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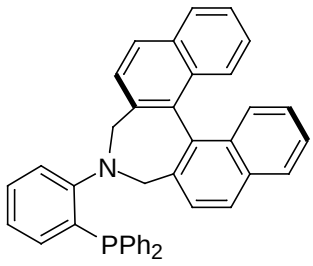
PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION USING CHIRAL P,N-LIGANDS

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 enantioselectives (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]



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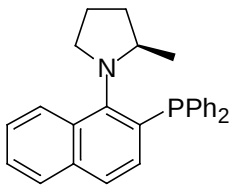

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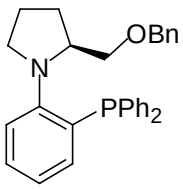

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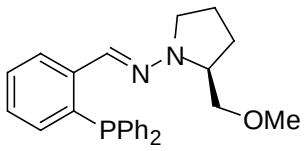
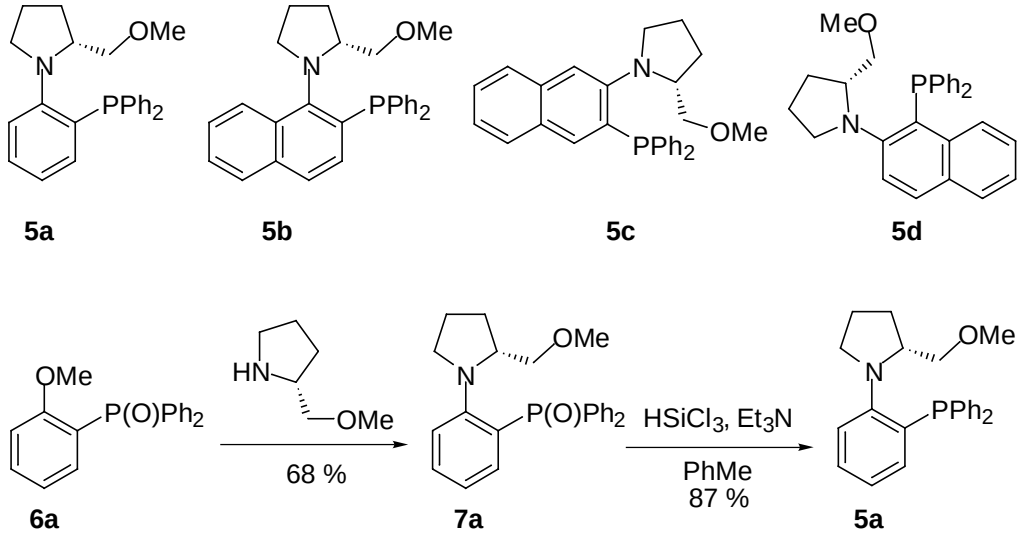


4

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 moeity of **4** for application to asymmetric catalysis. Here, we report palladium-catalyzed asymmetric allylic alkylation (AAA reaction) using chiral P,N-ligands (**5**).

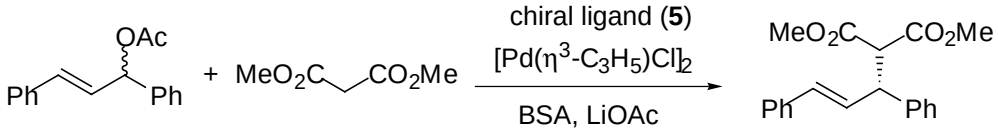
The synthesis of chiral P,N-ligand such as (*R*)-1-[2-(diphenylphosphino)phenyl]-2-(methoxymethyl)pyrrolidine (**5a**) was shown to Scheme 1. Nucleophilic aromatic substitution (SNAr) reactions[8] of the corresponding phosphine oxide compound such as diphenyl(2-

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-triethylmine 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 conditions[7] (2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 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).



8 **9** **10**

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 regioisomeres 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 (*R*)-**10**/ %[b]	ee of (*R*)-**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_2Cl_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] Determing 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.

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10. **5a**: $[\alpha]_D^{20}$ = +8.2° (c=1.00, $CHCl_3$); ^{1}H NMR (300 Mz, $CDCl_3$) 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); ^{31}P NMR (121 Mz, $CDCl_3$) δ -12.14; FAB-MS *m / z* 376 (M^++H, 64).; **5b**: $[\alpha]_D^{20}$ = -12.3° (c=1.00, $CHCl_3$); ^{1}H NMR (300 Mz, $CDCl_3$) 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); ^{31}P NMR (121 Mz, $CDCl_3$) δ -16.22; FAB-MS *m / z* 426 (M^++H, 57).; **5c**: $[\alpha]_D^{20}$ = -31.0° (c=1.00, $CHCl_3$); ^{1}H NMR (300 Mz, $CDCl_3$) δ1.57-1.91 (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); ^{31}P NMR (121 Mz, $CDCl_3$) δ -10.46.; **5d**: $[\alpha]_D^{20}$ = +32.0° (c=1.00, $CHCl_3$); ^{1}H NMR (300 Mz, $CDCl_3$) δ1.60-1.81 (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) ; ^{31}P NMR (121 Mz, $CDCl_3$) δ -16.05.
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