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ASYMMETRIC ALLYLIC ALKYLATION USING PLANAR CHIRAL PHOSPHINE-HYDRAZONE LIGANDS

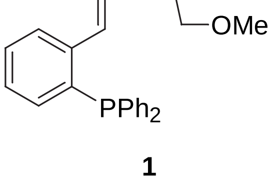
Takashi Mino, [a]* Teruhiro Ogawa[b], and Masakazu Yamashita[b]

[a] Department of Materials Technology, Faculty of Engineering, Chiba University, Inage, Chiba 263-8522 Japan
[b] Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0394, Japan

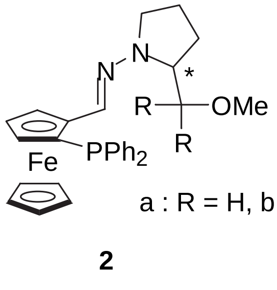
***Abstract* –** Palladium-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate (**3**) with a dimethyl malonate-BSA-lithium acetate system has been successfully carried out in the presence of chiral ferrocene hydrazone such as (*S*)-α-(diphenylphosphino)ferrocenecarboxaldehyde SAMP hydrazone (DPPFA-SAMP) ((*S*,*S*)-**2a**) in high yields with high enantioselectives (up to 96% ee).

Synthesis of chiral ferrocene derivatives has attracted much interest in various research fields.[1] Planar chiral ferrocenes have shown efficiency as catalysts for asymmetric synthesis. Palladium-catalyzed allylic substitution is a versatile and widely used process in organic synthesis,[2] and the development of an efficient enantioselective catalysis for this reaction is an important goal of current research in this area.[3] Recently, therefore, chiral ferrocene ligands with planar chirality have begun to be used in palladium-catalyzed allylic substitution.[4]

We previously described palladium-catalyzed asymmetric allylic substitution, using 2-diphenylphosphinobenzaldehyde SAMP hydrazone (DPPB-SAMP) (**1**) as a chiral ligand.[5] Here we report novel phosphine-hydrazone ligands (**2**) with planar chirality which give good results in asymmetric allylic substitution.



1



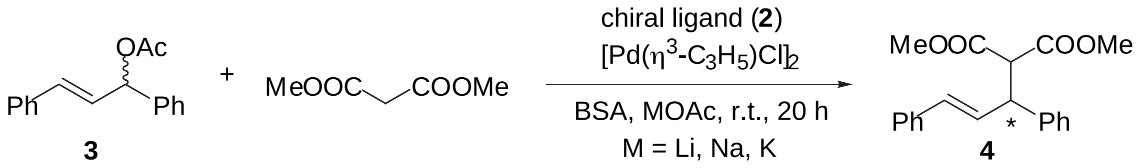
a : R = H, b = Me, c : R = Et

2

Phosphine-hydrazone ligands (**2**) can be easily prepared from (*S*)-α-(diphenylphosphino)ferrocenecarboxaldehyde[4c] with SAMP ((*S*)-1-amino-2-(methoxymethyl)pyrrolidine), SADP ((*S*)-amino-2-(1’-

methoxy-1’-methylethyl)pyrrolidine), SAEP ((*S*)-amino-2-(1’-methoxy-1’-ethylpropyl)pyrrolidine), and RAMP ((*R*)-1-amino-2-(methoxymethyl)pyrrolidine) which is enantiomer of SAMP in good yields.[6]

These ligands were examined in palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**3**)[7] with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[8] at room temperature (Scheme 1, Table 1). Using SAMP hydrazone ((*S*,*S*)-**2a**) and lithium acetate in CH_2Cl_2 (Entry 1), product (**4**) was obtained in an 86% yield and 92% ee. When toluene was used instead of CH_2Cl_2, the enantioselectivity of **4** increased to 96% ee (Entry 4). When sodium acetate or potassium acetate was used instead of lithium acetate in toluene, the yield and/or enantioselectivity of **4** decreased (Entries 6 and 7 vs Entry 4). The optimized result was therefore obtained when the reaction was carried out in the presence of lithium acetate as a base in toluene.



