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Asymmetric catalysis of ene reactions with trifluoropyruvate catalyzed by dicationic palladium(II) complexes

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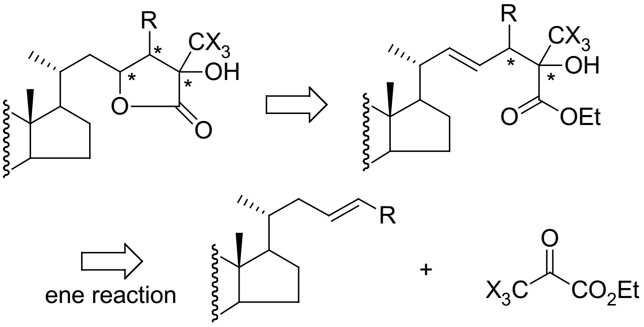
Abstract—Chiral dicationic SEGPHOS–Pd(II) complex achieves a high chemical yield, (*E*)-olefin selectivity, *anti*-diastereoselectivity, along with high enantioselectivity even with less reactive mono- and 1,2-disubstituted olefins in this much less reactive ketone–ene reactions. The high levels of enantioselectivity stem from the effective shielding with diphenyl groups on phosphines caused by the narrow dihedral angle of metal complexes with SEGPHOS.

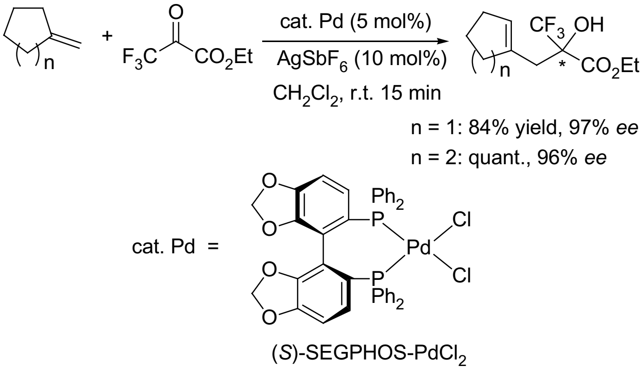
Carbonyl–ene reactions with ketones are synthetically important as a short access to chiral tertiary alcohols with homo-allylic functionality.[1] However, there has been essentially no successful example on the asymmetric catalysis of ketone–ene reactions except for the recent report by Evans,[2] because of low ene reactivities of ketones as compared with aldehydes. We report herein the success in asymmetric catalysis of the ketone–ene reaction by a dicationic SEGPHOS–Pd(II) complex [SEGPHOS = (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diarylphosphine)][3] rather than the nitrile-coordinated dicationic BINAP–Pd(II) complexes[4] to construct the corresponding quaternary carbon centers[5] as conceptually exemplified in the retro-synthesis of steroid side chains (Scheme 1).

The asymmetric catalysis of ketone–ene reactions was first investigated with 1,1-disubstituented olefins and ethyl trifluoropyruvate by dicationic Pd(II) complex bearing chiral diphosphine ligands, SEGPHOS, in particular. The dicationic SEGPHOS–Pd(II) was prepared in situ from SEGPHOS–$PdCl_2$ and two equimolar amount of $AgSbF_6$ in CH_2Cl_2. Fortunately, the ene products were obtained with high chemical yield and high enantioselectivity (96–97% ee) in the catalytic reactions at room temperature within 15 min (Scheme 2).[6]

As suggested by the results above, the SEGPHOS–Pd(II) complex is the suitable catalyst for ketone–ene



Scheme 1.



Scheme 2.

Keywords: carbonyl–ene reaction; palladium; BINAP; SEGPHOS; trifluoropyruvate.

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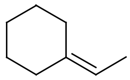
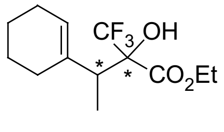
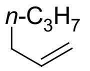
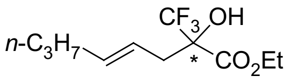
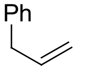
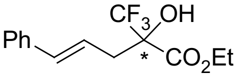
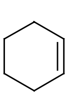
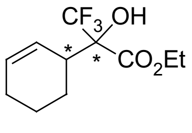
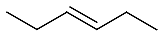
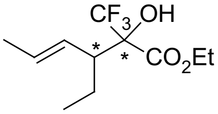
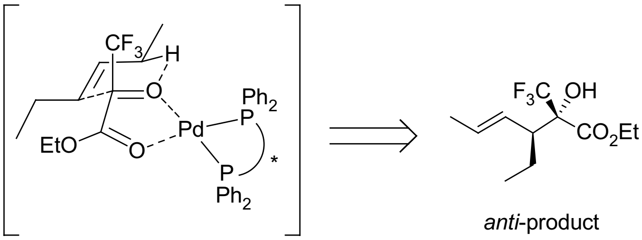
Table 1. Asymmetric ene reactions with a variety of olefins

