

Highly Efficient Ligands for Palladium-Catalyzed Asymmetric Alkylation of Ketone Enolates

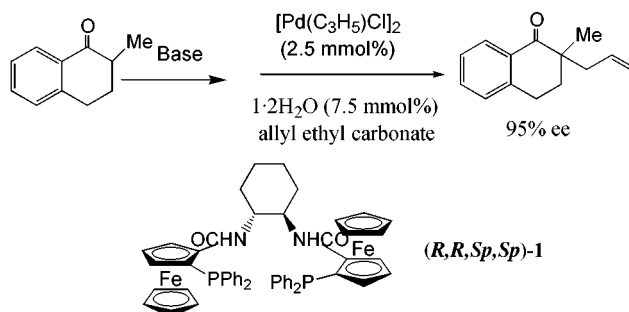
Shu-Li You, Xue-Long Hou,* Li-Xin Dai,* and Xia-Zhen Zhu

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

xlhou@pub.sioc.ac.cn

Received October 8, 2000

ABSTRACT



Ferrocene-modified chiral pocket ligands have been studied in the palladium-catalyzed asymmetric allylation of simple ketone enolates, in which (*R,R,Sp,Sp*)-1 containing two pairs of matched chiralities, central chirality and planar chirality, behaved very efficiently in this reaction and up to 95% ee value was achieved.

Asymmetric construction of quaternary carbon centers is a difficult but interesting project.¹ For initial attempts, the asymmetry was mainly induced through stoichiometric chiral auxiliary or self-replicating chirality.² Asymmetric catalytic methods in this area were very limited. However, several advances have been made recently. Palladium-catalyzed asymmetric allylic alkylation (AAA) of prochiral nucleophiles has been used effectively to create quaternary carbon centers, in which the prochiral nucleophiles were usually stabilized nucleophiles.^{3,4} For example, Ito used BINAP as ligand to realize the AAA reaction of β -keto- α -aminoesters with ee values of 76–95%.^{3a} Simple ketone enolates are an

important class of nucleophiles, but the AAA reaction was more difficult to effect because they are nonstabilized nucleophiles. The situation is changed now. Trost realized the construction of a quaternary carbon center with high enantioselectivity recently by using simple ketone enolates through palladium-catalyzed AAA reaction;^{5a} the allylation of 2-methyltetralone with allyl acetate may reach 88% ee and 99% yield with their chiral pocket ligand. Although there

(3) (a) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (b) Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837. (c) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (d) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (e) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228

(4) For reviews of the palladium-catalyzed allylic alkylation reaction, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (c) Frost, C. G.; Howarth, J. M. *J. Tetrahedron: Asymmetry* **1992**, *3*, 1089. (d) Consiglio, G.; Waymouth, R. *Chem. Rev.* **1989**, *89*, 257.

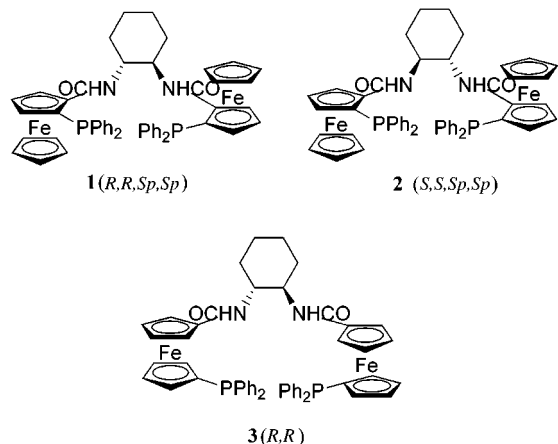
(5) (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Ahman, J.; Wofle, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (c) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

* E-mail address for second corresponding author: dailx@pub.sioc.ac.cn.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Fujii, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) (a) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930. (b) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fujii, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155. (c) J. Seyden-Penne *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

have been a few successful methods to date, any virtual improvement of asymmetric synthesis of quaternary carbon centers will be noteworthy. Ferrocene derivatives have been found to be the versatile and highly efficient ligands in certain asymmetric reactions.⁶ As a result of the special structure of ferrocene, planar chirality is easily introduced,⁷ and it plays a decisive role in the enantiocontrol in many reactions. It can be concluded that better enantiocontrol will be achieved when a matched planar chirality with the existed central chirality is introduced into the ligand.^{8,9} Recently, we synthesized bis-*N*-[2-(diphenylphosphino)ferrocenylcarbonyl]-diaminocyclohexane derivatives **1** and **2** and used them as



ligands in the palladium-catalyzed asymmetric allylic alkylation to synthesize α -alkylated amino ester derivatives with a quaternary chiral carbon center.¹⁰ These ligands can be easily synthesized from ferrocene and diaminecyclohexane and are stable in air also. Most interestingly, they are seemingly somewhat similar to Trost's chiral pocket but different in size and backbone environment. Furthermore, they could be modified with planar chirality, which might

(6) (a) Blaser, H. U.; Spindler, F. *Chimia* **1997**, *51*, 297. (b) Imwinkelried, R. *Chimia* **1997**, *51*, 300.

