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The Enantioselective Addition of Alkyne Nucleophiles to Carbonyl Groups

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Abstract

Over the past decade, large strides have been achieved in the invention of methods for the direct enantioselective addition of alkynes and metal alkynylide nucleophiles into prochiral aldehydes, ketones, and imines. This review highlights and compares the available methods for these transformations.

Keywords

alkynylation; propargylic amine; propargylic alcohol; catalytic asymmetric

1 Introduction

Enantioenriched propargylic alcohols and amines are useful and versatile building blocks in asymmetric synthesis.[i] For example, optically active propargylic alcohols and amines serve as precursors for a variety of chiral materials since the heteroatom and alkyne are handles for further transformations. This is demonstrated in the case of propargylic alcohol **1** (Figure 1). Activation of the alcohol and direct displacement with a nucleophile or in an S_N2' fashion can lead to quarternary carbon stereogenic centers (**2**) or optically active allenes (**3**). Selective reduction can afford the alkane (**4**) or alkene (**5**). Metal-catalyzed [2+2+2] cycloadditions afford benzylic alcohols (**6**),[ii] and hydrosilylation can furnish vinyl silanes (**7**)[iii] which can be further functionalized to tri-substituted olefins (**8**) or oxidized to hydroxy ketones (**9**). For this reason, propargyl alcohols[iv] and analogously propargyl amines[v,vi] have been used intermediates in the efficient synthesis of many natural products.

The two most common methods to prepare optically active propargylic alcohols are through i) asymmetric reduction of an ynone (Scheme 1, eq 1), and ii) asymmetric metal-catalyzed alkynylation of a carbonyl group (Scheme 1, eq 2).[vii]

Although a tremendous amount of work has led to highly enantioselective catalytic hydrogenations, application of these methods is ultimately limited by the necessity of an alkynyl ketone starting material. Ynones are accessible, however the functional group suffers from a propensity to decompose, to isomerize to allenyl ketones, or to react as potent Michael acceptors. Also, by virtue of hydrogen addition, reduction cannot give access to tertiary alkynols. One solution to this problem is the application of alkyl additions to an

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Dedicated to Professor Armin de Meijere on his 70th birthday.

ynone. Despite research addressing this problem,[viii] alkyl additions are often complicated by ynone instability as well as the high reactivity of the metalated alkyl group.

The addition of a terminal acetylide to a carbonyl[vii] (eq 2) alleviates both of these strategic concerns. There is no necessity for an ynone or ynal as the carbonyl partner; any aldehyde or ketone can be attacked to furnish a propargylic alcohol. Alkynylation of a ketone ($R^2 \neq H$) or imine would grant access to tertiary carbinol centers or propargylic amines respectively. The addition of an acetylide has the possibility to yield a convergent synthesis, adjoining two complex pieces while forming a stereocenter. This review will entail the development of effective technology for the enantioselective direct addition of alkyne nucleophiles to prochiral carbonyl groups.

2 Enantioselective Alkynylation of Aldehydes

2.1 Lithium Acetylide Addition to Aldehydes

The first example of an enantioselective alkyne addition to an aldehyde was published by Mukaiyama and coworkers.[ix] Trimethylsilylacetylene was deprotonated with *n*-BuLi and a superstoichiometric amount of **16** was added (Scheme 2). Lithium acetylides add to aldehydes at −78 °C and this background reaction led to moderate ee (78%). Fortunately, lowering of the temperature to −123 °C increased the enantiomeric excess to 92%. Additionally, it was found that a slow addition of the aldehyde minimized the background reaction. The substrate scope of this methodology featured benzyaldehyde and a range of silyl acetylenes (TES-, TBS-, Ph_3Si-, Ph_2MeSi-).

2.2 Alkylzinc-Mediated Enantioselective Alkynylations of Aldehydes

The use of alkylzinc compounds for the chemoselective addition to aldehydes has been an active area of research since its disclosure in 1978.[x] Alkynylzincs feature a high functional group tolerance and a slow rate of addition to carbonyl groups in the absence of a Lewis basic ligand.[xi] The use of alkynylzinc or alkylalkynylzinc reagents for the addition of an alkyne to an aldehyde was developed on the shoulders of the well-established alkyl additions,[viic] and the first examination of this process was carried out by Soai and co-workers.[xii] Heating of an alkyne with diethylzinc in THF to form bisalkynyl zinc (**19**), and subsequent treatment with amino alcohol **20** and an aldehyde furnished propargylic alcohol **21** in excellent yields (up to 99%), but in low enantioselectivities (Scheme 3). This research proved the viability of alkynylzinc species as a nucleophile for asymmetric addition to aldehydes.

The rationale for enantioselectivity is in agreement with the model proposed by Noyori for the addition of alkyl groups from dialkylzincs to aldehydes catalyzed by ephedrine derivatives (Scheme 4).[xiii] One zinc atom is bound to the amino alcohol and another equivalent of dialkyl- or dialkynylzinc binds the oxygen. The aldehyde binds the Lewis acidic zinc atom and alkyl or alkynyl transfer furnishes the product. The enantioselectivity is governed by which of the two lone pairs of the aldehyde binds the catalyst. The steric clash depicted in the unfavorable binding event (**23**) between the R group on the zinc and the R_1 group of the aldehyde dictates the enantioselectivity. This model provides a rationale for the absolute chemistry observed.

The report from Niwa and Soai[xii] prompted researchers at Ciba-Geigy AG to disclose their enantioselective alkynylations (Scheme 5).[xiv] While operating with stoichiometric amounts of *N*-methylephedrine (**25**) and a different experimental procedure much-improved enantioselectivities were observed. Initial results from the phenylacetylene ethylzinc (**26**) and neutral catalyst gave desired propargylic alcohol **28** in 68% yield (42% ee). Preforming the lithium salt of *N*-methylephedrine and using the phenylacetylene zinc bromide (**27**)

resulted in 80% yield and 88% ee. Similarly, pyridyl ligands were employed in the enantioselective alkynylation of aromatic aldehydes by Falorni (**34**)[xv] and by Oshino (**35**),[xvi] furnishing propargylic alcohols in moderate ee (Scheme 6). Researchers at Merck studied the addition of zinc alkynylides to aldehydes catalyzed by 10 mol% of ephedrine derivative **31** (Scheme 6).[xvii] The reactions were ligand accelerated. The background reaction went to 30% conversion in 17 hours, and the catalyzed reaction was complete after only 3 hours. Additionally, the zinc alkynylide species was made via a 1:1 mixture of dimethylzinc and the alkyne. NMR studies showed that no deprotonation occured in toluene at room temperature until the amino alcohol ligand **31** was added. Thus, the zinc-ligand complex catalyzed the deprotonation of terminal alkynes with alkyl zincs. Additionally, dimethylzinc was used instead of diethylzinc to avoid alkyl addition. While 5–12% methyl addition was observed as a by-product in pure toluene, by changing the solvent to a 3:1 mixture of toluene and THF, no methyl addition was observed.

A small non-linear effect[xiii] was observed (40% ee ligand produced 53% ee product), implying the reactive intermediates were not monomeric in ligand. Good yields and selectivities were obtained with only 10 mol% catalyst. This study focused on the use of phenyl acetylene and aromatic aldehydes, however 1-pentyne was proven effective. In analogy to these conditions, Chan described the efficient alkynylation of aromatic aldehydes with BINOL-derived amino alcohol **36**.[xviii]

Several research groups aimed at using new ligands and reaction conditions to increase the substrate scope of the reaction. Wang and co-workers developed methodology utilizing an excellent stoichiometry of zinc alkynylide to aldehyde (1.4:1) with bifunctional pyridine-containing amino alcohol ligand **38** (Scheme 7).[xix] The authors propose that the pyridine acts as a Lewis base to activate the alkynyl ethylzinc for nucleophilic addition (**40**). Excellent scope of aldehydes was observed for the addition of phenyl acetylene. Similar results were garnered by substituting the pyridine for an *N*-Tf moiety.[xx]

Trost's commercially available ProPhenol catalyst (**41**)[xxi] was shown to facilitate the enantioselective addition of zinc alkynylides to unsaturated aldehydes (Scheme 8).[xxii] The authors proposed that treatment of **41** with dimethylzinc formed the active bifunctional catalyst (**42**), capable of binding both the nucleophile and the electrophile within the chiral space (**43**). Sensitive α,β-unsaturated aldehydes and a wide variety of alkynes including alkyl alkynes and TMS–acetylene were employed yielding propargylic alcohols in high chemical and optical yields.

This methodology was used in the context of the total synthesis of several natural products[xxii] including adociacetylene B (Scheme 8).[xxiib] Bis-aldehyde **44**, previously shown to be an unsuitable substrate for Carreira's conditions,[xxiii] was treated with ProPhenol (**41**), TMS–acetylene, and dimethylzinc to furnish desired diol **45** in 60% yield with >99% ee.

Dahmen surveyed a large library of chiral ligands (including salen, quinine, ephedrine, prolinol, and [2.2]-paracyclophane-based ligands (**47**, Figure 2)) in the alkynylation of benzaldehyde. Optimal enantioselectivity was obtained in the presence of DiMPEG (poly(ethyleneglycol) dimethyl ether).[xxiv] Optimized conditions effected the alkynylation of aliphatic aldehydes and were tolerant of TMSacetylene albeit with slightly diminished ee's (<80%). The author speculates that the additive could prevent the formation of dialkynylzinc, a material shown to alkynylate aldehydes in lower ee. DiMPEG was also found to be an effective additive in the asymmetric alkynylation of aldehydes catalyzed by ferrocenyl amino alcohols (**46**).[xxv]

The number of amino- and imino alcohol ligands capable of effecting alkynylations is growing. Mono[xxvi] and bisoxazolidines[xxvii] (**48**) have been successfully employed in the asymmetric alkynylation of aldehydes, and generally function best with aromatic aldehydes. Pu found the use of substituted BINOL ligands[xxviii] and chiral macrocycle (**49**) for the addition of phenyl acetylene to aliphatic and α,β-unsaturated aldehydes to be effective.[xxix]

2.3 Titanium-Catalyzed Zinc Alkynylide Additions to Aldehydes

Another successful strategy for the enantioselective alkynylation of aldehydes involves the use of a chiral ligand bound to titanium. It is possible that the titanium catalyst acts only as a chiral Lewis acid, binding the aldehyde to increase the rate of zinc alkynylide addition. However, recent mechanistic studies on the titanium-catalyzed alkyl addition[xxx] indicate that the alkyl group is likely bound to the titanium catalyst through a transmetalation, and the organotitanium complex is responsible for addition to the aldehyde.[xxxi]

The titanium-BINOL-catalyzed enantioselective alkynylation of aldehydes was independently developed by both Pu and Chan (Scheme 9). Pu and co-workers accomplished the alkynylation of aromatic aldehydes with a variety of different alkynes (eq 1). It was found that zinc alkynylide formation required refluxing of the alkyne and diethylzinc in toluene for five hours under a nitrogen atmosphere. It was later found that the addition of two equivalents of HMPA allows for this step to run at room temperature to increase the functional group tolerance of the process.[xxxii] Subsequent addition of Ti(O-*i*-Pr)$_4$ then BINOL and the aldehyde afforded the corresponding propargylic alcohols in high yield and >92% ee.[xxxiii] Increasing the catalyst loading to 40 mol% BINOL and the use of 1 equivalent of titanium was necessary for the effective alkynylation of aliphatic and α,β-unsaturated aldehydes.[xxxiv] Additionally, Pu showed that functionalized octahydro-BINOL ligands increased the enantioselectivity of these alkynylations.[xxxv]

Chan's experimental setup was similar to Pu's although dimethylzinc was used, and the zinc alkynylide was treated with preformed titanium-BINOL after 15 minutes at room temperature (eq 2).[xxxvi] Additionally, only 1.3 equivalents of the alkyne and 1.2 equivalents of dimethylzinc were required (as opposed to 2 equivalents used by Pu). Chan used only phenyl acetylene as the donor, and produced the corresponding propargylic alcohol **39a** from benzaldehyde in high yield and ee. The enantioselectivity was lower in the case of aliphatic aldehydes and *ortho*-substituted benzaldehydes. It was later determined that the addition of chiral additives could increase the enantioselectivity of the alkynylation reaction.[xxxvii] When N-tosyl norephedrine (10 mol%) combined with BINOL (10 mol%) and titanium(IV) isopropoxide (15 mol%), aromatic aldehydes were alkynylated in up to 99% ee. The addition of phenol increased the ee's across the board and allowed for the alkynylation of alphatic aldehydes with high ee.[xxxviii]

In Marshall's synthesis of cytostatin, Pu's conditions were proven effective for a catalystcontrolled diastereoselective alkynylation of aliphatic aldehydes containing an α-stereocenter with TMSacetylene in contrast to several other methods.[xxxix] Recently, bisoxazolidine and bis(β-hydroxy amide) ligands have been shown effective BINOL substitutes under identical reaction conditions.[xl,xli]

2.4 Zinc Salt-Promoted Alkynylation of Aldehydes

While relatively strong bases are required to deprotonate a terminal alkyne, coordination of the π-system with an appropriate metal salt can drastically increase the acidity. This strategy was originally exploited for the alkynylation of aldehydes by Yamaguchi and co-workers with tin(II) triflate and an amine base (Scheme 10, eq 1),[xlii] and later accomplished with gallium(III) iodide.[xliii] Utilization of copper or silver salts accomplished the metalation,

however the resultant metalated species were generally not nucleophilic enough to alkynylate carbonyl compounds.

In surveying various metal salts and reaction conditions, Carreira and co-workers accomplished an *in situ* generation of nucleophilic metalated alkynylides (Scheme 10, eq 2).[xliv,xlv] In the presence of catalytic zinc(II) triflate and Hünig's base in dichloromethane a variety of alkynes were metalated and rendered nucleophilic for the addition to nitrones, aldehydes, ketones, and N-tosyl imines. Spectroscopic evidence of in situ metalation was garnered via the ^{13}C NMR shifts of the *sp*-hybridized carbons in analogy to the Cu(I) or Ag(I) alkynylides,[xlvi] and by infrared spectroscopy.[xlvii]

The enantioselective variant of this strategy was achieved by the use of stoichiometric amounts of zinc(II) triflate, Hünig's base, and (+)-*N*-methylephedrine (**25**) (Scheme 11).[xlviii,xlix,l] Excellent yields and enantioselectivities were observed for aliphatic aldehydes with broad tolerance of alkyne substitution including acetylene gas (**57b**).[li] Aromatic and unsaturated aldehydes (**57c** and **57d**) were alkynylated in lower yield due to a competitive Cannizzaro disproportionation reaction. The robust reaction was shown to perform well without purfication of reagents and in reagent-grade toluene containing up to 300 ppm water.[lii] Jiang accomplished this transformation with zinc(II) chloride in the presence of TMS-chloride as an exogenous Lewis acid.[liii]

This process was rendered catalytic in zinc salt, base, and chiral ligand by raising the reaction temperature to 60 °C, employing triethylamine, and increasing the concentration (Scheme 12).[liv] Aromatic substrates were not reported, but the chemical and optical yields associated with aliphatic aldehydes (especially α-branched aldehydes) were high. The addition products of linear aldehydes were isolated in lower yields due to self-condensation of the starting aldehydes. In a feat of atom economy, this transformation was performed under solvent-free conditions.

Since the report of the catalytic asymmetric alkynylation of aldehydes via soft metalation, several groups have reported improved protocols. Jiang and co-workers introduced a new amino alcohol ligand (**59**),[lv] while Davis and co-workers utilized carbohydrate-derived ligands.[lvi] This methodology has received a tremendous amount of attention from the community, and several natural products have been synthesized using this type of alkynylation as a key reaction by both the Carreira group[lvii] and others.[lviii] Inconsistent results of these alkynylations in the context of total synthesis have led to the speculation that the commercial supply of zinc(II) triflate is of variable quality.[lix,lx]

The soft metalation strategy for alkynylation is not limited to zinc, and was effectively extended to indium salts by Shibasaki and co-workers (Scheme 13).[lxi] The non-stereoselective version of this reaction was previously developed[lxii] and was based on the the dual nature of indium(III): acting as both a hard Lewis acid[lxiii] and an alkynyl activator.[lxiv] Enantioselective addition of alkynes to aldehydes was accomplished in the presence of BINOL (10 mol%), indium(III) bromide (10 mol%), and dicyclohexylmethylamine (50 mol%) in refluxing dichloromethane. The reaction conditions were not sensitive to air, and the catalyst loading could be dropped to only 2 mol% at higher concentrations (10 M). A strong non-linear effect was observed wherein 20% ee BINOL furnished **39a** in 94% ee. Excellent scope was observed with respect to both reacting species with the exception of silylalkynes, which were not tolerated. Subsequent work found that the reaction could tolerate 2-methyl-3-butyn-2-ol as a removable group on the alkyne.[lxv]

2.5 Alkynylations with Propiolate Nucleophiles

2.5.1 γ-Hydroxy-α,β-Acetylenic Ester Utility—The product resulting from the addition of propiolate to an aldehyde is an γ-hydroxy-α,β-acetylenic ester (**61**), an extremely versatile synthetic intermediate. Functional group transformations such as alkyne reduction (**64**), conjugate addition (**65**), amidation (**66**), saponification, and decarboxylation(**63**)[lxvi] can elaborate adduct **61** into a variety of useful building blocks. Additionally, complexity can be introduced by using metalcatalyzed rearrangements and additions such as tetronic acid formation (**67**)[lxxi] or the Ru-catalyzed alkene-alkyne coupling reaction (**68**).[lxvii] Owing to the flexibility of these adducts, it is not surprising that γ-hydroxy-α,β-acetylenic esters have been used as intermediates in the synthesis of many natural products.[lxviii] In spite of their synthetic utility, access to these adducts through enantioselective alkynylation of aldehydes has only recently been accomplished.

The first published attempt at the asymmetric addition of a propiolate nucleophile was in the context of a total synthesis by Koide and co-workers (Scheme 14).[lxix] Subjection of methyl propiolate (**70**) to the conditions of Carreira (zinc triflate, Hünig's base, and N-methylephedrine)[xlviii] did not lead to the desired alkyne addition product (**72**). Instead, the Lewis acidic conditions promoted the conjugate addition of the amine base with subsequent loss of an isopropyl group to furnish vinylogous carbamate **71** as the only observable product.

2.5.2 Zinc-Mediated Propiolate Additions—Methyl propiolate was shown to be an effective nucleophile in the alkynylation of aldehydes using the ProPhenol catalyst (Scheme 15).[xxii] Trost and coworkers pointed to the bifunctional nature of the catalyst (Scheme 8, **43**), which enabled the use of catalyst-bound zinc alkyoxides which are more weakly Lewis acidic than zinc triflate. These reaction conditions avoided decomposition of the sensitive alkynoic ester functionality, and yielded γ-hydroxy-α,β-acetylenic esters such as **74** in high yield and enantioselectivity.

2.5.3 Titanium-Catalyzed Propiolate Additions—Pu and co-workers examined the enantioselective addition of propiolate nucleophiles from the standpoint of their titanium-BINOL methodology. Initial attempts were frustrated by the decomposition of the propiolate when heating in toluene at reflux in the presence of diethylzinc. The formation of the zinc alkynylide was found to occur under more mild conditions at ambient temperature in the presence of hexamethylphosphoramide (HMPA).[xxxii] Under these new reaction conditions, the addition product was isolated, albeit in low yield. Optimization found that prolonging the treatment of methyl propiolate with HMPA, diethylzinc, and BINOL for 16 hours at room temperature followed by addition of the titanium and the aldehyde produced the desired transformation with a wide variety of aromatic[lxx] and aliphatic[lxxi] aldehydes (Scheme 16). Additionally, the products were selectively hydrated with Ziese's dimer to form optically active tetronic acids (Figure 3, **67**).

Chan and Wang attacked the propiolate addition problem with their *N*-tosyl alcohol ligand (**76**, Scheme 17).[lxxii] Surveying the literature, the authors showed that the ratio of alkynyl to alkyl transfer from the titanium-mediated zinc alkynylations was quite dependent on the ligand used, and this was attributed to the Lewis acidity of the catalyst. *N*-Tosyl alcohol (**72**) was shown to be less Lewis acidic than BINOL and therefore chosen to be used in the case of Lewis acid-sensitive propiolate donors. Additionally, the oxygens on the sulfonamide could serve as a Lewis base to catalyze the deprotonation of the alkyne in place of Pu's HMPA. Optimization showed that an exogenous Lewis base was required, and DME was used as an alternative to HMPA. Methyl propiolate served as a donor to furnish γ-hydroxy-α,β-acetylenic ester **77** in good yields and ee's with a variety of aldehydes.

