Tetrahedron Letters 50 (2009) 1596–1599

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

B-Alkyl Suzuki–Miyaura cross-coupling of tri-*n*-alkylboranes with arylbromides bearing acidic functions under mild non-aqueous conditions

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ARTICLE INFO

Article history:
Received 9 July 2008
Revised 9 January 2009
Accepted 19 January 2009
Available online 23 January 2009

ABSTRACT

An efficient and chemoselective Pd-catalyzed *B*-alkyl Suzuki–Miyaura cross-coupling of tri-*n*-alkylboranes with arylbromides possessing acidic functions is described. This protocol features the relatively weak base Cs_2CO_3 and mild non-aqueous conditions. Aldehydes, ketones, nitriles, and chloro substitution are all tolerated.

Alkylarenes are omnipresent in all fields of organic chemistry. Classical methods of preparation for alkylarenes include the Friedel–Crafts alkylation[1] and Friedel–Crafts acylation[2]-reduction[3] sequence. Since the 1980s, the Suzuki–Miyaura,[4] Negishi[5], and Stille–Migita–Kosugi[6] cross-couplings of alkyl-metal species with aryl halides or sulfonates have emerged as excellent alternatives, due to their site-specificity, selectivity, and the mildness of palladium catalysis. Among them, the Suzuki coupling is particularly popular, thanks to the environmental friendliness as well as the ease of preparation and workup of organoboron compounds. The alkyl-metal reagents in the Suzuki coupling were normally *B*-alkyl-9-BBNs, which were usually prepared via hydroboration and used in situ necessitating prior protection for many sensitive functions. It should also be noted that hydroboration of lower alkenes is inconvenient. The groups of Molander and Falck have widened the scope of the reaction by using alkyltrifluoroborates[7] and alkylboronic acids[8] as stable coupling partners. On the other hand, Suzuki coupling using tri-*n*-alkylboranes[9] has only been documented sporadically in which the electrophiles were the most reactive aryl iodides or activated triflates.[4b,10] Thus, the advantage of using tri-*n*-alkylboranes for the introduction of lower alkyls has not been fully explored and recognized. Nonetheless, systematic study on the direct coupling in the presence of acidic functions (e.g., carboxylic acids and phenols) is lacking. Indeed, considering the protolysis of trialkylboranes by carboxylic acids and phenols,[11] this type of direct coupling is non-trivial. For example, reaction of 4-bromobenzoic acid with methylboronic acid was unsatisfactory.[12] 4-Bromophenol failed to couple with alkyltrifluoroborates.[7b] Unprotected indole NH was often detrimental.[13] In this respect, Blum and co-workers achieved cross-methylation using aluminum and indium reagents.[14] Excess Grignard reagents did couple with halobenzoic acids, but apparently aldehydes and ketones cannot survive.[15] Herein, we report our results for direct cross-alkylation of arylbromides bearing unmasked acidic functions as well as common polar groups.

4-Bromobenzoic acid (**1a**) was chosen as a reference substrate to explore the reaction conditions (Table 1). Commercial Pd(0) catalyst with added mono- and bi-dentate phosphane ligands was inactive (entries 1–4). Pd(0) prepared in situ showed promising results at a high catalyst loading (10 mol %), while $Pd(PPh_3)_2Cl_2$ improved the conversion marginally. Gratifyingly, with 2 mol % $Pd(dppf)Cl_2$, the reaction was complete within 2–3 h in excellent yield (99%). Triethylborane (3 equiv) was used to drive the reaction to completion, similar to results reported for alkyl-aluminum and indium reagents[14] (entries 7–9). Next, several bases were screened, among them Cs_2CO_3 (2 equiv) was the most effective, while K_2CO_3 and K_3PO_4 (in DMF–THF) both gave inferior results in terms of conversion and yield. It is also interesting to note that the protocol in Suzuki's seminal paper[4b] (3 M aq KOH) resulted in somewhat lower yields. In this connection, the anhydrous condition seems to be superior for aryl bromides, probably with some obscure mechanistic causes.[8a] This was contrary to the general observation that water was beneficial or even indispensable for the Suzuki coupling in various catalytic systems. A similar rare exception was also noted by Molander's group in the coupling of aryltriflates with potassium alkynyltrifluoroborates.[16]

Next, the scope and limitation of the reaction were examined with a series of bromo-substituted aromatic acids (Table 2). For

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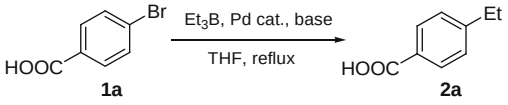
doi:10.1016/j.tetlet.2009.01.090

Table 1
Optimization of reaction conditions[a]



