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Arylboronic Acids and Arylpinacolboronate Esters in Suzuki Coupling Reactions Involving Indoles. Partner Role Swapping and Heterocycle Protection

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Yields of Suzuki couplings involving indoles depended upon (i) whether arylboronic acids or arylpinacolboronate esters were used, (ii) whether the heterocycle was the aryl halide or the arylboron coupling partner, and (iii) whether the heterocycle was protected or not. Highest yields, which were unaffected by incorporating Boc or Tos protection at the heterocyclic nitrogen, were obtained when indole bromides were reacted with phenylboronic acids. When indolylboronic acids were reacted with phenyl bromides, yields were somewhat lower and depended on the nitrogen substituent, being highest in the absence of protection, lower in the presence of the Boc group, and lowest of all with the Tos group. Arylpinacolboronate esters were less reactive than arylboronic acids. They required considerably longer reaction times and furnished generally lower yields of biaryl. Furthermore, irrespective of whether the heterocycle was the aryl bromide or the arylpinacolboronate ester, these yields were highest when it was protected with the Tos group. Yields were lower with the Boc group, and unprotected heterocycles gave only traces of biaryl. Careful selection of arylboron reagent, of coupling partner roles, and of protecting groups are essential to ensuring optimum results in these Suzuki couplings. These results may also be relevant to couplings involving other substrates.

Introduction

The Suzuki coupling reaction[1−6] has, over the past decade or so, established itself as a powerful method for the formation of carbon−carbon bonds, especially those involving sp^2-hybridized centers. It has, consequently, been widely applied in the formation of biaryl compounds where it usually involves the Pd(0)-mediated linking of an aryl halide with an arylboronic acid or arylboronate ester. The mechanism by which it proceeds is known to be complex in its details,[7−10] and the oxidative addition,[2,6,11] transmetalation,[12,13] and reductive elimination[14] steps have all been reported to be rate-determining in certain cases. Nonetheless, there is broad consensus that the main stages involved are those shown in Scheme 1.

Extensive investigation has allowed the performance of different palladium salts, ligands, bases and solvent systems to be evaluated and optimized.[3−6,15] Nevertheless, the reaction is still not fully understood and much remains to be clarified. Although both arylboronic acids and arylboronate esters can be used as reagents, no systematic comparative study of their performance has, to our knowledge, been reported. This is surprising since we have found that the choice of arylboron reagent may profoundly affect the outcome of a given coupling reaction, particularly since it usually determines the selection of other key reaction parameters such as solvent, base, and palladium(0) source. In contemporary practice, Suzuki couplings often employ widely differing reaction chemistries depending upon whether arylboronic acids or arylboronate esters are used as reagents. The decision of which to adopt may be crucial to success.

All other factors being equal, best results are usually obtained when the aryl halide coupling partner is electron-deficient and the arylboron partner electron-rich, a situation that favors oxidative addition and transmeta-

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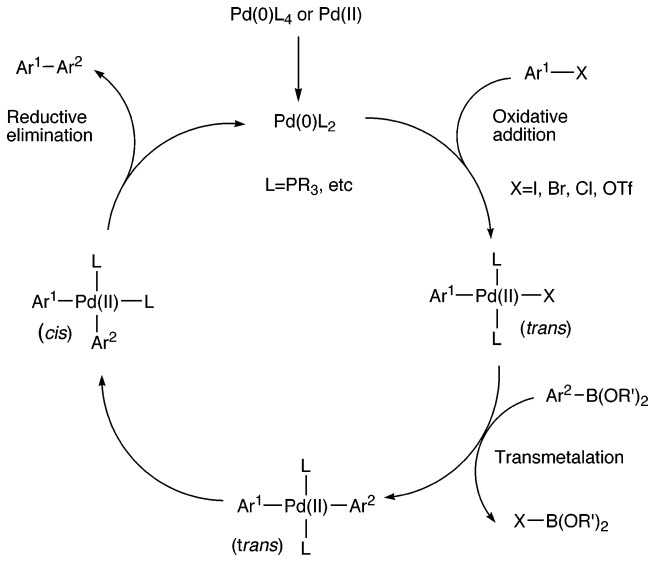
SCHEME 1



lation, respectively.[6] However, with complex, polyfunctionalized substrates it may not always be easy to judge which ring should be which component. Alternatively, tactical considerations may require that a particular coupling reaction be carried out with the coupling partner roles inverted or swapped with respect to those that are a priori desirable. The outcome of a given coupling may be significantly affected by the assignment of partner roles.

The indole ring is a key substructure in both organic and medicinal chemistry,[16,17] and a number of studies document its arylation as a starting-point for further elaboration.[18−26] We were interested in carrying out Suzuki couplings between 5-, 6- and 7-substituted indole[27−30] derivatives **1** and simple phenyl compounds **2** (see Scheme 2) with a view toward optimizing reaction conditions and yields. Although isolated examples of similar Suzuki couplings have been reported,[24−26] we wished to carry out a more extensive and systematic study that would allow us to evaluate the effect on biaryl coupling yields of:

(1) The use of arylboronate esters as an alternative to arylboronic acids. More specifically, we were interested in comparing the performances of arylboronic acids and pinacol-derived arylboronate esters.

(2) Swapping the partner roles, such that couplings in which the heterocycle functioned as the aryl halide might be compared with those in which it functioned as the arylboron derivative.

(3) Protection at the heterocyclic nitrogen atom, which also provides a means whereby the consequences of modulation of the electronic character of the heterocycle may be explored. In particular, we wished to compare the behavior of substrates lacking protection at this atom with those in which it was afforded by the Boc or the Tos group,[31−33] both commonly used in peptide synthesis involving tryptophan.[34]

To investigate these issues we carried out four series of Suzuki couplings using the following combinations of partners: (i) indole bromides and phenylboronic acids, (ii) indolylboronic acids and phenyl bromides, (iii) indole bromides and phenylpinacolboronate esters, and (iv) indolylpinacolboronate esters and phenyl bromides (see Scheme 2). Here we report the results of this study, which supplement and extend earlier work in this area and which may have a wider relevance to couplings involving other substrates.

Results and Discussion

All Suzuki chemistry was carried out using aryl bromides since they are inexpensive and easily prepared. They are somewhat less reactive than the more expensive aryl iodides but considerably more reactive than the corresponding aryl chlorides. A given series of couplings was carried out under similar reaction conditions with regard to stoichiometry, catalyst batch, solvent composition, concentration, reaction time, and temperature. For the series employing arylboronic acids, $Pd(Ph_3P)_4$ was used as the catalyst, Na_2CO_3 as the base, and a mixture of toluene−EtOH−H_2O as the solvent. For the series employing arylboronate esters, $PdCl_2$(dppf) was used as the Pd(0) source, K_3PO_4 as the base, and 1,4-dioxane as the solvent. These conditions reflect typical current practice for these chemistries. Each reaction was performed at least twice and repeated as necessary to establish yield reproducibility.

