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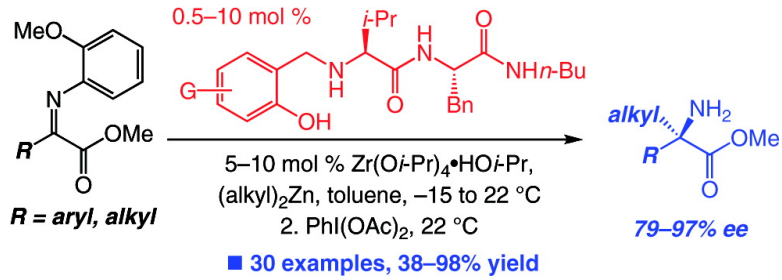

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Catalytic Asymmetric Alkylations of Ketoimines. Enantioselective Synthesis of *N*-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed Additions of Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluoroalkyl-Substituted Ketoimines

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Abstract: Catalytic enantioselective alkylations of three classes of ketoimines are reported. Reactions are promoted in the presence 0.5–10 mol % of a Zr salt and a chiral ligand that contains two inexpensive amino acids (valine and phenylalanine) and involve Me_2Zn or Et_2Zn as alkylating agents. Requisite aryl- and alkyl-substituted α-ketoimine esters, accessed readily and in >80% yield on gram scale through a two-step sequence from the corresponding ketones, undergo alkylation to afford quaternary α-amino esters in 79–97% ee. Aryl-substituted trifluoroketoimines are converted to the corresponding amines by reactions with Me_2Zn, catalyzed by a chiral complex that bears a modified *N*-terminus. The utility of the catalytic asymmetric protocols is illustrated through conversion of the enantiomerically enriched alkylation products to a range of cyclic and acyclic compounds bearing an *N*-substituted quaternary carbon stereogenic center.

Introduction

The search for efficient and enantioselective methods for formation of quaternary carbon stereogenic centers constitutes a crucial challenge in chemical synthesis.[1] Within this context, development of catalytic transformations that furnish *N*-substituted quaternary carbons, including enantiomerically enriched quaternary α-amino acids or related derivatives, is a particularly compelling objective.[2] α,α-Disubstituted amino acids are found in medicinally relevant agents[3] and lend conformational rigidity within biologically active peptides.[4] A direct route to this class of compounds involves enantioselective additions to ketoimines,[5] substrates with a sterically congested and relatively unreactive C=N bond (vs a C=O). Ketone-derived imines bear substituents that are more similar in size than those of an aldimine.[6] Ketoimines, unlike ketones, exist as an *E* and/or a *Z* isomer. Such factors, collectively, render differentation of enantiotopic faces of a ketoimine especially difficult. As a result, an effective catalyst for additions to ketoimines must, while maintaining high levels of enantioselectivity, exhibit an order of activity that is superior to what is sufficient for additions to aldimines or ketones.

Herein, we disclose catalytic enantioselective protocols for alkylations of three classes of ketoimines with dialkylzinc reagents (Scheme 1). The Zr-catalyzed processes deliver quaternary α-amino esters efficiently and in 79%–97% ee, require easily prepared substrates, and are promoted by ligands

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

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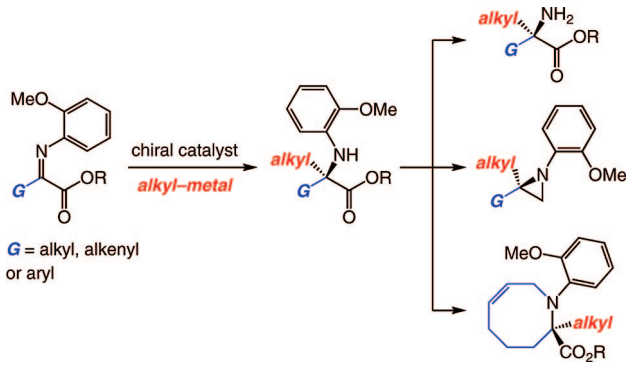
(5) For a recent review on catalytic enantioselective additions to ketoimines, see: Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888.

(6) For representative catalytic asymmetric additions of alkylmetal reagents to aldimines, see: (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (b) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055–12056. (c) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878. (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984–985. (e) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410. (f) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941. (g) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692–1693. (h) Boezio, A. A.; Pytkowicz, J.; Coté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260–14261. (i) Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, T. *J. Org. Chem.* **2003**, *68*, 9723–9727. (j) Coté, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6525–6528. (k) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979–981. (l) Basra, S.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 2659–2662. (m) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940–947.

10.1021/ja8001343 CCC: $40.75

Scheme 1. Catalytic Asymmetric Alkylation Reactions of α-Ketoimine Esters and Synthesis of Compounds with N-Substituted Quaternary Carbon Stereogenic Centers



with inexpensive amino acid components (valine and phenylalanine). As represented in Scheme 1, enantiomerically enriched products can be converted to useful, and otherwise difficult-to-access, acyclic or cyclic amines.

Catalytic enantioselective protocols for alkylations of ketoimines are uncommon; the only known example appeared only recently:[7] Charette and Lauzon reported that additions of Me_2Zn and Et_2Zn to trifluoromethyl keto-*N*-phosphinoylimines, promoted by a Cu complex of a chiral bisphosphine monoxide, result in the enantioselective formation of the derived amines (up to >98% ee). The efficiency of the protocols used for preparation of the ketoimine substrates, however, proved to be less than optimal: Ti-mediated generation of hemiaminal precursors from the trifluoromethyl ketones proceeds in 46–63% yield. It is important to note that, compared to that of aldimines, synthesis of ketoimines is generally less efficient; this is a complication that, due to competitive enamine formation, is exacerbated with substrates that carry an alkyl substituent. (Further discussion will be provided later.)

There are a limited number of catalytic methods for enantioselective transformations of ketoimines involving carbon-based nucleophiles.[8] Several catalysts for additions of HCN or TMSCN (Strecker reaction) have been mentioned in the literature.[9] Cu-catalyzed enantioselective reactions of allylboronates with ketoimines have been outlined as well.[10] There are two classes of Mannich-type additions,[11] and an Al-catalyzed asymmetric Reissert-type process involving TMSCN and 1-alkyl- and 1-aryl-substituted isoquinolines is worthy of note.[12] With only rare (and less enantioselective) exceptions,[11c] the reported investigations involve ketoimines that carry an aryl and a methyl substituent. In the few reported instances, alkyl-substituted substrates have proven to be less reactive, requiring the use of more active catalysts and/or altered conditions that result in lower enantioselectivity.[11] The preference for aryl-substituted substrates is likely because the size difference between an aryl and the smallest possible alkyl (a methyl) group is expected to maximize enantiotopic face differentiation. In one case, at the cost of limiting substrate generality, such complications are addressed through the use of ketoimines that are embedded within a rigid bicyclic structure.[11a,b]

Our focus on catalytic asymmetric alkylation (AA) reactions of α-ketoimine esters originates from the importance of α-quaternary amino acids.[2–4] A recent disclosure regarding Al-catalyzed additions of dialkylzinc reagents to α-ketoesters[13] and previous findings vis-à-vis the related Zr-catalyzed processes with aryl- and alkyl-substituted aldimines,[14] all reactions promoted by amino acid-based catalysts,[15] serve as the foundation for this study. The absence of an existing report on catalytic enantioselective additions to α-ketoimine esters provided further impetus for the investigations described herein.[16,17]

Results and Discussion

1. Catalytic Asymmetric Alkylation Reactions of Aryl-Substituted α-Ketoimine Esters. a. Catalytic AA Reactions with Me_2Zn. We first probed the possibility of utilizing **1**, a small peptide that consists of the inexpensive amino acids valine and phenylalanine, to promote the Zr-catalyzed AA reactions of α-ketoimine esters. The substrates initially examined differ in the identity of the alkoxy unit of the ester group. The four ketoimines selected for this preliminary study undergo reaction with high enantioselectivity (Table 1). All transformations proceed with minimal side product formation, indicated by the negligible differences between percent conversion and yields of isolated products (Table 1). The high enantioselectivity in reactions of alkyl esters **2a** and **3** (*E*:*Z* = 20:1, entries 1 and 2, Table 1), benzyl ester **4** (*E*:*Z* = 20:1, entry 3), and *tert*-butyl

