Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Synthesis of sterically encumbered C10-arylated benzo[*h*]quinolines using *ortho*-substituted aryl boronic acids†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 31

Received 14th September 2012,
Accepted 4th October 2012

DOI: 10.1039/c2ob26806j

www.rsc.org/obc

Marko Weimar and Matthew J. Fuchter*

The challenging coupling of 10-halobenzo[*h*]quinolines with *ortho*-substituted aryl boronic acids has been achieved using Pd(OAc)$_2$/P(O)Ph$_3$ as the catalytic system. High yields were obtained for diversely functionalised substrates under mild reaction conditions.

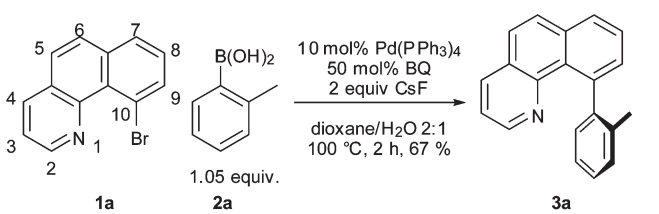
The Suzuki–Miyaura cross-coupling reaction is a highly reliable method to form aryl–aryl bonds starting from an aryl boronic acid and an aryl halide under palladium catalysis.[1] It has already reached an upper level of maturity and is ubiquitously applied in synthetic chemistry, facts recently recognised by the award of a Nobel prize for one of its discoverers.[2] In contrast, the highly researched field of C–H arylation is comparatively still in its infancy.[3] The advantage of this methodology over standard cross-coupling reactions is the fact that it allows the coupling of (at least one) non-functionalised aromatic compounds, thus potentially saving preparative steps and chemical waste.

Benzo[*h*]quinoline represents a prevalent substrate for the development of new directed C–H arylation protocols.[4] However, there is a dearth of examples of reactions using *ortho*-substituted arylating agents,[4b,e] which would afford highly sterically encumbered heterobiaryls. Through restricted rotation about the aryl–aryl bond, such bulky products would likely exist as isolatable atropoisomers and therefore be of significant interest in further conformational and stereochemical studies.[5] We were surprised by this omission from C–H arylation methodology, given that in the field of conventional cross-coupling chemistry,[6] especially the Suzuki–Miyaura reaction,[7] the coupling of bulky substrates is an actively investigated topic. We therefore elected to study the C10-arylation of benzo[*h*]quinoline with bulky *ortho*-substituted arylating agents under both C–H arylation and more conventional coupling conditions.

Initially we screened a significant number of published procedures to examine the feasibility of arylating benzo[*h*]quinoline directly with *ortho*-substituted halobenzenes. In all cases we found that, in the case of such substrates, C–H arylation chemistry was not successful. The only procedure we found to be preparatively viable (to prepare **3a**), was palladium-catalyzed C–H arylation using mixed aryl iodonium salts as reported by Sanford and co-workers.[8] Since this procedure requires prior preparation of bespoke iodonium arylating agents however, the advantages of using direct arylation as opposed to more conventional coupling conditions is less clear. Consequently, we decided to study whether the Suzuki–Miyaura reaction would stand up to these challenging substrates.

Using 10-halobenzo[*h*]quinoline[9] substrates (**1a** or **1b**), no cross-coupling with *o*-toluene boronic acid (**2a**) occurred under standard Suzuki–Miyaura reaction conditions (10 mol% Pd(PPh$_3$)$_4$, 2 equiv. CsF, dioxane–H$_2$O, 100 °C).

We reasoned that the failure of the reaction may be due to stability of the oxidative addition product,[10] shutting down catalysis. Since it has been known for some time that *p*-benzoquinone (BQ) can function as a useful additive to promote transmetallation and reductive elimination of organopalladium complexes,[11] we decided to test the effect it would have on this Suzuki reaction. To our delight, we found that the addition of 0.5 equiv. of BQ to the reaction mixture lead to the formation of **3a** in 67% isolated yield (Scheme 1). While conducting control experiments, we made the surprising



Scheme 1 Suzuki–Miyaura cross-coupling reaction with BQ.

