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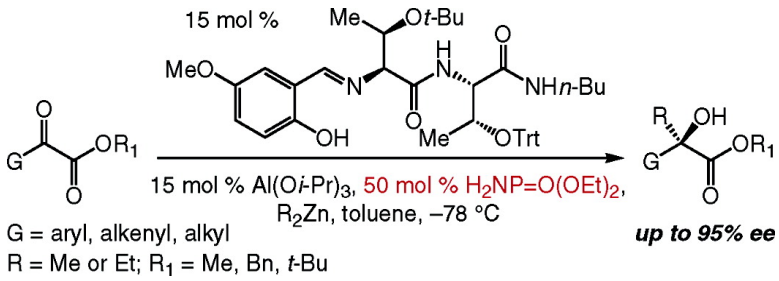

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Al-Catalyzed Enantioselective Alkylation of α-Ketoesters by Dialkylzinc Reagents. Enhancement of Enantioselectivity and Reactivity by an Achiral Lewis Base Additive

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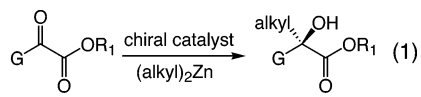
Abstract: An Al-catalyzed enantioselective method for additions of Me_2Zn and Et_2Zn to α-ketoesters bearing aromatic, alkenyl, and alkyl substituents is disclosed. Transformations are promoted in the presence of a readily available amino acid-based ligand and afford the desired products in excellent yields and in up to 95% ee. Investigations described illustrate that the presence of a Lewis basic additive can lead to significant enhancements in efficiency and enantioselectivity. A mechanistic model that provides a rationale for such effects is provided.

Introduction

Catalytic enantioselective addition of a carbon nucleophile to a ketone is perhaps the most efficient approach to the synthesis of an optically enriched tertiary alcohol. However, development of catalytic alkylations of ketones, in contrast to related processes involving aldehyde substrates,[1] has been the subject of relatively few reports.[2,3] Efficient enantioselective additions to ketones, as opposed to aldehydes, are significantly more challenging; ketones are less reactive, and because of the diminished size difference between the carbonyl substituents, the task of achieving effective enantiotopic face differentiation is more demanding.

α-Ketoesters represent a more reactive class of ketones that, upon alkylation, provide synthetically versatile and readily functionalizable tertiary alcohols (eq 1). The higher reactivity of α-ketoesters may at first appear as an advantage. However, with the more reactive alkylating agents (e.g., alkylmetals), such substrates demand that the chiral catalyst provides sufficient activity at lower temperatures; otherwise, uncatalyzed and nonenantioselective background processes can prove detrimental to product optical purity. Three reports have appeared regarding catalytic asymmetric additions of Zn-based reagents to α-ketoesters. In one study carried out by Kozlowski and co-workers,[4] chiral Ti complexes were used to effect additions of Et_2Zn to afford tertiary alcohols in up to 78% ee (−40 °C, THF). Higher enantioselectivities were observed with ketones bearing an aromatic substituent. Jiang and co-workers have employed chiral amino alcohols as ligands in Zn-catalyzed enantioselective alkynylations of aromatic α-ketoesters (up to 94% ee; 70 °C, toluene);[5] alkynylzinc reagents are prepared in situ from the reaction of a terminal alkyne and $Zn(OTf)_2$.[6] Shibasaki et al. have developed a related method for Zn-catalyzed asymmetric additions of Me_2Zn (up to 96% ee).[7] In the latter study, high substrate activity proves costly: slow addition (over 30 h at −20 °C) of the alkylzinc reagent is required to minimize uncatalyzed (nonenantioselective) alkylation. Examples of reactions of the more reactive Et_2Zn were not provided, and, with one exception (substrate with alkynyl substituent), only outcomes for reactions of aromatic substrates were disclosed.



G = aryl, alkenyl, alkyl

Herein, we report an Al-catalyzed protocol for enantioselective additions of Me_2Zn and Et_2Zn to α-ketoesters bearing

(1) For recent reviews, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886.

