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A New Entry to Pd–H Chemistry: Catalytic Asymmetric Conjugate Reduction of Enones with EtOH and a Highly Enantioselective Synthesis of Warfarin

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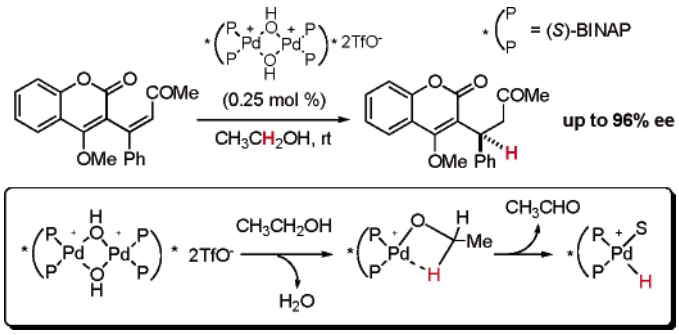
ABSTRACT



We report here the catalytic asymmetric conjugate reduction of enones using ethanol as a hydride source. The reaction was carried out in the presence of a chiral Pd complex at ambient temperature in ethanol, and the desired products were obtained in high chemical yield and high enantioselectivity. We applied this novel reaction to the catalytic asymmetric synthesis of warfarin (96% ee), and on the basis of *d*-labeling experiments, the reaction mechanism is proposed.

Catalytic asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated carbonyl compounds has recently emerged as a powerful method. Following the early work using chiral Co complexes combined with $NaBH_4$,[1] excellent enantioselectivity was achieved by the use of optically active Cu−bisphosphine or Rh−Phebox complex as a catalyst and hydrosilane as a reducing agent.[2−3] Further, the reduction of α,β-unsaturated aldehydes became feasible using chiral secondary amines with Hantzsch esters.[4] However, these reactions require a more-than-stoichiometric amount of reducing agents. In terms of atom economy and environmental concerns, a conjugate reduction using environmentally benign alcohols, such as ethanol as a hydride source and solvent, would be extremely beneficial.

(1) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60−61. (b) Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 967−970. (c) Geiger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249−254.

(2) Cu: esters: (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreria, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253−11258. (c) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352−8353. Nitroolefins: (d) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793−4795. Enones: (e) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797−6798. (f) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789−4792. (g) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273−1275. (h) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 1259−1264.

(3) Rh: esters: (a) Tsuchiya, Y.; Kanazawa, Y.; Shiomi, T.; Kobayashi, K.; Nishiyama, H. *Synlett* **2004**, 2493−2496. Enones: (b) Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chem.−Eur. J.* **2006**, *12*, 63−71.

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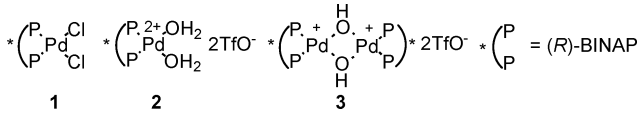
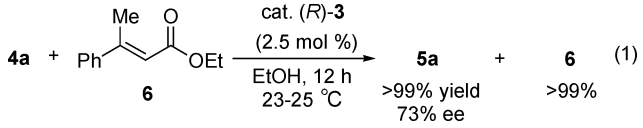
We have already reported various asymmetric reactions catalyzed by the chiral Pd−bisphosphine complexes **2** and **3**,[5] and we recently found that an α,β-unsaturated carbonyl compound was reduced in ethanol in the presence of **2** or **3**. Pd hydride species have been proposed to be key intermediates in the Pd-catalyzed oxidation of alcohols, but they are usually decomposed to Pd(0), which is reoxidized to complete the catalytic cycle.[6−7] We speculated that the Pd hydride species generated under our conditions might act as a reducing agent. While Pd−H species are known to be important intermediates in several reactions,[8] their use in the asymmetric conjugate reduction of enones has, to the best of our knowledge, not previously been reported.[9] In this paper, we describe an efficient enantioselective conjugate reduction of enones using ethanol as a hydride source and its application to the asymmetric synthesis of (*S*)-warfarin, a clinically important anticoagulant.



1 **2** **3**

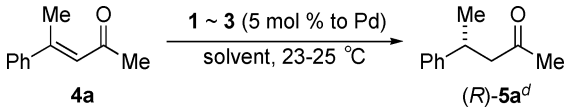
Initially, we examined the reaction of (*E*)-4-phenyl-3-penten-2-one **4a** in the presence of 5 mol % of chiral Pd−bisphosphine complexes in ethanol (1 M) at ambient temperature (Table 1). No reaction was observed when the chloride complex **1** was used as a catalyst (entry 1). However, when the aqua complex **2** was used, the reaction was complete after 6 h to give **5a** in 88% yield with 74% ee (entry 2). In entry 2, a small amount (8%) of acetophenone was isolated as a byproduct, probably due to hydration of the enone followed by a retro-aldol reaction. In contrast, no acetophenone formation was observed in the reaction using **3** as a catalyst, which afforded **5a** in quantitative yield with 74% ee (entry 3). The reaction in 2-propanol was considerably slower (entry 4), and ethanol was found to give the best result. No reduction of the carbonyl group was observed, indicating high functional group selectivity (1,2 reduction vs 1,4 reduction). Furthermore, when a mixture of **4a** and ethyl (*E*)-β-methylcinnamate **6** was subjected to the conjugate reduction, only **4a** was reduced, and the ester **6** was recovered quantitatively (eq 1). It is noteworthy that this reaction does not require the tedious Schlenck technique or special equipment and proceeds even in an open flask.



