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Catalytic Asymmetric Addition of Dimethylzinc to α-Ketoesters, Using Mandelamides as Ligands

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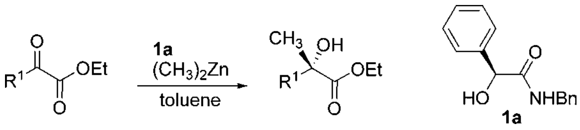
ABSTRACT



A strategy based on the control of the electron-donating capabilities of the coordinating groups of the ligand has been applied in the catalytic asymmetric addition of organometallic reagents to ketoesters. Mandelamides having deprotonated alcohol and carboxyamido groups catalyzed the addition of dimethylzinc to α-ketoesters with good yields and ee (up to 90%).

The catalytic enantioselective construction of stereogenic tetrasubstituted carbon centers is a very challenging goal in organic chemistry.[1] The addition of dialkylzinc reagents to ketones appears as an attractive procedure for this purpose since these organometallic reagents can be easily prepared and stored and are compatible with many functional groups. However, because of the low reactivity of these reagents toward the ketone carbonyl group the use of catalysts that strongly activate the carbonyl group or the organometallic reagent is required. So far, only a few systems that catalyze the addition of dialkylzinc reagents to simple ketones have been reported.[2]

On the other hand, the addition of carbon nucleophiles to α-ketoesters affords α-hydroxyesters containing stereogenic quaternary centers which are versatile synthetic precursors for natural products and medicinal agents.[3] Although diastereoselective additions of organometallics to chiral α-ketoesters with use of chiral auxiliaries have been studied extensively,[4] the number of catalytic enantioselective methods is scarce,[5] and most of the methods are limited to soft nucleophiles.[6] A serious issue that arises when considering the addition of dialkylzinc to α-ketoesters is the competing background addition. Unlike with aldehydes and ketones, the uncatalyzed reaction of Et_2Zn with α-ketoesters is fairly rapid since the substrate itself can act as a chelating ligand, thereby

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(1) For some recent examples on the catalytic enantioselective formation of quaternary stereogenic centers see: (a) Hird, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988−14989. (b) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584−4585. (c) Mauleon, P.; Carretero, J. P. *Chem. Commun.* **2005**, 4961−4963. (d) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749−760. (e) Mikami, K.; Yusa, Y.; Hatano, M.; Wakabayashi, K.; Aikawa, K. *Chem. Commun.* **2004**, 98−99.

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(6) See for instance: (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−689. (b) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211−2212. (c) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231−6233. (d) Jensen, K.; Thorbauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163. (e) Kwiatkowski, P.; Chaladaj, W.; Jurczak, J. *Tetrahedron Lett.* **2004**, 5343−5346.

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activating the alkylzinc reagent.[7] Therefore, the chiral catalyst must provide sufficient activity; otherwise, uncatalyzed and nonenantioselective background reaction may be detrimental to optical purity.

To date, only three methods for the enantioselective addition of dialkylzinc to ketoesteres have been reported. Kozlowski et al. have used titanium-salen type catalysts obtaining good yields of Et_2Zn addition products with fair enantioselectivities (up to 78%).[8] Shibashaki et al. have developed a system based on a proline-derived aminodiol. With this system high enantioselectivities can be attained (up to 96%) with the addition of Me_2Zn, although the reaction requires a slow addition of the reagent at low temperature (−20 °C) and long reaction times.[9] Et_2Zn was completely unreactive with this system.

In the two methods mentioned above, the background reaction is minimized by using bifunctional Lewis acid/Lewis base (LA/LB) catalysts (Figure 1), which unlike other bifunctional catalysts, bear electronically decoupled LA/LB sites.[10] These ligands provide activation of the substrate by a Lewis acid metal and independent Lewis base activation of the nucleophilic reagent by a heteroatom-containing moiety properly positioned on the ligand framework. This double activation results in the acceleration of the catalyzed reaction. Very recently, Hoveyda et al. have described an Al-catalyzed enantioselective method for the addition of dialkylzinc to α-ketoesters. Transformations are promoted in the presence of amino acid-based ligands to afford the products in high yields and in up to 93% ee.[11] In this case, the use of a LB additive leads to a significant improvement in efficiency and enantioselectivity by enhancing the nucleophilicity of the alkylzinc reagent.

