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Palladium catalyzed cross-coupling between phenyl- or naphthylboronic acids and benzylic bromides

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Abstract

The Suzuki–Miyaura palladium-catalyzed coupling reaction was extended to achieve mixed cross-coupling between substituted aryl and naphthyl mono- and bisbromomethanes with phenylboronic acid, 1-methoxy-2-naphthyl-, 3-methoxy-2-naphthyl-, or 4-methoxy-1-naphthylboronic acid to form the corresponding disubstituted methanes. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Suzuki–Miyaura reactions; palladium catalysts; benzylic bromides; boronic acids; calixnaphthalenes.

The Suzuki–Miyaura palladium-catalyzed cross-coupling reaction[1] between arylboronic acids and aryl halides or triflates has proven to be a very popular and versatile method for forming the carbon–carbon single bonds of simple or complex biaryls. There are many examples which demonstrate diverse and creative applications of the reaction towards challenging synthetic targets such as, for example, the michellamines,[2] macrocyclic oligophenylenes[3] and Cram's cyclic dibenzofuran 'saddle shaped host' compounds.[4] Snieckus' group has developed elegant strategies which combine directed *ortho*- and remote-metalation reactions with Suzuki–Miyaura cross-coupling in the synthesis of kinamycins, and a diverse array of other natural products.[5]

A wide range of aryl and 1-alkenylborane reagents undergo the Pd(0)-catalyzed cross-coupling reactions with alkyl, allylic, 1-alkenyl, aryl, and 1-alkynyl substrates.[1] However, there is only one reported example in which a benzylic halide, namely 2,4-dimethoxybenzyl chloride, has been employed with Suzuki–Miyaura-type conditions. In this example, the benzylic chloride was coupled with 1-naphthylboronate which was generated in situ from 1-bromonaphthalene in a modification of the Suzuki–Miyaura reaction conditions.[6] Negishi had earlier reported Pd(0)- and Ni(0)-catalyzed syntheses of unsymmetrical diarylmethanes via the corresponding benzylzinc bromides or benzylmagnesium chlorides with aryl bromides or iodides.[7] There are other instances in which Pd(0)-catalyzed coupling of benzylic halides under Stille-type conditions have been reported.[8] Brandsma et al.[9] evaluated benzyl–aryl cross-couplings for the syntheses of various tetrachlorobenzyltoluenes using four different transition metal catalysts with a number of different aryl metal compounds, however, they did not employ Suzuki–Miyaura conditions.

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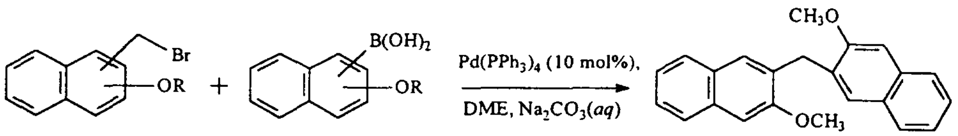
In connection with our work on convergent syntheses of calixnaphthalenes,[10] we were interested in evaluating the suitability of using the Suzuki–Miyaura methodology to produce synthetic bisnaphthylmethane intermediates which contain functionalized naphthyl units connected by methylene bridges (Scheme 1).



(Table 2, Entry 4)

Scheme 1.

As a model study to evaluate the chemistry of bromomethyl-functionalized naphthalenes, preliminary investigations were carried out using benzyl bromide and several representative methyl-, chloro- or nitro-substituted benzyl bromides with phenylboronic acid. Aryl bromomethyl derivatives were chosen for this study mainly because they can conveniently be prepared by a variety of different methods including, e.g., light-initiated bromination of methylaryls with *N*-bromosuccinimide, or direct bromomethylation of phenols or naphthols, using formaldehyde and HBr in acetic acid.

