ORGANIC LETTERS

2009
Vol. 11, No. 8
1801−1804

One-Pot Double Suzuki−Miyaura Couplings: Rapid Access to Nonsymmetrical Tri(hetero)aryl Derivatives

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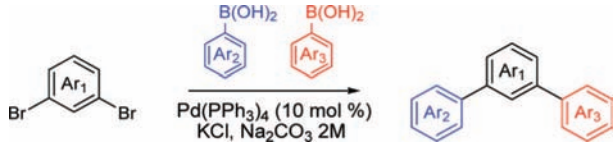
Received February 18, 2009

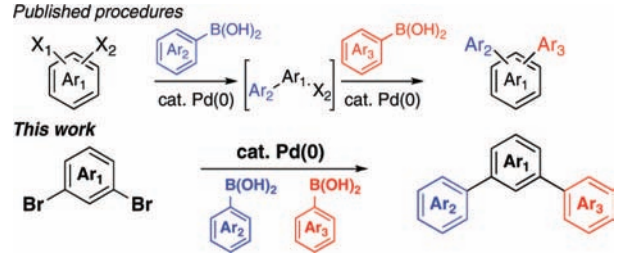
ABSTRACT



We describe a one-pot, simultaneous Suzuki−Miyaura cross-coupling of two different aryl boronic acids with symmetrical dibromo aryl and heterocyclic substrates to give as major products the unsymmetrical disubstituted tri(hetero)aryl derivatives. Yields of unsymmetrical dicoupled products were generally in the 52−75% range. This methodology is particularly suited to the generation of chemical libraries, as well as to the synthesis of biologically active or natural product analogs.

Poly- and heteropolyaromatic systems are found in a wide range of compounds useful as drugs[1] or materials.[2] They also form important classes of natural compounds, such as the *p*-terphenyl derivatives.[3] Although a large variety of methods has been described for the preparation of such species,[4] one of the most useful and versatile strategies is that of palladium-catalyzed cross-coupling reactions, notably the Suzuki−Miyaura coupling reaction.[5] Whereas the latter allows straightforward introduction of two identical aryl substituents starting from a dihaloaryl precursor,[6] the introduction of two different aromatic units onto the central aryl core presents a considerably more difficult synthetic challenge that to date has been taken up only by application of stepwise procedures (Scheme 1).[7] These rely on the application of sequential couplings the selectivity of which is

Scheme 1. General Context of the Study



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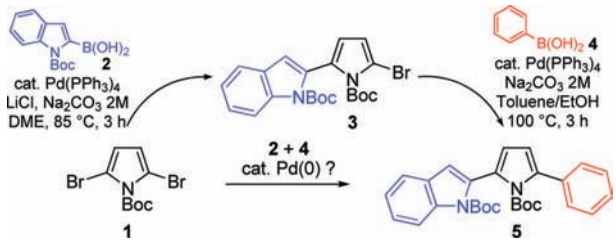
10.1021/ol900358n CCC: $40.75
Published on Web 03/26/2009

generally controlled by the introduction of differentially reactive halogen atoms on the central aromatic ring (e.g., Cl and Br/I)[8] or by the use, as starting materials, of dibromo or -iodo substrates with each halogen being discriminated by its electronic and/or steric environment.[9] The case of symmetrical dihalo compounds is even more delicate, and the question of selective introduction of two different aromatic substituents via controlled sequential monoarylations has been only rarely addressed.[10] It is therefore in this context that we wish to describe the direct synthesis of tri(hetero)aryl products of type Ar_1-Ar_2-Ar_3 by application of simultaneous double Suzuki−Miyaura couplings to symmetrical dibromoaryl substrates.

We initially envisaged the synthesis of diarylpyrroles starting from symmetrical dibromopyrroles via palladium-catalyzed coupling reactions. This has received considerable attention recently[1a,11] for the preparation of both natural products[12] and biologically active compounds[1a,13] and was accomplished by application of the aforementioned sequential couplings[10a] or by prior monobromine−lithium exchange.[14] We have thus recently shown that the 2,5-dibromopyrrole **1** reacts with 1 equiv of *N*-Boc-indole-2-boronic acid (**2**) under palladium catalysis to give the product of monocoupling **3**, a second coupling with phenylboronic acid **4** then affording the 2,5-unsymmetrically substituted pyrrole **5** (Scheme 2).[15]

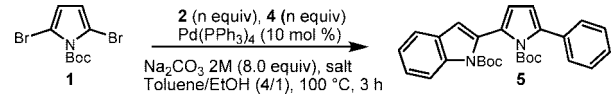
Scheme 2. From a Stepwise to a One-Pot Procedure



