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Radical Addition of Arylboronic Acids to Various Olefins under Oxidative Conditions

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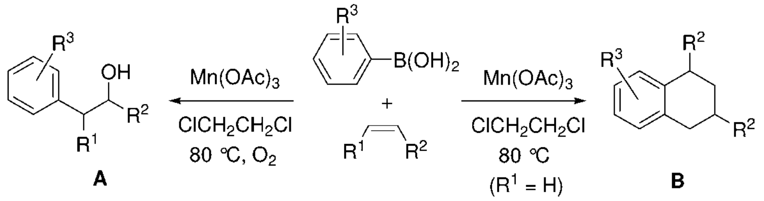
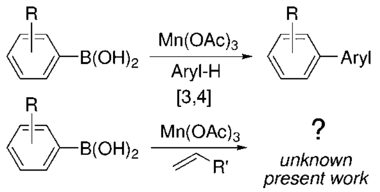
ABSTRACT



Arylboronic acids are shown to be valuable precursors for aryl radicals upon treatment with manganese triacetate. Under these oxidative conditions the intermediately generated aryl radicals undergo addition to olefins to give the arylhydroxylation products A in the presence of dioxygen. In the absence of dioxygen, for some olefins double olefin addition and subsequent homolytic aromatic substitution provide tetrahydronaphthaline derivatives B in moderate to good yields.

It is well-known that trialkylboron compounds react with O-centered radicals to liberate the corresponding alkyl radicals.[1] More recently, Renaud showed that alkylcatecholboron derivatives are valuable precursors for alkyl radicals upon reaction with heteroatom centered radicals.[2] Unfortunately, these methods do not allow generation of more reactive aryl radicals. However, Demir published a radical biaryl synthesis by reacting arylboronic acids with Mn(OAc)$_3$ in the presence of an arene as a solvent (Scheme 1).[3] Upon applying microwaves, this reaction could be conducted in EtOH by using only a slight excess of the arene acceptor.[4] Herein we present the first results on the application of arylboronic acids as aryl radical precursors in intermolecular addition reactions to various activated olefins. To our knowledge, oxidative radical addition of arylboronic acids to olefins is unknown.[5]

Scheme 1. Aryl Boronic Acids as Aryl Radical Precursors



We found that reaction of commercially available phenylboronic acid with vinyl dimethylphosphonate (6 equiv) in dichloroethane (DCE, 0.2 M) in the presence of Mn(OAc)$_3$ (3 equiv) under argon at 80 °C for 6 h provided tetrahydronaphthaline **1a** in 65% isolated yield as a 6.3:1 (*cis*/*trans*) mixture of diastereoisomers (Scheme 2, Table 1, entry 1). Product **1a**

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(1) (a) Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692. (b) Davies, A. G.; Roberts, B. P. *Acc. Chem. Res.* **1972**, *5*, 387.

(2) (a) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415. (b) Darmeceny, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71.

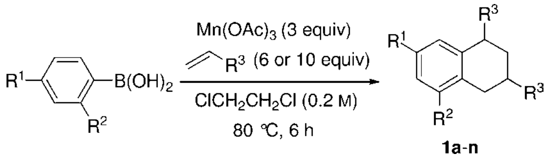
(3) Demir, A. S.; Ömer, R.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578.

(4) Guchhait, S. K.; Kashyap, M.; Saraf, S. *Synthesis* **2010**, 1166.

(5) Intermolecular aryl radical additions to olefins by using aryldiazonium salts as precursors; see: Heinrich, M. R. *Chem.—Eur. J.* **2009**, *15*, 820.

