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2637

The Directed *ortho*-Lithiation of Aryl Tetramethylphosphorodiamidates[1]

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Aryl tetramethylphosphorodiamidates were effectively *ortho*-lithiated with *sec*-BuLi in tetrahydrofuran at $-105\,^\circ$C. The resulting lithiated species were trapped with a variety of electrophiles at $-105\,^\circ$C to provide *ortho*-substituted phosphorodiamidates. When the lithiation was carried out at $-78\,^\circ$C, $O \rightarrow C$ migration of the bis(dimethylamino)phosphoryl group took place rapidly and 2-hydroxyarylphosphonic tetramethyldiamides were produced regioselectively. The *ortho*-directing ability of the phosphorodiamidates was investigated by intermolecular competition experiments with other directed metalation groups.

Keywords lithiation; phenol; bis(dimethylamino)phosphoryl group; phosphate; aryl tetramethylphosphorodiamidate; 2-hydroxyarylphosphonic tetramethyldiamide

During the last decade, heteroatom-directed aromatic lithiation reactions have been developed for the regioselective construction of highly substituted aromatic compounds.[2] A number of directing groups have been devised to prepare *ortho*-disubstituted aromatics which are not readily available through classical electrophilic aromatic substitutions. Although phenol itself (1) can be *ortho*-lithiated under rather stringent conditions,[3] a superior strategy involves protection of the phenolic hydroxyl with a suitable group which allows *ortho*-lithiation to be performed under milder conditions (compounds **2—8** in Chart 1).[2] Among them, the methoxymethyl[2,4] and the
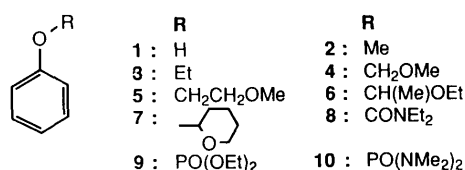
carbamoyl groups[2g,5] (**4** and **8** respectively) have shown great versatility and have been applied to syntheses of several natural products.[2g,6] In search of new *ortho*-directing groups, we have developed the bis(dimethylamino)phosphoryl function and report herein on its application to the facile *ortho*-lithiation of phenols.[1] We also describe the superior directing ability of the bis(dimethylamino)phosphoryl group on the basis of intermolecular competition experiments[7] with other *ortho*-directing groups such as **4** or **8**, as well as with non-phenolic directing groups such as *tert*-butylsulfone and tertiary amide.

The required aryl tetramethylphosphorodiamidates (**10a—h** and **11a**)[8] were easily prepared in 86—98% yields by the reaction of phenols or naphthols with bis(dimethylamino)phosphoryl chloride in the presence of sodium hydride according to the procedure of Dhawan and Redmore[9c,e,f] (Chart 2). For the synthesis of 3-(*tert*-butyldimethylsilyloxy)phenyl tetramethylphosphorodiamidate (**10i**), resorcinol was first mono-phosphorylated with one equivalent of sodium hydride/bis(dimethylamino)phosphoryl chloride

R

1 : H   2 : Me
3 : Et   4 : CH₂OMe
5 : CH₂CH₂OMe   6 : CH(Me)OEt
7 : (furanyl)   8 : CONEt₂
9 : PO(OEt)₂   10 : PO(NMe₂)₂

Chart 1

TABLE I. Physical Properties and Spectral Data of Aryl Tetramethylphosphorodiamidates (**10**)

Compd. No.	Formula (MS, m/z, M⁺)	bp (°C)	Analysis (%) Calcd (Found)			UV λ_{max}^{EtOH} nm (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	¹H-NMR[a] δ (CDCl₃)
			C	H	N			
10a	C₁₀H₁₇N₂O₂P (228)	125/5	52.62 (52.27)	7.51 7.50	12.27 11.97)	258 (s, 2.55), 264 (2.65), 270 (2.53)	3460, 2925, 2890, 1595, 1490, 1310, 1230, 1210, 995, 920	2.72 (d, $J=9.9$, 12H), 7.09—7.33 (m, 5H)[b]
10b	C₁₁H₁₉N₂O₃P (258)	125/0.8	51.15 (51.14	7.41 7.43	10.84 10.71)	217 (3.79), 273 (3.29), 279 (3.24)	3454, 2930, 1595, 1505, 1460, 1310, 1265, 1210, 1175, 1115, 1000, 915	2.74 (d, $J=10.3$, 12H), 3.84 (s, 3H), 6.86—7.31 (m, 4H)[b]
10c	C₁₁H₁₉N₂O₃P (258)	120/0.8	51.15 (51.04	7.41 7.43	10.84 10.74)	218 (3.89), 272 (3.33), 278.5 (3.28)	3450, 2930, 1605, 1490, 1455, 1310, 1285, 1220, 1145, 1000, 960	2.72 (d, $J=10.6$, 12H), 3.79 (s, 3H), 6.67 (dd, $J=8.4$, 2.6, 1H), 6.76 (br s, 1H), 6.78 (d, $J=8.1$, 1H), 7.20 (dd, $J=8.4$, 8.1, 1H)[b]
10d	C₁₁H₁₉N₂O₃P (258)	110/0.25	51.15 (50.80	7.41 7.44	10.84 10.90)	224 (3.01), 281 (2.31), 285 (s, 2.27)	3450, 2940, 1505, 1300, 1200, 1000, 905	2.71 (d, $J=9.9$, 12H), 3.77 (s, 3H), 6.83 (d, $J=8.8$, 2H), 7.10 (d, $J=8.8$, 2H)[b]
10e	C₁₂H₂₁N₂O₄P (288)	150/0.5	49.99 (49.78	7.34 7.21	9.72 9.63)	220 (s, 3.87), 274 (2.87)	3450, 2940, 1600, 1460, 1310, 1210, 1156, 1066	2.72 (d, $J=9.9$, 12H), 3.77 (s, 6H), 6.24 (br s, 1H), 6.38 (s, 2H)[b]
10f	C₁₅H₂₆N₃O₃P (327)	180/3	54.99 (55.19	8.00 7.89	12.89 12.56)	218 (s, 4.15)	3440, 2940, 1630, 1460, 1315, 1235, 1220, 1000, 910	1.14 (t, $J=7.2$, 6H), 2.73 (d, $J=10.3$, 12H), 3.20—3.59 (m, 4H), 7.22 (d, $J=8.8$, 2H), 7.35 (d, $J=8.8$, 2H)[b]
10g	C₁₄H₁₉N₂O₂P (278)	145/0.4	60.43 (60.21	6.88 6.91	10.07 9.88)	223 (4.81), 284 (3.89)	3450, 2930, 1595, 1460, 1395, 1310, 1220, 1090, 1000, 915	2.75 (d, $J=9.6$, 12H), 7.36—7.70 (m, 6H), 8.08—8.31 (m, 1H)[c]
10h	C₁₅H₂₁N₂O₃P (308)	190/0.6	58.43 (58.10	6.87 6.95	9.09 9.12)	240 (4.38), 301 (3.80), 312 (3.76), 326 (3.66)	3450, 2940, 1595, 1460, 1390, 1265, 1240, 1220, 1095, 1000, 980	2.72 (d, $J=9.6$, 12H), 3.93 (s, 3H), 6.65 (d, $J=6.0$, 1H), 7.36—7.63 (m, 3H), 8.02—8.32 (m, 2H)[c]
10i	C₁₆H₃₁N₂O₃PSi (358)	150/0.8	53.58 (53.38	8.71 8.62	7.85 7.78)	214.5 (3.89), 269.5 (3.14), 274 (s, 3.08)	3450, 2940, 1600, 1480, 1290, 1140, 990	0.20 (s, 6H), 0.98 (s, 9H), 2.71 (d, $J=9.9$, 12H), 6.61 (dd, $J=8.1$, 2.2, 1H), 6.70 (dd, $J=3.3$, 2.2, 1H), 6.81 (ddd, $J=8.4$, 3.3, 2.2, 1H), 7.14 (dd, $J=8.4$, 8.1, 1H)[b]