Scheme 1

Table 1. Enantioselective Allylic Alkylation Catalyzed by Palladium Complexes with Chiral Hydrazone Ligands (**2**).[a]

Entry	Ligand	Solv.	M	Yield of **4** / %[b]	Ee of **4** / %[c]	Config. of **4**
1	(*S*,*S*)-**2a**	CH_2Cl_2	Li	86	92	*R*
2	(*S*,*S*)-**2a**	THF	LI	88	92	*R*
3	(*S*,*S*)-**2a**	MeCN	Li	90	90	*R*
4	(*S*,*S*)-**2a**	PhMe	Li	93	96	*R*
5	(*S*,*S*)-**2a**	Et_2O	Li	90	92	*R*
6	(*S*,*S*)-**2a**	PhMe	Na	87	95	*R*
7	(*S*,*S*)-**2a**	PhMe	K	82	89	*R*
8	(*S*,*S*)-**2b**	PhMe	Li	90	90	*R*
9	(*S*,*S*)-**2c**	PhMe	Li	88	74	*R*
10	(*S*,*R*)-**2a**	PhMe	Li	94	46	*S*

[a] Molar ratio : $[Pd(\eta^3-C_3H_5)Cl]_2$ (0.02 eq.), ligand (0.04 eq.), dimethyl malonate (3.0 eq.), BSA (3.0 eq.), MOAc (0.01 eq.).

[b] Isolated yields.

[c] The *ee* values were determed by HPLC analysis using a chiral column (Chiralcel OD (Hexane:*i*-PrOH=99:1)).

In this condition, SADP hydrazone ((*S*,*S*)-**2b**) and SAEP hydrazone ((*S*,*S*)-**2c**) were used instead of (*S*,*S*)-**2a**, and the enantioselectivity of **4** decreased (Entries 8 and 9 vs Entry 4). Product (**4**) was formed with the (*R*)-(+)-enantiomer predominating, as determined from the sign of the optical rotation.[9]

We next investigated the asymmetric allylic alkylation using the diastereomer of (*S*,*S*)-**2a** as ligand. The enantioselectivity of **4** decreased and the configuration of **4** was inverted using the ligand ((*S*,*R*)-**2a**) which was prepared from (*S*)-α-(diphenylphosphino)ferrocenecarboxaldehyde and RAMP (Entry 4 vs Entry 10). This observation indicates that the central chirality in the hydrazone unit is more influential factor determining the stereochemical outcome in the allylic alkylation than the planar chirality.

In summary, this study has shown that phosphine-hydrazone ligands with planar chirality such as **2a** can be used in palladium-catalyzed asymmetric allylic alkylation with high enantiomeric excess.

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6. **Typical Procedure for the Preparation of 2**. A mixture of (*S*)-α-(diphenylphosphino)-ferrocenecarboxaldehyde (0.38 mmol), chiral hydrazine (0.46 mmol), and benzene (10 mL) was heated at 100°C for 6 h under an argon atmosphere, and then cooled to room temperature. The reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography.

   (*S*)-α-(Diphenylphosphino)ferrocenecarboxaldehyde SAMP hydrazone ((*S*,*S*)-**2a**): 99%; $[\alpha]^{D}_{25}$ = +138.0 ° (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 Mz, $CDCl_3$) δ 1.72–1.99 (m, 4H), 2.73 (dd, 8.0 and 16.8 Hz, 1H), 3.14–3.30 (m, 2H), 3.25 (s, 3H), 3.31–3.39 (m, 1H), 3.39–3.45 (m, 1H), 3.65–3.71 (m, 1H), 4.07 (s, 5H), 4.31 (t, 2.4 Hz, 1H), 4.75–4.86 (m, 1H), 7.13–7.25 (m, 6H), 7.32–7.43 (m, 3H), 7.48–7.48 (m, 2H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 21.98, 26.41, 49.41, 59.06, 63.01, 68.41 (d, 3.1 Hz), 69.79, 70.12, 72.05 (d, 3.8 Hz), 74.08, 74.36 (d, 10.0 Hz), 88.73 (d, 17.7 Hz), 127.50, 127.96 (d, 6.0

Hz), 128.08 (d, 7.7 Hz), 129.01, 131.50 (d, 7.0 Hz), 132.16 (d, 17.8 Hz), 135.26 (d, 21.1 Hz), 137.92 (d, 10.2 Hz), 140.33 (d, 11.1 Hz); ^{31}P NMR (121 Mz, $CDCl_3$) δ -19.80; FAB-MS *m / z* 510 (M^+, 30); HRMS (FAB) calcd for $C_{29}H_{31}N_2OPFe$ (M^+) 510.1523, found 510.1499.

