

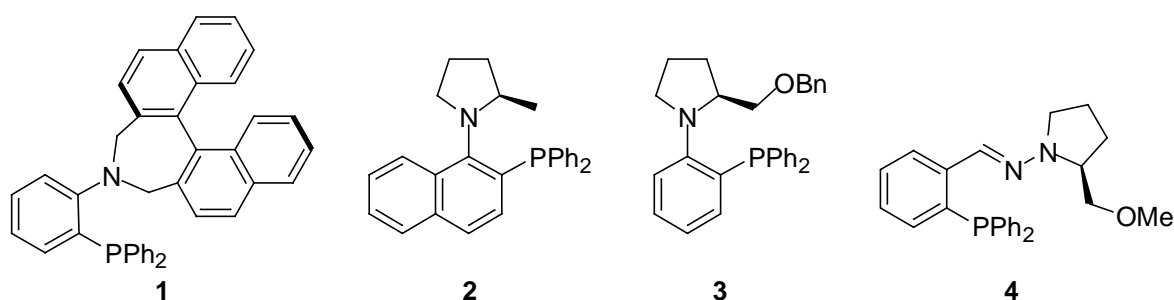
PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION USING CHIRAL P,N-LIGANDS

Takashi Mino,* Youichi Tanaka, Masami Sakamoto, and Tsutomu Fujita

Department of Materials Technology, Faculty of Engineering, Chiba University, Inage, Chiba 263-8522, Japan

Abstract – Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**8**) with a dimethyl malonate-BSA-LiOAc system has been successfully carried out in the presence of new chiral P,N-ligands **5** in good yields with good enantioselectivities (up to 83% ee).

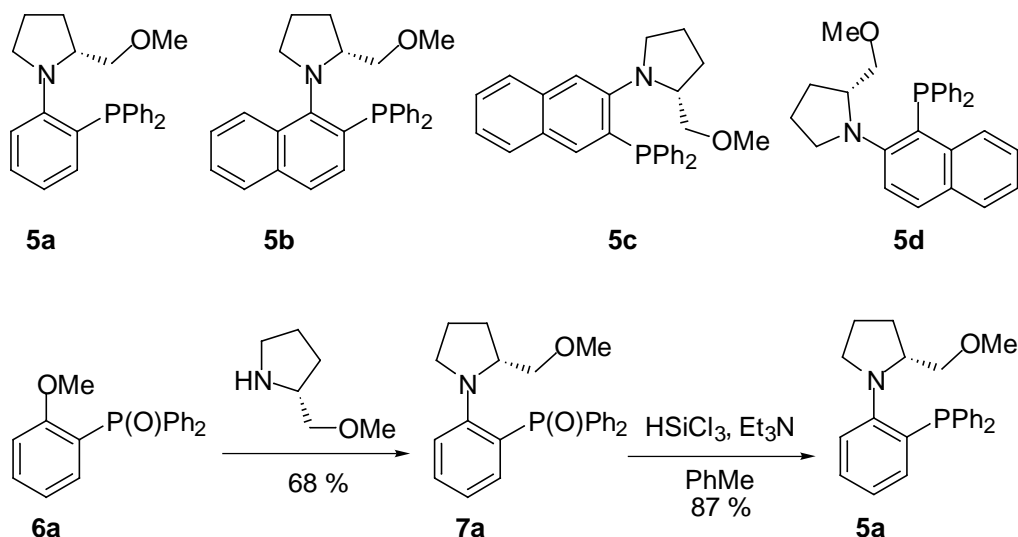
Palladium-catalyzed allylic alkylation is a widely used process in organic synthesis,¹ and the development of efficient enantioselective catalysis for this reaction is awaited.² Recently, P,N-bidentate ligands were found to be efficient chiral sources for this reaction.³ A sort of this ligand is aminophosphine such as Wimmer's C_2 -symmetric ligand (**1**),⁴ Miyano's ligand (**2**)⁵ and Hiroi's ligand (**3**).⁶ On the other hand, we previously reported phosphine-hydrazone bidentate ligands such as 2-diphenylphosphinobenzaldehyde SAMP hydrazone (DPPB-SAMP) (**4**).⁷



We were interested in aminophosphine ligands which have a methoxymethyl moiety. This ether bond was expected to interact with the incoming nucleophile to bring about good stereoselectivity. Thus we designed a chiral P,N-ligand which was cut out a hydrazone moiety of **4** for application to asymmetric catalysis. Here, we report palladium-catalyzed asymmetric allylic alkylation (AAA reaction) using chiral P,N-ligands (**5**).

