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Catalytic Asymmetric Addition of Dialkylzinc Reagents to α-Aldiminoesters

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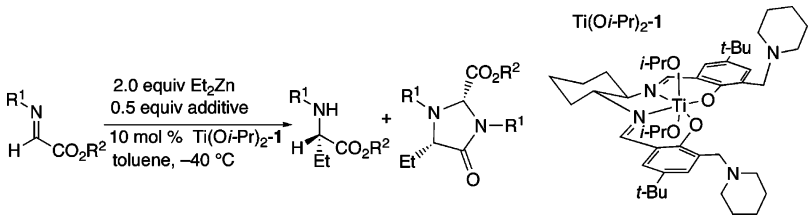
ABSTRACT



The first catalytic, enantioselective addition of organozinc reagents to α-aldiminoesters is described. The use of a Lewis acid/Lewis base containing bifunctional catalyst preorganizes both reactive substrates to promote enantioselective addition over the racemic background reaction and alternative addition modes. Alcohol additives were found to enhance the enantioselection. The addition product was also found to cyclize with remaining substrate to provide imidazolidines.

Optically active natural and non-natural amino acids are versatile building blocks for a range of biologically important molecules.[1] Enantioselective addition to α-iminoesters as a route to the synthesis of important chiral amino acids has been achieved[2] via the imino-ene reaction,[3] Friedel−Crafts reaction,[4] enol ether addition,[5] and enolizable ketone[6] and aldehyde[7] addition.

In comparison, the enantioselective addition of unstabilized anions to α-iminoesters, which provides entry to key congeners of α-amino acids, has not been reported. While related diastereomeric processes have been forthcoming,[8] the enantioselective processes have proven to be more difficult. To date, only enantioselective additions of stoichiometric allyl zinc reagents have appeared.[9]

On the other hand, the corresponding aldimine additions have met with greater success.[10] α-Iminoesters are significantly more challenging due to their higher reactivity and the presence of a bicoordinate metal binding site (Figure 1);

(1) For selected reviews on α-amino acid synthesis, see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989. (b) Hanessian, S.; McNaughton-Smith, G.; Lombardt, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (c) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(2) For reviews, see: (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102 and references therein.

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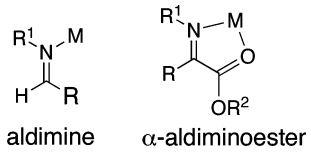


Figure 1. Metal binding to aldimines versus α-iminoesters.

both factors lead to substantial racemic background processes.

We have previously reported the enantioselective addition of Et_2Zn to α-ketoesters using salen-derived independent Lewis acid/Lewis base bifunctional catalysts.[11] In these systems, the electrophile coordinates to the Lewis acid, while the electronically decoupled Lewis base activates the nucleophile. These independent moieties facilitate enantioselective addition (Figure 2). Here we report the first enantio-

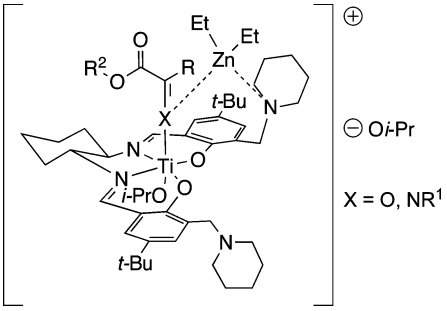


Figure 2. Proposed transition state.

selective addition of organozinc reagents to α-iminoesters using these bifunctional catalysts.

Our initial experiments showed that the addition of Et_2Zn to α-ketiminoesters (Figure 3, R ≠ H) proceeded with poor

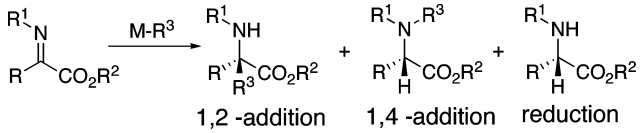
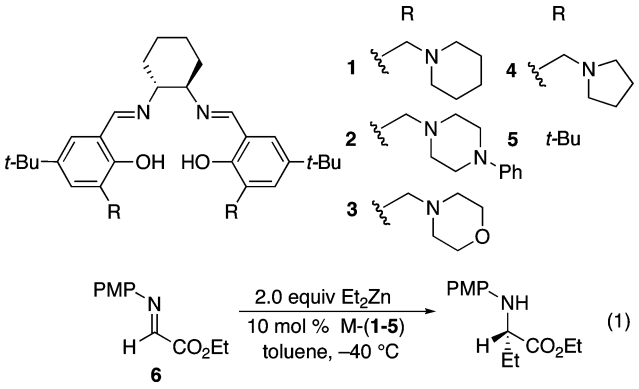