2.6 Other Strategies for the Enantioselective Alkynylation of Aldehydes

Corey and Cimprich developed the enantioselective boron alkynylide addition to aldehydes in the presence of an oxazaborolidine (Scheme 18).[lxxiii] In a one-pot procedure, bromodimethylborane was added to the alkynyl stannane (**78**) to generate the dimethyl alkynyl borane (**79**) and one equivalent of tributyltin bromide. The oxazaborolidine catalyst (**80**) was then added (0.25–1.0 equivalents), followed by the aldehyde. Excellent enatioselectivities and yields were observed for the addition of both phenyl acetylene and 1-heptyne to a variety of aldehydes.

The proposed mechanism of this transformation (eq 2) features coordination of the Lewis basic nitrogen of oxazaborolidine **80** with dimethyl alkynyl borane **79** to form complex **82**. The Lewis acidic boron atom in the oxazaborolidine binds the aldehyde, and this promotes the transfer of the alkyne to the aldehyde. Both the high degree of enantioselectivity and the preference for the (*R*)-carbinols can be understood by the proposed transition state model (**83**) as a close analogy to the CBS reduction of ketones.[lxxiv] The shielding of one face of the oxazaborolidine by the aryl groups favors coordination of the reagents to the opposite face. The lone pair on the aldehyde *anti* to the large alkyl group binds preferentially to avoid a steric clash with the R group of the oxazaborolidine catalyst.

The equivalent of tributyltin bromide formed in the reaction presumably does not affect the reaction, and was deemed unnecessary. In fact, in a single example the authors synthesized the alkynyl borane from the corresponding lithium acetylide (Scheme 18, eq 3) forming the desired optically active propargylic alcohol (**87**) in 72% yield with 88% ee (compared to 96% with 90% ee via the alkynyl stannane). This experiment shows that the tin salt is likely not crucial to the success of this reaction.

Maruoka and co-workers developed an enantioselective Meervein-Ponndorf-Verley (MPV) alkynylation (Scheme 19).[lxxv,lxxvi] In an analogy to the MPV reduction[lxxvii] (**92**) an aluminum catalyst binds both an alcohol and a carbonyl and affects an alkyne transfer in a six-membered transition state (**93**).[lxxviii] Chiral diol **90** in the presence of trimethylaluminum formed an active catalyst capable of binding a propargylic alcohol (**89**) and a suitably activated aldehyde (**88**) to initiate alkyne transfer in high yields and ee's. Substoichiometric amounts of aluminum catalyst could be used in some cases at the expense of enantioselectivity (50–60% ee), and the alkynylation of unactivated aldehydes was unsuccessful due to low conversion. This represents an interesting strategy for the synthesis of propargyl alcohols owing to the potential for high chemoselectivity in the presence of multiple alkyne functional groups.

3 Enantioselective Alkynylation of Ketones

The enantioselective alkynylation of ketones represents the most convergent and efficient strategy for the synthesis of optically active tertiary alcohols,[lxxix,lxxx] valuable intermediates for the synthesis of natural products. Additionally, tertiary alcohols are not available through reduction methods, making the alkynylation strategy particularly desirable. Recently, great strides have been made toward the realization of a general and efficient alkynylation of ketones.[viia,b,e]

The first enantioselective alkynylation of a ketone was developed at Merck and Dupont for the synthesis of anti-AIDS drug efavirenz (Scheme 20).[lxxxi,lxxxii] Pyrrolidine ephedrine derivative **31** was treated with dimethylzinc then a metal acetylide (**95**) to form zincate **96**. Addition of trifluoromethylketone **97** furnished the resultant tertiary alcohol **98**. Interestingly, the counter ion of the metal acetylide greatly affected the stereoselectivity of

addition to ketone **97**. In addition, Collum has reported thorough mechanistic studies in the case where lithium acetylides were employed.[lxxxib]

Aliphatic alkynes and phenyl acetylene were shown to be viable nucleophiles for alkynylation of α-ketoesters in the presence of catalytic zinc(II) triflate and amino alcohol **59** (Scheme 21).[lxxxiii] Excellent yields and enantioselectivities were observed for both linear and cyclic keto esters, however, enolizeable ketones were not tolerated.

The first general catalytic alkynylation of ketones was achieved by Cozzi.[lxxxiv] Dimethylzinc-mediated addition of terminal alkynes to a variety of unactivated ketones in the presence of Jacobsen's chiral salen ligand **104** afforded the corresponding tertiary alcohol product (**105**) in good yield (Scheme 22). This method was particularly outstanding with respect to substrate scope in both the alkyne and the aldehyde partners. The products were afforded in moderate to good yields and enantioselectivities. A more sterically bulky salen ligand was employed by Katsuki and co-workers to increase the enantioselectivity.[lxxxv] The difficulty in ketone alkynylation is generally ascribed to their extremely low reactivity toward nucleophilic addition of zinc alkynylides. The author proposed a mechanism involving complex **107** featuring activation of both the ketone and the reacting zinc acetylide to overcome this low reactivity. The enantiomeric excess of the corresponding alcohol products was shown to linearly correlate with the enantiomeric excess of salen ligand **104** suggesting a single molecule of catalyst in the enantiodetermining step.

Another successful strategy to affect the alkynylation of ketones was developed by Chan.[lxxxvi] To increase the electrophilicity of the ketone, a strongly Lewis acidic catalyst composed of sulfonamide **109** and $Cu(OTf)_2$ (10 mol %) was utilized, and zinc phenylacetylide was added to arylmethylketones in high yield and enantioselectivities (Scheme 23, eq 1). While extremely efficient with aryl ketones and phenylacetylene, the use of TMSacetylene or aliphatic ketones resulted in low chemical and optical yields. A full account of this material[lxxxvii] was recently published including a large screen of chiral ligands (including BINOL, pybox, and ephedrine derivatives) and the full optimization of reaction conditions.

Recently, Wang[lxxxviii] has utilized the same strategy with catalytic *N*-tosylproline (8 mol%) and $Cu(OTf)_2$ (8 mol%) to catalyze the addition of zinc phenylacetylide (4 equiv) to aromatic ketones (eq 2). Aliphatic ketones such as **111** were also excellent substrates for these conditions.

Independently, Cozzi[lxxxix] and Wang[xc] developed a titanium BINOL system to catalyze the alkynylation of ketones. Cozzi employed stoichiometric amounts of titanium phenylacetylides in the presence of catalytic BINOL for the addition to aryl ketones (Scheme 24, eq 1). Wang used a preformed BINOL titanium(IV) complex to be used as a catalyst for the addition of zinc phenylacetylides to both aryl and aliphatic ketones (Scheme 24, eq 2).

Instead of relying on a more Lewis acidic catalyst, Wang and co-workers observed ketone alkynylation utilizing only zinc phenylacetylide formed by the addition of phenyl acetylene to dimethylzinc and phenylglycine-derived Schiff base **118** (Scheme 25).[xci] An uncharacteristically low catalyst loading of amino alcohol **118** was tolerated, and aryl ketones such as 2-fluoroacetophenone (**117**) were alkynylated with phenyl acetylene in the presence of only 0.1 mol % **118**. The substrate scope was limited to arylmethylketones, phenyl acetylene and more recently, ethynylcyclohexene.[xcii] Recently, a solid supported version of the catalyst was developed for easy removal, although the enantioselectivity was generally lower than in the case of the solution phase catalyst.[xciii]

Shibasaki recently disclosed preliminary results in the enantioselective alkynylation of activated trifluoromethyl ketones using chiral bidentate phosphine ligand (**121a**) or pybox (**121b**) and a catalytic copper salt as a base (Scheme 26).[xciv] This represents the most atom economical strategy for the asymmetric alkynation of ketones as it is substoichiometric in both metal and ligand.

4 Enantioselectieve Addition of Alkyne Nucleophiles to Imines

4.1 Background

While a large number of methods to add an alkyne to an imine without stereocontrol have been developed,[xcv] the enantioselective variant of such reactions has received relatively little attention.[xcvi]

The first example of an enantioselective alkynylation of an imine was published by Huffman and co-workers at Merck (Scheme 27).[xcvii] The enantioselective addition of lithium acetylides in the presence of stoichiometric quinine alkoxide to *N*-acyl ketimine **123** was pursued for the synthesis of HIV reverse transcriptase inhibitor **126**. Extensive optimization showed that the enantioselectivity in these lithium acetylide additions was highly dependent on both the concentration and the temperature of the reaction. This dependency was attributed to a temperature-dependant aggregation state of the reactive lithium acetylide in solution. It was observed that the lithium acetylide was only partially soluble in THF, however, the addition of the quinine lithium salt fully solubilized the alkynylide. This methodology remained substrate specific, and has not been generally applicable to the synthesis of propargyl amines.

4.2 Copper-Based Methods

The copper-catalyzed alkynylation of imines was introduced by Li and co-workers,[xcviii,xcix,c,ci] and represents a much more general strategy for the synthesis of optically pure propargyl amines. The imines were generated *in situ* via dehydration of the aldehyde and amine components prior to the addition of phenyl acetylene, CuOTf, and pybox **129** (Scheme 28). While the substrate scope was quite limited to only aryl imines, the corresponding propargyl amines were isolated in excellent yields and enantioselectivities in either toluene or water. Bisia and Singh further optimized the enantioselectivity of these addition reactions by surveying other pybox ligands,[cii] and Weissberg et al demonstrated the viability of this process with a solid supported pybox catalyst.[ciii]

The scope of the alkyne to be used was increased upon the substitution of the ligand for binaphthyl imine **133**.[civ,cv] The use of 1-decyne was tolerated in the presence of bis-imine **133** to furnish the corresponding propargyl amine **134c** in 91% yield and 73% ee (Scheme 29). This represents the first example of an enantioselective addition of an aliphatic alkyne to an imine. Phenyl acetylene addition to substituted aryl imines produced the corresponding propargyl amines in <50% ee.

The catalytic system developed by Knochel and co-workers exhibited excellent substrate scope with respect to the aldehyde, amine, and alkynes used (Scheme 30).[cvi] This system was a direct analogy to the previously-developed alkynylation of enamines,[cvii] and functions without the formation and isolation of sensitive enamines. This alkynylation functioned with enolizable aldehydes to form propargyl amines such as **139c**. Both bis-benzyl and bis-allyl amines are tolerated, and can be mono protected for further funtionalization in the context of a chemical synthesis. The authors proposed a dimeric copper complex as the catalytically active species based on a large non-linear effect (70% ee product when using 10 % ee QUINAP). Excellent enantioselectivity in these additions was also observed by the utilization of the easily accessible modular ligand, PINAP (**140**).[cviii]

Recently, Chan and co-workers screened basic additives in the copper-catalyzed alkynylation of aryl imines with phenylacetylene.[cix] An increase in enantioselectivity was observed when one equivalent of dimethylzinc was added to the reaction mixture. Additionally, when the ratio of copper salt to pybox ligand (**129**) was varied in the phenylacetylene addition to α-imino ester **141** an interesting effect was observed (Table 1).[cx] The absolute stereochemistry of the alkyne addition adduct completely inverted from 1:1 ratio of copper salt to pybox ligand (entry 1, 63% ee) to the opposite antipode when a 1.5:1 ratio of copper salt to pybox ligand was used (entry 5, −70% ee). Additionally, a large effect was seen by the careful exclusion of water (entry 1 vs. 2) by the inclusion of molecular sieves.

4.3 Alkynylation of Imines Using Other Metals

Hoveyda and Snapper developed a Zr-catalyzed method for the enantioselective alkynylation of *N*-aryl imines in the presence of a mixed alkynylzinc species (Scheme 31).[cxi] The authors proposed that the zirconium could act as a Lewis acid by chelating the substrate (explaining the necessity of the 2-methoxy group). Interestingly, when dimethylzinc and TMS-acetylene are used in the absence of **145** and **146**, methyl addition product **148** is the only observed addition product.

The practicality and feasibility of a zinc-alkynylide addition was shown by the alkynylation of cyclic acyl imine **149** towards the synthesis of the drug Efavirenz (Scheme 32).[cxii] Treatment of cyclopropylacetylene with zinc triflate, triethylamine and stoichiometric quantities of amino alcohol **100** in toluene allowed for the formation of propargyl amine **150** in excellent yield and enantioselectivity even in the context of the industrial synthesis. Ligand **100** is potentially recovered and was reused up to three times. Additionally, other alkynes performed well under these reaction conditions.

In an ongoing effort to demonstrate the applicability of alkynylboranes in enantioselective additions, the Chong group established new alkynylation conditions for the synthesis of propargyl amines (Scheme 33).[cxiii] The moisture sensitive *N*-acylimines were prepared *in situ*[cxiv] from the corresponding *N*-TMS imines, and used without purification. A variety of substituted *N*-acylbenzaldimines (**151**) were tolerated in the alkynylation and this method was used towards the formal synthesis of (−)-*N*-acetylcolchinol.[cxv]

A solution of dimethylzinc and a terminal alkyne were shown to alkynylate a variety of protected imines in the absence of a chiral Lewis basic ligand.[cxvi] In spite of this potential setback, an enantioselective dimethylzinc-mediated alkynylation of *N*-aryl imines was developed by Bolm and coworkers, mediated by stoichiometric quantities of a norephedrine-based amino alcohol.[cxvii] A highly efficient catalytic alkynylation of *N*-tosyl arylimines was accomplished by the use of aryl-substituted BINOL (**156**) and dimethylzinc (Scheme 34).[cxviii] The reaction showed tolerance to phenylacetylene, 1-hexyne and 4-phenyl-1-butyne, and a variety of arylimines. Although aliphatic imines were surveyed, the corresponding propargyl amine products were isolated in low yields (<40%). The facile cleavage of the tosyl group from the product with SmI_2[cxix] renders this method useful in the arena of fine chemical synthesis.

5 Conjugate Addition of Metal Alkynylides to Enones

The conjugate addition of alkynyl groups to unsaturated ketones is a particularly difficult synthetic challenge. Organocuprates commonly employed for such additions of alkyl groups are not suited for the addition of alkynes due to the exceptionally strong bonding between copper and alkynes.[cxx] This trait has been exploited by using alkynyl ligands on mixed organocuprates as a nontransferable “dummy” ligand.[cxxi] For this reason, initial examples of

1,4-additions of alkynes featured alkynyl boranes[cxxii] and alanes.[cxxiii] The enantioselective variant of such reactions remains in its infancy, and only a handful of examples have been reported.

5.1 Conjugate Addition of Alkynyl Boranes and Boronates

The enantioselective conjugate addition of alkynylboronates to enones was first accomplished by Chong and co-workers.[cxxiv] The boronate BINOL ester of phenyl acetylene (**159**) was preformed, and added to enone **158** to form the corresponding alkynylated product **160** selectively (Scheme 35). The authors postulated a six-membered transition state with the chirality of the BINOL dictating the facial selectivity of the enone. Transition state **162** was disfavored due to an undesirable steric clash between the alkyne and the BINOL, favoring **161**. It should be noted that this mechanism requires enone to be in the *s-cis* conformation that is unavailable for cyclic enones such as cyclohexenone. Cyclohexenone was unreactive under these conditions, in support of the six-membered transition state hypothesis. This reactivity profile was previously observed in the racemic addition of alkynylborane reagents to Michael acceptors.[cxxii]

The BINOL-mediated conjugate addition was rendered catalytic in BINOL **164** by taking advantage of the propensity for alkoxy ligand on boron to exchange, and a rare example of a ligand accelerated process (Scheme 36).[cxxv] Both aliphatic and aromatic boron alkynylides were added to aromatic substituted enones in high yield and ee. Utilization of a catalytic amount of BINOL **164** had little effect on the optical purity of the corresponding alkynylated adducts such as **160**.

5.2 Nickel-Catalyzed Conjugate Addition of an Alkynylalane

The 1,4-addition to cyclic enones remains a difficult problem due to the inaccessibility of the more reactive *s-cis* conformation. This type of addition was previously accomplished in a nonstereoselective manner with zinc-[cxxvi] or aluminum acetylides.[cxxvii] The enantioselective conjugate addition of an alkyne nucleophile to 2-cyclohexen-1-one was reported by Corey and co-workers (Scheme 37).[cxxviii] Using cyanobisoxazoline nickel complex **167**, the addition of alane **166** to cyclohexenone (**165**) proceeded in 86% yield and with 82–88% ee. This preliminary communication only detailed the optimization of this single reaction, but the strategy is promising for the conjugate alkynylation of cyclic enones.

5.3 Conjugate Alkynylation with Zinc alkynylides

The enantioselective alkynylation of nitroolefins mediated by NME-**25** was achieved by Tomioka and co-workers (Scheme 38, eq 1).[cxxix] Three equivalents of dimethylzinc, phenylacetylene, and **25** in the presence of nitroolefin **169** furnished the desired adduct **170** in 65% yield. It was observed that inclusion of a radical inhibitor (galvinoxyl, 3 mol%) increased the isolated yield of **170** to 83%. A variety of substituted nitroolefins were tolerated under these conditions, and enolizeable electrophiles produced lower yields. Included in this research was a rare example[cxxvi] of a zinc-mediated asymmetric conjugate alkynylation (eq 2). Utilization of previous conditions in the presence of chalcone **158** for 4 days at 70 °C furnished the conjugate addition product **160** in 92% yield and 82% ee.

5.4 Copper-Catalyzed Conjugate Alkynylation

Although copper acetylides are generally considered to be inert to conjugate additions, Carreira and co-workers observed such a reaction (Scheme 39).[cxxx,cxxxi] The authors note that the reaction mixture is heterogeneous because the phenylacetylene is not soluble in the water. On small scale (0.25 mmol), 10 equivalents of phenyl acetylene must be used to affect the heterogeneous reaction. Increasing the scale to 1.25 mmol allows for much more

desirable stoichiometry (1 equiv phenylacetylene). The substrate scope included phenyl acetylene and reactive acceptors such as alkylidene Meldrum's acid derivatives. As a control experiment, (−)-sodium ascorbate was used, and the chirality of the ascorbate was shown to be inconsequential to the enantioselectivity of the addition reaction.

5.5 Rhodium-Catalyzed Conjugate Alkynylations

Rhodium-catalyzed asymmetric conjugate addition of organometallics to enones is an increasingly important strategy for the construction of chiral materials due to the broad substrate scope and excellent chemo- and stereoselectivity.[cxxxii] The alkynylation is faced with the problem that an acetylene is generally more reactive than the enone toward the Rh-alkynylide, resulting in alkyne dimerization. Recently, Hayashi and co-workers developed two strategies for the rhodium-catalyzed asymmetric conjugate addition of alkynes to enones (Scheme 40).[cxxxiii,cxxxiv] The first strategy featured a rearrangement of racemic alkynyl alkenyl alcohols such as **173** to the conjugate addition product (**174**). This rearrangement was proposed to occur by rhodium coordination to the alcohol, and a β-alkyne elimination to form a chiral rhodium complex bound to the alkyne and enone (**178**). This process was shown to be effective on a number of enones with TBS-acetylene **174** was formed in 88% yield with excellent ee (94%).

The second strategy for Rh-catalyzed conjugate alkynylation featured the bimolecular addition of an alkyne to an enone, and relied on the careful tuning of the catalyst and substrates (Scheme 40, eq 2). Increasing the size of the alkyne to (triisopropylsilyl)acetylene and employing bulky DTBM-segphos (**176**) as a chiral ligand increased the chemoselectivity to favor the alkynylation of enones in preference to alkyne dimerization. The desired alkynylation products were produced in uniformly high chemical and optical yields. Interestingly, cyclic enones were also alkynylated in excellent ee albeit in lower yields (55% for indenone).

6 Summary and Outlook

The enantioselective addition of alkyne nucleophiles to a variety of electrophiles has received a great deal of attention from the synthetic community over the last ten years. As a result of this research, great progress has been made towards the development of general and reliable methods.