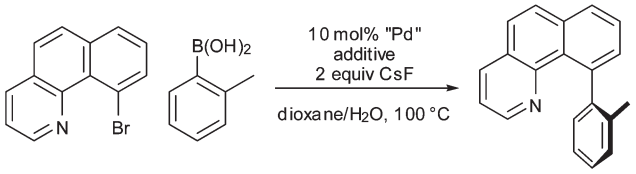
Department of Chemistry, Imperial College London, London SW7 2AZ, UK. E-mail: m.fuchter@imperial.ac.uk; Fax: +44 (0) 2075945805; Tel: +44 (0) 2075945815

†Electronic supplementary information (ESI) available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c2ob26806j

observation that an old batch of $Pd(PPh_3)_4$ furnished the desired product *without* additional BQ. We therefore concluded that one role of BQ may be the oxidation of the PPh_3 ligands to $P(O)Ph_3$ during the course of the reaction (*cf.* slow aerobic degradation of $Pd(PPh_3)_4$). Moreover, we found that PPh_3 suppressed the reaction: An experiment with the "old" $Pd(PPh_3)_4$ catalyst and additional PPh_3 did not yield any product.

In light of these results, we turned our attention to phosphine-free palladium precatalysts and found that a combination of $Pd(OAc)_2$ and $P(O)Ph_3$ led to a fast reaction with complete consumption of **1a** within 10 min at 100 °C (Table 1, entry 2). Denmark and co-workers have previously reported the beneficial effect of $P(O)Ph_3$ in cross-coupling reactions of electron-rich arylsilanolates.[12] At this temperature, comparable results were obtained when a Pd(0) or a Pd(II) source was used (Table 1, entries 3 and 4). Only the heterogeneous catalyst Pd black afforded an incomplete conversion even after 18 h (Table 1, entry 5). Interestingly, with a Pd(0) source ($Pd(dba)_2$) as the catalyst, the addition of $P(O)Ph_3$ was not necessary for the reaction to occur at 100 °C (Table 1, entry 7) whereas with a Pd(II) source ($Pd(OAc)_2$) only traces of **3a** were formed in the absence of $P(O)Ph_3$ (Table 1, entry 6). Upon lowering the reaction temperature however, we observed that a quantitative yield of **3a** was afforded even at ambient temperature when a Pd(II) precatalyst and $P(O)Ph_3$ was used (Table 2, entry 1), whereas the use of a Pd(0) source ($Pd(dba)_2$) was far less effective (Table 2, entry 2). This result highlights the preparative usefulness of a Pd(II) source combined with $P(O)Ph_3$. Furthermore, to our surprise chlorobenzo[*h*]-quinoline **1b** gave a much faster reaction time than with bromo compound **1a**. Indeed, the coupling of substrate **1b** proceeded quantitatively within 0.5 or 2 h, respectively, with CsF or Na_2CO_3 as the base (Table 2, entries 3 and 4), while for **1a** stirring overnight was necessary to reach full conversion.

Table 1 Initial screening of reaction conditions[a]

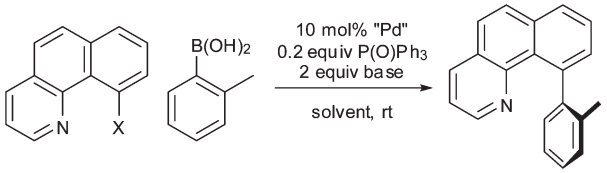


1a **2a** **3a**

Entry	Catalyst	Additive (equiv.)	Time (h)	Conversion[b] (%)
1	$Pd(PPh_3)_4$	BQ (0.5)	2	67[c]
2	$Pd(OAc)_2$	$P(O)Ph_3$ (0.2)	10 min	86
3	$PdCl_2$	$P(O)Ph_3$ (0.2)	0.5	98
4	$Pd(dba)_2$	$P(O)Ph_3$ (0.2)	0.5	83
5	Pd black	$P(O)Ph_3$ (0.2)	18	64
6	$Pd(OAc)_2$	—	1	1
7	$Pd(dba)_2$	—	0.5	86

[a] Reactions were performed on a 0.2 mmol scale with 1.05 equiv. **2a** in 1.5 ml dioxane–H_2O 2 : 1. [b] Determined by NMR based on the ratio of **1a** and **3a**. [c] Isolated yield.

