Asymmetric Catalysis

DOI: 10.1002/anie.200705344

Catalytic Enantioselective Aldol-type Reaction of β-Ketosters with Acetals**

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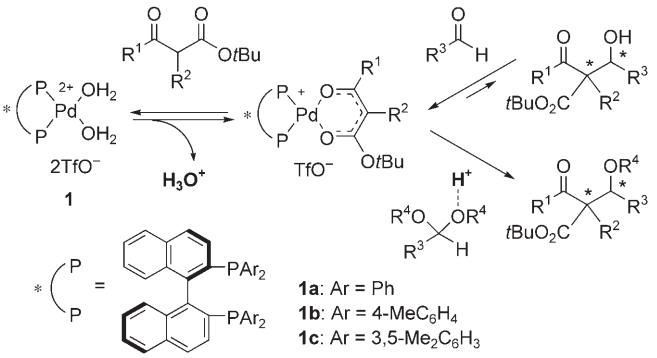
In memory of Yoshihiko Ito

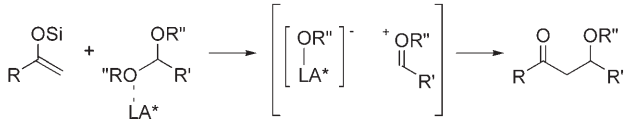
Optically active β-oxycarbonyl compounds are useful intermediates in synthetic organic chemistry and great efforts have been devoted to the development of catalytic asymmetric aldol reactions. Excellent methods have been developed with secondary amines as well as chiral Lewis acids, whereby ketones and their silyl derivatives react with aldehydes in a highly enantioselective manner.[1] In contrast, readily enolizable 1,3-dicarbonyl compounds, such as β-ketoesters and malonates, have rarely been used as nucleophiles[2] because of the insufficient nucleophilicity of the metal enolates of such compounds; a plausible alternative explanation is that the products are unstable and readily undergo retro-aldol reactions (Scheme 1). Because of these general difficulties, there are only a few examples of the synthesis of optically active β-oxymalonates by using π-allyl Pd chemistry,[3] aldol reactions,[4] and oxy-Michael reactions.[5] As for catalytic aldol reactions of 1,3-dicarbonyl compounds, we recently reported a catalytic asymmetric hydroxymethylation of β-ketoesters by using paraformaldehyde as a C1 unit.[6,7] However, reactions with less reactive aldehydes were difficult to perform (vide infra), and we were unable to find literature precedent on similar reactions.

Previously, we showed that chiral Pd enolates formed by the reaction of chiral Pd^{II}–bisphosphine complexes **1** with β-ketoesters were accompanied by the formation of a protic acid (Scheme 1).[8] We envisaged that this proton might activate acetals to give an oxonium intermediate, which would undergo an aldol-type reaction with the β-ketoester. Since the product is O protected, we expected that the undesired retro-aldol reaction would be suppressed. The use of an acetal as a synthetic equivalent of an aldehyde has been extensively investigated in Lewis acid mediated or catalyzed aldol-type reactions with silyl enolates.[9] In general, chiral induction is hard to achieve in these reactions because the chiral Lewis acid interacts only weakly with the prochiral electrophile (Scheme 2). To our knowledge, an asymmetric version of this type of reaction has not been reported. Herein, we disclose the first example of a catalytic asymmetric aldol-type reaction of acetals by using chiral Pd^{II} and Pt^{II} complexes, where the chiral metal enolates of prochiral β-ketoesters are the key intermediates.



Scheme 1. Aldol-type reaction of β-ketoesters.

We chose *tert*-butyl-2-oxo-cyclohexane carboxylate (**2a**) and cinnamaldehyde diethyl acetal (**3a**)[10a] as model substrates (Table 1). The reaction of **2a** with **3a** was carried out in the presence of 10 mol% of Pd–binap complex **1a** (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) in THF at 0°C. As expected, the desired aldol-type adduct **4aa** was obtained in excellent yield. To our delight, the enantioselectivity of the product was excellent (98%), although the diastereoselectivity was insufficient (Table 1, entry 1). When the reaction was carried out at −20°C the diastereoselectivity was improved (Table 1, entry 2). As shown in entry 3 in Table 1, the amounts of the catalyst and the acetal used could be reduced. Careful



Scheme 2. Lewis acid catalyzed Mukaiyama-type aldol reaction with acetals.

