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Catalytic Asymmetric Aldol Reaction via Chiral Pd(II) Enolate in Wet DMF

Mikiko Sodeoka, Kazuhiko Ohrai, and
Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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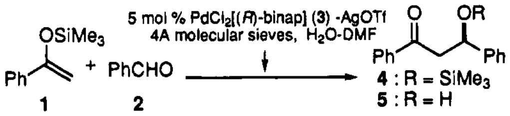
The catalytic aldol reaction that employs a transition metal enolate has attracted much attention from organic chemists because of its possible application to catalytic asymmetric synthesis. Several pioneering methods using achiral transition metal complexes as catalysts have already been reported.[1] For example, Tsuji *et al.* reported a catalytic aldol-like reaction that proceeds via a Pd(II) enolate generated from allyl β-keto carboxylate and a Pd(0) complex.[1d] A detailed study of a Rh(I) complex-catalyzed condensation of silyl enol ethers and aldehydes was reported by Bergman and Heathcock[1b] after an early report by Matsuda *et al.*[1a] To our knowledge, however, there has been no report of a catalytic asymmetric aldol reaction that proceeds with high enantioselectivity via a chiral transition metal enolate.[2,3] In this paper we describe the first synthetically useful example of a catalytic asymmetric aldol reaction that proceeds via a Pd(II) enolate. Using a Pd(II)−(*R*)-BINAP-derived complex as the catalyst, good chemical and optical yields (up to 73% ee) have been attained in the addition of silyl enol ethers to aldehydes.

After examination of a variety of palladium complexes and reaction conditions, we have found that the cationic Pd complex, PdCl[(*R*)-binap]$^+$, generated from $\mathrm{PdCl_2}$[(*R*)-binap] (**3**)[4] and AgOTf (1 equiv to **3**) in wet DMF (1.8 v/v % H_2O) in the presence of 4A molecular sieves (stirred at 23 °C for 20 min and then filtered), is a very effective catalyst for the asymmetric condensation of silyl enol ethers and aldehydes.[5] For example, addition of benzaldehyde (**2**) and acetophenone silyl enol ether (**1**) (1.5 equiv to **2**) to this catalyst solution (5 mol % to **2**) and stirring at 23 °C for 13 h afforded the aldol products in 96% yield (**4**, 87%, **5**, 9%). The optical yields of these products were 71% ee and 73% ee, respectively.[6−8] A number of experiments have shown that *water plays an important role in this reaction*. Rigorous drying of DMF (freshly distilled from CaH_2) and AgOTf (dried at 60 °C under vacuum) drastically slowed the reaction (**1** was consumed after 115 h at 23 °C) and afforded **4** as the only product in 19% yield and 68% ee. Addition of extra water (0.5 equiv to **2**) to a filtered solution of the catalyst prepared in *wet DMF* (1.8 v/v %) did not drastically disturb the condensation process, affording **4** and **5** in 6% yield (69% ee) and 54% yield (68% ee), respectively, after 2 h at 23 °C. However, addition of water together with the substrates to a filtered solution of the catalyst prepared in *dry DMF* largely enhanced decomposition of **1** to acetophenone (**1** was consumed after 2 h at 23 °C), and the yield of **5** decreased to 17% (67% ee). None of the product **4** was observed. These results may indicate that different Pd complexes are formed in the absence or presence of water. The cationic Pd complex, PdCl[(*R*)-binap](DMF)$^+$TfO$^-$ (**6**), may be formed from **3** and AgOTf in dry DMF. Reaction of this complex with **1** may then generate trimethylsilyl triflate, which could catalyze the nonspecific addition of **1** to **2** and promote acid hydrolysis of **1** if water is present. In the presence of water and 4A molecular sieves, however, **6** may be converted to PdCl[(*R*)-binap](DMF)$^+$· OH$^-$ (or its covalent complex, PdCl(OH)[(*R*)-binap])[9] (**7**), and this species may be responsible for catalysis of the enantioselective aldol process. It is likely that 4A molecular sieves effectively trap the triflic acid produced in the formation of **7** preventing its catalysis of substrate decomposition. Scheme 2 demonstrates a possible mechanism for this catalytic asymmetric aldol reaction. Nucleophilic attack of hydroxide anion on the silyl group may play a key role in the transmetalation step.

Scheme 1



Three forms of transition metal enolates are known, oxygen-bound enolates such as **8**, carbon-bound enolates such as **9**, and oxo-π-allyl complexes such as **10**. To determine which species play a major role in this catalytic asymmetric aldol reaction, we decided to study the reaction progress by NMR. Initially, **3** and AgOTf (1 equiv) were mixed in wet DMF-d_7 in the presence of 4A molecular sieves, stirred at 23 °C for 20 min, and then filtered. A ^{1}H-NMR spectrum of the filtrate clearly showed the formation of a new Pd complex, tentatively assigned as **7** (or a mixture of **6** and **7**). To this solution

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[1] Rh catalysts: (a) Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5517. (b) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. (c) Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3122. Pd catalysts: (d) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126. Ru catalysts: (e) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S. *J. Am. Chem. Soc.* **1989**, *111*, 5954 and references cited therein.

