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Catalytic Asymmetric Aldol Reactions of Enolizable Carbon Pronucleophiles with Formaldehyde and Ethyl Glyoxylate

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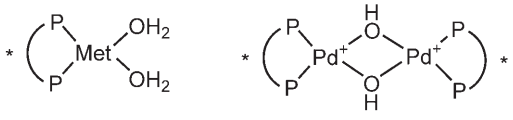
This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

Abstract: We herein describe novel catalytic asymmetric aldol reactions of acidic carbon pronucleophiles including β-keto esters and specific ketones with reactive electrophiles such as formaldehyde and ethyl glyoxylate. In the presence of a catalytic amount of chiral Pd(II)-BINAP complexes, the hydroxymethylation of β-keto esters with paraformaldehyde or formalin was examined, and the corresponding adducts were obtained in good yields with good to high enantioselectivity (*ca.* 86% *ee*). In some cases, the similar Pt(II) complex also worked well to give the products with better enantioselectivity. Furthermore, these complexes were found to promote the aldol reactions of less acidic ketones, and ethyl glyoxylate underwent reaction with 3-coumaranone and β-tetralone, affording the aldol products with a significant level of enantioselectivity of up to 83% *ee*.

Keywords: aldol reactions; asymmetric catalysis; formaldehyde; glyoxylates; palladium; platinum

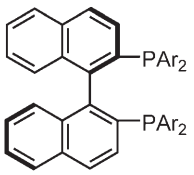
The catalytic asymmetric aldol reaction is one of the most important carbon-carbon bond forming reactions in organic synthesis.[1] After the pioneering work on the intermolecular direct catalytic asymmetric aldol reaction by Shibasaki et al.,[2] considerable attention has been paid to *in situ* activation of carbonyl compounds as nucleophiles with various catalysts including not only chiral metal complexes but also organocatalysts, and direct aldol reactions represent the current state of the art.[3] However, probably due to the high reactivity, the use of formaldehyde and glyoxylate as useful C_1 and C_2 units has been relatively limited. Recently, the number of catalytic asymmetric aldol reactions with such molecules is rapidly increasing. For example, catalytic enantioselective hydroxymethylation reactions of enol silanes and ketones were reported using chiral Lewis acids[4] and organocatalysts,[5] respectively. As for active methine compounds, the reaction of α-cyanopropionate with formaldehyde was developed using a chiral Rh complex,[6] and 2-nitrocyclohexanone was tested in the presence of *Cinchona* alkaloids.[7] Furthermore, highly enantioselective aldol reactions of glyoxylates with silyl enolates were developed using chiral Lewis acids, affording optically active α-hydroxy esters.[8]

We already reported various catalytic asymmetric reactions including the Michael reaction, Mannich-type reaction, and electrophilic fluorination reactions using chiral Pd(II)-bisphosphine complexes **1** and **3**.[9] In these reactions, active methine compounds such as β-keto esters reacted with **1** to form chiral palladium enolates **I**. This enolate reacted with highly reactive electrophiles such as iminium ions in a highly enantioselective manner. Therefore, we expected that it would also react with highly electrophilic aldehydes. In this communication, we describe a novel catalytic

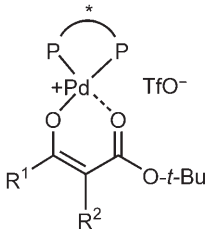


1: Met = Pd^{2+}
2: Met = Pt^{2+}

3



a: Ar = Ph
b: Ar = 4-MeC_6H_4
c: Ar =3,5-$Me_2C_6H_3$

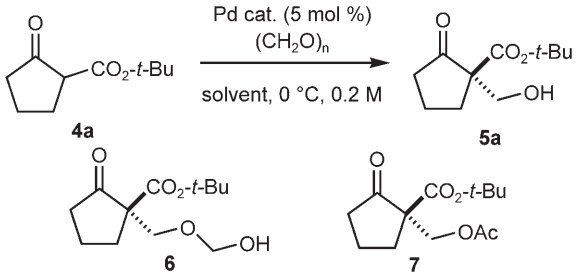


I

asymmetric hydroxymethylation of β-keto esters with formaldehyde using the Pd and Pt complexes **1** and **2** (*ca.* 86% *ee*). In addition, we also found that the Pd complex **1** could promote the direct aldol reactions of less acidic ketones with ethyl glyoxylate with a significant level of enantioselectivity (up to 83% *ee*).