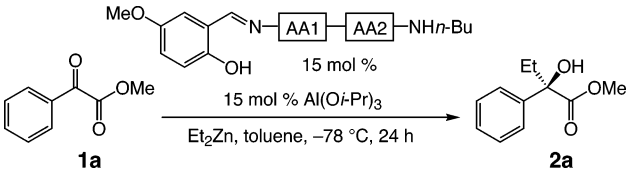
(2) For examples of catalytic enantioselective alkylations, arylations, and allylations of ketones, see: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (b) Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−1242. (c) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651−5666. (d) Celina, G.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (e) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291−2293. (f) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545. (g) Yus, M.; Ramon, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745−2748. (h) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103−1114. (i) Prieto, O.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955−1957. (j) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898. (k) Garcia, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641−3644. (l) Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749−760. (m) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539. (n) Li, H.; Garcia, C.; Walsh, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425−5427. (o) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910−8911. (p) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147−4149. (q) Jeon, S.-J.; Li, H.; Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455.

(3) For catalytic enantioselective aldol additions 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) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (d) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233−4235. (e) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984−5987. (f) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, in press.

(4) (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781−3784. (b) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668−12669.

(5) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453.

Table 1. Representative Data from Initial Screening of Chiral Ligands



entry	AA1	AA2		conv. (%)[a]	ee (%)[b]
1	L-Thr(*t*-Bu)	L-Thr(Trt)	**3**	>98	75
2	D-Thr(*t*-Bu)	L-Thr(Trt)	**4**	80	−15
3	Gly	L-Thr(Trt)	**5**	20	−30
4	L-Thr(*t*-Bu)	Gly	**6**	15	<10

[a] Determined by GLC. [b] Determined by chiral GLC (see the Supporting Information for details).

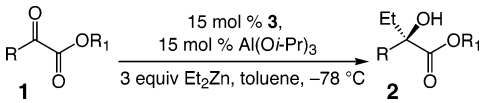
aromatic, alkenyl, and alkyl substituents. Transformations are promoted in the presence of a readily available chiral amino acid-based ligand and a commercially available achiral additive to afford the desired products in high yield and up to 95% ee. We illustrate that the presence of a Lewis base additive leads to enhancements in efficiency and enantioselectivity. Moreover, a model that provides a rationale for such effects is provided.

Results and Discussion

1. Identification of Optimal Catalyst through Ligand Screening: Enantioselective Additions with Et_2Zn. On the basis of the catalyst screening methods developed in our laboratories,[8] we initiated our investigation by examining the ability of a range of chiral amino acid-based ligands (total of ~60) in the presence of various transition metal salts to promote enantioselective addition of Et_2Zn to α-ketoester **1a**.[9] These studies led us to establish that, in the presence of 15 mol % of $Al(Oi\text{-}Pr)_3$[10] and dipeptide **3** (entry 1, Table 1), tertiary alcohol **2a** can be obtained efficiently (>98% conv. after 24 h at −78 °C) and in 75% ee.[11] As the representative data in Table 1 indicate, both residues must be an L or a D amino acid (entry 2 vs 1). Moreover, the presence of chirality at *both* amino acid residues proves to be critical in obtaining appreciable levels of asymmetric induction (entries 3 and 4, Table 1).

