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PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION USING CHIRAL PYRIDYL-HYDRAZONE LIGANDS

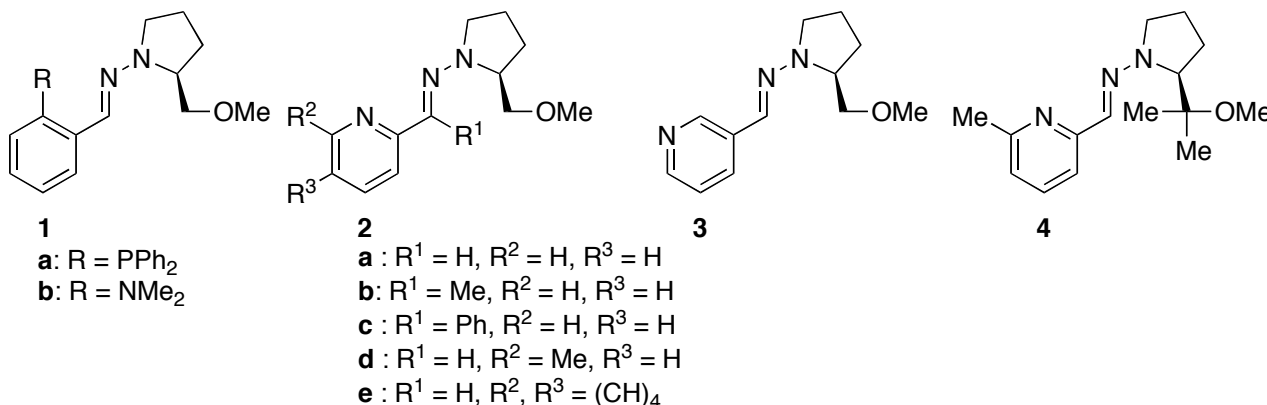
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Abstract – Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with a dimethyl malonate-BSA-LiOAc system has been successfully carried out in the presence of chiral pyridyl-hydrazone ligands such as **2c** with moderate enantioselectivities (up to 67% ee).

Palladium-catalyzed asymmetric allylic substitutions are one of the most effective methods for the enantioselective construction of carbon-carbon or carbon-heteroatom bonds.¹ Since chiral 2-(phosphinoaryl)oxazoline² can induce high enantiomeric excesses in palladium-catalyzed reactions of racemic and achiral allylic substrates with nucleophiles, a number of *P,N*-chelate chiral ligands³ have been reported. We previously described palladium-catalyzed asymmetric allylic substitution using 2-diphenylphosphinobenzaldehyde SAMP hydrazone (DPPB-SAMP) (**1a**) as a chiral ligand.⁴ Recently, Moberg, Chelucci, and Zhou were introduced the use of *N,N*-chelate chiral ligands such as oxazolonylpridines and oxazolonylquinolines as ligands for palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with a dimethyl malonate.⁵



configuration of the product (**6**) in these reactions was proved to be *R* as determined from the sign of the optical rotation.⁸

Table 1. Asymmetric allylic alkylation catalyzed by palladium complexes with chiral hydrazone ligand.^a

| Entry | Ligand | Yield ^b / % | Ee ^c / % |
|-------------------|-----------|------------------------|---------------------|
| 1 | 1b | N. R. ^d | – |
| 2 | 2a | 98 | 38 |
| 3 | 2b | 86 | 25 |
| 4 | 2c | 94 | 49 |
| 5 | 2d | 15 | 55 |
| 6 | 2e | <5 | 43 |
| 7 | 3 | N. R. ^d | – |
| 8 | 4 | <5 | 32 |
| 9 ^{e,f} | 2c | 78 | 62 |
| 10 ^{e,g} | 2c | 14 | 67 |

^a Molar ratio : [Pd(η^3 -C₃H₅)Cl]₂ (0.02 eq.), ligand (0.04 eq.), dimethyl malonate (3.0 eq.), BSA (3.0 eq.), LiOAc (0.02 eq.), THF, 24 h.

^b Isolated yields.

