Development of a New Chiral Spiro Oxazolinylpyridine Ligand (Spymox) for Asymmetric Catalysis

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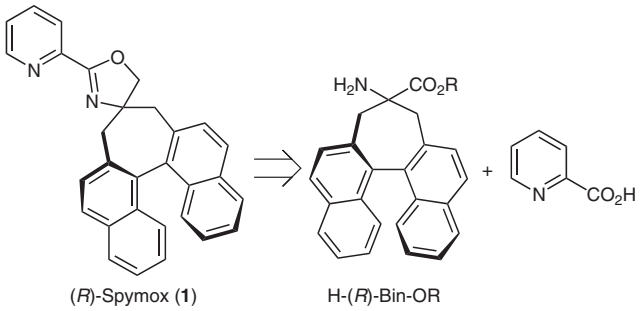
Abstract: A novel optically active 2-(oxazolinyl)pyridine ligand (Spymox) having a spiro binaphthyl backbone was synthesized from an α,α-disubstituted α-amino acid (H-Bin-OH), and successfully used in palladium-catalyzed asymmetric allylic alkylations to afford the corresponding alkylated products with 99% ee.

Key words: ligand design, α-amino acid, spiro compounds, asymmetric catalysis, allylic substitution

Development of new chiral ligands for asymmetric synthesis is an important research subject in synthetic organic chemistry. Recently, optically active spiro compounds have attracted significant attention as a new class of chiral ligands because their rigid spiro structure can result in a fairly rigid transition-state geometry during the course of asymmetric metal catalysis.[1] However, there are few reports on the successful development of spiro chiral ligands, especially which have spiro structure on their side arm, because of the difficulty involved in the preparation of these ligands in optically pure form.[2,3] Herein, we have designed chiral spiro 2-(oxazolinyl)pyridine (Spymox) as a novel *N*,*N*-bidentate ligand.[4] Spymox was efficiently synthesized from 2-picolinic acid and H-Bin-OR,[5] which is an α,α-disubstituted α-amino acid with an axial chiral binaphthyl backbone (Scheme 1). Surprisingly, no report have been appeared on the application of this unique artificial amino acid to asymmetric catalysis, though chiral α-amino acids have been frequently used as synthons for numerous chiral ligands[6] and organocatalysts.[7] In this paper, we discuss the concise synthesis of spymox and its successful application to palladium-catalyzed asymmetric allylic alkylations.[8]



Scheme 1 Design of novel chiral spiro oxazolinylpyridine ligand

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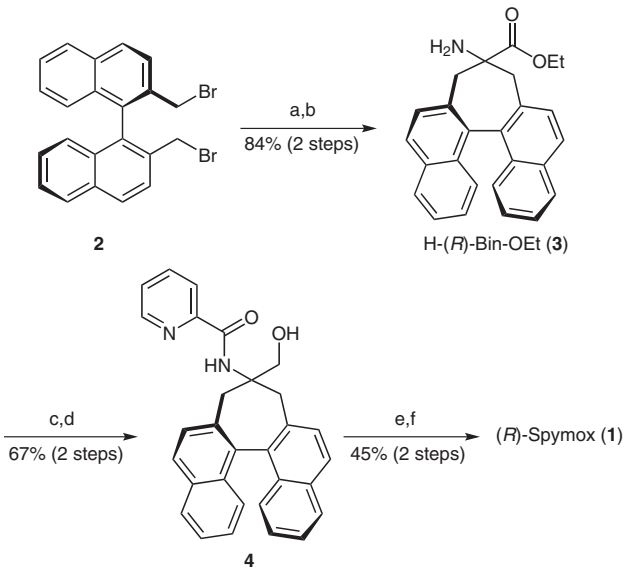
The synthesis of Spymox (**1**) is shown in Scheme 2. H-[(*R*)-Bin]-OEt (**3**) was synthesized from (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl (**2**) and ethyl isocyanoacetate using a phase-transfer catalyst in 84% yield. This procedure is much more concise than the previous report using glycine *tert*-butyl ester Schiff base.[5] The amido alcohol **4** was obtained by the condensation of **3** with 2-picolinoyl chloride, followed by reduction of the ethyl ester with $LiBH_4$. After chlorination of the primary alcohol with $SOCl_2$, the oxazoline ring was formed under basic conditions to afford (*R*)-**1** with 45% yield (25% overall yield).

