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Transition-Metal-Free Borylation of Aryltriazene Mediated by $BF_3 \cdot OEt_2$

Chuan Zhu and Motoki Yamane*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

yamane@ntu.edu.sg

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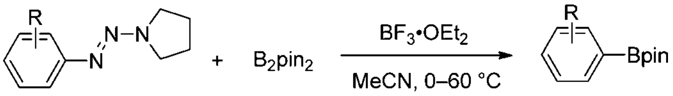
ABSTRACT



A practical and simple method for deaminoborylation of aryltriazene with bis(pinacolato)diboron has been developed that is mediated by $BF_3 \cdot OEt_2$. Various arylboronic esters are prepared in moderate to good yields with this facile transition-metal-free procedure.

Arylboronic acid and ester have been widely used to create carbon–carbon and carbon–heteroatom bonds in organic synthesis over the past several decades.[1] As they are one of the most powerful synthetic tools, various methods for the synthesis of arylboronic acid derivatives have been developed.[2] Conventional methods to prepare these boron compounds usually involve a stoichiometric amount of air and moisture sensitive aryl-metal reagents in harsh reaction conditions.[3] In this aspect, transition metal-catalyzed borylation of aryl halides which possess tremendous versatility and functional group compatibility is a more reliable route.[4] Remarkably, this methodology recently expanded to include a C–H bond activation strategy and significant progress was achieved.[5] As transition metal catalysts are expensive and sometimes cause a problem of metal residue in the final medicinal products, more attention has been focused on the transition-metal-free process in organic synthesis.[6] Recently, borylation of arylamine via oxidative deamination by alkylnitrite was reported.[7] It provides a direct conversion of arylamine to arylboronic ester under metal-free conditions which brought an innovative development to arylboronic ester synthesis. However, the substrate scope was still limited.

Aryltriazene could be readily prepared from corresponding arylamine in high yield and easy to handle.[8] Traditionally, aryltrizene is used as equiverlant of aryldiazonium salt in the presence of Lewis or Brønsted acid in nucleophilic substitution reactions or Pd-catalyzed coupling reactions.[9] In particular, $BF_3 \cdot OEt_2$ is an efficient reagent to activate aryltriazene in Pd-catalyzed

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(1) For review, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N. *Cross-Coupling React.* **2002**, *219*, 11.

(2) For review, see: Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2009**, *110*, 890.

(3) For selected examples, see: (a) Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-k. *J. Org. Chem.* **2002**, *67*, 1041. (b) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312.

(4) For selected examples, see: (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 8683. (c) Zhu, W.; Ma, D. *Org. Lett.* **2005**, *8*, 261. (d) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (e) Yamamoto, T.; Morita, T.; Takagi, J.; Yamakawa, T. *Org. Lett.* **2011**, *13*, 5766. (f) Zhang, J.; Wang, X.; Yu, H.; Ye, J. *Synlett* **2012**, *23*, 1394.

(5) For selected examples, see: (a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271. (c) Frey, G. D.; Rentzsch, C. F.; von Preysing, D.; Scherg, T.; Mühlhofer, M.; Herdtweck, E.; Herrmann, W. A. *J. Organomet. Chem.* **2006**, *691*, 5725. (d) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kugel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem.—Eur. J.* **2010**, *16*, 8155. (e) Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.

(6) For transition-metal-free arylboronic ester synthesis, see: (a) Del Grosso, A.; Pritchard, R. G.; Muryn, C. A.; Ingleson, M. J. *Organometallics* **2009**, *29*, 241. (b) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2102. (c) Niu, L.; Yang, H.; Wang, R.; Fu, H. *Org. Lett.* **2012**, *14*, 2618.

(7) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1846.

(8) For review, see: Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3338.

