ORGANIC LETTERS

2002
Vol. 4, No. 22
3781−3784

The First Catalytic Asymmetric Addition of Dialkylzincs to α-Ketoesters

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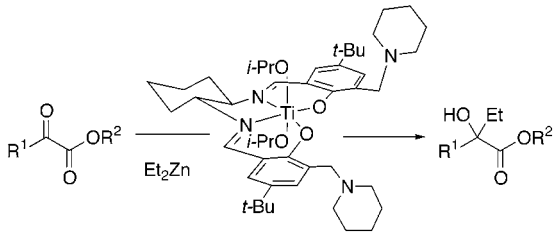
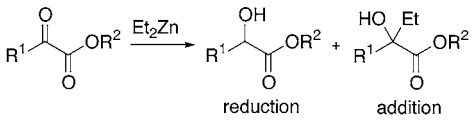
Received June 6, 2002

ABSTRACT



The first catalytic, enantioselective addition of organozinc reagents to α-ketoesters is described. Modular bifunctional salen catalysts that contain Lewis acid and Lewis base activating groups accelerate the carbonyl addition to a much greater extent than the competing carbonyl reduction. α-Hydroxyesters containing new quaternary stereogenic centers are obtained in high yield and moderate enantiomeric excess. Enrichment to 98% ee can be effected by recrystallization of the corresponding α-hydroxy acid.

α-Hydroxyesters arising from addition of organometallics to α-ketoesters (eq 1) contain stereogenic quaternary centers[1] and are versatile synthetic precursors.[2] Diastereoselective additions of organometallics to chiral α-ketoesters have been studied extensively.[3] The development of catalytic, enantioselective methods has lagged,[4] and current methods are limited to soft nucleophiles.[5] To the best of our knowledge, there are no reports of the catalytic enantioselective addition of alkyl groups to α-ketoesters.



(1)

Numerous catalysts have been reported for the related asymmetric addition of dialkylzincs to aldehydes,[6] but significant additional challenges arise for the asymmetric addition of organometallics to the much less reactive ketones. Despite the utility of the adducts, only three systems for the catalytic, enantioselective addition of alkyls to ketones have been reported.[7] We anticipated that α-ketoesters would display reactivity intermediate to that of aldehydes and ketones. Furthermore, the resultant α-alkyl-α-hydroxyesters are amenable to derivatization and are useful starting components for the synthesis of pharmaceutical agents and natural products.[2]

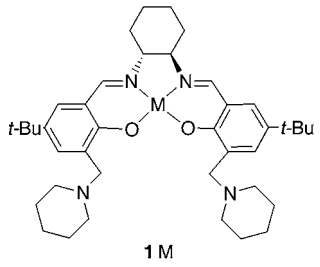
(1) For reviews of the enantioselective construction of quaternary centers, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460. (b) Corey, E. J.; Guzman-Peresz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597.

(2) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis;* VCH: Weinhein, Germany, 1997.

(3) (a) Sugimura, H.; Watanabe, T. *Synlett* **1994**, 175−177. (b) Tamai, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 439−445. (c) Akiyama, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447−450. (d) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802. (e) Boireau, G.; Deberly, A.; Loupy, A.; Monteux, D. *Tetrahedron Lett.* **1999**, *40*, 6919−6922. (f) Loupy, A.; Monteux, D. A. *Tetrahedron* **2002**, *58*, 1541−1549 and references therein.

(4) Methods that use ≥1 equiv of chiral ligand in the enantioselective alkylation of α-ketoesters have been developed, but few (see 4e) are synthetically useful. (a) Abenhaim, D.; Boireau, G.; Sabourault, B. *Tetrahedron Lett.* **1980**, *21*, 3043−3046. (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597−1606. (c) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128. (d) Zadel, G.; Breitmaier, E. *Chem. Ber.* **1994**, *127*, 1323−1326. (e) Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301−2308. (f) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711−713.

10.1021/ol026315w CCC: $22.00
Published on Web 10/09/2002



1 M

Figure 1.

