Further Application of an N-Ar Axially Chiral Mimetic-Type Ligand: Asymmetric Grignard Cross-Coupling Reaction

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Abstract: A novel chiral ligand mimicking N-Ar axial chirality, (*S*)-*N*-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-(piperidinylmethyl)piperidine, was found to exhibit good enantioselectivity (up to 80% ee) in the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride with β-bromostyrene derivatives. Additionally, this type ligand is appealing, because it allows the synthesis of a wide variety of analogues.

Key words: N-Ar axis, chiral mimetics, optically active ligand, Grignard cross-coupling, asymmetric Kumada–Corriu reaction

Quite recently, we have developed a novel chiral ligand **1** mimicking N-Ar axial chirality based on the following concept:[1] the chiral ligand **1** may have the two diasteromers due to the N-Ar axis and the chiral carbon in solution (Figure 1). But, if the N-Ar axis in **1** is configurationally flexible, and the complexation of **1** and a metal is largely reflected by the asymmetric center of the heterocyclic ring in **1**, one of the two diastereomer complexes due to the N-Ar axis, is expected to be selectively formed (**2a** in Figure 2), leading to the creation of a favorable asymmetric environment. The designed ligand **1i** has been found to exhibit 99% ee with the use of (*E*)-1,3-diphenyl-2-propenyl acetate as the standard substrate, and has achieved better results than the representative Pfaltz[2] and Trost[3] ligands with the use of (*E*)-1-phenyl-3-trimethylsilyl-2-propenyl acetate as the substrate, in the palladium-catalyzed asymmetric allylic substitution with dimethyl malonate as the pronucleophile.[1] In order to explore further application of the ligand **1**, we planned to search for a suitable asymmetric reaction. Our interest in this ligand focused on its use in the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride with alkenyl halides, which has met with success using Kumada's P,N-ligands.[4,5] Many ligands have been developed for the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride with alkenyl halides, but the best substrate showing more than 80% ee was vinyl bromide.[5a,5c–e,6,8,9] One type of substrate with which it has been more difficult to achieve high selectivity is a styrene derivative such as β-bromostyrene.[5b,d,7] There are, to date, only two examples by Knochel[8] and Saigo[9] that give good enantioselectivity with β-bromostyrene. Herein we would like to report our investigation of this reaction using β-bromostyrene as a substrate with the ligand **1** mimicking N-Ar axial chirality.[10] The results obtained with the ligand **1** are, to the best of our knowledge, the third best enantioselectivity in the reported literature. Additionally, the ligand **1** is appealing, because it allows the synthesis of a wide variety of analogues.

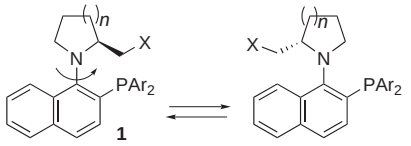

Figure 1

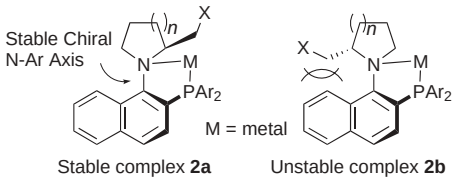

Figure 2

We screened a variety of ligands **1** (>20) in the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride with β-bromostyrene. Selected results are shown in Table 1. Reactions were carried out with $PdCl_2(CH_3CN)_2$ (5 mol%), the ligands **1a**–**n** (5 mol%, Figure 3), and 1-phenylethylmagnesium chloride (2 equiv, 0.5–0.7 mol/L in Et_2O) in α,α,α-trifluorotoluene[11] at 0 °C.[12] First, the effect of a pendant substituent with the pyrrolidine-based ligands **1a**–**e** was examined.[13] As shown in entries 1–5, the pendant substituent played an important role. The ligands **1a**–**c** possessing a pendant oxygen group exhibited faster reaction rate than **1d** and **1e** possessing a pendant nitrogen group. Among the oxygen-containing ligands **1a**–**c**, **1b** gave better results (entry 2, 66% yield, 66% ee). The ee of **5a** was determined by HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH = 100:1), and its absolute configuration was determined by comparison with the reported **5a**.[8] The inhibition of the reactivity observed with the ligands **1d** and **1e** possessing the pendant nitrogen substituent, a strong coordinating group, is considered to