As illustrated in Table 2, α-ketoesters undergo enantioselective alkylation with 15 mol % of **3** and $Al(Oi\text{-}Pr)_3$ to afford the desired tertiary alcohols in 63−98% yield and up to 83% ee. Significant levels of product optical purity are observed in all cases, except with the reaction of **1f** (entry 6, Table 2), which requires a longer reaction time (48 h vs 20−45 min) to proceed to >98% conv. In all reactions, adventitious ketone reduction is not observed (<2% by 400 MHz ^{1}H NMR analysis).[4]

Table 2. Al-Catalyzed Enantioselective Reaction Et_2Zn with α-Ketoesters



entry	R	R_1		time	yield (%)[a]	ee (%)[b]
1	Ph	Me	**a**	20 min	95	75
2	Ph	Bn	**b**	20 min	95	80
3	Ph	*t*-Bu	**c**	20 min	63	70
4	*p*-$OMeC_6H_4$	Me	**d**	45 min	96	83
5	*p*-IC_6H_4	Me	**e**	20 min	84	60
6	*o*-$OMeC_6H_4$	Me	**f**	48 h	87	<5
7	3-furyl	Me	**g**	20 min	88	44
8	Me	Me	**h**	20 min	>98[c]	39

[a] Isolated yields. [b] Determined by chiral GLC (see the Supporting Information for details). For stereochemical proofs and optical rotations, see the Supporting Information. [c] Percent conversion (accurate yield difficult to measure due to product volatility).

2. Effect of Achiral Additives on Reaction Efficiency and Enantioselectivity. Next, we examined whether an appropriate additive,[12] particularly a Lewis basic entity, could give rise to improved reaction outcomes. We studied the effect of a number of additives, including commercially available achiral P- and N-oxides, on the enantioselectivity and rate of reactions of Et_2Zn with α-ketoesters (representative data are summarized in Table 5).

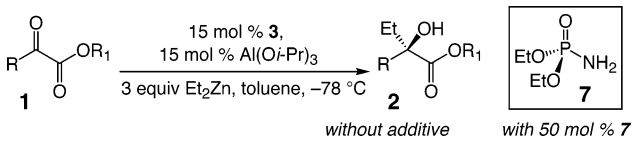
As illustrated in Table 3, we established that with 50 mol % of diethylphosphoramidate (**7**),[13] enantioselectivity is noticeably improved. In certain cases, such as those shown in entries 5−8 of Table 3, such enhancements are significant. Particularly noteworthy is the reaction of **1f**, where an otherwise nonselective (<5% ee) transformation delivers tertiary alcohol **2f** in 75% ee.

3. Catalytic Enantioselective Additions with Me_2Zn. The influence of additive **7** on enantioselectivity and reaction rate is more pronounced in the case of transformations involving the less reactive Me_2Zn. As the results summarized in Table 4 indicate, in all cases, the desired tertiary alcohol is obtained at a substantially higher level of optical purity and more efficiently when 50 mol % of **7** is included in the reaction mixture. Thus, Al-catalyzed transformations that do not proceed to completion within 24 h and afford tertiary alcohols in 30−77% ee occur more readily (83 to >98% conv.) and in 56−95% ee in the presence of **7**. The reaction of **1i** to afford **8i** in 92% ee (entry 4, Table 4) is especially noteworthy and represents a significant improvement over the previously reported protocols (30% ee).[7]

4. Rationale for the Effect of Achiral Additive on Reactivity and Enantioselectivity. The above observations can be rationalized based on seminal studies of Gutmann[14] and, more recently, Denmark.[15] Thus, as depicted in Scheme 1, association of Lewis basic additive **7** (deprotonated form shown) with the transition metal center[16] of the alkylzinc reagent (**I** → **II**)[17] may

(6) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807.
(7) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489−5492.
(8) (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671. (b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707. (c) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem.—Eur. J.* **1998**, *4*, 1885−1889. (d) Hoveyda, A. H. *Chem. Biol.* **1998**, *5*, R187−R191. (e) Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 991−1016.
(9) See the Supporting Information for details.
(10) For Al-catalyzed enantioselective cyanation of ketones in the presence of the same class of peptide-based ligands, see: Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012.
(11) There is 5−10% conv. in the absence of the chiral ligand.
(12) For a review on additives in asymmetric catalysis, see: (a) Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577. For examples of additives in reactions promoted by the present class of ligands, see: (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (c) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734−3735.
(13) Amount (50 mol %) of **7** was found to be optimal (see the Supporting Information for details).
(14) Gutmann, V. *The Donor−Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978.