We chose paraformaldehyde as a C_1 unit, because we surmised that its polymeric structure would allow gradual release of monomeric formaldehyde under the catalytic conditions. In the presence of 5 mol% of the Pd complexes with several chiral bisphosphine ligands **a–c**, **4a** was treated with paraformaldehyde (5 equivs.) in various solvents (Table 1, entries 1–9). Optimization of the reaction conditions revealed that the reaction proceeded efficiently when THF and **1a** were used, and the desired hydroxymethyl β-keto ester **5a** was obtained in 82% yield with 86% *ee* at 0°C (Table 1, entry 5). Although **5a** was prone to react with another formaldehyde to form a small amount of **6** as a by-product (6% yield), this could be removed by silica gel column chromatography. Direct acetylation was possible by adding AcCl (10 equivs.) and pyridine (5 equivs.) to the reaction mixture (room temperature, 6 h), and the corresponding *O*-acetylated product **7** was obtained in 91% yield with 86% *ee*, indicating that **5a** is stable and the enantioselectivity of the product is maintained during the purification (entries 5 and 6). It is likely that monomeric formaldehyde is formed from the polymeric acetal structure of paraformaldehyde, and a protic acid (TfOH) and water molecules, resulting from the reaction of **4a** with the Pd complex **1** to form the enolate **I**, play a role in the generation of formaldehyde. Indeed, the neutral Pd(μ-OH) complex **3**, which gives only a water molecule during the formation of **I**,[9a] did not promote the hydroxymethylation reaction efficiently, and **5a** was obtained in only 14% yield with 17% *ee* (room temperature, 100 h) (entry 9).

Table 1. Optimization of the hydroxymethylation of **4a**.

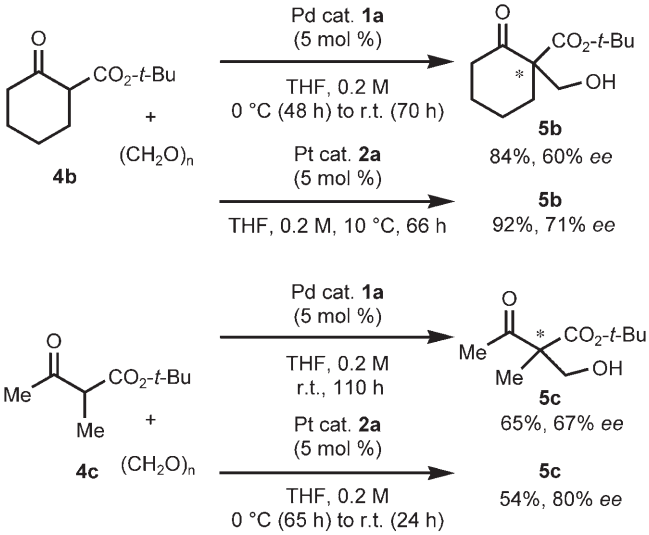


Entry	Solvent	Catalyst	Time [h]	Yield [%]	ee [%]
1	CH_2Cl_2	**1a**	18	72	55
2	Acetone	**1a**	21	83	53
3	Et_2O	**1a**	44	87	60
4	*i*-Pr_2O	**1a**	45	71	65
5	THF	**1a**	30	**82**	**86**
6	THF	**1a**	30	**91**[a]	**86**
7	THF	**1b**	47	82	65
8	THF	**1c**	49	73	39
9[b]	THF	**3a**	100	14	17
10[c]	*i*-Pr_2O	**1a**	45	88	77

[a] The product was isolated as *O*-acetylated compound **7**.
[b] The reaction was carried out at room temperature.
[c] Formalin (35% in water, 5 equivs.) was used.

Moreover, the use of formalin (35–37% in water) was examined in place of paraformaldehyde. The reaction in THF proceeded smoothly, but only modest asymmetric induction (35% *ee*) was observed. Gratifyingly, however, the *ee* was improved to 77% when *i*-Pr_2O was used as a solvent (entry 10), although it did not exceed the maximum value obtained in entry 5.[10] The fact that the reaction of **4a** with formalin in THF proceeded without the catalyst at 0°C (>70% yield after 24 h) led us to speculate that the low concentration of formaldehyde in the organic layer was maintained because an aqueous solution of formalin was hardly soluble in *i*-Pr_2O, thereby suppressing the uncatalyzed racemic reaction to improve the enantioselectivity.

