Highly Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation and Amination of Monosubstituted Allylic Acetates with Novel Ferrocene *P,N*-Ligands

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

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

Received May 2, 2001
Revised Manuscript Received June 18, 2001

Palladium-catalyzed allylic substitution reaction is one of the brightest focuses in asymmetric synthesis during the past decades because of its great potential in organic synthesis.[1] Various ligands have been synthesized and used in this reaction, especially with 1,3-symmetrically disubstituted substrates, and high ee is realized.[2] Despite this, little success was achieved with the unsymmetrical substrate such as **1** or **2**, and achiral linear product **4** was usually given (Figure 1).[3]

High regio- and enantioselectivity for certain substrates in allylic alkylation reactions were, however, achieved by employing other chiral metal complexes such as W, Mo, and Ir.[4] Even so, the use of palladium aiming at the asymmetric reaction of the monosubstituted substrates has never been abandoned,[5] and several specially designed ligands have been tested accordingly. Hayashi found that 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ligand (MeO-MOP) gave good regio- and enantioselectivity in palladium-catalyzed alkylation of **2**, but a very low regioselectivity for substrate **1**.[6] Pfaltz developed phosphite-oxazoline ligands and used them to control the regio- and enantioselectivity in the palladium-catalyzed allylic alkylation of **1** or **2**.[7] High regio- and enantioselectivity were achieved for 3-(1-naphthyl)-3-allylic acetate. However, only moderate to low regioselectivity was obtained for other aryl- and alkyl-substituted substrates.[7] For the regio- and enantioselective allylic amination reactions,[8] pioneering work has been done by Hayashi and Ito with butenyl acetate as the only substrate.[9] Therefore, the regio- and enantioselectivity of monosubstituted substrates in palladium-catalyzed allylic substitution reaction remain to be solved.

On the basis of our previous results[10] and those of others,[6,7,11] we designed and synthesized a series of novel ferrocene ligands.

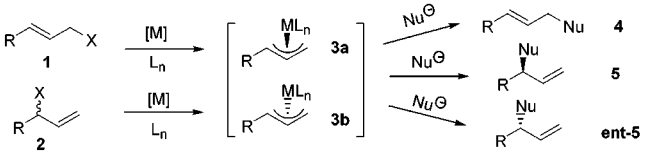


Figure 1. Transition-metal catalyzed allylic alkylation with unsymmetrical monosubstituted π-allyl intermediate.

High regio- and enantioselectivity were realized in Pd-catalyzed allylic alkylation and amination of monosubstituted allylic acetates employing these chiral ligands. In this paper, we would like to report the preliminary results of our studies.

Ligands **8**−**11** were synthesized as shown in Scheme 1. A new chiral center was formed on the P atom during the reaction with BINOL, and all diastereoisomers were easily isolated as orange solids by column chromatography. The preparation of these ligands is fairly easy even in gram quantity although the structure is seemingly rather complex. They are very stable in air, and no change in NMR spectra was observed after 2 months. The absolute configuration at the phosphorus atom was determined by X-ray diffraction analysis.[12] Although Pfaltz[7] and Hayashi[6] have also developed ligands by incorporating a binaphthyl skeleton on the P-atom, ligands **8**−**11** are entirely different from them. A cyclic phosphite structure was found in that of Pfaltz, while in our ligands, a new chiral center was introduced to the P-atom, and a free OH functionality was retained, which is crucial in these reactions, particularly in the amination reaction (vide infra).

For the allylic alkylation reaction of **1a** or **2a**, all ligands gave branched product **5a** in good regioselectivity, among which (S,S_{phos},R)-**8d** was the best. Under the optimized condition by using ligand **8d**, wide ranges of substrates were investigated (eq 1). All results are summarized in Table 1.

All reactions provided the branched products **5** with high regio- and enantioselectivity, except the substrate **1g** with 2-thienyl group, which gave a relatively lower regio- and enantioselectivity (entry 8, Table 1). In the literature, the regioselectivity was dramatically reduced or even reversed to the achiral linear product for substrates with electron-withdrawing groups on aryl rings, and it was claimed that it was controlled by electronic factors.[7] In our case, 94/6 regioselectivity in favor of **5** (94% ee) was recorded for **1e** with *p*-chlorophenyl group (entry 6, Table 1). Even with a very strong electron-withdrawing group such as CN group in **1f**, the reaction still gave a 90/10 regioselectivity in favor of **5** (95% ee, entry 7, Table 1). Despite the fact that high regioselectivity in Pd-catalyzed allylic substitution reactions of **1h** containing a methyl substituent has been reported with N[9] or S[13] nucleophile, no satisfactory results for **1h** in the alkylation reaction have ever been reported. However, with ligand **8d** the alkylation

(1) Reviews: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2.

(2) For examples, see: (a) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (b) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (c) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047.

