ORGANIC LETTERS

2005
Vol. 7, No. 13
2523–2526

Directed *ortho* Metalation-Based Methodology. Halo-, Nitroso-, and Boro-Induced *ipso*-Desilylation. Link to an *in situ* Suzuki Reaction†

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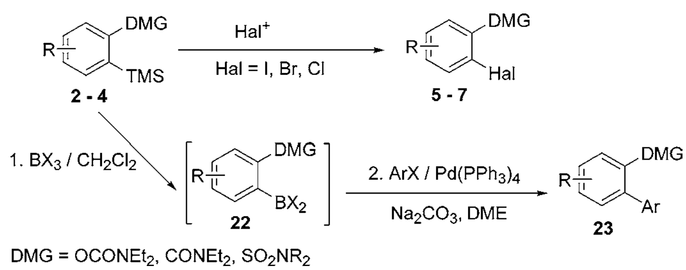
Received March 28, 2005

ABSTRACT



Treatment of DoM-derived silylated aromatics 2–4 under standard electrophilic halogenation conditions cleanly affords *ipso*-desilyation products 5–7, while nitration of methoxy-substituted analogues 8, 9 leads to non-*ipso* isomers 10, 12 and 11, 13, controlled by a silicon steric effect. Sequential *ipso*-borodesilylation of 2a, 3a, and 20 followed by treatment with aryl halides under Pd-catalyzed conditions constitutes an in situ Suzuki–Miyaura cross-coupling protocol to biaryls and heterobiaryls 23.

In the 30 year evolution of modern organosilicon chemistry,[1] during which its rich and broad impact on organic methodology, total synthesis, and industrial applications has been amply demonstrated, the total output of arylsilane chemistry has constituted a minor component[1a] despite the comprehensive and careful physical organic studies of Eaborn[2] and others,[3] which have potentially set a platform for a synthetic playground. A salient feature is marked by kinetic studies that show *ipso*-protodesilyation/proton−deuterium exchange rates[4] $k_{deSi}/k_{H,D} = 10^4$, which stimulated brief studies of other electrophile-induced desilylation reactions.[1a,5] Our longstanding interest[6] and that of others[7] have stimulated an exploratory study of electrophile-induced desilylation reactions for arylsilanes derived by directed ortho metalation

† Dedicated to the memory of Colin Eaborn (1923−2004) in appreciation of his insightful mechanistic work in organosilicon chemistry.

(1) (a) Colvin, E. *Silicon in Organic Synthesis*; Butterworth: New York, 1981; p 125. (b) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (c) Brook, M. *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley: New York, 2000, p 569. (d) Fleming, I. *Science of Synthesis*; Thieme: Stuttgart, 2002; Vol. 4, p 685.

(2) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.

(3) (a) Freiser, H.; Eagle, M. V.; Speier, J. *J. Am. Chem. Soc.* **1953**, *75*, 2821. (b) Bott, R. W.; Eaborn, C.; Greasley, P. M. *J. Chem. Soc.* **1964**, 4804. (c) Berwin, H. J. *Chem. Commun.* **1972**, 237. (d) Al-Omran, F.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1185. (e) Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, *3*, 1629.

(4) Eaborn, C.; Pande, K. C. *J. Chem. Soc.* **1960**, 1566.

(5) (a) Dey, K.; Eaborn, C.; Walton, D. R. M. *Organomet. Chem. Synth.* **1970/1971**, *1*, 151. (b) Felix, G.; Dunoguès, J.; Calas, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 402. (c) Bennetau, B.; Dunoguès, J. *Synlett* **1993**, 171.

(6) (a) Reed, J. N. Ph.D. Thesis, University of Waterloo, Waterloo, Canada, 1984. (b) Mills, R. J.; Horvath, R.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145. (c) Bourguignon, M. L.; Snieckus, V. Unpublished results, University of Waterloo, Waterloo, Canada, 1987. (d) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372. (e) Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508. (f) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662. For an intramolecular carbodesilylation, see: Sibi, M. P.; Shankaran, K.; Alo, B. I.; Hahn, W. R.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 2933.