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

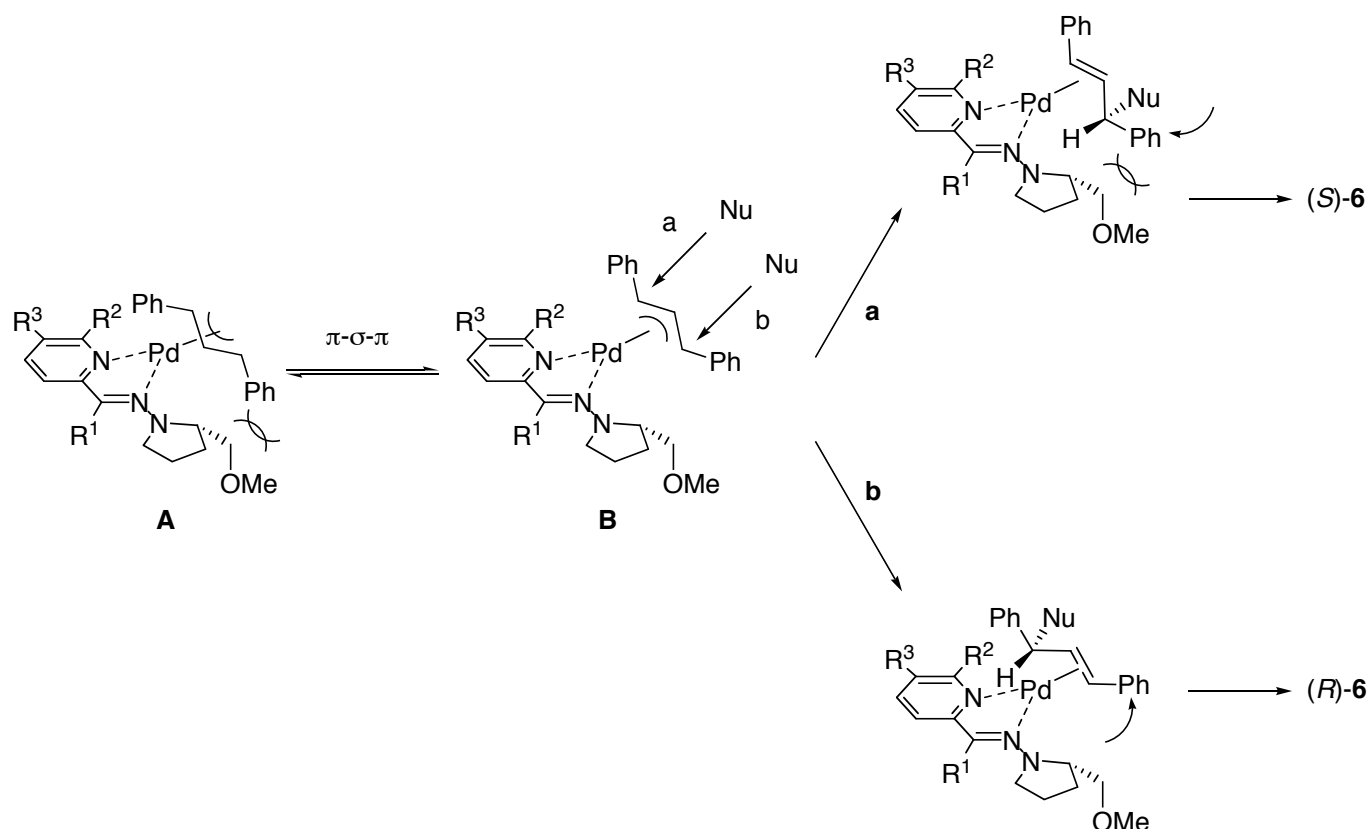
^d No reaction.

^e This reaction was carried out using 0.10 eq. of [Pd(η^3 -C₃H₅)Cl]₂ and 0.20 eq. of ligand.

^f This reaction was carried out at –20 °C for 72 h.

^g This reaction was carried out at –40 °C for 7 d.

According to the generally accepted mechanism of palladium-catalyzed allylic alkylation, there are two candidates, **A** and **B**, which are considerable reaction intermediates formed from chiral ligand **2**. However, **A** has been proved unstable due to steric hindrance of the phenyl rings of the allylic substrate and the methoxymethyl group of the ligand. Therefore, the reaction probably proceeds through a W-type intermediate **B** rather than an M-type intermediate **A**. The enantioselectivity of the reaction is determined by the regioselectivity in the attack of nucleophile to one of the two allylic termini in the intermediate **B**. From the absolute configuration of the product (**6**) obtained with ligand (**2**), we proposed that the nucleophile preferentially attacks the allylic terminus trans to the hydrazone nitrogen. This selectivity explained that pathway **b** is more stable than pathway **a** by a late transition state related to the steric interaction between ligand and allyl in a product like the Pd(0)–olefin complex.



