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2.10 Alkynylation of Carbonyl and Imino Groups

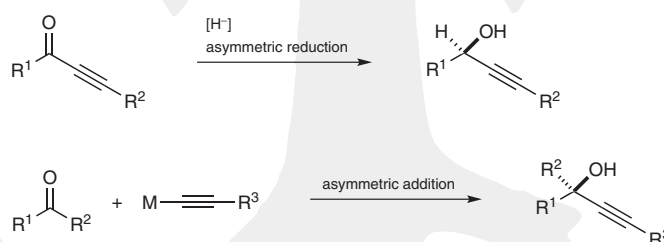
2.10.1 Enantioselective Addition of Acetylide Nucleophiles to Carbonyl Compounds

E. M. Carreira and D. E. Frantz

General Introduction

Chiral propargylic alcohols can be found as structural motifs in several natural products and pharmaceuticals. However, their most important attribute is their use as versatile chiral building blocks in organic synthesis.^[1] This has only recently become true due to the dramatic development of new methodologies within the past decade that have provided access to these substrates with unprecedented enantioselectivities. Undoubtedly, most modern asymmetric approaches to chiral propargylic alcohols involve the addition of metal acetylides to carbonyl compounds mediated through the use of chiral external ligands. The advantage of this approach over classical asymmetric reductions of alkynyl ketones is the simultaneous formation of a carbon–carbon bond and stereogenic center in a single step (Scheme 1). This area has been recently reviewed and a comprehensive summary of the various approaches toward enantioselective addition of alkyne nucleophiles to both aldehydes and ketones can be found within these references.^[1–7] Thus, what will be presented here is a selection of the most successful reactions with respect to yield and enantioselectivity while keeping practicality, costs, and the availability of starting materials as equally important considerations.

Scheme 1 General Approaches to Chiral Propargylic Alcohols



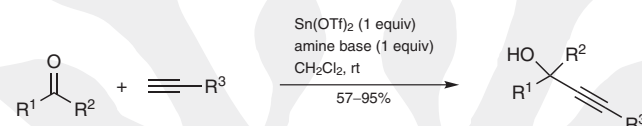
To perform a successful enantioselective alkynylation of a carbonyl compound, judicious choices have to be made up front based on the carbonyl derivative employed (i.e., aldehyde vs ketone and aliphatic vs aromatic) and the electronic nature of the alkyne nucleophile (i.e., electron rich vs electron poor). Additional factors to consider include the degree of selectivity, the availability of reagents and catalysts, functional group compatibility, and whether the process can provide viable access to either enantiomer. For larger-scale preparations, criteria such as robustness, catalyst and/or ligand recovery, costs, environmental impact, and safety also have to be considered in addition to those mentioned previously. In the following sections, these practical issues are considered and addressed whenever possible.

for references see p 514

2.10.1.1 Enantioselective Addition of Terminal Alkynes to Aliphatic Aldehydes via Zinc(II) Salts

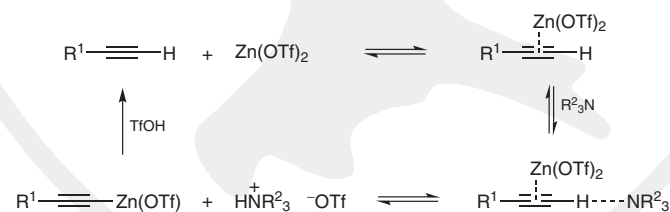
Traditional processes to generate nucleophilic metal (i.e., lithium or magnesium) acetylides capable of addition to carbonyl compounds have required an initial deprotonation step using either a strong amide base or alkyllithium at low temperatures to provide the corresponding metalated alkyne in stoichiometric quantities. This preactivation step imparts severe limitations with respect to functional group compatibility, scalability, and catalysis. In contrast, the mild generation of metal acetylides (room temperature and amine base) from copper(I) salts in catalytic cross-coupling methods (i.e., Sonogashira) is a well-known process.^[8] Unfortunately, copper acetylides are in most cases poor nucleophiles toward C=O bonds [copper(I) acetylides, in contrast, can add to imine derivatives^[9]]. In 1991, Yamaguchi was able to demonstrate that tin(II) salts are capable of inducing a mild deprotonation of terminal alkynes with amine bases and that the corresponding tin acetylides can effectively add to aldehydes and ketones (Scheme 2).^[10]

Scheme 2 Alkynylation of Aldehydes or Ketones Promoted by Tin(II) Salts^[10]



In 1999, the Carreira group reported a similar process to generate nucleophilic zinc acetylides in situ from terminal alkynes using a simple combination of zinc(II) trifluoromethanesulfonate and amine bases in the synthesis of propargylic hydroxylamines from nitrones.^[11] Subsequent mechanistic studies through the use of in situ infrared spectroscopy provide evidence that a zinc acetylide is generated.^[12] In these experiments, the reversible deprotonation of phenylacetylene in the presence of triethylamine and zinc(II) trifluoromethanesulfonate can be monitored by the disappearance of the terminal C–H stretch. Subsequent addition of trifluoromethanesulfonic acid leads to the reappearance of the alkyne C–H stretch. No reaction is observed in the absence of zinc(II) trifluoromethanesulfonate. This led to the proposed process for the metalation of terminal alkynes by zinc(II) salts and amine bases as outlined in Scheme 3.

Scheme 3 Proposed Mechanism for the In Situ Formation of Zinc Acetylides from Zinc(II) Salts and Amine Bases^[12]



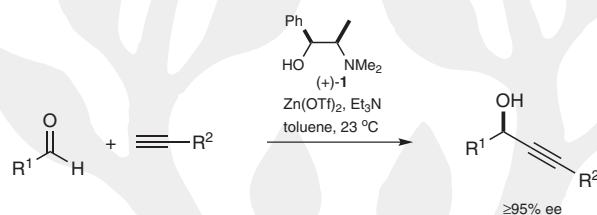
The advantages of this mild method for the generation of nucleophilic zinc acetylides are numerous. Firstly, prior activation of the alkyne (via an initial stoichiometric deprotonation) is obviated, allowing for greater functional group tolerance with respect to the starting alkyne. Secondly, the lower basicity of the zinc acetylide (as compared to either lithium or magnesium acetylides) also provides greater functional group tolerance with respect to the carbonyl compound while simultaneously reducing the absolute reliance on

inert reaction conditions. Finally, the handling of pyrophoric reagents, such as alkylolithiums or dialkylzinc compounds, is also circumvented, providing a much safer process toward propargylic alcohols, making this method attractive for large-scale preparations.

2.10.1.1.1 Stoichiometric Zinc(II)-Mediated Enantioselective Alkynylations

The preferred method for the enantioselective addition of terminal alkynes to aliphatic aldehydes is the method developed by the Carreira group.^[13–16] This strategy involves the use of stoichiometric amounts of zinc(II) trifluoromethanesulfonate, *N*-methylephedrine (**1**), and triethylamine at room temperature in toluene (Scheme 4).

