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Chiral Palladium(II)-Catalyzed Asymmetric Glyoxylate–Ene Reaction: Alternative Approach to the Enantioselective Synthesis of α-Hydroxy Esters

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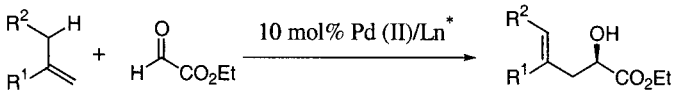
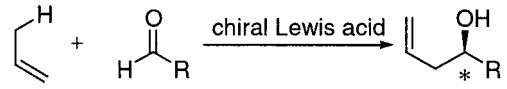
ABSTRACT



An effective chiral palladium catalyst [Pd(CH_3CN)$_2$(*S*)-Tol-BINAP](SbF$_6$)$_2$ (2b) is developed for asymmetric glyoxylate–ene reactions. This palladium dicationic catalyst provides a simple but efficient approach to the asymmetric synthesis of α-hydroxy esters in excellent yields with high enantioselectivities at relatively higher reaction temperature (60 °C).

As one of the most important methodologies for carbon−carbon bond construction, asymmetric ene reactions catalyzed by chiral Lewis acids have received great attention in recent years.[1] Among those, a number of examples of glyoxylate−ene reactions, which afford α-hydroxy esters, versatile synthons in organic synthesis, have been described.[2]



We have reported asymmetric glyoxylate−ene reactions catalyzed by titanum(IV) complexes with chiral binaphthol (BINOL) ligands at low reaction temperature (ca. −30 °C) to produce the α-hydroxy esters in excellent enantioselectivities and chemical yields.[3] However, the BINOL−Ti catalysts are only successful with 1,1-disubstituted olefins. The reaction with monosubstituted olefins is still a limitation. To further explore the possibility of asymmetric glyoxylate−ene reaction with monosubstituted olefins and at room temperature or higher reaction temperature, we focused our attention on the new type of chiral metal complexes, such as chiral palladium(II) complexes.[4] Herein, we report the enantioselective glyoxylate−ene reaction catalyzed by chiral BINAPs coordinated palladium diantimonate catalysts (**2**). These catalysts provide a simple but efficient way to the enantioselective synthesis of the α-hydroxy esters in excellent chemical yields with high enantioselectivities at relatively

(1) (a) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: New York, 1996. (b) Whitesell, J. K. *Stereoselective Synthesis*; Houben-Weyl: 1996; Vol. 5; pp 3271−3297. (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021−1050. (d) Snider, B. B. *Comprehensive Organic Synthesis*; Pergamon: London, 1991; Vol. 5, pp 1−27.

(2) (a) Mikami, K.; Nakai, T. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000; pp 543−568. (b) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305−342. (c) Mikami, K.; Terada, M. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, Heidelberg, 1999; Vol. III, pp 1143−1176. (d) Mikami, K. *Advances in Asymmetric Synthesis*; JAI Press: Greenwich, CT, 1995; Vol. 1, pp 1−44.

(3) (a) Mikami, K. *Pure Appl. Chem.* **1996**, 68, 639−644. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954; **1989**, *111*, 1940−1941. (c) Mikami, K.; Terada, M.; Nakai, T. Annual Meeting of the Chemical Society of Japan, Tokyo, 1988, April 1−4, Abstract 1XIB43.

(4) For our highly enantioselective ene-type cyclizations catalyzed by chiral palladium complexes bearing BINAP derivatives, see: Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* In press.

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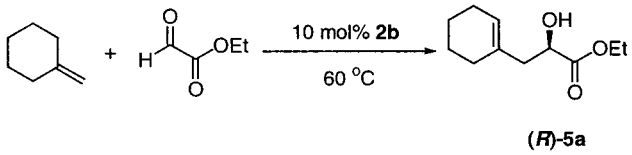
Scheme 1. [Pd(CH_3CN)$_2$(*S*)-Tol-BINAP](SbF_6)$_2$ (**2b**)-Catalyzed Glyoxylate−Ene Reaction between Methylenecyclohexane and Ethyl Glyoxylate



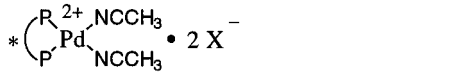
(*R*)-5a

2b, [Pd(CH_3CN)$_2$(*S*)-Tol-BINAP](SbF_6)$_2$ 88% ee, 97% yield

Reaction was carried out in CH_2ClCH_2Cl/toluene = 1/2 by volume.

higher reaction temperature (60 °C) with 1,1-disubstituted and trisubstituted olefins.

