JOC *Note*

Single and Double Suzuki−Miyaura Couplings with Symmetric Dihalobenzenes

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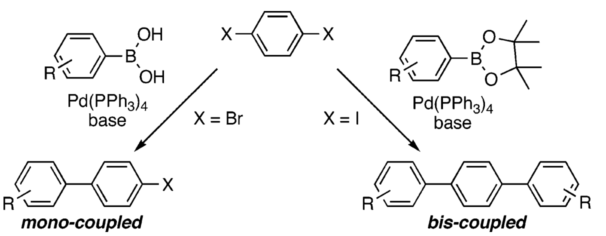
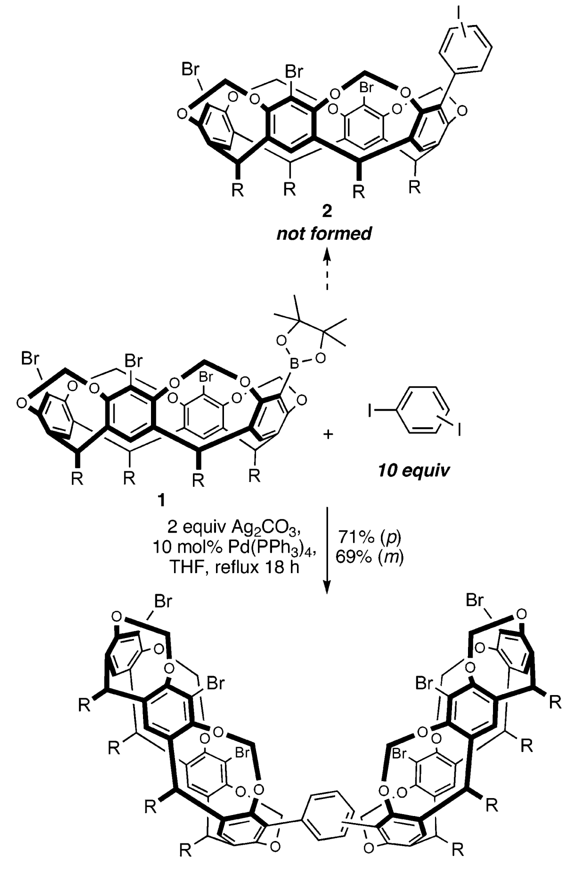


m- or *p*-diiodobenzene undergoes selective double coupling reactions with arylboronic acids and esters. Selectivity for double coupling over single coupling is remarkably strong: even with a diiodobenzene:monoboronic acid ratio of 10:1, the products of double coupling are formed in good yields. Steric hindrance and electronic influences of the boronic acid or ester, and reaction conditions do not appear to impact significantly upon the outcome of the reaction. In contrast, *m*- and *p*-dibromobenzenes undergo single couplings with aryl boronic acids with high selectivity.

The Suzuki−Miyaura cross-coupling reaction is one of the most widely used transformations in synthesis.[1] Many examples involving di- and trihaloaromatic precursors have been reported.[2] The most common outcome of such reactions is exhaustive multiple coupling, and often an excess of the boronic acid or ester coupling partner is employed to drive the reaction to completion. A significant number of reports of selective single couplings with di- or trihaloaromatics have, however, also been reported. These latter examples employ a low molar ratio of monoboronic acids:polyhalobenzenes to encourage single couplings.[3] In sharp contrast to this general pattern, during an attempt to obtain monocoupled products **2** by reacting cavitand boronic ester **1** with 10 molar equiv of *m*- or *p*-diiodobenzene, we were surprised to obtain only the double coupled product **3** (Scheme 1).[4] Single coupling of cavitand boronic ester **1** was readily achieved by using the unsymmetrical coupling partner, *m*- or *p*-bromoiodobenzene, a well-established method for such conversions.[5] Nevertheless, we were intrigued by the results depicted in Scheme 1 and this Note describes the results of our investigations in this regard.

SCHEME 1



A survey of the literature uncovered three isolated reports of related “counter-statistical” outcomes in Pd-catalyzed coupling reactions of *p*-diiodobenzene,[6] and one

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[1] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 49−97. (c) Miyaura, N. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, UK, 1998; Vol. 6, pp 187−243. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (e) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83−90. (f) de Miejere, A.; von Zezschwitz, P.; Nüske, H.; Stulgies, B. *J. Organomet. Chem.* **2002**, *653*, 129−140. (g) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (h) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (i) Suzuki, A. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley/Interscience: New York, 2002; pp 249−262. (j) Miyaura, N. *Metal-Catalysed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 41−123.

