

Asymmetric synthesis using palladium catalysts

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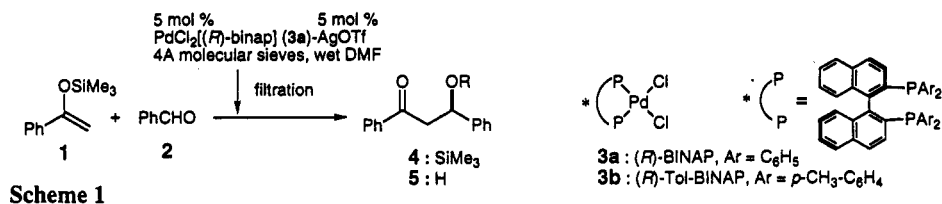
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Abstract: A catalytic asymmetric aldol reaction proceeding via a chiral palladium(II) enolate is described. The novel chiral diaquo palladium(II) complexes of (*R*)-BINAP (**9a**), and (*R*)-Tol-BINAP (**9b**) were prepared in good yield, and their structures were determined by X-ray crystallography. These air- and moisture-stable complexes were found to be excellent catalysts for the asymmetric aldol reaction, and up to 89% ee of asymmetric induction was achieved using these catalysts.

The development of new catalytic asymmetric carbon-carbon bond-forming reaction has become a popular interest in recent years, as such reactions can provide routes to a variety of optically active chiral building blocks for the synthesis of natural products and chiral drugs. Among the various catalyst systems, we have focused on the use of chiral palladium complexes. We have developed an asymmetric Heck reaction and applied this reaction to the synthesis of various natural products.¹ We have also reported a tandem carbon-carbon bond-forming reaction using the asymmetric Heck reaction in combination with a palladium-catalyzed π -allylic substitution reaction² and Suzuki coupling reaction.³ More recently we started a project to develop a novel palladium-catalyzed asymmetric aldol reaction.⁴ The catalytic aldol reaction that proceeds via a transition metal enolate has attracted much attention from organic chemists, and several pioneering works using achiral transition metal complexes as catalysts have already been reported.⁵ To our knowledge, however, there has been no example of a catalytic asymmetric aldol reaction which proceeds with high enantioselectivity via a chiral transition metal enolate.^{6,7} In this paper we describe the first synthetically useful example of a catalytic asymmetric aldol reaction that proceeds via a Pd(II) enolate.⁴ Using a Pd(II)-(*R*)-BINAP-derived complex as the catalyst, good chemical and optical yields (up to 89% 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 first found that the cationic Pd complex generated from PdCl₂(*R*)-binap] (**3a**)⁸ and AgOTf (1 eq relative to **3**) in wet DMF (1.8 v/v % H₂O) 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. For example, addition of benzaldehyde (**2**) and acetophenone silyl enol ether (**1**) (1.5 eq relative to **2**) to this catalyst solution (5 mol % relative to **2**) and stirring at 23 °C for 13 h afforded the aldol products in 96% yield (**4** : 87%, **5** : 9%) and in 71% and 73% ee respectively. A quite interesting feature of this reaction is *the requirement for water and molecular sieves in the preparation of an active catalyst*. Rigorous drying of DMF (freshly distilled from CaH₂) 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.



Scheme 1

Although three forms of transition metal enolates, oxygen-bound enolates such as **6**, carbon-bound enolates such as **7** and oxo- π -allyl complexes such as **8** are known, NMR experiments have shown that this reaction proceeds via an oxygen-bound enolate. Initially **3a** and AgOTf (1 eq) were mixed in wet DMF- d_7 in the presence of 4A molecular sieves, stirred at 23 °C for 20 min and then filtered. To the filtrate **1** (1 eq, methylene chemical shifts of **1**: 4.51, 5.11 ppm) was then added, and the rapid formation of three singlets at 4.41, 4.68, and 9.54 ppm was observed. Addition of **2** (1 eq) to this mixture caused the rapid formation of **4** and **5** with the disappearance of these three singlets (Figure 1c). The optically active aldol products **4** (5%, 76% ee) and **5** (21%, 70% ee) were isolated after 1 h. No starting material remained. The two singlets observed at 4.41 and 4.68 ppm are consistent with the formation of the palladium oxygen-bound enolate of acetophenone.^{5c,9} Integration of the singlet at 9.54 ppm decreased when same reaction was carried out in a mixture of D_2O and DMF. This fact and the requirement for water in this reaction suggest that some oxygen ligand such as OH, H_2O , or Me_3SiOH is involved in the formation of this palladium oxygen-bound enolate.