Table 2 Optimisation of reaction conditions[a,b]



1a or **1b** **2a** **3a**

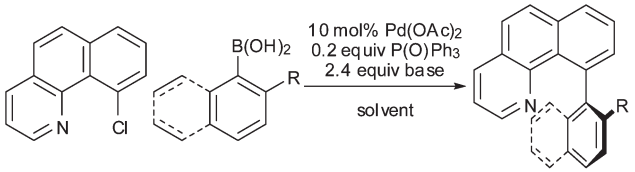
Entry	X	Catalyst	Base	Solvent	Time (h)	Yield[c] (%)
1	Br	$Pd(OAc)_2$	CsF	Dioxane–H_2O 2 : 1	18	98
2	Br	$Pd(dba)_2$	CsF	Dioxane–H_2O 2 : 1	18	52
3	Cl	$Pd(OAc)_2$	CsF	Dioxane–H_2O 2 : 1	0.5	100
4	Cl	$Pd(OAc)_2$	Na_2CO_3	Dioxane–H_2O 2 : 1	2	99
5	Cl	$Pd(OAc)_2$	Na_2CO_3	Dioxane	18	92
6	Cl	$Pd(OAc)_2$	Na_2CO_3	MeOH	5 min	100
7	Cl	$Pd(OAc)_2$[d]	Na_2CO_3	MeOH	0.25	84

[a] Reactions were performed on a 0.1 mmol scale with 1.05 equiv. **2a** in 0.75 ml dioxane–H_2O 2 : 1 or 0.5 ml dioxane or 0.5 ml MeOH. [b] For more results, see ESI.† [c] Isolated yield. [d] 1 mol% $Pd(OAc)_2$.

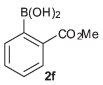
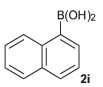
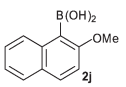
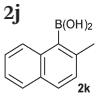
In terms of suitable solvents, we found that under non-aqueous conditions (for example anhydrous dioxane) the reaction took up to 18 h to go to completion (Table 2, entry 5), whereas it was fastest in MeOH where the reaction was complete after about 5 min (Table 2, entry 6). Pleasingly, when the catalyst loading was reduced to 1 mol%, the reaction was still suitably fast, although the product yield dropped slightly (Table 2, entry 7). While we surveyed other phosphine oxide additives, for example $P(O)Cy_3$ or XPhos(O), we found these to be less effective than $P(O)Ph_3$. Additional optimisation conditions can be found in Table S1, ESI.†

Next, the scope of the coupling reaction was examined (Table 3). A variety of *ortho*-substituents were tolerated. In general, electron donating (Me, OMe) and electron withdrawing substituents (CF_3 and Cl) all furnished a high product yield (Table 3, entries 1 to 4). To our surprise, 2-bromobenzeneboronic acid (Table 3, entry 5) was also a suitable substrate, giving the corresponding product in 99% yield; the *ortho*-bromo group proving inert to the reaction conditions. Additional substituents on the aromatic ring did not generally alter the reactivity of the boronic acids (compare Table 3, entry 1 with entry 7) unless the 6-position was occupied in addition to the 2-position. For example, 2,6-dimethylbenzeneboronic acid (Table 3, entry 8) only underwent coupling when the reaction was performed at elevated temperature. Indeed, more sterically encumbered substrates reduced the reaction rate and, depending on the solvent used, led to a side reaction where **1a** or **1b** were converted to the 10-methoxy derivative (in methanol) or the 10-hydroxy derivative (in dioxane–H_2O), respectively. Pleasingly, this side reaction could be avoided simply by switching to THF as solvent. While 10 mol% catalyst was arbitrarily selected from our optimisation studies, we were delighted to observe that analogous results were obtained using 5 mol% (Table 3, entries 4 and 12). The robustness of our method could be demonstrated when the reaction of

Table 3 Scope of the cross-coupling reaction[a,b]



1b **2a-k** **3a-k**

Entry	Boronic acid	Solvent	Base	T (°C)	Time (h)	Yield[c] (%)
1	**2a**	Dioxane–H_2O 2 : 1	CsF	rt	0.5	100
2	 **2b**	Dioxane–H_2O 2 : 1	CsF	rt	18	74
3	 **2c**	Dioxane–H_2O 2 : 1	CsF	rt	18	100
4	 **2d**	Dioxane–H_2O 2 : 1	CsF	rt	10 min	93 (96[d])
5	 **2e**	Dioxane–H_2O 2 : 1	CsF	rt	2 min	99
6	 **2f**	THF	Na_2CO_3	60	18	51
7	 **2g**	Dioxane–H_2O 2 : 1	CsF	rt	0.5	100
8	 **2h**	THF	CsF	60	18	84
9	 **2i**	Dioxane–H_2O 2 : 1	Na_2CO_3	rt	18	85
10	 **2j**	THF	CsF	60	2	88
11[e]	**2j**	THF	CsF	60	2	92
12	 **2k**	THF	CsF	60	18	72 (84[d])

[a] Reactions were performed on a 0.1 mmol scale with 1.2 equiv. boronic acid in 0.75 ml dioxane–H_2O 2 : 1 or 0.5 ml THF. [b] For more results, see ESI.† [c] Isolated yield. [d] Isolated yield using 5 mol% $Pd(OAc)_2$. [e] On gram scale (4.2 mmol **1b**).

