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Enantioselective Propargylation and Allenylation Reactions of Ketones and Imines

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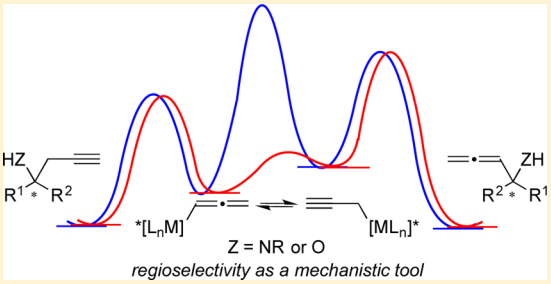
ABSTRACT: Enantioselective propargylation and allenylation reactions pose an interesting challenge because they require control of regioselectivity as well as enantioselectivity. This review presents recent advances in enantioselective propargylation and allenylation reactions of ketones and imines. In this context, a brief discussion of the possible mechanisms of these transformations and consequences for regioselectivity is provided.



INTRODUCTION

Enantioselective methods for addition to carbonyl electrophiles constitute an important class of carbon−carbon bond-forming reactions. In particular, addition reactions of propargyl and allenyl nucleophiles construct orthogonally functionalized building blocks with convenient handles for further elaboration. For this reason, propargylation reactions of aldehydes have been employed in total syntheses of complex polyketides. Figure 1 depicts a subset of natural products that featured a propargylation reaction in their respective synthetic sequences (the resultant homopropargylic alcohol fragment is highlighted in red). The monomeric unit of rhizopodin,[1] the bongkrekic acids,[2] and bryostatin[3] were synthesized using an indium-catalyzed addition to an aldehyde,[4,5] while addition of a chiral borane to an aldehyde[6] was featured in the synthesis of octalactins A and B.[7] Although the majority of these applications have utilized a chiral auxiliary to set the stereochemistry of the homopropargylic alcohol, new enantioselective methods to accomplish this bond construction have since been established. Identification of catalysts capable of providing both high enantioselectivity and regioselectivity is necessary to fully realize the potential of propargylation and allenylation reactions. The impressive body of work in enantioselective addition to aldehydes is beyond the scope of this review;[8−11] however, it forms the foundation of this field. Recently, there have been many exciting advances in propargylation and allenylation reactions of ketones and imines with control of enantio- and regioselectivity. Herein, we will discuss these developments and examine the mechanistic implication of the observed regioselectivity of these reactions.

For the purposes of this review, reactions will be split into two groups based on mechanism (Scheme 1). Propargylation and allenylation reactions involving *direct addition* of the allenyl- or propargylmetal reagent will be classified as group I (Scheme 1a). Alternatively, reactions which undergo an oxidative addition or transmetalation to form a new organometallic species capable of *isomerization*, followed by addition, will be classified as group II (Scheme 1b).[12−14] While controlling regioselectivity makes these reactions challenging to develop, inferences concerning reaction mechanism can often be gleaned from product distribution, allowing for classification of reactions as either group I or group II. Since C1 and C3 of propargyl and allenyl fragments are at different oxidation states, their positions can be easily traced from the starting material to the product.

Group I reactions can be identified by examining the regiochemical outcome when isomeric organometallic reagents are employed (Scheme 1a). These reactions typically proceed through direct addition of the organometallic reagent to the electrophile by an S_E2'-type mechanism. Therefore, when allenylmetal reagent **1** is used, propargyl product **2** forms preferentially. In contrast, the use of propargylmetal reagent **3** affords allenyl product **4**. Therefore, as a preliminary test of mechanism, the isomeric reagent can be employed: if the opposite product isomer is generated, the transformation may proceed through a group I reaction mechanism. These reactions often utilize tin, silicon, or boron organometallic reagents and are typically catalyzed by Lewis acids or bases.

In contrast, group II reactions proceed through a metal-mediated isomerization, followed by addition, and can afford a range of regiochemical outcomes (Scheme 1b). Product distributions are determined by a balance between rate of isomerization, relative stability, and relative nucleophilicity of allenyl- and propargylmetal complexes (Figure 2). Each of these factors depends upon the identity and concentration of the metal, ligand manifold, and reaction conditions. When isomerization is fast and reversible on the reaction time scale, the transformation follows the Curtin−Hammett principle and regioselectivity is governed by the difference in rates of addition to the carbonyl derivative (Figure 2a).[15,16] When this mechanistic scenario is operative, use of either allenylmetal reagent **1** or propargylmetal reagent **3** will yield the same major product.[17−21] Related cross-coupling reactions of allenyl and propargylmetal species often

