

Generation of Aryl Radicals from Arylboronic Acids by Manganese(III) Acetate: Synthesis of Biaryls and Heterobiaryls

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The efficient generation of aryl radicals from arylboronic acids by manganese(III) acetate is described. In aromatic solvents, in situ generated aryl radicals afford the corresponding biaryls in very good yields. This method works selectively, and yields are better than those from similar, previously described methods. Arylboronic acids carrying sensitive functional groups also work efficiently.

Introduction

C–C bond-forming reactions leading to biaryls are very important because this approach is the key step in the synthesis of many natural and unnatural biaryls. There are various biaryl coupling methods, and the applications of these methods are reviewed comprehensively in the literature.¹ In the classical Ullmann reaction, arylhalides are reacted with copper, forming the corresponding biaryls. The original Ullmann reaction employs high temperatures and is greatly affected by the nature of the substituents and the steric environment. An ambient-temperature variant of this reaction was developed and has been used by many researchers.² Catalytic coupling reactions are also well-known in biaryl synthesis, the four most commonly used being the Kharasch, Negishi, Stille, and Suzuki reactions.^{1d,3} Today, catalytic coupling reactions are a routine means of access to biaryls in laboratories. In these catalytic coupling methods, the course of the reaction is determined by the position of the functional group specific to the method employed so that perfect regioselective coupling is possible. Thus, the selectivity of the coupling site is now reduced to the introduction of that functional group into the desired coupling position.

Another common method for the synthesis of simple unsymmetrical biaryls is the generation of aryl radicals in the presence of aromatic solvents. Although the product range of this approach is somewhat limited, it provides an easy access to a variety of unsymmetrical biaryls. The classical Gomberg–Bachmann (GB) biaryl

synthesis uses arenediazonium ions in an aqueous heterogeneous mixture of the aromatic reactant and base.⁴ The yields of this classical reaction are low for most cases, possibly related to the instability of arenediazonium salts in the reported reaction conditions, where many competing reactions are probably taking place. Beadle et al. developed a phase-transfer GB (PTGB) reaction, and under their conditions the yields are greatly improved.⁵ Patrick et al. reported that aryltriazenes react with aromatic solvents in the presence of trifluoroacetic acid to produce biaryls via aryl radicals.⁶ Although the yields approach those of the PTGB reaction in some cases, the PTGB reaction is far better.

Manganese(III) acetate is a one-electron oxidant, largely used as a radical generator. Since the pioneering work of Heiba et al. and Bush et al. in 1968,⁷ manganese(III)-mediated oxidations have been extensively studied. Fristad et al. showed that the rate of radical generation with manganese(III) acetate with bridging acetates correlates with the enolizability and CH acidity of the substrates.⁸ Thus, it is this reagent's ability to generate radicals in such systems that leads to highly efficient C–C bond-forming reactions, especially for the construction of cyclic systems, a topic reviewed by Snider.⁹ We recently showed that arylhydrazines can be efficiently oxidized by manganese(III) acetate to produce aryl radicals that afford biaryls in benzene with very good yields.¹⁰ Although the

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TABLE 1. Yields of Biaryls^a

entry	arylboronic acid, R	solvent	biaryl, yield (%)	PTGB yield (%)	arylhydrazine yield (%)	mp (°C)	lit. mp (°C)
1	1a , H	benzene	2a , 95	62	75	68–69	69 ⁵
2	1b , 2-Br	benzene	2b , 90	81	70	oil	
3	1c , 3-Br	benzene	2c , 89	NR	73	oil	
4	1d , 4-Br	benzene	2d , 80	81	81	90	90 ⁵
5	1e , 2-OMe	benzene	2e , 82	NR	NR	oil	
6	1f , 3-OMe	benzene	2f , 85	NR	NR	oil ^{14a}	
7	1g , 4-OMe	benzene	2g , 84	80	83	90	89 ⁵
8	1h , 2-CHO	benzene	2h , 40	NR	NR	oil ^{14b}	
9	1i , 3-CHO	benzene	2i , 60	NR	NR	oil ^{14c}	
10	1j , 4-CHO	benzene	2j , 80	73	NR	58–59	60 ^{13a}
11	1a , H	thiophene	6a , 73	43	70	42	42–43 ⁵
12	1b , 2-Br	thiophene	6b , 74	NR	65	oil ^{14d}	
13	1c , 3-Br	thiophene	6c , 77	NR	68	oil ¹¹	
14	1d , 4-Br	thiophene	6d , 75	56	54	99	99–100 ⁵
15	1e , 2-OMe	thiophene	6e , 70	NR	NR	oil ^{14e}	
16	1f , 3-OMe	thiophene	6f , 55	NR	NR	oil ^{14f}	
17	1g , 4-OMe	thiophene	6g , 66	NR	62	105	106–107 ¹⁰
18	1h , 2-CHO	thiophene	6h , 50	NR	NR	oil ^{14g}	
19	1i , 3-CHO	thiophene	6i , 67	NR	NR	oil ^{14h}	
20	1j , 4-CHO	thiophene	6j , 73	NR	NR	66	67–68 ^{13b}
21	1a , H	furan	7a , 62	NR	60	oil ¹⁴ⁱ	
22	1b , 2-Br	furan	7b , 55	NR	53	oil ¹¹	
23	1c , 3-Br	furan	7c , 63	NR	60	oil ^{14j}	
24	1d , 4-Br	furan	7d , 67	55	65	85	85–86 ⁵
25	1e , 2-OMe	furan	7e , 36	NR	NR	oil	
26	1f , 3-OMe	furan	7f , 32	NR	NR	oil ^{14f}	
27	1g , 4-OMe	furan	7g , 34	NR	30	36	37–38 ¹⁰
28	1h , 2-CHO	furan	7h , 19	NR	NR	oil ^{14k}	
29	1i , 3-CHO	furan	7i , 24	NR	NR	oil	
30	1j , 4-CHO	furan	7j , 27	NR	NR	40–41	41–42 ^{13b}

