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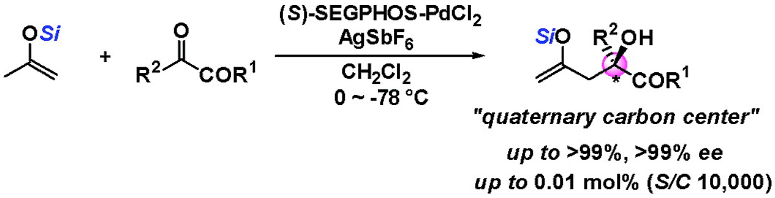

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Enantioselective Catalysis of Ketoester-ene Reaction of Silyl Enol Ether to Construct Quaternary Carbons by Chiral Dicationic Palladium(II) Complexes

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Development of synthetic methods for optically active and highly functionalized silyl enol ethers are in great demand in organic synthesis.[1] Since the optically active β-hydroxy silyl enol ethers are valuable as chiral building blocks for many bioactive compounds,[2] an asymmetric carbonyl-ene reaction with silyl enol ether is one of the most efficient synthetic methods. The problems associated in this reaction, however, are the decomposition of silyl enol ethers under the Lewis acid conditions and competition with the Mukaiyama aldol reaction.[3,4] There are only two types of asymmetric carbonyl-ene reactions using silyl enol ether as an ene substrate. We have reported a BINOL-derivated chiral Ti complex-catalyzed asymmetric glyoxylate-ene reaction of trimethylsilyl enol ether to give chiral β-hydroxy silyl enol ether (ene-type) products in high yield and enantioselectivity instead of secondary β-hydroxy ketone (Mukaiyama aldol-type product).[5] Recently, Jacobsen has also reported a chiral Cr complex-catalyzed ene reaction between aldehyde and trimethylsilyl enol ether to give the ene-type product in an excellent yield with enantioselectivity.[6] These reactions produce silyl enol ethers, however, with the chiral tertiary carbon centers. There is so far no report on silyl enol ether to afford quaternary carbon centers.[7] Herein we report a chiral dicationic Pd complex-catalyzed asymmetric ketoester-ene reaction of silyl enol ether, which constructs an optically active β-hydroxy silyl enol ether with a quaternary carbon center.[8−10]

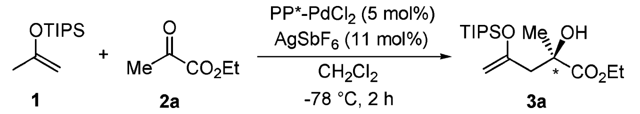
The asymmetric ketoester-ene reaction was first investigated with acetone silyl enol ether **1** bearing TIPS group and ethyl pyruvate **2a** (Table 1). The active dicationic Pd catalyst as Lewis acid was in situ generated from 5 mol % of chiral PP*-$PdCl_2$ complex and 11 mol % of $AgSbF_6$ in dichloromethane.[8a] (*S*)-BINAP-$PdCl_2$ bearing C_2 symmetric binaphthyl-backbone gave ene-type product **3a** in 77% yield and 92% ee without aldol-type product (entries 1−3 vs 4).[11] While the use of (*S*)-tol-BINAP increased the enantioselectivity up to 95% ee, the yield was decreased by decomposition of **1** (entry 5). The sterically more demanding (*S*)-xylyl-BINAP-$PdCl_2$ gave lower yield and enantioselectivity (entry 6). (*S*)-SEGPHOS[12] was found to be the most effective to give **3a** with 93% ee in 96% yield without decomposition of **1** (entry 8).[13]

Several *Si* groups in **1** were further examined by (*S*)-SEGPHOS-$PdCl_2$ under the same conditions (Scheme 1). The less hindered TMS enol ether yielded only aldol product **4a** bearing the same absolute configuration (46%, 80% ee).[14] The use of TBDMS decreased the enatioselectivity of the ene product. In addition, the sterically more hindered TBDPS gave ene product **3a** in higher enantioselectivity (96% ee), but the reactivity of TBDPS ether significantly decreased.

The reactions of various ketoester substrates **2b**−**f** and TIPS enol ether **1** were examined by (*S*)-SEGPHOS-$PdCl_2$ under the optimized conditions (Table 2). Methyl pyruvate **2b** produced ene product **3b** quantitatively (85% ee) (entry 2). The absolute configuration of ene product **3c** from benzyl pyruvate **2c** was determined to be *R* (entry 3).[15] The substrate **2d**,**e** bearing CF_3 and β-phenyl ethyl groups gave high enantioselectivity (88 and 87% ee, respectively) (entries 4, 5). Benzoylformate **2f** yielded ene product **3f** in higher enantioselectivity (98% ee) (entry 6). The construction of quaternary carbon center was thus succeeded with high enantioselectivity from various ketoester substrates. Significantly, less reactive diketone **2g**,**h** could be employed in the reaction. Dimethyl diketone **2g** afforded the corresponding desymmetrized[16] product in good yield with high enantioselectivity (entry 7). The more significant result was obtained with unsymmetrical diketone **2h**, leading to the complete regioselectivity and enantioselsectivity (entry 8).