An important observation made during the course of this study was that the coupling order could not be reversed, very little dicoupled product being obtained when boronic acid **4** was used in the first coupling reaction. This difference in reactivity prompted us to attempt an unprecedented simultaneous one-pot Pd-catalyzed preparation of **5** from 2,5-dibromopyrrole **1** and the two boronic acids **2** and **4**. We reasoned that, provided the indoleboronic acid **2** coupled more rapidly than the phenyl counterpart, the monocoupled 2-indole-5-pyrrole derivative **3** would first be formed preferentially and could then react with the arylboronic acid present in the reaction mixture to give the desired 2,5-substituted pyrrole **5**.

Despite the statistical bias against appreciable formation of the desired 2-indole-5-arylpyrrole **5**,[16] an initial three-component palladium-catalyzed coupling was performed using the following procedure. Thus, *N*-Boc-2,5-dibromopyrrole and 1.5 equiv of each boronic acid in a 4:1 mixture of toluene/ethanol were treated with 10 mol % $Pd(PPh_3)_4$ and Na_2CO_3 for 3 h at 100 °C. While unsurprisingly many side products were obtained, 18% of the expected disubstituted pyrrole derivative **5** could indeed be isolated from the reaction mixture by chromatography (Table 1, entry 1).

Table 1. Optimization of the One-Pot Strategy



entry	**2** (equiv)	**4** (equiv)	salt (equiv)	yield (%)[a]
1	1.5	1.5	none	18
2	1.0	1.0	none	37
3	1.0	1.0	LiCl (1.0)	50
4	**1.0**	**1.0**	**LiCl (3.0)**	**67**
5	1.0	1.0	LiBr (3.0)	59
6	**1.0**	**1.0**	**KCl (3.0)**	**69**
7	1.0	1.0	KCl (5.0)	55

[a] Isolated yields after flash chromatography.

Encouraged by this result, we set out to optimize the reaction conditions. Interestingly, decreasing the proportion of both boronic acids to only 1 equiv led to a doubling of the yield

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(7) For recent examples, see: (a) Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.-P.; Balme, G. *Org. Lett.* **2007**, *9*, 271–274. (b) Era, I.; Pohl, R.; Klepetov, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389–5392. For a review, see: (c) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267.

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(13) (a) Banwell, M. G.; Hamel, E.; Hockless, D. C. R.; Verdier-Pinard, P.; Willis, A. C.; Wong, D. J. *Bioorg. Med. Chem.* **2006**, *14*, 4627–4638. (b) Kobayashi, N.; Kaku, Y.; Higurashi, K.; Yamauchi, T.; Ishibashi, A.; Okamoto, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1747–1750. (c) Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380.

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(16) In addition to compound **5**, up to eight other products could be expected from such a reaction: the monocoupled compound **3**, monocoupled 2-arylpyrrole of type **6** (and their dehalogenated 2-indolyl- and 2-arylpyrrole analogs), 2,5-diindolylpyrrole **7**, 2,5-diarylpyrrole **8**, and the two homocoupling products **9** and **10** (see Figure 1).

of **5** (entry 2, 37%). We then investigated the effect of adding inorganic salts to the reaction mixture.[17] Thus, the presence of 1 equiv of LiCl led to a net increase to 50% in the isolated yield of **5** (entry 3), which rose to 67% when 3 equiv of LiCl was employed (entry 4). While replacement of LiCl by LiBr led to a minor decrease in yield of **5** (59%, entry 5), use of KCl led to a slight increase in yield (69%, entry 6). Increasing the amount of KCl to 5 equiv, however, had a detrimental effect on the yield of **5** (55%, entry 7). Thus, the optimal yield of **5** using this one-pot, three-component procedure (69%) compares favorably with previously described stepwise protocols.[8−10]

To better appreciate the sequence and time-scale of the two different successive couplings, the course of the reaction was investigated by ^{1}H NMR spectroscopy.[18]

As shown in Figure 1, in the first 5 min of the reaction, the monocoupled indolylpyrrole product **3** is by far prepon-