1. Suzuki Couplings Using Arylboronic Acids: (a) Reactions of Indole Bromides with Phenylboronic Acids. Couplings between indole bromides (**1a**−**g**, X^1 = 5-, 6-, or 7-Br, R^1 = H, Boc, or Tos) and commercially available substituted phenylboronic acids [**2a**−**d**, X^2 = $B(OH)_2$, R^2 = 4-Me, 4-OMe, 2-Me, or 2-OMe] all occurred in good to excellent yield (66−99%) (Table 1, entries 1−20). Although this range is perhaps wider than anticipated, and possibly indicates a certain degree of irreproducibility in the chemistry, certain general trends can, nevertheless, still be discerned. First, as might be expected, the position of the bromine atom in the indoles

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SCHEME 2

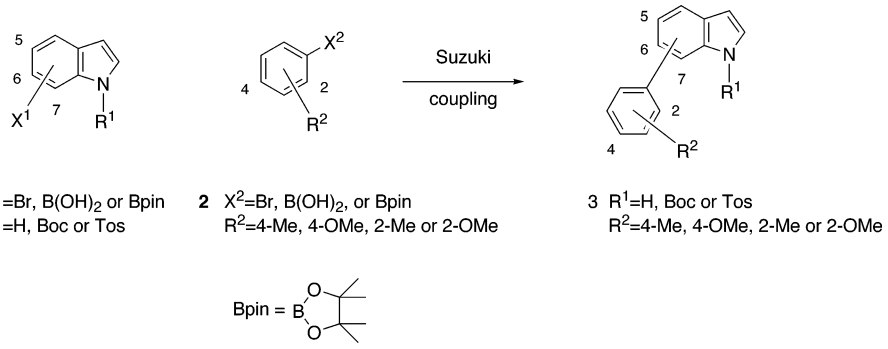

TABLE 1. Suzuki Couplings between Indoles and Phenyl Derivatives Using Arylboronic Acids

entry	aryl bromide	arylboronic acid	biaryl yield[a] (%)
1	**1a**, X^1 = 5-Br, R^1 = H	**2a**, X^2 = $B(OH)_2$, R^2 = 4-Me	**3a**, 97
2	**1a**, X^1 = 5-Br, R^1 = H	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3b**, 85
3	**1a**, X^1 = 5-Br, R^1 = H	**2c**, X^2 = $B(OH)_2$, R^2 = 2-Me	**3c**, 99
4	**1a**, X^1 = 5-Br, R^1 = H	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3d**, 91
5	**1b**, X^1 = 6-Br, R^1 = H	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3e**, 76
6	**1b**, X^1 = 6-Br, R^1 = H	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3f**, 80
7	**1c**, X^1 = 7-Br, R^1 = H	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3g**, 67
8	**1c**, X^1 = 7-Br, R^1 = H	**2d** X^2 = $B(OH)_2$, R^2 = 2-OMe	**3h**, 66
9	**1d**, X^1 = 5-Br, R^1 = Boc	**2a**, X^2 = $B(OH)_2$, R^2 = 4-Me	**3i**, 79
10	**1d**, X^1 = 5-Br, R^1 = Boc	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3j**, 70
11	**1d**, X^1 = 5-Br, R^1 = Boc	**2c**, X^2 = $B(OH)_2$, R^2 = 2-Me	**3k**, 99
12	**1d**, X^1 = 5-Br, R^1 = Boc	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3l**, 94
13	**1e**, X^1 = 6-Br, R^1 = Boc	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3m**, 67
14	**1e**, X^1 = 6-Br, R^1 = Boc	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3n**, 84
15	**1f**, X^1 = 5-Br, R^1 = Tos	**2a**, X^2 = $B(OH)_2$, R^2 = 4-Me	**3o**, 70
16	**1f**, X^1 = 5-Br, R^1 = Tos	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3p**, 93
17	**1f**, X^1 = 5-Br, R^1 = Tos	**2c**, X^2 = $B(OH)_2$, R^2 = 2-Me	**3q**, 74
18	**1f**, X^1 = 5-Br, R^1 = Tos	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3r**, 97
19	**1g**, X^1 = 6-Br, R^1 = Tos	**2b**, X^2 = $B(OH)_2$, R^2 = 4-OMe	**3s**, 80
20	**1g**, X^1 = 6-Br, R^1 = Tos	**2d**, X^2 = $B(OH)_2$, R^2 = 2-OMe	**3t**, 89
21	**2e**, X^2 = Br, R^2 = 4-Me	**1h**, X^1 = 5-$B(OH)_2$, R^1 = H	**3a**, 65
22	**2f**, X^2 = Br, R^2 = 4-OMe	**1h**, X^1 = 5-$B(OH)_2$, R^1 = H	**3b**, 80
23	**2g**, X^2 = Br, R^2 = 2-Me	**1h**, X^1 = 5-$B(OH)_2$, R^1 = H	**3c**, 60
24	**2h**, X^2 = Br, R^2 = 2-OMe	**1h**, X^1 = 5-$B(OH)_2$, R^1 = H	**3d**, 94
25	**2f**, X^2 = Br, R^2 = 4-OMe	**1i**, X^1 = 6-$B(OH)_2$, R^1 = H	**3e**, 75
26	**2h**, X^2 = Br, R^2 = 2-OMe	**1i**, X^1 = 6-$B(OH)_2$, R^1 = H	**3f**, 65
27	**2f**, X^2 = Br, R^2 = 4-OMe	**1j** X^1 = 7-$B(OH)_2$, R^1 = H	**3g**, 52
28	**2h**, X^2 = Br-, R^2 = 2-OMe	**1j**, X^1 = 7-$B(OH)_2$, R^1 = H	**3h**, 87
29	**2e**, X^2 = Br, R^2 = 4-Me	**1k**, X^1 = 5-$B(OH)_2$, R^1 = Boc	**3i**, 34
30	**2f**, X^2 = Br, R^2 = 4-OMe	**1k**, X^1 = 5-$B(OH)_2$, R^1 = Boc	**3j**, 50
31	**2g**, X^2 = Br, R^2 = 2-Me	**1k**, X^1 = 5-$B(OH)_2$, R^1 = Boc	**3k**, 18
32	**2h**, X^2 = Br, R^2 = 2-OMe	**1k**, X^1 = 5-$B(OH)_2$, R^1 = Boc	**3l**, 8
33	**2f**, X^2 = Br, R^2 = 4-OMe	**1l**, X^1 = 5-$B(OH)_2$, R^1 = Tos	**3p**, 10
34	**2h**, X^2 = Br, R^2 = 2-OMe	**1l**, X^1 = 5-$B(OH)_2$, R^1 = Tos	**3r**, traces[b]

[a] All yields refer to isolated products after column chromatography on silica gel. [b] Product only detected by mass spectrometry of the reaction crudes.

studied has little influence on the yield. Second, the effect of increased steric hindrance in the phenylboronic acid, occasioned by the presence of an ortho substituent, is negligible. Third, yields were not significantly affected by whether the heterocyclic nitrogen was protected or not. These results are in line with expectations and indicative of optimal choices both in the partner roles and in the reaction conditions used.