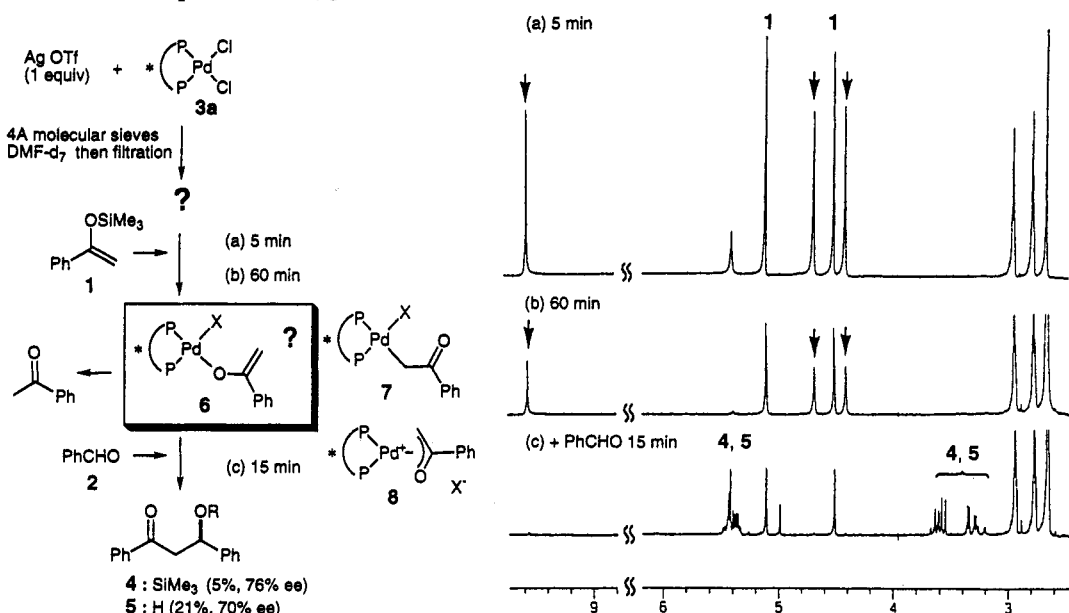


Figure 1

When the ratio of silver triflate to PdCl₂[(*R*)-tol-binap] (**3b**)¹⁰ was increased (10 mol % AgOTf, 5 mol % Pd) in the catalyst preparation, the reaction proceeded quite smoothly and a greater than 90% yield of the aldol products (mixture of **4** and **5**) was obtained after only 2.5 h.¹¹ This was much faster than the reaction using equimolar amounts (5 mol %) of AgOTf and Pd that required 19 h for completion. The enantioselectivity of the products obtained from both reactions were almost identical (71% ee) suggesting the participation of the same catalytic species in these reactions. In addition, these experimental results strongly suggest that chloride ion is not involved in the catalytically active complex.¹²

Because our original procedure for the preparation of the active catalyst was somewhat difficult (mixing the Pd complex, silver salt, and water in DMF, and then filtration), we attempted to isolate the active complex. After examination of various reaction conditions (reactions of **3a** or **3b** with a number of silver salts in a variety of wet solvents in the presence or absence of molecular sieves), we found that reaction of PdCl₂[(*R*)-binap] (**3a**) or PdCl₂[(*R*)-tol-binap] complex (**3b**) with 2 equiv of silver tetrafluoroborate in wet acetone (0.5 v/v % H₂O/acetone) gave a crystalline, yellow complex in good yield (75% for the (*R*)-BINAP complex, and 76% for the (*R*)-Tol-BINAP complex, respectively, after removal of AgCl by filtration and recrystallization).^{11,13} The structures of these complexes were determined by X-ray crystallography to be the diaquo Pd²⁺ complexes **9a** and **9b**. The structure of [Pd((*R*)-tol-binap)(H₂O)₂]²⁺(BF₄)₂ (**9b**) is shown as an example in figure 2. These complexes are quite stable to air and moisture, and can be stored for several months at room temperature without problem.

