CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc Europe

DOI: 10.1002/chem.201202085

Development of Zn–ProPhenol-Catalyzed Asymmetric Alkyne Addition: Synthesis of Chiral Propargylic Alcohols

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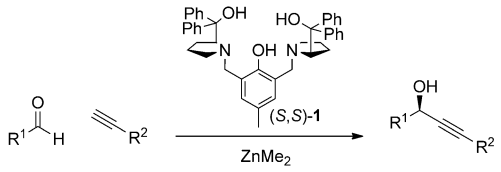
Abstract: The development of a general and practical zinc-catalyzed enantioselective alkyne addition methodology is reported. The commercially available ProPhenol ligand (**1**) has facilitated the addition of a wide range of zinc alkynylides to aryl, aliphatic, and α,β-unsaturated aldehydes in high yield and enantioselectivity. New insights into the mechanism of this reaction have resulted in a significant reduction in reagent stoichiometry, enabling the use of precious alkynes and avoiding the use of excess dimethylzinc. The enantioenriched propargylic alcohols from this reaction serve as versatile synthetic intermediates and have enabled efficient syntheses of several complex natural products.

Keywords: alkynes · alkynylide · asymmetric catalysis · nucleophilic addition · total synthesis

Introduction

The design and development of the ProPhenol ligand, **1**,[1] as an enantioselective catalyst for base-mediated nucleophilic addition reactions has led to the discovery of a number of highly efficient transformations.[2] The combination of the ProPhenol ligand and a dialkylzinc reagent has been shown to catalyze asymmetric Mannich and Henry reactions,[3,4] the desymmetrization of *meso*-1,3-diols,[5] and the direct aldol reaction.[6] The success of this catalyst system with stabilized nucleophiles, such as enolates and nitronates, prompted us to investigate zinc alkynylides and their addition to aldehydes (Scheme 1). Herein, we provide a full account of the development of a practical and general methodology for zinc-catalyzed enantioselective alkynylation of aldehydes by using the commercially available ProPhenol ligand, **1**.[7]



Scheme 1. ProPhenol-catalyzed alkyne addition.

Propargyl alcohols serve as robust and versatile intermediates in the synthesis of fine chemicals, natural products, and therapeutic agents (Figure 1).[8] The broad synthetic utility of this motif lies in the bifunctional reactivity of alkynes. The terminal alkyne can act as a nucleophile through deprotonation and subsequent alkylation or metal-catalyzed cross-coupling. Conversely, the latent electrophilicity of alkynes can be chemoselectively activated by complexation with a transition metal. Furthermore, the reactivity of propargyl alcohols toward S_N2 displacement extends the activation to the propargylic position as well. This synthetic versatility makes the catalytic enantioselective preparation of propargylic alcohols especially valuable. Three general approaches have been utilized for the synthesis of secondary propargyl alcohols: enantioselective ynone reduction (A),[9] asymmetric alkyne addition to aldehydes (B),[10] and ynal alkylation (C).[11] Although a number of catalysts have been developed to facilitate both ynone reduction and ynal alkylation, the application of these methods is limited by the propensity of these alkynes to decompose, isomerize, and act as Michael acceptors. The addition of a terminal acetylene to an alde-

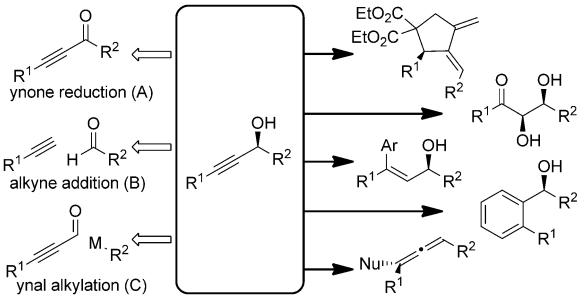


Figure 1. Formation and reactivity of propargylic alcohols.[12]

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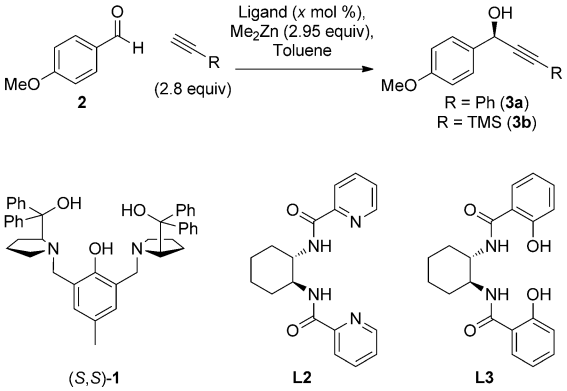
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202085. It contains full experimental details.

hyde avoids these problems and provides a convergent approach to the desired propargyl alcohol.

The mild reactivity of organozinc reagents has enabled the enantioselective addition of alkyl, vinyl, and alkynyl groups to a variety of carbonyl compounds with excellent functional group tolerance.[13] The asymmetric addition of alkynylzinc nucleophiles to aldehydes has recently generated a large amount of interest in the chemical community.[14] Early reports by Carreira et al. demonstrated that stoichiometric (+)-*N*-methyl ephedrine, $Zn(OTf)_2$, and triethylamine could be used to achieve alkyne metalation and addition to aliphatic aldehydes under particularly mild conditions.[15] High enantioselectivity and yield were obtained with a variety of alkynes, although aryl and α,β-unsaturated aldehydes typically gave lower yields. The initial conditions requiring stoichiometric zinc and ephedrine were ultimately rendered catalytic by increasing the reaction temperature to 60 °C.[15f] The groups of Pu and Chan independently reported the use of (*S*)-1,1′-bi-2-naphthol ((*S*)-BINOL), in conjunction with $Ti(OiPr)_4$ and either Et_2Zn or Me_2Zn to facilitate nucleophilic addition of alkynes to aldehydes.[16,17] These conditions require an excess of alkyne and dialkylzinc but ultimately provide good yield and enantioselectivity with a range of substrates. A number of other chiral zinc catalysts have also been reported to enable the enantioselective addition of alkynes to aldehydes.[18] Efficient asymmetric alkyne addition often requires the use of relatively high catalyst loadings and an excess of alkyne and dialkylzinc reagents.[19] Our aim was to develop an efficient chiral catalyst system capable of adding functionalized alkynes to a wide range of aldehydes while minimizing the use of excess reagents and stoichiometric additives, improving the atom economy of this transformation.[20] This would ultimately enable facile access to chiral propargyl alcohols and entry into alkyne-based strategies in the synthesis of natural products.