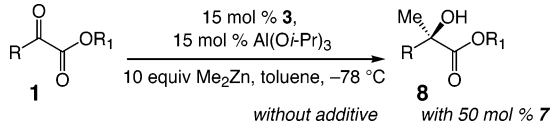
Table 3. Al-Catalyzed Enantioselective Reaction of Et_2Zn with α-Ketoesters



					without additive		with 50 mol % of **7**	
entry	R	R_1		time	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]; config.
1	Ph	Me	**a**	20 min	95	75	98	83; (+)
2	Ph	Bn	**b**	20 min	95	80	75	86; (−)
3	Ph	*t*-Bu	**c**	20 min	63	70	95	78; (+)
4	*p*-$OMeC_6H_4$	Me	**d**	45 min	96	83	98	89; (+)
5	*p*-IC_6H_4	Me	**e**	20 min	84	60	98	84; (+)
6	*o*-$OMeC_6H_4$	Me	**f**	48 h	87	<5	92	75; (−)
7	3-furyl	Me	**g**	20 min	88	44	90	72; (+)
8	Me	Me	**h**	20 min	98[c]	39	>98[c]	56; nd

[a] Isolated yields. [b] Determined by chiral GLC (see the Supporting Information for details). For stereochemical proofs and optical rotations, see the Supporting Information. nd = not determined. [c] Percent conversion (accurate yield difficult to measure due to product volatility).

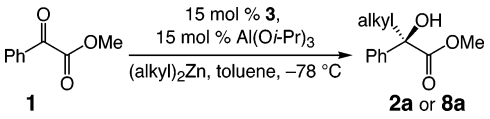
Table 4. Al-Catalyzed Enantioselective Reaction of Me_2Zn with α-Ketoesters



					without additive		with 50 mol % of **7**	
entry	R	R_1		time	conv. (%)[a]; yield (%)	ee (%)[a]	conv.[a]; yield (%)[b]	ee (%)[a]; config.
1	Ph	Me	**a**	24 h	92; nd	67	>98; 97	95; (−)
2	Ph	*t*-Bu	**c**	24 h	43; nd	50	83; 71	85; (−)
3[c]	*p*-$OMeC_6H_4$	Me	**d**	24 h	66; 53	77	98; 71	84; (−)
4[d]	Et	Me	**i**	24 h	93; nd	70	>98; 44	92; (−)
5	PhHC=CH	Me	**j**	24 h	>98; 97	30	>98; 91	56; (−)

[a] Determined by chiral GLC (see the Supporting Information for full details). For stereochemical proofs and optical rotations, see the Supporting Information. [b] Isolated yields. [c] Reaction carried out at −60 °C. [d] Low yield is due to product volatility. nd = not determined.

Table 5. Effect of Additives on Al-Catalyzed Enantioselective Reaction of Me_2Zn and Et_2Zn with α-Ketoesters[a]



entry	$(alkyl)_2Zn$	additive	conv. (%)[b]	ee (%)[c]
1	Me_2Zn	none	90	67
2	Et_2Zn	none	>98	75
3	Me_2Zn	**7**	>98	95
4	Et_2Zn	**7**	>98	83
5	Me_2Zn	$Me_2NPO(OEt)_2$	47	45
6	Et_2Zn	$Me_2NPO(OEt)_2$	>98	75
7	Me_2Zn	Ph_3PO	42	47
8	Et_2Zn	Ph_3PO	>98	90
9	Me_2Zn	$(t\text{-}Bu)_3PO$	80	76
10	Et_2Zn	$(t\text{-}Bu)_3PO$	>98	77
11	Me_2Zn	NMO	93	86
12	Et_2Zn	NMO	>98	74

[a] Conditions: 3 equiv of Et_2Zn (20 min), 10 equiv of Me_2Zn (24 h). [b] Determined by GLC analysis. [c] Determined by chiral GLC (see the Supporting Information for details).

lead to a beneficial redistribution of electron density, enhancing the nucleophilicity of the alkylzinc reagent (due to build-up of electron density at the alkyl ligands)[18] and stronger Zn chelation with the Lewis basic amide (resulting from enhanced Lewis acidity of Zn). Such electronic alteration, achieved by involvement of an appropriate Lewis basic additive (cf. **II**), would facilitate and promote directed delivery of the alkylzinc reagent by the AA2 moiety (vs nondirected addition, which may lead to attack on the alternative face of the Al-bound carbonyl).

