Asymmetric Catalysis

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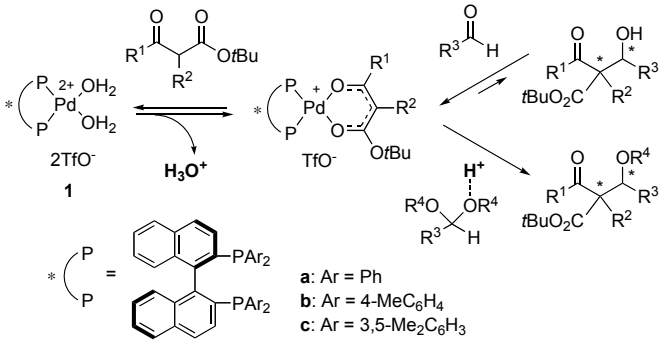
Catalytic Enantioselective Aldol-type Reaction of β-Keto Esters with *O,O*-Acetals**

*Natsuko Umebayashi, Yoshitaka Hamashima, Daisuke Hashizume, and Mikiko Sodeoka**

This paper is dedicated to the late Professor 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 chiral Lewis acids and chiral secondary amines, in which 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-keto esters and malonates have rarely been used as nucleophiles,[2] probably because of insufficient nucleophilicity of the metal enolates of such compounds, although a plausible alternative explanation is that the products are unstable and readily undergo retro-aldol reaction (Scheme 1). Because of these general difficulties, there are only a few examples of the synthesis of optically active β-oxymalonates using π-allyl Pd chemistry,[3] aldol reaction,[4] and oxy-Michael reaction.[5] As for catalytic aldol reactions of 1,3-dicarbonyl compounds, we recently reported a catalytic asymmetric hydroxymethylation of β-keto esters using paraformaldehyde as a C1 unit.[6],[7] However, reactions with less reactive aldehydes were difficult (vide infra), and we found no precedents in the literature.

Previously, we showed that chiral Pd enolates were formed by the reaction of chiral Pd^{II}-bisphosphine complexes **1** with β-keto esters, being accompanied with the formation of a protic acid (Scheme 1).[8] We envisaged that this proton might activate *O,O*-acetals to give an oxonium intermediate, so that aldol-type reactions with β-keto esters would proceed smoothly. Since the product is *O*-protected, we expected that the undesired retro-aldol reaction would be suppressed. The use of *O,O*-acetals as a synthetic equivalent of aldehydes has been extensively investigated in Lewis acid-mediated or catalyzed aldol-type reactions with silyl enolates.[9] A general principle of these reactions is that chiral induction is hard to achieve, since the chiral Lewis acid interacts only weakly with the prochiral electrophile (Scheme 2). To our knowledge, no asymmetric version of such reactions has been reported. Here, we disclose the first example of a catalytic asymmetric aldol-type reaction of *O,O*-acetals using chiral Pd^{II} and Pt^{II} complexes, in which the chiral metal enolates of prochiral β-keto esters are the key intermediates.



Scheme 1. Aldol-type reaction of β-keto esters.

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

We chose *tert*-butyl 2-oxo-cyclohexanecarboxylate (**2a**) and cinnamaldehyde diethyl acetal (**3a**)[10a] as model substrates (Table 1). In the presence of 10 mol% of the Pd-binap complex **1a**, the reaction of **2a** with **3a** was carried out in THF at 0 °C. As we 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 (entry 1). When the reaction was carried out at -20 °C, the diastereoselectivity was improved (entry 2). As shown in entry 3, the amounts of the catalyst and the acetal could be reduced. Careful observation revealed that **3a** was almost entirely consumed after only 3 h, affording **4aa** in 85% yield with a 5/1 diastereomeric ratio and almost perfect enantioselectivity (major: 99% ee) (entry 3). With a bulkier complex **1c**, high diastereoselectivity was observed, although both the reaction rate and the enantioselectivity decreased

[*] N. Umebayashi, Dr. Y. Hamashima, Prof. M. Sodeoka
Synthetic Organic Chemistry Laboratory, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)
Fax: (+81)48-467-9373
E-mail: sodeoka@riken.jp

Dr. D. Hashizume
Molecular Characterization Team, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)