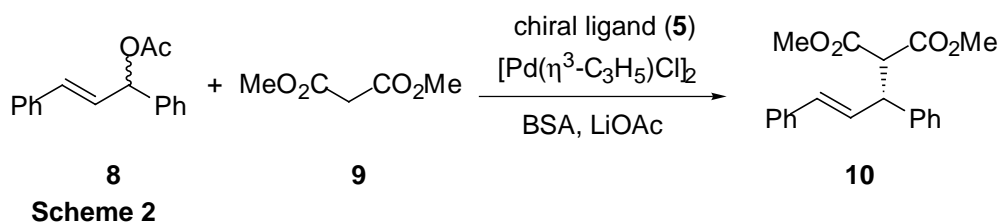
The synthesis of chiral P,N-ligand such as (*R*)-1-[2-(diphenylphosphino)phenyl]-2-(methoxymethyl)pyrrolidine (**5a**) was shown to Scheme 1. Nucleophilic aromatic substitution (S_NAr) reactions⁸ of the corresponding phosphine oxide compound such as diphenyl(2-

methoxyphenyl)phosphine oxide (**6a**) with lithiated (*R*)-1-(methoxymethyl)pyrrolidine gave phosphine oxide (**7a**). Phosphine oxide (**7a**) was converted into the desired chiral P,N-ligand (**5a**) using trichlorosilane-triethylimine in good yield.⁹ The other ligands (**5b-d**) were prepared in the same manner.¹⁰



Scheme 1

These chiral P,N-ligands (**5**) were applied to the palladium-catalyzed AAA reaction of 1,3-diphenyl-2-propenyl acetate (**8**) with a dimethyl malonate (**9**). This reaction was carried out under our previously reported conditions⁷ (2 mol% of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, 4 mol% of chiral ligand, and a mixture of *N,O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol% of LiOAc in THF) (Scheme 2, Table 1).



Scheme 2

Using ligand (**5a**), the product (**10**) was obtained in good chemical yield (93%), but enantiomeric excess was low (49% ee) (Entry 1). However, using ligand (**5b**)¹¹ which have a naphthyl backbone, the product (**10**) was obtained in good enantioselectivity (74% ee) (Entry 2). Using regioisomers of **5b** such as **5c** and **5d**, the enantioselectivities of **10** were decreased (Entry 3 and 4). When the reaction was carried out in toluene, the chemical yield and enantiomeric excess were increased (Entry 2 vs Entry 5). The reaction at 0 °C further improved the enantioselectivity to 79% ee (entry 9). Although enantioselectivity was improved to 83% ee by further depressing the temperature (-20 °C), the reaction rate became slow (Entry 10). In each case, the product (**10**) was formed with the (*R*)-(+)-enantiomer predominating, as determined from the sign of the optical rotation.¹² When 2-diphenylphosphinobenzaldehyde RAMP hydrazone (*ent*-**4**) was used as a catalyst, palladium-catalyzed AAA reaction with *ent*-**4** was gave (*S*)-isomer of **10**.⁷

RAMP ((*R*)-1-amino-2-(methoxymethyl)pyrrolidine) was prepared from (*R*)-1-(methoxymethyl)pyrrolidine. So we can show that palladium-catalyzed AAA reactions gave each enantiomer products (**10**) using chiral ligands which were prepared from one chiral source such as (*R*)-1-(methoxymethyl)pyrrolidine.