After careful examination of various palladium(II) complexes and counterions, we found that the combination of palladium(II) dication species with its strongly anionic ligand, such as BF_4^- and SbF_6^-, could be employed as an efficient catalyst in glyoxylate−ene reactions. Among those, the (*S*)-Tol-BINAP-coordinated palladium(II) diantimonate complex (**2b**), which can be stored under argon atmosphere at room temperature, provides not only high enantioselectivities but also excellent control of regioselectivity leading to homoallylic rather than allylic alcohols in glyoxylate−ene reactions (Scheme 1).



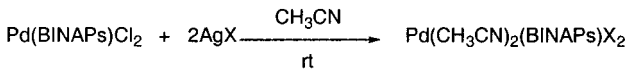
1, X = BF_4^-; **2**, X = SbF_6^-

a: * = (*S*)-BINAP; **b**: * = (*S*)-Tol-BINAP;

c: * = (*S*)-Xylyl-BINAP

The palladium complexes **1**, a yellowish green powder, and **2**, a chocolate powder, employed in this reaction were prepared from Pd(BINAP)Cl_2 [5] with $AgBF_4$ [6] and $AgSbF_6$ in CH_3CN at room temperature, respectively (Scheme 2).

Scheme 2. Preparation of **1** and **2** from Pd(BINAPs)Cl_2



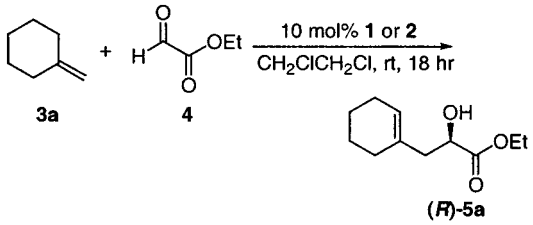
1, X = BF_4, 90% ~ 94%
2, X = SbF_6, 95% ~ 97%

BINAP: (*S*)-BINAP, (*S*)-Tol-BINAP, (*S*)-DM-BINAP;

The initial results of the effect of ligands and counterions of palladium complexes **1** and **2** on glyoxylate−ene reactions

(5) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188−4196.

Table 1. Effect of Ligand and Counterion in Glyoxylate−Ene Reaction



(*R*)-5a

		5a	
entry	Pd(II)	yield (%)[a]	ee (%)[b]
1	**1a**	72	48
2	**1b**	76	72
3	**2a**	82	61
4	**2b**	88	78
5	**2c**	87	42

[a] Isolated yield. [b] Determined by chiral GC using CP-Cyclodextrin-B-2,3,6-M-19 column.

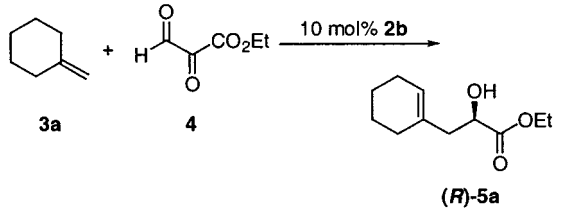
were obtained in the reaction using methylene−cyclohexane (**3a**) and ethyl glyoxylate (**4**) as starting materials (Table 1). Both palladium complexes **1** and **2** provided good chemical yields and enantioselectivities in glyoxylate−ene reaction. The reaction of **3a** with **4** by using the (*S*)-Tol-BINAP-coordinated palladium diantimonate (**2b**) in CH_2ClCH_2Cl proceeded smoothly at room temperature to give **(*R*)-5a** in 88% yield with 78% ee (entry 4). This result was better than that obtained using the complexes **1** as catalyst because of the higher electron negativity of the SbF_6^- group compared to that of the BF_4^- group. Steric effect of BINAP ligands was observed in this reaction. The sterically less demanding BINAP gives lower ee (entries 1 and 3), while the middle size of the Tol-BINAP ligand offers better enantioselectivity (entries 2 and 4). More sterically bulky DM (i.e., Xylyl)-BINAP[7] gives lower ee (entry 5), which is much worse than that using BINAP as chiral ligand.