10.1021/ol101818k

Scheme 2. Synthesis of Tetrahydronaphthaline Derivatives



was derived from a double olefin addition with subsequent homolytic aromatic substitution (see discussion on the mechanism below).[6] This remarkable cascade reaction comprises three C−C bond forming steps![7] Transition-metal-mediated addition of arylboronic acids to 2 equiv of an alkyne and subsequent cyclization to give naphthalene derivatives have been reported.[8] However, analogous metal-mediated reactions by using alkenes as acceptors leading to tetrahydronaphthalenes, as reported herein, are unknown. The assignment of the relative configuration was based on NMR spectroscopy by careful analysis of the vicinal ^3J(CCCP) coupling constants.[9]

Table 1. Reaction of Various Arylboronic Acids with Various Olefins

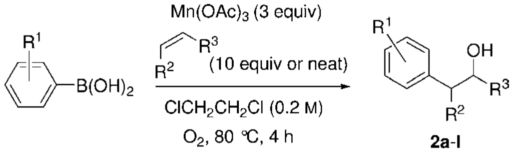
entry	R^1	R^2	R^3	solvent	*dr*(*cis*/*trans*)	no.	yield[%]
1	H	H	$PO(OMe)_2^a$	DCE	6.:1	**1a**	65
2	H	H	$PO(OMe)_2^a$	DCM	5.3:1	**1a**	45
3	H	H	$PO(OMe)_2^a$	TFT	7.0:1	**1a**	20
4^b	H	H	$PO(OMe)_2^a$	DCE	–	**1a**	0
5^c	H	H	$PO(OMe)_2^a$	DCE	6.2:1	**1a**	10
6^d	H	H	$PO(OMe)_2^a$	DCE	–	**1a**	0
7	CH_3	H	$PO(OMe)_2^a$	DCE	7.0:1	**1b**	64
8	Ph	H	$PO(OMe)_2^a$	DCE	4.5:1	**1c**	67
9	F	H	$PO(OMe)_2^a$	DCE	4.8:1	**1d**	57
10	Cl	H	$PO(OMe)_2^a$	DCE	4.1:1	**1e**	60
11	Br	H	$PO(OMe)_2^a$	DCE	3.9:1	**1f**	45
12	I	H	$PO(OMe)_2^a$	DCE	3.5:1	**1g**	44
13	OCH_3	H	$PO(OMe)_2^a$	DCE	7.0:1	**1h**	34
14	H	F	$PO(OMe)_2^a$	DCE	3.4:1	**1i**	33
15	H	H	SO_2Ph^a	DCE	1.8:1	**1j**	48
16	Cl	H	SO_2Ph^a	DCE	1:1.3	**1k**	44
17	Ph	H	SO_2Ph^a	DCE	1.3:1	**1l**	49
18	H	H	CO_2Me^e	DCE	1.7:1	**1m**	27
19	H	H	CN^e	DCE	1:4.0	**1n**	19

^{a} 6 equiv of olefin were used. ^{b} Diacetoxyiodobenzene was used as oxidant. ^{c} 2-Iodoxybenzoic acid was used as oxidant. ^{d} $FeCl_3$ was used as an oxidant. ^{e} 10 equiv of olefin were used.

In other solvents (dichloromethane (DCM), α,α,α-trifluorotoluene (TFT)) with $Mn(OAc)_3$ or by using other oxidants such as diacetoxyiodobenzene, 2-iodoxybenzoic acid, and $FeCl_3$ in dichloroethane, either the cascade reaction failed or lower yields were achieved (entries 2−6).

Various arylboronic acids were then reacted with vinyl dimethylphosphonate in DCE with $Mn(OAc)_3$ as an oxidant under optimized conditions (Table 1).[10,11] *Para*-substituted phenylboronic acids provided the corresponding naphthaline derivatives **1b**−**h** with moderate to good yields (entries 7−13). A lower yield was achieved with the *ortho*-F-substituted phenyl boronic acid (→ **1i**, entry 14) and by using *ortho*-tolylboronic or *ortho*-ethoxyboronic acid the reaction failed (not shown in the table) clearly documenting that steric effects, as expected, play an important role in the initial intermolecular aryl radical addition reaction. We found that phenylvinylsulfone is a suitable radical acceptor for our double addition/homolytic substitution process. Products **1j**−**l** were isolated in acceptable yields (entries 15−17). However, with methyl acrylate and with acrylonitrile as acceptors, only low yields of the corresponding tetrahydronaphthalene derivatives **1m** and **1n** were obtained in the reaction with phenylboronic acid under the applied conditions (entries 18 and 19).