Table 1. Initial optimization.[a]



	R	Conc. [M][b]	*T* [°C]	*t* [h]	X [mol %]	Yield [%]	*ee* [%][c]
ligand screening							
1	Ph	0.18	RT	22	20 (**1**)	78	80
2	Ph	0.18	0	16	20 (**L2**)	26	35
3	Ph	0.18	0	16	20 (**L3**)	36	−66
time, temperature and catalyst loading, X = (*S*,*S*)-**1**							
4	Ph	0.18	RT	72	20	95	79
5	Ph	0.18	RT	48	10	77	83
6	Ph	0.18	−20	45	10	60	77
7	Ph	0.18	−20	45	5	32	72
reaction concentration, X = (*S*,*S*)-**1**							
8	TMS	0.18	3	21	10	35	85
9	TMS	0.26	3	21	10	50	85
10	TMS	0.38	3	24	10	74	85
11	TMS	0.69	3	21	10	87	75
catalyst loading at higher concentration, X = (*S*,*S*)-**1**							
12	Ph	0.38	3	24	10	86	74
13	Ph	0.38	3	24	5	73	58
14	Ph	0.38	3	21	2.5	68	46

[a] Reactions run on a 0.325 mmol scale with 2.7 or 2.8 equivalents of an alkyne and 2.6 or 2.95 equivalents of dimethylzinc, respectively. Yields of the isolated product are reported. [b] Reaction concentration (in molarity) is reported with respect to the alkyne and includes the toluene added as part of the dimethylzinc solution. [c] Enantiomeric excess determined by chiral HPLC analysis. TMS = trimethylsilyl.

Results and Discussion

Initial optimization: Optimization of the enantioselective addition of phenyl- and TMS-acetylene to *para*-anisaldehyde (**2**) commenced with the screening of several C2-symmetric ligands, (*S*,*S*)-**1**, **L2**, and **L3**, designed in our group (Table 1). Stoichiometric zinc alkynylide was required for adequate enantioselectivity, and all optimization was initially carried out by using nearly three equivalents of the dialkylzinc and alkyne. Further experiments to improve the atom economy of this alkynylation methodology will be discussed below. Ligand screening revealed that the ProPhenol ligand, (*S*,*S*)-**1**, provided the best results in terms of both yield and enantioselectivity, with the desired propargyl alcohol being isolated in 78% yield and 80% *ee* (Table 1, entry 1). Ligands **L2** and **L3**, resembling a Salen ligand and the backbone of our phosphine ligands for Pd-catalyzed asymmetric allylic alkylation, also provided the desired product, albeit with a lower enantioselectivity of 35 and −66% *ee*, respectively (Table 1, entries 2 and 3). These results contrast with Cozzi's asymmetric alkyne addition reaction to ketones, which utilizes a similar Salen ligand to obtain excellent results.[21] Enantiomeric induction from (*S*,*S*)-**1** was found to be a robust process and provided excellent selectivity for the (*R*)-propargylic alcohol **3a**, at a range of temperatures and catalyst loadings (Table 1, entries 4–7).[22] Consequently, the majority of optimization experiments focused primarily on improving reactivity and catalyst turnover. Reducing the catalyst loading to 10 mol% and increasing the reaction time to 48 h produced the desired product in 77% yield and 83% *ee* (Table 1, entry 5). These results are similar to those given in Table 1, entry 1 with 20 mol% of (*S*,*S*)-**1**. In an attempt to obtain even better enantioselectivity, the alkyne addition was performed at −20 °C with both 5 and 10 mol% of (*S*,*S*)-**1** (Table 1, entries 6 and 7). These reactions provided similar levels of enantioselectivity, but resulted in a substantial decrease in reactivity.

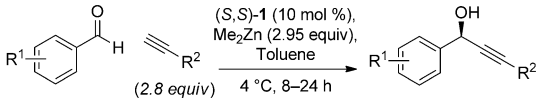
TMS-acetylene was found to be significantly less reactive in ProPhenol-catalyzed alkyne addition reactions than phenylacetylene. However, by increasing the reaction concentration, improved reactivity could be obtained with TMS-acetylene to ultimately provide the desired product in 74% yield and 85% *ee* (Table 1, entry 10). The optimal alkyne concentration was found to be 0.38 M and a further increase in concentration, to 0.69 M, resulted in decreased enantioselectivity (Table 1, entry 11). At higher reaction concentrations (ca. 2 M) the ligand-free background reaction proceeds readily, and is presumably the cause of the slight decrease in enantioselectivity.[23] Unfortunately, decreasing the catalyst loading further (<10 mol%) provided a lower yield and significantly lower *ee* (Table 1, entries 13 and 14).

The optimization of reaction temperature, time, concentration, and catalyst loading has enabled the addition of either TMS-acetylene or phenylacetylene to *para*-anisaldehyde in good yield (>70%) and *ee* (>70%) with just 10 mol% catalyst loading. Interestingly, similar results were generally observed for dimethyl- and diethylzinc; however, others have noted that alkyl transfer from dimethylzinc is significantly slower than from diethylzinc, and therefore, dimethylzinc was chosen to avoid the formation of potential alkyl addition side products.[24] Utilizing the optimized conditions outlined in Table 1, entries 10 and 12, we set out to investigate the scope of this reaction.

Alkynylation of aryl aldehydes: A variety of aryl aldehydes underwent efficient alkyne addition by using the previously optimized conditions (Table 2). High yields and enantioselectivities were obtained in addition reactions to benzaldehydes containing both electron-donating and electron-withdrawing substituents. Substitution on each aromatic carbon atom was tolerated and particularly good results were obtained with *ortho*-substituted benzaldehydes. However, the steric encumbrance of 2,6-dimethylbenzaldehyde resulted in a decreased yield and *ee* (Table 2, entry 20) although 2,6-dimethoxybenzaldehyde performed very well (Table 2, entry 16). Good functional group tolerance was observed, with only *N*-(4-formylphenyl)acetamide providing poor results (Table 2, entry 7). Good results were obtained with a variety of alkynes and only small variations in yield and enantioselectivity were observed.

Alkynylation of α,β-unsaturated aldehydes: Alkyne addition to α,β-unsaturated aldehydes provides a particularly valuable extension of the substrate scope. The resulting alkenyl alkynyl carbinols contain three orthogonal functional groups primed for further synthetic manipulation. ProPhenol-catalyzed addition of TMS-acetylene to a range of α,β-unsaturated aldehydes proceeded in excellent yield and enantioselectivity (Table 3) although the substitution pattern of the α,β-unsaturated aldehyde has a significant effect on the enantioselectivity of alkyne addition. (*E*)-Cinnamaldehyde provides the desired propargyl alcohol in 91% *ee* (Table 3, entry 1). However, replacement of the phenyl substituent with a methyl or hexyl group produces the desired product

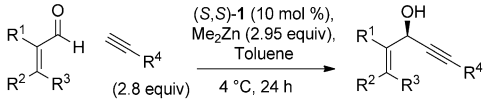
Table 2. Alkynylation of aryl aldehydes.



	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	H	Ph	95	81
2	2-NO_2	Ph	84	92
3	3-NO_2	Ph	91	68
4	4-NO_2	Ph	78	83
5[c,d]	4-F	Ph	77	85
6[c,d]	4-Cl	Ph	98	83
7	4-NHAc	Ph	trace	–
8	2-furyl	TMS	81	84
9[c]	2-furyl	Ph	90	85
10	C_4H_4 (2-naphth)	Ph	89	75
11[c,d]	2-MeO	Ph	100	86
12	2-MeO	CH_2OMe	86	84
13[c,d]	3-MeO	Ph	86	76
14	4-MeO	TMS	74	85
15[c]	4-MeO	Ph	86	74
16	2,6-$(MeO)_2$	Ph	87	99
17	2,6-$(MeO)_2$	TMS	79	97
18	3,5-$(MeO)_2$	$CH_2CH(OEt)_2$	90	82
19	3,5-$(MeO)_2$	CH_2CH_2OTBS	82	87
20[c]	2,6-$(Me)_2$	Ph	27	35
21	2,4-(MeO_2)-3-Me	Ph	87	92

[a] Yield of the isolated product. Reactions performed on a 0.325 mmol scale. [b] Enantiomeric excess determined by chiral HPLC analysis. [c] Reaction performed with 2.5 equivalents of the alkyne and 2.5 equivalents of Me_2Zn. [d] Reaction run at a concentration of 0.2 M with respect to alkyne. Naphth = naphthyl.