(b) Reactions of Indolylboronic Acids with Phenyl Bromides. Swapping the chemical roles of the coupling partners required the synthesis of indolylboronic acids[35] [**1h**−**l**, X^1 = 5-, 6-, or 7-$B(OH)_2$, R^1 = H, Boc, or Tos] from the corresponding indole bromides (**1a**−**d**,**f**, X^1 = 5-, 6-, or 7-Br, R^1 = H, Boc, or Tos). This was done using previously reported methods.[6,24,27] However, since we found that satisfactory purification and characterization of the required indolylboronic acids was not easy to accomplish, and since others[2] have commented on the difficulties of preparating and isolating of boronic acids in a pure state, we used the crude products directly. The possibility that impurities might affect the yields for this series of couplings cannot be discounted, but we have no evidence that this is the case.

In Suzuki couplings with substituted phenyl bromides (**2e**−**h**, X^2 = Br, R^2 = 2-Me, 4-Me, 2-OMe, or 4-OMe), yields showed effectively no dependence on the position of the boronic acid group within the indole. Neither was the effect of increased steric hindrance in ortho-substituted phenyl bromides appreciable in those cou-

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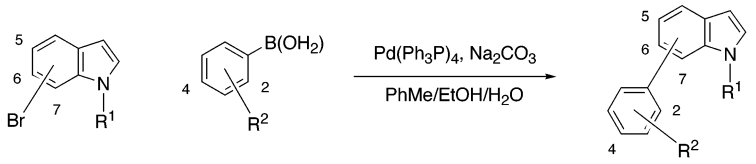
SCHEME 3



1a 5-Br, R^1=H
1b 6-Br, R^1=H
1c 7-Br, R^1=H
1d 5-Br, R^1=Boc
1e 6-Br, R^1=Boc
1f 5-Br, R^1=Tos
1g 6-Br, R^1=Tos

2a R^2=4-Me
2b R^2=4-OMe
2c R^2=2-Me
2d R^2=2-OMe

3a indol-5-yl, R^1=H, R^2=4-Me
3b indol-5-yl, R^1=H, R^2=4-OMe
3c indol-5-yl, R^1=H, R^2=2-Me
3d indol-5-yl, R^1=H, R^2=2-OMe
3e indol-6-yl, R^1=H, R^2=4-OMe
3f indol-6-yl, R^1=H, R^2=2-OMe
3g indol-7-yl, R^1=H, R^2=4-OMe
3h indol-7-yl, R^1=H, R^2=2-OMe
3i indol-5-yl, R^1=Boc, R^2=4-Me
3j indol-5-yl, R^1=Boc, R^2=4-OMe
3k indol-5-yl, R^1=Boc, R^2=2-Me
3l indol-5-yl, R^1=Boc, R^2=2-OMe
3m indol-6-yl, R^1=Boc, R^2=4-OMe
3n indol-6-yl, R^1=Boc, R^2=2-OMe
3o indol-5-yl, R^1=Tos, R^2=4-Me
3p indol-5-yl, R^1=Tos, R^2=4-OMe
3q indol-5-yl, R^1=Tos, R^2=2-Me
3r indol-5-yl, R^1=Tos, R^2=2-OMe
3s indol-6-yl, R^1=Tos, R^2=4-OMe
3t indol-6-yl, R^1=Tos, R^2=2-OMe

plings involving unprotected heterocycles (Table 1, entries 21−28). It did, however, become noticeable in couplings involving Boc-protected indolylboronic acids (Table 1, entries 29−32). Yields for couplings involving the Tos-protected counterparts were too low to allow any such relationship to be reliably established.

The conspicuous dependence of yield on the substituent present at the heterocyclic nitrogen atom (Table 1, entries 21−34) is the most noteworthy feature of this series of reactions. With indolylboronic acids in which this atom was unprotected, they ranged between 52 and 94% (Table 1, entries 21−28). Protection with the Boc group caused them to drop to the range 8−50% (Table 1, entries 29−32), and with the Tos group they fell further to 10% at best (Table 1, entry 33).

These results show that swapping the partner roles caused Suzuki coupling yields to become more sensitive to steric and electronic factors. The lower overall values in comparison to the first series of reactions [see Section 1a above], the incipient sensitivity to steric impediment in ortho-substituted phenyl bromides, and the clear variation observed with regard to the substituent at the heterocyclic nitrogen atom are all indicative of this.

The diminished yields may be a consequence of the reduced effectiveness with which the more electron-rich phenyl bromides participate in the oxidative addition to Pd(0) catalyst.[11] The variation with respect to the substituent at the heterocyclic nitrogen atom is in agreement with the supposition that more electron-deficient indolylboronic acids undergo transmetalation more reluctantly.[6] However, it should be borne in mind that the results of this second series of reactions may also reflect, to a greater or lesser extent, the yields in which the different indolylboronic acids themselves were formed.

2. Suzuki Couplings Using Arylpinacolboronates. Arylboronate esters provide an attractive alternative to arylboronic acids, and the pinacol derivatives have been among the most widely used.[36−41] They can be formed under mild conditions by Pd(0)-catalyzed reaction[36] between aryl halides and bis(pinacolato)diboron via a mechanism similar to that shown in Scheme 3. This method may be advantageously applied to substrates incorporating easily epimerizable stereogenic carbon atoms or sensitive functional groups, since the use of organolithiums or other strong bases is avoided.

The arylpinacolboronate esters we describe in this study are among the first reported in Suzuki arylations of indoles. To expedite the coupling reactions, the crude products were not purified prior to use; instead, they were employed directly. Nevertheless, unlike the indolylboronic acids described above in Section 1b, arylpinacolboronate esters were much more amenable to chromatographic purification and spectroscopic characterization (see Experimental Section and Supplementary Information).