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(14) (a) See ref 6d. (b) See ref 6e. (c) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244–4247. (d) Akullian, L. C.; Porter, J. R.; Traverse, J. F.; Snapper, M. L.; Hoveyda, A. H. *Adv. Synth. Catal.* **2005**, *347*, 417–425.
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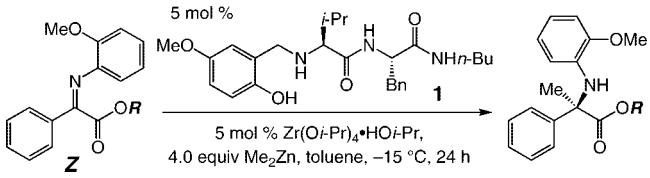
Table 1. Effect of Carboxylic Ester Structure on Zr-Catalyzed AA Reactions of α-Ketoimine Esters[a]



entry	R		*Z*:*E*[b]	conv (%)[c]	yield (%)[d]	ee (%)[e]
1	Me	**2a**	20:1	92	86	95
2	Et	**3**	20:1	81	71	96
3	Bn	**4**	20:1	91	78	96
4	*t*-Bu	**5**	5:1	36	34	94

[a] All reactions were performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of unpurified product mixtures (d_8-toluene). [c] Determined through analysis of 400 MHz ^{1}H NMR spectra of unpurified product mixtures (d_8-toluene). [d] Yields of products after purification. [e] Enantioselectivities were determined by chiral HPLC analysis; see Supporting Information for details.

ester **5** (*E*:*Z* = 5:1, entry 4), together with the uniform identity of the major product enantiomers and recovery of unreacted **5** with an identical *E*:*Z* ratio, suggest that the two isomers interconvert and one ketoimine might react preferentially (see below for the significance of this attribute to mechanistic models).

The facility of ketoimine isomerization is underlined by variations in ketoimine *E*:*Z* ratios that occur upon changing the solvent in which ^{1}H NMR spectra are recorded. For example, in chloroform, in contrast to the values measured in toluene and shown in Table 1, methyl ester **2a** exists as a 7:1 *Z*:*E* mixture of isomers. Examination of freshly prepared samples of *tert*-butyl ester **5** indicates a 10:1 *E*:*Z* ratio (isomerization occurs within 6–12 h). DFT calculations[18] suggest that the *Z* isomers are lower in energy for **2a** ($\Delta H \approx 1.8$ kcal/mol) and **5** ($\Delta H \approx 3.3$ kcal/mol); the most favored conformations of *Z* and *E* isomers of *tert*-butyl ester **5** are illustrated in Figures 1 and 2. It should be noted, however, that such calculations represent energies in the gas phase and coordination of the chiral catalyst to a ketoimine likely alters the identity of the preferred or reactive isomer, particularly since, as mentioned above, it is evident that such interconversions can occur readily.

A range of aryl-substituted α-ketoimine esters can be alkylated with high enantioselectivity (88–97% ee; Tables 2 and 3); α-quaternary amino esters are isolated in excellent yields after silica gel purification (91–98%; Tables 2 and 3). Substrates with a sterically hindered *ortho*-substituted aryl group, such as **2b** (entry 2, Table 2), **2d** (entry 4), and **2g** (entry 7), are efficiently alkylated. The higher catalyst loadings (10 mol % vs 5 mol %) indicated for entries 2, 4, and 7 point to transformations that are relatively sluggish and require higher temperatures (22 or 4 °C vs −15 °C) to proceed to complete (>98%) conversion. Product enantiopurity might suffer slightly due to adjustments in conditions so that maximum conversion is achieved. The relatively lower selectivities involve substrates that require elevated temperatures (88% and 91% ee with *o*-methoxyphenyl- and *o*-bromophenyl-substituted ketoimines **2d** and **2g** in entries 4 and 7, respectively). The stereochemical identity of products was established through X-ray crystallographic analyses for Br-containing quaternary α-amino esters **6g** and **6 h** (entries 7 and 8, Table 2), illustrated in Figure 3.

(18) All structures were minimized according to the following sequence. The promising conformers from conformer distributions, obtained with the PM3 semi-empirical method, were optimized at the B3LYP level of theory. Conformer distributions were calculated with the Spartan '04 suite. Final stationary points on the potential energy surface were calculated with the Gaussian 03.D02 suite. Electronic configurations of the molecular systems were described by 6–31G(d,p) double-ζ basis set on H, C, N, and O; the basis sets for N and O were augmented with a single *sp*-type and a single *d*-type diffuse functions as supplied by Gaussian 03.D02. All basis sets are as supplied by the Gaussian 03.D02 suite. The valley nature of stationary points was confirmed by frequency calculation at the same level of theory: (a) Spartan 04: Pople, J. A.; et al. *J. Comput. Chem.* **2000**, *21*, 1532–1548. (b) Gaussian 03.D02: Pople, J. A.; et al. *Gaussian 03*, revision D02; Gaussian, Inc.: Wallingford, CT, 2004. (c) 6-31G(d,p): Hehre, W. J.; Ditchfield, R.; Pople, J. A *J. Chem. Phys.* **1972**, *56*, 2257–2261.

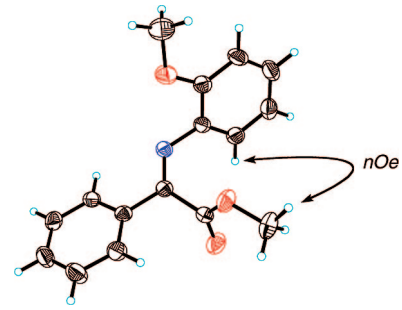


Figure 1. X-ray crystal structure of α-ketoimine ester **2a** and a key NOE.

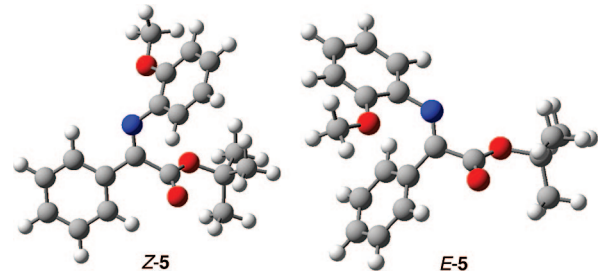
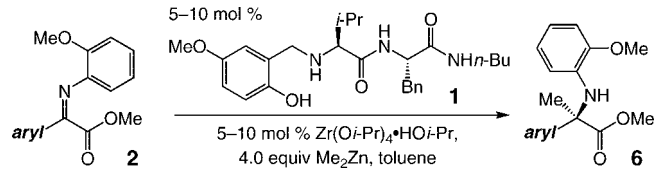


Figure 2. Calculated (DFT) minimized conformations of *E* and *Z* isomers of *tert*-butyl ester **5**.

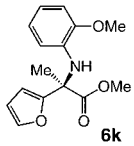
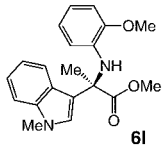
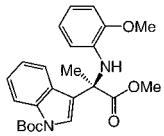
Table 2. Zr-Catalyzed AA Reactions of Aryl-Substituted α-Ketoimine Esters with Me_2Zn[a]



entry	aryl		mol % **1**	mol % Zr salt	temp (°C); time (h)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	C_6H_5	**a**	5	7	−15; 24	>98; 94	95
2	1-naphthyl	**b**	10	10	4; 48	>98; 91	92
3	2-naphthyl	**c**	5	7	−15; 24	>98; 98	96
4	*o*-$OMeC_6H_4$	**d**	10	10	22; 56	>98; 91	88
5	*p*-$OMeC_6H_4$	**e**	5	5	4; 24	>98; 95	96
6	*p*-$CF_3C_6H_4$	**f**	5	5	−15; 24	>98; 94	96
7	*o*-BrC_6H_4	**g**	10	10	4; 24	>98; 98	91
8	*p*-BrC_6H_4	**h**	5	5	−15; 24	>98; 98	95
9	*m*-ClC_6H_4	**i**	5	5	−15; 24	>98; 91	95
10	*p*-IC_6H_4	**j**	5	5	−15; 24	>98; 95	94

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

Table 3. Zr-Catalyzed AA Reactions of Heterocycle-Substituted α-Ketoimine Esters with Me_2Zn[a]

entry	product	mol % **1**	mol % Zr salt	temp (°C); time (h)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	 **6k**	5	5	4; 24	>98; 94	94
2	 **6l**	5	7	22; 48	>98; 98	91
3	 **6m**	5	5	−15; 24	>98; 93	97

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

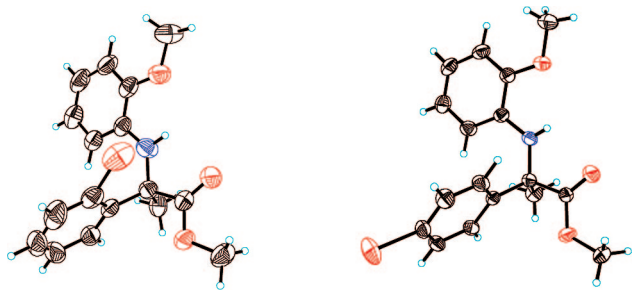
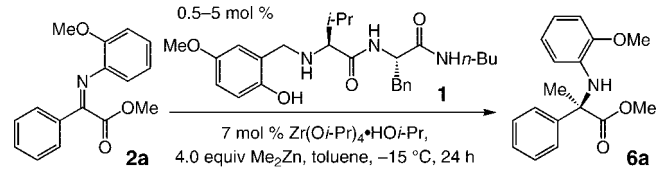


Figure 3. X-ray crystal structures of α-quaternary amino esters **6g** (left) and **6h** (right).