In the case of aldehyde alkynylation, thorough examination of reaction conditions and catalyst design have led to an ever increasing substrate scope and functional group tolerance. Due to the diminished electrophilicity, ketone alkynylation technology lags behind that of aldehydes, but bifunctional catalysts are beginning to solve the problem. Tremendous advances have been made in the case of imines, and several general methods have been developed for their alkynyation catalytic in metal. By far the least amount of attention has been applied to conjugate alkynylations, however recent advances in both alkynylboronates and rhodiumcatalyzed direct additions have made steady progress towards general enone alkynylations.

While the wealth of research in this area has produced effective methodology for the alkynylation of many electrophiles, there exists room for improvement. Future technology will likely feature increasing substrate scope, reaction efficiency, and improved catalyst loadings.

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Biographies

Barry Trost was born in Philadelphia, PA, in 1941 where, in 1959, he began his university training at the University of Pennsylvania (BA degree, 1962). He obtained his Ph.D. degree in Chemistry just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin, where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor of Chemistry in 1982. He joined the faculty at Stanford University as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In recognition of his many contributions, Professor Trost has received numerous awards, a few of which are the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Herbert C. Brown Award for Creative Research in Synthetic Methods (1999), the Yamada Prize (2001), the ACS Cope Award (2004), Thomson Scientific Laureate (2007), and the Nagoya Medal (2008). Professor Trost has been elected a fellow of the American Academy of Sciences (1992) and a member of the National Academy of Sciences (1990). He has published two books and over 830 scientific articles. Professor Trost's research interests include the invention and development of new synthetic reactions largely based upon catalysis using transition-metal complexes and their use to define strategies that result in the total synthesis of complex molecules of biological importance.

Andrew Weiss was born in Champaign, IL, in 1981. He obtained his B.S. degree from the University of Michigan in Ann Arbor with a double major in Chemistry and Biochemistry under the guidance of Professor Edwin Vedejs in 2003. Shortly after, he began his graduate studies with Professor Barry Trost at Stanford University focusing on the development of enantioselective alkynylation chemistry and application to the total synthesis of natural products. After completion of his Ph.D. degree in 2008, he joined the group of Professor David Evans at Harvard University as a postdoctoral fellow.

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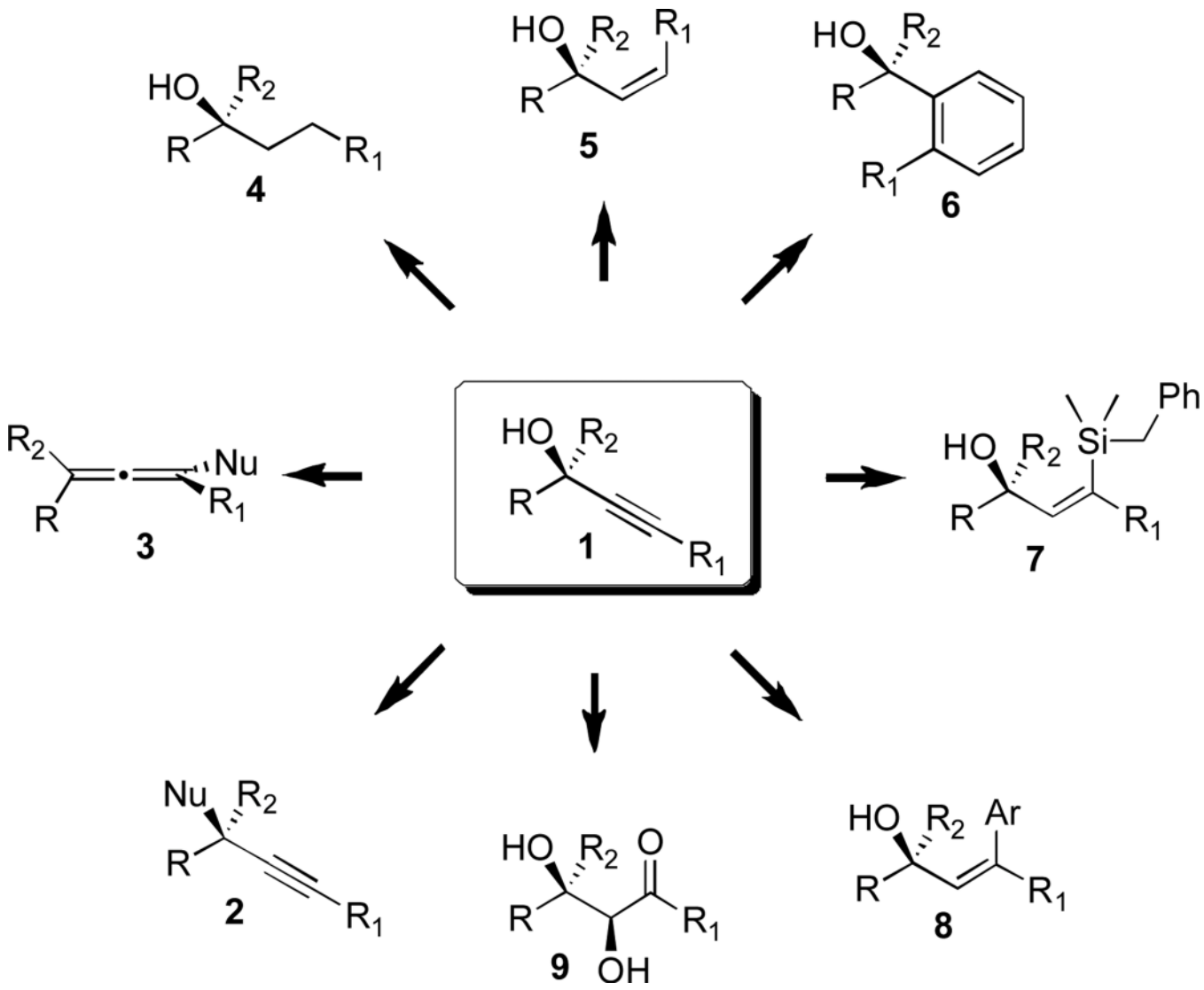


Figure 1.
Propargyl alcohols as synthetic intermediates.

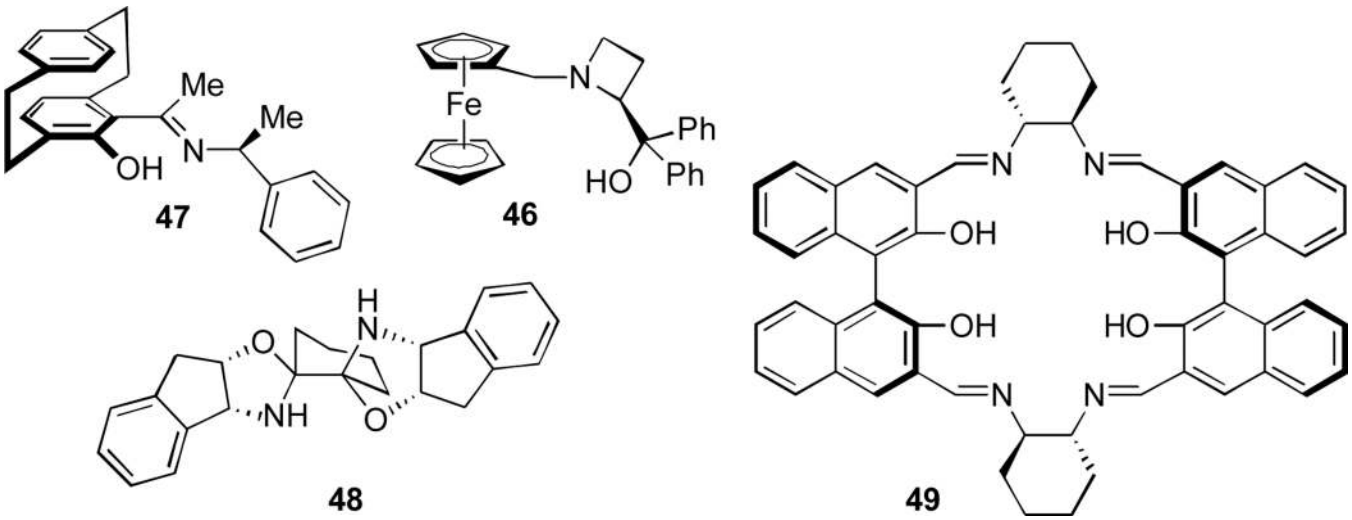


Figure 2.
Ligands for the alkynylation of aldehydes.

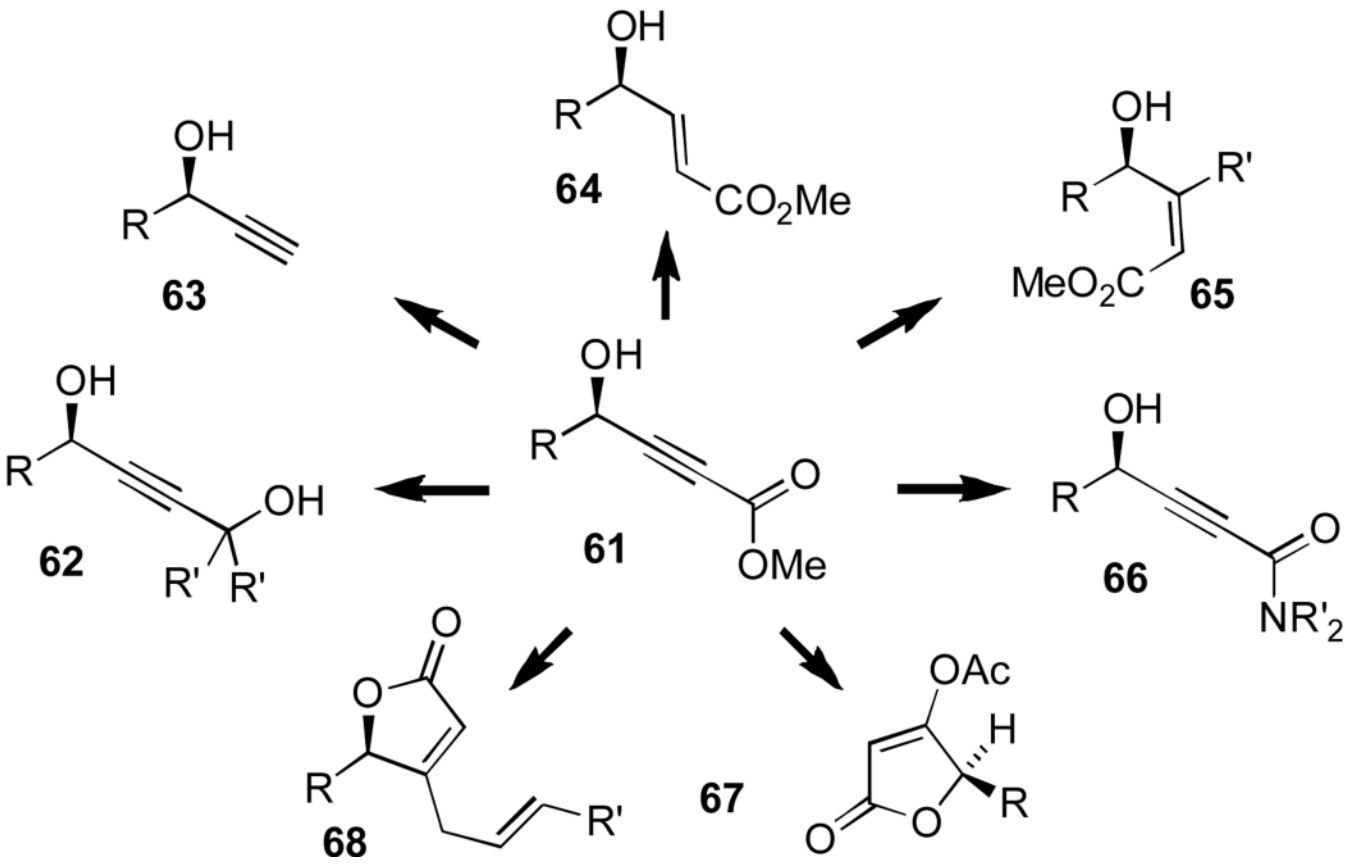
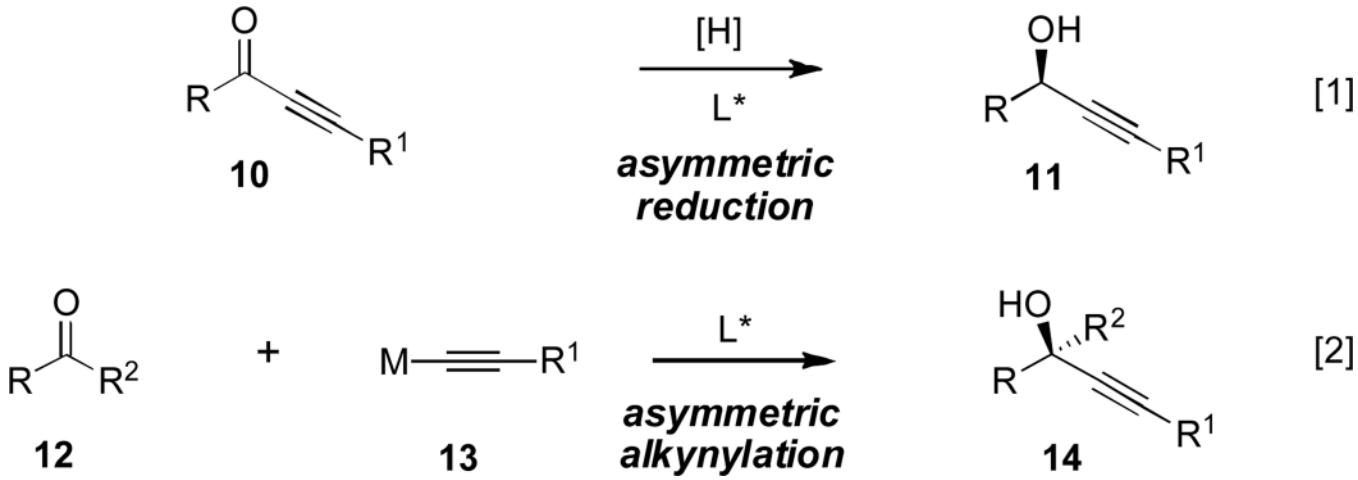
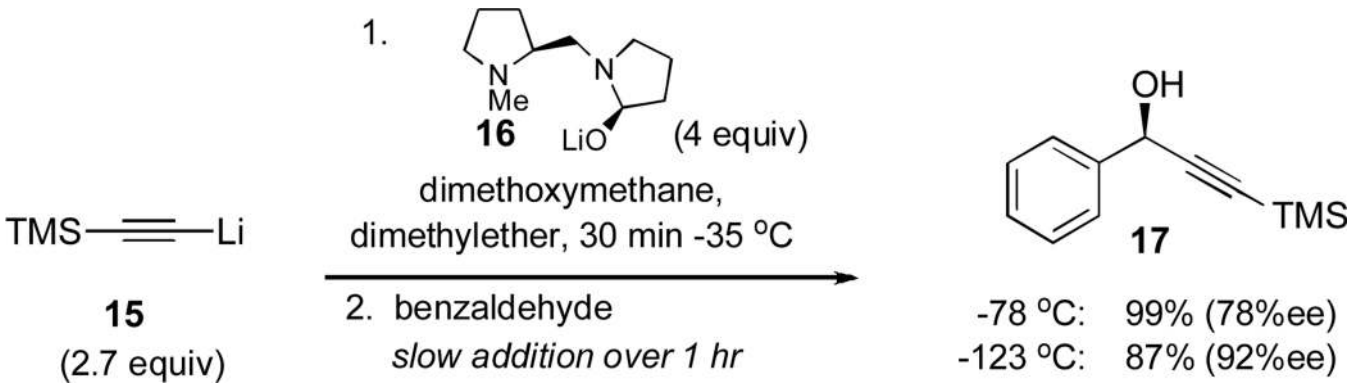


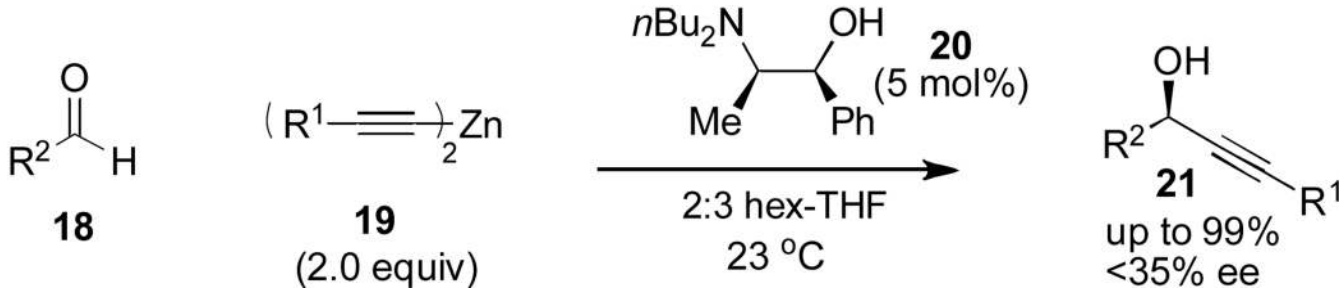
Figure 3.
γ-Hydroxy-α,β-acetylenic ester transformations.



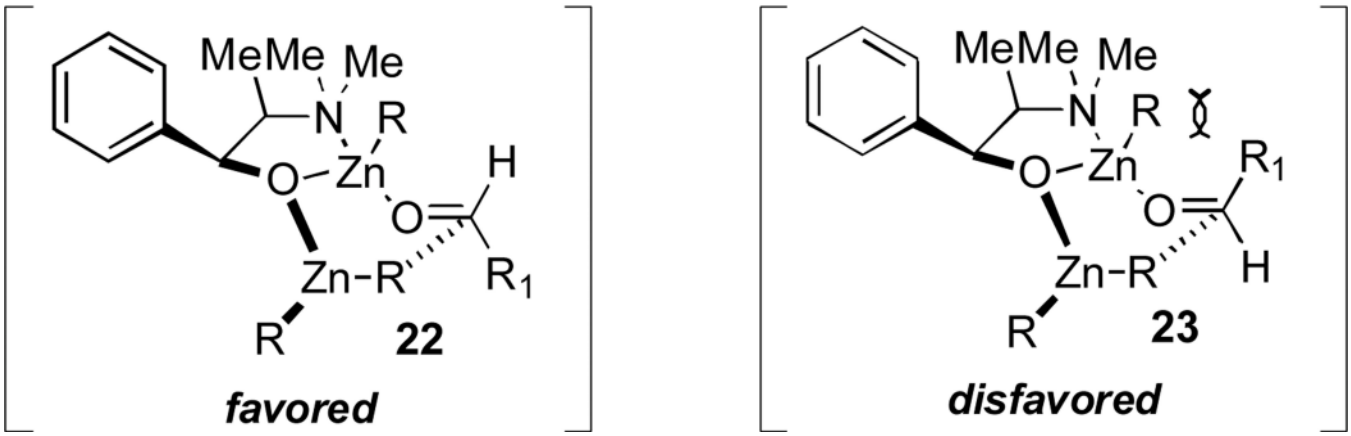
Scheme 1.
Common methods for the synthesis of propargylic alcohols.