Entry	Olefin	Ene product	Time (h)	Yield (%)	% ee	Ratio
1			0.5	80	84	*anti*/*syn* = 98/2
2			0.5	79	97	100% (*E*)
3			0.5	quant.	96	100% (*E*)
4			1	64	92	*anti*/*syn* = 91/9
5			1	65	96	100% (*E*) *anti*/*syn* = 96/4

reactions with ethyl trifluoropyruvate. A variety of olefins were then examined under the same conditions (Table 1). Trisubstituted olefin gave the ene product in good yield and enantioselectivity (entry 1). Significantly, the reaction of mono-substituted olefins with low ene reactivity proceeded with high levels of enantioselectivity and exclusively (*E*)-selectivity (entries 2 and 3). In spite of decreased yield, less reactive 1,2-disubsituted olefins also exhibited high diastereo- and enantioselectivity (entries 4 and 5). An electron-withdrawing trifluoromethyl substituent might be important for accelerating inter-molecular electrophilic attack onto the less ene reactive mono- and 1,2-disubstitued olefins. The dicationic SEGPHOS–Pd(II) complex-catalyzed ketone–ene reactions can proceed only 1,1-di-substituted methylenecyclohexane with the less electrophilic nonfluorinated ethyl pyruvate (47% yield, 98% ee).

The stereochemical assignment of the diastereomeric products deserves comment. Based on the similarity of the *anti*-diastereoselective reaction catalyzed by $SnCl_4$, the major isomers of the ene products were determined to be *anti* (Scheme 3).[7]



65% yield, 100% (*E*), *anti/syn* = 96/4, 96% *ee*
cf. $SnCl_4$; 34% yield, 100% (*E*), *anti/syn* = 91/9

Scheme 3.

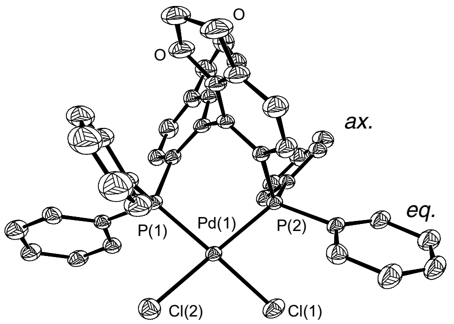


Figure 1. ORTEP drawing of (*S*)-SEGPHOS–$PdCl_2$.

Encouraged by the success in ketone–ene reactions with SEGPHOS–Pd(II) complex, the dihedral angle of metal complexes with various diphosphine ligands was examined. Indeed, the X-ray analysis of SEGPHOS–$PdCl_2$ complex[8] shows that the dihedral angle is significantly narrower (60.1°) than that of BINAP–$PdCl_2$ complex (70.2°)[9] (Fig. 1). As already reported dihedral angle of SEGPHOS–Ru is narrower (64.99°) than BINAP–Ru 73.49°.[3] The enantioselectivity with methylenecyclohexane is thus inversely correlated to the dihedral angles of the diphosphine ligands from SEGPHOS (96% ee) to BINAP (95% ee), by virtue of the effective shielding with diphenyl groups on phosphines caused by the narrower dihedral angle of metal complexes with SEGPHOS, in particular.

In summary, we have demonstrated the ketone–ene reactions of even with the less ene reactive mono- and 1,2-

disubstitued olefins catalyzed by chiral dicationic SEGPHOS–Pd(II) complex, which provides an important and short access to chiral quaternary carbon with homoallylic tertiary alcohol and trifluoromethyl functionalities of which the latter is of material and pharmaceutical interests.

