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Asymmetric Addition of Dimethylzinc to α-Ketoesters Catalyzed by (−)-MITH

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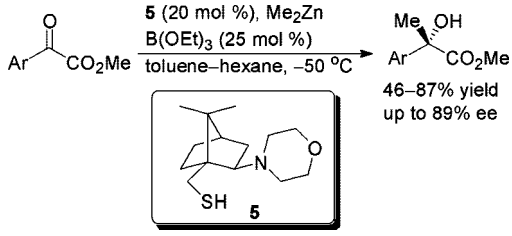

This investigation describes the catalytic asymmetric addition of dimethylzinc to α-ketoesters in the presence of (−)-MITH (**5**) and triethyl borate as an additive to give the corresponding chiral α-hydroxy esters with good yields and high enantioselectivities.

Catalytic asymmetric carbon−carbon bond-forming reactions are important in the synthesis of natural products and active pharmaceutical compounds. Enantioselective addition of organozincs to carbonyl compounds, one of the most powerful methods for constructing chiral carbon−carbon bonds, has been widely studied. The enantio-enriched alcohols thus obtained are valuable building blocks and intermediates. However, since ketones are less reactive than aldehydes, the development of chiral ligands for the asymmetric addition of organozinc reagents to aldehydes is more popular than that to simple ketones.[1] Recently, effective ligand systems have been reported to catalyze the asymmetric addition of organozinc reagents to ketones;[2] they exhibited levels of reactivity and enantioselectivity similar to those of aldehydes. This method is an effective tool for constructing tetrasubstituted chiral centers but still raises a tremendous interest for synthetic chemists.

α-Hydroxy esters that contain quaternary stereogenic centers, which are synthesized by the addition of nucleophiles to

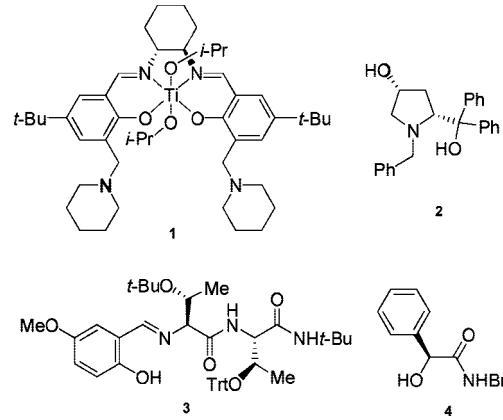

FIGURE 1. Catalysts of catalytic addition of dialkylzinc to α-ketoesters.

α-ketoesters, are important precursors in synthetic organic chemistry because they can be further functionalized to complex and biologically active molecules. The optically active α-hydroxy esters can be prepared by the diastereoselective addition of organometallic reagents to α-ketoesters with the employment of chiral auxiliaries.[3] Only a few catalytic enantioselective methods have been developed for such a purpose.[4] Unlike aldehydes and ketones, α-ketoesters can act as chelating agents: alkylzinc reagents are self-activated, so that the rapid background reaction of alkylzincs with α-ketoester proceeds without enantioselection. A method that is based on the bifunctional titanium−salen catalyst **1**[4a,b] effects the catalytic asymmetric Et_2Zn addition to α-ketoesters (Figure 1). This approach was recently applied as a key step in constructing the quaternary chiral center in the synthesis of (*S*)-camptothecin.[5] A chiral prolinol derivative **2**[4c] was developed to promote the asymmetric addition of Me_2Zn to α-ketoesters, providing the corresponding α-hydroxy esters with up to 96% ee. These two ligand systems exploit the concept of bifunctional catalysts, in which the substrate is activated by a Lewis acid metal center and the alkylzinc reagent is independently activated by a Lewis base center in a cooperative manner; therefore, the reaction was accelerated through the dual activation of both a substrate and a nucleophile. The enantioselective Al-catalyzed transformation of Me_2Zn and Et_2Zn to α-ketoesters in the presence of an amino acid-based ligand **3**[4d] has been reported to afford the product in high yields and ee's. Recently, mandelamide **4**[4e] was utilized in the addition of Me_2Zn to α-ketoesters to generate good yields

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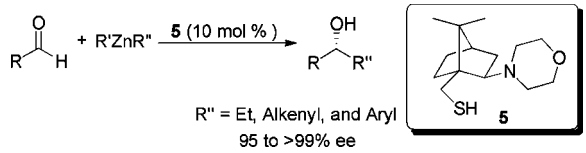
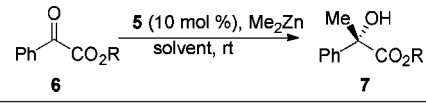


FIGURE 2. Asymmetric addition of organozincs to aldehydes catalyzed by ligand **5**.