2-methoxy-1-naphthylboronic acid with **1b** was conducted on gram scale affording the coupling product in 92% isolated yield (Table 3, entry 11).

In conclusion, we have developed a highly robust and versatile method to prepare bulky C10-arylated benzo[*h*]quinoline products. We envisage these products will be of significant interest in the study of dynamic conformation chemistry and as stereochemical switches. In the developed method, the use of $P(O)Ph_3$ as an additive enabled the formation of a number of sterically encumbered, functionalised products. It is worth reiterating that use of chlorobenzo[*h*]quinoline (**1b**) lead to shorter reaction times than the bromo compound (**1a**), a fact that is counterintuitive for the known reactivity profile of oxidative addition of a Pd(0) species into the carbon–halide bond.[13] Future studies will be aimed at elucidating the mechanistic nature of this interesting transformation and its use in target based synthesis.

We would like to thank the Leverhulme Trust (grant F/07058/BG) for funding this work.

Notes and references

1 (*a*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*c*) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*,

ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, Germany, 1998, p. 49.

2 X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 9047.

3 For reviews discussing C–H arylation, see: (*a*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (*b*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*c*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*d*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*e*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (*f*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.

4 (*a*) L. Ilies, M. Kobayashi, A. Matsumoto, N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.*, 2012, **354**, 593; (*b*) T. W. Lyons, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 4455; (*c*) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109; (*d*) H. Miura, K. Wada, S. Hosokawa and M. Inoue, *Chem.–Eur. J.*, 2010, **16**, 4186; (*e*) N. Luo and Z. Yu, *Chem.–Eur. J.*, 2010, **16**, 787; (*f*) W. Jin, Z. Yu, W. He, W. Ye and W.-J. Xiao, *Org. Lett.*, 2009, **11**, 1317; (*g*) M. Kim, J. Kwak and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 8935; (*h*) X. Zhao and Z. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 8136; (*i*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 11904.

5 (*a*) J. Clayden, S. P. Fletcher, S. J. M. Rowbottom and M. Helliwell, *Org. Lett.*, 2009, **11**, 2313; (*b*) J. Clayden, S. P. Fletcher, J. J. W. McDouall and S. J. M. Rowbottom, *J. Am. Chem. Soc.*, 2009, **131**, 5331; (*c*) M. S. Betson, A. Bracegirdle, J. Clayden, M. Helliwell, A. Lund, M. Pickworth, T. J. Snape and C. P. Worrall, *Chem. Commun.*, 2007, **18**, 754.

6 (*a*) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah and M. G. Organ, *Angew. Chem., Int. Ed.*, 2012, **51**, 3314; (*b*) G. C. Fortman and S. P. Nolan, *Chem. Soc. Rev.*, 2011, **40**, 5151; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555; (*d*) W. Su, S. Urgaonkar, P. A. McLaughlin and J. G. Verkade, *J. Am. Chem. Soc.*, 2004, **126**, 16433.

7 (*a*) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin and S. P. Nolan, *Chem.–Eur. J.*, 2012, **18**, 4517; (*b*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.

8 D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330.

9 (*a*) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Tetrahedron*, 2006, **62**, 11483; (*b*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300.

10 M. Alami, C. Amatore, S. Bensalem, A. Choukchou-Brahim and A. Jutand, *Eur. J. Inorg. Chem.*, 2001, 2675.

11 (*a*) C. Sköld, J. Kleimark, A. Trejos, L. R. Odell, S. O. Nilsson Lill, P.-O. Norrby and M. Larhed, *Chem.–Eur. J.*, 2012, **18**, 4714; (*b*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 9651 and references cited therein.

12 S. E. Denmark, R. C. Smith and S. A. Tymonko, *Tetrahedron*, 2007, **63**, 5730.

13 (*a*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (*b*) V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.