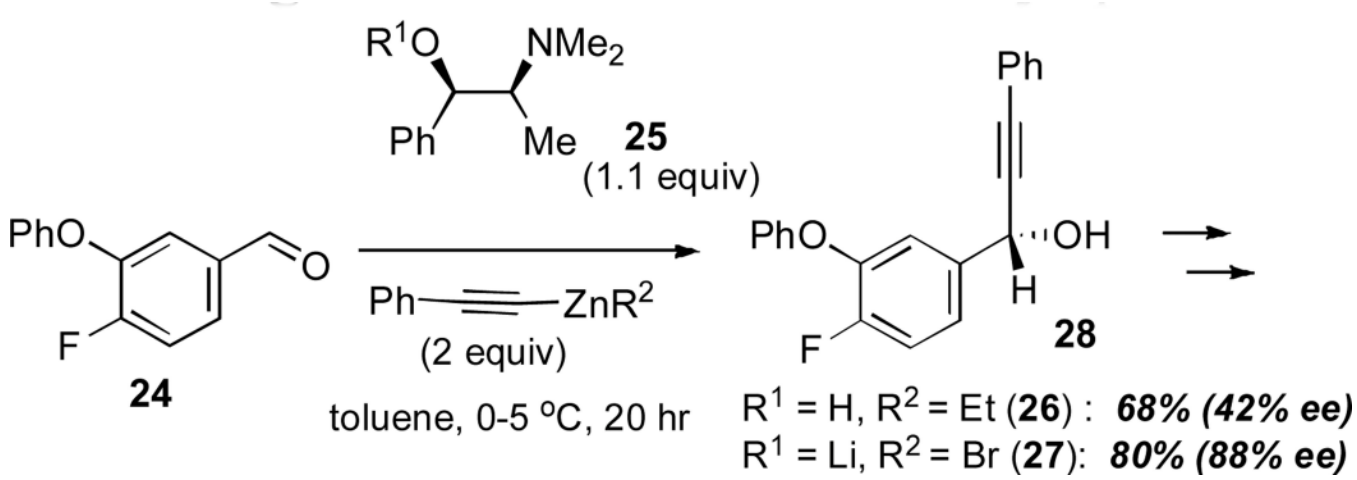
Scheme 2.
First example of an enantioselective alkynylation of an aldehyde.



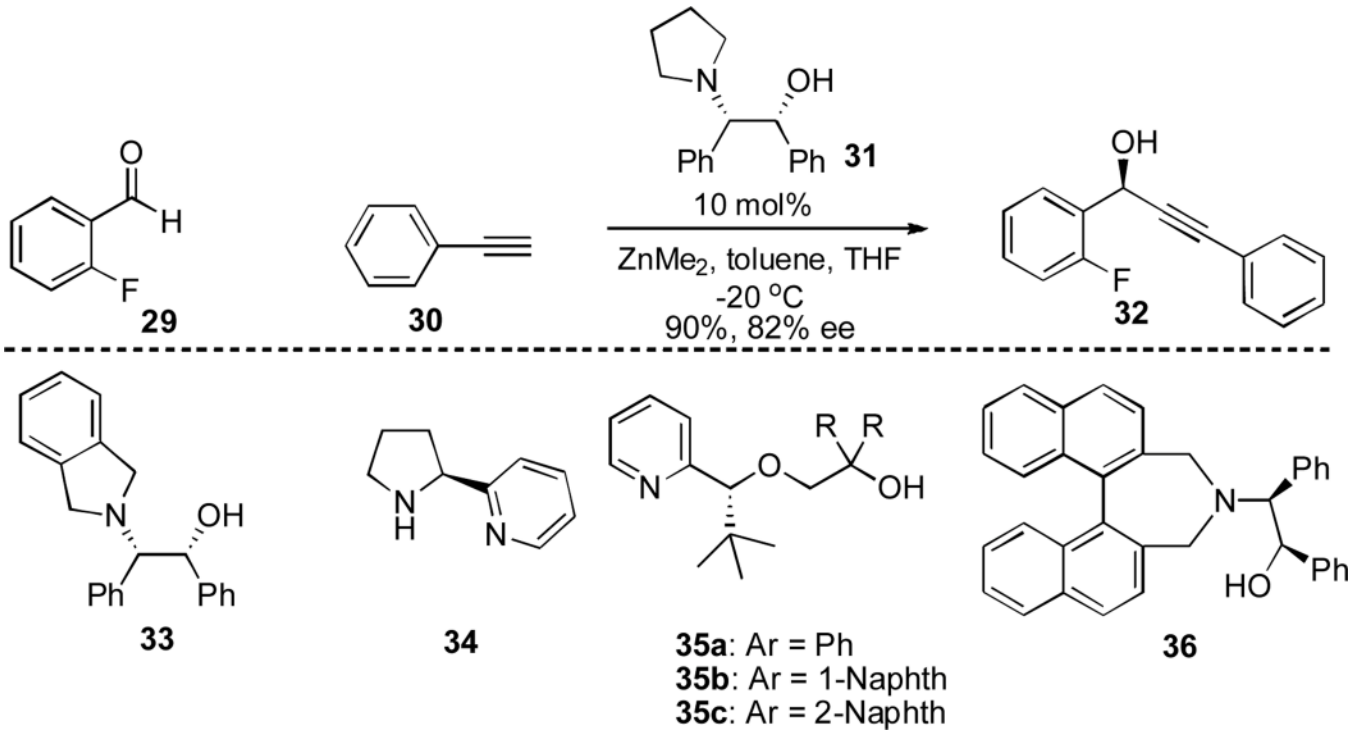
Scheme 3.
Catalytic asymmetric zinc alkynylation of aldehydes.



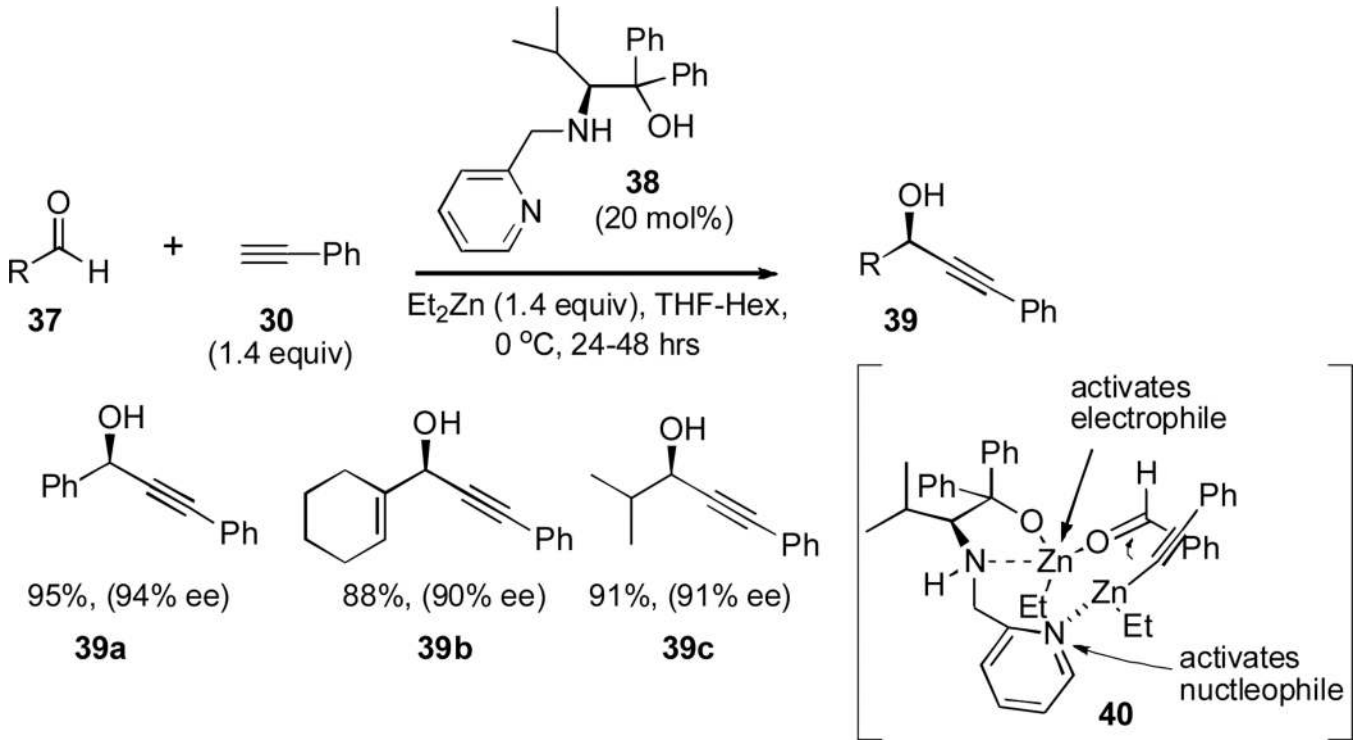
Scheme 4.
Rationale for enantioselectivity of alkyne or alkyl (R) addition to an aldehyde.



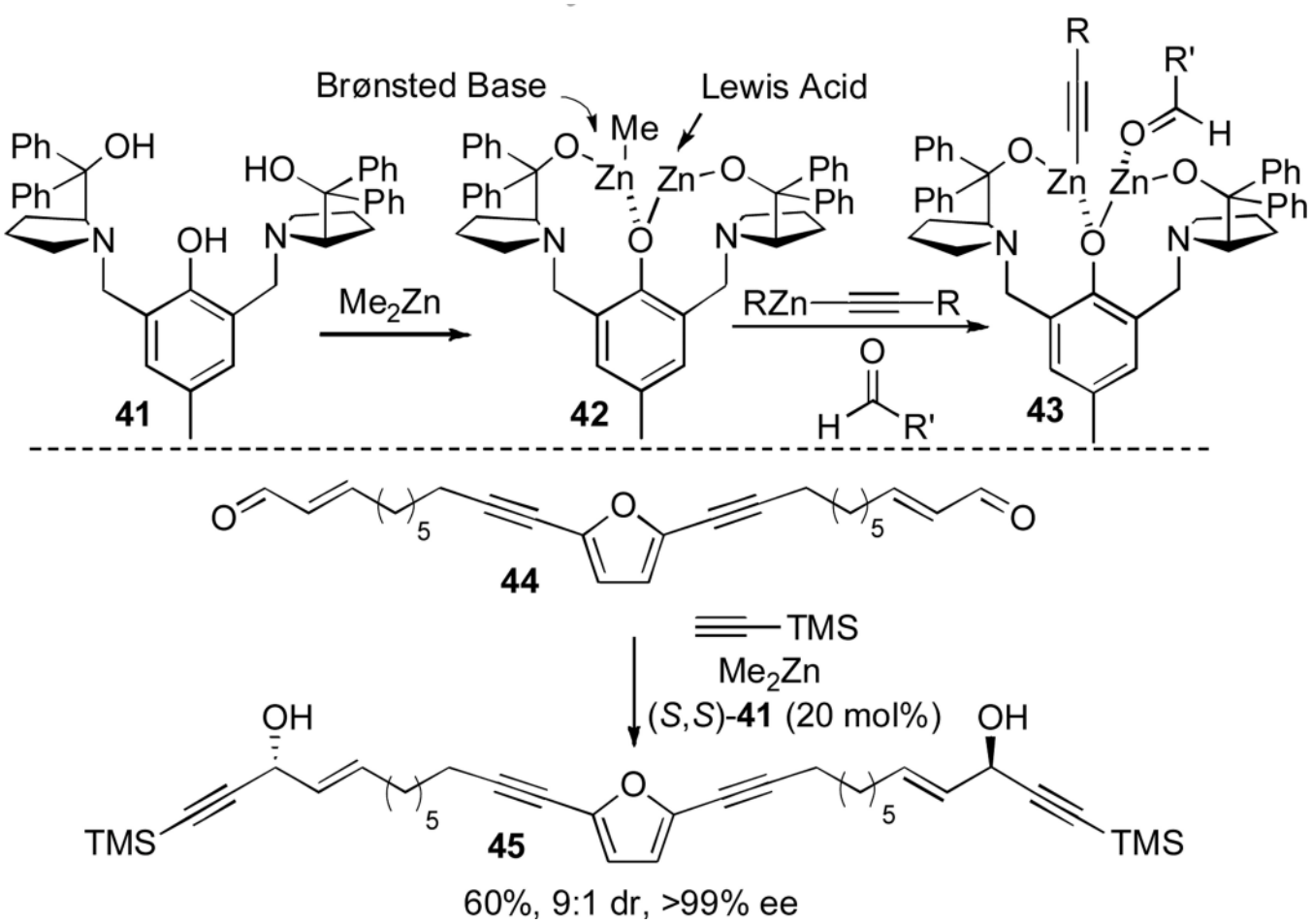
Scheme 5.
(+)-NME-mediated enantioselective addition of zinc alkynylides.



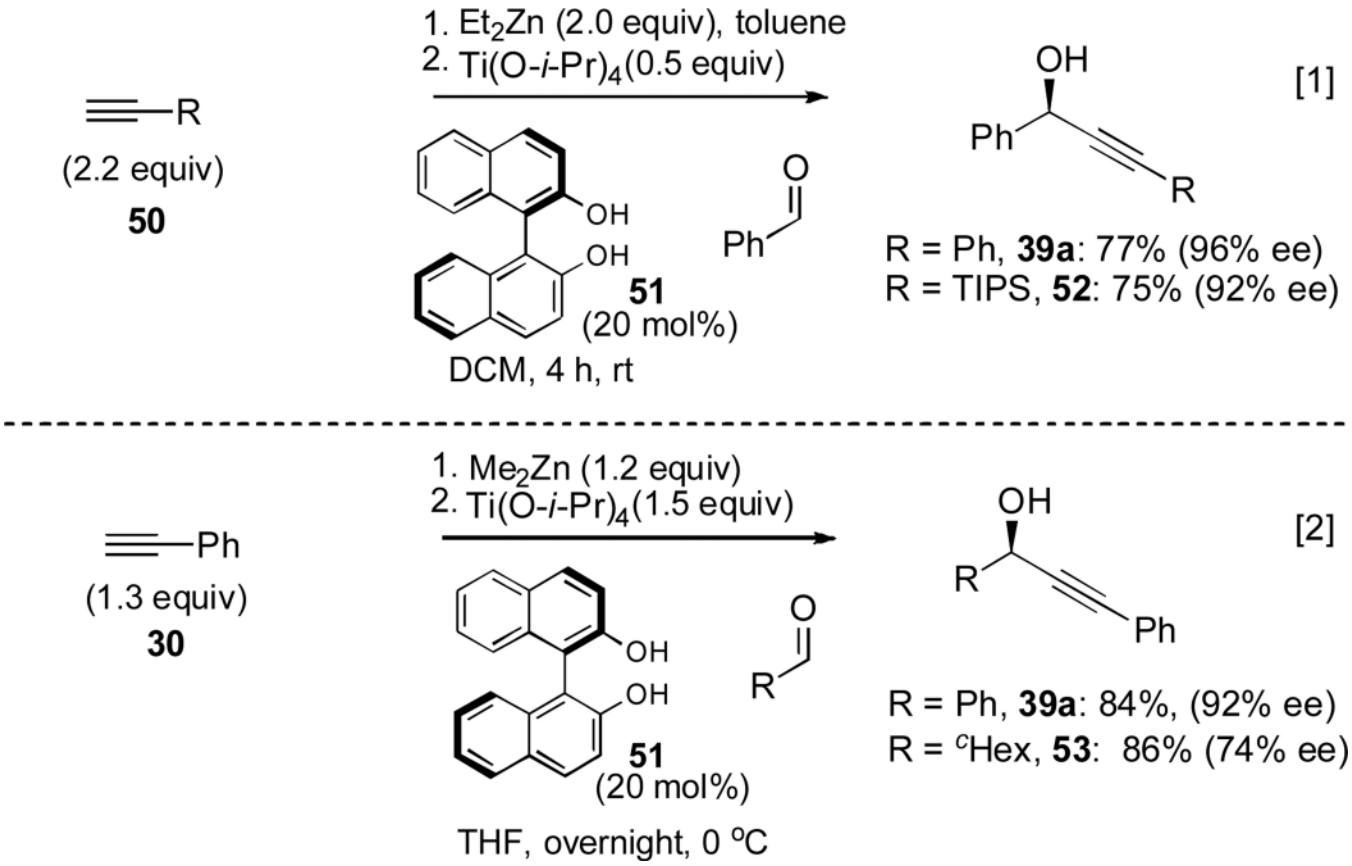
Scheme 6.
Alternative conditions employing catalytic amino alcohol ligands.



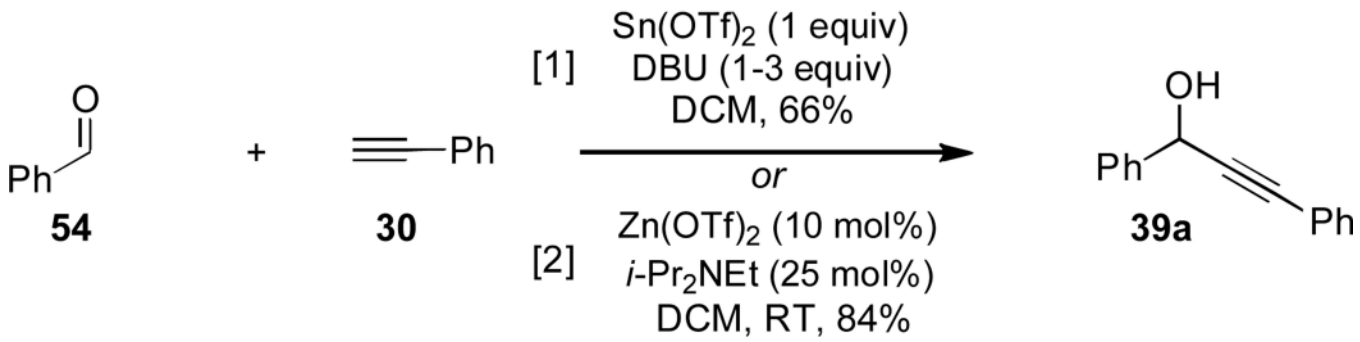
Scheme 7.
Wang's bifunctional catalyst for the asymmetric alkynylation of aldehydes.



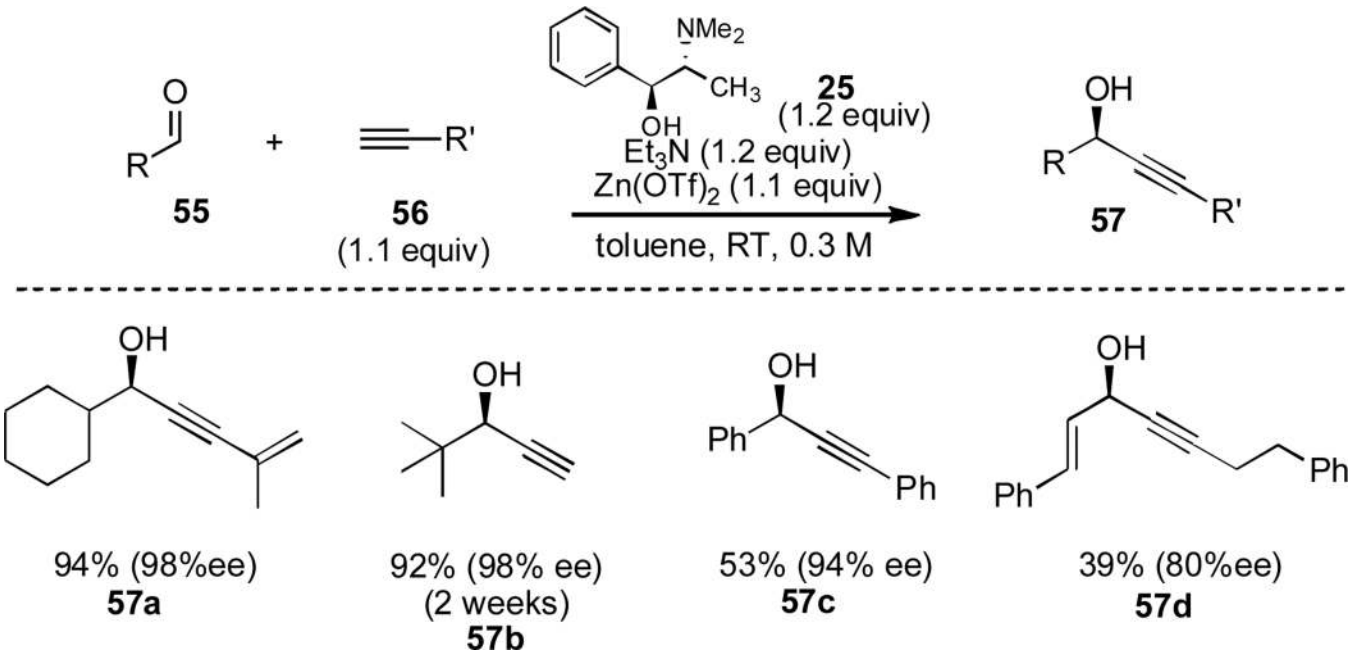
Scheme 8.
Trost's bifunctional ProPhenol catalyst for the enantioselective alkynylation of unsaturated aldehydes.