Scheme 2

In conclusion, we have prepared chiral pyridyl-hydrazone ligands (**2–4**) from the corresponding aldehydes and chiral hydrazines. These ligands such as **2c** can be used in palladium-catalyzed asymmetric allylic alkylation with moderate enantiomeric excess.

EXPERIMENTAL

All the experiments were carried out under an argon atmosphere. IR spectra were taken on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on a JEOL LA-400 spectrometer or a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ ppm referenced to an internal SiMe_4 standard for ^1H and ^{13}C NMR. Mass spectra were recorded on a JEOL JMS-HX110. Optical rotations were measured on a JASCO DIP-370.

Typical procedure for the preparation of **1b** and **2-4**.

A mixture of the corresponding aldehyde (1.0 mmol), chiral hydrazine (1.5 mmol), catalytic amount of trifluoroacetic acid and benzene (5 mL) was added to a flask under an argon atmosphere. The mixture was heated under reflux for 5 h, 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.

2-*N,N*-Dimethylaminobenzaldehyde SAMP hydrazone (**1b**)

98%; $[\alpha]_D^{25} = -169.7^\circ$ (*c* 0.57, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ : 1.86-2.06 (m, 4H), 2.72 (s, 6H), 3.06 (dd, $J=7.7$ and 16.5 Hz, 1H), 3.41 (s, 3H), 3.51-3.59 (m, 2H), 3.63-3.72 (m, 2H), 6.98-7.03 (m, 2H), 7.17 (td, $J=1.5$ and 7.3 Hz, 1H), 7.57 (s, 1H), 7.82 (dd, $J=1.7$ and 7.7 Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ : 22.1, 26.8, 45.0, 49.3, 59.2, 63.1, 74.7, 118.1, 122.7, 125.6, 127.6, 130.3, 132.0, 151.3; IR (neat): 3060, 2976, 2937, 2875, 2827, 2785, 1738, 1597, 1577, 1554, 1485, 1452, 1340, 1308, 1236, 1192, 1149, 1120, 1047, 972, 945, 901, 764, 555 and 526 cm^{-1} ; FAB-MS *m/z*: 262 ($\text{M}^+ + 1$, 40); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}$ ($\text{M}^+ + \text{H}$) 262.1919, found 262.1907.

2-Pyridinecarboxaldehyde SAMP hydrazone (2a)⁹

75%; $[\alpha]_D^{25} = -24.0^\circ$ (*c* 0.75, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ : 1.89-2.09 (m, 4H), 3.14-3.19 (m, 1H), 3.39 (s, 3H), 3.44-3.54 (m, 2H), 3.67 (dd, $J=3.6$ and 9.5 Hz, 1H), 3.76-3.80 (m, 1H), 7.04 (ddd, $J=1.2$, 4.9 and 7.3 Hz, 1H), 7.25 (s, 1H), 7.56-7.60 (m, 1H), 7.77 (d, $J=8.2$ Hz, 1H), 8.47 (qd, $J=0.9$ and 4.9 Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ : 22.3, 27.0, 48.5, 59.3, 62.8, 74.7, 118.4, 121.1, 131.6, 136.0, 149.0, 156.4; IR (neat): 3900, 3770, 3370, 3080, 3000, 2950, 2925, 2850, 2350, 2325, 1990, 1030, 1780, 1740, 1720, 1700, 1680, 1640, 1600, 1580, 1560, 1540, 1520, 1500, 1460, 1380, 1360, 1140, 980, 760, 740 and 700 cm^{-1} ; FAB-MS *m/z*: 220 ($\text{M}^+ + 1$, 7).