Acknowledgements

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References and Notes

1. (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vols. 2 and 5; (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021; (c) Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, Heidelberg, 1999; Vol. III, p 1143; (d) Mikami, K.; Nakai, T. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000. p 543.
2. Evans reported the excellent example of asymmetric catalysis of glyoxylate–ene reaction with a variety of olefins by chiral bis-oxazoline Cu^{2+} complexes; Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. In relation to the glyoxylate–ene reaction, pyruvate is also examined as an enophile to give, however, low yield of the corresponding ene product even with a reactive 1,1-disubstituted olefin, methylenecyclohexane (5 equiv), at room temperature to heated conditions (40 °C) for 2 days. The use of large excess of methylenecyclohexane gave 84% yield using 20 mol% of the Cu^{2+} catalyst under the heated conditions for 2 days.
3. Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264, EP 850945A, 1998, US 5872273, 1999.
4. (a) Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996**, *37*, 6351; (b) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017; (c) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660; (d) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059; (e) Becker, J. J.; Van Orden, L. J.; White, P. S.; Gagne, M. R. *Org. Lett.* **2002**, *4*, 727.
5. Reviews: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037; (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Ind. Ed.* **1998**, *37*, 388.
6. Typical experimental procedure: To a solution of (*S*)-SEGPHOS–$PdCl_2$ (15.8 mg, 0.02 mmol) in CH_2Cl_2 (2.0 ml) was added silver hexafluoroantimonate (15.1 mg, 0.044 mmol) under argon atmosphere. After the mixture was stirred at room temperature for 30 min, ethyl trifluoropyruvate (80 μl, 0.60 mmol) and methylenecyclohexane (48 μl, 0.40 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 15 min, directly loaded onto a silica gel column and eluted with hexane/ethyl acetate = 5/1 to give ene product quantitatively as a colorless oil. GC (column, CP-Cyclodextrin-β-2,3,6-M-19, i.d. 0.25 mm × 25 m, CHROMPACK; carrier gas, nitrogen 75 kPa; column, 120 °C; injection temp, 150 °C), t_R of major isomer 25.9 min, t_R of minor isomer 27.2 min. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, $J = 7.2$ Hz, 3H), 1.45–1.59 (m, 4H), 1.82–2.09 (m, 4H), 2.47 (d, $J = 14.1$ Hz, 1H), 2.63 (d, $J = 14.1$ Hz, 1H), 3.77 (d, $J = 0.9$ Hz, 1H), 4.25–4.34 (m, 2H), 5.52 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.9, 22.8, 25.4, 29.8, 39.6, 63.5, 78.2 (q, $J_{C\text{–}F} = 27.9$ Hz), 123.4 (q, $J_{C\text{–}F} = 285.2$ Hz), 127.7, 130.9, 169.7.
7. Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6305.
8. X-ray crystallographic was performed with a Rigaku AFC7R diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71069$ Å) at 253 K. Crystal data for (*S*)-SEGPHOS–$PdCl_2 \cdot 2C_6H_6$: experimental formula $C_{38}H_{28}Cl_2O_4P_2Pd$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 17.5015(19)$ Å, $b = 19.825(3)$ Å, $c = 12.6610(19)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 4393.1(10)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.191\ g\,cm^{-3}$, range for date collection $2\theta\,max = 55.00°$. The structures were solved by direct methods (SHELXL-97). The final cycle of full-matrix least-squares was based on 5567 observed reflections ($I > 2\sigma(I)$) and 521 variable parameters and converged to $R = 0.0464$, $R_w = 0.1804$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC-186409. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Selective bond lengths [Å], bond angles [°]: Pd(1)–P(1) 2.255(2), Pd(1)–P(2) 2.261(2), Pd(1)–Cl(1) 2.355(2), Pd(1)–Cl(2) 2.352(3): P(1)–Pd(1)–P(2) 90.95(8), Cl(2)–Pd(1)–P(1) 89.79(9), Cl(1)–Pd(1)–Cl(2) 89.29(1), Cl(1)–Pd(1)–P(2) 91.32(9). ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, $J = 1.5$ Hz, 2H), 5.89 (d, $J = 1.2$ Hz, 2H), 6.36 (dd, $J = 8.1$, 1.5 Hz, 2H), 6.47 (dd, $J = 12.0$, 8.4 Hz, 2H), 7.28–7.52 (m, 20H), 7.62–7.73 (m, 4H), 7.94 (m, 4H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.19 (s, 2P).
9. X-ray crystallographic analysis was performed in our hands with a Rigaku R-AXIS CS (Imaging Plate) diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71069$ Å) at 223 K. Crystal data for (*S*)-BINAP–$PdCl_2$: experimental formula $C_{44}H_{32}Cl_2P_2Pd$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 15.81470(10)$ Å, $b = 22.2991(2)$ Å, $c = 12.7147(6)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 4483.9(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.155\ g\,cm^{-3}$. The structures were solved by direct methods (SHELXL-97). The final cycle of full-matrix least-squares was based on 4761 observed reflections ($I > 2\sigma(I)$) and 422 variable parameters and converged to $R = 0.1221$, $R_w = 0.3173$. Also see: Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188.