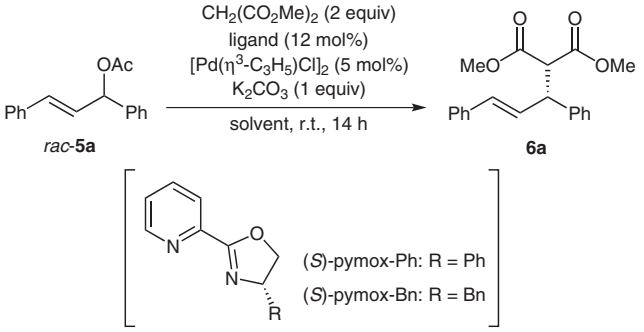


Scheme 2 *Reagents and conditions*: (a) $CNCH_2CO_2Et$ (1.2 equiv), *n*-$Bu_4N^+HSO_4^-$ (20 mol%), K_2CO_3 (10 equiv), MeCN, reflux, 18 h; (b) concd HCl, EtOH, r.t., 6 h; (c) 2-picolinoyl chloride·HCl (1.1 equiv), Et_3N (4 equiv), CH_2Cl_2, r.t., 4 h; (d) $LiBH_4$ (5 equiv), THF, r.t., 12 h; (e) $SOCl_2$ (10 equiv), $CHCl_3$, reflux, 6 h; (f) 2.5 N aq NaOH (10 equiv), 1,4-dioxane, 60 °C, 20 h.

The asymmetric induction of Spymox was evaluated by using it in the palladium-catalyzed asymmetric alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**5a**).[9] Fortunately, the palladium complex of (*R*)-**1** catalyzed the alkylation of **5a** with dimethyl malonate to afford the desired product **6a** with 99% ee. As sumarized in Table 1, excellent enantioselectivities were observed in a variety of solvents, including highly polar solvents and protic solvents. Notably, the use of *tert*-butyl methyl ether (TBME) as the solvent resulted in a dramatic enhancement of the catalytic activity to afford **6a** in a high yield, even at ambient

temperature (entry 7). Moderate enantioselectivities were observed when monosubstituted 2-(oxazolinyl)pyridine ligands (pymox) were used in the same reaction (entries 8 and 9).[10] These results clearly show that our ligand with a spiro bicyclic oxazoline backbone is very advantageous for asymmetric induction.

Table 1 Asymmetric Allylic Alkylation of **5a** with Dimethyl Malonate Catalyzed by Pd-Spymox Complex[a]



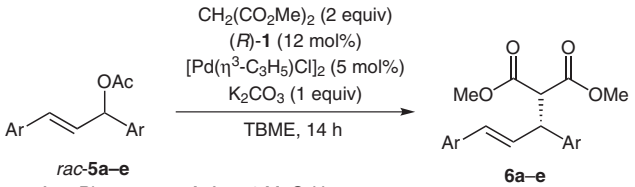
Entry	Solvent	Ligand	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	(*R*)-**1**	29	99 (*R*)
2	THF	(*R*)-**1**	29	99 (*R*)
3	*i*-PrOH	(*R*)-**1**	26	99 (*R*)
4	DMF	(*R*)-**1**	15	99 (*R*)
5	toluene	(*R*)-**1**	23	99 (*R*)
6[d]	toluene	(*R*)-**1**	91	99 (*R*)
7	TBME	(*R*)-**1**	90	99 (*R*)
8	TBME	(*S*)-pymox-Bn	65	14 (*S*)
9[e]	TBME	(*S*)-pymox-Ph	15	45 (*S*)

[a] All reactions were carried out with 2 equiv of dimethyl malonate and 1 equiv of K_2CO_3 in the presence of palladium complex prepared from ligand (12 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol%).
[b] Isolated yield.
[c] Determined by HPLC analyses.
[d] The reaction run at 80 °C.
[e] The reaction run for 48 h.

Next, the scope of the substrate was expanded to various substituted 1,3-diphenyl-2-propenyl acetates. As shown in Table 2, excellent enantioselectivities (97–99% ee) were observed in all the examples, though substrates possessing electron-withdrawing or electron-donating groups required high temperatures or the use of NaH as a base to facilitate a high rate of conversion.

Finally, we tested several malonates (**7a**–**e**) as nucleophiles (Table 3). The reactions of **5a** with dialkyl malonates **7a**,**b** proceeded smoothly to afford the desired products **8a**,**b** with 98–99% ee (entries 1 and 2). The use of α-substituted malonates, including the α-fluorinated malonate **7d**,[11] also afforded the corresponding allylated products **8c**,**d** with excellent enantioselectivities (entries 3 and 4).

