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S3S63 Terminal Ynamides: Synthesis, Coupling Reactions and Additions to Common Electrophiles

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Abstract

Ynamides consist of a polarized triple bond that is directly attached to a nitrogen atom carrying a sulfonyl, an alkoxycarbonyl, an acyl or another electron withdrawing group. The triple bond polarization renders ynamides broadly useful building blocks with synthetic opportunities that go far beyond traditional alkyne chemistry. The versatile reactivity of ynamides in cycloadditions, cycloisomerizations, regioselective additions with various nucleophiles or electrophiles, ring-closing metathesis, and many other reactions has been investigated in detail during the past decades. A common feature of these methods is that the triple bond is consumed and either cleaved or transformed to a new functionality. The wealth of reports on these ynamide reactions is in stark contrast to the dearth of carbon-carbon bond formations that leave the triple bond of terminal ynamides intact. The recent introduction of effective synthetic methods for the preparation of terminal ynamides has set the stage to fully explore the synthetic potential of this intriguing class of compounds. This digest letter summarizes the most effective routes to terminal ynamides and the current state of selective nucleophilic addition, substitution and coupling reactions, including the first examples of asymmetric synthesis.

Keywords

Terminal ynamides; nucleophilic additions; coupling reactions

1. Introduction

The distinctive chemical properties and synthetic versatility of ynamines and ynamides have attracted rapidly increasing attention among synthetic chemists. The reactivity of the electron-rich, strongly polarized triple bond in ynamines and analogues thereof varies significantly from that of simple alkynes. Ynamines are rather unstable and readily hydrolyze toward amides, which complicates the synthesis, storage and use of these intriguing building blocks. Because the presence of an electron withdrawing acyl or sulfonyl

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group effectively dimishes the triple bond polarization, ynamides have become practical alternatives that facilitate handling and improve reaction control (Figure 1).

The emergence of ynamides in the last 20 years has created new synthetic opportunities and challenges at the same time. Internal ynamides exhibiting a *C*-substituted triple bond have been used in many reactions and have been applied in the total synthesis of natural compounds.[1] In stark contrast to alkynes, which have been employed extensively in Sonogashira couplings and nucleophilic addition 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,[2] and cycloadditions,[3] cycloisomerizations,[4] Heck-Suzuki-Miyaura domino reactions,[5] ring-closing metathesis,[6] radical additions,[7] and titanium-mediated carbon-carbon bond formations are among the most common synthetic transformations.[8] 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 (Scheme 1). This review discusses the current state of terminal ynamide synthesis and focusses on transformations that maintain the alkynyl motif.

2. Synthesis of terminal ynamides

To date, three major routes for the preparation of terminal ynamides have been developed.[1,9] 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. More recently, the use of alkynyl iodonium salts and the extension of copper catalyzed C-N bond formation to ynamide synthesis have significantly improved the general scope and functional group compatibility. 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, *vide infra*. Trimethylsilylated alkynyl iodonium salts were initially used to form silyl ynamides which were then subjected to deprotection with TBAF, but it was later found that terminal ynamides can be made directly from terminal alkynyl iodonium salts. 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, the alkyne moiety must be protected by a silyl group which is finally removed to yield the terminal ynamide (Scheme 2). Altogether, these three synthetic strategies provide convenient access to a variety of terminal ynamides that can easily be produced on the gram scale.

2.1. 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.[10] Deprotonation of thymine, **1**, and cytosine, **2**, with sodium hydride followed by addition of tetrachloroethylene, **3**, and heating to 60 °C gave the trichloro enamides **4** and **5** in only up to 25% yield (Scheme 3). Treatment of **4** and **5** with *n*-butyllithium at −70 °C then furnished the terminal ynamides **6** and **7** 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.

Several years later, Brückner utilized dihalo enamides to develop a general synthetic entry to tosyl ynamides (Scheme 4).[11] Inspired by the Corey-Fuchs transformation of aldehydes to alkynes,[12] formamide **8** was transformed to the corresponding β, β-dibromo enamide **9** in 92% yield. Unfortunately, the conversion of **9** via **10** to ynesulfonamide **11** 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 **12**. This problem was solved by the replacement of carbon tetrabromide with carbon tetrachloride. Several β, β-dichloro enamide intermediates **14a–f** were obtained in excellent yields and gave tosyl ynamides **15a–f** under essentially the same conditions in 80–97% yield. Brückner's method has been employed to make analogous ynamides **16** and **17** for use in coupling reactions and nucleophilic additions discussed below and ynamides **18**–**20** which were employed in Ru,[13] Pt,[4a] and Au[14] catalyzed isomerization reactions (Figure 2).

The superior results observed with chloro enamides **14** compared to the low yield obtained with the brominated analogue **9** have been attributed to competing reaction pathways that may occur with the latter (Scheme 5).[11b] The dichloro enamides probably follow the Corey-Fuchs reaction course (pathway A). In this case, the dihalo enamide **21** preferentially undergoes deprotonation to **25** and subsequent lithium chloride elimination to chloro ynamide **26** which then reacts with another equivalent of butyllithium to the terminal ynesulfonamide **15**. Alternatively, lithium-halide exchange of the diahalo enamide **21** can generate the lithiated enamide **22** which may eliminate tosylamide **23** (path B) or form an alkylidene carbene **27** that spontaneously rearranges to **15** (path C). The outcome of the reaction with **9** suggests that the lithium-bromide exchange predominates over the deprotonation path and thus leads to **12** as the major product.

2.2. 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,[15] provides new opportunities for terminal ynamide synthesis They employed trimethylsilylethynyl(phenyl)iodonium triflate, **29**, which can be prepared from a stanna- or silaacetylene precursor, in the coupling reaction with amides and sulfonamides (Scheme 6).[16] In this one-pot procedure, amides **28** are first deprotonated with butyllithium and then treated with **29** at room temperature.[17] It is generally believed that the reaction proceeds through alkylidene carbene intermediates **30** which undergo spontaneous 1,2-migration of the silyl group to form silylated ynamides **31** in moderate to high yields. Interestingly, intramolecular CH-insertion to dihydropyrroles **33** was not observed. Desilylation of **31** with TBAF in wet THF at 0 °C gave the terminal ynamides **32** in high yields. Some of the ynamides prepared with this method were applied to inter- and intramolecular cycloadditions.[16]

The scope of alkynyl iodoinum 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[3j] and carbazoles,[3l] and other ynamides used in [4+2]cycloadditions[18] or Pauson-Khand reactions (Scheme 7).[3i] It is noteworthy that this method tolerates several functional groups, including alkenyl, alkynyl, carbamoyl, alkoxy, acetal, and alkoxycarbonyl moieties, albeit yields vary significantly. Interestingly, terminal ynamides can also be obtained directly from ethynyl(phenyl)iodonium triflate, **34**, which eliminates the desilylation step. Comparison of the two methods shows that *N*-alkynylation with **34** gives consistently higher yields than the reaction with the silylated iodonium salt **29**.

The Witulski group also applied alkynyl iodonium triflate **34** in the synthesis of ynamides carrying a chiral substituent such as **36**. Several *N*-sulfonyl protected allylglycine methyl esters **35** were found to undergo smooth amidation in the presence of cesium carbonate as base within 3 hours at room temperature and no sign of racemization was observed. Yields for **36a–d** were generally high and ranged from 70% to 95%, but *N*-Boc and *N*-acetyl derivatives did not react and the corresponding ynamides **36e** and **36f** were not detected (Scheme 8).[19]

Other important ynamides synthesized by this method include the *N*-ethynylcarbamates **32c** and **37** which have been employed in gold catalyzed cyclizations forming oxazolinones,[20] and the oxazolidinone **38**, another example of a chiral ynamide synthesized with Witulski's method, which was used in Cadiot-Chodkiewicz reactions, *vide infra* (Figure 3).[21]

2.3. Copper catalyzed C-N bond formation

The coupling of silyl protected alkynyl halides and amides pioneered by the Hsung group has become the most versatile method for the synthesis of terminal ynamides (Scheme 9).[22] 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 **28** 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 *N*,*N*'-dimethyl ethylendiamine (DMEDA) and excess of potassium phosphate at 110–150 °C, the coupling of oxazolidinone nucleophiles with 1-bromo-2-triisopropylacetylene, **39**, gave cyclic ynecarbamates **40a–c** in 70–85% yield. The camphor-derived ynamide **40d** and acylic ynecarbamates **40e** and **40f**, however, were obtained in poor yields with this method. The TIPS protected ynamides are readily converted to the corresponding terminal ynamides. For example, **40a** was desilylated with TBAF in 71% yield within 5 minutes.

Under essentially the same conditions as shown in Scheme 9, Urabe *et al.* prepared several TMS protected ynesulfonamides **41a–e** as well as **15e** using 5 mol% of CuI as catalyst for the coupling of cyclic and acyclic substrates with 1-bromo-2-trimethylsilylacetylene, **42** (Figure 4).[23] Although the free terminal ynamides were not isolated in this study, they are easily obtained via TBAF desilylation as has been shown by Witulski for ynesulfonamide **15e**.[16]

Danheiser introduced a stepwise approach to extend the scope of this approach and accomplished copper promoted ynamide formation under mild conditions.[24] The amide

substrate **43** was first converted to a copper complex with stoichiometric amounts of CuI and KHMDS and then treated with trialkylsilylethynyl halide **39** or **42** (Scheme 10). While this protocol is not catalytic, the reaction occurs at room temperature and several silyl protected ynecarbamates **44** were prepared in superior yields. As expected, **44b** was successfully desilylated with TBAF to the corresponding terminal ynamide **44c** in 81% yield.