a) Listed as chemical shifts (multiplicity, coupling constant in Hz, number of protons).   *b*) 400 MHz NMR.   *c*) 60 MHz NMR.

and subsequently treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole[10] in dimethylformamide (DMF) to give 10i in 45% overall yield. The structures of all compounds were established by examination of infrared (IR), ultraviolet (UV), proton nuclear magnetic resonance (^{1}H-NMR), mass spectral (MS) data and elemental analyses as summarized in Tables I (for 10) and VI (for 11).

At the outset of this work, we noticed that although the bis(dimethylamino)phosphoryl group has been used as a directing group for the α-lithiation of tetrahydroisoquinolines[11] and for the 3-lithiation of 2-furanols,[12] there was no report on its use for the *ortho*-lithiation of phenols.[13] However, *ortho*-lithiation of the closely related aryl diethylphosphates (9) using lithium diisopropylamide (LDA) or *n*-BuLi at −78 or 0 °C has been studied and results in a rapid $O \rightarrow C$ diethylphosphoryl migration to give the corresponding diethyl 2-hydroxyarylphosphonates.[9]

With a view to minimizing the $O \rightarrow C$ phosphoryl migra-

tion, we first reexamined the lithiation of phenyl diethylphosphate (9)[9] with *sec*-BuLi at −105 °C (Chart 3). However, only the migration product, diethyl 2-hydroxyphenylphosphonate (13),[9] was obtained in 94% yield after quenching with saturated NH_4Cl solution at −105 °C. The incipient *ortho*-lithiated species (12) could not be trapped by an electrophile such as MeI or PhCHO and only the migration product (13) was obtained. When phenyl tetramethylphosphorodiamidate (10a) was lithiated by LDA or *sec*-BuLi at −78 °C for 1 h, an analogous migration product (16a) *via* 15a was obtained in 80% or 78% yield (Chart 4). This base-induced phosphoryl migration was studied for the various substituted aryl tetramethylphosphorodiamidates (10b—h and 11a) under the conditions described above (1.2 eq of *sec*-BuLi/tetrahydrofuran (THF)/−78 °C→ room temperature (r.t.)) and the results are summarized in Table II. In every case, the 2-hydroxyarylphosphonic diamide (16) was formed as a single product in high yield. The regioselectivity of the migration in 10c and 10e could be attributable to dual directing ability of the methoxy and the phosphorodiamidate groups, directing the lithiation at the carbon center to both functions.[2] In the case of

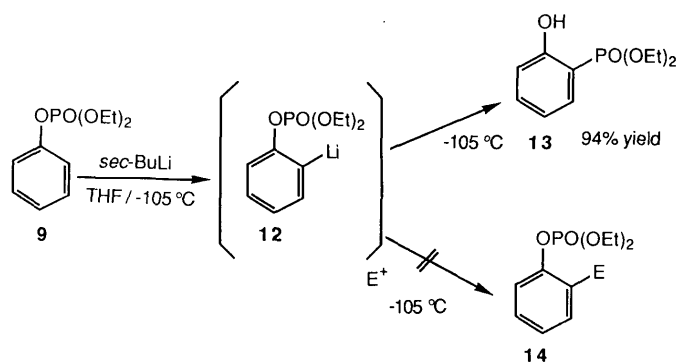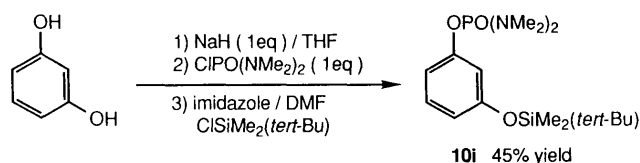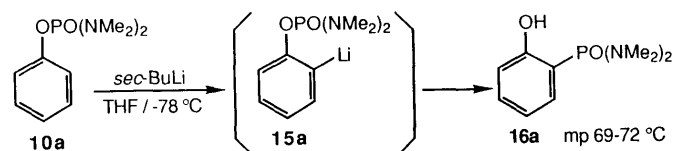|	R¹	R²	R³	R⁴	yield (%)
10a :	H	H	H	H	92
10b :	OMe	H	H	H	98
10c :	H	OMe	H	H	93
10d :	H	H	OMe	H	96
10e :	H	OMe	H	OMe	95
10f :	H	H	CONEt₂	H	91
10g :	-(CH=CH)₂-		H	H	88
10h :	-(CH=CH)₂-		OMe	H	86
11a :	Me	H	H	H	90

Chart 3

Chart 2

Chart 4

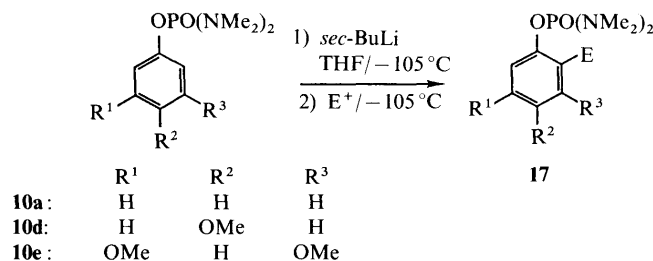TABLE II. Base-Induced Rearrangement of Aryl Tetramethylphosphorodiamidates (10, 11)

Aryl phosphorodiamidate (10 and 11)	2-Hydroxyarylphosphonic diamide (16)				
		R¹	R²	R³	R⁴	Yield (%)
10a	16a	H	H	H	H	80
10b	16b	OMe	H	H	H	80
10c	16c	H	H	H	OMe	90
10d	16d	H	H	OMe	H	90
10e	16e	H	OMe	H	OMe	95
10f	16f	H	H	CONEt₂	H	79
10g	16g	-(CH=CH)₂-		H	H	90
10h	16h	-(CH=CH)₂-		OMe	H	92
11a	16i	Me	H	H	H	83