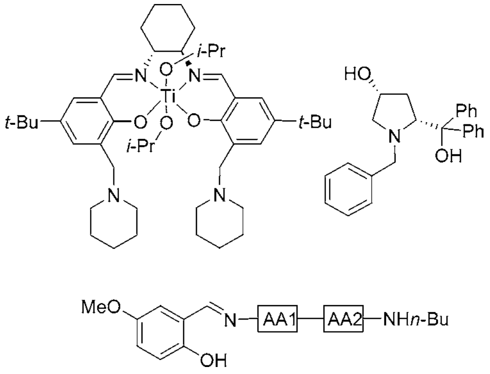

Figure 1. Catalysts used in the addition of dialkylzinc to α-ketoesters.

In this Letter we report a different strategy in the design of a catalytic system for this particular reaction, the addition of dimethylzinc to α-ketoesters. As starting models for our ligands we considered bifunctional amino alcohols bearing tertiary amines, which have been extensively used as catalysts for the enantioselective addition of dialkylzinc to aldehydes.[12] We envisioned that in the competition between the chiral ligand and the substrate to coordinate the zinc metal ion, the chiral ligand−Zn complex may be favored by increasing the electron-donating ability of the ligand, and this would favor the enantioselective reaction with respect to the competing nonenantioselective background "substrate-catalyzed" reaction. However, it also should be kept in mind that a too strong electron-donating coordinating group on the ligand may decrease the Lewis acidity of the metal center, therefore preventing coordination and activation of the carbonyl group. We thought that deprotonated *N*-monosubstiuted carboxy amides would serve perfectly for this purpose. Amide and carbamate type ligands have been used by Seto as catalysts for the enantioselective addition of dialkyl- and vinylzinc reagents to aldehydes.[13]

Simple mandelamides are easily prepared in one step starting from mandelic acid and amines. We have shown that these compounds can be used as ligands in the asymmetric addition of dialkylzinc to aldehydes catalyzed by titanium isopropoxide.[14] These compounds bear a hydroxyl group and a *N*-monosubstituted carboxyamide that may be deprotonated in the reaction media, and therefore fulfill the requirements stated above to be used as ligands for the addition to α-ketoesters.

The investigation started with the reaction between methyl (phenyl)oxoacetate **2** (R^1 = Ph, R^2 = Me) and dimethylzinc. As is shown in Table 1, all mandelamides **1a**−**e** were able to catalyze the reaction at acceptable rates and with moderate enantioselectivites. The fastest reaction was found with mandelamides derived from benzylamine **1a** and picolylamine **1c** (entries 1 and 4); amide **1a** gave the highest enantioselectivity under these conditions. The introduction of an additional methyl group in the vicinity of the amide (entries 2 and 3) or the use of *N*-*tert*-butyl amide had a deleterious effect, and the reaction required longer reaction times to reach completion, although the final yield and ee did not show big variations. On the other hand, the reaction with amino alcohol **1f** (entry 9) was not complete after 24 h and the product was obtained in only 15% ee, in good agreement with our expectations. The reaction catalyzed by **1a** was carried out at different temperatures. The results had little variation in the range between room temperature and −20 °C, except for the reaction times required. However,

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[10] Catalysts such as Zn-amino alcohols are LA/LB interdependent catalysts, since the LA is directly coordinate to the LB moiety.

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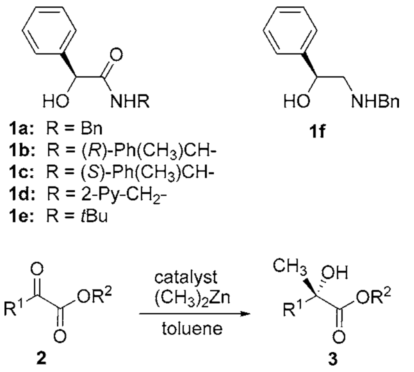
Table 1. Addition of Dimethylzinc to Methyl Oxo(phenyl)acetate **2** (R^1 = Ph, R^2 = Me) Catalyzed by Mandelamide[a]



entry	catalyst	T [°C]	t [h]	yield [%][b]	ee [%]
1	**1a**	0	5	80	65
2	**1b**	0	24	78	42
3	**1c**	0	23	78	49
4	**1d**	0	6	82	48
5	**1e**	0	22	75	54
6	**1a**	rt	1.5	78	62
7	**1a**	−20	20	78	64
8	**1a**	−40	40	74	47
9	**1f**	0	24	38[c]	15