As summarized in Table 1 (all yields reported in Tables 1 and 2 are isolated, unoptimized yields), good yields of mixed diarylmethanes were obtained by the Pd(0)-catalyzed cross-coupling procedure.[11] The yields were relatively unaffected by the presence of either an electron-donating or withdrawing group

Table 1

Cross-coupling products of benzyl halides with phenylboronic acid and 3-methoxy-2-naphthylboronic acid

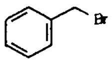
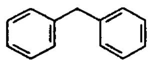
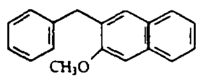
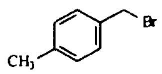
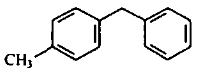
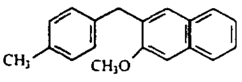
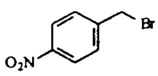
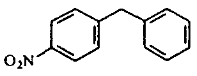
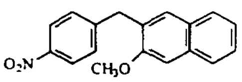
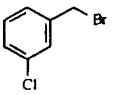
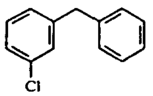
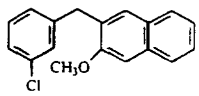
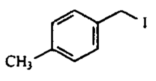
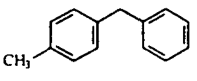
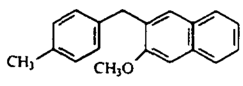
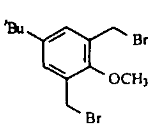
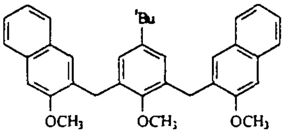
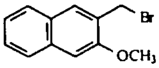
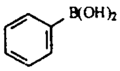
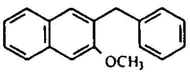
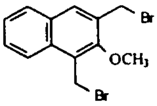
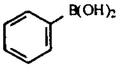
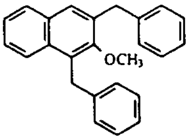
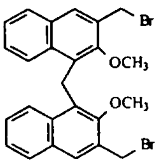
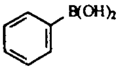
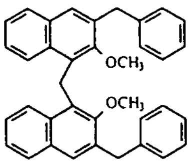
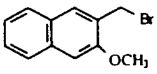
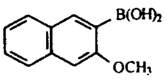
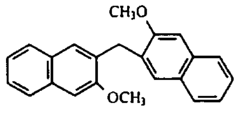
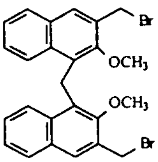
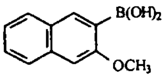
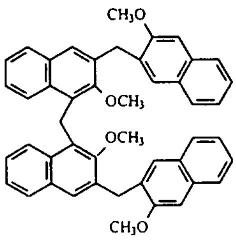
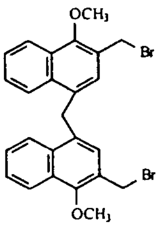
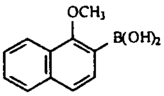
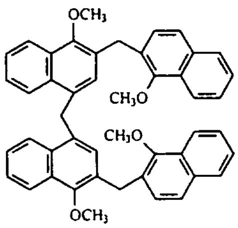
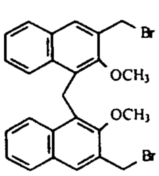
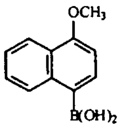
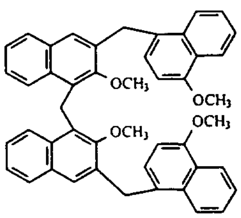
Entry	Benzyl halide	Product with PhB(OH)$_2$	Yield (%)	Product with NaphB(OH)$_2$	Yield (%)
1			80		75
2			75		57
3			82		68
4			85		70
5			81		61
6					42

Table 2
Cross-coupling products of bromomethylnaphthalenes with phenylboronic acid and methoxynaphthylboronic acids

Entry	Naphthyl halide	Boronic acid	Product	Yield (%)
1				65
2				35
3				45
4				80
5				58
6				80
7				60

on the benzyl halide. By contrast, Miyaura et al. has reported that the presence of electron-donating groups lead to diminished yields of aryl–aryl cross-coupled products.[12] A slightly higher yield of coupled product only was obtained with benzyl iodide versus benzyl bromide. Table 1 also presents the products and the respective yields of the cross-coupled products obtained with the benzyl halides and 3-methoxy-2-naphthylboronic acid. Entry 7 shows that the bisbromomethyl compound also gave a good yield of the corresponding bisnaphthyl product. Longer reaction times and higher catalyst loadings[11] were required for substrates containing two bromomethyl functional groups (Table 1, entry 6; Table 2, entries 2, 3 and 5–7), as compared to those which contain only one (Table 1, entries 1–5; Table 2, entries 1 and 4). $Pd(PPh_3)_4$ was found to be the most convenient catalyst to use, although other Pd catalysts gave similar results.