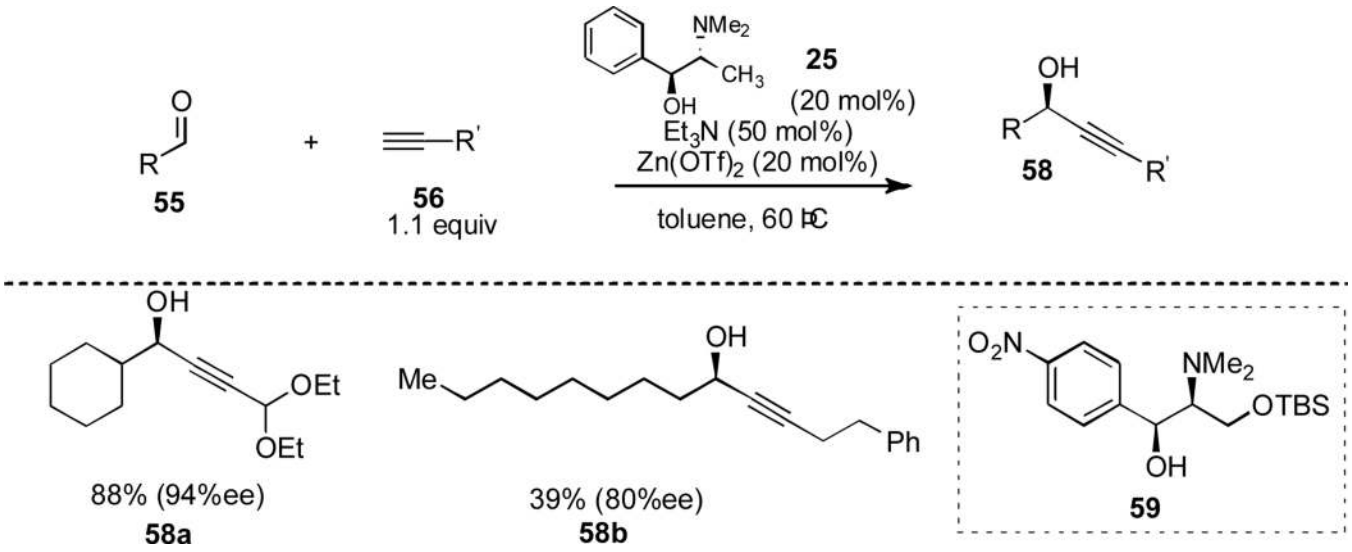
Scheme 9.
Enantioselective titanium-catalyzed addition of zinc alkynylides to aldehydes.



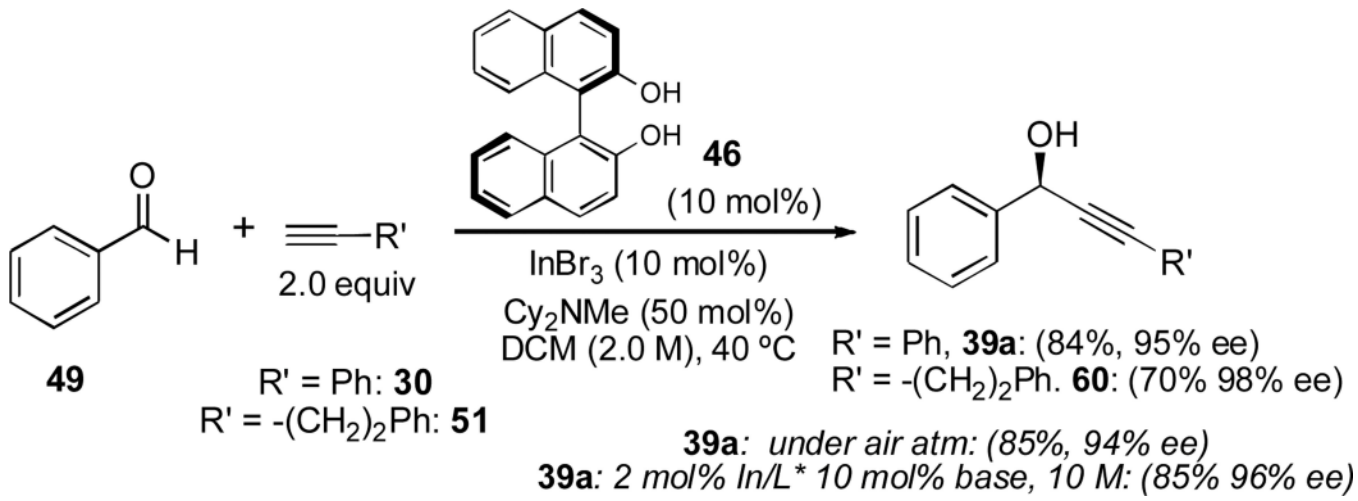
Scheme 10.
Metal salt-mediated alkynylation of aldehydes.



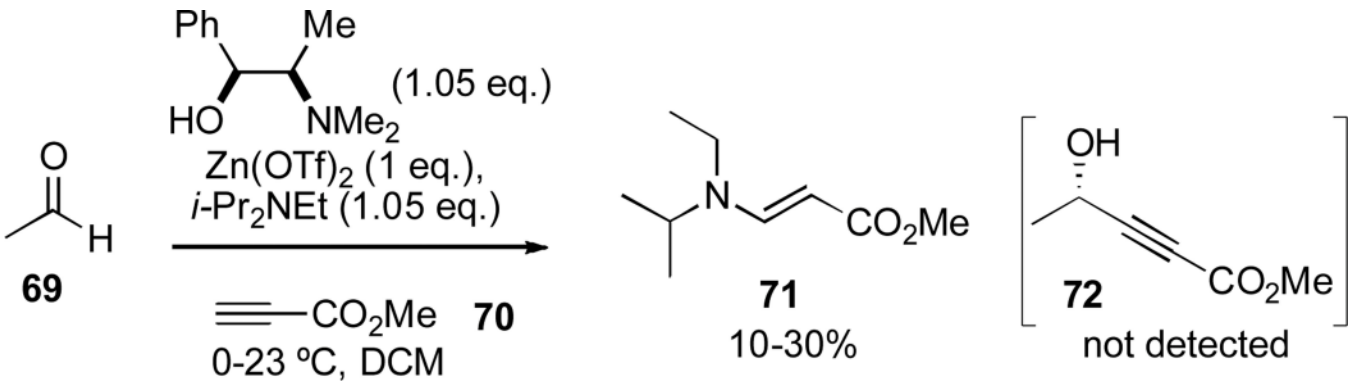
Scheme 11.
Stoichiometric *N*-methylephedrine-mediated alkynylation methodology.



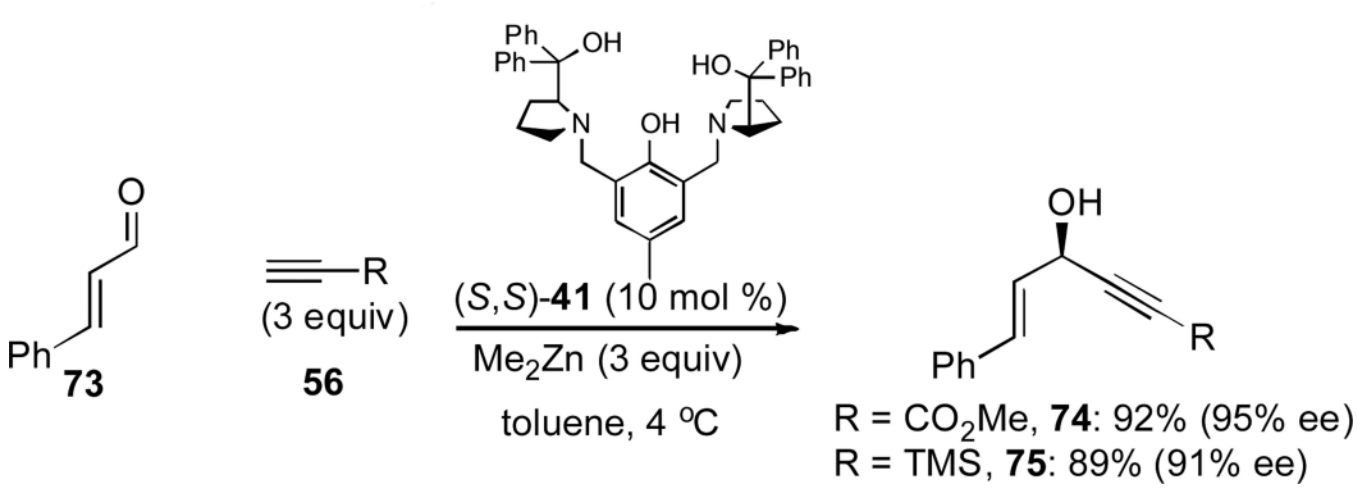
Scheme 12.
Catalytic *N*-methylephedrine-mediated alkynylation methodology.



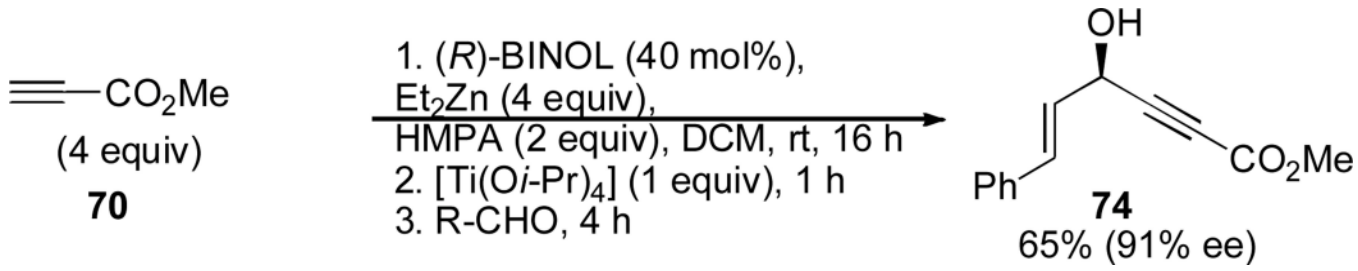
Scheme 13.
Shibasaki's In(III)/BINOL-catalyzed alkynylation.



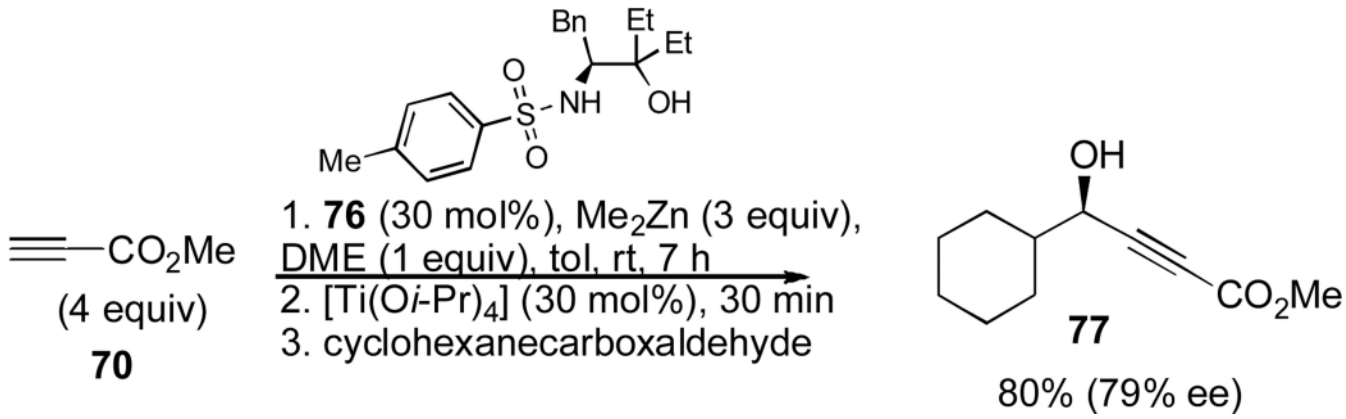
Scheme 14.
Attempted propiolate addition with Carriera's conditions.



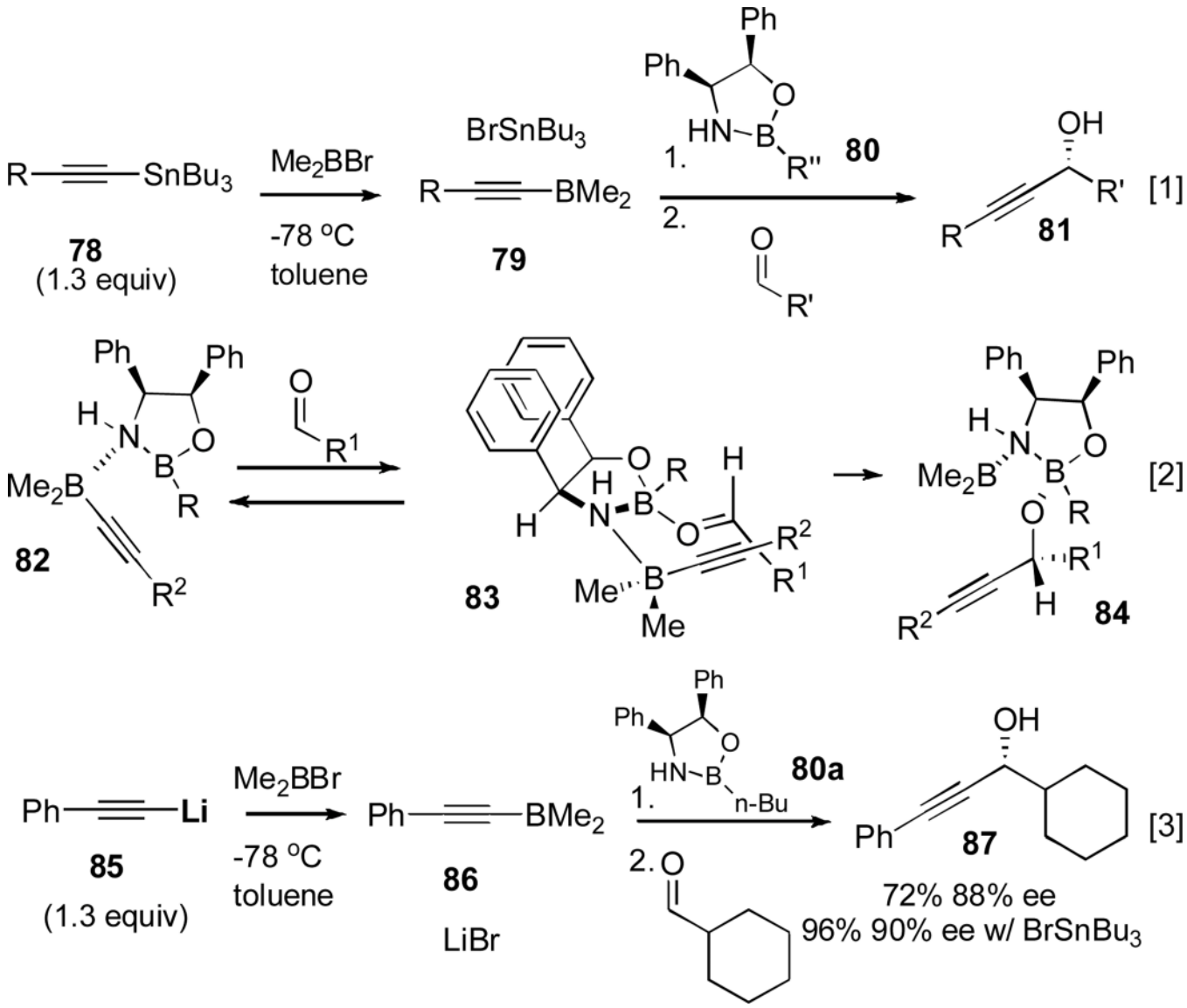
Scheme 15.
ProPhenol-catalyzed enantioselective propiolate addition.



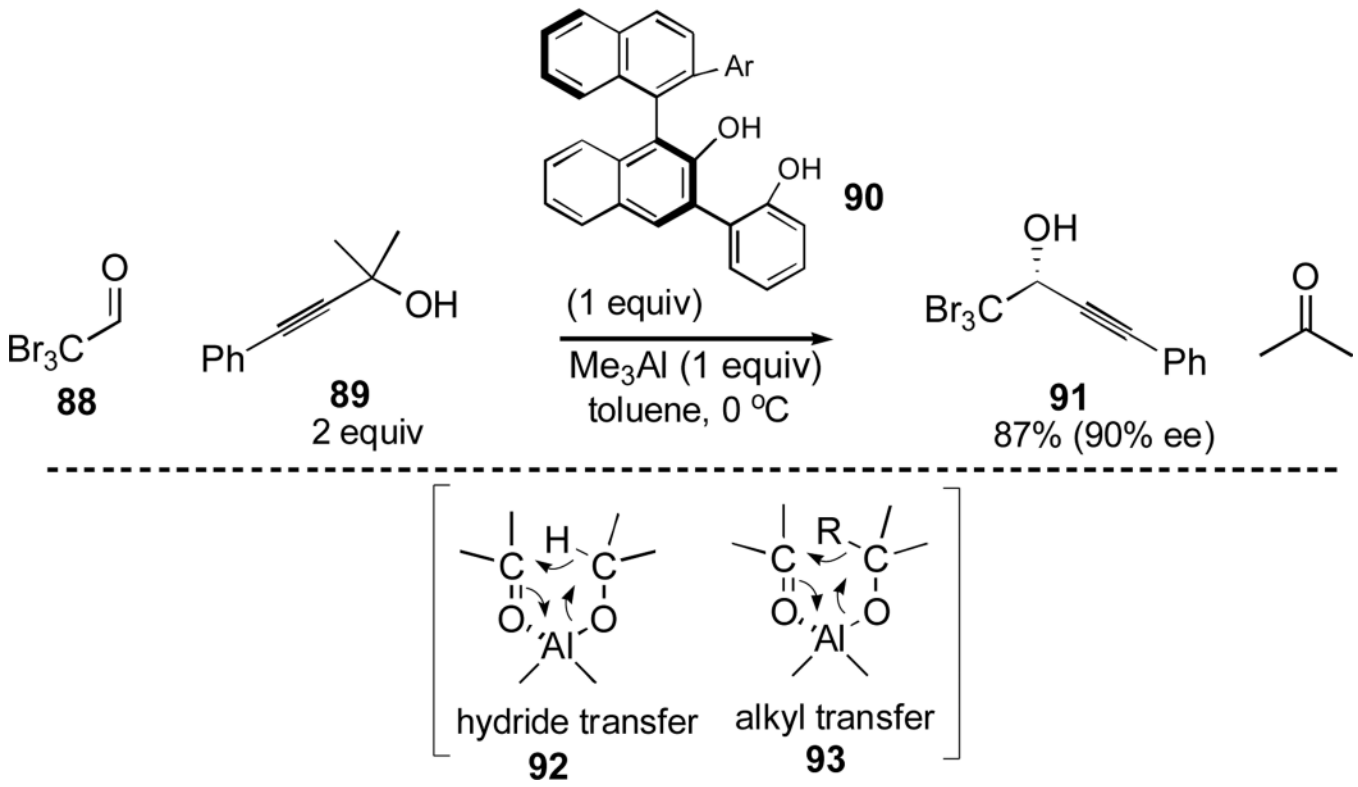
Scheme 16.
Pu's titanium-BINOL-HMPA catalyst for the zinc propiolate addition to aldehydes.