Hsung,[25] Tam[26] 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.[27] With these modifications, remarkable results have been obtained with several imidazolidinone, carbamate, 3-alkoxycarbonylindole, sulfonamide and phosphoramidate nucleophiles **28** and bromoalkyne **39**, and the C-N bond formation was found to occur at lower temperatures than previously reported (Scheme 11). An impressive variety of terminal ynamides, including **40a–b** and **40g–x**, has been prepared by this method. For example, the cyclic ynecarbamate **40b** was prepared in gram quantities on the 100 mmol scale with up to 97% yield which compares favorably with the CuCN method.[25c] It is noteworthy that Zhang *et al.* reported an iron catalyzed amidation protocol that uses $FeCl_3$ under otherwise very similar conditions.[28] The yields of the silylated ynamides prepared by this method were generally lower than those obtained by the copper catalyzed processes shown in Scheme 11 and the amidation reaction may have been partly affected by the presence of small copper impurities in the iron salt used.[29] As discussed above, the silyl compounds **40** are readily cleaved with TBAF or potassium carbonate to furnish the corresponding terminal ynamides.[24b]

Evano's group introduced potassium trifluoroborates, which can be prepared from terminal alkynes by subsequent lithiation, addition of trimethyl borate and treatment with potassium hydrogen difluoride, as alkynyl transfer agents to copper catalyzed ynamide synthesis and obtained **31d** from **45** in 51% yield.[30] Remarkable features of this approach are that the reaction occurs under air at room temperature and in the absence of strong base (Scheme 12). The sparse solubility of the alkynyl trifluoroborate **46** in dichloromethane is critical to the success of the catalytic C-N coupling. The use of DMSO as solvent, in which **46** is readily soluble, led to exclusive formation of the undesired alkyne homodimer. The heterogeneous reaction conditions, however, 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.[31] They developed an aerobic oxidative procedure that directly couples amides **28** and terminal alkynes **47**, thus avoiding the requirement for a halogenated alkyne precursor (Scheme 13). This method provides convenient access to a variety of silylated ynamides **48a–i** 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 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.[32] For example, the silyl group of **48i** was quantitatively removed with TBAF within 5 minutes at room temperature.

A mechanism explaining the reaction course was proposed by the same group (Scheme 14).[31] During formation of **48d** the copper catalyst **49** probably first reacts with trimethylsilylacetylene, **47a**, to form the acetylide complex **50** in the presence of base. Complex **50** can then either accept a second acetylide to yield **51** and subsequently dialkyne **52** or react with the sulfonamide **53** to the copper(II) species **54**. The latter direction should be favored and outperform the homocoupling pathway toward **52** when **53** is present in excess. Finally, reductive elimination and reoxidation of the copper catalyst produces ynamide **48d** and regenerates **49**.

Few TMS protected ynimides have been synthesized by coupling of succinimide or phthalimide **55** with alkynyl bismuthonium salts **56** which first have to be prepared from the corresponding potassium alkynyltrifluoroborate precursors (Scheme 15).[33] The yields of the silylated ynimides were initially poor due to significant side reactions forming the homocoupled dialkyne derivatives and *N*-aryl imide byproducts. Following Stahl's work, the homocoupling pathway was suppressed by using the imide in excess and **57a** and **57b** were produced with 52 to 57% yield. Terminal ynimides cannot be directly synthesized with ethynyl bismuthonium salts, but **57b** was desilylated to the corresponding free terminal ynimide with TBAF at 0 °C in 88% yield.

3. Nucleophilic addition and substitution reactions

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.[34] 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, they resorted to *in situ* formation of the lithiated ynamide **58** from its β, β-dichloro enamide precursor **14**.[35] Treatment of **14** with two equivalents of butyllithium at −78 °C and subsequent reaction of the lithiated ynamide with various electrophiles gave the expected products **59** in good to high yields (Table 1). For example, addition of TMSCl and dimethyl sulfate gave **59a** and **59b** in 78% and 74% yield, respectively (entries 1 and 2). With the exception of *tert*-butyl isocyanate, which gave **59f** in only 53% yield, benzaldehyde and other carbonyl nucleophiles were converted to the corresponding 1,2-addition products **59c–g** in 88% to 96% yield and the procedure was also successfully applied to diethyl chlorophosphate, producing **59h** in 73% yield (entries 3–8). As expected, similar results were obtained by acetylation of other tosyl ynamides to **59i–l** (entries 9–12).

Careful deprotonation of terminal ynamides and ynehydrazides such as **60** and **62** with lithium hexamethyldisilazide (LHMDS) or another strong base has remained an attractive alternative to Saá's *in situ* generation of lithium ynamides shown above.[4b,22,36] Additions of the alkylnyllithium intermediates to ethyl chloroformate gave **61** and **63** in 90% and 47% yield, respectively. A particularly interesting example is the S_N2 methylation of the

phosphoramidate-derived ynamide **64** to the farnesol derivative **65** which produced a mixture of bicyclic enamine **66** and tricyclic imine **67** upon heating (Scheme 16).[37] In analogy to the addition to carbonyl electrophiles, the deprotonation of terminal ynamides **68** 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-γ-amino ynamides **70a–h** in good yields.[38]

We recently demonstrated that copper iodide catalyzes the addition of ynesulfonamide **14f** to acyl chlorides **71** and several *N*-heterocycles **73** activated *in situ* with ethyl chloroformate at room temperature.[39] The reaction with aromatic acyl chlorides **71** gave a series of 3-aminoynones **72a**–**f** in high yields ranging from 79 to 99% (Scheme 17). Steric hindrance does not seem to affect the reaction and the ynamide addition to pivaloyl chloride gave **72g** in 90% yield. Aliphatic acyl chlorides that can undergo ketene formation and related side reactions remain suitable substrates for 3-aminoynone synthesis at slightly reduced temperatures. For example, **72h** was obtained in 70% yield when the reaction was performed at 15 °C.

We found that the copper catalyzed addition of **14f** to alkyl chloroformates does not occur under the same conditions. This observation prompted us to investigate if this ynamide can be added to pyridine and other *N*-heterocycles activated *in situ* with ethyl chloroformate. Again, copper iodide catalysis proved successful and we were able to produce 1,2-dihydropyridines **74a**–**e** in 71–96% yield (Scheme 17). The addition product obtained from 4-methoxypyridine was unstable and hydrolyzed during chromatographic purification to ketone **74f** which was isolated in 71% yield. Several quinolines and phenanthridine were then employed in the same protocol to give **74g**–**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. A proposed catalytic cycle of the ynamide addition to the activated *N*-heterocyclic substrate **77** formed *in situ* from quinoline, **73g**, is shown in Scheme 18. It is assumed that **14f** reacts with CuI via **75** to a copper acetylide complex **76**. Nucleophilic attack at **77** then produces the 1,2-dihydroquinoline derivative **74g** and regenerates the copper catalyst.

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.[40] They observed that lithiation of *N*-sulfonyl ynamides **78** with LHMDS followed by addition of chiral *N*-*tert*-butanesulfinyl imines **79** at −40 °C affords the corresponding 1,2-addition products **80a**–**g** in good to high yields and with impressive diastereoselectivity (Scheme 19). The reactions between the *N*-benzyl-*N*-tosyl ynamide **78** with 4 different activated aldimines carrying a *tert*-butanesulfinyl moiety gave the propargylic amines **80a**–**d** in 63-77% yield and with at least 20:1 dr. For example, **80a** 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 **78** by a methoxy group increases the yield to 95% while the diastereomeric ratio remains unchanged. The para-nitro analogue, however, gives

80f 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.

Interestingly, addition of selected Lewis acids can completely reverse the sense of asymmetric induction (Scheme 20). When stoichiometric amounts of boron trifluoride diethyl etherate were added to the lithiated ynamide, the reaction with **79** gave the (*R*)-configured addition products **80a**–**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.

The first catalytic enantioselective nucleophilic 1,2-addition with ynamides was accomplished in our laboratory.[32] We realized that terminal ynamides undergo zinc catalyzed addition with aldehydes under mild conditions and started with the development of an asymmetric procedure. Screening of a wide range of chiral ligands, solvents, base and variation of the prenucleophile revealed that indole derived ynamides are particularly useful and give the corresponding propargylic alcohols in superior yields and ee compared to ynesulfonamides and ynecarbamates. The initial reaction between 3-benzoylindolyl ynamide **48j** and 4-bromobenzaldehyde, **81a**, in the presence of catalytic amounts of zinc triflate and *N*-methyl ephedrine in toluene gave **82a** in 87% yield and 77% ee. An interesting feature of this reaction is that it is reversible. We observed considerable racemization of the product leading to reduced ee's unless apolar solvents in which the addition products precipitate are used. We therefore switched to toluene/hexane mixtures to impede racemization and isolated **82a** in 97% yield and 93% ee (Table 2, entry 1). The procedure is operationally simple and has a wide substrate scope. Very high yields and ee's were obtained with other electron-rich and electron-deficient aromatic aldehydes **81b**–**l** and the 3-aminopropargylic alcohols **82b**–**l** were isolated in 81–93% yield and up to 96% ee (entries 2–12). Similar results were also obtained with aliphatic aldehydes **81m** and **81n** (entries 13 and 14).

4. Coupling reactions

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.[41] Saá and coworkers successfully applied a Glaser-Hay coupling protocol to a few ynesulfonamides **15** and obtained diynes **83a**–**e** in excellent yields. The oxidative coupling is catalyzed by CuI in the presence of TMEDA and atmospheric dioxygen, and it is generally complete within 3 hours at room temperature (Scheme 21).[42] Alternatively, copper catalyzed Cadiot-Chodkiewicz cross-coupling of sulfonyl and carbamoyl ynamides **32** with the electron-deficient bromoalkyne **84** has been reported to proceed at ambient temperatures. The push-pull diynes **85** were isolated in up to 93% yield.[21]

Saá and coworkers also reported palladium catalyzed cross coupling of zinc ynamides with aryl iodides. This coupling procedure requires lithiation of dichlorovinyl amides **14** and subsequent treatment with zinc dibromide. The *in situ* formed zinc ynamides **86** were then

employed in palladium catalyzed coupling reactions to afford a variety of *C*-substituted ynamides **87** (Scheme 22).[43] The coupling with simple aryl iodides furnished **87a–c** in moderate 63–69% yield. The reaction is of limited use when electron-rich aryl iodides are employed and the methoxy-derived products **87d–f** and **87j** 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 **87g–i**, **87k**, and **87l** in up to 92% yield.

