DOI: 10.1002/ejoc.200800544

One-Pot Dual Substitutions of Bromobenzyl Chloride, 2-Chloromethyl-6-halogenoimidazo[1,2-*a*]pyridine and -[1,2-*b*]pyridazine by Suzuki–Miyaura Cross-Coupling Reactions

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Keywords: Suzuki–Miyaura cross-coupling / Nitrogen heterocycles / Halides / Palladium / Diarylmethanes

A very simple, mild and inexpensive palladium-catalyzed cross-coupling of (hetero)arylboronic acids with benzylic halides occurs in good yield. This method was successfully expanded to two heterocyclic electrophiles and allowed one-pot dual substitutions of bromobenzyl chloride, 2-chloromethyl-6-halogenoimidazo[1,2-*a*]pyridine or -[1,2-*b*]pyridazine, leading to numerous new unsymmetrical methylene-linked biaryl systems.

Introduction

Unsymmetrical methylene-linked biaryl systems are important building blocks in organic chemistry, and are commonly found in numerous classes of biologically active compounds and pharmaceuticals.[1] They can be obtained by a Suzuki–Miyaura reaction by using benzylic halides, carbonates or acetates as electrophilic substrates. High functional group tolerance, easy separability, nontoxic byproducts, and increasing commercial availability of boron coupling partners have made the Suzuki–Miyaura coupling a popular and effective tool. However, relatively few results have been reported for palladium-catalyzed benzylic substitutions, and the different methods reported in the literature to access methylene-linked biaryl systems possess distinct drawbacks.[2] Thus, in various methods, the electrophile,[3] the boron coupling partner[2] or the palladium complex have to be preformed, e.g., the palladacycles used by Botella and Nájera.[4] The development of direct catalytic reactions in which products are obtained from the reaction of prior unmodified substrates is an important task notably for industrial applications. Some of the reported procedures also engendered significant stoichiometric inefficiencies, requiring 1.5[4a,4b,4d,5] or 2.0[6] equiv. of boronic acid. Moreover, the proposed methods may require long reaction times,[2,3,6a,7] with reactions lasting sometimes more than a few days at room temperature.[4a,4b] Finally, previous work synthesizing diarylmethanes by a Suzuki–Miyaura cross-coupling demonstrated only few examples of heteroaryl substrates as either coupling partner. Few methods have been reported for the coupling of benzylic electrophiles to heteroarylboron coupling partners,[3,4b,6a,7] and only a few results have been reported on the coupling of heterocyclic electrophiles.[4a,4b]

During the course of our work to synthesize highly functionalized imidazo[1,2-*a*]pyridines as potential biologically active compounds, we previously reported the reactivity of this heterocycle toward the Suzuki cross-coupling reaction.[8] Surprisingly, the conventional Suzuki conditions applied to the 6-bromo-2-chloromethylimidazo[1,2-*a*]pyridine led to the monosubstitution of the chlorine atom. From the literature, it appeared that Chowdhury and Georghiou had previously described a similar procedure for the cross-coupling between phenyl or naphthylboronic acids and benzylic bromides.[9] However, this procedure was criticized notably by Botella and Nájera,[4a] as it required heating for 18 h under argon and a high catalyst loading, and explored only phenyl and naphthyl substrates.

In this paper, we wish to report that a simplified and milder Suzuki–Miyaura procedure using $Pd(PPh_3)_4$ as catalyst is able to perform the cross coupling of benzylic halides and arylboronic acids. We expand the scope of this method to two chloromethylheterocycles and various (hetero)arylboronic acids. A high degree of flexibility with regard to functional groups is tolerated. Moreover, we expand the scope of this method to the one-pot dual substitution of bromobenzyl bromide, 2-chloromethyl-6-halogenoimidazo[1,2-*a*]pyridine or -[1,2-*b*]pyridazine.

Results and Discussion

Our studies began using the reaction conditions we previously described in the imidazo[1,2-*a*]pyridine series: benzyl chloride (0.5 mmol), boronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (2 mol-%) and Na_2CO_3 (2.1 equiv.) in a mixture of DME

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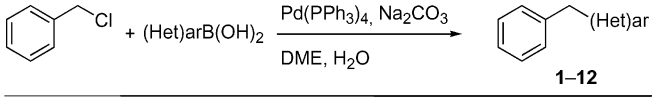
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