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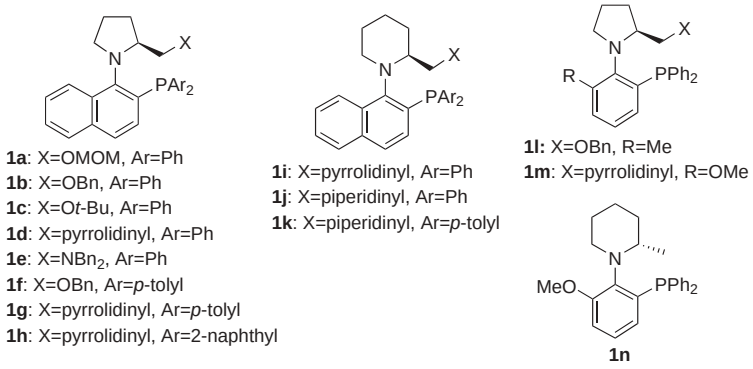
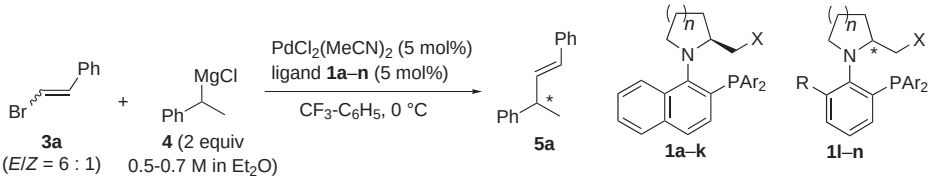


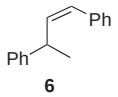
Figure 3

Table 1 Ligand Screening[a]



Entry[b]	Ligand	X	n	Ar	R	Time (h)	Yield (%)	Ee (%)[c]	Absolute configuration
1	**1a**	OMOM	1	Ph		1	59	7	R
2	**1b**	OBn	1	Ph		1	66	66	S
3	**1c**	*t*-BuO	1	Ph		1	42	47	S
4	**1d**	Pyrrolidinyl	1	Ph		24	35	62	S
5	**1e**	NBn_2	1	Ph		24	20	9	R
6	**1i**	Pyrrolidinyl		Ph		1	53	61	S
7[d]	**1i**	Pyrrolidinyl		Ph		24	25	52	S
8	**1j**	Piperidinyl		Ph		1	58	66	S
9	**1f**	OBn	1	*p*-tolyl		24	15	9	R
10	**1g**	Pyrrolidinyl	1	*p*-tolyl		24	37	65	S
11	**1h**	Pyrrolidinyl	1	2-naphthyl		24	43	56	S
12	**1k**	Piperidinyl		*p*-tolyl		1	56	55	S
13	**1l**	OBn	1	Ph	Me	24	42	63	S
14	**1m**	Pyrrolidinyl	1	Ph	MeO	24	26	69	S
15	**1n**	H		Ph	MeO	1	52	7	S

[a] A mixture of (*E*)- and (*Z*)-β-bromostyrene (6:1) was used. The reactions were performed using 5 mol % of $PdCl_2(MeCN)_2$ and ligand **1a**–**n**, and 2 equiv of **4** in CF_3-C_6H_5 at 0 °C.
[b] In all entries, a small amount of **6** was obtained with no enantioselectivity (for example, **1d** afforded 2% yield and 0% ee).



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[c] Determined by HPLC analysis.
[d] 1-Phenylethylmagnesium bromide was used.

be due to the internal coordination of the pendant nitrogen group to palladium. Molecular modeling studies suggested that the piperidine based-ligand **1i** avoids such a problem, because coordination of the pendant nitrogen group to the internal palladium seemed to be torsionally unfavorable. As expected, replacement of the piperidine ring on the naphthalene ring enhanced the reaction rate while the chemical yield was increased to 53% from 35% (entries 4 vs. 6). The use of 1-phenylethylmagnesium bromide in place of the corresponding chloride decreased both chemical yield and enantioselectivity (entries 6 vs. 7). Furthermore, employing the piperidine-based ligand **1j** possessing the pendant piperidinyl group gave better results (58% yield, 66% ee) than **1i** (entries 6 vs. 8). The effects of the diarylphosphino groups, the aromatic part and so on, were also examined as shown in entries 9–15. However, the ligands **1f**–**h** and **1k**–**n** gave less satisfactory results. Thus, in terms of both chemical yield and enantioselectivity, the two ligands **1b** and **1j** were chosen as candidates for the next screening. The effect of temperature on the reaction was examined (Table 2). In the case of the ligand **1b**, reduction of the temperature from 0 to –10 °C resulted in no reaction (entry 1). On the other hand, in the case of the ligand **1j**, the enantioselectivity was improved (entry 2: 71% ee).[14] Furthermore, the use of (*E*)-β-bromostyrene (**3a**) in place of a 6:1 mixture of (*E*)- and (*Z*)-isomers gave a slight improvement of chemical yield and enantioselectivity (entry 3: 69% yield, 72% ee).

