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Aluminum-Catalyzed Asymmetric Alkylations of Pyridyl-Substituted Alkynyl Ketones with Dialkylzinc Reagents

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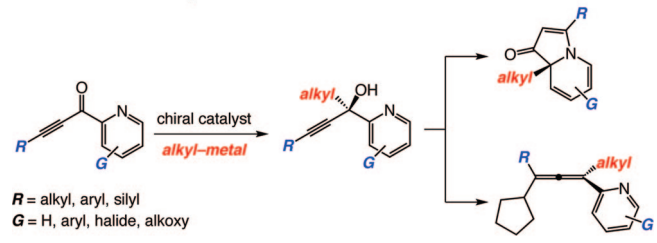
Abstract: Alkylations of pyridyl-substituted ynones with Et_2Zn and Me_2Zn, promoted by amino acid-based chiral ligands in the presence of Al-based alkoxides, afford tertiary propargyl alcohols efficiently in 57% to >98% ee. Two easily accessible chiral ligands are identified as optimal for reactions of the two dialkylzinc reagents. Catalytic alkylations with Et_2Zn require a chiral ligand carrying two amino acid moieties (valine and phenylalanine) along with a *p*-trifluoromethylphenylamide *C*-terminus. In contrast, reactions with Me_2Zn are most effectively promoted in the presence of a chiral ligand containing a single amino acid (benzyl cysteine), capped by an *n*-butylamide. Enantiomerically enriched tertiary alcohols bearing a pyridyl and an alkyne substituent can be functionalized in a variety of manners to furnish a wide range of difficult-to-access acyclic and heterocyclic structures; two noteworthy examples are Cu-catalyzed protocols for conversion of tertiary propargyl alcohols to enantiomerically enriched tetrasubstituted allenes and bicyclic amides that bear an *N*-substituted quaternary carbon stereogenic center. Mechanistic models that account for the trends and enantioselectivity levels are provided.

Introduction

Development of chiral catalysts for enantioselective synthesis of tertiary alcohols is a challenging and important goal of modern chemical synthesis.[1] Nevertheless, in spite of recent advances,[2] catalytic additions of carbon-based nucleophiles to ketones, perhaps the most direct route to synthesis of enantiomerically enriched tertiary alcohols, remain underdeveloped.[3,4] Of particular significance are approaches that furnish modifiable and synthetically versatile allylic, homoallylic, propargylic, or benzylic tertiary carbinols.[3,4] Herein, we report methods for Al-catalyzed asymmetric alkylation (AA) reactions of pyridyl-substituted propargyl ketones with dialkylzinc reagents (Scheme 1). Enantiomerically enriched tertiary alcohols are obtained through reactions promoted by easily accessible amino acid-based catalysts. Enantiomerically enriched products, obtained in up to >98% ee, bear a hydroxyl-substituted quaternary carbon stereogenic center flanked by an alkyne and a pyridyl unit, a combination that is found in biologically active molecules[5] and can be exploited for accessing heterocyclic organic molecules that would otherwise be difficult to prepare (Scheme 1).

Scheme 1. Catalytic Asymmetric Alkylations of Pyridyl Ynones and Applications to Enantioselective Synthesis of Difficult-to-Access Molecules



Our focus on catalytic AA reactions of ynones stemmed from several considerations:

(1) Au-,[6] Cu-,[7] and Pt-catalyzed[8] reactions of pyridyl-substituted propargyl alcohols, furnishing an assortment of useful

(1) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds; Wiley-VCH: Weinheim, 2006.

(2) For examples of catalytic asymmetric protocols that deliver enantiomerically enriched tertiary alcohols (non-propargylic) but are not additions to ketones, see: (a) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (b) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353–3356. (c) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449. (d) Jung, B.; Hong, M. S.; Kang, S. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2616–2618. (e) Zhao, Y.; Mitra, A.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8471–8474.

(3) For a recent review on catalytic enantioslective additions to ketones, see: Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888.

(4) For representative examples of catalytic enantioselective additions of carbon-based nucleophiles to ketones, see: (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894. (b) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446. (c) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196. (d) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235. (e) Celina, G.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971. (f) Yus, M.; Ramon, D.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745–2748. (g) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911. (h) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965. (i) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353–3356. (j) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733. (k) Lou, S.; Moquist, P. N.; Shaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. (l) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441. (m) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449. (n) Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122–7124. (o) Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535–4538.

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heterocyclic compounds, have recently been developed. The utility of such methods would be elevated by the availability of a catalytic asymmetric protocol that allows for synthesis of the requisite substrates in high enantiomeric purity.

(2) The acetylene moiety of the tertiary propargyl alcohols can be used to synthesize useful heterocyclic structures. For example, alkyl and alkenyl (*cis* and *trans*) tertiary allylic alcohols would be accessed through catalytic hydrogenation procedures. Alternatively, deprotonation of a terminal alkyne may be followed by treatment with a range of electrophiles.

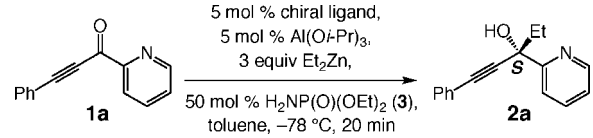
(3) To the best of our knowledge, there are no existing examples of catalytic AA reactions of pyridyl ketones with alkylmetal reagents, and enantioselective additions of C-based nucleophiles to ynones are relatively uncommon.[9,10] It should be noted that the significant majority of catalytic alkylations of acyclic ketones involve methyl-substituted substrates,[4,10,11] presumably to ensure maximum levels of enantioselectivity (due to optimal size difference between carbonyl substituents).

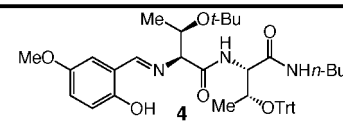
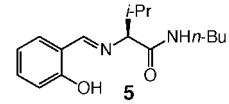
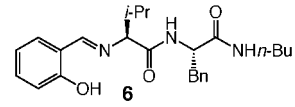
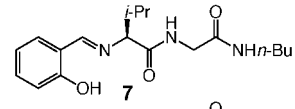
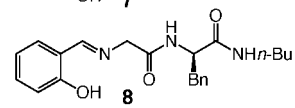
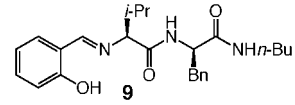
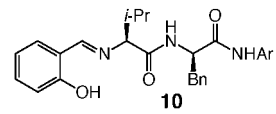
Our goal was to investigate catalytic AA reactions of pyridyl ynones through the use of readily accessible and easily modifiable amino acid-based chiral ligands developed in these laboratories.[12] One class of reactions promoted in the presence of the aforementioned ligands is catalytic enantioselective additions of C-based nucleophiles to ketones,[13] including Al-catalyzed cyanide additions of aryl- and alkyl-substituted unactivated ketones[9a] and Al-catalyzed AA reactions of α-ketoesters with dialkylzinc reagents.[14]

Results and Discussion

1. Catalytic Asymmetric Alkylation Reactions of Ynones with Et_2Zn. a. Identification of an Effective Chiral Ligand. We began by probing the ability of several amino acid-based ligands to catalyze the enantioselective addition of Et_2Zn to ynone **1a** in the presence of $Al(Oi\text{-}Pr)_3$, a combination formerly identified as optimal in catalytic alkylations of α-ketoesters.[14] Key findings from initial studies are summarized in Table 1. All transforma-

Table 1. Screening of Chiral Ligands for Catalytic AA Reactions of Propargyl Ketone **1a** with Et_2Zn[a]



entry	chiral ligand	ee (%);[b] abs. conf.
1	 **4**	75; *R*
2	 **5**	<2; nd
3	 **6**	59; *R*
4	 **7**	15; *R*
5	 **8**	<10; nd
6	 **9**	70; *S*
7	 **10** **10a** Ar = C_6H_5	95; *S*
8	**10b** Ar = *p*-$OMeC_6H_4$	97; *S*
9	**10c** Ar = *p*-$CF_3C_6H_4$	***>98***; ***S***

[a] All reactions were performed under a N_2 atmosphere; see the Supporting Information for experimental details. All catalytic alkylations proceed to >98% conversion. [b] Enantioselectivities were determined by chiral HPLC analysis; see the Supporting Information for details. nd = not determined; abs. conf. = absolute configuration of major product enantiomer.