(1)

With these results in hand, we next examined the reactions of other substrates (Table 2). The reaction of the ethyl-substituted substrate **4b** was completed after 3 h in the presence of 2.5 mol % of **3**, affording **5b** in 97% yield with 84% ee. Interestingly, as the bulkiness of the β-substituent was increased, the reaction rate was significantly enhanced. The reaction of the substrate bearing *i*-Pr or *c*-Hex was completed within 1 h, affording the reduced products **5c** and **5d** in excellent yields in a highly enantioselective manner

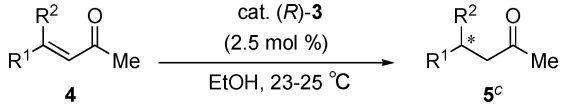
Table 1. Optimization of the Reaction Conditions



entry	cat.	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	**1**	EtOH	24	*c*	
2	**2**	EtOH	6	88	74
3	**3**	EtOH	12	>99	74
4	**3**	*i*-PrOH	12	29	72

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Recovery of the starting material. [d] For determination of the absolute stereochemistry, see Supporting Information.

Table 2. Catalytic Asymmetric Conjugate Reduction of Enones



entry	R^1	R^2	product **5**	time (h)	yield[a] (%)	ee[b] (%)
1	Ph	Et	**5b**	3	97	84 (*R*)
2	Ph	*i*-Pr	**5c**	1	>99	92 (*S*)
3	Ph	*c*-Hex	**5d**	0.5	97	86
4	Ph	CF_3	**5e**	1	85	84
5	2-BrC_6H_4	Me	**5f**	6	>99	80

[a] Isolated yield. [b] Determined by chiral HPLC. [c] For determination of the absolute stereochemistry, see Supporting Information.

(4) Organocatalysis: (a) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110. (b) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33.

(5) (a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531. (d) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164−10165. (e) Sodeoka, M.; Hamashima, Y. *Pure Appl. Chem.* **2006**, *78*, 477−494 and references therein.

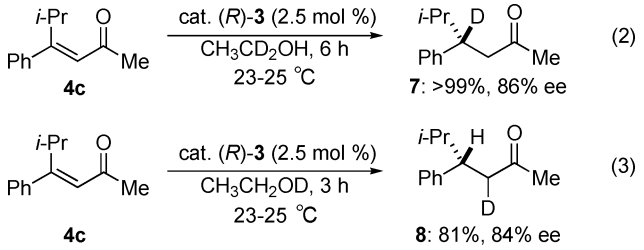
(6) (a) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755. (c) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726.

(7) Mechanistic studies on formation of Pd hydride in oxidation of alcohols: (a) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734. (b) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904−2907 and references therein.

(8) Tsuji, J., Ed. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons: Chichester, UK, 2004.

(9) Putative Pd hydride species generated from Pd(0) and metal hydrides were used in non-enantioselective conjugate reduction. Haskel, A.; Keinan, E. In *Handbook of Organopalladium Chemistry in Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, Chapter VII 2.3, pp 2767−2782.

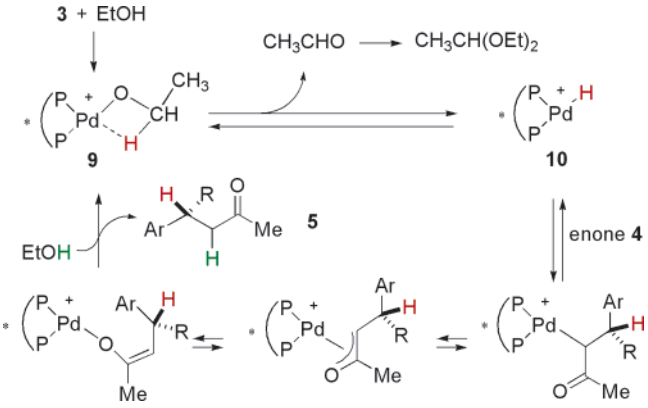
(92 and 86% ee, respectively) (entries 2 and 3). Reaction of the β-CF_3-enone **4e** also proceeded smoothly to give **5e** in 85% yield with 84% ee (entry 4), which would be valuable in medicinal chemistry. Notably, the conjugate reduction of the Br−arene-substituted enone **4f** proceeded without difficulty to afford **5f** in >99% yield with 80% ee (entry 5). No reduction of the Br group or Heck-type reaction was observed, suggesting that no Pd(0) species is involved in the reaction.



To examine the mechanism of the reaction, we conducted the reaction in *d*-ethanol. The reaction of **4c** in CH_3CD_2OH (ethyl-1,1-d_2 alcohol) afforded **7** in >99% yield with 86% ee (eq 2). In this reaction, selective deuterium incorporation at the β-position was observed.[10] On the other hand, the use of CH_3CH_2OD (ethyl alcohol-*d*) afforded **8**, having a deuterium at the α-position (eq 3).