(2 mL) and H_2O (1 mL).[8] The only specificity of these Suzuki–Miyaura conditions was the use of sealed tubes in which the reaction was heated at 100 °C for 4 h. These conditions are very close to those described by Langle et al.[7] but led to better yields in shorter reaction times. To gain some insight into the effect of the ring substituents and the nature of the boronic acid, a number of competitive experiments were performed. In the first approach, these reaction conditions were applied to the coupling of various (hetero)arylboronic acids to benzyl chloride. As shown in Table 1, six diversely substituted phenylboronic acids were evaluated, providing the attempted coupling products in around 94% yield. All the reported yields are given after purification of the compounds and no starting material was recovered at the end of the reaction. A high degree of diversity in the aryl substituents was tolerated, including electron-withdrawing groups (entries 1 and 5) and electron-donating groups (entries 2, 3, 4 and 6), whatever the position of the substitution. Even a sterically hindered aryl boronic acid (entry 6) was efficiently coupled to benzyl chloride in 99% yield. The same diversity was allowed using heteroarylboronic acids, as all the substrates investigated gave the diarylmethane products in good yields (83 to 99%). These results indicate that the cross-coupling reaction of benzyl chloride with various boronic substrates is not sensitive to steric and electronic effects.

Table 1. Coupling of benzyl chloride with (hetero)arylboronic acids.[a]



1–12

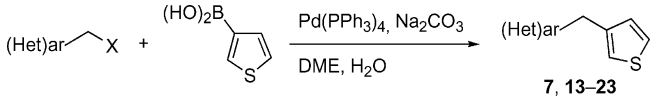
Entry	(Het)ar	Compd.	Yield [%][b]
1	3-bromophenyl	**1**	91
2	4-methoxyphenyl	**2**	84
3	3-methoxyphenyl	**3**	93
4	2-methoxyphenyl	**4**	99
5	3-nitrophenyl	**5**	93
6	2,4,6-trimethylphenyl	**6**	99
7	thien-3-yl	**7**	95
8	thien-2-yl	**8**	95
9	fur-3-yl	**9**	87
10	fur-2-yl	**10**	83
11	pyridin-4-yl	**11**	99
12	pyridin-3-yl	**12**	94

[a] Reaction conditions: benzyl chloride (0.5 mmol), boronic acid (0.6 mmol), $Pd(PPh_3)_4$ (2 mol-%), Na_2CO_3 (1.05 mmol), DME (2 mL), H_2O (1 mL) at 100 °C for 4 h in a sealed tube. [b] Isolated yields.

We then considered it interesting to compare our method to the procedure described by Nobre and Monteiro,[5] which was applied only to phenylboronic acids without exploring heteroarylboronic acids. We decided to apply their conditions using 1 mol-% of $Pd(OAc)_2$, 2 mol-% of PPh_3 and 2 equiv. of K_3PO_4 in toluene, for the coupling of thien-3-ylboronic acid and benzyl chloride. After 19 h of heating at 80 °C, only 61% of the attempted coupling product was obtained along with 22% of starting material, compared to 95% yield with our method after 4 h.

Next, the influence of the nature of the electrophile was explored using diversely substituted arylmethyl halides and thien-3-ylboronic acid. The reason for choosing this boronic acid was that the heteroarylboronic acids were less studied than the phenyl substrates. As shown in Table 2, the attempted coupling products were obtained in around 95% yield. As previously observed, electron-withdrawing or electron-donating groups present on the benzyl chloride had no effect on the coupling efficacy, whatever the position of the substituent. Replacing the chlorine atom with a bromine had no significant effect on the yield, as the coupling of benzyl bromide with thien-3-ylboronic acid provided 99% of phenylthienylmethane (entry 10, Table 2) compared to 95% starting from benzyl chloride (entry 7, Table 1). Interestingly, the 2-, 3-, and 4-bromobenzyl chlorides were substituted specifically on the alkyl group (entries 7–9, Table 2).

Table 2. Coupling of diversely substituted arylmethyl halides and thien-3-ylboronic acid.[a]



7, 13–23

Entry	(Het)ar	X	Compd.	Yield [%][b]
1	4-methylphenyl	Cl	**13**	93
2	3-methylphenyl	Cl	**14**	90
3	2-methylphenyl	Cl	**15**	99
4	4-methoxyphenyl	Cl	**16**	93
5	3-methoxyphenyl	Cl	**17**	98
6	2-methoxyphenyl	Cl	**18**	92
7	4-bromophenyl	Cl	**19**	94[c]
8	3-bromophenyl	Cl	**20**	93[c]
9	2-bromophenyl	Cl	**21**	90[c]
10	phenyl	Br	**7**	99
11	6-bromoimidazo[1,2-*a*]pyridin-2-yl	Cl	**22**	66[c,d]
12	6-chloroimidazo[1,2-*b*]pyridazin-2-yl	Cl	**23**	95[c]

[a] Reaction conditions: benzyl chloride (0.5 mmol), boronic acid (0.6 mmol), $Pd(PPh_3)_4$ (2 mol-%), Na_2CO_3 (1.05 mmol), DME (2 mL), H_2O (1 mL) at 100 °C for 4 h in a sealed tube. [b] Isolated yields. [c] 0.5 mmol of boronic acid was used. [d] 8% of disubstituted derivatives were recovered.