Table 2 Asymmetric Allylic Alkylation of Various 1,3-Diaryl-2-propenyl Acetates[a]

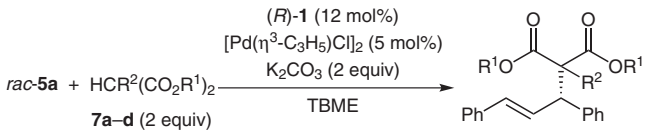


a: Ar = Ph **d**: Ar = 4-MeC_6H_4
b: Ar = 4-$O_2NC_6H_4$ **e**: Ar = 3-MeC_6H_4
c: Ar = 4-ClC_6H_4

Entry	Substrate	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**5a**	r.t.	90	99 (*R*)
2	**5b**	r.t.	<5	n.d.
3	**5b**	55	<5	n.d.
4[d]	**5b**	55	84	99
5	**5c**	r.t.	27	99
6	**5c**	55	92	99
7	**5d**	r.t.	30	97
8	**5d**	55	73	97
9	**5e**	55	94	98

[a] All reactions were carried out with 2 equiv of dimethyl malonate and 1 equiv of K_2CO_3 in the presence of palladium complex prepared from (*R*)-**1** (12 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol%) unless otherwise noted.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] NaH (1 equiv) was used instead of K_2CO_3.

Table 3 Asymmetric Allylic Alkylation of **5a** with Various Malonates[a]



a: R^1 = Et, R^2 = H **c**: R^1 = Me, R^2 = Me
b: R^1 = Bn, R^2 = H **d**: R^1 = Me, R^2 = F

Entry	Nucleophile	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**7a**	55	24	82	>99 (*R*)
2	**7b**	55	14	90	>99
3	**7c**	55	14	94	99 (*S*)
4	**7d**	rt	48	58	>99

[a] All reactions were carried out with 2 equiv of dimethyl malonate and 2 equiv of K_2CO_3 in the presence of palladium complex prepared from (*R*)-**1** (12 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol%).
[b] Isolated yield.
[c] Determined by HPLC analysis.

A plausible transition-state model is proposed in Figure 1. One of naphthyl rings on the ligand shields the upper right-hand side of the π-allyl palladium complex; thus, the position of nucleophilic attack as well as the formation of the π-allyl complex (two phenyl groups would be located below) are properly controlled.

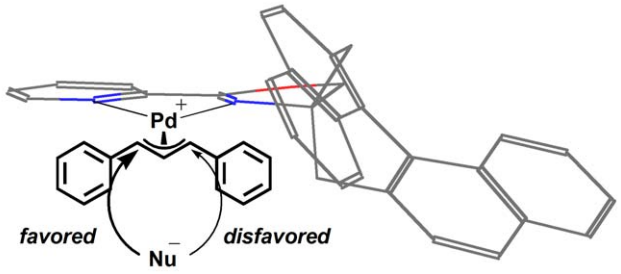


Figure 1 A plausible transition-state model

In conclusion, we have synthesized a novel optically active spiro ligand from H-Bin-OH; this has been successfully applied to palladium-catalyzed asymmetric allylic alkylations. To the best of our knowledge, this is the first example of the use of H-Bin-OH derivatives for asymmetric catalysis. Further study on the application of H-Bin-OH and its derivatives to the preparation of novel chiral catalysts are under way.

Typical Procedure for Asymmetric Allylic Alkylations

A flame-dried flask under argon was charged with (*R*)-**1** (0.024 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol). Dichloromethane (1 mL) was added to this mixture. After the reaction mixture was stirred for 1 h at r.t., CH_2Cl_2 was evaporated in vacuo. Residual Pd complex was dissolved into TBME (5 mL). 1,3-Diphenyl-2-propenyl acetate (**5a**, 0.2 mmol), dimethyl malonate (0.4 mmol), and K_2CO_3 (0.4 mmol) were added to this solution. The reaction mixture was stirred for 14 h at r.t. The reaction was quenched with sat. aq NH_4Cl, and the mixture was extracted by CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on SiO_2 to give **6a** in 90%yield with 99% ee.

Products **6a–d** and **8a–d** were identical in all respects to the known literature compounds.[12–15]

See the references section for analytical details of new compounds **1**, **4**, **5e**, and **6e**.[16–19]

CAS Registry Numbers

5a: 73930-97-9; **5b**: 881397-70-2; **5c**: 195192-51-9; **5d**: 881397-68-8; pymox-Ph: 153880-57-0; pymox-Bn: 108915-08-8; **7d**: 344-14-9.