For α-ketoesters, the development of an enantioselective alkylation, is complicated by competing reaction pathways. Two main products (reduction and addition) are encountered in the reaction with anionic organometallics containing a *β*-hydrogen (eq 1).[8] Thus, several factors must be considered in developing asymmetric catalysts for the reaction in eq 1. First, the catalyst must accelerate the addition reaction faster than the uncatalyzed, racemic addition or reduction. With ketones, this issue does not arise since there is no uncatalyzed reaction with Et_2Zn at room temperature. In contrast, the uncatalyzed reaction of Et_2Zn with α-ketoesters is fairly rapid since the substrate itself can act as a chelating ligand, thereby activating the Et_2Zn (Table 1, entries 1 and 2).[9] Second, the catalyst must accelerate addition to a greater degree than reduction. We found that the reduction pathway can be a major contributor in the addition of EtMgBr and Et_2Zn.[9] Bifunctional amino salen complexes developed in our laboratory[10,11] catalyze the addition of Et_2Zn to α-ketoesters with excellent chemoselectivity for the addition product (Table 1, entries 3−5).[9] In this communication, we discuss the degree of asymmetric induction that is conveyed by these catalysts as well as their scope and generality. This work represents the first asymmetric addition of alkyl nucleophiles to α-ketoesters using a catalytic amount of a chiral additive.

Table 1. Addition of Et_2Zn to $PhCOCO_2Et$ (eq 1: R^1 = Ph, R^2 = Et)[a]

	catalyst[b]	*T* (°C)	*t* (h)	reduction conversion (%)[c]	addition conversion (%)[c]	addition ee (%)[c]
1	none	0	24	86	11	
2	none	−40	2	45	23	
3	**1**·Zn	0	24	6	93	20 (*R*)
4	**1**·Mg	−40	2	0	99	34 (*R*)
5	**1**·Ti(O*i*-Pr)$_2$	−40	2	0	99	56 (*R*)

[a] Addition of 1.2 equiv of Et_2Zn with 10 mol % catalyst in $PhCH_3$. [b] Complexes with **1** were prepared by stirring with MR_2 (M = Zn, Mg) or $MY(Oi\text{-}Pr)_n$ (M = Ti, V, Al, Zr) for 1 h. For the *i*-PrO sources, the released *i*-PrOH was removed in vacuo and the catalyst was redissolved for the reaction. [c] Determined by chiral GC (Cyclodex b). Absolute configuration was assigned by comparison to the literature.

Utilizing the most reactive and selective Ti(O*i*-Pr)$_2$ salen catalyst as a starting point (Table 1, entry 5), we wished to assess how the three remaining salen components (diamine, pendant amine, and alkoxide) effect the reactivity and selectivity in the addition of Et_2Zn to ethyl oxo(phenyl)-acetate. The reactivity and selectivity of titanium morpholine catalysts containing other diamine backbones such as (*R*)-BINAM (18% reduction, 18% addition with 15% ee *S*) and (*S*,*S*)-1,2-diphenylethylenediamine (5% reduction, 39% addition with 38% ee *S*) were poor compared to those of the (*S*,*S*)-cyclohexanediamine analogue (Table 2, entry 3).

The pendant amine of these catalysts is crucial to the reactivity and selectivity, indicating that it may act as a Lewis basic activating group. For example, the Ti(O*i*-Pr)$_2$ complexes **2** and **3**, which contain similar pendant amines (piperidine, pyrrolidine), display comparable reactivity and selectivity (Figure 2, Table 2, entries 1 and 2). In contrast, analogue **4** containing the less basic morpholine is less reactive, while analogue **5** containing the sterically smaller dimethylamine is less selective (Table 2, entries 3 and 4).