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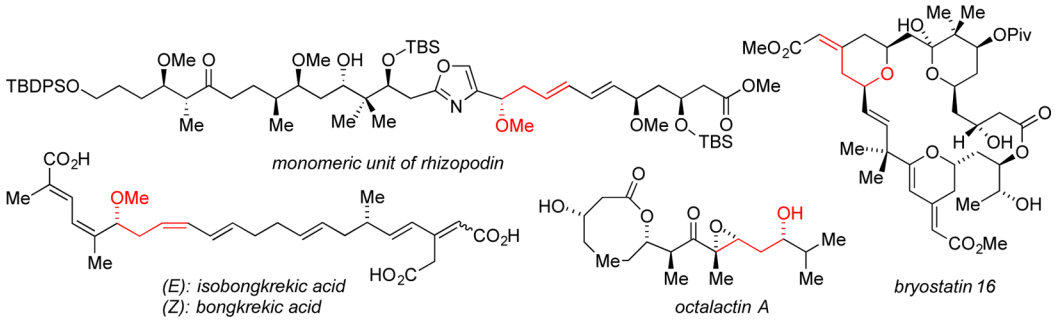
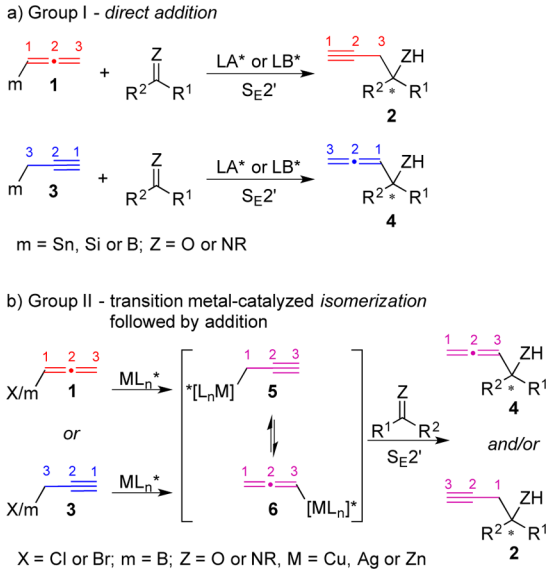


Figure 1. Polyketide natural products prepared via propargylation reactions.

Scheme 1. Regioselectivity in Different Mechanisms of Addition



conform to this mechanistic scenario and relative stability of the propargyl- and allenylmetal intermediates is directly reflected in the product distributions.[22,23]

In contrast, if the barrier to isomerization is much higher than that of nucleophilic attack (Figure 2b), then the first species formed (**5** or **6**) will react to form the corresponding product (**4** or **2**, respectively).[24−26] In this scenario, use of allenylmetal reagent provides a different product from the isomeric propargylmetal reagent. Therefore, distinguishing this mechanism from a group I mechanism is often difficult and requires evidence of a transmetalation or an oxidative addition event.

Previous work regarding addition to aldehydes, as well as related palladium-catalyzed cross-coupling reactions, has demonstrated that both mechanistic scenarios presented in Figure 2 are plausible.[27] In 2011, Fandrick and co-workers performed detailed studies on the addition of allenyl and propargylzinc reagents to aldehydes.[20] They proposed that isomerization of these intermediates is bimetallic;[28−33] therefore, modulating the amount of diethylzinc could be used to control the rate of isomerization. At low concentrations of diethylzinc, the isomerization was slower than addition to the aldehyde. Under these conditions, the use of propargylboronic acid pinacol ester **7** resulted in formation of homopropargylic alcohol **11** (Scheme 2). Likewise, the use of the isomeric allenylboronic acid pinacol ester **8** afforded homoallenyl alcohol **12** exclusively. Performing the reaction at higher concentrations of diethylzinc accelerated isomerization and resulted in reaction via the thermodynamically favored allenylzinc **9** to provide homopropargylic alcohol **11**. Related experiments have been critical to delineation of the mechanisms of propargylation and allenylation reactions, and are the basis for assignment of reactions as following either a group I or group II mechanism in this review.

■ PROPARGYLATION REACTIONS OF KETONES

Metal-Catalyzed Propargylation Reactions. Recent advances in propargylation reactions have addressed the significant reactivity and selectivity challenges posed by ketones. Ketones are less electrophilic than aldehydes and require a more active catalytic system. In addition, selection between the *re* and *si* faces of ketones is more difficult because the large and small substituents may be sterically similar. In 2010, Shibasaki and co-workers reported the first enantioselective propargylation reaction of ketones.[34] This method employed a copper catalyst along with a modular ligand scaffold and allenylboronic acid pinacol ester **8**. A range of electron-rich acetophenone derivatives

