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A New Protocol for the One-Pot Synthesis of Symmetrical Biaryls

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Biaryls play an important role in modern organic chemistry. Although a large number of protocols for the synthesis of symmetrical and unsymmetrical biaryls already exist, most of them are not generally applicable. In our studies toward the total synthesis of the secalonic acids, we were interested in bis(pinacolato)diboron as a reagent for transforming haloarenes into arylboronic esters. By optimizing the reaction conditions, we were able to obtain biaryls containing various functional groups in good to excellent yields.

Biaryls play an important role in modern organic chemistry. Many natural products, often possessing biological activity, contain symmetrical or unsymmetrical biaryl units.[1] Prominent examples for such molecules are Michellamine A (**1**) or the secalonic acids **2** (Figure 1).[2]

Since the first coupling reaction performed by Ullmann over a century ago,[3] considerable efforts have led to a variety of procedures to form biaryls, which have recently been reviewed.[4] Whereas the first coupling reactions were performed with stoichometric amounts of metal, the catalytic use of metals, especially palladium, is nowadays established. Palladium-catalyzed cross-coupling reactions with organometallic compounds based on tin,[5] boron,[6] or zinc,[7] for example, are among the most popular reactions. Recently, several papers for the synthesis of symmetrical biaryls have been published which reflect the current efforts in this field of research.[8] Because of their high compatibility with functional groups and the low toxicity of organoboronic compounds,[9] Suzuki cross-coupling reactions are frequently used in natural product syntheses.[10] Nevertheless, the formation of the boronic acid

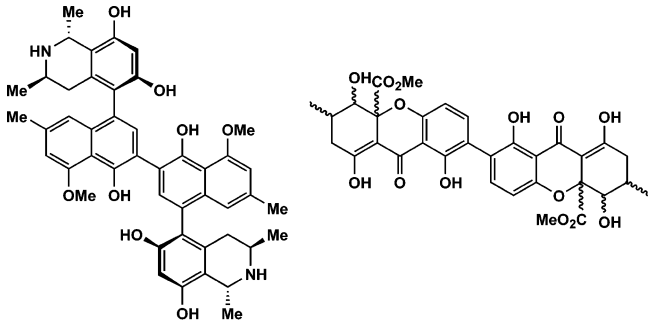

FIGURE 1. Structures of Michellamine A (1) and the secalonic acids **2**.

derivatives remains challenging as it often requires the use of strong bases, such as organolithium compounds. In 1995, Miyaura et al. introduced bis(pinacolato)diboron as a reagent for the transformation of arylhalides to arylboronic esters under mild conditions (Scheme 1).[11]

This procedure allows the synthesis of arylboronic esters in good yields while tolerating various functional groups. In another publication, the Miyaura group described the cross-coupling of aryl triflates to arylboronic esters as well as the synthesis of unsymmetrical biaryls using a modified protocol.[12,13] In both cases, the authors used KOAc as base since stronger bases such as K_2CO_3 afforded symmetrical biaryls as byproducts. The proposed mechanism of this reaction is depicted in Scheme 2. Oxidative addition of the catalyst to haloarene **3** followed by displacement of the halide leads to the corresponding

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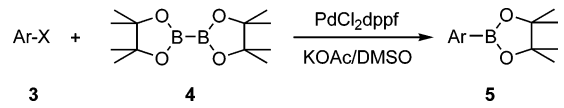
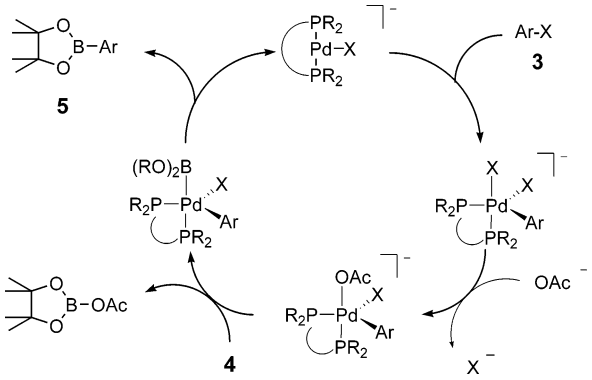
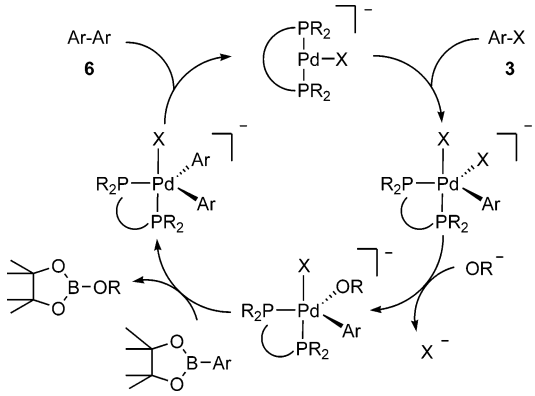
SCHEME 1. Transformation of Haloarenes 3 into Arylboronic Esters 5