(3) Some exceptional examples: (a) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074. (c) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Williams, J. M. J. *Org. Lett.* **1999**, *1*, 1969.

(4) Examples of other metal-catalyzed allylic substitutions: (a) W: Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (b) Mo: Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416. (c) Ir: Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (d) Fe: Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974. (e) Rh: Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (f) Ru: Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanable, Y. *Organometallics* **1995**, *14*, 1945. (g) Pt: Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Humphries, M. E.; Williams, J. M. J. *Chem. Eur. J.* **2000**, *6*, 353.

(5) (a) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J., Ed.; VCH: Wiley: England, 1995. (b) Tenaglia, A.; Heumann, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2180.

(6) (a) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681.

(7) (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.

(8) Selected examples for regioselective Pd-catalyzed allylic amination reaction: (a) Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Mashmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S.; Oldroyd, R.; Gladden, L.; Mantle, M. D. *Chem. Commun.* **1999**, 1167. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (c) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451.

(9) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743.

(10) (a) You, S.-L.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X. *Chem. Commun.* **1998**, 2765. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933. (c) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149. (d) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285.

(11) (a) *Ferrocene*; Hayashi, T., Togni, A., Eds.; VCH: Weiheim, Germany, 1995. (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377 and references therein.

(12) The absolute configurations on P-atom in **8a**, **8b**, **9c**, **8d**, and **10** were determined by X-ray diffraction (see Supporting Information).

(13) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297.

10.1021/ja016121w CCC: $20.00
Published on Web 07/10/2001

Scheme 1. Synthesis of Ligangs **8**−**11**

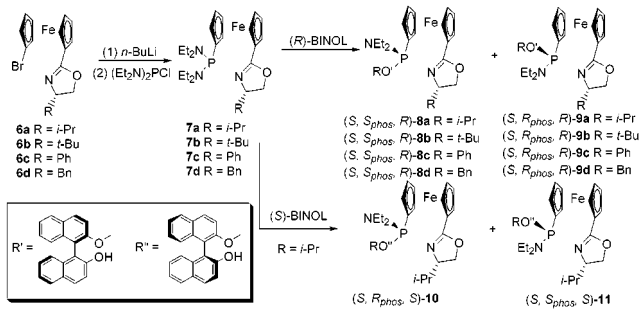
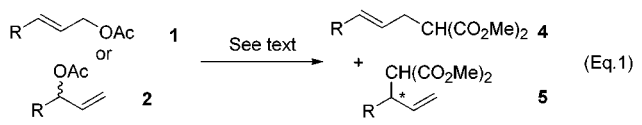


Table 1. Pd-catalyzed Allylic Alkylation with Ligand **8d**[a]



entry	substrate, **R**	*T* °C	time h	yield %[b]	**5**/**4**[c]	ee %[d]
1	**1a**, phenyl	0	2	98	95/5	95
2	**1b**, 1-naphthyl	0	1	95	>99/1	93
3	**1b**, 1-naphthyl	−43	7	97	>99/1	97
4	**1c**, 4-Meo-Ph	−20	2	97	93/7	97
5	**1d**, 4-Me-Ph	0	9	91	98/2	92
6	**1e**, 4-Cl−Ph	0	1	97	94/6	94
7	**1f**, 4-CN−Ph	0	1	96	90/10	95
8	**1g**, 2-thienyl	0	1	95	80/20	87
9	**1h**, methyl	0	2	83	>97/3	94

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**8d**/KOAc/substrate/$CH_2(CO_2Me)_2$/BSA = 2/4/3/100/300/300. CH_2Cl_2 and toluene were the solvents. [b] Isolated yield. [c] Determined by 300 MHz ^{1}H NMR of the crude product after column chromatography. [d] Determined by chiral HPLC.

of **1h** gave >97/3 regioselectivity in favor of **5** with 94% ee (entry 11, Table 1). For substrates **2a** and **2b** an excellent regioselectivity but a slightly lower enantioselectivity were achieved (the data were not showed).

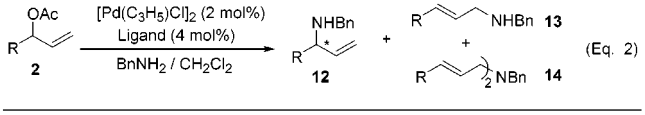
The above ferrocene-based *P*,*N*-ligands were also applied successfully to Pd-catalyzed allylic amination reactions, a more challenging but very useful reaction to synthesize allylic amines.[14] Benzylamine was chosen as the nucleophile. First, **1a** or **2a** was used as the substrate, and the reaction was optimized by varying the ligands, solvents, and temperature. It was surprising that all the (S,S_{phos},R)-**8** and (S,R_{phos},S)-**10** ligands, which gave excellent results in the alkylation reactions, provided the linear product with high ratio. Fortunately, high regio- and enantioselectivity for **2** were given by utilizing (S,R_{phos},R)-**9** and (S,S_{phos},S)-**11** ligands; products with opposite absolute configuration were obtained from **9** and **11**. With (S,R_{phos},R)-**9c** as ligand, 0 °C in CH_2Cl_2 was found to be the best reaction condition, and wide ranges of substrates were investigated (eq 2). The results are summarized in Table 2.