Using 5 mol % of the novel optically active diaquo palladium complex **9b** the asymmetric condensation of **1** and **2** in *dry* (freshly distilled from CaH₂) DMF gave a near quantitative yield of the aldol products **4**

and **5** in only 1.5 h at room temperature.¹¹ The optical yield of the products **4** and **5** are 72% ee and 73% ee, respectively. With this complex as a catalyst, the addition of extra water is not necessary for reaction of this trimethylsilyl enol ether substrate. When the amount of catalyst was reduced to 1 mol %, aldol product **5** (after HCl treatment) was obtained in 84% yield after 42 h without any loss of the asymmetric induction (74% ee). Interestingly, again, the addition of a trace amount of water (0.2 mol equiv to **2**) accelerated this reaction to give **5** (83%, 74% ee) after only 18 h.¹⁴

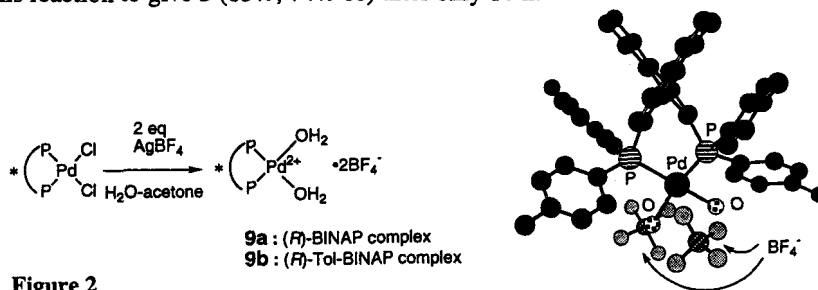
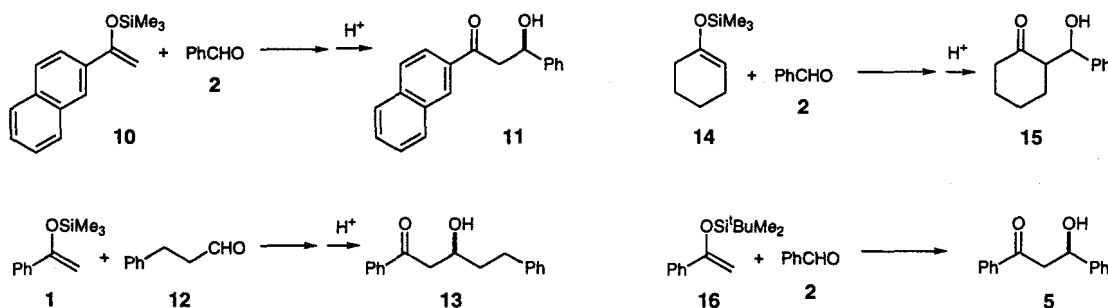


Figure 2

To define the scope of this novel catalytic aldol reaction, several other substrates were examined using the diaquo palladium complex $[\text{Pd}((R)\text{-tol-binap})(\text{H}_2\text{O})_2]^{2+}(\text{BF}_4^-)_2$ (**9b**).¹¹ Condensation of **10** and **2** using 1 mol % of **9b** in wet DMF (0.2 mol equiv of H_2O relative to **2** was added) proceeded smoothly (at 22 °C, 18 h) affording **11** in 82% yield after desilylation (72% ee). In the case of the aliphatic aldehyde **12**, reaction with 1 mol % of **9b** was very slow and gave a lower chemical yield; however, **13** was obtained in good chemical (78%) and optical yield (74% ee) when 2.5 mol % of **9b** was used as the catalyst (23 °C, 44 h). This latter example demonstrates the utility of these reaction conditions with enolizable aldehydes. While Pd(II) enolates generated from silyl enol ethers and $\text{Pd}(\text{OAc})_2$ are known to provide α , β -unsaturated ketones through β -hydrogen elimination,¹⁵ reaction of cyclohexanone silyl enol ether **14** with **2** (1 mol % **9b**, 20 °C, 43 h) proceeded to give the desired aldol product **15** in 56% yield (*syn/anti*: 44 (70% ee)/12 (13% ee)). No cyclohexenone formation was observed. Reaction of *tert*-butyldimethylsilyl enol ether **16** in dry DMF was quite slow even with 5 mol % of **9b**, and only 17% yield of the aldol product **5** (OH form only, without any acid treatment) was obtained after 17 h. Addition of a large amount of water (1.8 v/v % in DMF, 2 mol equiv relative to **2**), however, accelerated the reaction affording **5** in 77% yield after 17 h, and the optical yield of **5** (74% ee) was comparable to the product of the reaction of the corresponding trimethylsilyl enol ether **1**. Since trimethylsilyl enol ethers are quite unstable to hydrolysis and difficult to purify, the use of this reaction for *tert*-butyldimethylsilyl enol ethers is noteworthy and should be useful for the synthesis of complex molecules.