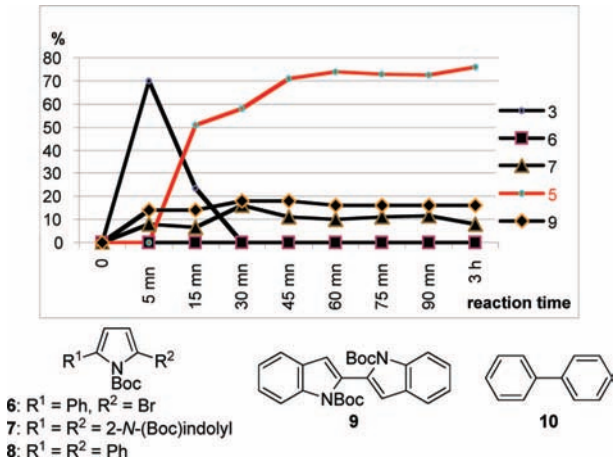
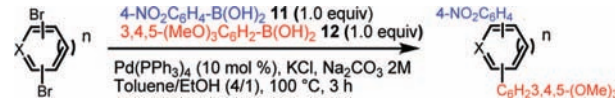


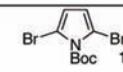
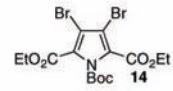
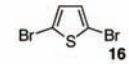
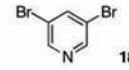
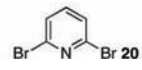
Figure 1. ^{1}H NMR study of the product mixture as a function of time.

derant (70%) with just traces of the expected product **5** being observed (<5%). After 15 min of reaction, the percentage of each compound is identical (38%), and after 45 min, the percentage of **5** reaches a plateau of 70% with practically no monocoupled intermediate **3** being observed. The rapid formation of **3** and then **5** therefore limits that of the two major side products observed in this reaction, the diindolylpyrrole **7** and indole homocoupled derivative **9** (in the 10−15% range), while the slower coupling of phenylboronic acid **4** is demonstrated by the observation of only traces of the monocoupled derivative **6**.

With the aim of extending the scope of this singular result, we then decided to apply this procedure to two different phenylboronic acids. Using the optimal reaction conditions developed for the preparation of **5** (Table 1, entry 6), it was observed that the combination of 2,5-dibromo-*N*-Boc-pyrrole **1** with 4-nitrophenylboronic acid **11** and 3,4,5-(trimethoxy)-phenylboronic acid **12** afforded the unsymmetrically disubstituted 2,5-diarylpyrrole **13** in 52% yield (Table 2, entry

Table 2. One-Pot Coupling with Dibromo Heterocycles



entry	substrate	product	yield (%)[a]
1	 1	**13**	52
2	 14	**15**	43
3	 16	**17**	54[b]
4	 18	**19**	54
5	 20	**21a**	65

[a] Isolated yields after flash chromatography. [b] ^{1}H NMR spectroscopic yield with traces of homocoupling products.

1). Using these two boronic acids but this time with pyrrole **14** as substrate, 43% yield of the unsymmetrically substituted product **15** was obtained (entry 2). This represents the first example of a differentially substituted 3,4-diaryl analogue of the naturally occurring lamellarin family of compounds.[2d,13c]

We then proceeded to investigate the use of other symmetrically substituted dibromoheterocycles in this reaction. Thus, the one-pot coupling reaction of arylboronic acids **11** and **12** with 2,5-dibromothiophene **16** gave coupling product **17** in 54% yield (entry 3).[19] Diarylpyridines also represent an interesting family of biologically active compounds that have only been prepared by application of sequential couplings.[9e,20] We thus observed that application of our one-pot three-component procedure to 3,5-dibromopyridine **18** led to formation of the expected unsymmetrical diphenylpyridine derivative **19** with a yield of 54% (entry 4). An even higher yield (65%) of the analogous product **21a** was obtained from the symmetrical 2,6-dibromopyridine **20** (entry 5).

The good yield obtained with the dibromopyridine **20** then encouraged us to study the scope of the three-component

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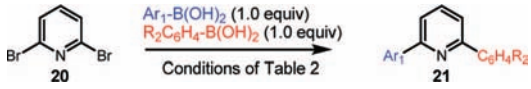
(18) Because the reaction is conducted in a sealed tube, it was stopped at regular 5−15 min intervals and worked up, and the crude product was investigated by ^{1}H NMR. In addition, the expected intermediates and byproducts were synthesized separately (see Supporting Information) in order to serve as controls for identification of the principal products in the reaction mixture.