[2] According to SciFinder Scholar, 278 papers containing Suzuki−Miyaura couplings of polyhaloaromatics (including pseudohalides and heteroaromatics) have been published between 1986 and 2004, with just over three-quarters (216) published in the last five years.

[3] Examples of multiple couplings were reported in 139 papers, regioselective monocouplings of unsymmetrical substrates in 34 papers, and monocouplings of symmetrical substrates in 37.

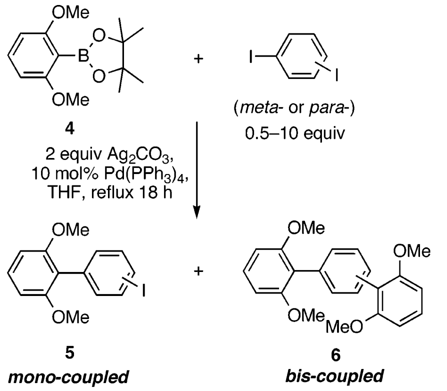
[4] Seitzberg, J. G.; Sinclair, D. J.; Sherburn, M. S. Manuscript in preparation.

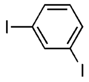
[5] (a) Unrau, C. M.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2773−2776. (b) Wong, K.-T.; Hung, T. S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.-M.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513−516. (c) Bo, Z.; Schlueter, A. D. *J. Org. Chem.* **2002**, *67*, 5327−5332. (d) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179−13184. (e) Greenfield, A. A.; Butera, J. A.; Caufield, C. E. *Tetrahedron Lett.* **2003**, *44*, 2729−2732. (f) Simoni, D.; Giannini, G.; Baraldi, P. G.; Romagnoli, R.; Roberti, M.; Rondanin, R.; Baruchello, R.; Grisolia, G.; Rossi, M.; Mirizzi, D.; Invidiata, F. P.; Grimaudo, S.; Tolomeo, M. *Tetrahedron Lett.* **2003**, *44*, 3005−3008. (g) Sailer, M.; Gropeanu, R.-A.; Mueller, T. J. J. *J. Org. Chem.* **2003**, *68*, 7509−7512.

[6] (a) Bunz, U. H. F.; Roidl, G.; Adams, R. D. *J. Organomet. Chem.* **2000**, *600*, 56−62. (b) Tsvetkov, A. V.; Latyshev, G. V.; Lukashev, N. V.; Beletskaya, I. P. *Tetrahedron Lett.* **2000**, *41*, 3987−3990. (c) Tietze, L. F.; Nordmann, G. *Synlett* **2001**, 337−340.

10.1021/jo050105q CCC: $30.25

TABLE 1



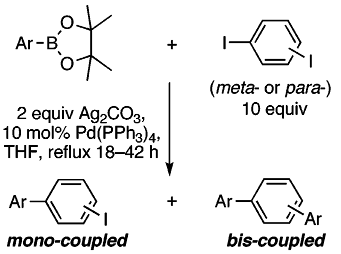
	product ratio (**5**:**6**)	
diiodide (equiv)		
0.5	0:100[a]	0:100[a]
1	10:90[b]	20:80[b]
2	18:82[b]	29:71[b]
5	20:80[a]	31:69[b]
10	26:74[a]	35:65[a]

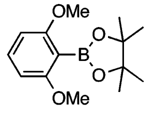
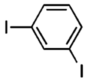
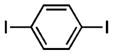
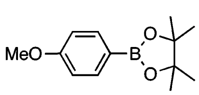
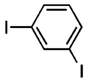
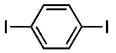
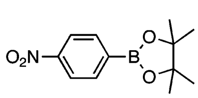
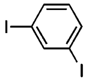
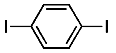
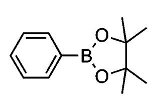
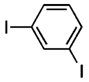
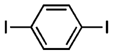
[a] Average of three runs. [b] Average of two runs (maximum variation of ±5%, most entries ±1%).

involving di- and trihalopyrimidines.[7] Whereas authors have expressed their surprise with these results,[6c] none report a detailed investigation into this unusual behavior. To study the impact of various parameters upon this transformation, we employed a simple model compound for cavitand boronic ester **1**, namely 2,6-dimethoxyphenylboronic pinacol ester **4**. The ratio of boronic ester: diiodobenzene was progressively decreased (2:1 → 1:10) and the ratio of mono- to biscoupling was determined by HPLC analysis, following the complete conversion of **4** (Table 1). While the amount of monocoupled product increases as a function of available diiodide, bis-coupling is still strongly favored, even with a 10-fold excess of the diiodide. Interestingly, an increase in available diiodobenzene has a slightly stronger impact upon the product ratio in the para series than in the meta series.[8]

To determine whether this unexpected preference for double coupling was a function of the electronic and/or steric requirements of boronic esters **1** and **4**, four different aryl boronic esters were treated with large excesses (10 equiv) of both *p*- and *m*-diiodobenzene under the usual reaction conditions (Table 2).