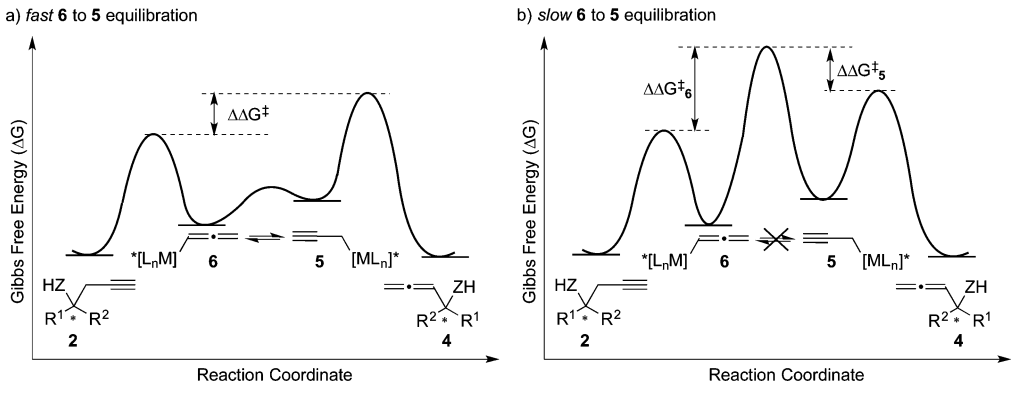


Figure 2. Possible mechanistic scenarios for group II additions: Isomerization of allenyl- and propargylmetal intermediates.

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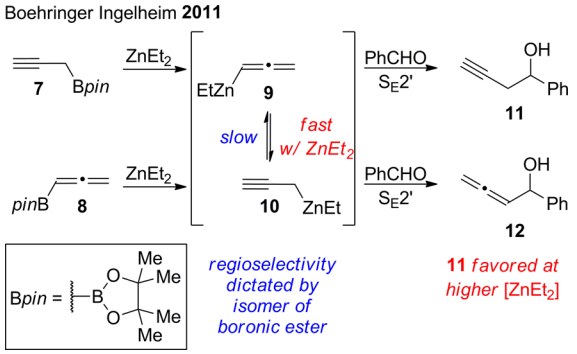
Scheme 2. Addition of Allenyl- and Propargylzinc to Aldehydes



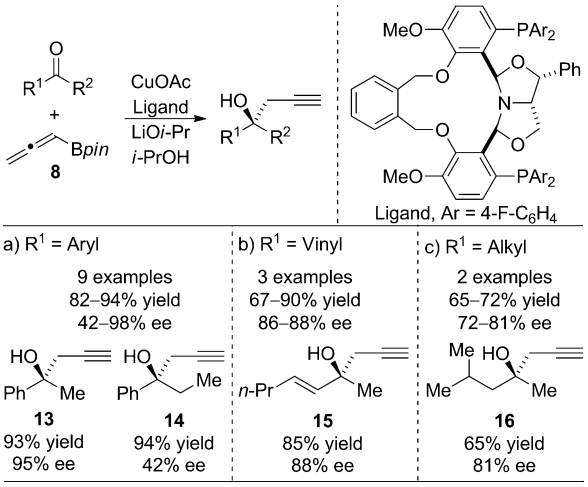


Figure 3. Copper-catalyzed propargylation of ketones. Conditions: allenylboronic acid pinacol ester **8** (1.5–3 equiv), CuOAc (2–5 mol %), ligand (2.4–6 mol %), LiO*i*-Pr (0.5–1 equiv), *i*-PrOH (1 equiv), CH_2Cl_2, −75 °C, 19–72 h.

and heteroaromatic methyl ketones afforded tertiary alcohols in both good yields and enantioselectivities (ee) (Figure 3a). Substituting the methyl substituent for an ethyl group resulted in decreased ee when forming **14**. Enones were also competent substrates in the reaction: products of 1,2-addition were isolated with high ee (≥86% ee, Figure 3b). Alkyl ketones could also be used in this transformation, although both the yield and ee were lower with these substrates (Figure 3c).

Shortly after Shibasaki's original report, Fandrick and co-workers disclosed a copper-catalyzed propargylation method.[35] The Boehringer Ingelheim team focused on propargylation of methyl ethyl ketone, a particularly challenging substrate for enantioselective addition reactions because the two substituents are very similar in size. The copper-catalyzed propargylation reaction utilized a commercially available ligand and trimethylsilyl (TMS)-protected propargylborolane **17**. A range of alkyl ketones afforded homopropargyl alcohols in good yields and high ee (Figure 4a). The catalytic system proved to be general: a range of both electron-poor and electron-rich acetophenone derivatives could be propargylated in high yields with high enantioselectivity (Figure 4b). Enones were also competent substrates and afforded 1,2-addition products (Figure 4c).