TABLE III. Physical Properties and Spectral Data of 2-Hydroxyarylphosphonic Tetramethyldiamides (16)

Compd. No.	Formula (MS, m/z, M$^+$)	mp (°C) (Recryst. solvent)	Analysis (%) Calcd (Found)			UV λ_{max}^{EtOH} nm (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	^{1}H-NMR$^{a)}$ δ (CDCl$_3$)
			C	H	N			
16a	C$_{10}$H$_{17}$N$_2$O$_2$P (228)	69—72 (Ether–hexane)	52.62 (52.71	7.51 7.39	12.28 12.08)	217 (s, 3.95), 290 (3.65)	2925, 1580, 1455, 1405, 1295, 1250, 1125, 980	2.67 (d, J = 10.3, 12H), 6.84 (dt, J = 7.8, 3.3, 1H), 6.95 (dd, J = 8.5, 5.6, 1H), 7.21 (ddd, J = 12.7, 7.8, 2.0, 1H), 7.37 (dt, J = 7.9, 2.4, 1H), 11.37 (br s, 1H)$^{b)}$
16b	C$_{11}$H$_{19}$N$_2$O$_3$P (258)	78—79 (Ether–hexane)	51.15 (51.35	7.42 7.32	10.85 10.77)	297 (3.74)	2935, 2890, 1580, 1440, 1250, 1125, 980	2.66 (d, J = 10.3, 6H), 2.68 (d, J = 10.3, 6H), 3.89 (d, J = 1.0, 3H), 6.79—6.85 (m, 2H), 6.95—6.98 (m, 1H), 11.67 (br s, 1H)$^{b)}$
16c	C$_{11}$H$_{19}$N$_2$O$_3$P (258)	94 (Ether–hexane)	51.15 (51.23	7.42 7.22	10.85 10.91)	242 (3.73), 296 (3.67)	3420, 2900, 2560, 1605, 1580, 1460, 1440, 1300, 1250, 1180, 1110, 1080, 990	2.65 (d, J = 10.3), 3.80 (s, 3H), 6.32 (dd, J = 8.1, 4.9, 1H), 6.56 (dd, J = 8.3, 4.9, 1H), 7.29 (dd, J = 8.1, 8.3, 1H), 12.66 (br s, 1H)$^{b)}$
16d	C$_{11}$H$_{19}$N$_2$O$_3$P (258)	66—68 (Ether–hexane)	51.15 (50.92	7.42 7.30	10.85 10.83)	227.5 (3.96), 314 (3.70)	2940, 2895, 1495, 1460, 1280, 1250, 985	2.68 (d, J = 10.3, 12H), 3.76 (d, J = 1.0, 3H), 6.72 (dd, J = 13.7, 2.9, 1H), 6.90 (dd, J = 9.3, 6.4, 1H), 6.99 (dd, J = 3.1, 9.0, 1H), 10.90 (br s, 1H)$^{b)}$
16e	C$_{12}$H$_{21}$N$_2$O$_4$P (288)	89—91 (Ether–hexane)	49.99 (49.89	7.34 7.17	9.72 9.69)	214.4 (4.61), 247 (4.08), 284 (3.41)	2935, 2550, 1610, 1580, 1420, 1395, 1295, 1220, 1200, 1150, 1110, 990	2.64 (d, J = 10.2, 12H), 3.78 (s, 6H), 5.87—5.97 (m, 1H), 6.03—6.13 (m, 1H), 12.75 (br s, 1H)$^{c)}$
16f	C$_{15}$H$_{26}$N$_3$O$_3$P (327)	75—77 (Ether–hexane)	54.99 (54.91	8.00 7.94	12.89 12.82)	295 (3.56)	2930, 2700, 2570, 1620, 1590, 1425, 1400, 1285, 1140, 980	1.19 (br s, 6H), 2.67 (d, J = 10.3, 12H), 3.42 (br s, 4H), 6.95 (dd, J = 8.6, 8.4, 1H), 7.33 (dd, J = 12.8, 2.2, 1H), 7.42 (ddd, J = 8.4, 2.2, 1.1, 1H), 11.59 (s, 1H)$^{b)}$
16g	C$_{14}$H$_{19}$N$_2$O$_2$P (278)	121—122 (Ether–hexane)	60.42 (60.45	6.88 6.73	10.07 10.10)	218 (4.65), 248.5 (4.59), 289 (3.70), 323 (3.65), 337 (3.72)	2890, 2660, 1570, 1395, 1295, 1160, 1120, 980	2.70 (d, J = 10.3, 12H), 7.19 (dd, J = 11.0, 8.3, 1H), 7.28 (dd, J = 8.3, 2.9, 1H), 7.50 (t, J = 8.3, 1H), 7.56 (t, J = 6.8, 1H), 7.75 (d, J = 8.3, 1H), 8.38 (d, J = 8.3, 1H), 12.45 (br s, 1H)$^{c)}$
16h	C$_{15}$H$_{21}$N$_2$O$_3$P (308)	127 (Ether)	58.44 (58.39	6.87 6.82	9.09 9.00)	214.5 (4.69), 257 (4.49), 336 (3.84), 347.5 (3.80)	2925, 2885, 1595, 1570, 1455, 1395, 1360, 1320, 1290, 1160, 1120, 1100, 980	2.67 (d, J = 10.3, 12H), 3.89 (s, 3H), 6.46 (d, J = 13.0, 1H), 7.44—7.68 (m, 2H), 8.09—8.42 (m, 2H), 11.99 (s, 1H)$^{c)}$
16i	C$_{11}$H$_{19}$N$_2$O$_2$P (242)	68—70 (Ether–hexane)	54.53 (54.50	7.90 7.73	11.56 11.51)	293.5 (3.66)	2925, 1590, 1460, 1420, 1290, 1250, 1125, 985	2.25 (s, 3H), 2.66 (d, J = 10.3, 12H), 6.75 (dt, J = 7.5, 3.4, 1H), 7.07 (dd, J = 12.8, 8.2, 1H), 7.23 (dd, J = 7.3, 1.0, 1H), 11.57 (br s, 1H)$^{b)}$

a) Listed as chemical shifts (multiplicity, coupling constant in Hz). *b*) 400 MHz NMR. *c*) 60 MHz NMR.