(5) For pyridyl-substituted tertiary propargyl alcohols that exhibit biological activity, see: Starck, J.-P.; Talaga, P.; Quéré, L.; Collart, P.; Christophe, B.; Lo Brutto, P.; Jadot, S.; Chimmanada, D.; Zanda, M.; Wagner, A.; Mioskowski, C.; Massingham, R.; Guyaux, M. *Bioorg. Med. Chem.* **2006**, *16*, 373–377.

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(7) (a) Jansen, A.; Krause, N. *Synthesis* **2002**, 1987–1992. (b) Jansen, A.; Krause, N. *Inorg. Chim. Acta* **2006**, *359*, 1761–1766. (c) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783–7786.

(8) Smith, C.; Bynnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169–1171.

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(10) For catalytic enantioselective additions of alkynyl metals to ketones, see: (a) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895–2898. (b) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557–1560. (c) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147–4149. (d) Liu, L.; Wang, R.; Kang, Y-F.; Chen, C.; Xu, Z-Q.; Zhou, Y-F.; Ni, M.; Cai, H-Q.; Gong, M-Z. *J. Org. Chem.* **2005**, *70*, 1084–1086.

(11) For additional examples, see: (a) Casolari, S. J.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061–1063. (b) Waltz, K. M.; Gavinonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697–3699. (c) Prieto, O.; Ràmon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957. (d) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539. (e) Cunningham, A.; Mokal-Parekh, V.; Wilson, C.; Woodward, S. *Org. Biomol. Chem.* **2004**, *2*, 741–748. (f) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743–2745. (g) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557. (h) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661.

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(13) For an example, see: Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532–6533.

(14) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456.

tions were performed in the presence of diethylphosphoramidate (**3**), based on the positive effect of this additive on the efficiency and enantioselectivity in the previously reported Al-catalyzed process.[15]

The need for a particularly active chiral catalyst became clear in the course of these initial investigations: in the *absence* of a metal salt and a chiral ligand, even at −78 °C, the reaction of Et_2Zn to **1a** proceeds readily to >98% conversion, affording *rac*-**2a** within only 20 min. Moreover, we discovered that, in addition to overcoming a facile uncatalyzed alkylation, the chiral catalyst would have to compete effectively with a side reaction: when Et_2Zn is used with 50 mol % **3** (in the absence of an Al salt and/or a chiral ligand), a nearly equal amount of the corresponding secondary alcohol is generated, presumably as a result of competitive hydride addition.

Thus, as depicted in entry 1 of Table 1, we established that, when catalytic AA is performed with 5 mol % **4**, a ligand identified as optimal for related reactions of α-ketoesters,[14] tertiary alcohol **2a** is obtained cleanly in 75% ee without *any* detectable amount of the undesired secondry propargyl alcohol (>98% conv, 20 min, −78 °C). Chiral ligands bearing a single amino acid does not give rise to effective catalysts (entry 2). The observation that Schiff base **6** (entry 3), consisting of two readily available and inexpensive amino acids (both antipodes), affords appreciable asymmetric induction (59% ee) was encouraging, leading us to probe the activity of **7**−**9** (entries 4−6, Table 1). The low selectivities obtained with **7** and **8** illustrate that two chiral amino acid residues are required for the Al-based catalyst to be able to compete effectively with uncatalyzed Et_2Zn addition.

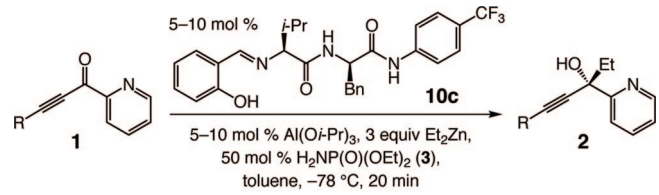
The catalytic AA reaction in the presence of ligand **9** (entry 6) proved critical for several reasons:

(1) The preferential formation of the opposite enantiomer, compared to reactions with ligands that bear two L-amino acids (e.g., **4** in entry 1 and **6** in entry 3), indicates that it is the AA2 unit (the *C*-terminus amino acid) that controls the identity of the major isomer.

(2) Since **9**, a ligand that bears D- and L-antipodes of two inexpensive amino acids, furnishes tertiary propargyl alcohol **2a** in 70% ee (entry 6), we focused our efforts on the ligand's *C*- and *N*-termini to establish whether alteration of the steric and electronic attributes of these segments would result in improvements in enantioselection.[16] Replacement of the *n*-butyl of the *C*-terminus amide with a phenyl group (**10a**, entry 7) leads to a significant change in enantioselectivity (95% vs 70% ee in entry 6). Such a variation offers the opportunity for modification of the *electronic* attributes of this part of the chiral ligand, which resulted in further improvements in enantioselectivity: incorporation of the corresponding *p*-CF_3 (**10c**, entry 9) affords **2a** with exceptional enantioselectivity (>98% ee by chiral HPLC analysis).

(3) Inclusion of a *p*-CF_3-phenyl group at the *C*-terminus of a ligand that bears two L-amino acids does not render it competitive with **10c**; such a ligand affords (*R*)-**2a** in only 65−75% ee (vs (*S*)-**2a** formed in >98% ee with **10c**).

Table 2. Al-Catalyzed AA Reactions with Et_2Zn[a]



				without 50 mol % **3**			with 50 mol % **3**		
entry	R		mol %	conv (%)[b]	yield (%)[c]	ee (%)[d]	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	C_6H_5	**a**	5	>98	61	95	>98	80	>98
2	*o*-MeC_6H_4	**b**	5	>98	64	82	>98	68	89
3	*o*-MeC_6H_4	**b**	10	>98	65	89	>98	65	>98
4	*m*-MeC_6H_4	**c**	10	>98	70	95	>98	62	>98
5	*p*-MeC_6H_4	**d**	10	>98	68	92	>98	74	>98
6	*p*-$OMeC_6H_4$	**e**	10	>98	64	96	>98	67	>98
7	*p*-$CF_3C_6H_4$	**f**	5	>98	80	81	>98	80	>98
8	*p*-$CF_3C_6H_4$	**f**	10	>98	83	93	>98	83	>98
9	*p*-IC_6H_4	**g**	10	>98	58	80	>98	72	>98
10	*p,m*-$Cl_2C_6H_3$	**h**	10	>98	54	81	>98	84	>98
11	*o*-BrC_6H_4	**i**	5	>98	46	77	>98	51	92
12	*o*-BrC_6H_4	**i**	10	>98	46	84	>98	87	>98
13	3-thiophene	**j**	10	>98	56	93	>98	77	>98
14	*n*-hex	**k**	10	79	63	75	>98	73	98
15	Cy	**l**	10	72	67	78	>98	74	>98
16	$(i\text{-}Pr)_3Si$	**m**	10	>98	74	85	>98	84	>98