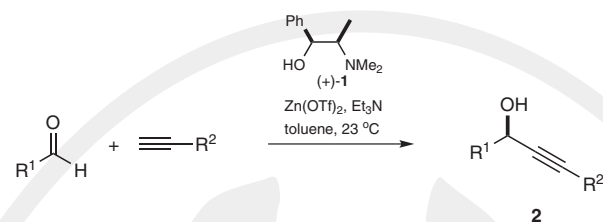
Scheme 4 Carreira's Stoichiometric Enantioselective Zinc Acetylide Addition to Aldehydes^[13]



This method provides several distinct advantages over other protocols that are available. Firstly, all of the reagents necessary to carry out the reaction are commercially available. Both enantiomers of *N*-methylephedrine are also readily available from reliable suppliers, providing convenient access to either enantiomer of the chiral propargylic alcohol of interest. Secondly, the reaction performs equally well without prior purification of the reagents or solvents, can be conducted in air, and can tolerate the presence of water (up to 6000 ppm).^[13] Thirdly, high enantioselectivities are observed across a broad range of aliphatic aldehydes and alkynes, with most reactions occurring in >95% ee (Table 1). Finally, the reaction is even amenable to acetylene itself, albeit with longer reaction times.^[16] With (+)-*N*-methylephedrine as the chiral ligand, attack of the zinc acetylide occurs from the *Si*-face of the aldehyde to produce the corresponding (*R*)-propargylic alcohol. The (*S*)-enantiomer can be obtained in similar yields and enantioselectivities using (–)-*N*-methylephedrine. For larger-scale preparations, recovery of the chiral amino alcohol is facilitated by simple acid/base extraction. Because most of the products are oils, purification of the products is usually achieved by normal-phase silica gel chromatography.

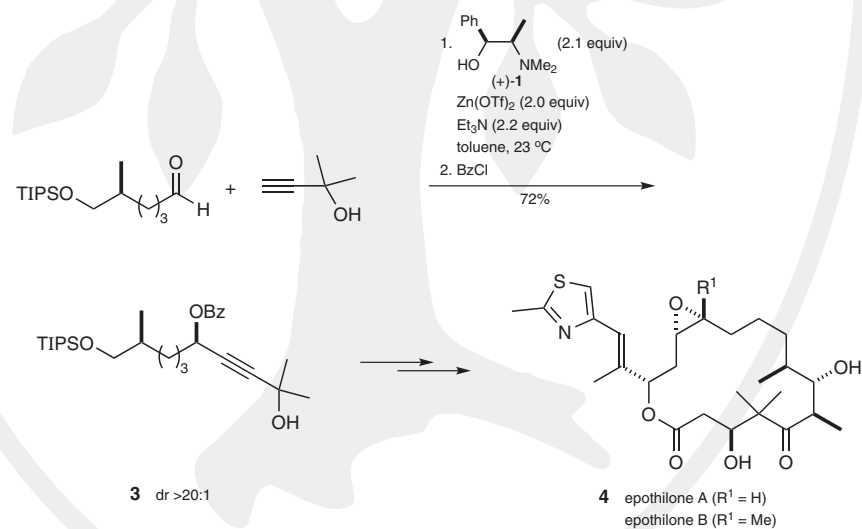
The extension of this method to several applications in natural product total synthesis also highlights its versatility and broad scope (Scheme 5). The Carreira group has demonstrated the usefulness of this approach in the total synthesis of epothilone A (**4**, R¹ = H) and epothilone B (**4**, R¹ = Me) via propargylic alcohol **3**, and leucascandrolide A (**6**) via propargylic alcohol **5** (Scheme 5).^[17,18] More recently, the Shair group at Harvard have employed this protocol for the enantioselective synthesis of (+)-cephalostatin **1** (**8**) via a highly diastereoselective alkynylation of aldehyde **7**.^[19]

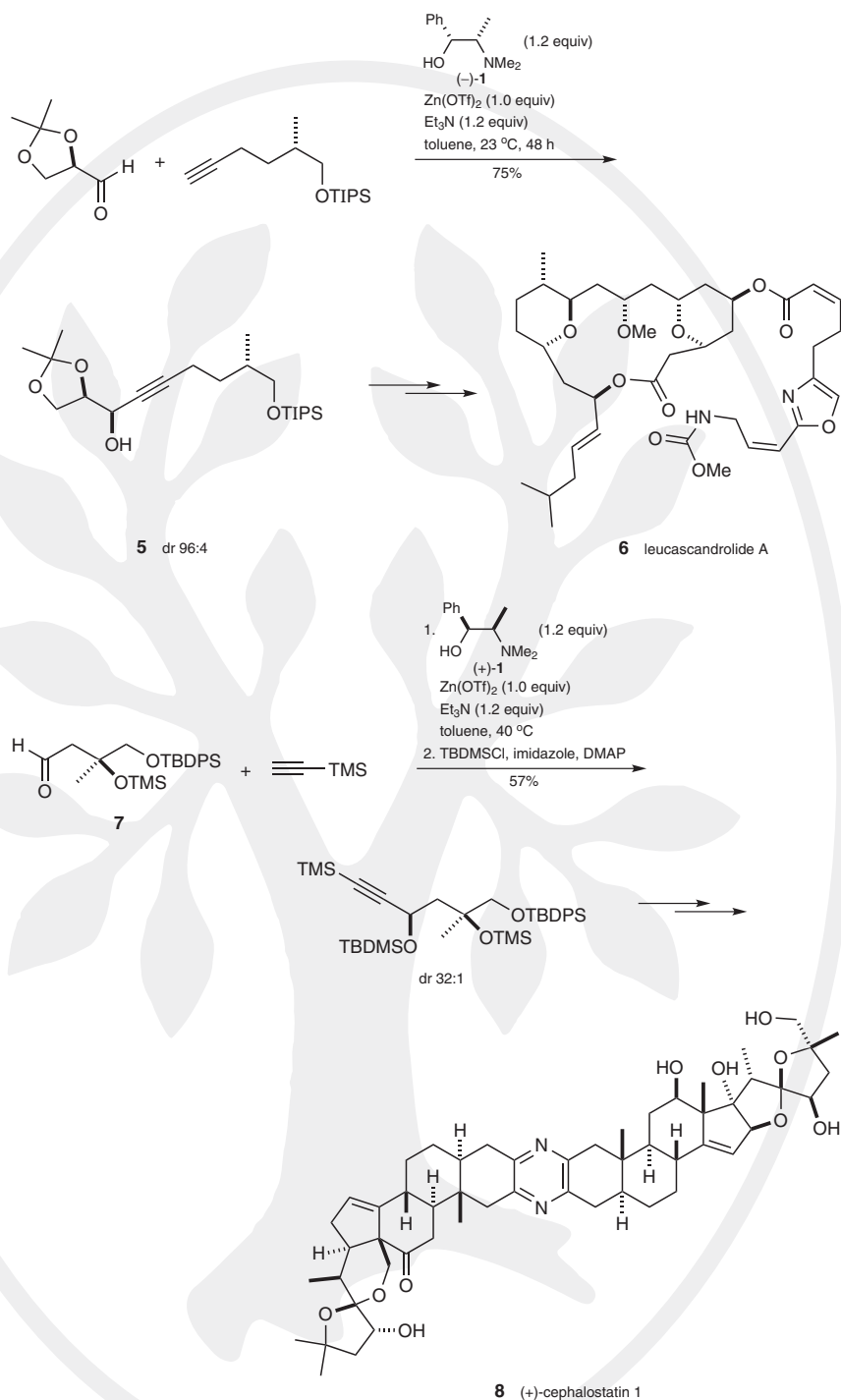
for references see p 514

Table 1 Enantioselective Addition of Alkynes to Aldehydes^[13]