Hsung demonstrated that terminal ynecarbamates **88** are suitable substrates for typical Sonogashira reaction protocols.[44] They used $Pd(PPh_3)_4$ as catalyst and CuI or CuCN as cocatalyst to affect smooth transmetallation with aryl iodides at room temperature (Scheme 23). The coupling products **89a–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.[45]

5. Iodination

2-Haloynamides such as **26** may not only serve as intermediate precursors in the synthesis of terminal ynamides but also as highly versatile, isolable reagents (Scheme 5). Danheiser's group recognized the synthetic potential of 2-iodoynamides and prepared **90a–c** by deprotonation of terminal ynamides with either *n*-butyllithium or KHMDS and subsequent addition of iodine or 1,2-diiodoethane as the iodination reagent (Scheme 24).[46] The use of 2-iodoynamides in [2+2] cycloadditions with ketenes was found to provide invaluable access to multifunctional iodocyclobutenones.

6. Outlook

The unique properties and the distinct reactivity of terminal ynamides continue to draw increasing attention to this synthetically very useful class of compounds. While most ynamides can be stored conveniently at room temperature and under air, which greatly facilitates preparation and use, they often do not react like simple alkynes. In stark contrast to terminal alkynes, reactions with the highly polarized ynamide analogues that leave the triple bond intact have rarely been investigated. It is evident that the progress with the development of orthogonal methods for the synthesis of a wide variety of terminal ynamides has greatly facilitated and inspired recent studies exploring efficient functionalization of these versatile building blocks. The general utility of terminal ynamides in catalytic cross-couplings, nucleophilic additions, asymmetric carbon-carbon bond formations and other reactions that do not consume the *N*-substituted alkyne moiety, however, remains to be fully explored. It is expected that the number of publications on both synthetic and mechanistic aspects of this emerging area will continue to rapidly increase and that terminal ynamides will soon find broad use in many applications including total synthesis.

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6. References and notes

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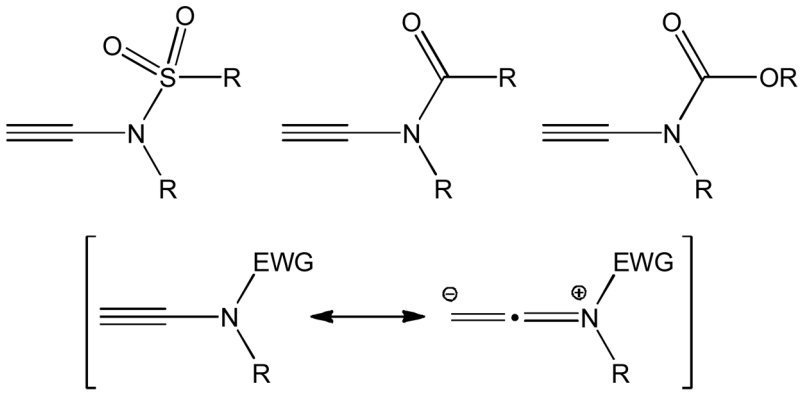


Figure 1.
Structures of terminal ynamides.

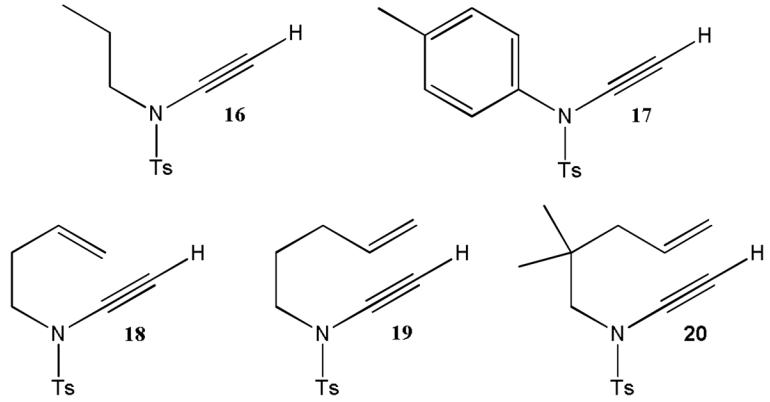


Figure 2.
Selected ynamides synthesized with Brückner's method.

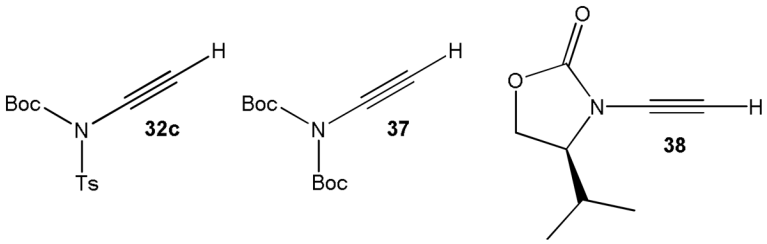


Figure 3.
Other important ynamides prepared by the alkynyl iodonium method.

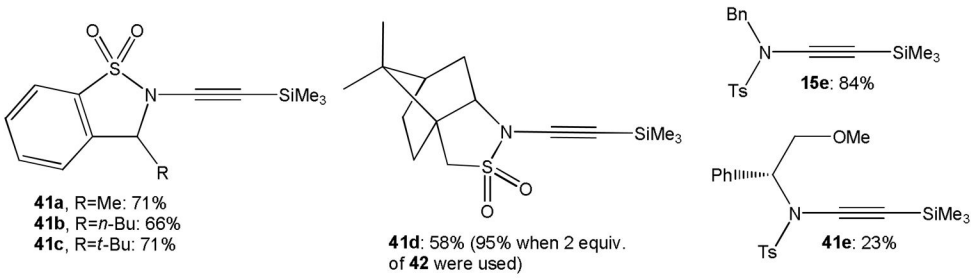
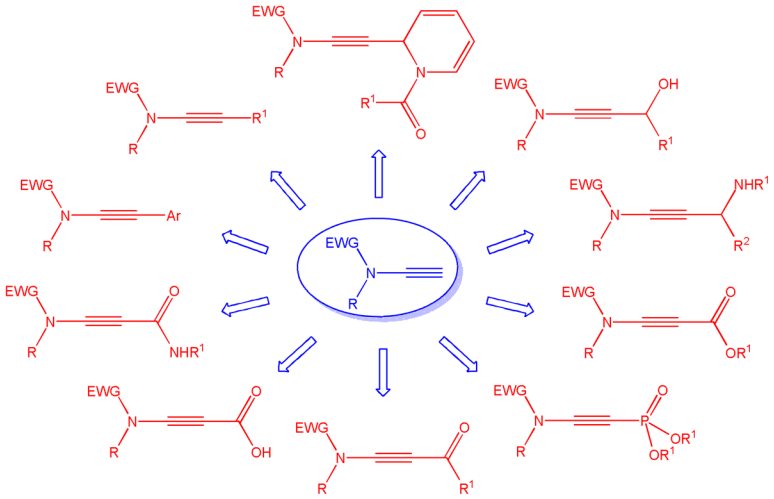
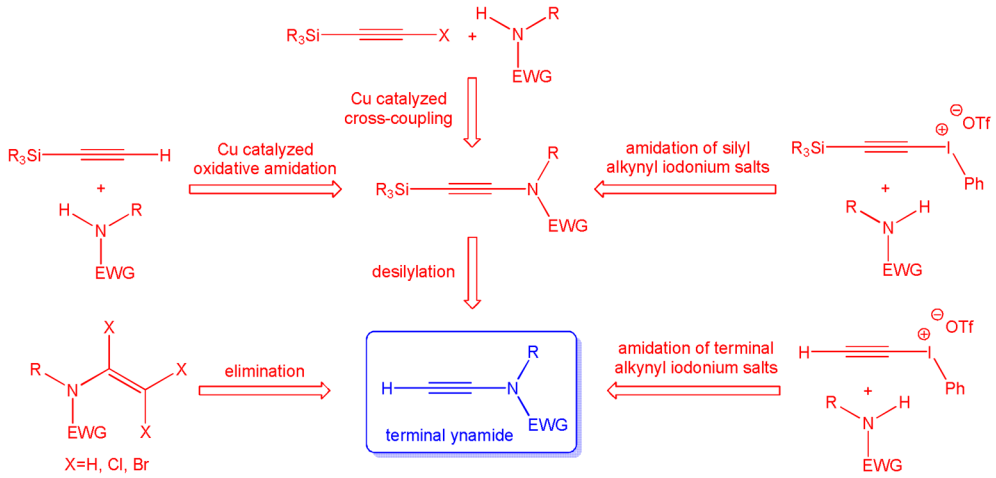


Figure 4.
Ynesulfonamides synthesized with CuI as catalyst.



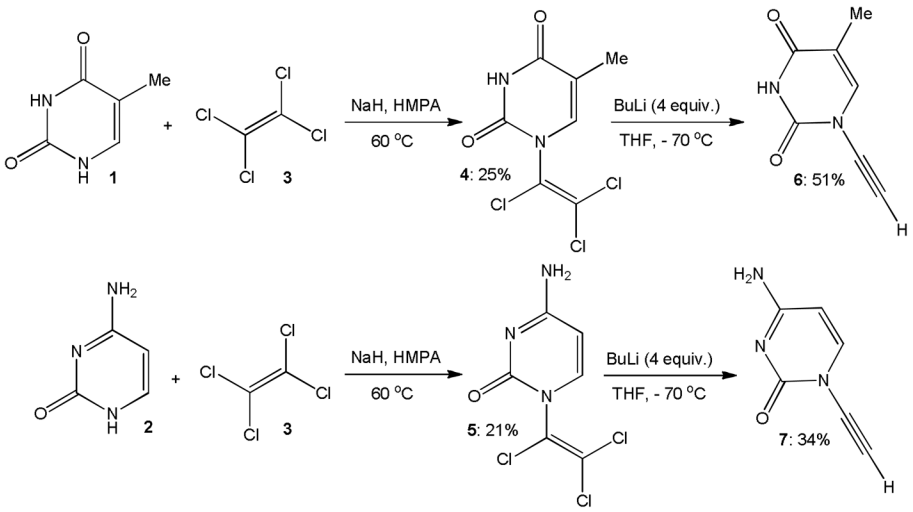
Scheme 1.