The data summarized in Table 5, regarding the effect of various additives on the efficiency and enantioselectivity of the addition process, indicate that the presence of acidic protons (NH_2) is critical to the effectiveness of the achiral additive (e.g., compare entries 3−4 and 5−6); use of di*methyl*phosphoramidate does not lead to improvement of reaction efficiency or enantioselectivity. One plausible explanation for this observation is

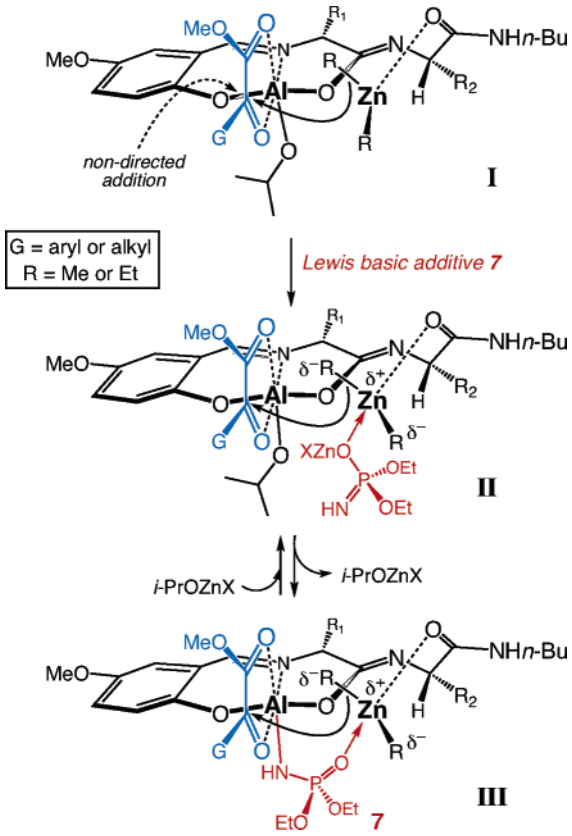
(15) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789 and references therein.

(16) For coordination chemistry of Al-based complexes, see: *Coordination Chemistry of Aluminum*; Robinson, G. H., Ed.; VCH: Weinheim, Germany, 1993.

(17) **I** and **II** are proposed based on previous mechanistic studies. See: (a) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599. Preliminary studies indicate that the presence of Al(+3) *and* Zn(+2) is required; for example, alkylations proceed to <10% conv. to afford racemic products with $EtAl(Oi\text{-}Pr)_2$ as the sole metal salt.

(18) Experimental and theoretical studies suggest that Lewis base coordination to a dialkylzinc reduces Zn−C bond order, increasing alkylmetal nucleophilicity. (a) Hursthouse, M. B.; Motevalli, M.; O'Brien, P.; Walsh, J. R.; Jones, A. C. *J. Mater. Chem.* **1991**, *1*, 139−140. (b) Haarland, A.; Green, J. G.; McGrady, G. S.; Downs, A. J.; Gullo, E.; Lyall, M. J.; Timberlake, J.; Tutukin, A. V.; Volden, H. V. Ostby, K.-A. *Dalton Trans.* **2003**, 4356−4366.