TABLE 2



boronic ester	dihalide	yield[a] (%)	mono:bis
 **4**		91	31:69
		86	35:65
 **7**		100	20:80
		96	17:83
 **8**		92	17:83
		63[b]	25:75
 **9**		100	21:79
		80	25:75

[a] Isolated yield based upon boronic ester. [b] Low yield due to product decomposition on silica.

For each aryl boronic ester substrate examined, regardless of the aromatic substituent location and type, the major products resulted from double coupling. While the number of substrates examined is not large, these results show that electron rich (**4**, **7**), electron poor (**8**), electronically neutral (**9**), sterically hindered (**4**), and unhindered (**7**, **8**, **9**) aromatic boronic esters all exhibit essentially the same reactivity pattern.

The reaction conditions used throughout this study, involving silver carbonate and an aprotic medium as reported by Chaumeil,[9] were found to be optimal for coupling reactions of cavitand boronic ester **1**. Attempted couplings of the boronic acid analogue of **1** were accompanied by the formation of varying amounts of the protiodeboronylation product—a common side reaction with ortho-substituted boronic acids[10]—under a variety of different reaction conditions. Aprotic conditions are somewhat unusual for Suzuki–Miyaura couplings but the presence of silver(I) salts has been shown to have an advantageous effect upon several such reactions.[11] Nevertheless, we suspected that either the reaction conditions or the use of boronic esters might be the origin of the double coupling. Cram reported a 50% yield of the product of monocoupling between 2,6-dimethoxyphenyl-

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[7] Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128.

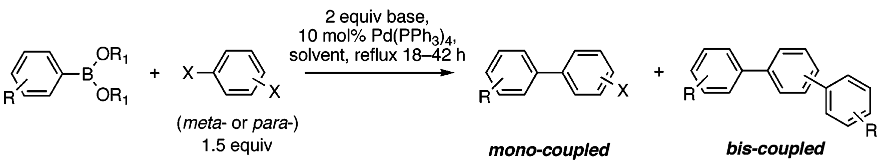
[8] This pattern is not followed in reactions between a 1:1 (or 10:1) ratio of *o*-diiodobenzene and boronic ester **4** under the same conditions, which instead gave the monocoupled product in 70% (or 60%) isolated yield. We speculate that steric hindrance inhibits the second oxidative addition step in the ortho series.

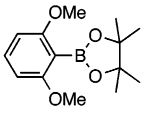
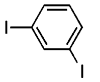
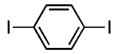
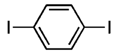
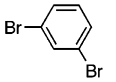
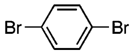
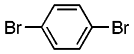
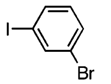
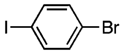
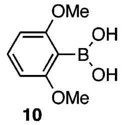
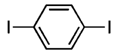
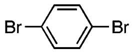
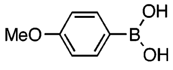
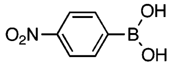
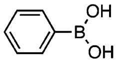
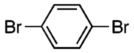
[9] Chaumeil, H.; Le Drian, C.; Defoin, A. *Synthesis* **2002**, 757–760.

[10] Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666–2670.

[11] (a) Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758. (b) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468–10477. (c) Chen, H.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 4444–4446. (d) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213–7215. (e) Chen, J.; Cammers-Goodwin, A. *Tetrahedron Lett.* **2003**, *44*, 1503–1506.