TABLE IV. Synthesis of *ortho*-Substituted Phenyl Tetramethylphosphorodiamidates (17)

	R^1	R^2	R^3
10a:	H	H	H
10d:	H	OMe	H
10e:	OMe	H	OMe

Run	Phosphorodiamidate (10)	Electrophile (E$^+$)	Product (17)	R^1	R^2	R^3	E	Yield (%)
1	10a	Me$_3$SiCl	17a	H	H	H	Me$_3$Si	79
2	10a	(PhS)$_2$	17b	H	H	H	PhS	64
3	10a	Me–CHO	17c	H	H	H	Me–CH(OH)	67
4	10a	p-MeO–C$_6$H$_4$–CHO	17d	H	H	H	p-MeO–C$_6$H$_4$–CH(OH)	67
5	10a	p-NO$_2$–C$_6$H$_4$–CHO	17e	H	H	H	p-NO$_2$–C$_6$H$_4$–CH(OH)	55
6	10a	PhCOPh	17f	H	H	H	Ph–C(OH)–Ph	72
7	10a	PhCOMe	17g	H	H	H	Ph–C(OH)–Me	64
8	10a	p-MeO–C$_6$H$_4$–COCl	17h	H	H	H	p-MeO–C$_6$H$_4$–CO	94
9	10d	p-MeO–C$_6$H$_4$–CHO	17i	H	OMe	H	p-MeO–C$_6$H$_4$–CH(OH)	51
10	10d	PhCOPh	17j	H	OMe	H	Ph–C(OH)–Ph	58
11	10e	p-MeO–C$_6$H$_4$–CHO	17k	OMe	H	OMe	p-MeO–C$_6$H$_4$–CH(OH)	57

ortho-tolyl tetramethylphosphorodiamidate (**11a**), lithiation might occur initially at the benzylic position, followed by rearrangement to the ring, because the benzylic lithiated species could be trapped with electrophiles, as described later, when the reaction was conducted at −105 °C.[14] The structures of the migration products were established by examination of *ortho* (*ca.* 15 Hz), *meta* (*ca.* 7 Hz), and *para* (*ca.* 2 Hz) P–H coupling constants in phosphorus

TABLE V. Physical Properties and Spectral Data of *ortho*-Substituted Aryl Tetramethylphosphorodiamidates (**17**)

Compd. No.	Formula (MS, *m/z*, M⁺)	mp (bp) (°C) (Recryst. solvent)	Analysis (%) Calcd (Found) C	H	N	UV λ_{max}^{EtOH} nm (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	¹H-NMR[a] δ (CDCl₃)
17a	C₁₃H₂₅N₂O₂PSi (300)	64—65 (Ether–hexane)	51.97 (51.73	8.39 8.53	9.33 9.27)	216 (3.95), 263 (s, 2.84), 269 (3.00), 277 (2.97)	3060, 2900, 1590, 1470, 1435, 1305, 1235, 1190, 1130, 1080, 1000, 920	0.28 (s, 9H), 2.73 (d, J=9.6, 12H), 6.86—7.49 (m, 4H)[b]
17b	C₁₆H₂₁N₂O₂PS (336)	160/0.6	57.12 (57.25	6.29 6.40	8.33 8.53)	233 (3.89), 249 (4.07), 276 (3.70)	3460, 2930, 1580, 1470, 1310, 1220, 1065, 1000, 920	2.67 (d, J=10.2, 12H), 6.98—7.15 (m, 4H), 7.28 (s, 5H)[b]
17c	C₁₂H₂₁N₂O₃P (272)	150/0.5	52.90 (52.40	7.77 7.61	10.37 10.01)	265 (2.54), 271 (2.48)	3370, 2930, 2900, 1605, 1590, 1490, 1455, 1365, 1310, 1215, 1180, 1130, 1080, 1050, 1000, 930	1.53 (d, J=6.6, 3H), 2.74 (d, J=9.5, 6H), 2.77 (d, J=10.3, 6H), 4.36 (br s, 1H), 5.22 (q, J=6.6, 1H), 7.01 (d, J=7.7, 1H), 7.19—7.27 (m, 2H), 7.54 (d, J=7.3, 1H)[c]
17d	C₁₈H₂₅N₂O₄P (364)	114—116 (CH₂Cl₂–hexane)	59.33 (59.00	6.92 6.89	7.69 7.60)	230 (4.12), 269 (s, 3.24), 274.5 (3.32), 283 (3.15)	3310, 2935, 1610, 1585, 1510, 1455, 1315, 1405, 1240, 1225, 1205, 1180, 1000, 925	2.64 (d, J=9.6, 6H), 2.73 (d, J=10.8, 6H), 3.79 (s, 3H), 4.85 (d, J=3.6, 1H), 6.16 (br s, 1H), 6.81—7.44 (m, 8H)[b]
17e	C₁₇H₂₂N₃O₅P (379)	115—120 (Ether–hexane)	53.82 (53.89	5.84 5.82	11.08 11.16)	276 (4.07)	3310, 2900, 1595, 1510, 1485, 1450, 1345, 1310, 1215, 1170, 1050, 1005, 910	2.68 (d, J=10.8, 6H), 2.78 (d, J=10.2, 6H), 5.84 (d, J=2.4, 1H), 6.21 (br s, 1H), 6.88—7.28 (m, 4H), 7.62 (d, J=9.0, 2H), 8.21 (d, J=9.0, 2H)[b]
17f	C₂₃H₂₇N₂O₃P (410)	138—139 (CH₂Cl₂–hexane)	67.30 (67.40	6.63 6.74	6.83 6.91)	255 (s, 2.79), 260 (2.91), 266 (2.94), 273 (s, 2.79)	3180, 2940, 1600, 1570, 1480, 1450, 1310, 1210, 1185, 1000	2.40 (d, J=10.2, 12H), 5.59 (s, 1H), 6.57—7.28 (m, 14H)[b]
17g	C₁₈H₂₅N₂O₃P (348)	112—114 (CH₂Cl₂–hexane)	62.06 (62.15	7.23 7.18	8.04 8.04)	261 (s, 2.45), 266 (2.70), 272 (2.53)	3310, 2900, 1600, 1580, 1490, 1450, 1310, 1240, 1215, 1190, 1170, 1010, 990, 945	1.84 (s, 3H), 2.41 (d, J=10.8, 12H), 4.74 ((br s, 1H), 7.28—7.73 (m, 9H)[b]
17h	C₁₈H₂₃N₂O₄P (362)	Oil	58.19 (57.99	6.51 6.39	7.58[d] 7.54)	289 (4.31)	3450, 3070, 3000, 2930, 2900, 2850, 2810, 1660, 1600, 1580, 1510, 1485, 1450, 1420, 1310, 1260, 1240, 1220, 1180, 1150, 1105, 1070, 1030, 1000, 940	2.44 (d, J=9.6, 12H), 3.82 (s, 3H), 6.89 (d, J=9.6, 2H), 7.16—7.53 (m, 4H), 7.81 (d, J=9.6, 2H)[b]
17i	C₁₉H₂₇N₂O₅P (394)	94—96 (Ether)	57.86 (57.85	6.90 6.81	7.10 7.09)	227 (4.33), 277 (s, 3.65), 283 (3.70)	3270, 2930, 2900, 1605, 1590, 1510, 1490, 1450, 1430, 1310, 1270, 1245, 1210, 1195, 1175, 1150, 1055, 1035, 995, 940	2.67 (d, J=9.5, 6H), 2.76 (d, J=10.3, 6H), 3.68 (s, 3H), 3.81 (s, 3H), 5.10 (br s, 1H), 6.11 (s, 1H), 6.67 (d, J=2.9, 1H), 6.75 (dd, J=8.8, 3.3, 1H), 6.87 (d, J=8.8, 2H), 6.92 (d, J=8.8, 1H), 7.34 (d, J=8.8, 2H)[c]
17j	C₂₄H₂₉N₂O₄P (440)	161—162 (CH₂Cl₂–hexane)	65.44 (65.20	6.64 6.57	6.36 6.43)	285 (3.53)	3250, 2930, 1600, 1575, 1485, 1450, 1305, 1210, 1190, 1185, 1045, 1005	2.46 (d, J=10.8, 12H), 3.62 (s, 3H), 5.80 (br s, 1H), 6.27—6.93 (m, 3H), 7.34 (s, 10H)[b]
17k	C₂₀H₂₉N₂O₆P (424)	128—130 (CH₂Cl₂–ether)	56.59 (56.64	6.89 6.77	6.60 6.60)	226 (4.29), 276.5 (3.54)	3350, 2940, 1605, 1505, 1455, 1430, 1320, 1215, 1145, 1105, 975	2.55 (d, J=10.0, 6H), 2.65 (d, J=10.0, 6H), 3.70 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.39 (d, J=11.4, 1H), 6.08 (br s, 1H), 6.31 (d, J=2.4, 1H), 6.65 (br s, 1H), 6.80 (d, J=8.7, 2H), 7.27 (d, J=8.7, 2H)[b]

