of particular interest with respect to Efavirenz, a commonly prescribed reverse transcriptase inhibitor. The possibility of an asymmetric formation of the important trifluoromethyl-derived propargylic alcohol pharmacophore was investigated. Addition of phenylacetylene to 3,3,3-trifluoroacetophenone was achieved in moderate to high yield and enantioselectivity using catalytic zinc(II) triflate and the chiral ligand cinchonine in triethylamine and acetonitrile as solvent. While more investigation is required to develop a reproducible procedure, the results indicate that excellent yields and ee are possible under mild conditions.

Ynamides derived from alkynes and electron-deficient amines have received increasing interest due to their huge synthetic potential, including utilization in the total synthesis of natural compounds. The addition of ynamides to acyl chlorides has been accomplished at room temperature using copper iodide as catalyst. This economical and practical carbon-carbon bond formation provides convenient access to a variety of 3-aminonyrones from aliphatic and aromatic acyl chlorides in up to 99% yield. Steric hindrance does not seem to affect the reaction and the ynamide addition to pivaloyl chloride gave was achieved in 90% yield.
The first catalytic asymmetric addition of ynamides to aliphatic and aromatic aldehydes is described. This reaction provides unprecedented access to a diverse family of $N$-substituted propargylic alcohols that are obtained in high yield and ee in the presence of 10 mol% of zinc triflate and $N$-methylephedrine. The use of apolar solvent mixtures is essential to avoid product racemization and to optimize ee’s without compromising conversion. Furthermore, asymmetric addition of terminal ynamides to trifluoromethyl ketones with a readily available chiral zinc catalyst is accomplished and gives CF$_3$-substituted tertiary propargylic alcohols in up to 99% yield and 96% ee. The exclusion of organozinc additives and base as well as the general synthetic utility of the products are key features of this reaction. The value of the $\beta$-hydroxy-$\beta$-trifluoromethyl ynamides is exemplified by selective transformations to chiral $Z$- and $E$-enamides, an amide, and $N,O$-ketene acetals. The highly regioselective hydration, stereoselective reduction, and hydroacyloxylation reactions proceed with high yields and without erosion of the ee value of the parent $\beta$-hydroxy ynamides.
ACKNOWLEDGEMENTS

My mentor, Dr. Christian Wolf, has provided unflagging support and indispensable guidance through six years of laboratory research. He pushed me to find success by systematically exhausting all possible solutions. His high standards for productivity and attention to detail drew out my best work and his encouragement through health and family issues was instrumental in completing my dissertation. I cannot thank him enough for all the time and effort he has invested in me and my training as an organic chemist.

My committee members, Dr. Timothy Warren, Dr. Travis Holman and Dr. Jennifer Swift, have been a great support through the years. In addition to supporting my research and honing my scientific thinking, Dr. Warren and Dr. Homan provided wonderful instruction through graduate courses and all three, in addition to my mentor, have supported my development as a teacher. Dr. Nagarjuna Gavvalapalli kindly agreed to step in as a reader for my dissertation defense in the absence of Dr. Travis Holman, for which I am truly grateful.

Current and former Wolf group members have contributed greatly to my productivity and success in the lab. Dr. Daniel Iwaniuk, Dr. Marwan Ghosn, Dr. Hanhui Xu, Dr. Peng Zhang, Max Moscowitz and Mikki Boswell were patient and helpful in training me when I first joined the group. Dr. Keith Bentley, Yangwei Liu, Ransheng Ding and Zeus De los Santos and Pegah Bakhshi were wonderful to work with in the ensuing years. I have also been lucky to have very diligent and hard-working undergraduate students, Jonathan Dannatt, Carlos Arnett-Guardado and Nicole Weiss.

I am grateful to the Department of Chemistry, the Graduate School of the Arts and Sciences and Georgetown University for the opportunity to complete my graduate studies. Ms. Kay Bayne, Ms. Inez Traylor, Dr. Mo Itani, Mr. Travis Hall, Dr. Ercheng Li and Ms. Yen Miller, Ms. Valencia Boyd, Ms. Tabi Lemlem, Ms. Nga Le and Mr. John Ndirtu have all provided vital administrative support during my
graduate studies. I am also grateful to the National Science Foundation and National Institutes of Health for the funding that enabled me to carry out my research.

I would like to thank my husband, Dave Cook for his unending support since the day I first thought about applying to graduate school. I couldn’t have done it without him. I’m also grateful to my parents for raising me to excel in school and providing encouragement throughout my studies. I would also like to thank my daughter, Ada Kate, for taking many naps and requiring relatively little attention while I wrote my dissertation.
# Table of Contents

Chapter 1. The chemistry of alkynes and ynamides

1.1. Properties and significance of alkynes and ynamides ........................................ 1
1.2. Synthesis of terminal alkynes ................................................................................. 3
1.3. Synthesis of terminal ynamides ............................................................................. 9
1.4. Coupling and Sn2 reactions with terminal alkynes and ynamides ......................... 26
1.5. Nucleophilic additions of terminal alkynes and ynamides to carbonyl electrophiles .......... 38

Chapter 2. Alkynylation of trifluoromethyl ketones

2.1. Introduction .............................................................................................................. 53
2.2. Evaluation of copper catalysis ............................................................................ 56
2.3. Zinc-mediated alkynylation .................................................................................... 59
2.4. Catalysis with Zn(OTf)2 ..................................................................................... 63
2.5. Conclusion ............................................................................................................ 69
2.6. Experimental section ............................................................................................ 70

Chapter 3. Copper catalyzed nucleophilic addition of ynamides to acyl chlorides

3.1. Introduction .............................................................................................................. 71
3.2. Results and discussion .......................................................................................... 72
3.3. Conclusion ............................................................................................................ 76
3.4. Experimental section ............................................................................................ 77

Chapter 4. Catalytic enantioselective addition of ynamides to aldehydes

4.1. Introduction .............................................................................................................. 82
4.2. Results and discussion ....................................................................................... 82
4.3. Conclusion ............................................................................................................ 90
4.4. Experimental section ............................................................................................ 91
Chapter 5. Efficient access to multifunctional trifluoromethyl alcohols through catalytic asymmetric C—C bond formation with terminal ynamides .......................................................... 105

5.1. Introduction ........................................................................................................................................ 105

5.2. Results and discussion .......................................................................................................................... 106

5.3. Conclusion ............................................................................................................................................. 115

5.4. Experimental section ............................................................................................................................ 115

References and notes .................................................................................................................................... 129
List of Figures

Figure 1.1. Biologically active alkynes ........................................................................................................... 2
Figure 1.2. Structures of terminal ynamides .................................................................................................. 3
Figure 1.3. Selected ynamides synthesized with Brückner’s method ............................................................. 13
Figure 1.4. Other important ynamides prepared by the alkynyl iodonium method ....................................... 19
Figure 1.5. Ynesulfonamides synthesized with CuI as catalyst ...................................................................... 20
Figure 2.1. Pharmaceuticals containing CF₃ groups ......................................................................................... 53
Figure 2.2. Structure of bisoxazolidine 11 .................................................................................................... 56
Figure 3.1. Structures of terminal ynamines, ynamides and ynesulfonamides ................................................ 71
Figure 3.2. Crystal structure of 2 ..................................................................................................................... 75
Figure 3.3. Proposed mechanism of the CuI catalyzed formation of aminoynone, 2 (top), and conversion of the ynamide to 2 vs time (bottom) ..................................................................................... 76
Figure 3.4. Crystal structure of N-(3-Phenyl-3-oxoprop-1-ynyl)-N-phenyl-4-tolylsulfonamide, 2 .... 81
Figure 4.1. Crystal structures of 13 (left) and 20 (right) ................................................................................ 89
Figure 4.2. Crystal structure of (3S)-3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl) propyne, 13 ................................................................. 103
Figure 4.3. Crystal Structure of 3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 20 ........ 104
Figure 5.1. ¹H NMR spectroscopic analysis of Zn(OTf)₂, L8 and ynamide 1 interactions ......................... 110
Figure 5.2. X-ray structures of (S, Z)-28 (left) and (S,E)-30 (right) ............................................................. 115
Figure 5.3. Crystal structure of (S, Z)-N-butyl-4-methyl-N-(4,4,4-trifluoro-3-hydroxy-3- phenylbut-1-en-1-yl)benzenesulfonamide, 28 .................................................................................. 127
Figure 5.4. Crystal Structure of (S,E)-2-((N-butyl-4-methylphenyl)sulfonamido)-4,4,4-trifluoro-3- hydroxy-3-phenylbut-1-en-1-yl benzoate, 30 .................................................................................. 128
LIST OF SCHEMES

Scheme 1.1. Synthesis of phenylacetylene from alkyl and alkenyl halide ........................................... 5
Scheme 1.2. Corey-Fuchs reaction. ........................................................................................................... 6
Scheme 1.3. Mechanism of the Corey-Fuchs reaction. ............................................................................ 7
Scheme 1.4. One-pot variations of the Corey-Fuchs reaction. ................................................................. 7
Scheme 1.5. Homologation of aldehydes using diazophosphonates. ..................................................... 8
Scheme 1.6. Homologation with Ohira-Bestmann reagent. ................................................................. 8
Scheme 1.7. One-pot transformations of esters, amides and alcohols to alkynes using Ohira-Bestmann reagent 14................................................................. 9
Scheme 1.8. Synthesis of alkynes from methyl ketones. ........................................................................ 9
Scheme 1.9. Synthetic routes to terminal ynamides. ............................................................................. 11
Scheme 1.10. Thymine and cytosine derived ynamides. ................................................................. 12
Scheme 1.11. Brückner’s general synthesis of tosyl ynamides. ............................................................. 13
Scheme 1.12. Possible reaction pathways of dihalo enamides. .......................................................... 14
Scheme 1.13. Anderson’s streamlined synthesis of dichloroenamides. ............................................. 15
Scheme 1.14. Terminal ynamide synthesis from 1,2-dichloroenamides. ............................................. 15
Scheme 1.15. Amidation with trimethylsilylthynyl(phenyl)iodonium triflate, 37............................ 16
Scheme 1.16. Amidations with free and TMS protected alkynyl iodonium salts 43 and 37............. 17
Scheme 1.17. N-alkynylation of enantiopure allylglycine derivatives. ............................................. 18
Scheme 1.18. CuCN catalyzed N-alkynylation of oxazolidinones, amides and carbamates............. 20
Scheme 1.19. Copper mediated N-alkynylation of selected carbamates. ........................................... 21
Scheme 1.20. Scope of the ynamide synthesis using catalytic amounts of copper and phenanthroline ........................................................................................................... 22
Scheme 1.21. Catalytic C-N bond formation with an alkynyl trifluoroborate ..................................... 23
Scheme 1.22. Oxidative alkynylation of various N-nucleophiles ......................................................... 24
Scheme 1.23. Mechanism of the copper catalyzed oxidative C-N bond formation with terminal
alkynes as postulated by Stahl ........................................................................................................ 25
Scheme 1.24. Ynimide synthesis with alkynyl bismuthonium salts ......................................................... 25
Scheme 1.25. Modified Glaser coupling .................................................................................................. 27
Scheme 1.26. Cadiot-Chodkiewicz coupling ....................................................................................... 27
Scheme 1.27. Selective heterocoupling of terminal alkynes using Au(I) or Cu$^0$ ....................................... 28
Scheme 1.28. Sonogashira and Heck couplings ..................................................................................... 29
Scheme 1.29. Mechanism of the Sonogashira reaction ............................................................................ 30
Scheme 1.30. Stille coupling of unsymmetrical alkynes .......................................................................... 31
Scheme 1.31. Nucleophilic substitution reactions with metal acetylide species ........................................ 31
Scheme 1.32. Examples of coupling reactions between terminal alkynes and alkyl substrates .......... 32
Scheme 1.33. Glaser-Hay coupling and Cadiot-Chodkiewicz cross-coupling of ynamides .............. 34
Scheme 1.34. Palladium catalyzed cross coupling of zinc ynamides with aryl iodides .................... 35
Scheme 1.35. Sonogashira coupling with ynamides .............................................................................. 36
Scheme 1.36. SN2 reactions with deprotonated terminal ynamides ..................................................... 37
Scheme 1.37. SN2 reactions using in situ generated lithium ynamide ................................................... 38
Scheme 1.38. Nucleophilic additions of terminal alkynes to carbonyl compounds and derivatives ...... 39
Scheme 1.39. Formation of alkynyl ketones with acetylide nucleophiles ............................................ 40
Scheme 1.40. Enantioselective alkyne addition to selected carbonyl compounds. ............................. 41
Scheme 1.41. Dialkyl zinc-mediated alkynylation of carbonyl compounds. ........................................ 43
Scheme 1.42. Catalytic alkynylation of carbonyl electrophiles using zinc triflate ............................. 44
Scheme 1.43. Catalytic asymmetric alkynylation of aldehydes using Zn(OTf)$_2$ and (+)-NME ............. 45
Scheme 1.44. Deprotonation of terminal ynamides for subsequent nucleophilic additions ............... 48
Scheme 1.45. Copper catalyzed nucleophilic ynamide addition to activated N-heterocycles.............49

Scheme 1.46. Catalytic cycle of the copper catalyzed ynamide addition to activated quinolone .......50

Scheme 1.47. Diastereoselective synthesis of propargylic amines 140 from tert- butanesulfinyl
derived imines 139..................................................................................................................51

Scheme 1.48. Boron promoted diastereoselective addition of sulfanyl ynamides 138 to N- tert-
butanesulfinyl imines 139 ...........................................................................................................52

Scheme 2.1. Shibasaki catalytic cycle ..........................................................................................55

Scheme 2.2. Alkynylation with Cu(OTf)₂ and Et₂Zn....................................................................57

Scheme 2.3. Asymmetric addition of 5a to 4a using Et₂Zn .........................................................60

Scheme 2.4. Competing ethylation and reduction with Et₂Zn.....................................................60

Scheme 2.5. Alkynylation mediated by Me₂Zn ..............................................................................61

Scheme 2.6. Alkynylation with Et₂Zn at reduced temperature ..................................................61

Scheme 2.7. Optimized conditions for the alkynylation of 4a with the bisoxazolidine ligand 11 ......64

Scheme 2.8. Ligand screening with catalytic Zn(OTf)₂ ..................................................................65

Scheme 2.9. Catalysis with binaphthyl diamines .........................................................................67

Scheme 2.10. Alkynylation with cinchona alkaloid 47 using different Et₃N sources .................68

Scheme 3.1. Synthesis of ynesulfonamide 1 ............................................................................72

Scheme 4.1. Noncatalytic nucleophilic addition of ynamides to aldehydes ...............................82

Scheme 4.2. Diastereoselective ynamide addition to citronellal ................................................90

Scheme 4.3. Synthesis of 3-benzoylindole ..................................................................................91

Scheme 4.4. Synthesis of 1-(3-benzoylindolyl)-2-(triisopropylsilyl)acetylene ..........................92

Scheme 4.5. Synthesis of (3-benzoylindolyl)acetylene .............................................................93

Scheme 5.1. Addition of ynamides to trifluoromethyl ketones provides practical access to several
functionalities containing a chiral CF₃-substituted alcohol group. .....................................106

Scheme 5.2. Selective transformations of β-hydroxy ynamides .............................................113
LIST OF TABLES

Table 1.1. Ynamide additions to carbonyl electrophiles..........................................................46
Table 2.1. Preliminary work by the Shibasaki group..................................................................54
Table 2.2. Me$_2$Zn-mediated alkynylation with copper catalyst .............................................59
Table 2.3. Ligand screening with Me$_2$Zn..................................................................................62
Table 2.4. Optimization with N-methylephedrine, 30 .................................................................66
Table 3.1. Copper(I) catalyzed addition to acyl chlorides............................................................73
Table 4.1. Screening of various ynamide nucleophiles .................................................................84
Table 4.2. Catalytic asymmetric ynamide addition to aldehydes ..................................................86
Table 5.1. Optimization of the zinc triflate catalyzed asymmetric addition of ynamides to 2 .... 107
Table 5.2. Further investigation with L8 .....................................................................................109
Table 5.3. Asymmetric catalytic addition of ynamides to trifluoromethyl ketones.....................111
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1’-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BOX</td>
<td>bisoxazoline</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>tert-butoxide</td>
</tr>
<tr>
<td>CN</td>
<td>cyanide</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N’-dicyclohexyl carbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutyl aluminum hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMEDA</td>
<td>N,N’-dimethyl ethylenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppm</td>
<td>bis(diphenylphosphino)methane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
</tbody>
</table>
ee ..................enantiomeric excess
Et ..................ethyl
GC-MS ..........gas chromatography-mass spectrometry
h ..................hours
HIV ...............human immunodeficiency virus
HMPA ..........hexamethylphosphoramide
HPLC .............high-performance liquid chromatography
Hz ..................hertz
IPA ..............2-propanol
IR ..................infrared
KHMDS ........potassium bis(trimethylsilyl)amide
LDA .............lithium diisopropylamide
LHMDS ........lithium bis(trimethylsilyl)amide
Me ..................methyl
Ms ..................methanesulfonate
MS ..................molecular sieves,
NCS ..............N-chlorosuccinimide
NME ..............N-methylephedrine
NMR .............nuclear magnetic resonance
Ph ..................phenyl
phen ..............phenanthroline
ppm ...............parts per million
Pr ..................n-propyl
i-Pr ...............isopropyl
Pro ..............proline
Py ..................pyridine
Red-Al ..........sodium bis(2-methoxyethoxy)aluminumhydride
ROMP ...........ring-opening metathesis polymerization
TEA ............... triethylamine
TBAF ............... tetra-$n$-butylammonium fluoride
TBAI ............... tetra-$n$-butylammonium iodide
TC ............... thiophene-2-carboxylate
THF ............... tetrahydrofuran
THP ............... tetrahydropyranyl
TIPS ............... triisopropylsilyl
TMEDA .......... $N,N,N',N'$-tetramethylethylenediamine
TLC ............... thin layer chromatography
TMS ............... trimethylsilyl, tetramethylsilane
Tf .................. trifluoromethanesulfonate
Ts .................. $para$-toluenesulfonate
TS .................. transition state
Chapter 1. The chemistry of alkynes and ynamides

1.1. Properties and significance of alkynes and ynamides

Acetylene produced from coal was one of the pillars of the chemical industry in the first half of the 20th century, providing a vital feedstock for the production of organic compounds. While global production of acetylene peaked in the 1960s, with the United States alone manufacturing 500,000 metric tons per year, acetylene remains an indispensable starting material for many industrially produced compounds, including substituted and functionalized alkynes. Terminal alkynes are weak acids, with pKa’s near 25, and undergo deprotonation in the presence of strong bases such as n-butyllithium and sodium amide. Acetylides are synthetically useful as nucleophiles for carbon-carbon bond forming reactions, such as SN2 reactions with primary alkyl halides or additions to carbonyl electrophiles, and have been used extensively in metal-catalyzed coupling reactions (see section 1.4.1. and 1.5.1.).

Alkynes occur naturally in plants, moss, fungi, algae, sponges, insects and frogs. Over 1,000 acetylenic natural products have been isolated to date. Many of these naturally occurring alkynes have medicinal potential as antibiotics, antifungals, antitumor and other classes of pharmaceuticals. Some examples of naturally occurring alkynes are shown in Figure 1.1. The alkyne-containing steroid Norethynodrel, 1, is an active ingredient in Enovid, the first marketed oral contraceptive. Alkynes 2 and 3 both show anti-cancer activity. The internal alkyne 2, known as Caulerpenyne, is the single major secondary metabolite of marine green macroalgae Caulerpa taxifolia. Caulerpenyne is known as “killer algae,” as it is cytotoxic to several cell lines, and has been shown to be especially effective for inhibiting colorectal cancer. Enediyne 3,

---

1 Part of this chapter’s content has been published by Elsevier (Tetrahedron Lett. 2015, 56, 2377 – 2392.) All copyrights are reserved by Elsevier Ltd.
N1999A2, is an antibiotic as well as a potent anticancer agent. It has been shown to inhibit the growth of tumor cell lines as well as bacteria.\textsuperscript{8} Hemiquinone 4 is a fungal metabolite isolated from ectotrophic fungus SDEF 678 and exhibits antifungal activity,\textsuperscript{9} while Dragomabin 5, an alkyne-containing peptide, inhibits a chloroquine-resistant strain of \textit{P. falciparum}.\textsuperscript{10}

\textbf{Figure 1.1. Biologically active alkynes.}

Nitrogen-substituted alkynes, known as ynamines, are not commonly found in nature. The first isolated ynamine was synthesized unintentionally by Zaugg and coworkers while attempting to furnish an isomeric alkyne.\textsuperscript{11} With the advent of Viehe’s practical synthesis of ynamines\textsuperscript{12} the synthetic potential of the electron-rich and strongly polarized triple bond became apparent.
However, ynamines proved difficult to prepare and handle because they readily react with water to amides. Ynamides have become practical alternatives to ynamines as electron-withdrawing groups on the nitrogen atom diminish the polarization of the triple bond, facilitating handling and improving reaction control. Several classes of ynamides are represented in Figure 1.2.

![Figure 1.2. Structures of terminal ynamides.](image)

Since the development of multiple practical approaches for the synthesis of ynamides (see Section 1.3.), the synthetic utility of ynamides has expanded enormously. Particular attention has been paid to cycloaddition and cycloisomerization reactions as the inherently polarized triple bond undergoes highly regioselective cyclization reactions. Indeed, ynamides have been used to selectively assemble nitrogen-containing heterocycles in the total syntheses of alkaloids Desbromoarborescidines A and C, Lennoxamine, Antiostatin A, and (−)-Herbindoles A, B and C.

1.2. Synthesis of terminal alkynes

Two primary industrial methods for producing acetylene, the simplest alkyne, exploit coal via calcium carbide and, more recently, cracking of natural gas. The storage and handling of acetylene is difficult because it is less thermodynamically stable than other hydrocarbons below 1200 °C and can form explosive mixtures with air. Acetylene is a natural building block for homologous alkynes; well-known processes include the reaction of sodium acetylde with alkyl
halides in liquid ammonia (the Picon synthesis),\textsuperscript{19} or metal-catalyzed Sonogashira\textsuperscript{20} coupling reactions. Alternatively, terminal alkynes can be synthesized from vinyl halides or carbonyl compounds. While early synthetic methods relied on elimination reactions with alkyl or vinyl halides in the presence of strong bases, a greater variety of alkyne targets can be obtained through one-carbon homologation of aldehydes or ketones.

1.2.1. Industrial methods for the production of acetylene

The reaction of calcium oxide and coal to produce calcium carbide is highly endothermic, requiring temperatures between 2000 and 2300 °C. Below 1600 °C, the starting materials are preferred thermodynamically (see Equation 1). In the second step, water is typically added in slight excess to form acetylene and calcium hydroxide; so-called dry generators have a production capacity of 5 tons of acetylene per hour.\textsuperscript{21} While this method dominated the industry when coal was a readily available fuel source, the move to petrochemistry decreased the demand for acetylene as an organic building block in favor of more accessible ethylene and propylene. Production of acetylene via calcium carbide is limited both by the energy requirement for operating the furnace as well as the necessary disposal of the calcium hydroxide by-product.\textsuperscript{1}

\begin{align*}
\text{CaO} \ (s) + 3 \text{C} \ (s) & \rightleftharpoons \text{CaC}_2 \ (s) + \text{CO} \ (g) \quad (1) \\
\text{CaC}_2 \ (s) + 2 \text{H}_2\text{O} \ (l) & \rightarrow \text{C}_2\text{H}_2 \ (g) + \text{Ca(OH)}_2 \ (s) \quad (2)
\end{align*}

Cracking natural gas or other carbon-containing fuels also produces acetylene. Generally, the fuel and a defined amount of oxygen are preheated, mixed and heated to about 1200 °C until covalent bonds of the hydrocarbon break homolytically. The resulting hydrogen and alkyl radicals recombine to form a variety of small organic molecules. Rapid quenching traps acetylene as one of the isolatable products.\textsuperscript{22}
1.2.2. Elimination method

Terminal alkynes such as phenylacetylene, 8, have traditionally been prepared by treating alkyl and alkenyl halides with strong base (Scheme 1.1). β-Bromostyrene, 6, has been converted into phenylacetylene with molten potassium hydroxide in 67% yield,\textsuperscript{22} with sodium amide and liquid ammonia in 75%\textsuperscript{23} as well as with organolithium compounds in near quantitative yields.\textsuperscript{24} 1,2-Dibromo-1-phenylethane 7, gave phenylacetylene in 53% yield when treated with sodium metal in liquid ammonia.\textsuperscript{25} The formation of alkynes by elimination reactions continues to be of general interest.\textsuperscript{26}

![Scheme 1.1. Synthesis of phenylacetylene from alkyl and alkenyl halides.](image)

1.2.3. Synthesis from carbonyl compounds

While terminal alkynes have been synthesized from acyl chlorides and esters,\textsuperscript{27} such transformations typically require multiple steps with moderate to low overall yield. This review will focus on more straightforward approaches for the synthesis of terminal alkynes, primarily from aldehydes. Following the pioneering work of Corey and Fuchs,\textsuperscript{28} several methods have been developed to synthesize terminal alkynes through the homologation of aldehydes. Research continues in this area, both in optimizing phosphorous reagents,\textsuperscript{29} and developing new methods to expand the scope of alkynes that may be obtained.\textsuperscript{30}
Corey and Fuchs initially described two methods for the homologation of an aldehyde to form a dibromoolefin (Scheme 1.2). In the first method, aldehyde 9 is combined with a prepared mixture of carbon tetrabromide and triphenylphosphine and stirred in dichloromethane at 0 °C for 5 minutes. In an alternate procedure, zinc dust, carbon tetrabromide and triphenylphosphine are first stirred for 24 hours followed by addition of the aldehyde which is then stirred for 1-2 hours at room temperature. It was reported that the second method involves less complicated product isolation and gives somewhat higher yields.