(9) For seleceted examples, see: (a) Naus, P.; Leseticky, L.; Smrcek, S.; Tislerova, I.; Sticha, M. *Synlett* **2003**, 2117. (b) Saeki, T.; Matsunaga, T.; Son, E.-C.; Tamao, K. *Adv. Synth. Catal.* **2004**, *346*, 1689. (c) Saeki, T.; Son, E. C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617. (d) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (e) Liu, C. Y.; Knochel, P. *Synlett* **2007**, 2081. (f) Liu, C. Y.; Gavryushin, A.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 1020. (g) Nan, G. M.; Ren, F.; Luo, M. M. *Beilstein J. Org. Chem.* **2010**, 6. (h) Nan, G. M.; Zhu, F. H.; Wei, Z. J. *Chin. J. Chem.* **2011**, *29*, 72. (i) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7242.

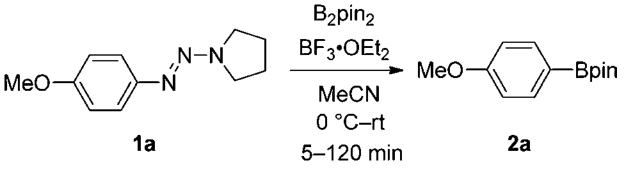
10.1021/ol302024m

Suzuki-Miyaura coupling reaction.[9c,g,h] Moreover, polymer-bonded triazenes have been extensively used in solid-supported synthesis.[10] Thus this method may potentially have wide application in combinatorial chemistry. Herein, we report $BF_3 \cdot OEt_2$-mediated deaminoborylation of a wide range of functionalized aryltriazenes.

Our initial study began with *p*-methoxyphenyltriazene **1a** which was reacted with 1 equiv of bis(pinacolato)-diboron (B_2pin_2) in the presence of 1.1 equiv of $BF_3 \cdot OEt_2$ in 1,2-dimethoxyethane (Table 1, entry 1). Gratifyingly, the reaction proceeded smoothly and the desired product, arylboronic ester **2a** was isolated in 41% yield after 10 min at room temperature. Next, the reaction solvents were screened in the same reaction conditions (entries 1–9), and acetonitrile gave the highest yield, 52% (entry 6). Only trace amount of product was observed when more polar solvents such as DMSO and DMF were used, and aryltriazene **1a** was recovered in a significant amount (entries 3 and 4). When the amount of $BF_3 \cdot OEt_2$ was reduced to 1 equiv, the yield of product was not affected at all (compare entries 6 and 10). Then catalytic amount of $BF_3 \cdot OEt_2$ was tested but only led to trace amount of product (entry 11). This means that $BF_3 \cdot OEt_2$ acted as a stoichiometric reagent rather than a catalyst. The yields obviously increased when the reaction was performed at lower temperatures (entries 12 and 13). The amount of B_2pin_2 was optimized in entries 14–17, and 1.5 equiv showed the highest efficiency (entry 15). The effect of the counteranion on the Lewis acid was investigated by using BCl_3 and BBr_3 in replacement of $BF_3 \cdot OEt_2$ (entries 19 and 20). The desired product **2a** was obtained in both cases, however the yields dropped to a large extent. It is known that radical initiators such as benzoyl peroxide (BPO) enhance the borylation of aryl amine which was proposed a radical mechanism, however, adding BPO gave no improvement for both yield and reaction time (entry 21).[7]

As shown in Table 2, a series of aryltriazene were then subjected to the above optimized reaction conditions. The reaction was successful for a variety of aryltriazenes and provided moderate to high yields of the corresponding arylboronic esters. The reactivity of substrates is relevant to the electronic effects of the substituent on the benzene ring. For example, 4-methoxyphenyltriazene gave rise to 73% of **2a** within 5 min (entry 2) at 0 °C, however the less electron rich 3-methoxyphenyltriazene rendered the reaction more sluggish, afforded **2b** in 58% yield after 30 min at room temperature (entry 2). Unsubstituted phenyltriazene displayed inferior reactivity and led to only 36% yield while 1-napthyltriazene furnished **2k** in 65% yield. The substrates bearing 4-thionyl or 4-amino group is considered to be unstable toward an oxidant such as nitrite which was used in the borylation of arylamines. Even with such a substrate, the reaction proceeded and gave the desired boronic ester which has a sulfur or nitrogen functionality although the yields are modest possibly due to the stronger coordination of sulfur and nitrogen atoms to BF_3 (entries 4 and 5).