TABLE 1. Asymmetric Addition of Me_2Zn to α-Ketoesters 6 Catalyzed by Ligand 5



entry		R	Me_2Zn (equiv)	solvent	time (h)		yield of **7**[a] (%)	ee[b] (%)
1	**6a**	Me	1.5	toluene	23	**7a**	52	22
2			3	toluene	23		75	29
3			6	toluene	12		80	32
4			6	hexane	5		99	37
5	**6b**	Et	6	hexane	5	**7b**	92	36
6	**6c**	*i*-Pr	6	hexane	7	**7c**	88	24
7	**6d**	*t*-Bu	6	hexane	5	**7d**	87	31
8[c]	**6a**	Me	6	hexane	24	**7a**	85	52
9[d]			6	hexane	65		78	61

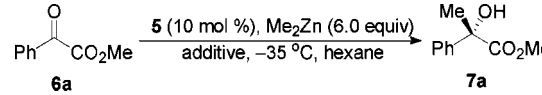
[a] Isolated yields after column chromatography. [b] Determination by chiral HPLC. [c] Reaction was conducted at −20 °C. [d] Reaction was conducted at −35 °C.

and ees, based on the concept of the control of electron-donating capabilities of the coordinating groups.

As part of our early endeavors to develop camphor-derived chiral ligands for use in catalytic asymmetric reactions,[6] (−)-2-*exo*-morpholinoisobornane-10-thiol (**5**)[7] ((−)-MITH), has been demonstrated to be an effective promoter of the asymmetric addition of Et_2Zn, alkenylzinc,[7a] and arylzinc[7b] reagents to aldehydes, affording the corresponding optically active alcohols with excellent enantioselectivities (95 to >99% ee) (Figure 2). In principle, the employment of ligand **5** for the asymmetric addition of Me_2Zn to α-ketoesters is anticipated to exhibit a level of asymmetric induction that is comparable to that of aldehydes. This work presents findings concerning the asymmetric addition of Me_2Zn to α-ketoesters catalyzed by ligand **5**.

Our study started with the addition of Me_2Zn to methyl benzoyl formate **6a** in the presence of 10 mol % of ligand **5** at 0 °C using toluene as a solvent. The reaction gave the corresponding product **7a** with 52% yield and 22% ee when 1.5 equiv of Me_2Zn was employed after 23 h (Table 1, entry 1). When the amount of Me_2Zn was increased to 6 equiv, the ee of **7a** was increased to 32% (entry 3). A better chemical yield and enantioselectivity were obtained when hexane was used as a reaction medium (entry 4), and notably, the reaction in toluene required a longer reaction time than that conducted in hexane (entries 3 and 4). Subsequently, α-ketoesters with diverse ester functional groups, including ethyl **6b**, isopropyl **6c**, and *tert*-butyl **6d**, were examined under the above-mentioned reaction conditions (entries 5−7). The corresponding products **7c**,**d** were obtained with lower yields and enantioselectivities

TABLE 2. Effects of Additives on Asymmetric Addition of Me_2Zn to α-Ketoester



entry	additive	time (h)	yield[a] (%)	ee[b] (%)
1[c]	10% D*i*MPEG	45	18	27
2	25% IPA	20	65	59
3	10% $B(OMe)_3$	20	75	62
4	25% $B(OMe)_3$	20	90	71
5	50% $B(OMe)_3$	20	74	63
6	100% $B(OMe)_3$	20	78	60
7	200% $B(OMe)_3$	20	79	51
8	25% $B(OEt)_3$	20	97	73
9	25% $B(O\textit{i}\text{-Pr})_3$	20	92	71
10	25% $B(O\textit{t}\text{-Bu})_3$	20	90	66
11	25% $B(OPh)_3$	20	38	15

[a] Isolated yields after column chromatography. [b] Determination by chiral HPLC. [c] Reaction was conducted in toluene.

when the ketoesters had bulkier ester substituents (entries 6 and 7). The enantioselectivity was improved (up to 61% ee) when the reaction was carried out at −35 °C as the reaction time increased (entry 9).