Using the ligand **1j**, we examined the cross-coupling reaction with several β-bromostyrenes as shown in Table 3. Styrene derivatives[15] bearing *p*-methyl (**3b**), *p*-isopropyl (**3c**) and *p*-chloro (**3d**) groups were found to be employable, giving the corresponding products in good enantioselectivities (entries 1–3, up to 80% ee), although, unfortunately, the reaction with **3e** bearing an electron-donating group did not proceed (entry 4).[16] The ee and absolute configuration of **5b**–**d** were determined by HPLC analysis (Daicel Chiralpak AD, hexane/*i*-PrOH/TFA=9:1:0.1) after conversion of **5b**–**d** to the known carboxylic acid **7**.[17]

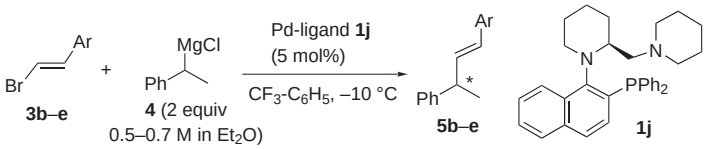
In summary, we have shown that an N-Ar axially chiral mimetic-type ligand is efficient in the asymmetric cross-coupling reaction[18–20] of 1-phenylethylmagnesium chloride with β-bromostyrene derivatives. Analogues of this ligand are being developed for use in other asymmetric reactions.[21,22]

Table 2 Temperature Effect with Ligand **1b** and **1j**[a]

Entry	Ligand	Conditions	Yield (%)	Ee (%)	Absolute configuration
1	**1b**	–10 °C, 24 h	NR[b]	–	–
2	**1j**	–10 °C, 12 h	66	71	S
3[c,d]	**1j**	–10 °C, 6 h	69	72	S

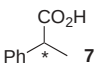
[a] A mixture of (*E*)- and (*Z*)-β-bromostyrene (6:1) was used except for entry 3. The reactions were performed using 5 mol % of $PdCl_2(MeCN)_2$ and ligand **1b** or **1j**, and 2 equiv of **4** in CF_3-C_6H_5.
[b] No reaction occurred.
[c] When the reaction was performed at –20 °C, no reaction occurred.
[d] (*E*)-β-Bromostyrene was used.

Table 3 Cross-Coupling Reaction of Several β-Bromostyrenes with Ligand **1j**[a]



Entry	Ar	Time (h)	Yield (%)	Ee (%)[b]	Absolute configuration
1	*p*-Me-C_6H_5 (**3b**)	3	50	78	S
2	*p*-*i*-Pr-C_6H_5 (**3c**)	4	49	80	S
3[c,d]	*p*-Cl-C_6H_5 (**3d**)	2	51	66	S
4[c]	*p*-MeO-C_6H_5 (**3e**)	24	NR	–	–

[a] (*E*)-β-Bromostyrene derivatives were used except for entry 3. The reactions were performed using 5 mol % of $PdCl_2(MeCN)_2$ and the ligand **1j**, and 2 equiv of **4** in CF_3-C_6H_5 at –10 °C.
[b] Determined by HPLC analysis of **7**, which was obtained by the successive treatment of **5b**–**d** with a catalytic amount of OsO_4 (*t*-BuOH-H_2O) and RuO_2 ($NaIO_4$ in CCl_4–MeCN–H_2O at 0 °C, Sharpless conditions).



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[c] The reaction was performed at 0 °C.
[d] A 3.9:1 mixture of (*E*)- and (*Z*)-isomers was used.