Table 1. Reaction of 4-Methoxyphenyltriazene with B_2pin_2 in the Presence of $BF_3 \cdot OEt_2$[a]



entry	molar Ratio (**1a**/B_2pin_2/ $BF_3 \cdot OEt_2$)	solvent	time (min)	temp (°C)	yield (%)
1	1/1/1.1	DME	90	rt	41
2	1/1/1.1	DCM	5	rt	27
3[b]	1/1/1.1	DMF	120	rt	trace
4[b]	1/1/1.1	DMSO	120	rt	trace
5	1/1/1.1	EtOH	90	rt	43
6	1/1/1.1	MeCN	5	rt	52
7	1/1/1.1	Benzene	5	rt	38[c]
8	1/1/1.1	Acetone	120	rt	trace
9	1/1/1.1	1,4-dioxane	120	rt	trace
10	1/1/1	MeCN	5	rt	52
11[b]	1/1/0.2	MeCN	30	rt	trace
12	1/1/1	MeCN	5	0	60
13	1/1/1.1	MeCN	15	−15	62
14	1/1.1/1	MeCN	5	0	62
15	1/1.5/1	MeCN	5	0	73
16	1/2/1	MeCN	5	0	75
17	1/0.5/1	MeCN	30	0	28
18[d]	1/1.5/1	MeCN	5	0	73
19[d,e]	1/1.5/1	MeCN	5	0	30
20[d,f]	1/1.5/1	MeCN	5	0	5
21[d,g]	1/1.5/1	MeCN	5	0	73

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale in 5.0 mL solvent. [b] *p*-Methoxyphenyltriazene was recovered. [c] 1-Methoxy-4-phenylbenzene was obtained as a side product in 6% yield. [d] 2.0 mL MeCN was used. [e] 1.0 equiv BCl_3 (1 mol/L hexane solution) was used in place of $BF_3 \cdot OEt_2$. [f] 1.0 equiv BBr_3 (1 mol/L dichloromethane solution) was used in place of $BF_3 \cdot OEt_2$. [g] 2 mol % BPO in comparison with literature.

The reactions of the phenyltriazene with a simple alkyl substituent at para-, ortho-position also proceeded to afford **2g**, **2h** and **2i** in 75%, 83%, and 71% yield, respectively (entries 7–9). The borylation of ortho-methyl substituted substrate (entry 8) led to good yield in contrast with ortho-methoxyl substituted one which gave no product (entry 3). The alkynyl moiety was found to be tolerated in the reaction conditions to give alkynylphenylboronic ester **2j** in 53% yield. As stated above, the reaction is suitable for rather electron rich aryltriazenes and it was revealed that strongly electron-defficient aryltriazenes such as acylphenyltriazene **1l** gave no desired product (entry 12). It is noteworthy that oxime derivative which is a synthetic equivalent of ketone could be applied for this borylation, and boronic ester **2m** which has an oxime functionality was obtained in 70% yield (entry 13). Development of the preparation of haloarylboronic esters, especially bromo- and iodo-substituted ones, is important because they are difficult to synthesize by the conventional transition metal-catalyzed borylation of arylhalides. It is notable that a variety of haloaryltriazenes are applicable