^a Yields are isolated except for **7e**. The presence and yield of compound **7e** were determined by GC–MS, but we were unable to isolate the pure compound from the complex crude mixture. New compound **7i** gave satisfactory analytical data (Experimental Section). All other compounds are known (**2b**, **2c**, and **2e** are commercially available), and all analytical data are in agreement with previously reported data.¹⁴ NR: not reported.

reaction is very efficient in benzene, it generally produces the corresponding heterobiaryls in furan and thiophene with moderate to good yields.¹¹

This drawback of arylhydrazines prompted us to find a more suitable substrate as the source of aryl radicals. A suitable candidate for this reaction should be much more reactive than arylhydrazinium salts under the reaction conditions yet stable enough to handle easily and not prone to side reactions. It is known that arylboronic acids decompose to aryl radicals in the presence of some oxidants.¹² Arylboronic acids are widely used as the organometallic counterpart in the Suzuki reaction. They are stable under atmospheric and aqueous conditions such that Suzuki coupling can be carried out with aqueous organic solvents.

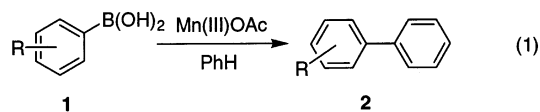
Therefore, we decided to investigate the oxidation of arylboronic acids with manganese(III) acetate in aromatic solvents. Herein we report the synthesis of a variety of unsymmetrical biaryls with in situ generated aryl radicals from arylboronic acids with manganese(III) acetate.

Results and Discussion

First, we examined the reaction of various arylboronic acids with manganese(III) acetate in benzene. A mixture of manganese(III) acetate and phenylboronic acid was

stirred at room temperature, and the reaction was monitored by GC–MS and TLC. The progress of the reaction was so slow that only a small amount of product could be detected after 24 h. Refluxing of the same reaction mixture quickly furnished the biphenyl in 30 min with an almost quantitative yield (Table 1, entry 1).

We examined a variety of arylboronic acids **1a–j** (Table 1, entries 1–10) and observed that biaryls **2a–j** can be prepared in very good yields by the reaction of arylboronic acids with manganese(III) acetate in benzene (eq 1). The yields are generally better than those from similar reactions reported previously. This shows that arylboronic acids are suitable substrates for the generation of aryl radicals. Products were obtained as a single isomer showing that the initial radical that forms does not isomerize as reported previously for the PTGB reaction⁵ and the oxidation of arylhydrazines:¹⁰ the unpaired electron is attached to the carbon that originally bore the leaving functionality.

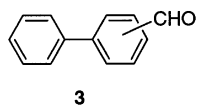


Formylphenylboronic acids were reacted similarly to other arylboronic acids with careful monitoring of the reaction mixture by TLC and GC–MS. We observed that the corresponding formylbiphenyls **2h–j** were formed in very good yields (Table 1, entries 8–10) without any oxidation products. Therefore, we showed that aryl

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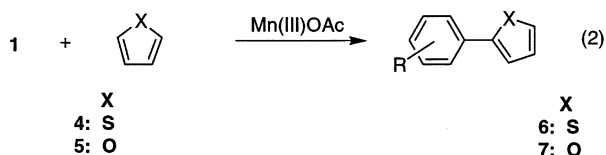
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radicals can be generated efficiently from formylphenylboronic acids for the synthesis of the formylbiphenyls **3**, which are valuable starting materials for a variety of important targets such as benzoin or pinacols.