N. Umebayashi, Prof. M. Sodeoka
Graduate School of Science and Engineering, Saitama University
255 Shimo-okubo, Sakura-ku, Saitama 338-8570 (Japan)

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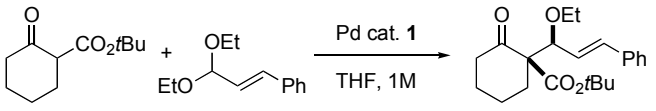
(entry 4). An acetal with *cis* configuration of the double bond[10b] also underwent the reaction to afford **4aa** with *trans* configuration (entry 5). The reaction with **3a** was chemoselective, and no 1,4-type adduct was formed (vide infra). A control experiment revealed that no aldol product was formed in the reaction with cinnamaldehyde in place of **3a**.

Table 1. Optimization of the reaction conditions.



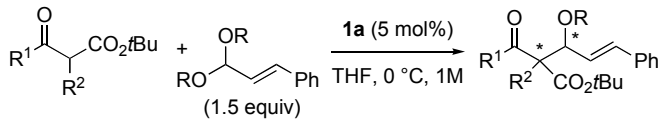
2a **3a** **4aa** (major)

Entry	**1** (mol%)	**3a** (equiv)	Temp. (°C)	Time (h)	Yield (%)	dr[a]	ee[b] (%)
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 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. [c] **3a** with *cis* configuration was used.

Using the optimized reaction conditions, we next examined the scope of the reaction (Table 2). Other substrates, including methyl, allyl, and benzyl acetals,[10c-e] underwent the desired aldol-type reaction, giving the products at synthetically useful levels (entries 1-3). The availability of allyl and benzyl groups is useful, since they can be removed easily. Reactions of other β-keto esters were also examined: the reactions of **2b** proceeded without difficulty, and the enantioselectivity was again excellent (entries 4,5). When the reaction was carried out at -20 °C, the diastereoselectivity was significantly improved without loss of the reaction efficiency (entry 6).

Table 2. Aldol-type reactions using other substrates.



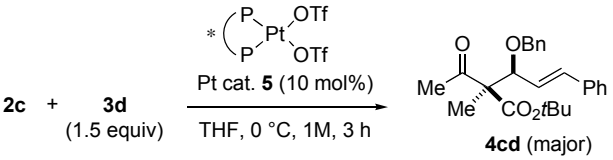
4

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

Entry	Keto ester	Acetal	Product	Time (h)	Yield (%)	dr[a]	ee[b] (%)
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]

[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. [c] -20 °C. [d] 10 mol% **1a**. [e] Not determined.

As in the case of our Michael reaction,[8a,b] the acyclic substrate **2c** was less reactive than the cyclic β-keto esters. The reactions of **2c** with **3c** and **3d** did not reach completion, and a color change of the reaction mixture was observed, indicating decomposition of the catalyst (entries 6, 7). We speculated that the Pd complex tended to undergo reduction by alcohol derived from the starting acetals,[11] because the complexation of **2c** and **1a** might be slow. To address this issue, we examined the use of Pt^{II} complex, expecting that it would give a Pt enolate similar to the Pd enolate, but more resistant to decomposition.[12][13] Gratifyingly, in the presence of 10 mol% of the Pt complex **5a**, the desired product **4cd** was formed in 71% yield after 3 h (Scheme 3). The reaction using **5b** gave **4cd** with better diastereoselectivity and excellent enantioselectivity (97%). Significant improvement in diastereoselectivity was observed in the reaction catalyzed by **5c**. Finally, when the reaction was carried out at -20 °C, better stereoselectivity (dr = 14/1, 89% ee) was achieved.



2c + **3d** (1.5 equiv)

4cd (major)

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

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

As shown in the Supporting Information, the relative and absolute stereochemistry of the major diastereomers of compounds **4aa** and **4cd** was unequivocally determined by X-ray analysis.[14] Taking this together with our previous results,[8] it is likely that the observed absolute stereochemistry arises from face selection of the metal enolate, and 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 was always high, regardless of the difference in the size of the acetals.