[2] Au(I) and Ag(I) complexes have been reported to catalyze the asymmetric aldol-type reaction of isonitriles with aldehydes. See: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. Recently, the Pd(II) complex-catalyzed reaction of isonitriles has also been reported (maximum 14% ee); see: (b) Nesper, R.; Pregosin, P. S.; Püntener, K.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 2239 and references cited therein.

[3] (a) Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.*, **1987**, *28*, 793 (maximum ee, 12%). (b) Roos, G. H. P.; Haines, R. J.; Raab, C. E. *Synth. Commun.* **1993**, *23*, 1251 (maximum ee, 23%).

[4] Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188.

[5] A representative procedure follows: To a mixture of **3** (160 mg, 0.20 mmol), AgOTf (51 mg, 0.20 mmol), and 4A molecular sieves (powder, 1.2 g) was added wet DMF (144 μL H_2O in 8 mL dry DMF), and the suspension was stirred at 23 °C for 20 min. After canula filtration, **2** (410 μL, 4.0 mmol) and **1** (1.23 mL, 6.0 mmol) were added to the resulting orange solution, and the mixture was stirred at 23 °C for 13 h. Dilution of the reaction mixture with ether, filtration through a short silica gel column, and concentration gave pale yellow oil. This mixture was purified by silica gel column chromatography to afford **4** (1.04 g, 87%) and **5** (82 mg, 9%).

[6] The ee of **4** was determined by HPLC analysis using Chiralcel OJ, hexane:^{i}PrOH 9:1, after conversion to **5** (1 N HCl−THF, 1:2). The absolute stereochemistry was determined to be *R* by comparison of the optical rotation of **4** (+32.4° (*c* 0.74, MeOH) (70% ee)) with the reported value. See: Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513.

[7] The use of other amide solvents such as NMP and DMA resulted in the comparable asymmetric induction to DMF. Reaction in acetonitrile or THF afforded moderate asymmetric induction (33−46% ee). Reaction in dry methylene chloride proceeded smoothly to give only **4**, but the ee of **4** was only 2%. It is likely that a trimethylsilyl cation-catalyzed aldol process predominates in methylene chloride.

[8] The effect of various silver salts (such as $AgClO_4$, $AgNO_3$, AgOAc, $AgBF_4$, $AgPF_6$, $AgOCOCF_3$, Ag_2O, Ag_3PO_4, and Ag_2CO_3) was examined. Similar asymmetric induction was observed for all salts except Ag_2CO_3 (only 10−18% ee).

[9] For transition metal hydroxo complex, see: Woerpel, K. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 7888 and references cited therein.

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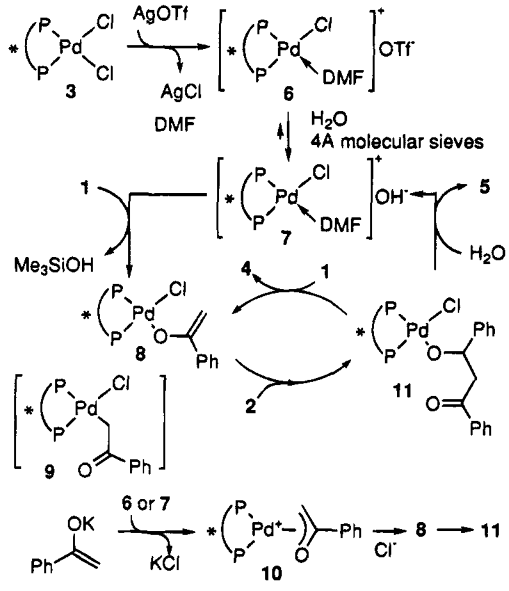
Scheme 2



1 (1 equiv, methylene chemical shifts of **1**: 4.51, 5.11 ppm) was then added, and rapid formation of two singlets at 4.41 and 4.68 ppm was observed consistent with the formation of **8** (Figure 1a).[1b] This complex was not stable at 23 °C under the conditions described above, and gradual formation of acetophenone (2.65 ppm) was observed.[1b] After 60 min, however, two singlets still remained (Figure 1b). Addition of **2** (1 equiv) to this mixture caused the rapid formation of **4** and **5** with disappearance of the two singlets (Figure 1c), and then remaining **1** reacted slowly to give more **4** and **5**. The optically active aldol products **4** (5%, 76% ee) and **5** (21%, 70% ee) were isolated after 1 h (no **1** remained).[10]

Reaction of the cationic complex **6** prepared in DMF-d_7 with the potassium enolate of acetophenone[1b] gave a completely different ^{1}H-NMR spectrum. Two new signals, doublet of doublets, at 3.98 ppm, and a multiplet, at 2.25–2.44 ppm, appeared suggesting formation of **10** (Figure 1d).[11] On addition of **2** very slow conversion to **5** was observed (Figure 1e). It is interesting that enantiomeric excess of this aldol product **5** (38% isolated yield) was almost the same as that of the product described above (73% ee). These facts appear to exclude a Lewis acid mediated pathway,[12] in which the aldehyde, activated by coordination of the cationic Pd complex, reacts with the silyl enol ether. The ^{1}H-NMR experiments described above strongly suggest that reaction via the chiral oxygen-bound Pd enolate **8** is the major pathway.

