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Manganese(III) acetate-mediated synthesis of biaryls under microwave irradiation

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ABSTRACT

Manganese(III) acetate ($Mn(OAc)_3$)-mediated synthesis of biaryls and heterobiaryls starting from arylboronic acid was developed under microwave irradiation in high yields. Microwaves were also used for the synthesis of $Mn(OAc)_3$ from $KMnO_4$ and acetic acid. Additional irradiation of this in situ generated $Mn(OAc)_3$ with arylboronic acids, which in turn furnished the biaryls in high yields in a one pot reaction. This is superior from the point of view of yield, short reaction time, sensitive functional group toleration, and more environmentally friendly than the reported methods with a minimum amount of benzene and thiophene as a reagent but not as a solvent.

1. Introduction

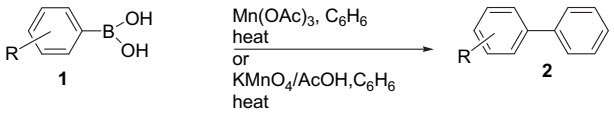
Metal-promoted radical reactions have found widespread use in organic synthesis, in which one of the well-known examples of this application is the $Mn(OAc)_3$-mediated reaction.[1] Manganese(III) acetate dihydrate ($Mn(OAc)_3 2H_2O$)-mediated free-radical reactions have emerged as important synthetic methods for a new bond formation as well as bond breaking. The application of $Mn(OAc)_3$ promoted free-radical reactions in numerous regio-, chemo-, and stereoselective carbon–carbon, carbon–heteroatom bond formations have been developed in both inter- and intramolecular reactions.[2a–c]

Biaryls are an important class of organic compounds, since the biaryl unit is represented in natural products, advanced materials, and molecules of medicinal interest. There are various biaryl coupling methods, in which the applications of these methods have been reviewed comprehensively in the literature.[3] Catalytic coupling reactions[3c,4] are commonly used methods for the formation of C–C bonds in turn leading to biaryls. The Suzuki–Miyaura protocol[4,5] is one of those catalytic methods wherein arylboronic acids are used as a reaction partner and where the position of the boronic acid functional group determines the course of the reaction regioselectively in order to yield aryl- and heterobiaryls.[6]

Another common method for the synthesis of simple unsymmetrical biaryls is the generation of aryl radicals in the presence of aromatic solvents. $Mn(OAc)_3$ is a one-electron oxidant and is generally used to generate radicals that lead to C–C bond forming reactions.[2c]

In our previous work, we developed a general method for the synthesis of biaryls starting from arylhydrazines/aromatic solvents and arylboronic acids/aromatic solvents in the presence of $Mn(OAc)_3$. We showed, for the first time, that $Mn(OAc)_3$ is a versatile reagent for the generation of aryl radicals from arylhydrazines and arylboronic acids.[7]

The potassium permanganate and acetic acid method were also developed for aryl coupling reactions. The reaction of arylboronic acids and arylhydrazines in benzene with potassium permanganate and acetic acid in turn furnished biaryls in 85–96% yield. We have shown that the potassium permanganate/carboxylic acid/organic solvent combination behaves as manganese(III)acetate. This system is also applied to an aryl coupling reaction, in which aryl coupling products are obtained in good yield (Scheme 1).[7]



Scheme 1.

As we have described in our previous papers,[8] microwave irradiation has been widely used as a powerful and easily controllable heating source for organic reactions. Furthermore, the use of microwave ovens in organic synthesis is an alternative green technology for heating. Reactions conducted under microwave usually have short reaction times, high yields and better selectivities.[9] The heating effect, that is, utilized in microwave-assisted organic transformations is due to the dielectric constant of the solvent. It is particularly convenient that, qualitatively, the larger the dielectric constant of the reaction medium, the greater the coupling with microwaves.[10]

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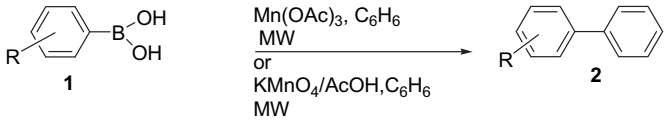
In the course of our studies on biaryl systems,[6,7] we decided to investigate the reaction of arylboronic acids with $Mn(OAc)_3$ and benzene as well as the $KMnO_4$/acetic acid system under microwave irradiation. Herein, we report the microwave-assisted synthesis of a variety of unsymmetrical biaryls with in situ generated aryl radicals from arylboronic acids/$Mn(OAc)_3$ system.