Fandrick and co-workers proposed a group II mechanism initiated by transmetalation of a copper precatalyst with propargylborolane **17** to afford an allenyl copper intermediate

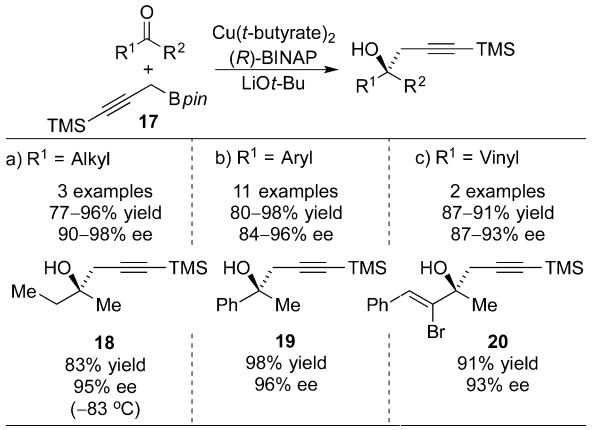
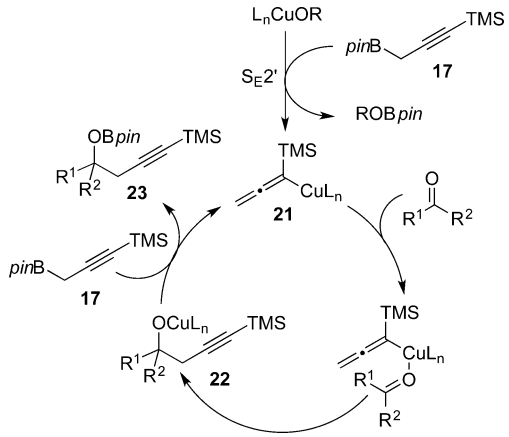


Figure 4. Copper-catalyzed propargylation of alkyl and aryl ketones. Conditions: propargyl borolane **17** (1.4 equiv), Cu(*tert*-butyrate)$_2$ (5–10 mol %), (*R*)-BINAP (7–15 mol %), LiO-*t*-Bu (8 mol %), THF, −62 °C, 18–35 h.

Scheme 3. Proposed Mechanism of Copper-Catalyzed Propargylation Reactions of Ketones



(**21**, Scheme 3). Subsequent coordination of the carbonyl activates the electrophile for addition. The resultant propargylated intermediate **22** transmetalates with borolane **17**, regenerating **21**.

Since both the Shibasaki and Fandrick reactions utilized a copper-based catalyst and a borolane transmetalating agent in the presence of an alkoxide base, by Occam's razor one may hypothesize that they proceeded through a similar mechanism. While Shibasaki used an allenylborolane **8** and Fandrick propargylborolane **17**, both systems afforded propargyl products. These results are most consistent with the Curtin–Hammett principle where formation of rapidly equilibrating allenyl- and propargylcopper intermediates leads to the same major product in both transformations (Figure 2a). An alternative explanation is that the Shibasaki and Fandrick reactions undergo two different mechanisms: both reactions would generate homopropargylic alcohol if the Shibasaki reaction proceeded through a Lewis acid-catalyzed, direct addition of allenylborolane (group I) and the Fandrick reaction went through the proposed group II mechanism.

Recently, Fandrick and co-workers expanded the scope of their transformation to include the highly reactive trifluoromethyl ketones.[36−38] A zinc catalyst ligated by proline derivative **24** was

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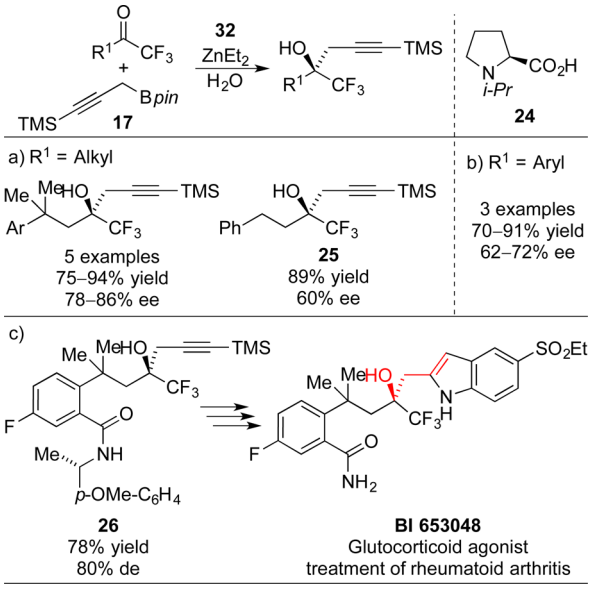

Figure 5. Zinc-catalyzed propargylation reaction of trifluoromethyl ketones. Conditions: propargyl borolane **17** (1.2 equiv), proline **24** (27 mol %), $ZnEt_2$ (25 mol %), H_2O (2 mol %), THF, −40 °C, 2 d.