(a) Reactions between Indole Bromides and Phenylpinacolboronate Esters. Suzuki couplings between indole bromides (**1a**,**b**,**d**−**g**, X^1 = 5- or 6-Br, R^1 = H, Boc, or Tos) and phenylpinacolboronate esters (**2i**−**j**, X^2 = Bpin, R^2 = 2-OMe or 4-OMe) occurred in yields that were, even at best, considerably lower than those obtained with the corresponding phenylboronic acids (cf. Table 2, entries 1−11, and Table 1, entries 1−20). Furthermore, a clear dependence on the substituent at the heterocyclic nitrogen was observed. Yields were highest (40−62%) when the heterocycle was protected with the Tos group

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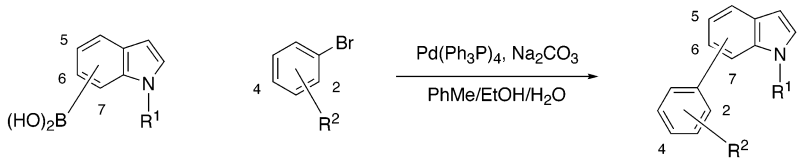
SCHEME 4



1h 5-B(OH)$_2$, R^1=H
1i 6-B(OH)$_2$, R^1=H
1j 7-B(OH)$_2$, R^1=H
1k 5-B(OH)$_2$, R^1=Boc
1l 5-B(OH)$_2$, R^1=Tos

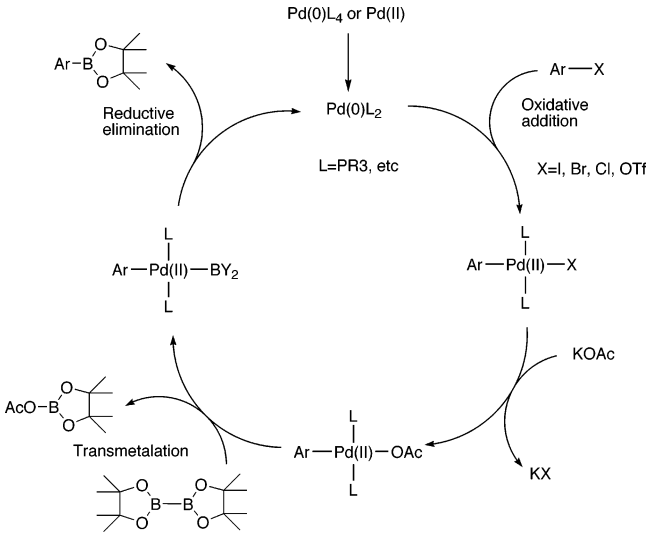
2e R^2=4-Me
2f R^2=4-OMe
2g R^2=2-Me
2h R^2=2-OMe

3a indol-5-yl, R^1=H, R^2=4-Me
3b indol-5-yl, R^1=H, R^2=4-OMe
3c indol-5-yl, R^1=H, R^2=2-Me
3d indol-5-yl, R^1=H, R^2=2-OMe
3e indol-6-yl, R^1=H, R^2=4-OMe
3f indol-6-yl, R^1=H, R^2=2-OMe
3g indol-7-yl, R^1=H, R^2=4-OMe
3h indol-7-yl, R^1=H, R^2=2-OMe
3i indol-5-yl, R^1=Boc, R^2=4-Me
3j indol-5-yl, R^1=Boc, R^2=4-OMe
3k indol-5-yl, R^1=Boc, R^2=2-Me
3l indol-5-yl, R^1=Boc, R^2=2-OMe
3p indol-5-yl, R^1=Tos, R^2=4-OMe
3r indol-5-yl, R^1=Tos, R^2=2-OMe

(Table 2, entries 8−11). With the less electron-withdrawing Boc group, yields dropped to the range of 8−34% (Table 2, entries 4−7), and when the indole was unprotected only traces of the desired biaryls could be detected in the reaction crudes (Table 2, entries 1−3). The effect of steric hindrance in the phenylboronate partner, occasioned by ortho substitution, was also evident. Ortho-substituted phenylpinacolboronates almost always gave lower yields than their para-substituted counterparts, in contrast to the series using phenylboronic acid partners, where this was not the case. All couplings with these boronate esters also required significantly longer reaction times than those necessary for arylboronic acids.

These data indicate that phenylpinacolboronate esters are less reactive than phenylboronic acids. The generally lower coupling yields obtained, the longer reaction times required, and the sensitivity to steric hindrance observed all corroborate this. This lower reactivity may have its origin in steric factors. The bulkiness occasioned by the presence of two pairs of geminal methyl groups in arylpinacolboronate esters may hamper their participation in the transmetalation stage of Suzuki coupling (see Scheme 1). This would disfavor completion of the catalytic cycle and lead to decreased formation of biaryl. It is also possible that the steric requirements of arylpinacolboronate esters impede the interaction of base with the boron atom, inhibiting its quaternization to give an "ate" complex. This step is known to be crucial for efficient transmetalation in the Suzuki coupling,[6,42,43] and its obstruction would be expected to have an adverse effect on yield. Some support for these hypotheses is to be found in the generally lower coupling yields observed for ortho-substituted arylpinacolboronate esters compared to their para-substituted counterparts. Steric congestion would be expected to be greater in the former cases, and the adverse effect on yield would be expected to be correspondingly more pronounced, in line with the experimental results obtained for this series.

SCHEME 5

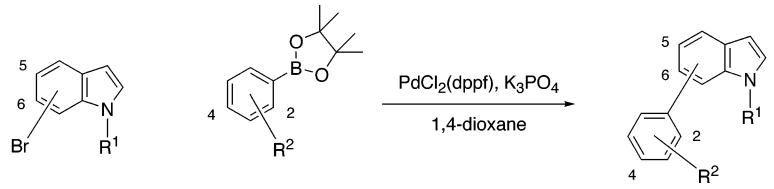


The correlation between coupling yields and the substituent at heterocyclic nitrogen may be explained by the greater facility with which more electron-deficient indole bromides participate in the oxidative addition to Pd(0). Indoles substituted with the more electron-withdrawing Tos group should undergo this step most readily, followed by those substituted with the Boc group. Unprotected indoles, on the other hand, would undergo oxidative addiion more reluctantly. The experimental results for this series of couplings support this view. As seen in Section 1a above, when phenylboronic acids were employed as coupling partners, the impact of any differences in the rates of oxidative addition on the coupling yields was not appreciable. However, in this series of couplings, under the different reaction conditions employed and with the less reactive phenylboronate esters its influence becomes discernible.

Nevertheless, the conspicuous difference in performance between phenylboronic acids and phenylpinacolboronate esters, when reacted with the same unprotected indole bromide partners, is striking. In the former case high yields of biaryl were obtained, whereas in the latter only traces were produced (cf. Table 1, entries 1−8, and Table 2, entries 1−3). This discrepancy would seem to be symptomatic of some other cause. Competing side reactions of the unprotected indoles with the Pd(II) or

(42) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
(43) Norrild, J. C.; Hanne, E. *J. Am. Chem. Soc.* **1995**, *117*, 1479.