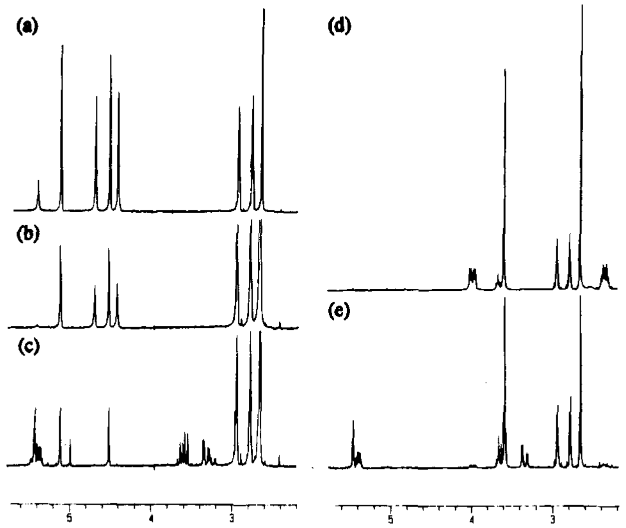
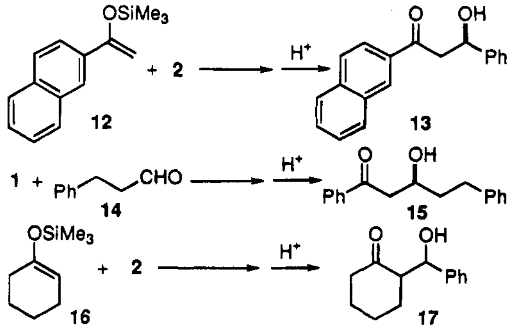


Figure 1. **1** was added to a solution of the cationic Pd complex solution in DMF-d_7 at 23 °C, and the ^{1}H-NMR spectra were taken after (a) 5 min and (b) 60 min. To this mixture **2** was added, and a spectrum was taken after 15 min (c). The potassium enolate of acetophenone was added to a solution of the cationic Pd complex solution in DMF-d_7 at 23 °C. The spectrum was taken after 5 min (d). To this mixture **2** was added, and a spectrum was taken after 20 h (e).

Scheme 3



To define the scope of this novel catalytic aldol reaction, several other substrates were examined using conditions similar to those described above (Scheme 3). Condensation of **12** and **2** proceeded smoothly (37 h), affording **13** in 80% yield after desilylation (73% ee). In addition, reaction of the enolizable aldehyde **14** with **1** (37 h) provided **15** of 73% ee and in 86% yield. While Pd(II) enolates generated from silyl enol ethers and Pd(OAc)$_2$ are known to provide α, β-unsaturated ketones through β-hydrogen elimination,[13] reaction of cyclohexanone silyl enol ether **16** and **2** proceeded to give the desired aldol products **17** in 58% yield (*syn*/*anti* = 43 (72% ee)/15 (18% ee). No cyclohexenone formation was observed.

In conclusion, we have found that the Pd(II)–BINAP complex catalyzes addition of silyl enol ethers to aldehydes smoothly at room temperature affording the corresponding aldol products in good chemical and optical yields. To our knowledge this is the first example of a catalytic asymmetric aldol reaction that occurs via a Pd(II) enolate. Although elegant examples of the Lewis acid-catalyzed asymmetric Mukaiyama aldol reaction have been reported recently,[14] *the catalytic asymmetric aldol reaction reported here is mechanistically different from such a Lewis acid-mediated process.* Investigations for further improvements in the enantioselectivity and further mechanistic studies are currently underway.

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[10] No obvious change in the ^{1}H-NMR spectrum was observed when **2** (1 equiv) was added to the cationic Pd complex in DMF-d_7. Upon addition of **1** (1 equiv) to this mixture the signals corresponding to **8** quickly appeared (5 min) and then resonances for **4** and **5** began to grow. After 12 h the signals of **1**, **8**, and **4** had completely disappeared, and **5** was isolated in 34% yield (73% ee).

[11] Burkhardt, E. R.; Doney, J. J. D.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *109*, 2022.

[12] Aldol reactions catalyzed by transition metal Lewis acids have been reported; see: Cozzi, P. G.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Synlett* **1994**, 857 and references cited therein.

[13] Ito, Y.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

[14] For a review of the Lewis acid-catalyzed asymmetric Mukaiyama aldol reaction, see: Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417 and references cited therein.