2. Results and discussion

In an initial reaction, which is shown in Scheme 2, to a mixture of $Mn(OAc)_3$ and 500 mg of zeolite (montmorilloite K10) in 5 mL benzene was added to arylboronic acid. This solution was stirred under different microwave conditions, such as 200-, 400-, 600-, and 800-W irradiation, in which the reaction is monitored by TLC. After all of the starting material is consumed (30 min), the product is isolated after a work up procedure. The best yield (91%) is obtained under the 600–800-W conditions (30 min). We examined a variety of aryl- and hetero-arylboronic acids and observed that biaryls **1**–**18** can be prepared in very good yields by the reaction of arylboronic acid with manganese(III) acetate in benzene under microwave irradiation (Scheme 2). These microwave yields are in some cases better than those from similar reactions that were reported previously.[7]



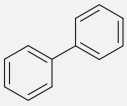
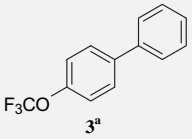
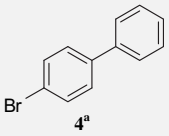
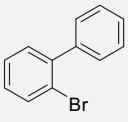
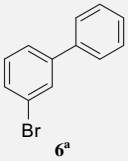
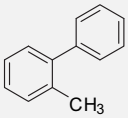
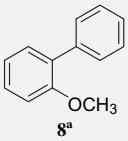
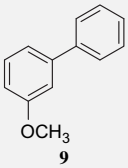
Scheme 2.

The same reaction was also performed with the $KMnO_4$/AcOH/benzene system. First, the $KMnO_4$/AcOH/benzene mixture was mixed with zeolite and irradiated under microwave (20–30 min). After the purple color of the mixture transformed into brown, arylboronic acid is added and the irradiation is continued (30 min). The products are obtained with similar yields with the $Mn(OAc)_3$ case as summarized in Table 1. Formylphenylboronic acids were reacted similarly to other arylboronic acids with careful monitoring of the reaction mixture by TLC. We observed that the corresponding formylbiphenyls were formed in good yields. Therefore, we showed that aryl radicals can be generated efficiently from formylphenylboronic acids for the synthesis of the formylbiphenyls, which are valuable starting materials for a variety of important targets, such as benzoins or pinacols,[11] most of the compounds are protected. We also examined the reaction of arylboronic esters. Phenylboronic acid is converted to the corresponding esters with 1,3-propanediol with the azeotropic removal of water in benzene. The reaction of phenylboronic acid ester furnished biphenyl in 5–6% yield. Therefore, the boronic acid esters seem to be unreactive toward MW assisted manganese(III) acetate 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, which is not easily applicable by using other methods.

For the synthesis of biaryls under microwave irradiation heteroaromatic compounds were also tried, such as furan, thiophene, and pyrimidine. Among these aromatic compounds, thiophene and pyrimidine gave biaryls with high yields but in the furan case, significant amounts of side products were formed and we could not obtain the desired product in acceptable yields.