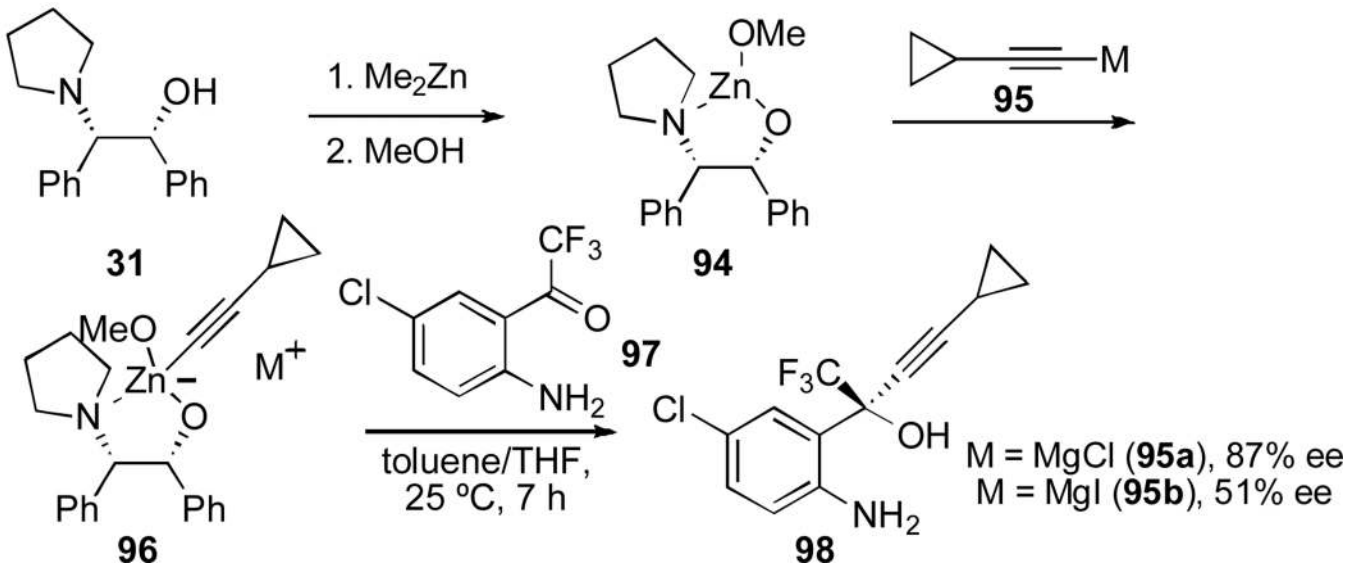
Scheme 17.
Chan and Wang's alternative propiolate addition.



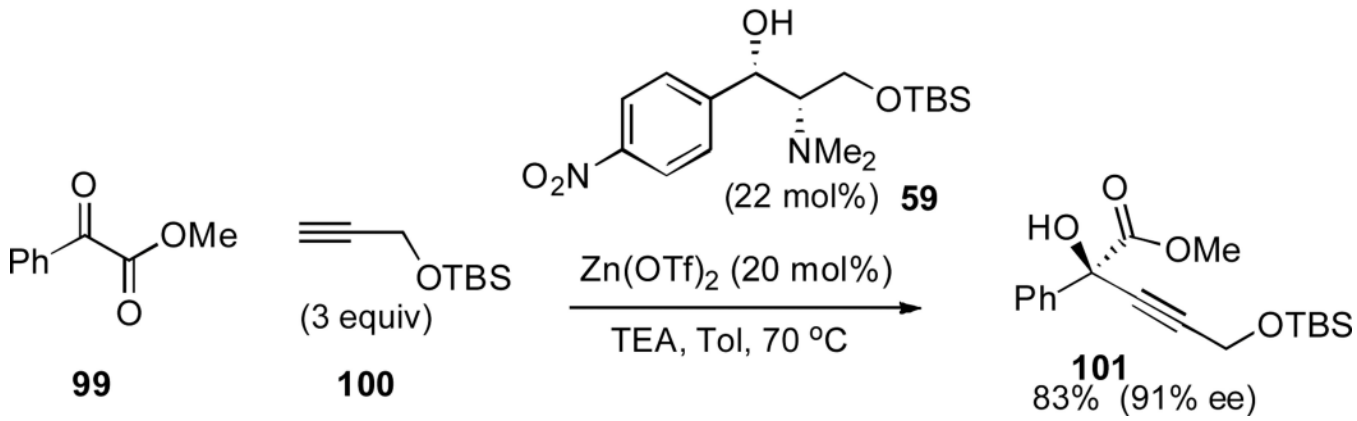
Scheme 18.
Corey's enantioselective boron alkynylide addition to aldehydes.



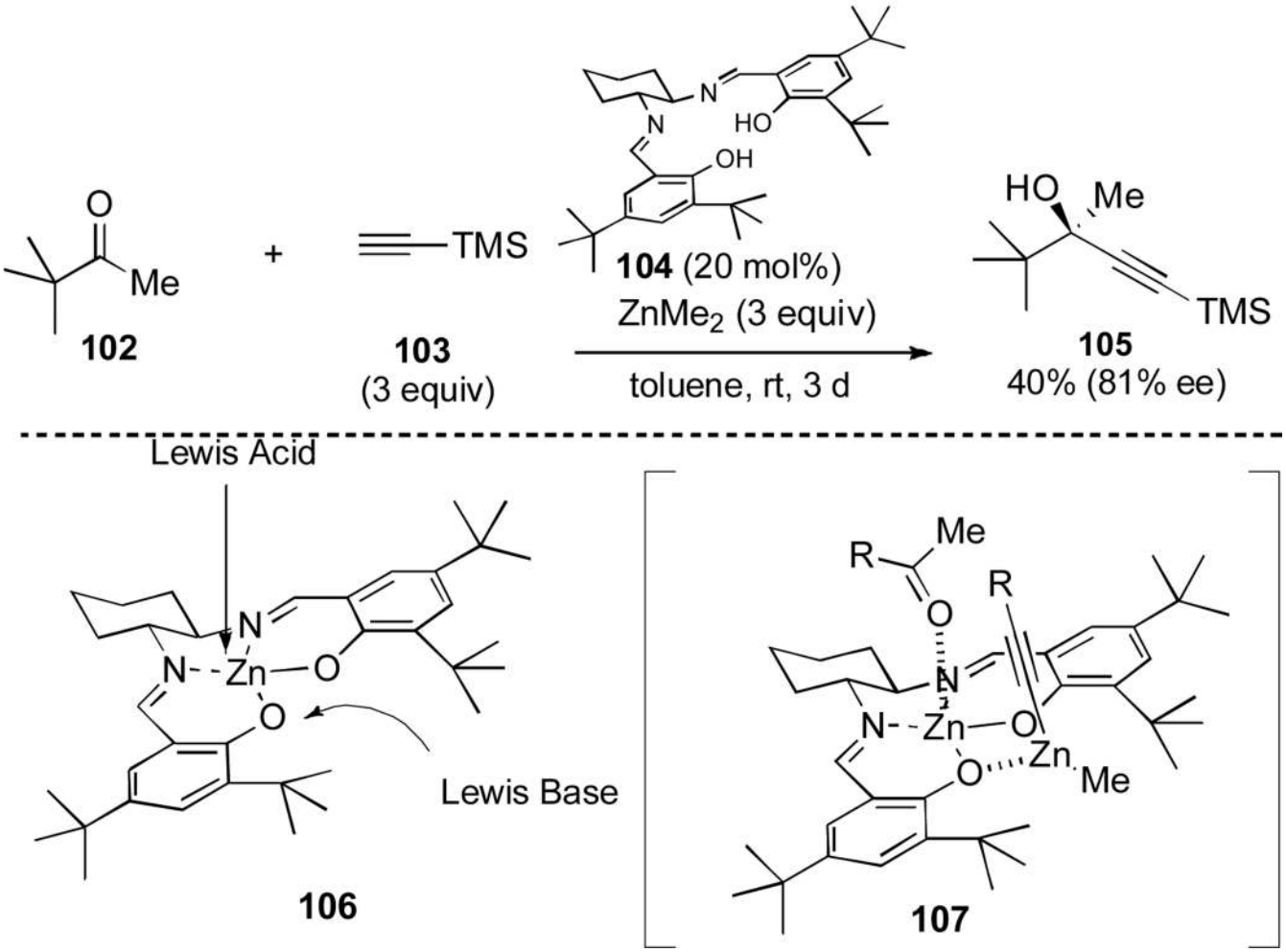
Scheme 19.
Enantioselective MPV alkyne addition to activated aldehydes.



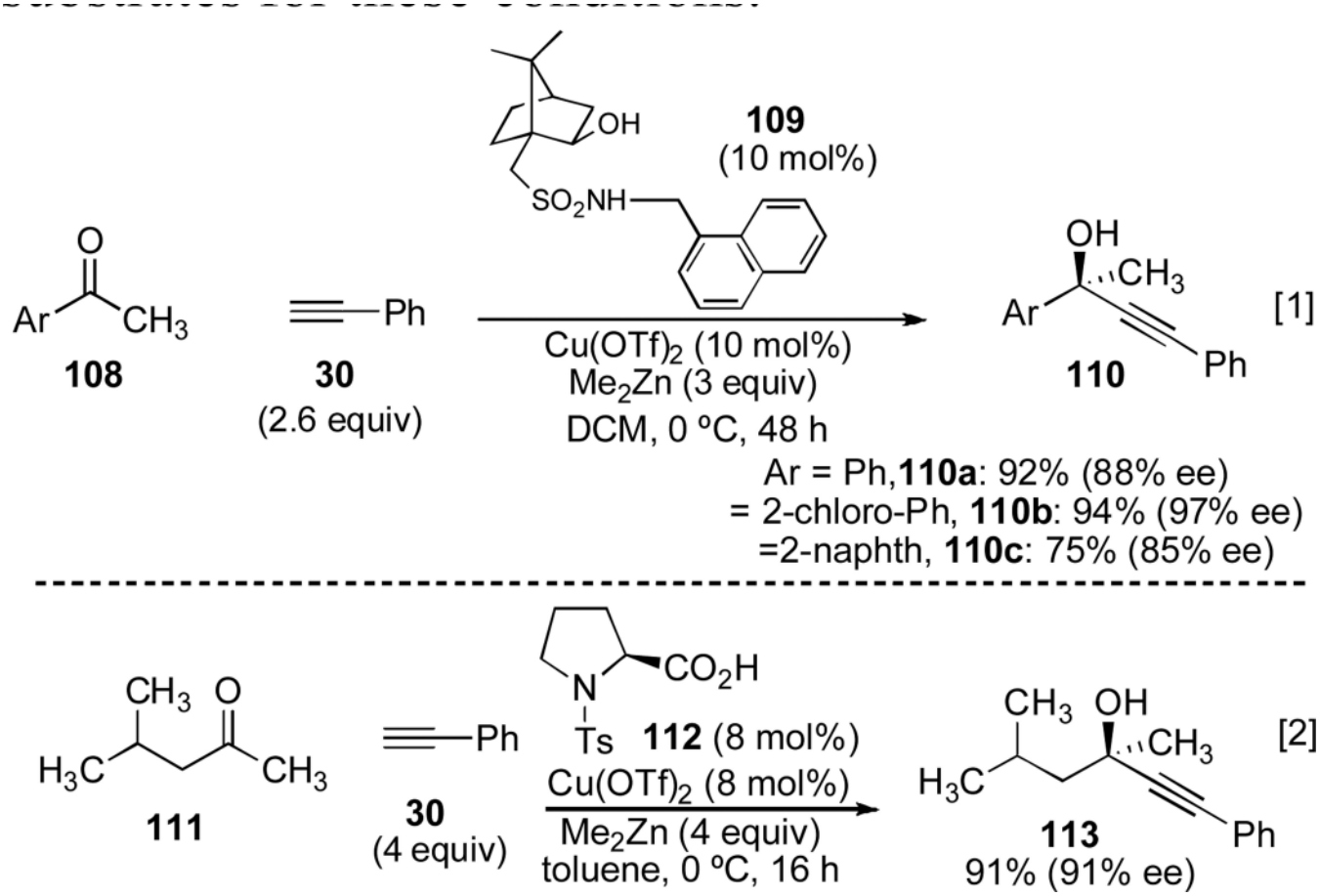
Scheme 20.
First example of enantioselective alkynylide addition to a ketone.



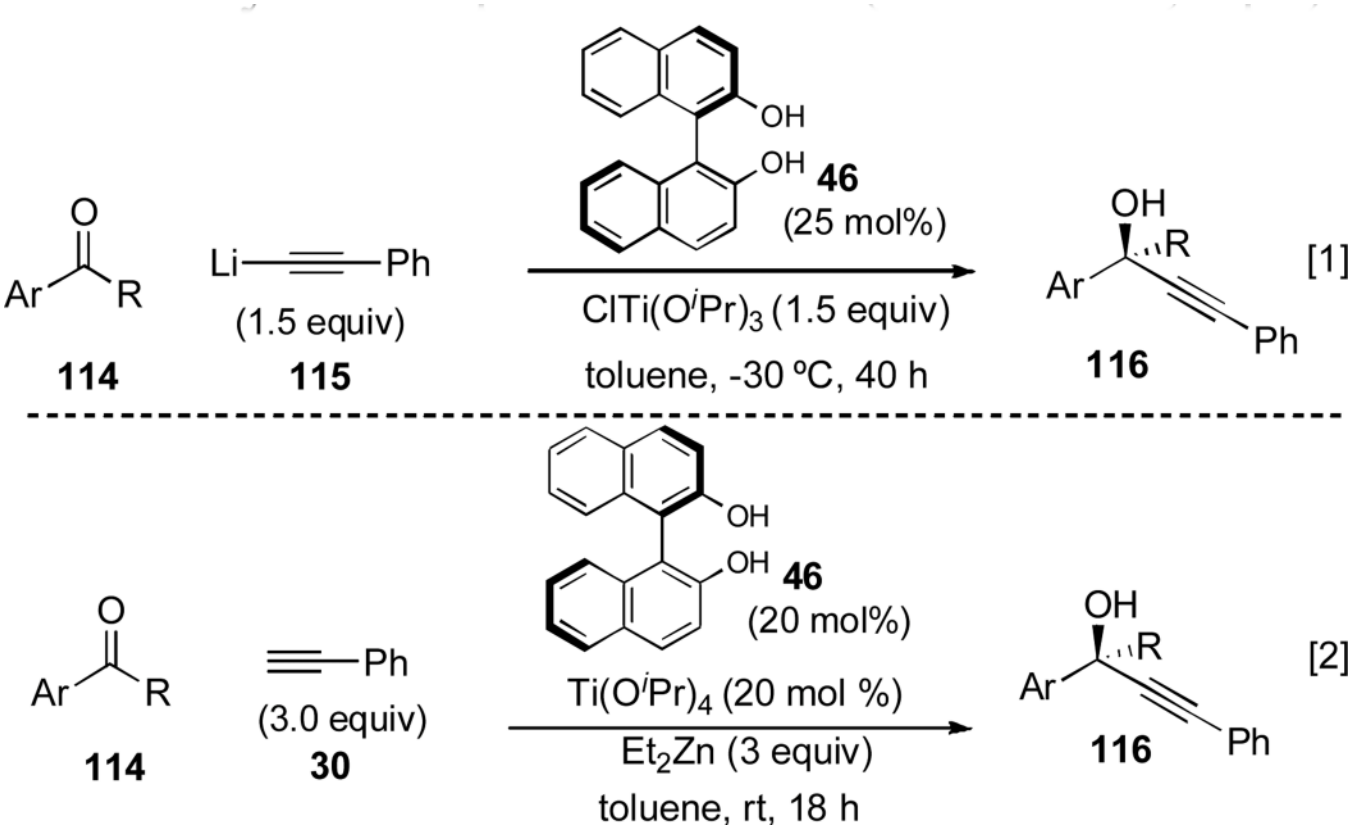
Scheme 21.
Enantioselective alkynylation of activated ketones with catalytic zinc.



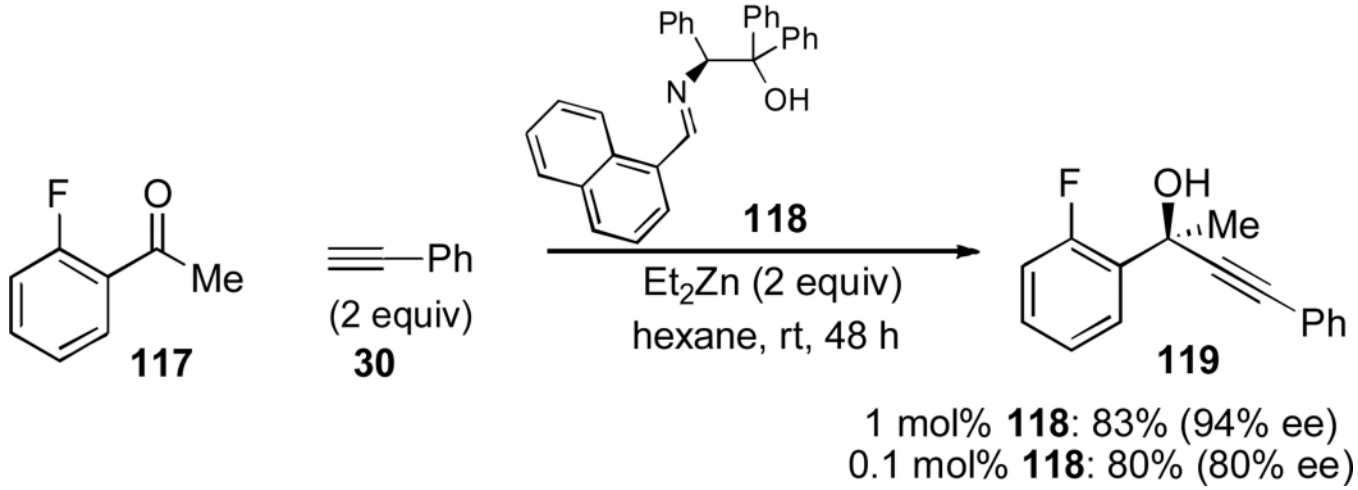
Scheme 22.
Cozzi's salen-catalyzed alkynylation of ketones.



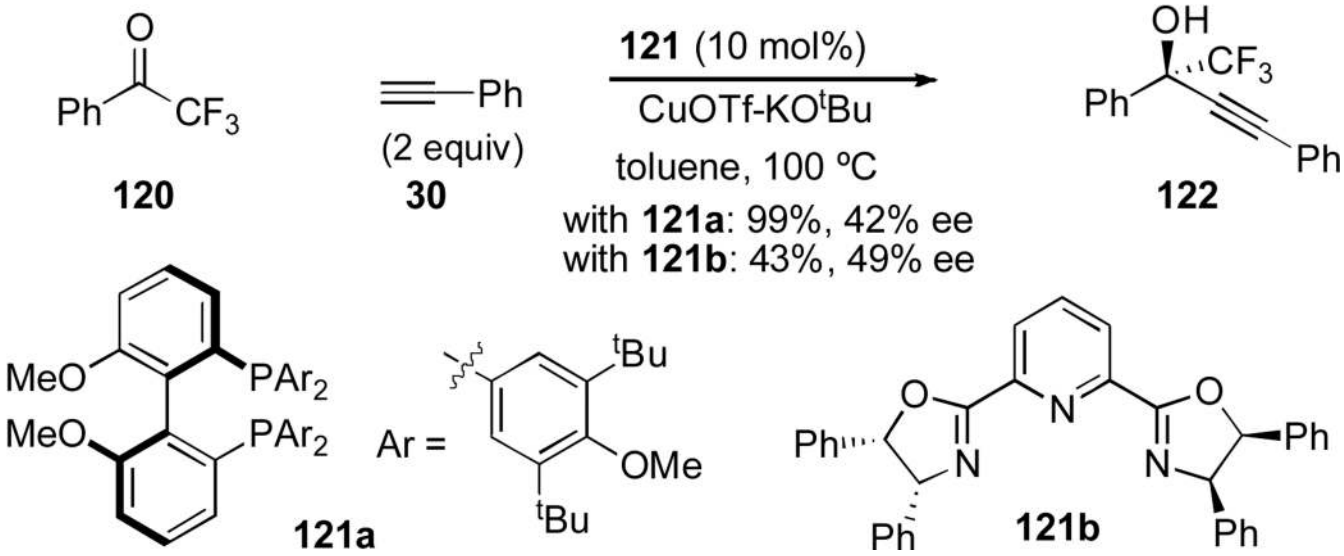
Scheme 23.
Enantioselective copper-catalyzed zinc alkynylide addition to ketones.