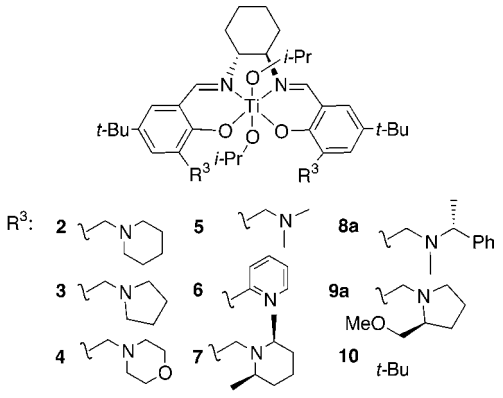


Figure 2.

(5) Mukaiyama aldol: (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. Isocyanoacetates: (b) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681−4684. Self-aldol: (c) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2000**, 2211−2212. [2 + 2]-Cycloaddition: (d) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125−2128. Hetero-Diels−Alder: (e) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231−6233. Friedel−Crafts: (f) Jensen, K. B.; Thorbauge, J.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163.

(6) For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911−922.

(7) Ph_2Zn: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. Me_2Zn and Et_2Zn: (b) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651−5666. (c) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971.

(8) For an example of this problem, see ref 3a. Diastereoselective additions to α-ketoesters are often limited to MeMgX and ArMgX which do not contain *β*-hydrogens (see ref 3b−d).

(9) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.*, in press. For example, EtMgBr + $PhCOCO_2Et$ at −10 °C gives 19% reduction and 60% addition.

(10) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053−3056.

(11) We had found that bifunctional Lewis acid−Lewis base salen catalysts were much more reactive compared to the Noyori DAIB catalysts (see ref 9). Under comparable conditions, these salen catalysts have among the fastest rates (catalytic in titanium) for the enantioselective addition of dialkylzincs to aldehydes. Separation of the Lewis acid and Lewis base sites in these salen catalysts, which is not possible in the DAIB-type catalyst, is proposed to account for these rate differences

Table 2. Addition of Et_2Zn to $PhCOCO_2Et$ Using Bifunctional Catalysts (eq 1: $R^1 = Ph$, $R^2 = Et$)[a]

entry	catalyst	reduction conversion (%)[c]	addition conversion (%)[c]	addition ee (%)[c]
1	**2**	0	99	56 (*R*)
2	**3**	3	94	54 (*R*)
3	**4**	9	72	54 (*R*)
4	**5**	0	91	44 (*R*)
5	**6**	0	91	57 (*R*)
6	**7**	10	84	20 (*S*)
7	**8a**	0	98	15 (*R*)
8	**8b**[b]	1	98	50 (*S*)
9	**9a**	3	76	12 (*R*)
10	**9b**[b]	6	66	3 (*S*)
11	**10**	20	56	4 (*S*)

[a] Addition of 1.2 equiv of Et_2Zn with 10 mol % catalyst. Reactions were in $PhCH_3$ at −40 °C for 2 h. [b] (1*S*,2*S*)-1,2-Cyclohexanediamine backbone. All other catalysts were generated from (1*R*,2*R*)-1,2-cyclohexanediamine. [c] Determined by chiral GC (Cyclodex β). Absolute configuration was assigned by comparison to the literature.

Salens containing structurally different pendant amines such as pyridine analogue **6** (Table 2, entry 5) can also provide results similar to piperidine analogue **2**. Catalysts containing more hindered amines such as 2,6-dimethylpiperidinyl **7** (Table 2, entry 6) are less reactive. Diastereomeric catalysts **8a** and **8b**, which contain chiral elements in the diamine backbone *and* the tethered amine Lewis base, were also examined (Table 2, entries 7 and 8). The two catalysts, which differ in the absolute configuration of the 1,2-cyclohexanediamine backbone, catalyze the addition with opposite facial selectivity, as expected. However, the different levels of stereoselection afforded by **8a** and **8b** indicate that the stereogenic centers of the amine portion also affect the transfer of asymmetry, providing further evidence for the direct involvement of the tertiary amine moieties. A double-stereodifferentiation effect was also seen with diastereomeric complexes **9a** and **9b** (Table 2, entries 9 and 10). The most reactive and chemoselective catalysts contain pendant amines that can effectively coordinate metal species (i.e., Et_2Zn). Overall, the data indicate that the pendant amine plays an important role in the reaction pathway. The lesser reactivity and chemoselectivity of the titanium complex of *tert*-butyl salen **10**, which lacks a pendant amine, (Table 2, entry 11) further support this proposal.