TABLE 3



entry	organoboron	dihalide	base/solvent	yield[a] (%)	product ratio mono:bis
1	 **4**		Ag_2CO_3/THF	96	15:85
2			Ag_2CO_3/THF	94	16:84
3			Cs_2CO_3/toluene/MeOH	96	15:85
4			Ag_2CO_3/THF	90	58:42
5			Ag_2CO_3/THF	94	57:43
6			Cs_2CO_3/toluene/MeOH	56	55:45
7			Ag_2CO_3/THF	95	91:9
8			Ag_2CO_3/THF	97	97:3
9	 **10**		Cs_2CO_3/toluene/MeOH	84	30:70
10			Cs_2CO_3/toluene/MeOH	81	88:12
11	 **11**		Cs_2CO_3/toluene/MeOH	85	82:18
12	 **12**		Cs_2CO_3/toluene/MeOH	70	59:41
13				81	89:11[b]
14	 **13**		Cs_2CO_3/toluene/MeOH	86	69:31
15				99	95:5[b]

[a] Isolated yield based upon organoboron starting material. [b] Reaction carried out with 10 molar equiv of dibromide.

boronic acid and 1.5 molar equiv of *p*-dibromobenzene using $Pd(PPh_3)_4$ catalyst and cesium carbonate as base in toluene/methanol, with no mention of biscoupling.[12] To determine whether this difference in selectivity was due to the conditions (silver carbonate/THF vs cesium carbonate/toluene/methanol) or the substrates (boronic ester vs boronic acid, and diiodide vs dibromide), a final series of coupling reactions was carried out (Table 3). The results of these experiments clearly demonstrate that reaction conditions have no effect on the monocoupling: biscoupling selectivity (compare entries 2 vs 3; 5 vs 6). The outcome is clearly influenced, however, by both the nature of the boron-containing species and the dihalide. Monocoupling is more pronounced in boronic acids than in their pinacolate ester derivatives (compare entries 9 vs 3; 10 vs 6); however, the identity of the halogen is the major factor in determining selectivity, with biscoupling being favored in reactions with diiodobenzenes and monocoupling with dibromobenzenes (compare entries 1 vs 4; 2 vs 5; 3 vs 6; 9 vs 10).[13]

These results show that diiodobenzenes are the best choice of electrophile if double coupling is desired, whereas selective single coupling can be obtained through reactions of dibromobenzenes with arylboronic acids (entries 10−15). The selectivity witnessed for these latter transformations approaches that seen with the considerably more expensive[14] bromoiodobenzenes (entries 7 and 8).[5]

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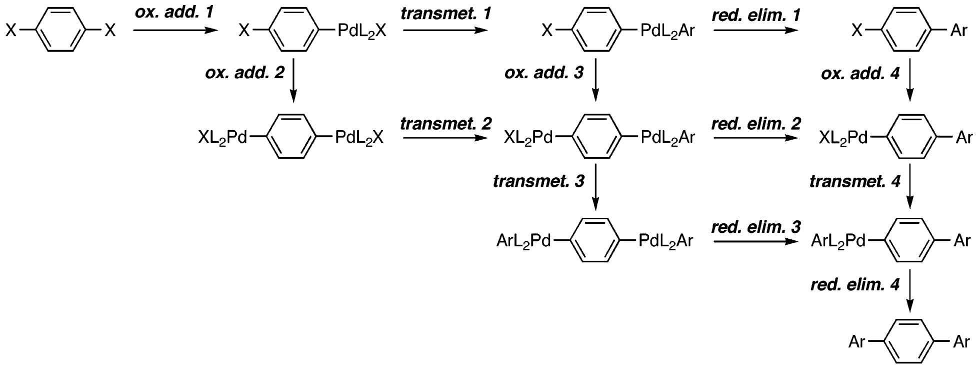
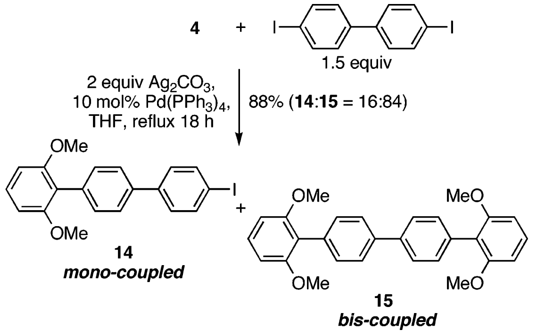
[12] (a) von dem Bussche-Hünnefeld, C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1085−1087. (b) von dem Bussche-Hünnefeld, C.; Helgeson, R. C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *Croat. Chim. Acta* **1996**, *69*, 447−458.

[13] In light of this result, it is interesting to note that of the 37 monocouplings of symmetrical substrates mentioned in ref 3, none were with diiodides.