Scheme 3. Oxidative Radical Hydroxyarylation



Interestingly, we found that reaction of phenylboronic acid and methyl acrylate with $Mn(OAc)_3$ in the presence of dioxygen (balloon, 1 atm) did not provide the targeted tetrahydronaphthalene derivative but delivered product **2a** as a result of a radical hydroxyarylation (Scheme 3, Table 1, entry 1).[11] Radical hydroxyalkylations are well established;[12] however, the corresponding arylhydroxylation process is not well investigated to date.[13] This is not unexpected since, due to the high reactivity of aryl radicals, intermolecular aryl radical additions are generally very difficult to achieve.[14] A slightly better yield was obtained for the reaction with acrylonitrile under the same

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(6) Reviews on homolytic aromatic substitutions: (a) Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P., Sibi, M., Eds; Wiley-VCH: Weinheim, 2001; p 62. (b) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649. (c) Bowmann, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803. (e) Vaillard, S. E.; Schulte, B.; Studer, A. In *Modern Arylation Methods*; Ackermann, L., Ed; Wiley-VCH: Weinheim, 2009; p *475*.

(7) Such a cascade, although in low yield, has been reported for the decomposition of dibenzoylperoxide in the presence of an olefin; see: Araneo, S.; Fontana, F.; Minisci, F.; Recupero, F.; Serri, A. *Tetrahedron Lett.* **1995**, *36*, 4307.

(8) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 5198.

(9) Thiem, J.; Meyer, B. *Org. Magn. Reson.* **1978**, *11*, 50.

(10) $Mn(OAc)_3$ (1.5 mmol) and vinyldimethylphosphonate (3.0 mmol) were added to a solution of the corresponding arylboronic acid (0.50 mmol) in $ClCH_2CH_2Cl$ (2.5 mL). The reaction mixture was stirred at 80 °C under an argon atmosphere for 6 h. The suspension was filtered through a pad of celite, and the volatiles were removed under reduced pressure. The residue was purified by FC (CH_2Cl_2/MeOH = 40:1).

(11) Oxidative formal hydroxyarylation of olefins; see: Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235.

(12) Radical hydroxyalkylation; see: Ueda, M.; Miyabe, H.; Kimura, T.; Kondoh, E.; Naito, T.; Miyata, O. *Org. Lett.* **2009**, *11*, 4632, and references cited therein.

(13) Formal radical hydroxyarylation; see: Heinrich, M. R.; Wetzel, A.; Kirschstein, M. *Org. Lett.* **2007**, *9*, 3833.

(14) For a highly efficient intermolecular aryl radical addition, see: Vaillard, S. E.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6533.

Table 2. Radical Hydroxyarylation

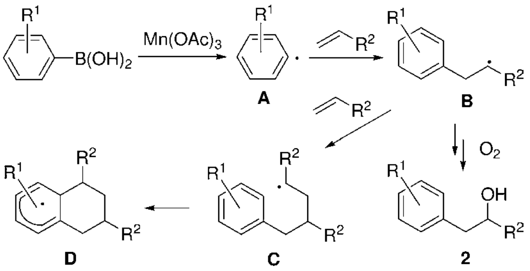
entry	R^1 inArB(OH)	R^2	R^3	*dr*	no.	yield[%]
1[a]	H	H	CO_2Me	–	**2a**	33
2[a]	H	H	CN	–	**2b**	39
3[a]	H	CO_2Me	CO_2Me	2.6:1	**2c**	43
4[b]	H	CO_2Me	CO_2Me	2.6:1	**2c**	48
5[b]	4-CH_3	CO_2Me	CO_2Me	1.5:1	**2d**	38
6[b]	3-CH_3	CO_2Me	CO_2Me	3.0:1	**2e**	27
7[b]	2-CH_3	CO_2Me	CO_2Me	2.2:1	**2f**	23
8[b]	4-F	CO_2Me	CO_2Me	2.4:1	**2g**	46
9[b]	4-Cl	CO_2Me	CO_2Me	1.9:1	**2h**	53
10[b]	4-Br	CO_2Me	CO_2Me	1.7:1	**2i**	46
11[b]	4-I	CO_2Me	CO_2Me	2.0:1	**2j**	34
12[b]	4-MeO	CO_2Me	CO_2Me	1.1:1	**2k**	37
13[b]	3-Cl	CO_2Me	CO_2Me	2.1:1	**2l**	40