We also examined the reaction of arylboronic esters. Phenylboronic acid and 2-formylphenylboronic acid were converted to the corresponding esters with 1,3-propanediol with the azeotropic removal of water in benzene. The 2-formylphenylboronic acid ester was unreactive in our reaction conditions, but the reaction of phenylboronic acid furnished biphenyl in 15% yield after 72 h of reflux. Therefore, the boronic acid esters seem to be unreactive toward manganese(III) acetate-mediated oxidation. The low-yield conversion of the phenylboronic acid ester to the biphenyl can be attributed to the slow hydrolysis of the ester, which in turn yields the reactive phenylboronic acid. This observation may find application in manganese(III) acetate-mediated synthesis as a protection or deprotection tool and for the controlled generation of aryl radicals from arylboronic acids.

As seen in Table 1, the generation and subsequent trapping of aryl radicals in heterobiaryl solvents have been reported to give lower yields than the corresponding reactions in benzene. Therefore, we examined the oxidation of arylboronic acids **1a–j** in thiophene (**4**; entries 11–20) or furan (**5**; entries 20–30). The arylation of furan and thiophene occurred with moderate to good yields and exclusively in the 2 position to furnish **6a–j** and **7a–j** (eq 2). Yields were lower than those for the reactions



carried out in benzene, as expected, based on previous reports by us and others.^{5,6,10} Although there was a good improvement of the yields in thiophene with the use of arylboronic acids instead of arylhydrazines, they were just comparable for the furan and below satisfactory. That shows us that, although arylboronic acids are more suitable for the generation of aryl radicals, furan is not as compatible as thiophene in the manganese(III) acetate-mediated synthesis that results in comparable or lower yields in furan. However, arylboronic acids furnished the corresponding heterobiaryls with higher yields than did PTGB. Formylphenylboronic acids were also studied under the same reaction conditions, and it was observed that they gave the corresponding formylheterobiaryls but the yields were lower than those of benzene and below satisfactory for furan.

To clarify the radical nature of the reaction, phenylboronic acid and 4-OMe-phenylboronic acid were reacted with manganese(III) acetate in bromobenzene. Phenyl-

boronic acid in bromobenzene afforded 49%, 30%, and 21% isomers, results very similar to those obtained from the oxidation of phenylhydrazinium chloride in bromobenzene where the O isomer predominates, but there is no substantial selectivity. 4-OMe-phenylboronic acid in bromobenzene shows a very similar distribution of isomers: 54%, 29%, and 17%. This observation is in agreement with the product distribution of the formation of aryl radicals by a substitution reaction of aryl radicals with arenes.

In conclusion, we showed that a variety of radicals can be generated from the corresponding arylboronic acids. In the presence of organic solvents, these radicals afford the monosubstituted biaryls with yields generally higher than those from similar previously reported reactions. Reactions in benzene gave higher yields than those in thiophene or furan; the former was better in terms of yield. Possible applications and extensions of this study are now under investigation.

Experimental Section

Typical Procedure for Biaryls. To a mixture of manganese(III) acetate¹⁵ (330 mg, 1.24 mmol Mn(OAc)₃·2H₂O) in 10 mL of benzene was added phenylboronic acid (50 mg, 0.41 mmol), and the resulting mixture was refluxed for 30 min (formation of the products was monitored by TLC and GC–MS). After the completion of the reaction, the mixture was filtrated through a pad of silica using hexane or petroleum ether as the eluent. Concentration under reduced pressure furnished the biphenyl **2a** (62 mg, 95%, solid), confirmed by NMR, IR, and GC–MS.

2-(3-Formylphenyl)furan (7i): yield 24%, colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 6.49 (1H, dd, *J* = 3.3, 1.7 Hz), 6.74 (1H, d, *J* = 3.3 Hz), 7.49 (1H, d, *J* = 1.7 Hz), 7.53 (1H, dd, *J* = 7.7, 7.6 Hz), 7.74 (1H, d, *J* = 7.6 Hz), 7.90 (1H, d, *J* = 7.7 Hz), 8.14 (1H, s), 10.1 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 106.6, 112.2, 125.2, 128.6, 129.5, 129.7, 132.2, 137.3, 143.0, 152.9, 191.8. Anal. Calcd for C₁₁H₈O₂: C, 76.73; H, 4.68. Found: C, 76.64; H, 4.61.

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