Entry	R ¹	R ²	Time (h)	Yield ^a (%)	ee (%)	Ref
1	Cy	Ph	1	99	96	[13]
2	Cy	TMS	2	93	98	[13]
3	Cy	CH(OEt) ₂	8	90	98	[13]
4	iPr	(CH ₂) ₂ Ph	2	90	99	[13]
5	iPr	CMe ₂ OH	4	97	98	[13]
6	<i>t</i> -Bu	Ph	2	99	94	[13]
7	<i>t</i> -Bu	(CH ₂) ₂ Ph	2	84	99	[13]
8	CH ₂ <i>t</i> -Bu	(CH ₂) ₂ Ph	2	72	99	[13]

^a The reaction was conducted using Zn(OTf)₂ (1.1 equiv), (+)-*N*-methylephedrine [(+)-1; 1.2 equiv], and Et₃N (1.2 equiv) in toluene (0.3 M) at 23 °C.

Scheme 5 Application of Carreira's Alkynylation Method to Natural Product Total Synthesis^[17–19]



Despite the documented success of this method by many synthetic groups, there are several limitations that should be highlighted. In general, simple α -unbranched aliphatic aldehydes give products in slightly lower enantiomeric excesses and yields because of competing self-condensation aldol products. This limitation, however, can be circumvented by slow addition of the aldehyde to the reaction over the course of several hours.^[14] Al-

for references see p 514

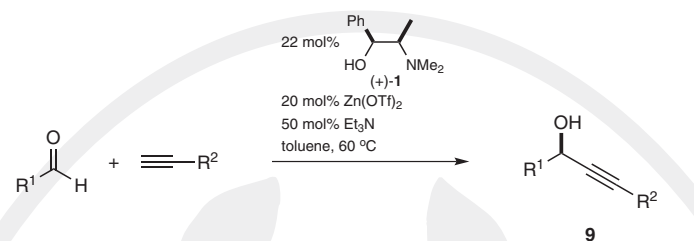
though both toluene and dichloromethane serve as suitable solvents for this reaction, coordinating solvents (i.e., tetrahydrofuran), in general, reduce the enantioselectivity of these reactions significantly (to ~80% ee).^[13] Finally, there have been several reports in the literature of failed alkynylations with this method.^[20–22] A significant amount of attention has been paid to the purity, particle size, and dryness of the zinc(II) trifluoromethanesulfonate obtained from commercial sources. Although a systematic study has not been performed to examine all of these factors simultaneously, the fact that a majority of these reactions are heterogeneous dictates careful attention to these parameters as well as efficient stirring and the purity of both starting materials (alkyne and aldehyde). It is interesting to note, however, that most failures are a result of reactions that simply do not provide any product, rather than reactions that are not enantioselective, suggesting a critical parameter may have been overlooked in these cases. Nonetheless, the number of successful examples of this method far outweighs the failures and this continues to be the first method of choice for the asymmetric alkynylation of aliphatic aldehydes.^[23–30]

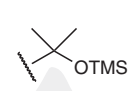
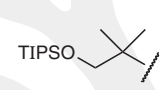
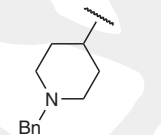
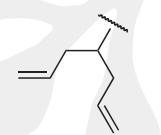
Propargylic Alcohols 2; General Procedure for the Enantioselective Alkynylation of Aliphatic Aldehydes Using Stoichiometric Amounts of Zinc(II) Trifluoromethanesulfonate:^[13]

A 10-mL flask was charged with Zn(OTf)₂ (0.200 g, 0.550 mmol, 1.1 equiv) and (+)-*N*-methylephedrine [(+)-**1**; 0.108 g, 0.600 mmol, 1.2 equiv], and purged with N₂ for ca. 15 min. Toluene (1.5 mL) and Et₃N (61.0 mg, 0.600 mmol, 1.2 equiv) were added. The resulting heterogeneous mixture was stirred at 23 °C for 2 h, after which the alkyne (0.600 mmol, 1.2 equiv) was added in one portion via syringe. After 15 min, the aldehyde (0.500 mmol, 1.0 equiv) was added via syringe. The reaction was stirred at 23 °C until full conversion of the aldehyde was evident by TLC. The reaction was quenched by the addition of sat. aq NH₄Cl (3 mL) and then poured into a separatory funnel containing Et₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with sat. aq NaCl (10 mL) and dried (Na₂SO₄). Concentration of the dried organic soln yielded the crude product mixture, which was purified by flash chromatography (silica gel) to provide the propargylic alcohol.

2.10.1.1.2 Catalytic, Asymmetric Additions of Alkynes to Aliphatic Aldehydes via Zinc(II) Salts

In 2001, the Carreira group reported a significant advancement over their prior stoichiometric enantioselective alkynylation via zinc(II) salts (see Section 2.10.1.1.1) by enabling the reaction to be catalytic in zinc, *N*-methylephedrine, and base.^[31] They found that simply by conducting the reaction at higher temperatures (60–100 °C), turnover of the initially formed zinc alkoxide is obtained with surprisingly little influence on the enantioselectivity of the reaction as compared to the stoichiometric version at room temperature. Using 20 mol% of zinc(II) trifluoromethanesulfonate, 22 mol% of *N*-methylephedrine (**1**), and 50 mol% of triethylamine, they were able to demonstrate the catalytic version on a broad range of aliphatic aldehydes and highly functionalized alkynes (Table 2).

Table 2 Catalytic Enantioselective Addition of Alkynes to Aldehydes via Zinc(II) Salts^[31]


Entry	R ¹	R ²	Time (h)	Yield ^a (%)	ee (%)	Ref
1	Cy	CH ₂ NBn ₂	2	91	97	[31]
2	Cy	TES	7	85	96	[31]
3	Cy	CH(OEt) ₂	8	88	94	[31]
4	iPr		5	77	98	[31]
5		CH ₂ NBn ₂	5	80 ^b	95	[31]
6		CH ₂ NBn ₂	5	81 ^b	94	[31]
7		(CH ₂) ₂ Ph	16	80	93	[31]
8	(CH ₂) ₆ Me	CH ₂ NBn ₂	24	55 ^c	91	[31]

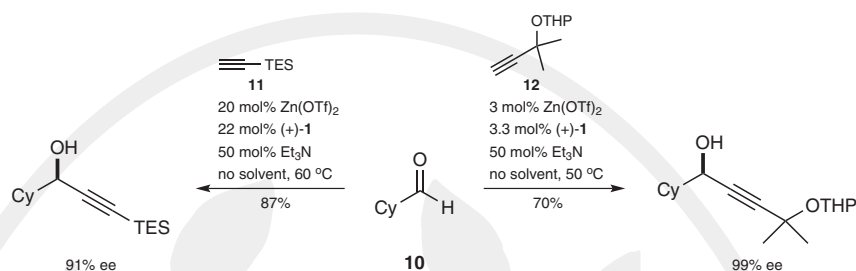
^a The reaction was conducted using 20 mol% of Zn(OTf)₂, 22 mol% of (+)-*N*-methylephedrine [(+)-**1**], and 50 mol% of Et₃N in toluene (1.0 M) at 60 °C unless otherwise noted.

