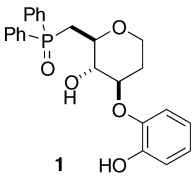
Asymmetric Alkylation of Ketones

Multicenter Strategy for the Development of Catalytic Enantioselective Nucleophilic Alkylation of Ketones: Me_2Zn Addition to α-Ketoesters**

*Ken Funabashi, Markus Jachmann, Motomu Kanai, and Masakatsu Shibasaki**

The catalytic construction of stereogenic tetrasubstituted carbon centers through the addition of carbon nucleophiles to ketones or ketoimines is very challenging, partly because of the lower reactivity of these substrates relative to aldehydes and aldoimines.[1] This task requires strong activation of the substrate and/or the nucleophile by an asymmetric catalyst. We developed Lewis acid–Lewis base two-center asymmetric catalysts (titanium and lanthanide complexes of **1**) that promote the cyanosilylation of ketones and ketoimines with broad substrate generality.[2] The fundamental concept for the catalyst design was that the Lewis acid metal and the Lewis base (the phosphane oxide) activate both the substrate and the nucleophile (TMSCN) simultaneously at defined positions in the transition state. A logical extension of this concept is to target the diorganozinc addition to ketones,[3] because both Lewis acid activation of the substrate and Lewis base activation of the reagent are required to promote the reaction.[4] We report herein our initial investigations toward this goal: the catalytic enantioselective addition of Me_2Zn to α-ketoesters. Our newly designed catalyst **2**, which



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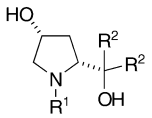
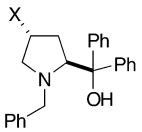


2: R^1 = Bn, R^2 = Ph
3: R^1 = Bn, R^2 = Me
4: R^1 = Bn, R^2 = *p*–ClC_6H_4
5: R^1 = Bn, R^2 = *p*–$MeOC_6H_4$
6: R^1 = allyl, R^2 = Ph
7: R^1 = β–naphthyl, R^2 = Ph
8: R^1 = 9–anthracenyl, R^2 = Ph



9: X = H
10: X = OH

[*] Prof. Dr. M. Shibasaki, K. Funabashi, Dr. M. Jachmann, Dr. M. Kanai
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-Ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp
Dr. M. Kanai
PRESTO, Japan Science and Technology Corporation
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-Ku, Tokyo 113-0033 (Japan)

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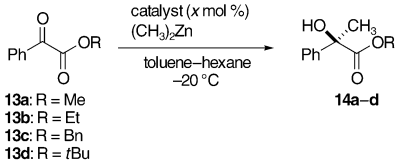
contains arranged multicenters (alcohols and an amine), produced the corresponding products with up to 96% *ee* from aromatic and acetylenic α-ketoesters. This type of catalytic enantioselective reaction was recently reported by DiMauro and Kozlowski; however the enantioselectivity and substrate generality were not necessarily high (up to 78% *ee*).[5] The products are useful chiral building blocks for the synthesis of pharmaceutical agents and natural products.[6]

Because **1** did not produce satisfactory catalyst activity and enantioselectivity in the reaction of Me_2Zn with ethyl benzoylformate (**13b**; see Table 1), we developed a new catalyst system. Based on the transition-state model initially proposed by Noyori and co-workers (Figure 1, **11**),[7] we expected that the presence of an additional Lewis base coordinating to Me_2Zn would more strongly activate the nucleophile (Figure 1, **12**). Moreover, we planned to use a zinc alkoxide as the additional Lewis base, because anionic Lewis bases have a greater electron-donating ability than neutral Lewis bases such as amines or phosphane oxides. The combination of these two factors should allow the reaction to proceed through a dual activation pathway with the strongly activated nucleophilic Me_2Zn, and both high catalyst activity and enantioselectivity should be observed. Based on these considerations, we designed new enantioselective catalysts **2**–**8**. These catalysts could be readily synthesized in two steps from commercially available 2,4-*cis*-4-hydroxy-D-proline methyl ester.[8] Catalyst **9**, which lacks the 4-hydroxy group,[9] and the 2,4-*trans* catalyst **10**[10] were also prepared as control catalysts.

Table 1: Optimization of the reaction conditions.[a]



Entry	13/14	Catalyst	*x* [mol%]	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	**b**	**2**	20	24	72	82
2	**b**	**9**	20	24	45	0
3	**b**	**10**	20	24	28	7[e]
4	**b**	**2**	10	36	63	53
5	**b**	**2**	10	30+12	69	83
6	**b**	**3**	10	30+12	89	4
7	**b**	**4**	10	30+12	85	80
8	**b**	**5**	10	30+12	89	77
9	**b**	**6**	10	30+12	78	33
10	**b**	**7**	10	30+12	55	56
11	**b**	**8**	10	30+12	89	33
12	**a**	**2**	10	30+12	85	81
13	**c**	**2**	10	30+12	74	40
14	**d**	**2**	10	30+12	17	n.d.[f]

[a] Me_2Zn: 1.8 equiv (entries 1–4) or 2.5 equiv (entries 5–14). [b] In entries 1–4, Me_2Zn was added in one portion, whereas in entries 5–14, Me_2Zn was added slowly over 30 h, and the reaction was continued for 12 h. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis. [e] The opposite enantiomer was the major isomer. [f] Not determined.