Substrates **2a**−**e** gave excellent ee values and branched regioselectivity. It differed from the results of the allylic alkylation, and high regio- and enantioselectivity were achieved in the amination of **2g** with a 2-thienyl group (**12g**/**13g**/**14g**: 90/9/1, ee of **12g**: 98%, entry 6, Table 2). High regio- and relatively lower enantioselectivity for **2h** with methyl as substituent were obtained (entry 7, Table 2). However, only moderate regioselectivity was achieved for substrate **1**.

The favored ligands for these two reactions are entirely different. Ligands **8** (S,S_{phos},R) and **10** (S,R_{phos},S) give better results in alkylation reactions, while the ligands **9** (S,R_{phos},R) and **11** (S,S_{phos},S) are better in amination reactions. The contradiction

(14) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

Table 2. Pa-catalyzed Allylic Amination with Ligand **9c**[a]



entry	substrate, **R**	time h	yield %[b]	**12**/**13**/**14**[c]	**B**/**L**[d]	ee %[e]
1	**2a**, phenyl	7	94	95/3/2	94/6	98
2	**2b**, 1-naphthyl	8	87	94/6/−	96/4	97
3	**2c**, 4-Meo-Ph	8	86	87/13/−	85/15	94
4	**2d**, 4-Me-Ph	6	89	94/6/−	90/10	95
5	**2e**, 4-Cl−Ph	3	76	86/9/5	87/13	97
6	**2g**, 2-thienyl	8	85	90/9/1	90/10	98
7	**2h**, methyl	4	78	>97/3/−	>97/3	84

[a] Proceeded at 0 °C in CH_2Cl_2 with molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**9c**/substrate/$BnNH_2$ = 2/4/100/300. [b] Isolated yield. [c] Determined by GC of the crude product after column chromatography. [d] Determined by 300 MHz ^{1}H NMR of the crude product after column chromatography, **B**/**L** represents ratio of **12**/(**13**+**14** × 2). [e] Determined by chiral HPLC.

between these two sets of ligands in two reactions could possibly be rationalized by the following considerations. In the amination reaction, a hydrogen bond between the free OH group in the ligand and the amine might be formed. Thus, the attack of the nucleophile may probably happen in an intramolecular mode. The X-ray structures of these ligands showed two types of disposition of the OH group. For **8** and **10**, the OH group is directed outwardly from the metal center. For **9** and **11**, the OH group is directed inwardly to the reaction center. For **8** and **10**, the intramolecular attack of a nucleophile may favor the formation of the linear product, while branched products with different configuration will be derived from **9** and **11**, which is consistent with the experimental results. To verify the above notion, the free OH group of **8a** and **9a** was converted to the Me-ether, and the corresponding methylated ligands (S,S_{phos},R)-**15** and (S,R_{phos},R)-**16** were prepared from **7a** and (*R*)-2-(2′-hydroxy-1,1′-binaphthyl) methyl ether. We therefore expected that the regioselectivity by using **15** would be higher than that of **8a**, and regioselectivity by using **16** would be lower than that of **9a**, accordingly. The results are almost the same as we expected. The regioselectivity by **15** is 50/43/7 for **2a**, which is higher than for **8a** (3/81/16) and that by **16** is 63/31/6, which is lower than for **9a** (89/8/3). The reaction rate by **15** and **16** was much slower (72 and 48 h, respectively) as a result of intermolecular reaction instead of the original intramolecular ones. It is therefore clear that the hydroxyl group in the ligands is crucial and important in the palladium-catalyzed allylic amination reaction.

Highly regio- and enantioselective Pd-catalyzed allylic alkylation and amination of monosubstituted allylic acetates were realized for a wide range of substrates for the first time. However, the difference of regio- and enantioselectivity between two types of substrates **1** and **2** in these two reactions is a problem that remains to be solved.

Acknowledgment. Financially supported by the Major Basic Research Development Program (G2000077506), the Natural Science Foundation of China, Outstanding Youth Fund, the Chinese Academy of Sciences. We thank Professor H. N. C. Wong for inspiring discussion. This paper is dedicated to Professor Wei-Yuan Huang on the occasion of his 80th birthday.

Supporting Information Available: Synthetic procedure and spectral characterization for all ligands, X-ray crystallographic files (CIF) of compound **8a**, **8b**, **9c**, **8d**, and **10**, general procedure for allylic alkylation, ^{1}H NMR and HPLC data for **5a**−**h**, **12a**−**e**, **12g**−**h**; ^{1}H NMR data for **13a**−**e**, **13g**, **14a**−**e**, **14g** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016121W