Table 3. Alkynylation of α,β-unsaturated aldehydes.



	R^1	R^2	R^3	R^4	Yield [%][a]	*ee* [%][b]
1	H	Ph	H	TMS	89	91
2[c]	H	Me	H	TMS	89	39
3	H	C_6H_{13}	H	TMS	90	36
4	H	*i*Pr	H	TMS	100	94
5	Me	H	H	TMS	74	91
6	Me	Et	H	TMS	67	87
7	$-(CH_2)_4-$		H	TMS	81	90
8	H	H	H	$(CH_2)_2OTBS$	55	90
9	H	Ph	Ph	TMS	80	76
10	Br	C_6H_{13}	H	TMS	66[d]	91
11	Br	Ph	H	TMS	68	95
12	Me	CO_2Et	H	TMS	75	86
13	H	Ph	H	BDMS	100	73
14	H	Ph	H	$CH(OEt)_2$	85	82
15	H	*i*Pr	H	$CH(OEt)_2$	85	87
16	H	Ph	H	C_6H_{13}	100	77

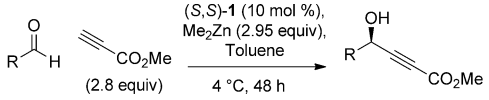
[a] Yield of the isolated product. Reactions performed on a 0.325 mmol scale. [b] Enantiomeric excess determined by chiral HPLC analysis. [c] Reaction performed with 2.7 equivalents of alkyne and 2.6 equivalents of Me_2Zn. [d] A 14% yield of the methyl addition side product was also isolated. TBS = *tert*-butyldimethylsilyl, BDMS = benzyldimethylsilyl.

in less than 40% *ee* (Table 3, entries 2 and 3, but also see Table 6, entry 2 below), which was, however, restored to over 90% by addition of an α-bromo group (see below). The difference in results between these β-substituents seems to result primarily from steric interactions. Following this notion, the incorporation of an isopropyl group at the β-position restored the excellent enantioselectivity (Table 3, entry 4). Interestingly, the absence of substitution at the β-position also led to high enantioselectivity (Table 3, entry 5 and 8). A number of functionalized substrates gave good results, including α-bromoenals (Table 3, entries 10 and 11), β-formyl propionates (Table 3, entry 12), propiolaldehyde diethyl acetals (Table 3, entries 14 and 15), and aliphatic alkynes (Table 3, entry 16).

Methyl propiolate represents a particularly attractive class of nucleophiles for alkyne addition.[25] The resulting γ-hydroxy-α,β-acetylenic esters are extremely versatile synthetic intermediates and have been used in a number of total syntheses.[26] Propiolate donors have traditionally been difficult substrates for asymmetric alkynylation due to their propensity to decompose in the presence of Lewis acids and nucleophiles.[27] Methyl propiolate ultimately proved to be one of the most effective alkynes under Zn–ProPhenol alkynylation conditions (Table 4). Excellent results were obtained with a range of α,β-unsaturated aldehydes, including (*E*)-non-2-enal, which provided a 97% *ee* with methyl propiolate (Table 3, entry 2), a major improvement on the 36% *ee* obtained with TMS-acetylene. The superior results are presumed to be a consequence of the stabilization of the alkynylide of this alkyne along with potential coordination of the propiolate ester with the bimetallic catalyst.

Aliphatic aldehydes: While the initial communication disclosed[7] only the use of unsaturated aldehydes, a variety of aliphatic aldehydes are suitable electrophiles for asymmetric alkynylation with the ProPhenol ligand, (*S*,*S*)-**1** (Table 5). The addition of methyl propiolate to α- and β-substituted aliphatic aldehydes proceeded in good yield and enantioselectivity. The addition of methyl propiolate to cyclopropanecarboxaldehyde gave the desired propargylic alcohol in 88% yield and 94% *ee*. *n*-Aliphatic aldehydes are particularly challenging substrates for alkynylation due to their propensity to enolize and undergo cross-aldol side reactions.[28] Modest yields and excellent enantioselectivities were ultimately achieved when utilizing the more acidic alkyne, methyl propiolate (Table 5). Aliphatic aldehydes with an increased propensity to enolize, such as cyclopentanecarboxaldehyde and 3-methylbut-3-enal, did not produce the desired products. On the other hand, the less easily enolized aldehyde cyclohexanecarboxaldehyde performed exemplarily. The increased steric hindrance of 2,2-dimethyl-substituted aldehydes often results in decreased enantioselectivity although addition of methyl propiolate to pivaldehyde provided the desired product in 88% *ee*. However, the analogous 3-chloro- and 3-oxopropanoate substrates provided significantly lower enantioselectivity. Extension of this methodology to aliphatic aldehydes further demonstrates the generality of the ProPhenol-catalyzed alkynylation with respect to both nucleophile and electrophile.

Table 4. Addition of methyl propiolate to α,β-unsaturated aldehydes.

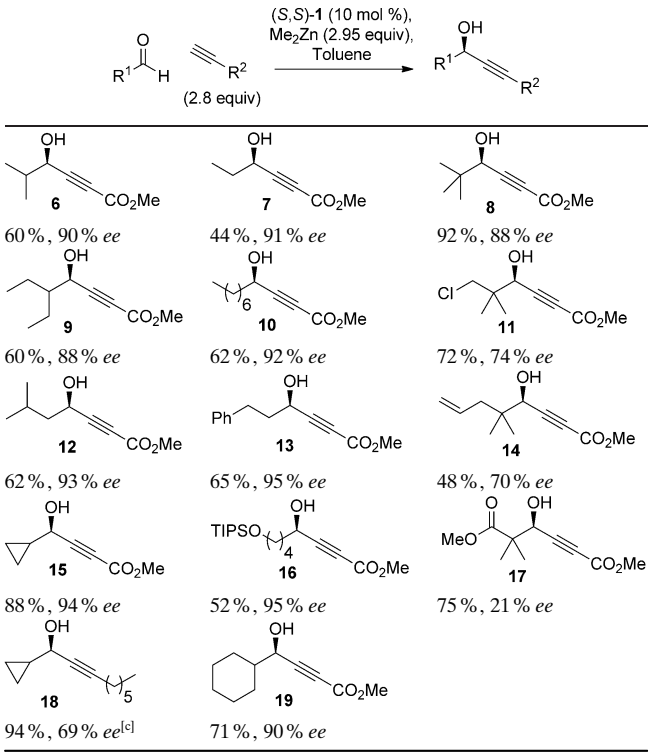


	Aldehyde	Product	Yield [%][a]	*ee* [%][b]
1	**4a**	**5a**	94	90
2	**4b**	**5b**	86	97
3	**4c**	**5c**	97	97
4	**4d**	**5d**	92	95
5[c]	**4e**	**5e**	71	90
6[d]	**4f**	**5f**	86	96
7[e]	**4g**	**5g**	95	82
8	**4h**	**5h**	97	72

[a] Yield of the isolated product. [b] Enantiomeric excess determined by chiral HPLC. [c] Reaction performed by using 3 equivalents of alkyne and 3 equivalents of Me_2Zn. [d] Reaction performed by using (*R*,*R*)-**1**. [e] Reaction performed by using ethyl propiolate.

