Ultrasound-Assisted Synthesis of Symmetrical Biaryls by Palladium-Catalyzed Homocoupling of Aryl *n*-Butyl Tellurides

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Received 11 June 2008

Abstract: An ultrasound-assisted synthesis of symmetrical biaryls with electron-withdrawing or -donating substituents is described and illustrated by palladium-catalyzed homocoupling reaction of aryl tellurides. This procedure offers easy access to biaryls in short reaction time, and the products are achieved in good to excellent yields.

Key words: homocoupling reaction, symmetrical biaryls, aryl *n*-butyl tellurides

The demand for biaryl scaffolds for both synthetic and medicinal purposes has increased dramatically during the past few decades. These scaffolds are common structural features found in many biologically important natural products such as michellamine A (**I**) and secalonic acid (**II**, Figure 1).[1] Besides their great diversity in complex natural products and pharmaceutical agents,[2] these compounds are fascinating and challenging research objects in the material and polymer sciences.[3,4] Axially chiral biaryls are useful as versatile auxiliaries for asymmetric synthesis,[5] as chiral phases for chromatography,[6] and important substrates for chiral liquid crystalline materials.[7]

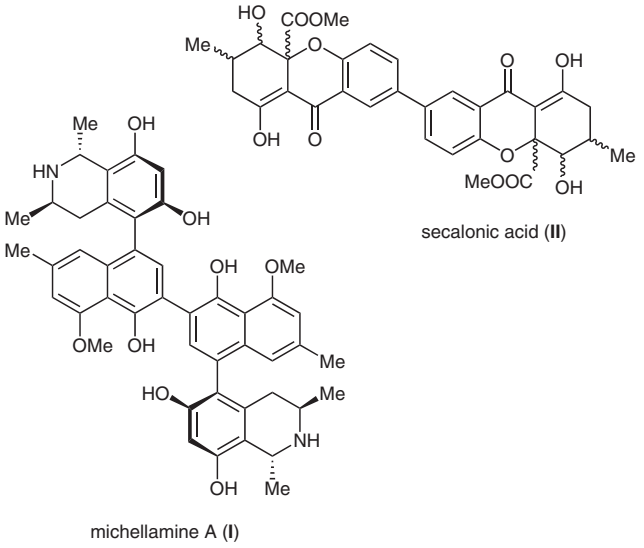

Figure 1 Structures of michellamine A (**I**) and secalonic acid (**II**)

SYNLETT 2008, No. 20, pp 3221–3225
Advanced online publication: 24.11.2008
DOI: 10.1055/s-0028-1087244; Art ID: S05908ST

Recently, Buchwald's chiral biaryl phosphine ligands with triisopropyl moieties (XPhos and *tert*-butyl XPhos) have emerged as versatile chiral ligands for palladium-catalyzed asymmetric syntheses.[8] Several biaryl compounds have recently been reported as potent glucagon receptor antagonists for the treatment of diabetes.[9] The biaryl Bay-27-9955, functionalized with two isopropyl units, has been reported to inhibit glucagon from the human glucagon receptor with an IC_{50} value of 110 nM.[10] In addition, some of the biaryl scaffolds have been identified as new class of antileishmanial agents.[11]

The construction of biaryl axis can be achieved either by intermolecular- or by intramolecular cross-coupling of two similar or dissimilar aromatic rings in the presence of organometallic complexes. Palladium-catalyzed cross-coupling reactions between the electrophilic compounds ArX (X being mainly Cl, Br, I, and OTf) and organometallic species ArM (M being Mg, Zn, Sn, and B) are on the verge of becoming truly general process for the construction of biaryl systems. Recently, the synthesis of unsymmetrical biaryls by the palladium-catalyzed cross-coupling of potassium aryltrifluoroborate salts and aryl tellurides was reported.[12]

Symmetrical biaryls were traditionally obtained by the Ullmann reaction[13] and some other methods.[14] In current decade the synthesis of symmetrical biaryl systems has been emphasized around the metal-assisted homocoupling of aryl halides,[15] boronic acids,[16]aryl Grignard reagents,[17] and arene diazonium salts.[18] Wong and Zhang reported the synthesis of these systems by the palladium-catalyzed homocoupling of aryl boronic acids but required phosphine or phosphate as ligands and harsh reaction conditions.[19] In the past decade some symmetrical biaryls have been reported by palladium-catalyzed coupling reactions of diaryltellurium(IV) dichlorides,[20a] aryltellurium(IV) trichlorides,[20b] and telluronium salts.[20c]

Recently, organotellurium compounds have attained remarkable development as synthons and intermediates in synthetic organic chemistry. In the current decade, the organotellurium compounds have been used instead of halogens as electrophilic partners in some palladium-catalyzed cross-coupling reactions.[21,22]

Herein, we report a new protocol for the synthesis of biaryl systems by palladium-catalyzed homocoupling of functionalized aryl *n*-butyl tellurides using ultrasonic waves as a source of energy.[23] The strength of the procedure lies in

the formation of the C–C bond and introduction of electron-donor or -acceptor functionalities into their molecular structure.