SCHEME 2. Proposed Reaction Mechanism for the Generation of Arylboronic Esters[13]



SCHEME 3. Proposed Reaction Mechanism for the Formation of the Biaryls

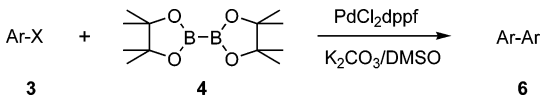


pentacoordinate palladium(II) species. Transmetalation with bis(pinacolato)diboron (**4**) followed by reductive elimination yields the arylboronic ester **5**.

The effect of stronger bases such as K_2CO_3 probably lies in their stronger nucleophilicity. After exchange of the halide against carbonate the neutral arylboronic ester **5** is coordinated leading to the formation of the corresponding biaryl **6** as shown in Scheme 3. This mechanism seems to be plausible regarding studies by Soderquist et al., who could show that halide exchange followed by reaction with the neutral borane species dominates the formation of rather unstable boronic ate complexes in the case of oxygenated organoboron compounds.[14] However, these studies did not make use of carbonate salts as base.

As a result, the reaction does not stop with the formation of the arylboronic ester **5** but continues with a Suzuki coupling step to yield the corresponding biaryls **6**. In following studies, Miyaura and co-workers also introduced an efficient protocol for the conversion of alkenyl halides and triflates into the corresponding alkenylboronic esters.[15] Despite the relatively high cost

SCHEME 4. Synthesis of Symmetrical Biaryls



of bis(pinacolato)diboron, the described procedures possess a high value for organic synthesis due to the mild coupling conditions. This reagent has consequently been used in several total syntheses for introducing boronic acid esters or biaryl units. In their studies toward the total synthesis of diazonamide A, Nicolaou and associates employed this reagent to synthesize one of the key intermediates.[16] Although there have been several studies on the synthesis of unsymmetrical biaryls by employing bis(pinacolato)diboron, the potential of this reagent for the synthesis of symmetrical biaryls has not been examined to date.[17] In the course of our investigations toward the total synthesis of the secalonic acids **2**, which contain a symmetrical biaryl core, we became interested in the possibility of a direct coupling reaction according to Scheme 4.

In our first attempts we applied the original protocol published by Miyaura and associates using K_2CO_3 as the base on several haloarenes and were pleased to obtain the corresponding biaryls in good to excellent yields (Table 1).

As shown in Table 1, the reaction tolerates a variety of functional groups such as cyano, acetoxy, or ester groups. However, limitations are clearly visible. The reaction is slow for substrates containing electron-donating or bulky substituents such as methoxy or *tert*-butyl groups and chloroarenes are not suitable substrates. One of the major disadvantages of the reaction is the fast degradation of the catalyst leading to a black palladium precipitate. As the reaction proceeds slowly for electron-rich or sterically-hindered substrates such as entry 3 or 13, we decided to add diphenylphosphinoferrocene (dppf) to slow the catalyst decomposition. According to Table 1, the additional ligand leads to good results even for difficult substrates such as entry 3 or 13. Recrystallization of bis-3,3′([1,3]-dioxolano)-4,4′-dimethoxybiphenyl (**14**) yielded colorless crystals which were suitable for single-crystal X-ray diffraction. The structure is included in the Supporting Information. To expand the range of substrates, we also used aryltriflates for this homocoupling reaction. As depicted in Table 2, aryltriflates are also excellent substrates for the synthesis of symmetrical biaryls. Interestingly, the reaction also worked with DMSO as the solvent whereas the reported transformation of aryltriflates into arylboronates is only successful when using dioxane.[12] In our case, DMSO as well as dioxane led to good results.