This reaction was also applicable to other substrates, and the hydroxymethyl β-keto esters **5b** and **5c** were obtained with good enantioselectivity, although a longer reaction time was required for satisfactory chemical yield (Scheme 1). In these reactions, the color of the reaction mixture changed to black during the reaction, indicating decomposition of the catalyst. Interestingly, when the similar platinum complex **2a** was employed for these reactions,[11] no change of the color was observed. The reactions using



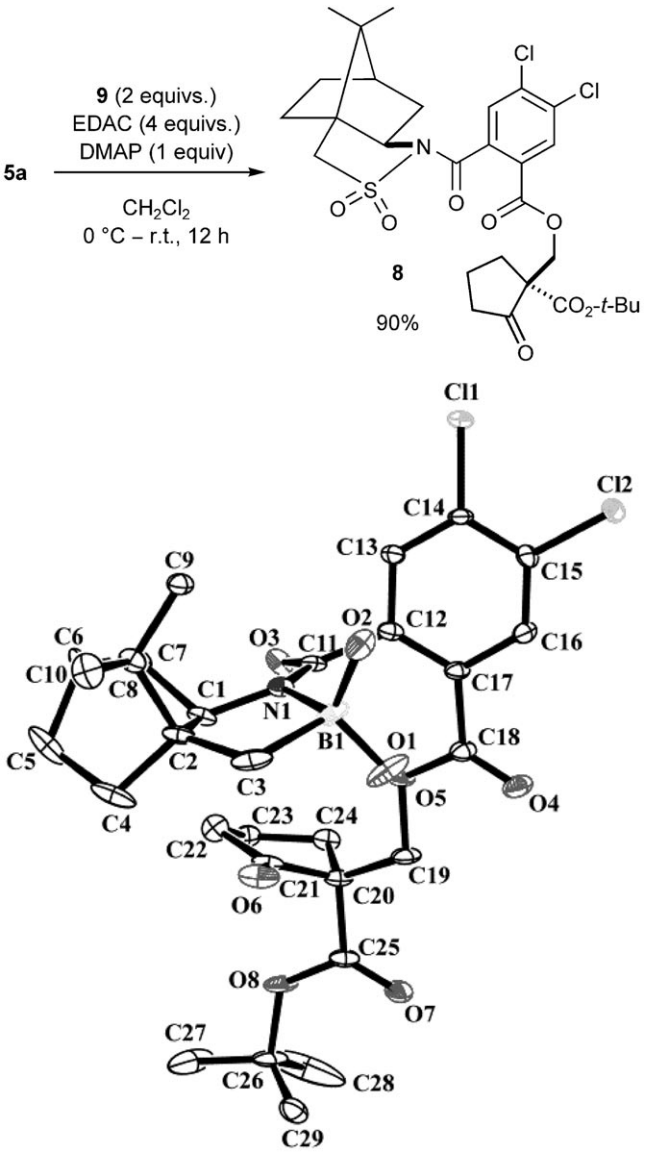
Scheme 1. Catalytic asymmetric hydroxymethylation of β-keto esters.

2a (5 mol%) proceeded at lower temperature, affording the desired products with improved enantioselectivity (**5b**: 71% *ee*, **5c**: 80% *ee*, respectively). It seems that the more suitable catalyst should be selected according to the nature of the substrates, because diminished enantioselectivity (60% *ee*) was observed in the case of the reaction of **4a** using **2a** (73% at 0°C after 24 h). These reactions could be performed without any precaution to exclude air and moisture. It should be noted that aldol products bearing a chiral quaternary carbon center were synthesized in these Pd(II)- or Pt(II)-catalyzed reactions. To the best of our knowledge, this is the first example of the catalytic asymmetric hydroxymethylation of β-keto esters.

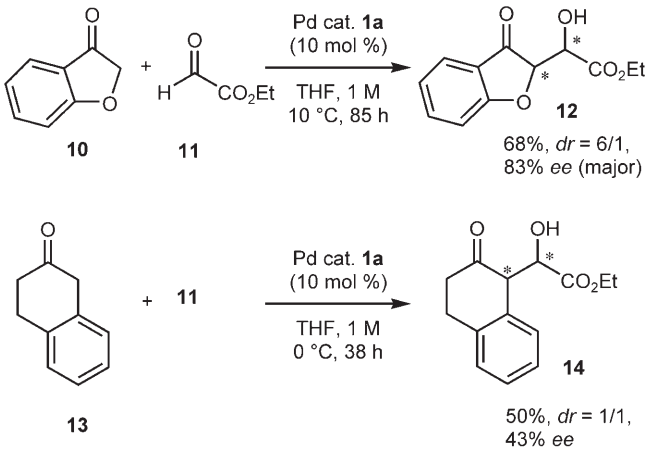
The absolute configuration of **5a** was unequivocally determined to be *R* by X-ray analysis of **8**, which was synthesized by esterification of **5a** with *N*-(2-carboxy-4,5-dichlorobenzoyl)-(−)-10,2-camphorsultam **9**[12] (Scheme 2).[13] This selectivity is in accord with the results observed in the reactions previously reported by our group, and it can be understood by postulating the involvement of the chiral square planer Pd enolate of β-keto esters.[9]