The mechanism for the Corey-Fuchs reaction is understood to proceed through a phosphorous ylide 12 formed from carbon tetrabromide and triphenylphosphine (Scheme 1.3). Ylide 12 subsequently reacts with aldehyde 9, proceeding through betaine and oxyphosphetane intermediates before eliminating triphenylphosphine oxide to form dibromoolefin 10. The second step of the Corey-Fuchs reaction entails elimination and lithium-halide exchange with two equivalents of n-BuLi to form a lithium acetylide which gives terminal alkyne 11 after aqueous work-up. An alternative elimination protocol was later developed using magnesium metal in refluxing THF, achieving comparable yields of 75-95%. This method is attractive for large scale syntheses where use the of n-BuLi is problematic.
Some notable improvements to the Corey-Fuchs protocol include the development of one-pot procedures that avoid isolation of the olefin intermediate (Scheme 1.4). One report demonstrated that dibromoolefin 10 can be converted to alkyne 11 using tert-butoxide in the presence of aldehyde 9.\textsuperscript{32} Alternatively, aldehydes converted into (Z)-1-iodo-alkenes can undergo dehydrohalogenation with TBAF, providing good yields with a wide range of aliphatic and aromatic substrates.\textsuperscript{33}

The transformation from an aldehyde to an alkyne can also be accomplished in one step using (diazomethyl)trimethylsilane\textsuperscript{34} or diazophosphonates (Scheme 1.5).\textsuperscript{35} The first general method for the homologation of aldehydes using diazophosphonates was reported by Gilbert,\textsuperscript{36} using Seyferth’s synthesis of diazophosphonate 13.\textsuperscript{37} Building on work by Ohira,\textsuperscript{38} Bestmann later expanded the scope and convenience of this reaction to include enolizable aldehydes using diazophosphonate 14 at room temperature under less basic conditions than those used by
Due to the popularity of Bestmann’s protocol, compound 14 is now commercially available. Alternatively, it can be synthesized from phosphonate 15 with various diazotransfer reagents.

Scheme 1.5. Homologation of aldehydes using diazophosphonates.

Either deprotonation of 13 with a strong base or base-catalyzed acyl cleavage of 14 gives resonance-stabilized phosphonate ion 16 (Scheme 1.6). The new carbon-carbon bond to the aldehyde is formed through a Horner-Wadsworth-Emmons-type reaction, giving a diazoalkene which rearranges to alkyne 11 after loss of molecular nitrogen. Bestmann originally reported that alkynes are formed in 70-97% yields from both aromatic and aliphatic aldehydes. The synthesis of terminal alkynes has also been accomplished with reagent 14 supported on ROMPgel and immobilized on a modular flow reactor with comparable results.

Scheme 1.6. Homologation with Ohira-Bestmann reagent.

The Ohira-Bestmann reagent is also suitable for one-pot syntheses of alkynes from esters, amides and primary alcohols in which the aldehyde is formed in situ (Scheme 1.7). Both esters and Weinreb amides are reduced to aldehydes by DIBAL-H. Bestmann’s conditions give the desired alkynes in moderate to good yield without isolation of the intermediate aldehyde. Taylor and coworkers oxidized primary alcohols to aldehydes in the presence of 5 equivalents of
manganese dioxide and found that the Bestmann alknylation proceeds smoothly in the presence of MnO₂, giving up to 99% yield of 11.⁴⁴

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{O} & \quad \text{R}^1 \\
\text{O} & \quad \text{R}^1 \quad \text{or} \\
\text{O} & \quad \text{R}^1 \\
1) \text{DIBAL-H} & \quad \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \\
2) \text{14, K}_2\text{CO}_3, \text{MeOH, 25} \degree \text{C} & \quad \text{R} \quad \text{H} \\
1) \text{MnO}_2, \text{THF} & \quad \text{HO} \quad \text{R} \\
2) \text{14, K}_2\text{CO}_3, \text{MeOH, 25} \degree \text{C}
\end{align*}
\]

**Scheme 1.7. One-pot transformations of esters, amides and alcohols to alkynes using Ohira-Bestmann reagent 14.**

Methyl ketones have been used for the synthesis of terminal alkynes (Scheme 1.8). A microwave-assisted dehydration with a new phosphorous reagent was recently developed, giving good yields of aromatic terminal alkynes in just a few minutes.⁴⁵ Alternatively, treatment of hydrazones with a halonium source such as N-chlorosuccinimide (NCS) in the presence of a phase transfer catalyst generates geminal dihalide intermediates that undergo elimination to alkynes, including phenylacetylene 8, in moderate to good yields.⁴⁶

\[
\begin{align*}
\text{R} & \quad \text{Cl} \\
\text{Cl} & \quad \text{R} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \quad \text{N} \\
\text{H} & \quad \text{N} \quad \text{N} \\
\text{H} & \quad \text{N} \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
50 - 82\% & \quad 78\%
\end{align*}
\]

**Scheme 1.8. Synthesis of alkynes from methyl ketones.**

### 1.3. Synthesis of terminal ynamides

To date, three major routes for the preparation of terminal ynamides have been developed.⁴⁷ The first viable syntheses of terminal ynamides were based on elimination reactions of dichloro
or trichloro enamides with \( n \)-butyllithium at low temperatures and subsequent quenching of the reaction with alcohol. A larger scope and the tolerance of additional functional groups is now possible with two milder methods, namely the use of alkynyl iodonium salts and through copper catalyzed C-N bond formation. The reaction between lithiated amides and electrophilic alkynyl iodonium salts is believed to proceed via alkylidene carbene intermediates which preferentially rearrange to the corresponding ynamides, \textit{vide infra}. Trimethylsilylated alkynyl iodonium salts were initially used to form silyl ynamides which were then subjected to deprotection with tetra-\( n \)-butylammonium fluoride (TBAF), but it was later found that terminal ynamides can be made directly from terminal alkynyl iodonium salt, providing a more efficient variant of the original method. The key step in the third main pathway to terminal ynamides is the copper catalyzed amidative cross-coupling of alkynyl halides, alkynyl trifluoroborates, alkynyl bismuthonium salts or terminal alkynes. In all cases of copper coupling, the alkyne moiety must be protected by a silyl group which is finally removed to yield the terminal ynamide (Scheme 1.9). Altogether, these three synthetic strategies provide convenient access to a variety of terminal ynamides that can easily be produced on the gram scale.
1.3.1. Elimination method

In 1994, Zemlicka and coworkers showed successful conversion of purine and pyrimidine derived chloro enamines and enamides to terminal ynamines and ynamides, respectively.\(^4\) Deprotonation of thymine, 17, and cytosine, 18, with sodium hydride followed by addition of tetrachloroethylene, 19, and heating to 60 °C gave the trichloro enamides 20 and 21 in up to 25% yield (Scheme 1.10). Treatment of 20 and 21 with \textit{n}-butyllithium at -70 °C then furnished the terminal ynamides 22 and 23 in 34-51% yield. While this reaction sequence required the use of strong base and gave low overall yields, it represents the first access to terminal ynamides and it led to the development of quite successful elimination methods.
Brückner later utilized dihalo enamides to develop a general synthetic entry to tosyl ynamides (Scheme 1.11). Inspired by the Corey-Fuchs transformation of aldehydes to alkynes, formamide $24c$ was transformed to the corresponding β,β-dibromo enamide $25c$ in 92% yield. Unfortunately, the conversion of $25c$ via $26c$ to ynesulfonamide $27c$ in the presence of n-butyllithium at -78 °C occurred with only 43% yield due to competing cleavage of the vinyl dibromide moiety and formation of considerable amounts of sulfonamide $28$. This problem was solved by the replacement of carbon tetrabromide with carbon tetrachloride. Several β,β-dichloro enamide intermediates $29a-f$ were obtained in excellent yields and gave tosyl ynamides $27a-f$ under essentially the same conditions in 80-97% yield. Brückner’s method has been employed to make analogous ynamides $27g-j$. Compound $27g$ was used for coupling reactions discussed below and ynamides $27h-j$ were employed in Ru,$^{50}$ Pt,$^{51}$ and Au$^{52}$ catalyzed isomerization reactions (Figure 1.3).
Scheme 1.11. Brückner’s general synthesis of tosyl ynamides.

The superior results observed with chloro enamides 29 compared to the low yield obtained with the brominated analogue 25c have been attributed to competing reaction pathways that may occur with the latter (Scheme 1.12).\textsuperscript{49b} The dichloro enamides probably follow the Corey-Fuchs reaction course (pathway A). In this case, the dihalo enamide 30 preferentially undergoes
deprotonation to 33 and subsequent lithium chloride elimination to chloro ynamide 34 which then reacts with another equivalent of butyllithium to form the terminal ynesulfonamide 27.

Scheme 1.12. Possible reaction pathways of dihalo enamides.

Alternatively, lithium-halide exchange of the dihalo enamide 30 can generate the lithiated enamide 31 which may eliminate to form tosylamide 32 (path B) or to form an alkylidene carbene 36 that spontaneously rearranges to 27 (path C). The outcome of the reaction with β,β-dibromo enamide 25c suggests that brominated enamides favor lithium-bromide exchange (path B) over deprotonation (path A), giving rise to the undesired cleavage product 28c (Scheme 1.11).

Anderson et al. recently developed a more streamlined synthesis of ynamides in which sulfonamides 36 are converted directly into dichloroenamides 38 (Scheme 1.13). This approach eliminates the need for preparing the intermediary formamides, 24, utilized in Brückner’s method. In contrast to the large excess of carbon tetrachloride necessary to form Brückner’s 2,2-dichloroenamides, many of Anderson’s 1,2-dichloroenamides are synthesized with a slight excess of trichloroethylene, 37 (TCE), and 1.5 equivalents of cesium carbonate (Method A). 1,2-Dichloroenamides 38 undergo elimination to form lithiated ynamides 26, and the terminal ynamides 27 are isolated after aqueous work-up (Scheme 1.14).
Scheme 1.13. Anderson’s streamlined synthesis of dichloroenamides.

Scheme 1.14. Terminal ynamide synthesis from 1,2-dichloroenamides.
1.3.2. Amidation of alkynyl iodonium salts

Witulski and Stengel were first to realize that C-N bond formation with alkynyl iodonium salts, originally introduced by Stang et al. for the preparation of ynamines, provides new opportunities for terminal ynamide synthesis. They employed readily available trimethylsilylethynyl(phenyl)iodonium triflate, 37, in the coupling reaction with amides and sulfonamides (Scheme 1.15).  

Scheme 1.15. Amidation with trimethylsilylethynyl(phenyl)iodonium triflate, 37.
In this one-pot procedure, amides 36 are first deprotonated with butyllithium and then treated with 37 at room temperature. It is generally believed that the reaction proceeds through alkylidene carbene intermediates 38 which undergo spontaneous 1,2-migration of the silyl group to form silylated ynamides 39 in moderate to high yields. Interestingly, intramolecular CH-insertion to dihydropyrrroles 41 was not observed. Desilylation of 39 with TBAF in wet THF at 0 °C gave the terminal ynamides 40 and 27 in high yields. Ynamides prepared by this method were utilized by Witulski and Stengel for inter- and intramolecular cycloadditions.

![Scheme 1.16. Amidations with free and TMS protected alkynyl iodonium salts 43 and 37.](image)

The scope of alkynyl iodonium salt amidation was further expanded to a variety of diynes which proved invaluable substrates for [2+2+2]cycloadditions producing an array of substituted indolines and carbazoles, and other ynamides used in [4+2]cycloadditions or Pauson-Khand
It is noteworthy that this method tolerates several functional groups, including alkenyl, alkynyl, carbamoyl, alkoxy, acetal, and alkoxy carbonyl moieties, albeit yields vary significantly. Interestingly, terminal ynamides can also be obtained directly from ethynyl(phenyl)iodonium triflate, 43, which eliminates the desilylation step. Comparison of the two methods shows that N-alkynylation with 43 gives consistently higher yields than the reaction with the silylated iodonium salt 37.

The Witulski group applied alkynyl iodonium triflate 43 in the first synthesis of chiral ynamides 46 from chiral sulfonamide precursors. Several N-sulfonyl protected allylglycine methyl esters 44 were found to undergo smooth amidation in the presence of cesium carbonate as base within 3 hours at room temperature with no observed racemization. Yields for 45a-d were generally high, from 70% to 95%, but N-Boc and N-acetyl derivatives did not react and the corresponding ynamides 45e and 45f were not detected (Scheme 1.17).

Scheme 1.17. N-alkynylation of enantiopure allylglycine derivatives.

*N*-ethynylcarbamates 27q and 40f were synthesized by this method and have been employed in gold catalyzed cyclizations forming oxazolinones. Another example of a chiral ynamide synthesized with Witulski’s method is oxazolidinone 40g which was used in Cadiot-Chodkiewicz reactions, *vide infra* (Figure 1.4).
Figure 1.4. Other important ynamides prepared by the alkynyl iodonium method.

1.3.3. Copper catalyzed C-N bond formation

The Hsung group’s pioneering work in coupling silyl protected alkynyl halides with amides has become the most versatile method for the synthesis of terminal ynamides (Scheme 1.18).\textsuperscript{64} Initial investigations with palladium catalysts, inspired by general progress with N-arylations of amides and amines, were unsuccessful due to predominant homocoupling toward 1,3-dialkynes. Copper-catalyzed coupling of amides \textbf{36} with alkynyl halides proved more promising, though competition with the homocoupling pathway persisted until alkynyl iodides were substituted with alkynyl bromides. In the presence of catalytic amounts of CuCN and \textit{N},\textit{N}'-dimethyl ethylenediamine (DMEDA) and excess of potassium phosphate at 110-150 °C, the coupling of oxazolidinone nucleophiles with 1-bromo-2-triisopropylsilylacetylene, \textbf{46b}, gave cyclic ynecarbamates \textbf{47a-c} in 70-85% yield. The camphor-derived ynamide \textbf{47d} and acyclic ynecarbamates \textbf{47e} and \textbf{47f}, however, were obtained in poor yields with this method. The resulting triisopropylsilyl (TIPS) protected ynamides are readily converted to the corresponding terminal ynamides using a fluoride nucleophile. For example, \textbf{47a} was desilylated with TBAF in 71% yield within 5 minutes.
Scheme 1.18. CuCN catalyzed N-alkynylation of oxazolidinones, amides and carbamates.

Under essentially the same conditions as shown in Scheme 18, Urabe et al. prepared several trimethylsilyl (TMS) protected ynesulfonamides 39e-g, 39i-j and 39p using 5 mol % of CuI as catalyst for the coupling of cyclic and acyclic substrates with 1-bromo-2-trimethylsilylacetylene, 46a (Figure 1.5). Although the free terminal ynamides were not isolated in this study, they may also be obtained via TBAF desilylation as has been shown by Witulski for ynesulfonamide 27e.

Danheiser was able to extend the scope of this approach with a stepwise approach that allowed copper promoted ynamide formation under mild conditions. The amide substrate 48 was first converted to a copper complex with stoichiometric amounts of CuI and KHMDS and then treated with a trialkysilylethynyl bromide 46 (Scheme 1.19). While this protocol is not
catalytic, the reaction occurs at room temperature and enabled the preparation of several silyl protected ynecarbamates 49 in superior yields. As expected, 49b was successfully desilylated with TBAF to the corresponding terminal ynamide 49c in 81% yield.

Scheme 1.19. Copper mediated N-alkynylation of selected carbamates.

Hsung, Tam and others later increased the efficiency and scope of the catalytic ynamide formation using either copper sulfate, copper thiophene-2-carboxylate (CuTC) or cuprous iodide in combination with 1,10-phenanthroline or DMEDA as ligand. With these modifications, remarkable results have been obtained with several imidazolidinone, carbamate, 3-alkoxycarbonylindole, sulfonamide and phosphoramidate nucleophiles and bromoalkyne 46b, and the C-N bond formation was found to occur at lower temperatures than previously reported (Scheme 1.20). An impressive variety of ynamides, including 47a-b and 47g-x, has been prepared by this method. For example, the cyclic ynecarbamate 47b was prepared in gram quantities on the 100 mmol scale with up to 97% yield which compares favorably with Hsung’s original procedure using CuCN.

21
Scheme 1.20. Scope of the ynamide synthesis using catalytic amounts of copper and phenanthroline.

It is noteworthy that Zhang et al. reported an iron catalyzed amidation protocol using FeCl₃ under otherwise very similar conditions. The yields of the silylated ynamides prepared by this method were generally lower than those obtained by the copper catalyzed processes described above; the amidation reaction may have been affected by the presence of small copper impurities in the iron salt used.
Evano’s group introduced trifluoroborates as alkynyl transfer agents to mediate copper catalyzed ynamide synthesis and obtained 39e from 50 in 51% yield. Remarkable features of this approach are that the reaction occurs under air at room temperature and in the absence of strong base (Scheme 1.21). The sparse solubility of the alkynyl trifluoroborate 51 in dichloromethane is critical to the success of the catalytic C-N coupling. The use of DMSO as solvent, in which 51 is readily soluble, led to exclusive formation of the undesired alkyne homodimer while the less polar solvent DCM favored the desired coupling product. The heterogeneous reaction conditions seem to be the major reason for the long reaction times. The overall scope of this method for the synthesis of terminal ynamides remains to be fully explored.


A significant contribution to this field came from the Stahl group. They developed an aerobic oxidative procedure that directly couples amides 36 and terminal alkynes 52, thus avoiding the requirement for a halogenated alkyne precursor (Scheme 1.22). This method provides convenient access to a variety of silylated ynamides 39aa-bb and 47a, 47p, 47y-z, and 47aa-cc, that were obtained with remarkable yields. The oxidative C-N coupling of carbamate, urea and sulfonamide nucleophiles occurs in the presence of catalytic amounts of copper chloride and mild base at 70 °C. The use of indole derived nucleophiles, however, typically requires stoichiometric copper amounts. A remaining drawback is that a large excess (5 equivalents) of the N-nucleophile is necessary to limit the formation of alkynyl chloride and homocoupled alkyne byproducts. Ynamides obtained by this method have been desilylated to provide terminal
alkynes. For example, the silyl group of 47cc was quantitatively removed with TBAF within 5 minutes at room temperature.

Scheme 1.22. Oxidative alkynylation of various N-nucleophiles.

A mechanism explaining the reaction course was proposed by the same group (Scheme 1.23). During formation of 39aa the copper catalyst 53 probably first reacts with trimethylsilylacetylene, 52a, to form the acetylide complex 54 in the presence of base. Complex 54 can then either accept a second acetylide to yield 55 and subsequently dialkyne 56 or react with the sulfonamide 33aa to form the copper(II) species 57. The latter direction should be favored and outperform the homocoupling pathway toward 56 when 33aa is present in excess. Finally, reductive elimination and reoxidation of the copper catalyst produces ynamide 39aa and regenerates 53.
Scheme 1.23. Mechanism of the copper catalyzed oxidative C-N bond formation with terminal alkynes as postulated by Stahl.

A few TMS protected ynamides have been synthesized by coupling of succinimide or phthalimide 58 with alkynyl bismuthonium salts 59 (Scheme 1.24). The yields of the silylated ynimides were initially poor due to significant side reactions forming the homocoupled dialkyn derivatives and N-aryl imide byproducts. Following Stahl’s work, the homocoupling pathway was suppressed by using the imide in excess and 60a and 60b were produced with 52 and 57% yield, respectively. 60b was desilylated to the corresponding free terminal ynimide with TBAF at 0 °C in 88% yield.

Scheme 1.24. Ynimide synthesis with alkynyl bismuthonium salts.
1.4. Coupling and S$_n$2 reactions with terminal alkynes and ynamides

Some of the earliest reported transformation in organic chemistry include the use of metals to promote the formation of carbon-carbon bonds.$^{76}$ Terminal alkynes have been popular substrates in Glaser’s copper-promoted homocoupling of phenylacetylene and palladium and copper catalyzed Sonogashira cross-coupling reactions. The scope of alkyne cross-coupling reactions has steadily increased and this reaction remains very important for the synthesis of complex organic molecules.

In stark contrast to alkynes, which have been employed extensively in Sonogashira couplings, nucleophilic additions and substitution reactions, the utilization of substrates carrying a terminal ynamide functionality typically trails behind the development of synthetic methods that exploit the more popular internal analogues. As a result, the majority of reactions of terminal ynamides reported to date do not conserve the triple bond,$^{77}$ and cycloadditions,$^{57-60,78}$ cycloisomerizations,$^{51,79}$ Heck-Suzuki-Miyaura domino reactions,$^{80}$ ring-closing metathesis,$^{81}$ radical additions,$^{82}$ and titanium-mediated carbon-carbon bond formations are among the most common synthetic transformations.$^{83}$

1.4.1. Coupling and S$_n$2 reactions with alkynes

The copper-mediated coupling of alkynes in the presence of an oxidant has been known since Glaser reported the homocoupling of phenylacetylene, $^8$, in 1869 using stoichiometric amounts of CuCl and atmospheric oxygen as the oxidant.$^{84}$ Glaser’s conditions have since been modified to improve the practicability and scope of this dimerization reaction.$^{85}$ For example, in 1962 Hay developed a catalytic version of the Glaser reaction using CuCl and TMEDA as a solubilizing agent, now known as the Glaser-Hay coupling.$^{86}$ After screening of copper salts and
bases, Balaraman and Kesavan found that optimal conditions for phenylacetylene homocoupling provide 10 mol% of copper(II) acetate hydrate and one equivalent of piperidine (Scheme 1.25).

![Scheme 1.25. Modified Glaser coupling.](image)

Cadiot and Chodkiewicz showed that a terminal alkyne and a bromoalkyne can be coupled selectively in the presence of 1-2 mol% of copper (Scheme 1.26).\(^7\) In this reaction alkyne 63 coordinates to the copper catalyst and is deprotonated to form a copper acetylide. Bromoalkyne 62 then adds to the copper center through oxidative addition, which is followed by reductive elimination to form dialkyne 64 and regeneration of the copper catalyst. This was a significant breakthrough, laying the groundwork for important cross-coupling protocols.

![Scheme 1.26. Cadiot-Chodkiewicz coupling.](image)

Selective heterocoupling of terminal alkynes has recently been accomplished with good selectivity using both gold(I) and copper powder as catalysts (Scheme 1.27). Shi and coworkers used bis(diphenylphosphino)methane bis(gold(I) bromide, dppm(AuBr)\(_2\), to selectively catalyze the cross-coupling of unfunctionalized alkynes (Method A).\(^8\) Under optimized conditions yields of up to 93% were achieved using dppm(AuBr)\(_2\) (2.5 mol%), phenanthroline ligand (10 mol %), PhI(OAc)\(_2\) (2 equiv.) as oxidant and a 3:1 mixture of acetonitrile to 1,4-dioxane as solvent. Both
electron rich and electron deficient aliphatic and aromatic alkynes, including heteroaromatic alkynes, furnished the desired product in good yields. The reaction features high functional group compatibility, and tolerance of alcohols, silanes, esters, ketal, ketones and carboxylic acid groups. Notably, only a slight excess of (1.3 equiv.) of one alkyne was used, demonstrating a significant advantage over alternative cross-coupling protocols that require a large excess of one alkyne or the prefunctionalization of one coupling partner, as in the Cadiot-Chodkiewicz coupling discussed above. However, the high selectivity demonstrated by Shi required that the alkyne reactants be distinct from one another; two aromatic alkynes gave no selectivity for heterocoupling over homocoupling.

Scheme 1.27. Selective heterocoupling of terminal alkynes using Au(I) or Cu0.

Selective catalytic cross-coupling of terminal alkynes has also been accomplished using copper. Su et al. found that under aerobic conditions copper powder gave higher yields and heterocoupling selectivity than copper(I) or (II) salts. While using higher catalyst loading than Shi’s procedure, the copper method has a larger substrate scope, tolerating thioesters, imides and acetals in addition to those reported by Shi and coworkers. Most significantly, the copper method furnishes selective cross-coupling between aliphatic as well as between aromatic alkynes (Scheme 1.27).
The coupling of alkynes with aryl and vinyl halides was first accomplished by Castro and Stevens using stoichiometric amounts of copper at elevated temperature, but this area saw a breakthrough in 1975, when palladium-catalyzed coupling reactions of terminal alkynes were concurrently reported by the Cassar, Heck and Sonogashira groups. The Heck and Cassar reactions are palladium-catalyzed and typically require elevated temperatures while Sonogashira coupling utilizes copper to greatly accelerate the reaction, enabling alkylation at room temperature (Scheme 1.28). While the exact mechanism of the Sonogashira reaction is not known, the addition of copper(I) is thought to activate alkyne by generating Cu-acetylide which is then transferred to palladium during the transmetallation step of the palladium catalytic cycle (Scheme 1.29). Oxidative addition of organohalide to the palladium center precedes transmetallation and C-C bond formation in is achieved during reductive elimination from the palladium catalyst. Sonogashira coupling chemistry has proven critical to the total synthesis of natural products containing enynes such as and (Figure 1.1) as well as targets obtained after the partial or full reduction of the triple bond.
Scheme 1.29. Mechanism of the Sonogashira reaction.

Through a series of metal screenings, Negishi and coworkers found that organometallic acetylene species formed from zinc, boron and tin could serve as coupling partners in palladium-catalyzed coupling with aryl iodides.\textsuperscript{96} Stille further developed palladium-catalyzed coupling of organostannanes, resulting in a versatile methodology with broad functional group compatibility.\textsuperscript{97} An example of a Stille coupling between terminal bromoalkynes 71 and alkynylstannane 72 under phase transfer catalysis conditions is shown in Scheme 1.30. The presence of cesium fluoride was found to improve the yield of the desired heterocoupled product. The authors theorize that the presence of fluoride facilitates transmetallation from tin to palladium.\textsuperscript{98}
Scheme 1.30. Stille coupling of unsymmetrical alkyne.

The formation of Csp-Csp$^3$ bonds has traditionally been accomplished through nucleophilic substitution of primary alkyl halides with metal acetylides. Early methods typically used an alkali or alkaline earth metal in liquid ammonia to form metal acetylides, as pioneered by Lebeau and Picon in 1913.$^{99}$ Vaughn et al. investigated sodium, potassium, calcium and barium acetylides and found sodium acetylides to be cheaper, more soluble and more stable in air while all metal acetylides reacted similarly towards alkyl halide substrates. Investigations of alkyl halide and sulfate reactivity towards nucleophilic substitution by sodium acetylide found that yield increased with the size of the halogen and decreased with the size of the alkyl group, but that reactions with alkyl sulfates were much more rapid than with any alkyl halide (Scheme 1.31).$^{100}$

Scheme 1.31. Nucleophilic substitution reactions with metal acetylide species.
The efficiency of nucleophilic substitution reactions has since been improved with the use of \( n \)-butyllithium to form lithium acetylides in highly polar solvents; Brattesani and Heathcock obtained high yields of certain internal alkynes using HMPA as solvent.\(^{101}\) Buck and Chong were able to avoid extremely polar solvents, obtaining good to excellent yields of substitutions with lithium acetylides using THF. At elevated temperatures, alkyl iodides reacted readily and good conversion of alkyl bromide and chloride substrates were obtained with the addition of 10 mol\% of TBAI or NaI.\(^{102}\)

Scheme 1.32. Examples of coupling reactions between terminal alkynes and alkyl substrates.
Coupling reactions using alkyl substrates is an attractive alternative to the strong bases required for SN2 reactions described above. Under typical coupling conditions alkyl halides have a propensity to undergo β-hydride elimination following oxidative addition to the metal catalyst but recent work demonstrates the efficacy of metal-catalyzed coupling reactions for Csp-Csp3 bond formation, including secondary alkyl substrates (Scheme 1.32).