We propose that the mechanism entails the departure of an alkoxide ligand to provide a cationic Ti species (Figure 3).[12] If such a pathway is relevant, then the nature of the alkoxide ligands should not dramatically effect the selectivity, as the remaining alkoxide ligand in **2**·adduct is distal from the site of stereochemical induction. Indeed, similar results were obtained when $Ti(Ot\text{-}Bu)_4$ was used in place of $Ti(Oi\text{-}Pr)_4$ (Figure 4, Table 3, entry 1 vs 2). When a chiral Ti-alkoxide[13] is used to generate the salen complex, the influence of the alkoxide configuration on the enantioselectivity is relatively small (Table 3, entries 3−5 vs entry 1). Further support for a monomeric catalyst species is provided by a lack of nonlinear behavior (Figure 5).

The optimal catalyst (*R*,*R*)-**2** was used to study the reaction scope and was found to greatly accelerate the addition

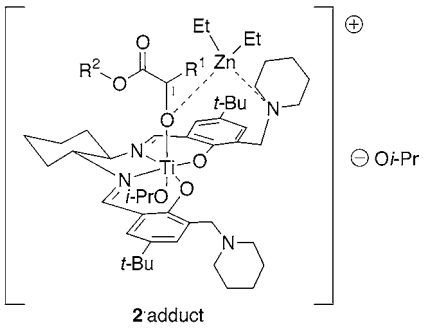


Figure 3.

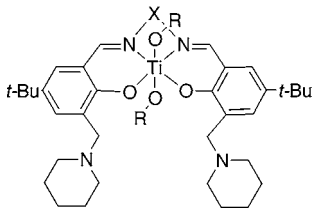
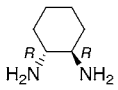
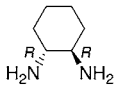
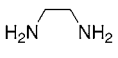
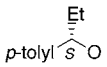
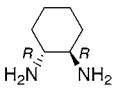
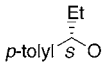
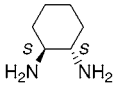
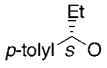


Figure 4.

Table 3. Addition of Et_2Zn to $PhCOCO_2Me$ Using $Ti(OR)_2$-Salen Catalysts (eq 1: $R^1 = Ph$, $R^2 = Me$)[a]

entry	catalyst H_2NXNH_2	catalyst RO	reduction conv. (%)[b]	addition conv. (%)[b]	addition ee (%)[b]
1		*i*-PrO	0	99	72 (*R*)
2		*t*-BuO	0	96	70 (*R*)
3			0	60	18 (*S*)
4			0	92	57 (*R*)
5			0	74	78 (*S*)

[a] Addition of 1.2 equiv of Et_2Zn with 10 mol % catalyst. Reactions were in $PhCH_3$ at −40 °C for 2 h. [b] Determined by chiral GC (Cyclodexβ).

(12) (a) Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron*, **1997**, *53*, 14327−14338. (b) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710−1740.

(13) We thank Prof. Patrick Walsh for a sample of titanium tetra[(*S*)-1-(4-methylphenyl)propoxide]: Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161−2164.

