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Enantiopure β-Hydroxysulfoxide Derivatives as Novel Chiral Auxiliaries in Asymmetric Biaryl Suzuki Reactions

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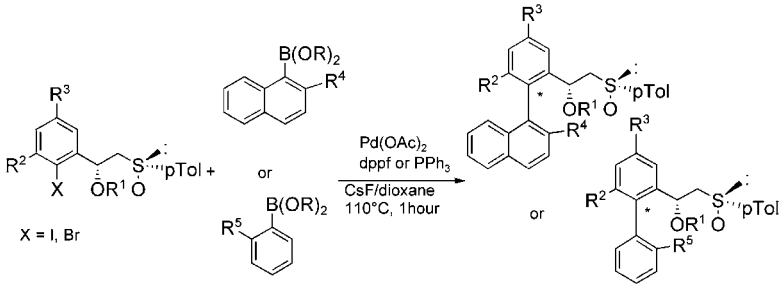
ABSTRACT



Highly diastereoselective biaryl Suzuki coupling reactions of (1*R*)-1-(2-iodo or bromophenyl)-2-(*R*)-(4-tolylsulfinyl)-1-ethanol derivatives with various aryl- or naphthylboronic acids (or esters) were performed with high yields (up to 99%) and an excellent control of the axial chirality (up to 98% de).

Axially chiral biaryls are of importance not only as chiral ligands[1] in asymmetric reactions but also as biologically active natural products, e.g., steganone,[2] vancomycin,[3] and michellamine....[4] A few successful methods using either chiral ligands, stoichiometric chiral auxiliaries, or chiral starting materials allow asymmetric synthesis of this biaryl subunit.[5] However, efficient examples of asymmetric Suzuki reactions are relatively rare and have been reported only in the past few years. The use of chiral ligands was first explored by Nicolaou[6] in the total synthesis of vancomycin. Cammidge[7] and Buchwald[8] very recently reported atropoenantioselective Suzuki couplings induced by chiral ligands for the synthesis of binaphthyl or phenylnaphthyl compounds. We recently communicated asymmetric Suzuki coupling with chiral phosphine ligands in the synthesis of 2,2′-dimethoxy-1,1′-dinaphthalene. The results show that the ratio of BINAP and Tol-BINAP to $Pd(OAc)_2$ or $(\eta^3$-allylPdCl$)_2$ influences the sense of the enantioselectivity.[9] Another example of

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(3) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172.

(4) Bringmann, G.; Pokorny, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 46, p 127.

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(6) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584.

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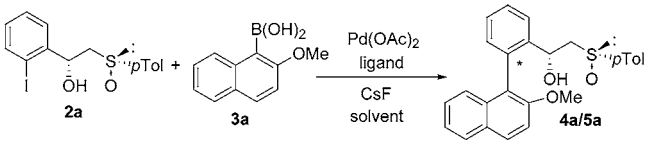
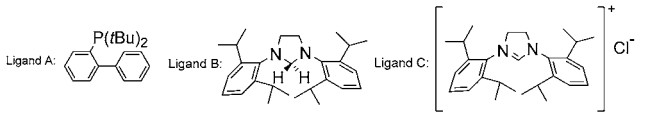
enantioselective Suzuki coupling was described by Baudoin in the synthesis of an axially chiral antimitotic biaryl.[10] Diastereoselective Suzuki couplings were only reported by Uemura[5j] using chiral arene(chromium)halide complexes.

It is surprising that the chiral auxiliary approach, presumably less substrate dependent, has been rarely investigated. Although sulfoxides have proved to be efficient chiral auxiliaries in asymmetric synthesis[11] especially in C−C bond formation such as Diels−Alder cycloadditions or nucleophilic additions, only a few examples are known in asymmetric transition-metal-catalyzed reactions.[12] In connection with our interest in the synthesis of biaryls with axial chirality, we report here the first examples of asymmetric biaryl Suzuki coupling reactions using enantiopure β-hydroxy- and β-methoxysulfoxides as chiral auxiliaries with a powerful control of the axial chirality.