Comparison of the data in entries 5 and 6 of Table 2, involving reactions of substrates bearing a *p*-methoxy- and a *p*-trifluoromethylphenyl group, respectively, implies that an electron-withdrawing group is beneficial to the rate of enantioselective alkylation. Thus, reaction of ketoimine **2f**, containing the electron-withdrawing CF_3, proceeds to >98% conversion at −15 °C (24 h), whereas **2e**, carrying a methoxy group, must be alkylated at 4 °C (24 h). Similarly, catalytic alkylation of *ortho*-substituted **2g** (entry 7, Table 2) requires 10 mol % catalyst to proceed to >98% conversion (4 °C, 24 h). These findings demonstrate that increased substrate electrophilicity is critical to the rate of Zr-catalyzed AA and suggest that the addition of the alkylating agent to the sterically encumbered C═N bond of the ketoimine, a process that engenders substantial steric congestion, might be the turnover-limiting step.

Ketoimines with a heterocyclic substituent can be used; three examples are presented in Table 3. Furyl-substituted **6k** (entry 1, Table 3) and Me- and Boc-protected indoles **6l** and **6m** (entries 2 and 3, Table 3) are obtained in 93–98% yield and 91–97% ee. The lower reactivity exhibited in entry 2 (22 °C, 48 h) versus the process illustrated in entry 3 (−15 °C, 24 h) is consistent with the suggestion that faster reaction rates should be expected when the ketoimine substituent is electron-withdrawing.

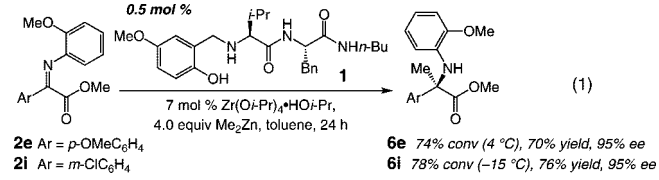
Table 4. Effect of Catalyst Loading on Zr-Catalyzed AA Reactions[a]



entry	mol % **1**	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	5	>98	94	95
2	2	>98	93	91
3	1	94	92	93
4	0.5	75	74	95

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

Several additional points merit mention: (1) Although the most efficient reactions are observed under the conditions shown in Tables 2 and 3, useful reactivity and enantioselectivity levels can be attained with lower amounts of the chiral ligand. Thus, as represented in Table 4 for the conversion of ketoimine **2a** to amine **6a**, in the presence of only 1 mol % **1** and 7 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr,[19] the desired product is obtained in 92% yield and 93% ee. Even with 0.5 mol % **1**, with the reaction proceeding to 75% conversion, **6a** is isolated in 74% yield and 95% ee. Two additional examples of transformations in the presence of 0.5 mol % of ligand **1** are provided in eq 1.

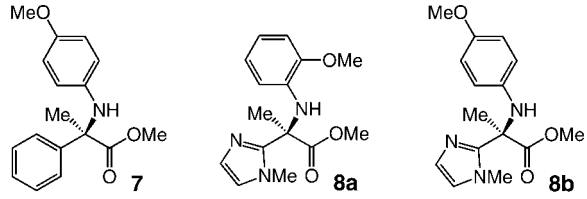


2e Ar = *p*-OMeC$_6$H$_4$ **6e** *74% conv (4 °C), 70% yield, 95% ee*
2i Ar = *m*-ClC$_6$H$_4$ **6i** *78% conv (−15 °C), 76% yield, 95% ee*

(2) The presence of the *o*-methoxy of the ketoimine's *N*-aryl group is required for high conversion and enantioselectivity. Thus, as shown in Scheme 2, amino ester **7** is obtained in <2% ee from the reaction of a *p*-anisidine imine; this alkylation proceeds only to 50% conversion under the same conditions that lead to complete transformation of **2a** to deliver **6a** in 94% yield and 95% ee (entry 1, Table 4). The presence of a competing *ortho*-chelating group, on the other hand, can diminish asymmetric induction, as illustrated in the case of *N*-methylimidazole-substituted amino ester **8a** (Scheme 2). As the formation of **8b** indicates (12% ee), in the absence of the methoxy group of *o*-anisidine, the heteroatom residing within the ketoimine substituent may not be able to provide a

(19) With 0.5 mol % of the chiral ligand, use of lower amounts of the Zr salt (<7 mol %) results in diminished reaction efficiency. Thus, with 1, 2, and 5 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr, under otherwise identical conditions, 27%, 34%, and 41% conversion to **6a** is observed, respectively. Similarly, when catalytic alkylation is performed in the presence of increased amounts of the transition metal salt, lower conversions are obtained (e.g., 33% and 26% conversion with 10 and 15 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr). It should be noted, however, that except for when 1–2 mol % of the Zr salt is used (87–88% ee), **6a** is obtained in 94–96% ee. The mechanistic implications of the above observations, which do not uniformly apply to all ketoimines, are not clear but might suggest that the identity (stoichiometry) of the active chiral complex is not comprised of a 1:1 combination of the Zr salt and the chiral ligand (see proposed predictive models in Figure 4).

Scheme 2. Effect of Chelating Heteroatoms on Zr-Catalyzed AA Reactions[a]



~50% conv, <2% ee >98% conv, 12% ee >98% conv, 12% ee

[a] Conditions: 5 mol % **1**, 5 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr, 4.0 equiv of Me_2Zn, 4 °C, 24 h.

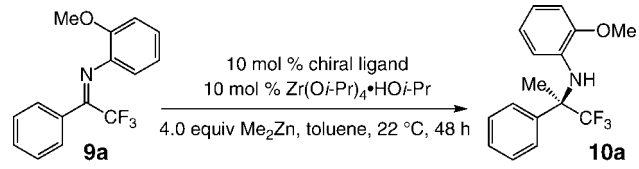
sufficiently effective chelate. Since furyl-substituted **6k** is obtained in 94% ee (entry 1, Table 3), however, it appears that the influence of a heteroatom-containing group depends on the nature of the neighboring Lewis base.

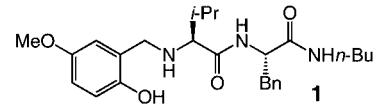
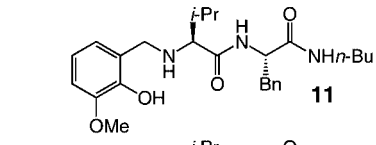
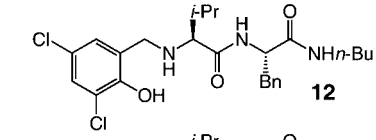
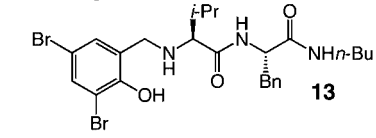
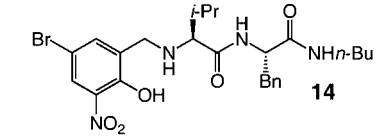
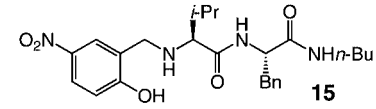
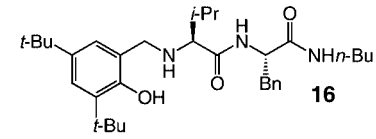
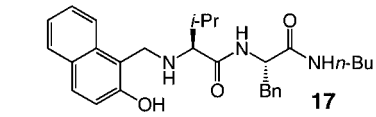
Next, we investigated whether the catalytic process can be used in reactions of another noteworthy (and the only previously reported[7]) class[20,21] of substrates: trifluoromethyl ketoimines. Our initial studies indicated that chiral ligand **1**, under the conditions that proved effective for transformations of α-ketoimine esters, promotes an enantioselective, albeit inefficient, alkylation. Thus, as shown in entry 1 of Table 5, subjection of ketoimine **9a** to the catalytic alkylation conditions described above leads to less than 20% conversion after 48 h at 22 °C, affording **10a** in 92% ee.