The effect of solvent and temperature in this reaction was also investigated (Table 2). Both dichloromethane and 1,2-dichloroethane provide high solubility of complexes **1** and **2**. The reactions carried out in these solvents are relatively faster so as to slightly decrease the enantioselectivity. Toluene itself is not a proper solvent for this palladium-catalyzed glyoxylate−ene reaction at room temperature as a result of the extremely low solubility of the palladium complexes therein (entry 8). Raising the temperature, for instance, to 60 °C, could greatly improve the solubility of the complex **2** and afford the ene product in 95% yield with 84% ee (entry 9). Therefore, toluene as a cosolvent could retard the reaction but improve the enantioselectivity at room

(6) [Pd(CH_3CN)$_2$(*R*)-BINAP](BF_4)$_2$: (a) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017−5023. (b) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660−8667.

(7) Mashima, K.; Matsumura, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *Chem. Commun.* **1991**, 609−610.

Table 2. Effect of Solvent and Temperature in Palladium Complex **2b**-Catalyzed Glyoxylate−Ene Reaction



				5a	
entry	solvent	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	rt	18	83	76
2	CH_2ClCH_2Cl	rt	18	88	78
3	CH_2ClCH_2Cl	40	8	97	82
4	CH_2ClCH_2Cl	60	4	97	86
5	CH_2ClCH_2Cl	80	2	98	75
6	CH_2ClCH_2Cl/toluene, 1/2	rt	20	85	84
7	CH_2ClCH_2Cl/toluene, 1/2	60	4	95	88
8	toluene	rt	20		
9	toluene	60	4	95	84
10[c]	CH_2ClCH_2Cl/toluene, 1/2	60	4	97	43

[a] Isolated yield. [b] Determined by chiral GC using CP-Cyclodextrin-B-2,3,6-M-19 column. [c] Using **2c** as catalyst.

temperature (entry 6). More sterically demanding chiral ligand (*S*)-Xylyl-BINAP gave only 43% ee (entry 10) even at 60 °C.

It is also interesting that the enantioselectivity of this reaction catalyzed by Pd(II) complex is somewhat temperature dependent. Increase of reaction temperature from ambient (ca. 25 °C) to 60 °C could improve the enantioselectivity from 78% to 86% in the case of CH_2ClCH_2Cl as a solvent (entries 2 and 4) (Figure 1). The chemical yield of this reaction was also increased from 88% to 97%. This unusual result suggests that there is a competitive factor, which may arise from the coordination of the hydroxy group of the ene product with the palladium center. Increase of reaction temperature could break down and reduce such

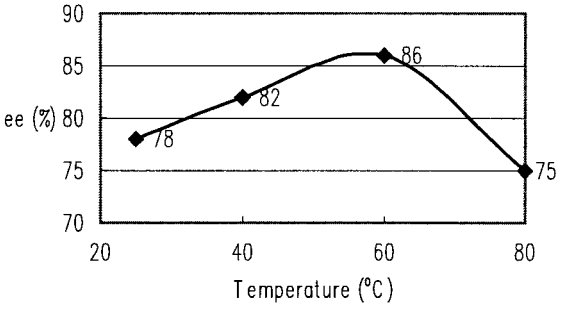
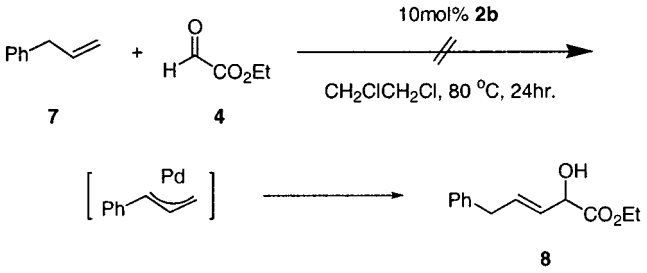


Figure 1. Temperature dependence in enantioselective glyoxylate−ene reactions catalyzed by Pd(II) complex (**2b**) in CH_2ClCH_2Cl as solvent.

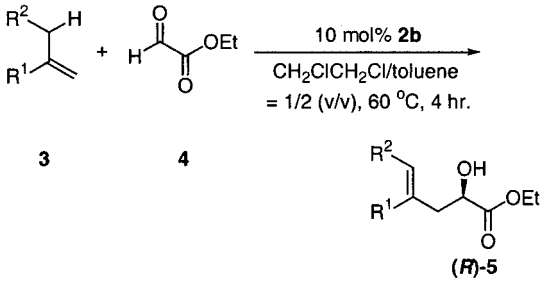
Scheme 3. Glyoxylate−Ene Reaction with Allylbenzene



coordination to improve the enantioselectivity. However, a too high reaction temperature, for instance, 80 °C (entry 5), would accelerate the reaction too much to reduce the enantioselectivity. The best result of the palladium complex catalyzed glyoxylate−ene reaction was obtained in the reaction using $[Pd(CH_3CN)_2(S)\text{-Tol-BINAP}](SbF_6)_2$ (**2b**) as a catalyst and toluene/1,2-dichloroethane (2/1 in volume) as a solvent system at 60 °C (entry 7).