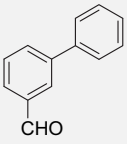
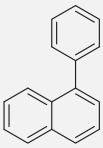
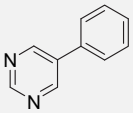
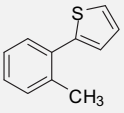
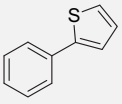
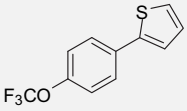
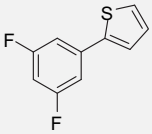
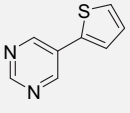
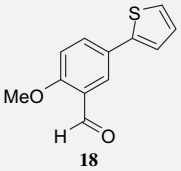
The reaction proceeds independent of the substituents of the arylboronic acid and hetero-arylboronic acids. Both arylboronic

Table 1
$Mn(OAc)_3$-mediated synthesis of biaryls

Product	Yield (%)		Yield (%) lit., mp °C (lit.)
	$Mn(OAc)_3$	$KMnO_4$/AcOH/benzene system	
 **1**[a]	91	90	96, 69–73 (69–72)[7a]
 **2**[a]	85	90	99, 56–58[12]
 **3**[a]	78	84	95, oil[7a]
 **4**[a]	84	87	100, 91–93 (92–93)[13,14]
 **5**[a]	**81**	80	95 (oil)[13,15]
 **6**[a]	**89**	91	90 (oil)[13,14]
 **7**[a]	87	93	61 (oil)[16]
 **8**[a]	76	75	90 (oil)[7a]
 **9**	92	98	85 (oil)[17]

(*continued on next page*)

Table 1 (*continued*)

Product	Yield (%)		Yield (%) lit., mp °C (lit.)
	$Mn(OAc)_3$	$KMnO_4$/AcOH/ benzene system	
 **10**[a]	71	77	60, 53–54 (semisolid)[18]
 **11**	81	88	87 (oil)[17]
 **12**	75	73	56, semisolid (54)[19,20]
 **13**	91	95	79, oil[20,21]
 **14**	92	90	70, oil (34–35)[22,23]
 **15**	82	88	—
 **16**	92	95	—
 **17**	78	81	92, 77–79 (77–78)[24,25]
 **18**	62	65	—

[a] Commercially available compound.

acids with electron withdrawing and electron donating groups at the *ortho*-, *para*- and *meta*- positions gave corresponding biaryls in excellent yields. This method tolerates sensitive groups and no isomerization in the arylboronic acid part is detected, but the changing of the benzene to substituted derivatives furnished a mixture of isomeric products. Similar results were also obtained with heating methods.[7d]

The progress of the reaction under microwave irradiation was so rapid that all of the reactions went to completion in a short time.

3. Conclusion

A rapid and efficient method for the manganese(III) acetate-mediated synthesis of biaryls and heterobiaryls has been developed under microwave irradiation. Microwaves are also used for the synthesis of $Mn(OAc)_3$ from $KMnO_4$ and acetic acid, and additional irradiation with arylboronic acids, which in turn furnished biaryls in high yields. This is superior from the point of view of yield, short reaction time, tolerates sensitive functional groups, and is more environmentally friendly than the reported methods. The boronic acid esters seem to be unreactive toward MW assisted $Mn(OAc)_3$ oxidation. Benzene and thiophene are not used as a solvent but rather as a reagent in very low amounts.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were obtained on Bruker Avance DPX 400 spectrometers at 300 MHz. All of the resonances are referenced to the residual solvent signals ($CDCl_3$ for ^1H NMR; $CDCl_3$ for ^{13}C NMR). Elemental analyses: Leco CHNS 932 Analyzer (Central laboratory from Hacettepe university and METU). The IR spectra were obtained on Bruker IFS 66/s. Column chromatography was conducted on silica gel 60 (40–63 mm). TLC was carried out on aluminum sheets that were pre-coated with silica gel $60F_{254}$ (Merck), in which the spots were visualized with UV light (λ 254 nm). Microwave reactions are carried out with Milestone start MW.

4.2. General procedure for the synthesis of biaryls with $Mn(OAc)_3$

To a solution of $Mn(OAc)_3$ (680 mg, 0.3 mmol) and 500 mg of zeolite in 5 mL benzene–AcOH (20:1) or thiophene–AcOH was added to 0.1 mmol of arylboronic acid. This solution was stirred under 800-W microwave radiation (30 min). The reaction is monitored by TLC. After all the starting material is consumed, the reaction mixture was diluted with 50 mL ether and neutralized with $NaHCO_3$ (10% solution). The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography by using EtOAc–hexane as an eluent. In most cases, the direct filtering of the reaction mixture was conducted through a pad of silica provided pure products.