The approach to prepare biaryl compounds **2a–h** was based on palladium-catalyzed homocoupling reaction of functionalized aryl *n*-butyl tellurides **1a–h**. The parent precursors aryl *n*-butyl tellurides **2a–h** were conveniently prepared in high yields by Grignard reaction of aryl halides followed by addition of tellurium and butylation by *n*-bromobutane.[12]

Initially, we paid our attention on the determination of the optimal conditions for the homocoupling of aryl tellurides **1**. Toward this end, *n*-butyl phenyl telluride **1a** was chosen as model substrate and a variety of conditions was screened (Table 1). The reactions were monitored by TLC or GC.

First of all, we determinated the palladium catalyst. The Pd(II) and (0) species were used in the homocoupling reactions and the best result was reached with $Pd(PPh_3)_4$ (Table 1, entry 4). It was used Ag_2O as additive, triethylamine as base, and methanol as solvent, and the reaction was irradiated for 45 minutes in an ultrasound bath. The product was obtained in 64% isolated yield.

Table 1 Study of Catalyst Effect on Homocoupling of *n*-Butyl Phenyl Telluride **1a**

Entry	Catalyst[a]	Yield (%)[b]
1	–	n.r.[c]
2	$PdCl_2$	15
3	$Pd(OAc)_2$	28
4	$Pd(PPh_3)_4$	64
5	$Pd(acac)_2$	n.r.

[a] Catalyst (8 mol%) was used.
[b] Isolated yields.
[c] n.r. = no reaction.

The next step was the determination of the best base and the necessity of an additive in the reaction. Initially, an organic base, such as triethylamine, in the presence of Ag_2O was used, and the desired compound was isolated in 64% yield. When the same reaction was performed with an inorganic base, such as sodium carbonate, the desired compound was achieved in 85% yield. Furthermore, to check the effect of base, we performed the same reaction without base, but no reaction was observed.

To investigate the effect of additive, the same reaction was performed with two different additives CuI and AgOAc, but no reaction was observed with CuI while the desired product **2a** was isolated in 53% yield with AgOAc. Furthermore, to establish the stoichiometry of the reaction, we performed this reaction with two equivalents of Ag_2O, but the reaction leads to the formation of side products. No reaction was observed in the absence of an additive.

The role of Ag_2O can be attributed to the removal of phosphine ligands of the catalyst or from one of the catalytic intermediates formed in the course of the reaction.[12] The catalyst loadings were analyzed, and the best result was afforded with 8 mol% of $Pd(PPh_3)_4$, in 85% yield.

Finally, to observe the effect of ultrasonic waves in this reaction, we put the same reaction under reflux conditions, and the reaction was completed in 10 hours while the desired compound **2a** was isolated in 52% yield.

During the optimization studies for biphenyl **2a**, it was observed that the reaction mixture of *n*-butyl phenyl telluride **1a** (1.0 equiv), Ag_2O (1.0 equiv), sodium carbonate (2.0 equiv), and of $Pd(PPh_3)_4$ (8 mol%) in methanol, irradiated under ultrasonic waves for 45 minutes, were the best condition for the synthesis of biphenyl **2a**. After achieving the best condition for the synthesis of the desired compound **2a**, we synthesized a series of functionalized biaryl compounds **2a–h** using the optimized conditions in 59–85% yields (see Table 2). Unfortunately, this reaction was not working with more hindered aryl *n*-butyl telluride **1i**. All the synthesized compounds were characterized by spectroscopic analysis.[24]

To generalize this approach, *n*-butyl naphthyl tellurides **3a–c** were prepared from functionalized bromo naphthalene using Grignard reaction, followed by the addition of tellurium and *n*-butylation, and attempted the same reaction under similar reaction conditions, which yielded binaphthyl **4a–c** in good yields (see Table 3).