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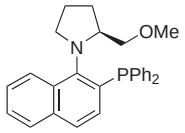
(12) The use of other solvents such as THF, CH_2Cl_2 and toluene, and the use of nickel salts in place of $PdCl_2(MeCN)_2$, gave less satisfactory results.
(13) Use of the ligand **1o** (Figure 4) possessing a pendant methoxy group resulted in no reaction. For the ligand **1o**, see: (a) Miyano, S.; Hattori, T.; Komuro, Y.; Kumobayashi, H. Jpn. Kokai Tokkyo koho, H09241277, **1997**; *Chem. Abstr.* **1997**, *127*, 302486h. (b) Kondo, K.; Fujita, H.; Iida, T.; Suzuki, T.; Murakami, Y. *30thCongress of Heterocyclic Chemistry, November 24–26th*; Hachioji: Japan, **1999**. (c) Mino, T.; Tanaka, Y.; Sakamoto, M.; Fujita, T. *Heterocycles* **2000**, *53*, 1485.



1o

Figure 4

(14) The use of ligand **1i** at ca.–20 °C afforded the coupling product with 25% yield and 80% ee.
(15) The physical data of **3a**, **3b**, **3d** and **3e** were comparable to those reported: (a) Graven, A.; Jorgensen, K. A.; Dahl, S.; Stanczak, A. *J. Org. Chem.* **1994**, *59*, 3543. (b) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 4102. (c) The new styrene derivative **3c** was characterized by IR, ^{1}H- and ^{13}C NMR, MS, and HRMS. The ^{1}H NMR data of **3c** are shown below: ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 3 H × 2), 2.88 (sept, *J* = 6.9 Hz, 1 H), 6.70 (d, *J* = 13.8 Hz, 1 H), 7.07 (d, *J* = 13.8 Hz, 1 H), 7.13–7.29 (m, 4 H).
(16) The use of vinyl bromide and 1-propenyl bromide as substrates resulted in no reaction.
(17) The racemic and optically active carboxylic acid **7** were purchased from Aldrich Co., Ltd.
(18) The ligands **1b**, **1d**, **1e**, and **1g–i** were reported by us.[1] The new ligands **1a**, **1c**, **1f**, **1j–l** and **1n** were characterized by IR, ^{1}H- and ^{13}C NMR, FABMS, and elemental analysis. All ligands **1a–n** were synthesized according to the typical procedure described below.

(*S*)-*N*-[2-(Diphenylphosphanyl)naphthalen-1-yl]-2-(piperidinylmethyl)piperidine (1j). To a stirred solution of (*S*)-2-(piperidinylmethyl)piperidine (700 mg, 3.84 mmol) in THF (4.0 mL) was gradually added BuLi (2.53 mL, 4.00 mmol, 1.58 M solution in hexane) at –30 °C, and the mixture was stirred for 2 h at the same temperature. To this solution was then added a solution of 1-methoxy-2-(diphenylphosphinoyl)naphthalene (680 mg, 1.90 mmol) in THF (2.0 mL) at –30 °C. The whole mixture was stirred for 1 h at the same temperature, quenched with H_2O and extracted with EtOAc. The organic extracts were successively washed with saturated aq NH_4Cl and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel column (Fuji Silysia Chromatorex NH, EtOAc/hexane=1:5) gave a mixture (724 mg) of 1-(*S*)-*N*-[2-(diphenylphosphonyl)naphthalen-1-yl]-2-(piperidinylmethyl)piperidine and small amounts of impurities. This mixture was used for the next step without further separation. IR (neat): ν = 1308, 1254, 1192, 1161 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.75–1.15 (m, 8 H), 1.24–1.45 (m, 2 H), 1.60–1.94 (m, 8 H), 2.46 (dd, *J* = 13.3, 5.9 Hz, 1 H), 2.92 (br d, *J* = 11.1 Hz, 1 H), 3.36 (dd, *J* = 11.1, 11.1 Hz, 1 H), 3.51–3.62 (br, 1 H), 6.97 (dd, *J* = 12.1, 8.6 Hz, 1 H), 7.35–7.57 (m, 10 H), 7.65–7.87 (m, 4 H), 8.23 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$): 24.29, 24.90, 25.47, 25.63, 31.38, 54.80, 56.09, 60.55, 62.23, 125.15, 125.42, 125.62, 126.21, 127.02, 127.95, 128.13, 128.65, 129.02, 129.22, 129.77, 130.74, 131.09, 131.23, 131.37, 131.94, 132.07, 134.15, 134.65, 135.09, 135.22, 135.66, 136.22, 136.63, 155.14. FABMS: *m*/*z* = 509 (M^+ + 1). The above mixture was dissolved in *p*-xylene (7.0 mL), and Et_3N (2.10 mL, 15.1 mmol) and $HSiCl_3$ (1.4 mL, 14 mmol) were added at 0 °C. The whole mixture was heated at 140 °C for 2 h. After being cooled to r.t., the reaction mixture was carefully poured into 10% NaOH, and the whole mixture was extracted with EtOAc. The organic extracts were successively washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by silica gel column (Fuji Silysia Chromatorex NH, hexane/EtOAc = 20:1) gave (*S*)-*N*-[2-(diphenylphosphanyl)naphthyl]-2-(piperidinylmethyl)piperidine (**1j**) (505 mg, 54% in 2 steps) as a colorless amorphous.

