

A Journal of the Gesellschaft Deutscher Chemiker A Deutscher Chemiker CDCh International Edition Www.angewandte.org

Accepted Article

Title: Metal-Free Radical Borylation of Alkyl and Aryl lodides

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201810782 Angew. Chem. 10.1002/ange.201810782

Link to VoR: http://dx.doi.org/10.1002/anie.201810782 http://dx.doi.org/10.1002/ange.201810782



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Metal-Free Radical Borylation of Alkyl and Aryl lodides

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Abstract: A metal-free radical borylation of alkyl and aryl iodides with bis(catecholato)diboron (B₂cat₂) as the boron source under mild conditions is introduced. The borylation reaction is operationally easy to conduct and shows high functional group tolerance and broad substrate scope. Radical clock experiments and density functional theory calculations provide insights into the mechanism and rate constants for C-radical borylation with B₂cat₂ are disclosed.

Boronic esters are highly valuable synthetic precursors, since the boronic ester moiety can be transformed into a wide range of useful functional groups.^[1] Therefore, methods that allow to efficiently prepare alkyl and aryl boronates are demanded.

A) Borylation of alkyl halides

 $\begin{array}{c} R_1^1 X \\ R^2 \uparrow_3^{-} + B_2 pin_2 \end{array} \xrightarrow[base/ligand]{} \begin{array}{c} Cu, Fe, Mn, Ni, Ir \\ \hline \\ base/ligand \end{array} \xrightarrow[R^1]{} \begin{array}{c} R_1^1 \\ R^2 \end{array}$

B) Borylation of aryl halides



C) Transition-metal-free borylation of alkyl and aryl iodides (this work)



Scheme 1. Borylation of alkyl and aryl halides with diboron reagents $[B_2pin_2 = bis(pinacolato)diboron]$.

In recent years, various processes for transition metal catalyzed borylation of alkyl halides with diborons to access alkyl boronate esters have been developed (Scheme 1A).^[2-6] Steel, Marder, and Liu disclosed a CuCl/Xantphos-catalyzed borylation

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of alkyl halides.^[2] The Ito group reported a similar reaction with diboron using a CuCl/Xantphos catalyst and stoichiometric KO'Bu.^[3] Fu reported borylation of various alkyl electrophiles with a NiBr₂/pybox catalyst,^[4] and Marder introduced a ZnCl₂/N-heterocyclic carbene catalyst system for the borylation of unactivated alkyl halides.^[5] Recently, Cook disclosed a MnBr₂/tetramethylethylenediamine-catalyzed borylation of alkyl halides using EtMgBr as a stoichiometric activator.^[6] However, all these valuable methods require a transition metal catalyst, a ligand and a stoichiometric amount of a base. To our knowledge, metal and additive-free radical borylation of alkyl halides with diborons is unknown.^[7]

Arylboronates can be obtained from haloarenes and diborons *via* reactive aryl radicals^[8-13] (Scheme 1B). Along these lines, Marder developed a zinc(II)-catalyzed borylation of aryl halides using a stoichiometric base^[8] and photoinduced aryl halide borylation was reported by Larionov^[9], Li^[10] and Fu^[11]. Recently, a pyridine-catalyzed radical borylation of aryl halides was disclosed by Jiao.^[12] We present herein mild radical borylation of both alkyl and aryl iodides with commercial bis(catecholato)diboron as the boron source (Scheme 1C).

We first explored the reaction of 1-iodooctane (1a) with bis(catecholato)diboron (2a) to alkyl boronate 3a under blue LED irradiation at ambient temperature using different solvents (Table 1).

Table 1: Optimization of the reaction conditions.[a]

			+ B ₂ cat ₂	1) Solvent blue LED, rt		oin
	~ ~	• •	2a	2) pinacol, NEt ₃	3a	
1 equiv		n equiv			_	
	Entry	n	Sc	olvent	Yield [%]	
	1	2	1,2-DCE MeCN THF MeOH DMF DMF DMF		0	_
	2	2			trace	
	3	2			trace	
	4	2			8	
	5	2			71	
	6 ^[b]	2			0	
	7 ^[c]	2			0	
	8 ^[d]	2	DI	MF	7	
	9	4	D	MF	88	
	10 ^[e]	4	D	MF	15	

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (n x 0.2 mmol), solvent (0.6 mL), 10 W blue LED, Ar, rt, 24 h; pinacol (0.8 mmol), NEt₃ (0.7 mL), 1 h, isolated yields. [b] B_2pin_2 was used. [c] B_2neo_2 was used. [d] $B_2(OH)_4$ was used. [e] In the dark.