4.3. General procedure for the synthesis of biaryl via the $KMnO_4$/acetic acid system under microwave radiation

$KMnO_4$ (47 mg, 0.3 mmol) and 500 mg of zeolite in 5 mL benzene–AcOH (20:1) or thiophene–AcOH was stirred under 800-W microwave radiation until the color of the solution turned brown. To this solution 0.1 mmol of arylboronic acid was added and stirred under 800-W microwave radiation (30 min). The reaction was monitored by TLC. After all of the starting material was consumed, the reaction mixture was diluted with ether (50 mL) and neutralized with $NaHCO_3$ (10% solution). The resulting organic phase was

dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography by using flash silica gel, EtOAc–hexane (1:10) as an eluent.

*4.3.1. Biphenyl (**1**)*[7a]. Yield (13.8 mg, 90%), white solid; mp 69–73 °C (lit. 69–72 °C). δ_H (400 MHz $CDCl_3$) 7.31–7.36 (m, 2H), 7.42–7.47 (m, 4H), 7.55–7.60 (d, 4H); δ_C (100 MHz $CDCl_3$) 127.2, 127.3, 128.8, 141.2.

*4.3.2. 3,5-Difluorobiphenyl (**2**)*[12]. Yield (19.1 mg, 90%), yellow oil. δ_H (400 MHz $CDCl_3$) 6.76 (1H, tt, J=8.8, 2.0 Hz), 7.14 (2H, dd, J=8.8, 2.4 Hz), 7.41 (1H, t, J=7.2 Hz), 7.47 (2H, t, J=7.2 Hz), 7.54 (2H, d, J=7.2 Hz); δ_C (100 MHz $CDCl_3$) 102.5 (t, J=100 Hz), 110.1 (dd, J=18, 6 Hz), 127.1, 128.6, 129.2, 139.2, 144.6 (t, J=10 Hz), 163.5 (dd, J=247, 13 Hz).

*4.3.3. 4-Trifluoromethoxybiphenyl (**3**)*[7a]. Yield (20 mg, 84%), white solid; mp 57–59 °C (lit. 56–58 °C). δ_H (400 MHz $CDCl_3$), 7.18 (d, J=8.6 Hz, 2H, CH), 7.27 (t, J=7.4 Hz, 1H, CH), 7.33 (d, J=7.4 Hz, 2H, CH, CH), 7.45 (t, J=7.4 Hz, 2H, CH, CH), 7.48 (t, J=8.6 Hz, 2H, CH, CH); δ_C (100 MHz $CDCl_3$) 121.2, 127.2, 127.6, 128.5, 128.8, 139.9, 140.2, 148.6.

*4.3.4. 4-Bromobiphenyl (**4**)*[13,14]. Yield (20.2 mg, 87%), white solid; mp 91–93 °C (lit. 92–93 °C). δ_H (400 MHz $CDCl_3$) 7.35–7.39 (m, 1H), 7.42–7.51 (m, 2H), 7.60–7.68 (m, 6H); δ_C (100 MHz $CDCl_3$) 121.6, 126.9, 127.6, 128.7, 128.8, 131.9, 140.1, 140.3.

*4.3.5. 2-Bromobiphenyl (**5**)*[13,15]. Yield (18.6 mg, 80%), colorless oil. δ_H (400 MHz $CDCl_3$) δ 7.12 (m, 1H, Ar), 7.26 (m, 2H, Ar), 7.33 (t, J=7.0 Hz, 1H, Ar), 7.36 (m, 4H, Ar), 7.59 (d, J=7.2 Hz, 1H); δ_C (100 MHz $CDCl_3$) 122.5, 127.3, 127.5, 127.8, 128.9, 129.2, 131.3, 133.1, 141.1, 142.3.