a) Listed as chemical shifts (multiplicity, coupling constant in Hz, number of protons). *b*) 60 MHz NMR. *c*) 400 MHz NMR. *d*) For C₁₈H₂₃N₂O₄P·1/2H₂O.

substituted benzenoids[15] in 400 MHz ¹H-NMR spectra. Physical properties and spectral data for **16** are listed in Table III.

On the other hand, when **10a** was lithiated with 1.2 eq of *sec*-BuLi at −105 °C for 1 h and subsequently treated with trimethylsilyl chloride at −105 °C, the *ortho*-silylated compound (**17a**) was obtained in 79% yield (Table IV; run 1). Under these conditions, none of the migration product was obtained. Using disulfide, aldehydes, ketones, and acid chlorides as electrophiles, again at −105 °C, the corresponding *ortho*-substituted products were regioselectively synthesized in moderate to good yields (Table IV; runs 2—8). The methoxy-substituted phosphorodiamidates (**10d** and **e**) behaved in a similar manner and the corresponding *ortho*-substituted phosphorodiamidates (**17i**—**k**) were obtained in moderate yields (Table IV; runs 9—11). The physical properties and spectral data for all the *ortho*-substituted products (**17a**—**k**) are summarized in Table V.

Regioselective methylation of **10a**—**h** was achieved by
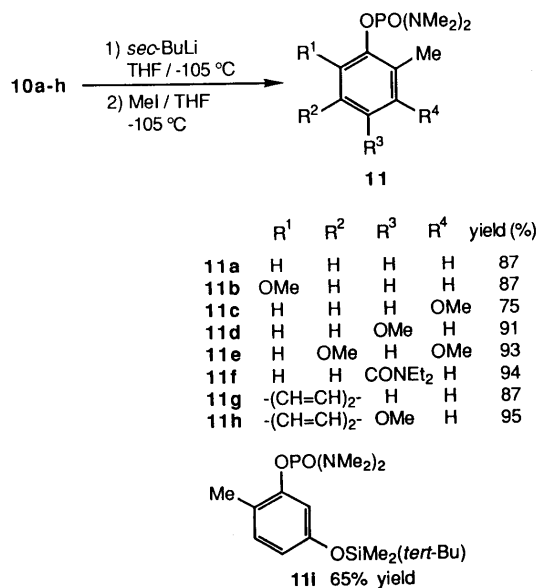
Chart 5

trapping the corresponding *ortho*-lithiated species at −105 °C with MeI to give various 2-methylaryl phosphorodiamidates in high yields (Chart 5). Using the 3-methoxy-substituted **10c** and 3,5-dimethoxy-substituted **10e** as starting phosphorodiamidates, exclusive methylation at the position between the phosphate and methoxy groups was effected, and 1,2,3-trisubstituted and 1,2,3,5-tetrasubstituted benzenes (**11c** from **10c** and **11e** from **10e**) were obtained as the sole products, respectively. In contrast, lithiation of **10i**, which has a bulky *tert*-butyldimethylsilyloxy group at the 3-position, occurred at the 6-position to give the 1,2,4-trisubstituted benzene (**11i**) in 65% yield. This demonstrates that the *tert*-butyldimethylsilyloxy group inhibits lithiation *ortho* to this group, presumably owing to

steric hindrance.[10,16) The regiochemistry of **11** was determined by 400 MHz ^{1}H-NMR spectroscopy.[15b) Physical and spectral data for the 2-methylaryl tetramethylphosphorodiamidates (**11**) are summarized in Table VI.

Intermolecular competition[7) between **10d** and other phenol derivatives (**4a** and **8a**) bearing directed metalation groups (DMG) was next examined (Chart 6). Phosphorodiamidate (**10d**) and 4-methoxy(methoxymethoxy)benzene (**4a**) were allowed to compete for 1.0 eq of *sec*-BuLi (THF/−105 °C) and then the reaction was quenched with excess MeI. Analysis of the products by gas chromatography (GC) revealed a 3.5:1 ratio for **11d** vs. **18**. In the intermolecular competition experiment between **10d** and 4-methoxyphenyl *N,N*-diethylcarbamate (**8a**), **11d** and **19**[5) were

TABLE VI. Physical Properties and Spectral Data of 2-Methylaryl Tetramethylphosphorodiamidates (**11**)