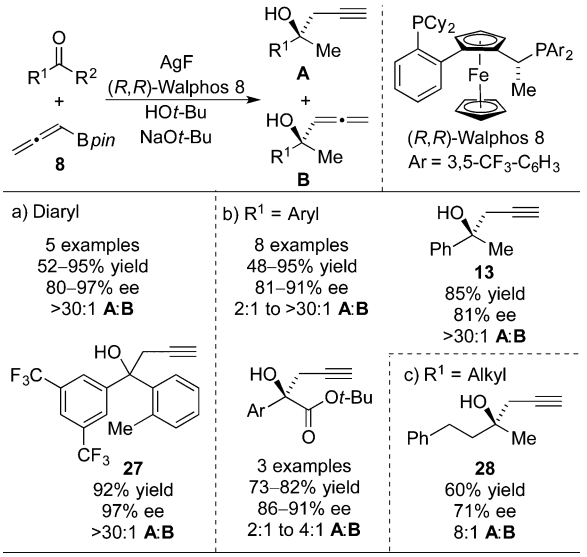

Figure 6. Silver-catalyzed propargylation reaction of ketones. Conditions: allenylboronic acid pinacol ester **8** (4 equiv), AgF (5−10 mol %), (*R*,*R*)-Walphos 8 (6−11 mol %), HO-*t*-Bu (1.1 equiv), NaO-*t*-Bu (15−30 mol %), MeOH then *t*-BuOMe, −20 °C, 6 h.

used to replace the copper catalyst. Ketones containing alkyl substituents with *β-gem*-dimethyl groups provided the desired products with highest enantioselectivity (Figure 5a). Removal of this structural feature reduced the ee of product **25** (60% ee, Figure 5a). In addition, aryl ketones were competent substrates and desired products were formed in yields ranging from 70 to 91% and with moderate ee (Figure 5b). This methodology was applied to the diastereoselective synthesis of **BI 653048**, a small molecule therapeutic for the treatment of rheumatoid arthritis (Figure 5c).

This transformation is proposed to proceed through a similar mechanism as the copper-catalyzed reaction. The observed regioselectivity, formation of homopropargylic alcohols, is most consistent with a group II mechanism since direct addition (group I) would likely lead to formation of allenyl products (Scheme 1).

In comparison to other ketone classes, methods for enantioselective addition reactions to diaryl ketones are limited because there is minimal steric differentiation between the two carbonyl substituents.[39] Recently, we have disclosed the first method for enantio- and regioselective propargylation of this substrate class.[40] We found that silver salts ligated by a ferrocene-based ligand, (*R*,*R*)-Walphos-**8**, afforded the desired product with *ortho*-substituted 1,1-diaryl ketones in moderate to excellent yield and with good to excellent enantioselectivities (Figure 6a). In all cases, the observed regioselectivity was excellent, favoring formation of the homopropargyl alcohol. The methodology was not limited by substrate class, and a range of ketones underwent smooth propargylation reactions. *α*-Ketoesters afforded desired product with good yields and good enantioselectivity (Figure 6b). In addition, both electron-rich and electron-poor acetophenone derivatives as well as alkyl ketones were competent substrates in this reaction (Figure 6b,c).

The preferential formation of propargyl products is consistent with both group I and group II mechanisms. However, the erosion of regioselectivity observed for the more electrophilic *α*-ketoesters (Figure 6b) supports a group II mechanism. As rate of nucleophilic attack increases, addition and isomerization are closer in energy resulting in a switch between scenarios a and b in Figure 2.

Organocatalytic Propargylation Reaction of Ketones. Addition to carbonyl electrophiles can also be accomplished in the absence of metal catalysts. Schaus and co-workers demonstrated that a chiral diol can catalyze addition of borolane **29** to a range of ketones when exposed to microwave irradiation.[41] This reaction featured a broad substrate scope and provided high yields of propargylation for an *α*-ketoester as well as acetophenone and its derivatives (**30** and **13** respectively, Figure 7a). Dialkyl ketones (Figure 7b) and enones (Figure 7c) were also competent electrophiles although slight variability in both yield and ee was observed.

The authors next investigated reactions of racemic mixtures of chiral allenes. In the presence of the BINOL catalyst, moderate to good diastereoselectivity was observed, and both diastereomers were formed in good ee (Figure 8). This reaction was the first example of a kinetic resolution of the nucleophile in an addition to a ketone. Using this strategy, highly substituted products were synthesized in a straightforward manner without recourse to enantioselective synthesis of chiral allenylborolane reagents.

The mechanism of this transformation is an example of direct addition (group I). Based on their related studies of enantioselective allylation reactions,[42] the authors postulated that the chiral diol partially displaces the ethylene glycol backbone of the borolane, providing a chiral nucleophile (Figure 9). Subsequent coordination of the carbonyl to the electrophilic boron center activates the ketone for addition. The authors proposed a closed transition state which favors formation of *syn* products.[43]

Redox Propargylation Reaction of Ketones. In contrast to the reactions described in the previous section, redox processes employ propargyl halides and require a redox-active metal catalyst or reagent. Since allenyl- or propargylmetal reagents are often synthesized from the corresponding halides, redox reactions offer a more step-economical approach to addition chemistry.[44] Sigman and co-workers utilized a combination of synthetic and computational approaches to identify an enantioselective catalyst for Nozaki−Hiyama−Kishi (NHK)