Overview of transformations of terminal ynamides leaving the triple bond intact.



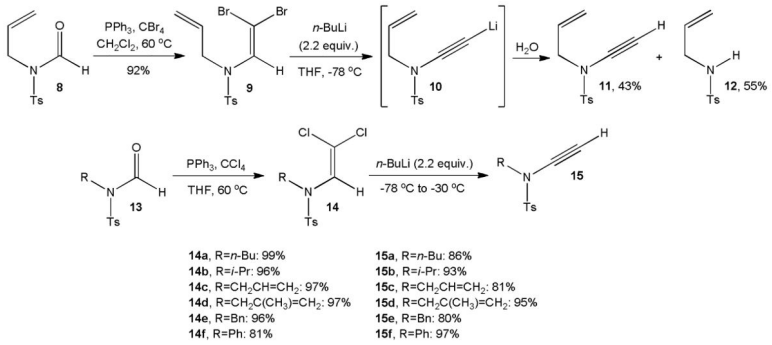
Scheme 2.

Synthetic routes to terminal ynamides.



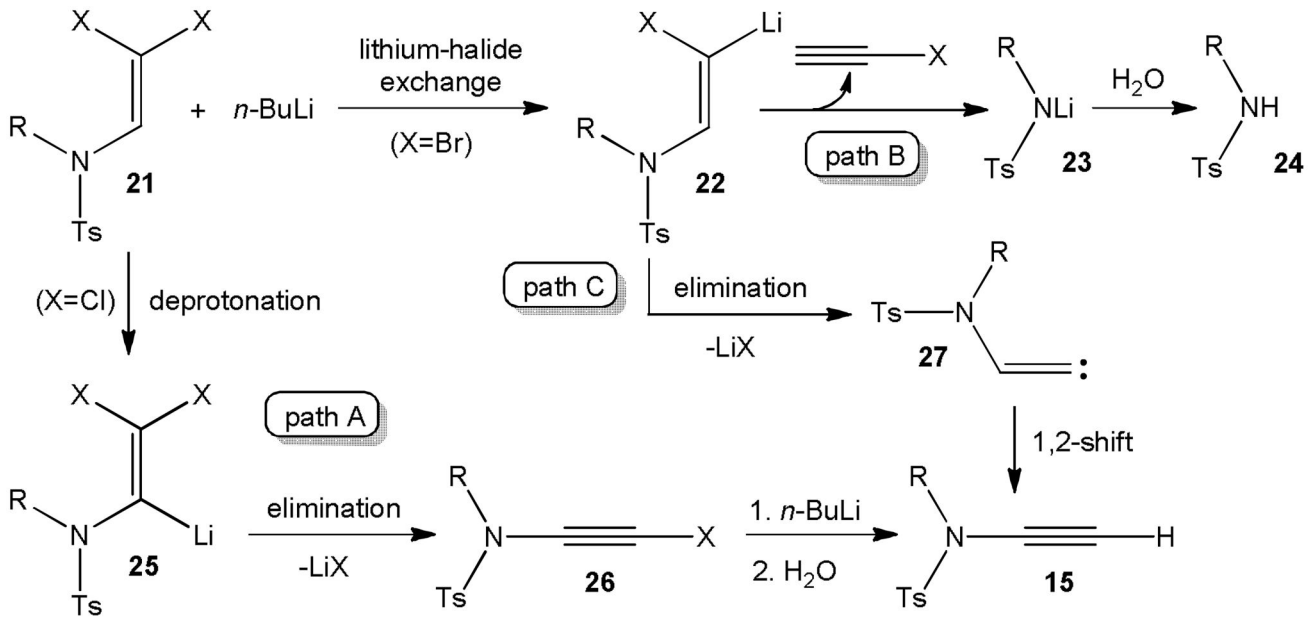
Scheme 3.

Thymine and cytosine derived ynamides.

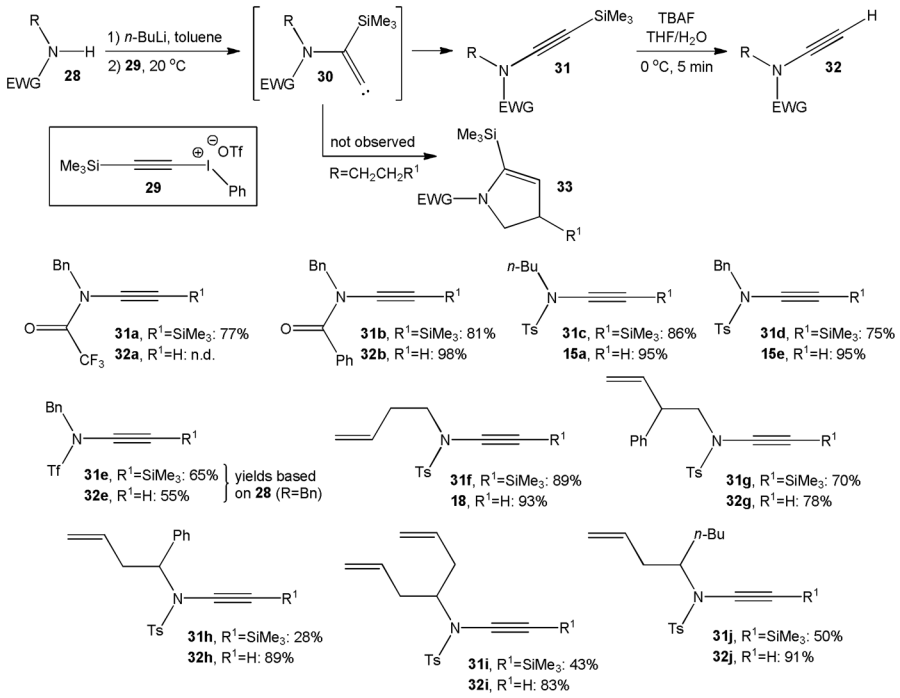


Scheme 4.

Brückner's general synthesis of tosyl ynamides.

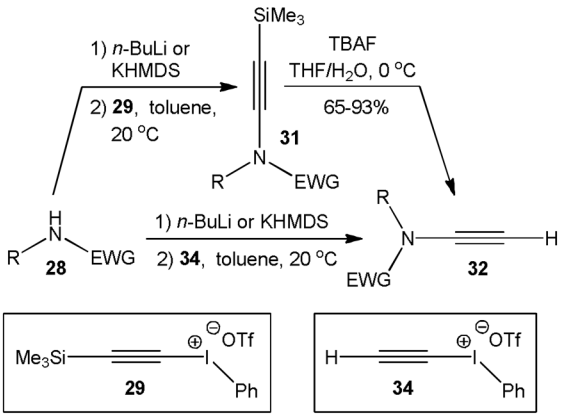


Scheme 5.
Possible reaction pathways of dihalo enamides.



Scheme 6.

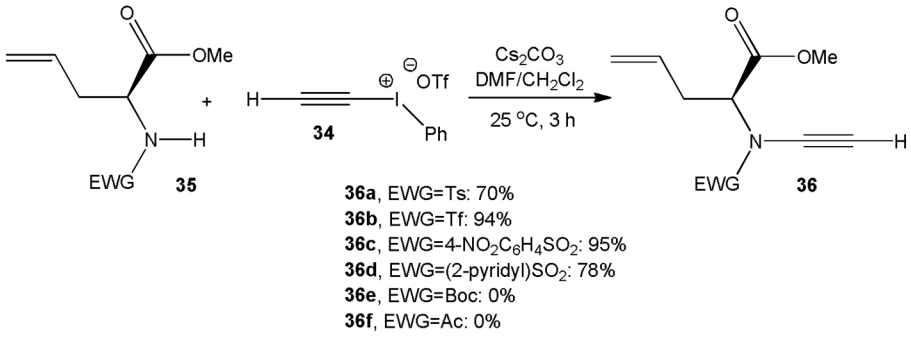
Amidation with trimethylsilylethynyl(phenyl)iodonium triflate, **29**.