1a 2a

Entry	Catalyst (mol %)	Base (equiv)	Conv. (%)	Yield[b] (%)
1	$Pd_2(dba)_3$-4 PPh_3 (5)	Cs_2CO_3 (2)	Trace	nd
2	$Pd_2(dba)_3$-2 dppf (5)	Cs_2CO_3 (2)	Trace	nd
3	$Pd_2(dba)_3$-2 dppp (5)	Cs_2CO_3 (2)	Trace	nd
4	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2)	Trace	nd
5	$Pd(OAc)_2$-4 PPh_3 (10)	Cs_2CO_3 (2)	40	38
6	$Pd(PPh_3)_2Cl_2$ (3)	Cs_2CO_3 (2)	58	54
7	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	100	99
8[c]	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	56	52
9[d]	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	70	66
10	$Pd(dppf)Cl_2$ (2)	K_2CO_3 (3)	<5	nd
11[e]	$Pd(dppf)Cl_2$ (2)	K_3PO_4 (3)	90	76
12	$Pd(dppf)Cl_2$ (2)	3 M KOH (3)	100	82

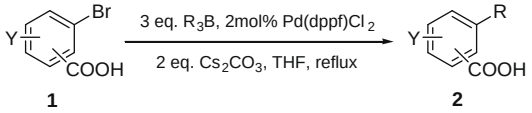
[a] All reactions run on 1.0 mmol scale with 3.0 equiv Et_3B in 5.0 mL THF under reflux for 2–3 h, unless otherwise noted.
[b] Isolated yield.
[c] With 1.2 equiv Et_3B.
[d] With 2.0 equiv Et_3B.
[e] In DMF–THF (1:1), no reaction in THF.

these compounds with diverse substitution patterns, including salicylic acid derivatives (entries 4 and 5), good to excellent yields were obtained. On the other hand, chloro substitution was not affected under the present conditions (entry 5). Variation of the nucleophiles was also carried out, using tri-*n*-butylborane, which gave the desired products in comparable yields (entries 3, 4, and 7). However, attempts to extend the reaction to α-branched nucleophiles (e.g., tri-2-propylborane) were unsuccessful, probably due to very high steric hindrance around boron that impeded the key process of transmetalation.

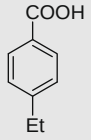
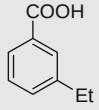
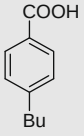
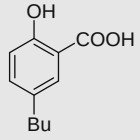
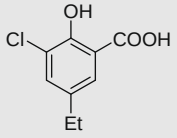
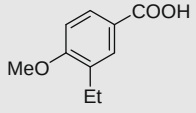
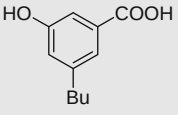
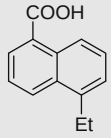
Results for substrates bearing other acidic OH and NH functions are summarized in Table 3. We focused on unactivated bromoarenes, as the coupling of these substrates is more challenging than those activated by electron-withdrawing groups in the *para*-position. In these cases, the amount of boranes can be reduced to 1.5–2.0 equiv to obtain full conversion. Free phenolic and benzylic hydroxyls did not interfere with the coupling. Moreover, aldehydes and enolizable methyl ketones were both intact (entries 4 and 5). The electronic effects of ring substitutions were not significant, although the electron-donating free hydroxyl *ortho*- to bromo substitution caused lower yields and the formation of minor amounts of reductive de-bromination byproducts (entries 2 and 5). Excellent yield was obtained for nitrile **2k**, which also possessed phenolic proton. Acidic NH groups in sulfonamide and sulfanilide posed no difficulty for the coupling either (entries 6 and 7). As expected, use of tri-*n*-butylborane gave coupling products in excellent yields (entries 3, 4, and 8). However, nitro group cannot survive and resulted in a complex mixture, similar to the reaction of *B*-alkyl-9-BBN.[17] Furthermore, our protocol also worked well with heterocyclic substrates, such as 3-bromopyridine (entry 8).

In summary, an efficient and chemoselective direct Suzuki–Miyaura cross-coupling of tri-*n*-alkylboranes with bromoarenes in the presence of unmasked acidic functions is described, featuring the weak base Cs_2CO_3 under mild non-aqueous conditions.[18] Aldehydes, ketones, nitriles, chloro substitution were all tolerated. Thus, it is especially useful for the incorporation of lower *n*-alkyls to complex aromatics. The reasonable catalyst loading, the non-aqueous environment and the short reaction time required (2–6 h) are additional advantages. Application of this protocol to the total synthesis of biologically active polysubstituted aromatics such as dibenzodioxocinone analogs[19] will be pursued. Mechanistic studies are in progress.

Table 2
Direct Suzuki cross-coupling of bromo aromatic acids

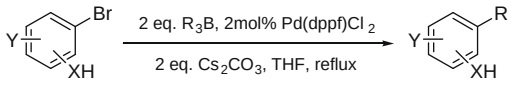


1 2

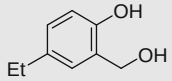
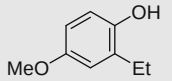
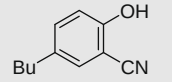
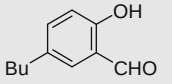
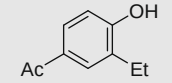
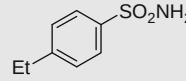
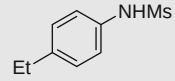
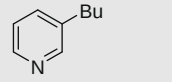
Entry	2	Yield[a] (%)
1	 **2a**	99
2	 **2b**	88
3	 **2c**	80
4	 **2d**	91
5	 **2e**	81
6	 **2f**	73
7	 **2g**	94
8	 **2h**	92

[a] Isolated yield.

