ORGANIC LETTERS

2009
Vol. 11, No. 22
5130−5133

Axial Chirality Control During Suzuki−Miyaura Cross-Coupling Reactions: The *tert*-Butylsulfinyl Group as an Efficient Chiral Auxiliary

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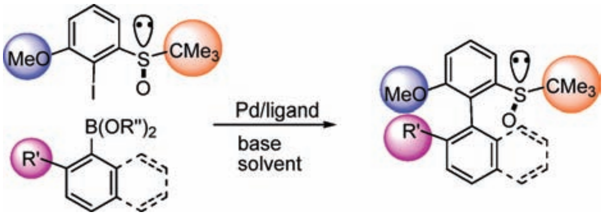
Received September 8, 2009

ABSTRACT



An efficient route to a new family of axially chiral biaryl ligands by a Suzuki−Miyaura cross-coupling reaction between ortho,ortho′-disubstituted aryl iodides bearing in ortho position a *tert*-butyl or *p*-tolylsulfinyl group and ortho-substituted phenyl boronic acids or esters is described. The comparison between the *t*-BuSO and *p*-TolSO groups as chiral controllers is reported. The modularity of the approach is demonstrated by the preparation of a variety of enantiopure axially chiral mixed S/N and S/P ligands.

Chiral atropo-isomeric biaryl compounds have attracted great interest in the past decade for two fundamental reasons. First, it has been shown that there is an intimate relationship between the absolute configuration of the axial axis and the activity of a number of pharmacologically relevant biaryl molecules.[1] Second, the large amount of data gathered on the structure activity relationship in the field of asymmetric catalysis reveal that axial chirality is one of the most important structural motifs within successful organic and organometallic catalysts.[2] Although several methods have been used for the preparation of axially chiral biaryl compounds, the most general and effective ones are those based on asymmetric aryl−aryl coupling reactions.

One of the well-known examples of such approaches is the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction.[3] Both enantioselective and diastereoselective procedures have been followed for the development of efficient asymmetric versions of this significant reaction. After the pioneering work of Uemura at the beginning of the nineties,[4] advances in this field have been very scarce, and it was not

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10.1021/ol9020755 CCC: $40.75

until the past few years that efficient enantioselective methods were reported.[5] However, the new methods on record, which include the use of palladium nanoparticles[5g] and solid supported catalysts,[5h] deal mainly with the coupling of rather simple substrates. Surprisingly, diastereoselective approaches with chiral auxiliaries, presumably less substrate dependent, have been rarely investigated, and up to now only three kinds of atropo-diastereoselective Suzuki−Miyaura coupling reactions were reported.[6] On the other hand, although sulfoxides have proved to be efficient chiral controllers in asymmetric synthesis especially in C−C bond formations,[7] only a few examples are known in asymmetric transition metal-catalyzed reactions,[8] and their use in a diastereoselective Suzuki−Miyaura cross-coupling is still unprecedented.

On the basis of these premises, we supposed that the use of aryl iodide having in the ortho position either the widely used *p*-tolyl sulfinyl group **1a** or the more hindered *tert*-butyl sulfinyl counterpart **1b** may be suitable for the development of a diastereoselective Suzuki−Miyaura cross-coupling reaction. Indeed, this was the case, as the condensation of iodide **1b** with various aryl boronic acids or esters **2a−g** afforded a new family of atropo-enantiopure biaryl ligands **3** bearing different ortho and ortho′ substituents on each aromatic unit (Figure 1). For the preparation of enantiopure iodides **1a**,**b**, we developed a practical two-step procedure starting from commercially available 3-bromoanisole. The synthesis depicted in Scheme 1 started with condensation of the Grignard reagent of the anisyl bromide either with enantiopure (S_S)-menthyl *p*-toluenesulfinate[9] **4** or with enantiopure (R_S)-diacetone-D-glucose *tert*-butylsulfinate[10] **5** to give the corresponding enantiopure sulfoxides in good to excellent yields. Ortholithiation with LDA (−78 °C, THF) followed by addition of iodine at −78 °C afforded the aryl iodides **1a**,**b**.

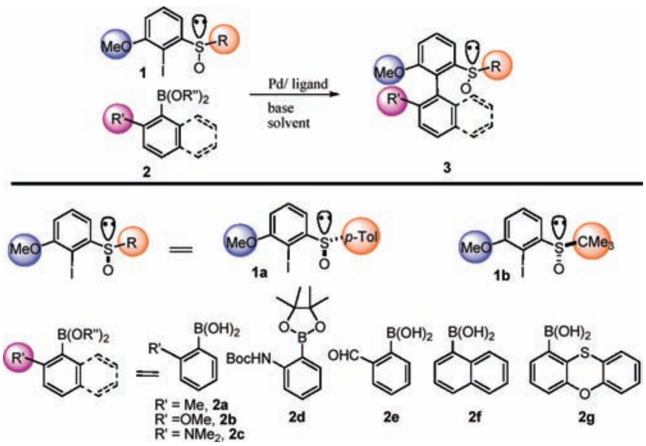
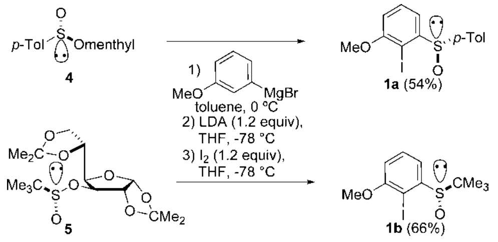


Figure 1. Atropo-diastereoselective Suzuki−Miyaura cross-coupling reaction.