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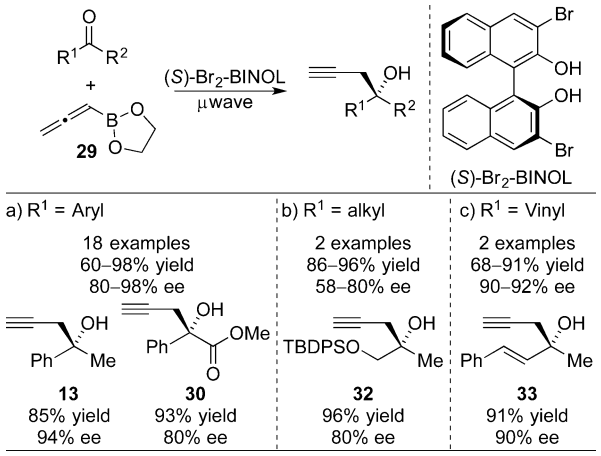

Figure 7. Microwave-promoted propargylation of ketones. Conditions: allenylboronic ester **29** (1.5 equiv), (*S*)-Br_2-BINOL (10 mol %), microwave.

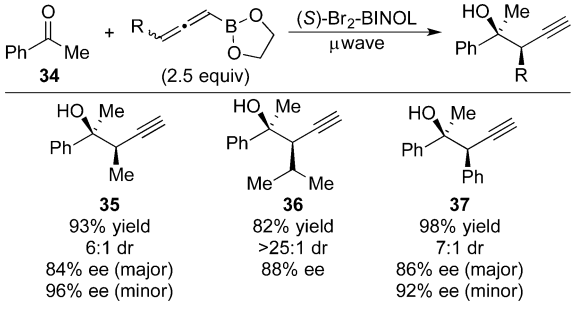

Figure 8. Kinetic resolution of racemic allenylborolane. Conditions: allenylboronic ester (2.5 equiv), (*S*)-Br_2-BINOL (10 mol %), microwave.

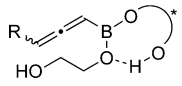

Figure 9. Chiral nucleophile.

propargylation of ketones.[45,46] In addition to tackling a synthetic challenge, this experiment served as a testing ground in the use of free energy relationships for rational design of enantioselective catalysts. Initially, oxazoline-proline based ligands were investigated. By varying the steric bulk at two different positions (R^1 and R^2, Figure 10a), the authors generated a preliminary data set to calibrate computational studies. Fitting the obtained data allowed them to predict that a maximum enantioselectivity of 50% would be expected with the oxazoline−proline scaffold.

To achieve synthetically useful levels of enantiomeric excess, a second ligand class was designed (Figure 10b). While the proline component was conserved, the oxazoline was replaced with a quinoline. Instead of varying sterics at two different positions, this design allowed for systematic variation of the electronic properties of the quinolone (R^1) and the steric properties of the proline moiety (R^2). This class of ligands showed a synergistic dependence of electronic and steric effects. In electron-rich systems, changes to the steric environment had a more pronounced effect on ee than when the ligand was electron-poor. In fact, a catalyst containing the methoxy-substituted quinoline moiety provided high ee, which approached the maximum calculated for this ligand class.

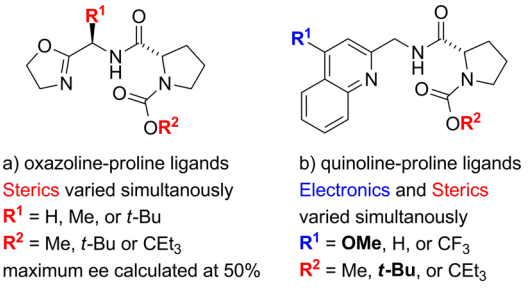

Figure 10. Ligand design for NHK propargylation.

Having identified the optimal catalyst for the NHK propargylation of ketones, the authors determined the substrate scope of the transformation. Both aryl (Figure 11a) and alkyl ketones (Figure 11b) performed well in the transformation, affording products in moderate to good yields. The authors noted that steric bulk of the substrate itself was important and increasing substitution α to the carbonyl provided desired products in higher ee. For example, phenyl ethyl ketone afforded **14** in 76% yield and 72% ee, while the bulkier phenyl isopropyl ketone reacted to form alcohol **39** in comparable yield but a much higher ee (92%, Figure 11a).