In summary, the ultrasound-assisted synthesis of functionally symmetrical biaryls by homocoupling reaction of easily accessible aryl tellurides was demonstrated. This methodology has the flexibility of introducing electron-donor or -acceptor functionalities in the biaryl architectures. Further applications of our methodology for the synthesis of biaryls are currently in progress.

Acknowledgment

The authors are grateful to FAPESP (07/51466-9, 07/59404-2) and CNPq (154976/2006-7) for the financial support.

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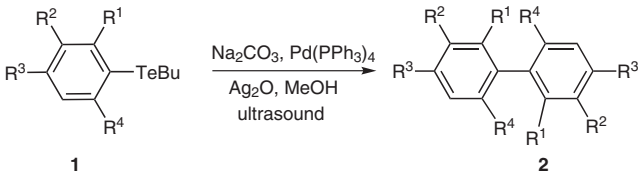
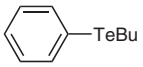
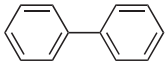
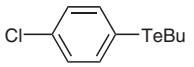
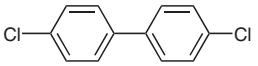
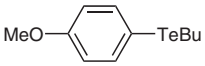
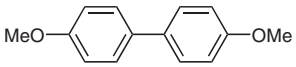
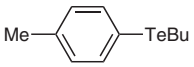
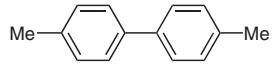
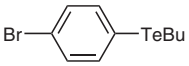
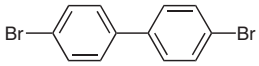
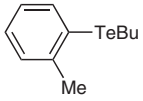
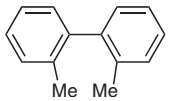
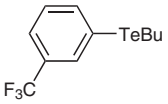
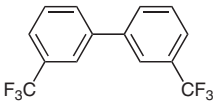
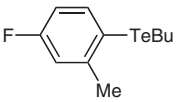
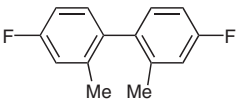
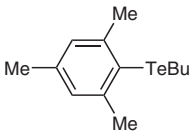
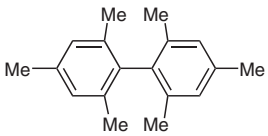
Table 2 Homocoupling Reaction of Functionalized *n*-Butyl Phenyl Tellurides **1a–h**



1 **2**

Entry	Aryl telluride **1**	Product **2**	Reaction time (min)	Yield (%)
1	 **1a**	 **2a**	45	85
2	 **1b**	 **2b**	60	71
3	 **1c**	 **2c**	45	78
4	 **1d**	 **2d**	45	78
5	 **1e**	 **2e**	60	78
6	 **1f**	 **2f**	90	59
7	 **1g**	 **2g**	60	82
8	 **1h**	 **2h**	120	62
9	 **1i**	 **2i**	16 h	n.r.[a]

[a] n.r. = no reaction.

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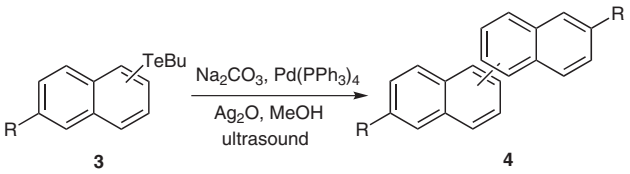
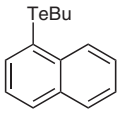
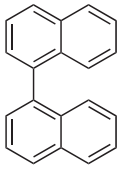
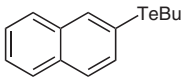
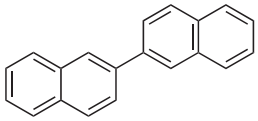
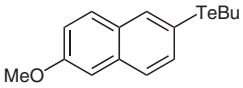
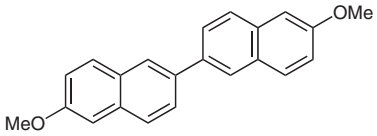
Table 3 Homocoupling Reaction of *n*-Butyl Naphthyl Tellurides **3a–c**



3 **4**

Entry	Naphthyl telluride **3**	Product **4**	Reaction time (min)	Yield (%)
1	 **3a**	 **4a**	90	21
2	 **3b**	 **4b**	60	82
3	 **3c**	 **4c**	60	79

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(24) **General Experimental Procedure for Biaryls 2a–h and 4a–c**

A suspension of aryl telluride (**1a**, 0.135 g, 0.5 mmol), $Pd(PPh_3)_4$ (0.45 g, 8 mmol), Na_2CO_3 (0.106 g, 1 mmol) and Ag_2O (0.116 g, 0.5 mmol) in MeOH (3 mL) was irradiated in a water bath of an ultrasonic cleaner for 45 min. Then, the reaction was diluted with EtOAc (30 mL). The organic layer was washed with sat. solution of NH_4Cl (2 × 10 mL) and H_2O (2 × 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash silica column chromatography using hexane as eluent and characterized as biphenyl **2a**.