Eckhardt and Fu developed a variant of the Sonogashira reaction using cesium carbonate base and carbene ligand 74 to couple aliphatic and aromatic alkynes with alkyl iodides and bromides in moderate to good yield with good functional group compatibility.\textsuperscript{103} Hu and coworkers utilized Ni(II) pincer complex 75 with CuI as co-catalyst to couple alkynes with alkyl chlorides in addition to bromides and iodides. Reactions with alkyl bromides and chlorides occur in the presence of an iodide additive, presumably facilitating conversion to the corresponding alkyl iodide in situ. Therefore, NaI (20 mol%) was added to reactions with alkyl bromides and n-Bu4NI (20 mol %) was used in reactions with alkyl chlorides to obtain moderate to good yields with a wide range of alkyl halides.\textsuperscript{104} Ren et al. reported highly efficient copper-catalyzed coupling reactions between aromatic terminal alkynes and secondary alcohols under ligand-, base- and additive-free reaction conditions.\textsuperscript{105}

1.4.2. Coupling and SN2 reactions with ynamides

Despite significant progress in the synthesis of terminal ynamides, carbon-carbon bond forming reactions that leave the triple bond intact are rare and have only recently been discovered. The Sonogashira reaction and oxidative dimerizations of terminal alkynes have become very popular methods for practical carbon-carbon bond formation. Surprisingly, the possibility of catalytic cross- and homocoupling with ynamides has rarely been explored.\textsuperscript{106} Saá and coworkers successfully applied a Glaser-Hay coupling protocol to a few ynesulfonamides 27
and obtained diynes 76a-e in excellent yields. The oxidative coupling is catalyzed by Cul in the presence of TMEDA and atmospheric dioxygen, and it is generally complete within 3 hours at room temperature (Scheme 1.33).\(^{107}\) Alternatively, copper catalyzed Cadiot-Chodkiewicz cross-coupling of sulfonyl and carbamoyl ynamides 40 with the electron-deficient bromoalkyne 77 has been reported to proceed at ambient temperatures. The push-pull diynes 78 were isolated in up to 93% yield.\(^{63}\)

![Scheme 1.33. Glaser-Hay coupling and Cadiot-Chodkiewicz cross-coupling of ynamides.](image)

Saá and coworkers also reported palladium catalyzed cross coupling of zinc ynamides with aryl iodides. This coupling procedure requires lithiation of dichlorovinyl amides 29 and subsequent treatment with zinc dibromide. The in situ formed zinc ynamides 79 were then
employed in typical Sonogashira coupling conditions to afford a variety of C-substituted
ynamides 80 (Scheme 1.34). The coupling with simple aryl iodides furnished 80a-c in
moderate 63-69% yield. The reaction is of limited use when electron-rich aryl iodides are
employed and the methoxy-derived products 80d-f and 80j were obtained in only 24-48% yield.
Not unexpectedly, the reaction with electron-deficient aryl halides such as 4-nitro-iodobenzene
and pyridine or pyrimidines gave 80g-i, 80k, and 80l in up to 92% yield.

Scheme 1.34. Palladium catalyzed cross coupling of zinc ynamides with aryl iodides.

Hsung demonstrated that terminal ynecarbamates 81 are suitable substrates for typical
Sonogashira reaction protocols. They used Pd(PPh3)4 as catalyst and Cul or CuCN as
cocatalyst to affect smooth transmetallation with aryl iodides at room temperature (Scheme
The coupling products 82a-d were obtained with varying yields and the screening of the copper source is apparently important. Unfortunately, bromobenzene gave poor results and effective ynamide coupling with aryl bromides and chlorides is still elusive to date. A noteworthy variation of the Sonogashira reaction with ynamides is the coupling with 2-iodoanilines. In this case, the C-arylation of the terminal ynamide is followed by spontaneous 5-endo-dig cyclization toward 2-amidoindoles.  

A variety of terminal ynamides have been used as nucleophiles in SN2 reactions, using methyl iodide as the electrophile to form methylated ynamides 83 (Scheme 1.36). In Hsung’s 2003 reported synthesis of chiral ynamides, lithium hexamethyldisilazide (LHMDS) was used to deprotonate a terminal ynamide in THF at -78 °C. Methyl iodide was subsequently added to form yne-carbamate 83a in 59% yield after aqueous work-up. The same conditions were used to form yne-amide 83b in 62% yield. Danheiser prepared yne-sulfonamide 83c in 90% yield.
using KHMDS,\textsuperscript{111} and Wang \textit{et al.} used Hsung’s procedure to generate yne-phosphoramidate $83d$ as a substrate for a carbocyclization cascade.\textsuperscript{112}

Scheme 1.36. \textit{S}_2\textit{N} reactions with deprotonated terminal ynamides.

In 2007, Saá and coworkers thoroughly investigated the potential of metal ynamide species as nucleophiles (Scheme 1.37).\textsuperscript{113} Initial screening of bases to deprotonate terminal ynamide $27f$ indicated that LDA was preferable to KHMDS, $n$-BuLi and EtMgBr for promoting nucleophilic substitution with TMSCl. However, higher yields were obtained by quenching the lithiated ynamide intermediate $26f$ with an electrophile suitable to an $S_2N_2$ reaction. This method is especially appealing as lithiated ynamides $26$ are generated during the eliminated method of terminal ynamide synthesis (see Section 1.3.1), allowing for the synthesis of ynamide substitution products from a tosylamide in fewer overall steps.
1.5. Nucleophilic additions of terminal alkynes and ynamides to carbonyl electrophiles

The addition of alkyne nucleophiles to carbonyl compounds has been a central topic in organic synthesis, particularly asymmetric alkynylation of aldehydes, ketones and imines (Scheme 1.38).\textsuperscript{114} Despite the general success and utility of carbon-carbon bond formation with terminal alkynes, few sporadic reports of nucleophilic 1,2-additions of terminal ynamides and ynamines to carbonyl compounds and other electrophiles have appeared in the literature.\textsuperscript{115}
Scheme 1.38. Nucleophilic additions of terminal alkynes to carbonyl compounds and derivatives.

1.5.1. Nucleophilic 1,2-additions of terminal alkynes

Traditionally, alkyne additions to carbonyl compounds have been mediated by strong air-sensitive bases such as alkyllithium reagents, Grignard reagents or metalated amides. For example, alkynyl ketones 86 were first formed by selective addition of alkynyl magnesium chloride or alkynyl lithium reagents to acid anhydrides, benzoyl cyanide, tertiary amides and esters, as discussed below (Scheme 1.39). Kroeger and Nieuwend found that alkynyl magnesium chlorides 94 reacted readily with acetic anhydride to form both tertiary alcohol 87 and ketone 86. The authors added an excess of anhydride dropwise to a cooled solution of Grignard reagent to achieve 58 – 64% yield of the desired ketone and 16 - 17% of the quaternary alcohol byproduct. In Yamaguchi’s acylation of lithium acetylides 95 with aliphatic esters,
higher yields of the desired alkynyl ketones 86 were achieved at low temperatures in the presence of boron trifluoride.\textsuperscript{120} Alkynyl ketones have also been furnished from acyl chlorides using softer copper and silver acetylides.\textsuperscript{121}

\section*{Scheme 1.39. Formation of alkynyl ketones with acetylide nucleophiles.}

Lithium acetylides have been used in asymmetric reactions with aldehydes, imines and trifluoromethyl ketones (Scheme 1.40). In the first example of an asymmetric alkyne addition to aldehydes, Mukaiyama and coworkers prepared lithium acetylides in the presence of excess chiral pyrrolidine 96 and subsequently added benzaldehyde dropwise to the mixture at low temperatures. Using trimethylsilyl acetylide 95a at -123 °C, 87\% yield and 92\% ee of the corresponding alkynyl alcohol 88a were obtained.\textsuperscript{122} Based on Mukaiyama’s method, Huffman used 3.2 equivalents of \textit{n}-butyllithium to form lithium acetylides in the presence of the cinchona alkaloid quinine, 97.
Scheme 1.40. Enantioselective alkyne addition to selected carbonyl compounds.

Asymmetric addition of lithium acetylides to ketimine 98 was accomplished with up to 84% yield and 97% ee during the synthesis of an HIV reverse transcriptase inhibitor. The same general conditions can also be applied to trifluoromethyl ketones, as demonstrated in the
synthesis of \textit{89b}, a precursor of the HIV pharmaceutical Efavirenz.\textsuperscript{124} Some drawbacks of the methods described above are that the lithium acetylides must be prepared in a separate step using an excess of the alkyl lithium reagent. While recent examples of lithium acetylide addition to carbonyls have been accomplished under catalytic conditions,\textsuperscript{125} quantitative amounts of a chiral ligand are typically required to control the stereochemical outcome of the product.

Building on numerous accounts of catalytic asymmetric organozinc additions to carbonyl compounds,\textsuperscript{126} the asymmetric alkynylation of carbonyl compounds mediated by alkyl zinc reagents has become a rich area of study. Zinc acetylides are less reactive than lithium acetylides, resulting in higher functional group tolerance and slow addition to carbonyl groups in the absence of a ligand, which is an undesirable background reaction.\textsuperscript{127} Typical procedures feature stoichiometric amounts of dimethyl or diethyl zinc and 10 – 20 mol\% of a chiral ligand \textsuperscript{102} – \textsuperscript{120} combined with an alkyne \textsuperscript{11} and carbonyl electrophile \textsuperscript{101} at reduced temperatures (Scheme 1.41). Early reports of this method adapted readily available amino alcohol ligands such as \textsuperscript{103} and \textsuperscript{104},\textsuperscript{128} or binapthyl-derived amino alcohol \textsuperscript{105}\textsuperscript{129} to provide moderate yields and ee’s for the alkynylation of aromatic aldehydes to form propargylic alcohols \textsuperscript{88}. Pyridine alcohol \textsuperscript{102}\textsuperscript{130} and bifunctional pyridine \textsuperscript{109}\textsuperscript{131} catalyze the enantioselective alkynylation of some aromatic and aliphatic aldehydes while amino alcohol \textsuperscript{108}\textsuperscript{132} catalyzes the formation of chiral propargylic amines from the alkynylation of imines generated \textit{in situ} from aromatic aldehydes, thus producing \textsuperscript{92}. Ferrocene ligands such as amino alcohol derived \textsuperscript{111} have also been employed as catalysts in the asymmetric alkynylation of aldehydes.\textsuperscript{133}
Scheme 1.41. Dialkyl zinc-mediated alkynylation of carbonyl compounds.

Trost achieved excellent yields and ee’s of propargylic alcohols from an array of aliphatic aldehydes using the C$_2$-symmetric ProPhenol ligand $106$. Notably, Wang’s alkynylation of ketones requires only 1 mol% of Schiff base $117$, and up to 90% yield and 98% ee of
Propargylic alcohols were obtained using 5 mol% of [2.2]paracyclophane-based ketimine 112. Oxazolidine ligands 107137 and 113138 have also been used for the alkylation of aldehydes, with the best results and largest scope reported for bisoxazolidine 114.139 Salens such as 118 were used in the first catalytic alkylation of ketones140 and further optimization resulted in up to 94% ee with the bulkier ligand 119.141 The well-studied BINOL class of ligands142 has also been exploited successfully for the alkylation of aromatic aldehydes (using BINOL 110),143 aliphatic aldehydes (using cyclic ligand 116),144 N-tosylarylimines (using 120)145 and α-ketoimine esters as an entry to chiral quaternary α-CF₃ α-amino acids (using BINOL 115).146

![Scheme 1.42. Catalytic alkylation of carbonyl electrophiles using zinc triflate.](image-url)
Carreira demonstrated the utility of zinc catalyzed 1,2-additions to aldehydes 123, ketone 124, N-tosyl aldimine 125 and nitrones 121 (Scheme 1.42). Unlike dialkyl zinc methods, Carreira’s procedure requires catalytic amounts of zinc triflate and an amine base to form zinc acetylides. The reaction was first optimized with aliphatic nitrones in racemic fashion, giving 93 in 62 – 96% yield. Aromatic derivates reacted more slowly; for example, 93a was obtained in 43% yield. Preliminary results with (+)-N-methylephedrine, 122, gave 93b in 60% ee and this was later further developed to achieve catalytic asymmetric alkynylation of aldehydes in excellent yields. The reaction with aldehydes was also accomplished under solvent-free conditions, thus improving atom economy while decreasing reaction time and streamlining work-up. Catalytic Zn(OTf)₂ with Et₃N base and an amino alcohol ligand have also been used to achieve enantioselective alkynylation of α-keto esters (Scheme 1.43).

\[
\begin{align*}
123 (R = \text{alkyl}) + 11 (1.2 \text{ equiv.}) & \rightarrow 88 \\
& \text{R}^1 = \text{aryl, alkyl, vinyl, silyl}
\end{align*}
\]

**Scheme 1.43.** Catalytic asymmetric alkynylation of aldehydes using Zn(OTf)₂ and (+)-NME.

### 1.5.2 Nucleophilic 1,2-additions of ynamides

Despite the general success and utility of carbon-carbon bond formation with terminal alkynes, few sporadic reports of nucleophilic 1,2-additions of terminal ynamides and ynamines to carbonyl compounds and other electrophiles have appeared in the literature. Saá and coworkers were first to show the broad potential of nucleophilic ynamide additions. Because deprotonation of tosyl ynamides with LDA and other strong bases followed by trapping with trimethylsilyl chloride or benzaldehyde gave unsatisfactory results due to incomplete
deprotonation, they resorted to *in situ* formation of the lithiated ynamide 26 from its β,β-dichloro enamide precursor 29. Treatment of 29 with two equivalents of butyllithium at -78 °C and subsequent reaction of the lithiated ynamide with various electrophiles gave the expected products 126 in good to high yields (Table 1.1). With the exception of *tert*-butyl isocyanate, which gave 126d in only 53% yield, benzaldehyde and other carbonyl nucleophiles were converted to the corresponding 1,2-addition products 126a-e in 88% to 96% yield and the procedure was also successfully applied to diethyl chlorophosphate, producing 126f in 73% yield (entries 3-8). As expected, similar results were obtained by acetylation of other tosyl ynamides to 126g-j (entries 7-10).

**Table 1.1. Ynamide additions to carbonyl electrophiles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>PhCHO</td>
<td><img src="image" alt="126a" /></td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ac₂O</td>
<td><img src="image" alt="126b" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>ClCO₂Et</td>
<td><img src="image" alt="126c" /></td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>t-BuNCO</td>
<td><img src="image" alt="126d" /></td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>CO₂</td>
<td><img src="image" alt="126e" /></td>
<td>90</td>
</tr>
</tbody>
</table>
Careful deprotonation of terminal tosyl ynamides and ynehydrazides such as 127 and 129 with LHMDS or another strong base has remained an attractive alternative to Saá’s in situ generation of lithium ynamides shown above.\textsuperscript{79a,64,151} Additions of the alkynyllithium intermediates to ethyl chloroformate gave 128 and 130 in 90% and 47% yield, respectively (Scheme 1.44). In analogy to the addition to carbonyl electrophiles, the deprotonation of terminal ynamides 131 with LHMDS at -50 °C followed by addition of activated aromatic imines 69 was reported to give a variety of \(N\)-carbamoyl- and \(N\)-sulfonyl-\(\gamma\)-amino ynamides 132a-h in good yields.\textsuperscript{152}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Ph</td>
<td>ClP(O)(OEt)(_2)</td>
<td><img src="126f.png" alt="Image" /></td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>4-MeC(_6)H(_4)</td>
<td>Ac(_2)O</td>
<td><img src="126g.png" alt="Image" /></td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>Ac(_2)O</td>
<td><img src="126h.png" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>Pr</td>
<td>Ac(_2)O</td>
<td><img src="126i.png" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)=CHCH(_2)</td>
<td>Ac(_2)O</td>
<td><img src="126j.png" alt="Image" /></td>
<td>77</td>
</tr>
</tbody>
</table>
Scheme 1.44. Deprotonation of terminal ynamides for subsequent nucleophilic additions.

Wolf recently demonstrated that copper iodide catalyzes the addition of ynesulfonamide 27f to several N-heterocycles 133 activated in situ with ethyl chloroformate at room temperature (Scheme 1.45).153 1,2-Dihydropyridines 134a-e were produced in 71-96% yield. The addition product obtained from 4-methoxypyridine was unstable and hydrolyzed during chromatographic purification to ketone 134f which was isolated in 71% yield. Several quinolines and phenanthridine were employed in the same protocol to give 134g-j in 82-95% yield. This reaction generally occurs with high conversion but yields can be compromised if 1,4-addition is
possible; significant amounts of the 1,4-regioisomer were obtained with pyridine and other substrates unless the para position was blocked.

Scheme 1.45. Copper catalyzed nucleophilic ynamide addition to activated N-heterocycles.

A proposed catalytic cycle of the ynamide addition to the activated N-heterocyclic substrate 137 formed in situ from quinoline, 133g, is shown in Scheme 1.46. It is assumed that 27f reacts with Cul via 135 to a copper acetylide complex 136. Nucleophilic attack at 137 then produces the 1,2-dihydroquinoline derivative 134g and regenerates the copper catalyst.
Scheme 1.46. Catalytic cycle of the copper catalyzed ynamide addition to activated quinoline.

The progress with nucleophilic ynamide additions to various electrophiles discussed above set the stage for stereoselective variants. Hsung and coworkers were first to show that ynamides can be practical prenucleophiles in asymmetric additions.\textsuperscript{154} They observed that lithiation of $N$-sulfonyl ynamides\textsuperscript{138} with LHMDS followed by addition of chiral $N$-tert-butanesulfinyl imines\textsuperscript{139} at $-40$ °C affords the corresponding 1,2-addition products 140a-g in good to high yields and with impressive diastereoselectivity (Scheme 1.47). The reactions between the $N$-benzyl-$N$-tosyl ynamide 138 with 4 different activated aldimines carrying a tert-butanesulfinyl moiety gave the propargylic amines 140a-d in 63-77% yield and with at least 20:1 dr. For example, 140a was obtained from the benzaldehyde derived $N$-tert-butanesulfinyl imine in 69% yield and 25:1 dr. The para-substituent in the arylsulfonyl group exerts a strong influence on the yield and diastereoselectivity of this reaction. Replacement of the para-methyl group in 138 by a methoxy group increases the yield to 95% while the diastereomeric ratio remains unchanged. The para-
nitro analogue, however, gives 140f in 79% yield and only 4:1 dr. In all cases, the presence of an (S)-tert-butanesulfinyl auxiliary was found to favor a Re-face attack leading to the (S)-propargylic amines. This was attributed to a Zimmermann-Traxler chair-like transition state.

**Scheme 1.47. Diastereoselective synthesis of propargylic amines 140 from tert-butanesulfinyl derived imines 139.**

Interestingly, addition of selected Lewis acids can completely reverse the sense of asymmetric induction (Scheme 1.48). When stoichiometric amounts of boron trifluoride diethyl etherate were added to the lithiated ynamide, the reaction with 139 gave the (R)-configured addition products 140a-g with high diastereoselectivity and yields were generally higher than under Lewis acid free conditions. The reversal of the chiral induction was rationalized with two possible open chain transition states, both favoring a Si-face attack on the (S)-tert-butanesulfinyl imine.
Scheme 1.48. Boron promoted diastereoselective addition of sulfonyl ynamides 138 to N-tert-butanesulfinyl imines 139.

140a, R=Ph, R¹=Me: ≥95%, dr([S₆,R];[S₆,S])≥25:1
140b, R=C₆H₃, R¹=Me: 93%, dr([S₆,R];[S₆,S])≥25:1
140c, R=C₆H₄, R¹=Me: 90%, dr([S₆,R];[S₆,S])≥25:1
140d, R=4-MeOC₆H₄, R¹=Me: ≥95%, dr([S₆,R];[S₆,S])≥25:1
140e, R=Ph, R¹=OMe: 93%, dr([S₆,R];[S₆,S])≥25:1
140f, R=Ph, R¹=NO₂: 91%, dr([S₆,R];[S₆,S])≥25:1
140g, R=Ph, R¹=F: 84%, dr([S₆,R];[S₆,S])≥25:1
Chapter 2. Alkynylation of trifluoromethyl ketones

2.1. Introduction

Although rare in nature, organofluorine compounds are of increasing interest to synthetic chemists due to the prominent role in materials sciences and pharmaceuticals.\textsuperscript{155} In fact, over 20\% of current pharmaceuticals contain at least one fluorine atom. The incorporation of fluorine can improve metabolic stability, bioavailability and protein-ligand interactions of drugs.\textsuperscript{156} The anticancer drug 1, Efavirenz, 2, and Prozac, 3, represent a few examples of pharmaceuticals containing at least one CF\textsubscript{3} group (Figure 2.1). Accordingly, there has been recent emphasis on enantioselective catalysis with trifluoromethyl compounds.\textsuperscript{157}

![Chemical structures of pharmaceuticals containing CF\textsubscript{3} groups.]

Figure 2.1. Pharmaceuticals containing CF\textsubscript{3} groups.

Of particular interest is Efavirenz, 2, a reverse transcriptase inhibitor that is among the most effective and best tolerated HIV drugs.\textsuperscript{2} The first synthesis for this important drug was developed by Merck laboratories in the 1990’s. They accomplished the asymmetric addition of lithium cyclopropylacetylide to a trifluoromethyl ketone with up to 98\% enantiomeric excess. The synthesis was later simplified into fewer steps with up to 99\% ee.\textsuperscript{158} However, quantitative amounts of a chiral auxiliary were required, a significant disadvantage compared to catalysis
when the drug is synthesized on a large scale. More recently, this key alkylation step has been accomplished with substoichiometric amounts of ligand as well as enantiopure product in an example of autocatalysis to improve the synthesis of Efavirenz.\textsuperscript{159}

Table 2.1. Preliminary work by the Shibasaki group.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Loading (x mol%)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>10</td>
<td>60</td>
<td>21</td>
<td>&gt;99</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>100</td>
<td>18</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>100</td>
<td>16</td>
<td>66</td>
<td>52</td>
</tr>
</tbody>
</table>

Asymmetric alkynylations of aldehydes and ketones have been accomplished by many groups,\textsuperscript{160} and alkynlation of trifluoromethyl ketones in racemic fashion has been reported.\textsuperscript{161} In 2007, Shibasaki reported a racemic copper catalyzed alkynylation of trifluoromethyl ketones that showed good to excellent yields, as well as preliminary results for an asymmetrically
catalyzed reaction with 2,2,2-trifluoroacetophenone, 4a, as substrate (Table 2.1).\textsuperscript{162} Catalysis with DTMB-SEGPHOS, 7, gave 6a in quantitative yield and 42% ee while PyBOX, 8, gave 4a in 66% yield and 52% ee. The propargylic alcohol 6a is also formed in 46% ee from an acetylide generated \textit{in situ} via desilylation of triethoxy(phenylethynyl)silane in the presence of ligand 7 and CuF.\textsuperscript{163} The Shibasaki group proposed a mechanism for alkynylation of trifluoromethyl ketones using free alkynes (Scheme 2.1).\textsuperscript{8} Nucleophilic addition of the copper(I) acetylide 9 to ketone 4 forms copper(I) alkoxide complex 10. The desired alkynylation product 6 is formed by deprotonation of alkyne 5, regenerating acetylide 9. Highly efficient asymmetric alkynylation of aromatic trifluoromethyl ketones has recently been accomplished using an octahedral ruthenium complex.\textsuperscript{164}

\begin{center}
Scheme 2.1. Shibasaki’s proposed catalytic cycle.
\end{center}
2.2. Evaluation of copper catalysis

The chiral bisoxazolidine ligand 11, previously developed by Wolf (Figure 2.2), was first applied in the method reported by the Shibasaki group. However, catalytic amounts of tert-butoxide base used by Shibasaki did not lead to measurable conversion using copper(I) or copper(II) triflate in the presence of ligand 11. Increasing the base to 2 equivalents in refluxing toluene achieved 80% conversion of ketone 4a to alkynylation product 6a after 5 hours, but without any stereoselectivity.

![Structure of bisoxazolidine 11.](image)

Figure 2.2. Structure of bisoxazolidine 11.

Considering milder conditions employed by Ma and ArndtSEN in the alkynylation of activated pyridinium salts, 10 mol% each of CuI and 11 with 3 equivalents of triethylamine were applied to the addition of 5a to 4a but this did not result in measurable conversion. It was hypothesized that transmetallation from lithium phenylacetylide would form a reactive copper phenylacetylide species in situ that would react with ketone 4a. Expecting the formation of an R₂CuLi species, 2 equivalents of lithium phenylacetylide were added relative to CuI and 4a in the presence of 10 mol% of 11. The reaction was complete after 16 hours, but GC-MS analysis indicated that 30% of the resulting material was a phenylacetylene dimer, and the isolated product 6a was racemic. An inherent drawback of generating a copper acetylide in situ is that extensive analysis is required to determine the exact nature of the species formed, or even that it is definitely forming at all. To this end, copper(I) phenylacetylide was purchased and used directly. This bright yellow solid was unreactive towards 4a in the presence of 11 in
toluene/hexanes mixtures, dichloromethane, THF and EtOH. The addition of 5 mol% of KOt-Bu and up to 40 mol% of triethylamine (TEA) at 90 °C did not affect the reaction. In contrast, Shibasaki used commercial copper phenylacetylide in the presence of ligand 7 and obtained 6a in yields and enantiomeric excess comparable to the CuOTf-KOt-Bu system. However, in the absence of a phosphine or amine ligand, only trace amounts of the product were observed. Furthermore, in a mechanistic study of aldehyde alkynylation catalyzed by copper(I) complexes, Asano et al. noted that copper acetylide, an air- and water-stable solid, is easily formed but exists as a stable polymeric complex that is unreactive towards aldehydes. Phosphine ligands were found to have significant rate-accelerating effects, particularly those with wide P-Cu-P bite angles such as xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene). Shibasaki also found that xantphos is highly effective in racemic alkynylations of trifluoromethyl ketones. With these studies in mind, copper phenylacetylide was added to 4a in the presence of either triphenylphosphine or ligand 8. Reactions with each ligand were performed separately in toluene and in THF, but only trace amounts of the desired alkynylation product were formed. Conditions developed for the nitroaldol reaction of trifluoromethyl ketones were also tested, but resulted in only 5% conversion.