^b The reaction was performed at 100 °C.

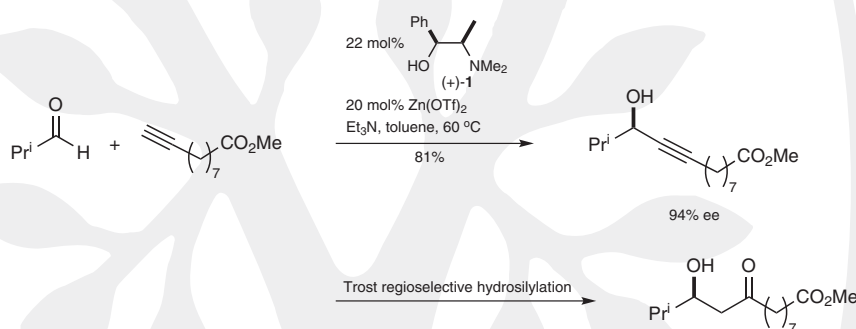
^c The aldehyde was added dropwise to the reaction mixture over 2.5 h.

Some analogies to the stoichiometric version were established with this initial report, including the relative insensitivity of these reactions to moisture and air, the same sense of facial selectivity [i.e., (+)-*N*-methylephedrine [(+)-**1**] gives (*R*)-alcohols, (–)-*N*-methylephedrine gives (*S*)-alcohols], and toluene as the preferred solvent. Furthermore, in an effort to increase the atom efficiency of the catalytic reaction, it was demonstrated that the reaction performs exceedingly well in the absence of solvent. By using 1.0 equivalents of aldehyde and 1.05 equivalents of alkyne, the asymmetric alkynylation of cyclohexanecarbaldehyde (**10**) using either alkyne **11** or **12** occurs in high yields and enantioselectivities with no added solvent (Scheme 6). This provides tangible advantages, including obviating the need to perform the chiral zinc complex (zinc salt, ligand, and amine), a reduction in reaction times, and the elimination of aqueous workups by direct chromatography of the reaction mixture on silica gel.

for references see p 514

Scheme 6 Solvent-Free Catalytic Enantioselective Alkynylation of Aldehydes^[31]

Although the application of the catalytic version of the Carreira alkynylation has seen much less use than the stoichiometric version, there are several published examples of its utility. The Trost group recently applied this approach in the development of a regioselective hydrosilylation/oxidation protocol of propargylic alcohols as a surrogate to the aldol reaction (Scheme 7).^[32]

Scheme 7 Application of Catalytic Alkynylation of Aldehydes toward β -Hydroxy Ketones^[32]

The most significant limitation of the catalytic method described here is that it cannot be applied to aromatic aldehydes because of a competing Cannizzaro process.

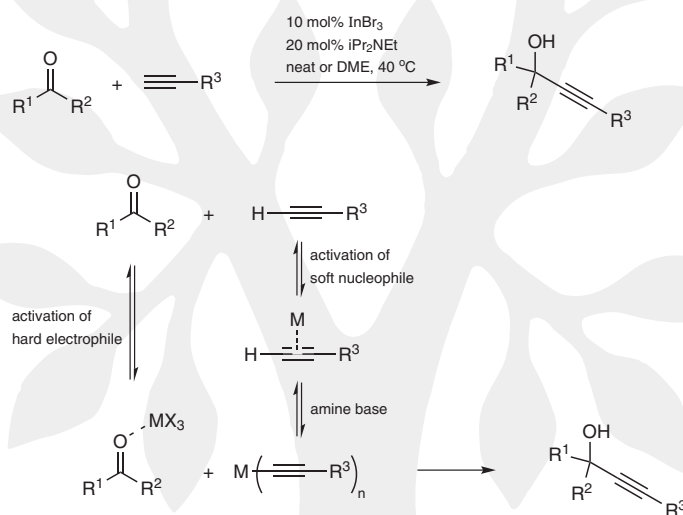
Propargylic Alcohols 9; General Procedure for the Zinc(II) Trifluoromethanesulfonate Catalyzed Enantioselective Alkynylation of Aliphatic Aldehydes:^[31]

A 10-mL flask was charged with $\text{Zn}(\text{OTf})_2$ (36 mg, 0.10 mmol, 20 mol%) and was then heated to 125 °C under vacuum (<0.38 Torr) for 2 h. After the system had been allowed to cool to 23 °C, (+)-*N*-methylephedrine [(+)-1; 20 mg, 0.11 mmol, 22 mol%] was added under N_2 . The flask was evacuated (<0.38 Torr) for 30 min, and then purged with N_2 prior to the addition of toluene (0.50 mL) and Et_3N (25 mg, 0.25 mmol, 50 mol%) by syringe. The resulting mixture was stirred for 2 h at 23 °C, after which the alkyne (0.60 mmol, 1.2 equiv) was added. After the mixture had been stirred for 15 min at 23 °C, the aldehyde (0.50 mmol, 1.0 equiv) was added in one portion, and the mixture was heated to 60 °C until full conversion was observed by TLC. The mixture was quenched with sat. aq NH_4Cl (3 mL) and then poured into a separatory funnel containing Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 \times 10 mL). The combined organic layers were washed with sat. aq NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (silica gel) provided the pure propargylic alcohol.