To address the above shortcoming, we probed the catalytic activity of a small selection of chiral ligands. We focused on modification of the *N*-terminus's aromatic moiety in order to retain an important advantage of the ligand class, namely, the inexpensive commercially available valine and phenylalanine amino acid components. The results of these studies are summarized in Table 5. The presence of an electron-withdrawing (and possibly chelating) group *ortho* to the hydroxyl unit gives rise to enhancement in enantioselectivity but causes little change in efficiency (ligand **11**, entry 2, Table 5). On the other hand, incorporation of halides at the C2 and C4 carbons of the aryl group leads to higher conversion; with chiral ligand **13** (entry 4, Table 5), bearing a dibromophenyl group at its *N*-terminus, 62% conversion is observed and the desired product is generated with improved enantiomeric purity (>98% ee). Modified ligands **14** (entry 5) and **15** (entry 6), containing the more electron-withdrawing nitro groups, prove to be more effective (vs **1**), but neither is superior to **13**. To determine whether the higher activity of **13** arises from steric factors, the catalytic AA reaction was performed with **16**[14c,d] (entry 7, Table 5), which proved optimal, affording 95% conversion to enantiomerically pure **10a** (>98% ee). The relative ineffectiveness of **17** (entry 8) suggests that the large group adjacent to the chelating hydroxyl unit might be crucial for higher catalyst activity.

Trifluoromethyl ketoimines are catalytically alkylated with high enantioselectivity (Table 6); products are obtained in 96

Table 5. Screening of Chiral Ligands for Catalytic AA Reactions of Trifluoromethylketoimines with Me_2Zn[a]



entry	ligand	conv (%)[b]	ee (%)[c]
1	 **1**	17	92
2	 **11**	18	98
3	 **12**	47	>98
4	 **13**	62	>98
5	 **14**	34	97
6	 **15**	55	98
7	 **16**	***95***	***>98***
8	 **17**	16	95

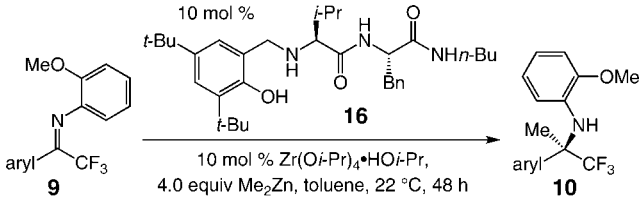
[a] All reactions performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra. [c] Enantioselectivities were determined by chiral HPLC analysis; see Supporting Information for details.

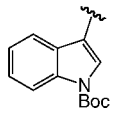
to >98% ee and 66–96% yield after purification. Catalytic alkylation of **9d** is performed at 40 °C to achieve 70% conversion after 48 h (entry 4, Table 6); tertiary amine **10d** is isolated in 66% yield and >98% ee after silica gel chromatography. In the case of **9e** (entry 5, Table 6), where diminished ketoimine electrophilicity is combined with the steric hindrance of an *o*-methoxy substituent, alkylation is not observed even at 60 °C (48 h). The significance of ketoimine electrophilicity to alkylation efficiency is consistent with observations regarding transformations of α-ketoimine esters (see Table 2 and related discussion). As illustrated in entry 6 of Table 6, trifluoroke-

(20) For an example of a medicinally relevant agent with a trifluoromethyl-substituted tertiary carbinol, see: (a) Pierce, M. E.; et al. *J. Org. Chem.* **1998**, *63*, 8536–8543. For a general discussion regarding the significance of F-containing molecules to modern medicine, see: (b) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.

(21) For catalytic asymmetric protocols that afford trifluoromethyl-substituted tertiary alcohols (in addition to ref 6), see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16. (b) Ma, J.-A.; Cahard, D *Chem. Rev.* **2004**, *104*, 6119–6146. (c) Tur, F.; Saà, J. M. *Org. Lett.* **2007**, *9*, 5079–5082. (d) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666–8669.

Table 6. Zr-Catalyzed AA Reactions of Trifluoromethylketoimines with Me_2Zn[a]



entry	aryl		conv (%)[b]	yield (%)[c]	ee (%)[d]
1	C_6H_5	**a**	95	93	>98
2	*p*-BrC_6H_4	**b**	94	92	>98
3	*p*-$CO_2MeC_6H_4$	**c**	74	70	96
4	*p*-$OMeC_6H_4$	**d**	70	66	>98[e]
5	*o*-$OMeC_6H_4$	**e**	<2	–	–
6		**f**	>98	96	98

[a] All reactions were performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of the unpurified product mixtures. [c] Yields of products after purification. [d] Enantioselectivities were determined by chiral HPLC analysis; see Supporting Information for details. [e] Reaction performed at 40 °C.

toimine **9f**, which bears a heterocyclic indole substituent, undergoes reaction to afford **10f** in 96% yield and 98% ee.

b. Catalytic AA Reactions with Et_2Zn. The higher reactivity of Et_2Zn (vs Me_2Zn) renders the corresponding alkylations more complicated, since the chiral catalyst must overcome particularly competitive noncatalytic alkylzinc additions. As the data summarized in entry 1 of Table 7 indicate, attempts at catalytic alkylation of α-ketoimine ester **2a** with Et_2Zn and ligand **1** delivered amino ester **21a** (93% ee; see Table 8). Only 50% of the product mixture, however, arises from 1,2-addition. Also present are 25% of *rac*-**22a** (G = H) and 25% of conjugate addition product *rac*-**23a** (G = H).[22] Control experiments indicate that formation of **22** and **23** is due to an uncatalyzed pathway that requires only the presence of Et_2Zn (Zr salt is not needed). [23] When the reaction is performed at −30 °C, in the hopes of improving selectivity, <10% conversion is observed.

We reasoned that the competitive conjugate addition pathway, if not the reduction process, might be rendered less favorable by electronic manipulation of the *N*-aryl substituent. Nonetheless, as shown in entries 2 and 3 of Table 7, the presence of an electron-donating methoxy (**18**; entry 2) or an electron-withdrawing nitro group (**19**; entry 3) does not lead to higher yields of the desired product **21a** (G = *p*-OMe and *p*-NO_2, respectively). With the substrate bearing a *p*-methoxy unit in entry 2 (**18**), an equal mixture of the three products is generated, suggesting that such an electronic alteration might reduce the rate of the desired alkylation by diminishing imine electrophilicity (see above for a discussion of the effect of electron-withdrawing aryl substituents). The presence of a *p*-nitro group in **19** (entry 3) leads to exclusive generation of the reduction product **22a** (G = *p*-NO_2). Finally, we reasoned that a more sterically demanding oxygen substituent within the *N*-aryl unit might discourage competitive conjugate addition (see **20**, entry 4, Table 7). This prediction was proven partly valid: <2% of **23b** is observed with *o*-phenoxyimine **20** as the substrate (Table 7); the presence of the larger phenoxy unit retards the rate of 1,2-alkylation, however, to render hydride addition more favorable, as 66% of the product mixture consists of secondary amine **22b**.[24]

The results from the studies involving Zr-catalyzed AA reactions of Et_2Zn and α-ketoimine esters are summarized in Table 8. The α-quaternary amino ester **21a**, easily separated from **22a** and **23a** through silica gel chromatography, is isolated in 48% yield and 93% ee.[25] Reaction of *p*-methoxyphenyl ketoimine (**21e**), shown in entry 2 of Table 8, is relatively sluggish (15 h vs 4 h for **2a**) but delivers a more favorable ratio of the α-quaternary amino ester versus the reduced and conjugate addition products (**21e**:**22e**:**23e** = 68:16:16); **21e** is obtained in 95% ee and 66% yield after purification. In contrast, when *p*-trifluoromethyl ketoimine **2f** serves as the substrate (entry 3, Table 8), only 4% of **21f** is obtained; the remainder of the mixture consists of the reduced (48%) and conjugate addition products (48%). It is plausible that, with the more electrophilic *p*-trifluoromethyl ketoimine, the rate of conjugate addition is sufficiently rapid that it does not allow for effective competition by the 1,2-addition pathway. The outcomes of the transformations illustrated in entries 4 and 5 of Table 8, involving Me- and Boc-protected indole-based ketoimines, are consistent with such a scenario. Alkylation of the slower-reacting *N*-methylindole (entry 4, Table 8) proceeds to >98% conversion in 56 h to afford the desired amino ester **21l** in 91% ee and 74% yield; 75% of the product mixture consists of the desired product, with only a total of 25% **22l** and **23l** formed. Alkylation of Boc-protected indole in entry 5 of Table 8 proceeds more readily (>98% conversion in 12 h); **21m**, formed in 96% ee and isolated in 52% yield, constitutes 56% of the mixture. With the more electrophilic imine, the uncatalyzed processes become more dominant, leading to the relatively lower yield of the quaternary α-amino ester **21m**.