Proposed mechanism: The proposed mechanism for ProPhenol-catalyzed alkyne addition involves the formation of the dinuclear zinc species **A** (Scheme 2). This complex contains both Brønsted basic and Lewis acidic sites, and can therefore act as a bifunctional catalyst, activating two reagents simultaneously. The relative acidity of a terminal alkyne (pK_a (DMSO) PhC≡CH = 28.7)[29] enables the formation of an alkynylzinc nucleophile, which undergoes nucleophilic addition to the *Si* face of an aldehyde. Product dissociation through metal exchange liberates a propargylic zinc alkoxide and regenerates the active catalyst. Turnover of the catalyst in this way necessitates the use of a stoichiometric amount of the organozinc reagent. In contrast, the ProPhenol-catalyzed direct aldol reaction requires only a catalytic amount of the dialkylzinc reagent and dissociation of the product alkoxide is postulated to occur through proton exchange.[6]

Table 5. Enantioselective alkynylation of aliphatic aldehydes.[a,b]



[a] Yield of the isolated product. [b] Enantiomeric excess determined by chiral HPLC analysis. [c] Enantiomeric excess determined by chiral HPLC analysis of the corresponding benzoate.

Additive effects and triphenylphosphine oxide (TPPO): During research into the ProPhenol-catalyzed addition of diynes, it was discovered that the presence of acetate groups in the substrate, far from the reacting alkyne terminus, resulted in significantly higher enantioselectivity.[30] It was hypothesized that this Lewis basic group interacts with the dinuclear zinc catalyst and reinforces the chiral pocket created by the ProPhenol ligand. The proposed coordination is supported by the X-ray crystal structure of the ProPhenol dinuclear zinc complex reported by Ding and co-workers (Figure 2).[31] The crystal structure contains a molecule of

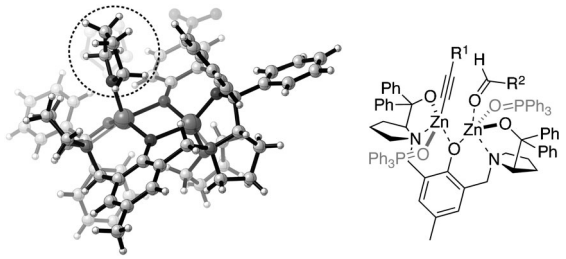
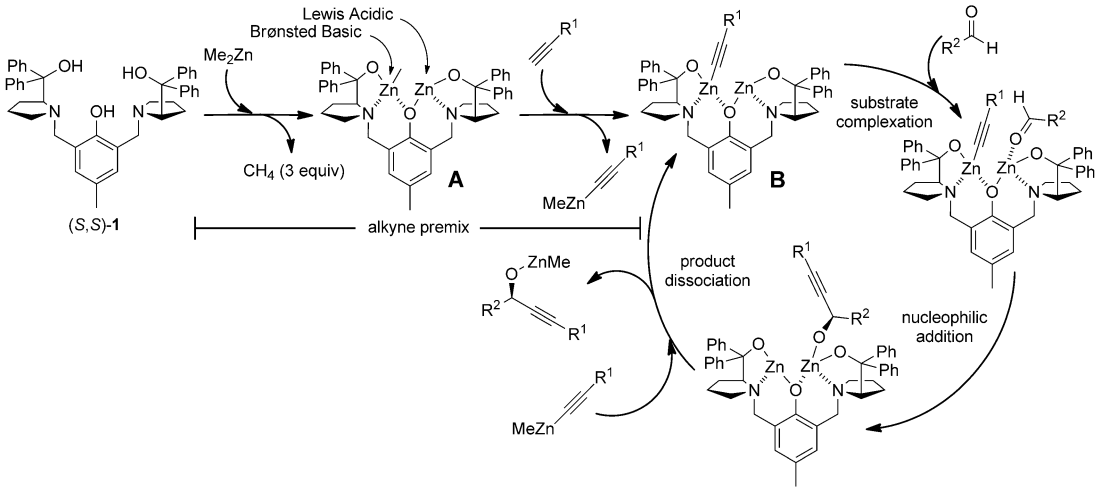


Figure 2. Zn-ProPhenol crystal structure and proposed interaction with Lewis basic additives.

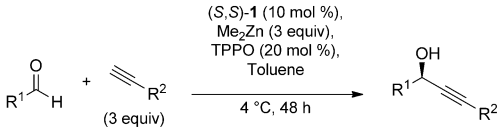
THF (dashed circle) coordinated to each of the zinc atoms, analogous to the postulated interaction with a Lewis base. Screening a variety of substoichiometric Lewis basic additives revealed that the addition of TPPO (20 mol %) provided optimal results. The largest improvements were observed in cases for which the substrates lacked potential Lewis basic sites (Table 6). A large improvement in enantioselectivity was observed for the addition of TMS-acetylene to (*E*)-nonenal (Table 6, entry 2). Methyl propiolate, an alkyne containing a Lewis basic ester, often shows little or no improvement with the addition of TPPO (Table 6, entry 4). The addition of TPPO to the reaction has enabled the successful addition of a silylated enyne to both unsaturated (Table 6, entry 5) and saturated aldehydes (Table 6, entries 6 and 7).

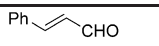
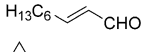
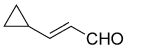
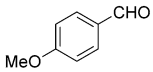
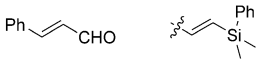
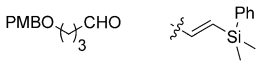
Reagent stoichiometry: To maximize the practicality and synthetic efficiency of this methodology, we sought to reduce reagent stoichiometry to a minimum. Ideally, the alkyne addition could be catalytic in metal with the resultant zinc alkoxide serving as a base for subsequent alkyne depro-



Scheme 2. Proposed mechanism for ProPhenol-catalyzed alkynylation of aldehydes.