[a] Me_2Zn: 6.0 equiv. Catalyst: 20 mol %. [b] Yields of isolated product after column chromatography. [c] Conversion determined by GLC

when the temperature was lowered to −40 °C, the reaction was not complete after 40 h and the ee dropped to 47%.

The influence of the ester group in the substrate was tested next (Table 2). The best results in terms of enantioselectivity were obtained with medium-sized esters, such as ethyl (Table 2, entry 2) and isopropyl (Table 2, entry 3). The small methyl and the very bulky *tert*-butyl esters gave lower ee (Table 2, entries 1 and 4, respectively). Therefore ethyl ketoesters were established as the best substrates for this reaction.

Table 2. Addition of Dimethylzinc to Ethyl Oxo(phenyl)acetate **2** (R^1 = Ph) Catalyzed by Mandelamide **1a** and Effects of the Ester Group and the Reagent Load[a]

entry	**2** [R^2]	Me_2Zn [equiv]	t [h]	yield [%][b]	ee [%]
1	Me	6	5	80	65
2	Et[c]	6	1.5	80	81
3	*i*-Pr	6	4.5	82	78
4	*t*-Bu	6	6	87	46
5	Et	6	2.5	71	75
6	Et	5	3.5	78	66
7	Et	3	24	44	66
8	Et	6	6 + 1[d]	85	74
9[e]	Et	6	2	97 [95][f]	74 [73]

[a] Catalyst **1a**: 20 mol %. 0 °C. [b] Yields of isolated product after column chromatography. [c] When 5 mol % of **1a** was used, the product was obtained in 71% yield and 75% ee. [d] Me_2Zn was added slowly over 6 h, and the reaction was continued for 1 h. [e] MeOH (or *i*-PrOH in brackets): 0.25 equiv was added after Me_2Zn. [f] Conversions determined by GLC.

Further study carried out with ethyl oxo(phenyl)acetate **2** (R^1 = Ph, R^2 = Et) involved variations in the load of catalyst and the number of equivalents of reagent. A reduction in the catalyst load to 5 mol % brought about a small drop in the yield (71%) and ee (75%). However, a small reduction in the number of equivalents of Me_2Zn from 6 to 5 caused a dramatic decrease in the enantiomeric excess from 81% to 66% (Table 2, entry 6). Further reduction of the number of equivalents of Me_2Zn to 3 did not caused a further effect in the enantioselectivity of the reaction (entry 7), although the yield of the reaction diminished to 44% because the reaction was not complete after 24 h. Since Shibashaki reported that the slow addition of the reagent and the use of protic additives increased the yield and enantioselectivity in the reaction catalyzed by a proline-derived amino alcohol, we tested these possibilities. However, the slow addition of 6 equiv of reagent over 6 h gave the expected product with 85% yield but lower ee (Table 2, entry 8). The use of MeOH or *i*-PrOH as additives did not improve the outcome of the reaction (Table 2, entry 9).

Substrate generality was then investigated under the optimized reaction conditions (Table 3). As is shown compound **1a** catalyzed the addition of dimethylzinc to α-ketoesters having aromatic and heteroaromatic substituents R^2 with good yields and ee from moderate (62%) to high (90%). In general, the reaction was complete in less than 6 h. Only the more hindered substrate ethyl (2-naphthyl)-oxoacetate (entry 8) required longer times. The presence of electron-donating groups increased the enantioselectivity of the reaction (entries 4−7), thus ethyl (4-methoxyphenyl)-oxoacetate (entry 5) gave the expected product in 82% yield and 90% ee. Remarkably, Shibashaki reported a low yield (42%) with similar enantioselectivity (92%) in the addition to methyl (4-methoxyphenyl)oxoacetate, while Hoveyda reported a lower yield (71%) and enantioselectivity (84%). The catalyst also catalyzed the reaction in ketoesters bearing an aliphatic substituent (entry 11) although with lower enantioselectivity.