2. Catalytic Asymmetric Alkylation Reactions of Alkyl-Substituted α-Ketoimine Esters. a. Synthesis of Alkyl-Substituted α-Ketoimine Esters. Removal of *o*-anisidyl groups requires oxidative procedures, an attribute that might be viewed as less attractive than imines bearing protecting/activating groups that are converted to unmasked amines upon subjection to hydrolytic conditions.[7] Arylimines used in this study, however, offer an important advantage: the electron-donating aryl unit stabilizes the C=N bond, allowing *alkyl*- as well as aryl-substituted substrates to be easily prepared and used in catalytic transformations.[26]

(22) For a related conjugate addition (non-asymmetric) involving Et_2AlCl, see: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720–3721.

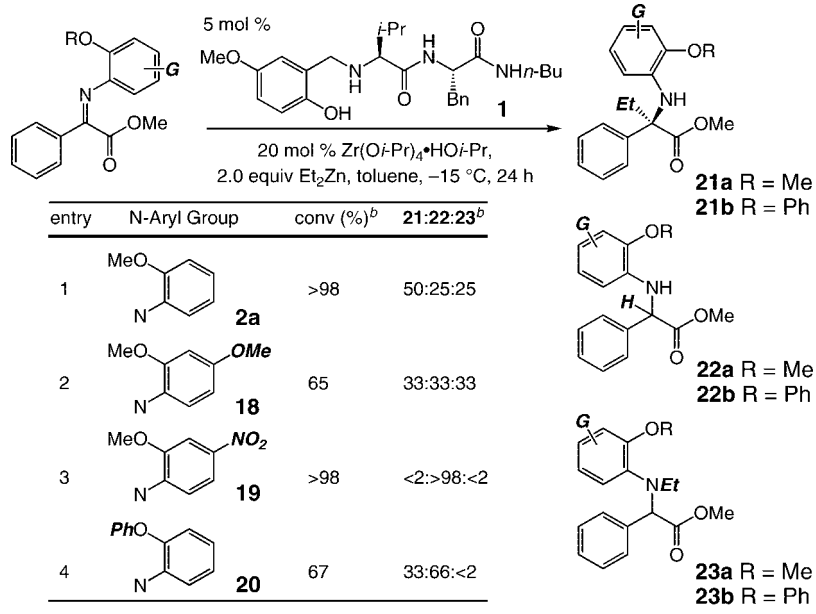
(23) Similar side products are observed, even in Ti-catalyzed reactions of the more reactive α-aldimine esters with Et_2Zn; see ref 6l .

(24) Extensive ligand screening studies did not lead to identification of a catalyst system that promotes alkylation with Et_2Zn with improved product selectivity. Furthermore, for transformation of **2a** to **21a**, slow addition of the dialkylzinc reagent (over 22 h), under otherwise identical conditions (Tables 7 and 8), results in only ~50% conversion and diminished enantioselectivity (82% ee vs 93% ee) without an improvement in product selectivity.

(25) Catalytic alkylations with lower amounts of the Zr salt lead to less favorable results. For example, when 5 mol % **1** and 10 mol % $Zr(Oi\text{-}Pr)_4 \cdot HOi\text{-}Pr$ (vs 20 mol %) are used, **21a**–**23a** are generated in nearly equal amounts. Increasing the amount of the chiral ligand is detrimental as well: with 10 mol % **1** and 10 mol % of the Zr salt, the reaction outcome is the same as mentioned above.

(26) (a) See ref 6e. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735.

Table 7. Effect of *N*-Aryl Group on Zr-Catalyzed AA Reactions with Et_2Zn[a]



entry	N-Aryl Group	conv (%)[b]	21:22:23[b]
1	**2a**	>98	50:25:25
2	**18**	65	33:33:33
3	**19**	>98	<2:>98:<2
4	**20**	67	33:66:<2

[a] All reactions performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of unpurified reaction mixtures.

High-yielding synthesis of ketoimines, particularly when gram-scale preparations are desired, can pose a challenge. Unlike that of aldimines, formation of ketoimines is typically slow, especially when parent ketones carry sterically hindered substituents. The route shown in Scheme 3, based on a recently reported procedure,[27] delivers aryl- as well as alkyl-substituted ketoimines in a practical and efficient manner. For example, the gram-scale synthesis of α-ketoimine ester **25a**, obtained in 86% overall yield, is accomplished in two straightforward steps from commercially available 2-methoxyaniline. Alkyl-substituted ketoimines such as **25a** are isolated in a high degree of purity through a simple aqueous wash (largely to remove trimethylphosphine oxide) but cannot be purified by silica gel chromatography. All α-ketoimine esters (alkyl- and aryl-substituted) can be stored at −30 °C for several months without significant hydrolysis or decomposition.

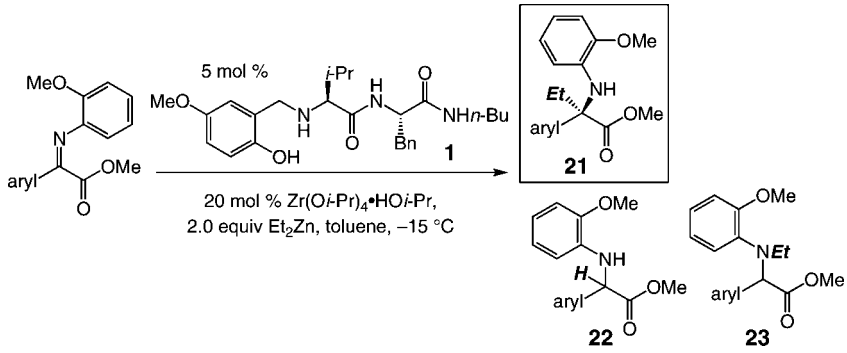
b. Identification of an Optimal Chiral Ligand. As the first step in examining catalytic enantioselective alkylations of alkyl-substituted ketoimines, we explored the effectiveness of the two chiral ligands identified as optimal in the above studies. α-Ketoimine ester **25a** was selected as the prototypical substrate, and its alkylation in the presence of Me_2Zn and various amounts of ligands **1** or **16** under different conditions was systematically probed (Table 9). As shown in entry 1 of Table 9, with 10 mol % **1** at 4 °C, catalytic AA proceeds to 93% conversion in 24 h to afford amine **26a** in 74% ee and 85% yield after purification. To improve selectivity, the reaction was performed at −15 °C (entry 2, Table 9), resulting in only 20% conversion to **26a**. When chiral ligand **16** is used under identical conditions at 4 °C (entry 3), alkylation proceeds to 93% conversion to afford **26a** in 85% yield and 93% ee. As the data in entries 4 and 5 of Table 9 indicate, when the Zr-catalyzed AA is carried out with 5 mol % catalyst loading (4 °C, 24 h), the desired product is still obtained in useful yields (69–73%) and in 92% ee. When 2 mol % of **16** is used (entry 6), however, there is 49% conversion after 24 h, and **26a** is isolated in only 31% yield (but still in 93% ee).

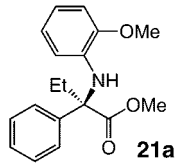
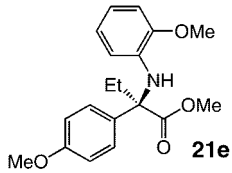
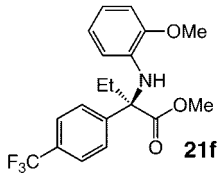
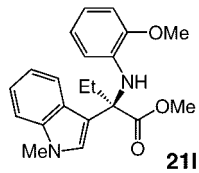
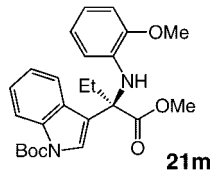
c. Zr-Catalyzed AA Reactions of Alkyl-Substituted α-Ketoimine Esters. A range of alkyl-substituted α-ketoimine esters undergo Zr-catalyzed AA with Me_2Zn (Table 10). Reactions of substrates bearing an *n*-alkyl group (entries 1–3, Table 10), as well as those that carry a substituent with a β branch (entry 4), proceed to >90% conversion within 24 h at 4 °C to afford α-quaternary amino esters in 86–93% ee and 52–85% yield after silica gel purification. Ketoimines that bear an α-branched alkyl group (entries 5 and 6, Table 10), on the other hand, are alkylated at a reduced rate; nonetheless, **26e** and **26f** are obtained in 82–83% ee. (See Scheme 6, below, for an additional example.) It should be noted that the yields of purified products shown in Table 10 correspond to a *two-step* process involving synthesis of the requisite ketoimine from *o*-methoxyphenylazide **24** (see Scheme 3) with a simple aqueous wash, followed by the catalytic AA reaction.