[a] All reactions were performed under a N_2 atmosphere; see the Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^1H NMR spectra. [c] Yields of products after purification. [d] Enantioselectivities were determined by chiral HPLC analysis; see the Supporting Information for details.

b. Catalytic AA with Et_2Zn. Through the use of chiral ligand **10c** and Al(O*i*-Pr)$_3$, a wide range of pyridyl-substituted ynones can be efficiently alkylated with Et_2Zn (Table 2).[17] The following points regarding the data in Table 2 are noteworthy:

(1) Reactions furnish products with high enantioselectivity in the presence of 5 mol % catalyst (e.g., entries 1, 2, 7, and 11 of Table 2). In many cases, however, asymmetric induction is enhanced when 10 mol % loading is utilized (compare entries 2−3 and 11−12). Lower amounts of catalyst have a detrimental effect on selectivity in transformations that involve alkyl-substituted ynones; Al-catalyzed AA of **1k** (entry 14, Table 2) thus affords **2k** in 61% ee, along with 10−15% of the racemic secondary alcohol, when 5 mol % catalyst is used. Presumably, catalytic alkylations of less reactive substrates do not effectively compete with the aforementioned uncatalyzed and facile addition of Et_2Zn.

(2) Catalytic AA reactions performed in the absence diethylphosphoramidate **3** proceed with lower enantioselectivity (see data in Table 2). In cases where the alkyne is alkyl-substituted, the influence of this additive is especially noticeable. For example, in alkylations of ynones **1k** and **1l** (entries 14 and 15, Table 2), enantioselectivities are improved from 75% and 78% ee to 98% and >98% ee, respectively. In most cases, purified products are isolated in higher yields when **3** is used.

(3) Alkynes bearing electron-deficient (entries 7−12, Table 2), electron-rich (entry 6), and sterically demanding aryl (entries 2 and 3) as well as alkyl (entries 14 and 15), heterocyclic (entry 13), and silyl (entry 16) substituents undergo facile alkylations in good yields and in up to >98% ee.

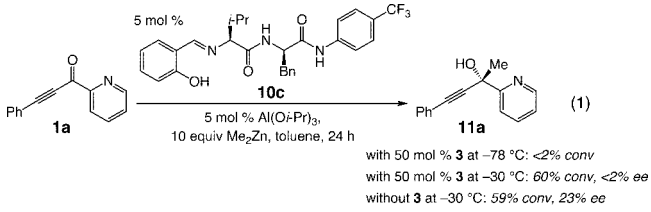
(15) For a review on the effect of additives in asymmetric catalysis, see: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577.

(16) For representative cases, where *C*-terminus modification in this class of chiral ligands has led to substantial improvement in efficiency and/or enantioselectivity, see: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019. (b) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829–2832.

(17) The identity of the major enantiomers in reactions with Et_2Zn is based on an X-ray crystal structure obtained for **2g** (entry 9, Table 2). See the Supporting Information for details.

(4) In certain instances, in the absence of **3**, substantial amounts of the undesired secondary alcohol are obtained (<2% ee). As an example, in reactions shown in entries 10−13, 15−20% of the reduced product is isolated in the absence of the additive.

2. Catalytic Asymmetric Alkylation Reactions with Me_2Zn. a. Identification of an Effective Chiral Ligand. Next, we turned our attention to transformations with Me_2Zn. This change can result in significant variations in the reaction regime; as will be illustrated below, such proved to be the case here. Thus, the chiral ligand identified as optimal for additions with Et_2Zn is not nearly as effective with this less reactive dialkylzinc reagent. As shown in eq 1, there is <2% conversion for alkylation of **1a** in the presence of ligand **10c** (at −78 °C). It is only at −30 °C that appreciable conversion is observed, albeit resulting in the formation of *racemic* **11a** (<2% ee). An unexpected observation in these preliminary investigations is also depicted in eq 1: in contrast to additions involving Et_2Zn, catalytic alkylation of **1a** with Me_2Zn proceeds with higher enantioselectivity in the *absence* of diethylphosphoramidate **3** (23% ee vs <2% ee). These findings suggested that an alternative ligand had to be identified for efficient Al-catalyzed alkylations with Me_2Zn and that the effect of **3** as an additive would have to be re-evaluated.

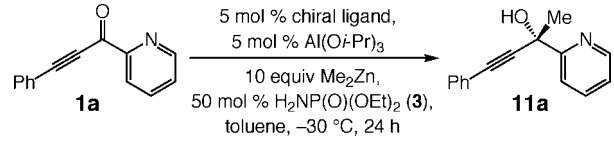


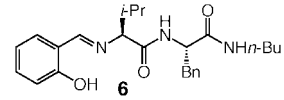
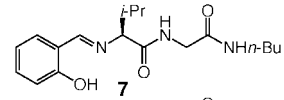
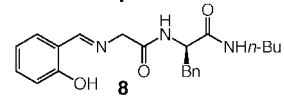
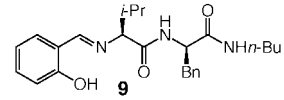
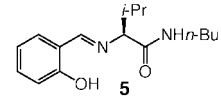
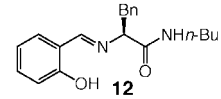
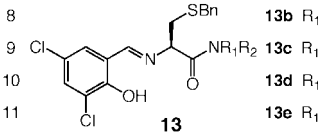
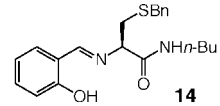
A number of amino acid-based Schiff bases were thus examined. Selected data from these studies are summarized in Table 3. These initial studies were carried out in the presence of additive **3** (see below for additional detail). The findings in entries 1−4 of Table 3 show that, in contrast to catalytic AA reactions involving Et_2Zn, ligands that bear two amino acid moieties deliver appreciable activity (68−73% conv after 24 h at −30 °C), but the desired tertiary alcohol (**11a**) is obtained either in the racemic form or with low selectivity (<10% ee).

Ligands containing a *single* amino acid unit give rise to significantly more discriminating catalysts (entries 5 and 6, Table 3). In the presence of Schiff base **5** (entry 5), bearing a valine unit, reaction proceeds with similar efficiency (67% conv) to furnish **11a** in 14% ee. When the amino acid moiety is changed to phenylalanine (ligand **12**, entry 6), ketone alkylation takes place with similar efficiency (77% conv), but **11a** is isolated with improved enantiopurity (65% ee). Further screening studies[18] led us to establish that the derived benzylcysteine **13a**, which contains a 3,5-dichlorosalicyl Schiff base, is more effective: Al-catalyzed AA proceeds to 91% conversion within 24 h to furnish **11a** in 73% ee. Alteration of the substituents at the *C*-terminus only leads to lowering of catalytic activity and/or asymmetric induction. Noteworthy is the significantly reduced degree of enantioselectivity observed with ligand **13e** (entry 11, Table 3), which bears a *p*-CF_3-phenylamide terminus (64% vs 91% conversion and 42% vs 73% ee compared to **13a**); this observation provides an additional distinction between reactions of the two dialkylzinc reagents (entries 6 and 9 of Table 1).

(18) See the Supporting Information for details of ligand screening studies.

