ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 1553–1555

www.rsc.org/chemcomm

COMMUNICATION

Aminoborylation/Suzuki–Miyaura tandem cross coupling of aryl iodides as efficient and selective synthesis of unsymmetrical biaryls†‡

Ludovic Marciasini,[a] Nicolas Richy,[b] Michel Vaultier[ab] and Mathieu Pucheault*[ab]

Received 27th July 2011, Accepted 20th September 2011
DOI: 10.1039/c1cc14605j

Sequential borylation of a first aryl iodide using a dialkylaminoborane followed by a Suzuki–Miyaura cross coupling of second aryl iodide ended up with an efficient, selective and practical synthesis of unsymmetrical biaryls. This tandem coupling shows a wide range of applicability.

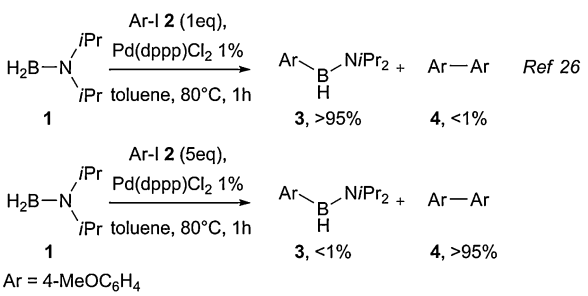
Facilitated by the generalization of transition metal catalysed cross coupling of organometallics, access to unsymmetrical biaryl compounds has witnessed a large increase in its application domains, from advanced material preparation to the synthesis of bioactive molecules.[1] Indeed, the classical preparation of the biaryl scaffold involves the reaction between an organometallic reagent, typically centred on B,[2–4] Si,[5,6] Zn,[7] Mg,[8,9] or Sn,[10] with an aryl halide or pseudo halide, in the presence of transition metal complexes based on Pd, Ni, Pt, Au or Rh. Despite its selectivity and efficiency these methods rely usually on separate organometallic preparation, involving tedious purification steps and stability issues.

Alternatively, reductive coupling of aryl halides could lead to similar products. Since Ullmann's discovery of copper mediated homocoupling of aryl iodides,[1] several advanced methods have been developed for the preparation of unsymmetrical biaryl compounds including catalytic version of the parent reaction. Homocoupling is now well documented and can be performed using Pd,[11–17] Ni,[18,19] or Co[20] complexes as catalysts. In many cases attempts to adapt these methods to the selective synthesis of unsymmetrical biaryls raise selectivity issues. Indeed, the random reaction of two different aryl halides putatively leads to a 1/2/1 mixture of homo- and hetero-coupled products. This statistical reaction outcome can be circumvented on the basis of a large reactivity difference between the two partners,[11,21] usually taking advantages of electronic variations on the aromatic rings as nicely shown by Jutand *et al.*[11] Although this approach would eventually be appealing in some cases, it dramatically decreases the reaction scope to the synthesis of few biphenyl compounds.

The other desymmetrisation approach is associated to the use of different halides, one reacting usually significantly faster than the other. In that regard, some nice methods have been proposed by Gosmini *et al.*,[18–20] using nickel[18,19] or cobalt[20] based catalysts, for the cross coupling of Ar–I with Ar–Br[16] or Ar–Cl,[19] and Ar–Br with Ar–Cl[19] using stoichiometric amounts of Mn[20] or a sacrificial anode[18,19] (Mg, Zn) as reducing agent.

The main method for selective cross coupling of aryl halides relies on generating organometallics from one of the halide, followed by an *in situ* cross coupling with the second partner. As such, many examples can be found in the literature related to *in situ* Negishi or Kumada crosscoupling, using zinc or magnesium[22] species as intermediates.

In our program focused on boron chemistry,[23–28] we thought about using aminoarylboranes **3** as a reagent for Suzuki Miyaura cross coupling. These compounds are simply prepared through palladium catalysed borylation of aryl halides and triflates with diisopropylaminoborane **1**. Although this reaction led in most cases to very little biaryl product **4**, we envisioned to perform a one pot cross coupling with an excess of aryl iodide **2**. Indeed when using 5 equivalents of 4-methoxyphenyl iodide **2a**, the biphenyl compound **4aa** was isolated in 71% yield, showing that these aminoarylboranes could efficiently be used as partners in Suzuki–Miyaura cross coupling. However, despite our effort to optimize the catalytic system, a decrease in aryl halide quantity systematically led to a mixture of the corresponding aminoborane **3a** and biaryl **4aa** as sole products (Scheme 1).