Whether additives enhance the level of enantioselectivity was examined. D*i*MPEG[8] and 2-propanol[2b,4c] are reportedly effective additives in parallel reactions and were tested first (Table 2, entries 1 and 2). The addition of these additives did not improve the reaction in terms of yields and enantioselectivities. Interestingly, the reaction rate increased when 10 mol % of $B(OMe)_3$[9] was added, giving the corresponding product **7a** with similar yield and ee as obtained without additives (Table 2, entry 3 vs Table 1, entry 9). The yield and enantioselectivity of **7a** depended on the amount of $B(OMe)_3$ and an optimal result of up to 90% yield and 71% ee was obtained in the presence of 25% $B(OMe)_3$ (entry 4). Increasing the amount of additive reduced enantioselectivities (entries 5−7). Next, various commercially available borates were studied (entries 8−11), and in the presence of 25% $B(OEt)_3$, the reaction gave **7a** with improved yield (97%) and ee (73%) (entry 8).

Higher asymmetric induction was anticipated when the reaction was conducted at a temperature lower than −35 °C. In the presence of 25 mol % of $B(OEt)_3$, the addition of Me_2Zn to α-ketoester **6a** catalyzed by 10 mol % of ligand **5** at −50 °C yielded compound **7a** with 74% ee (Table 3, entry 1). The reaction, using 20 mol % of ligand **5**, gave compound **7a** in a better yield and ee (entry 2). No improvement in the enantioselectivity was observed when the reaction was conducted at −65 °C (entry 3); at −80 °C, the yield of the product was less than 5% (entry 4). The slow addition (24 h) of compound **6a** was investigated to diminish the competitive self-catalyzed background reaction of substrate and Me_2Zn. The product **7a** was obtained in 81% ee and 85% yield (entry 5), giving results similar to those obtained without the slow addition of the starting material (entry 2).

To elucidate substrate generality, various α-ketoesters **8** were subjected to the reaction conditions described in Table 3, entry 2. The ee of the corresponding product obtained from an

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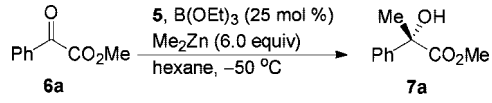
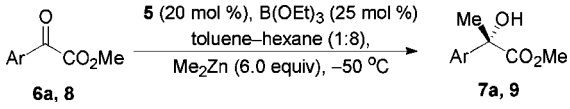
TABLE 3. Optimization of Reaction Conditions



entry	**5** (mol %)	time (h)	yield[a] (%)	ee[b] (%)
1	10	26	83	74
2	20	22	85	79
3[c]	20	68	43	75
4[d]	20	92	<5	-[e]
5[f]	20	(24 + 20)	85	81

[a] Isolated yields after column chromatography. [b] Determination by chiral HPLC. [c] Reaction was conducted at −65 °C. [d] Reaction was conducted at −80 °C. [e] Not determined. [f] Toluene solution of compound **6a** was introduced within 24 h.

TABLE 4. Asymmetric Addition of Me_2Zn to Various α-Ketoesters



entry[a]		Ar	time (h)		yield[b] (%)	ee[c] (%)
1	**6a**	Ph	22	**7a**	85	79
2	**8a**	4-Me-Ph	24	**9a**	84	85
3	**8b**	3-Me-Ph	27	**9b**	76	84
4	**8c**	2-Me-Ph	72	**9c**	46[d]	76
5	**8d**	4-MeO-Ph	96	**9d**	54[e]	89
6	**8e**	4-Cl-Ph	41	**9e**	79	59
7	**8f**	4-Br-Ph	22	**9f**	52[f]	55
8	**8g**	4-CF_3-Ph	12	**9g**	71	16
9	**8h**	2-furyl	96	**9h**	82	75
10	**8i**	2-thienyl	18	**9i**	87	85
11	**8j**	2-naphthyl	23	**9j**	70	82
12	**8k**	$PhCH_2CH_2$	24	**9k**	83	19

[a] In entries 2−11, α-ketoesters were added as a mixture with toluene. [b] Isolated yields after column chromatography. [c] Determination by chiral HPLC. [d] **8c** was recovered in 25% yield. [e] **8d** was recovered in 32% yield. [f] **8f** was recovered in 18% yield.