Table 3. Addition of Dimethylzinc to Ethyl α-Ketoesters **2** (R^2 = Et) Catalyzed by Mandelamide **1a**[a]

entry	**2** [R^1]	t [h]	yield [%][b]	ee [%]
1	Ph	1.5	80	81
2	4-Cl-C_6H_4−	4	87	63
3	4-Me-C_6H_4−	3.5	82	81
4	4-MeO-C_6H_4−	2.5	82	90
5	3,4-(CH_2O_2)-C_6H_3−	4	87	84
6	3,4-$(MeO)_2$-C_6H_3−	4	82	85
7	3,4,5-$(MeO)_3$-C_6H_2−	6	83	78
8	*β*-naphthyl−	24	70	74
9	α-thiophenyl−	2	66	72
10	α-furanyl−	2.5	56	78
11	$PhCH_2CH_2$−	2	73	35

[a] Me_2Zn: 6.0 equiv. Catalyst **1a**: 20 mol %. 0 °C. [b] Yields refer to isolated product after column chromatography.

The stereochemistry of the newly formed stereogenic center in the resulting products was assigned to be *S* by comparison of the optical rotation of methyl 2-hydroxy-2-phenylpropanoate **3** ($R^1 = Ph$, $R^2 = Me$) with values reported in the literature[9] and the same configuration was assigned to the rest of the hydroxyesters under the assumption of a uniform mechanistic pathway. Although a detailed mechanistic discussion is difficult at present, the stereochemical course of the reaction may be rationalized in terms of the transition state outlined in Figure 2, which is similar to the transition state proposed for the addition of dialkylzinc to aldehydes catalyzed by amino alcohols.[15] We assume that the hydroxyamide ligand coordinates the metal through deprotonated hydroxy and carboxy amido groups.[16] Deprotonation of the amide hydrogen by dialkylzinc has been demonstrated by Seto, on the basis of ^{1}H NMR experiments.[13] Furthermore, deprotonation can take place even with weaker bases as has been shown in IR experiments by the significant shift of the carbonyl stretching band to lower frequencies in other related systems.[16b,17]

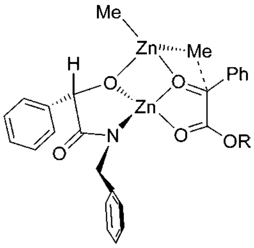


Figure 2. Proposed TS for the addition of dimethylzinc to α-hydroxy esters catalyzed by mandelamide **1a**.

In summary, we have developed a new enantioselective catalyst for the addition of dimethylzinc to α-ketoesters.[18] Our strategy is based on the control of the electron-donating capability of the coordinating groups of the catalyst. The yields are good and ee values obtained with our system are higher than those obtained with titanium-bifunctional salen catalysts and do not require the use of an additional Lewis acid. On the other hand, the yields and enantioselectivities are comparable to those obtained by Shibashaki with a bifunctional proline-derived amino alcohol. An advantage of our system is that the catalysts are easily prepared in a one-step procedure, and a modular design of the catalyst is possible by varying the starting hydroxy acid and amine (also, both enantiomers of the catalyst may be available from the corresponding mandelic acid enantiomer). Furthermore, the reaction times are short and no slow addition of the reagent is required, leading to simplified procedures. Studies toward clarifying the reaction mechanism, increasing the efficiency, and developing new addition reactions to ketoesters are underway.

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Supporting Information Available: General procedure for the catalytic asymmetric addition of dimethylzinc to α-ketoesters, characterization data, ^{1}H NMR and ^{13}C NMR spectra for compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In our case, we observed a shift from 1651 to 1573 cm^{-1} in the carbonyl stretching band of compound **1a** after treatment with Me_2Zn.

(18) Reaction of ethyl oxo(phenyl)acetate **2** ($R^1 = Ph$) with Et_2Zn under our conditions yielded the corresponding racemic reduction product.