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Suzuki arylation at positions 2 and 2′ of 1,1′-binaphthyls: stereochemical result depending on the sense of polarity of substrates ☆

Peter Kasák, Henrich Brath, Margaréta Dubovská, Michal Juríček and Martin Putala*

Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, 842 15 Bratislava, Slovak Republic

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Abstract—The first preparation of enantiomerically pure 1,1′-binaphthyl-2,2′-diboronic acid (by resolution) is reported. Optimization of the cross-coupling conditions was found to be crucial to achieve good yields in Suzuki arylation in approaches from both 2,2′-diiodide or 2,2′-diboronic acid (52–56%, with model *p*-tolyl reagents). Stereochemical results in these reactions were dramatically different: almost complete racemization starting from the 2,2′-diiodide versus complete conservation of stereogenic information from the 2,2′-diboronic acid. This novel synthetic approach, a stereoconservative Suzuki arylation of the diboronic acid, should be a valuable method for the synthesis of a new group of 2,2′-diarylated (including functionalized) binaphthyl derivatives.

During the last decades, the synthesis and applications of chiral 1,1′-binaphthyl derivatives[1,2] have become a subject of intensive studies by many research groups, especially because of their unique stereochemical properties (axial chirality). The synthesis and application of 1,1′-binaphthyl derivatives bearing carbon groups in the positions 2 and 2′ are limited almost exclusively to those bearing monocarbon groups because of the lack of suitable synthetic approaches. Attempts to synthesize nonracemic 2,2′-diaryl derivatives **1** by substitution reactions at positions 2 and 2′, reported in the literature,[3,4] were not successful except for the synthesis of binaphthyl bridged metallocenes.[5,6]

The Suzuki cross-coupling reaction[7] represents a valuable method for the formation of C–C bonds, especially when at least one of the carbons involved is sp^2-hybridized. The main advantages of organoboronic acids as the organometallic component in Suzuki reactions, are low toxicity, inertness towards air and water and tolerance to many functional groups. This makes the Suzuki reaction a valuable candidate for the development of cross-coupling synthetic methodology leading to enantiopure 2,2′-diaryl-1,1′-binaphthyl derivatives, including functionalized ones. The Suzuki reaction is known not to be particularly sensitive to steric factors, also important because binaphthyl substrates for reactions in the positions 2 and 2′ must be considered as highly strained, possessing a large group in the neighboring position (2-substituted 1-naphthyl in position 1).

Schilling and Kaufmann[3] studied the Suzuki arylation of the racemic dibromide **2a** with various arylboronic acids and of the racemic diboronic acid **3** with aryl halides in the presence of Na_2CO_3 as a base. Formation of only traces (<3%) of the diarylated products **1** was observed at best, and monoarylated hydro-dehalogenated or hydro-deboronated derivatives **4** were obtained as the main products (23–67%). In our recently published study on the synthesis of the binaphthyl bridged ferrocene **1a**,[6] Suzuki coupling of the more reactive binaphthyl dielectrophile, diiodide **2b**,[8] in the presence of K_3PO_4 afforded the desired product **1a** in yields of up to 12%[6] (Scheme 1).

We succeeded in obtaining the desired diarylated product **1b** in 52% yield (together with 10% of **4b**) by

Keywords: Arylboronic acid; Binaphthyl; Cross-coupling; Palladium; Stereoconservative; Suzuki reaction.