31k, EWG=Ts, R=$(CH_2)_2C{\equiv}CSiMe_3$: 69%
31l, EWG=Ts, R=$(CH_2)_2C{\equiv}C(CH_2)_2NHTs$: 28%
31m, EWG=Ts, R=$(CH_2)_2C{\equiv}C(CH_2)_2OTBDMS$: 80%
31n, EWG=Ts, R=$(CH_2)_2C{\equiv}C(CH_2)_2OBn$: 66%
31o, EWG=Ts, R=$(CH_2)_2C{\equiv}C(CH_2)_2OTHP$: 43%
31p, EWG=Ts, R=$(CH_2)_2C{\equiv}CCH_2OTHP$: 60%
31q, EWG=Ts, R=$(CH_2)_2C{\equiv}CH$: 64%
31r, EWG=Ts, R=$(CH_2)_2C{\equiv}CPh$: 72%
31d, EWG=Ts, R=Bn: 75%
31s, EWG=Ts, R=Boc: 54%
31t, EWG=Ns, R=Bn: 60%
31u, EWG=Ts, R=$(CH_2)_2CH{=}CHCH{=}CH_2$: 80%

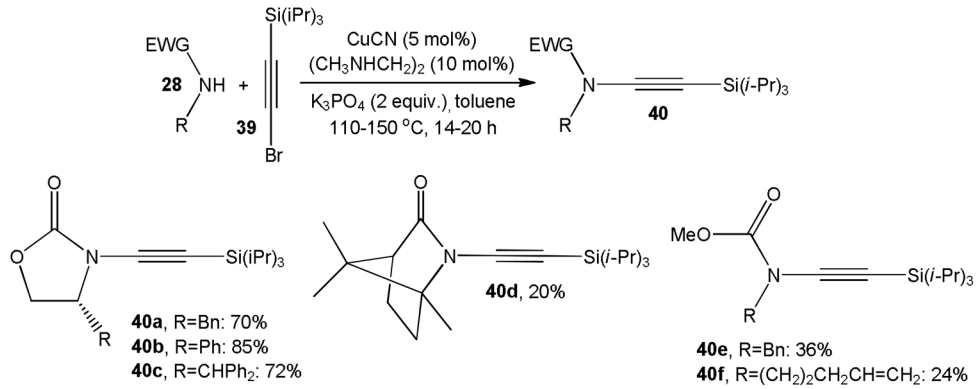
32a, EWG=Ts, R=$(CH_2)_2C{\equiv}CPh$: 85%
32b, EWG=Ts, R=$(CH_2)_2C{\equiv}CCO_2Me$: 35%
15e, EWG=Ts, R=Bn: 90%
32c, EWG=Ts, R=Boc: 84%
} direct synthesis with **34**
32d, EWG=Ts, R=$(CH_2)_2CH{=}CHCH{=}CH_2$: 93% from **31u**

Scheme 7.
Amidations with free and TMS protected alkynyl iodonium salts **29** and **34**.



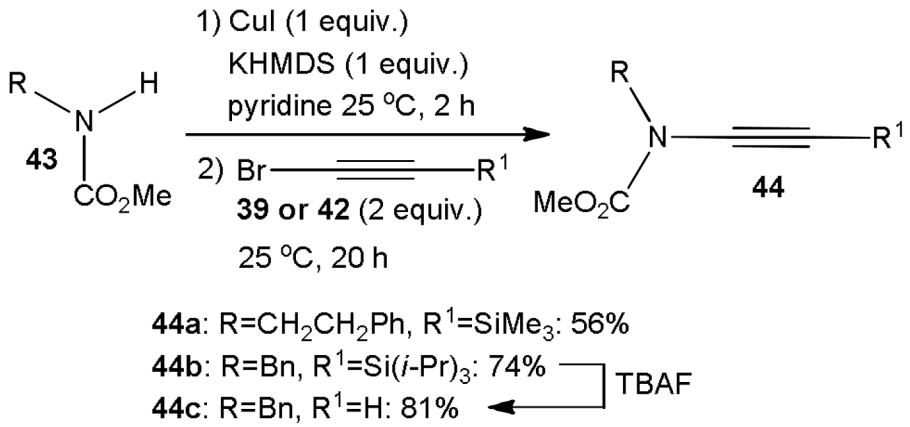
36a, EWG=Ts: 70%
36b, EWG=Tf: 94%
36c, EWG=4-$NO_2C_6H_4SO_2$: 95%
36d, EWG=(2-pyridyl)SO_2: 78%
36e, EWG=Boc: 0%
36f, EWG=Ac: 0%

Scheme 8.
N-alkynylation of enantiopure allylglycine derivatives.

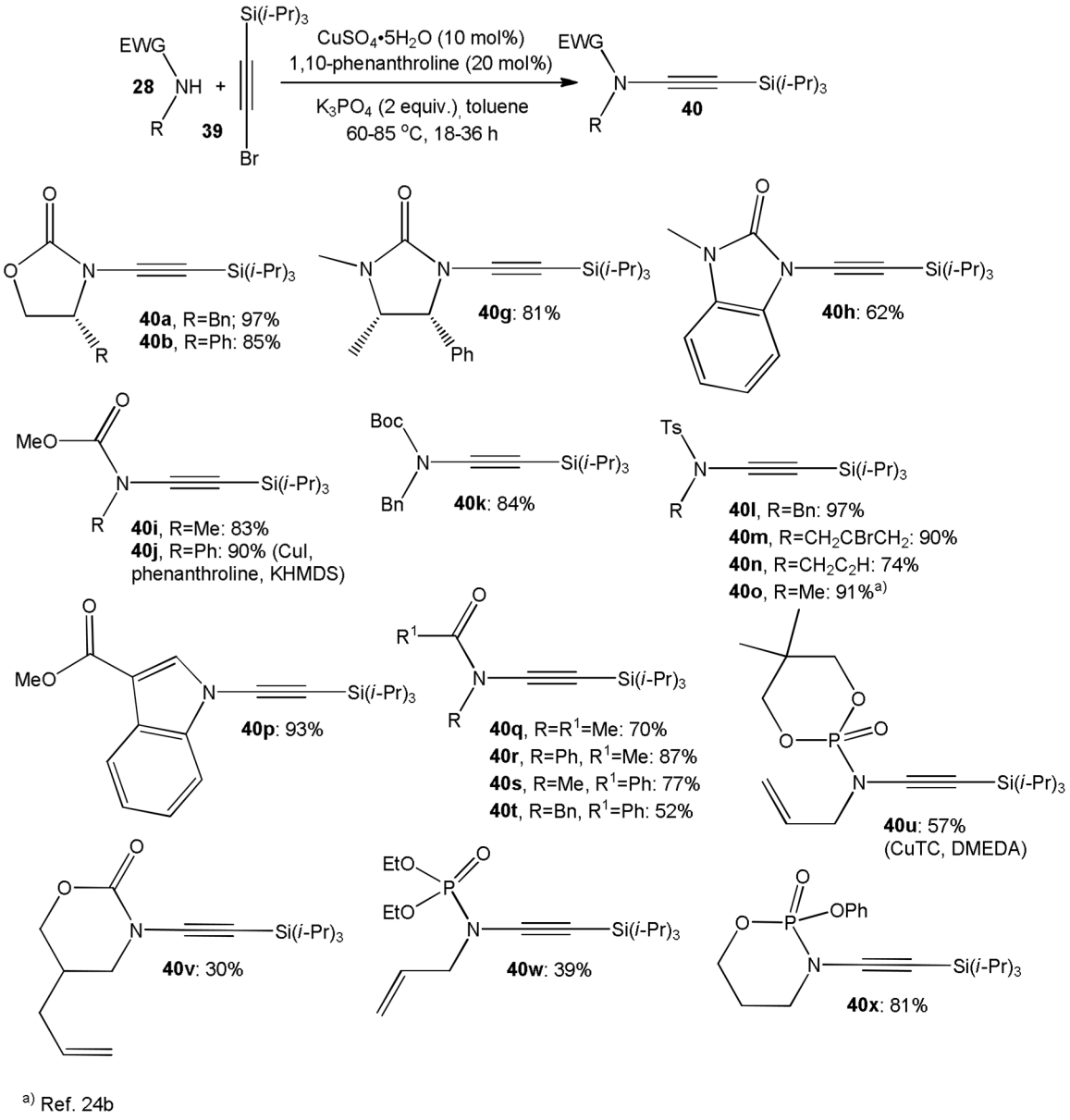


Scheme 9.

CuCN catalyzed *N*-alkynylation of oxazolidinones, amides and carbamates.



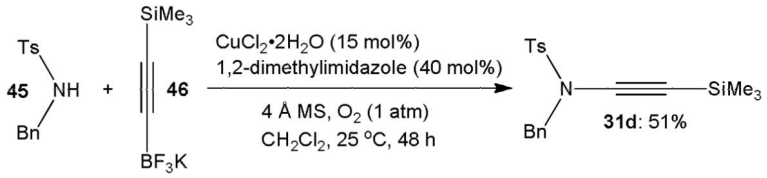
Scheme 10.
Copper mediated *N*-alkynylation of selected carbamates.



a) Ref. 24b

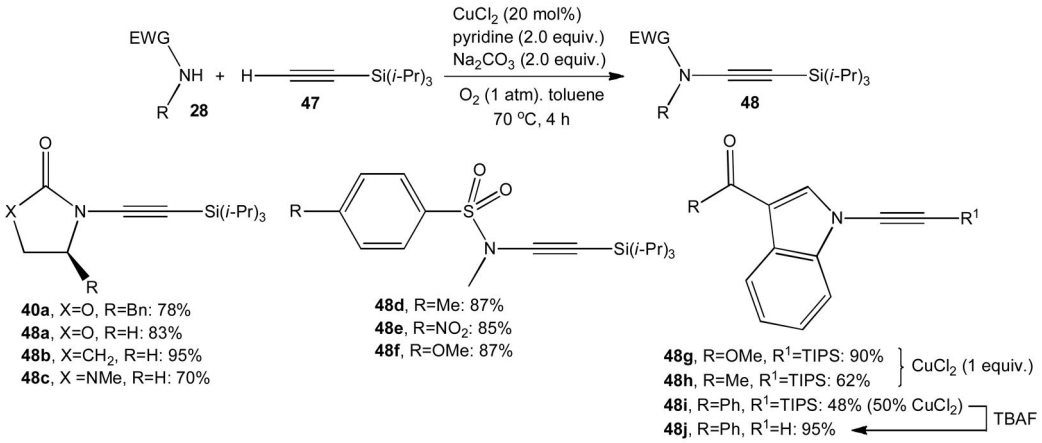
Scheme 11.