Although the palladium complex (**2b**) gave a promising result in the reaction of 1,1-disubstituted olefin with glyoxylate at relatively high reaction temperature, we could not

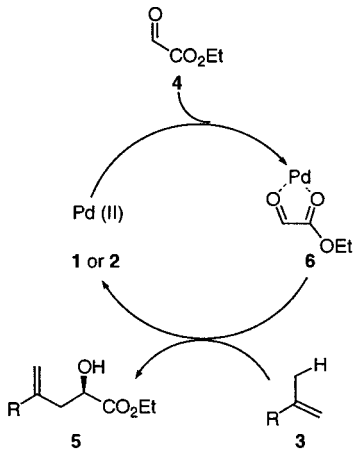
Table 3. Enantioselective Glyoxylate-Ene Reactions with 1,1-Disubstituted and Trisubstituted Olefins



		5		
entry	3	yield (%)[a]	ee (%)[b]	diastereomer ratio
1		97	88	
2		93	74	
3		92	73 (major)	5.6/1
4		94	81 (major)	2.2/1
5[c]		83	75 (major)	5.6/1

[a] Isolated yield. [b] Determined by chiral GC using CP-Cyclodextrin-B-2,3,6-M-19 column. [c] At room temperature.

Scheme 4. Proposed Mechanism for Palladium(II)-Catalyzed Glyoxylate−Ene Reaction



make a breakthrough in the reaction with monosubstituted olefin at present. Palladium complex (**2b**) catalyzed ene reaction with monosubstituted olefin, such as allylbenzene (**7**), unfortunately gave no desired product (**8**) even at 80 °C but only recovery of starting materials (Scheme 3). It suggests that the initial step should not include the C−H activation of an ene olefin to give π-allyl palladium species in this glyoxylate−ene reaction.

On the basis of the results described above, the mechanism of palladium(II) complex catalyzed glyoxylate−ene reaction is exemplified in Scheme 4. The reaction is considered totake place through the complexation of the carbonyl groups of glyoxylate with dicationic palladium catalyst at the initial step to form the bidentate intermediate **6**. Subsequent addition of the ene component to the carbonyl−Pd complex leads to the formation of the ene product **5** and regeneration of Pd complex **1** or **2** in situ for the next catalytic cycle. This catalytic system is generally applicable to other 1,1-disubstituted olefins, such as α-methylstyrene and 2-ethyl-1-butene, and furthermore to trisubstituted olefin, such as ethylidenecyclohexane (Table 3).[8]

In conclusion, an effective chiral palladium catalyst [Pd-$(CH_3CN)_2$(*S*)-Tol-BINAP]$(SbF_6)_2$ (**2b**) is developed for the asymmetric glyoxylate−ene reaction with 1,1-disubstituted olefins at relatively higher temperature (60 °C). This palladium cationic catalyst provides a simple but efficient approach to asymmetric synthesis of α-hydroxy esters in excellent yields with high enantioselectivities. This reaction is currently still under investigation to further expand the scope of this process with, in particular, monosubstituted olefins.[9]

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(8) **General Procedure (Table 3).** To a solution of [Pd$(CH_3CN)_2$-(BINAP)]X_2 (**1** or **2**) (0.025 mmol, 10 mol % of ethyl glyoxylate) in 2 mL of CH_2ClCH_2Cl was added 0.5 mmol of olefin **3** and 0.25 mmol of ethyl glyoxylate **4** in 4 mL of toluene at room temperature under an atmosphere of argon. This yellow solution was then stirred at 60 °C for 4 h (reaction was monitored by TLC, AcOEt/hexane = 1/2), solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane = 1/3) to afford α-hydroxy ester (**5**) as colorless oil.

(9) Recently, Evans D. A. et al reported the first example using chiral box copper(II) complexes for catalytic enantioselective carbonyl−ene reactions with monosubstituted olefins in up to 98% ee: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (c) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.