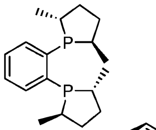
With these successful results in terms of catalyst activity and enantioselectivity, we attempted to decrease the catalyst loading (Scheme 2). Ene product **3a** was quantitively obtained in 92% ee with the less catalyst loading (0.05 mol %). Even with the smallest

Table 1. Enantioselective Ketoester-ene Reaction with Silyl Enol Ether **1** and Ethyl Pyruvate **2a** by Chiral Dication Pd Catalysts

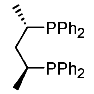


entry	PP*-ligand	yield (%)[a]	ee (%)[b]
1	(*R*,*R*)-DUPHOS	68	5[c]
2	(*S*,*S*)-BDPP	52	75[c]
3	(*S*)-QUINAP	9	76[c]
4	(*S*)-BINAP	77	92
5	(*S*)-tol-BINAP	62	95
6	(*S*)-xylyl-BINAP	47	61
7	(*S*)-SYNPHOS	79	92
8	(*S*)-SEGPHOS	96	93

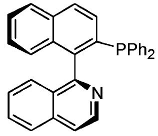
[a] Isolated yield. [b] Enantiopurity was determinded by HPLC analysis after desilylation to β-hydroxyketone **4a**. [c] Opposite configuration.



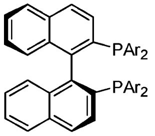
(*R*,*R*)-DUPHOS



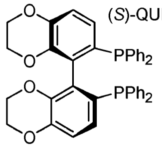
(*S*,*S*)-BDPP



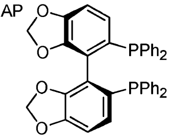
(*S*)-QUINAP



(*S*)-BINAP (Ar = Ph)
(*S*)-tol-BINAP (Ar = 4-Me-Ph)
(*S*)-xylyl-BINAP (Ar = 3,5-Me_2-Ph)

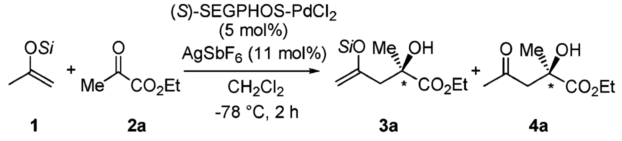


(*S*)-SYNPHOS



(*S*)-SEGPHOS

Scheme 1. Silyl Effects on SEGPHOS-Pd^{2+}-Catalyzed Ketoester-ene Reaction

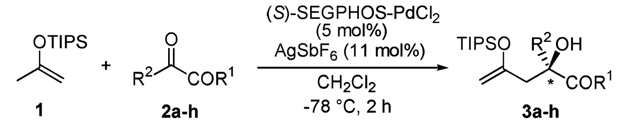


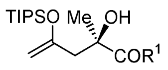
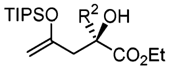
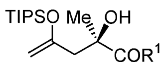
Si =	3a	4a
TMS	-	46%, 80% *ee*
TBDMS	95%, 85% *ee*	-
TIPS	96%, 93% *ee*	-
TBDPS[a]	68%, 96% *ee*	-

[a] Reaction time was 24 h.

10.1021/ja076539f CCC: $37.00

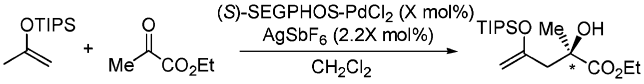
Table 2. Enantioselective Ene Reaction with Various Enophiles



entry	product		yield (%)[b]	ee (%)
1		R^1 = OEt (**3a**)	96	93[c]
2		R^1 = OMe (**3b**)	>99	85[d]
3		R^1 = OBn (**3c**)	91	81(*R*)[c]
4		R^2 = CF_3 (**3d**)	70	88[d]
5		R^2 = CH_2CH_2Ph (**3e**)	40	87[c]
6		R^2 = Ph (**3f**)	72	98[c]
7[a]		R^1 = Me (**3g**)	81	94[d]
8[a]		R^1 = Et (**3h**)	84	>99[d]

[a] Reaction time was 18 h. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis after desilylation to *β*-hydroxyketone **4**. [d] Enantiopurity was determined by GC analysis after desilylation to *β*-hydroxyketone **4**.

Scheme 2. Low Catalyst Loading of SEGPHOS−Pd Complex



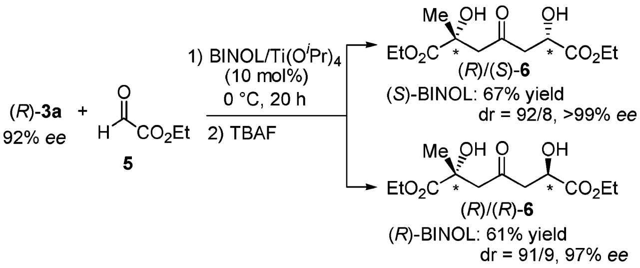
1 2a 3a

0.05 mol%, -40 °C, 20 h >99% yield, 92% *ee* *S/C = 2,000*

0.02 mol%, -10 °C, 20 h 97% yield, 92% *ee* *S/C = 5,000*

0.01 mol%, 0 °C, 48 h 85% yield, 90% *ee* *S/C = 10,000*

Scheme 3. Hetero Two-Directional Reaction by BINOL/$\text{Ti(O}^i\text{Pr)}_4$ Catalyst



substrate/catalyst ratio, namely S/C 10,000 at 0 °C, the high yield and enantioselectivity could be obtained.