On the basis of these results, we propose the catalytic cycle depicted in Scheme 1. First, the Pd complex **3** acts as a

Scheme 1. Proposed Catalytic Cycle

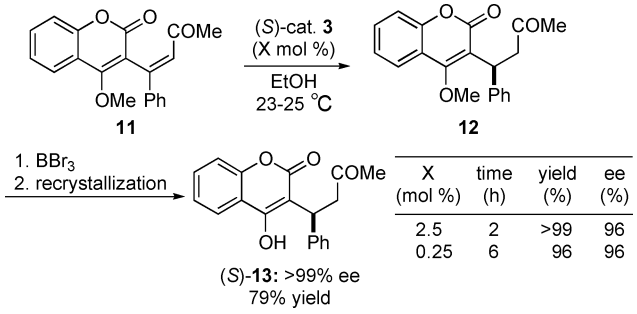


Brønsted base[5] to generate the Pd−ethoxide **9**, which subsequently gives the Pd hydride **10** via β-hydride elimination.[6,7] The enones **4** coordinating to the Pd complex would undergo hydride transfer, and the resulting Pd enolate is protonated by ethanol to reproduce the Pd−ethoxide complex **9**. In this proposed mechanism, the hydrogen atoms in ethanol (indicated in red and green, respectively) are selectively incorporated into the reduced product, which is in accord with the results of the labeling experiments.[11]

(10) Reaction in CH_3CD_2OH was much slower than that in ethanol, suggesting that the formation of the Pd hydride species may be a rate-determining step. See ref 7.

Finally, we applied our novel conjugate reduction to the asymmetric synthesis of warfarin, a well-known anticoagulant (Scheme 2). Although the biological activity of

Scheme 2. Asymmetric Synthesis of Warfarin



X (mol %)	time (h)	yield (%)	ee (%)
2.5	2	>99	96
0.25	6	96	96

the *S* enantiomer is about 5−8 times higher than that of the *R* enantiomer, warfarin has been prescribed as a racemate for a long time.[12] Several approaches to the enantioselective synthesis of optically active warfarin have been reported.[13] Considering that our reaction favors substrates bearing a bulky substituent at the β-position, we examined the conjugate reduction of 4-Me-dehydrowarfarin **11** (Scheme 2).[14] As we expected, the reaction proceeded smoothly in the presence of the (*S*)-Pd complex **3** (2.5 mol %) to afford the reduced product **12** quantitatively. To our delight, the enantiomeric excess of **12** was as high as 96%. Furthermore, the amount of catalyst could be reduced to as little as 0.25 mol % without any loss of enantioselectivity. Demethylation with BBr_3, followed by a single recrystallization, gave optically pure (*S*)-warfarin **13**.[15] To the best of our knowledge, this is the most enantioselective reaction currently available for the catalytic asymmetric synthesis of warfarin.

In conclusion, we have shown that the cationic Pd hydride generated from the Pd(μ-OH) complex **3** and ethanol can act as a reactive chiral reducing agent. An efficient catalytic asymmetric conjugate reduction of enones, having potential for industrial use, has been developed. This reaction was shown to be applicable to the asymmetric synthesis of (*S*)-

(11) The results of the labeling experiments cannot exclude the possibility that reduction occurs through direct hydride transfer from Pd-bound ethanol to the β-position of the enone, which is relevant to the mechanism of Meerwein−Ponndorf−Verley reduction. However, our preliminary NMR and ESI-MS studies suggest that a Pd hydride is formed as a key intermediate in our reaction.

(12) (a) O'Reilly, R. A. *New Engl. J. Med.* **1976**, *295*, 354−357. (b) Wingard, L. B.; O'Reilly, R. A.; Levy, G. *Clin. Pharmacol. Ther.* **1978**, *23*, 212−217. (c) Rang, H. P.; Dale, M. M.; Ritter, J. M.; Gardner, P. *Pharmacology*, 4th ed.; Churchill Livingstone: Philadelphia, 2001.

(13) For the synthesis of optically active warfarin, see: (a) Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H. *Turk. J. Chem.* **1996**, *20*, 139−145. (b) Robinson, A.; Li, H.-Y.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321−8324. (c) Li, H.-Y.; Robinson, A. U.S. Patent 5,856,525, 1999. (d) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707−709. (e) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955−4957.

(14) Reaction of dehydrowarfarin was unsuccessful because of facile intramolecular cyclization to give the corresponding mixed ketal. Similar reaction was observed in ref 13b.

(15) For the absolute configuration of warfarin, see: West, B. D.; Preis, S.; Schroeder, C. H.; Link, K. P. *J. Am. Chem. Soc.* **1961**, *83*, 2676−2679.

warfarin **13** with excellent yield and selectivity (96% ee). Further work to expand the scope of the reaction and to establish the mechanism in detail is underway.

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Supporting Information Available: Experimental details of the conjugate reduction and the spectroscopic characterization of new compounds (PDF) are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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