We have reported efficient conditions for sterically hindered Suzuki cross-couplings,[9] e.g., DME and cesium fluoride in the presence of $Pd(OAc)_2$ and triphenylphosphine. Therefore, we studied the Suzuki coupling reaction between 2-methoxy-1-naphthyl boronic acid **3a** and the readily available enantiopure (1*R*)-1-(2-iodophenyl)-2-(*R*)-(4-tolylsulfinyl)-1-ethanol **2a** as a model reaction (Table 1.).

Table 1. Suzuki Reactions of **2a** with 2-Methoxy-1-naphthylboronic Acid **3a**[a]





entry	ligand	solvent	biaryl yield[b] (%)	dr[c] **4a**/**5a**	starting material yield (%)	reduction product yield (%)
1	dppf	dioxane	70	97/3	9	20
2	dppf	THF	50	98/2	33	17
3	rac BINAP	dioxane	0		85	<15
4	A	dioxane	0		>85	
5	B	dioxane	50	15/85	50	0
6	C	dioxane	20	15/85	80	

[a] Reaction conditions: **2a** (1 equiv), 2-methoxy-1-naphthyl boronic acid **3a** (2 equiv), $Pd(OAc)_2$ (10 mol %), bidentate ligand (15 mol %), monodentate ligand (30 mol %), CsF (4 equiv), 70 °C, 3−5 h. [b] Isolated product after chromatography. [c] Determined by ^{1}H NMR on the crude mixtures.

Condensation of the lithiated anion of (+)-(*R*)-methyl-*p*-tolyl sulfoxide to the 2-iodo-1-methylbenzoate afforded the β-ketosulfoxide **1a** in 80% yield. Diastereoselective reduction with DIBAL in the presence of $ZnCl_2$ is known to provide the desired [2(*R*),S(*R*)]-β-hydroxy sulfoxide **2a** in which the OH group is syn to the bulky substituant of the sulfoxide (Scheme 1.).[13]

Scheme 1. Synthesis of the β-Hydroxysulfoxide **2a**

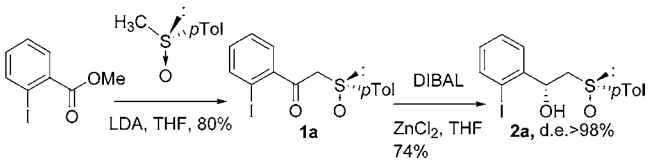


Table 1 summarizes the results obtained in the palladium-catalyzed Suzuki coupling of 2-methoxy-1-naphthylboronic acid **3a** and the enantiopure (1*R*)-1-(2-iodophenyl)-2(*R*)-(4-tolylsulfinyl)-1-ethanol **2a**.

Dppf with $Pd(OAc)_2$ in dioxane or THF was found to give remarkable stereocontrol (de 94−96%)[14] with a yield of 70% in dioxane at reflux (Table 1, entries 1 and 2). However, we observed the hydrodehalogenation of the aryl iodide (20% in the case of the coupling reaction performed in dioxane). Use of the racemic BINAP or 2-(di-*tert*-butylphosphino)-biphenyl (ligand A) did not provide any coupling product. Surprisingly, 1,3-bis-(2,6-diisopropylphenyl)imidazolidine (ligand B) and its imidazolium salt (ligand C) gave the coupling product with opposite axial chirality (de 70%), a surprising result probably due to the Pd complexes (Table 1, entries 5 and 6). In this case, mono crystals of the major diastereomer **5a** were obtained from ethyl acetate at 20 °C. Analysis by X-ray crystallography[15] revealed that the configuration of the chiral axis was *aS* (Figure 1).

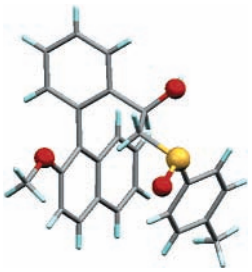


Figure 1. Crystal structure of **5a**.