Next, our attention was focused on heterocombination of ene reaction sequence[17] with **3a** (92% ee *R*) by using chiral BINOL-Ti catalyst (Scheme 3).[18] In the presence of 10 mol % (*S*)-BINOL/$\text{Ti(O}^i\text{Pr)}_4$, the reaction with ethyl glyoxylate **5** afforded the mixture of ene,[18] Friedel−Crafts,[19] and aldol products.[20] However, diol (*R*)/(*S*)-**6** bearing both quaternary and tertiary carbon centers was obtained in 67% yield and >99% ee (92% diastereoselectivity) after desilylation by TBAF. In contrast, the treatment with (*R*)-BINOL-Ti catalyst led to the diol (*R*)/(*R*)-**6** in 61% yield and 97% ee (dr = 91/9).

In summary, we have succeeded in dicationic SEGPHOS-Pd complex-catalyzed ketoester-ene reaction, which constructs highly optically active *β*-hydroxy silyl enol ether with quaternary carbon center. We have also succeeded in lowering the catalyst loading up to 0.01 mol % without significant decrease in the yield and enantioselectivity. This low catalyst loading will open the door to industrial applications of the present chiral Lewis acid catalysis. Further investigations on engineered Lewis acid catalysis of tandem reactions are currently in progress.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Carreira, E. M. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8B2. (d) Machajewski, T. D.; Wong, C.-H.; Lerner, R. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (e) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.

(2) Examples of chiral alcohols with quaternary carbon centers: (a) Harris, G. H.; Jones, E. T. T.; Meinz, M. S.; Nallin-Omstead, M.; Helms, G. L.; Bills, G. F.; Zink, D.; Wilson, K. E. *Tetrahedron Lett.* **1993**, *34*, 5235. (b) Tan, L.; Chen, C.-Y.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3961. (c) Oxybutynin: Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819.

(3) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *2*, 1011.

(4) Examples of asymmetric Mukaiyama-aldol reactions. (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (b) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (d) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984.

(5) (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077.

(6) (a) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882. (b) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771.

(7) Reviews on the construction of quaternary carbon centers: (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., Int. Ed.* **1998**, *37*, 388. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

(8) We have reported Pd-catalyzed asymmetric ene reactions. (a) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183. (b) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059.

(9) Cu-catalyzed asymmetric ketoester-ene reactions. (a) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. Sc-catalyzed asymmetric carbonyl-ene reactions. (b) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006.

(10) Catalytic asymmetric reactions by using ketoester. (a) Dimauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (b) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. (c) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki *J. Am. Chem. Soc.* **2002**, *124*, 12668.

(11) Whether AgCl was filtered or not, the condition of 10 mol % $AgSbF_6$ to 5 mol % Pd complex gave almost the same result. We had confirmed that $AgSbF_6$ did not catalyze the reaction. Therefore, there is no participation of silver salt in this reaction.

(12) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(13) The use of 2-(triisopropyl)siloxy-1-butene instead of **1** gave the ene product in 91% yield, *E*/*Z* = 7/3, 85% ee (enantiopurity was determined after desilylation of *E*- and *Z*-isomer mixture).

(14) Sodeoka and Shibasaki reported Pd-catalyzed asymmetric aldol reaction via Pd enolate. The aldol product would be obtained via Pd enolate. (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (b) Hamashima, Y.; Sodeoka, M. *Chem. Rec.* **2004**, *4*, 231.

(15) The absolute configuration was determined in comparison of the value of optical rotation. Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

(16) (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Mikami, K.; Yoshida, A. *J. Syn. Org. Chem. Jpn.* **2002**, *60*, 732. (c) Rovis, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: New York, 2007; Chapter 10.

(17) Reviews on tandem (domino) reactions: (a) Ziegler, F. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 6, p. 875. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. Wender, P. A., Ed. *Chem. Rev.* **1996**, *96* (thematic issue). (c) Nakai, T.; Mikami, K. *Kagaku no Ryoiki* **1982**, *36*, 661; *Chem. Abstr.* **1982**, *96*, 16001.

(18) Homo two-directional glyoxylate-ene reaction: Mikami, K.; Matsukawa, S.; Nagashima, M.; Funabashi, H.; Morishima, H. *Tetrahedron Lett.* **1997**, *38*, 579.

(19) Ishii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, *1*, 2013.

(20) These three products were incompletely separated by silica-gel chromatography and transformed into **6** with TBAF.

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