Two heterocycles were evaluated in these Suzuki conditions. On 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine, the substitution took place specifically on the methylene group (entry 12, Table 2). In the case of the 6-bromo-2-chloromethylimidazo[1,2-*a*]pyridine, only 8% of the disubstituted product was obtained, which was easily separated from the monosubstituted compound (entry 11, Table 2). This provides a new method to rapidly functionalize the 2-position of the imidazo[1,2-*a*]- and -[1,2-*b*]pyridazine series.

The catalyst loading of our method can be considered quite high as compared to methods given in the literature. However, this is due to the low mass of starting material we decided to use in our study and the difficulty we encountered in weighing precisely very low quantities of catalyst. To determine if the catalyst loading could be reduced, a few more experiments were performed using 1 mol-%, 0.1 mol-% or 0.01 mol-% of $Pd(PPh_3)_4$ to catalyze the coupling of

benzyl chloride and thien-3-ylboronic acid in the conditions given in Table 1. Only the reaction using 0.01 mol-% of $Pd(PPh_3)_4$ was performed in a round-bottomed flask starting from 500 mg of benzyl chloride in a refluxing mixture of 15 mL of DME and 7.5 mL of water. No significant variation of the coupling yields was observed whatever the catalyst loading (95 to 98% yields). This also demonstrates that this method can be efficiently applied to larger scale of starting material, in a conventional flask and at lower temperature.

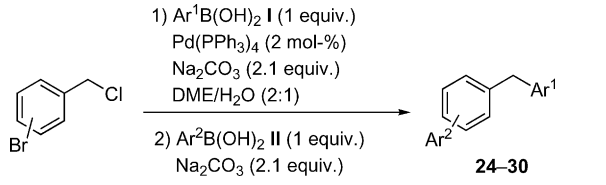
The temperature of heating could also be considered as a detrimental criterium. We experimented with the coupling of benzyl chloride and thien-3-ylboronic acid under the conditions described in Table 1 at room temperature. After 18 h of stirring, a 93% yield of coupling product was obtained.

Nevertheless, the following experiments were performed in sealed tubes at 100 °C, with the aim of making the small volumes introduced easier to handle and shortening the reaction times.

From the previously observed monosubstitution of the bromobenzyl chloride (Table 2), we envisaged realizing a one-pot dual Suzuki coupling to substitute successively the aliphatic then the aromatic halogens with distinct (hetero)-aryl groups in one step. This could provide a very interesting and straightforward route for obtaining of diversely substituted aryl(substitutedaryl)methanes (Table 3). Thus, 4-bromobenzyl chloride was treated with one equivalent of thien-3-ylboronic acid in the presence of $Pd(PPh_3)_4$ (2 mol-%) and 2.1 equiv. of sodium carbonate, in a mixture of DME and water (2:1). After 4 h of heating at 100 °C, one equivalent of phenylboronic acid and 2.1 equiv. of sodium carbonate were added to the reaction mixture. The reaction mixture was stirred 4 h at 100 °C, yielding, after workup, 76% of the desired 3-(biphen-4-ylmethyl)thiophene (**24**; entry 1, Table 3). The average yield of the one-pot dual Suzuki couplings was 64%. Depending on the reactivity of the both boron coupling partners, the attempted heterocoupling products **25**–**29** were obtained along with around 15–20% of homocoupling derivatives, either with the first arylboronic acid introduced **I** or with the second arylboronic acid **II**. The elimination of the byproducts was performed by chromatography.

Finally, two different aromatic rings were successively introduced onto 6-bromo-2-chloromethylimidazo[1,2-*a*]pyridine (Table 4), yielding the attempted coupling products **31**–**34** in 48–74% yield. The same results were obtained using 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine as starting material (Table 5), leading to **35**–**38** in 48–62% yield. As previously observed, some homocoupling products were recovered at the end of the reaction and were eliminated by column chromatography.