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



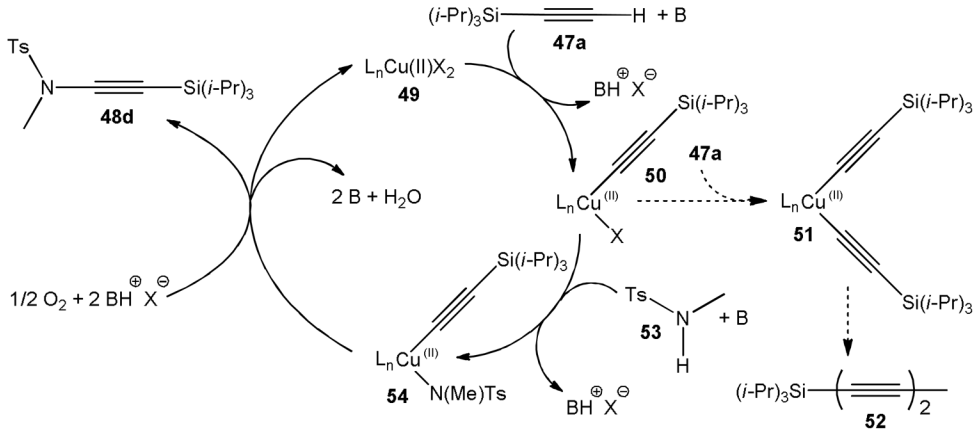
Scheme 12.

Catalytic C-N bond formation with an alkynyl trifluoroborate.



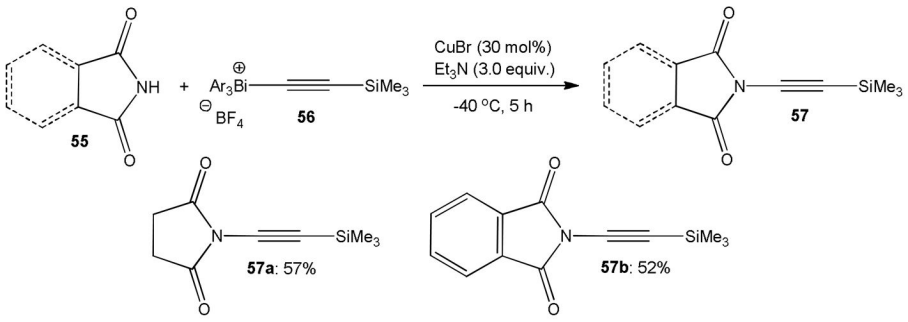
Scheme 13.

Oxidative alkynylation of various *N*-nucleophiles.



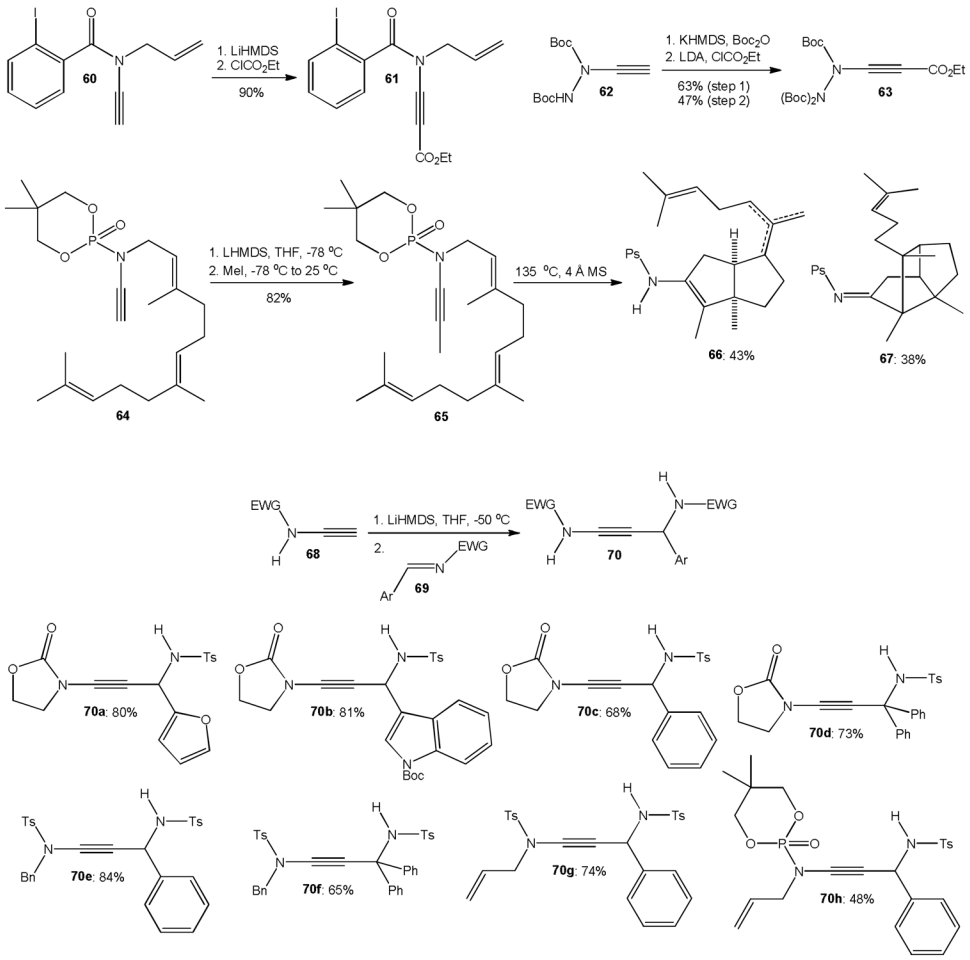
Scheme 14.

Mechanism of the copper catalyzed oxidative C-N bond formation with terminal alkynes as postulated by Stahl.



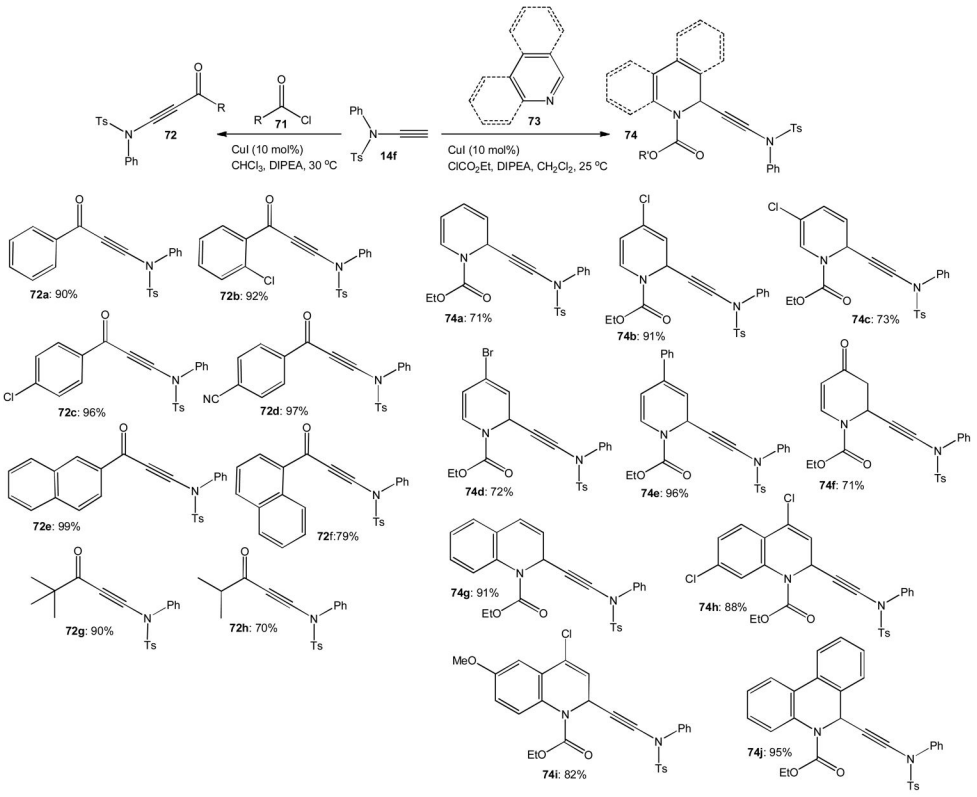
Scheme 15.

Ynimide synthesis with alkynyl bismuthonium salts.



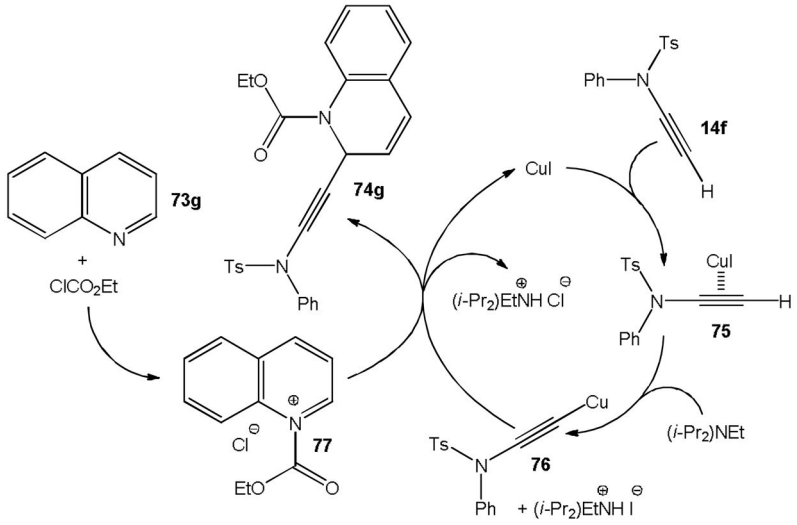
Scheme 16.

Deprotonation of terminal ynamides for nucleophilic addition and substitution reactions.



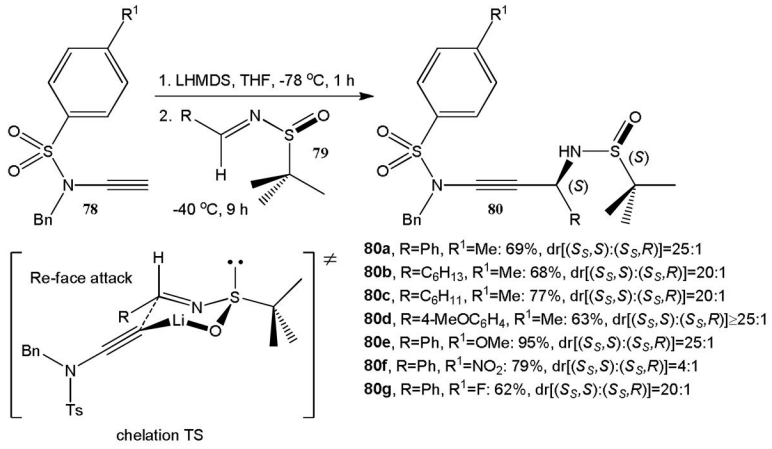
Scheme 17.