3. Practical Utility and Functionalization of α-Quaternary Amino Esters Obtained through Zr-Catalyzed AA Reactions. a. Zr-Catalyzed AA Carried Out on Gram Scale and Removal of the *N*-Aryl Group. The reactions developed through this study are promoted by a chiral ligand that can be readily prepared from two commercially available and inexpensive amino acids and salicyl aldehydes that benefit from the same attributes. Dipeptides **1** and **16** are prepared in four steps and ~60% overall yield without the need for silica gel chromatography; ligands are purified through a simple precipitation. Moreover, as the example in Scheme 4 illustrates, reactions can be performed on gram scale to obtain quaternary amino esters in high yield and enantiomeric purity. Through a simple precipitation procedure, the enantiomerically enriched products can be purified to >98% ee (Scheme 4), a useful property that may, at least partly, be due to the *N*-aryl unit. Perhaps the only

(27) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690–7696.

Table 8. Zr-Catalyzed AA of Aryl-Substituted α-Ketoimine Esters with Et_2Zn[a]



entry	desired product	time (h)	conv (%)[b]	**21**:**22**:**23**[b]	yield of **21** (%)[c]	ee of **21** (%)[d]
1	 **21a**	4	>98	50:25:25	48	93
2	 **21e**	15	>98	68:16:16	66	95
3	 **21f**	15	>98	4:48:48	nd	nd
4	 **21l**	56	>98	75:12.5:12.5	74	91
5	 **21m**	12	>98	56:22:22	52	96

[a] All reactions were performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of the unpurified product mixtures; conversion relates to the formation of all three products (**21**–**23**). [c] Yields of products after purification. [d] Enantioselectivities were determined by chiral HPLC analysis; see Supporting Information for details. nd = not determined.

aspect of the present protocol that is less economically attractive is the relatively high cost of dialkylzinc reagents. To address this issue, we show by the reaction in Scheme 4 that 1.5 equiv of Me_2Zn (in contrast to 4 equiv used in the studies detailed above) is sufficient for achieving high conversion.[28]

b. Enantioselective Synthesis of Allylic Amines, Amino Alcohols, and Aziridines Bearing an *N*-Substituted Quaternary Carbon Stereogenic Center. Some of the notable attributes of *o*-anisidine imines as electrophiles for enantioselective additions to aldimines and ketoimines were briefly discussed before. We have reported previously that *o*-anisidine groups can be removed oxidatively to afford the corresponding amines or related derivatives in 65–80% yield.[14] One possible complication is that, with quaternary amino esters, the increase in steric congestion at the nitrogen could result in significant diminution of the rates of oxidation reactions; these concerns arise from the accepted mechanism for such oxidations performed in the presence of $PhI(OAc)_2$, which is often the optimal oxidant.[29] In such transformations, it is likely that the reaction is initiated through displacement of an acetate group of the iodoacetate by the

(28) Attempts to prepare dialkylzinc reagents through reaction of the corresponding alkyllithium reagents with $ZnCl_2$ for in situ use in Zr-catalyzed AA reactions resulted in variable conversions and complete lack of enantioslectivity (<2% ee).

Scheme 3. Representative Synthesis of an α-Ketoimine Ester

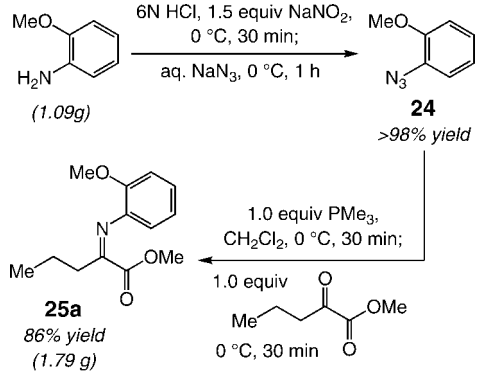
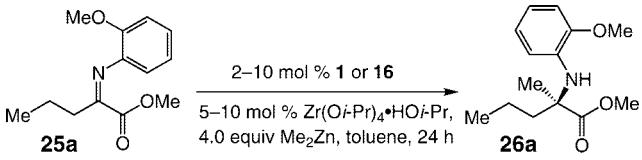


Table 9. Initial Screening Studies for Zr-Catalyzed AA Reactions of Alkyl-Substituted α-Ketoimine Esters with Me_2Zn[a]



entry	ligand; mol %	Zr salt; mol %	temp (°C); conv (%)[b]	yield (%)[c]	ee (%)[d]
1	**1**; 10	10	4; 93	85	74
2	**1**; 10	10	−15; 20		73
3	**16**; 10	10	4; 93	85	93
4	**16**; 5	10	4; 84	73	92
5	**16**; 5	5	4; 81	69	92
6	**16**; 2	10	4; 49	31	93

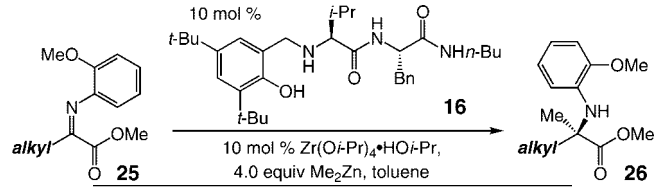
[a] All reactions were performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of the unpurified product mixtures. [c] Yields of products after purification. [d] Enantioselectivities were determined by chiral HPLC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

aniline nitrogen. As the examples in Scheme 5 illustrate, products from catalytic AA reaction involving an aryl- or an alkyl-substituted ketoimine can be converted to amines **27**–**29** in >70% yield after purification.

The catalytic protocols involving alkyl-substituted ketoimines allow for incorporation of functional groups that can be utilized, in conjunction with the nucleophilic amine of the product, toward synthesis of enantiomerically enriched *cyclic N*-containing molecules. Two examples are presented in Scheme 6. Alkylation of α-ketoimine ester **25g** and concomitant reaction of the resulting metal amide with the neighboring carboxylic ester leads to five-membered ring lactam **26g**, isolated in 63% yield after silica gel purification and in 79% ee. Synthesis of the allylamine derived from unsaturated amino ester **26b**, followed by catalytic ring-closing metathesis promoted by 2 mol % Ru carbene **30**,[30] furnishes azacene **31** in 81% overall yield (86% ee).

The carboxylic ester that resides within catalytic AA products offers opportunities for a variety of functionalization procedures; representative examples are shown in Scheme 7. The ester group can be cleanly reduced to afford the α-quaternary amino

Table 10. Zr-Catalyzed AA of Alkyl-Substituted α-Ketoimine Esters with Me_2Zn[a]



entry	product		temp (°C); time (h)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	*n*-Pr	**a**	4; 24	93; 85	93
2		**b**	4; 48	>98; 56	86
3[e]	Ph	**c**	4; 24	>98; 52	86
4	*i*-Bu	**d**	4; 24	94; 74	87
5[e]	*i*-Pr	**e**	22; 120	52; 38	82
6	Cy	**f**	22; 120	62; 58	83

[a] All reactions were performed under N_2 atmosphere; see Supporting Information for experimental details. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of the unpurified product mixtures. [c] Yields of products after purification. Yields are overall for two steps starting with aryl azide **24** and synthesis of ketoimine esters. [d] Enantioselectivities were determined by chiral HPLC analysis; see Supporting Information for details. [e] Reaction performed on the derived ethyl ester.

aldehyde in quantitative yield after treatment with DIBAL-H (e.g., **32**; <2% over-reduction). The corresponding α-quaternary amino alcohol (e.g., **34**) is obtained upon subjection of the AA product with LAH (>98% yield after purification). Amino aldehydes and alcohols may be used to access an assortment of *N*-containing molecules of high enantiomeric purity. Conversion to allylic amine **33** in 87% yield, which can be further manipulated by diastereoselective conjugate addition processes, and the three-step transformation to afford aziridine **35** in 74% overall yield (and 94% ee) are two illustrative cases. It should be noted that there are no existing catalytic asymmetric aziridination[31] protocols that can be used to access synthetically versatile small-ring heterocycles such as **35**.