2.10.1.2 Catalytic Enantioselective Addition of Terminal Alkynes to Aromatic Aldehydes

Although the stoichiometric Carreira asymmetric alkynylation reaction conditions are able to provide chiral propargylic alcohols derived from aromatic aldehydes in good yields and high enantioselectivities,^[13,15] the catalytic version is not applicable in these cases. Because of this, several groups have developed alternative methods to add terminal alkynes to aromatic aldehydes in both high yields and enantioselectivities. Three methods from the groups of Trost,^[33] Wolf,^[34] and Shibasaki^[35] have all received a significant amount of attention. Of these, the protocol of Shibasaki involving the use of commercially available indium(III) salts and 1,1'-binaphthalene-2,2'-diol (BINOL) ligands offers the most attractive approach in terms of practicality, scope, and generality. The initial report from this group demonstrates the feasibility of this approach in racemic fashion through the addition of terminal alkynes to both aldehydes and ketones (Scheme 8).^[36]

Scheme 8 Shibasaki's Alkynylation of Carbonyl Derivatives through Dual Activation of Electrophile and Nucleophile^[36]



The premise behind this method is the simultaneous dual activation of both the electrophile (aldehyde or ketone) and the nucleophile (alkyne) through the use of catalytic amounts of indium(III) bromide and *N,N*-diisopropylethylamine (Hünig's base). By the use of in situ infrared studies as well as NMR analysis (both ¹H and ¹³C), Shibasaki's group has provided convincing evidence that supports their hypothesis of this dual-activation role of indium(III) salts. In the same year, they followed up on these findings to report an asymmetric alkynylation of both aliphatic and aromatic aldehydes promoted by a chiral indium(III)/BINOL complex (Table 3). The reaction provides a complementary approach to the Carreira catalytic alkynylation by providing propargylic alcohols **13** in good yields (61–85%) and high enantioselectivities (83–99% ee) with aromatic aldehydes. In addition, the present reaction shows remarkable relative insensitivity to both moisture and air (entry 8) similar to the Carreira alkynylation and a common advantage of this soft metalation strategy. Furthermore, catalyst loadings can be reduced to 2 mol% for both indium(III) bromide and BINOL when the reaction is performed at high concentration (10 M), with no apparent influence on yield or enantioselectivity (entry 1 vs entry 9). In

for references see p 514

all of the examples provided, when (*R*)-BINOL is used as the chiral ligand, the resulting (*R*)-propargylic alcohols are formed. Interestingly, a strong nonlinear effect is observed in these reactions, where BINOL at 20% ee provides the product in 94% ee.

Table 3 Catalytic Enantioselective Addition of Terminal Alkynes to Aromatic Aldehydes via a Chiral Indium(III)/BINOL Complex^[35]

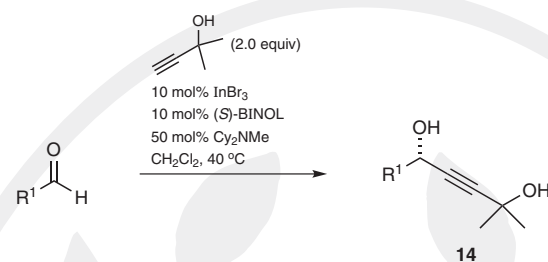
$R^2 \text{—} \text{C} \equiv \text{C—H}$ (2.0 equiv)
 10 mol% InBr₃
 10 mol% (*R*)-BINOL
 50 mol% Cy₂NMe
 CH₂Cl₂, 40 °C

Entry	R ¹	R ²	Time (h)	Yield (%)	ee (%)	Ref
1	Ph	Ph	24	84	95	[35]
2	Ph	(CH ₂) ₂ Ph	48	70	98	[35]
3	Ph		48	77	89	[35]
4	Ph	cyclopropyl	48	74	83	[35]
5	4-FC ₆ H ₄	Ph	24	75	95	[35]
6	3-MeOC ₆ H ₄	Ph	48	77	97	[35]
7	3-furyl	Ph	20	84	98	[35]
8 ^a	Ph	Ph	24	85	94	[35]
9 ^b	Ph	Ph	48	85	96	[35]

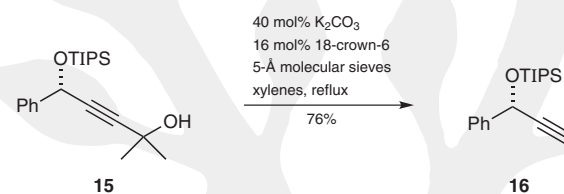
^a The reaction was performed under an air atmosphere.

^b The reaction was performed using InBr₃ (2 mol%), (*R*)-BINOL (2 mol%), and Cy₂NMe (10 mol%) in CH₂Cl₂ (10 M).

Despite the generality exhibited by the Shibasaki asymmetric alkynylation, there are some notable limitations that have yet to be solved in its current state of development. Firstly, the reaction times are significantly long (usually 48 hours) for most aromatic aldehydes. The fact that the reactions are performed at the boiling point of dichloromethane dictates that they are performed under reflux (rather than a sealed flask for safety reasons) to reduce solvent loss. Secondly, to achieve good yields, 2 equivalents of the alkyne is needed, which places a significant burden on the reaction if the alkyne starting material is difficult to obtain. Finally, the successful implementation of prototypical synthetic equivalents of acetylene [i.e., (trimethylsilyl)acetylene] is not demonstrated in the original report^[36] or in the subsequent asymmetric version discussed above. These are viewed as critical to the overall generality of any asymmetric alkynylation because of the versatility of the products that are formed with these alkynes that permit the introduction of additional functional groups through subsequent deprotection/deprotonation or cross-coupling protocols. To address this limitation, Shibasaki's group subsequently reported the asymmetric addition of 2-methylbut-3-yn-2-ol to aldehydes via their indium(III)/BINOL method.^[37] Using the same conditions as originally documented, they have demonstrated the successful asymmetric alkynylation on a series of aromatic aldehydes in good yields and high enantioselectivities with this acetylene equivalent (Scheme 9). Using conditions similar to those developed by the Carreira group,^[14] removal of acetone from protected propargylic alcohol **15** [derived from propargylic alcohol **14** (R¹ = Ph)] is accomplished to provide the terminal alkyne **16** in 76% isolated yield.

Scheme 9 Catalytic Enantioselective Addition of 2-Methylbut-3-yn-2-ol to Aromatic Aldehydes via Shibasaki's Method^[37]

R ¹	Yield (%)	ee (%)	Ref
Ph	88	97	[37]
4-MeOC ₆ H ₄	62	99	[37]
2-furyl	89	93	[37]

**Propargylic Alcohols 13; General Procedure for the Catalytic Asymmetric Addition of Terminal Alkynes to Aromatic Aldehydes via Indium(III)/BINOL Complexes:**^[35]

To a dry flask was added (*R*)-BINOL (28.6 mg, 0.10 mmol) and InBr₃ (35.5 mg, 0.10 mmol) under an atmosphere of argon. To the flask was added CH₂Cl₂ (0.5 mL) followed by the aldehyde (1.0 mmol) at rt. The resulting soln was stirred for 15 min followed by addition of Cy₂NMe (106 μL, 0.50 mmol). After stirring for an additional 10 min, the alkyne was added (2.0 mmol) and the mixture was warmed to 40 °C. The reaction was monitored for complete conversion of the aldehyde by TLC and then quenched with sat. aq NH₄Cl and small amounts of 1 M HCl. The mixture was extracted with Et₂O and dried (Na₂SO₄). The crude product obtained after concentration was purified by flash chromatography (silica gel) to give the pure propargylic alcohol.