We performed the asymmetric Suzuki reaction on other coupling partners using $Pd(OAc)_2$ with dppf in dioxane (Table 2.). The various β-hydroxysulfoxides **2** were obtained using the same methodology as for the synthesis of the

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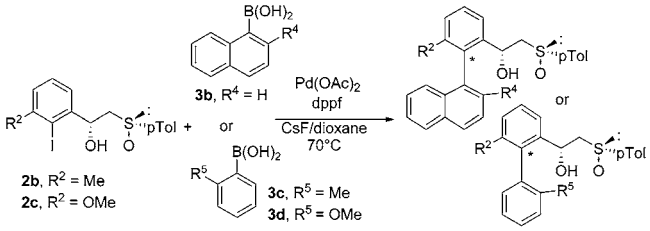
Table 2. Suzuki Coupling Reactions between β-Hydroxysulfoxides **2** and Boronic Acids **3**[a]



entry	2	3	biaryl yield (%)[b]	dr[c]	starting material yield (%)	reduction product yield (%)
1	**2b**	**3b**	0			99
2	**2b**	**3c**	0			>90
3	**2b**	**3d**	60	70/30		30
4	**2c**	**3b**	27	90/10		62
5	**2c**	**3c**	0			88
6	**2c**	**3d**	61	93/7		23

[a] Reaction conditions: **2** (1 equiv), **3** (2 equiv), $Pd(OAc)_2$ (10 mol %), dppf (15 mol %), CsF (4 equiv), 70 °C, 3−5 h. [b] Isolated product after chromatography. [c] Determined by ^1H NMR on the crude mixtures.

β-hydroxysulfoxide **2a** with good yields and diastereoselectivities (Scheme 1).

The *o*-methoxyphenyl iodide **2c** in coupling reaction with *o*-methoxyphenylboronic acid **3d** gave good yield and diastereoselectivity (Table 2, entry 6). However, with the other coupling partners major hydrodehalogenation of the aryl halide occurred.

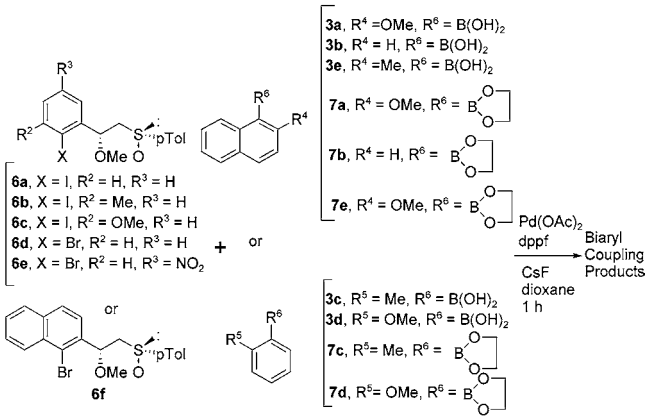
Either the free hydroxy group or the acidic protons of the boronic acid might be responsible for the reduction of the aryl halide. Therefore, we decided to protect the hydroxy group of the β-hydroxysulfoxides **2** (as a methoxy) in the presence of NaH and methyliodide in DMF at −20 °C. Excellent yields were obtained for the formation of the corresponding β-methoxysulfoxides **6a**−**f**.

Furthermore, we synthesized in good yields the boronic esters **7a**−**e** by condensation of ethylene glycol with the boronic acids **3a**−**e** in the presence of CaH_2 in refluxing THF.

Table 3 summarizes the results obtained in the palladium-catalyzed Suzuki coupling of various boronic acids **3** or esters **7** with various β-methoxysulfoxides **6**.