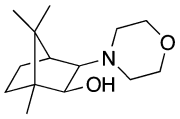
Figure 3. Regioselection and chemoselection in additions of organometallic reagents to α-iminoesters.

regioselectivity, yielding 1,2-addition, 1,4-addition, and reduction. A survey of prior work revealed similar regioselectivity problems. Mg-, Al-, and Cu-mediated alkylations have resulted in 1,4-additions, whereas Zn-mediated additions lead to mainly 1,2-additions (Figure 3).[12]

Upon screening aldiminoester substrates (Figure 3, R = H) against metal adducts of bifunctional salens **1**−**4**, we found that PMP (*para*-methoxyphenyl)-protected aldiminoester **6** gave only 1,2-addition (eq 1) and was chosen for further exploration. Pure **6** can be synthesized on a large scale by condensation of ethylglyoxylate and *para*-methoxyaniline and subsequent distillation.[13]



Importantly, treating **6** with Et_2Zn at −40 °C in the absence of catalyst led to the formation of significant racemic addition product within 2 h. Thus, these substrates are much more challenging than most aldehydes (no background reaction) and parallel the reactivity encountered with the α-ketoesters.[11] Thus, an effective catalyst for this process needs to (1) control the enantioselective addition of Et_2Zn to **6**, and (2) be more rapid than the background reaction. Conventional ligands used in the enantioselective addition of Et_2Zn to aldehydes, such as (−)-MIB,[14] are not effective, providing little product and no selectivity.



Gratifyingly, a screen with the bifunctional salen catalysts[11,15] revealed that regio- *and* enantioselective additions to this problematic substrate class are viable. A number of metals were investigated using the (*R*,*R*)-piperidine ligand (**1**) (Table 1, entries 1−4); Ti(O*i*-Pr)$_2$ was clearly superior and was used in the screening of other salens (**2**−**5**) (entries 5−8). Importantly, the ligand with a *t*-Bu group (**5**) exhibited practically no stereochemical control (Table 1, entry 8), confirming the need for a Lewis base moiety. Overall, the

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(12) (a) Chiev, K. P.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2205. (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415 and references therein. For Et_2AlCl additions, see: (c) Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720. (d) Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829.

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(14) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369.

(15) DiMauro, E. F.; Mamai, A.; Kozlowski, M. C. *Organometallics* **2003**, *22*, 850.

Table 1. Addition of Diethylzinc to α-Aldiminoester **6** (eq 1) Using Metal Complexes of Salens **1**−**5**

entry	ligand	metal	ee (%)[a]
1	**1**	Zn	28 (*S*)
2	**1**	Mg	57 (*S*)
3	**1**	Al(O*i*-Pr)	22 (*S*)
4	**1**	Ti(O*i*-Pr)$_2$	62 (*S*)
5	**2**	Ti(O*i*-Pr)$_2$	36 (*S*)
6	**3**	Ti(O*i*-Pr)$_2$	40 (*S*)
7	**4**	Ti(O*i*-Pr)$_2$	40 (*S*)
8	**5**	Ti(O*i*-Pr)$_2$	4 (*S*)

[a] Determined by HPLC (see Supporting Information).

Ti(O*i*-Pr)$_2$−(*R*,*R*)-piperidine salen catalyst provided the best metal−ligand combination (Table 1, entry 4).

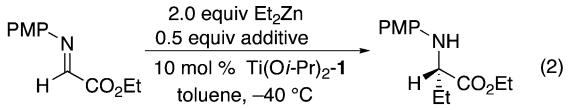
To improve the reaction, the effect of temperature on enantioselectivity (eq 1) was examined. The optimal temperature was −40 °C as a loss of selectivity was observed at both higher (−10 °C) and lower (−78 °C) temperatures. Upon increasing catalyst loading from 10 to 20 or 100 mol %, no selectivity improvements were observed. This key experiment indicates that none of the inherent selectivity (at 100 mol %) from the catalyst is lost under turnover conditions (10 mol %). A catalyst loading of 10 mol % at −40 °C was used in all further studies.