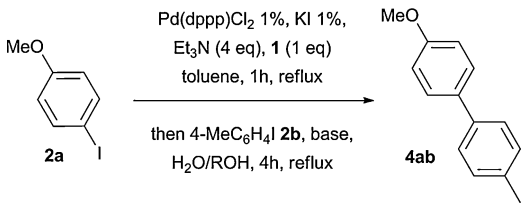
Scheme 1 Synthesis and reactivity of aminoarylboranes.

[a] *Institut des Sciences Moléculaires, UMR CNRS 5255, Université Bordeaux 1, 351 Cours de la Libération, F-33405 Talence Cedex, France. E-mail: m.pucheault@ism.u-bordeaux1.fr*
[b] *Chimie et Photonique Moléculaires, UMR CNRS 6510, Université Rennes 1, Campus de Beaulieu, 263 Avenue du Général Leclerc, F-35042 Rennes Cedex, France*

† This article is part of the *ChemComm* 'Emerging Investigators 2012' themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR spectra. See DOI 10.1039/c1cc14605j

Table 1 Reaction condition optimization



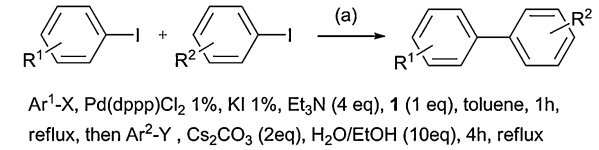
Entry	ROH	H_2O	Base	Conv. (yield[a])
1	—	—	K_2CO_3 2 eq.	80% (76%)
2	MeOH	10 eq.	Cs_2CO_3 2 eq.	85% (74%)
3	EtOH	10 eq.	Cs_2CO_3 2 eq.	100% (quant.)
4	Glycol	10 eq.	Cs_2CO_3 2 eq.	75% (71%)
5	EtOH	30 eq.	Cs_2CO_3 2 eq.	72% (68%)

[a] Isolated yield after purification by flash chromatography.

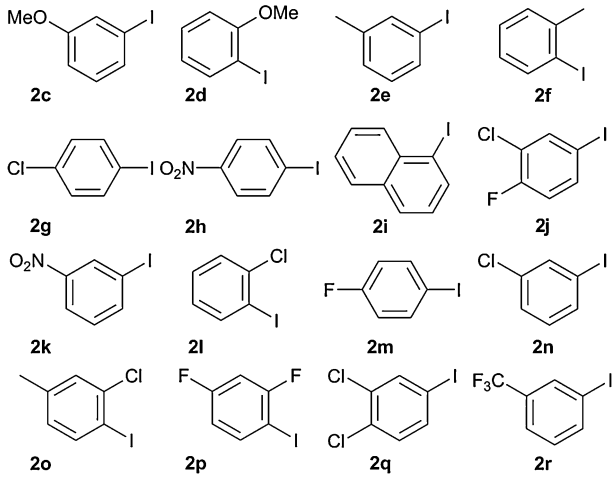
Encouraged by these promising results, we decided to take advantage of the borylation selectivity to perform an *in situ* cross coupling with a second aryl iodide. This borylation Suzuki–Miyaura tandem sequence has been exploited nicely on aryl chlorides using tetrahydroxydiboron[29] to generate a boronic acid intermediate through the addition of an aqueous solution of K_2CO_3. Other scarce examples can be found using dialkoxyborane in the borylation step;[30,31] evaporation between the two steps was required to remove excess borane and for toluene to DMF solvent swap.[31] Interestingly, aminoarylboranes are sufficiently stable to resist aqueous work up, even following a short flash column chromatography. However, in the presence of alcohols, they readily transform into the corresponding boronates, the latter being more easily hydrolyzed. Optimization of the reaction conditions for the second step of the sequence led to the use of a 1/1 mixture of ethanol and water as additive and Cs_2CO_3 as a base under refluxing conditions. The presence of water was found not to be detrimental to the reaction. Palladium source and KI additive were optimized for the borylation step in previous studies,[26,27] and therefore remained unchanged. Keeping Et_3N as sole base for the second step led to decent yields but in average 5–10% below those obtained with inorganic bases (Table 1).