The first attempt between the iodide **6a** and 2-methoxy-1-naphthylboronic acid **3a** using $Pd(OAc)_2$ and dppf gave

Table 3. Suzuki Coupling Reactions between β-Methoxysulfoxides **6** and Boronic Acids **3** or Boronic Esters **7**[a]



entry	6	3 or 7	ligand	biaryl yield[d] (%)	dr[e]
1	**6a**	**3a**	Dppf[b]	99	>99/1
2	**6a**	**3a**	PPh_3[c]	93	>99/1
3	**6a**	**3e**	Dppf[b]	99	>99/1
4	**6d**	**3a**	Dppf[b]	98	>99/1
5	**6b**	**7b**	PPh_3[c]	88	90/10
6	**6b**	**7c**	PPh_3[c]	78	75/25
7	**6b**	**7d**	PPh_3[c]	89	80/20
8	**6c**	**7b**	PPh_3[c]	86	95/5
9	**6c**	**7c**	PPh_3[c]	86	90/10
10[f]	**6c**	**3d**	Dppf[b]	80	85/15
11	**6f**	**7b**	Dppf[b]	87	85/15
12	**6f**	**7c**	PPh_3[c]	70	75/25
13	**6f**	**7d**	PPh_3[c]	75	80/20
14	**6e**	**3a**	PPh_3[c]	93	>99/1
15	**6e**	**3e**	PPh_3[c]	84	>99/1

[a] Reaction conditions: **6** (1 equiv), **3** or **7** (2 equiv), CsF (4 equiv), reflux dioxane, 1 h. [b] $Pd(OAc)_2$ (10 mol %), dppf (15 mol %). [c] $Pd(OAc)_2$ (3 mol %), PPh_3 (9 mol %). [d] Isolated product after chromatography. [e] Determined by ^1H NMR on the crude mixtures. [f] 70 °C.

in only 1 h the coupling product with an excellent yield (>99%) and a complete control of the diastereoselectivity (>98% de) (Table 3, entry 1).

No trace of the other diastereomer was detected by ^{13}C and ^1H NMR.[16] Furthermore, using PPh_3 (9 mol %) as ligand with 3 mol % of $Pd(OAc)_2$ afforded the coupling product with the same diastereoselectivity and slightly lower yield (Table 3, entry 2). With the bromide **6d** instead of the iodide the results are identical (Table 3, entry 3). In the same way, a coupling reaction of **6a** with 2-methyl-1-naphthyl boronic acid **3e** occurred with excellent yield and diastereoselectivity (Table 3, entry 4). Starting from the bromide **6e** with a nitro group in the para position and 2-methoxy-1-naphthylboronic acid **3a** or 2-methyl-1-naphthylboronic acid **3e**, the coupling products were obtained very efficiently (Table 3, entries 14 and 15). β-Methoxysulfoxide bearing a naphthyl moiety **6f**

(12) Recent references: (a) Buezo, N. D.; De la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890 and references therein. (b) Henrich, M.; Delgado, A.; Molins, E.; Roig, A.; Llebaria, A. *Tetrahedron Lett.* **1999**, *40*, 4259. (c) Paley, R. S.; Estroff, L. A.; McCulley, D. J.; Martinez-Cruz, L. A.; Jimenez Sanchez, A.; Cano, F. H. *Organometallics* **1998**, *17*, 1841.

(13) Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649.

(14) The diastereomeric ratio was established by ^1H NMR studies: the chemical shifts of the methoxy and the methyl(*p*-tolyl) groups were significantly different.

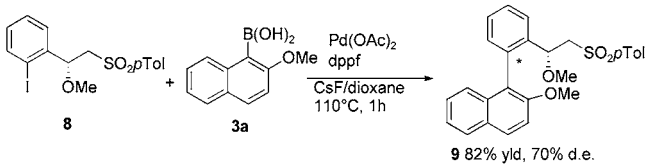
(15) We thank Dr. Nathalie Gruber for assistance with the analysis of the crystal structure (Service commun Rayons X, 4 rue Blaise Pascal, 67070 Strasbourg cedex, e-mail: sercomrx@chimie.u-strasbg.fr).

(16) We did the synthesis of the other diastereomer with opposite axial chirality by synthesis of the methyl ether of the coupling biaryl product obtained with ligand B, and we noticed by ^1H and ^{13}C NMR studies the different chemical shifts for the two axial diastereomers (cf. the Supporting Information).

in Suzuki coupling with various boronic esters **7b**−**d** gave good yields but control of the axial chirality was slightly lower (up to 70% de) (Table 3, entries 11−13). The coupling reaction between aryl iodides bearing a methoxy group in an ortho′ position **6c** or a methyl group in an ortho′ position **6b** and phenyl or naphthylboronic acid or ester afforded the coupling products in very good yields and selectivity up to 90% de (Table 3, entries 5−10).