Table 3. Screening of Chiral Ligands for Catalytic AA Reactions of Ketone **1a** with Me_2Zn[a]



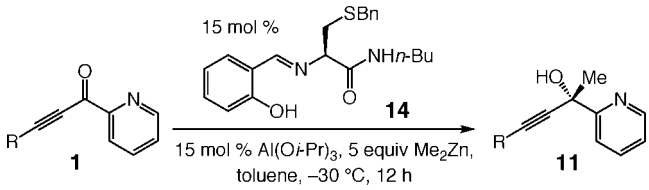
entry	chiral ligand	conv (%)[b]	ee (%)[c]; opt. rot.
1	 **6**	72	<2; nd
2	 **7**	68	<10; nd
3	 **8**	73	<2; nd
4	 **9**	71	<10; nd
5	 **5**	67	14; (+)
6	 **12**	77	65; (+)
7	**13a** R_1 = H, R_2 = *n*-Bu	***91***	***73*; (+)**
8	**13b** $R_1 = R_2$ = Et	73	<2; nd
9	 **13c** R_1 = H, R_2 = Ph	63	10; (+)
10	**13d** R_1 = H, R_2 = *p*-$OMeC_6H_4$	74	<2; nd
11	**13**; **13e** R_1 = H, R_2 = *p*-$CF_3C_6H_4$	64	42; (+)
12	 **14**	***89***	***70*; (+)**

[a] All reactions were performed under a N_2 atmosphere; see the Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra. [c] Enantioselectivities were determined by chiral HPLC analysis; see the Supporting Information for details. nd = not determined.

Subsequently, we established that the related chiral ligand **14**, prepared from the less expensive non-halogenated salicyl aldehyde, performs at a similar level of efficiency (entry 12, Table 3; 89% conv after 24 h and 70% ee).

b. Catalytic AA Reactions with Me_2Zn. The initial studies summarized in eq 1 indicated that, unlike reactions with Et_2Zn, catalytic alkylations involving Me_2Zn may proceed with higher selectivity in the absence of diethylphosphoramidate. Accordingly, we examined the Al-catalyzed enantioselective synthesis of tertiary propargyl alcohol **11a** in the absence of this additive. As illustrated in entry 1 of Table 4, catalytic AA proceeds readily to afford **11a** in 95% ee (vs 70% ee in the presence of **3**) and 74% yield after silica gel purification.[19] A variety of pyridyl-substituted ynones containing electron-donating (entry 2, Table 4), electron-withdrawing (entries 3−6, Table 4), heterocyclic (entry 7, Table 4), and *n*-alkyl (entry 8, Table 4)

Table 4. Al-Catalyzed AA Reactions with Me_2Zn[a]

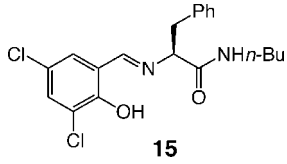


entry	R		conv (%)[b]	yield (%)[c]	ee (%)[d]
1	C_6H_5	**a**	>98	74	95
2	*p*-$OMeC_6H_4$	**e**	>98	77	96
3	*p*-$CF_3C_6H_4$	**f**	>98	70	87
4	*p*-IC_6H_4	**g**	>98	58	79
5	*p,m*-$Cl_2C_6H_3$	**h**	>98	53	95
6	*o*-BrC_6H_4	**i**	>98	57	96
7	3-thiophene	**j**	>98	74	91
8	*n*-hex	**k**	>98	59	89
9	(*i*-Pr)$_3$Si	**m**	>98	65	57[e]

[a] All reactions were performed under a N_2 atmosphere; see the Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra. [c] Yields of products after silica gel purification. [d] Enantioselectivities were determined by chiral HPLC analysis; see the Supporting Information for details. [e] Reaction performed at −50 °C with ligand **15**.

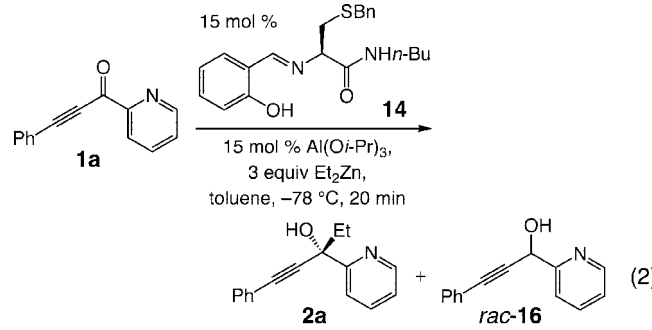
substituents can be catalytically alkylated with high selectivity (79−96% ee).

Alkylation of silyl-substituted ynone **1m** (entry 9, Table 4), performed at −50 °C and requiring ligand **15** for optimized selectivity, proceeds with moderate enantioselectivity. Reaction of **1m** in the presence of ligand **14** (at −50 °C) affords **11m** in only 22% ee and 45% yield. Ynone **1m**, at −30 °C, undergoes a particularly facile alkylation in the absence of a chiral ligand *and* without an Al salt present. Such uncatalyzed processes[20] occur with alkyl-substituted ynones such as **1k**, but at a slower rate and to a lesser degree with aryl-substituted alkynes.[21] The lower selectivity for the formation of silyl-substituted **11m** serves as an additional point of contrast with reactions involving Et_2Zn, which can be used to alkylate **1m** in >98% ee (85% ee

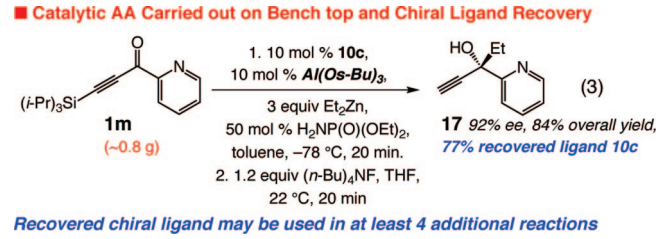


in the absence of additive **3**; see entry 16, Table 2).

The difference in the two classes of catalytic alkylations is further highlighted by the findings shown in eq 2. In the presence of 15 mol % ligand **14**, optimal for reactions of Me_2Zn, and 50 mol % diethylphosphoramidate **3**, alkylation of **1a** with Et_2Zn proceeds to 82% conversion to furnish **2a** in only 15−20% ee with an equal amount of secondary alcohol *rac*-**16**; <2% of *rac*-**16** is generated when ligand **10c** is used (as well as **6**−**9** and **10a**,**b**, illustrated in Table 1). Thus, catalytic AA with chiral ligand **14**, performed in the absence of **3**, proceeds somewhat more efficiently and enantioselectively (25−30% ee vs 15−20% ee) even for reactions that involve Et_2Zn. Such findings suggest that the effectiveness of the additive is catalyst-dependent: it is when a chiral ligand bearing *two* amino acid moieties (with Et_2Zn) is used that the presence of diethylphosphoramidate **3** is advantageous.



3. Catalyst Recycling and Matters of Practicality. Enantioselective alkylations can be performed on a useful laboratory scale, as the example in eq 3 illustrates (∼0.8 g of ynone **1m**). Terminal alkyne **17**, which cannot be accessed through direct alkylation,[22] is obtained in 92% ee and 84% overall yield (catalytic AA and removal of the silyl group).



Several points regarding the representative transformation in eq 3 merit specific mention:

(1) Al(O*i*-Pr)$_3$ can be used easily only when it is freshly distilled and exists as a soluble (in toluene) oil, but it solidifies upon exposure to air. In contrast, Al(O*s*-Bu)$_3$ persists as a toluene-soluble oil, even when exposed to air.[23] As a result, for reactions run on relatively larger scale, use of commercially

(19) The identity of the major enantiomers in reactions with Me_2Zn is based on an X-ray crystal (Cu irradiation) structure obtained for **11a** (entry 1, Table 4). See the Supporting Information for details.

(20) Although initial screening studies were performed with 5 mol % catalyst loading (see Table 3), we subsequently established that larger amounts of catalyst (see Table 4) generally deliver improved levels of enantioselectivity, presumably due to minimization of nonselective (uncatalyzed) alkylations.

