Nucleophilic Aromatic Substitution Reactions of 1-Methoxy-2-(diphenylphosphinyl)naphthalene with *C*-, *N*-, and *O*-Nucleophiles: Facile Synthesis of Diphenyl(1-substituted-2-naphthyl)phosphines

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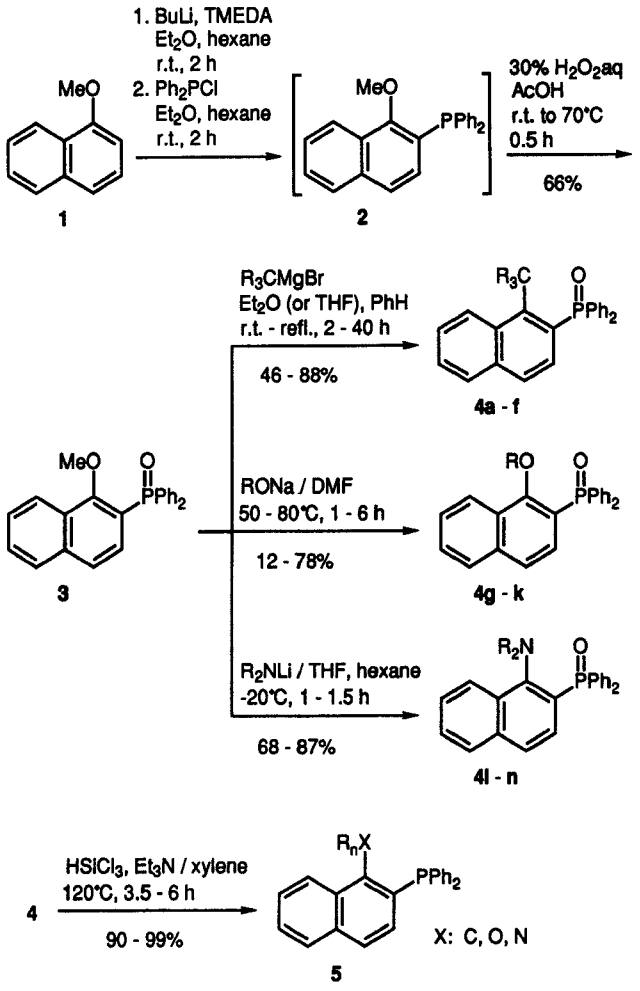
A novel nucleophilic aromatic substitution reaction is described in which the methoxy group of 1-methoxy-2-(diphenylphosphinyl)-naphthalene is readily replaced with Grignard reagents, alkoxides, and amides. Reduction of the resulting phosphine oxides provides a convenient route to diphenyl(1-substituted-2-naphthyl)phosphines.

Organic synthesis catalyzed by transition metals bearing phosphine ligands has enjoyed tremendous success over the past 30 years. It is well known that a combination of the metal center and phosphine ligands plays a critical role for a reaction to proceed successfully, and hence, there has been continuing efforts to develop novel phosphine ligands, especially chiral phosphines.[1,2] On the other hand, nucleophilic aromatic substitution (S_NAr) is an important process in synthetic aromatic chemistry, but generally requires severe reaction conditions or the presence of highly electron-withdrawing, so-called "activating" groups on the aromatic nucleus.[3] In previous papers, we have reported facile construction of the biaryl skeleton via the reaction of 1-alkoxy-2-naphthoates or -benzoates with aryl Grignard reagents.[4] The reaction is postulated to proceed via a Michael-type addition of the aryl carbanion across the aromatic system followed by elimination of the alkoxy group to complete the net biaryl coupling reaction.[5] This implies that the ester function, which is not regarded as a potent electron-withdrawing group,[3] effectively activates the *o*-alkoxy group for the apparent S_NAr displacement,[6] which has tempted us to exploit novel S_NAr reactions by use of unconventional activating substituents. Herein we report the first successful example of our efforts in this line, where the diphenylphosphinyl group activates the *o*-methoxy substituent for the S_NAr reaction of 1-methoxy-2-(diphenylphosphinyl)naphthalene (**3**) with *C*-, *N*-, and *O*-nucleophiles (Scheme 1).[7]



Scheme 1

The substrate **3** was easily prepared via the selective *o*-lithiation of 1-methoxynaphthalene (**1**) with butyllithium in the presence of tetramethylethylenediamine (TMEDA),[8] and then treatment with chlorodiphenylphosphine followed by oxidation with hydrogen peroxide in acetic acid.