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[**] We thank Prof. Teiji Chihara of RIKEN for his generous support. This work was supported by a Grant-in-Aid for the Encouragement of Young Scientists (B) from JSPS (No. 18790005), a Grant-in-Aid for Scientific Research on Priority Areas from MEXT (No. 19028065, "Chemistry of Concerto Catalysis"), and Special Project Funding for Basic Science from RIKEN.

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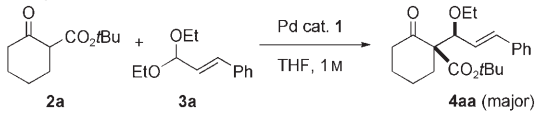
Table 1: Optimization of the reaction conditions.



2a **3a** **4aa** (major)

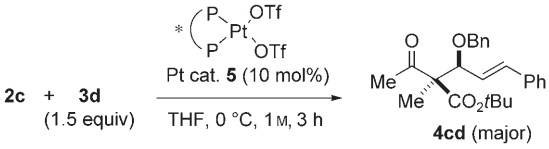
Entry	**1** (mol%)	**3a** (equiv)	*T* [°C]	*t* [h]	Yield [%]	d.r.[a]	*ee* [%][b] major	*ee* [%][b] minor
1	**1a** (10)	4	0	24	96	2.3:1	98	98
2	**1a** (10)	4	−20	24	61	7.7:1	>99	>99
3	**1a** (5)	1.5	0	3	85	5.0:1	99	95
4	**1c** (10)	4	0	12	58	11:1	72	34
5[c]	**1a** (5)	1.5	0	3	64	5.3:1	99	95

[a] The diastereomeric ratio was determined by comparing the integration values of the allylic methine protons in the ^{1}H NMR spectrum of the crude product mixture. [b] Enantioselectivity was determined by chiral HPLC analysis. The numbers represent the enantiomeric excess of the major and minor diastereomers. [c] **3a** with *cis* configuration was used.

observation revealed that **3a** was almost entirely consumed after 3 hours, affording **4aa** in 85% yield with a 5:1 diastereomeric ratio and almost perfect enantioselectivity (major diastereomer: 99% *ee*; Table 1, entry 3). With a bulkier complex such as **1c**, high diastereoselectivity was observed, although both the reaction rate and the enantioselectivity decreased (Table 1, entry 4). An acetal with a *cis* configured double bond[10b] underwent reaction to afford **4aa** with a *trans* configuration (Table 1, entry 5). The reaction with **3a** was chemoselective, and no 1,4-type adduct was formed (vide infra). A control experiment revealed that an aldol product was not formed in the reaction where cinnamaldehyde was used in place of **3a**.

We next examined the scope of the reaction by using the optimized reaction conditions (Table 2). Other substrates, including methyl, allyl, and benzyl acetals,[10c–e] underwent the desired aldol-type reaction to give products at synthetically useful levels (Table 2, entries 1–3). The ability to make aldol-type products with allyl and benzyl groups is useful because such groups can be easily removed. Reactions of other β-ketoesters were also examined; for example, the reactions of **2b** proceeded without difficulty, and the enantioselectivity was again excellent (Table 2, entries 4 and 5). When the reaction was carried out at −20°C, the diastereoselectivity was significantly improved without any loss in the efficiency of the reaction (Table 2, entry 6).

As in the case of our Michael reaction,[8a,b] acyclic substrate **2c** was less reactive than the cyclic β-ketoesters. The reactions of **2c** with **3c** and **3d** did not go to completion, and a color change of the reaction mixture was observed, indicating decomposition of the catalyst (Table 2, entries 7 and 8). We speculated that the Pd complex tended to undergo reduction by the alcohol, derived from the starting acetals,[11] because the complexation of **2c** with **1a** was slow. To address this issue, we examined the use of a Pt^{II} complex with the expectation that it would give a Pt enolate, similar to the Pd enolate, that would be more resistant to decomposition.[12,13] Gratifyingly, in the presence of 10 mol% of Pt complex **5a**, the desired product **4cd** was formed in 71% yield after 3 hours (Scheme 3). The reaction with **5b** gave **4cd** in better