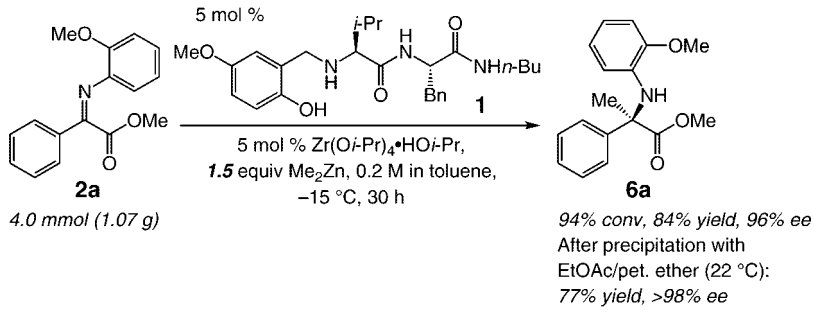
4. Mechanistic Working Models. The stereochemical outcome of the catalytic process may be predicted, as illustrated by complex **I** in Figure 4, through a reactive complex consistent

(29) (a) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 69136916. For an overview of the utility of hypervalent reagents in organic synthesis, see: (b) Kitamura, T.; Fujiwara, Y *Org. Prep. Proc.* **1997**, *29*, 409–458.

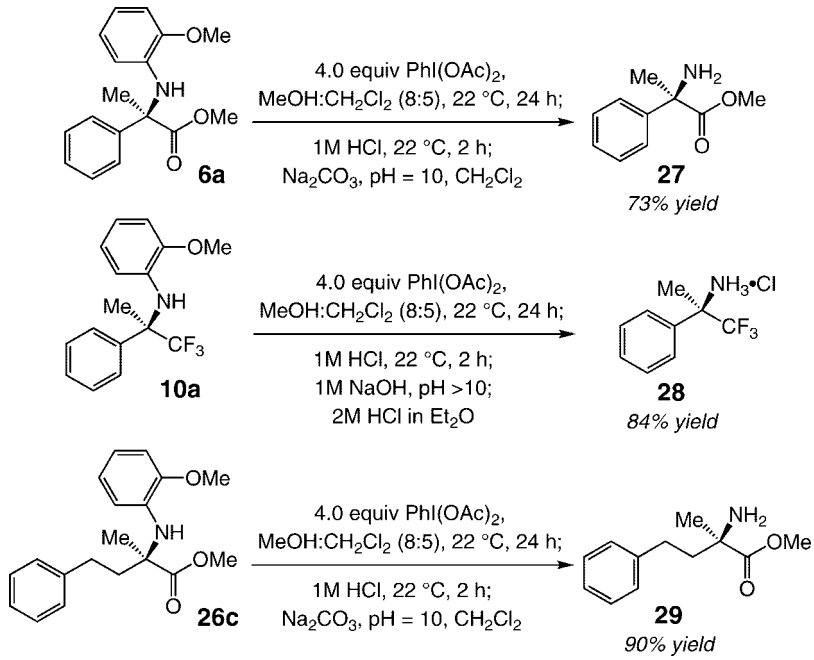
(30) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(31) For studies on catalytic asymmetric aziridination reactions, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327. (c) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631–4634. (d) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 354–355. (e) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. C.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917–5920. (f) Xu, J.; Ma, L.; Jiao, P. *Chem. Commun.* **2004**, 1616–1617. (g) Fioravanti, S.; Mascia, M. G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2004**, *60*, 8073–8077. (h) Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 3965–3968. (i) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987–8990. (j) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019–1026. (k) Ma, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2005**, *70*, 10155–10158. (l) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022–2028. (m) Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3718–3734. (n) Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 1571–1574. (o) Shen, Y.-M.; Zhao, M.-X.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005–8008. (p) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351–353.

Scheme 4. Zr-Catalyzed AA Reaction Performed on Gram Scale



Scheme 5. Synthesis of Unprotected Amine through Oxidative Removal of the *o*-Anisidine Group



with the previously reported mechanistic models put forth for reactions of this class of amino acid-based ligands.[32] The significance of the *o*-methoxy group of the *N*-activating unit, likely required for two-point binding with the transition metal, has been demonstrated by the data in Scheme 2. Previous studies have underlined the significance of the AA2 moiety (see Figure 4), resulting in a conformationally restricted peptide backbone that allows effective association of the *C*-terminus amide with the alkylzinc reagent.[32] Electron donation by association of the Lewis basic amide (or its deprotonated form) with the dialkylzinc reagent likely results in redistribution of electron density such that it leads to enhancement of the Zn center Lewis acidity[33] and increased alkylmetal nucleophilicity.[34] The stereogenic center at one amino acid unit (AA1) of the chiral ligand causes the ketoimine substrate to coordinate *anti* to its *i*-Pr group. As was suggested before, it is plausible that the amine group of the chiral ligand allows for the formation of a Zr−N bond, stabilizing a Lewis acidic cationic metal center, and resulting in a more favorable complex caused by the dissociation of a sterically demanding isopropoxide ligand. Coordination of the carboxylic ester unit of the α-ketoimine ester with the Zr center may provide additional transition-state organization, requiring reaction through the thermodynamically less favored *E* ketoimine stereoisomer (see Table 1). It has already been mentioned that ketoimine isomers can interconvert readily, and association with the chiral ligand may lead to alteration of the stereochemical preferences of the unbound substrate; it is therefore plausible that it is the less favored stereoisomer that serves as the active form of an α-ketoimine ester.[35]

A similar model can be proposed for reactions involving trifluoromethyl ketoimines (**II**, Figure 4). A noteworthy difference with the model proposed for reactions of α-ketoimine esters

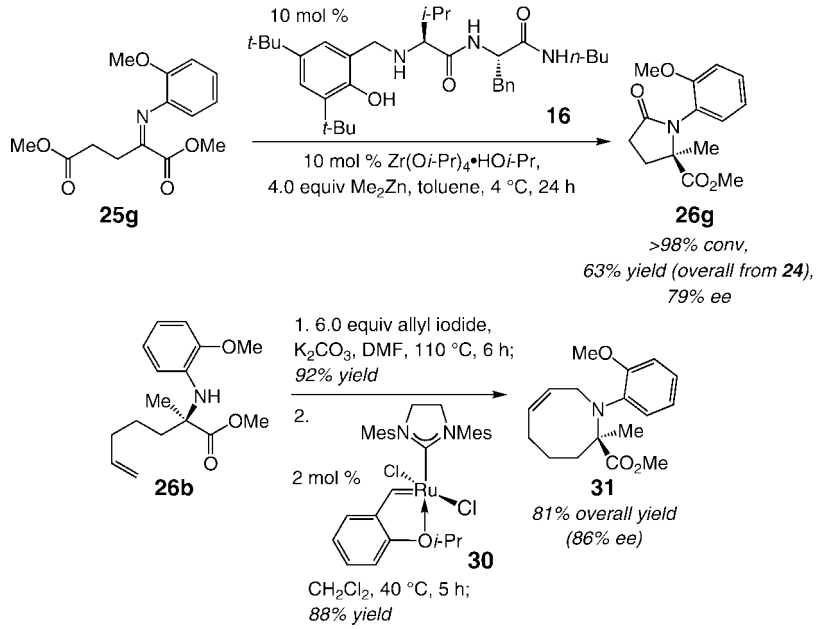
(32) For example, see: (a) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594–11599. (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233.

(33) Theoretical studies (HF and B3LYP level of theory) indicate 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* **2000**, *20*, 713–720.