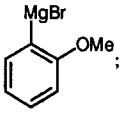
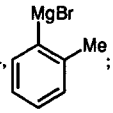
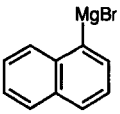
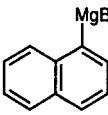
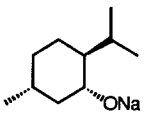
Table 1 summarizes the result of the S_NAr reaction. Alkyl and aryl Grignard reagents reacted with **3** to give **4a–f** in good to moderate yield (Entries 1–6); **3** was treated with 1.8 equiv of 2-methoxy-1-naphthylmagnesium bromide in THF–benzene at reflux for 18 h to give 2-diphenylphosphinyl-2′-methoxy-1,1′-binaphthyl (**4f**) in 59% yield, reduction of which by use of trichlorosilane quantitatively gave, though in racemic modification, the tertiary phosphine 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (**5f**), a compound of much recent interest.[9] However, it should be added that treatment of **3** with 1.1 equiv of phenyllithium in THF at −78 °C did not afford the methoxy displacement product but 1-methoxynaphthalene and triphenylphosphine in 85 and 57% yield, respectively, by aryl exchange at phosphorus.[7] As for nucleophiles other than carbanions, alkoxides also reacted with **3** in DMF at 50–80 °C to give **4g–k**, the yield of which varied depending on the bulkiness and nucleophilicity of the alkoxide employed (Entries 7–11). Although the reaction medium and counter cation should be taken into consideration, amides were most reactive among the nucleophiles examined (Entries 12–14); even lithium diisopropylamide reacted smoothly at −20 °C to give **4m** in good yield.

It should be noted that the S_NAr reaction by use of chiral nucleophiles opens a facile route for the synthesis of novel types of chiral phosphine ligands (e.g. **5k** and **5n**), which may be rather difficult to access by other methods. Fur-

Table 1. The S_NAr Reaction of **3** with *C*, *N*, and *O*-Nucleophiles and the Reduction of **4** to **5**

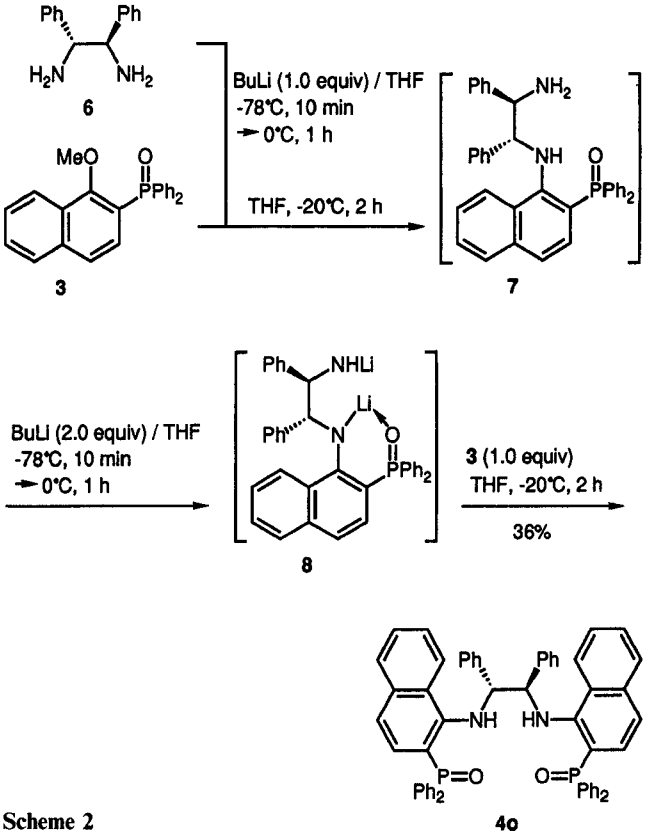
Entry	S_NAr Reaction				Reduction		
	Nucleophile[b] (equiv)/Solvent	Temp. (°C) [Time (h)]	**4**	Yield (%)[a]	Time (h)	**5**	Yield (%)[a]
1	BuMgBr (1.8)/Et_2O, PhH	refl. (10)	**4a**	73			
2	*i*-PrMgBr (1.8)/Et_2O, PhH	refl. (40)	**4b**	46			
3	(1.8)/Et_2O, PhH	r.t. (1) → refl. (1)	**4c**	88			
4	(1.8)/Et_2O, PhH	refl. (40)	**4d**	70			
5	(1.8)/Et_2O, PhH	refl. (40)	**4e**	64			
6	(1.8)/THF, PhH	refl. (18)	**4f**	59	3.5	**5f**	94
7	BuONa (10)/DMF	50 (1)	**4g**	78	6	**5g**	99
8	*i*-PrONa (10)/DMF	50 (2)	**4h**	57			
9	(*S*)-C_6H_{13}(Me)CHONa (1.8)/DMF	50 (6)	**4i**	55			
10	(*S*)-Ph(Me)CHONa (1.8)/DMF	50 (6)	**4j**	12			
11	(3.0)/DMF	80 (2)	**4k**	29	6	**5k**	95
12	BuNHLi (2.0)/THF, hexane	−20 (1)	**4l**	87			
13	*i*-Pr_2NLi (2.0)/THF, hexane	−20 (1)	**4m**	68			
14	(*S*)-Ph(Me)CHNHLi (2.0)/THF, hexane	−20 (1.5)	**4n**	87	6	**5n**	90