Table 1. Asymmetric allylic alkylation using chiral P,N-ligands (**5**).^a

Entry	Ligand	Solv.	Yield of (<i>R</i>)- 10 / % ^b	ee of (<i>R</i>)- 10 / % ^c
1	5a	THF	93	49
2	5b	THF	79	74
3	5c	THF	91	24
4	5d	THF	96	35
5	5b	PhMe	94	76
6	5b	MeCN	94	60
7	5b	CH ₂ Cl ₂	95	64
8	5b	DMF	63	64
9 ^d	5b	PhMe	99	79
10 ^e	5b	PhMe	88	83

^a The reaction was carried out at rt. for 24 h.

^b Isolated yields.

^c Determining by HPLC analysis using a chiral column (Chiralcel OD).

^d This reaction was carried out at 0 °C for 96 h.

^e This reaction was carried out at -20 °C for 7 days.

In conclusion, we showed the palladium-catalyzed AAA reaction using chiral P,N-ligands (**5**) with a good enantiomeric excess. Further studies on the optimization of ligands and application to other asymmetric reactions are in progress in our laboratory.

REFERENCES AND NOTES

- (a) J. Tsuji and I. Minami, *Acc. Chem. Res.*, 1987, **20**, 140. (b) B. M. Trost and T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*; ed. by G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon, Oxford, 1982, Vol. 8, p. 799. (c) B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385.
- (a) B. M. Trost and D L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395. (b) J. M. J. Williams, *Synlett*, 1996, 705. (c) A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339. (d) T. Hayashi, in *Catalytic Asymmetric Synthesis*; ed. by I. Ojima, VCH Publishers, New York, 1993, p. 325. (e) G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257 and references cited therein.
- Some recent examples of AAA reaction using P,N-ligand: (a) M. Bourghida and M. Widhalm, *Tetrahedron: Asymmetry*, 1998, **9**, 1073. (b) M. Ogasawara, K. Yoshida, H. Kamei, K. Kato, Y.