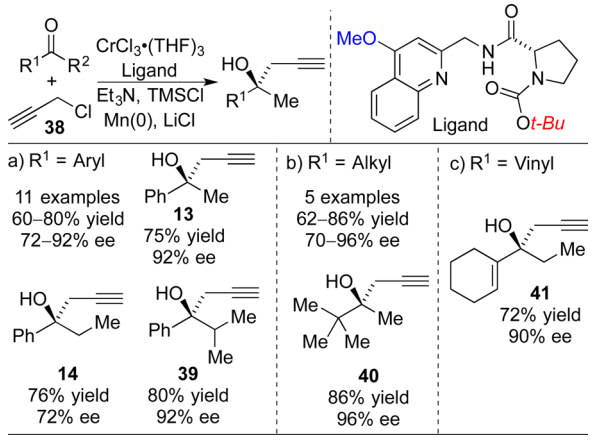

Figure 11. Substrate scope of NHK propargylation. Conditions: propargyl chloride **38** (3.0 equiv), $CrCl_3$·$(THF)_3$ (10 mol %), ligand (11 mol %), Et_3N (20 mol %), TMSCl (4 equiv), Mn(0) (2 equiv), LiCl (1 equiv), THF, rt, 72 h.

Classification of the mechanism of this redox reaction according to the schema in this review is straightforward: since the reaction proceeds via a metal-catalyzed oxidative addition event to generate an allenyl- or propargylmetal species in situ before addition to the carbonyl can occur, it is a group II reaction. Further interpretation of the results to distinguish between fast and slow isomerization of the resultant organometallic intermediates is not possible since the observed regioselectivity could arise from either mechanistic scenario described in Figure 2.

■ PROPARGYLATION REACTIONS OF IMINES

Despite the wealth of methods for enantioselective addition to imines, propargylation reactions remained a challenge until recently.[47−49] In 2002, Akiyama reported catalytic enantioselective propargylation reactions of α-iminoesters.[50] Both propargyl- and allenyltin reagents were employed in this copper-catalyzed transformation. Addition of unfunctionalized allenyltributyltin

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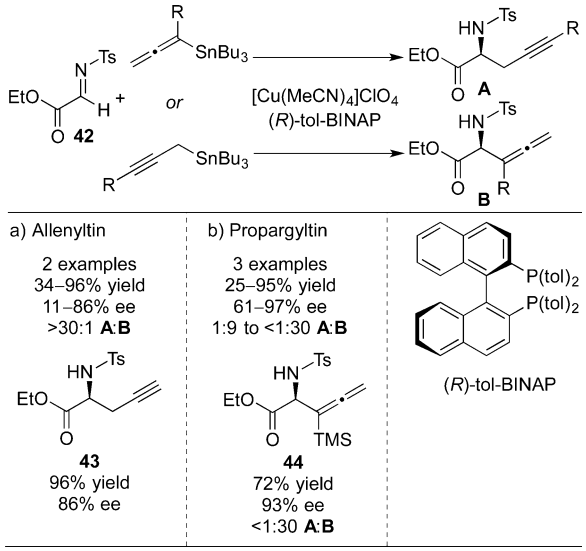

Figure 12. Enantioselective propargylation and allenylation of α-iminoesters. Conditions: α-imino ester (2.0 equiv), $[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP (1 mol %), Et_2O, −30 °C.

afforded **43** in 96% yield and 86% ee (Figure 12a). Propargyltin reagents were also used in this reaction to afford allenyl products ranging from 25% to 95% yield and with enantioselectivites up to 97% (Figure 12b).

This transformation is an example of Lewis acid catalyzed direct addition (group I). Consistent with this mechanism, allenyltin reagents afforded propargylic products and propargyltin reagents provided allenylic products. The observed regioselectivity of this reaction contrasts Fandrick's copper-catalyzed propargylation of ketones which proceeds by a group II mechanism. When TMS-protected propargyltributyltin was used in conjunction with copper, allene **44** was formed as the major product (Figure 12b); however, addition of TMS-protected propargylborolane **17**, also catalyzed by copper, afforded propargyl products (Figure 4). It is likely that the observed regioselectivity can be attributed to the relative nucleophilicity of the propargylmetal reagent: the more nucleophilic propargyltin complex favors direct addition (group I) while the less nucleophilic propargylborolane complex undergoes transmetalation with copper prior to addition (group II).

Our laboratory reported enantioselective propargylation of imines in 2011.[51] This reaction employed a silver catalyst analogous to the one used for propargylation of ketones.[39] We found that the transformation was general for a range of aryl aldimines of varying electronic properties (Figure 13a). We also showed that while a sulfonyl protecting group was necessary for the reaction to proceed, the easily deprotected nosyl group was well tolerated and **46** was formed in good yield and ee. An α,β-unsaturated imine could also be propargylated with good enantioslectivitiy, although **47** was formed in diminished yield (Figure 13b). Sterically congested alkyl imines were also competent substrates, although both the yield and the ee suffered as compared to aryl imines (Figure 13c). Since the use of allenylborolane **8** to form propargyl products is consistent with both group I and group II reactions, further experiments are necessary to elucidate the mechanism of this reaction.