Table 6. Alkynylation with TPPO.[a,b]

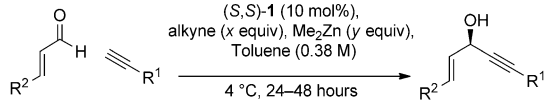


	Aldehyde	R^2	No TPPO Yield [%] (*ee* [%])	With TPPO Yield [%] (*ee* [%])
1		C_6H_{13}	100 (77)	79 (93)
2		TMS	90 (36)	79 (94)
3		CO_2Me	71 (90)	85 (95)
4		TMS	74 (85)	83 (81)
5			–	85 (91)
6			–	56 (66)
7			–	58 (74)

[a] Yield of the isolated product. [b] Enantiomeric excess determined by chiral HPLC analysis. PMB = *para*-methoxybenzyl.

tonation reactions. Carreira and co-workers were able to achieve alkynylation that was catalytic in zinc triflate in some cases by increasing the reaction temperature to 60 °C.[15f] Attempts to use a catalytic amount of dimethylzinc and elevated reaction temperatures in the ProPhenol-catalyzed alkynylation resulted only in recovered starting material (Table 7, entry 4). Previous attempts to use just a slight excess of the alkyne and dimethylzinc have resulted in a significant drop in enantioselectivity.

Table 7. Alkynylation with reduced stoichiometry.



	R^1	R^2	X/Y	Comments[a]	Yield [%][b]	*ee* [%][c]
1	CO_2Me	*i*Pr	3.0:3.0	–	97	97
2	CO_2Me	*i*Pr	1.5:1.5	–	79	97
3	CO_2Me	Ph	1.2:1.5	0.48 M	81[d]	94
4	CO_2Me	Ph	1.2:0.2	60 °C, 24 h	–	–
5	$(CH_2)_5CH_3$	Ph	3.0:3.0	–	83	81
6	$(CH_2)_5CH_3$	Ph	1.5.1.5	–	60	75
7	$(CH_2)_5CH_3$	Ph	1.2:1.5	TPPO (20 mol %), 0.48 M	80	93
8	TMS	*i*Pr	3.0:3.0	–	100	94
9	TMS	*i*Pr	1.2:1.2	–	71	50
10	TMS	Ph	3.0:3.0	–	75	90
11	TMS	Ph	1.2:1.2	–	52[e]	50
12	TMS	Ph	1.2:1.5	TPPO (20 mol %), 0.48 M	83	88

[a] Reaction concentration is reported with respect to the alkyne. [b] Yield of the isolated product. [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Isolated along with a 16% yield of the methyl addition side product. [e] 17% of the starting material was recovered.

Zinc alkoxides are known to form aggregates,[32] and it was hypothesized that the aggregation state of the reactive zinc species plays an important role in enantioselectivity. Since the aggregation state is likely to be concentration dependent, a number of experiments were performed with the concentration of the alkyne and dimethylzinc held constant, while reducing the stoichiometry of each. Consequently, the ProPhenol-catalyzed addition of methyl propiolate was found to give the same high enantioselectivity with less than half the amount of alkyne (Table 7, entry 3). 1-Octyne addition by using 1.5 equivalents of the alkyne also provided good enantioselectivity, although a drop in yield was observed. The lower yield is presumably a consequence of decreased reactivity and to counter this, the reaction concentration was increased to 0.5 M (Table 7, entry 6). When this adjustment was used in conjunction with TPPO (20 mol %), the desired product was obtained in 80% yield and 93% *ee* by using just 1.2 equivalents of alkyne. TMS-acetylene also required a higher reaction concentration and TPPO (20 mol %) to provide a high yield and enantioselectivity.

The concentration dependence of this reaction led us to investigate the possibility of a dimeric active catalyst.[33] A number of dimeric zinc amino alcohol catalysts have been reported previously and display characteristic nonlinear asymmetric induction in alkyl addition to aldehydes.[34] To evaluate potential nonlinear effects in ProPhenol-catalyzed alkyne addition reactions, the addition of methyl propiolate to (*E*)-nonenal was performed under the original superstoichiometric conditions with (*S*,*S*)-**1** of varying optical purity (Figure 3, see the Supporting Information for full experimental details). The enantiomeric excess of the product displayed a linear correlation ($R^2 = 0.99$) with the enantiopurity of the ProPhenol ligand used to catalyze the reaction. When the ligand is not enantiomerically pure a dimeric active catalyst could potentially form three different association complexes: Zn–[(*S*,*S*)-**1**+(*S*,*S*)-**1**], Zn–[(*S*,*S*)-**1**+(*R*,*R*)-**1**], and Zn-[(*R*,*R*)-**1**+(*R*,*R*)-**1**]. It is likely that the homo- and heterochiral complexes would display significantly different catalytic activities and, therefore, display nonlinear asymmetric induction. The results shown in Figure 3 suggest that a

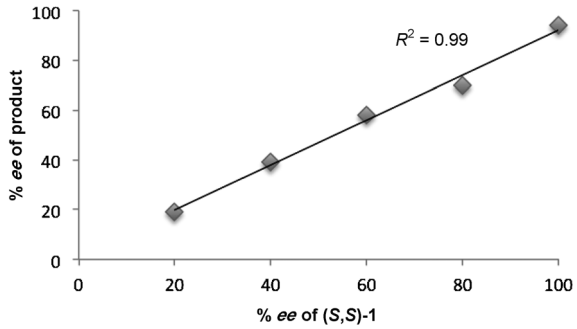


Figure 3. The absence of nonlinear effects in the addition of methyl propiolate to (*E*)-nonenal with (*S*,*S*)-**1**.

single ProPhenol ligand is present in the enantiodetermining step.

Alkynylzinc formation and analysis of the alkyne premix: Reducing the number of equivalents of alkyne used in addition reactions to enolizable aldehydes represents a much more challenging prospect. These reactions produce undesired cross-aldol side products and reducing the number of equivalents of alkyne exacerbates the problem (Table 8, entries 1–3). We hypothesized that this side reaction occurs as a result of incomplete alkynylzinc formation and the presence of unreacted dimethylzinc in the reaction mixture. Formation of the alkynylzinc species is driven, in part, by the entropically favored release of methane gas. However, a number of additional factors also contribute to the overall composition of the alkyne premix. Nonpolar solvents have been shown to disfavor formation of the alkynylzinc species. In the case of phenylacetylene in heptane, no formation of the methylalkynylzinc species is observed.[35] A number of other Zn–alkyne addition methodologies rely on the use of additives to aid in the formation of the alkynylzinc nucleophile.[36]

A stepwise ^{1}H NMR analysis of the methyl propiolate/Me_2Zn/(*S*,*S*)-**1** premix in [D_8]toluene was used to evaluate alkyne deprotonation. By using a 1.2:1.5:0.1 ratio of methyl propiolate/Me_2Zn/(*S*,*S*)-**1**, integration of the peaks at $\delta =$ 0.17 (s, 3H; $CH_3ZnC{\equiv}C$) and −0.69 ppm (s, 6H; $(CH_3)_2Zn$) revealed that approximately 30% of the desired alkynylzinc species was being formed during the standard 1 hour premixing reaction at room temperature (Figure 4, see the Supporting Information for full experimental details).[37] Deprotonation of the terminal alkyne was not observed in the absence of the ProPhenol ligand. Analysis of the alkyne premix by volumetric gas titration of methane revealed that the initial rate of deprotonation is rapid but tapers off after about 15 min. The volume of methane obtained over the standard premixing time was in good agreement with the results of the ^{1}H NMR spectroscopy.