We then embarked into exploring the scope of this reaction and were pleased to find that conversion was reaching in most cases 100%, affording unsymmetrical biaryls in 80–90% isolated yield (Table 2). The borylation step tolerates a wide range of substituents from electron-donating (Table 2, entries 3–11, 14, 15, 18, and 21–25) to electron-withdrawing groups (Table 2, entries 12, 16, and 26). The substituent position on the first aryl iodide has almost no incidence on yields (Table 2, entries 1, 8 and 11). Very similarly for the second step, electronic demand of the substituent has little influence on yields (Table 2, electron rich: entries 1 and 2; electron poor entries 12, 22). Indeed, Suzuki Miyaura cross coupling is known to be favoured using electron rich boron derivatives, prone to transmetallation and electron deficient aryl halides, prone to faster oxidative addition. This general trend can be found in most cases; best yields are obtained with methoxy derived arylaminoborane intermediates, lower yield being obtained when methoxyaryl iodides are employed in the

Table 2 Palladium catalysed selective unsymmetrical biaryl synthesis



Ar^1-X, Pd(dppp)Cl_2 1%, KI 1%, Et_3N (4 eq), **1** (1 eq), toluene, 1h, reflux, then Ar^2-Y , Cs_2CO_3 (2eq), H_2O/EtOH (10eq), 4h, reflux



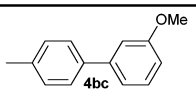
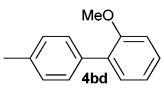
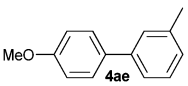
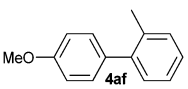
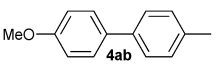
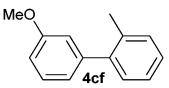
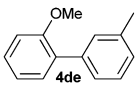
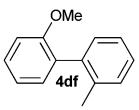
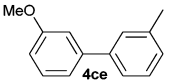
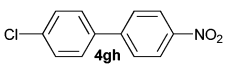
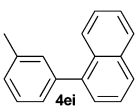
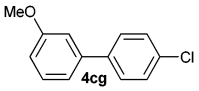
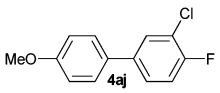
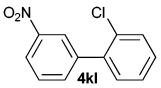
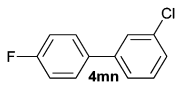
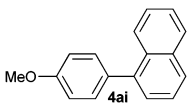
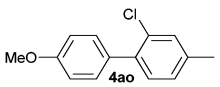
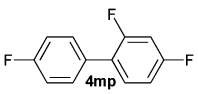
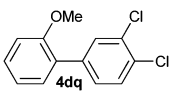
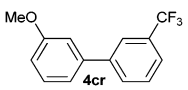
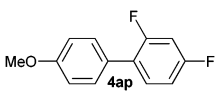
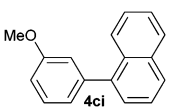
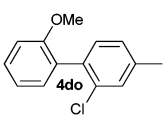
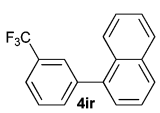
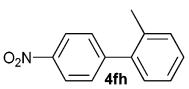
Entry	Ar^1I	Ar^2I	Product	Yield[a]
1	**2b**	**2c**	 **4bc**	64%
2	**2b**	**2d**	 **4bd**	84%
3	**2a**	**2e**	 **4ae**	91%
4	**2a**	**2f**	 **4af**	85%
5	**2a**	**2b**	 **4ab**	Quant.
6	**2b**	**2a**		56%
7	**2c**	**2f**	 **4cf**	80%
8	**2d**	**2e**	 **4de**	87%
9	**2d**	**2f**	 **4df**	81%
10	**2f**	**2d**		39%
11	**2c**	**2e**	 **4ce**	80%
12	**2g**	**2h**	 **4gh**	78%
13	**2e**	**2i**	 **4ei**	73%

Table 2 (*continued*)

Entry	Ar^1I	Ar^2I	Product	Yield[a]
14	**2c**	**2g**	 **4cg**	83%
15	**2a**	**2j**	 **4aj**	68%
16	**2k**	**2l**	 **4kl**	64%
17	**2m**	**2n**	 **4mn**	88%
18	**2a**	**2i**	 **4ai**	89%
19	**2a**	**2o**	 **4ao**	84%
20	**2m**	**2p**	 **4mp**	61%
21	**2d**	**2q**	 **4dq**	97%
22	**2c**	**2r**	 **4cr**	90%
23	**2a**	**2p**	 **4ap**	81%
24	**2c**	**2i**	 **4ci**	79%
25	**2d**	**2l**	 **4do**	94%
26	**2r**	**2i**	 **4ir**	83%
27	**2f**	**2h**	 **4fh**	91%