Relating to the total synthesis of the secalonic acids (**2**), we were also interested in applying the present protocol to functionalized xanthones which represent the core of the secalonic acids. Due to the acidic protons next to the xanthone carbonyl function, we chose racemic xanthenol methyl ether **22** as the substrate for homo-

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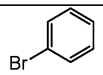
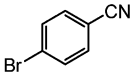
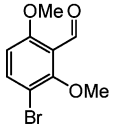
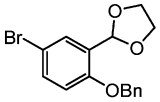
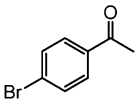
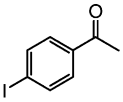
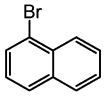
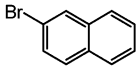
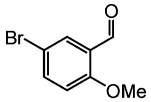
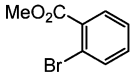
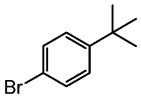
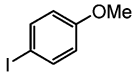
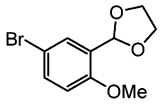
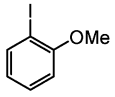
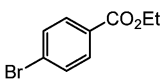
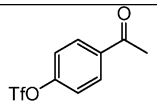
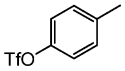
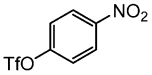
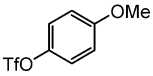
TABLE 1. Synthesis of Symmetrical Biaryls from Haloarenes (Scheme 4)[a]

Product Number	Haloarene	yield (%)[b]
1		98
2		94
3		62[c]
4		65[c]
5		68
6		90
7		82
8		76
9		88
10		42
11		72
12		49
13		77[c]
14		60
15		40
16		54
17		81

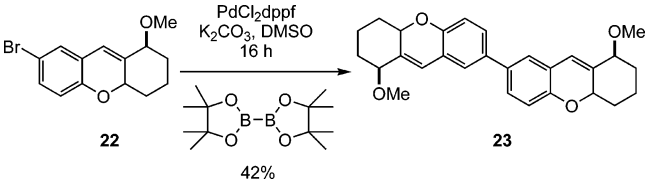
[a] All reactions were performed at 80 °C in DMSO, using haloarene (1 equiv), **4** (0.5 equiv), $PdCl_2$dppf (4 mol %), and K_2CO_3 (3 equiv). [b] Isolated yields. [c] 4 mol % of dppf was added.

TABLE 2. Synthesis of Symmetrical Biaryls from Aryltriflates[a]

Product number	arenetriflate	yield (%)[b]
18		82[d,e]
19		84
20		75[d,e]
21		55

[a] All reactions were performed at 80 °C in DMSO or dioxane, using haloarene (1 equiv), **4** (0.5 equiv), $PdCl_2$dppf (4 mol %), and K_2CO_3 (3 equiv). [b] Isolated yields. [c] Solvent DMSO. [d] Solvent dioxane. [e] 4 mol % of dppf was added.

SCHEME 5. Synthesis of Bisxanthene 23



coupling. The bromide **22** is readily available from 5-bromosalicylic aldehyde and 2-cyclohexenone in a 3-step synthesis.[18,19] As shown in Scheme 5, when subjected to the cross-coupling conditions, the xanthone gave the bisxanthene **23** in reasonable yield. However, we could only isolate one apparent diastereomer of **23** and there were no traces of other diastereomers detectable by NMR or GC.

In summary, we have developed an easy and widely applicable procedure for the synthesis of symmetrical biaryls. Bromo- and iodoarenes as well as arenetriflates are suitable substrates for the reaction and due to its mild conditions, a large variety of functional groups can be tolerated. As shown before, the reaction is also applicable to complex and sterically hindered substrates such as tetrahydroxanthones. Further studies on the scope of this reaction, as well as its application in the total synthesis of the secalonic acids, are currently in progress.

Experimental Section

All reactions were carried out according to the following procedure: A dry flask with an argon atmosphere was charged with haloarene or arenetriflate (1.0 equiv), **4** (0.5 equiv), $PdCl_2$dppf (4.0 mol %), and K_2CO_3 (3.0 equiv). In some cases, 4.0 mol % of dppf was added. After addition of 6 mL of DMSO or dioxane, the reaction was stirred at 80 °C for 14 h. The reaction mixture was cooled to room temperature and ex-

(18) 7-Bromo-2,3,4,4a-tetrahydroxanthene-1-one (**24**), which was synthesized following a literature procedure,[17] was reduced to 7-bromo-2,3,4,4a-tetrahydroxanthene-1-ol (**25**) yielding only one diastereomer. The last step included the protection of the alcohol function as methyl ether. Further details are included in the Supporting Information.