$[\alpha]_D^{28}$ +115 (*c* 1.60, dioxane). IR(nujol): ν = 1300, 1275, 1206, 1159 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.83–2.22 (m, 18 H), 2.66 (br d, *J* = 11.5 Hz, 1 H × 4/5), 3.01 (br d, *J* = 11.2 Hz, 1 H × 1/5), 3.30 (br dd, *J* = 11.5, 10.6 Hz, 1 H × 4/5), 3.45–3.53 (br, 1 H × 1/5), 3.55–3.73 (br, 1 H × 4/5), 4.13–4.28 (br, 1 H × 1/5), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1 H × 4/5), 7.09 (dd, *J* = 8.6, 3.8 Hz, 1 H × 1/5), 7.14–7.57 (m, 13 H), 7.72–7.77 (m, 1 H × 1/5), 7.81 (dd, *J* = 6.3, 3.5 Hz, 1 H × 4/5), 8.05 (dd, *J* = 6.3, 3.5 Hz, 1 H × 4/5), 8.63 (dd, *J* = 6.3, 3.5 Hz, 1 H × 1/5). ^{13}C NMR ($CDCl_3$): 24.05, 24.29, 24.41, 25.27, 25.71, 25.93, 26.02, 27.47, 29.75, 31.59, 32.34, 54.10, 54.32, 54.93, 55.10, 57.17, 57.38, 59.20, 61.70, 62.50, 62.59, 124.80, 124.94, 125.49, 125.57, 125.78, 125.95, 126.02, 126.71, 127.44, 127.90, 127.97, 128.00, 128.13, 128.17, 128.27, 128.37, 128.63, 129.50, 131.91, 132.72, 133.00, 133.29, 133.54, 133.80, 133.95, 134.10, 134.26, 134.54, 134.66, 135.01, 135.19, 136.92, 137.40, 137.60, 138.35, 138.54, 138.81, 139.00, 139.63, 139.87, 150.99, 151.30, 153.92, 154.28. FABMS: *m*/*z* = 493 (M^+ + 1). Anal. Calcd for $C_{33}H_{37}N_2P$: C, 80.46; H, 7.57; N, 5.69, Found: C, 80.27; H, 7.56; N, 5.85.

Typical Procedure for Grignard Cross-Coupling Reaction of (*E*)-β-Bromostyrene(3a) with Ligand 1j (entry 3, Table 2). 1-Phenylethylmagnesium chloride (**4**) (2.10 mL, 1.50 mmol, 0.70 mol/L in Et_2O) was added to the mixture of $PdCl_2(MeCN)_2$ (9.3 mg, 0.036 mmol) and the ligand **1j** (18.2 mg, 0.0369 mmol) in α,α,α-trifluorotoluene (2.10 mL) at 0 °C, and the solution was stirred at the same temperature for 30 min (CAUTION: stirring at 0 °C for 30 min for the favorable complexation of Pd and ligand **1j** is needed.). To the solution was added (*E*)-β-bromostyrene (**3a**) (133 mg, 0.727 mmol) at –10 °C. The resulting solution was stirred for 6 h at –10 °C. After usual work-up, purification by silica gel column(hexane) afforded the coupling product **5a** (105 mg, 69%, 72% ee) as a colorless oil. The ee was determined by HPLC analysis (Daicel chiralcel OD, hexane/*i*-PrOH = 100:1, 0.3 mL/min, 254 nm): t_R/min = 34.9 (*S*), 37.1 (*R*).

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(22) During the completion of this manuscript, we became aware of a recent report by Mino, T. et al. of the Pd-catalyzed asymmetric allylic alkylation with the ligand **1m**: Mino, T.; Tanaka, Y.; Sato, Y.; Saito, A.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2003**, *44*, 4677.