Scheme 2.2. Alkynylation with Cu(OTf)2 and Et2Zn.
To accomplish the alkynylation of trifluoroacetophenone, 4a, zinc acetylides were formed with stoichiometric amounts of diethyl zinc while copper(II) triflate was employed to catalyze the alkynylation step, as had been reported for alkynylations of other ketones.\textsuperscript{170} After 17, hours GC-MS analysis indicated that 85\% of the mixture consisted of the reduction product 12, 5\% was identified as the desired alkynylation product 6a and 9\% was 1-phenylbutene, 13, a side product resulting from the addition of Et\textsubscript{2}Zn to phenylacetylene (Scheme 2.2). Dimethylzinc proved to be a more suitable zinc source than diethylzinc. For example, alkynylation product 6a was obtained in 43\% ee and 57\% isolated yield using Me\textsubscript{2}Zn (Table 2.2, entry 6) compared to 5\% conversion using Et\textsubscript{2}Zn (Scheme 2.2). The presence of different copper salts had a notable effect on enantioselectivity. Replacing copper(II) with copper(I) triflate caused a 20\% decrease in enantiomeric excess (entries 4, 6), while copper(II) acetate and copper(I) thiophene-2-carboxylate catalyzed the formation of the opposite enantiomer (entries 2 – 3). By contrast, Shibasaki reported that copper(II) and copper(I) triflate gave comparable yield and %ee which can be attributed to the reduction of copper(II) in the course of the reaction.\textsuperscript{8} It was noted that the copper(I) triflate complex was not completely soluble in toluene or in the toluene-hexanes mixture used which could explain the observed decrease in enantioselectivity. Finally, the reaction occurs in the absence of a copper catalyst and the opposite enantiomer was obtained in 26 %ee (entry 11).

To explore the relationship between copper and zinc in the catalysis of the reaction, the ratios of Me\textsubscript{2}Zn, Cu(OTf)\textsubscript{2}, and phenylacetylene were varied (Table 2.2, entries 5-11). No clear trend was observed when the amount of Cu(OTf)\textsubscript{2} was varied from 5 mol\% to 100 mol\% (entries 5 – 8). In fact, increasing Cu(OTf)\textsubscript{2} from catalytic amounts to a full equivalent resulted in the formation of opposite enantiomer, which was also observed in the absence of a copper catalyst.
In view of these difficulties and the observation that comparable enantioselectivity was achieved with Me₂Zn in the absence of copper, the screening of copper catalysts was abandoned. Ma and coworkers later accomplished alkynylation of trifluoromethylketones using both Me₂Zn and Ti(Oi-Pr)₄ metal salts in the presence of a cinchona alkaloid ligand and BaF₂ additive.\textsuperscript{171}

Table 2.2. Me₂Zn-mediated alkynylation with copper catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Cu loading (mol%)</th>
<th>5a (equiv.)</th>
<th>Me₂Zn (equiv.)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSC₄H₄CO₂</td>
<td>10</td>
<td>2.6</td>
<td>3.0</td>
<td>21</td>
<td>19\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂</td>
<td>10</td>
<td>2.6</td>
<td>3.0</td>
<td>25</td>
<td>6\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>CuOTf</td>
<td>10</td>
<td>2.6</td>
<td>3.0</td>
<td>&lt;31</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂</td>
<td>5</td>
<td>2.6</td>
<td>3.0</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)₂</td>
<td>10</td>
<td>2.6</td>
<td>3.0</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)₂</td>
<td>50</td>
<td>2.6</td>
<td>3.0</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>100</td>
<td>2.6</td>
<td>3.0</td>
<td>31</td>
<td>31\textsuperscript{a}</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>10</td>
<td>2.6</td>
<td>1.0</td>
<td>32</td>
<td>15\textsuperscript{a}</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)₂</td>
<td>100</td>
<td>2.6</td>
<td>1.0</td>
<td>29</td>
<td>4\textsuperscript{a}</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)₂</td>
<td>10</td>
<td>1.0</td>
<td>1.0</td>
<td>28</td>
<td>6\textsuperscript{a}</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>--</td>
<td>2.6</td>
<td>3.0</td>
<td>25</td>
<td>26\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Opposite enantiomer favored
2.3. Zinc-mediated alkylnylations

Zinc-mediated alkylnylations using both dimethyl and diethylzinc have been accomplished with a wide variety of ligands and carbonyl substrates (see Section 1.5.1). Of particular interest for this project were protocols developed for aldehydes\textsuperscript{172} and ketones\textsuperscript{173}.

![Scheme 2.3. Asymmetric addition of 5a to 4a using Et\textsubscript{2}Zn.]

The use of diethylzinc for \textit{in situ} formation of zinc acetylides in the presence of 11 favored the reduction of trifluoromethylketone 4a (Scheme 2.3), although more alkylnylation product was obtained with Et\textsubscript{2}Zn alone than in the presence of copper (compare to Scheme 2.2). The undesired reduction reaction was expected and in accordance with literature reports\textsuperscript{174}. Reducing agents such as DIBAL-H, LiAlH\textsubscript{4} and NaBH\textsubscript{4} reduce 4a and acetophenone to comparable extents but Et\textsubscript{2}Zn reduces 4a exclusively\textsuperscript{175}. The reason for this discrepancy is not completely understood, but one possible explanation is that the increased bulkiness of the trifluoromethyl group favors the so called Grignard reduction which is often observed with bulky ketones. It is assumed that two equivalents of alkyl zinc are required for nucleophilic addition (Scheme 2.4 A), but in sterically hindered systems where two equivalents cannot be accomodated, reduction is possible via β-hydride elimination with one equivalent of Et\textsubscript{2}Zn (Scheme 2.4 B). The electron withdrawing nature of the CF\textsubscript{3} group renders the carbonyl carbon more electrophilic and a harder Lewis acid which may favor the reduction pathway.
Scheme 2.4. Competing ethylation and reduction with Et₂Zn.

To avoid this complication, Et₂Zn was substituted with Me₂Zn, which cannot undergo β-hydride elimination (Scheme 2.5). Under these conditions reduction to 12 was not observed, but the reaction proceeded more slowly, with only 30% conversion at 5 hours. Furthermore, 6a was produced in only 10% ee with Me₂Zn compared to 29% ee in the presence of Et₂Zn under the same conditions. Concluding that Et₂Zn gave a better starting point for asymmetric catalysis, other means of inhibiting the reduction pathway were investigated.

Scheme 2.5. Alkynylation mediated by Me₂Zn.

Scheme 2.6. Alkynylation with Et₂Zn at reduced temperature.
Table 2.3. Ligand screening with Me₂Zn.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion to 6a (%)</th>
<th>Ee of 6a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>46⁺</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>16ᵇ</td>
<td>2</td>
</tr>
</tbody>
</table>

a) 29% methylation product 21 by GC-MS. b) 69% methylation product 21 by GC-MS.

A decrease in the reaction temperature improved the ratio of the reduction to alkynylation product, from 4:1 at room temperature to 3:1 at -5 °C. Decreasing the amount of Et₂Zn to 1.5 equivalents and further lowering the temperature to -20 °C resulted in a 3:2 ratio of reduction product 12 to alkynylation product 6a. However, at -20 °C the reaction was still not complete after two days and GC-MS analysis indicated substantial formation of the additional side
products 1-phenylbutene 13 and the ethylation product 20 (Scheme 2.6). In another approach to zinc-mediated catalysis, transmetalation reactions using (phenylethynyl)magnesium bromide and ZnCl₂ as well as (phenylethynyl)lithium with Zn(OTf)₂ were conducted in the presence of 11. Both reactions gave near quantitative amounts of racemic product.

At this point, Me₂Zn was re-examined as the metal source. The use of Me₂Zn was screened with new bisoxazolidine ligands,¹⁷⁶ and commercially available bisoxazolines (Table 2.3). Bisoxazolidine ligands 22 and 23 gave comparable yields to ligand 11 (entries 1 – 3) and the bisoxazoline ligands gave nearly racemic alkynylation product 6a (entries 4 – 6). Furthermore, t-BuBOX, 25 and PyBOX, 8, produced the undesired methylated compound 21 in 29% and 69%, respectively, at room temperature. Continued optimization of the solvent, zinc reagent, catalyst loading, reaction time and concentration did not lead to significant improvement. Hayashi and coworkers later reported the alkynylation of aromatic trifluoromethyl ketones using 2.3 equivalents of Me₂Zn and 5 mol% of a chiral Schiff base at room temperature. They obtained 6a in 96% yield and 64% ee.¹⁷⁷

2.4. Catalysis with Zn(OTf)₂

While initial attempts to apply Carreira’s protocol for the catalytic asymmetric alkynylation of aldehydes¹⁷⁸ to trifluoromethyl ketones were not promising, it was discovered that an increase in the concentration by using very small volumes of solvent improved results. Interestingly, the reaction can also be conducted without solvent. It was found that the combination of zinc triflate and TEA reported for the alkynylation of nitrones,¹⁷⁹ aldehydes²¹ and α-ketoesters,¹⁸⁰ was also optimal for trifluoromethyl ketones, but somewhat surprising was that other combinations of metal salts and bases gave little to no conversion of starting materials. Copper, palladium, gold, silver, magnesium and nickel salts gave less than 5% conversion. The same was observe with
other available zinc(II) salts: Zn(OAc)$_2$, Zn(BF$_4$)$_2$, Zn(CN)$_2$, ZnCl$_2$, Zn(ClO$_4$)$_2$, Zn(SbF$_6$)$_2$, and Zn(N(Tf)$_2$)$_2$. Likewise, commonly used bases such as pyridine, 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-bis(dimethylamino)naphthalene (proton sponge) did not promote the reaction at all. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) gave 20% conversion after 20 h, but without any enantioselectivity.

Increasing the amount of ligand 11 from 10 to 20 mol% improved the enantioselectivity and the use of an excess of Zn(OTf)$_2$ (25 or 30 mol%) increased the yield substantially without decreasing ee. Under solvent-free conditions the yield improved further with a slight decrease in the ee. Using 11 (20 mol%), Zn(OTf)$_2$ (25 mol%), Et$_3$N (10 equiv.) and 5a (3 equiv.), 6a was obtained in 99% yield and 55% ee (Scheme 2.7). At lower temperatures, 6a was produced in 64% ee but in only 63% yield after 1 day at 10 °C. The addition of 2-30 mol% of various additives including TMSOTf, Ph$_3$PO, Ph$_3$PS, 2,2,2-trifluoroethanol, and lithium chloride did not improve the results.

Scheme 2.7. Optimized conditions for the alkynylation of 4a with bisoxazolidine ligand 11.

While investigation with ligand 11 was underway, a variety of nitrogen- and oxygen-based ligands were screened, including bisoxazolidines synthesized according to published procedures$^{20}$ and commercially available bisoxazolines and amino alcohols (Scheme 2.8). In all reactions, 0.1 mL toluene was used as solvent, accounting for less than half of the reaction volume.
Scheme 2.8. Ligand screening with catalytic Zn(OTf)$_2$. 

* double catalyst loading
*N*-Methylephedrine, 30, was soon identified as a promising starting point for catalysis. However, the background reaction caused significant problems; as the reaction progressed stereoselectivity decreased in almost every instance (Table 2.4). Altering the ratio of ligand to zinc produced large variations in yield and ee. When the ligand was used in excess of the metal (20 mol % vs 10 mol %), the product was obtained in 9% yield with 79% ee (entry 1). When the catalyst loading of zinc triflate was increased to 30 mol%, 6a was obtained in 94% yield with 30% ee (entry 2). A decrease in the amount of TEA gave consistently higher yields but lower ee’s (entries 3-5). In a final attempt, the reaction was conducted at elevated temperatures (entries 6-8). At 90 °C, 6a was produced in quantitative amounts and with 46% ee after 1 day (entry 8). The replacement ligand 30 with (1R, 2S)-2-(dibutylamino)-1-phenylpropan-1-ol gave 6a in 26% ee compared to 74% ee with 30 under the same conditions.

**Table 2.4. Optimization with *N*-methylephedrine, 30.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>30 (mol%)</th>
<th>Zn(OTf)₂ (mol%)</th>
<th>Et₃N (equiv.)</th>
<th>Alkyne (equiv.)</th>
<th>T (°C)</th>
<th>Time (days)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>30</td>
<td>1</td>
<td>9</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>30</td>
<td>5</td>
<td>2</td>
<td>30</td>
<td>2</td>
<td>94</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>20</td>
<td>5</td>
<td>1.2</td>
<td>30</td>
<td>1</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>20</td>
<td>2</td>
<td>1.2</td>
<td>30</td>
<td>1</td>
<td>63</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>20</td>
<td>0.5</td>
<td>1.2</td>
<td>30</td>
<td>1</td>
<td>68</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>60</td>
<td>1</td>
<td>81</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>60</td>
<td>1</td>
<td>39</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>90</td>
<td>1</td>
<td>96</td>
<td>46</td>
</tr>
</tbody>
</table>
BINAM, 37, was tested with different zinc salts and varying ligand/zinc catalyst ratio, but unlike NME, 30, the stereoselectivity with BINAM did not change significantly; the best results are shown in Scheme 2.9. It was hypothesized that BINAM derivative 48 would give better results, as previously screened ligands containing tertiary amines had performed better than ligands containing primary or secondary amino groups, but ligand 48 unexpectedly gave racemic product.

Scheme 2.9. Catalysis with binaphthyl diamines.

Initially encouraging results were produced with the cinchona alkaloid 47 using acetonitrile as solvent, which produced a homogeneous reaction mixture (Scheme 2.10). However, yields and ee’s were not reproducible. Generally, the use of higher grade, >99.5% pure, Et$_3$N gave lower ee’s than Et$_3$N sold as 99% pure. The use of Et$_3$N purified by distillation immediately prior to use likewise gave low yield and ee. The best yields of 6a were obtained with Et$_3$N that had been stored in a clear glass vial inside of a glove box at approximately 30 °C for several months. Even a few weeks’ storage under these conditions gave up to 20% increase in yield. Storage of the zinc salt, ligand and ketone in the glove box had no effect on the reaction, while storage of the alkyne in the glove box for even a few days resulted in slower conversion and lower yield.
Various additives were employed in an attempt to reproduce the best results. The effect of common additives as well as possible Et$_3$N decomposition products, including hexamethylphosphoramidite, 2,2,2-trifluoroethanol, triphenylphosphine oxide, triphenylphosphine sulfide, dimethylammonium chloride and $N,N$-dimethylhydroxylamine were tested. Attempts to identify impurities in Et$_3$N by $^1$H-NMR, GC-MS and ICP-OES (Inductively coupled plasma optical emission spectroscopy) were all unsuccessful.

It was found that the reaction was tolerant to, and actually benefitted from small amounts of water, as results with ultra-pure Et$_3$N improved somewhat with the addition of 0.1 wt.% of H$_2$O, but no conversion was observed when 0.4 wt.% or greater amounts of H$_2$O were added. Water tolerance was also a concern with respect to the zinc salt; while some batches of Zn(OTf)$_2$ gave the expected results when used as purchased, other batches gave no conversion of starting materials until the zinc salt was heated to 110 °C overnight under vacuum. Carreira and coworkers noted that the alkynylation of aldehydes using Zn(OTf)$_2$ and an amine base was tolerant to moisture,\textsuperscript{24} while multiple groups that employed the same procedure report that drying of Zn(OTf)$_2$ is necessary for best results,\textsuperscript{24,181} and specifically that presence of water lead to a dramatic decrease in ee for the alkynylation of aldehydes.\textsuperscript{27c} Several groups have had difficulty in applying Carreira’s conditions to alkynylation reactions. Unsuccessful attempts include the

Scheme 2.10. Alkynylation with cinchona alkaloid 47 using different Et$_3$N sources.

Various Scheme 2.10. Alkynylation with cinchona alkaloid 47 using different Et$_3$N sources.

Various additives were employed in an attempt to reproduce the best results. The effect of common additives as well as possible Et$_3$N decomposition products, including hexamethylphosphoramidite, 2,2,2-trifluoroethanol, triphenylphosphine oxide, triphenylphosphine sulfide, dimethylammonium chloride and $N,N$-dimethylhydroxylamine were tested. Attempts to identify impurities in Et$_3$N by $^1$H-NMR, GC-MS and ICP-OES (Inductively coupled plasma optical emission spectroscopy) were all unsuccessful.

It was found that the reaction was tolerant to, and actually benefitted from small amounts of water, as results with ultra-pure Et$_3$N improved somewhat with the addition of 0.1 wt.% of H$_2$O, but no conversion was observed when 0.4 wt.% or greater amounts of H$_2$O were added. Water tolerance was also a concern with respect to the zinc salt; while some batches of Zn(OTf)$_2$ gave the expected results when used as purchased, other batches gave no conversion of starting materials until the zinc salt was heated to 110 °C overnight under vacuum. Carreira and coworkers noted that the alkynylation of aldehydes using Zn(OTf)$_2$ and an amine base was tolerant to moisture,\textsuperscript{24} while multiple groups that employed the same procedure report that drying of Zn(OTf)$_2$ is necessary for best results,\textsuperscript{24,181} and specifically that presence of water lead to a dramatic decrease in ee for the alkynylation of aldehydes.\textsuperscript{27c} Several groups have had difficulty in applying Carreira’s conditions to alkynylation reactions. Unsuccessful attempts include the
alkynylation of aliphatic unbranched aldehydes,$^{182}$ branched aldehydes,$^{183}$ unsaturated aldehydes,$^{184}$ and β-lactam aldehydes.$^{185}$ For the most part challenges were attributed to the substrate sensitivity of the reaction. Carreira’s catalytic procedure is known to give lower yields of unbranched aliphatic aldehydes and unsaturated aldehydes due to competing self-aldol$^{24}$ and Cannizzaro disproportionation$^{27c}$ reactions, respectively. However, examples of the reaction using unbranched aliphatic, vinyl and aromatic aldehydes have been accomplished using catalytic$^{24}$ and stoichiometric$^{186}$ amounts of Zn(OTf)$_2$ and a chiral ligand, and it is curious that some groups were unable to achieve any conversion when using similar substrates. While attempting to apply Carreira’s conditions to the alkynylation of an aliphatic aldehyde, Dake and coworkers obtained yields ranging from 0 – 60%.$^{187}$ Although attempts gave consistently high ee’s, the Dake group abandoned Carreira’s alkynylation in favor of an alternate synthetic route.

2.5. Conclusion

A wide range of catalytic protocols have been screened to optimize the asymmetric alkynylation of trifluoromethyl ketones. While the use of Zn(OTf)$_2$ and amino alcohol ligands is attractive and appears promising, small amounts of water and other impurities that may be present in the zinc salt and triethylamine base seem to have a profound effect on both the yield and enantioselectivity this reaction. Excellent results were obtained using catalytic zinc triflate and (+)-cinchonine in triethylamine and acetonitrile. However, further investigation is necessary to develop a protocol for the zinc catalyzed alkynylation of trifluoromethyl ketones that gives high yields and ee’s with high reproducibility.
2.6. Experimental section

Commercially available trifluoroacetophenone, phenylacetylene, (+)-cinchonine and solvents were used as purchased without further purification. Zinc triflate was heated to 110 °C under vacuum overnight before use. NMR spectra were obtained at 400 MHz (\(^1\)H NMR) and 100 MHz (\(^{13}\)C NMR) in deuterated chloroform. Chemical shifts are reported in ppm relative to TMS.

Procedure for the Zinc catalyzed alkynylation of trifluoroacetophenone.

Zinc triflate (14.8 mg, 0.04 mmol), (+)-cinchonine (12 mg, 0.04 mmol), 3,3,3-trifluoroacetophenone (35.2 mg, 0.2 mmol) and phenylacetylene (62.4 mg, 0.60 mmol) were dissolved in triethylamine (0.28 mL, 2 mmol) and acetonitrile (0.1 mL) under nitrogen atmosphere. The clear yellow solution was stirred at 30 °C for 15 h. Solvents were evaporated under a stream of nitrogen and the crude residue was purified by flash chromatography on silica gel (particle size 40-63 μm) using CH\(_2\)Cl\(_2\) and pentane (1:1) as the mobile phase giving 32 – 92% yield and 56 – 97% ee. \(^1\)H NMR (400 MHz) \(\delta = 7.84 - 7.78\) (m, 2H), 7.50 – 7.56 (m, 2H), 7.48 – 7.29 (m, 6H), 3.12 (s, 1H). The ee was determined by HPLC on Chiralcel® AD using hexanes/IPA (90:10) as the mobile phase at 1.0 mL/min. \(t_1 = 8.5\) min, \(t_2 = 11.9\) min.
Chapter 3. Copper catalyzed nucleophilic addition of ynamides to acyl chlorides

3.1. Introduction

The unique chemistry of ynamines has received continuous attention due to the huge synthetic potential of these remarkably versatile building blocks. In particular, C-substituted ynamines exhibiting an internal triple bond have found widespread use in a variety of reactions and in the total synthesis of natural compounds. The reaction scope of ynamines and derivatives thereof differs considerably from that of enamines and alkynes as the reactivity of the electron-rich triple bond is dominated by the adjacent, strongly polarizing amine moiety. The increasing availability of terminal ynamides, ynesulfonamides and ynecarbamates based on practical procedures developed by Witulski, Bruckner, Saa and others has further extended the general utility of ynamide chemistry (Figure 3.1). Among the most noteworthy reactions are cycloadditions, cycloisomerizations, homo- and cross-couplings, ring-closing metathesis, radical additions, and titanium-mediated carbon-carbon bond formations.

Surprisingly, few examples of nucleophilic additions of terminal ynamides, ynesulfonamides and ynecarbamates to aldehydes, ketones and other electrophiles, all requiring strongly basic

---

ii This content of this chapter has been published by the American Chemical Society (J. Org. Chem. 2014, 79, 4167 – 4173.) All copyrights are reserved by the ACS.
conditions, can be found in the literature. The absence of a catalytic procedure that allows mild carbon-carbon bond formation with acyl chlorides is in stark contrast to the wealth of reports on this reaction with terminal alkynes.

3.2. Results and discussion

Propargylic ketones are key intermediates for the preparation of natural products and heterocyclic compounds and most conveniently prepared through catalytic alkynylation of acyl chlorides or via carbonylative Sonogashira coupling. Many procedures require heating and long reaction times and are not applicable to ynamides which lack the thermal stability of alkynes. Carbon-carbon bond formation with the readily available N-ethynyl-N-phenyl-4-tolylsulfonamide, 1, under mild reaction conditions was therefore investigated. Following a literature procedure, gram amounts of 1 were synthesized from N-tosyl aniline (Scheme 3.1).

![Scheme 3.1. Synthesis of ynesulfonamide 1.](image)

Initial analysis of the reaction between ynesulfonamide 1 and benzyol chloride showed that copper(I) salts were superior over both zinc and palladium complexes commonly used in alkynylation reactions. Using 10 mol% of cuprous iodide and 2 equivalents of diisopropylethylamine in THF, the desired N-(3-phenyl-3-oxoprop-1-ynyl)-N-phenyl-4-tolylsulfonamide, 2, was obtained in 50% yield after 20 hours. The screening of various copper(I) salts, organic solvents, base and temperature revealed that 2 can be isolated in 90% yield when the reaction is performed in the presence of 10 mol% of copper iodide in chloroform at 30 °C (Table 3.1, entry 1), representing the first catalytic addition of an ynamide to an acyl
chloride. It is noteworthy that the order of addition of the reagents is important for this reaction. The best yields were obtained when the catalyst, base and the ynamide were stirred for 30 minutes prior to addition of the acyl chloride. The reaction also proceeds with high yields when other aromatic substrates are employed; ynones 3-7 were isolated in 79-99% yield (entries 2 – 6).

Among the impressive number of high-yielding catalytic cross couplings of aromatic acyl chlorides with terminal alkynes, very few examples with aliphatic electrophiles have been reported, typically producing ynones in only moderate yields.\textsuperscript{14a,c} This can probably be attributed to fast ketene formation and subsequent side reactions when acyl chlorides exhibiting \( \alpha \)-hydrogens are used in the presence of base. While the reaction with pivaloyl chloride gave the corresponding propargylic ketone 8 in high yield as expected, ynone formation with \( \alpha \)-hydrogen-containing 2-methylpropanoyl chloride also proceeds smoothly at 15 °C, providing 9 in 70% yield (entries 7 – 8).

**Table 3.1. Copper(I) catalyzed addition to acyl chlorides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acyl Chloride</th>
<th>Product</th>
<th>t (h)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td>22</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>18</td>
<td>92</td>
</tr>
</tbody>
</table>
Table 3.1. (Cont.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acyl Chloride</th>
<th>Product</th>
<th>t (h)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( \text{Cl} \text{C} \text{O} \text{Cl} )</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>( \text{NC} \text{C} \text{O} \text{Cl} )</td>
<td>( \text{NC} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>18</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>( \text{C} \text{C} \text{O} \text{Cl} )</td>
<td>( \text{C} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>12</td>
<td>99</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>( \text{Cl} \text{C} \text{O} \text{Cl} )</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>38</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>( \text{Cl} \text{C} \equiv \text{N} \text{Ph} )</td>
<td>52</td>
<td>70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> 20 °C. <sup>c</sup> 15 °C.
**Figure 3.2. Crystal structure of 2.** Selected crystallographic separations [Å]: N1—C3 1.345 Å, C3—C2 1.197 Å, C2—C1 1.448 Å, C1—O1 1.224 Å.