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* Corresponding author. Tel.: +421-2-60296-323; fax: +421-2-60296-690; e-mail: putala@fns.uniba.sk

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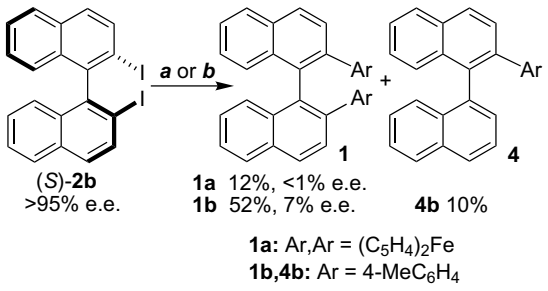
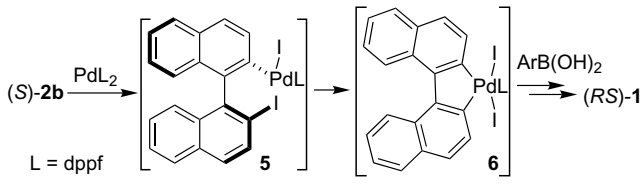


Scheme 1. Suzuki arylation of diiodide **2b**. Reagents and conditions: (a)[6] $Fe[C_5H_4B(OCH_2)_2]_2$ (2.0 equiv), $Pd(dba)_2$ (0.1 equiv), K_3PO_4 (10 equiv), THF, reflux, 24 h; (b) $4\text{-}MeC_6H_4B(OH)_2$ (2.4 equiv), $Pd(PPh_3)_4$ (0.1 equiv), $Ba(OH)_2{\cdot}8H_2O$ (6.0 equiv), THF–H_2O, reflux, 24 h.

changing the base to $Ba(OH)_2$ in the reaction of the diiodide **2b** with the model substrate—*p*-tolylboronic acid (Scheme 1). However, starting from enantiopure diiodide **2b**, the product **1b** obtained was almost racemic (as was also found in the case of **1a**[6]). In contrast to this stereochemical result (racemization), Suzuki reactions on 1,1′-binaphthyls in positions other than 2 and 2′ (e.g., 3,3′ or 6,6′) are known[9] to proceed without lost of enantiopurity. Only reactions at positions 2 and 2′ take place, where mutual nonbonding interaction between groups (being replaced in the course of the reaction) is decisive for configurational stability of these derivatives.[1] The origin of racemization of the binaphthyl moiety during the reaction in the positions 2 and 2′ has to lie in the specific mechanism,[6] which might involve bonding interactions between these positions. We presume that the insertion of palladium into one of the carbon–iodine bonds of the diiodide **2b** results in a normal Pd(II)-complex **5**. Transmetallation of the complex **5** should be slow, so the insertion of palladium into the neighboring carbon–iodine bond in the position 2′ could then take place, affording palladacyclic Pd(IV)-complex **6**. The latter would be configurationally unstable: other 1,1′-binaphthyl derivatives bridged across the 2 and 2′ positions with one atom have racemization barriers[1] in the range from 45 to 65 kJ/mol. The complex **6** should be more reactive in the transmetallation step with boronic acids and after reductive elimination affords only racemic products **1** (Scheme 2).[6]

Our mechanistic proposal is supported by the ^{31}P NMR spectra of intermediate Pd complexes[6] (two signals from C_1-symmetric complex **5** and a single signal from C_2-symmetric complex **6**). In addition, evidence for the migration of Pd in the Pd(II)-complex from the position 2 to the position 2′ on 1,1′-biphenyl derivatives was reported recently.[10] Pt(IV)-complexes containing a biphenyl moiety similar to that in the complex **6**, were characterized.[11] Also, structurally related *Pd*,*Pd*-dibromopallada(IV)cyclopentadiene species stabilized with an *N*,*N*-ligand were observed as intermediates.[12]



Scheme 2. Proposed mechanism for Suzuki arylation of **2b**.