In order to evaluate the efficacy of the procedure using bromomethylnaphthalenes, phenylboronic acid was coupled with 3-bromomethyl-2-methoxynaphthalene, 1,3-bisbromomethyl-2-methoxynaphthalene, and bis(3-bromomethyl-2-methoxynaphthyl)methane (Table 2, entries 1, 2 and 3, respectively). Cross-coupling could also be effected in reasonable yields when the substituted naphthylboronic acids, 3-methoxy-2-naphthylboronic acid, 1-methoxy-2-naphthylboronic acid and 4-methoxy-1-naphthylboronic acid were employed with the bromomethylnaphthalenes shown in Table 2 (entries 4–7, respectively). Syntheses of both 1-methoxy- and 3-methoxy-2-naphthylboronic acids were achieved using Biehl's method[13] to generate the corresponding *o*-lithiated intermediates, which were subsequently quenched in situ with trimethylborate, followed by acidic workup.

In summary, we have shown that the Suzuki–Miyaura methodology can be extended to achieve cross-coupling between phenylboronic acid and benzylic bromides, iodides or bromomethylnaphthalenes in synthetically useful yields. Also, efficient cross-coupling could be effected between various bromomethylnaphthalenes and methoxy-substituted 1- and 2-naphthylboronic acids. In particular, the naphthalene ring-containing cross-coupled products shown as entries 4–7 in Table 2 allow for potential convergent synthesis of 'mixed' *endo*- and *exo*-functionalized calix[4]naphthalenes. With these compounds in hand, experiments are currently on-going to effect cyclization to the corresponding C_{2v}-symmetrical calix[4]napthalenes.

Acknowledgements

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References

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
2. Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940–7942, and references cited therein.
3. Hensel, V.; Lützow, K.; Jacob, J.; Gessler, K.; Saenger, W.; Schlüter, A.-D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2654–2656.
4. Schwartz, E. B.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 10775–10784.
5. Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072–7273, and references cited therein.
6. Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501–6503.
7. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823.
8. Kamlage, S.; Sefkow, M.; Peter, M. G. *J. Org. Chem.* **1999**, *64*, 2938–2940, and references cited therein.
9. de Lang, R.-J.; van Hooijdonk, M. J. C. M.; Brandsma, L. *Tetrahedron* **1998**, *54*, 2953–2966.
10. Georghiou, P. E.; Ashram, M.; Li, Z.-P.; Chaulk, S. G. *J. Org. Chem.* **1995**, *60*, 7284–7289.

11. Typical Pd(0)-catalyzed cross-coupling procedure: A 3-neck flask equipped with a reflux condenser, septum and stirring bar was charged with halide (1 mmol) and $Pd(PPh_3)_4$ (3 mol% or 5–10 mol% for mono- or bisbromomethyl-substrates, respectively) in DME (10 mL), under argon. The mixture was stirred at 50°C for 10 min. To this solution was added the boronic acid (1.5 mmol) dissolved in a minimum amount of EtOH:DME (1:2) and aqueous 2 M Na_2CO_3 (2 mL). The reaction mixture was heated at reflux for 16–18 h (up to 36–48 h for bisbromomethyl-containing substrates), cooled and extracted with CH_2Cl_2. The solution of the extract was dried over $MgSO_4$ and filtered. Evaporation of the solvent gave a crude product which was flash column chromatographed to afford the cross-coupled product.
12. Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993–2996.
13. Biehl, E. R.; Deshmukh, A. R.; Dutt, M. *Synthesis* **1993**, 885–888.