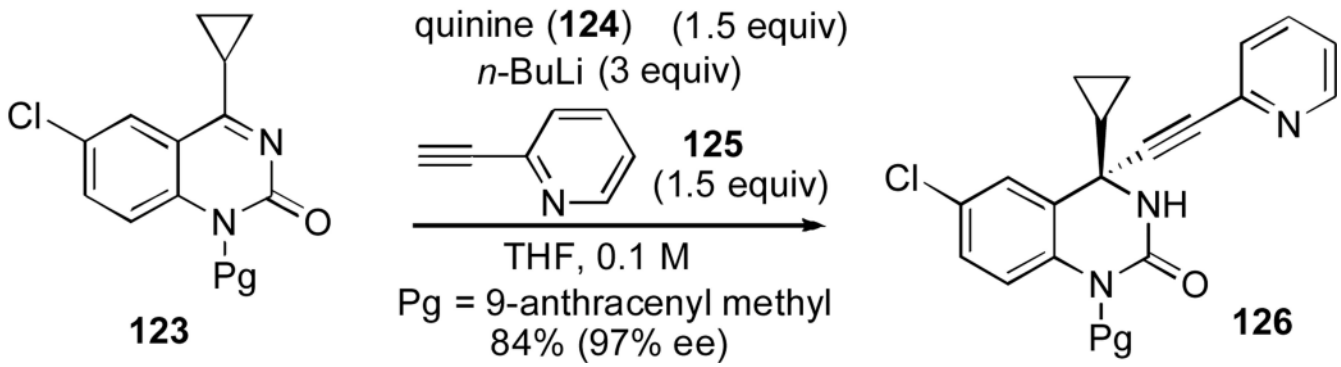
Scheme 24.
Titanium(IV)-BINOL catalyzed alkynylations of ketones.



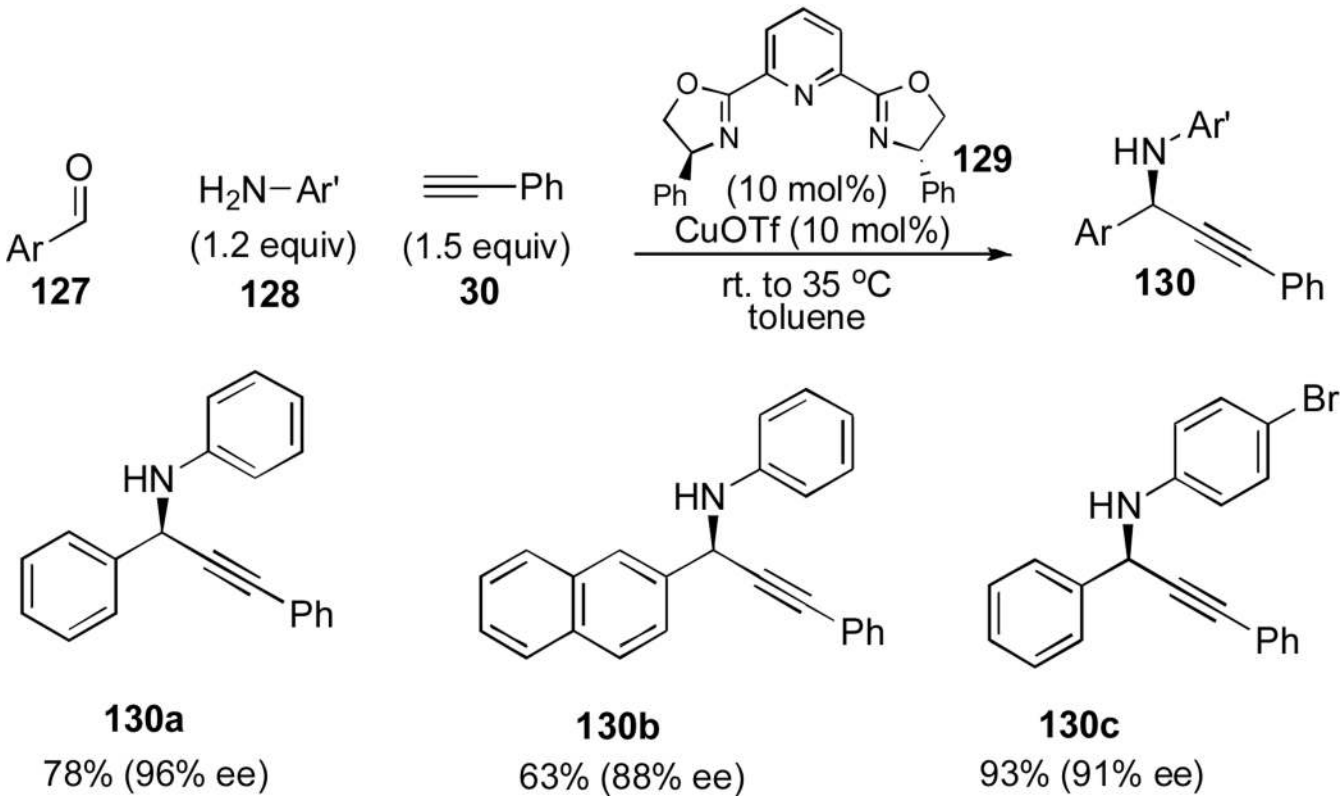
Scheme 25.
Wang's enantioselective addition of zinc alkynylides to unactivated ketones.



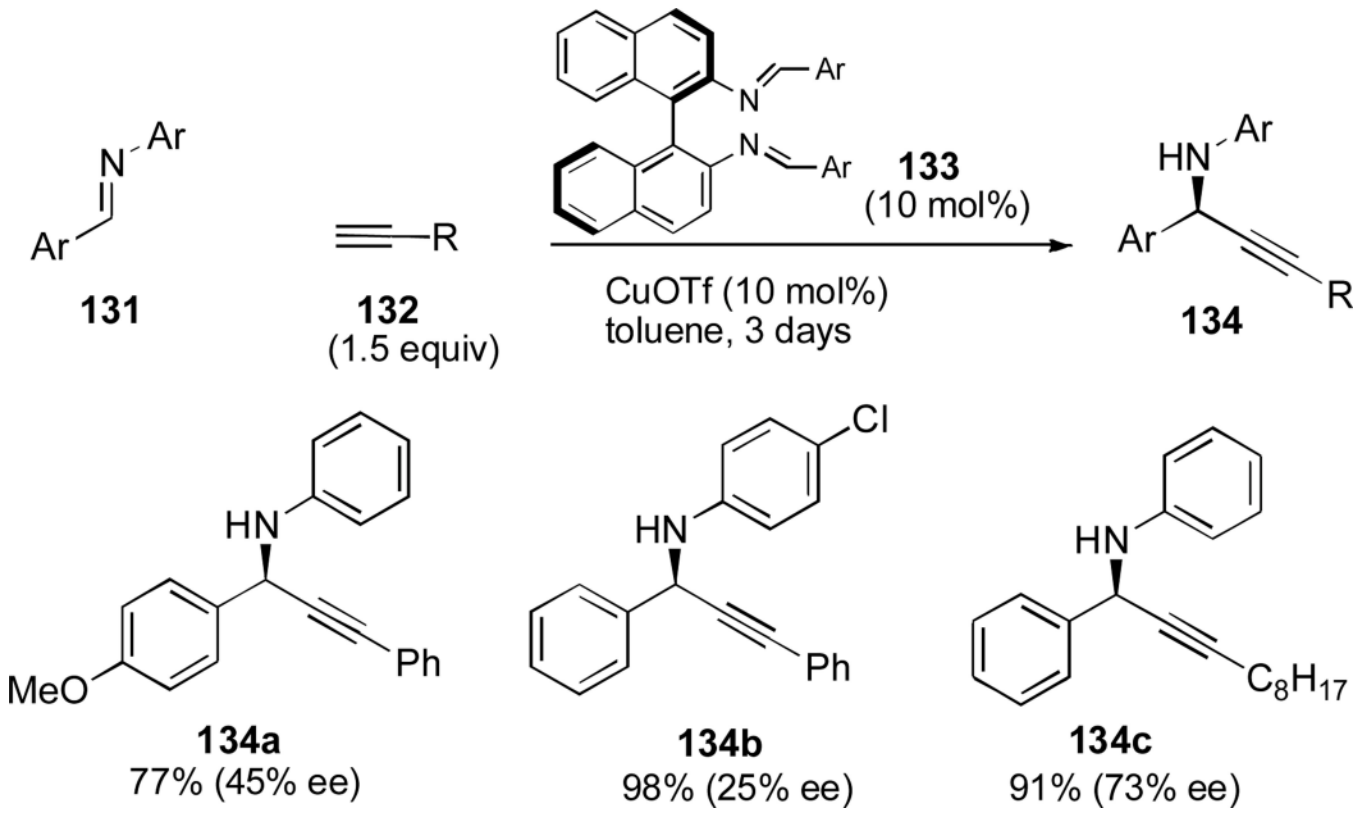
Scheme 26.
Catalytic enantioselective alkynylation of trifluoromethyl ketones.



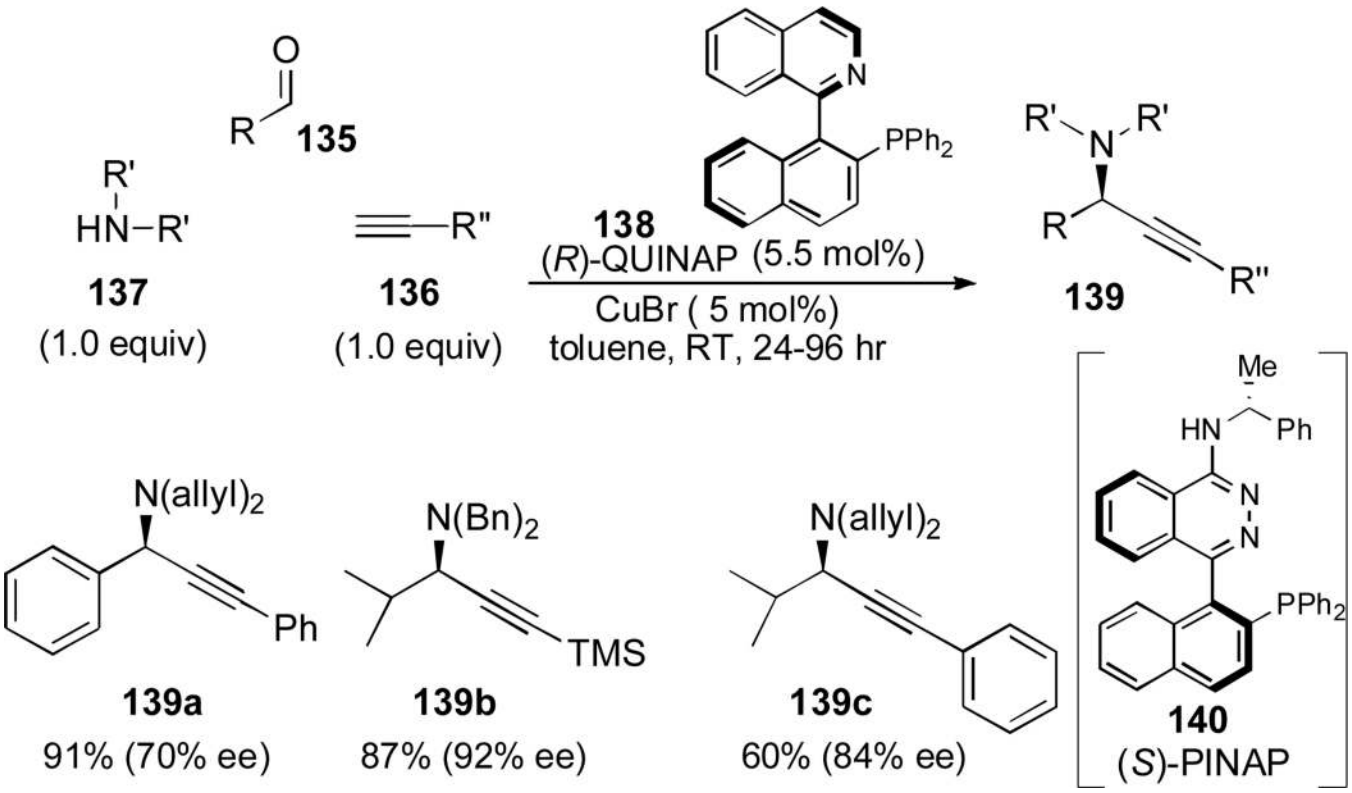
Scheme 27.
First example of an enantioselective imine alkynylation.



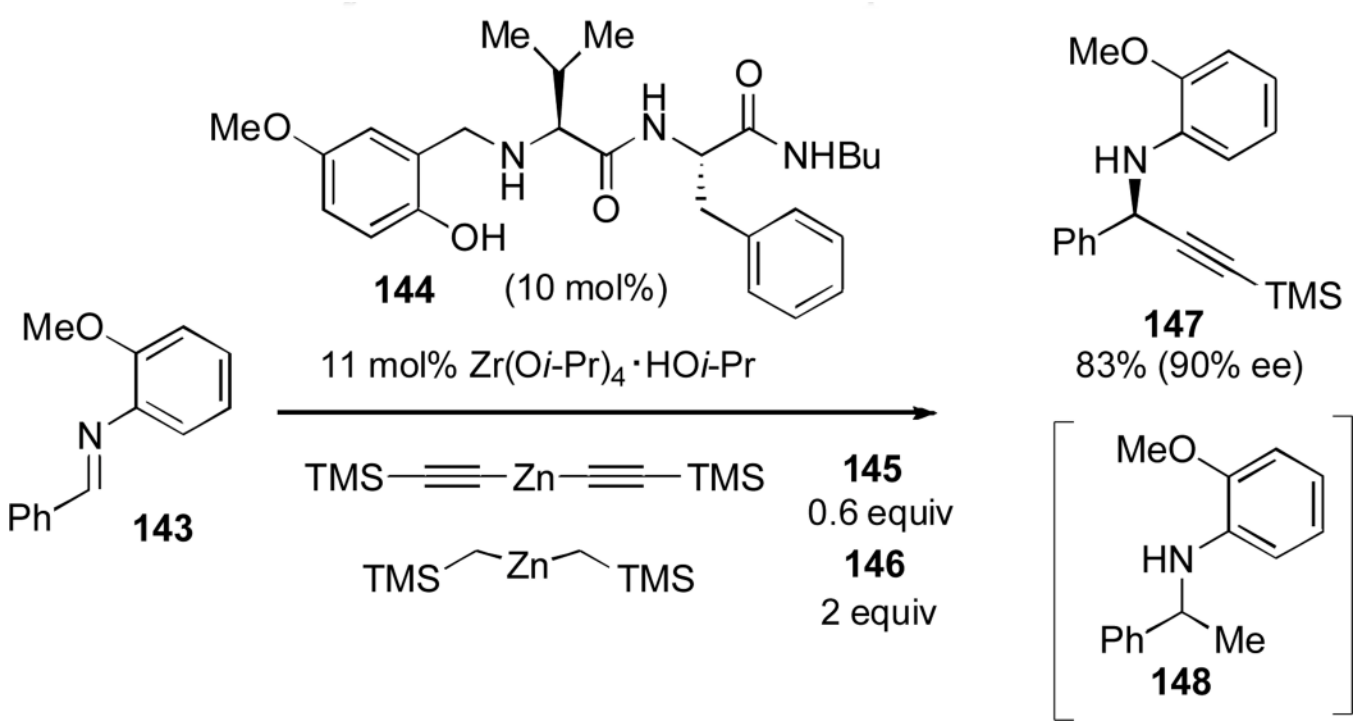
Scheme 28.
Li's three-component coupling reaction.



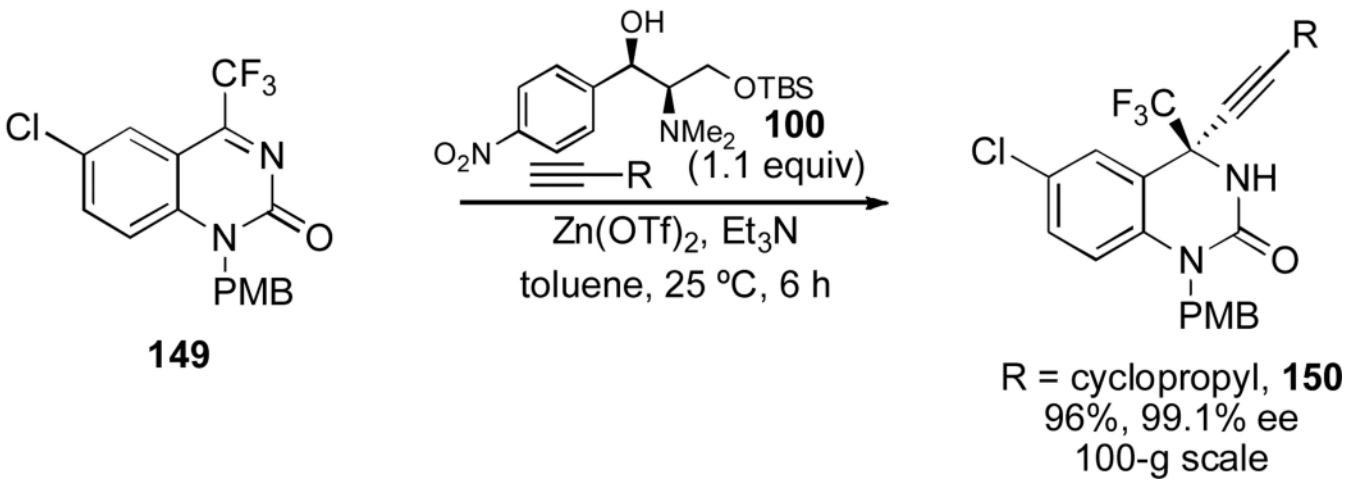
Scheme 29.
Alternative ligand for alkynylation of *N*-aryl imines.



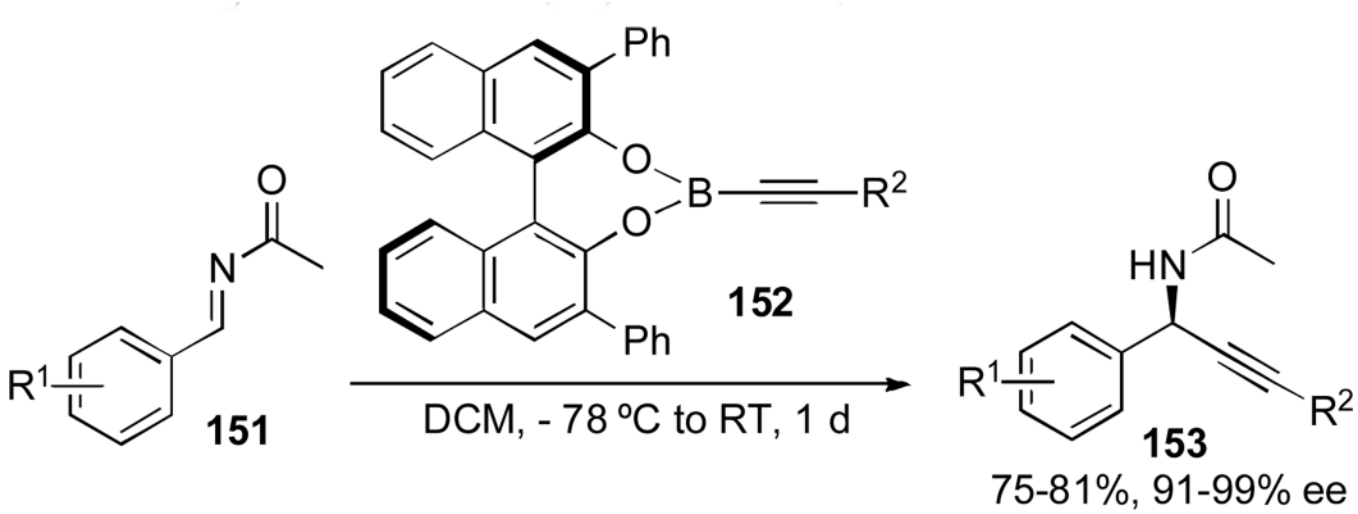
Scheme 30.
Knochel's QUINAP system for the alkynylation of imines.