Compd. No.	Formula (MS, m/z, M$^+$)	bp (mp) (°C) (Recryst. solvent)	Analysis (%) Calcd (Found)			UV λ_{max}^{EtOH} nm (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	^{1}H-NMR$^{a)}$ δ (CDCl$_3$)
			C	H	N			
11a	C$_{11}$H$_{19}$N$_2$O$_2$P (242)	110/0.6	54.53 (54.09	7.91 7.81	11.56 11.32)	266 (2.25), 272 (2.19)	3460, 2925, 1590, 1495, 1460, 1310, 1240, 1180, 1115, 1000, 915	2.28 (s, 3H), 2.70 (d, $J=9.6$, 12H), 6.92 —7.20 (m, 4H)$^{b)}$
11b	C$_{12}$H$_{21}$N$_2$O$_3$P (272)	135/2.5	52.93 (53.13	7.77 7.69	10.29 10.19)	272 (3.21), 277.5 (3.21)	3430, 2930, 1580, 1490, 1310, 1280, 1220, 1180, 1080, 1000, 910	2.36 (s, 3H), 2.75 (d, $J=9.9$, 12H), 3.84 (s, 3H), 6.76 (d, $J=8.4$, 2H), 6.97 (t, $J=8.4$, 1H)$^{c)}$
11c	C$_{12}$H$_{21}$N$_2$O$_3$P (272)	140/0.7	52.93 (52.88	7.77 7.73	10.29 10.32)	218 (3.90), 272 (3.06), 277 (3.06)	3460, 2940, 1595, 1475, 1310, 1270, 1220, 1110, 1000, 945	2.17 (s, 3H), 2.73 (d, $J=9.9$, 12H), 3.82 (s, 3H), 6.63 (d, $J=8.4$, 1H), 6.94 (d, $J=8.4$, 1H), 7.06 (t, $J=8.4$, 1H)$^{c)}$
11d	C$_{12}$H$_{21}$N$_2$O$_3$P (272)	145/0.8	52.93 (52.52	7.77 7.74	10.29 10.17)	225 (3.88), 281 (3.29), 285 (s, 3.26)	3450, 2940, 1610, 1505, 1465, 1310, 1220, 1200, 1110, 1050, 1000, 945, 900	2.29 (s, 3H), 2.73 (d, $J=9.9$, 12H), 3.75 (s, 3H), 6.66 (dd, $J=8.8$, 2.9, 1H), 6.71 (d, $J=2.9$, 1H), 7.13 (d, $J=8.8$, 1H)$^{c)}$
11e	C$_{13}$H$_{23}$N$_2$O$_4$P (302)	165/2	51.65 (50.88	7.67 7.59	9.27 8.75)	276 (3.23)	3450, 2930, 1620, 1590, 1500, 1460, 1310, 1220, 1150, 1110, 1000	2.08 (s, 3H), 2.73 (d, $J=9.9$, 12H), 3.77 (s, 3H), 3.79 (s, 3H), 6.25 (d, $J=1.1$, 1H), 6.59 (d, $J=1.1$, 1H)$^{c)}$
11f	C$_{16}$H$_{28}$N$_3$O$_3$P (341)	160/0.3	56.29 (56.37	8.27 8.11	12.31 12.43)	277 (2.54)	3530, 3460, 2970, 2930, 2880, 1630, 1500, 1460, 1430, 1295, 1230, 1205, 1165, 1125, 1095, 1065, 1000, 935, 900	1.16 (t, $J=7.0$, 6H), 2.30 (s, 3H), 2.73 (d, $J=10.2$, 12H), 3.40 (q, $J=7.0$, 4H), 7.21—7.31 (m, 3H)$^{b)}$
11g	C$_{15}$H$_{21}$N$_2$O$_2$P (292)	Oil	61.60 (61.49	7.24 7.13	9.57 9.67)	226.5 (4.90), 283 (3.78), 292 (s, 3.70)	3450, 2925, 2810, 1630, 1600, 1570, 1460, 1380, 1310, 1235, 1175, 1085, 995, 930	2.56 (s, 3H), 2.75 (d, $J=9.6$, 12H), 7.26 —8.00 (m, 6H)$^{b)}$
11h	C$_{16}$H$_{23}$N$_2$O$_3$P (322)	123 (Ether)	59.61 (59.52	7.19 7.12	8.69 8.76)	211 (4.86), 240 (4.76), 302 (4.06), 313 (s, 3.98), 327 (s, 3.80)	2920, 2890, 1600, 1460, 1360, 1310, 1235, 1220, 1090, 995, 980, 940	2.55 (s, 3H), 2.73 (d, $J=10.2$, 12H), 3.93 (s, 3H), 6.60 (s, 1H), 7.37—7.54 (m, 2H), 7.96—8.25 (m, 2H)$^{b)}$
11i	C$_{16}$H$_{33}$N$_2$O$_3$PSi (372)	155/0.6	54.81 (54.44	8.93 8.78	7.52 7.51)	277 (3.38)	3450, 2925, 2550, 1610, 1510, 1300, 1240, 1155, 1110, 990, 910	0.19 (s, 9H), 0.97 (s, 6H), 2.22 (s, 3H), 2.73 (d, $J=9.9$, 12H), 6.52 (dd, $J=8.1$, 2.2, 1H), 6.83 (dd, $J=2.2$, 1.1, 1H), 6.98 (d, $J=8.1$, 1H)$^{c)}$

a) Listed as chemical shifts (multiplicity, coupling constant in Hz, number of protons). *b)* 60 MHz NMR. *c)* 400 MHz NMR.
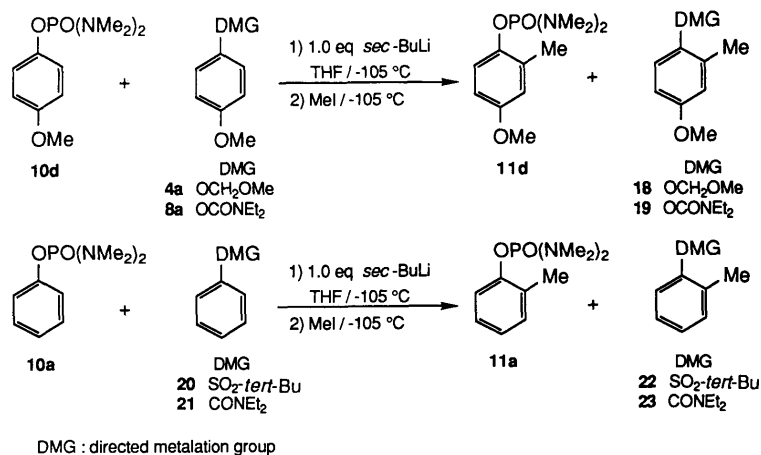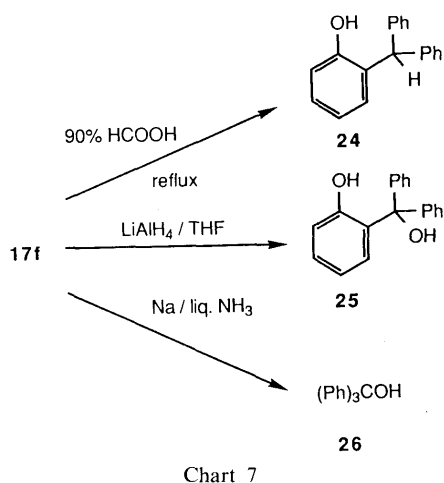