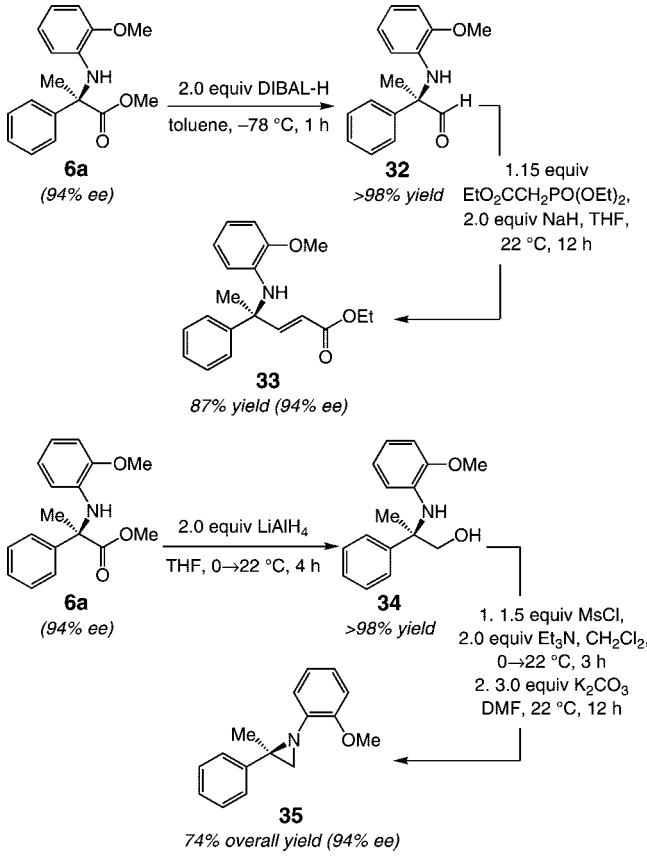
(34) Experimental and theoretical studies suggest that Lewis base coordination to a dialkylzinc reduces Zn−C bond order, increasing alkylmetal nucleophilicity. See: (a) Hursthouse, M. B.; Motevalli, M.; O'Brien, P.; Walsh, J. R.; Jones, A. C. *J. Mater. Chem.* **1991**, *1*, 139–140. (b) Haaland, A.; Green, J. C.; 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. For a general discussion, see: (c) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199–6200.

(35) In one instance, catalytic asymmetric additions of HCN to aldimines have been shown to proceed through the thermodynamically less favored *Z* substrate isomer: Vachal, P.; Jacobsen, E. N *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.

Scheme 6. Application to Synthesis of Enantiomerically Enriched N-Containing Heterocycles



Scheme 7. Reduction of Catalytic AA Products and Representative Functionalizations



(**I**) is the origin of preference for reaction through the ketoimine isomer shown. One possibility that can serve to organize the reactive complex in a way similar to that proposed for **I** involves chelation of a fluoride atom with the Lewis acidic Zr center. Indeed, F→Zr association,[36] including those involving a cationic metal center and a trifluoromethyl group,[36h] has been observed on a number of occasions in complexes characterized through X-ray crystallography.

Although the complexes shown in Figure 4 provide a rationale for the stereochemical outcomes of AA reactions, it should be noted that there are subtle issues that cannot be explained by such models. As an example, modes of addition represented by **I** and **II** do not offer an explanation as to why the identity of the *N*-terminus aromatic ring is different for the optimal ligand in reactions of trifluoromethylketoimines versus α-ketoimine esters. It is the unpredictable effect of such seemingly minor modifications that underlines the significance of the modular character of the present amino acid-based class of chiral catalysts.[15b]

Conclusions

We have developed the first catalytic protocol for enantioselective alkylations of α-ketoimine esters with dimethyl- and diethylzinc. Reactions proceed in the presence of as little as 0.5 mol % of a readily available chiral ligand. Catalytic alkylations afford a variety of α-quaternary amino esters with high enantioselectivity (from 79% up to >98% ee) and in yields that are often at useful levels (38%–98% after purification).

(36) (a) Catala, R. M.; Cruz-Garritz, D.; Hills, A.; Hughes, D. L.; Richards, R. L.; Sosa, P.; Torrens, H. *J. Chem. Soc., Chem. Commun.* **1987**, 261–262. (b) Siedle, A. R.; Newmark, R. A.; Lamanna, W. M. *Organometallics* **1993**, *12*, 1491–1492. (c) Memmler, H.; Walsh, K.; Gade, L. H.; Lauher, J. W. *Inorg. Chem.* **1995**, *34*, 4062–4068. (d) Temme, B.; Erker, G.; Karl, J.; Luftmann, H.; Fröhlich, R.; Kotila, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1755–1757. (e) Ruwwe, J.; Erker, G.; Fröhlich, R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 80–82. (f) Karl, J.; Erker, G.; Fröhlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 11165–11173. (g) Lancaster, S. J.; Thornton-Pett, M.; Dowson, D. M.; Bochmann, M. *Organometallics* **1998**, *17*, 3829–3831. (h) Benedikt, G. M.; Goodall, B. L.; Iyer, S.; McIntosh, L. H.; Mimna, R.; Rhodes, L. F. *Organometallics* **2001**, *20*, 2565–2569. (i) Hannig, F.; Fröhlich, R.; Bergander, K.; Erker, G.; Petersen, J. L. *Organometallics* **2004**, *23*, 4495–4502. (j) Bach, M. A.; Beweries, T.; BUrlakov, V. V.; Arndt, P.; Baumann, W.; Spannenberg, A.; Rosenthal, U. *Organometallics* **2005**, *24*, 5916–5918. For related reviews, see: (k) Kulawiec, R. J.; Crabtree, R. H. *Coord. Chem. Rev.* **1990**, *99*, 89–115. (l) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373–431. (m) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363–3384.

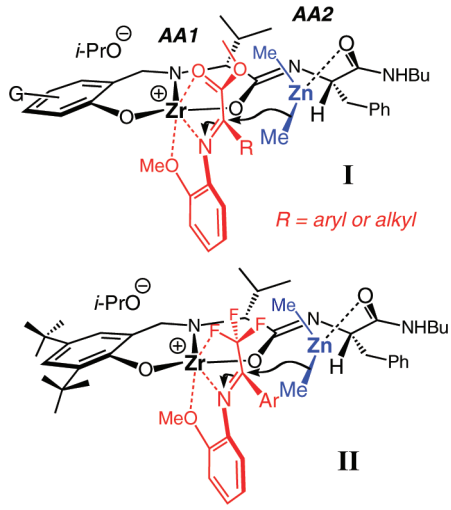


Figure 4. Proposed model for Zr-catalyzed AA reactions.

Among the positive attributes of the Zr-catalyzed protocol are the ease and efficiency with which the chiral ligand, consisiting of commercially available and inexpensive amino acids and salicyl aldehydes, and ketoimine substrates can be prepared on gram scale. That catalytic AA reactions can be carried out on alkyl- as well as aryl-substituted α-ketoimines is noteworthy; this characteristic arises from the stabilizing effects of the *o*-anisidyl imines, which are resistant to enolization (enamine formation) but are readily activated upon association with the Lewis acidic chiral Zr complex. Oxidative removal of the *N*-activating group is not adversely affected by a neighboring quaternary carbon center; the unprotected amine is obtained in >70% yield (after purification) through a one-pot procedure. The presence of a carboxylic ester within the enantiomerically enriched products provides opportunities for functionalization: enantiomerically enriched products are readily and efficiently converted to an assortment of useful compounds such as the derived lactams, azacenes, amino aldehydes, amino alcohols, and aziridines.

Although we have succeeded in securing advances on several fronts in the area of catalytic asymmetric ketoimine alkylations, the studies outlined herein raise a variety of questions that point to the need for substantial future investigations. Perhaps the most notable is that catalytic AA reactions are limited to transformations involving two dialkylzinc reagents; processes with longer-chain alkylmetals give rise to non-enantioselective reduction of the ketoimines. A chiral catalyst that effectively competes with such undesired pathways is needed in the same way that the presence of ligand **1** largely overcomes competitive imine reduction (see Table 8). Such a chiral catalyst would be especially attractive if reactions were to be promoted at minimal catalyst loadings (e.g., <2 mol %). The relatively high cost of dialkylzinc reagents is another issue that should be kept in mind. Efficient protocols that utilize more economically attractive alkylating agents, such as trialkylaluminum reagents, represent one possible attractive option.

Studies that address the above shortcomings in chiral ligand/catalyst design and methodology, as well as development of other catalytic enantioselective methods for additions of C-based nucleophiles to ketoimines and applications to synthesis of biologically relevant molecules, are the focus of ongoing investigations in these laboratories.

Acknowledgment. This work is dedicated to Professor T. Ross Kelly on the occasion of his 65th birthday. Financial support was provided by the NIH (Grant GM-57212). We thank Professor K. Mikami (Tokyo Institute of Technology) for providing us with physical data for enantiomerically pure **10a**. We are grateful to Mr. Adil R. Zhugralin (Boston College) for calculations and numerous helpful discussions. Dr. John Boylan provided us with invaluable support regarding NMR measurements, and Ms. Kyoko Mandai and Ms. Stephanie Ng (Boston College) provided assistance in connection with X-ray crystal structures. The X-ray facilities at Boston College are supported by Schering-Plough.

Supporting Information Available: Experimental procedures and spectral data for substrates and products (PDF); complete refs 18 and 20 (PDF); X-ray crystal data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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