(19) Dang, T. T.; Rasool, N.; Dang, T. T.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 845–847.

reaction with regard to the variety of arylboronic acids that could be used to ensure unsymmetrical coupling. Thus, reaction of **20** with boronic acid **12** and, instead of 4-nitrophenylboronic acid **11**, its 4-methyl analogue **22**, led to an even higher yield (75% vs 65%) of the expected product **21b** (Table 3, entry 2 vs entry 1), whereas coupling with **12**

Table 3. Scope of Boronic Acids Used for Coupling with **20**



entry	Ar_1	R_2	product	yield[a]
1	**12**: 3,4,5-$(MeO)_3C_6H_2$	**11**: 4-NO_2	**21a**	65
2	**12**: 3,4,5-$(MeO)_3C_6H_2$	**22**: 4-CH_3	**21b**	75
3	**12**: 3,4,5-$(MeO)_3C_6H_2$	**4**: 4-H	**21c**	59
4	**23**: 4-$MeOC_6H_4$	**4**: 4-H	**21d**	62
5	**11**: 4-$NO_2C_6H_4$	**4**: 4-H	**21e**	53
6	**24**: C_6H_5-CH=CH	**4**: 4-H	**21f**	48

[a] Isolated yields after flash chromatography.

and unsubstituted phenylboronic acid **4** provided product **21c** with a yield of 59% (entry 3). Replacement of the trimethoxyphenylboronic acid **12** by the less electron-donating 4-methoxy derivative **23** or even the highly electron-withdrawing 4-nitro derivative **11** still led to good yields of the pyridine derivatives **21d** (62%) and **21e** (53%), respectively (entries 4 and 5) starting from **20**. Finally, coupling of **20** with (*E*)-styrylboronic acid **24** and **4** afforded 2-phenyl-6-(*E*)-styrylpyridine **21f** in 48% yield (entry 6).

We finally investigated the more difficult case of dibromobenzenes. Application of a sequential coupling procedure to such substrates generally leads to symmetrical terphenyl derivatives after the first coupling,[6b] a nonstatistical phenomenon that has recently been overcome by applying chemoselective coupling to bromochlorobenzenes.[8b] We were thus very pleased to observe that 1,3-dibromobenzene leads under our three-component cross-coupling reaction with **11** and **12** to 47% of the unsymmetrically coupled product **25a** (Table 4, entry 1), a similar result being obtained using the 4-methoxy- or 4-nitrophenylboronic acids (**23** or **11**) in combination with phenylboronic acid **4** (entries 2 and 3). While these yields are somewhat lower than those obtained

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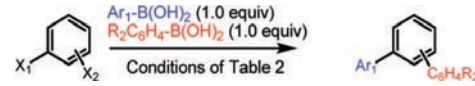
Table 4. Double Coupling with 1,*n*-Dihalobenzene



entry	1,*n*-dihalo	Ar_1	R_2	product	yield[a]
1	1,3-diBr	3,4,5-$(MeO)_3C_6H_2$	**11**: 4-NO_2	**25a**	47
2	1,3-diBr	4-$MeOC_6H_4$	**4**: 4-H	**25b**	40
3	1,3-diBr	4-$NO_2C_6H_4$	**4**: 4-H	**25c**	43
4	1,3-diI	3,4,5-$(MeO)_3C_6H_2$	**11**: 4-NO_2	**25a**	54
5	1,2-diBr	3,4,5-$(MeO)_3C_6H_2$	**11**: 4-NO_2	**25d**	37
6	1,4-diBr	3,4,5-$(MeO)_3C_6H_2$	**11**: 4-NO_2	**25e**	44

[a] Isolated yields after flash chromatography.

using 2,6-dibromopyridine (Table 3, entries 1, 4, and 5), use instead of 1,3-diiodobenzene as substrate now provided the dicoupled compound **25a** in a more satisfactory 54% yield (entry 4).[21] Finally and interestingly, 1,2-dibromobenzene did afford the expected dicoupled product despite considerable steric impediment, albeit in modest yield (37%, entry 5), and 1,4-dibromobenzene gave the *p*-terphenyl derivative **25e** in 44% yield (entry 6).

In conclusion, we have shown that starting from a symmetrical dibromo heterocycle (pyrrole, thiophene, pyridine) or benzene, it is possible to obtain high yields of the unsymmetrically substituted diaryl products using a double Suzuki−Miyaura cross-coupling reaction in which both arylboronic acids are *simultaneously* present in the reaction mixture. Whereas previous strategies to obtain such compounds have relied on tedious stepwise protocols, the success of the present procedure resides in the difference in reactivities, even minor, of each boronic acid. Such a one-pot double cross-coupling strategy should allow the efficient preparation of chemical libraries of potentially bioactive compounds or of natural product analogues.

Acknowledgment. We wish to thank the Institut de Chimie des Substances Naturelles for financial support and a fellowship (F.B.).

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

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(21) It should be mentioned that 1,3-dichlorobenzene failed to react with boronic acids **11** and **12** under our standard coupling conditions.