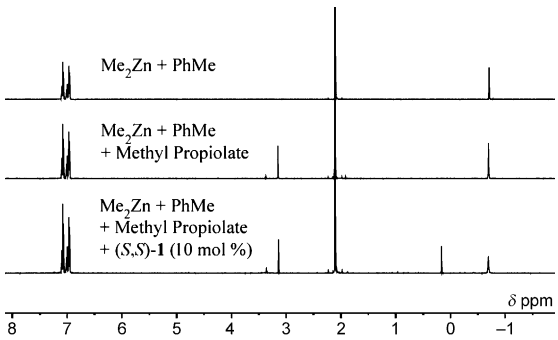
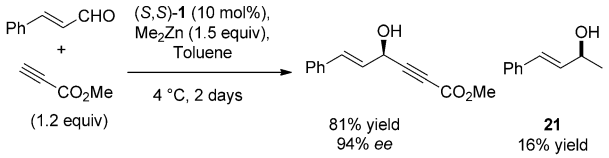
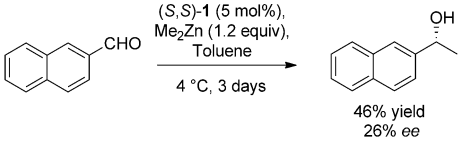


Figure 4. ^{1}H NMR analysis of the alkyne premix.

In contrast to enolizable aldehydes, the presence of significant amounts of dimethylzinc has little effect on the outcome of the alkyne addition reactions to aryl and α,β-unsaturated aldehydes.[38] Minor quantities of methyl addition side products, such as compound **21**, have been isolated in only a small number of cases (Scheme 3). ProPhenol-catalyzed methyl addition is a relatively slow process and required 3 days to react with approximately half of the starting aryl aldehyde (Scheme 4).

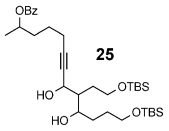


Scheme 3. ProPhenol-catalyzed methyl addition.



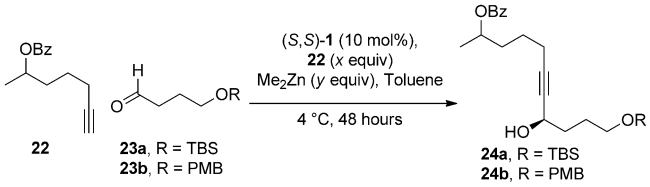
Scheme 4. Competing methyl addition.

These observations prompted the investigation of methods to facilitate the formation of the alkynylzinc nucleophile and, therefore, reduce the amount of dimethylzinc present (Table 8). The addition of aliphatic alkyne **22** to the enolizable aldehyde **23a** provided the desired propargylic alcohol **24a** in low yield under the original superstoichiometric conditions (Table 8, entry 1). The low yield is a consequence of competing aldol side reactions, which provide a complex mixture of oligomers including compound **25**, which was isolated in 19% yield as a mixture of diastereomers from the reaction in Table 8, entry 1. The use of Lewis basic additives, such as *N*-methyl imidazole (NMI), DMSO, and DMF, to aid the formation of the desired alkynylzinc nucleophile provided a low yield of the desired product **24a** (Table 8, entries 4–6).[37] However, extending the alkyne premixing time from 1 hour to 24 h provided a 19% increase in the yield (Table 8, entry 7). Combining this discovery with a higher catalyst loading (20 mol%) led to an optimized result of 69% yield and 67% *ee* for this challenging alkyne–aldehyde pairing (Table 8, entry 8). Thus, applying our mechanistic understanding of the reaction led to a modest improvement in the addition of a nonstabilized alkyne nucleophile (**22**) to an enolizable aliphatic aldehyde (**23**), the most challenging combination for this methodology.



In contrast to the previous example, enolizable aliphatic aldehydes were shown to be excellent electrophiles in the ProPhenol-catalyzed alkynylation when more stabilized nucleophilic alkynes were employed. For example, the higher

Table 8. Optimization of alkyne addition with an enolizable substrate.



22

23a, R = TBS
23b, R = PMB

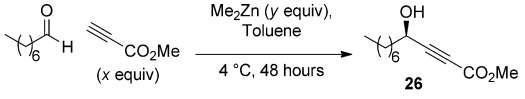
24a, R = TBS
24b, R = PMB

	CHO	X/Y	Conditions	Yield [%][a]	*ee* [%][b]
1	**23a**	2.8:2.95	–	35[c]	45
2	**23a**	2.8:2.95	TPPO (20 mol%)	39	62
3	**23a**	1.2:1.5	TPPO (20 mol%)	22	54
4	**23a**	1.2:1.3	NMI (30 mol%)	11	72
5	**23a**	1.2:1.4	DMSO (4 equiv)	4	14
6	**23a**	1.2:1.4	DMF (4 equiv)	10	17
7	**23b**	2.8:2.95	TPPO (20 mol%), 24 h alkyne premix	58	50[d]
8	**23b**	2.8:2.95	(*S*,*S*)-**1** (20 mol%), TPPO (40 mol%), 24 h alkyne premix	69	67[d]

[a] Yield of the isolated product. All reactions were run on a 0.1625 mmol scale. [b] Enantiomeric excess determined by chiral HPLC analysis. [c] Isolated along with a 19% yield of the cross-aldol side product **25**. [d] Enantiomeric excess determined by ^{1}H NMR analysis of the corresponding (*S*)-methyl mandelate. Bz = benzoyl.

acidity of methyl propiolate provides improved results with enolizable aldehydes relative to other alkynes (Table 9). Addition of methyl propiolate to octanal under the initial conditions provides propargylic alcohol **26** in 62% yield. Lowering the reaction stoichiometry from 2.8 to 1.2 equivalents of alkyne results in a significantly decreased yield (Table 9, entry 4). Longer alkyne premixing times result in visible decomposition of methyl propiolate (Table 9, entry 5). Therefore, a higher catalyst loading was used to aid the consumption of dimethylzinc through alkynylzinc formation (Table 9, entries 6 and 7). Ultimately, a 57% yield and 90% *ee* of the desired propargyl alcohol were obtained by using 1.2 equivalents of the alkyne.

Table 9. Optimization of methyl propiolate addition to octanal.



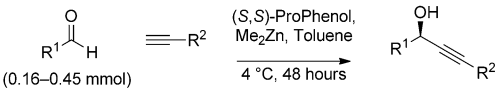
26

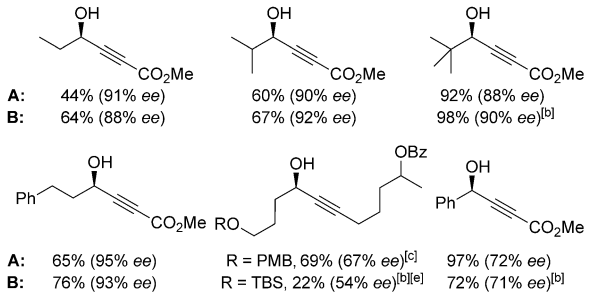
	X/Y	Conditions	Yield [%][a]	*ee* [%][b]
1	2.8:2.95	–	62	92
2	1.5:1.5	–	37	86
3	1.5:1.5	TPPO (20 mol%)	35	90
4	1.2:1.5	–	42	91
5	2.8:2.95 (Et_2Zn)	4 h alkyne premix	60	70
6	1.2:1.5	(*S*,*S*)-**1** (20 mol%)	57	90
7	2.8:2.95	(*S*,*S*)-**1** (20 mol%)	72	87

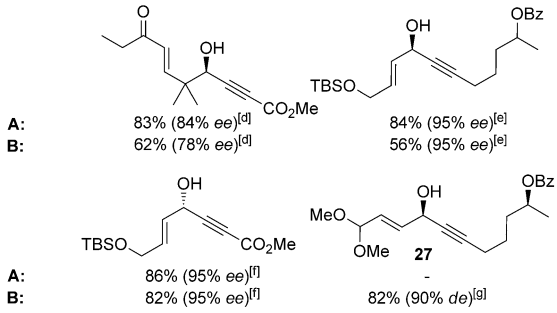
[a] Yield of the isolated product. All reactions were run on a 0.325 mmol scale. [b] Enantiomeric excess determined by chiral HPLC analysis.