(7) (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (b) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (c)Yamamoto, Y.; Yanagi, A. *Heterocycles* **1982**, *19*, 168. (d) Effenberger, F.; Krebs, A. *J. Org. Chem.* **1984**, *49*, 4687. (e) Hari, Y.; Shoji, Y.; Aoyama, T. *Synthesis* **2004**, *8*, 1183.

10.1021/ol0506563 CCC: $30.25
Published on Web 05/20/2005

(DoM) protocols. Herein, we report preliminary studies on electrophilic halo-, nitroso-, and boro-induced *ipso*-desilylations (Figure 1, **1**, path a), the steric effect of silicon groups promoting non-*ipso* electrophilic substitution (particularly with $E^+ = NO_2^+$) in the presence of electron-donating groups (EDGs) (**1**, path b), and the conjunction of the borodesilylation procedure (**1**, path a, $E^+ = BX_2^+$)[8,9] with the Suzuki cross-coupling regimen. Considered in sum, these results provide new extensions and opportunities in DoM-mediated, regioselective construction of aromatics and certain complementarity with the direct usage of arylboronic acids for the synthesis of biaryls and heterobiaryls.[10]

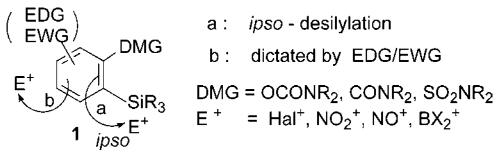
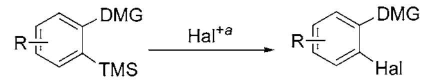


Figure 1.

Results of halo-induced *ipso*-desilylation studies using I^+-, Br^+-, and Cl^+-generating[11] reagents for three prototypical, powerful, and commonly used directed metalation group (DMG)-bearing aromatics **2**−**4** are summarized in Table 1. All substrates show highly regioselective *ipso* reactivity to give products **5**−**7**. In sharp contrast, all of the corresponding nonsilylated derivatives show no reaction, leading to recovery of starting material. As expected, the para-directing effect of the moderate *O*-carbamate EDG is evident at least in iodination and bromination reactions but at higher temperatures.[12]

To obtain initial appreciation of *ipso*-desilylative NO_2^+ reactivity, a series of unsubstituted (**8a**, **9a**), TMS-substituted (**8b**, **9b**) and TIPS-substituted (**8c**, **9c**) benzamides and *O*-carbamates containing the powerful OMe EDG were tested under standard electrophilic nitration conditions.[12,13] As gleaned from Table 2, instead of *ipso*-desilylation, electrophilic nitration occurred, assumably dictated by the OMe group. Synthetically useful trends in nitration selectivity were observed in the series **8b**,**c**, **9b**,**c** to **10b**,**c**, **12b**,**c** conversions although only a minor steric effect was noted in the change from TMS **9b** to TIPS **9c** in the *O*-carbamate series. However, a change of conditions to ammonium nitrate[10a] on the ortho-silylated *O*-carbamate **2a** led to the formation of the corresponding 4-, 2-, and *ipso*-nitro-substituted products, **17**, **18**, and **19**, respectively, in a ratio of 7.5:1.5:1 in quantitative yield (Scheme 1). The observed selectivity may be due to the milder nitration conditions. Furthermore, when nitrosating conditions[14] were adapted to the ortho-silylated *O*-carbamates **2a**, the *ipso* nitroso product **15** was obtained in modest yields in addition to recovered starting material.