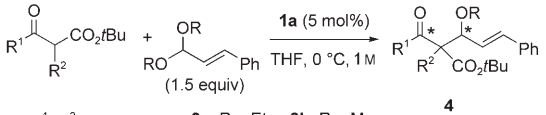


2c + **3d** (1.5 equiv) → **4cd** (major)

Pt cat. **5a**: 71%, d.r. = 1.3:1, *ee* = 97% (major), 96% (minor)
Pt cat. **5b**: 71%, d.r. = 2.5:1, *ee* = 97% (major), 96% (minor)
Pt cat. **5c**: 67%, d.r. = 10:1, *ee* = 85% (major), 66% (minor)
Pt cat. **5c** (–20 °C, 24 h): 71%, d.r. = 14:1, *ee* = 89% (major)

Scheme 3. Aldol-type reactions of **2c** with **3d** by using Pt complexes. Tf = trifluoromethanesulfonyl.

Table 2: Aldol-type reactions by using other substrates.



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2a: R^1–R^2 = –$(CH_2)_4$–
2b: R^1–R^2 = –$(CH_2)_3$–
2c: R^1=R^2 = Me
3a: R = Et **3b**: R = Me
3c: R = Allyl **3d**: R = Bn

Entry	Ketoester	Acetal	Product	*t* [h]	Yield [%]	d.r.[a]	*ee* [%][b] major	*ee* [%][b] minor
1	**2a**	**3b**	**4ab**	3	43	4.2:1	>99	98
2	**2a**	**3c**	**4ac**	3	70	4.5:1	>99	92
3	**2a**	**3d**	**4ad**	3	71	5.2:1	99	99
4	**2b**	**3a**	**4ba**	3	86	3.2:1	99	98
5	**2b**	**3c**	**4bc**	1	86	2.2:1	98	98
6[c]	**2b**	**3c**	**4bc**	1	82	6.3:1	99	98
7[d]	**2c**	**3c**	**4cc**	3	41	4.5:1	97	–[e]
8[d]	**2c**	**3d**	**4cd**	3	22	3.6:1	–[e]	–[e]

[a] The diastereomer ratio was determined by comparing the integration ratio of the allylic methine protons in the ^{1}H NMR spectrum of the crude products. [b] Enantioselectivity was determined by chiral HPLC analysis. The numbers represent the enantiomeric excess of the major and minor diastereomers. [c] −20°C. [d] 10 mol% **1a**. [e] Not determined.

diastereoselectivity and excellent enantioselectivity (97% *ee*). Significant improvement in the diastereoselectivity was observed in the reaction catalyzed by **5c**. Finally, a better stereoselectivity (d.r. = 14:1, 89% *ee* for major diastereomer) was achieved when the reaction was carried out at −20°C.

As shown in the Supporting Information, the relative and absolute stereochemistry of the major diastereomers of compounds **4aa** and **4cd** were unequivocally determined by X-ray crystallographic analysis.[14] Taken together with our previous results[8] it is likely that the observed absolute stereochemistry arises from facial selection of the metal enolate, and that the relative stereochemistry is biased by the geometry of the approaching oxonium ion (Figure 1). This idea is in accord with the fact that the enantioselectivity is high, regardless of the difference in the size of the acetals.

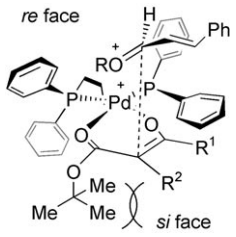
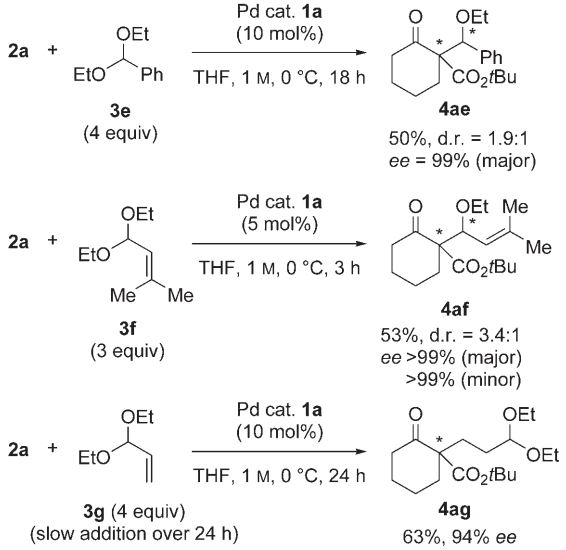


Figure 1. Proposed transition-state model.