(21) The amount of uncatalyzed (background) reaction depends on the substrate and likely its inherent electrophilicity. For instance, there is 20−25% conversion with *p*-CF_3-aryl ketone **1f** (entry 3, Table 4) under otherwise identical conditions (−30 °C) but in the absence of the chiral ligand.

(22) Terminal alkynes undergo facile uncatalyzed alkylation under the reaction conditions (−78 °C for Et_2Zn and −30 °C for Me_2Zn), even in the absence of an Al salt, to afford racemic tertiary propargylic alcohols.

(23) Al(O*i*-Pr)$_3$ (purchased from Strem) is a white powder with a tetrameric structure and is insoluble in toluene, which is the solvent used for Al-catalyzed AA reactions described in this study. After distillation, however, Al(O*i*-Pr)$_3$ exists as a readily soluble clear liquid. The oil readily turns to a white powder when exposed to air or after standing for longer periods of time (under nitrogen or vacuum). (See: Shiner, V. J., Jr.; Whittaker, D.; Fernandez, V. P. *J. Am. Chem. Soc.* **1963**, *85*, 2318–2322) It is the oil (distilled) form of Al(O*i*-Pr)$_3$ that is effectively used for catalytic alkylations. In contrast, Al(O*s*-Bu)$_3$ is an oil and remains as such in air; it is thus a more practical salt for use, particularly for transformations performed on a relatively large scale (e.g., gram quantities of ketone substrate). Al(O*s*-Bu)$_3$ should be stored under nitrogen, since, after extended periods of time (months), it turns into a solid, presumably due to the formation of aluminum oxides.

available Al(O*s*-Bu)$_3$ is preferred. Under such conditions, Al-catalyzed AA can be carried out on a bench top under inert atmosphere without resorting to rigorous protocols or glovebox techniques.

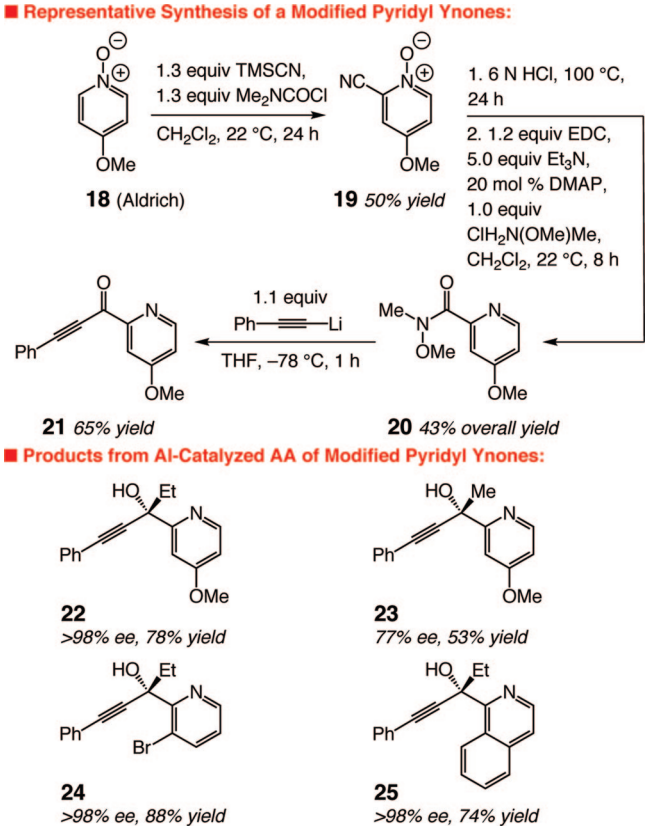
(2) The chiral ligand can be recovered after the reaction in 71−87% yield after purification and reused for at least four additional transformations without diminution in efficiency or product enantiopurity.

4. Synthesis and Catalytic AA Reactions of Modified Pyridyl Substrates and Other Functionalization Procedures.

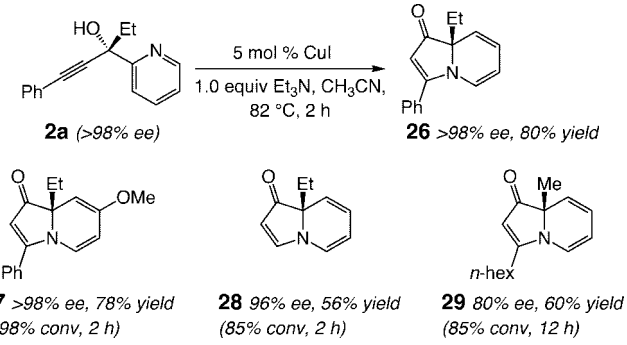
a. Synthesis and Al-Catalyzed AA Reactions of Substrates Bearing Modified Pyridines. As illustrated below, one of the advantages of the present method is that the alkyne and the pyridyl group residing within AA products offer opportunities for useful functionalization procedures. Beyond changes in the substituents of the ynones, demonstrated above, substrates with different pyridyl groups can be used in the Al-catalyzed AA reactions. The synthesis route illustrated in Scheme 2, involving the four-step synthesis of 4-methoxy-substituted pyridine **21**,[24] is representative and demonstrates the feasibility of structural modifications at the pyridyl site. Thus, tertiary propargyl alcohols **22**−**24**,[25] accessed in 77% to >98% ee and in 53−88% yield (under conditions shown for Tables 2 and 4), are obtained through enantioselective alkylations of substrates with modified pyridines.

b. Functionalizations Involving the Pyridyl Groups of Products. A number of recent disclosures have involved catalytic (non-asymmetric) transformations of pyridyl-substituted propargyl alcohols to the corresponding *N*-fused bicyclic structures (Scheme 3). Au-,[6] Cu-,[7] and Pt-based[8] catalysts have been reported to promote such processes with various levels of efficiency; the majority of the cases involve reactions of secondary alcohols. The pyridyl-substituted tertiary alcohols, now available in high enantiomeric purity, through a subsequent and facile Cu-catalyzed transformation,[26] can be converted to synthetically versatile bicyclic systems that contain a quaternary α-amino carbonyl group. Representative examples are illustrated in Scheme 3. Treatment of enantiomerically pure tertiary propargyl alcohol **2a** with 5 mol % CuI (82 °C) results in complete conversion (>98%) within 2 h, providing **26** in 80% yield after chromatography. Synthesis of bicycle **27** (78% yield after purification) represents a reaction of an enantiomerically pure substrate that bears a modified pyridyl group (see **22**, Scheme 2). Catalytic cyclization of terminal alkyne **17** (see eq 3) affords **28** at a slower rate compared to the aforementioned two processes, presumably because the developing positive charge β to the developing carbonyl unit is less stabilized due to the lower degree of substitution. Nonetheless, the desired bicycle is obtained in 56% yield after silica gel chromatography. Cu-catalyzed reaction of alkyl-substituted tertiary propargyl alcohol **2k** (see entry 14, Table 2) proceeds less readily than that of the unsubstituted derivative (**17** → **28**).