- Uozumi, and T. Hayashi, *Tetrahedron: Asymmetry*, 1998, **9**, 1779. (c) W. Zhang, Y. Yoneda, T. Kida, Y. Nakatsuji, and I. Ikeda, *Tetrahedron: Asymmetry*, 1998, **9**, 3371. (d) J. P. Cahill, and P. J. Guiry, *Tetrahedron: Asymmetry*, 1998, **9**, 4301. (e) Y. Imai, W. Zhang, T. Kida, Y. Nakatsuji, and I. Ikeda, *Tetrahedron Lett.*, 1998, **39**, 4343. (f) B. Wiese and G. Helmchem, *Tetrahedron Lett.*, 1998, **39**, 5727. (g) K. Yonehara, T. Hashizume, K. Mori, K. Ohe, and S. Uemura, *Chem. Commun.*, 1998, 415. (h) A. Saitoh, M. Misawa, and T. Morimoto, *Synlett*, 1999, 483. (i) Y. Suzuki, Y. Ogata, and K. Hiroi, *Tetrahedron: Asymmetry*, 1999, **10**, 1219. (j) J. C. Anderson, R. J. Cubbon, and J. D. Harling, *Tetrahedron: Asymmetry*, 1999, **10**, 2829. (k) J. W. Han, H-Y. Jang, and Y. K. Chung, *Tetrahedron: Asymmetry*, 1999, **10**, 2853. (l) K. Ito, R. Kashiwagi, K. Iwasaki, and T. Katsuki, *Synlett*, 1999, 1563.
- P. Wimmer and M. Widhalm, *Tetrahedron: Asymmetry*, 1995, **6**, 657.
 - T. Hattori, Y. Komuro, N. Hayashizaka, H. Takahashi, and S. Miyano, *Enantiomer*, 1997, **2**, 203.
 - (a) K. Hiroi and Y. Suzuki, *Heterocycles*, 1999, **50**, 89. (b) K. Hiroi, Y. Suzuki, and I. Abe, *Tetrahedron: Asymmetry*, 1999, **10**, 1173.
 - T. Mino, W. Imiya, and M. Yamashita, *Synlett*, 1997, 583.
 - T. Hattori, J. Sakamoto, N. Hayashizaka, and S. Miyano, *Synthesis*, 1994, 199.
 - (a) Y. Uozumi, N. Suzuki, A. Ogiwara, and T. Hayashi, *Tetrahedron*, 1994, **50**, 4293. (b) J. -M. Valk, T. D. W. Claridge, and J. M. Brown, *Tetrahedron: Asymmetry*, 1995, **6**, 2597.
 - 5a**: $[\alpha]_D^{20} = +8.2^\circ$ (c=1.00, CHCl₃); ¹H NMR (300 Mz, CDCl₃) δ 1.54-1.86 (m, 3H), 2.01-2.16 (m, 1H), 2.63 (t, 8.9 Hz, 1H), 2.72 (q, 7.1 Hz, 1H), 3.03 (dd, 3.7 and 9.2 Hz, 1H), 3.12 (s, 3H), 3.45-3.56 (m, 1H), 3.63-3.77 (m, 1H), 6.81 (dq, 1.3 and 3.8 Hz, 1H), 6.94 (t, 7.4 Hz, 1H), 7.18-7.39 (m, 12H); ³¹P NMR (121 Mz, CDCl₃) δ -12.14; FAB-MS *m/z* 376 (M⁺+H, 64).; **5b**: $[\alpha]_D^{20} = -12.3^\circ$ (c=1.00, CHCl₃); ¹H NMR (300 Mz, CDCl₃) δ 2.00 (br, 3H), 2.39 (br, 1H), 2.89 (br, 1H), 3.09 (s, 3H), 3.22 (br, 3H), 4.08 (br, 1H), 7.06 (br, 1H), 7.14-7.38 (m, 11H), 7.47 (br, 2H), 7.60 (d, 8.5 Hz, 1H), 7.85 (br, 1H); ³¹P NMR (121 Mz, CDCl₃) δ -16.22; FAB-MS *m/z* 426 (M⁺+H, 57).; **5c**: $[\alpha]_D^{20} = -31.0^\circ$ (c=1.00, CHCl₃); ¹H NMR (300 Mz, CDCl₃) δ 1.57-1.91 (m, 3H), 2.02-2.20 (m, 1H), 2.43 (t, 8.9 Hz, 1H), 2.75 (q, 7.7 Hz, 1H), 2.97 (dd, 3.7 and 9.2 Hz, 1H), 3.08 (s, 3H), 3.70-3.88 (m, 2H), 6.95-7.18 (m, 2H), 7.22-7.43 (m, 11H), 7.53 (d, 8.4 Hz, 1H), 7.56 (d, 4.5 Hz, 1H), 7.70 (d, 8.1 Hz, 1H); ³¹P NMR (121 Mz, CDCl₃) δ -10.46.; **5d**: $[\alpha]_D^{20} = +32.0^\circ$ (c=1.00, CHCl₃); ¹H NMR (300 Mz, CDCl₃) δ 1.60-1.81 (m, 3H), 2.01-2.19 (m, 1H), 2.92-3.02 (m, 1H), 3.11 (s, 3H), 3.15 (dd, 7.2 and 9.3 Hz, 1H), 3.34 (dd, 4.3 and 9.3 Hz, 1H), 3.66-3.78 (m, 1H), 3.98-4.11 (m, 1H), 6.80-6.87 (m, 1H), 6.96-7.17 (m, 6H), 7.19-7.28 (m, 3H), 7.38-7.49 (m, 4H), 7.61 (d, 7.9 Hz, 1H), 7.76 (d, 9.0 Hz, 1H); ³¹P NMR (121 Mz, CDCl₃) δ -16.05.
 - The enantiomer of **5b** was previously synthesized: S. Miyano, T. Hattori, Y. Komuro, H. Kumobayashi, *Jpn. Kokai Tokkyo Koho*, H09241277 (*Chem. Abstr.*, 1997, **127**, 302486h).
 - T. Hayashi, A. Yamamoto, T. Hagihara, and Y. Ito, *Tetrahedron Lett.*, 1986, **27**, 191.