In the present reaction, conversion of the acetal into the oxonium ion by protonation is crucial. In fact, the reaction efficiency was affected by the partial structure of the acetal (Scheme 4). A substrate that gives an oxonium ion stabilized



Scheme 4. Reactions using various acetals.

by an adjacent π system reacts with β-ketoesters, but a product is not formed in the reaction with simple acetals. For example, the reaction of **2a** with the diethyl acetal of hydrocinnamaldehyde catalyzed by **1a** did not proceed, even at room temperature. However, an acetal of benzaldehyde reacted with **2a** under the standard conditions. Although the chemical yield was less satisfactory, probably because of steric repulsions, almost perfect enantioselectivity was achieved (major diastereomer: 99% *ee*). An acetal of a simple α,β-unsaturated aldehyde was also available, and **4af** was obtained in 53% yield with 99% *ee*. In contrast, the reaction of acrolein diethyl acetal (**3g**) was dramatically different, and formal 1,4-addition product **4ag** was obtained as a major product.[15]

With regard to the reaction mechanism, alkylation of the β-ketoester with a π-allyl Pd intermediate generated from Pd^0 and **3** is also plausible.[3] If this were the case, the high enantioselectivity that is observed would arise from the facial selectivity of the chiral π-allyl Pd species, and not from the chiral enolate. High selectivity should, therefore, be observed in the reaction with malonate, but the reaction of dibenzyl malonate with **3a** gave the corresponding aldol-type product in 55% yield with only 23% *ee* and a diene derived from β-elimination of ethanol in 15% yield (see the Supporting Information). These results suggest that the π-allyl Pd species is not involved in the reaction.

In conclusion, we have developed a highly enantioselective aldol-type reaction of β-ketoesters with acetals. Our Pd complex can act as an acid/base catalyst, and simultaneous activation of both the nucleophile and the electrophile is possible. Formation of the enolate under acidic conditions is the key to the success of the reaction and allows the use of acetals as a coupling partner; basic conditions are unfavorable. Whereas a straightforward aldol reaction of β-ketoesters with aldehydes hardly gives the corresponding product, the present method affords the aldol-type product in good yield with up to 99% *ee*. Thus, we have demonstrated the utility of the metal enolates under acidic conditions, and additional studies in this area are in progress.

Received: November 21, 2007
Revised: March 9, 2008
Published online: April 25, 2008

Keywords: β-ketoester · acetal · aldol reaction · palladium · platinum

[1] a) *Modern Aldol Reactions*, *Vol. 1, 2* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**; b) E. M. Carreira in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 513–542; c) M. Sawamura, Y. Ito in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 493–512; d) H. Nishiyama, T. Shiomi, *Top. Curr. Chem.* **2007**, *279*, 105–137.

[2] Other active methylene compounds have been used successfully in catalytic asymmetric addition reactions to aldehydes. Representative examples include: α-isocyanoacetate: a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; nitroalkane: b) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; c) B. M. Trost, V. S. Yeh, *Angew. Chem.* **2002**, *114*, 889–891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; d) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055; e) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; f) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595–3597; α-cyanopropionate: g) R. Kuwano, H. Miyazaki, Y. Ito, *Chem. Commun.* **1998**, 71–72.

[3] a) B. M. Trost, C. B. Lee, J. M. Weiss, *J. Am. Chem. Soc.* **1995**, *117*, 7247–7248. They also reported the reaction of Meldrum's acid and azalactone with benzyloxyallene to give related products; b) B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438–4439; c) B. M. Trost, A. B. C. Simas, B. Plietker, C. Jäkel, J. Xie, *Chem. Eur. J.* **2005**, *11*, 7075–7082.