Alkynylation scope with reduced alkynylide stoichiometry: The use of a stoichiometric amount of the alkyne would enable the use of precious alkynes to access complex synthetic targets in a highly efficient manner. Thus, we were pleased to observe that the newly developed reaction conditions allowed for the use of only 1.2 equivalents of the alkyne (Table 10). In line with our previous results, the nature of the alkyne affected the results of the alkynylation. When methyl propiolate was used, good enantioselectivity and yield were observed with each class of aldehydes: aliphatic, α,β-unsaturated and aryl. However, when only 1.2 equivalents of a nonstabilized aliphatic alkyne, such as **22**, is added to an α,β-unsaturated aldehyde, TPPO is required as an additive to provide a high yield and *ee*. The addition of **22** to enolizable aldehydes is particularly challenging and gives only a moderate yield and enantioselectivity when an excess of the alkyne is used in conjunction with TPPO, increased catalyst loading, and a 24 hours of alkyne premixing. The synthesis of propargyl alcohol **27** in 88% yield and 90% *ee* was achieved by using a single equivalent of both the alkyne and aldehyde.

Table 10. Scope and evaluation of the alkynylation with reduced stoichiometry.[a]

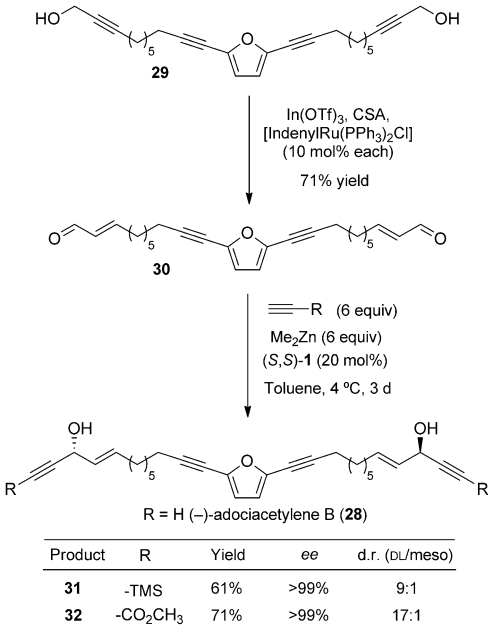






[a] Conditions A: alkyne (2.8 equiv), Me_2Zn (2.95 equiv), ProPhenol (10 mol%), 0.34 M in toluene. Conditions B: alkyne (1.2 equiv), Me_2Zn (1.5 equiv), ProPhenol (20 mol%), 0.48 M in toluene. [b] (*S*,*S*)-**1** (10 mol%) was used in the reaction. [c] (*S*,*S*)-**1** (20 mol%) and TPPO (40 mol%) were used in conjunction with a 24 h premixing time. [d] (*S*,*S*)-**1** (20 mol%) was used in the reaction. [e] TPPO (20 mol%) was used in this reaction. [f] 3.0 equivalents of Me_2Zn were used in the reaction. [g] Reaction performed with (*R*,*R*)-**1**.

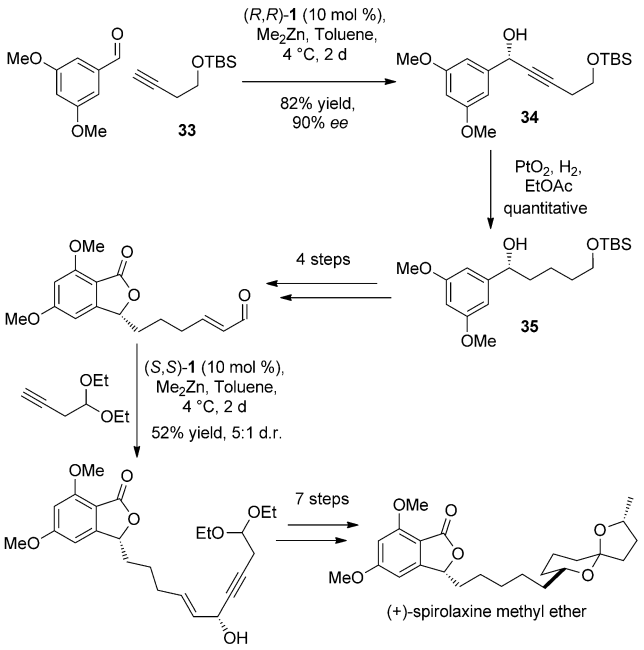
Synthetic Applications: The Zn–ProPhenol-catalyzed alkyne addition methodology has enabled the total synthesis of a wide range of complex natural products.[39] The synthetic utility of this transformation is a direct consequence of the mild reaction conditions and broad substrate scope that has become a focal point of this methodology. The propargylic alcohol moiety is present in a number of biologically and structurally interesting polyacetylenic natural products. The ProPhenol ligand enables the direct and convergent installation of this functionality, as shown in the total synthesis of adociacetylene B, **28** (Scheme 5).[40] The key intermediate,



Product	R	Yield	*ee*	d.r. (DL/meso)
31	-TMS	61%	>99%	9:1
32	$-CO_2CH_3$	71%	>99%	17:1

Scheme 5. Total synthesis of adociacetylene B. Tf = triflyl, CSA = camphorsulfonic acid.