[a] Isolated yield

[b] Entry 3,  ; Entry 4,  ; Entry 5,  ; Entry 6,  ; Entry 11, 

thermore, the S_NAr methodology can be applied to the synthesis of a chiral bis(phosphine oxide) **4o** as follows (Scheme 2): Treatment of **3** with 1.0 equiv of lithium amide of (1*R*,2*R*)-diphenylethylenediamine **(6)** in THF at −20 °C gave **7**. Addition of 2.0 equiv of butyllithium to **7** seemingly afforded diamide **8**, which was then added to a solution of 1.0 equiv of **3** in THF to give **4o** in 36% yield. It seems that the initial 1.0 equiv of butyllithium added to **7** is preferentially used for the abstraction of a proton from the secondary amino group to give the chelate-stabilized amide. Hence, treatment of dilithium amide of **6** with 2.0 equiv of **3** afforded **4o** in less than 10% yield.

In conclusion, it is shown that the methoxy group of 1-methoxy-2-(diphenylphosphinyl)naphthalene **(3)** is substantially activated for S_NAr reaction, providing a new method for convenient preparation of diphenyl(1-substituted-2-naphthyl)phosphines **(5)**.



Scheme 2

Melting points were taken using a Yamato MP-21 apparatus and are uncorrected. IR spectra were obtained using a Shimadzu IR-430 grating spectrophotometer. ^1H NMR spectra were obtained using a Bruker AC-250T spectrometer. Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University. Silica gel columns were prepared by use of Nacalai Tesque silica gel 60 (70–230 mesh). Et_2O, THF, PhH, and xylene were distilled from sodium diphenylketyl just before use. DMF was distilled from calcium hydride and stored under an N_2 atmosphere. Other reagents and solvents were of commercial quality from freshly opened containers. Water- and air-sensitive reactions were routinely carried out under an N_2 atmosphere.

1-Methoxy-2-(diphenylphosphinyl)naphthalene (3):
To a mixture of **1** (1.58 g, 9.99 mmol), TMEDA (1.16 g, 9.98 mmol), and Et_2O (25 mL) was added dropwise 1.58 M BuLi in hexane (6.80 mL, 10.7 mmol) over 10 min and the mixture was stirred at r.t. for 2 h. To it was added Ph_2PCl (2.21 g, 10.0 mmol) and the resulting mixture was stirred for further 2 h. Then it was poured into 2 N HCl (200 mL) and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with 2 N Na_2CO_3 (100 mL) and water (2 × 100 mL), and dried ($MgSO_4$). After the solvents were evaporated, the residue was dissolved in AcOH (50 mL). To it was added 30% H_2O_2 (1.0 mL) and the mixture was gradually heated to 70 °C over 20 min, and stirred at 70 °C for 10 min. After being cooled to r.t., it was diluted with PhH (100 mL). To it was carefully added 20% NaOH (200 mL) at 0 °C and the two layers were sepa-