[4] a) S. Marumoto, H. Kogen, S. Naruto, *Chem. Commun.* **1998**, 2253–2254; b) S. Marumoto, H. Kogen, S. Naruto, *J. Org. Chem.* **1998**, *63*, 2068–2069.

[5] D. J. Buchanan, D. J. Dixon, F. A. Hernandez-Juan, *Org. Lett.* **2004**, *6*, 1357–1360.

[6] I. Fukuchi, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2007**, *349*, 509–512.

[7] Recently, nonasymmetric hydroxymethylation of β-ketoesters with formalin catalyzed by an iron salt was reported: C. Ogawa, S. Kobayashi, *Chem. Lett.* **2007**, *36*, 56–57.

[8] Michael reaction: a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241; b) Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki, M. Sodeoka, *Adv. Synth. Catal.* **2005**, *347*, 1576–1586; Mannich-type reaction: c) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549–1553; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525–1529; *Angew. Chem.* **2005**, *117*, 1549–1553; d) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010–14011; for a short review: e) M. Sodeoka, Y. Hamashima, *Pure Appl. Chem.* **2006**, *78*, 477–494; f) M. Sodeoka, Y. Hamashima, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941–956.

[9] For selected examples: a) T. Mukaiyama, M. Hayashi, *Chem. Lett.* **1974**, 15 – 16; b) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 3248 – 3249; c) S. Murata, M. Suzuki, R. Noyori, *Tetrahedron* **1988**, *44*, 4259 – 4275; d) W.-D. Z. Li, X.-X. Zhang, *Org. Lett.* **2002**, *4*, 3485 – 3488; e) B. Jiang, X. Zhang, G. Shi, *Tetrahedron Lett.* **2002**, *43*, 6819 – 6821; f) J. Cossy, F. Lutz, V. Alauze, C. Meyer, *Synlett* **2002**, 45 – 48; g) X. Li, A. Kurita, S. Man-e, A. Orita, J. Otera, *Organometallics* **2005**, *24*, 2567 – 2569. Boron enolates generated in situ was also employed; h) L.-S. Li, S. Das, S. C. Sinha, *Org. Lett.* **2004**, *6*, 127 – 130.

[10] Acetals were prepared according to the following reports. Ethyl acetal: a) J. A. Vanallan, *Org. Synth. Collect. Vol. IV* **1963**, 21 – 22; b) B. Byrne, L. M. Lafleur Lawter, K. J. Wengenroth, *J. Org. Chem.* **1986**, *51*, 2607 – 2609; Methyl acetal: c) K. Mikami, H. Ohmura, *Org. Lett.* **2002**, *4*, 3355 – 3357; Allyl acetal: d) J. B. Brogan, J. E. Richard, C. K. Zercher, *Synth. Commun.* **1995**, *25*, 587 – 593; Benzyl acetal: e) T. Watahiki, Y. Akabane, S. Mori, T. Oriyama, *Org. Lett.* **2003**, *5*, 3045 – 3048.

[11] We recently found that ethanol was oxidized in the presence of **1a** to give a Pd–H species, which underwent asymmetric conjugate reduction of enones. See, Y. Tsuchiya, Y. Hamashima, M. Sodeoka, *Org. Lett.* **2006**, *8*, 4851 – 4854.

[12] We recently reported that the Pt–binap complex gave better results in the addition reaction of β-ketoesters to paraformaldehyde. See, reference [6].

[13] [Ni{(*R*)-segphos}](OTf)$_2$ and [Cu{(*S*,*S*)-*tert*-Bu-box}](OTf)$_2$ gave poor results (11% yield and 0% *ee* after 45 h, 0% yield after 24 h, respectively).

[14] CCDC-662229 (**4aa**) and CCDC-677026 (**4cd**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. In the case of **4cd**, X-ray analysis was carried out after the conversion to the corresponding camphor derivative. Details of the conversion and the crystallographic studies are described in the Supporting Information.

[15] A similar methyl acetal was formed when a catalytic asymmetric Michael reaction with acrolein was carried out in MeOH in the presence of **1a**. See reference [8b].