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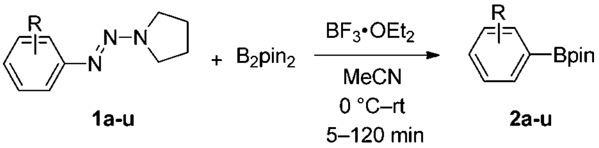
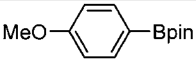
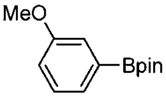
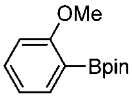
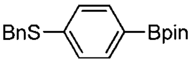
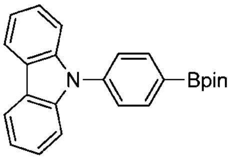
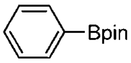
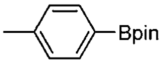
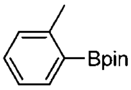
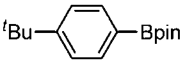
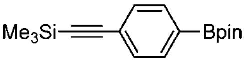
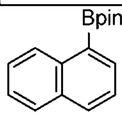
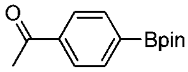
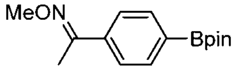
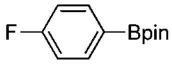
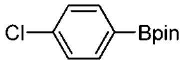
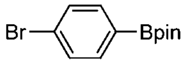
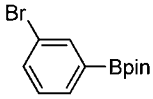
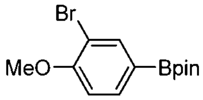
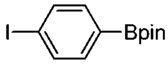
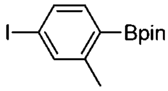
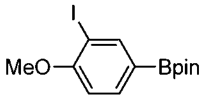
(10) For reviews, see: (a) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805. (b) Gil, C.; Bräse, S. *J. Comb. Chem.* **2008**, *11*, 175.

Table 2. Substrates Scope for the Borylation of Aryltriazene[a]



entry	product		temp	time	yield
1		**2a**	0	5	73
2		**2b**	rt	30	50
3		**2c**	60	30	trace
4[b,c]		**2d**	rt	15	62
5[b,c]		**2e**	rt	30	52
6		**2f**	0	60	36
7		**2g**	0	20	75
8		**2h**	0	20	83
9		**2i**	0	20	71
10		**2j**	rt	90	53
11		**2k**	0	30	65
12		**2l**	rt	60	trace
13[b,c]		**2m**	0	60	70
14		**2n**	60	60	54
15		**2o**	60	60	44
16		**2p**	60	60	44
17		**2q**	60	120	30
18		**2r**	0	90	72
19		**2s**	60	60	34
20[c]		**2t**	0	120	64
21		**2u**	0	90	62

[a] Unless otherwise noted, all the reactions were carried out by adding $BF_3 \cdot OEt_2$ (0.5 mmol) to a solution of **1** (0.5 mmol) and B_2pin_2 (0.75 mmol) in 2 mL MeCN under nitrogen atmosphere. [b] 5 mL solvent was used. [c] $BF_3 \cdot OEt_2$ was added at 0 °C and the reaction mixture was warm to rt gradually.

for this borylation (entries 14–21). Although it required higher temperature (60 °C) and longer reaction time (1–2 h) for the consumption of the starting material, 4-fluoro-, 4-chloro-, 4-bromo-, and 4-iodophenyltriazenes were converted to the corresponding boronic esters **2n**–**p**, **2s** in 34–54% yields (entries 14–16, 19). The reactivity and yield were improved when electron-donating substituents were attached on the phenyl ring (entries 18, 20, 21).

A plausible mechanism for this borylation is depicted in Scheme 1. The formation of triazene-BF_3 complex **A** is followed by the generation of arenediazonium salt **B**.[9c,g–i] This step is supported by the observed electronic effect of the substituent on the phenyl group of aryltriazenes which affects the reactivity of aryltriazenes. The formation of diazoniumsalt **B** is also supported by a preliminary investigation of a simple Hammett plot which gave a negative ρ value (−2.06).[11] The fluoride anion transfers from the trifluoroborate anion onto B_2pin_2 to give diboronate **C**. Then, nucleophilic substitution of N_2 in arenediazonium part takes place to give the desired product, arylboronic ester **2** together with F-Bpin. This mechanism is also supported by the direct reaction of aryldiazonium salt (Scheme 2). The same borylation product **2a** was obtained in 45% yield in the reaction of methoxybenzenediazonium tetrafluoroborate with B_2pin_2.