Scheme 2. Synthesis and Al-Catalyzed AA of Substrates with a Modified Pyridine



Scheme 3. Functionalization of Pyridyl-Substituted Tertiary Carbinols: Application to Cu-Catalyzed Enantioselective Synthesis of Indolizinones



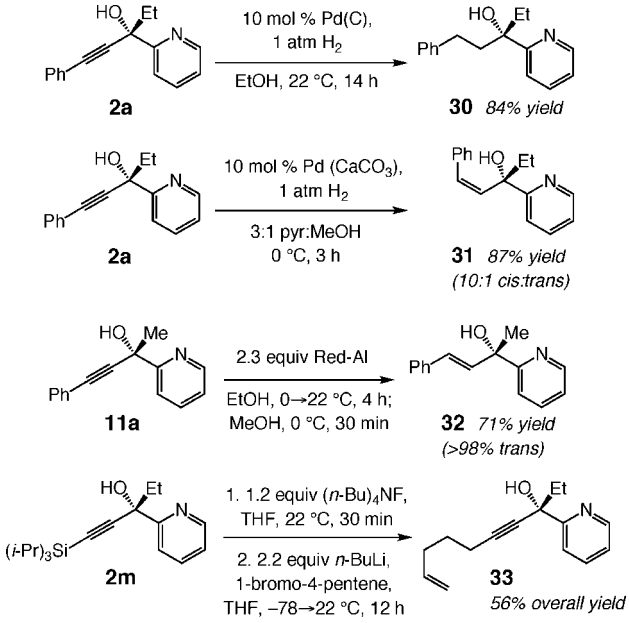
A critical point regarding the Cu-catalyzed reactions relates to the retention of the stereochemical integrity of the tertiary carbinol sites in the cyclization process. With the availability of enantiomerically enriched tertiary propragyl alcohols, such issues can be investigated. Formation of enantiomerically pure **26** and **27** (Scheme 3) illustrates that, in cases where catalytic cyclization is facile (reaction proceeds to >98% conversion within 2 h), there is complete retention of stereochemistry. When the Cu-catalyzed process is relatively sluggish, however, some enantiomeric purity is lost. Bicyclic amide **28** is thus obtained in 96% ee from a sample of **2m** that is isolated in >98% ee, and the slowest-forming alkyl-substituted **29** is generated in 80% ee from a substrate (**11k**) which is prepared in 89% ee. It is plausible that, with the slower cyclizations, the Cu−alkyne complex, serving as an intermediate in the catalytic cycle, coordinates to the neighboring Lewis basic hydroxyl group and facilitates epimerization at the carbinol center by a C−O bond dissociation/re-formation process.

(24) The Reissert−Henze cyanation of pyridine oxides in Scheme 2 is based on the following reported procedure: Fife, W. *J. Org. Chem.* **1983**, *48*, 1375–1377.

(25) Pyridyl ketone **24** is prepared from the commercially available carboxylic acid (via the derived Weinreb amide and subsequent alkylation with the alkynyl lithium).

(26) Attempts to promote similar cyclizations with a number of alkylation products (including alkyl-substituted **2l**) in the presence of 15−30 mol % $PtCl_2$ (see ref 10) resulted in generation of complex mixtures of products.

Scheme 4. Representative Functionalizations of Alkyne Group of the Catalytic AA Products

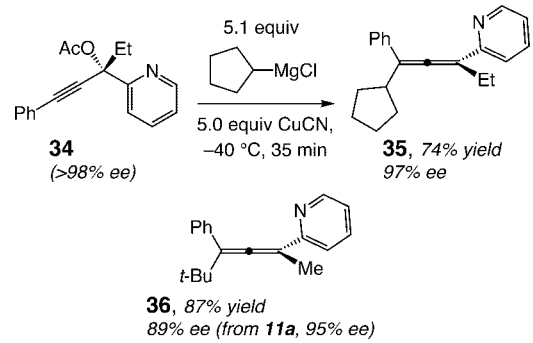


c. Functionalizations Involving the Alkyne Groups of AA Products. The alkyne unit of the enantiomerically enriched products can be readily hydrogenated to afford the corresponding fully saturated alkyl-substituted tertiary alcohols without complications from the relatively sensitive tertiary benzylic alcohol; synthesis of **30** in 84% yield through a simple Pd-catalyzed hydrogenation is representative (Scheme 4). Similarly, hydrogenation of tertiary carbinol **2a** in the presence of 10 mol % $Pd(CaCO_3)$ results in stereoselective reduction of the alkyne, furnishing allylic alcohol **31** as a 10:1 mixture of *cis*:*trans* isomers and in 87% yield (Scheme 4). Through treatment of **11a** with Red-Al,[27] the derived *trans* tertiary alcohol **32** is obtained as a single alkene isomer (>98% *trans*) and in 71% yield after silica gel chromatography.

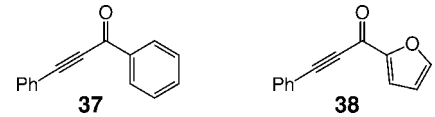
It was mentioned previously that silyl-substituted products offer access to enantiomerically enriched terminal alkynes, which can be alkylated to provide functionalities that can be used for further structural modification. The desilylation/alkylation sequence illustrated in Scheme 4, leading to the conversion of **2m** to **33**, which is a potential substrate for a number of enyne cyclization reactions,[28] illustrates this point.

The stereochemically defined tertiary propargyl alcohol presents numerous opportunities for conversion of the AA products to a wide variety of compounds that are otherwise difficult to access in high enantiomeric purity. A representative case is illustrated in Scheme 5. Treatment of acetate **34**, obtained in quantitative yield from enantiomerically enriched **2a**, with cyclopentylmagnesium chloride in the presence of CuCN at −40 °C leads to the formation of enantiomerically pure tetrasubstituted allene **35** in 74% yield;[29] synthesis of **36**, involving the reaction of *tert*-butyllithium, provides an additional example. In both examples in Scheme 5, there is limited loss of enantiopurity. Similar observations have been disclosed for transformations that involve enantiomerically enriched secondary propargyl alcohols; electron-transfer processes involving the allene product and the cuprate reagents have been suggested to rationalize such observations.[7c] Access to nonracemic tertiary propargyl alcohols thus leads to the generation of fully substituted allenes in high enantiomeric purity.[30]

Scheme 5. Application to Enantioselective Synthesis of Tetrasubstituted Allenes



5. Mechanistic Considerations. The presence of the pyridyl unit is critical to effective alkylation: there is <2% conversion when aryl ketone **37** and furyl ketone **38** are used as substrates under the conditions used for reactions with Et_2Zn described in Table 2. These observations underline the importance of two-point chelation, involving Lewis acidic Al and the Lewis basic carbonyl and N atom of the pyridine.



a. Reactions with Et_2Zn. Al-catalyzed AA reactions of Et_2Zn with ligands that bear an L-valine and a L-phenylalanine (or vice versa) can be explained by the intermediacy of **I**−**III**, illustrated in Figure 1. The Lewis basic amide at the *C*-terminus of the ligand chelates with and enhances the nucleophilicity of the alkylzinc reagent[31] toward addition to a substrate molecule (**I** and **II**), and the Lewis acidic Al associates with and activates the substrate molecule, which undergoes enantioselective alky-

(27) Corey, E. J.; Katzellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245–4247.

(28) For recent examples of enyne cyclization reactions, see: (a) Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656–1661. (b) Negishi, E-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346. (c) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (d) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180–10181. (e) Jiménez-Núñez, E.; Echevarren, A. M. *Chem. Commun.* **2007**, 333–346.

(29) For other methods that furnish enantiomerically enriched tetrasubstituted allenes, see: (a) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2003**, *6*, 305–307. (b) Miura, T.; Shimada, M.; Ku, S-Y.; Tamai, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101–7103. For a protocol for synthesis of Ti-substituted tetrasubstituted allenes, see: (c) Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551–4554.

(30) For reviews on stereoselective synthesis of allenes, see: (a) Krause, N.; Hoffman-Röder, A. *Tetrahedron* **2004**, *60*, 11671–11694. (b) Miesch, M. *Synthesis* **2004**, 746–752. (c) Brummond, K. M.; De Forrest, J. *Synthesis* **2007**, 795–818. (d) For allene-containing natural products or biologically active molecules, see Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216.