(7) (a) Ahn, K. H.; Cho, C.-W.; Beak, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937. (b) Nishibayashi, Y.; Semura, S. *Synlett* **1995**, 79. (c) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 79. (d) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (e) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002. (f) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629. (g) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.

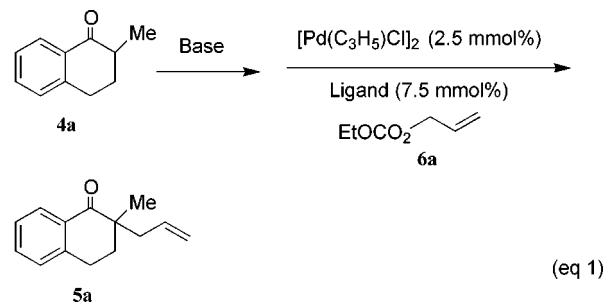
(8) For papers on planar chirality, see: (a) You, S.-L.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X. *Chem. Commun.* **1998**, 2765. (b) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285. (c) Dai, L.-X.; Hou, X.-L.; Deng, W.-P.; You, S.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 1401. (d) You, S.-L.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2000**, *11*, 1495. (e) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 1331. (f) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483. (g) Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195.

(9) (a) Bolm, C.; Muniz-Fernandez, K.; Seger, A.; Raabe, G.; Gunther, K. *J. Org. Chem.* **1998**, *63*, 7860. (b) Bolm, C.; Muniz-Fernandez, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491; (c) Muniz, K.; Bolm, C. *Chem. Eur. J.* **2000**, *6*, 2309.

(10) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933. About the same time, Zhang's group also synthesized the same ligands **1** and **2**; see: Longmire, J. M.; Wang, B.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 5435.

give an enhancement in enantioselectivity of the asymmetric reaction. As we expected, with ligand containing a pair of matched chiralities, the product was achieved with good enantioselectivity with the simplest allylic system. This success emboldened us to apply these ligands to a more challenging asymmetric reaction. In this paper, we report the application of them to palladium-catalyzed alkylation of simple ketone enolates.

First, we chose 2-methyl-1-tetralone with allylic ethyl carbonate and $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ as the test reaction (eq 1).



The choice of solvent had a moderate effect on the enantioselectivity of the reaction. Several solvents were examined, and THF gave the best result with ligand **1** (90% yield, 82% ee; Table 1, entry 2). DME has been reported as the best

Table 1. Optimizing Reaction Condition for Alkylation with **4a**^a

entry	ligand	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	1	DME	1	96	66
2	1	THF	3	90	82
3	2	THF	1	90	29
4	3	THF	1	88	0
5	1 ·2H ₂ O	THF	0.5	96	92
6 ^d	1 ·2H ₂ O	THF	1	93	95
7 ^{d,e}	1	THF	2	68	87
8 ^{d,f}	1 ·2H ₂ O	THF	2	73	89
9 ^{d,g}	1	THF	1.5	78	83
10 ^{d,h}	1	THF	1	85	79

^a All reactions were performed with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ /ligand/**4a**/LDA/allyl ethyl carbonate (2.5/7.5/100/150/150). ^b Isolated yield. ^c Determined by HPLC. ^d $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ and ligand were heated at 50 °C for 1 h before use. ^e 15 mol % H₂O was used as additive during preparation of catalyst. ^f Reaction was performed at 0 °C. ^g 15 mol % MeOH was used as additive during preparation of catalyst. ^h 15 mol % *t*-BuOH was used as additive during preparation of catalyst.

solvent,^{5a} but it only gave 66% ee (Table 1, entry 1). With ligand **2**, the product was obtained in 90% yield and 29% ee (Table 1, entry 3), and the absolute configuration of the product was opposite to that with ligand **1**. Obviously ligand **1** containing two pairs of matched chiralities was a better ligand, as we found in our previous work.¹⁰ Ligand **3** was synthesized in our laboratory, and the larger ring was formed on chelating the two phosphorus atoms with the palladium. However, ligand **3** led to the product in 88% yield but 0% ee. The easy rotation of the diphenylphosphorus-substituted Cp ring may be the reason for this low selectivity.