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(15) For compound **8d**, see: Jiang, B.; Huang, Z.-G.; Cheng, K.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 942.
(16) Compound **1**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (m, 1 H), 8.08 (m, 1 H), 7.95 (m, 4 H), 7.77 (m, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.46–7.38 (m, 4 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 7.27–7.20 (m, 2 H), 4.65 (d, *J* = 8.8 Hz, 1 H), 3.95 (d, *J* = 8.8 Hz, 1 H), 2.94 (d, *J* = 13.1 Hz, 1 H), 2.88 (d, *J* = 13.3 Hz, 1 H), 2.72 (d, *J* = 13.3 Hz, 1 H), 2.65 (d, *J* = 13.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 149.8, 147.0, 136.7, 135.4, 134.7, 134.5, 133.7, 133.1, 133.0, 132.1, 131.9, 128.7, 128.5, 128.4, 128.4, 128.3, 127.5, 127.4, 127.2, 126.0, 125.7, 125.4, 125.1, 124.4, 82.5, 77.3, 44.4, 43.5. IR (neat): 3847, 3741, 3475, 3053, 2938, 1635, 1577, 1469, 1361, 1302, 1092, 968, 813, 751, 696, 615 cm^{-1}. Anal. Calcd (%) for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.67; H, 5.15; N, 6.36. $[\alpha]_D$ –72.4 (*c* 1.25, $CHCl_3$).
(17) Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (m, 1 H), 8.23 (m, 2 H), 7.96–7.86 (m, 5 H), 7.55 (m, 1 H), 7.48–7.37 (m, 6 H), 7.29–7.23 (m, 2 H), 5.19 (dd, *J* = 5.2, 8.0 Hz, 1 H), 4.01 (dd, *J* = 8.0, 11.5 Hz, 1 H), 3.83 (dd, *J* = 5.2, 11.5 Hz, 1 H), 3.23 (d, *J* = 13.7 Hz, 1 H), 3.11 (d, *J* = 12.4 Hz, 1 H), 2.54 (d, *J* = 13.7 Hz, 1 H), 2.45 (d, *J* = 12.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 149.6, 148.2, 137.8, 135.4, 135.4, 134.8, 134.6, 134.4, 133.2, 133.2, 133.1, 132.0, 132.0, 128.6, 128.4, 128.4, 128.1, 128.1, 127.4, 126.6, 126.1, 126.0, 125.6, 125.4, 122.3, 70.2, 66.9, 41.0, 38.9. IR (neat): 3846, 3343, 3053, 2928, 1667, 1525, 1457, 1324, 1245, 1058, 817, 752, 697, 621, 436 cm^{-1}. Anal. Calcd (%) for $C_{30}H_{24}N_2O_2$: C, 80.06; H, 5.44; N, 6.30. Found: C, 81.34; H, 5.74; N, 6.03. $[\alpha]_D$ –90.5 (*c* 1.0, $CHCl_3$).
(18) Compound **5e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.05 (m, 8 H), 6.60 (d, *J* = 15.3 Hz, 1 H), 6.41–6.28 (m, 2 H), 2.36 (s, 3 H), 2.32 (s, 3 H), 2.13 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 139.3, 138.4, 138.2, 136.2, 132.6, 129.0, 128.9, 128.63, 128.57, 127.8, 127.5, 124.2, 124.0, 76.4, 21.6, 21.49, 21.45. Anal. Calcd (%) for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19; O, 11.41. Found: C, 81.06; H, 6.62.
(19) Compound **6e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.00 (m, 8 H), 6.44 (d, *J* = 15.6 Hz, 1 H), 6.29 (dd, *J* = 15.6 Hz, 1 H), 4.21 (dd, *J* = 10.8, 8.4 Hz, 1 H), 3.94 (d, *J* = 10.8 Hz, 1 H), 3.70 (s, 3 H), 3.53 (s, 3 H), 2.33 (s, 3 H), 2.31 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 168.0, 140.3, 138.4, 138.1, 136.9, 131.9, 129.1, 128.7, 128.5, 128.0, 127.2, 124.8, 123.7, 57.7, 52.76, 52.74, 52.60, 52.57, 49.3. Anal. Calcd (%) for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86; O, 18.16. Found: C, 74.69; H, 6.86. $[\alpha]_D$ +24.1 (*c* 0.63, $CHCl_3$). The er was determined by HPLC [hexane–2-PrOH (96:4), 0.5 mL/min] using a CHIRALPAK AD column (0.46 cm × 25 cm): t_R (major isomer) = 23.0 min; t_R (minor isomer) = 26.5 min.