(31) For a detailed discussion of Lewis base activation of Lewis acids, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638. For recent applications of this concept toward development of new chiral catalysts and catalytic enantioselective protocols from these laboratories, see: (b) Reference 14. (c) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67–70. (d) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604–15605.

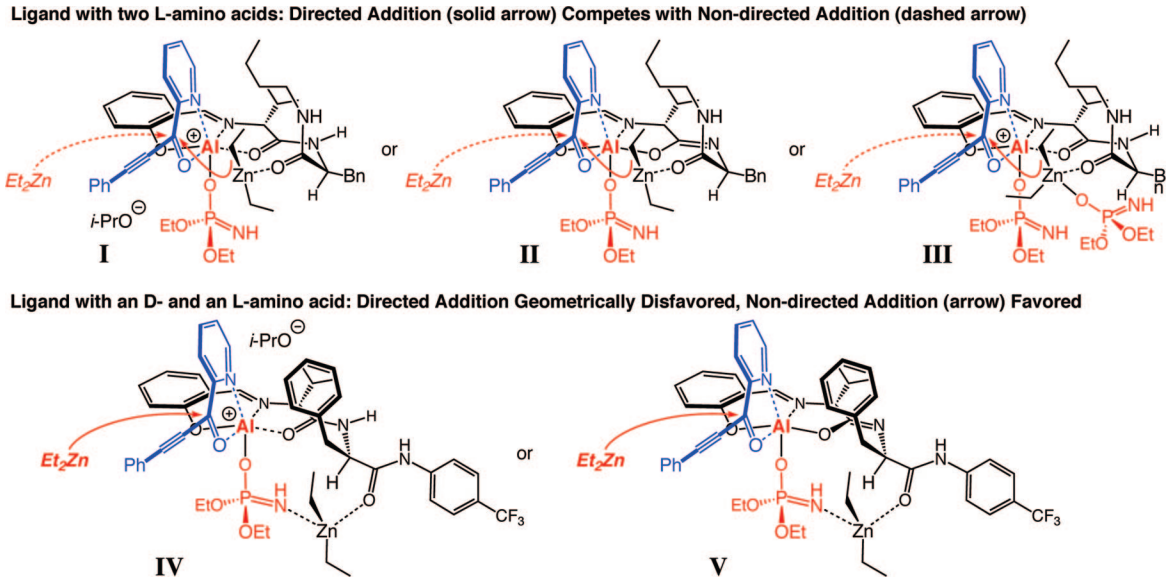


Figure 1. Mechanistic models for Al-catalyzed AA reactions with Et_2Zn based on calculations performed at the MMFF94 level in Spartan.

lation.[32] The competing mode of addition is represented in **I**−**III** (dotted arrows, Figure 1): the alkylmetal adds to the bound substrate without activation by the chiral ligand's amide terminus. It is unclear, however, whether it is the cationic complex **I** or the neutral complex **II** (or **III**), that promotes alkylation.

In all cases (**I**−**III**),[33] we suggest that the strongly Lewis basic phosphoramidate additive, by replacing an isopropoxy ligand, increases Al Lewis acidity[31] and catalytic activity. Activation of the Al center by the phosphoramidate is identical in nature to the interaction involving amide carbonyl interaction with the dialkylzinc reagent. Modeling studies indicate that a second molecule of phosphoramidate might interact with the amide-bound alkylzinc reagent (**III**, Figure 1), further elevating Zn Lewis acidity[34] as well as alkylmetal nucleophilicity. Such considerations offer a rationale for the need for the presence of relatively significant amounts of the Lewis basic additive (50 mol %).

In contrast to the transformations promoted by L,L-dipeptides, catalytic AA reactions with chiral ligands that bear an L-valine and a D-phenylalanine (or vice versa) may proceed through complexes **IV** and/or **V** (Figure 1); the previously favored (with L,L-ligands in **I**−**III**) diastereotopic face is now blocked by the substituent of the AA2 moiety, thus favoring the nondirected mode of addition and causing a reversal in the sense of enantioselective alkylation. The proposed scenario is consistent with the finding that the absolute stereochemistry of the AA product is predicated on the identity of the chiral ligand's AA2 moiety (see Table 1 and the accompanying discussion). Examination of molecular models indicates that, in ligands that carry an L-valine and a D-phenylalanine (or vice versa; see **IV** and **V**), the diethylzinc coordinated to the AA2 (phenylalanine) carbonyl cannot be directed to add to the Al-bound pyridyl ketone due to geometric constraints.

Molecular mechanics calculations[35] suggest that a Zn bridge consisting of the Lewis basic phosphoramidate (additive) with the carbonyl of the ligand's *C*-terminus leads to a high degree of rigidity in complexes **IV** and **V**, resulting in the enhanced enantioselectivity observed for L,D-dipeptide **10c** versus an L,L-ligand such as **6** (see entry 3, Table 1). The elevated enantioselectivity obtained through the use of ligands that contain an *aryl*amide *C*-terminus (e.g., **10a**−**c** in entries 7−9 of Table 1) vs alkylamides such as **9** (entry 6, Table 1) may originate from the more acidic amide proton which undergoes deprotonation, thus increasing the Lewis basicity of the amide carbonyl, which in turn helps to strengthen the proposed Zn bridge.

Two additional points regarding complexes **I**−**V** are noteworthy:

(1) Coordination of the phosphoramidate additive (**3**) at the apical position, anti to the *i*-Pr substituent of the AA1 moiety (valine), is likely due to minimization of unfavorable steric interactions. Such mode of phosphoramidate association determines the manner in which the pyridyl ynone binds to the Al center, which in turn, as is discussed below, establishes whether the chiral ligand can participate in directed alkylation (delivery of the dialkylzinc by the Lewis basic amide at the *C*-terminus).

(2) The proposed function of the phosphoramidate additive,[15] particularly its role to provide structural rigidity through Zn chelation in complexes **IV** and **V**, finds support in the data summarized in Table 5. Thus, although use of $Me_2NP(O)(OEt)_2$ (**38**; entry 2, Table 5) leads to complete conversion, **2k** is obtained in only 25% ee (vs 98% ee with $H_2NP(O)(OEt)_2$, entry 1). This difference in enantioselectivity may be attributed to the absence of a Zn bridge as a result of the presence of the alkylated phosphoramidate (additive cannot participate in ligand exchange with an isopropoxyaluminum), giving rise to a complex of reduced structural rigidity where the two enantiotopic faces of the bound carbonyl are less effectively differentiated. The diminution in enantioselectivity versus that

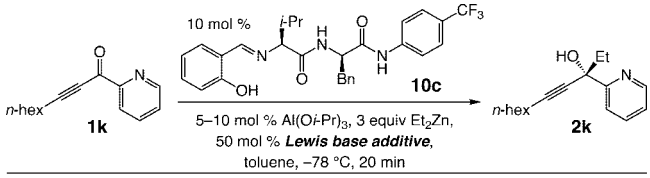
(32) (a) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594–11599. (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233.

(33) For a recent review regarding bifunctional chiral catalysis, see: Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583.

(34) Theoretical studies (HF and B3LYP level of theory) illustrate that chelation of TMEDA with Me_2Zn causes an increase in the positive charge on Zn ($q_{Zn} = +1.247$ to $+1.364$); see: Weston, J. *Organometallics* **2001**, *20*, 713–720.