The copper catalyzed carbon-carbon bond formation with terminal ynamides probably proceeds through a mechanism generally accepted for similar alkyne reactions. In analogy to metal catalyzed nucleophilic additions with alkynes, side-on coordination of the ynamide to copper(I) likely increases the acidity of the terminal CH bond. Deprotonation by the tertiary amine base then produces a copper complex that reacts with the electrophilic acyl chloride or activated N-heterocycle and regenerates the catalyst (Figure 3.3). Ynamide additions to acyl chlorides are sluggish in the absence of CuI; synthesis of aminonynone, 2, from 1 and benzoyl chloride is almost complete after 10 hours (Figure 3), but less than 50% ynamide consumption and formation of unidentified byproducts were observed when the reaction was performed without the catalyst.
3.3. Conclusion

In conclusion, the first catalytic addition of a readily available ynesulfonamide to aliphatic and aromatic acyl chlorides has been accomplished. The reaction occurs under mild conditions and provides unprecedented access to a variety of 3-aminoynones in good to high yields. The convenient access to these synthetically versatile ynamide derivatives is expected to prove invaluable to medicinal chemistry and natural product synthesis.
3.4. Experimental section

Commercially available reagents and solvents were used without further purification. Anhydrous solvents were used as purchased and not dried any further. NMR spectra were obtained at 400 MHz ($^1$H NMR) and 100 MHz ($^{13}$C NMR) in deuterated chloroform. Chemical shifts are reported in ppm relative to TMS.

General procedure for the copper catalyzed ynamide addition to acyl chlorides.

Copper iodide (2.3 mg, 12 μmol), N-ethynyl-N-phenyl-4-tolylsulfonamide (32.5 mg, 0.12 mmol) and N,N-diisopropylethylamine (31.0 mg, 0.24 mmol) were dissolved in chloroform (0.15 mL) under nitrogen. After 30 minutes an acyl chloride (0.18 mmol) was added and stirred until completion as determined by TLC. Solvents were evaporated under a stream of nitrogen and the crude residue was purified by flash chromatography on silica gel (particle size 40-63 μm) as described below.

$N$-(3-Phenyl-3-oxoprop-1-ynyl)-$N$-phenyl-4-tolylsulfonamide, 2.

The reaction with benzoyl chloride (25.1 mg, 0.18 mmol) and the ynamide (32.5 mg, 0.12 mmol) was performed at 30 ℃ for 22 hours. The concentrated crude residue was purified by column chromatography (2:1 dichloromethane: hexanes) to give 40.5 mg (0.108 mmol, 90%) of a white solid. $^1$H NMR (400 MHz) $\delta$ = 8.19 (d, $J = 6.9$ Hz, 2H), 7.67 – 7.57 (m, 3H), 7.52 (dd, $J = 8.4$ Hz, 6.9 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.30 – 7.22 (m, 4H), 2.42 (s, 3H). $^{13}$C NMR (100 MHz) $\delta$ = 176.8, 145.9, 137.2, 136.9, 133.6, 132.9, 129.9, 129.5, 129.17, 129.15, 128.6, 128.1, 126.5, 90.1, 74.9, 21.6. Anal. Calcd. For C$_{22}$H$_{17}$NO$_3$S: C, 70.38; H, 4.56; N, 3.73. Found: C, 70.51; H, 4.73; N, 3.86. mp 139 - 140 ℃.
**N-(3-(2-Chlorophenyl)-3-oxoprop-1-ynyl)-N-phenyl-4-tolylsulfonamide, 3.**

The reaction with 2-chlorobenzoyl chloride (32.6 mg, 0.186 mmol) and the ynamide (32.5 mg, 0.12 mmol) was performed at 30 °C for 18 hours. The concentrated crude residue was purified by column chromatography (5:2 dichloromethane: hexanes) to give 45 mg (0.11 mmol, 92%) of a white solid. $^1$H NMR (400 MHz) δ = 8.06 (d, $J = 7.6$ Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 3.6$ Hz, 2H), 7.45 – 7.31 (m, 4H), 7.31 – 7.21 (m, 4H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz) δ = 175.3, 145.9, 137.1, 135.4, 133.1, 133.0, 132.9, 132.4, 131.4, 129.9, 129.4, 129.2, 128.2, 126.8, 126.5, 91.0, 76.3, 21.7. Anal. Calcd. For C$_{22}$H$_{16}$ClNO$_3$S: C, 64.47; H, 3.93; N, 3.42. Found: C, 64.65; H, 4.07; N, 3.41. mp > 105 °C (decomp.)

**N-(3-(4-Chlorophenyl)-3-oxoprop-1-ynyl)-N-phenyl-4-tolylsulfonamide, 4.**

The reaction with 4-chlorobenzoyl chloride (31.4 mg, 0.18 mmol) and the ynamide (32.5 mg, 0.12 mmol) was performed at 30 °C for 20 hours. The concentrated crude residue was purified by column chromatography (2:1 dichloromethane: hexanes) to give 47 mg (0.115 mmol, 96%) of a white solid. $^1$H NMR (400 MHz) δ = 8.09 (d, $J = 8.6$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.39 – 7.28 (m, 3H), 7.28 – 7.18 (m, 4H), 2.39 (s, 3H). $^{13}$C NMR (100 MHz) δ = 175.4, 146.0, 140.2, 137.0, 135.4, 132.9, 130.5, 129.9, 129.5, 129.3, 128.9, 128.1, 126.4, 90.7, 74.7, 21.6. Anal. Calcd. For C$_{22}$H$_{16}$ClNO$_3$S: C, 64.47; H, 3.93; N, 3.42. Found: C, 64.38; H, 4.05; N, 3.46. mp 105 - 107 °C.

**N-(3-(4-Cyanophenyl)-3-oxoprop-1-ynyl)-N-phenyl-4-tolylsulfonamide, 5.**

The reaction with 4-cyanobenzoyl chloride (30.0 mg, 0.18 mmol) and the ynamide (32.7 mg, 0.12 mmol) was performed at 30 °C for 18 hours. The concentrated crude residue was purified by column chromatography (3:1 dichloromethane: hexanes) to give 46.5 mg (0.116 mmol, 97%) of a white solid. $^1$H NMR (400 MHz) δ = 8.29 (d, $J = 8.3$ Hz, 2H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 2H), 7.45 – 7.31 (m, 4H), 7.31 – 7.21 (m, 4H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz) δ = 175.5, 146.1, 139.8, 137.1, 135.4, 134.0, 132.9, 130.9, 129.9, 129.8, 129.3, 128.9, 128.1, 126.5, 90.7, 74.7, 21.5. Anal. Calcd. For C$_{22}$H$_{16}$ClNO$_3$S: C, 64.47; H, 3.93; N, 3.42. Found: C, 64.38; H, 4.05; N, 3.46. mp 105 - 107 °C.
Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.47 – 7.34 (m, 3H), 7.29 (d, J = 8.1 Hz, 2H), 7.27 – 7.23 (m, 2H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz) δ = 174.8, 146.2, 139.8, 136.8, 136.7, 132.8, 132.4, 130.0, 129.6, 129.4, 128.1, 126.4, 117.9, 116.8, 92.3, 75.1, 21.7. Anal. Calcd. for C$_{23}$H$_{16}$N$_2$O$_3$S: C, 68.98; H, 4.03; N, 7.00. Found: C, 68.67; H, 4.14; N, 6.92. mp > 155 °C (decomp.)

$N$-(3-(2-Naphthyl)-3-oxoprop-1-ynyl)-$N$-phenyl-4-tolylsulfonamide, 6.

The reaction with 2-naphthoyl chloride (35.0 mg, 0.18 mmol and the ynamide (32.9 mg, 0.121 mmol) was performed at 30 °C for 12 hours. The concentrated crude residue was purified by column chromatography (1:1 dichloromethane: hexanes) to give 51.5 mg (0.12 mmol, 99%) of a white solid. $^1$H NMR (400 MHz) δ = 8.88 (s, 1H), 8.19 (dd, J = 8.6, 1.7 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.65 – 7.54 (m, 2H), 7.44 – 7.34 (m, 3H), 7.35 – 7.27 (m, 2H), 7.28 – 7.22 (m, 2H), 2.41 (s, 3H). $^{13}$C NMR (100 MHz) δ = 176.8, 145.9, 137.1, 135.9, 134.5, 132.9, 132.6, 132.5, 130.0, 129.9, 129.5, 129.2, 128.8, 128.4, 128.1, 127.8, 126.8, 126.6, 123.6, 90.2, 75.0, 21.7. Anal. Calcd. for C$_{26}$H$_{19}$NO$_3$S: C, 73.39; H, 4.50; N, 3.29. Found: C, 73.32; H, 4.77; N, 3.32.

$N$-(3-(1-Naphthyl)-3-oxoprop-1-ynyl)-$N$-phenyl-4-tolylsulfonamide, 7.

The reaction with 1-naphthoyl chloride (55.0 mg, 0.28 mmol) and the ynamide (54.5 mg, 0.20 mmol) was performed at 20 °C for 38 hours. The concentrated crude residue was purified by column chromatography (1:1 dichloromethane: hexanes) to give 67 mg (0.16 mmol, 79%) of a colorless oil. $^1$H NMR (400 MHz) δ = δ 9.21 (d, J = 8.5 Hz, 1H), 8.56 (d, J = 7.1 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.68 – 7.57 (m, 4H), 7.54 (dd, J = 7.6, 7.4 Hz, 1H), 7.41 - 7.33 (m, 3H), 7.32 – 7.26 (m, 2H), 7.23 (d, J = 8.1 Hz, 2H), 2.38 (s, 3H). $^{13}$C NMR (100 MHz) δ = 178.7, 145.9, 137.2, 134.6, 134.0, 133.9, 132.8, 132.7, 130.7, 129.9, 129.5, 129.2,
128.7, 128.5, 128.2, 126.6, 126.5, 125.9, 124.7, 88.7, 76.0, 21.7. Anal. Calcd. for C$_{26}$H$_{19}$NO$_3$S: C, 73.39; H, 4.50; N, 3.29. Found: C, 73.30; H, 4.89; N, 3.30.

N-(4,4-Dimethyl-3-oxopent-1-ynyl)-N-phenyl-4-tolylsulfonamide, 8.

The reaction with pivaloyl chloride (21.6 mg, 0.179 mmol) and the ynamide (33.5 mg, 0.124 mmol) was performed at 30 °C for 18 hours. The concentrated crude residue was purified by column chromatography (2:1 dichloromethane: hexanes) to give 39.5 mg (0.111 mmol, 90%) of a white solid. $^1$H NMR (400 MHz) δ = 7.56 (d, $J = 7.9$ Hz, 2H), 7.36 – 7.28 (m, 3H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.21 – 7.13 (m, 2H), 2.40 (s, 3H), 1.19 (d, $J = 1.3$ Hz, 9H). $^{13}$C NMR (100 MHz) δ = 193.0, 145.8, 137.4, 133.1, 129.8, 129.3, 129.0, 128.1, 126.4, 89.2, 73.6, 44.6, 26.2, 21.6. Anal. Calcd. For C$_{20}$H$_{21}$NO$_3$S: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.68; H, 6.29; N, 3.86. mp 98 - 101 °C.

N-(4-Methyl-3-oxopent-1-ynyl)-N-phenyl-4-tolylsulfonamide, 9.

The reaction with isobutryl chloride (30.4 mg, 0.28 mmol) and the ynamide (54.0mg, 0.20 mmol) was performed at 15 °C for 52 hours. The concentrated crude residue was purified by column chromatography (2:1 dichloromethane: hexanes) to give 47.3 mg (0.14 mmol, 70%) of a colorless oil.$^1$H NMR (400 MHz) δ = 7.58 (d, $J = 7.9$ Hz, 2H), 7.40 – 7.26 (m, 5H), 7.23 – 7.14 (m, 2H), 2.63 (hept, $J = 7.1$ Hz, 1H), 2.42 (s, 3H), 1.20 (d, $J = 7.1$ Hz, 6H). $^{13}$C NMR (100 MHz) δ = 190.9, 145.9, 137.3, 132.9, 129.9, 129.4, 129.1, 128.1, 126.5, 89.1, 74.3, 42.7, 21.7, 18.1. Anal. Calcd. For C$_{19}$H$_{19}$NO$_3$S: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.59; H, 5.86; N, 4.00.
A single crystal was obtained by slow evaporation of a solution of the ketone in CDCl$_3$ (Figure 3.4). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structure was solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: C$_{22}$H$_{17}$NO$_3$S, $M = 375.44$, colorless rod, 0.58 x 0.46 x 0.41 mm$^3$, monoclinic, space group $P2_1$, $a = 5.587(2)$, $b = 18.446(7)$, $c = 17.936(7)$ Å, $β = 97.283(8)$, $V = 1857$ Å$^3$, $Z = 4$. 

Figure 3.4. Crystal structure of $N$-(3-Phenyl-3-oxoprop-1-ynyl)-$N$-phenyl-4-tolylsulfonamide, 2.
Chapter 4. Catalytic enantioselective addition of ynamides to aldehydes

4.1. Introduction

The unique synthetic versatility of ynamines and ynamides has attracted increasing attention in recent years. In particular, substituted ynamides have been applied in a wide array of carbon-carbon bond forming reactions and several total syntheses of natural products using these multifaceted building blocks as key intermediates have been reported. A few examples of nucleophilic additions of lithium or sodium ynamides to aldehydes, imines and ketones toward racemic N-substituted propargylic alcohols have been reported, however, at the time of writing a broadly applicable, mild variant that avoided the use of butyllithium, sodium amide or another strong base had not been developed. The first catalytic enantioselective nucleophilic 1,2-addition with ynamides was accomplished using a zinc salt and amine base at room temperature (Scheme 4.1).

![Scheme 4.1. Noncatalytic nucleophilic addition of ynamides to aldehydes.](image)

4.2. Results and discussion

As little information on the reactivity, in particular with regard to acidity and the propensity toward formation of transition metal alkynyl σ-complexes and nucleophilicity, was available for terminal ynamides, the possibility of a catalytic enantioselective nucleophilic addition to

---

iii The content of this chapter has been published by the Royal Society of Chemistry (Chem. Commun. 2014, 50, 3151 – 3154.) All copyrights are reserved by the Royal Society of Chemistry.
aldehydes was investigated using readily available N-phenyl-N-tosyl ynamide 1 and alkyne addition protocols introduced by Carreira, Trost, Shibasaki and others.\textsuperscript{205} Ynesulfonamide 1 was prepared in three high-yielding steps on the gram scale from commercially available N-tosyl aniline following a literature procedure.\textsuperscript{206} With this prototype ynamide in hand, the search for a catalytic reaction with 4-bromobenzaldehyde was begun by screening a variety of metal salts and chiral ligands, including bisoxazolines, bisoxazolidines, cinchona alkaloids, amino alcohols and diamines, in several solvents. The use of 4-bromobenzaldehyde over benzaldehyde was preferred during initial screening due to its superior shelf life. The reaction did not occur in the absence of a transition metal or under conditions typically used for nucleophilic additions with enamides or enecarbamates.\textsuperscript{207}

It was discovered that nucleophilic addition occurs in the presence of catalytic amounts of zinc triflate and N-methylephedrine (NME) in toluene at room temperature, providing the N-substituted propargylic alcohol 2 in high yield and 60\% ee (Table 4.1, entry 1). Encouraged by this finding, other ynamides were prepared, including novel 3-acylindole-stabilized vinylogous ynamides, via TBAF-promoted desilylation of TIPS-protected precursors that were obtained as previously described by Stahl.\textsuperscript{208} As expected, incorporation of the ynamide nitrogen atom into a slightly less electron-withdrawing moiety increases the reactivity while substantially decreasing enantioselectivity. Excellent yields were obtained with ynamides 3 and 4 but the ee’s dropped below 40\% (Table 4.1, entries 2 – 3). The introduction of the indole-derived terminal ynamides 5-8 gave superior results; the ee’s generally improved to 80\% (entries 4-7). The reaction with the 3-benzoylindolyl derived ynamide 7 gave the corresponding propargylic alcohol 13 in 87\% yield and 77\% ee (entry 6).
Table 4.1. Screening of various ynamide nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ynamide</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield$^a$ (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Ynamide 1" /></td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>2.5</td>
<td>87</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Ynamide 3" /></td>
<td><img src="image4.png" alt="Product 9" /></td>
<td>3</td>
<td>91</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Ynamide 4" /></td>
<td><img src="image6.png" alt="Product 10" /></td>
<td>5</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Ynamide 5" /></td>
<td><img src="image8.png" alt="Product 11" /></td>
<td>18</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Ynamide 6" /></td>
<td><img src="image10.png" alt="Product 12" /></td>
<td>18</td>
<td>58</td>
<td>78</td>
</tr>
</tbody>
</table>
Further optimization of the catalytic asymmetric addition of 7 to bromobenzaldehyde revealed an unexpected feature that has not been observed for additions of ynamines, ynamides or even simple alkynes to aldehydes. During extensive screening of the effects of catalyst loading, solvents and base on the yield and enantioselectivity, it was observed that the ee of 13 decreased over time when the reactions were allowed to proceed to full completion. Stirring enantioenriched 13 under typical reaction conditions for several hours proved that the C-C bond formation is reversible as the decrease of the ee of 13 coincided with the formation of the starting materials.

Comparison of bases showed that the reaction is sluggish when DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DMAP (4-dimethylaminopyridine) are used while the best results were obtained with sterically hindered amines and 2,6-lutidine. The presence of the latter, however, was found to strongly promote the racemization reaction which was most evident in THF and diethyl ether. The ee of 13 dropped from 93% to only 23% when the reaction was
performed in the presence of one equivalent of 2,6-lutidine in THF for 20 hours. It was then discovered that the undesired racemization process can be substantially reduced or eliminated when the reaction is carried out in apolar solvents. Because 13 precipitates in toluene and most of its derivatives are barely soluble in hexane/toluene mixtures, racemization can be avoided with these solvent choices even when relatively long reaction times are required to achieve high yields. Under optimized conditions, 13 was produced in 97% yield and 93% ee (Table 4.2, entry 1).

Table 4.2. Catalytic asymmetric ynamide addition to aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\text{PhCO} = \text{H}
\] to [13] | \[\begin{array}{c}
\text{OH} \\
\text{NR}_2 \text{R}_3
\end{array}\] | 18 | 97 | 93 |
| 2     | \[
\text{ClCO} = \text{H}
\] to [15] | \[\begin{array}{c}
\text{OH} \\
\text{NR}_2 \text{R}_3
\end{array}\] | 16 | 92 | 95 |
| 3     | \[
\text{FCO} = \text{H}
\] to [16] | \[\begin{array}{c}
\text{OH} \\
\text{NR}_2 \text{R}_3
\end{array}\] | 18 | 85 | 93 |
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1.png" alt="" /></td>
<td><img src="image2.png" alt="" /></td>
<td>18.5</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td><img src="image3.png" alt="" /></td>
<td><img src="image4.png" alt="" /></td>
<td>13</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>6(^b)</td>
<td><img src="image5.png" alt="" /></td>
<td><img src="image6.png" alt="" /></td>
<td>18</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="" /></td>
<td><img src="image8.png" alt="" /></td>
<td>17</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9.png" alt="" /></td>
<td><img src="image10.png" alt="" /></td>
<td>18</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td><img src="image11.png" alt="" /></td>
<td><img src="image12.png" alt="" /></td>
<td>15</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td><img src="image13.png" alt="" /></td>
<td><img src="image14.png" alt="" /></td>
<td>20</td>
<td>80</td>
<td>88</td>
</tr>
</tbody>
</table>
Having optimized the catalytic reaction between bromobenzaldehyde and 7 toward 3-(4-bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 13, a variety of aldehydes were employed to determine the substrate scope. The reaction with aromatic substrates generally proceeded with high yields and ee’s (Table 4.2). Screening of several other halogenated benzaldehyde derivatives showed that the corresponding products 15-18 can be obtained with excellent results with the exception of 2-fluorobenzaldehyde which was obtained in high yield but somewhat lower ee (Table 2, entries 2 – 5). This cannot be attributed to steric hindrance because the ynamide addition to 2-methylbenzaldehyde produced 22 in 93% yield and 95% ee (entry 9). The method was extended to include aliphatic aldehydes.

### Table 4.2. (Cont.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td><img src="11.png" alt="Benzaldehyde" /></td>
<td><img src="11.png" alt="Product" /></td>
<td>26</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td><img src="12.png" alt="Furan" /></td>
<td><img src="12.png" alt="Product" /></td>
<td>21</td>
<td>81</td>
<td>87</td>
</tr>
<tr>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="13.png" alt="Cyclohexanone" /></td>
<td><img src="13.png" alt="Product" /></td>
<td>15</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td><img src="14.png" alt="Butanone" /></td>
<td><img src="14.png" alt="Product" /></td>
<td>13</td>
<td>87</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> Toluene used as solvent. <sup>c</sup> The absolute configuration of 13 was determined by crystallographic analysis. All other assignments are by analogy.
cyclohexanecarboxaldehyde and decanal afforded 26 and 27 in 87-89% yield and 90-95% ee, respectively (entries 13 – 14). Single crystals of products 13 and 20 were obtained by slow evaporation of a chloroform solution. Crystallographic analysis of 13 revealed S-configuration (Figure 4.1).

![Crystal structures of 13 (left) and 20 (right).](image)

**Figure 4.1.** Crystal structures of 13 (left) and 20 (right). Selected crystallographic separations [Å] for 13: C(sp)-C(sp): 1.191, N-C(sp) 1.358. 20: C(sp)-C(sp): 1.191, N-C(sp) 1.359.

The Zn(II)-(−)-NME catalyst system is tolerant of a chiral center in the substrate. The reaction between (R)-citronellal and ynamide 7 gave 28 in 88% yield and 98% de within 3 hours (Scheme 2). The same aldehyde reacted more slowly and with lower diastereoselectivity when (+)-NME was used as chiral ligand under otherwise identical conditions. As a result, 29 was isolated in only 56% yield and 73% ee. The reduced yield is mostly a result of slow conversion; 25% of the unreacted ynamide were recovered after 3 hours. These results show that the sense of asymmetric induction is overwhelmingly controlled by the chiral catalyst while the chirality in the substrate may still have a distinctive effect on the reaction outcome. The Zn(II)-(−)-NME catalyzed reaction with the (R)-enantiomer of citronellal represents a matched pair whereas the reduced reaction rate and the lower asymmetric induction observed with Zn(II)-(+)NME is in accordance with a mismatched pair.209
4.3. Conclusion

The first catalytic asymmetric addition of ynamides to aldehydes has been developed. The zinc catalyzed method is operationally simple, applicable to aliphatic and aromatic aldehydes, proceeds under mild conditions at room temperature, and provides practical access to a variety of $N$-substituted propargylic alcohols that are obtained in high yields and ee’s. The use of apolar solvent mixtures proved essential to avoid product racemization and to achieve high ee’s without compromising conversion. The unique reactivity and diversity of the polar ynamide functionality bear remarkable potential for asymmetric synthesis. The introduction of terminal ynamides to catalytic enantioselective additions described herein is expected to provide unprecedented entries to complex chiral building blocks.
4.4. Experimental section

4.4.1. Synthetic procedures

Commercially available reagents and solvents were used without further purification. Anhydrous solvents were used as purchased and not dried any further. Aldehydes were purified by column chromatography on silica gel prior to use unless noted otherwise. NMR spectra were obtained at 400 MHz ($^1$H NMR) and 100 MHz ($^{13}$C NMR) in deuterated chloroform. Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 40-63 μm) as described below.

Scheme 4.3. Synthesis of 3-Benzoylindole.\textsuperscript{210}

To a solution of indole (1.53 g, 13.1 mmol) in anhydrous 1,1-dichloroethane (15 mL) under nitrogen at 0 °C was added benzoyl chloride (1.40 g, 10.0 mmol) in anhydrous dichloromethane (15 mL) and zirconium tetrachloride (3.50 g, 15.0 mmol) in one portion. The bright yellow solution was stirred vigorously as it warmed to room temperature. After 4 hours the mixture was quenched with water (50 mL), transferred to a separatory funnel with acetone (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under vacuum. The resulting red solid was washed with acetone to give a light purple solid (1.33 g, 6.0 mmol 60% yield) which was used without further purification (Scheme 4.3). $^1$H NMR (400 MHz) $\delta = 8.58$ (bs, 1H), 8.42 (m, 1H), 7.84 (m, 2H), 7.56 (m, 1H), 7.52 – 7.42 (m, 3H), 7.37 – 7.30 (m, 2H). $^{13}$C NMR (100 MHz) $\delta = 189.7, 140.7, 136.4, 133.4, 131.3, 128.8, 128.3, 126.4, 124.1, 122.8, 122.7, 117.4, 111.2.
Scheme 4.4. Synthesis of 1-(3-Benzoylindolyl)-2-(triisopropylsilyl)acetylene.\(^6\)

Copper(II) chloride (0.40 g, 3.0 mmol), sodium carbonate (1.27 g, 12.0 mmol), (triisopropylsilyl)acetylene (1.64 g, 9.0 mmol) and pyridine (0.95 g, 12.0 mmol) were combined in a round bottomed flask with toluene (50 mL) and a solution of 3-benzoylindole (1.33 g, 6.0 mmol) in DMSO (5 mL) was added. The resulting heterogeneous mixture was purged with dioxygen gas for approximately 10 minutes and stirred at 70 °C under oxygen for 4 hours. The crude mixture was concentrated by rotary evaporation. Unreacted 3-benzoylindol (0.49 g, 2.3 mmol, 38%) was recovered from a short silica plug (DCM/EtOAc) as a white solid. The crude product mixture was further purified by flash chromatography (30:1 hexanes:EtOAc) to give a colorless oil (1.15 g, 2.88 mmol, 48%). \(^1\)H NMR (400 MHz) \(\delta = 8.38\) (d, \(J = 7.8\) Hz, 1H), 7.86 (d, \(J = 7.6\) Hz, 2H), 7.68 (s, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 (dd, \(J = 7.5, 7.5\) Hz, 1H), 7.40 (dd, \(J = 7.5, 7.4\) Hz, 1H), 1.16 (s, 18H), 1.16 (s, 3H). \(^{13}\)C NMR (100 MHz) \(\delta = 190.5, 139.9, 138.7, 136.7, 131.8, 128.8, 128.5, 125.9, 125.2, 124.2, 123.0, 118.3, 111.3, 92.7, 71.3, 18.7, 11.3.\)
Tetrabutylammonium fluoride (1M THF, 3.5 mL) was added to a solution of 1-(3-benzoylindolyl)-2-(triisopropylsilyl)acetylene (1.15 g, 2.88 mmol) in dichloromethane (5mL) and the mixture was stirred for 5 minutes at room temperature. The resulting solution was extracted with dichloromethane (3 x 30 mL) from H₂O. The concentrated crude residue was purified by column chromatography (40:30:1 CH₂Cl₂:hexanes:EtOAc) to give a white solid (0.68 g, 2.77 mmol, 95% yield) after solvents were removed by rotary evaporation at room temperature. \(^1\)H NMR (400 MHz) δ = 8.38 (m, 1H), 7.85 (m, 2H), 7.69 (s, 1H), 7.64 – 7.54 (m, 2H), 7.50 (m, 2H), 7.47 – 7.36 (m, 2H), 3.18 (s, 1H). \(^{13}\)C NMR (100 MHz) δ = 190.5, 139.7, 138.5, 136.7, 131.9, 128.8, 128.5, 125.9, 125.3, 124.3, 122.9, 118.6, 111.2, 72.7, 60.4. Anal. Calcd. For C\(_{17}\)H\(_{11}\)NO\(_2\): C, 83.25; H, 4.52; N, 5.71. Found: C, 82.93; H, 4.59; N, 5.81. mp > 120 °C (decomp).