Table 2. Compounds **4** and **5** Prepared

Product[a]	mp (°C)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a[b]	115–116	1429, 1194	0.79 (t, 3H, J = 7.1, $C_3H_6CH_3$), 1.22–1.47 (m, 4H, $CH_2C_2H_4Me$), 3.44 (t, 2H, J = 7.8, CH_2Pr), 7.10–8.15 (m, 16H, H_{arom})
4b[b]	193–196	1438, 1187	1.37 (d, 6H, J = 7.2, $2CH_3$), 4.36 (sept, 1H, J = 7.2, CH), 7.08–8.43 (m, 16H, H_{arom})
4c[b]	amorphous solid	1429, 1188	3.30 (s, 3H, OCH_3), 6.36–7.88 (m, 20H, H_{arom})
4d[b]	amorphous solid	1437, 1194	1.66 (s, 3H, CH_3), 6.85–7.92 (m, 20H, H_{arom})
4e[b]	215–217	1427, 1192	6.87–8.00 (m, 23H, H_{arom})
4f[c]	amorphous solid	1428, 1177	3.57 (s, 3H, OCH_3), 6.79–8.01 (m, 22H, H_{arom})
4g[b]	108–110	1438, 1187	0.85 (t, 3H, J = 7.3, $C_3H_6CH_3$), 1.14–1.30 (m, 2H, $C_2H_4CH_2Me$), 1.54–1.65 (m, 2H, CH_2CH_2Et), 3.97 (t, 2H, J = 6.8, CH_2Pr), 7.26–8.10 (m, 16H, H_{arom})
4h[b]	152–154	1438, 1191	1.06 (d, 6H, J = 6.1, $2CH_3$), 5.07 (sept, 1H, J = 6.1, OCH), 7.07–8.26 (m, 16H, H_{arom})
4i[b]	amorphous solid	1436, 1200	0.86 (t, 3H, J = 6.1, $C_5H_{10}CH_3$), 1.00 (d, 3H, J = 6.1, CH_3), 1.00–1.50 (m, 10H, $C_5H_{10}Me$), 4.94 (hex, 1H, J = 6.1, OCH), 7.07–8.24 (m, 16H, H_{arom})
4j[b]	amorphous solid	1430, 1198	1.44 (d, 3H, J = 6.4, CH_3), 5.90 (q, 1H, J = 6.4, OCH), 7.08–7.99 (m, 21H, H_{arom})
4k[b]	amorphous solid	1438, 1200	0.64–1.80 (m, 18H, $H_{menthyl}$), 4.52–4.65 (m, 1H, OCH), 7.08–8.18 (m, 16H, H_{arom})
4l[b]	105–107	1431, 1176	0.77 (t, 3H, J = 7.2, $C_3H_6CH_3$), 1.18–1.32 (m, 2H, $C_2H_4CH_2Me$), 1.34–1.46 (m, 2H, CH_2CH_2Et), 3.13 (t, 2H, J = 6.8, CH_2Pr), 6.76 (br, 1H, NH), 6.82–8.26 (m, 16H, H_{arom})
4m[b]	amorphous solid	1428, 1196	0.87 (d, 6H, J = 6.4, $2CH_3$), 1.08 (d, 6H, J = 6.4, $2CH_3$), 3.93 (sept, 2H, J = 6.4, 2NCH), 7.11–8.46 (m, 16H, H_{arom})
4n[b]	162–165	1434, 1158	1.36 (d, 3H, J = 6.3, CH_3), 4.80–4.93 (m, 1H, NCH), 7.90 (br, 1H, NH), 6.84–8.20 (m, 21H, H_{arom})
4o[b]	226–227	1432, 1150	5.53 (d, 2H, J = 9.0, 2NCH), 6.74–8.64 (m, 42H, H_{arom}), 8.90 (d, 2H, J = 9.0, 2NH)
5f[c]	156–159	1423	3.35 (s, 3H, OCH_3), 6.92–7.99 (m, 22H, H_{arom})
5g[b]	106–109	1424	0.94 (t, 3H, J = 7.3, $C_3H_6CH_3$), 1.41–1.56 (m, 2H, $C_2H_4CH_2Me$), 1.80–1.91 (m, 2H, CH_2CH_2Et), 4.08 (t, 2H, J = 6.6, CH_2Pr), 6.89–8.13 (m, 16H, H_{arom})
5k[b]	amorphous solid	1430	0.57–2.50 (m, 18H, $H_{menthyl}$), 4.50–4.62 (m, 1H, OCH), 6.91–8.23 (m, 16H, H_{arom})
5n[b]	amorphous solid	1430	1.53 (d, 3H, J = 6.7, CH_3), 4.79 (q, 1H, J = 6.7, NCH), 5.41 (br, 1H, NH), 6.97–8.18 (m, 21H, H_{arom})

[a] $[\alpha]_D^{21}$ (c, $CHCl_3$): **4i**, 0° (1.00); **4j**, + 49.0° (1.14); **4k**, + 5.4° (1.46); **4n**, − 80.3° (1.33); **4o**, + 58.7° (1.00); **5k**, − 17.1° (1.01); **5n**, − 71° (0.42).