Table 1. *ipso*-Halodesilylation Reactions of Compounds **2**−**4**



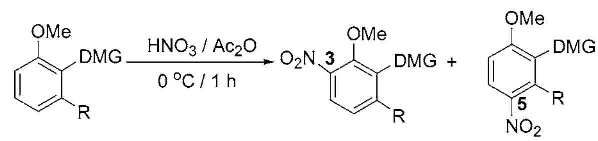
2, 3, 4 **5, 6, 7**

2, 5: DMG = $OCONEt_2$; **3, 6:** DMG = $CONEt_2$; **4, 7:** DMG = SO_2NEt_2

compd	R	hal+/solvent/temp	product	hal	R	yield %
2a	H	ICl/CH_2Cl_2/rt	**5a**	I	H	86
2a	H	Br_2/CH_2Cl_2/0 °C−rt	**5b**	Br	H	92 (82)[b]
2b	4-NO_2	Br_2/CH_2Cl_2/mw[c]	**5c**	Br	4-NO_2	70
2a	H	NCS/MeCN/reflux	**5d**	Cl	H	70
3a	H	ICl/CH_2Cl_2/rt	**6a**	I	H	71
3a	H	Br_2/CH_2Cl_2/reflux	**6b**	Br	H	78
3a	H	NCS/MeCN/mw[d]	**6c**	Cl	H	65
4a	H	ICl/CH_2Cl_2/rt	**7a**	I	H	66
4b	4-Me	ICl/CH_2Cl_2/rt	**7b**	I	4-Me	76
4a	H	Br_2/CH_2Cl_2/reflux	**7c**	Br	H	77
4b	4-Me	Br_2/CH_2Cl_2/reflux	**7d**	Br	4-Me	76[e]
4c	5-Me	Br_2/CH_2Cl_2/reflux	**7e**	Br	5-Me	53
4a	H	NCS/MeCN/mw[d]	**7f**	Cl	H	NR

[a] Hal^+ = 1.5−5 equiv, *t* = 3−15 h. [b] NBS/MeCN/reflux. [c] Microwave: 150 W/25′ min. [d] On SiO_2/250 W/10′ min. [e] See ref 6f.

Table 2. Nitration of Benzamides **8** and *O*-Aryl Carbamates **9**



8, 9 **10, 12** **11, 13**

DMG	R		C3:C5		yield (%)
$CONEt_2$	H	**8a**	1:1	**10a**:**11a**	76[a]
	TMS	**8b**	4:1	**10b**:**11b**	95[a]
	TIPS	**8c**	19:1	**10c**:**11c**	83[b]
$OCONEt_2$	H	**9a**	2:1	**12a**:**13a**	76
	TMS	**9b**	14:1	**12b**:**13b**	82
	TIPS	**9c**	15:1	**12c**:**13c**	78

[a] See ref 6c. [b] See ref 6d.

(8) (a) Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1. (b) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. (c) Kaufmann, D. *Chem. Ber.* **1987**, *120*, 853, 901. (d) Gross, U.; Kaufmann, D. *Chem. Ber.* **1987**, *120*, 991. (e) Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *Chem. Commun.* **1995**, 2523. (f) Fu, J.-m.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 227. (g) Hupe, E.; Calaza, M. I.; Knochel, P. *Chem. Commun.* **2002**, 1390.

(9) Recently, a Merck group has reported an in situ metalation−electrophile quench method that adds convenience to the synthesis of silylated and boronated indole derivatives; see: Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

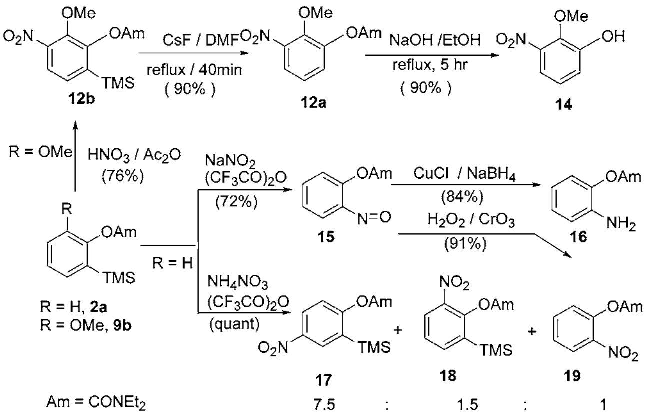
(10) For recent reports of electrophile-induced *ipso*-deboronation studies, see: (a) Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, *10*, 1485. (b) Prakash, G. K. S.; Panja, C.; Mathew, V. S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205.

(11) Chlorination using chlorine was not convenient due to an inability to control amounts of chlorine added, resulting in the formation of some dichlorination (15%) and side products.

(12) For details, see General Procedure in Supporting Information.

(13) (a) Eaborn, C.; Salih, Z. S.; Walton, D. R. M. *J. Chem. Soc.***,** *Perkin Trans. 2* **1972**, 172. (b) Dwyer, C. L.; Holzapfel, W. *Tetrahedron*, **1998**, *54*, 7843.