**General zinc catalyzed ynamine addition procedure.**

Zinc triflate (7.4 mg, 20 μmol), (1R,2S)-(−)-N-methylephedrine (3.9 mg, 22 μmol), 3-benzoyl-1-ethynylindole (50.0 mg, 0.20 mmol), aldehyde (0.30 mmol) and \(N,N\)-diisopropylethylamine (25.8 mg, 0.20 mmol) were dissolved in either toluene or a 1:1 toluene/hexane mixture (0.5 mL) under nitrogen atmosphere. The mixture was stirred at room temperature until completion as determined by \(^1\)H NMR analysis. Solvents were evaporated
under a stream of nitrogen and the crude residue was purified by flash chromatography or crystallization as described below.

3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 13.

The reaction with 4-bromobenzaldehyde (62 mg, 0.33 mmol) was performed using the ynamine (55 mg, 0.22 mmol) in toluene (0.55 mL). After 18 hours, a white precipitate was isolated and washed twice with hexanes (1 mL). Additional product was isolated from the concentrated supernatant by flash chromatography (5% EtOAc, CH₂Cl₂). The combined fractions gave 92 mg (0.21 mmol, 97%, 93% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.38 (m, 1H), 7.84 (d, $J = 7.4$ Hz, 2H), 7.66 (s, 1H), 7.62 – 7.55 (m, 3H), 7.55 – 7.48 (m, 5H), 7.46 – 7.38 (m, 2H), 5.77 (d, $J = 5.5$ Hz, 1H), 2.37 (d, $J = 5.5$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.6, 139.6, 139.2, 138.5, 136.7, 132.0, 131.9, 128.8, 128.5, 128.2, 126.0, 125.4, 124.4, 123.0, 122.7, 118.8, 111.2, 76.8, 71.7, 64.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, $t_1$ (minor) = 12.4 min, $t_2$ (major) = 14.7 min, $\alpha = 1.23$. Anal. Calcd. for C$_{24}$H$_{16}$NO$_2$Br: C, 66.99; H, 3.75; N, 3.26. Found: C, 66.93; H, 4.12; N, 3.14. mp 140 °C (decomp).

3-(4-Chlorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 15.

The reaction with 4-chlorobenzaldehyde (35 mg, 0.25 mmol) was performed using the ynamine (55 mg, 0.22 mmol) in 1:1 toluene-hexanes (0.55 mL). After 16 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH₂Cl₂) to give 78 mg (0.20 mmol, 92%, 95% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.37 (m, 1H), 7.83 (m, 2H), 7.64 (s, 1H), 7.62 – 7.46 (m, 6H), 7.46 – 7.35 (m, 4H), 5.79 (d, $J = 5.9$ Hz, 1H), 2.48 (d, $J = 5.9$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.5, 139.6, 138.6, 138.5, 136.7, 134.5, 131.9, 129.0, 128.8, 128.5, 127.8, 126.0, 125.3, 124.4, 123.0, 118.8, 111.1, 76.8, 71.7, 64.0. The ee was determined
by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, \( t_1 \) (minor) = 11.3 min, \( t_2 \) (major) = 13.2 min, \( \alpha = 1.21 \). Anal. Calcd. For \( \text{C}_{24}\text{H}_{16}\text{ClNO}_2 \): C, 74.71; H, 4.18; N, 3.63. Found: C, 74.63; H, 4.15; N, 3.72. mp 166-167°C.

3-(4-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 16.

The reaction with 4-fluorobenzaldehyde (39 mg, 0.31 mmol) was performed using the ynamine (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 18 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, \( \text{CH}_2\text{Cl}_2 \)) to give 69 mg (0.19 mmol, 92%, 93% ee) of a white solid. \( ^1\text{H} \) NMR (400 MHz) \( \delta = 8.34 \) (m, 1H), 7.79 (d, \( J = 7.8 \) Hz, 2H), 7.62 – 7.56 (m, 3H), 7.55 (s, 1H), 7.52 – 7.43 (m, 3H), 7.40 – 7.32 (m, 2H), 7.09 (dd, \( J = 8.6, 8.6 \) Hz, 2H), 5.78 (d, \( J = 5.8 \) Hz, 1H), 2.96 (d, \( J = 5.9 \) Hz, 1H). \( ^{13}\text{C} \) NMR (100 MHz, \( \text{CDCl}_3 \)) \( \delta = 190.7, 162.8 \) (d, \( J_{(C,F)} = 247.6 \) Hz), 139.6, 138.5, 136.8, 136.1 (d, \( J_{(C,F)} = 3.2 \) Hz), 131.9, 128.8, 128.5, 128.3 (d, \( J_{(C,F)} = 8.3 \) Hz), 125.9, 125.3, 124.4, 123.0, 118.7, 115.7 (d, \( J_{(C,F)} = 21.8 \) Hz), 111.2, 71.9, 64.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, \( t_1 \) (minor) = 9.9 min, \( t_2 \) (major) = 11.4 min, \( \alpha = 1.20 \). Anal. Calcd. For \( \text{C}_{24}\text{H}_{16}\text{FNO}_2 \): C, 78.04; H, 4.37; N, 3.79. Found: C, 77.75; H, 4.53; N, 3.88. mp 123-124°C.

3-(3-Fluorophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 17.

The reaction with 3-fluorobenzaldehyde (48 mg, 0.39 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 18.5 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, \( \text{CH}_2\text{Cl}_2 \)) to give 84 mg (0.23 mmol, 87%, 88% ee) of a white solid. \( ^1\text{H} \) NMR (400 MHz) \( \delta = 8.36 \) (m, 1H), 7.84 (d, \( J = 7.2 \) Hz, 2H), 7.65 (s, 1H), 7.63 – 7.46 (m, 4H), 7.46 – 7.38 (m, 4H), 7.35 (d, \( J = 9.9 \) Hz, 1H), 7.07 (m, 1H), 5.81 (d, \( J = 6.0 \) Hz, 1H), 2.47 (d, \( J = 6.0 \) Hz, 1H). \( ^{13}\text{C} \) NMR (100 MHz) \( \delta \)
= 190.8, 162.9 (d, \( J_{(C,F)} = 246.8 \) Hz), 142.7 (d, \( J_{(C,F)} = 7.0 \) Hz), 139.5, 138.4, 136.9, 132.0, 130.3 (d, \( J_{(C,F)} = 8.1 \) Hz), 128.8 , 128.5 , 125.8, 125.3, 124.4, 122.9, 122.0 (d, \( J_{(C,F)} = 3.1 \) Hz), 118.6, 115.4 (d, \( J_{(C,F)} = 21.3 \) Hz), 113.5 (d, \( J_{(C,F)} = 22.8 \) Hz), 111.1, 76.6 , 71.8 , 63.9 (d, \( J_{(C,F)} = 2.1 \) Hz). The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, \( t_1 \) (minor) = 21.0 min, \( t_2 \) (major) = 22.5 min, \( \alpha = 1.08 \). Anal. Calcd. For \( C_{24}H_{16}FNO_2 \): C, 78.04; H, 4.37; N, 3.79. Found: C, 77.64; H, 4.22; N, 3.87. mp > 136 °C (decomp).

3-(2-Fluorophenyl)-3-hydroxy-1-(3-benzyllindolyl)propyne, 18.

The reaction with 2-fluorobenzaldehyde (42 mg, 0.34 mmol) was performed using the ynamine (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 13 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, \( \text{CH}_2\text{Cl}_2 \)) to give 70.5 mg (0.19 mmol, 95%, 70% ee) of a white solid. \(^1\)H NMR (400 MHz) \( \delta = 8.35 \) (m, 1H), 7.81 (d, \( J = 7.4 \) Hz, 2H), 7.70 (ddd, \( J = 7.6, 7.6, 1.8 \) Hz, 1H), 7.58 (s, 1H), 7.57 – 7.44 (m, 4H), 7.42 – 7.31 (m, 3H), 7.21 (ddd, \( J = 7.6, 7.6, 1.2 \) Hz, 1H), 7.11 (ddd, \( J = 10.5, 8.2, 1.2 \) Hz, 1H), 6.03 (d, \( J = 5.9 \) Hz, 1H), 2.98 (d, \( J = 5.9 \) Hz, 1H). \(^{13}\)C NMR (100 MHz) \( \delta = 190.7 , \) 160.0 (d, \( J_{(C,F)} = 248.3 \) Hz), 139.7 , 138.5 , 136.9 , 131.9 , 130.5 (d, \( J_{(C,F)} = 8.3 \) Hz), 128.8 , 128.5 , 128.1 (d, \( J_{(C,F)} = 3.4 \) Hz), 127.6 (d, \( J_{(C,F)} = 13.1 \) Hz), 125.9 , 125.3 , 124.6 (d, \( J_{(C,F)} = 3.6 \) Hz), 124.4 , 122.9 , 118.7 , 115.9 (d, \( J_{(C,F)} = 21.2 \) Hz), 111.2 , 76.3 , 71.1 , 59.3 (d, \( J_{(C,F)} = 4.9 \) Hz). The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, \( t_1 \) (minor) = 9.6 min, \( t_2 \) (major) = 11.4 min, \( \alpha = 1.25 \). Anal. Calcd. For \( C_{24}H_{16}FNO_2 \): C, 78.04; H, 4.37; N, 3.79. Found: C, 78.17; H, 4.48; N, 3.93. mp 105-107 °C.
3-(1-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 19.

The reaction with 1-naphthaldehyde (52 mg, 0.33 mmol) was performed using the ynamine (55 mg, 0.22 mmol) in toluene (0.55 mL). After 18 hours, the precipitate was isolated from the yellow supernatant to give 81 mg (0.20 mmol, 92%, 96% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.42 (d, $J = 8.4$ Hz, 1H), 8.37 (m, 1H), 7.96 – 7.87 (m, 3H), 7.83 (m, 2H), 7.67 (s, 1H), 7.64 – 7.47 (m, 7H), 7.44 – 7.36 (m, 2H), 6.45 (d, $J = 5.6$ Hz, 1H), 2.49 (d, $J = 5.6$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.5, 139.8, 138.6, 136.8, 135.3, 134.2, 131.9, 130.3, 129.7, 128.9, 128.8, 128.5, 126.7, 126.2, 126.0, 125.3, 124.6, 124.4, 123.8, 123.0, 118.7, 111.3, 71.8, 63.4. The ee was determined by HPLC on Chiralcel OD using hexanes:IPA (80:20) as the mobile phase at 1.0 mL/min, $t_1$ (minor) = 19.4 min, $t_2$ (major) = 27.1 min, $\alpha = 1.45$. Anal. Calcd. For C$_{28}$H$_{19}$NO$_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.67; H, 4.63; N, 3.62. mp > 190 °C (decomp).

3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 20.

The reaction with 2-naphthaldehyde (52 mg, 0.33 mmol) was performed using the ynamine (55 mg, 0.22 mmol) in 1:1 toluene/hexane (0.55 mL). After 17 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH$_2$Cl$_2$) to give 83 mg (0.20 mmol, 92%, 90% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.37 (m, 1H), 8.05 (s, 1H), 7.91 (d, $J = 8.6$ Hz, 1H), 7.87 (m, 2H), 7.84 – 7.78 (m, 2H), 7.73 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.62 (s, 1H), 7.60 – 7.44 (m, 6H), 7.43 – 7.34 (m, 2H), 5.96 (d, $J = 5.9$ Hz, 1H), 2.73 (d, $J = 5.9$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.6, 139.7, 138.5, 137.5, 136.9, 133.3, 133.2, 131.9, 128.9, 128.8, 128.5, 128.2, 127.7, 126.5, 126.0, 125.4, 125.3, 124.4, 124.2, 123.0, 118.7, 111.2, 76.8, 72.1, 64.9. The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (85:15) as the
mobile phase at 1.5 mL/min, $t_1$ (minor) = 19.8 min, $t_2$ (major) = 23.4 min, $\alpha = 1.21$. Anal. Calcd. For $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.41; H, 4.93; N, 3.57. mp 165-166 °C.

3-Phenyl-3-hydroxy-1-(3-benzoylindolyl)propyne, 21.

The reaction with benzaldehyde (63 mg, 0.59 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 18 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH$_2$Cl$_2$) to give 80 mg (0.23 mmol, 87%, 84% ee) of a white solid. $^1$H NMR (400 MHz) $\delta = 8.34$ (m, 1H), 7.78 (d, $J = 7.9$ Hz, 2H), 7.61 (d, $J = 7.8$ Hz, 2H), 7.58 – 7.52 (m, 2H), 7.52 – 7.31 (m, 8H), 5.78 (d, $J = 6.0$ Hz, 1H), 3.09 (d, $J = 6.1$ Hz, 1H). $^{13}$C NMR (100 MHz) $\delta = 190.7$, 140.3, 139.6, 138.5, 137.0, 131.9, 128.8, 128.6, 128.5, 126.5, 125.9, 125.2, 124.3, 122.9, 118.5, 111.2, 76.4, 72.2, 64.7. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, $t_1$ (minor) = 10.5 min, $t_2$ (major) = 12.8 min, $\alpha = 1.28$. Anal. Calcd. For $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99. Found: C, 82.14; H, 4.94; N, 4.12. mp > 102 °C (decomp).

3-(2-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 22.

The reaction with 2-tolyl aldehyde (47 mg, 0.39 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 15 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH$_2$Cl$_2$) to give 88 mg (0.24 mmol, 93%, 95% ee) of a white solid. $^1$H NMR (400 MHz) $\delta = 8.38$ (m, 1H), 7.84 (m, 2H), 7.73 (m, 1H), 7.66 (s, 1H), 7.62 – 7.54 (m, 2H), 7.50 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.33 – 7.27 (m, 2H), 7.23 (m, 1H), 5.96 (d, $J = 5.7$ Hz, 1H), 2.52 (s, 3H), 2.29 (d, $J = 5.7$ Hz, 1H). $^{13}$C NMR (100 MHz) $\delta = 190.5$, 139.8, 138.6, 138.0, 136.9, 135.7, 131.9, 131.0, 128.8, 128.8, 128.5, 126.5, 126.0, 125.3, 124.4, 123.0, 118.7, 111.2, 76.5, 71.7, 62.6, 19.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase.
at 1.0 mL/min, $t_1$ (minor) = 13.6 min, $t_2$ (major) = 16 min, $\alpha = 1.21$. Anal. Calcd. For C$_{25}$H$_{19}$NO$_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.91; H, 5.27; N, 3.93. mp 144-147 °C.

3-(4-Tolyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 23.

The reaction with 4-tolyl aldehyde (48 mg, 0.40 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 20 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH$_2$Cl$_2$) to give 77 mg (0.21 mmol, 80%, 88% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.38 (m, 1H), 7.84 (d, $J = 6.8$ Hz, 2H), 7.68 (s, 1H), 7.63 – 7.55 (m, 2H), 7.55 – 7.47 (m, 4H), 7.47 – 7.37 (m, 2H), 7.25 (d, $J = 7.4$ Hz, 2H), 5.77 (d, $J = 6.0$ Hz, 1H), 2.39 (s, 3H), 2.24 (d, $J = 6.1$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.6, 139.8, 138.7, 138.6, 137.4, 136.9, 131.9, 129.5, 128.8, 128.5, 126.5, 126.0, 125.3, 124.3, 123.0, 118.6, 111.3, 76.4, 72.2, 64.7, 21.2. The ee was determined by HPLC on Chiralpak IA using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, $t_1$ (minor) = 23.0 min, $t_2$ (major) = 25.9 min, $\alpha = 1.14$. Anal. Calcd. For C$_{25}$H$_{19}$NO$_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.77; H, 5.20; N, 3.90.

3-(3-Methoxyphenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 24.

The reaction with 3-methoxybenzaldehyde (14 mg, 0.10 mmol) was performed using the ynamine (15 mg, 0.06 mmol) in 1:1 toluene-hexanes (0.15 mL). After 26 hours, the concentrated crude residue was purified by column chromatography (3% EtOAc, CH$_2$Cl$_2$) to give 21 mg (0.055 mmol, 92%, 87% ee) of a white solid. $^1$H NMR (400 MHz) δ = 8.37 (m, 1H), 7.83 (d, $J = 7.8$ Hz, 2H), 7.64 (s, 1H), 7.62 – 7.53 (m, 2H), 7.50 (m, 2H), 7.45 – 7.37 (m, 2H), 7.35 (dd, $J = 8.0$, 8.0 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.91 (dd, $J = 8.2$, 2.5 Hz, 1H), 5.77 (d, $J = 6.0$ Hz, 1H), 3.84 (s, 3H), 2.47 (d, $J = 6.1$ Hz, 1H). $^{13}$C NMR (100 MHz) δ = 190.6, 160.0, 141.8, 139.7, 138.5, 136.9, 131.9, 129.9, 128.8, 128.5, 126.0, 125.3, 124.4, 123.0, 118.7, 114.2, 112.1, 111.2, 109.4, 102.6, 100.0, 99.7.
76.6, 72.0, 64.7, 55.4. The ee was determined by HPLC on Chiralpak OD using hexanes:EtOH (85:15) as the mobile phase at 1.2 mL/min, \( t_1 \) (major) = 17.0 min, \( t_2 \) (minor) = 21.2 min, \( \alpha = 1.29 \). Anal. Calcd. For C\(_{25}\)H\(_{19}\)NO\(_3\): C, 78.72; H, 5.02; N, 3.67. Found: C, 78.49; H, 5.03; N, 3.71. mp 96-99 °C.

3-(3-Furyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 25.

The reaction with 3-furanal (30 mg, 0.30 mmol) was performed using the ynamine (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). The aldehyde was used as purchased without further purification. After 21 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH\(_2\)Cl\(_2\)) to give 56 mg (0.16 mmol, 81%, 87% ee) of a white solid. \(^1\)H NMR (400 MHz) \( \delta = 8.36 \) (m, 1H), 7.82 (d, \( J = 6.9 \) Hz, 2H), 7.61 (m, 1H), 7.60 (s, 1H), 7.59 – 7.43 (m, 5H), 7.43 – 7.34 (m, 2H), 6.60 (dd, \( J = 1.8, 0.9 \) Hz, 1H), 5.74 (dd, \( J = 6.5, 1.0 \) Hz, 1H), 2.69 (d, \( J = 6.5 \) Hz, 1H) \(^{13}\)C NMR (100 MHz) \( \delta = 190.6, 143.9, 140.0, 139.6, 138.4, 136.8, 131.9, 128.8, 128.5, 126.1, 125.9, 125.3, 124.4, 122.9, 118.6, 111.1, 109.0, 75.2, 71.6, 57.5. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, \( t_1 \) (minor) = 11.0 min, \( t_2 \) (major) = 13.5 min, \( \alpha = 1.29 \). Anal. Calcd. For C\(_{22}\)H\(_{15}\)NO\(_3\): C, 77.41; H, 4.43; N, 4.10. Found: C, 77.23; H, 4.47; N, 4.17. mp > 118 °C (decomp).

3-(Cyclohexyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 26.

The reaction with cyclohexanecarboxaldehyde (44 mg, 0.39 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 15 hours, the concentrated crude residue was purified by column chromatography (2% EtOAc, CH\(_2\)Cl\(_2\)) to give 82 mg (0.23 mmol, 89%, 90% ee) of a colorless oil. \(^1\)H NMR (400 MHz) \( \delta = 8.38 \) (m, 1H), 7.83 (d, \( J = 6.9 \) Hz, 2H), 7.63 (s, 1H), 7.61 – 7.54 (m, 2H), 7.50 (dd, \( J = 7.4, 7.3 \) Hz, 2H), 7.46 – 7.35 (m, 2H),
4.49 (d, \(J = 5.8, 5.8\) Hz, 1H), 2.11 (d, \(J = 5.7\) Hz, 1H), 1.96 (m, 2H), 1.82 (m, 2H), 1.72 m, 2H), 1.40 – 1.10 (m, 5H). \(^{13}\)C NMR (100 MHz) \(\delta = 190.6, 139.8, 138.6, 137.0, 131.9, 128.8, 128.5, 125.9, 125.2, 124.3, 122.9, 118.4, 111.2, 75.7, 72.1, 67.4, 44.2, 28.7, 28.4, 26.3, 25.9, 25.8. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (90:10) as the mobile phase at 1.5 mL/min, \(t_1\) (minor) = 9.5 min, \(t_2\) (major) = 10.8 min, \(\alpha = 1.18\). Anal. Calcd. For C\(_{24}\)H\(_{23}\)NO\(_2\): C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.54; N, 4.14.

3-Nonyl-3-hydroxy-1-(3-benzoylindolyl)propyne, 27.

The reaction with decanal (66 mg, 0.42 mmol) was performed using the ynamine (65 mg, 0.26 mmol) in 1:1 toluene-hexanes (0.65 mL). After 13 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH\(_2\)Cl\(_2\)) to give 90 mg (0.23 mmol, 87%, 95% ee) of a colorless oil. \(^1\)H NMR (400 MHz) \(\delta = 8.36\) (m, 1H), 7.79 (d, \(J = 7.8\) Hz, 2H), 7.57 – 7.42 (m, 5H), 7.37 – 7.31 (m, 2H), 4.68 (q, \(J = 6.3\) Hz, 1H), 2.90 (bs, 1H), 1.86 (m, 2H), 1.56 (m, 2H), 1.46 – 1.18 (m, 12H), 0.87 (t, \(J = 6.7\) Hz, 3H). \(^{13}\)C NMR (100 MHz) \(\delta = 190.7, 139.7, 138.4, 137.1, 131.9, 128.8, 128.4, 125.8, 125.1, 124.2, 122.8, 118.2, 111.1, 74.7, 73.4, 62.5, 37.9, 31.8, 29.51, 29.49, 29.3, 29.2, 25.3, 22.6, 14.1. The ee was determined by HPLC on Chiralpak AD using hexanes:EtOH (85:15) as the mobile phase at 1.5 mL/min, \(t_1\) (major) = 4.8 min, \(t_2\) (minor) = 6.5 min, \(\alpha = 1.71\). Anal. Calcd. For C\(_{27}\)H\(_{31}\)NO\(_2\): C, 80.76; H, 7.78; N, 3.49. Found: C, 80.61; H, 8.02; N, 3.57.

3-((2R)-2,6-Dimethylhept-5-enyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 28.

The reaction with (\(R\))-citronellal (46 mg, 0.30 mmol) was performed using the ynamine (50 mg, 0.20 mmol) in 1:1 toluene-hexanes (0.5 mL). After 3 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc, CH\(_2\)Cl\(_2\)) to give 70.5 mg (0.18 mmol, 88%, 98% de) of a colorless oil. \(^1\)H NMR (400 MHz) \(\delta = 8.38\) (m, 1H), 7.82 (d, \(J = 6.9\) Hz, 2H),
7.59 (s, 1H), 7.58 – 7.51 (m, 2H), 7.50 (dd, 7.6, 7.4 Hz, 2H), 7.42 – 7.34 (m, 2H), 5.10 (m, 1H),
4.76 (m, 1H), 2.10 (m, 1H), 2.08 – 1.98 (m, 2H), 1.92 – 1.67 (m, 3H), 1.65 (s, 3H), 1.60 (s, 3H),
1.44 (m, 1H), 1.26 (m, 2H), 0.99 (d, J = 6.2 Hz, 3H).  
$^{13}$C NMR (100 MHz) $\delta$ = 190.6, 139.7, 138.5, 137.0, 131.8, 131.5, 128.8, 128.4, 125.9, 125.2, 124.4, 124.2, 122.9, 118.4, 111.1, 74.8, 73.6, 60.7, 45.3, 37.0, 29.1, 25.7, 25.3, 19.3, 17.7. The de was determined by HPLC on
Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5 mL/min, $t_1$ (major) = 10.5
min, $t_2$ (minor) = 12.5 min, $\alpha$ = 1.25. Anal. Calcd. For C$_{27}$H$_{29}$NO$_2$: C, 81.17; H, 7.32; N, 3.51.
Found: C, 81.20; H, 7.32; N, 3.51.

The reaction with (R)-citronellal (23 mg, 0.15 mmol) was also performed using (1S,2R)-(+)-
$N$-methylephedrine and the ynamine (25 mg, 0.10 mmol) in 1:1 toluene-hexanes (0.1 mL). After
3 hours, the concentrated crude residue was purified by column chromatography (1% EtOAc,
CH$_2$Cl$_2$) to give 22.5 mg (0.056 mmol, 56%, 73% de) of a colorless oil.  
$^1$H NMR (400 MHz) $\delta$ =
8.38 (m, 1H), 7.83 (d, J = 7.0 Hz, 2H), 7.62 (s, 1H), 7.61 – 7.53 (m, 2H), 7.50 (dd, 7.6, 7.4 Hz,
2H), 7.45 – 7.35 (m, 2H), 5.10 (m, 1H), 4.77 (m, 1H), 2.10 (m, 1H), 2.08 – 1.98 (m, 2H), 1.92 –
1.67 (m, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.44 (s, 1H), 1.26 (m, 2H), 0.99 (d, J = 6.2 Hz, 3H).  
$^{13}$C
NMR (100 MHz) $\delta$ = 190.6, 139.8, 138.5, 137.0, 131.9, 131.5, 128.9, 128.5, 126.0, 125.2, 124.4,
124.3, 122.9, 118.5, 111.1, 75.1, 73.2, 61.3, 45.2, 37.0, 29.6, 25.7, 25.3, 19.7, 17.7. The de was
determined by HPLC on Chiralpak AD using hexanes:EtOH (92:8) as the mobile phase at 1.5
mL/min, $t_1$ (minor) = 10.6 min, $t_2$ (major) = 12.4 min, $\alpha$ = 1.22.
4.4.2. Crystallographic analysis of selected products

![Crystal Structure](image)

Figure 4.2. Crystal structure of (3S)-3-(4-Bromophenyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 13.