Recently, Hoveyda and co-workers reported a copper-catalyzed propargylation of phosphonoyl imines.[52] The enantioselectivity of this system was exceptionally high across

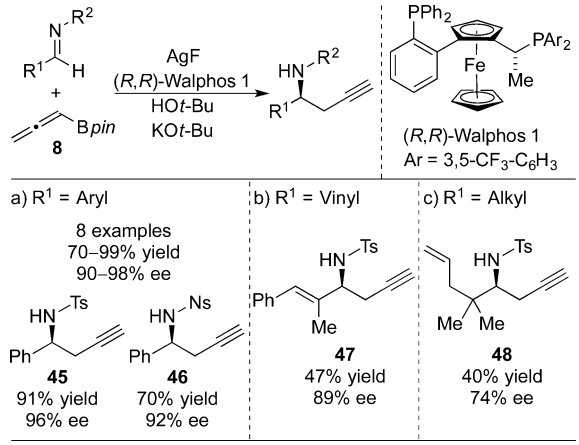

Figure 13. Silver-catalyzed propargylation of aldimines. Conditions: allenylboronic acid pinacol ester **8** (2−4 equiv), AgF (10 mol %), (*R,R*)-Walphos 1 (12 mol %), HO-*t*-Bu (1.1 equiv), KO-*t*-Bu (20 mol %), MeOH then THF, − 20 °C, 8 h.

many substrate classes including alkyl imines (Figure 14). The protecting group was easily cleaved to afford the free homopropargylic amines. The authors propose a group II mechanism, which proceeds through an allenylcopper intermediate to afford propargyl products preferentially, similarly to the Shibasaki (Figure 3) and Fandrick (Figure 4) reactions.

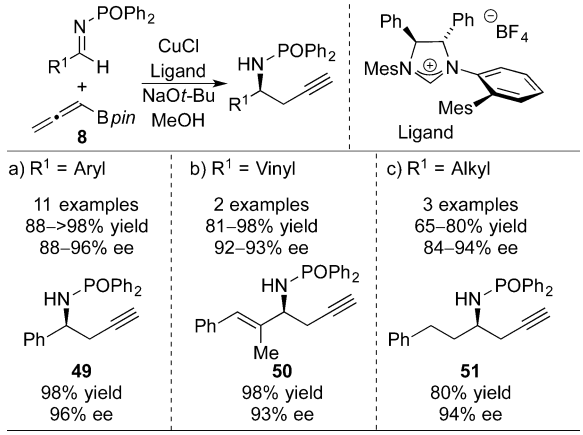

Figure 14. Copper-catalyzed propargylation of imines. Conditions: allenylboronic acid pinacol ester **8** (1.4 equiv), CuCl (1 mol %), ligand (1 mol %), NaO-*t*-Bu (3−5 mol %), MeOH (2 equiv), THF, rt, 1−6 h.

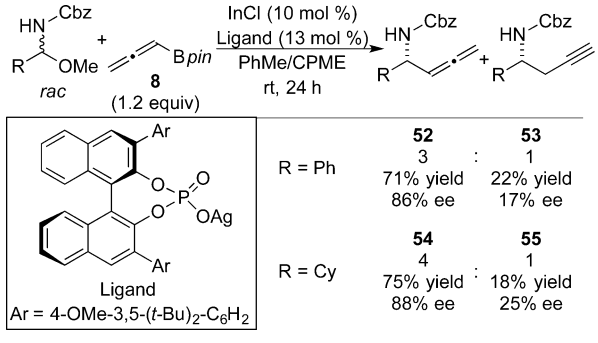

Figure 15. Allenylation of imines.

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Allenylation Reaction of Imines. To date, there has only been one report of an enantioselective allenylation reaction of imines. Kobayashi and co-workers demonstrated moderate selectivity for allenylation over propargylation when *N*,*O*-aminals were treated with allenylborolane **8** in the presence of indium and a chiral phosphate (Figure 15).[53] The substrate decomposes in situ to reveal an imine which undergoes the allenylation reaction. The regioselectivity of this reaction is consistent with a group II mechanism since direct addition of borolane **8** would most likely result in the formation of propargyl products (Scheme 1a).

CONCLUSIONS

Propargylation and allenylation reactions provide powerful tools for construction of orthogonally functionalized building blocks. Despite the challenges associated with the development of methods that require control of enantioselectivity and regioselectivity, the utility of these transformations has inspired multiple groups to address this bond construction. As new methods emerge, they further our understanding of the reactivity of propargyl and allenyl nucleophiles, allowing for development of more powerful catalysts that enable synthesis of increasingly complex structures. As understanding of the key intermediates in these reactions is further refined by mechanistic experiments, the scope of these transformations continues to grow. While several methods now exist for propargylation of ketones and imines, many new directions are in sight, including reactions of substituted nucleophiles and enantioselective allenylation reactions.

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Notes

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Photo provided by Elizabeth Swift.

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Photo provided by Tommaso Baldacchini.

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