Scheme 1



These results illustrate advantages for the synthesis of oxidized (**19**) and reduced (**16**) products as well as 1,2,3-contiguously substituted aromatics (**14** from **12b)**, which are difficult to prepare by classical electrophilic chemistry.[15]

While attempts to date in electrophilic fluorination, cyanation, amination, and Friedel−Crafts acylation[16] have been relatively unproductive, *ipso*-borodesilyation has led to useful results (Table 3). Thus, treatment of ortho-silylated DMG aromatics **2a**, **3a**, and **20**, usually cleanly obtained by DoM chemistry, with either BCl_3 or BBr_3 at ambient temperatures followed by derivatization with pinacol[17,18] afforded good to excellent yields of the *ortho*-boronopinacolates **21**.[12] In the carboxamide series, tertiary (entry 1) and secondary amides, including the TFA-labile cumyl amide[19] (entry 2), are successful reactants. 2-Silylated *O*-carbamates (entry 3),[20] a secondary sulfonamide (entry 5), and an indole (entry 6)[9] also furnish pure, usually crystalline, boronated derivatives. Interestingly, the bis-TMS substrate (entry 4) provides the monoborodesilylated product, a result with implications for further *ipso*-desilylative chemistry.

Although the boronopinacolates described in Table 3 are useful Suzuki cross-coupling partners, the development of an in situ *ipso*-borodesilyation−coupling procedure was undertaken for the potential convenient utility in medicinal chemistry and library generation programs. Thus, under mild conditions using either BCl_3 or BBr_3 interchangeably without significant change in yield, substrates **2a**, **3a**, and **20** were converted over a 2 h period into their intermediate dihaloboranes **22**,[8c] which, when treated with aryl bromides or iodides under typical Suzuki−Miyaura coupling conditions, afforded the biaryl or heterobiaryl products **23** (Table 4).[21]

(14) (a) Birkofer, L.; Franz, M. *Chem. Ber.* **1971**, *104*, 3062. (b) Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc*.**,** *Perkin Trans. 1* **1978**, 1076.

(15) For example, nitration of 2-methoxyphenol affords a 1:1 mixture of the 4- and 6-nitro derivatives; see ref 12b.

(16) Various Lewis acid ($AlCl_3$)-catalyzed acylation attempts led to protodesilylation products together with recovery of starting material.

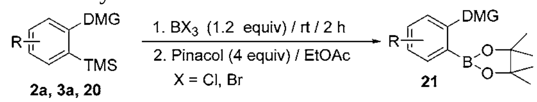
(17) Wong, K.; Chien, Y.; Liao, Y. L.; Lin, C.; Chou, M.; Leung, M. *J. Org. Chem*. **2002**, *67*, 1041.

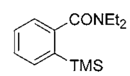
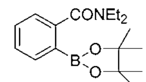
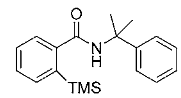
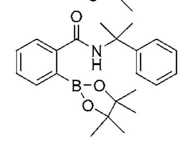
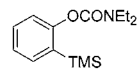
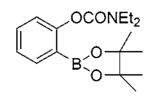
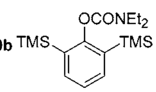
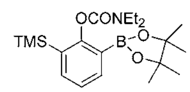
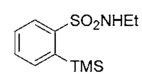
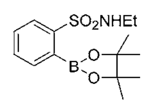
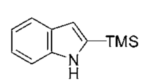
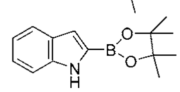
(18) For the preparation of stable diethanolamine adducts of boronic acids, see ref 8b.

(19) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.

(20) For a phenanthrene *O*-carbamate case, see ref 8e.