Table 3. One-pot dual arylations of bromobenzyl chloride.[a]

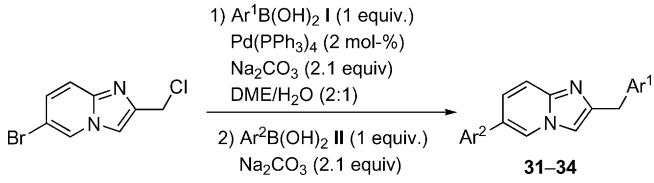


24–30

Entry	Compd.	Ar^2	Ar^1	Yield [%][b]
1	**24**	4-(phenyl)	thien-3-yl	76
2	**25**	4-(thien-3-yl)	4-methoxyphenyl	58
3	**26**	4-(3-trifluoromethyl)	2,4,6-trimethylphenyl	68
4	**27**	4-(fur-3-yl)	phenyl	53
5	**28**	4-(fur-2-yl)	thien-3-yl	58
6	**29**	3-(thien-3-yl)	3-methoxyphenyl	81
7	**30**	3-(4-fluorophenyl)	fur-3-yl	78

[a] Reaction conditions: bromobenzyl chloride (0.5 mmol), boronic acid **I** (0.5 mmol), $Pd(PPh_3)_4$ (2 mol-%), Na_2CO_3 (1.05 mmol), DME (2 mL), H_2O (1 mL) at 100 °C for few hours in a sealed tube, then boronic acid **II** (0.5 mmol) and Na_2CO_3 (1.05 mmol) at 100 °C for 4 h. [b] Isolated yields.

Table 4. One-pot dual arylations of 6-bromo-2-chloromethylimidazo[1,2-*a*]pyridine.[a]

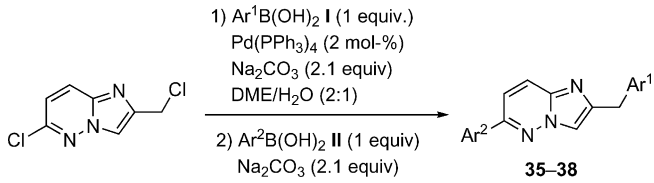


31–34

Entry	Compd.	Ar^2	Ar^1	Yield [%][b]
1	**31**	phenyl	thien-3-yl	74
2	**32**	thien-3-yl	fur-3-yl	65
3	**33**	thien-3-yl	phenyl	62
4	**34**	4-methoxyphenyl	4-fluorophenyl	48

[a] Same reaction conditions as those given in Table 3. [b] Isolated yields.

Table 5. One-pot dual arylations of 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine.[a]



35–38

Entry	Compd.	Ar^2	Ar^1	Yield [%][b]
1	**35**	thien-3-yl	fur-3-yl	48
2	**36**	thien-3-yl	phenyl	49
3	**37**	4-methoxyphenyl	4-fluorophenyl	62
4	**38**	phenyl	fur-3-yl	58

[a] Same reaction conditions as those given in Table 3. [b] Isolated yields.

Conclusions

In conclusion, we present herein a very simple, inexpensive and mild method for the Suzuki–Miyaura coupling of benzyl halides with various (hetero)aryl boronic acids. This reaction is performed on unmodified starting materials using a common palladium source, $Pd(PPh_3)_4$, and sodium carbonate in a mixture of DME/water (2:1). We demon-

strated that this procedure is efficient using as low as 0.01 mol-% of catalyst, and can be performed at room temperature. This method was successfully expanded to two heterocyclic electrophiles and allowed one-pot dual substitutions of bromobenzyl chloride, 2-chloromethyl-6-bromoimidazo[1,2-*a*]pyridine, and 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine, leading to numerous new unsymmetrical methylene-linked biaryl systems.

Experimental Section

General Method for the Preparation of Compounds 1–18: Into a dried sealed-tube was introduced, under argon, benzyl chloride (0.5 mmol), Na_2CO_3 (1.05 mmol), the corresponding boronic acid (0.6 mmol), tetrakis(triphenylphosphane)palladium (0.01 mmol), 1,2-dimethoxyethane (2 mL) and water (1 mL). The tube was sealed and heated at 100 °C for 4 h. After cooling, the resulting mixture was diluted in water, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness. The residue was purified by column chromatography.

General Method for the Preparation of Compounds 19–23: The reaction was carried out as described in the previous method using 0.5 mmol of boronic acid.

General Method for the Preparation of Compounds 24–38: Into a dried, sealed tube was introduced, under argon, (ar)alkyl halide (0.5 mmol), Na_2CO_3 (1.05 mmol), boronic acid **I** (0.5 mmol), tetrakis(triphenylphosphane)palladium (0.01 mmol), 1,2-dimethoxyethane (2 mL) and water (1 mL). The tube was sealed and heated at 100 °C for 4 h. The reaction was followed by TLC. After cooling, boronic acid **II** (0.5 mmol) and Na_2CO_3 (1.05 mmol) were introduced. The tube was sealed, and the mixture was heated at reflux at 100 °C for 4 h. The reaction was followed by TLC. After cooling, the resulting mixture was diluted with water, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness. The residue was purified by column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectral data of all compounds.

Acknowledgments

We express grateful acknowledgement to Frederic Montigny (SAVIT) for the NMR spectroscopic data.

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Received: June 5, 2008
Published Online: August 26, 2008