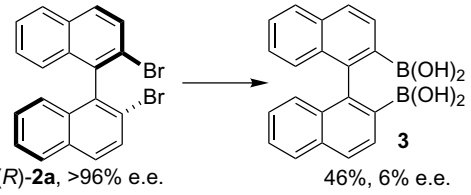
The negative stereochemical results (racemization) but acceptable yields in the Suzuki arylation given above led us to explore an approach with reversed polarity of the substrates for cross-coupling—from the diboronic acid **3** and aryl halides, however, the preparation of the required enantiomerically pure diboronic acid **3** has not been described. Firstly, we tried to exploit the method published by Kaufmann and co-workers[13] for the synthesis of racemic **3**—lithiation of the dibromide **2a** and quenching the corresponding dilithio derivative with a large excess of methyl borate. An analogous route gave access to other nonracemic 2,2′-dimetallo-1,1′-binaphthyls.[14] However, using enantiopure dibromide **2a**[8] at low temperature, the isolated diboronic acid **3** was almost racemic (Scheme 3).

We succeeded in resolving racemic diboronic acid **3** by chromatographic separation of the diastereoisomers of its ester **7** with chiral diol **8** accessible from L-tartaric acid[15] (Scheme 4). The diastereoisomeric purity of the boronate **7**[16] was easily determined from its ^1H NMR spectra and after flash chromatography twice on silica gel, it was found to be >98% de (Fig. 1). Acidic hydrolysis afforded enantiopure diboronic acid **3**.[17]

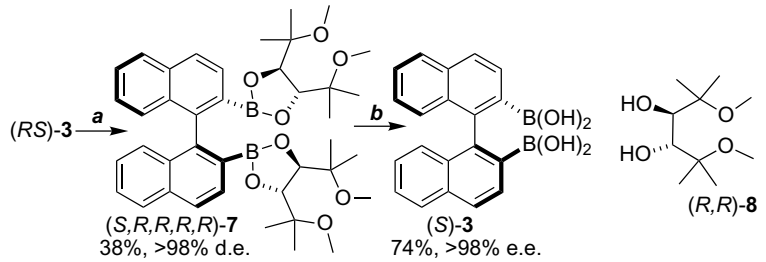
Having a method for the resolution of the diboronic acid **3** in hand, we optimized the conditions for Suzuki coupling of diboronic acid **3** with the model aryl halide—*p*-tolyl iodide. By variation of catalyst (Table 1, entries 1–3 and 15), base (entries 4–9 and 15) and solvent (entries 10–15) we succeeded in obtaining the desired diarylated product **1b** in reasonable yield (56%). Starting from enantiopure diboronic acid (*S*)-**3**, the isolated product **1b** was proved to be enantiopure (HPLC).

The absolute configurations of the compounds **1b**, **3** and **7** were assigned on the basis of the sign of optical rotation of the product **1b** prepared from **3**, compared to that of the product **1b** obtained from the diiodide **2b** of known configuration (Scheme 1).

In conclusion, we have developed an effective synthetic approach for the synthesis of a new group of nonrace-



Scheme 3. Synthesis of the diboronic acid **3**. Reagents and conditions: (i) *n*-BuLi (2.1 equiv), THF, −78 °C, 1 h; (ii) $B(OMe)_3$ (6.0 equiv), THF, −78 °C → rt, 12 h; (iii) 10% HCl aq, rt.



Scheme 4. Resolution of the diboronic acid **3**. Reagents and conditions: (a) (i) **8** (2.2 equiv), PhMe, reflux, 48 h; (ii) flash chromatography on silica gel, hexanes/ether 6/1; (b) BBr_3 (4.0 equiv), CH_2Cl_2, −20 °C → rt, 12 h.

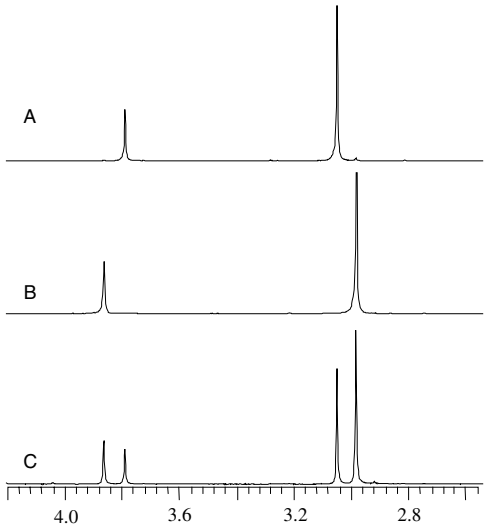


Figure 1. Expansions from the ^1H NMR spectra of (*aR*,*R*,*R*,*R*)-**7** (A), (*aS*,*R*,*R*,*R*)-**7** (B) and their mixture (C).