2-Acetylpyridine SAMP hydrazone (2b)⁹

94%; $[\alpha]_D^{25} = +1141^\circ$ (*c* 0.94, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ : 1.67-1.80 (m, 1H), 1.85-1.97 (m, 2H), 2.03-2.14 (m, 1H), 2.36 (s, 3H), 2.67 (td, $J=6.5$ and 9.5 Hz, 1H), 3.34-3.41 (m, 1H), 3.40 (s, 3H), 3.54-3.67 (m, 3H), 7.19 (ddd, $J=1.2$, 4.9 and 7.5 Hz, 1H), 7.63 (td, $J=1.8$ and 7.5 Hz, 1H), 8.04 (dt, $J=0.9$ and 8.1 Hz, 1H), 8.55 (ddd, $J=0.9$, 1.7 and 4.9 Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ : 15.8, 23.3, 27.1, 54.9, 59.3, 67.0, 75.9, 120.3, 122.8, 135.8, 148.3, 154.4, 157.2; IR (neat): 3053, 2970, 2924, 2873, 2735, 1701, 1576, 1466, 1431, 1360, 1282, 1244, 1194, 1101, 1074, 991, 960, 903, 783, 742, 696, 621 and 538 cm^{-1} ; FAB-MS *m/z*: 234 ($\text{M}^+ + 1$, 100).

Phenyl-2-pyridylketone SAMP hydrazone (mixture of syn and anti) (2c)

88%; $[\alpha]_D^{25} = +570^\circ$ (*c* 0.43, CHCl_3); m.p. 79-81°C; $^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.77 (m, 3H), 1.92-2.04 (m, 1H), 2.48-2.80 (m, 2H), 3.40-3.50 (m, 1H), 3.41 (s, 3H), 3.72-3.80 (m, 2H), 7.09 (ddd, $J=1.1$, 4.9 and 7.3 Hz, 0.5H), 7.20-7.45 (m, 6H), 7.60 (td, $J=1.8$ and 7.5 Hz, 0.5H), 7.70-7.79 (m, 1H), 8.50 (dd, $J=4.0$ and 6.1 Hz, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ : 24.1, 24.2, 27.2, 27.3, 55.2, 55.8, 59.66, 59.72, 66.7, 66.8, 76.0, 76.2, 121.8, 122.0, 122.8, 126.1, 127.2, 128.0, 128.1, 128.2, 128.4, 130.5, 136.1, 136.4, 137.9, 139.9, 144.7, 144.9, 149.2, 149.9, 157.7, 158.7; IR (KBr): 3678, 3633, 3057, 2978, 2927, 2873, 2825, 2725, 2056, 1957, 1884, 1820, 1757, 1581, 1547, 1462, 1423, 1338, 1282, 1223, 1192, 1136, 1092, 989, 966, 903, 845, 791, 768, 696, 652, 611 and 567 cm^{-1} ; EI-MS *m/z*: 295 (M^+ , 5); HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}$ ($\text{M}^+ + \text{H}$) 296.1763, found 296.1755.

6-Methyl-2-pyridinecarboxaldehyde SAMP hydrazone (2d)

79%; $[\alpha]_D^{25} = -175$ (*c* 0.10, CHCl₃); ¹H-NMR (CDCl₃) δ : 1.88-2.08 (m, 4H), 2.52 (s, 3H), 3.16 (dd, *J*=6.5 and 17.4 Hz, 1H), 3.40 (s, 3H), 3.43-3.53 (m, 2H), 3.66-3.69 (m, 1H), 3.72-3.79 (m, 1H), 6.92 (d, *J*=7.5 Hz, 1H), 7.26 (s, 1H), 7.49 (t, *J*=7.7 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H); ¹³C-NMR (CDCl₃) δ : 22.2, 24.4, 26.9, 48.6, 59.3, 62.8, 74.4, 115.3, 120.6, 132.0, 136.3, 155.8, 157.2; IR (neat): 3377, 3060, 2924, 2879, 1730, 1562, 1454, 1412, 1360, 1221, 1155, 1120, 982, 868, 789, 739 and 621 cm⁻¹; EI-MS *m/z*: 233 (M⁺, 72); HRMS (FAB) calcd for C₁₃H₂₀N₃OP (M⁺+H) 234.1606, found 234.1591.

2-Quinolinecarboxaldehyde SAMP hydorazone (2e)

9%; $[\alpha]_D^{25} = -176$ (*c*=0.09, CHCl₃); ¹H-NMR (CDCl₃) δ : 1.86-2.11 (m, 4H), 3.20-3.30 (m, 1H), 3.42 (s, 3H), 3.50-3.59 (m, 2H), 3.71 (dd, *J*=3.7 and 9.5 Hz, 1H), 3.80-3.90 (m, 1H), 7.43 (m, 2H), 7.65 (td, *J*=1.2 and 8.2 Hz, 1H), 7.73 (dd, *J*=0.4 and 8.1 Hz, 1H), 7.96-8.01 (m, 3H); ¹³C-NMR (CDCl₃) δ : 22.3, 26.7, 48.4, 59.3, 62.8, 74.3, 117.3, 125.4, 127.2, 127.5, 128.4, 129.3, 131.4, 135.5, 147.9, 156.7; IR (neat): 3388, 3059, 2974, 2925, 2877, 2083, 1957, 1712, 1599, 1558, 1502, 1460, 1425, 1367, 1342, 1306, 1252, 1228, 1196, 1115, 1016, 974, 901, 872, 831, 787, 756 and 621 cm⁻¹; EI-MS *m/z*: 269 (M, 29); HRMS (FAB) calcd for C₁₆H₂₁N₃O (M⁺+H) 270.1606, found 270.1609.