[b] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.25, N ± 0.27%.

[c] Showed the same IR and ^1H NMR spectra as those of the authentic sample prepared before.[10]

rated. The water layer was extracted with Et_2O (2 × 100 mL) and the combined extracts were washed with water (3 × 100 mL), and dried ($MgSO_4$). After volatiles were evaporated, the residue was chromatographed on a silica gel column eluting with hexane–EtOAc to give **3** as colorless crystals; yield: 2.37 g (66%); mp 140–141 °C.

$C_{23}H_{19}O_2P$ (358.4) calc. C 77.08 H 5.34
found 77.16 5.37

IR (KBr): ν = 1431, 1198 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.67 (s, 3H, OCH_3), 7.42–8.12 (m, 16H, H_{arom}).

1-Alkyl(or Aryl)-2-(diphenylphosphinyl)naphthalenes (4a–e); General Procedure:

To Mg turnings (220 mg) was added a solution of 1,2-dibromoethane (200 μL) in dry Et_2O (1.0 mL) and the mixture was irradiated with ultrasound for 10 min. To the activated magnesium was added a solution of the appropriate alkyl (or aryl) bromide (1.80 mmol) in Et_2O (6.0 mL) over 10 min under ultrasonic irradiation and the mixture was irradiated under gentle reflux for 2 h. To it was added dry PhH (7.0 mL) and the resulting mixture was irradiated for a further 10 min. After being cooled to r.t., it was added dropwise to a solution of **3** (359 mg, 1.00 mmol) in PhH (5.0 mL) over 10 min and the mixture was stirred for 2–40 h at the appropriate temperature. To the cooled mixture was added 2 N HCl (30 mL) and the two layers were separated. The water layer was extracted with Et_2O (3 × 20 mL) and the combined extracts were washed with 2 N Na_2CO_3 (30 mL) and water (2 × 30 mL), and dried ($MgSO_4$). Chromatography on a silica gel column was employed for purification of the product using hexane–EtOAc as the eluent (Tables 1 and 2).

2-Diphenylphosphinyl-2′-methoxy-1,1′-binaphthyl (4f):

Compound **4f** was prepared by a similar procedure to that used for **4a**, using THF instead of Et_2O as the solvent: To the Mg turnings (220 mg) which were treated with 1,2-dibromoethane (200 μL) in dry THF (1.0 mL) was added a solution of 1-bromo-2-methoxynaphthalene (427 mg, 1.80 mmol) in THF (6.0 mL) and the mixture was irradiated under gentle reflux for 2 h. After being cooled to r.t., it was added dropwise to a solution of **3** (359 mg, 1.00 mmol) in PhH (7.0 mL) and the mixture was refluxed for 18 h. The cooled mixture was worked up as mentioned above. Chromatography on a silica gel column eluting with hexane–EtOAc gave **4f**; yield: 288 mg (Tables 1 and 2).

1-Alkoxy-2-(diphenylphosphinyl)naphthalenes (4g and h); General Procedure:

To the appropriate alcohol (2.5 mL) was added Na (120 mg, 5.22 mmol) and the mixture was heated at 50 °C until hydrogen evolution ceased. After the excess alcohol was distilled off, the residue was heated at 110 °C in vacuo for 30 min to give the sodium alkoxide, which was dissolved in dry DMF (2.5 mL). To it was added **3** (180 mg, 0.502 mmol) and the mixture was heated at 50 °C for 1–2 h. After being cooled to r.t., it was poured into 2 N HCl

(20 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with 2 N Na_2CO_3 (20 mL) and water (2 × 30 mL), and dried ($MgSO_4$). Chromatography on a silica gel column was employed for purification of the product using hexane–EtOAc as the eluent (Tables 1 and 2).

1-Alkoxy-2-(diphenylphosphinyl)naphthalenes (4i and j); General Procedure:

To NaH (60% dispersion in mineral oil, 72.0 mg, 1.8 mmol) was added the appropriate alcohol (2.00 mmol) and the mixture was heated at 50°C for 1 h. To it was added dry DMF (1.0 mL) and **3** (359 mg, 1.00 mmol), and the resulting mixture was heated at 50°C for 6 h. After being cooled to r.t., it was worked up as mentioned for **4g**. Chromatography on a silica gel column was employed for purification of the product using hexane–EtOAc as the eluent (Tables 1 and 2).