α-ketoester bearing *ortho*-substituted benzene ring (Table 4, entry 4) is lower than those obtained from *meta*- or *para*-substituted ones (entries 2 and 3). The reaction depends on the electronic nature of the substituent; high ee's were obtained with aromatic ketoesters that bore electron-donating groups (entries 1−5), while addition to those with electron-withdrawing groups gave moderate ee's (entries 6−8). Heteroaromatic α-ketoesters are good reaction partners, and the corresponding products were isolated in good yields and ee's (entries 9 and 10). An aliphatic α-ketoester was also examined, though with lower asymmetic induction (entry 12).

To understand the mechanism and the role of additive in the catalytic reaction, investigations of nonlinear effect[10] with and without the additive were conducted.[11] As shown in Figure 3, positive nonlinear effects were observed in the reactions with and without additives, suggesting that a dimeric species exists in the catalytic reaction. It is conceivable that the presence of $B(OEt)_3$ is favorable to the turnover of the active complex, which facilitates the whole catalytic cycle and thus enhances the reaction rate.

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(11) For detailed reaction conditions, see the Supporting Information.

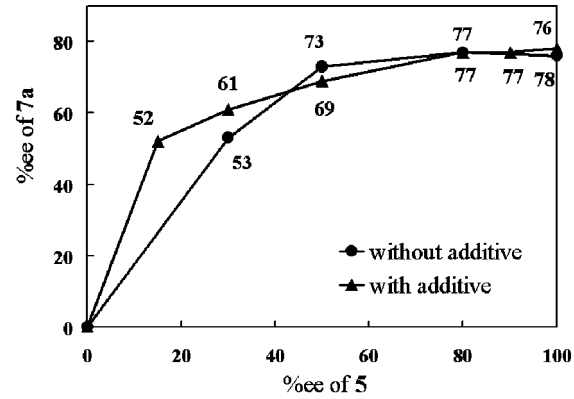

FIGURE 3. Correlation, with and without the additive, of ee between adduct and ligand **5** using 0.73 M Me_2Zn, 0.12 M $PhCOCO_2Me$, and 20% of ligand **5** in hexane at −35 °C.

In conclusion, the application of ligand **5** for the catalytic asymmetric addition of Me_2Zn to α-ketoesters using $B(OEt)_3$ as an additive is described. Notably, the adduct **9d** obtained from the reaction of methyl 4-methoxylbenzoyl formate (**8d**) was isolated with up to 89% ee and 54% yield. Good to moderate ee's and yields of the corresponding product were normally obtained. This result is comparable to those obtained using bifunctional prolinol **2** and activated mandelamide derivative **4**. The advantages of this methodology are that ligand **5** can be employed to prepare tetrasubstituted α-hydroxyl esters with good enantioselectivities without the modification of its parent structure, and both enantiomers are easily prepared. Studies of nonlinear effect with and without $B(OEt)_3$ exhibited positive nonlinearity. The role of additive, $B(OEt)_3$, in this reaction and the studies concerning the asymmetric addition of various dialkylzinc reagents to α-ketoesters catalyzed by ligand **5** are currently under investigation.

Experimental Section

Representative Experimental Procedures of (−)-MITH Catalyzed Asymmetric Methylation to α-Ketoesters. To a flame-dried flask containing (−)-MITH (25.5 mg, 0.1 mmol) was added dimethylzinc solution (3.0 mmol, 0.73 M in hexane). After the mixture was stirred at room temperature for 10 min, triethyl borate (21 μL, 0.125 mmol) was added. The mixture was kept at room temperature for another 5 min before it was cooled to −50 °C. After 10 min, methyl benzoylformate (71 μL, 0.5 mmol) was added to the mixture, and the mixture was stirred at −50 °C for another 22 h. Saturated $NH_4Cl_{(aq)}$ (3 mL) was added to stop the reaction, and the mixture was acidified with 1 N $HCl_{(aq)}$ (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated to give a light yellow oil, which was purified through column chromatography (ethyl acetate/hexanes = 1:6) to yield a colorless oil (77 mg, 85%). Chiral HPLC analysis (Chiralcel OD-H, 2-propanol/hexane (2:98), 0.5 mL/min flow rate, uv 254 nm) showed 79% ee.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support.

Supporting Information Available: Experimental procedures and spectroscopic data of the addition products, including ^1H NMR spectra and HPLC chromatographs. This material is available free of charge via the Internet at http://pubs.acs.org.

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