mic 1,1′-binaphthyl derivatives–2,2′-diarylated derivatives **1**, showing that proper choice of conditions and the sense of the polarity of the substrates are crucial to obtain these derivatives in good yields and optical purity. The scope and limitations of this method and its exploitation for the preparation of functionalized diarylated derivatives **1** with potential applications in stereoselective synthesis and material science are the subject of intensive study in our laboratory. Other applications of the novel enantiomerically pure diboronic acid **3** are also under investigation.

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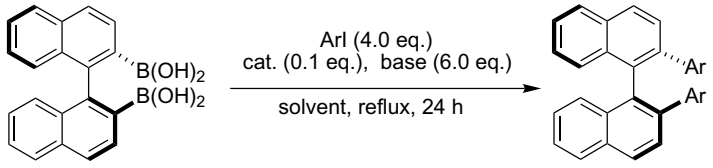
Table 1. Optimization of the coupling conditions from **3**[18]



Entry	Catalyst	Base	Solvent	Isolated yield of **1b** (%)
1	$Pd(OAc)_2$ or $Pd(dba)_2$	$Ba(OH)_2$	THF–H_2O (5:1)	Traces
2	$Pd(dppe)_2$ or $Pd(dppp)_2$	$Ba(OH)_2$	THF–H_2O (5:1)	10
3	$Pd(dppf)_2$	$Ba(OH)_2$	THF–H_2O (5:1)	25
4	$Pd(PPh_3)_4$	CsF	THF	Traces
5	$Pd(PPh_3)_4$	KF	THF	7
6	$Pd(PPh_3)_4$	Cs_2CO_3	THF	28
7	$Pd(PPh_3)_4$	Na_2CO_3	THF	0
8	$Pd(PPh_3)_4$	K_3PO_4	PhMe	Traces
9	$Pd(PPh_3)_4$	Bu_4NOH	MeOH–THF (1:5)	39
10	$Pd(PPh_3)_4$	$Ba(OH)_2$	MeOH	44
11	$Pd(PPh_3)_4$	$Ba(OH)_2$	Dioxane	25
12	$Pd(PPh_3)_4$	$Ba(OH)_2$	PhMe	54
13	$Pd(PPh_3)_4$	$Ba(OH)_2$	THF	52
14	$Pd(PPh_3)_4$	$Ba(OH)_2$	THF–MeOH (5:1)	52
15	**$Pd(PPh_3)_4$**	**$Ba(OH)_2$**	**THF–H_2O** (5:1)	**56**