Table 3
Direct Suzuki coupling of bromoarenes with trialkylboranes



1 2

Entry	2	Yield[a] (%)
1	 **2i**	73
2	 **2j**	72
3	 **2k**	95
4	 **2l**	93
5	 **2m**	70
6	 **2n**	88
7	 **2o**	84
8	 **2p**	88

[a] Isolated yield.

Acknowledgments

Financial support from the National Natural Science Foundation of China (20602008, 20832005) and Fudan University is gratefully acknowledged.

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18. *Representative experimental procedure*: To a mixture of bromoarene (1.0 mmol), Cs_2CO_3 (977 mg, 3.0 mmol), and Pd(dppf)Cl_2 (15 mg, 2 mol %) in a Schlenk tube under Ar atmosphere was added freshly distilled THF (2.0 mL). To the stirred suspension was added trialkylborane (3.0 mL, 1 M solution in THF, 3.0 mmol) in one portion, and the mixture was refluxed for 2–6 h. The reaction was cooled to 0 °C and quenched by 10% aq NaOH and 30% aq H_2O_2. After stirring for 30 min at rt, the mixture was acidified by dilute aq HCl, and extracted with ether (3 × 10 mL). The combined organic layer was washed successively with aq $FeSO_4$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography. Alternative acidic workup: To the cooled reaction mixture was added 50% aq HOAc (2 mL) and the whole was refluxed for 30 min. The cooled solution was extracted with ether (3 × 10 mL). The combined organic layer was washed successively with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography. *5-Butyl-2-hydroxybenzoic acid* (**2d**): Mp 85 °C; ^{1}H NMR ($CDCl_3$) δ 10.26 (br s, 1H), 7.70 (d, 1H, J = 2.4 Hz), 7.35 (dd, 1H, J = 8.4, 2.1 Hz), 6.93 (d, 1H, J = 8.7 Hz), 2.57 (t, 2H, J = 7.5 Hz), 1.57 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 175.0, 160.3, 137.5, 134.0, 129.9, 117.6, 110.8, 34.5, 33.6, 22.2, 13.9. *3-Chloro-5-ethyl-2-hydroxybenzoic acid* (**2e**): Mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.48 (s, 1H), 2.60 (q, 2H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 155.8, 136.9, 135.8, 128.2, 122.1, 112.1, 27.7, 15.4. *5-Butyl-2-hydroxybenzonitrile* (**2k**): Mp 58 °C; ^{1}H NMR ($CDCl_3$) δ 7.33–7.25 (m, 2H), 6.89 (d, 1H, J = 8.7 Hz), 5.83 (br s, 1H), 2.55 (t, 2H, J = 7.5 Hz), 1.55 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 156.4, 135.7, 135.0, 131.9, 116.6, 116.4, 99.1, 34.2, 33.3, 22.1, 13.8. *5-Butyl-2-hydroxybenzaldehyde* (**2l**): ^{1}H NMR ($CDCl_3$) δ 10.86 (s, 1H), 9.87 (s, 1H), 7.38–7.32 (m, 2H), 6.91 (d, 1H, J = 9.1 Hz), 2.60 (t, 2H, J = 7.5 Hz), 1.59 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 196.6, 159.7, 137.4, 134.3, 132.8, 120.3, 117.4, 34.4, 33.5, 22.1, 13.9. *1-(2-Ethyl-4-hydroxyphenyl)ethanone* (**2m**): Mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1H, J = 2.1 Hz), 7.74 (dd, 1H, J = 8.1, 1.8 Hz), 6.82 (d, 1H, J = 8.1 Hz), 5.72 (s, 1H), 2.68 (q, 2H, J = 7.8 Hz), 2.56 (s, 3H), 1.26 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 198.2, 158.7, 130.4, 130.3, 130.0, 128.6, 114.9, 112.3, 26.3, 23.0, 13.8. *4-Ethyl-benzenesulfonamide* (**2n**):

Mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 8.7 Hz), 7.34 (d, 2H, J = 8.7 Hz), 4.84 (br s, 2H), 2.73 (q, 2H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 149.7, 139.2, 128.6, 126.5, 28.8, 15.2. *3-Butylpyridine* (**2p**): ^{1}H NMR ($CDCl_3$) δ 8.44 (br s, 2H), 7.48 (d, 1H, J = 7.8 Hz), 7.20 (dd, 1H, J = 7.5, 5.1 Hz), 2.61 (q, 2H, J = 7.5 Hz), 1.60 (quintet, 2H, J = 7.8 Hz), 1.36 (sextet, 2H, J = 6.9 Hz), 0.93 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 149.8, 147.0, 137.9, 135.7, 123.2, 33.2, 32.6, 22.1, 13.8.

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