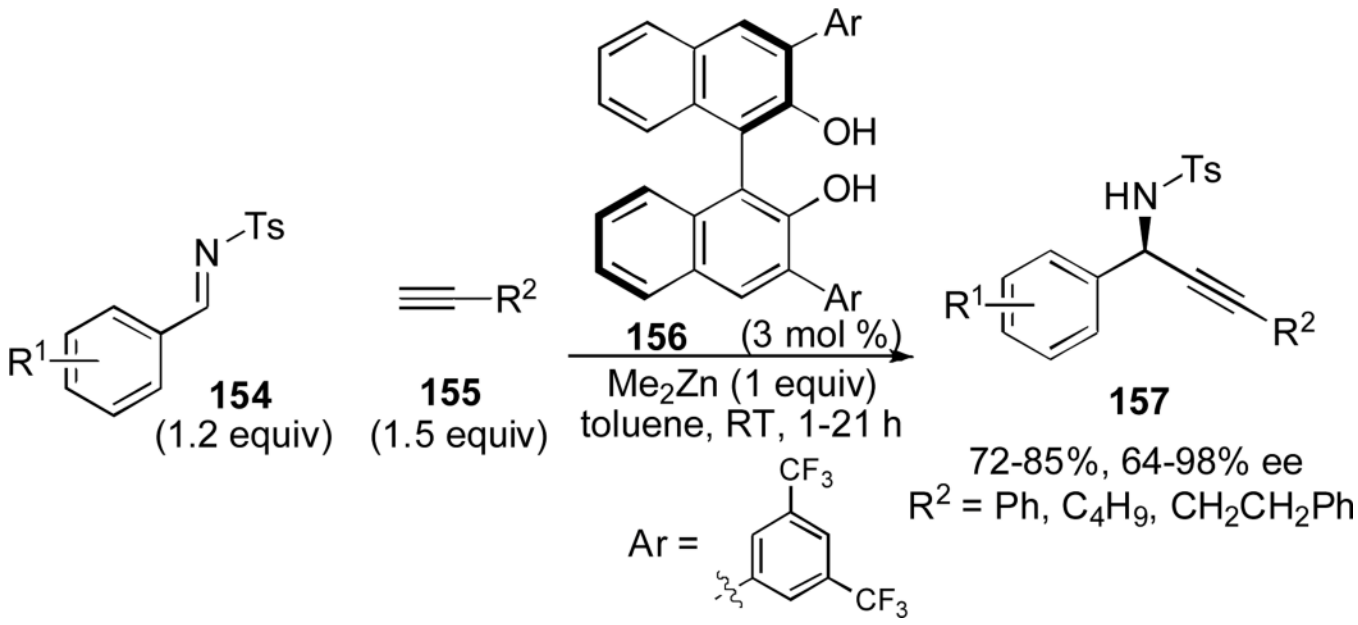
Scheme 31.
Zirconium-catalyzed alkynylation with mixed zinc species.



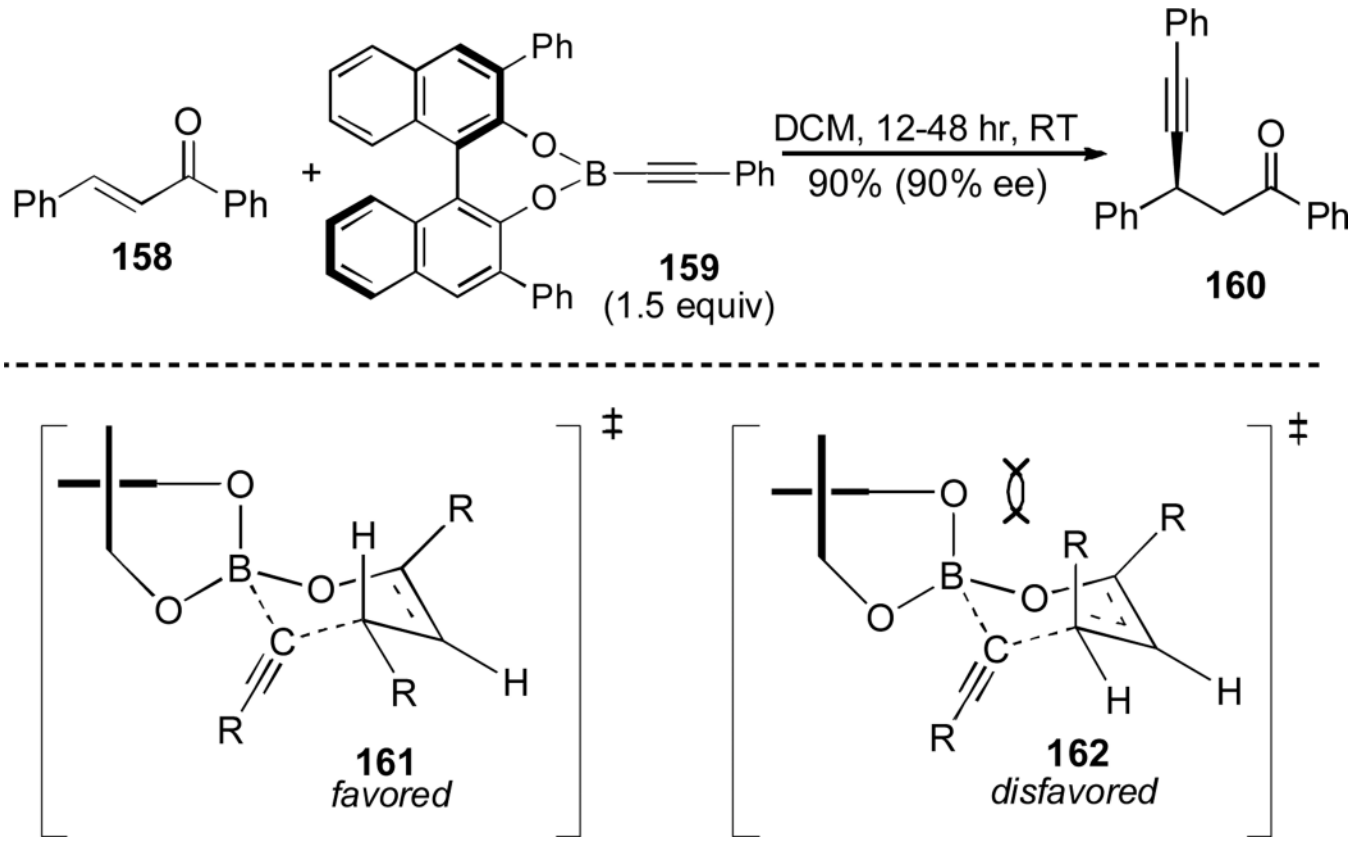
Scheme 32.
Zinc alkynylide addition to cyclic ketimine **150**.



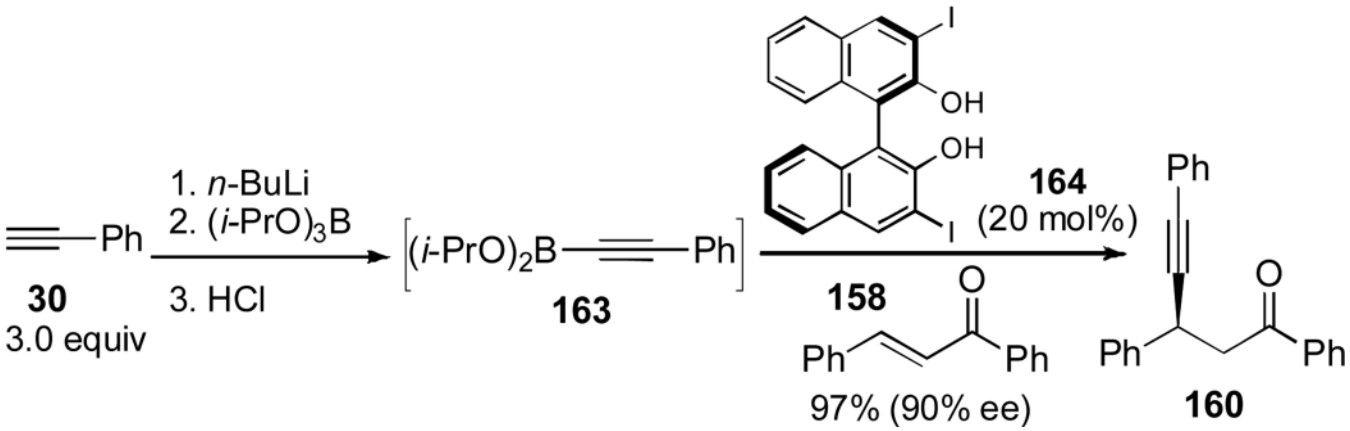
Scheme 33.
Enantioselective addition of alkynyl borane to *N*-acyl imines.



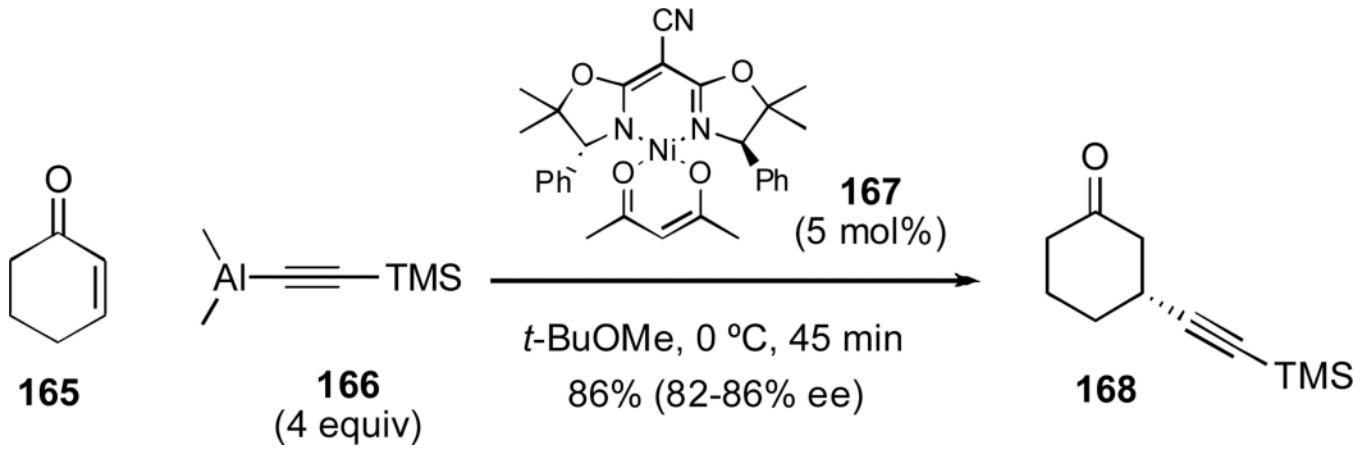
Scheme 34.
Dimethylzinc-mediated alkynylation of *N*-tosyl imines.



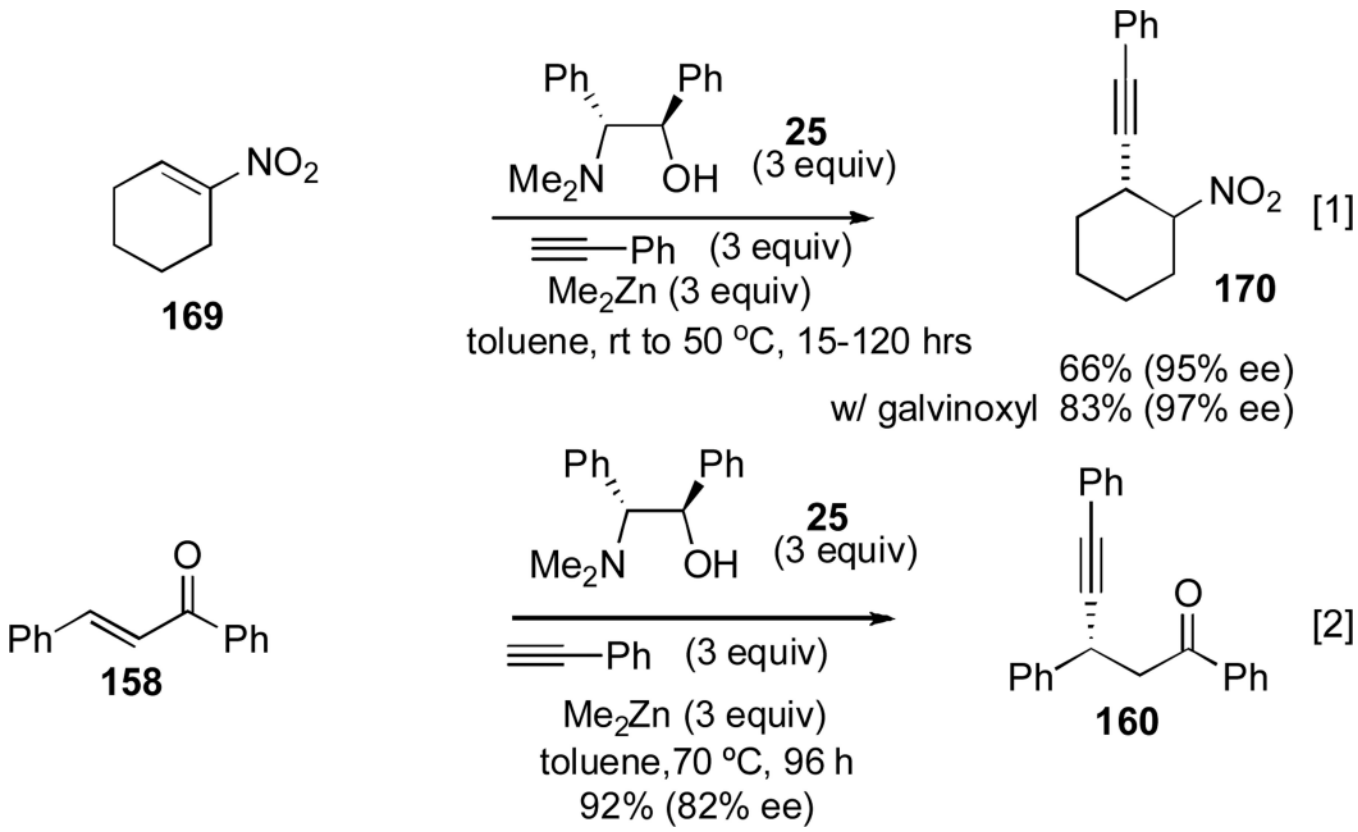
Scheme 35.
First example of enantioselective conjugate addition of an alkyne.



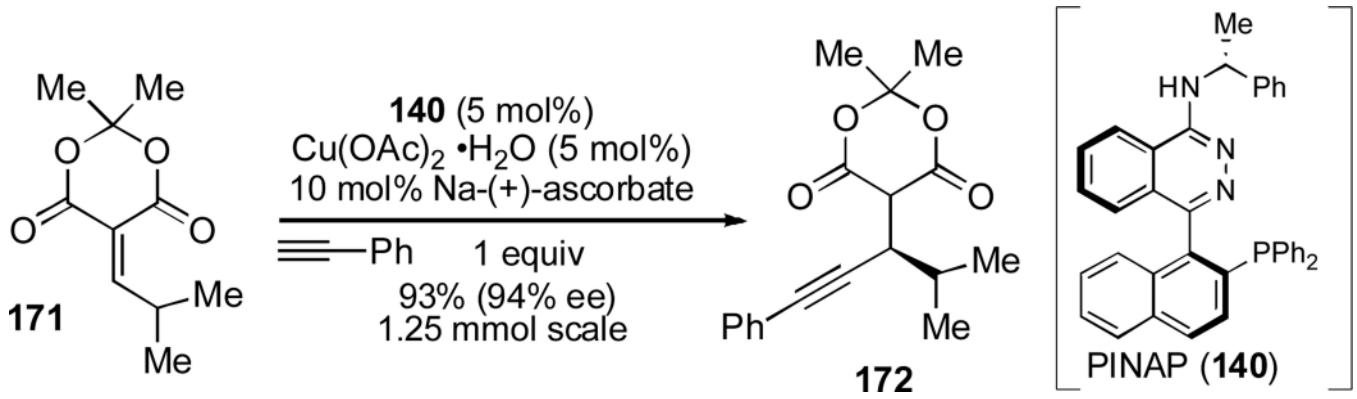
Scheme 36.
Asymmetric conjugate addition of alkynyl boronates.



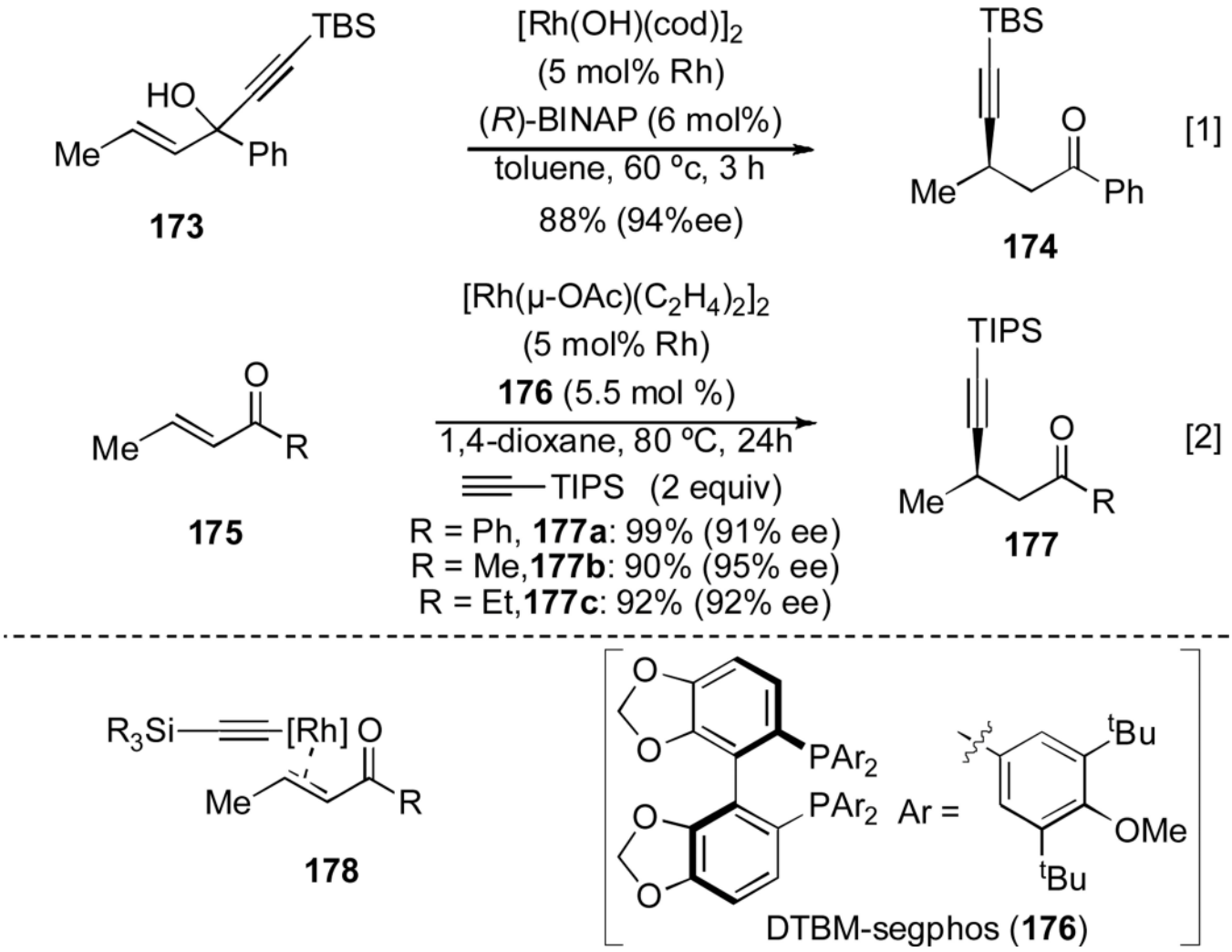
Scheme 37.
Corey's enantioselective conjugate addition to cyclic enone.



Scheme 38.
Aminoalcohol zinc alkynylide-mediated asymmetric conjugate additions.



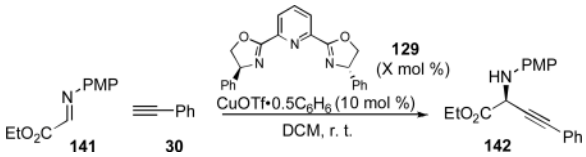
Scheme 39.
Copper-catalyzed enantioselective conjugate alkynylation of alkylidene Meldrum's acids.



Scheme 40.
Rh-catalyzed asymmetric conjugate addition of alkynes to enones.

Table 1

Copper/pybox ratio affects enantioselectivity.



entry	X	time	yield(%)	ee(%)
1	10	24 h	80	63
2	10	24 h	71	−23[a]
3	12	36 h	64	23
4	13	36 h	57	−36
5	15	6 d	60	−70[a]

a) molecular sieves (4 Å) added