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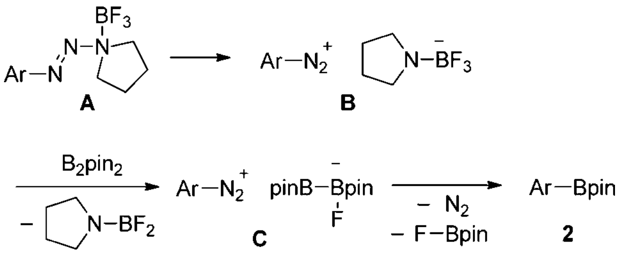
(11) See Supporting Information for details.

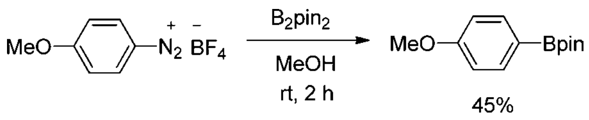
(12) (a) Pryor, W. A.; Gu, J. T.; Church, D. F. *J. Org. Chem.* **1985**, *50*, 185. (b) Nishino, H.; Kamachi, H.; Baba, H.; Kurosawa, K. *J. Org. Chem.* **1992**, *57*, 3551.

(13) (a) Rahm, A.; Amardeil, R.; Degueilcastaing, M. *J. Organomet. Chem.* **1989**, *371*, C4. (b) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

Scheme 1. Plausible Mechanism of $BF_3 \cdot OEt_2$-Mediated Borylation of Aryltriazene



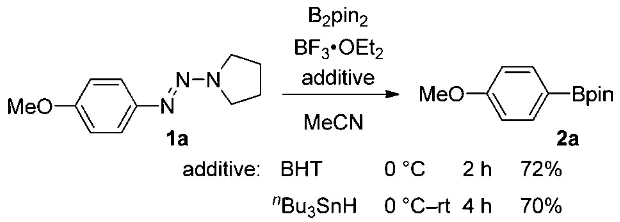
Scheme 2. Borylation of Aryldiazonium Salt[a]



[a] The reaction was performed by mixing methoxybenzenediazonium tetrafluoroborate (0.5 mmol), B_2pin_2 (0.5 mmol) in 2 mL MeOH and stirred at rt for 2 h.

To get some information on more detailed mechanism of this last nucleophilic arene substitution, we performed the reaction in the presence of hydrogen radical donors (Scheme 3). Di-*t*-butylhydroxytoluene (BHT)[12] and tributyltin hydride[13] were tested as the hydrogen donor and it was found that any of the trapping reagents did not affect much to the reaction and the borylation product was obtained in around 70% yield with no significant loss. This fact indicates that the nucleophilic arene substitution step may not involve a free phenyl radical process. At this stage, we cannot have a conclusion on the mechanism of the aromatic substitution step.[14] It requires further study to clarify the detailed mechanism.

Scheme 3. Reaction in the Presence of Hydrogen Radical Donor[a]



[a] Reactions were carried out by adding of $BF_3 \cdot OEt_2$ (0.5 mmol) to a solution of **1a** (0.5 mmol), B_2pin_2 (0.75 mmol) and additive (0.5 mmol) in MeCN (2 mL).

In summary, we have demonstrated a novel synthesis of arylboronic ester via direct borylation of aryltriazene. The reaction is simply mediated by $BF_3 \cdot OEt_2$ and completes within 5−120 min at 0 to 60 °C. The absence of metal reagents, transition metal catalyst or radical initiator makes this approach very easy to handle. This method is complementary to the existing arylboronic ester synthesis with the advantages of high efficiency, unique selectivity, and an environmentally friendly nature. Moreover, the reaction conditions are very mild and can tolerate many functional groups. Further experiments to expand the scope of this transformation are still under investigation.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of all newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For the review of mechanism of nucleophilic aromatic substitution, see: (a) Zollinger, H. *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*; VCH: Weinheim, 1994. For recent examples, see: (b) Romsted, L. S.; Zhang, J.; Zhuang, L. *J. Am. Chem. Soc.* **1998**, *120*, 10046. (c) Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* **2004**, *126*, 10632. (d) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958.