Additives have been reported to modulate catalytic activity and increase enantioselectivity in many transformations.[16] For the related case of Et_2Zn addition to α-ketoesters, we have shown that the use of excess Ti(O*i*-Pr)$_4$ leads to enhancement of enantioselectivity,[11c] and Hoveyda and coworkers have shown the benefit of $H_2NPO(OEt)_2$ addition.[17] Unfortunately, with α-aldiminoesters, the addition of either excess Ti(O*i*-Pr)$_4$ (Table 2, entry 2) or $H_2NPO(OEt)_2$ (Table 2, entry 3) resulted in reduced enantioselection. A range of other additives, including acids (Table 2, entry 4), amines (Table 2, entries 6−8), phenols (Table 2, entries 9−11), and alcohols (Table 2, entries 12−22), was then explored.

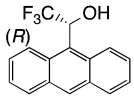
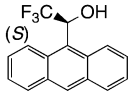
The temperature at which the additive was introduced proved crucial. In the case of CF_3CH_2OH, high enantioselectivities were achieved on addition at −40 °C (Table 2, entry 13). If the additive was introduced at room temperature, however, the enantioselectivity was drastically reduced to 7% ee. Apparently, the selective catalyst is not an equilibrated species, but rather a kinetic adduct.

Of all the additives investigated, alcohols with a pK_a range of 12−14[18] were superior (Table 2, entries 12 and 13) and were screened further (Table 2, entries 15−22). Matched and

Table 2. Effect of Additives on the Addition of Diethylzinc to α-Aldiminoester **6** (eq 2)



(2)

entry	additive	ee (%)[a]
1	none	64 (*S*)
2	Ti(O*i*-Pr)$_4$	3 (*S*)
3	$H_2NPO(OEt)_2$	58 (*S*)
4	$ClCH_2COOH$	13 (*S*)
5	H_2O	69 (*S*)
6	morpholine	44 (*S*)
7	Et_3N	64 (*S*)
8	pyridine	64 (*S*)
9	C_6H_5OH	60 (*S*)
10	*p*-$MeOC_6H_5OH$	62 (*S*)
11	*p*-$CF_3C_6H_5OH$	64 (*S*)
12	$C_6H_5CH_2OH$	70 (*S*)
13	CF_3CH_2OH	75 (*S*)
14	$(CF_3)_2CHOH$	29 (*S*)
15	(*R*,*R*)-BINOL	18 (*S*)
16	(*1R,2S,5R*)-menthol	57 (*S*)
17	L-(−)-borneol	56 (*S*)
18	D-(+)-borneol	48 (*S*)
19		69 (*S*)
20		69 (*S*)
21		80 (*S*)
22		55 (*S*)

[a] Determined by HPLC (see Supporting Information).

mismatched cases were observed with certain chiral alcohols (Table 2, entries 21 and 22). Apparently, a chiral alcohol with a relatively small aromatic substituent, as in (*R*)-trifluoromethyl benzyl alcohol, optimizes the stereochemical environment.

Once the selectivity screening was completed, the scope and yields were examined using the best catalyst combination: 10 mol % of Ti(O*i*-Pr)$_2$−(*R*,*R*)-piperidine salen at −40 °C with alcohols having a pK_a between 12 and 14 (Table 3). Upon purification of the 1,2-addition product, a dimer was also observed that likely arises from an intermolecular reaction of the initially formed amide anion with the starting material (Scheme 1). The *cis* stereochemistry of **8** was established by crystallographic analysis. The selectivity of **8** is comparable to that of **7**, suggesting that **8** is formed from **7**. Even so, monomeric adduct **7** was the predominant adduct and could be obtained with moderate to good yield and up to 80% ee (Table 3).

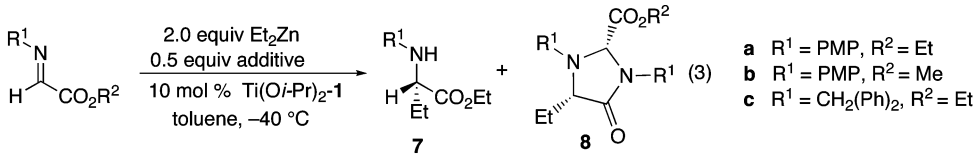
Modification of the α-iminoester substrate by changing from the ethyl ester to methyl ester had very little effect on

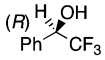
(16) For a review on additives in asymmetric catalysis, see: Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570.