(35) All structures were minimized through the use of MMFF94 method, as supplied by Spartan '04, Wavefuncton, Inc. Irvine, CA. Merck Molecular Force Field 94 was selected due to its ability to handle peptide bonds with reasonable accuracy.

Table 5. Effect of Additive Structure on Catalytic AA Reactions with Et_2Zn[a]



entry	additive	conv (%)[b]	ee (%)[c]
1	$H_2NP(O)(OEt)_2$ (**3**)	>98	98
2	$Me_2NP(O)(OEt)_2$ (**38**)	>98	25
3	$H_2NP(O)(O\textit{i}\text{-}Pr)_2$ (**39**)	77	85
4	$Ph_3P{-}O$	85	30

[a] All reactions were performed under a N_2 atmosphere. [b] Determined through analysis of 400 MHz ^1H NMR spectra. [c] Enantioselectivities were determined by chiral HPLC analysis.

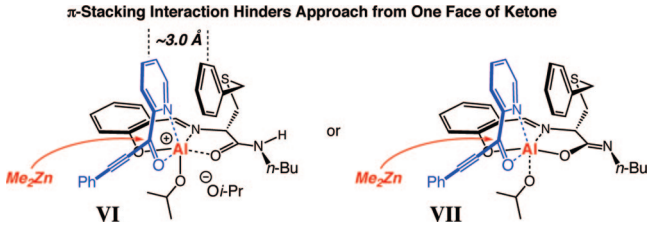


Figure 2. Model for Al-catalyzed AA reactions with Me_2Zn based on calculations performed at the MMFF94 level in Spartan.

observed when an additive is not used (25% ee in entry 2, Table 5, vs 75% ee in entry 14, Table 2) may be due to Lewis base activation of unbound dialkylzinc, culminating in substantially more competitive uncatalyzed alkylation rates. Diisopropylphosphoramidate **39** (entry 3, Table 5) can participate in the formation of a Zn bridge, but perhaps less efficiently than **3** (entry 1, Table 5) because of the larger alkoxy groups (*i*-PrO vs EtO). The low enantioselectivity observed when triphenylphosphine oxide is used as the additive (entry 4, Table 5) is likely based on reasons similar to those outlined above for phosphoramidate **38**.

Catalytic AA reactions in entries 3 and 4 of Table 5 do not proceed to >98% conversion, in spite of facile and complete alkylation with Et_2Zn, even in the absence of an Al salt or chiral ligand. This difference in reactivity may suggest that the Lewis basic additives might associate with the dialkylzinc reagent (in addition to the Al center), as suggested previously (see **III**, Figure 1), giving rise to a Et_2Zn·phosphoramidate complex that is significantly bulkier; this, in turn, results in diminished alkylation rates in spite of the (possibly) enhanced alkylmetal nucleophilicity. The involvement of a sterically demanding Et_2Zn·**3** complex would result in an increase in enantioselectivity when reactions proceed through complex **IV** or **V**, where stereocontrol depends largely on steric blockage of one face of the ketone substrate.

b. Reactions with Me_2Zn. The models that account for enantioselective AA reactions with Me_2Zn are illustrated in Figure 2 (**VI** and **VII**). Calculations and examination of molecular models indicate that the requirement for the presence of an aryl-containing amino acid moiety within the chiral ligand (see entries 6−12, Table 3) is due to the structural organization gained through a π-stacking interaction[36] involving the electron-deficient pyridyl ring of the Al-bound substrate.[37] Such $\pi-\pi$ association can inhibit addition from one face of the activated ketone, leading to selective generation of one enantiomer through reaction via complexes **VI** and/or **VII**.[38] The adverse effect of **3** in reactions with Me_2Zn may be attributed to the facilitation of the noncatalyzed process by this additive. Such an effect is perhaps absent with processes involving Et_2Zn, as such transformations can be performed at −78 °C (vs −30 °C for Me_2Zn); at lower reaction temperatures, there may be minimal activation of Et_2Zn by **3** or, as suggested above, the resulting complex may not be involved in alkylation due to steric factors. The L,D-ligand **10c**, effective for AA reactions with Et_2Zn, does not promote enantioselective additions of Me_2Zn since, in the absence of phosphoramidate additive and the Zn-bridged complexes, differentiation of the diastereotopic faces of the catalyst-bound substrate cannot be achieved.

Conclusions

We have developed protocols for catalytic enantioselective synthesis of tertiary propargyl alcohols bearing a pyridyl substituent through Al-catalyzed alkylations with dialkylzinc reagents. Chiral ligands can be prepared readily on gram-scale, and the requisite substrates are accessible in no more than four steps. The simplicity with which the present class of ligands can be structurally modified has been exploited in identifying the optimal chiral catalysts furnishing the highest possible level of enantioselectivity in reactions involving Et_2Zn and Me_2Zn as alkylating agents.

The protocols outlined herein furnish enantiomerically enriched products that contain a quaternary carbon stereogenic center bearing three highly versatile substituents: an alcohol, a pyridine, and an alkyne. As a result, a wide range of functionalization procedures can be used to prepare small organic molecules of high enantiomeric purity that would otherwise be far more difficult to access. Transformation of the alkylation product to bicyclic amide by a Cu-catalyzed process that converts a tertiary carbinol to an *N*-substituted quaternary carbon stereogenic center is a noteworthy example. Moreover, the accessibility of tertiary propargyl alcohols by catalytic asymmetric alkylation of ynones allows for the synthesis of enantiomerically enriched tetrasubstituted allenes through Cu-catalyzed allylic alkylation of the derived tertiary acetates by Li-based or Grignard reagents.

In spite of the advances described above, a number of significant objectives remain to be addressed. Identification of chiral catalysts that allow for alkylations with a wider range of alkylating agents and at lower catalyst loadings is one goal of

(36) It should be noted that the proposal that $\pi-\pi$ interactions give rise to the observed enantioselectivities is not based on calculations, since intermolecular aromatic $\pi-\pi$ stacking interactions have not been parameterized in MMFF94 (Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490–519). Attempts at performing calculations at higher levels of theory proved prohibitive due to the large size of the complexes.

(37) For reviews of π-stacking interactions in organic synthesis, see: (a) Jones, G. B.; Chapman, B. J. *Synthesis* **1994**, 475–497. (b) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999–8016. For recent examples where π-stacking interactions are proposed to account for the stereochemical outcome of catalytic asymmetric reactions, see: (c) Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3718–3734. (d) Jiang, H.; Birman, V. B. *Org. Lett.* **2005**, *7*, 3445–3447. (e) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405–2408. (f) Ginorta, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2006**, *4*, 4370–4374. (g) Ma, L.; Jiao, P.; Zhang, Q.; Du, D-M.; Xu, J. *Tetrahedron: Asymmetry* **2007**, *18*, 878–884. (h) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764.

(38) Such $\pi-\pi$ interactions are expected to remain operative in toluene, which is a molecule with significantly lower ability to interrupt such associations compared to benzene. This difference manifests itself in the substantial difference in the respective melting points of these two aromatic molecules (benzene mp = +5.5 °C; toluene mp =−93 °C).

future studies. With the present class of catalysts, reactions with longer chain dialkylzinc reagents (e.g., n-Bu_2Zn or $(i\text{-}Pr)_2Zn$) or Ph_2Zn lead to low conversion and/or formation of racemic secondary alcohols.

Investigations to identify catalytic systems that effectively address the above problems and development of catalytic enantioselective additions to other classes of ketones, as well as applications to the synthesis of biologically active molecules, constitute the focus of ongoing studies in these laboratories.

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Supporting Information Available: Experimental procedures and spectral data for substrates and products (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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