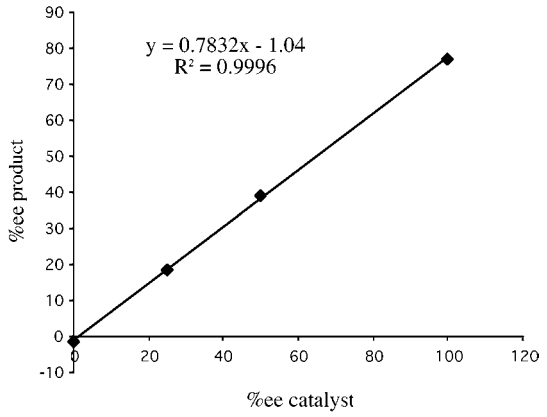


Figure 5. Linear relationship between catalyst enantiomeric excess and product enantiomeric excess (Et_2Zn + $PhCOCO_2Me$ using 10 mol % **2** at −78 °C for 2 h).

pathway in all cases (Table 4). The best enantioselectivity was obtained with smaller ester groups (i.e., Me, Table 4, entries 1−4). A variety of aryl ketones could be employed without significantly lowering the enantioselectivity (Table 4, entries 3 vs 7−10). Alkyl ketoesters (Table 4, entries 11−13) were less selective. Although results comparable to those of the aryl ketoesters (Table 4, entries 3 and 7−9) were seen with the *tert*-butyl ketoester (Table 4, entry 14), reduction (13%) became problematic with this hindered ketoester.

Importantly, this addition can be extended to other dialkylzincs without a significant drop in selectivity. For example, Me_2Zn gave 48% ee when it was employed in place of Et_2Zn (56% ee) for the reaction in entry 3 of Table 4. To demonstrate the efficacy of this catalyst, an addition was performed on a 5 mmol scale using 5 mol % (*R*,*R*)-**2** (Table 4, entry 5). The α-hydroxyester was isolated in 96% yield (0.92 g) with 78% ee. After ester hydrolysis, the corresponding α-hydroxy acid could be readily enriched to 98% ee by recrystallization (72% yield from the methyl ester).

Lewis acid−Lewis base salen complexes have been identified as effective catalysts for the addition of dialkylzincs to α-ketoesters. Further work is underway to investigate the mechanism of this reaction and to extend our collection of bifunctional catalysts to include more reactive and selective complexes.

Table 4. Addition of Et_2Zn to α-Ketoesters Using (*R*,*R*)-**2** (eq 1)[a]

entry	R^1	R^2	addition conversion (%)[c]	addition ee (%)[c]
1	Ph	*t*-Bu	99	30 (*R*)
2	Ph	Bn	99	48 (*R*)
3	Ph	Et	99 (92)	56 (*R*)
4	Ph	Me	99 (93)	72 (*R*)
5	Ph	Me	99 (96)	78 (98) (*R*)[c]
6	Ph	Me	96	74 (*R*)[d]
7	*p*-MeO−C_6H_4	Et	99	52 (*R*)
8	*p*-Br−C_6H_4	Et	96	42 (*R*)
9	*β*-naphthyl	Et	96	46 (*R*)
10	*o*-Me-C_6H_4	Et	67[e]	20 (*R*)
11	Me	Et	92	30 (*R*)
12	*i*-Pr	Et	98	30 (*R*)
13	Cy	Et	84	24 (*R*)
14	*t*-Bu	Et	57[f]	47 (*R*)
15	-$C(CH_3)_2CH_2^-$		100	26 (*R*)

[a] Addition of 1.2 equiv of Et_2Zn with 10 mol % catalyst. Reactions were in $PhCH_3$ at −40 °C for 2 h. [b] Determined by chiral GC (Cyclodex*β*) or HPLC (Chiracel AD). Isolated yields are in parentheses. Absolute configuration was assigned by comparison to the literature for entries 3 and 4. For all others, absolute configuration assigned by analogy. [c] 5 mol % catalyst, 5 mmol scale. The enantiomeric excess in parentheses was obtained after hydrolysis, recrystallization, and re-esterification. [d] Reaction at −78 °C for 2 h. [e] Conversion to reduction product = 7%. [f] Conversion to reduction product = 13%.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM59945), Merck Research Laboratories, and DuPont. E.F.D. thanks the University of Pennsylvania for an SAS Dissertation Fellowship. We thank Professors Patrick Walsh and Gary Molander for helpful discussions and use of GC instrumentation.

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

OL026315W