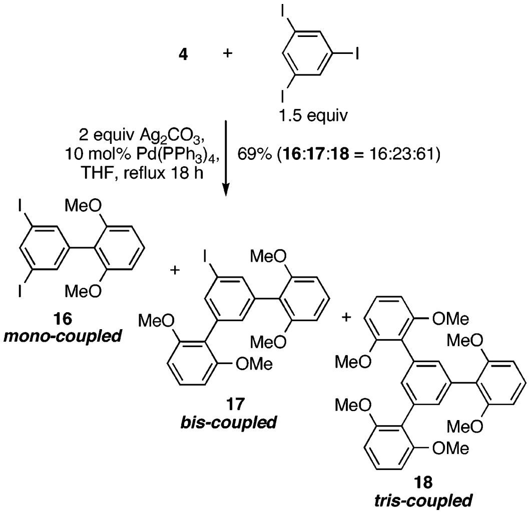
SCHEME 2



SCHEME 3



SCHEME 4



Attempts to explain the reactivity of dihalobenzenes in terms of the relative coupling rates of dihalobenzenes and halobiaryls proved unsatisfactory, with simple competition experiments providing conflicting results. Each Ar−*X* → Ar−*Ar* transformation requires three steps: oxidative addition, transmetalation, and reductive elimination, therefore a double coupling reaction proceeds through six discrete steps. Five different pathways from starting material to double-coupled product are possible and only the first and last steps are known (Scheme 2). We speculate that the difference in reactivity between dibromides and diiodides stems from the first branch point in the mechanistic pathway: *ox. add. 2* successfully competes with *transmet. 1* for diiodobenzenes, favoring double coupling,[15] whereas a slower oxidative addition step for the bromide leads to more transmetalation and thus more monocoupling. The complexity of the mechanism is such that confirmation of this proposal must await a thorough investigation.

Nevertheless, selective multiple couplings appear to be a general trait for di- and triiodoaryls, as exemplified by the results of couplings between pinacolyl 2,6-dimethoxyphenylboronate and both 4,4′-diiodibiphenyl (Scheme 3) and 1,3,5-triiodobenzene (Scheme 4).[16]

Experimental Section

Representative Procedure for the Suzuki−Miyaura Couplings. An oven-dried round-bottomed flask and condenser were placed under a nitrogen atmosphere and charged with pinacolyl 2,6-dimethoxyphenylboronate (**4**; 100 mg, 0.38 mmol), *p*-diiodobenzene (1.25 g, 3.8 mmol), silver(I) carbonate (209 mg, 0.76 mmol), and tetrakis(triphenylphosphine)palladium (44 mg, 38 μmol). The flask was evacuated and re-filled with nitrogen three times, then tetrahydrofuran (5 mL) was added and the reaction mixture was heated to reflux for 18 h. When the reaction was complete, inorganic solids were removed by filtration through Celite and washing with several portions of dichloromethane, then the solvent was evaporated. The residue was absorbed onto silica then subjected to flash chromatography (0 → 100% dichloromethane/hexane) giving 2,6-dimethoxy-4′-iodobiphenyl (**5**-*para*; 38 mg, 30%) followed by 2,2″,6,6″-tetramethoxy-1,1′:4′,1"-terphenyl (**6**-*para*; 37 mg, 56%).

Supporting Information Available: Characterization data, including ^{1}H and ^{13}C NMR spectra, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Bromo-4-iodobenzene is 28 times more expensive per mole than 1,4-dibromobenzene, based upon 2004 catalogue prices for 25 and 500 g pack sizes, respectively.

[15] While the preparation of 4-iodophenylbis(triphenylphosphine)-palladium iodide has been reported, a lack of experimental detail prevents any conclusions being drawn regarding the ease of a second palladation reaction. (a) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576−8581. (b) Vicente, J.; Lyakhovych, M.; Bautista, D.; Jones, P. G. *Organometallics* **2001**, *20*, 4695−4699.

[16] Selective single couplings of 1,3,5-tribromobenzene have been reported: (a) Manabe, K.; Okamura, K.; Date, T.; Koga, K. *J. Org. Chem.* **1993**, *58*, 6692−6700. (b) Caneschi, A.; Dei, A.; Mussari, C. P.; Shultz, D. A.; Sorace, L.; Vostrikova, K. E. *Inorg. Chem.* **2002**, *41*, 1086−1092. (c) Grilli, S.; Lunazzi, L.; Mazzanti, A.; Pinamonti, M. *J. Org. Chem.* **2002**, *67*, 5733−5738.