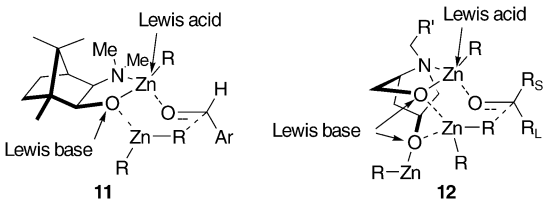


Figure 1. Fundamental concepts of catalyst design.

The function of catalysts **2**, **9**, and **10** (20 mol%) was first investigated for the reaction of Me_2Zn and **13b** in toluene at −20 °C for 24 h. As shown in Table 1, 2,4-*cis* catalyst **2** gave product **14b** in 72% yield with 82% *ee* (entry 1). Catalysts **9** and **10**, however, gave the product in only moderate yield with very low enantioselectivity (Table 1, entries 2 and 3). It can therefore be concluded that the 2,4-*cis* configuration of the diols is essential for high yield and enantioselectivity. Based on molecular-modeling studies, these two oxygen atoms must be in close proximity so that the two alkoxides can chelate Me_2Zn, which acts as a nucleophile. The sharp contrast between the catalytic activity and enantioselectivity of **2** and **9** or **10** might be due to the ability of the zinc alkoxides to chelate the nucleophile.[11]

Next, we investigated a decrease in the catalyst loading. When the amount of **2** was decreased to 10 mol%, the enantioselectivity was significantly decreased to 53% *ee* (Table 1, entry 4). This might be due partly to the competitive catalyst-independent background reaction. Thus, we tried slow addition (30 h) of Me_2Zn. The product was obtained with 83% *ee* (Table 1, entry 5), which was comparable to the results obtained with 20 mol% of the catalyst. Under these optimized reaction conditions, the catalyst structure was further modified. When the diaryl alcohol was changed into a dimethyl alcohol (catalyst **3**), a significant loss of enantioselectivity occurred (Table 1, entry 6). The electron-withdrawing or -donating group on the aryl group, however, did not have a significant effect (Table 1, entries 7 and 8). Finally, catalyst **2**, which contains a benzyl substituent on the nitrogen atom, produced the best enantioselectivity, and catalysts that bear smaller (*N*-allyl; Table 1, entry 9) and larger (*N*-β-naphthyl and *N*-9-anthracenyl; Table 1, entries 10 and 11) substituents gave lower enantioselectivity. The yield of the product was dependent on the bulkiness of the ester moiety of the substrate (Table 1, entries 12–14), and the best results were obtained with the small methyl ester **13a** as the substrate (Table 1, entry 12).

To improve the enantioselectivity further, several additives were screened.[12] Although neither coordinating additives such as $Ph_3P(O)$, Et_3N, Ph_3P, or LiBr, nor Brönsted acids such as trifluoromethanesulfonic acid or trifluoroacetic acid produced positive effects, the addition of protic additives such as MeOH, EtOH, *i*PrOH, or *t*BuOH improved both the yield and enantioselectivity (Figure 2). Although the tendency was slightly different depending on the alcohol, the chemical yield increased up to 96% (in the presence of 27 mol% EtOH) and the enantioselectivity up to 95% *ee* (in the presence of 18 mol% EtOH). The best results in terms of yield and enantioselectivity were obtained in the presence of 27 mol%

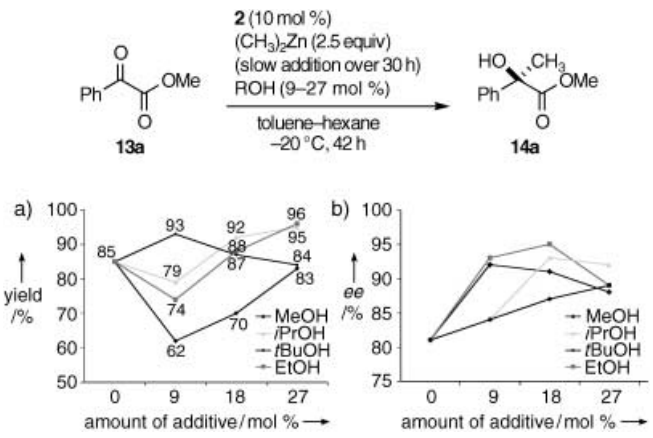


Figure 2. Effect of additive alcohol on yield and enantioselectivity. a) Relationship between yield and amount of additive. b) Relationship between *ee* and amount of additive.

*i*PrOH, and product **14a** was obtained in 95% yield with 92% *ee*.