To determine the relative contribution of both stereogenic centers to the asymmetric induction of the coupling reaction, we oxidized the sulfoxide to the corresponding sulfone with *m*-CPBA in CH_2Cl_2 and we performed the coupling reaction of sulfone **8** with 2-methoxy-1-naphthylboronic acid **3a**. The corresponding biaryl product **9** was obtained in 82% yield and 70% diastereomeric excess. Therefore, the presence of the sulfinyl group is essential for total control of the axial chirality (98% de). However, this result indicates that the diastereoselectivity of the coupling reaction is mainly controlled by the stereogenic carbon atom which is closer to the biaryl C−C bond formed (Scheme 2.).

Scheme 2. Suzuki Coupling between the Sulfone **8** and 2-Methoxy-1-naphthylboronic Acid **3a**

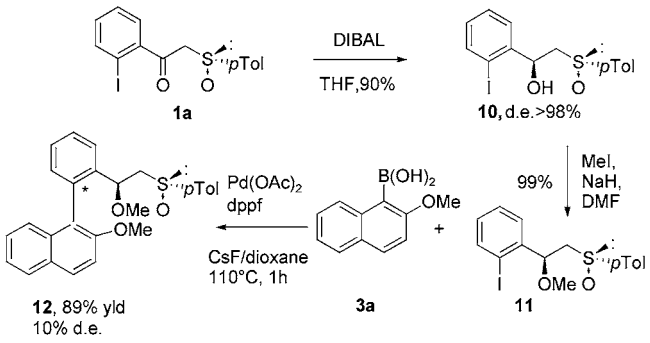


8 **3a** **9** 82% yld, 70% d.e.

We also synthesized the [2(*S*),S(*R*)]-*β*-hydroxy sulfoxide **10**, the epimer of **6a** at the stereogenic carbon atom by diastereoselective reduction of the *β*-ketosulfoxide **1a** with DIBAL. Hence, the hydroxy group is anti to the bulky substituent of the sulfoxide. After protection of the hydroxy-group as methoxy **11**, we performed the coupling reaction of **11** with 2-methoxy-1-naphthylboronic acid **3a**. The coupling product **12** was obtained in 89% yield but only 10% diastereomeric excess (Scheme 3.).

In conclusion, we have shown that the *β*-methoxysulfinyl group with the methoxy syn to the *p*-tolyl substituant is able

Scheme 3. Suzuki Coupling between **11** and 2-Methoxy-1-naphthylboronic Acid **3a**



1a **10**, d.e.>98% **12**, 89% yld 10% d.e. **3a** **11**

to act as an efficient stereochemical controller in Suzuki cross-coupling reactions between aryl and naphthyl moieties giving either binaphthyl or biphenyl or phenylnaphthyl compounds. The coupling products were obtained with excellent yields. Another interesting result is the dependence of the stereoselectivity with the ligand (dppf or imidazolidine).

Further studies on the coupling reaction with some specific substrates are ongoing in order to propose a model to understand this high diastereoselectivity.

Given our interest in total synthesis, these asymmetric cross-coupling reactions are promising because of the possible transformation of the chiral sulfoxide group in other functions (by desulfurization, Pummerer reaction, etc.).[17]

Acknowledgment. This work was supported by the CNRS and Ministère de la Recherche. P.-E.B. thanks la région Alsace for a fellowship.

Supporting Information Available: General experimental procedure for the biaryl Suzuki cross-coupling reaction. ^1H and ^{13}C NMR chemical shifts of the enantiopure biaryl compound formed by coupling reaction of **6a** and **3a** and its axial diastereomer obtained with ligand B. This material is available free of charge via the Internet at http://pubs.acs.org.

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