A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in CDCl$_3$ (Figure 4.2). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data:

C$_{23}$H$_{16}$NO$_2$Br, $M = 430.29$, colorless rod, 1.4 x 4.4 x 5.0 mm$^3$, orthorhombic, space group $P2_12_1$, $a = 6.6770(8)$, $b = 13.3668(16)$, $c = 21.243(3)$ Å, $V = 1895.9(4)$ Å$^3$, $Z = 4$. Absolute structure parameter = 0.0194(73) (Flack, H. D. Acta Cryst. 1983, A39, 876-881).
Figure 4.3. Crystal Structure of 3-(2-Naphthyl)-3-hydroxy-1-(3-benzoylindolyl)propyne, 20.

A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in CDCl₃ (Figure 4.3). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: C₂₈H₁₉NO₂, \( M = 401.16 \), colorless needle, 1.35 x 4.5 x 7.4 mm, monoclinic, space group \( P2_1 \), \( a = 8.0022(10) \), \( b = 7.1348(9) \), \( c = 16.892(2) \) Å, \( \beta = 92.7060(10) \) °C, \( V = 963.3(2) \) Å³, \( Z = 2 \).
Chapter 5. Efficient access to multifunctional trifluoromethyl alcohols through catalytic asymmetric C—C bond formation with terminal ynamides

5.1. Introduction

The significance of the trifluoromethyl-substituted propargylic alcohol moiety, for example, in the anti-HIV drug Efavirenz, has stimulated the development of several methods that furnish this motif in racemic form. In contrast to the general advance with asymmetric alkynylation of aldehydes, ketones, and imines, trifluoromethyl ketones have remained challenging substrates, and initially required the use of stoichiometric amounts of lithium or zinc aminoalkoxides. Shibasaki and coworkers first demonstrated the feasibility of asymmetric catalysis, and generated CF$_3$-substituted propargylic alcohols in up to 52% ee. Significant progress in this field emerged in 2011, when Carreira and coworkers reported an intriguing autocatalytic procedure that is tailored to the production of an Efavirenz precursor. At the same time, Ma and co-workers introduced an alkynylation method that gives 55 – 98% yield and 65 – 94% ee with nonenolizable trifluoromethyl ketones when 2.5 equivalents of the alkyne, 3 equivalents of Me$_2$Zn, and 2 equivalents of Ti(OiPr)$_4$ are used in addition to catalytic amounts of a cinchona alkaloid and BaF$_2$. It was thought that a catalytic asymmetric method that allows addition of terminal ynamides to trifluoroacetophenone and derivatives thereof had potential to overcome the remaining drawbacks of the reaction with alkynes, in particular the use of excess pyrophoric dimethylzinc. At the same time, the enantioselective synthesis of ynamide-derived, CF$_3$-substituted propargylic alcohols would provide unprecedented access to a variety of highly functionalized chiral building blocks if one could exploit the unique reactivity of the polarized N-substituted triple bond (Scheme 5.1). The recent introduction of a very practical two-step
synthesis of terminal ynamides from tosylamides and trichloroethylene by Anderson and co-workers provided an excellent starting point for this study.221

Scheme 5.1 Addition of ynamides to trifluoromethyl ketones provides practical access to several functionalities containing a chiral CF₃-substituted alcohol group.

5.2. Results and discussion

At the onset of this investigation, N-ethynyl-N-butylbenzenesulfonamide, 1, and other ynamides were employed in several literature procedures previously developed for catalytic enantioselective alknylations of carbonyl electrophiles. While these screening efforts were mostly unsuccessful, asymmetric addition of an ynamide to trifluoroacetophenone, 2, was found to occur in the presence of catalytic amounts of zinc triflate, N-methylephedrine, and excess Et₃N or i-Pr₂NEt. Further investigation then revealed that the yield and ee value varied substantially depending on the source of the tertiary amine employed.222 Careful purification of the amines used as well as investigation of possible effects of impurities and amine degradation products that may be present in small amounts but could possibly affect the ynamide addition did not resolve this problem. A method was therefore developed to avoid amine additives.
Table 5.1. Optimization of the zinc triflate catalyzed asymmetric addition of ynamides to 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 20 h</td>
<td>75</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 20 h</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 20 h</td>
<td>89</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 20 h</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>L7</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>72</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>L8</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>L9</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 20 h</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>L10</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>93</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>L11</td>
<td>n-Bu</td>
<td>DCE, 25 °C, 16 h</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>L8</td>
<td>allyl</td>
<td>DCE, 25 °C, 16 h</td>
<td>88</td>
<td>86</td>
</tr>
</tbody>
</table>
Comprehensive screening of zinc and copper complexes, a large variety of chiral ligands in several solvents, and analysis of the effect of (MeO)$_3$PO, (EtO)$_3$PO, Ph$_3$PO, Ph$_3$PS, tBu$_3$P, HMPA, and other additives on the asymmetric induction and turnover gave mixed results. Initially, moderate ee values were obtained with 10 mol% zinc triflate and L1 – L4. However, the reaction between the readily available ynamide 1 and 2 occurs with these catalysts even in the absence of triethylamine or Hüning’s base, thereby providing 3 in up to 95% yield at 25 °C (Table 5.1, entries 1–4). Although encouraging results were obtained with quinine,\textsuperscript{223} attention was turned to Trost’s Bis-ProPhenols, which can be more easily modified if ligand fine-tuning becomes necessary.\textsuperscript{224} The employment of L5 – L7, with either N-methylephedrine or diphenylprolinol units attached to a phenol core, did not show improvement (entries 5–7).

However, the introduction of C$_2$-symmetric L8 gave 3 in 87% yield and 89% ee within 16 h and essentially the same results were obtained with the N-allyl analogue of 1, thereby indicating that this method tolerates different ynamides (compare entries 8 and 12). The presence of the free

\begin{table}
\centering
\caption{5.1. (Cont.)}
\begin{tabular}{cccccc}
\hline
Entry & Ligand & R & Conditions & Yield (%) & Ee (%) \\
\hline
13 & L8 & n-Bu & CH$_2$Cl$_2$, 25 °C, 20 h & 95 & 87 \\
14 & L8 & n-Bu & CHCl$_3$, 25 °C, 20 h & 95 & 86 \\
15 & L8 & n-Bu & toluene, 25 °C, 16 h & 70 & 78 \\
16 & L8 & n-Bu & THF, 25 °C, 16 h & 55 & 66 \\
17 & L8 & n-Bu & ACN, 25 °C, 20 h & 90 & 31 \\
18 & L8 & n-Bu & EtOH, 25 °C, 20 h & 5 & n.d. \\
19 & L8 & n-Bu & DCE, 0 °C, 45 h & 78 & 93 \\
20 & L8 & n-Bu & DCE, -10 °C, 51 h & 73 & 91 \\
21\textsuperscript{a} & L8 & n-Bu & DCE, -20 °C, 24 h & 96 & 96 \\
\hline
\textsuperscript{a}) (EtO)$_3$PO (20 mol%). DCE = 1,2-dichloroethane.
\end{tabular}
\end{table}
phenol group appears to be essential to the catalytic activity of L8 as very low yields were obtained with L9. The use of the naphthyl analogue L10 further improved the yield, but at the expense of the enantioselectivity, while L11 gave poor results (entries 10 and 11). The effect of different solvents and temperatures were thus investigated with L8 and 10 mol% Zn(OTf)2 (entries 13–20). Chlorinated solvents proved superior and gave consistently high yields and ee values. When using dichloroethane as the solvent, ee values improved above 90% when the temperature was decreased to at least 0 °C, but the reaction time increased to approximately 2 days. This was addressed through the addition of catalytic amounts of triethyl phosphate to affect catalytic turnover, enabling the isolation of 3 in 96% yield and 96% ee at 20 °C in 24 hours (entry 21).

Table 5.2. Further investigation with L8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (equiv.)</th>
<th>2 (equiv.)</th>
<th>L8 (mol%)</th>
<th>Time</th>
<th>Conversion (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>1.0</td>
<td>10</td>
<td>16 h</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.5</td>
<td>10</td>
<td>16 h</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>1.5</td>
<td>10</td>
<td>2 h</td>
<td>41</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>4 h</td>
<td>82</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>8 h</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>1.5</td>
<td>0</td>
<td>26</td>
<td>47</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction analysis at 30 °C showed that the same results can be obtained using either 1.5 equivalents of the ynamide 1 or 1.5 equivalents of the trifluoromethyl ketone 2 (Table 5.2,
entries 1 – 2). Monitoring the reaction by $^1$H and $^{19}$F NMR showed that the catalysis is ligand accelerated. In the presence of 10 mol% of $\text{L8}$ the reaction is almost complete after 8 hours while in the absence of the ligand the conversion to 3 is only 47% after 26 hours (entries 5 – 6). The ynamide addition does not occur in the absence of a zinc catalyst and the replacement of $\text{Zn(O Tf}_2$ by $\text{Et}_2\text{Zn}$ gave racemic 3. When phenylacetylene was employed in the base-free procedure instead of ynamide 1, conversion was sluggish with low yield of the propargylic alcohol.

![5: BisProPhenol ligand](image)

![4: BisProPhenol ligand + Zn(O Tf)_2](image)

![3: BisProPhenol ligand + Zn(O Tf)_2 + ynamide stirred for 1 h](image)

![2: BisProPhenol ligand + Zn(O Tf)_2 + ynamide stirred for 5 h](image)

![1: Ynamide](image)

Figure 5.1. $^1$H NMR spectroscopic analysis of $\text{Zn(O Tf}_2$, L8 and ynamide 1 interactions.
Table 5.3. Asymmetric catalytic addition of ynamides to trifluoromethyl ketones.

\[
\begin{align*}
\text{R} & \quad \text{CF}_3 \quad \text{ketone} \\
\text{H} & \quad \text{H} \quad \text{β-Hydroxy ynamide} \\
\text{Zn(OEt)}_2, \text{ L8} (10 \text{ mol%)} \\
\text{CH}_2\text{Cl}_2, -20 \degree \text{C, 24 h} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>CF₃ ketone</th>
<th>β-Hydroxy ynamide</th>
<th>Yield(^a) (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>7</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>9</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>11</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>13</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>15</td>
<td>97</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 5.3. (Cont.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>CF&lt;sub&gt;3&lt;/sub&gt; ketone</th>
<th>β-Hydroxy ynamide</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>99</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>91</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> 0 °C, 50 h. The absolute configuration of 3 was determined by crystallographic analysis of the partial reduction and hydroacyloxylation derivatives 28 and 30.

<sup>1</sup>H NMR spectroscopic analysis of a stoichiometric mixture of zinc triflate, the Bis-ProPhenol ligand, and ynamide 1 showed formation of a Zn-<sup>L8</sup> complex in deuterated chloroform which is evident from line broadening and shifts of ligand NMR signals. No sign of coordination and activation of the ynamide in the presence of Zn-<sup>L8</sup> was observed. The signal of the terminal alkyne proton remained unchanged after 5 hours (Figure 5.1). The reaction presumably involves an intermediate side-on or end-on zinc-ynamide species which does not
form in the absence of the trifluoromethyl ketone. In accordance with a study by Cozzi,\textsuperscript{225} the substrate may, therefore, play a pivotal role in promoting the ynamide activation and its own consumption. Altogether, these observations reveal the strikingly different reactivity of terminal ynamides compared to simple alkynes and the distinct behavior of trifluoromethyl ketones. Results of the substrate scope evaluation for the asymmetric addition of readily available ynamides to \textit{2} are summarized in Table 5.3. The introduction of simple trifluoroacetophenone analogues gave the β-hydroxy ynamides \textit{5}, \textit{7}, and \textit{9} in 96 – 97\% yield and in 94 – 96\% ee (entries 2 – 4). Similar results were obtained with a series of functionalized analogues (entries 5 – 12).

The intrinsic synthetic value of the β-hydroxy ynamides shown below stems from the high density of functional groups that are combined into a relatively small chiral building block. The trifluoromethylated tertiary chiral alcohol moiety is an increasingly attractive motif with potential use in medicinal applications,\textsuperscript{226} and the adjacent ynamide unit provides unique synthetic versatility that is orthogonal to the chemistry of C-substituted propargylic alcohols. With this in mind, transformations that would generate unprecedented access to new or generally challenging structures were investigated. In contrast to alkynes, the ynamide unit can be considered a masked amide bond, thus a method to exploit regioselective hydration was developed. After screening of several acids and solvents, smooth conversion of \textit{3} into \textit{26} was achieved in the presence of dilute sulfuric acid at room temperature. β-Hydroxy sulfonamide \textit{26} was obtained in 91\% yield and without compromising the ee value of the starting material (Scheme 5.2, equation 1).
Scheme 5.2. Selective transformations of β-hydroxy ynamides.

\[ \text{Regioselective Hydration} \]

(1) \[ \text{Ts} - N - \text{Bu} \quad 3, 94\% \text{ ee} \]

\[ \text{1 M H}_2\text{SO}_4 \quad \text{ACN, 25 °C, 1 h.} \]

\[ \begin{align*}
\text{Ts} - N - \text{Bu} & \rightarrow \text{Ts} - N - \text{Bu} \\
\text{26, 91\%, 94\% ee}
\end{align*} \]

\[ \text{Stereoselective Reduction} \]

(2) \[ \text{Ts} - N - \text{Bu} \quad 3, 94\% \text{ ee} \]

\[ \text{Red-Al} \quad \text{THF, 0 °C, 2 h} \]

\[ \text{Ts} - N - \text{Bu} \quad 27, 82\%, 93\% \text{ ee} \]

\[ \text{Stereoselective Hydroacyxylation} \]

(3) \[ \text{Ts} - N - \text{Bu} \quad 3, 94\% \text{ ee} \]

\[ \text{H}_2, (10 \text{ bar}) \quad \text{Pd/C (5 wt\%)} \quad \text{CH}_2\text{Cl}_2, 25 \text{ °C, 15 h} \]

\[ \text{Bu} - \text{N} - \text{Ts} \quad 28, 86\%, 93\% \text{ ee} \quad 89:11 \text{ (Z/E)} \]

\[ \text{Stereoselective Hydroacyxylation} \]

(4) \[ \text{Ts} - N - \text{Bu} \quad 3, 87\% \text{ ee} \]

\[ \text{AcOH (10 equiv.)} \quad \text{CH}_2\text{Cl}_2, 25 \text{ °C, 65 h} \]

\[ \text{Bu} - \text{N} - \text{Ts} \quad 29, 89\%, 88\% \text{ ee} \quad >99:1 \text{ (E/Z)} \]

(5) \[ \text{Ts} - N - \text{Bu} \quad 3, 87\% \text{ ee} \]

\[ \text{PhCO}_2\text{H (10 equiv.)} \quad \text{CH}_2\text{Cl}_2, 25 \text{ °C, 65 h} \]

\[ \text{Bu} - \text{N} - \text{Ts} \quad 30, 93\%, 89\% \text{ ee} \quad >99:1 \text{ (E/Z)} \]

\[ N\text{-Tosyl } \beta\text{-hydroxy enamines were considered next as they are viable substrates for the synthesis of a variety of compounds, including aminocyclopropyl carbinols and 1,3-amino alcohols.}^{227} \text{ Urabe and co-workers originally developed a diastereoselective method that utilizes a chiral sulfonamide auxiliary to afford } N\text{-tosyl } (E)\text{-β-hydroxy enamines through Ti-mediated ynamide addition to aldehydes.}^{228} \text{ Walsh and co-workers introduced an asymmetric route toward} \]

\[ 114 \]
a series of $E$-isomers that is based on sequential hydroboration of internal $N$-tosyl ynamides, boron-to-zinc transmetalation, and catalytic nucleophilic addition to aldehydes in one pot.\textsuperscript{17a} This method provides stereoselective access to both ($Z$-) and ($E$-) $N$-tosyl $\beta$-hydroxy enamines with a tertiary chiral carbinol group. Selective reduction of $3$ with either Red-Al or by Pd-catalyzed hydrogenation gave $27$ and $28$ in one step in 82 and 86\% yield and 93\% ee (Scheme 5.2, equations 2 – 3).

Finally, the possibility of a mild diastereoselective addition of carboxylic acids to ynamide $3$ was explored. The Lam research group was the first to prepare $\alpha$-acyloxyenamides by palladium-catalyzed hydroacyloxylation of ynamides at 70 °C and demonstrated the synthetic utility of these $N,O$-ketene acetals in rearrangement reactions.\textsuperscript{229} Recently, a metal-free procedure that gives moderate to high yields although at even higher temperatures (100 °C) was reported.\textsuperscript{230} Hydroacyloxylation of $3$ with acetic and benzoic acid were accomplished in dichloromethane at room temperature without loss of the enantiomeric purity. In both cases, the $E$-isomers were produced with high diastereoselectivity ($E/Z$$>$$99$:1) and $29$ and $30$ were obtained in yields of 89\% and 93\%, respectively (Scheme 5.2, equations 4 – 5).\textsuperscript{231}

![Figure 5.2. X-ray structures of (S, Z)-28 (left) and (S,E)-30 (right). Selected bond lengths for 28 [Å]: C=C: 1.325, N-C(sp$^2$): 1.437; 30: C=C: 1.319, N-C(sp$^2$): 1.421, O-C(sp$^2$): 1.411.](image-url)
Slow evaporation of concentrated solutions of 28 and 30 in chloroform and dichloromethane, respectively, gave single crystals suitable for X-ray determination of the absolute and relative configurations (Figure 5.2). These enamides have relatively short C=C bonds (1.319–1.325 Å) and significantly longer C—N bonds (1.421–1.437 Å) compared to typical enamines, which explains the increased thermal stability and ease of isolation.

5.3. Conclusion

The first catalytic enantioselective addition of terminal ynamides to trifluoromethyl ketones has been accomplished. The reaction occurs in the presence of catalytic amounts of Zn(OTf)₂, a bis(prolinol)phenol ligand, and triethyl phosphate, and it provides practical access to synthetically versatile CF₃-substituted tertiary propargylic alcohols that are obtained in high yields and enantiomeric excess. The utility of the tertiary-β-hydroxy-β-trifluoromethyl ynamides was demonstrated with highly regioselective hydration, stereoselective reductions, and hydroacyloxyations, which afforded trifluoromethylated chiral alcohols with adjacent Z- and E-enamide, amide and N,O-ketene acetal functionalities.

5.4. Experimental section

5.4.1. Synthetic procedures

Commercially available trifluoromethyl ketones and solvents were used as purchased without further purification. NMR spectra were obtained at 400 MHz (¹H NMR) and 100 MHz (¹³C NMR) in deuterated chloroform. Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 40-63 μm) as described below.
General zinc catalyzed ynamide addition procedure.

Zinc triflate (7.4 mg, 0.02 mmol), \((R, R)-(-)-2,6\)-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol (14.8 mg, 0.022 mmol), \(N\)-butyl-\(N\)-ethynyl-4-tolylsulfonamide (75.3 mg, 0.30 mmol), ketone (0.20 mmol) and triethyl phosphate (7.3 mg, 0.04 mmol) were dissolved in 1,2-dichloroethane (0.2 mL) under nitrogen atmosphere. The mixture was stirred at -20 to -17 °C for 22-24 h. The crude mixture was purified by flash chromatography with 1% NEt₃ in CH₂Cl₂ as mobile phase on silica gel.

Acid mediated hydration of \(N\)-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-\(N\)-butyl-4-toluenesulfonamide.

To a solution of \(N\)-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-\(N\)-butyl-4-toluenesulfonamide (90 mg, 0.21 mmol) in CH₃CN (2 mL) was added 1M H₂SO₄ (1 mL). The resulting mixture was stirred vigorously for 1 hour and then extracted with Et₂O (3 x 15 mL). The combined organics were washed with brine (1 x 5 mL), and dried over MgSO₄ followed by removal of solvents under reduced pressure. The resulting colorless oil was purified by flash chromatography on silica gel (2:1 hexanes:CH₂Cl₂) to give 86 mg (0.19 mmol, 91%) of a cloudy white oil (Scheme 2, equation 1).

Stereoselective partial reduction of \(N\)-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-\(N\)-butyl-4-toluenesulfonamide.

a) Formation of the (E)-enamide

Adopting a procedure from Meyer,²³² a solution of \(N\)-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-\(N\)-butyl-4-toluenesulfonamide (120 mg, 0.28 mmol) in THF (2 mL) was added to a solution of Red-Al (0.12 mL, 3.4 M in toluene) in THF (2 mL) at 0 °C under nitrogen atmosphere. After stirring for 1 hour an additional portion of Red-Al (0.12 mL, 3.4 M in toluene) was added and the solution was stirred for an additional 1 hour. A saturated solution of
Rochelle’s salt (10 mL) was added and the resulting mixture was stirred for 2 hours and then extracted with EtOAc (3 x 15 mL). The combined extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The resulting cloudy oil was purified by flash chromatography on silica gel with hexanes and CH$_2$Cl$_2$ (6:4) as the mobile phase to give 99 mg (0.23 mmol, 82%) of a colorless oil (Scheme 2, equation 2).

b) Formation of the (Z)-enamide

$N$-(3-Phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-4-toluenesulfonamide (80 mg, 0.19 mmol) and 10 wt.% Pd on carbon (4 mg, 5 wt.%) were added to CH$_2$Cl$_2$ (15 mL) and stirred under H$_2$ atmosphere (10 bar) for 15 hours. The mixture was filtered through celite and concentrated under reduced pressure. The resulting white solid was purified by flash chromatography on silica gel with hexanes and CH$_2$Cl$_2$ (4:3) as the mobile phase to give 69 mg (0.16 mmol, 84%, 89:11 Z:E) of a white solid (Scheme 2, equation 3).

Stereoselective acylation of $N$-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-4-toluenesulfonamide

To a solution of $N$-(3-phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-4-toluenesulfonamide (87 mg, 0.20 mmol) in CH$_2$Cl$_2$ were added 8-10 equivalents of a carboxylic acid. The resulting mixture was stirred for 3 days and then purified directly by flash chromatography on silica gel with CH$_2$Cl$_2$: hexanes (1:1) as the mobile phase (Scheme 2, equations 4 – 5).

5.4.2. Product characterization.

$N$-(3-Phenyl-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-4-toluenesulfonamide, 3.

The reaction with 2,2,2-trifluoroacetophenone (35 mg, 0.20 mmol) was performed using $N$-butyl-$N$-ethynyl-4-toluenesulfonamide (75 mg, 0.30 mmol) at -20 ºC to give 82 mg (0.19 mmol,
96%, 96% ee) of a colorless oil after 24 hours.\(^1\)H NMR (400 MHz) \(\delta = 7.76\) (d, \(J = 8.1\) Hz, 2H), 7.69 (m, 2H), 7.43 – 7.36 (m, 3H), 7.32 (d, \(J = 8.1\) Hz, 2H), 3.44 – 3.32 (m, 2H), 3.05 (s, 1H), 3.05 (s, 3H), 1.67 – 1.58 (m, 2H), 1.40 – 1.29 (m, 2H), 0.90 (t, \(J = 7.3\) Hz, 3H).\(^{13}\)C NMR (100 MHz) \(\delta = 145.0, 135.4, 134.3, 129.9, 129.4, 128.2, 127.7, 127.2, 123.4\) (q, \(J = 285.6\) Hz), 81.7, 73.4 (q, \(J = 32.5\) Hz), 67.4, 50.9, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. \(t_1 = 6.4\) min (minor), \(t_2 = 9.9\) min (major). \(\alpha = 2.18\). Anal. Calcd. for C\(_{21}\)H\(_{22}\)F\(_3\)NO\(_3\)S: C, 59.28; H, 5.21; N, 3.29. Found: C, 59.02; H, 5.12; N, 3.29.

\(\text{N-(3'-(3'-Tolyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-N-butyl-4-toluenesulfonamide, 5.}\)

The reaction with 3’-methyl-2,2,2-trifluoroacetophenone (38 mg, 0.20 mmol) was performed using N-butyl-N-ethynyl-4-toluenesulfonamide (75 mg, 0.30 mmol) at -20 °C to give 85 mg (0.19 mmol, 97%, 95% ee) of a colorless oil after 24 hours.\(^1\)H NMR (400 MHz) \(\delta = 7.76\) (d, \(J = 8.3\) Hz, 2H), 7.53 (m, 1H), 7.48 (m, 1H), 7.35 – 7.26 (m, 3H), 7.22 (m, 1H), 3.16 (s, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 1.67 – 1.58 (m, 2H), 1.40 – 1.29 (m, 2H), 0.90 (t, \(J = 7.3\) Hz, 3H).\(^{13}\)C NMR (100 MHz) \(\delta = 145.0, 137.9, 135.3, 134.3, 130.2, 129.9, 128.0, 127.7, 127.6, 124.3, 123.4\) (q, \(J = 284.5\) Hz), 81.6, 73.4 (q, \(J = 32.0\) Hz), 67.5, 50.9, 29.8, 21.7, 21.5, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. \(t_1 = 6.3\) min (minor), \(t_2 = 7.4\) min (major). \(\alpha = 1.34\). Anal. Calcd. for C\(_{22}\)H\(_{24}\)F\(_3\)NO\(_3\)S: C, 60.12; H, 5.50; N, 3.19. Found: C, 60.06; H, 5.88; N, 3.25.