*4.3.6. 3-Bromobiphenyl (**6**)*[13,14]. Yield (21.2 mg, 91%), colorless oil. δ_H (400 MHz $CDCl_3$) 7.28–7.69 (m, 8H), 7.77 (s, 1H); δ_C (100 MHz $CDCl_3$) 122.9, 125.8, 127.1, 127.9, 128.9, 130.2, 130.3, 139.7, 143.4.

*4.3.7. 2-Methylbiphenyl (**7**)*[16]. Yield (15.6 mg, 93%), colorless oil. δ_H (400 MHz $CDCl_3$), 2.34 (s, 3H), 7.28–7.32 (m, 4H), 7.36–7.41 (m, 3H), 7.46–7.51 (m, 2H); δ_C (100 MHz $CDCl_3$) 20.4, 125.8, 126.6, 127.1, 128.1, 128.8, 129.1, 129.6, 130.3, 135.2, 141.8.

*4.3.8. 2-Methoxybiphenyl (**8**)*[7a]. Yield (13.8 mg, 75%), colorless oil. δ_H (400 MHz $CDCl_3$) 3.86 (s, 3H), 7.04 (d, J=8.6 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 7.41–7.35 (m, 3H), 7.47 (t, J=8.0 Hz, 2H), 7.59 (d, J=7.9 Hz, 2H); δ_C (100 MHz $CDCl_3$) δ 55.6, 111.3, 120.8, 126.7, 127.8, 128.6, 129.6, 130.8, 130.9, 138.5, 156.5.

*4.3.9. 3-Methoxybiphenyl (**9**)*[17]. Yield (15.7 mg, 85%), colorless oil. δ_H (400 MHz $CDCl_3$) 3.84 (s, 1H), 6.90–6.93 (m, 1H), 7.15–7.23 (m, 2H), 7.35–7.49 (m, 4H), 7.61–7.65 (m, 2H); δ_C (100 MHz $CDCl_3$) 55.5, 112.6, 113.1, 119.6, 127.2, 127.4, 128.8, 129.8, 141.1, 142.8, 161.0.

*4.3.10. Biphenyl-3-carbaldehyde (**10**)*[18]. Yield (12.3 mg, 77%), colorless semisolid (lit.[7d] mp 53–54 °C). δ_H (400 MHz $CDCl_3$) 7.22(m, 1H), 7.34 (m, 2H), 7.51 (m, 3H), 7.77 (m, 2H), 8.03 (m, 1H), 9.88 (s, 1H); δ_C (100 MHz $CDCl_3$) 127.2, 127.8, 128.6, 129.3, 129.4, 129.7, 133.4, 136.5, 137.2, 137.3, 191.2.

*4.3.11. 1-Phenylnaphthalene (**11**)*[17]. Yield (18.0 mg, 88%), colorless oil. δ_H (400 MHz $CDCl_3$) 7.45–7.57 (m, 9H), 7.89–7.95 (m, 3H); δ_C (100 MHz $CDCl_3$) 125.5, 125.8, 126.1, 127.2, 127.5, 127.9, 128.4, 130.2, 131.7, 133.9, 140.5, 140.8.

*4.3.12. 5-Phenylpyrimidine (**12**)*[19]. Yield (10.0 mg, 73%), semisolid (lit.[15] mp 41 °C). δ_H (400 MHz $CDCl_3$) 7.50–7.54 (m, 2H), 7.56 (d, J=7.5 Hz, 2H), 7.56–7.67 (m, 1H), 8.96 (s, 2H), 9.21 (s, 1H); δ_C (100 MHz $CDCl_3$) 126.8, 129.1, 129.5, 134.2, 134.3, 154.8, 157.3.

*4.3.13. 2-o-Tolylthiophene (**13**)*[20,21]. Yield (16.5 mg, 95%), colorless oil. δ_H (400 MHz $CDCl_3$) 2.45 (s, 3H), 7.06–7.10 (m, 1H), 7.08–7.12 (m, 1H), 7.24–726 (m, 3H), 7.33–7.37 (m, 1H), 7.39–7.44 (m, 1H); δ_C (100 MHz $CDCl_3$) 21.1, 124.09, 125.8, 126.6, 127.2, 127.9, 130.6, 134.2, 136.1, 143.2.