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

(18) Additives of Table 3 entries 2−6: (a) Lide, D. R. Dissociation Constants of Organic Acids and Bases. In *Handbook of Chemistry and Physics*, 85th ed.; CRC Press: Boca Raton, FL, 2004−2005; Vol. 1. (b) *Advanced Chemistry Development (ACD/Labs) Software*, version 8.14 for Solaris; ACD/labs, 1994−2005; CA Registry File (Scifinder Scholar), CAS RN 75-89-8, 100-51-6, 98-85-1, 91-01-0 (accessed December 2005).

Table 3. Addition of Diethylzinc to α-Iminoester (eq 3): Substrate Scope

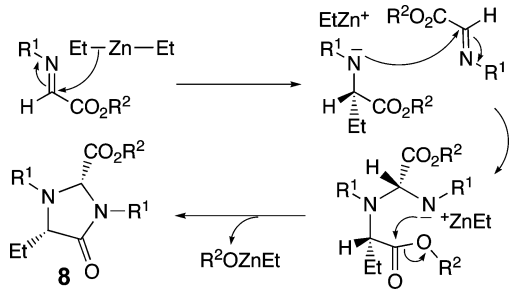


entry	R_1	R_2	additive	% ee **7**[a]	% ee **8**[a]	% yield **7**[b]	% yield **8**[b]	ratio **7**:**8**
1	PMP	Et	none	64 (*S*)	60 (2*S*, 5*S*)	50	11	4.5:1
2	PMP	Et	CF_3CH_2OH	75 (*S*)	70 (2*S*, 5*S*)	47	19	2.5:1
3	PMP	Et	$C_6H_5CH_2OH$	70 (*S*)	73 (2*S*, 5*S*)	46	7	6.8:1
4	PMP	Et		62 (*S*)	60 (2*S*, 5*S*)	55	5	11:1
5	PMP	Et		59 (*S*)	52 (2*S*, 5*S*)	59	14	4.2:1
6	PMP	Et		80 (*S*)	75 (2*S*, 5*S*)	63	6	10.5:1
7[c]	PMP	Et	none	64 (*R*)	66(2*R*, 5*R*)	44	10	2.3:1
8[c,d]	PMP	Et		78 (*R*)	80 (2*R*, 5*R*)	72	2	36:1
9	PMP	Me	none	71 (*S*)	70 (2*S*, 5*S*)	49	11	4.4:1
10	PMP	Me	CF_3CH_2OH	73 (*S*)	63 (2*S*, 5*S*)	19	35	1:1.8
11	PMP	Me	$C_6H_5CH_2OH$	71 (*S*)	73 (2*S*, 5*S*)	54	11	4.9:1
12	diphenylmethyl	Et	none	8 (*S*)	-	68	-	>100:1
13	diphenylmethyl	Et	CF_3CH_2OH	38 (*S*)	-	74	-	>100:1
14	diphenylmethyl	Et	$C_6H_5CH_2OH$	24 (*S*)	-	53	-	>100:1

[a] Determined by HPLC (see Supporting Information). [b] Isolated yields. [c] Ti(O*i*-Pr)$_2$-(*S*,*S*)-piperidine salen used. [d] 0.25 equiv of additive used.

the selectivity (Table 3, entries 9−11). It is interesting to note that the enantioselectivities for the methyl ester do not vary on addition of additive. When the *N*-PMP was replaced with *N*-diphenylmethyl, none of the cyclization product **8** was obtained. However, poorer enantioselectivities were observed (Table 3, entries 12−14), although use of additive did provide an increase in selectivity even in this system.

Scheme 1. Proposed Mechanism for the Formation of **8**



The first enantioselective addition of Et_2Zn to α-aldiminoesters has been reported. Independent bifunctional catalysts have been shown to facilitate this addition with moderate selectivity. The use of additives has also been shown to further enhance enantioselectivity under specific conditions. Alcohols with a pK_a of 12−14 were found to be most effective. A cyclized product was also obtained with complete diastereocontrol. Further results with organozinc reagents lacking β-hydrogens and with α-ketiminoesters are promising and will be reported in due course.

Acknowledgment. We are grateful to the NIH (GM 59945) and the GAANN program (M.W.F. fellowship) for financial support. We thank Carla Taylor for the synthesis of the substrate used in Table 3 (entries 12−14).

Supporting Information Available: Experimental details and characterization of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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