Scheme 1. Transition State Models



that the deprotonated additive (as illustrated in **II**, Scheme 1) is a significantly more effective Lewis base. Alternatively, it is possible that **7** allows for electronic activation by association with the alkylzinc reagent *intra*molecularly, as depicted in **III** in Scheme 1. Through the latter mode of reaction (**III**), the Al-bound additive can direct the dialkylzinc reagent toward addition to the α-ketoester substrate. In the absence of the acidic NH bonds, the Al−N bond cannot form, and intramolecular mode of activation (**III**, Scheme 1) is no longer feasible. In certain cases, such as entries 9 and 11, reaction efficiency and enantioselectivity do improve with additives that most likely do not provide two-point contact with the Al-based chiral complex. Nonetheless, overall, the data summarized in entries 7−12 of Table 5 support the notion that to achieve the most optimal results it may be that the additive must be able to be converted to a highly Lewis basic entity or provide intramolecular activation.[19]

Conclusions

We have developed an Al-catalyzed method for enantioselective alkylations of a variety of α-ketoesters. In contrast to previously reported procedures, the present protocol can be used with Me_2Zn and Et_2Zn,[20] aliphatic substrates can be alkylated with high enantioselectivity, and slow addition of the dialkylzinc reagents is not required. The present method affords superior (in the case of Et_2Zn) or similar enantioselectivities (in the case of Me_2Zn) compared to previously reported protocols. We have demonstrated that in the presence of a P-oxide additive (**7**), enantioselectivities and reaction rates can be improved significantly. These studies provide a striking example of how an external Lewis base, introduced as an additive,[21] can influence the outcome of a catalytic cycle, enhancing selectivity and efficiency. The alternative approach would involve covalent attachment of a Lewis basic moiety to the chiral catalyst.[22,23] An advantage of the present strategy is that it allows for a more facile reaction optimization through rapid screening of different Lewis base additives.

Al-catalyzed enantioselective alkylations of α-ketoesters is the newest addition to a growing list of metal-catalyzed enantioselective C−C bond forming reactions[8,10,12b,c,24] that are promoted by readily accessible and modifiable amino acid-based chiral ligands. Development of additional catalytic asymmetric methods, involving this class of chiral ligands and based on catalyst activation principles discussed above, is in progress.

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

JA053259W

(19) Enantioselectivity measurements with chiral ligands of various degrees of optical purity indicate that the presence of **7** does not significantly alter the slight degree of nonlinearity observed. See the Supporting Information for details. For an excellent review of nonlinear effects in asymmetric catalysis, see: Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411.

(20) Reactions with the more nucleophilic Ph_2Zn and $(i\text{-Pr})_2Zn$ under the present conditions led to >98% conv. and <2% ee, presumably due to uncatalyzed alkylation. Studies aimed at identification of chiral catalysts that promote a broader range of alkylations are in progress.

(21) For catalytic asymmetric reactions involving P-oxide additives, see: (a) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805−814. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636−3638. (c) Kinoshita, T.; Okada, S.; Park, S. R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680−4684. (d) Kino, R.; Daikai, K.; Kawanami, T.; Furuno, H.; Inanaga, J. *Org. Biol. Chem.* **2004**, 1822−1824. (e) Casa, J.; Najera, C.; Sansano, J. M.; Saa, J. M. *Tetrahedron* **2004**, *60*, 10487−10496.

(22) For representative examples, see: (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (b) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491−6493.

(23) For recent examples involving significant increase in reactivity and enantioselectivity of a catalytic asymmetric C−C bond forming reaction in the presence of a Lewis basic additive, see: Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592−11593 and references therein.

(24) For representative examples of Zr-catalyzed alkylations of alkylzinc reagents to imines: (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. Cu-catalyzed conjugate additions of alkylzinc reagents to carbocyclic enones: (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. Cu-catalyzed allylic alkylations with alkylzinc reagents: (c) Luchaco-Cullis, C.-A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460. Cu-catalyzed conjugate additions of alkylzinc reagents to nitroalkenes: (d) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584−4585. Cu-catalyzed conjugate additions of alkylzinc reagents to unsaturated heterocycles: (e) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306−5310.