SCHEME 6

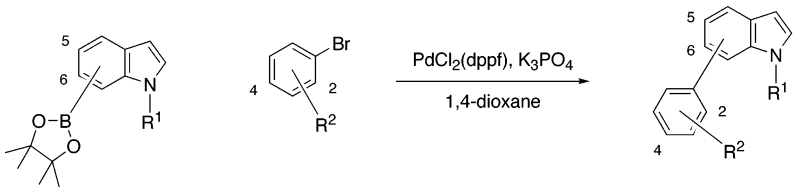


1a 5-Br, R^1=H
1b 6-Br, R^1=H
1d 5-Br, R^1=Boc
1e 6-Br, R^1=Boc
1f 5-Br, R^1=Tos
1g 6-Br, R^1=Tos

2i R^2=4-OMe
2j R^2=2-OMe

3b indol-5-yl, R^1=H, R^2=4-OMe
3d indol-5-yl, R^1=H, R^2=2-OMe
3e indol-6-yl, R^1=H, R^2=4-OMe
3j indol-5-yl, R^1=Boc, R^2=4-OMe
3l indol-5-yl, R^1=Boc, R^2=2-OMe
3m indol-6-yl, R^1=Boc, R^2=4-OMe
3n indol-6-yl, R^1=Boc, R^2=2-OMe
3p indol-5-yl, R^1=Tos, R^2=4-OMe
3r indol-5-yl, R^1=Tos, R^2=2-OMe
3s indol-6-yl, R^1=Tos, R^2=4-OMe
3t indol-6-yl, R^1=Tos, R^2=2-OMe

SCHEME 7



1m 5-Bpin, R^1=H
1n 6-Bpin, R^1=H
1o 5-Bpin, R^1=Boc
1p 6-Bpin, R^1=Boc
1q 5-Bpin, R^1=Tos
1r 6-Bpin, R^1=Tos

2f R^2=4-OMe
2h R^2=2-OMe

3b indol-5-yl, R^1=H, R^2=4-OMe
3d indol-5-yl, R^1=H, R^2=2-OMe
3e indol-6-yl, R^1=H, R^2=4-OMe
3j indol-5-yl, R^1=Boc, R^2=4-OMe
3k indol-5-yl, R^1=Boc, R^2=2-Me
3l indol-5-yl, R^1=Boc, R^2=2-OMe
3m indol-6-yl, R^1=Boc, R^2=4-OMe
3n indol-6-yl, R^1=Boc, R^2=2-OMe
3p indol-5-yl, R^1=Tos, R^2=4-OMe
3r indol-5-yl, R^1=Tos, R^2=2-OMe
3s indol-6-yl, R^1=Tos, R^2=4-OMe
3t indol-6-yl, R^1=Tos, R^2=2-OMe

Pd(0) species present suggest themselves as possibilities, among others.

(b) Reactions between Indolylpinacolboronates and Phenyl Bromides. In a final series of couplings, partner roles were swapped and indolylpinacolboronates (**1m**−**r**, X^2 = 5- or 6-Bpin, R^1 = H, Boc, or Tos), derived from the corresponding indole bromides (**1a**,**b**,**d**−**g**, X^1 = 5- or 6-Br, R^1 = H, Boc or Tos), were reacted with substituted phenyl bromides (**2**, X^2 = Br, R^2 = 2-Me, 4-Me, 2-OMe, or 4-OMe). Reaction times similar to those necessary for the reactions of the previous series were required to achieve optimum yields. Even so, these were consistently lower than those obtained with indolylboronic acids (cf. Table 2, entries 12−22, and Table 1, entries 21−34). The effect of increased steric hindrance, occasioned by ortho-substitution in the phenyl bromide was again clearly noticeable. Ortho-substituted phenyl bromides always gave lower yields than their para-substituted counterparts in couplings with indolylpinacolboronate partners. This contrasts, to some extent, with the series of reactions employing indolylboronic acids, which displayed less sensitivity to this factor.

However, the most noteworthy characteristic of this series of couplings is the inversion in the trend of the yields for the Tos- and Boc-protected and unprotected heterocycles in comparison to the series of reactions employing indolylboronic acids. As seen in Section 1b above, when the latter were coupling partners, highest yields were obtained in the absence of indole protection and lowest ones in the presence of the Tos group, with Boc-protected heterocycles presenting intermediate values. In the present series of couplings, this trend was inverted. Only traces of biaryls were produced in couplings involving indolylpinacolboronates having an unprotected heterocyclic nitrogen (Table 2, entries 12−14). The presence of Boc and Tos protection led to improved yields, which were higher (24−62%) for the more electron-withdrawing Tos group (Table 2, entries 19−22) than for the Boc group (16−39%) (Table 2, entries 15−18).

The results of this series confirm the previously observed lower reactivity and greater sensitivity to steric effects of arylpinacolboronate esters in comparison to arylboronic acids. There is, however, an inversion in the yield trend, and the difference in performance between unprotected indolylboronic acids, which gave good yields of biaryls, and unprotected indolylpinacolboronate esters, which gave only traces, in couplings with the same phenyl bromide partners is remarkable (cf. Table 1, entries 21−28, and Table 2, entries 12−14). This result parallels that seen in the previous series of reactions [see

TABLE 2. Suzuki Couplings between Indoles and Phenyl Derivatives Using Arylpinacolboronate Esters

entry	aryl bromide	arylboronate	biaryl yield[a] (%)
1	**1a**, X^1 = 5-Br, R^1 = H	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3b**, traces[b]
2	**1a**, X^1 = 5-Br, R^1 = H	**2j**, X^2 = Bpin, R^2 = 2-OMe	**3d**, traces[b]
3	**1b**, X^1 = 6-Br, R^1 = H	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3e**, traces[b]
4	**1d**, X^1 = 5-Br, R^1 = Boc	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3j**, 22
5	**1d**, X^1 = 5-Br, R^1 = Boc	**2j**, X^2 = Bpin, R^2 = 2-OMe	**3l**, 8
6	**1e**, X^1 = 6-Br, R^1 = Boc	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3m**, 19
7	**1e**, X^1 = 6-Br, R^1 = Boc	**2j**, X^2 = Bpin, R^2 = 2-OMe	**3n**, 34
8	**1f**, X^1 = 5-Br, R^1 = Tos	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3p**, 62
9	**1f**, X^1 = 5-Br, R^1 = Tos	**2j**, X^2 = Bpin, R^2 = 2-OMe	**3r**, 45
10	**1g**, X^1 = 6-Br, R^1 = Tos	**2i**, X^2 = Bpin, R^2 = 4-OMe	**3s**, 55
11	**1g**, X^1 = 6-Br, R^1 = Tos	**2j**, X^2 = Bpin, R^2 = 2-OMe	**3t**, 40
12	**2f**, X^2 = Br, R^2 = 4-OMe	**1m**, X^1 = 5-Bpin, R^1 = H	**3b**, traces[b]
13	**2h**, X^2 = Br, R^2 = 2-OMe	**1m**, X^1 = 5-Bpin, R^1 = H	**3d**, traces[b]
14	**2f**, X^2 = Br, R^2 = 4-OMe	**1n**, X^1 = 6-Bpin, R^1 = H	**3e**, traces[b]
15	**2f**, X^2 = Br, R^2 = 4-OMe	**1o**, X^1 = 5-Bpin, R^1 = Boc	**3j**, 36
16	**2h**, X^2 = Br, R^2 = 2-OMe	**1o**, X^1 = 5-Bpin, R^1 = Boc	**3l**, 16
17	**2f**, X^2 = Br, R^2 = 4-OMe	**1p**, X^1 = 6-Bpin, R^1 = Boc	**3m**, 39
18	**2h**, X^2 = Br, R^2 = 2-OMe	**1p**, X^1 = 6-Bpin, R^1 = Boc	**3n**, 30
19	**2f**, X^2 = Br, R^2 = 4-OMe	**1q**, X^1 = 5-Bpin, R^1 = Tos	**3p**, 43
20	**2h**, X^2 = Br, R^2 = 2-OMe	**1q**, X^1 = 5-Bpin, R^1 = Tos	**3r**, 24
21	**2f**, X^2 = Br, R^2 = 4-OMe	**1r**, X^1 = 6-Bpin, R^1 = Tos	**3s**, 62
22	**2h**, X^2 = Br, R^2 = 2-OMe	**1r**, X^1 = 6-Bpin, R^1 = Tos	**3t**, 42