2-(Diphenylphosphinyl)-1-(1-*p*-menth-3-yloxy)naphthalene (4k):

Compound **4k** was prepared by a similar procedure to that used for **4i**: A mixture of *l*-menthol (3.13 g, 20.0 mmol) and NaH (60% dispersion in mineral oil, 720 mg, 18.0 mmol) was heated at 80°C for 1 h. To it was added DMF (5.0 mL) and **3** (2.15 g, 6.00 mmol), and the mixture was heated at 80°C for 2 h. After being cooled to r.t., it was poured into 2 N HCl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with 2 N Na_2CO_3 (50 mL) and water (2 × 50 mL), and dried ($MgSO_4$). After the volatiles were evaporated, excess *l*-menthol was distilled off (150°C, 2.0 mbar). Chromatography on a silica gel column eluting with hexane–EtOAc gave **4k**; yield: 827 mg (Tables 1 and 2).

1-Amino-2-(diphenylphosphinyl)naphthalenes (4l–n); General Procedure:

The lithium amides were prepared as follows: To a pertinent amine (1.10 mmol) in dry THF (2.0 mL) was added slowly 1.58 M BuLi in hexane (635 μL, 1.00 mmol) at −78°C and the mixture was stirred at −78°C for 10 min, and then at 0°C for 1 h. The amide solution thus obtained was added to a solution of **3** (180 mg, 0.502 mmol) in THF (2.0 mL) at −20°C and the mixture was stirred for 1–1.5 h. After being allowed to warm to r.t., it was poured into sat NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with water (2 × 20 mL) and dried ($MgSO_4$). Chromatography on a silica gel column was employed for purification of the product using hexane–EtOAc as the eluent (Tables 1 and 2).

(1*R*,2*R*)-*N*,*N*'-Bis(2-diphenylphosphinyl-1-naphthyl)-1,2-diphenylethylenediamine (4o):

The mono lithium amide of **6** was prepared from the parent amine (26.5 mg, 0.125 mmol) and 1.68 M BuLi (75 μL, 0.126 mmol) in THF (0.5 mL) in a similar manner as above. The prepared amide solution was added to a solution of **3** (44.8 mg, 0.125 mmol) in THF (1.0 mL) at −20°C and the mixture was stirred for 2 h to give crude **7**, whose diamide **8** was in turn prepared by treatment of the solution with 1.68 M BuLi (150 μL, 0.252 mmol) in a similar manner as above. Then the amide solution was added to a solution of **3** (44.8 mg, 0.125 mmol) in THF (1.0 mL) at −20°C and the mixture was stirred for 2 h. After being allowed to warm to r.t., it was worked up as above. Chromatography on a silica gel column eluting with hexane–EtOAc gave **4o**; yield 38.4 mg (Scheme 2 and Table 2).

Diphenyl(1-substituted-2-naphthyl)phosphines 5; General Procedure:

A mixture of **4** (0.150 mmol), Et_3N (d = 0.726, 85 μL, 0.61 mmol), $HSiCl_3$ (d = 1.34, 60 μL, 0.59 mmol), and dry xylene (1.0 mL) was heated at 120°C for 3.5–6 h. After being cooled to r.t., it was poured carefully into 10% NaOH (30 mL) and extracted with PhH (3 × 20 mL). The combined extracts were washed with water (2 × 20 mL) and dried ($MgSO_4$). Chromatography on a silica gel column was employed for purification of the product eluting with hexane–PhH for **5f** and hexane–EtOAc for **5g–n**, respectively (Tables 1 and 2).

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(1) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.
(2) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945, and references cited therein.
(3) March, J. *Advanced Organic Chemistry*; 4th ed.; Wiley: New York, 1992.
(4) Suzuki, T.; Hotta, H.; Hattori, T.; Miyano, S. *Chem. Lett.* **1990**, 807.
Hattori, T.; Suzuki, T.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1375.
(5) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 613.
(6) *Cf.* the S_NAr reaction by use of oxazolines as the activating group:
Reuman, M.; Meyers, A.I. *Tetrahedron* **1985**, *41*, 837.
(7) After this work had been started, we saw a report describing a conjugate addition of *t*-BuLi to 2-(diphenylphosphinyl)naphthalene:
Alcock, N.W.; Brown, J.M.; Pearson, M.; Woodward, S. *Tetrahedron Asymm.* **1992**, *3*, 17.
(8) Shirley, D.A.; Cheng, C.F. *J. Organomet. Chem.* **1969**, *20*, 251.
(9) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.
(10) Hattori, T.; Shijo, M.; Kumagai, S.; Miyano, S. *Chem. Express* **1991**, *6*, 335.