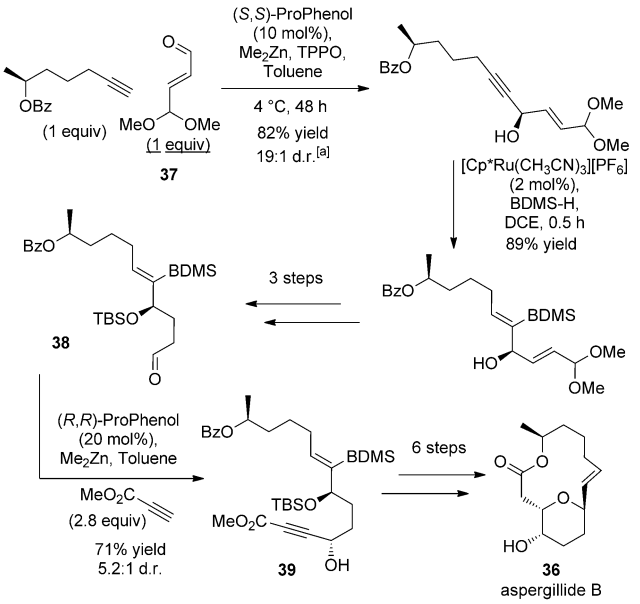
bis(enal) **30**, was prepared from the symmetric propargylic alcohol **29** by using a Ru-catalyzed redox/isomerization.[41] This atom-economic transformation avoids the use of protecting groups and multiple redox operations often used with conventional olefination chemistry. Bis(alkynylation) of **30** with TMS-acetylene provided the desired product **31** in excellent enantioselectivity and a 9:1 mixture of DL- and *meso*-diastereomers. Alkynylation with the conditions from the original optimization [Me_2Zn (3 equiv), alkyne (3 equiv), and (*S*,*S*)-**1** (10 mol%)] resulted in significant amounts of the monoalkynylation product and the starting material, even after an extended reaction time of 3 days. The superior performance of methyl propiolate as an alkynylzinc nucleophile was once again illustrated by the increased yield and d.r. obtained relative to reaction with TMS-acetylene. The resulting γ-hydroxy-α,β-acetylenic ester **32** was saponified and decarboxylated to provide (−)-adociacetylene B (**28**) in a highly efficient manner. Ligand (*R*,*R*)-**1** was also used to facilitate this reaction, providing access to both enantiomers of the natural product.



Scheme 6. Alkyne additions in the total synthesis of spirolaxine methyl ether.

The orthogonal reactivity of alkynes was utilized to great effect in the total synthesis of (+)-spirolaxine methyl ether (Scheme 6).[42] ProPhenol-catalyzed addition of the aliphatic alkyne **33** to 3,5-dimethoxybenzaldehyde provided propargylic alcohol **34** in high *ee* and yield. Mild and selective alkyne reduction was subsequently achieved by using Adam's catalyst, providing access to the chiral benzyl alcohol **35**. An additional asymmetric alkynylation/hydrogenation sequence was used to install a second chiral alcohol in the presence of a relatively sensitive phthalide group. This alkyne strategy ultimately led to the total synthesis of spirolaxine methyl ether in 13 linear steps. This work highlights the utility of asymmetric alkyne addition as a surrogate for a saturated alkyl group addition in the preparation of chiral alcohols.

The formal total synthesis of aspergillide B (**36**) was enabled by an alkyne addition linchpin strategy, whereby (*S*)-hept-6-yn-2-yl benzoate (**22**) and methyl propiolate were added to each end of a butane dialdehyde equivalent **37** (Scheme 7).[43] Substrate and reaction optimization enabled alkynylation by using just 1 equivalent of the precious alkyne **22** (see Table 8). Subsequent Ru-catalyzed hydrosilylation was used to achieve an *E*-selective reduction while also differentiating the two alkenes present in the product and enabling selective hydrogenation.[44] The late-stage addition of methyl propiolate to aliphatic aldehyde **38** proceeded in good yield. Chemoselective reduction of **39** was then achieved by using our hydrosilylation/protodesilylation protocol for the formation of (*E*)-alkenes. The basic reaction conditions used for this transformation triggered spontaneous oxy-Michael addition to produce the desired tetrahydrofuran ring and complete the formal total synthesis of aspergilli-



Scheme 7. Alkyne addition in the synthesis of aspergillide B. [a] The d.r. was determined by chiral HPLC analysis. Cp* = pentamethylcyclopentadienyl, BDMS-H = benzyldimethylsilane, DCE = 1,2-dichloroethene.

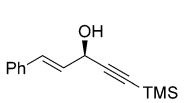
de B. In this case, the asymmetric alkynylation served as a surrogate for a vinylation.

Conclusion

Continued optimization of the Zn–ProPhenol-catalyzed alkyne addition has led to the development of practical and general conditions for the asymmetric alkynylation of aldehydes. This synthetically efficient methodology operates with relatively low catalyst loading and can avoid the use of excess alkyne and dialkylzinc reagents. The chiral propargylic alcohols produced in this reaction are versatile synthetic intermediates and have enabled the synthesis of various natural products. Further research into the asymmetric alkynylation of enolizable aldehydes is currently underway.

Experimental Section

Representative alkynylation procedure with reduced reagent stoichiometry: Preparation of 1-phenyl-5-trimethylsilanylpent-1-en-4-yn-3-ol:



Dimethylzinc (406 μL, 1.2 M solution in toluene, 0.488 mmol, 1.5 equiv) was added to a solution of the (*S*,*S*)-ProPhenol ligand (20.8 mg, 0.0325 mmol, 10 mol%), triphenylphosphine oxide (18 mg, 0.065 mmol, 20 mol%), and TMS-acetylene (56 μL, 0.39 mmol, 1.2 equiv) in anhydrous toluene (0.44 mL) at 0 °C (0.813 mL total toluene, 0.48 M alkyne concentration). The reaction mixture was warmed to room temperature and stirred for 60 min before addition of *trans*-cinammaldehyde (43 mg, 0.325 mmol, 1 equiv) at 0 °C. The reaction was stirred for 48 h at 4 °C before it was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted three times with Et_2O and the combined organic layers were concentrated in vacuo. The crude product was purified by flash column chromatography. 1-Phenyl-5-trimethylsilanylpent-1-en-4-yn-3-ol was isolated as a white solid (67 mg, 83% yield). M.p. 57–58 °C; $[\alpha]_D^{25} = +2.16$ ($c = 1.05$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.43 (m, 2H), 7.32–7.36 (m, 2H), 7.25–7.29 (m, 1H), 6.77 (dd, $J = 16$, 1.2 Hz, 1H), 6.29 (dd, $J = 16$, 6 Hz, 1H), 5.05 (dt, $J = 6$, 1.2 Hz, 1H), 1.96 (t, $J = 6$ Hz, 1H), 0.21 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 136.0$, 132.0, 128.6, 128.1, 127.8, 126.8, 104.1, 91.3, 66.3, −0.2 ppm; IR (film): $\tilde{\nu} = 3300$ (br, OH), 2960, 2172, 1654, 1496, 1449, 1407, 1251 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}OSi$: 230.1127; found: 230.1126, ±0.6 ppm; Chiral HPLC: Chiralcel AD column, heptane/*i*PrOH = 90:10, 1.0 mL min^{-1}, $\lambda = 254$ nm: 6.97/8.79 min (88% *ee*); this characterization data matches the literature data.[45]

Acknowledgements

We thank the National Science Foundation (CHE-0846427) and the National Institutes of Health (GM-33049) for their generous support of our programs. M.J.B. is grateful to Victoria University of Wellington for a Ph.D. scholarship. A.H.W. thanks GlaxoSmithKline (ACS Division of Organic Chemistry Fellowship) and Bristol–Myers Squibb (for a graduate fellowship). A.J.v.W. thanks the DAAD for a postdoctoral fellowship. We also thank Sigma–Aldrich for donating the ProPhenol ligand.

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Received: June 13, 2012
Revised: August 29, 2012
Published online: October 23, 2012