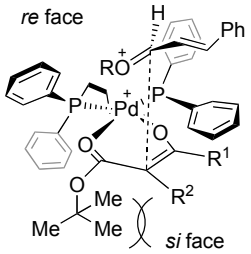
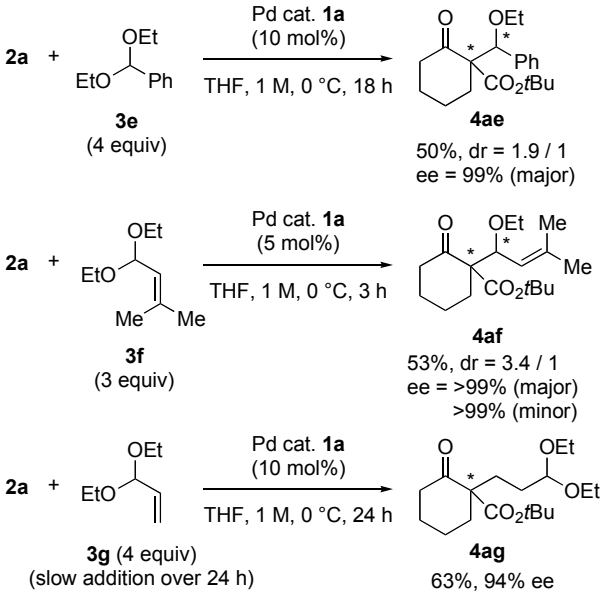


Figure 1. Proposed transition state model.

In the present reaction, conversion of the acetal to 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 by an adjacent π-system reacts with β-keto esters, but no product is formed in the reaction with simple acetals. For example, the reaction of **2a** with 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 due to the steric repulsion, almost perfect enantioselection was achieved (major: 99% ee). An acetal of a

simple α,β-unsaturated aldehydes was also available, and **4af** was obtained in 53% yield with 99% ee. In contrast, the reaction course of acrolein diethyl acetal (**3g**) was dramatically different, and the formal 1,4-addition product **4ag** was obtained as a major product.[15]



Scheme 4. Reactions using various *O,O*-acetals.

As regards the reaction mechanism, alkylation of the β-keto ester with a π-allyl Pd intermediate generated from Pd(0) and **3** is also plausible.[3] If this were the case, the high enantioselectivity observed above would arise from the face selectivity of the chiral π-allyl Pd species, and not the chiral enolate. Therefore, high selectivity should be observed even in the reaction with malonate. However, the reaction of dibenzyl malonate with **3a** gave the corresponding aldol-type product in 55% yield with only 23% ee, together with a diene derived from β-elimination of ethanol in 15% yield (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-keto esters with *O,O*-acetals. Our Pd complex can act as an acid-base catalyst, and simultaneous activation of both nucleophile and electrophile is possible. Formation of the enolate under acidic conditions is the key to success, allowing the use of *O,O*-acetals as a coupling partner; basic conditions are unfavorable. While a straightforward aldol reaction of β-keto esters with aldehydes hardly gives the corresponding product, the present method afforded 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. Further studies along this line are in progress.

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[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-keto esters 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] The crystallographic data of **4aa** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 662229. In the case of **4cd**, X-ray analysis was carried out after the conversion to the corresponding camphor derivative. The crystallographic data of this compound have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 677026. These data can be obtained online free of charge. Details of the conversion and the crystallographic studies are described in 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.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

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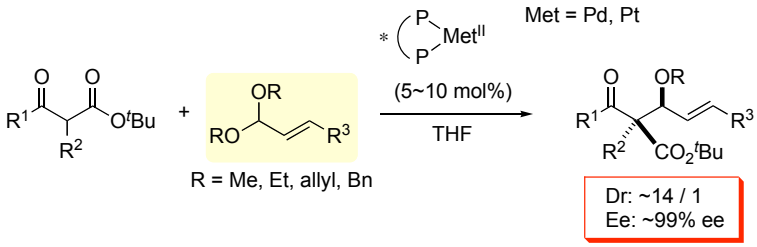

Two activations with one catalyst: Using cationic Pd and Pt complexes, a catalytic enantioselective aldol-type reaction of β-keto esters with *O,O*-acetals has been developed. Because the formation of metal enolates occurs under acidic conditions, *O,O*-acetals can be used as electrophiles. Whereas reactions of β-keto esters with simple aldehydes are basically difficult, the desired reactions proceeded smoothly under the present conditions.