Substrate generality was then investigated under the optimized reaction conditions. High *ee* values were obtained with aromatic and heteroaromatic ketones (Table 2, entries 1–7). Although the enantioselectivity was moderate, the present reaction could also be applied to acetylenic ketoester **13j** (Table 2, entry 8). The product is a versatile precursor for functionalized or α,α-dialkyl-substituted hydroxy esters. Ketoester **13k** that is constrained to the *s-cis* form of the ketone and amide carbonyls gave 76% *ee* (Table 2, entry 9). Thus, this is the first example of a catalytic enantioselective addition of Me_2Zn to α-ketoesters that affords products with high enantioselectivity.[13,14]

Although a detailed mechanistic discussion is difficult at present owing to the lack of information on the structure of the catalyst, we obtained important information regarding the role of the additive, based on the differences in the nonlinear effects[15] in the absence or presence of *i*PrOH (Figure 3).

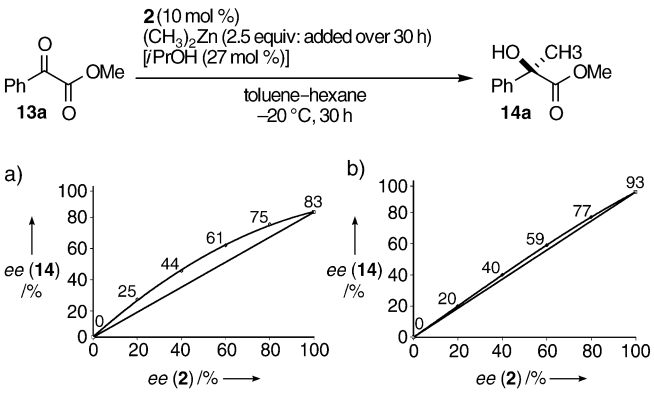
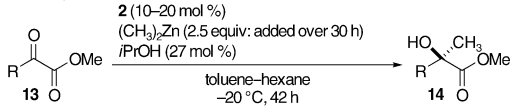


Figure 3. Nonlinear effects a) in the absence of and b) in the presence of *i*PrOH.

Positive nonlinear effects were observed in the absence of *i*PrOH, however the nonlinearity almost disappeared in the presence of 27 mol% *i*PrOH. These results suggest that the additive *i*PrOH (thus, zinc isopropoxide in the reaction mixture) changes the catalyst structure into a monomeric form by mixed aggregate formation, which might be the actual catalytic species that results in the high enantioselectivity and reactivity.

In summary, we developed a new enantioselective catalyst for the addition of Me_2Zn to α-ketoesters. The *cis* arrangement of the two hydroxy groups on the pyrrolidine ring is essential for high catalyst activity and enantioselectivity. Addition of a catalytic amount of *i*PrOH improved the yield and enantioselectivity. The nonlinear effects suggest that the additive forms a monomeric catalyst species. The information obtained in the present study will be useful for the development of an enantioselective catalyst of diorganozinc addition to simple ketones. Studies toward this end and to clarify the reaction mechanism are underway.

Table 2: Catalytic enantioselective addition of Me_2Zn to α-ketoesters.[a]



Entry	**13**	**2** [mol%]	Yield [%][b]	*ee* [%][c]
1	R = Ph (**13a**)	10	95	92[d]
2[f]	R = Ph (**13a**)	10	70 (91)	85[d]
3	R = *p*-Br-C_6H_4 (**13e**)	10	89	85
4	R = *p*-MeO-C_6H_4 (**13f**)	10	42	92
5	 (**13g**)	10	77	80
6	 (**13h**)	10	91	96
7	 (**13i**)	20	89	72
8	 (**13j**)	10	75	59[d]
9	 (**13k**)	20	82	76[e]

[a] For experimental procedure, see reference [13]. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined to be *R*. [e] The absolute configuration was determined to be *S*. [f] Reaction carried out on a 1.6-g scale. Conversion yield is in parenthesis. Recovery of chiral ligand **2**: 98%.

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[13] General procedure: Me_2Zn (1.0 M in hexane, 18 μL, 0.018 mmol) was added to a solution of the catalyst **2** (7.2 mg, 0.020 mmol) in toluene (0.45 mL), and the mixture was stirred for 30 min at room temperature. *i*PrOH (4.13 μL) in toluene (0.050 mL) was then added and the mixture was stirred for 30 min. The mixture was cooled to −20 °C and the α-ketoester (0.20 mmol) was added, followed by the dropwise addition of Me_2Zn (1.0 M in hexane, 482 μL, 0.482 mmol) over 30 h by using a syringe pump. The reaction vessel has to be strictly sealed so as not to lose the volatile Me_2Zn. After all the Me_2Zn was added, the reaction was stirred for 12 h and then quenched with aqueous citric acid (10%). Extraction with EtOAc and purification by column chromatography (SiO_2, EtOAc/hexane, 1:8→1:4) provided the product.
[14] Further scope and limitations: A vinyl-substituted ketoester [R = (*E*)-PhCH=CH] gave the product in 92% yield with 15% *ee*. An alkyl-substituted ketoester ($R = PhCH_2CH_2$) gave a complex mixture of products. The reaction of Et_2Zn and **13a** did not give any products, and **13a** was recovered.