Chart 6

OH Ph

90% HCOOH → (structure) Ph / H

24

reflux

LiAlH₄ / THF → OH Ph (structure) Ph / OH

17f

25

Na / liq. NH₃

(Ph)₃COH

26

Chart 7

TABLE VII. Intermolecular Competition for Lithiation

Run	Compd.	Methylated product (yield, %)				Starting material (yield, %)			
1	10d+4a	11d	76.9	18	21.9	10d	<1	4a	71.9
2	10d+8a	11d	65.1	19	33.9	10d	23.4	8a	61.0
3	10a+20	11a	55.3	22	12.5	10a	37.5	20	84.5
4	10a+21	11a	74.9	23	24.2	10a	12.0	21	60.7

obtained in approximately 2 : 1 ratio. Furthermore, similar intermolecular competition between **10a** and phenyl-*tert*-butylsulfone **(20)**[7c] or *N,N*-diethylbenzamide **(21)** was carried out, and a greater ratio (4.4 : 1 or 3.1 : 1) of **11a** to **22**[7c] or **23** was obtained (Table VII). The above results suggest that the tetramethylphosphorodiamidate group is a better *ortho* metalating group than the carbamoyl,[2g,5] methoxymethoxy,[2,4] *tert*-butylsulfonyl,[7c] or the *N,N*-diethylamido groups.[2b]

Removal of the bis(dimethylamino)phosphoryl group was easily achieved by two methods. *ortho*-Tolyl and *ortho*-naphthyl phosphorodiamidates **(11a, d, g)** were hydrolyzed with 90% formic acid (HCOOH) under reflux for 1 h[12] to give *ortho*-cresol, 4-methoxy-2-methylphenol,[17] and 2-methyl-1-naphthol[18] in quantitative, 69% and 87% yields, respectively. Alternatively, treatment of **10c** or **11c** with 1.1 eq of LiAlH₄ in refluxing THF for 1 h led to 3-methoxyphenol or 3-methoxy-2-methylphenol[19] in 70% or 56% yield. The behavior of tetramethylphosphorodiamidate as a latent directed metalation group[7c] was demonstrated by the reaction of **17c** with 3 eq of sodium (Na) in liquid ammonia (NH₃) to afford 1-phenylethanol[20] in 93% yield.[21] Thus, by choosing an appropriate deprotecting method, **17f** may be converted to (2-hydroxyphenyl)diphenylmethane **(24)**[22] (with 90% HCOOH), (2-hydroxyphenyl)diphenylmethanol **(25)**[23] (with LiAlH₄), and triphenylmethanol **(26)**[24] (with Na/liquid NH₃) in 63%, 67%, and 92% yields, respectively (Chart 7).

In conclusion, we have found that the aryl tetramethylphosphorodiamidates can be effectively *ortho*-lithiated with *sec*-BuLi at −105°C and the resulting *ortho*-lithiated species can be trapped with electrophiles as long as the reaction temperature is kept at −105°C. By intermolecular competition with other *ortho*-directing groups, aryl tetramethylphosphorodiamidates were revealed

as superior for lithiation. In addition, aryl tetramethylphosphorodiamidates are easily converted into *ortho*-substituted phenols by acidic or reductive hydrolysis and into substituted aromatics by reductive dehydroxylation. Thus, *ortho*-lithiation of aryl tetramethylphosphorodiamidates provides a new and useful procedure for the regioselective synthesis of highly substituted aromatics.

Experimental

All melting points are uncorrected. The IR spectra were obtained in KBr disk using a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The ¹H-NMR spectra were obtained with JEOL FX 90Q, JEOL JNM-PMX 60, and JEOL JNM GX-400 spectrometers using CDCl₃ as a solvent and tetramethylsilane as an internal reference. The mass spectra (MS) were determined on a JEOL-DX 303 mass spectrometer. The GC was performed by use of a Shimadzu GC-8A gas chromatograph equipped with a Silicon GE SE-30 column. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reactions were freshly distilled from sodium benzophenone ketyl before use. Flash chromatography was carried out with a Kieselgel 60 (230—400 mesh) column.

General Procedure for the Syntheses of Aryl Tetramethylphosphorodiamidates (10 and 11a) The following procedure for the synthesis of 4-methoxyphenyl tetramethylphosphorodiamidate **(10d)** is representative; the other amidates **(10a—c, 10e—h, and 11a)** were obtained similarly.

4-Methoxyphenyl Tetramethylphosphorodiamidate (10d) 4-Methoxyphenol (7.44 g, 60 mmol) in THF (100 ml) was added to a stirred suspension of NaH (60% NaH, 3.60 g, 90 mmol) in THF (50 ml) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, and was then cooled in an ice bath and bis(dimethylamino)phosphoryl chloride (20.47 g, 120 mmol) in THF (50 ml) was added dropwise. The reaction mixture was stirred at room temperature for 12 h. After removal of the solvent, saturated NH₄Cl solution and methylene chloride were added to the residue. The organic layer was separated, dried over Na₂SO₄ and then evaporated to yield crude 4-methoxyphenyl tetramethylphosphorodiamidate **(10d)** as an oil. Purification by distillation gave pure **10d** (14.47 g, 96%), bp 110 °C (0.25 mmHg) (see Tables I and VI).

3-(*tert*-Butyldimethylsilyloxy)phenyl Tetramethylphosphorodiamidate (10i) Resorcinol (13.2 g, 120 mmol) was mono-phosphorylated under the conditions described above (60% NaH, 3.6 g, 90 mmol; bis(dimethylamino)phosphoryl chloride, 10.23 g, 60 mmol). The residue was chromatographed using benzene as an eluent to give 3-hydroxyphenyl tetramethylphosphorodiamidate (9.14 g), which was used without further purification in the next step. *tert*-Butyldimethylsilyl chloride (5.06 g, 33 mmol) was added into a stirred solution of imidazole (2.29 g, 33.6 mmol) and mono-phosphorylated resorcinol (9.14 g, 33.6 mmol) in DMF (20 ml) at room temperature. The reaction mixture was stirred at room temperature for 12 h. Water and *n*-hexane were added to the reaction mixture. The organic layer was separated, washed with 5% NaHCO₃ solution, and dried over Na₂SO₄. The solvent was removed to give a residue, which was distilled to give **10i** (9.67 g, 80% yield, 45% overall yield), bp 150 °C (0.8 mmHg) (see Table I).

Base-Induced Rearrangement of Aryl Tetramethylphosphorodiamidates (10a—h and 11a) The following procedure for the synthesis of 2-hydroxyphenylphosphonic tetramethyldiamide **(16a)** is representative; the other phosphoronic diamides **(16b—i)** were obtained similarly.

2-Hydroxyphenylphosphonic Tetramethyldiamide (16a) A solution of *sec*-BuLi (1.00 M in cyclohexane, 6.0 ml, 6.0 mmol) was injected into a stirred solution of phenyl tetramethylphosphorodiamidate **(10a**, 1.14 g, 5.0 mmol) in THF (50 ml) at −78 °C (dry ice-acetone) under a nitrogen atmosphere. The mixture was stirred at −78 °C for 30 min, then the cooling bath was removed and stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated NH₄Cl solution, and evaporated under reduced pressure. The residue was extracted with methylene chloride and the methylene chloride layer was separated and dried over Na₂SO₄. The extract was evaporated to give a residue, which was chromatographed using methylene chloride–acetone (9 : 1) as an eluent to give 2-hydroxyphenylphosphonic tetramethyldiamide **(16a)**. Further purification by recrystallization from ether–*n*-hexane gave pure **16a** (0.91 g, 80%), mp 69—72 °C (see Tables II and III).