It was very interesting to note that ligand **1** easily crystallized with two water molecules.¹¹ We found that the crystalline ligand was easily formed as a dark-red solution with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ in THF. When this catalyst was subjected to the identical reaction, 92% ee of the product was obtained. This value is higher than that obtained by using water-free **1** as ligand. This result suggests that the crystal water may be important in this reaction though the reaction system included lithium reagents that react with the water immediately. To get better coordination, $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ and the crystalline ligand were stirred for 1 h at 50 °C before being used as the catalyst. The ee of the product increased to 95% (Table 1, entry 6). Although there were some reports about the enhancement of reactivity of aldol reaction by the presence of a small amount of water, the role of water here should be further examined.¹² For this aim, the following reaction was performed. Palladium and water-free ligand were stirred in THF with 15 mol % water at 50 °C for 1 h and product was obtained in 68% yield and 87% ee (Table 1, entry 7), which was still better than the result of entry 2. The result also indicated the presence of a little water might assist the coordination. The reaction was also done with other hydroxy-containing reagents such as MeOH and *t*-BuOH as additives. The reactions ran smoothly to give product in 83% ee and 78% yield and in 79% ee and 85% yield, respectively (Table 1, entry 9 and 10). With the same condition in entry 6 but with the reaction performed at 0 °C, the yield and enantioselectivity decreased a little (Table 2, entry 8).

Table 2. Palladium-Catalyzed Asymmetric Alkylation with Different Ketone Enolates^a

entry	R ¹	allylic reagent	time (h)	yield (%) ^b	ee (%) ^c	ee (%) ^d
1	Et	6a	1	95	66	80
2	Bn	6a	1.5	91	84	85
3	Me	6b	2	77	87	47

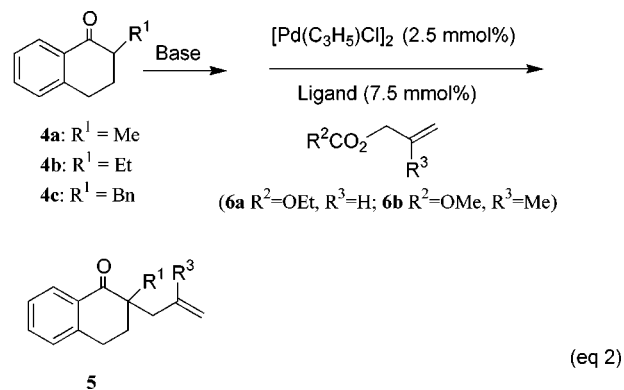
^a All reactions were performed with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2 / \mathbf{1} \cdot 2\text{H}_2\text{O} / \mathbf{4a} / \text{LDA} /$ allylic reagent (2.5/7.5/100/150/150). ^b Isolated yield. ^c Determined by HPLC. ^d Data from literature.^{5a}

Under the optimized reaction condition, several ketone substrates and allylic reagents were investigated.¹³ We found

(11) The X-ray structure has been reported in our former paper (see ref 10).

(12) A similar water effect has been reported, see: (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (b) Sodeoka, M.; Takunoh, R.; Miyazaki, F.; Shibasaki, M. *Synlett* **1997**, 463. (c) Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *Enantiomer* **2000**, *5*, 71.

that ketones **4** having different R substituents reacted with allylic reagent **6a** (eq 2) to give rise to good yields and high



enantioselectivities except for **4b**, which only gave moderate enantioselectivity (66% ee) (entry 3 in Table 2). Fortunately, when allylic reagent **6b** was used in this reaction with **4a**, high enantioselectivity (87% ee) was also achieved (entry 4 in Table 2). The ee values obtained from ref 5a are also listed in the table.

In conclusion, (*R,R,Sp,Sp*)-**1** was found to be an efficient ligand in the palladium-catalyzed asymmetric alkylation of simple ketone enolates. The reaction could construct a quaternary carbon center with high enantioselectivity up to 95% ee. And interestingly, two molecules of crystalline water of the ligand **1** gave better results albeit no clear explanation can be given for the moment.

Acknowledgment. This research was financially supported by the Major Basic Research Development Program (grant G2000077506), National Natural Science Foundation of China, National Outstanding Youth Fund, Chinese Academy of Sciences, and Shanghai Committee of Science and Technology.

OL0067033

(13) **Typical Procedure for the Palladium-Catalyzed Allylic Alkylation of Ketone Enolates.** A test tube was charged with 1 mL of THF and 64 mg (0.4 mmol) of 2-methyl-1-tetralone **4a**. The solution was cooled to -78 °C, and 0.3 mL (0.6 mmol, 2 M in heptane/THF/ethylbenzene) of LDA was added. The solution was stirred at -78 °C for 1 h and then charged with a solution containing 3.7 mg (0.01 mmol) of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, 28 mg (0.03 mmol) of chiral ligand **1**·2H₂O in 0.5 mL of THF, and a solution of 78 mg (0.6 mmol) allyl ethyl carbonate **6a** in 0.5 mL of THF (which was heated for 1 h before use). Immediately after the addition, the cooling bath was removed and the reaction allowed proceeding at room temperature. The reaction was completed in 1 h. The reaction mixture was diluted with ether (20 mL) and washed twice with brine. The organic phase was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/petroleum ether = 1/40) to afford 74 mg of **5a** in 93% yield, 95% ee, ($[\alpha]_D^{20} = -18.0$, *c* 0.75 CHCl₃), determined by HPLC (Chiralcel OD Column, 99.9:0.1 hexane/2-propanol, flow = 0.7 mL/min); *t*_R = 16.46, 17.96 min.