3-Pyridinecarboxaldehyde SAMP hydorazone (3)

93%; $[\alpha]_D^{25} = -168$ (*c* 0.23, CHCl₃); ¹H-NMR (CDCl₃) δ : 1.80-2.10 (m, 4H), 3.11 (dd, *J*=7.7 and 17.2 Hz, 1H), 3.41 (s, 3H), 3.42-3.56 (m, 2H), 3.63-3.73 (m, 2H), 7.12 (s, 1H), 7.22 (dd, *J*=4.8 and 7.9 Hz, 1H), 7.90 (dt, *J*=1.8 and 8.0 Hz, 1H), 8.40 (dd, *J*=1.6 and 4.7 Hz, 1H), 8.67 (d, *J*=1.9 Hz, 1H); ¹³C-NMR (CDCl₃) δ : 22.3, 26.9, 48.6, 59.3, 63.0, 74.5, 123.4, 127.7, 131.4, 133.3, 147.4, 147.6; IR (neat): 3396, 2976, 2879, 2237, 1581, 1552, 1460, 1419, 1377, 1342, 1252, 1198, 1120, 1020, 972, 904, 804, 731, 710, 627 and 536 cm⁻¹; EI-MS *m/z*: 219 (M⁺, 97); HRMS (FAB) calcd for C₁₂H₁₈N₃O (M⁺+H) 220.1450, found 220.1434.

6-Methyl-2-pyridinecarboxaldehyde SADP hydorazone (4)

91%; $[\alpha]_D^{25} = -35.5$ (*c* 0.22, CHCl₃); ¹H-NMR (CDCl₃) δ : 1.18 (s, 3H), 1.31 (s, 3H), 1.78-2.18 (m, 4H), 2.52 (s, 3H), 3.02-3.17 (m, 1H), 3.27 (s, 3H), 3.45-3.58 (m, 1H), 3.65-3.75 (m, 1H), 6.91 (d, *J*=7.4 Hz, 1H), 7.27 (s, 1H), 7.47 (t, *J*=7.8 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 1H); ¹³C-NMR (CDCl₃) δ : 21.0, 23.3, 23.4, 24.4, 24.9, 49.6, 49.7, 70.6, 76.6, 115.1, 120.5, 131.5, 136.3, 156.2, 157.2; IR (neat): 3060, 2972, 2924, 2825, 1739, 1562, 1456, 1410, 1360, 1217, 1155, 1076, 984, 870, 789 and 739 cm⁻¹; EI-MS *m/z*: 261 (M⁺, 4); HRMS (FAB) calcd for C₁₅H₂₄N₃O (M⁺+H) 262.1919, found 262.1932.

General procedure for the palladium-catalyzed allylic alkylation.

To mixture of [Pd(η^3 -C₃H₅)Cl]₂ (0.01 or 0.05 mmol), chiral hydrazone (0.02 or 0.10 mmol), and lithium acetate (0.01 mmol) in a THF (1 mL) was added BSA (1.5 mmol), racemic 1,3-diphenyl-2-propenyl acetate (**5**) (0.5 mmol), and dimethyl malonate (1.5 mmol) at various temperature under an argon atmosphere. After being stirred corresponding times, 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: 14% yield; 67% ee (Entry 10, Table 1); $[\alpha]_D^{25} +10.3$ (c 1.08, CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 3.52 (s, 3H), 3.70 (s, 3H), 3.96 (d, $J = 11.0$ Hz, 1H), 4.26 (dd, $J = 8.5$ and 11.0 Hz, 1H), 6.32 (dd, $J = 8.5$ and 15.8 Hz, 1H), 6.48 (d, $J = 15.8$ Hz, 1H), 7.21-7.33 (m, 10H).

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