[a] Isolated yield after purification by flash chromatography.

second step. Overall, halides, nitro, trifluoromethyl, alkyl, alkoxygroup, naphthyl substituent can equally be utilized. So far the only found limitation is related to the competitive reduction of carbonyl groups by the dialkylaminoborane **1** and is yet to be applied to heteroaromatics. The reaction was even slightly halide selective as 4,4′-dibromobiphenyl could be synthesized in 47% yield using 4-bromo-1-iodobenzene **2s** as sole reagent; less than 5% of iodine containing aromatics were isolated from the reaction mixture other than the starting material.

Overall, we have developed an efficient and straightforward access to unsymmetrical biphenyls directly from aryl iodides by using a tandem borylation/Suzuki–Miyaura cross coupling. It is noteworthy that the same reaction using bromoarenes in lieu of aryl iodides led to the same products, showing the wide applicability of that sequence for the practical preparation of such unsymmetrical biaryl compounds.

Johnson, Matthey and Co., Ltd. is gratefully acknowledged for a loan of palladium.

Notes and references

1 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1470.
2 S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633–9695.
3 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.
4 N. Miyaura, in *Cross-Coupling Reactions*, ed. N. Miyaura, Springer, Berlin/Heidelberg, 2002, pp. 11–59.
5 Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918–920.
6 T. Hiyama, *J. Organomet. Chem.*, 2002, **653**, 58–61.
7 E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821–1823.
8 R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 1972, 144a.
9 K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 4374–4376.
10 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524.
11 C. Amatore, E. Carré, A. Jutand, H. Tanaka, Q. Ren and S. Torii, *Chem.–Eur. J.*, 1996, **2**, 957–966.
12 J.-Z. Jiang and C. Cai, *Colloids Surf., A*, 2007, **305**, 145–148.
13 X. Chen and L. Wang, *Chin. J. Chem.*, 2009, **27**, 2037–2042.
14 J. Moon, H. Nam, J. Ju, M. Jeong and S. Lee, *Chem. Lett.*, 2007, 1432–1433.
15 S. Venkatraman, T. Huang and C.-J. Li, *Adv. Synth. Catal.*, 2002, **344**, 399–405.
16 J. Hassan, C. Hathroubi, C. Gozzi and M. Lemaire, *Tetrahedron*, 2001, **57**, 7845–7855.
17 L. Wang, Y. Zhang, L. Liu and Y. Wang, *J. Org. Chem.*, 2006, **71**, 1284–1287.
18 C. Gosmini, J. Y. Nédélec and J. Périchon, *Tetrahedron Lett.*, 2000, **41**, 5039–5042.
19 C. Gosmini, J. Y. Nédélec and J. Périchon, *Tetrahedron Lett.*, 2000, **41**, 201–203.
20 M. Amatore and C. Gosmini, *Angew. Chem., Int. Ed.*, 2008, **47**, 2089–2092.
21 L. Wang and W. Lu, *Org. Lett.*, 2009, **11**, 1079–1082.
22 A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 5010–5014.
23 M. Vaultier and M. Pucheault, *Sci. Synth.*, 2011, **6**, in press.
24 N. Joubert, E. Baslé, M. Vaultier and M. Pucheault, *Tetrahedron Lett.*, 2010, **51**, 2994–2997.
25 M. Vaultier, C. Duriez, L. Euzenat, Y. Ribourdouille and G. Alcaraz, (CNRS, UR1). FR2833957, 2003, p. 15.
26 L. Euzenat, D. Horhant, Y. Ribourdouille, C. Duriez, G. Alcaraz and M. Vaultier, *Chem. Commun.*, 2003, 2280–2281.
27 L. Euzenat, D. Horhant, C. Brielles, G. Alcaraz and M. Vaultier, *J. Organomet. Chem.*, 2005, **690**, 2721–2724.
28 K. K. Kukkadapu, A. Ouach, P. Lozano, M. Vaultier and M. Pucheault, *Org. Lett.*, 2011, 4132–4135.
29 G. A. Molander, S. L. J. Trice and S. D. Dreher, *J. Am. Chem. Soc.*, 2010, **132**, 17701–17703.
30 P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux and F. Colobert, *Org. Lett.*, 2004, **6**, 4419–4422.
31 N. Praveen Ganesh and P. Y. Chavant, *Eur. J. Org. Chem.*, 2008, 4690–4696.