Due to instability of n-octylcatecholborane, the crude product was transesterified with pinacol and NEt₃ to give **3a**. In 1,2-dichloroethane (1,2-DCE), borylation did not proceed and **1a** was

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recovered (Table 1, entry 1). In acetonitrile or tetrahydrofuran (THF), trace amounts of **3a** were detected (entries 2, 3), but in methanol an encouraging 8% yield was obtained (entry 4). Significant improvement of the yield to 71% was achieved by using N,N-dimethylformamide (DMF)^[14] (entry 5). Replacing B₂cat₂ by bis(pinacolato)diboron (B₂pin₂) or bis(neopentyl-glycolato)diboron (B₂neo₂) under otherwise identical conditions did not lead to any product formation (entries 6, 7). Using tetrahydroxydiboron [B₂(OH)₄] as the trapping reagent and subsequent treatment with pinacol and magnesium sulfate, only 7% of **3a** was obtained (entry 8). Increasing the amount of B₂cat₂ to 4 equivalents led to a further improvement (88%, entry 9). A control experiment in the absence of light irradiation proceeded in low yield (entry 10).

Under optimized conditions, substrate scope was investigated. Borylation of 3-methylbutyliodide (1b) to 3b proceeded in 80% vield (Scheme 2). With 1-chloro-6-iodohexane (1c) containing both an iodine and a chlorine atom, the borvlation occurred chemoselectively by replacing the I-atom (3c. 94%). The primary alkyl iodide 1d bearing a perfluoroalkyl chain worked well (see 3d) and an alkyl iodide containing a carbazole moiety participated to provide **3e** (70%). (2-lodoethyl)benzene (**1f**) and 4-(iodomethyl)cyclohex-1-ene (1g) were also borylated in good yields (91% and 82%). Alkynyl- (1h), nitrile- (1i), ester- (1j), ketone- (1k), and aldehyde-functionalities (1l) are tolerated and the products 3h-I were isolated in good yields (56-80%). Borodeiodination of secondary alkyl iodides worked well, as shown for 2-iodoheptane (1m) and 6-iodo-2-methylhept-2-ene (1n) to provide 3m and 3n in 91% and 89% yield. lodides tetrahydropyran, containing cyclohexane, Boc-protected piperidine (Boc = tert-butoxycarbonyl), arene and phenyl alkyl ether (10-s) turned out to be good substrates for the borylation. Compound 1t with both naphthyl and perfluorobutyl groups performed well to give 3t in 86% yield. 1-lodoadamantane (1u) was smoothly converted to 3u (90%), but tert-butyliodide could not be borylated under the standard conditions.

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 $\begin{array}{l} \textbf{Scheme 2. Scope of alkyl iodides. Reaction conditions: 1a-u (0.2 mmol), 2a (0.8 mmol), DMF (0.6 mL), 10 W blue LED, Ar, rt, 24 h; pinacol (0.8 mmol), NEt_3 (0.7 mL), 1 h, isolated yields. [a] 2 equiv of 2a was used. \end{array}$

We were very pleased to find that under the same conditions aryl iodides can also be borylated (Scheme 3). However, as compared to the alkyl iodides slightly lower yields are generally achieved. Iodobenzene (4a) afforded phenyl pinacolboronate (5a, 61%) and iodoarenes 4b-g bearing *para*-substituents performed well to give the aryl boronates 4b-g in 46-71% yield. *Meta* and *ortho*-substituted aryl iodides 4h and 4i provided 5h and 5i in good yields (73% each). Borylation of 1-iodonaphthalene (4j), 9iodophenanthrene (4k) and 3-iodothiophene (4I) was also successful (5j-I). Our method, albeit less efficiently, is also applicable to the preparation of vinyl boronates, as documented by the borylation of 1-iodocyclohex-1-ene (5m, 32%).

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 $\begin{array}{l} \mbox{Scheme 3. Scope of aryl iodides. Reaction conditions: 4a-m (0.2 mmol), 2a (0.8 mmol), DMF (0.6 mL), 10 W blue LED, Ar, rt, 24 h; pinacol (0.8 mmol), NEt_3 (0.7 mL), 1 h, isolated yields. \end{array}$

The facts that light was required and that conditions are similar to those reported by us and Aggarwal for alkyl radical borylations^[7a,7d,14a] indicated that these transformations are likely radical in nature. We therefore carried out radical clock experiments (Scheme 4). Cyclopropylmethyl iodide (6) gave exclusively the ring opening product **7**, but 6-lodo-1-hexene (**8**) reacted mainly to the uncyclized boronate **9a**. Still, formation of small amounts of the cyclized product **9b** indicated that trapping of a primary C-radical with B₂cat₂ to be very fast. Successful cyclizing borylation of aryl iodide **10** to **11b** further supported the radical mechanism. Such cyclizing borylations cannot be achieved using ionic type borylation processes.