[a] All yields refer to isolated products after column chromatography on silica gel. [b] Product only detected by mass spectrometry of the reaction crudes.

Section 2a above] between indole bromide and phenylpinacolboronate ester partners. The trend in yield was similar, with the unprotected indoles again giving rise to only traces of biaryl. Also worth mentioning is the difference in performance between Tos-protected indolylboronic acids and Tos-protected indolylpinacolboronate esters. In these cases, it was the former that gave rise to poor yields of biaryl. Indolylpinacolboronates, on the other hand, underwent Suzuki coupling most satisfactorily and produced the corresponding biaryls in acceptable yields (cf Table 1, entries 33−34, and Table 2, entries 19−22).

This inversion of the trend in yields probably does not have one single cause but is, rather, the outcome of a combination of different factors. We believe that the following three points are relevant. First, although Suzuki couplings involving unprotected indolylpinacolboronates gave only traces of biaryl, this was not because the boronate esters themselves (**1m**−**n**, R^1 = H) did not form. On the contrary, they were the main products isolated after reaction workup and chromatography. Their reluctance to participate in Suzuki couplings is intriguing and parallels the similar reluctance displayed by unprotected indole bromide partners in the previous series of reactions [see Section 2a, above]. As in that previous case, we can only speculate that this may have its origin in competing side-reaction between the unprotected indoles and the Pd(II) or Pd(0) species present under the reaction conditions used.

Second, the yields of those couplings involving Boc-protected indolylboronates are diminished by a partial instability of the protecting group to the reaction conditions. This contributes to the lowering of the yields of couplings involving Boc-protected indolylboronate partners compared to their Tos-protected counterparts, in contrast to the results observed with indolylboronic acids. (Reduction of reaction times and/or temperatures led to lower yields of biaryls). Both unprotected (**1m**, X^1 = 5-Bpin, R^1 = H; **1n**, X^1 = 6-Bpin, R^1 = H) and Boc-protected indolylpinacolboronate esters (**1o**, X^1 = 5-Bpin, R^1 = Boc; **1p**, X^1 = 6-Bpin, R^1 = Boc) were isolated after workup of these reactions, demonstrating both the instability of the Boc group and the reluctance to react of the indolylpinacolboronate esters.

Third, the different results obtained when Tos-protected indolylboronic acids and Tos-protected indolylboronates were reacted with the same phenyl bromide partners (only very poor yields of biaryl in the former case; good yields in the latter) may reflect the relative ease with which the arylboron intermediates themselves are formed, bearing in mind the quite different mechanisms involved.

We suggest that, in this series of reactions, the overall result is to produce a yield trend that is inverted with respect to that which would be predicted on the basis of a consideration of the relative electron deficiencies of the indoles themselves. As has been seen in Section 1b above, this contrasts with the results obtained using indolylboronic acids, which could be rationalized in terms of the relative electronic characters of the heterocycle.

Conclusions

In Suzuki couplings involving 5-, 6-, or 7-substituted indoles, yields were found to depend on the following interrelated factors:

(1) Whether arylboronic acids or arylpinacolboronate esters were used as coupling partners. The former were more reactive and almost always furnished biaryls in higher yields, the exceptions being Tos-protected indolylboronic acids, which performed poorly. Arylpinacolboronate esters, on the other hand, were considerably less reactive and generally gave lower yields of biaryl, especially in couplings involving unprotected indoles where they gave only traces of the desired biaryls.

(2) The assignment of partner roles. Reactions employing arylboronic acids gave different results when partner roles were swapped. Biaryl formation proceeded most efficiently when the heterocycle was the bromoaryl

partner. When indolylboronic acids were coupled with phenyl bromides, yields were generally lower.

In contrast, partner role swapping had a very limited impact in couplings employing arylpinacolboronates, with similar results being obtained irrespective of whether the heterocycle was the aryl bromide or the arylboronate ester.

(3) Whether the indole was protected or not. The influence of the substituent at nitrogen was unimportant in couplings between indole bromides and phenylboronic acids. It was, however, substantial in couplings between phenyl bromides and indolylboronic acids where yields diminished as the electron-withdrawing capacity of the substituent increased.

On the other hand, couplings employing either phenyl- or indole-derived arylpinacolboronate esters gave only traces of biaryl with unprotected indoles: yields were acceptable only when protection was afforded by the strongly electron-withdrawing Tos group.

The different influences on yield discerned in this study may also operate in couplings involving other substrates, making it difficult to predict the best choices of reagents and reaction conditions. Nevertheless, it seems clear that careful selection both of protecting groups and of the arylboron reagent, together with a judicious assignment of the component roles, is crucial to ensure optimum results in some Suzuki couplings.

Experimental Section

1. General Methods. All chemicals and reagents used in this study were purchased commercially and used as received. THF and 1,4-dioxane were freshly distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride. Toluene was used as received. H_2O refers to deionized water. Organic layers were dried over anhydrous magnesium or sodium sulfate. Evaporation of solvents was carried out on a rotary evaporator at reduced pressure.

Column chromatography was performed using silica gel 60 (70−230 mesh). Solvent ratios are given as v/v.

^{1}H NMR spectra were recorded at 200, 300, or 400 MHz on Varian spectrometers in $CDCl_3$ with tetramethylsilane as an internal reference. Signals are quoted in parts per million as δ downfield from tetramethylsilane (δ 0.00) as an internal standard. Coupling constants (J values) are given in hertz. ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz, respectively. Chemical shifts were referenced to the deuterated solvent signals.