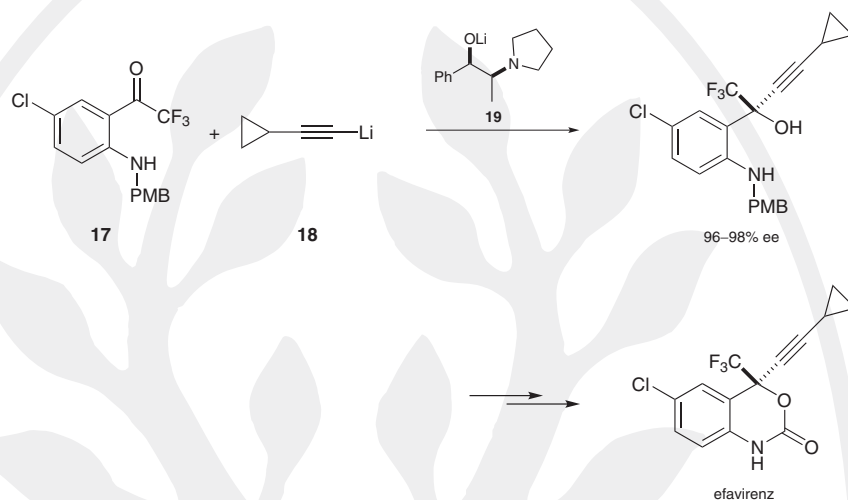
2.10.1.3 Enantioselective Addition of Terminal Alkynes to Ketones

Although the asymmetric addition of terminal alkynes to aldehydes has enjoyed tremendous success, the corresponding additions to ketones are considerably less well developed, and these additions require additional examination before they can be deemed general. The importance of accessing chiral tertiary propargylic alcohols via an enantioselective alkynylation of ketones cannot be overstated, because alternative approaches through simple asymmetric reductions (as with chiral secondary propargylic alcohols) are not feasible. The lack of success with ketones has been attributed to their lower electrophilicity compared to aldehydes, given that most systems that work with aldehydes simply do not react with ketones. Consequently, the most successful approaches have involved activated electrophiles, including α -oxo esters and trifluoromethyl ketones.^[1,6] In fact, the first successful enantioselective alkynylation of a ketone was reported by the Department of Process Research at Merck & Co., Inc., involving trifluoromethyl ketone **17**, lithium cyclopropylacetylide (**18**), and the chiral amino alkoxide **19** en route to the HIV

for references see p 514

reverse transcriptase inhibitor efavirenz (Scheme 10).^[38] Subsequent detailed studies of this reaction have led to further refinement and the use of a zinc acetylide that obviates the 4-methoxybenzyl protecting group on nitrogen.^[39–41]

Scheme 10 Merck's Synthesis of Efavirenz via the First Reported Asymmetric Alkynylation of Ketones^[38]

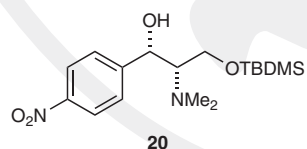


Despite the limitations that ketones present, new approaches toward catalytic alkynylations of unactivated ketones have recently been developed based on the concept of bifunctional catalysts (i.e., dual activation of both electrophile and nucleophile) that have shown dramatic success in the enantioselective addition of other alkylmetal species to ketones.^[36,42,43] Although these new avenues have shown promise in overcoming the low reactivity of ketones to provide tertiary propargylic alcohols in good yields, achieving high enantioselectivities (>95%) through absolute control of facial selectivity with chiral catalysts on a broad scope of substrates remains an ongoing challenge that has yet to be achieved.

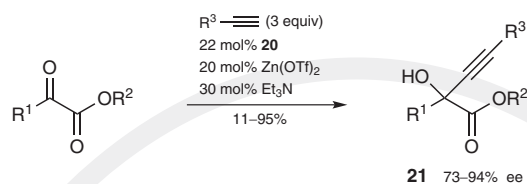
2.10.1.3.1 Enantioselective Addition of Terminal Alkynes to α -Oxo Esters

In 2002, Jiang and co-workers reported the catalytic enantioselective addition of terminal alkynes to α -oxo esters to give propargylic alcohols **21** based on the Carreira protocol for aldehydes (Scheme 11).^[44]

Scheme 11 Catalytic, Asymmetric Addition of Terminal Alkynes to α -Oxo Esters^[44]



2.10.1 Enantioselective Addition of Acetylide Nucleophiles to Carbonyl Compounds 509



The reaction is typified by the use of catalytic amounts of zinc(II) [20 mol% $\text{Zn}(\text{OTf})_2$], chiral amino alcohol **20** (22 mol%), and triethylamine (30 mol%). However, to achieve high yields, the reaction must be performed neat using the corresponding alkyne as solvent (usually at least 3 equiv). In general, the reaction works well with aromatic oxo esters and either aromatic or aliphatic alkynes, providing the corresponding propargylic alcohols in good yields and moderate to high enantioselectivities (Table 4, entries 1–6). The scope of the reaction appears to be limited to non-enolizable keto esters; for example, methyl pyruvate provides the desired tertiary alcohol in 92% ee, albeit in only 11% yield (entry 7). A limitation of this approach is the use of chiral amino alcohol **20**, which is not commercially available and requires a multistep synthetic sequence for its preparation. Interestingly, a single example is shown using (–)-*N*-methylephedrine [(–)-**1**] that provides the product in almost exactly the same yield and enantioselectivity (entry 2), suggesting that this commercially available chiral amino alcohol could serve as a surrogate to **20**. The absolute stereochemical assignment of the products when using chiral amino alcohol **20** was indirectly determined to be *R* based on the transformation outlined in Scheme 12. Comparison of the optical rotation of the hydrogenated product **23** $\{[\alpha]_{\text{D}} -26$ (*c* 0.26, CHCl_3)}, derived from propargylic alcohol **22**, with an authentic sample of (*S*)-methyl 2-hydroxy-2-methyl-4-phenylbutanoate $\{[\alpha]_{\text{D}} +29.6$ (*c* 2.4, CHCl_3)} was used to secure the assignment.

Table 4 Catalytic Enantioselective Addition of Terminal Alkynes to α -Oxo Esters^[44]

Entry	Reactants		Product	Yield ^a (%)	ee (%)	Ref
	α -Oxo Ester	Alkyne				
1				91	89 (+)	[44]
2				87 ^b	88 (–)	[44]
3				93	73 (+)	[44]

for references see p 514

Table 4 (cont.)

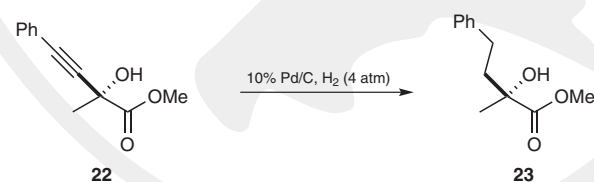
Entry	Reactants		Product	Yield ^a (%)	ee (%)	Ref
	α -Oxo Ester	Alkyne				
4				76 ^c	86 (+)	[44]
5				88	94 (+)	[44]
6				83	91 (+)	[44]
7				11	92 (-)	[44]
8				95	93 (+)	[44]

^a Unless otherwise noted, reactions were performed using 20 mol% of chiral amino alcohol **20**, 20 mol% of $\text{Zn}(\text{OTf})_2$, 30 mol% of Et_3N , and the alkyne as solvent (3 equiv) at 70 °C for 2 days.