\(\text{N-(3-(4'-Tolyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-N-butyl-4-toluenesulfonamide, 7.}\)

The reaction with 4’-methyl-2,2,2-trifluoroacetophenone (38 mg, 0.20 mmol) was performed using N-butyl-N-ethynyl-4-toluenesulfonamide (75 mg, 0.30 mmol) at -20 °C to give 85 mg (0.19 mmol, 97%, 95% ee) of a colorless oil after 24 hours.\(^1\)H NMR (400 MHz) \(\delta = 7.76\) (d, \(J = 8.1\) Hz, 2H), 7.69 (m, 2H), 7.43 – 7.36 (m, 3H), 7.32 (d, \(J = 8.1\) Hz, 2H), 3.44 – 3.32 (m, 2H), 3.05 (s, 1H), 3.05 (s, 3H), 1.67 – 1.58 (m, 2H), 1.40 – 1.29 (m, 2H), 0.90 (t, \(J = 7.3\) Hz, 3H).\(^{13}\)C NMR (100 MHz) \(\delta = 145.0, 135.4, 134.3, 129.9, 129.4, 128.2, 127.7, 127.2, 123.4\) (q, \(J = 285.6\) Hz), 81.7, 73.4 (q, \(J = 32.5\) Hz), 67.4, 50.9, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. \(t_1 = 6.4\) min (minor), \(t_2 = 9.9\) min (major). \(\alpha = 2.18\). Anal. Calcd. for C\(_{21}\)H\(_{22}\)F\(_3\)NO\(_3\)S: C, 59.28; H, 5.21; N, 3.29. Found: C, 59.02; H, 5.12; N, 3.29.
86 mg (0.19 mmol, 97%, 94% ee) of a colorless oil after 24 hours. \( ^1 \text{H NMR (400 MHz)} \) \( \delta = 7.76 \) (d, \( J = 8.3 \) Hz, 2H), 7.57 (d, \( J = 8.0 \) Hz, 2H), 7.33 (d, \( J = 8.2 \) Hz, 2H), 7.20 (d, \( J = 8.0 \) Hz, 2H), 3.44 – 3.31 (m, 2H), 3.00 (s, 1H), 2.45 (s, 3H), 2.38 (s, 3H), 1.68 – 1.57 (m, 2H), 1.40 – 1.27 (m, 2H), 0.90 (t, \( J = 7.3 \) Hz, 3H). \( ^{13} \text{C NMR (100 MHz)} \) \( \delta = 145.0, 139.4, 134.3, 132.5, 129.9, 128.9, 127.7, 127.0, 123.4 \) (q, \( J = 285.0 \) Hz), 81.5, 73.3 \( (q, J = 32.1 \) Hz), 67.5, 50.9, 29.8, 21.7, 21.2, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. \( t_1 = 6.3 \) min (minor), \( t_2 = 9.8 \) min (major). \( \alpha = 2.22 \). Anal. Calcd. for C\(_{22}\)H\(_{24}\)F\(_3\)NO\(_3\): C, 60.12; H, 5.50; N, 3.19. Found: C, 59.76; H, 5.84; N, 3.28.

**N-(3-**\( ^4' \)-**Tert-butylphenyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)**-*N*-butyl-4-toluenesulfonamide, 9.

The reaction with \( 4' \)-**tert**-butyl-2,2,2-trifluoroacetophenone (46 mg, 0.20 mmol) was performed using \( N \)-butyl-\( N \)-ethynyl-4-toluenesulfonamide (75 mg, 0.30 mmol) at -18 °C to give 92 mg (0.19 mmol, 95%, 96% ee) of a colorless oil after 24 hours. \( ^1 \)H NMR (400 MHz) \( \delta =7.77 \) (d, \( J = 8.3 \) Hz, 2H), 7.60 (d, \( J = 8.5 \) Hz, 2H), 7.41 (d, \( J = 8.4 \) Hz, 2H), 7.33 (d, \( J = 8.6 \) Hz, 2H), 3.44 – 3.32 (m, 2H), 3.02 (s, 1H), 2.45 (s, 3H), 1.68 – 1.58 (m, 2H), 1.40 – 1.30 (m, 2H), 1.33 (s, 9H), 0.90 (t, \( J = 7.4 \) Hz, 3H). \( ^{13} \)C NMR (100 MHz) \( \delta = 152.53, 145.0, 134.3, 132.4, 129.9, 127.7, 126.9, 125.1, 123.5 \) (q, \( J = 284.6 \) Hz), 81.5, 73.3 \( (q, J = 32.1 \) Hz), 67.5, 50.9, 34.6, 31.3, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Chiralcel OD using hexanes: EtOH (98:2) as the mobile phase at 1.0 mL/min. \( t_1 = 6.9 \) min (minor), \( t_2 = 9.3 \) min (major). \( \alpha = 1.66 \). Anal. Calcd. for C\(_{25}\)H\(_{30}\)F\(_3\)NO\(_3\): C, 62.35; H, 6.28; N, 2.91. Found: C, 62.32; H, 6.58; N, 3.01.
\(N-(3-(4'-\text{Fluorophenyl})-4,4,4\text{-trifluoro}-3\text{-hydroxy-but-1-yn-1-yl})-N\text{-butyl-4-toluenesulfonamide}, 11.\)

The reaction with 4'-fluoro-2,2,2-trifluoroacetophenone (39 mg, 0.20 mmol) was performed using \(N\text{-butyl}-N\text{-ethynyl-4-toluenesulfonamide}\) (75 mg, 0.30 mmol) at -20 °C to give 86 mg (0.19 mmol, 97%, 94% ee) of a colorless oil after 24 hours.\(^1\)H NMR (400 MHz) \(\delta = 7.75\) (d, \(J = 8.3\) Hz, 2H), 7.67 (m, 2H), 7.33 (d, \(J = 8.2\) Hz, 2H), 7.08 (m, \(J = 8.6\) Hz, 2H), 3.45 – 3.30 (m, 2H), 3.03 (s, 1H), 2.46 (s, 3H), 1.67 – 1.58 (m, 2H), 1.40 – 1.28 (m, 2H), 0.90 (t, \(J = 7.4\) Hz, 3H).\(^13\)C NMR (100 MHz) \(\delta = 164.64, 162.16, 145.2, 134.3, 131.3, 129.9, 129.3\) (d, \(J = 85.4\) Hz), 127.6, 123.5 (q, \(J = 284.0\) Hz), 115.1 (d, \(J = 21.7\) Hz), 81.9, 73.0 (q, \(J = 32.6\) Hz), 67.2, 50.9, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min \(t_1 = 6.2\) min (minor), \(t_2 = 7.1\) min (major). \(\alpha = 1.32.\)

Anal. Calcd. for \(C_{21}H_{21}F_{4}NO_{3}S:\) C, 56.88; H, 4.77; N, 3.16. Found: C, 56.78; H, 5.13; N, 3.25.

\(N-(3-(4'-\text{Chlorophenyl})-4,4,4\text{-trifluoro}-3\text{-hydroxy-but-1-yn-1-yl})-N\text{-butyl-4-toluenesulfonamide}, 13.\)

The reaction with 4'-chloro-2,2,2-trifluoroacetophenone (44 mg, 0.21 mmol) was performed using \(N\text{-butyl}-N\text{-ethynyl-4-toluenesulfonamide}\) (75 mg, 0.30 mmol) at -20 °C to give 86 mg (0.20 mmol, 95%, 93% ee) of a colorless oil after 24 hours.\(^1\)H NMR (400 MHz) \(\delta = 7.74\) (d, \(J = 8.3\) Hz, 2H), 7.62 (d, \(J = 8.6\) Hz, 2H), 7.36 (d, \(J = 8.6\) Hz, 2H), 7.32 (d, \(J = 8.3\) Hz, 2H), 3.44 – 3.30 (m, 2H), 3.40 (s, 1H), 2.45 (s, 3H), 1.67 – 1.57 (m, 2H), 1.40 – 1.28 (m, 2H), 0.90 (t, \(J = 7.4\) Hz, 3H).\(^13\)C NMR (100 MHz) \(\delta = 145.1, 135.6, 134.2, 134.0, 129.9, 128.6, 128.3, 127.6, 123.2\) (q, \(J = 284.7\) Hz), 81.9, 72.9 (q, \(J = 32.6\) Hz), 67.0, 50.8, 29.8, 21.6, 19.3, 13.4. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (95:5) as the mobile
phase at 1.0 mL/min. $t_1 = 8.2$ min (minor), $t_2 = 9.6$ min (major). $\alpha = 1.29$. Anal. Calcd. for C$_{21}$H$_{21}$ClF$_3$NO$_3$S: C, 54.84; H, 4.60; N, 3.05. Found: C, 54.71; H, 4.77; N, 3.09.

$N$-(3-(4'-Bromophenyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-$N$-toluenesulfonamide, 15.

The reaction with 4'-bromo-2,2,2-trifluoroacetophenone (50 mg, 0.20 mmol) was performed using $N$-butyl-$N$-ethynyl-4-toluenesulfonamide (75 mg, 0.30 mmol) at -17 °C to give 98 mg (0.19 mmol, 97%, 90% ee) of a colorless oil after 24 hours.$^1$H NMR (400 MHz) \( \delta = 7.74 \) (d, $J = 8.3$ Hz, 2H), 7.58 – 7.49 (m, 4H), 7.33 (d, $J = 8.3$ Hz, 2H), 3.44 – 3.31 (m, 2H), 3.32 (s, 1H), 2.46 (s, 3H), 1.67 – 1.57 (m, 2H), 1.40 – 1.28 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H).$^{13}$C NMR (100 MHz) \( \delta = 145.2, 134.6, 134.2, 131.3, 129.9, 129.0, 127.6, 123.9, 123.1 \) (q, $J = 284.7$ Hz), 82.0, 73.0 (q, $J = 32.6$ Hz), 67.0, 50.9, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (98:2) as the mobile phase at 1.0 mL/min. $t_1 = 17.1$ min (minor), $t_2 = 18.8$ min (major). $\alpha = 1.12$. Anal. Calcd. for C$_{21}$H$_{21}$BrF$_3$NO$_3$S: C, 50.01; H, 4.20; N, 2.78. Found: C, 50.08; H, 4.54; N, 2.73.

$N$-(3-(4'-Trifluoromethylphenyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-$N$-toluenesulfonamide, 17.

The reaction with 4'-trifluoromethyl-2,2,2-trifluoroacetophenone (50 mg, 0.21 mmol) was performed using $N$-butyl-$N$-ethynyl-4-toluenesulfonamide (77 mg, 0.31 mmol) at -18 °C to give 98 mg (0.20 mmol, 99%, 92% ee) of a colorless oil after 22 hours.$^1$H NMR (400 MHz) \( \delta = 7.82 \) (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.66 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 3.49 (s, 1H), 3.45 – 3.33 (m, 2H), 2.45 (s, 3H), 1.66 – 1.58 (m, 2H), 1.39 – 1.29 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H).$^{13}$C NMR (100 MHz) \( \delta = 145.2, 139.3, 134.1, 131.6 \) (q, $J = 32.6$ Hz), 129.9, 127.7, 127.6, 125.1 (q, $J = 3.8$ Hz), 123.8 (q, $J = 270.9$ Hz), 123.1 (q, $J = 284.5$ Hz), 82.2, 73.0
(q, \( J = 32.5 \) Hz), 66.8, 50.8, 29.8, 21.6, 19.3, 13.4. The ee was determined by HPLC on Phenomenex® Cellulose-4 using hexanes: EtOH (98:2) as the mobile phase at 1.0 mL/min. \( t_1 = 13.7 \) min (minor), \( t_2 = 14.6 \) min (major). \( \alpha = 1.09. \) Anal. Calcd. for C\(_{22}\)H\(_{21}\)F\(_6\)NO\(_3\)S: C, 53.55; H, 4.29; N, 2.84. Found: C, 53.54; H, 4.42; N, 2.87.

\( N-(3-(4'-\text{Cyanophenyl})-4,4,4-\text{trifluoro}-3-\text{hydroxy-but-1-yn-1-yl})-\text{N-butyl-4-toluenesulfonamide}, 19. \)

The reaction with 4'-cyano-2,2,2-trifluoroacetophenone (42 mg, 0.21 mmol) was performed using N-butyl-N-ethynyl-4-toluencesulfonamide (77 mg, 0.31 mmol) at -17 °C to give 86 mg (0.19 mmol, 91%, 90% ee) of a colorless oil after 22 hours.\(^1\)H NMR (400 MHz) \( \delta =7.83 \) (d, \( J = 8.2 \) Hz, 2H), 7.77 – 7.67 (m, 4H), 7.34 (d, \( J = 8.1 \) Hz, 2H), 3.60 (s, 1H), 3.46 – 3.30 (m, 2H), 2.46 (s, 3H), 1.66 – 1.57 (m, 2H), 1.38 – 1.27 (m, 2H), 0.90 (t, \( J = 7.4 \), 3H).\(^{13}\)C NMR (100 MHz) \( \delta = 145.3, 140.4, 134.1, 131.9, 129.9, 128.1, 127.5, 123.0 \) (q, \( J = 285.6 \) Hz), 118.2, 113.4, 82.5, 72.9 (q, \( J = 32.5 \) Hz), 50.8, 61.2, 50.8, 29.8, 21.6, 19.3, 13.4. The ee was determined by HPLC on Phenomenex® Cellulose-4 using hexanes: EtOH (97:3) as the mobile phase at 1.0 mL/min. \( t_1 = 23.4 \) min (minor), \( t_2 = 26.3 \) min (major). \( \alpha = 1.14. \) Anal. Calcd. for C\(_{22}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_3\)S: C, 58.66; H, 4.70; N, 6.22. Found: C, 58.77; H, 5.10; N, 6.14.

\( N-(3-(4'-\text{Ethoxycarbonylphenyl})-4,4,4-\text{trifluoro}-3-\text{hydroxy-but-1-yn-1-yl})-\text{N-butyl-4-toluenesulfonamide}, 21. \)

The reaction with 4'-ethoxy-2,2,2-trifluoroacetophenone (50 mg, 0.20 mmol) was performed using N-butyl-N-ethynyl-4-toluencesulfonamide (75 mg, 0.30 mmol) at -17 °C to give 99 mg (0.20 mmol, 99%, 89% ee) of a colorless oil after 22 hours.\(^1\)H NMR (400 MHz) \( \delta =8.06 \) (d, \( J = 8.5 \) Hz, 2H), 7.79 – 7.71 (m, 4H), 7.33 (d, \( J = 8.1 \) Hz, 2H), 4.40 (q, \( J = 7.1 \) Hz, 2H), 3.73 (s, 1H), 3.46 – 3.31 (m, 2H), 2.46 (s, 3H), 1.68 – 1.56 (m, 2H), 1.41 (t, \( J = 7.1 \) Hz, 3H), 1.38 – 1.29 (m,
$^1$H NMR (400 MHz) $\delta = 7.75$ (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 3.44 – 3.30 (m, 2H), 3.39 (s, 1H), 2.50 (s, 3H), 2.45 (s, 3H), 1.66 – 1.58 (m, 2H), 1.39 – 1.28 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz) $\delta = 145.9, 141.2, 134.9, 132.7, 130.6, 128.3, 128.2, 126.3, 124.0 (q, $J = 285.8$ Hz), 82.0, 73.5 (q, $J = 32.5$ Hz), 67.7, 51.1, 29.9, 21.8, 19.4, 15.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. $t_1 = 10.9$ min (minor), $t_2 = 18.8$ min (major). $\alpha = 2.06$. Anal. Calcd. for $C_{22}H_{24}F_3NO_3S_2$: C, 57.94; H, 5.27; N, 2.82. Found: C, 57.92; H, 5.53; N, 2.88.

$N$-((4'-Methoxyphenyl)-4,4,4-trifluoro-3-hydroxy-but-1-yn-1-yl)-$N$-butyl-4-toluenesulfonamide, 25.

The reaction with 4'-methoxy-2,2,2-trifluoroacetophenone (41 mg, 0.20 mmol) was performed using $N$-butyl-$N$-ethynyl-4-toluenesulfonamide (74 mg, 0.29 mmol) at 0 °C to give 85
mg (0.19 mmol, 91%, 85% ee) of a colorless oil after 52 hours. $^1$H NMR (400 MHz) $\delta = 7.76$ (d, $J = 8.3$ Hz, 2H), 7.61 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 2H), 6.91 (d, $J = 8.9$ Hz, 2H), 3.82 (s, 3H), 3.44 – 3.30 (m, 2H), 3.26 (s, 1H), 2.44 (s, 3H), 1.67 – 1.57 (m, 2H), 1.39 – 1.28 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz) $\delta = 161.0, 145.6, 134.7, 130.4, 129.0, 128.1, 128.0, 123.9 (q, $J = 285.6$ Hz), 113.9, 81.8, 73.4 (q, $J = 32.4$ Hz), 67.7, 55.5, 51.1, 29.8, 21.7, 19.4, 13.5. The ee was determined by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (95:5) as the mobile phase at 1.0 mL/min. $t_1 = 13.8$ min (minor), $t_2 = 26.2$ min (major). $\alpha = 2.20$. Anal. Calcd. for C$_{22}$H$_{24}$F$_3$NO$_4$S: C, 58.01; H, 5.31; N, 3.08. Found: C, 57.70; H, 5.54; N, 3.13.

$N$-Butyl-4,4,4-trifluoro-3-hydroxy-3-phenyl-$N$-tosylbutanamide, 26.

$^1$H NMR (400 MHz) $\delta = 7.76$ (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.34 – 7.21 (m, 5H), 5.45 (s, 1H), 3.86 (d, $J = 17.1$ Hz, 1H), 3.79 – 3.63 (m, 2H), 3.23 (d, $J = 17.0$ Hz, 1H), 2.48 (s, 3H), 1.56 – 1.36 (m, 2H), 1.28 – 1.14 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz) $\delta = 171.5, 145.7, 137.1, 136.2, 130.2, 128.6, 128.3, 127.4, 126.2, 124.2 (q, $J = 283.5$ Hz), 76.2 (q, $J = 28.7$ Hz), 46.8, 39.4, 31.3, 29.7, 21.6, 19.8, 13.5. The ee was determined as 94% ee (starting material: 94% ee) by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (95:5) as the mobile phase at 1.0 mL/min. $t_1 = 8.2$ min (minor), $t_2 = 10.0$ min (major). $\alpha = 1.38$. Anal. Calcd. for C$_{22}$H$_{24}$F$_3$NO$_4$S: C, 56.88; H, 5.46; N, 3.16. Found: C, 57.17; H, 5.78; N, 3.18.

$(E)$-$N$-(4,4,4-Trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl)-$N$-butyl-4-toluenesulfonamide, 27.

$^1$H NMR (400 MHz) $\delta = 7.57$ (d, $J = 8.2$ Hz, 2H), 7.56 – 7.52 (m, 2H), 7.43 – 7.36 (m, 3H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.09 (d, $J = 14.4$ Hz, 1H), 5.24 (d, $J = 14.4$ Hz, 1H), 3.40 – 3.26 (m, 2H), 2.60 (s, 1H), 2.42 (s, 3H), 1.60 – 1.51 (m, 2H), 1.39 – 1.28 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz) $\delta = 140.1, 133.7, 131.9, 128.1, 125.9, 124.9, 124.3, 122.9, 122.8 (q, $J = 1.5$ Hz), 121.0 (q, $J = 284.6$ Hz), 103.0, 72.9 (q, $J = 29.0$ Hz), 41.6, 24.9, 17.6 (q, $J = 1.3$ Hz), 125...
9.6. The ee was determined as 93% ee (starting material: 94% ee) by HPLC on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. $t_1 = 10.0$ min (minor), $t_2 = 14.9$ min (major). $\alpha = 1.75$. Anal. Calcd. for C$_{21}$H$_{24}$F$_3$NO$_3$S: C, 59.00; H, 5.66; N, 3.28. Found: C, 59.17; H, 6.01; N, 3.30.

(Z)-N-(4,4,4-Trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl)-N-butyl-4-toluenesulfonamide, 28.

$^1$H NMR (400 MHz) $\delta = 7.64 – 7.58$ (m, 4H), 7.40 – 7.29 (m, 5H), 6.30 (d, $J = 8.9$Hz, 1H), 5.46 (d, $J = 8.9$ Hz, 1H), 5.41 (s, 1H), 3.00 (m, 1H), 2.75 (m, 1H), 2.44 (s, 3H), 1.10 – 1.01 (m, 4H), 0.69 – 0.63 (m, 3H). $^{13}$C NMR (100 MHz) $\delta = 144.5, 137.7, 133.0, 131.3, 129.8, 129.6, 128.5, 128.0, 127.8, 126.7, 124.7 (q, $J = 285.3$ Hz), 76.5 (q, $J = 28.4$ Hz), 51.0, 29.7, 21.5, 19.6, 13.4. The ee was determined by HPLC as 93% ee (starting material: 94% ee) on Phenomenex® Cellulose-3 using hexanes: EtOH (90:10) as the mobile phase at 1.0 mL/min. $t_1 = 6.5$ min (minor), $t_2 = 7.5$ min (major). $\alpha = 1.33$. Anal. Calcd. for C$_{21}$H$_{24}$F$_3$NO$_3$S: C, 59.00; H, 5.66; N, 3.28. Found: C, 59.23; H, 5.81; N, 3.23. mp 117 – 120 °C.

(E)-N-(2-Acetoxy-4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl)-N-butyl-4-toluenesulfonamide, 29.

Employing acetic acid (103 mg, 1.72 mmol) in the procedure described above gave 88 mg (0.18 mmol, 89%) of a colorless oil. $^1$H NMR (400 MHz) $\delta = 7.75 – 7.63$ (m, 4H), 7.41 – 7.27 (m, 5H), 6.39 (s, 1H), 5.16 (s, 1H), 3.03 (m, 1H), 2.79 (m, 1H), 2.43 (s, 3H), 1.81 (s, 3H), 1.05 – 0.75 (m, 4H), 0.64 – 0.47 (m, 3H). $^{13}$C NMR (100 MHz) $\delta = 168.2, 145.2, 140.6, 138.4, 135.3, 130.0, 129.1, 128.7, 128.4, 127.8, 125.1 (q, $J = 286.8$ Hz), 122.3, 75.5 (q, $J = 29.0$ Hz), 48.7, 29.6, 21.6, 20.4, 19.7, 13.3. The ee was determined as 88% ee (starting material : 87% ee) by HPLC on Chiralcell OJ using hexanes: EtOH (98:2) as the mobile phase at 1.0 mL/min. $t_1 = 11.3$
min (minor), \( t_2 = 14.2 \) min (major). \( \alpha = 1.36 \). Anal. Calcd. for C\(_{23}\)H\(_{26}\)F\(_3\)NO\(_5\)S: C 56.90; H, 5.40; N, 2.88. Found: C, 57.00; H, 5.57; N, 2.91.

\textit{(E)}-N-(2-Benzoyloxy-4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl)-N-butyl-4-toluenesulfonamide, 30.

Employing benzoic acid (244 mg, 2.0 mmol) in the procedure described above gave 105 mg (0.19 mmol, 93\%) of a white solid.\(^1\)\(^1\)H NMR (400 MHz) \( \delta = 7.82 – 7.71 \) (m, 4H), 7.56 (m, 1H) 7.46 – 7.27 (m, 9H), 6.58 (s, 1H), 5.40 (s, 1H), 3.23 (m, 1H), 2.86 (m, 1H), 2.42 (s, 3H), 1.15 – 0.85 (m, 4H), 0.65 – 0.45 (m, 3H).\(^{13}\)C NMR (100 MHz) \( \delta = 164.1, 145.2, 140.5, 138.6, 135.8, 134.6, 130.4, 129.1, 128.9, 128.7, 128.5, 127.9, 125.2 (q, J = 287.0 Hz), 123.1, 76.5 (q, J = 28.7 Hz), 48.6, 29.8, 21.6, 19.8, 13.3. The ee was determined by HPLC as 89\% ee (starting material: 87\% ee) on Phenomenex® Cellulose-4 using hexanes: EtOH (98:2) as the mobile phase at 1.0 mL/min. \( t_1 = 12.4 \) min (minor), \( t_2 = 13.4 \) min (major). \( \alpha = 1.11 \). Anal. Calcd. for C\(_{28}\)H\(_{28}\)F\(_3\)NO\(_5\)S: C, 61.42; H, 5.15; N, 2.56. Found: C, 61.33; H, 5.36; N, 2.56. mp 120 – 123 °C.

\textbf{5.4.3. Crystallographic analysis}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.3.png}
\caption{Crystal structure of (S, Z)-N-butyl-4-methyl-N-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl)benzenesulfonamide, 28.}
\end{figure}
A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in CHCl₃ (Figure 5.3). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the APEX 2 program. The structures were solved by intrinsic phasing and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: C₂₁H₂₄F₃NO₃S, M = 427.42, colorless needle, 0.04 x 0.06 x 0.18 mm³, orthorhombic, space group P2₁2₁2₁, a = 5.6103(5), b = 10.5760(9), c = 36.083(3) Å, V = 2141.0(3) Å³, Z = 4. Absolute structure parameter = 0.01(3).

![Figure 5.4. Crystal Structure of (S,E)-2-((N-butyl-4-methylphenyl)sulfonamido)-4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-en-1-yl benzoate, 30.](image)

A single crystal was obtained by slow evaporation of a solution of the chiral alcohol in CH₂Cl₂ (Figure 5.4). Single crystal X-ray analysis was performed at 173 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the APEX 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: C₂₁H₂₄F₃NO₃S, M = 427.42, colorless needle, 0.04 x 0.06 x 0.18 mm³, orthorhombic, space group P2₁2₁2₁, a = 5.6103(5), b = 10.5760(9), c = 36.083(3) Å, V = 2141.0(3) Å³, Z = 4. Absolute structure parameter = 0.01(3).
C$_{28}$H$_{30}$F$_3$NO$_5$S, CH$_2$Cl$_2$, $M = 632.50$, colorless needle, 0.04 x 0.05 x 0.18 mm$^3$, orthorhombic, space group $P2_12_12_1$, $a = 7.6073(6)$, $b = 17.9032(13)$, $c = 21.8189(16)$ Å, $V = 2971.6(4)$ Å$^3$, $Z = 4$. Absolute structure parameter = 0.015(10).
References and notes


4 Minto, R. E.; Blacklock, B. J. *Prog. Lipid Res.* **2008**, *47*, 233-306.


106 One example of a palladium catalyzed dimerization of an ynesulfonamide to a 2,4-disulfonamido-1-penten-3-yne has been reported: Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338 – 4341.


202 It was observed that the ynesulfonamide used in this study undergoes thermal decomposition at 60 °C.


231 The hydroacyloxylations were carried out using batches of 3 with slightly lower ee values obtained during reaction optimization studies.