(19) Lesch, B.; Bräse, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 115−118; *Angew. Chem.* **2004**, *116*, 118−120.

tracted with CH_2Cl_2, and the combined organic layers were washed with water and aqueous sodium hydroxide solution (20%). Drying over anhydrous sodium sulfate followed by column chromatography yielded the corresponding biaryls.

8,8′-Dimethoxy-5,7,8,10a,5′,7′,8′,10′a-octahydro-6*H*,6′*H*-[2,2′]bixanthenyl (23). Yellow solid (71 mg, 165 μmol, 42% yield). Analytical TLC (silica gel 60, cyclohexane/EtOAc 5/1 v/v) R_f 0.28; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28−1.46 (m, 4H), 1.75−1.92 (m, 4H), 2.11−2.21 (m, 4H), 3.50 (s, 6H), 3.58 (dd, J = 11.0, 4.7 Hz, 2H), 4.90 (dd, J = 11.3, 5.0 Hz, 2H), 6.33 (s, 2H), 6.70 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 2.2 Hz, 2H), 7.19 (dd, J = 8.5, 2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 33.5, 35.2, 57.9, 77.0, 79.9, 113.8, 115.3, 121.0, 124.9, 126.9, 134.0, 138.2, 151.9; IR (cm^{-1}, KBr) 2938 (m, ν Ar−H); EI-MS *m*/*z* (rel intensity) 430 (18%) [M$^+$]; HR-MS (EI) for $C_{28}H_{30}O_4$ (M$^+$) calcd 430.2144, found 430.2147.

2-(4,4′-Dimethoxy-3′-methylbiphenyl-3-yl)-[1,3]dioxolane (14). Colorless solid (106 mg, 296 μmol, 60% yield). Analytical TLC (silica gel 60, cyclohexane/EtOAc 2/1 +2% NEt_3 v/v) R_f 0.08; mp 112−114 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 6H), 4.04−4.18 (m, 8H), 6.20 (s, 2H), 6.95 (d, J = 8.5 Hz, 2H), 7.51 (dd, J = 8.5, 2.5 Hz, 2H), 7.73 (d, J = 2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.2, 65.7, 99.8, 111.4, 125.6, 126.3, 128.9, 133.7, 157.2; IR (cm^{-1}, KBr): 3046 (w, ν Ar−H); EI-MS *m*/*z* (rel intensity) 358 (3%) [M$^+$], 43 (100%) [$C_2H_3O^+$]; HR-MS (EI) for $C_{20}H_{22}O_6$ (M$^+$) calcd 358.1416, found 358.1419. Anal. Calcd for $C_{20}H_{22}O_6$: C 67.03, H 6.19. Found: C 66.94, H 6.20.

4-(4,4′-Bisbenzyloxy-3′-methylbiphenyl-3-yl)[1,3]-dioxolane (4). Colorless solid (166 mg, 325 μmol, 65% yield). Analytical TLC (silica gel 60, cyclohexane/EtOAc 5/1 +2% NEt_3 v/v) R_f 0.12; mp 178−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03−4.17 (m, 8H), 5.18 (s, 4H), 6.28 (s, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.32−7.48 (m, 12H), 7.73 (d, J = 2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.7, 70.8, 99.9, 113.1, 125.9, 126.9, 127.5, 128.2, 128.9, 129.1, 133.9, 137.4, 156.4; IR (cm^{-1}, KBr) 3029 (w, ν Ar−H); EI-MS *m*/*z* (rel intensity) 510 (55%) [M$^+$], 419 (28%) [(M − Bn)$^+$], 91 (100%) [Bn$^+$]; HR-MS (EI) for $C_{32}H_{30}O_6$ (M$^+$) calcd 510.2042, found 510.2043. Anal. Calcd for $C_{32}H_{30}O_6$: C 75.28, H 5.92. Found: C 75.11, H 5.95.

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Supporting Information Available: Spectroscopic and analytical data for all products not described in the text as well as X-ray structure data for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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