(*S*)-α-(Diphenylphosphino)ferrocenecarboxaldehyde SADP hydrazone ((*S*,*S*)-**2b**): 89%; $[\alpha]^{D}_{25}$ = +576.0 ° (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.11 (s, 3H), 1.17 (s, 3H), 1.77-1.98 (m, 4H), 2.63 (dd, 8.5 and 15.9 Hz, 1H), 3.22 (s, 3H), 3.40-3.49 (m, 2H), 3.71-3.72 (m, 1H), 4.04 (s, 5H), 4.33 (t, 2.4 Hz, 1H), 4.89-4.91 (m, 1H), 7.12-7.23 (m, 5H), 7.25 (s, 1H), 7.36-7.39 (m, 3H), 7.50-7.58 (m, 2H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 21.03, 23.07, 23.69, 24.64, 49.59, 51.12, 67.71 (d, 3.5 Hz), 69.96, 70.06, 71.17, 71.76 (d, 3.5 Hz), 74.31 (d, 9.4 Hz), 77.69, 89.09 (d, 18.5 Hz), 127.62, 128.06, 127.07 (d, 13.4 Hz), 129.08, 130.22 (d, 9.7 Hz), 132.16 (d, 17.7 Hz), 135.16 (d, 21.0 Hz), 137.53 (d, 9.4 Hz), 140.00 (d, 10.5 Hz); ^{31}P NMR (121 Mz, $CDCl_3$) δ -20.84; FAB-MS *m / z* 538 (M^+, 38); HRMS (FAB) calcd for $C_{31}H_{35}N_2OPFe$ (M^+) 538.1836, found 538.1852.

(*S*)-α-(Diphenylphosphino)ferrocenecarboxaldehyde SAEP hydrazone ((*S*,*S*)-**2c**): 84%; $[\alpha]^{D}_{25}$ = +526.0 ° (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.88 (t, 7.5 Hz, 3H), 0.90 (t, 7.1 Hz, 3H), 1.42-2.05 (m, 8H), 2.64 (dd, 9.5 and 17.5 Hz, 1H), 3.26 (s, 3H), 3.33-3.42 (m, 1H), 3.64 (dd, 2.5 and 8.5 Hz, 1H), 3.71 (dt, 1.2 and 2.3 Hz, 1H), 4.03 (s, 5H), 4.33 (t, 2.5 Hz, 1H), 4.94 (dt, 1.2 and 2.3 Hz, 1H), 7.13-7.24 (m, 5H), 7.25 (s, 1H), 7.36-7.40 (m, 3H), 7.51-7.58 (m, 2H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 7.89, 8.62, 23.55, 23.69, 24.38, 26.25, 50.36, 50.66, 67.50 (d, 3.5 Hz), 69.97, 70.09, 70.34, 71.75 (d, 3.6 Hz), 74.19 (d, 9.2 Hz), 80.40, 89.22 (d, 18.6 Hz), 127.68, 128.09, 127.10 (d, 12.8 Hz), 129.05 (d, 9.9 Hz), 129.12, 132.15 (d, 17.6 Hz), 135.15 (d, 20.9 Hz), 137.44 (d, 9.2 Hz), 139.93 (d, 10.3 Hz); ^{31}P NMR (121 Mz, $CDCl_3$) δ -20.99; FAB-MS *m / z* 566 (M^+, 22); HRMS (FAB) calcd for $C_{33}H_{39}N_2OPFe$ (M^+) 566.2150, found 566.2157.

(*S*)-α-(Diphenylphosphino)ferrocenecarboxaldehyde RAMP hydrazone ((*S*,*R*)-**2a**): 93%; $[\alpha]^{D}_{25}$ = +282.0 ° (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.71-2.05 (m, 4H), 2.84 (dd, 8.1 and 16.6 Hz, 1H), 3.21-3.41 (m, 3H), 3.33 (s, 3H), 3.54 (dd, 5.6 and 9.2 Hz, 1H), 3.71 (t, 1.1 Hz, 1H), 4.04 (s, 5H), 4.33 (t, 2.4 Hz, 1H), 4.87 (t, 1.0 Hz, 1H), 7.11-7.24 (m, 5H), 7.29 (s, 1H), 7.36-7.40 (m, 3H), 7.50-7.59 (m, 2H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 22.01, 26.58, 49.73, 59.15, 63.23, 68.76 (d, 3.2 Hz), 70.03, 70.24, 72.00 (d, 4.0 Hz), 74.36, 74.49, 88.60 (d, 18.3 Hz), 127.56, 127.92 (d, 5.8 Hz), 128.08 (d, 7.6 Hz), 129.04, 132.12 (d, 9.9 Hz), 132.17 (d, 17.6 Hz), 135.26 (d, 21.1 Hz), 137.81 (d, 9.9 Hz), 139.99 (d, 10.5 Hz); ^{31}P NMR (121 Mz, $CDCl_3$) δ -20.99; FAB-MS *m / z* 510 (M^+, 61); HRMS (FAB) calcd for $C_{29}H_{31}N_2OPFe$ (M^+) 510.1523, found 510.1542.

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