The radical clock experiment with iodide 8 was chosen to estimate the rate constant for trapping of a primary C-radical with B_2 cat₂. To this end, a series of reactions with 6-iodo-1-hexene (8) were conducted varying the concentration of diboron 2a. Using the ratio of non-cyclized 9a to cyclized product 9b at a given diboron concentration and considering the known rate constant (2.3 x 10⁵ s⁻¹ at 25 °C^[15]) for the 5-exo-cyclization of the 5-hexenyl radical, the second order rate constant for the borylation of the primary C-radical derived from 8 with B₂cat₂ was estimated to be 3.8 x 10⁶ M⁻¹•s⁻¹ (for details, see the Supporting Information (SI)). In analogy, we estimated the rate constant for trapping of the aryl radical derived from 1-(3-butenyl)-2-iodo-benzene (10) with B₂cat₂ to lie at 7.4 x 10⁷ M⁻¹•s⁻¹. Hence, alkyl radical trapping with B₂cat₂ is a very fast process and its rate constant lies in the region of that for the reduction of a primary alkyl radical with Bu₃SnH.^[15] However, the rate constant for the reaction of B₂cat₂ with the aryl radical derived from 10 is around one order of magnitude smaller than that of the tin hydride reduction of a phenyl radical.^[16] Likely, steric effects exerted by the ortho-substituent and the bulky diborane play a role. Notably, kinetic data on radical borylation are currently unavailable in the literature.







Scheme 5. Proposed mechanism.

Based on these experiments and previous results,^[14a] a plausible mechanism is depicted in Scheme 5. Initiation proceeds via light mediated C-I bond homolysis of iodide 1 to generate the alkyl/aryl radical **A** which adds to B₂cat₂ to give the radical **B**. We found that for radicals **B** derived from secondary alkyl radicals, B-B bond homolysis is higher in energy than degenerate B-C bond homolysis to give B₂cat₂ and the starting radical **A**.^[14a] The unusual large solvent effect can readily be understood involving the solvent. Hence, the radical **B** is trapped by DMF in an exothermic process to give **C**, best described by a weak B-B one electron σ -bond,^[14] which readily homolyzes to give product boronate **3** along with the DMF-complexed boryl radical **D/E**. The chain is closed by an I-atom transfer reaction^[17] of the iodide **1** via **F** to eventually give **G** and radical **A**.

The I-atom transfer was further investigated using DFT calculations (see SI for details). We looked at the spin density plots of the DMF-complexed boryl radical \mathbf{D} and found highest spin density at the C-atom and only little spin at the boron atom

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(Figure 1). Therefore, the complexed boryl radical **D** is best described by resonance structure **E**, which certainly also influences its reactivity. In fact, I-transfer from CH₃I to the C-atom in **E** to give **F** proceeds *via* a low barrier (9.5 kcal/mol), whereas the barrier for I-transfer to the B-atom leading directly to **G** occurs at significantly higher barrier (18.3 kcal/mol) (Figure 2). In a polar solvent, however, iodide **F** is not stable and easily isomerizes ($\Delta G = -8$ kcal/mol) to the zwitterion **G**. The barrier in vacuum is only 3.7 kcal/mol, but becomes negative when solvation energies are included. Thus, **F** is most likely not a minimum structure under polar solvation conditions, but rather an ion pair (**E**⁺/I⁻) which is formally formed by heterolytic fission of the C–I bond in **F** or by charge transfer from **E** to the I-atom. Zwitterion **G** is immediately formed by collapse of this ion pair.



Figure 1. Calculated spin density of radical D/E (PBE0-D3/def2-TZVP, isosurface value: 0.01 a.u.).

In summary, a method for metal and additive-free borylation of alkyl and aryl iodides was introduced. The reaction proceeds under very mild conditions in good to excellent yields with a broad range of alkyl and aryl iodides. As compared to the reactions with aryl iodides, alkyl iodides generally lead to higher yields. Radical clock experiments and DFT calculations support the suggested radical chain mechanism.





Figure 2. Transition structures for I-atom transfer from CH_3I to radical D/E (PBE0-D3/def2-TZVP).

Acknowledgements

We thank the European Research Council (ERC Advanced Grant agreement No. 692640) for financial support.

Keywords: borylation • metal-free • alkyl lodides • aryl iodides • radical process

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Layout 2:

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Metal-free Radical Borylation of Alkyl and Aryl lodides

I to B: A metal and additive-free radical borylation using a commercial diboron reagent is introduced. Alkyl and aryl iodides are borylated under very mild conditions in good to excellent yields.

R¹ R^{2} R-R³ diboron reagent R^2 R

metal and additive-free borylation

34 examples, up to 94% yield