[a] 10 equiv of olefin were used. [b] Neat in olefin.

conditions (→ **2b**, entry 2). We tried to increase the yield by increasing the concentration of the aryl radical acceptor. However, upon running these two reactions in neat olefin, polymerization occurred. Dimethylmaleate reacted with phenylboronic acid under oxidative conditions producing hydroxy ester **2c** which was isolated in 43% yield as a 2.6:1 mixture of diastereoisomers (entry 3).[15] The yield was further improved to 48% upon increasing the concentration of the olefin (entry 4). *Para*- and *meta*-substituted phenylboronic acid derivatives reacted with acceptable yields with dimethyl maleate (entries 5, 6, and 8−13). As expected, the lowest yield was achieved for the *ortho*-substituted tolylboronic acid (entry 7). With vinyl dimethylphosphonate as an acceptor, we obtained the double olefin addition/homolytic aromatic substitution product **1a** even in the presence of dioxygen. It is important to note that aryl halides, which are substrates under radical tin hydride conditions, are not transformed under the reaction conditions.

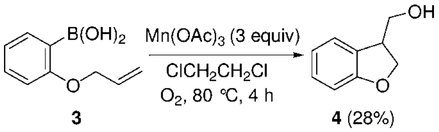
We suggest the following mechanism for our reactions. Reaction of $Mn(OAc)_3$ with an arylboronic acid provides an aryl radical **A** which undergoes intermolecular addition to the olefin acceptor to give **B** (Scheme 4). If the reaction of **B** with the alkene is slow and if oxygen is present, radical **B** is trapped by O_2 to give the corresponding peroxyl radical which is eventually further transformed to the hydroxy derivative **2**.[16] In the absence of dioxygen, adduct radical **B** undergoes renewed addition to the olefin to generate radical **C** which then further cylizes onto the arene to give the cyclohexadienyl radical **D**. This radical is readily oxidized to give the tetrahydronaphthalene derivative **1**.

Scheme 4. Suggested Mechanism



To further establish the radical nature of our reactions we reacted arylboronic acid **3** with $Mn(OAc)_3$ in the presence of dioxygen (Scheme 5). Hydroxylated dihydrobenzofurane **4** was obtained in 28% yield. That cyclization reaction strongly supports the radical character of our Mn-mediated oxidative processes.

Scheme 5. Oxidative Cyclization



In summary, we presented the first intermolecular aryl radical additions to various olefins starting with readily available arylboronic acids. Arylboronic acids upon reaction with $Mn(OAc)_3$ are valuable aryl radical precursors. In the presence of electron-poor olefins, aryl radical addition to the olefin is followed by renewed addition and subsequent homolytic aromatic substitution to eventually give tetrahydronaphthaline derivatives. These cascade reactions that comprise three C−C bond forming steps are experimentally very easy to conduct (simply mixing commercially available compounds and heating). In the presence of dioxygen, the initially generated adduct radical may react with O_2 to give the corresponding arylhydroxylation products.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We were not able to unambiguously assign the relative configuration of the major isomer.

(16) The mechanism for conversion of the alkyl peroxyl radical to the corresponding hydroxy compound under oxidative conditions is unknown.