Low-resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a ThermoFinnigan TRACE DSQ apparatus run by the Servei de Espectrometria de Masses (SCT) of the University of Barcelona. High-resolution mass spectrometry (HRMS) in both EI and CI modes were obtained from the Unidad de Masses of the Univeristy of Santiago de Compostela.

Elemental analyses were performed by the Laboratorio de Analisis Elemental, Instituto de Química Médica (CSIC), Madrid.

Melting points are uncorrected.

2. Selected Examples of General Reaction Procedures. (a) Preparations of 5-(4-Methoxyphenyl)indole 3b: (i) From 5-Bromoindole 1a and 4-Methoxyphenylboronic Acid 2b. Aqueous Na_2CO_3 (4 mL of a 1 M solution, 4 mmol) and $Pd(Ph_3P)_4$ (0.04 g, 0.03 mmol) in 1:1 toluene−EtOH (4 mL) were added to a solution of 5-bromoindole (0.32 g, 1.70 mmol) and 4-methoxyphenylboronic acid (0.50 g, 3.40 mmol) in 1:1 toluene−EtOH (4 mL), and the resulting mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.04 g, 0.03 mmol) in 1:1 toluene−EtOH (4 mL) was added, and heating at reflux under argon was continued for a further 4 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.31 g, 85%).

(ii) From Indol-5-ylboronic Acid 1h and 4-Bromoanisole 2f. KH (0.10 g, 2.60 mmol) was suspended in THF (4 mL) under argon at 0 °C. 5-Bromoindole (0.50 g, 2.6 mmol) was added, and the mixture was stirred for 15 min. The resulting solution was cooled to −78 °C, and ^{t}BuLi (3.4 mL of a 1.5 M solution in pentane, 5.1 mmol) was added over 1 min. The cooling bath was removed, and the mixture was stirred for 10 min. After the mixture was recooled to −78 °C, $B(OMe)_3$ (0.60 mL, 5.10 mmol) was added and the mixture was allowed to warm to rt and stirred for 3 h. H_2O was added, and the mixture was extracted with EtOAc. The aqueous phase was acidified to pH 1 with 10% HCl and extracted with EtOAc. The combined organic extracts were dried, and the solvent was removed, furnishing the crude indolylboronic acid as a light-brown oil.

The crude boronic acid (0.41 g, 2.60 mmol) in 1:1 toluene−EtOH (4 mL) was added to 4-bromoanisole (0.12 mL, 0.64 mmol), 1 M aqueous Na_2CO_3 (1.8 mL, 1.8 mmol), and $Pd(Ph_3P)_4$ (0.037 g, 0.03 mmol) in 1:1 toluene−EtOH (1.5 mL), and the mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.037 g, 0.03 mmol) in 1:1 toluene−EtOH (1.5 mL) was added, and heating at reflux under argon was continued for a further 4 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.11 g, 80%): mp 102−106 °C (lit.[26] 118−200 °C); δ_H (200 MHz, $CDCl_3$) 3.85 (s, 3H), 6.58 (m, 1H), 6.98 (d, J 8.8, 2H), 7.19 (m, 1H), 7.40 (d, J 1.4, 2H), 7.57 (d, J 8.8, 2H), 7.80, (s, 1H), 8.11 (bs, 1H); δ_C (50 MHz, $CDCl_3$) 55.3 (CH_3), 102.9 (CH), 111.1 (CH), 114.1 (CH), 118.7 (CH), 121.7 (CH), 124.7 (CH), 128.3 (CH), 128.4 (C), 133.0 (C), 135.0 (C), 135.2 (C), 158.0 (C); m/z (%) 224 [(M + 1), 100]; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.099714, found 223.100298. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.47; H, 5.59; N, 5.99.

(b) Preparations of 1-*tert*-Butoxycarbonyl-5-(4-methylphenyl)indole 3i: (i) From 1-Boc-5-bromoindole 1d and 4-Methylphenylboronic Acid 2a. Aqueous Na_2CO_3 (3 mL of a 1 M solution, 3 mmol) and $Pd(Ph_3P)_4$ (0.06 g, 0.06 mmol) in 1:1 toluene−EtOH (10 mL) were added to a solution of 1-Boc-5-bromoindole (0.34 g, 1.20 mmol) and 4-methylphenylboronic acid (0.33 g, 2.20 mmol) in 1:1 toluene−EtOH (4 mL), and the resulting mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.06 g, 0.06 mmol) in 1:1 toluene−EtOH (4 mL) was added, and heating at reflux under argon was continued for a further 4 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.38 g, 79%).

(ii) From 1-Boc-indol-5-ylboronic Acid 1k and 4-Bromotoluene 2e. KH (0.07 g, 1.72 mmol) was suspended in THF (4 mL) under argon at 0 °C. 1-Boc-5-bromoindole (0.51 g, 1.73 mmol) was added, and the mixture was stirred for 15 min. The resulting solution was cooled to −78 °C, and ^{t}BuLi (2.0 mL of a 1.5 M solution in pentane, 3.0 mmol) was added over 1 min. The cooling bath was removed, and the mixture was stirred for 10 min. After the mixture was recooled to −78 °C, $B(OMe)_3$ (0.40 mL, 3.40 mmol) was added and the mixture was allowed to warm to rt and stirred for 3 h. H_2O was added, and the mixture was extracted with EtOAc. The aqueous phase was acidified to pH 1 with 10% HCl and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried, and the solvent was removed, furnishing the crude indolylboronic acid as a light-brown oil.

The crude boronic acid (0.45 g, 1.70 mmol) in 1:1 toluene−EtOH (4 mL) was added to 4-bromotoluene (0.08 mL, 0.45 mmol), 1 M aqueous Na_2CO_3 (1.2 mL of a 1 M solution, 1.2 mmol), and $Pd(Ph_3P)_4$ (0.025 g, 0.02 mmol) in 1:1 toluene−

EtOH (1.5 mL), and the mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.025 g, 0.02 mmol) in 1:1 toluene−EtOH (1.5 mL) was added, and heating at reflux under argon was continued for a further 4 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.15 g, 34%): mp 85−87 °C; δ_H (200 MHz, $CDCl_3$) 1.68 (s, 9H), 2.39 (s, 3H), 6.59 (d, *J* 3.6, 1H), 7.25 (m, 2H), 7.55 (m, 4H), 7.75 (d, *J* 1.4, 1H), 8.16 (d, *J* 8.8, 1H); δ_C (50 MHz, $CDCl_3$) 21.1 (CH_3), 28.2 (CH_3), 83.5 (C), 107.5 (CH), 115.2 (CH), 119.1 (CH), 123.6 (CH), 126.3 (CH), 126.7 (CH), 129.4 (CH), 136.2 (C), 136.6 (C), 137.1 (C), 138.9 (C), 164.7 (C); *m*/*z* (%) 325 [$(M + NH_4)^+$, 100], 308 [(M + 1), 64]; HRMS (EI) calcd for $C_{20}H_{21}NO_2$ 307.157229, found 307.157840. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.94; H, 6.76; N, 4.45.