Copper catalyzed nucleophilic ynamide addition to acyl chlorides and activated *N*-heterocycles.



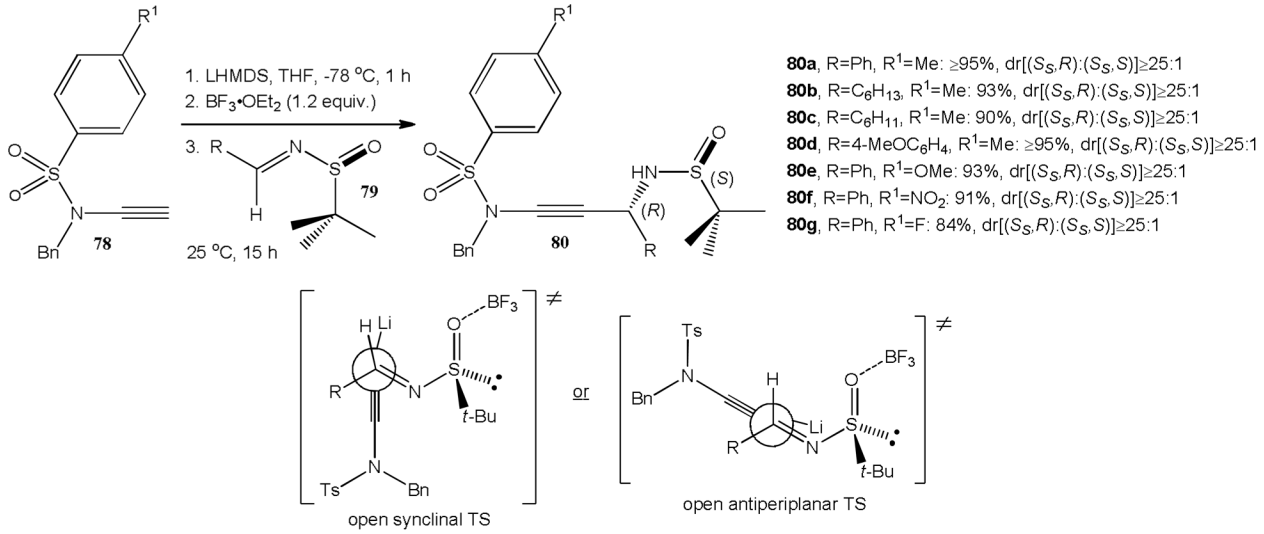
Scheme 18.

Catalytic cycle of the copper catalyzed ynamide addition to activated quinoline.



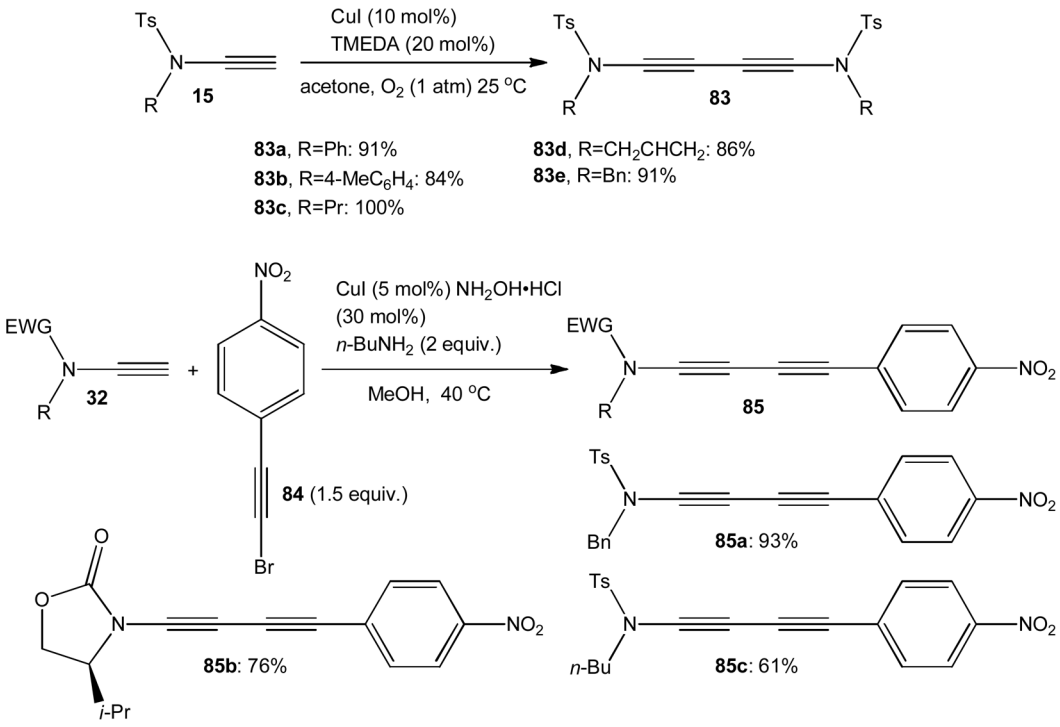
Scheme 19.

Diastereoselective synthesis of propargylic amines **80** from *tert*-butanesulfinyl derived imines **79**.



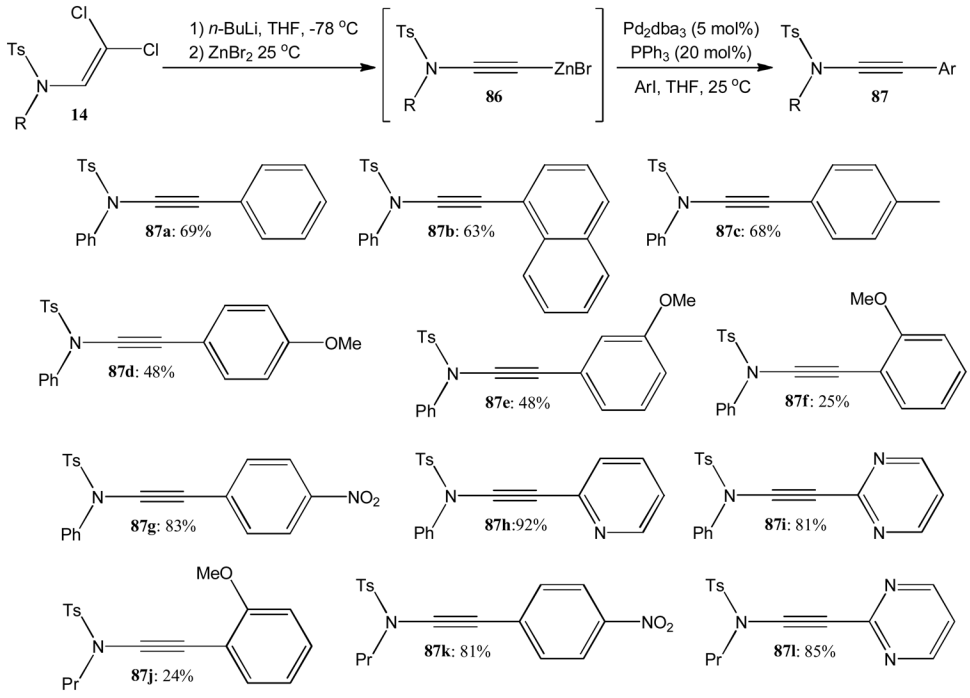
Scheme 20.

Boron promoted diastereoselective addition of sulfonyl ynamides **78** to *N*-*tert*-butanesulfinyl imines **79**.



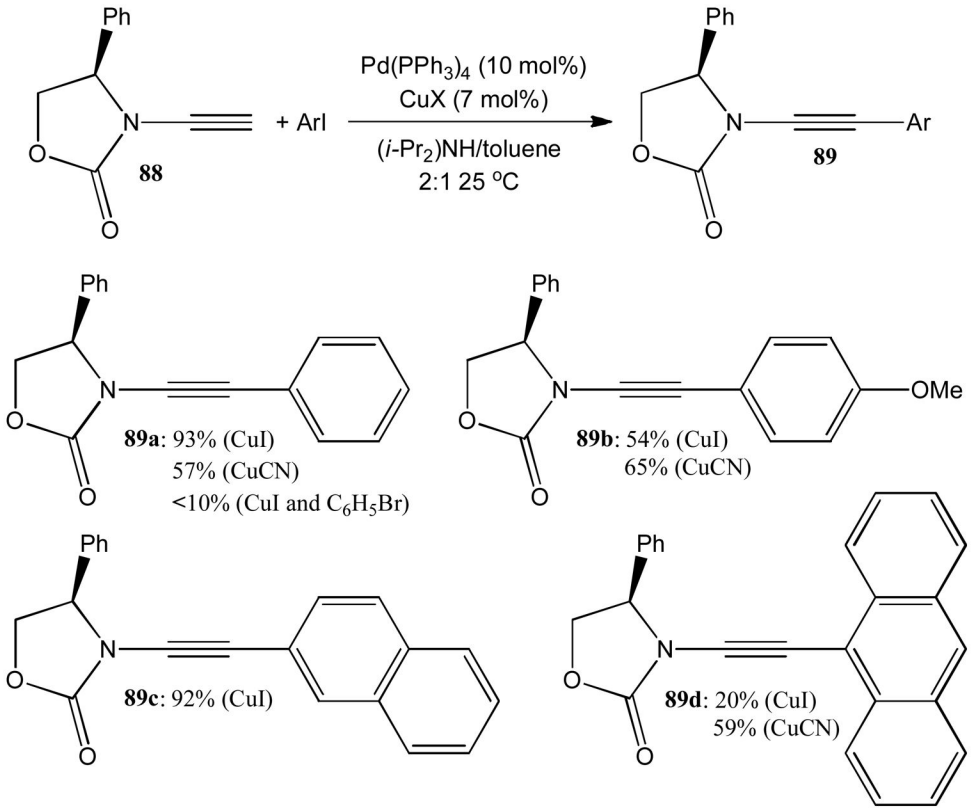
Scheme 21.