Table 3. Ortho-DMG-Substituted Arylboronopinacolates **21** by *ipso*-Borodesilylation



entry	arylsilanes		boronic esters		yield (%)[a]
1	**3a**			**21a**	76[b], 100[c,d], 84[e,f]
2	**20a**			**21b**	95[b]
3	**2a**			**21c**	85, 98[c,g], 83[e,f]
4	**20b**			**21d**	89
5	**20c**			**21e**	90[h]
6	**20d**			**21f**	80[i]

[a] Yields of isolated products. [b] Contains pinacol; calculated by NMR. [c] Yields of corresponding arylboronic acids via DoM, which was used directly in the subsequent cross-coupling reactions. [d] Fu, J.-m.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459. [e] Yields of corresponding boroxazine derivatives. [f] Sharp, M. J. M.S. Thesis, University of Waterloo, Waterloo, Canada, 1986. [g] See ref 8b. [h] Performed with 3 equiv of BBr_3 and microwave conditions (50 W/80 °C/30 min). [i] Addition of pinacol and NEt_3 at room temperature for 1.5 h instead of evaporation in a vacuum.

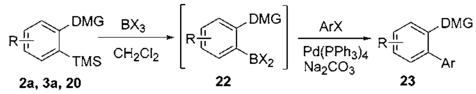
Thus, borono tertiary (entries 1 and 2) and secondary benzamides (entries 3 and 4) afforded clean coupling results with bromobenzene as a partner. Phenyl *O*-carbamates underwent coupling with a range of aryl bromides (entries 5 and 6) and 2-bromonaphthalene (entry 7), as well as 3-bromopyridine (entry 8), to afford synthetically useful yields of biaryl products. A secondary sulfonamide (entry 9) and the 2-TMS, *N*-carbamoyl indole (entries 10 and 11), a useful substance for C-7 DoM chemistry,[22] give coupled products in good yields.

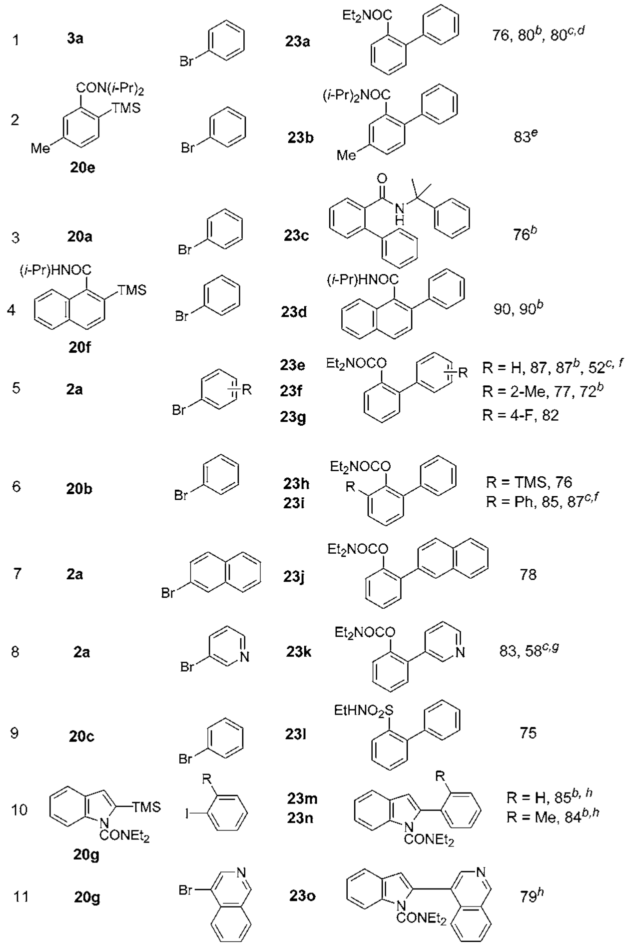
This *ipso*-borodesilylative methodology offers the following features: (a) the starting arylsilanes are stable, readily

(21) **Typical One-Pot *ipso*-Borodesilylation−Cross-Coupling Procedure.** A solution of BBr_3 (1.0 M, 0.48 mL) in CH_2Cl_2 was added dropwise by syringe to a stirred solution of arylsilane (0.4 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h after which time TLC monitoring indicated completion of the reaction. After evaporation to dryness, bromobenzene (0.33 mmol) and $Ph(PPh_3)_4$ (3 mol %) were added, and the whole was degassed for 15 min. Degassed glyme (4 mL) and 2 M Na_2CO_3 solution (1 mL) were added by syringe. The mixture was then heated to reflux for 5 h, cooled to room temperature, and poured into water (10 mL), and the whole was extracted with Et_2O (3 × 10 mL). The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and subjected to filtration, and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:5) to afford the biaryl compound.