*4.3.14. 2-Phenylthiophene (**14**)*[22,23]. Yield (14.4 mg, 90%), yellow oil (lit.[17] mp 34–35 °C). δ_H (400 MHz $CDCl_3$) 7.12–7.14 (m, 1H), 7.28–7.34 (m, 1H), 7.35–7.38 (m, 1H), 7.42–7.46 (m, 3H), 7.69–7.71 (m, 2H); δ_C (100 MHz $CDCl_3$) 123.1, 124.6, 125.7, 127.5, 128.2, 128.7, 134.2, 144.4.

*4.3.15. 2-(4-Trifluoromethoxyphenyl)thiophene (**15**).* Yield (19.5 mg, 88%), brown solid; mp=72.5–75.3 °C. IR ($CHCl_3$): 3120–3080, 1620, 1525 cm^{-1}. δ_H (400 MHz $CDCl_3$) 6.98 (t, J=4.2 Hz, 1H, CH), 7.13–7.32 (m, 4H, CH), 7.52 (d, J=8.6, 2H,); δ_C (100 MHz $CDCl_3$) 121.3, 121.4, 123.6, 125.3, 126.1, 127.2, 127.7, 128.0, 133.3, 142.8, 148.5. Anal. Calcd for $C_{11}H_7F_3OS$ (244.23): C, 54.09; H, 2.89. Found: C, 54.27; H, 3.12.

*4.3.16. 2-(3,5-Difluorophenyl)thiophene (**16**).* Yield (95, 18.6 mg), brown oil; IR ($CHCl_3$): 3118–3092, 1616, 1522 cm^{-1}. δ_H (400 MHz $CDCl_3$) 6.57–6.63 (m, CH, 1H), 6.95–7.02 (m, CH, 3H,), 7.20 (2H, d, J=5.2 Hz, CH); δ_C (100 MHz $CDCl_3$) 102.5 (t, J_{CF}=24.7 Hz), 108.8 (dd, J_{CF1}=7.5, J_{CF2}=18.5 Hz), 121.7, 124.4, 126.0, 126.7, 128.1, 137.5 (t, J_{CF}=9.9 Hz), 141.9, 163.4 (dd, J_{CF1}=247, J_{CF2}=12.6 Hz). Anal. Calcd for $C_{10}H_6F_2S$ (196.22): C, 61.21; H, 3.08. Found: C, 61.11; H, 3.22.

*4.3.17. 5-(Thiophen-2-yl)pyrimidine (**17**)*[24,25]. Yield (13.1 mg, 81%), white solid; mp 77–79 °C (lit.[18] 77.2–78.1 °C). δ_H (400 MHz $CDCl_3$) 7.16–7.20 (m, 1H), 7.42–7.44 (m, 1H), 7.45–7.47 (m, 2H), 8.97 (s, 1H), 9.14 (s, 1H); δ_C (100 MHz $CDCl_3$) 125.3, 127.1, 128.5, 128.6, 136.1, 153.5, 157.3.

*4.3.18. 2-Methoxy-5-thiophene-2-yl-benzaldehyde (**18**).* Yield (14.18 mg, 65%), green oil; IR ($CHCl_3$): 3210–3075, 1695, 1616, 1533 cm^{-1}. δ_H (400 MHz $CDCl_3$) 3.89 (3H, s, CH_3), 6.90–6.98 (2H, m, CH), 7.15–7.19 (2H, m, CH), 7.67 (1H, dd, J_1=2.5, J_2=8.7 Hz, CH), 7.96 (1H, d, J=2.5 Hz, CH), 10.39 (1H, s, CH); δ_C (100 MHz $CDCl_3$) 54.4, 110.9, 121.8, 123.5, 123.9, 124.6, 126.6, 126.9, 131.9, 141.7, 159.9, 187.6. Anal. Calcd for $C_{12}H_{10}O_2S$ (218.27): C, 66.03; H, 4.62. Found: C, 66.19; H, 4.44.

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