Glaser-Hay coupling and Cadiot-Chodkiewicz cross-coupling of ynamides.

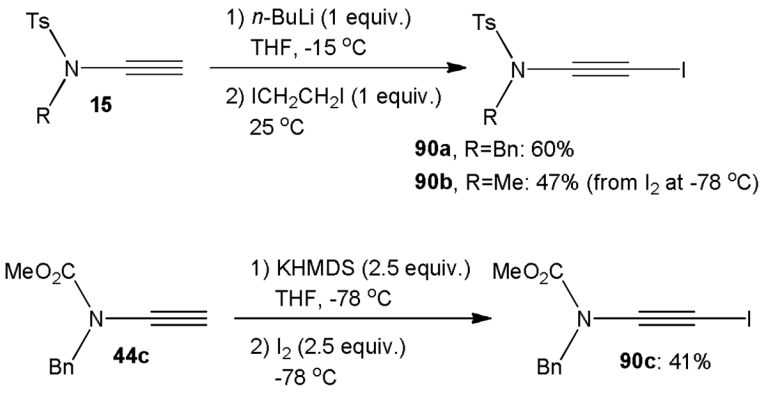


Scheme 22.

Palladium catalyzed cross coupling of zinc ynamides with aryl iodides.



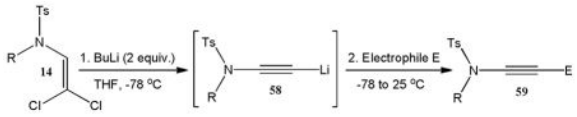
Scheme 23.
Sonogashira coupling with ynamides.

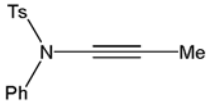
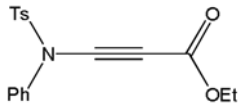
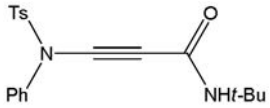
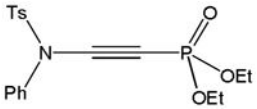


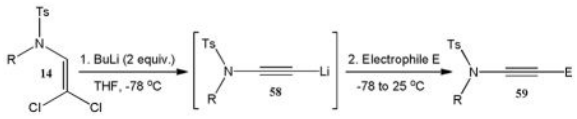
Scheme 24.
Iodination of terminal ynamides.

Table 1

Ynamide additions to common nucleophiles.



Entry	R	Electrophile	Product	Yield (%)
1	Ph	TMSCl	 **59a**	78
2	Ph	Me_2SO_4	 **59b**	74
3	Ph	PhCHO	 **59c**	88
4	Ph	Ac_2O	 **59d**	90
5	Ph	$ClCO_2Et$	 **59e**	96
6	Ph	*t*-BuNCO	 **59f**	53
7	Ph	CO_2	 **59g**	90
8	Ph	$ClP(O)(OEt)_2$	 **59h**	73



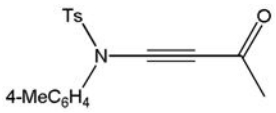
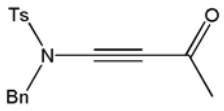
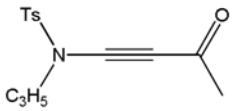
Entry	R	Electrophile	Product	Yield (%)
9	4-MeC_6H_4	Ac_2O	 **59i**	86
10	Bn	Ac_2O	 **59j**	84
11	Pr	Ac_2O	 **59k**	84
12	CH_2=$CHCH_2$	Ac_2O	 **59l**	77

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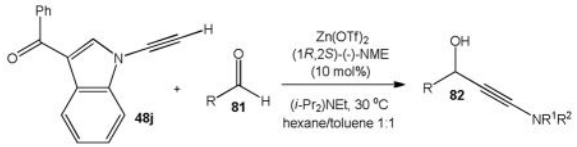
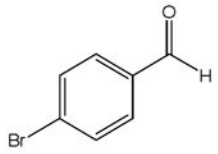
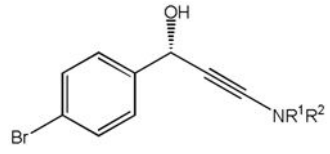
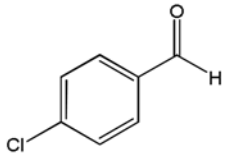
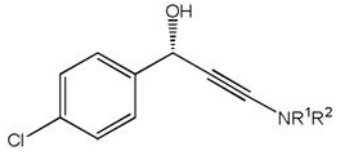
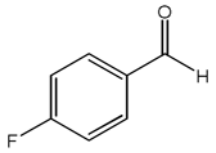
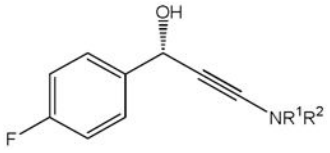
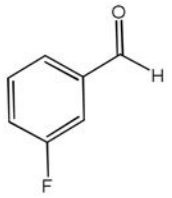
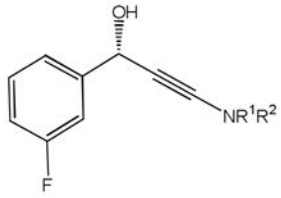
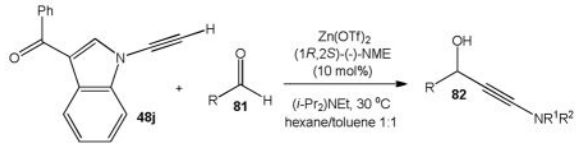
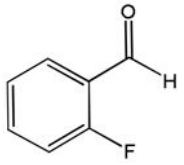
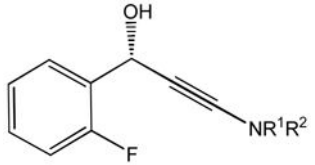
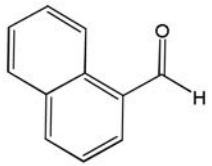
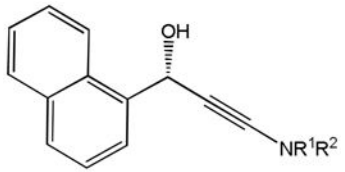
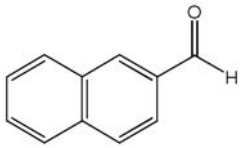
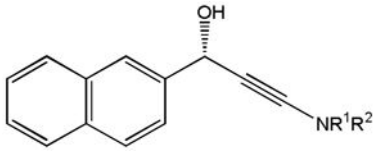
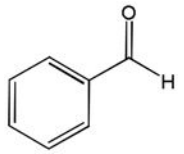
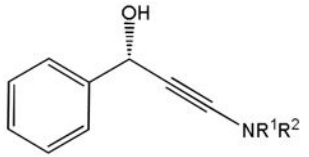
Table 2

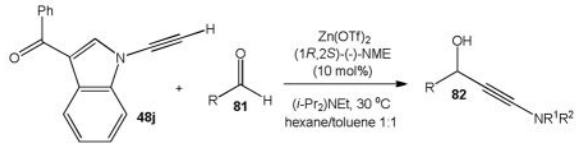
Catalytic asymmetric ynamide addition to aldehydes.

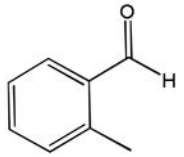
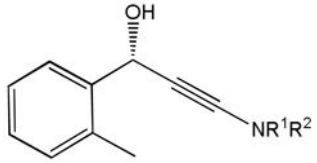
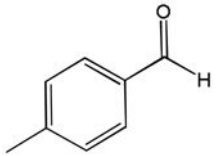
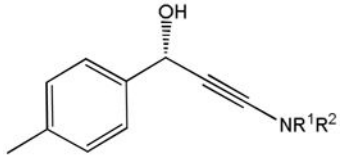
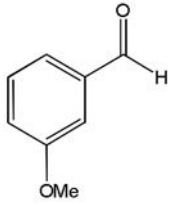
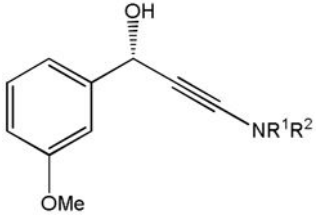
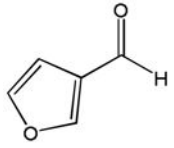
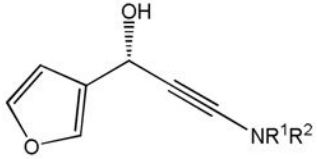


Entry	Aldehyde	Product	Time (h)	Yield (%)	Ee (%)
1	 **81a**	 **82a**	18	97	93
2	 **81b**	 **82b**	16	92	95
3	 **81c**	 **82c**	18	85	93
4	 **81d**	 **82d**	18.5	87	88



Entry	Aldehyde	Product	Time (h)	Yield (%)	Ee (%)
5	 **81e**	 **82e**	13	92	71
6[b]	 **81f**	 **82f**	18	92	96
7	 **81g**	 **82g**	17	92	90
8	 **81h**	 **82h**	18	87	84



Entry	Aldehyde	Product	Time (h)	Yield (%)	Ee (%)
9	 **81i**	 **82i**	15	93	95
10	 **81j**	 **82j**	20	80	88
11	 **81k**	 **82k**	26	92	87
12	 **81l**	 **82l**	21	81	87

Entry	Aldehyde	Product	Time (h)	Yield (%)	Ee (%)
13[b]			15	89	90
	81m	**82m**			
14			13	87	95
	81n	**82n**			