Scheme 2

For the purpose of further improvement of optical yield, we re-examined solvent effects using the diaquo complex **9a**.¹⁶ The optical yields of **5** from the reaction of **2** (ca. 0.1 M in various solvents)¹⁷ with **1** (1.5 equiv) using 5 mol % of **9a** as a catalyst were as follows: DMF, 74% ee; THF, 49% ee; CH_2Cl_2 , 73% ee; NMP, 72% ee; CH_3CN , 67% ee; DMSO, 72% ee; benzene, 4% ee; HMPA, 54% ee; DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone), 81% ee; DMI (1,3-dimethyl-2-imidazolidinone), 82% ee; TEU (1,1,3,3-tetraethylurea), 70% ee; and TMU (1,1,3,3-tetramethylurea), 84% ee. Apparently urea solvents give better asymmetric induction, with the best selectivity (84% ee) could be achieved on reaction in TMU. Finally we were pleased to find that the aldol product **5** could be obtained in 92% chemical yield and 89% ee when the reaction was carried out at 0 °C.¹⁸ Using a similar procedure,

optical yields for the condensation of **10** and **2** (89%, 87% ee), and **1** and **12** (88%, 81% ee) were improved.

In summary, we have found that the Pd(II)-BINAP complex catalyzes the addition of silyl enol ethers to aldehydes smoothly at ambient 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. Furthermore, the novel chiral diaquo palladium(II) complexes **9a**, and **9b** were prepared in good yield, and their structures were characterized by X-ray structural analysis. These air- and moisture-stable complexes were found to be excellent catalysts for the asymmetric aldol reaction. Mechanistic studies on this unique asymmetric aldol reaction are in progress.

Acknowledgements. We are greatly indebted to our talented co-workers, Dr. Kazuhiko Ohrai, Dr. Ryosuke Tokunoh, Mr. Futoshi Miyazaki, Ms. Emiko Hagiwara, and Dr. Akio Fujii. We thank Takasago International Corporation for the generous gift of (*R*)-Tol-BINAP. We also thank Rigaku Corporation, for X-ray analyses. This study was financially supported by a Grant-in-Aid for Encouragement of Young Scientists from Ministry of Education, Science and Culture, Japan.

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10. PdCl₂[(*R*)-tol-binap] (**3b**) was prepared in a similar manner to PdCl₂[(*R*)-binap] (**3a**).⁸ Since these two complexes were found to show basically the same reactivity and asymmetric induction, we used both complexes for this research.
11. M. Sodeoka, R. Tokunoh and M. Shibasaki, unpublished results.
12. A complex prepared from [Pd(CH₃CN)₄]²⁺(BF₄⁻)₂ (5 mol %) and (*R*)-Tol-BINAP (5 mol %) in wet DMF in the presence of 4A molecular sieves also effectively catalyzed the condensation of **1** with **2** to give **4** (98%, 69% ee) and **5** (2%, 64% ee).
13. M. Sodeoka, E. Hagiwara, K. Ohrai and M. Shibasaki, unpublished results.
14. Addition of too much water caused decomposition of **1** and decreased the chemical yield of the product (addition of 0.5 mol equiv of H₂O: 45%, 70% ee; addition of 1 mol equiv of H₂O: 4%, 67% ee).
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16. M. Sodeoka and E. Hagiwara, unpublished results.
17. Reaction concentration was important for the reactivity and asymmetric induction when TMU was used as the solvent. Reaction at ca. 0.67 M of **2** in TMU was slower than that at 0.1 M, and the optical yield of the product decreased from 84% ee to 76% ee. No dependence of optical yield on concentration was observed for the reaction in DMF.
18. A representative procedure follows: To a solution of **9a** (4.9 mg, 0.005 mmol) and **2** (10 μL, 0.1 mmol) in TMU (3.0 mL, distilled from CaH₂) was added **1** (31 μL, 0.15 mmol) in three portions at 30 min intervals at 0 °C. The mixture was stirred at 0 °C for 24 h. Dilution of the reaction mixture with ether, filtration through a short silica gel column, and concentration gave pale yellow oil. To this mixture was added a mixture of 2N HCl and THF (1:1, 4 mL). After stirring at room temperature for 30 min, the reaction mixture was diluted with water, and extracted with ether. The combined organic layer was washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was purified by preparative silica gel thin layer chromatography (AcOEt:hexane, 3:17) to afford **5** (20.3 mg, 92%). The ee of **5** was determined to be 89% by HPLC analysis using Chiralcel OJ, (hexane:ⁱPrOH, 9:1).