(c) Preparations of 1-(*p*-Toluenesulfonyl)-5-(4-methoxyphenyl)indole 3p: (i) From 1-Tos-5-bromoindole 1f and 4-Methoxyphenylboronic Acid 2b. Aqueous Na_2CO_3 (2.2 mL of a 1 M solution, 2.2 mmol) and $Pd(Ph_3P)_4$ (0.05 g, 0.04 mmol) in 1:1 toluene−EtOH (10 mL) were added to a solution of 1-Tos-5-bromoindole (0.31 g, 0.90 mmol) and 4-methoxyphenylboronic acid (0.20 g, 1.30 mmol) in 1:1 toluene−EtOH (4 mL), and the resulting mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.05 g, 0.04 mmol) in 1:1 toluene−EtOH (4 mL) was added, and heating at reflux under argon was continued for a further 4 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.31 g, 93%).

(ii) From 1-Tos-indol-5-ylboronic Acid 1l and 4-Bromoanisole 2f. KH (0.07 g, 1.72 mmol) was suspended in THF (4 mL) under argon at 0 °C. 1-Tos-5-bromoindole (0.33 g, 1.72 mmol) was added, and the mixture was stirred for 15 min. The resulting solution was cooled to −78 °C, and ^{t}BuLi (2.3 mL of a 1.5 M solution in pentane, 3.5 mmol) was added over 1 min. The cooling bath was removed, and the mixture was stirred for 10 min. After the mixture was recooled to −78 °C, $B(OMe)_3$ (0.40 mL, 3.40 mmol) was added and the mixture was allowed to warm to rt and stirred for 3 h. H_2O was added, and the mixture was extracted with EtOAc. The aqueous phase was acidified to pH 1 with 10% HCl and extracted with EtOAc. The combined organic extracts were dried, and the solvent was removed, furnishing the crude indolylboronic acid as a light-brown oil.

The crude boronic acid (0.30 g, 0.94 mmol) in 1:1 toluene−EtOH (4 mL) was added to 4-bromoanisole (0.03 mL, 0.47 mmol), 1 M aqueous Na_2CO_3 (0.6 mL of a 1 M solution, 0.60 mmol), and $Pd(Ph_3P)_4$ (0.01 g, 0.01 mmol) in 1:1 toluene−EtOH (1.5 mL), and the mixture was heated at reflux under argon for 1 h. $Pd(Ph_3P)_4$ (0.01 g, 0.01 mmol) in 1:1 toluene−EtOH (1.5 mL) was added, and heating at reflux under argon was continued for a further 5 h. After the mixture was cooled, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.009 g, 10%).

(iii) From 1-Tos-5-bromoindole 1f and Pinacol 4-Methoxyphenylboronate 2i. KOAc (0.23 g, 2.29 mmol), bis(pinacolato)diboron (0.22 g, 1.1 mmol), 4-bromoanisole (0.097 mL, 0.76 mmol), and $PdCl_2$(dppf) (0.04 g, 0.05 mmol) in 1,4-dioxane (4 mL) were heated at 80 °C under argon for 14 h. After the mixture was cooled, the solvent was removed, leaving the crude boronate as a pale brown oil.

This boronate (0.071 g, 0.31 mmol), potassium phosphate (0.28 g, 1.26 mmol), $PdCl_2$(dppf) (0.008 g, 0.008 mmol), and 1-Tos-5-bromoindole (0.134 g, 0.38 mmol) in 1,4-dioxane (2 mL) were heated at 100 °C under argon for 1 h. $PdCl_2$(dppf) (0.004 g, 0.004 mmol) and boronate (0.036 g, 0.15 mmol) were added, and the mixture was heated at 100 °C for a further 1 h. The addition of catalyst and boronate were repeated twice more at hourly intervals, and the mixture was then kept at 100 °C under argon for a further 24 h. After the mixture was cooled and filtered, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1] giving the product as a white solid (0.09 g, 62%).

(iv) From Pinacol 1-Tos-5-indolylboronate 1q and 4-Bromoanisole 2f. KOAc (0.23 g, 2.29 mmol), bis(pinacolato)diboron (0.22 g, 1.1 mmol), 1-tos-5-bromoindole (0.267 g, 0.76 mmol), and $PdCl_2$(dppf) (0.04 g, 0.05 mmol) in 1,4-dioxane (4 mL) were heated at 100 °C under argon for 48 h. After the mixture was cooled, the solvent was removed, leaving the crude boronate as a pale brown oil.

This boronate (0.12 g, 0.31 mmol), potassium phosphate (0.28 g, 1.26 mmol), $PdCl_2$(dppf) (0.008 g, 0.008 mmol), and 4-bromoanisole (0.05 mL, 0.38 mmol) in 1,4-dioxane (2 mL) were heated at 100 °C under argon for 1 h. $PdCl_2$(dppf) (0.004 g, 0.004 mmol) and boronate (0.06 g, 0.15 mmol) were added, and the mixture was heated at 100 °C under argon for a further 1 h. The addition of catalyst and boronate were repeated twice more at hourly intervals, and the mixture was then kept at 100 °C under argon for a further 70 h. After the mixture was cooled and filtered, the solvent was removed and the resulting crude was purified by chromatography [silica, hexanes−EtOAc, 9:1], giving the product as a white solid (0.09 g, 43%): mp 135−137 °C; δ_H (200 MHz, $CDCl_3$) 2.33 (s, 3H), 3.84 (s, 3H), 6.67 (d, *J* 3.6, 1H), 6.96 (d, *J* 8.8 2H), 7.22 (d, *J* 8.0, 2H), 7.59 (m, 4H), 7.65 (s, 1H), 7.78 (d, *J* 8, 2H), 8.01 (d, *J* 8.4, 1H); δ_C (50 MHz, $CDCl_3$) 21.6 (CH_3), 55.3 (CH_3), 109.2 (CH), 113.6 (CH), 114.2 (CH), 119.2 (CH), 123.9 (CH), 126.8 (CH), 128.2 (CH), 129.8 (CH), 131.3 (C), 133.7 (CH), 135.2 (C), 136.4 (C), 144.9 (C), 158.9 (C); *m*/*z* (%) 378 [$(M + H)^+$, 100]; HRMS (EI) calcd for $C_{22}H_{19}NO_3S$ 377.108565, found 377.108398. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.92; H, 5.33; N, 3.77.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **1b**, **1d**−**g**, **1m**−**o**, **2i**, **3a**, **3c**−**h**, **3j**−**o**, and **3q**−**t**, together with their characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for compounds **1b**, **1d**−**g**, **1m**−**o**, **2i** and **3a**−**t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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