^b (-)-(1*R*,2*S*)-*N*-Methylephedrine [(-)-**1**] was used as the chiral ligand.

^c 5 equivalents of alkyne was used.

Scheme 12 Assignment of Absolute Stereochemistry via Hydrogenation of a Chiral Tertiary Propargylic Alcohol^[44]



Tertiary Propargylic Alcohols **21; General Procedure for Catalytic Asymmetric Addition of Terminal Alkynes to α -Oxo Esters:^[44]**

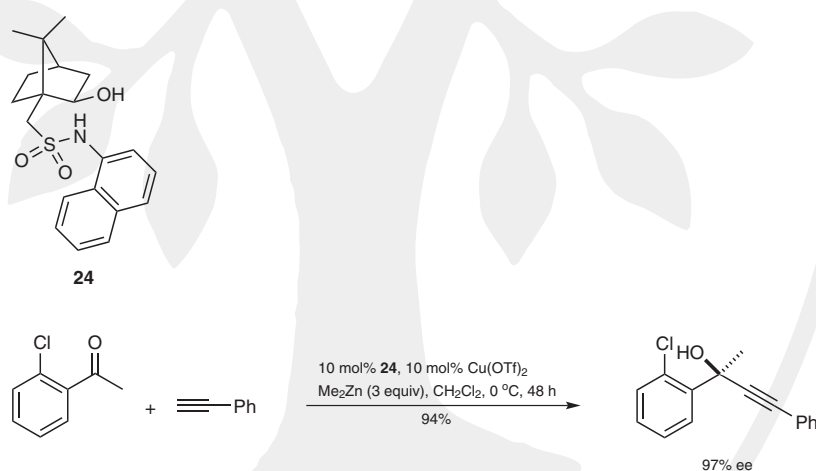
To a soln of $\text{Zn}(\text{OTf})_2$ (0.1 mmol, 0.2 equiv) and chiral ligand **20** (0.11 mmol, 0.22 equiv) in a terminal alkyne (1.5 mmol, 3 equiv) was added Et_3N (0.15 mmol, 0.3 equiv) at rt under an atmosphere of N_2 and the mixture was then stirred for 2 h. To this was added the α -oxo

ester (0.5 mmol, 1.0 equiv) via syringe and then the mixture was heated to 70 °C for 2 d. The mixture was then diluted with petroleum ether (20 mL) and washed with 0.5 M HCl (3 × 10 mL) while maintaining the pH above 4. The organic layer was then washed with sat. aq NaCl and deionized H₂O and dried (Na₂SO₄). The solvent was then removed and the resulting crude product was purified via flash chromatography (silica gel, petroleum ether/EtOAc 7:1) to give the desired tertiary propargylic alcohol.

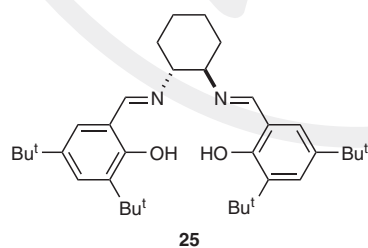
2.10.1.3.2 Enantioselective Addition of Terminal Alkynes to Unactivated Ketones

To date, a general and robust method for the asymmetric addition of acetylide nucleophiles to unactivated ketones that exhibits broad scope with respect to both alkyne and ketone (i.e., aromatic and aliphatic substrates) has yet to be identified. Nonetheless, there are several reported methods that have achieved very high enantioselectivities with either aromatic or aliphatic ketones, but these methods are limited to very specialized alkynes (most notably phenylacetylene).^[45–48] However, in 2003, two reports appeared from the laboratories of Chan^[49] and Cozzi^[50] that appear to complement each other and provide the broadest substrate scope (albeit still modest with respect to the alkyne) through the use of in situ generated zinc acetylides (Schemes 13 and 14). The source of asymmetric induction in Chan's method is the use of chiral sulfonamide **24** in tandem with catalytic amounts of copper(II) trifluoromethanesulfonate to activate the ketone toward nucleophilic addition. In Cozzi's work, the chiral salen ligand **25** is used to generate a proposed bifunctional zinc–salen, Lewis acid–Lewis base complex capable of simultaneous activation of both the zinc acetylide and ketone in the transition state.

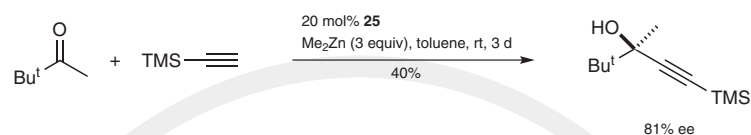
Scheme 13 Chan's Approach to the Asymmetric Alkynylation of Ketones^[49]



Scheme 14 Cozzi's Approach to the Asymmetric Alkynylation of Ketones^[50]



for references see p 514



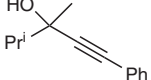





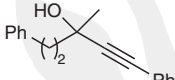








Subsequent to his initial report, Chan published a full, detailed account describing the approach that included a screen of various chiral ligands, elaboration of the substrate scope (including aliphatic ketones and alkynes), and provided optimized reaction conditions to access chiral tertiary propargylic alcohols **26**.^[51] This method is the most developed protocol to date. On the basis of the published work, there are some limitations, however, that have been pointed out. Only phenylacetylene, cyclopropylacetylene, and (trimethylsilyl)acetylene have been shown to work as reactants, and the reported selectivities are modest (Table 5, entries 9 and 10). In addition, although phenylacetylene is capable of adding to aliphatic ketones with remarkable selectivity in select cases (entry 6), other aliphatic ketones do not elicit the same success (entries 7 and 8). Furthermore, in all cases reported, excess alkyne is needed (at least 2.5 equiv) to achieve high yields. Finally, the utilization of the highly pyrophoric reagent, dimethylzinc(II), in excess presents a practical challenge on larger scale that may limit its application in these settings.

Table 5 Catalytic Enantioselective Addition of Terminal Alkynes to Ketones^[49,51]

Entry	Reactants		Product	Yield (%)	ee (%)	Ref
	Ketone	Alkyne				
1				92	88 (+)	[49]
2				91	96 (-)	[49]
3				91	70 (-)	[51]
4				77	92 (+)	[49]
5				57	71 (+)	[49]

Table 5 (cont.)