Syntheses of *ortho*-Substituted Aryl Tetramethylphosphorodiamidates (17 and 11) The following procedure for the synthesis of *ortho*-tolyl

tetramethylphosphorodiamidate (**11a**) is representative; the other *ortho*-substituted tetramethylphosphorodiamidates (**17a—k** and **11b—i**) were obtained similarly.

***ortho*-Tolyl Tetramethylphosphorodiamidate (11a)** A solution of *sec*-BuLi (1.00 M in cyclohexane, 6.0 ml, 6.0 mmol) was injected into a stirred solution of phenyl tetramethylphosphorodiamidate (**10a**, 1.14 g, 5.0 mmol) in THF (50 ml) at −105 °C (liquid nitrogen–ethanol) under a nitrogen atmosphere. The mixture was stirred at −105 °C for 1 h, then a solution of MeI (0.99 g, 7.0 mmol) in THF (20 ml) was injected into the lithiated solution at −105 °C. Stirring was continued for an additional 1 h at −105 °C. The reaction mixture was quenched with saturated NH_4Cl solution at −90 °C and the solution was allowed to warm to room temperature. THF was removed under reduced pressure. The residue was extracted with ether and the ether layer was washed with 5% $Na_2S_2O_3$ solution, dried over Na_2SO_4, and then evaporated to give crude *ortho*-tolyl tetramethylphosphorodiamidate (**11a**) as an oil, which was distilled to give pure **11a** (1.05 g, 87%), bp 110 °C (0.6 mmHg) (see Tables V and VI).

Intermolecular Competition Reaction A solution of *sec*-BuLi (1.00 M in cyclohexane, 3.0 ml, 3.0 mmol) was injected into a solution of **10d** (0.77 g, 3.0 mmol) and **4a** (0.50 g, 3.0 mmol) in THF (60 ml) at −105 °C under a nitrogen atmosphere. The mixture was stirred at −105 °C for 1 h, then a solution of MeI (0.43 g, 3.0 mmol) in THF (10 ml) was injected at −105 °C. The reaction mixture was stirred for an additional 1 h at −105 °C and then was quenched with saturated NH_4Cl solution at −90 °C. THF was removed and the residue was extracted with ether. The ether layer was washed with 5% $Na_2S_2O_3$ solution, dried over Na_2SO_4, and then evaporated to give a mixed residual oil. The residue was chromatographed with methylene chloride as an eluent to give a mixture (0.48 g) of **18** and **4a**, and with methylene chloride–acetone (9 : 1) as an eluent to give a mixture (0.64 g) of **10d** and **11d**. The ratio of the components of the mixture was determined by GC analyses (see Table VII). Compound **18** was synthesized in 83% yield by the procedure of ref. 6. 2-Methoxymethoxy-5-methoxytoluene (**18**), bp 90 °C (0.3 mmHg). MS *m/z*: 182 (M⁺). ¹H-NMR δ: 2.24 (s, 3H), 3.49 (s, 3H), 3.75 (s, 3H), 5.11 (s, 2H), 6.65 (dd, $J=$ 9.0, 3.0, 1H), 6.72 (d, $J=3.0$, 1H), 6.97 (d, $J=9.0$, 1H). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.27; H, 7.92.

Similarly, intermolecular competition experiments between **10d** and **8a**, **10a** and **20**, and **10a** and **21** were carried out and the results are summarized in Table VII.

Removal of Bis(dimethylamino)phosphoryl Group i) Using 90% HCOOH: A solution of **11d** (1.50 g, 5.50 mmol) in 90% HCOOH (5 ml) was refluxed for 1 h. After the removal of HCOOH under reduced pressure, 5% $NaHCO_3$ was added to the residue and the mixture was extracted with methylene chloride. The organic layer was separated, dried over Na_2SO_4, and evaporated to give a residue, which was chromatographed using methylene chloride as an eluent to give 4-methoxy-2-methylphenol. Further purification by recrystallization from ether–*n*-pentane gave 4-methoxy-2-methylphenol (mp 64—65 °C, 0.53 g, 69%) (lit.[17] mp 71 °C). Similarly, *ortho*-cresol, 2-methyl-1-naphthol (mp 57—59 °C) (lit.[18] mp 63—64 °C), and (2-hydroxyphenyl)diphenylmethane (**24**) (mp 120 °C) (lit.[22] mp 124 °C) were obtained in quantitative, 87% and 63% yields, respectively.

ii) Using LiAlH₄: A solution of **17f** (0.82 g, 2.0 mmol) and LiAlH₄ (0.08 g, 2.2 mmol) in THF (50 ml) was refluxed for 1 h, then allowed to cool. Water was added to the solution. Standard work-up and chromatographic purification gave (2-hydroxyphenyl)diphenylmethanol (**25**) (mp 138—139 °C, 0.37 g, 67%) (lit.[23] mp 140 °C). Similarly, 3-methoxyphenol and 3-methoxy-2-methylphenol (oil) (lit.[19] mp 47 °C) were obtained in 70% and 56% yields, respectively.

Reductive Dehydroxylation Triphenylmethanol (**26**): A dried, 100 ml, three-necked, round-bottomed flask equipped with dry ice condenser, NH_3 gas inlet, septum, and magnetic stirring bar was flushed with nitrogen, immersed in a dry ice–acetone bath and filled with liquid NH_3 (*ca.* 50 ml). A solution of **17f** (0.82 g, 2.0 mmol) in THF (10 ml) was injected into the flask and then a small piece of Na (0.14 g, 6.0 mmol) was added with stirring. Stirring was continued for 15 min. The blue color disappeared, and then the reaction mixture was quenched with saturated NH_4Cl solution. The ammonia was boiled off, and the mixture was extracted with ether. The ether layer was dried over Na_2SO_4, and evaporated to give a residue, which was chromatographed using ether as an eluent to give triphenylmethanol (**26**). Further purification by recrystallization from *n*-hexane–ether gave pure **26** (mp 158—160 °C, 0.48 g, 92%) (lit.[24] mp 162.4—162.5 °C). In a similar manner, 1-phenylethanol (bp 100 °C (20 mmHg)) (lit.[20] bp 100 °C (18 mmHg)) was obtained in 93% yield

starting from **17c**.

References and Notes

1) Part of this work has appeared in preliminary form: M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki, and S. Furukawa, *Chem. Pharm. Bull.*, **37**, 2564 (1989).

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