We next examined the reactions of β-keto esters with other reactive aldehydes such as acetaldehyde, chloroacetaldehyde, and ethyl glyoxylate. Unfortunately, however, only a low enantioselectivity of less than 10% was observed in each case, which was revealed to be due to spontaneous reaction to give the racemic compounds. In order to suppress undesired uncatalyzed reactions, we planned to use less acidic carbonyl compounds as the nucleophile. Among the ketones examined, we found that 3-coumaranone **10** underwent the aldol reaction with ethyl glyoxylate **11** at 0°C in the presence of **1a** (10 mol%), and the desired product **12** was obtained in 68% yield with 83% *ee* (major diastereomer) (Scheme 3).[14,15] In addition, the reaction of β-tetralone **13** with ethyl glyoxylate was also promoted by the Pd complex, and the corresponding adduct **14** was produced in 50% yield as a 1:1 diastereomixture. The enantiomers of the more polar diastereoisomer were separable on chiral HPLC, and the *ee* was determined to be 43%.[14] The reaction mechanism of these examples is not clear at the present, but we speculate that the chiral Pd enolate is generated from these ketones with relatively high acidity compared to simple ketones such as acetone, and the reaction might proceed through a closed transition state.[16] Catalytic asymmetric aldol reactions with glyoxylate described in the literature were usually performed using masked nucleophiles such as enol silanes in the presence of chiral Lewis acids,[8] but unmodified ketones could be used in our reactions.

In summary, we have developed novel catalytic asymmetric aldol reactions using formaldehyde and ethyl glyoxylate. β-Keto esters and some specific keto



Scheme 2. Conversion and X-ray structure of **8**.



Scheme 3. Pd(II)-catalyzed asymmetric aldol reactions.

compounds were examined, and the corresponding aldol adducts were obtained with up to 86% *ee*. In the present study, we found that the Pt(II) complexes as well as the Pd(II) complexes catalyze the aldol reactions of some acidic carbonyl compounds. Further investigation to improve the enantioselectivity and the scope of the reaction is under way in our group.

Experimental Section

Hydroxymethylation of 4a; Typical Procedure

To a stirred solution of the Pd complex **1a** (8 mg, 0.0075 mmol, 5 mol%) in THF (0.75 mL) was added β-keto ester **4a** (28 mg, 0.15 mmol). To this solution was added paraformaldehyde (22 mg, 0.75 mmol) at 0 °C, and the resulting suspension was stirred for 30 h. The mixture was diluted with ether, and the precipitate was removed by Celite filtration. After the filtrate was concentrated, flash column chromatography (hexane/ethyl acetate = 3/1) was carried out to give the desired product **5a** as a colorless oil; yield: 26.3 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H), 1.95–2.39 (m, 6H), 2.74 (dd, $J = 3.7$, 8.0 Hz, 1H), 3.71 (dd, $J = 8.0$, 11.2 Hz, 1H), 3.80 (dd, $J = 3.7$, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.7$, 27.8, 31.2, 38.4, 62.1, 63.7, 82.5, 170.7, 215.3; $[\alpha]_D^{27}$: −5.9 (*c* 1.25, $CHCl_3$, 86% *ee*); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 95/5, 0.5 mL min^{-1}, 280 nm): t_r (minor) = 32.7 min, t_r (major) = 36.8 min.

Acknowledgements

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[10] The reaction was carried out in the mixture of *i*-Pr_2O and water (19/1). The catalyst was almost insoluble.

[11] The Pt complex tested in this paper was prepared according to the procedure for the synthesis of **1**, see: A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458. The exact structure of the complex **2a** has not yet been confirmed by X-ray analysis.

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[13] Crystallographic data for the structure of **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 624275. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223–336–003, or mail to: deposit@ccdc.cam.ac.uk].

[14] Unfortunately, the enantiomers of other diastereomer were inseparable on chiral HPLC.

[15] The reaction of **10** with paraformaldehyde was unsuccessful because of the facile formation of Pd black.

[16] We cannot rule out the possibility that the Pd complexes activated ethyl glyoxylate and the enol tautomer of the ketones reacted.