(22) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

Table 4. In Situ *ipso*-Borodesilylation and Suzuki Cross-Coupling of Ortho-DMG-Substituted Arylsilanes





entry	arylsilane	aryl halide	product	yield (%)[a,b]
1	3a	Br	23a	76, 80[b], 80[c,d]
2	20e	Br	23b	83[e]
3	20a	Br	23c	76[b]
4	20f	Br	23d	90, 90[b]
5	2a	Br, R	23e 23f 23g	R = H, 87, 87[b], 52[c,f] R = 2-Me, 77, 72[b] R = 4-F, 82
6	20b	Br	23h 23i	R = TMS, 76 R = Ph, 85, 87[c,f]
7	2a	Br	23j	78
8	2a	Br, N	23k	83, 58[c,g]
9	20c	Br	23l	75
10	20g	I, R	23m 23n	R = H, 85[b,h] R = Me, 84[b,h]
11	20g	Br, N	23o	79[h]

[a] Yields of isolated products using ArBr coupling partners. [b] Yields of isolated products using ArI coupling partners. [c] Yields obtained by direct coupling with boronic acids. [d] Fu, J.-m. Ph.D Thesis, University of Waterloo, Waterloo, Canada, 1990. [e] Performed with 1.5 mol % $Pd(PPh_3)_4$. [f] See ref 8b. [g] See Table 3, footnote f. [h] BBr_3 was added at −25 °C, and the reaction mixture was stirred at this temperature for 1 h.

purified (chromatography, crystallization), and obtained by clean, high-yielding DoM reactions under conditions (e.g., Martin conditions[7a,b]) not requiring −78 °C[9] and hence amenable to scale-up; (b) since *ipso*-borodesilyations proceed quantitatively, as evidenced by high yields of isolated boronopinacolates, the uncertainty associated with the boron intermediates (boronic acid, half-ester acid, borinic acid, boroxane) obtained by direct treatment with $B(OR)_3$ electrophiles,[23] as also reflected in product yields, is eliminated; (c) in contrast to the coupling reactions of the boronic acid derivatives, those of the solutions of the intermediate dihaloboranes proceed under homogeneous conditions and involve simple evaporative rather than acidic or aqueous workup to give comparable yields of products (Table 4); and (d) although requiring an extra step for the preparation of the silanes, the *ipso*-borodesilyation reaction constitutes a general and efficient route to stable arylboronates (Table 3).

In summary, preliminary results of electrophile-induced *ipso*-desilylation chemistry have shown that (a) facile halo- and nitroso-induced *ipso* reactions proceed on simple DMG-bearing substrates (**2**−**4** and **2a**, respectively), (b) nitration conditions lead to non-*ipso* but substitution products **10b** and **12b**, which can be converted to synthetically useful 1,2,3-substituted aromatics, e.g., **14**, and (c) *ipso*-borodesilylation provides[24] a method for the convenient synthesis of pure boronopinacolates **21** (Table 3) and also serves as part of a DoM-initiated method for an in situ Suzuki cross-coupling synthetic protocol for biaryls and heterobiaryls (Table 4). Mechanistic and further preparative studies are in progress.

Acknowledgment. NSERC Canada is warmly acknowledged for consistent support of our synthetic programs. Z.Z.D. is grateful for an R.S. McLaughlin Fellowship. We thank Justin Morin for providing some starting materials.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0506563

(23) For other stable pyridyl boronates that participate in cross-coupling, see: Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. For a review on heterocyclic boronic acids, see: Tyrrell, E.; Brookes, P. *Synthesis* **2003**, *4*, 469.

(24) Fluoride-mediated carbodesilylation is another synthetically useful E^+-induced FG transfer reaction of arylsilanes; see refs 6b and 7d and: Effenberger, F.; Spiegler, W. *Chem. Ber*. **1985**, *118*, 3900. For *ipso*-cyanodesilylation, see: (a) Bennetau, B.; Dunoguès, J.; Babin, P. *Tetrahedron* **1993**, *49*, 10843. (b) Calle, M.; Cuadrado, P.; Gonzalez-Nogal, A. M.; Valero, R. *Synthesis* **2001**, 1949.