Entry	Reactants		Product	Yield (%)	ee (%)	Ref
	Ketone	Alkyne				
6				90	88	[51]
7				93	5	[51]
8				89	35	[51]
9				81	60	[51]
10				76	54	[51]

Tertiary Propargylic Alcohols 26; General Procedure for Catalytic Asymmetric Addition of Terminal Alkynes to Ketones:^[51]

A soln of sulfonamide ligand **24** (0.04 mmol, 0.1 equiv) and $\text{Cu}(\text{OTf})_2$ (0.04 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was stirred at rt for 30 min. In a separate flask, phenylacetylene (1.0 mmol, 2.5 equiv) and 2.0 M Me_2Zn in toluene (1.2 mmol, 3 equiv) were stirred at 0°C under an atmosphere of N_2 for 15 min. The Cu complex was then added to the flask containing the Me_2Zn /phenylacetylene soln via syringe. The resulting homogeneous soln was stirred at 0°C for 30 min before the ketone (0.4 mmol, 1.0 equiv) was added. The reaction was allowed to proceed at 0°C for 48 h. The reaction was quenched with 5% aq HCl (2.0 mL) and the product was extracted into EtOAc (3×2 mL). The resulting organic layer was dried (Na_2SO_4) and then concentrated to provide the crude product. The propargylic alcohol was purified by flash chromatography (silica gel, EtOAc/hexanes 1:9). The enantiomeric excess was determined by chiral HPLC analysis using either a Chiralcel OD or OD-H column.

for references see p 514

References

- [1] Trost, B. M.; Weiss, A. H., *Adv. Synth. Catal.*, (2009) **351**, 963.
- [2] Tyrrell, E., *Curr. Org. Chem.*, (2009) **13**, 1540.
- [3] Mao, J.; Xie, G., *Curr. Org. Chem.*, (2009) **13**, 1553.
- [4] Lin, L.; Wang, R., *Curr. Org. Chem.*, (2009) **13**, 1565.
- [5] Aschwanden, P.; Carreira, E. M., In *Acetylene Chemistry: Chemistry, Biology and Material Science*, Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, (2005); p 101.
- [6] Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C., *Coord. Chem. Rev.*, (2005) **249**, 1736.
- [7] Pu, L., *Tetrahedron*, (2003), **59**, 9873.
- [8] Chinchilla, R.; Nájera, C., *Chem. Rev.*, (2007) **107**, 874.
- [9] Wei, C.; Li, C.-J., *Synlett*, (2004), 1472.
- [10] Yamaguchi, M.; Hayashi, A.; Minami, T., *J. Org. Chem.*, (1991) **56**, 4091.
- [11] Frantz, D. E.; Fässler, R.; Carreira, E. M., *J. Am. Chem. Soc.*, (1999) **121**, 11245.
- [12] Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M., *Proc. Natl. Acad. Sci. U. S. A.*, (2004) **101**, 5843.
- [13] Frantz, D. E.; Fässler, R.; Carreira, E. M., *J. Am. Chem. Soc.*, (2000) **122**, 1806.
- [14] Boyall, D.; López, F.; Sasaki, H.; Frantz, D. E.; Carreira, E. M., *Org. Lett.*, (2000) **2**, 4233.
- [15] Boyall, D.; Frantz, D. E.; Carreira, E. M., *Org. Lett.*, (2002) **4**, 2605.
- [16] Diez, R. S.; Adger, B.; Carreira, E. M., *Tetrahedron*, (2002) **58**, 8341.
- [17] Bode, J. W.; Carreira, E. M., *J. Am. Chem. Soc.*, (2001) **123**, 3611.
- [18] Fettes, A.; Carreira, E. M., *Angew. Chem.*, (2002) **114**, 4272; *Angew. Chem. Int. Ed.*, (2002) **41**, 4098.
- [19] Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D., *J. Am. Chem. Soc.*, (2010) **132**, 275.
- [20] Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E., *Tetrahedron*, (2005) **61**, 7219.
- [21] Marshall, J. A.; Bourbeau, M. P., *Org. Lett.*, (2003) **5**, 3197.
- [22] López, F.; Castedo, L.; Mascareñas, J. L., *Org. Lett.*, (2005) **7**, 287.
- [23] Dieter, R. K.; Yu, H., *Org. Lett.*, (2001) **3**, 3855.
- [24] Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T., *Org. Lett.*, (2002) **4**, 2977.
- [25] Maezaki, N.; Hirose, Y.; Tanaka, T., *Org. Lett.*, (2004) **6**, 2177.
- [26] Molander, G. A.; Dehmel, F., *J. Am. Chem. Soc.*, (2004) **126**, 10313.
- [27] Davidson, M. H.; McDonald, F. E., *Org. Lett.*, (2004) **6**, 1601.
- [28] Trost, B. M.; Ameriks, M. K., *Org. Lett.*, (2004) **6**, 1745.
- [29] Crimmins, M. T.; She, J., *J. Am. Chem. Soc.*, (2004) **126**, 12790.
- [30] Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J., *J. Am. Chem. Soc.*, (2004) **126**, 15348.
- [31] Anand, N. K.; Carreira, E. M., *J. Am. Chem. Soc.*, (2001) **123**, 9687.
- [32] Trost, B. M.; Ball, Z. T.; Jöge, T., *Angew. Chem.*, (2003) **115**, 3537; *Angew. Chem. Int. Ed.*, (2003) **42**, 3415.
- [33] Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A., *J. Am. Chem. Soc.*, (2006) **128**, 8.
- [34] Wolf, C.; Liu, S., *J. Am. Chem. Soc.*, (2006) **128**, 10996.
- [35] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M., *J. Am. Chem. Soc.*, (2005) **127**, 13760.
- [36] Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M., *Org. Lett.*, (2005) **7**, 1363.
- [37] Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M., *Chem. Commun. (Cambridge)*, (2007), 948.
- [38] Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J., *Tetrahedron Lett.*, (1995) **36**, 8937.
- [39] Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B., *J. Am. Chem. Soc.*, (1998) **120**, 2028.
- [40] Tan, L.; Chen, C.-y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J., *Angew. Chem.*, (1999) **111**, 724; *Angew. Chem. Int. Ed.*, (1999) **38**, 711.
- [41] Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C., *J. Am. Chem. Soc.*, (2000) **122**, 11212.
- [42] Garcia, C.; LaRochelle, L. K.; Walsh, P. J., *J. Am. Chem. Soc.*, (2002) **124**, 10970.
- [43] Waltz, K. M.; Gavenonis, J.; Walsh, P. J., *Angew. Chem.*, (2002) **114**, 3849; *Angew. Chem. Int. Ed.*, (2002) **41**, 3697.
- [44] Jiang, B.; Chen, Z.; Tang, X., *Org. Lett.*, (2002) **4**, 3451.
- [45] Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z., *Org. Lett.*, (2004) **6**, 4147.
- [46] Chen, C.; Hong, L.; Xu, Z.-Q.; Liu, L.; Wang, R., *Org. Lett.*, (2006) **8**, 2277.
- [47] Motoki, R.; Kanai, M.; Shibasaki, M., *Org. Lett.*, (2007) **9**, 2997.

- ^[48] Cozzi, P. G.; Alesi, S., *Chem. Commun. (Cambridge)*, (2004), 2448.
- ^[49] Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C., *Angew. Chem.*, (2003) **115**, 5211; *Angew. Chem. Int. Ed.*, (2003) **42**, 5057.
- ^[50] Cozzi, P. G., *Angew. Chem.*, (2003) **115**, 3001; *Angew. Chem. Int. Ed.*, (2003) **42**, 2895.
- ^[51] Lu, G.; Li, X.; Li, Y.-M.; Kwong, F. Y.; Chan, A. S. C., *Adv. Synth. Catal.*, (2006) **348**, 1926.