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16. (*aS*,*R*,*R*,*R*)-**7**: Colorless oil. $[\alpha]_D^{27}$ +25.7° (*c* 0.27, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.87 (d, $^3J = 8.2$ Hz, 2H, Ar-*H*), 7.85 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.41 (ddd, $J = 2.2$, 6.6, 8.3 Hz, 2H, Ar-*H*), 7.15 (m, 4H, Ar-H), 3.78 (s, 4H, C-*H*), 3.04 (s, 12H, OCH_3), 0.80 (s, 12H, CH_3), 0.72 (s, 12H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.69, 134.50, 133.74, 130.60, 127.68, 127.38, 126.33, 126.23, 125.33, 82.40, 75.59, 49.53, 20.88, 18.77. UV (MeOH): 228, 286, 296, 321. IR ($CHCl_3$, cm^{-1}): 3055, 1715, 1608, 1550, 1520, 1480, 1432, 1422, 1402, 1380, 1352, 1245, 1210, 1113, 1105, 1012, 950, 846, 712, 680, 648. $R_F = 0.38$ (hexanes/diethyl ether, 4/1). Anal. Calcd for $C_{40}H_{52}B_2O_8$: C, 70.40; H, 7.68. Found: C, 70.69; H, 7.74.
(*aR*,*R*,*R*,*R*)-**7**: Colorless oil. $[\alpha]_D^{27}$ −41.1° (*c* 0.44, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz,): δ 8.05 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.90 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.86 (d, $^3J = 8.2$ Hz, 2H, Ar-*H*), 7.40 (ddd, $J = 2.2$, 5.6, 8.3 Hz, 2H, Ar-*H*), 7.13 (m, 4H, Ar-*H*), 3.86 (s, 4H, C*H*), 2.98 (s, 12H, OCH_3), 0.76 (s, 12H, CH_3), 0.56 (s, 12H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.14, 134.85, 133.58, 131.12, 127.55, 127.42, 126.37, 126.22, 125.47, 82.20, 75.51, 49.47, 20.95, 18.37. $R_F = 0.36$ (hexanes/diethyl ether, 4/1). CD (MeOH, nm): 332 (−m), 313 (+m), 302 (+s), 278 (−s), 272 (+m), 266 (−w), 262 (+m), 254 (−m), 249 (+w). Anal. Calcd for $C_{40}H_{52}B_2O_8$: C, 70.40; H, 7.68. Found: C, 70.25; H, 7.62. GC–MS (70 eV, EI): *m*/*z* (%) [M^+] not observable, 341 (26), 340 (92), 267 (73), 265 (100), 252 (60).
17. (*R*)-**3**: $[\alpha]_D^{25}$ +86.3° (*c* 0.27, $CHCl_3$). (*S*)-**3**: $[\alpha]_D^{25}$ −87.3° (*c* 0.31, $CHCl_3$).
18. General procedure for Suzuki coupling from (*S*)-**3**: A mixture of 0.5 mmol (170.5 mg) (*S*)-**3**, 1.2 mmol (262 mg) *p*-tolyl iodide, 3 mmol of base and 0.05 mmol of palladium catalyst in 5 mL of the solvent was heated under an inert atmosphere to reflux with stirring for 24 h. After cooling, the reaction mixture was poured into 5% aq HCl and extracted with CH_2Cl_2. After drying and evaporation of solvent, the residue obtained was purified by chromatography on silica gel (eluent hexanes/CH_2Cl_2, 9/1) affording (*S*)-**1b**. Enantiomeric purity was determined by HPLC analysis using a Chiralcel Daicel OD-H column. (*S*)-**1b**: White solid. Mp 179–183 °C. $[\alpha]_D^{22}$ −169.8° (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 7.91 (d, 2H, $^3J = 8.1$ Hz, C_{AR}-*H*), 7.97 (d, 2H, $^3J = 8.4$ Hz, C_{AR}-*H*), 7.23–7.48 (m, 8H, C_{AR}-*H*), 6.69 (d, 4H, $^3J = 7.8$ Hz, C_{AR}-*H*), 6.36 (d, 4H, $^3J = 8.1$ Hz, C_{AR}-*H*), 2.18 (s, 6H, Ar-CH_3). ^{13}C NMR ($CDCl_3$, δ): 140.0, 139.0, 136.0, 135.0, 134.6, 132.6, 129.4, 129.0, 128.4, 128.2, 128.1, 127.9, 126.8, 125.7, 31.3. UV (hexanes, nm): 226, 256, 294. IR (cm^{-1}): 3045, 1620, 1600, 1520, 1510, 1220, 1120, 1030, 870, 820, 720. Anal. Calcd for $C_{34}H_{26}$ (434.58): C, 93.94; H, 6.06. Found: C, 94.04; H, 5.57. GC–MS (70 eV, EI): *m*/*z* (%) [M^+] 434 (100), 326 (26), 343 (24), 163 (18).