Compound **2a**: white solid; mp 70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.28 (m, 6 H, ArH), 7.45 (d, *J* = 7.2 Hz, 4 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 122.6, 126.95, 130.11, 141.61. GC-MS (%): 154 (100), 153 (57), 152 (39), 76 (44).

Compound **2b**: white solid; mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.0 Hz, 4 H, ArH), 7.45 (d, *J* = 8.0 Hz, 4 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ =

128.00, 129.12, 133.52, 138.20. GC-MS (%): 222 (100), 152 (63), 93 (21), 75 (47).

Compound **2c**: white solid; mp 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 6 H, 2 OMe), 6.95 (d, *J* = 8.4 Hz, 4 H, ArH), 7.47 (d, *J* = 8.4 Hz, 4 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 54.89, 113.70, 127.28, 133.04, 158.24. GC-MS (%): 214 (100), 199 (87), 171 (21), 128 (16).

Compound **2d**: white solid; mp 122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 6 H, 2 Me), 6.96 (d, *J* = 7.6 Hz, 4 H, ArH), 7.64 (d, *J* = 7.6 Hz, 4 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.93, 127.28, 129.94, 137.88, 138.76. GC-MS (%): 182 (68), 167 (100), 165 (45), 152 (19), 89 (21).

Compound **2e**: white solid; mp 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.2 Hz, 4 H, ArH), 7.48 (d, *J* = 8.2 Hz, 4 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 128.23, 129.05, 133.76, 138.45. GC-MS (%): 312 (66), 152 (89), 76 (100).

Compound **2f**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 6 H, 2 Me), 7.02 (t, *J* = 8.4 Hz, 2 H, ArH), 7.18 (t, *J* = 8.4 Hz, 4 H, ArH), 7.50 (d, *J* = 8.0 Hz, 2 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.70, 124.74, 127.02, 127.10, 130.62, 132.13, 137.65. GC-MS (%): 182 (77), 167 (100), 166 (22), 165 (48).

Compound **2g**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 7.8 Hz, 2 H, ArH), 7.58 (d, *J* = 7.8 Hz, 2 H, ArH), 7.70 (d, *J* = 7.8 Hz, 2 H, ArH), 7.80 (s, 2 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 121.39, 122.71, 123.80, 130.34, 131.80, 134.95. GC-MS (%): 290 (100), 271 (24), 201 (28), 152 (19), 89 (21).

Compound **2h**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 6 H, 2 Me), 6.86–7.05 (m, 6 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.99, 114.48, 117.77, 118.89, 133.34, 139.93, 160.12, 163.37. GC-MS (%): 218 (92), 203 (100), 201 (52), 183 (60).

Compound **3a**: white solid; mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.8 Hz, 2 H, ArH), 7.36–7.52 (m, 4 H, ArH), 7.66–7.76 (m, 6 H, ArH), 8.18 (d, *J* = 8.4 Hz, 2 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 122.94, 126.26, 126.78, 127.19, 127.42, 128.02, 128.40, 129.99, 132.09, 134.56. GC-MS (%): 254 (90), 253 (100), 252 (80), 250 (25), 126 (98), 125 (47).

Compound **3b**: white solid; mp 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.58 (m, 6 H, ArH), 7.66–7.83 (m, 6 H, ArH), 8.00 (s, 2 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 119.37, 125.84, 126.45, 126.57, 127.42, 128.80, 129.15, 129.49, 131.39, 134.06. GC-MS (%): 254 (100), 252 (34), 126 (25). Compound **3c**: white solid; mp >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 6 H, 2 OMe), 7.03 (s, 2 H, ArH), 7.10 (d, *J* = 9.0 Hz, 2 H, ArH), 7.44 (d, *J* = 9.0 Hz, 2 H, ArH), 7.50–7.60 (m, 4 H, ArH), 7.85 (s, 2 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.11, 105.56, 116.83, 119.57, 128.18, 128.29, 129.40, 129.45, 129.81, 132.85, 157.69. GC-MS (%): 314 (100), 299 (29), 271 (29), 228 (25), 157 (25).