Scheme 1. Synthesis of Enantiopure Aryl Iodides **1a**,**b**



Next, we studied the Suzuki−Miyaura cross-coupling reaction between the aryl iodide tethered sulfoxides **1a**, **1b** and the boronic acids **2a−g**, and the results are summarized in Table 1. In the case of aryl iodide **1a** with a *p*-tolylsulfinyl group (Table 1, entries 1−5), we found that the use of conditions established for hindered Suzuki−Miyaura coupling reactions afforded the biaryl compounds in good to excellent yields and modest to variable diastereoselectivities.[11] Disappointingly low atropo-diastereoinduction was obtained especially in the reaction between the iodide **1a** and the *o*-methoxyphenyl boronic acid **2b** (Table 1, entry 2).

To explain the low diastereoselectivity for compound **3ab** (45:55, Table 1, entry 2), we studied its racemization rate at different temperatures. At 100 °C, complete racemization was obtained after 45 min. Thus, the torsional barrier of this compound is too low, resulting in a rapid racemization under the coupling conditions. On the other hand, the highest atropo-diastereoselectivity was observed in the coupling reaction between the iodide **1a** and naphthyl boronic acid **2f** affording the corresponding biaryl compound in 50% yield and 80:20 diastereomeric ratio (Table 1, entry 5).

The use of the iodide **1b** bearing the more sterically hindered *tert*-butylsulfinyl group in the Suzuki−Miyaura cross coupling turned out to be a more challenging synthetic

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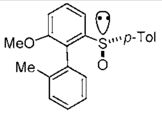
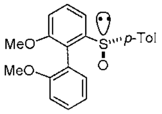
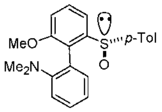
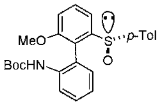
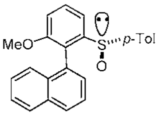
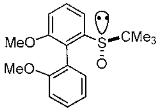
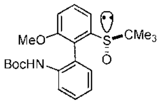
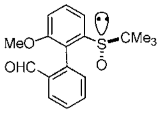
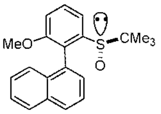
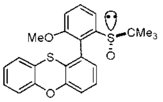
Table 1. Atropo-Diastereoselective Suzuki−Miyaura Cross-Coupling Reaction with a *p*-Tolyl and a *tert*-Butylsulfinyl Group As Chiral Auxiliary[a]

entry	product	method	yield (%)[d]	diastereomeric Ratio[b]
1	 **3aa**	A	90	66 : 44
2	 **3ab**	A	77	45 : 55
3	 **3ac**	A	92	75 : 25
4	 **3ad**	B	83	65 : 35
5	 **3af**	B	50	80 : 20
6[c]	 **3bb**	B	65	90 : 10
7	 **3bd**	B	86	95 : 5
8	 **3be**	B	60	75 : 25
9	 **3bf**	B	66	97 : 3
10	 **3bg**	B	50	85 : 15

[a] Reaction conditions: Method A: aryliodide (1 equiv), boronic acid (2 equiv), $Pd(OAc)_2$ (10 mol %), dppf (30 mol %), CsF (4 equiv), dioxane, reflux. Method B: $Pd(OAc)_2$ (10 mol %), S-Phos (15 mol %), Cs_2CO_3 (4 equiv), dioxane/H_2O, 70 °C. [b] Determined by ^1H NMR on the crude mixture. [c] DMF/H_2O was used as solvent. [d] Mixture of both diastereomers.

goal. After testing several Suzuki−Miyaura coupling reaction conditions, we have found that those described by Buchwald, slightly modified,[12] afforded the coupling products in good yields and in good to excellent diastereoselectivities (Table 1, 6−10). The Suzuki−Miyaura coupling reaction between the iodide **1b** and the boronic ester **2d** afforded product **3bd** in high yield (86%) and an excellent 95:5 diastereomeric ratio (Table 1, entry 7). It is worth mentioning that under the same conditions, the Suzuki−Miyaura coupling reaction between the *p*-tolylsulfinyl derivative **1a** and the same boronic ester **2d** gave the biaryl compound **3ad** in 83% yield and with low diastereoselectivity (65:35 ratio of both atropo-diastereomers) (Table 1, entry 4). Better diastereoselectivity was obtained in the case of the coupling of **1b** and the naphthyl boronic acid **2f**, where the biaryl compound **3bf** was obtained in an excellent 97:3 diastereomeric ratio. Interestingly, even the electron poor boronic acid **2e** and the boronic acid **2g** with a coordinating sulfur atom could be coupled under these conditions, affording the functionalized biaryl compounds with interesting 75:25 and 85:15 diastereomeric ratios, respectively (Table 1, entries 8 and 10). Taken all together, these results show the superiority of the *tert*-butylsulfinyl group compared to the widely used *p*-tolylsulfinyl group as chiral auxiliary in the diastereoselective Suzuki−Miyaura coupling reaction.

One of the main characteristics of the present method is its ability to afford functionalized and modular biaryl systems. Hence, in order to prepare enantiopure biarylamines, important intermediates in the synthesis of biologically relevant compounds, and in the synthesis of nitrogen based chiral ligands, we performed the deprotection of enantiopure Boc-protected biaryls. Treatment of the biarylamines **3ad** and **3bd** with TFA in CH_2Cl_2 gave, after flash chromatography, the free biaryl amines **4ad** and **4bd** as a single atropoisomer in 75% and 76% yield, respectively (Scheme 2). The versatility of enantiopure biarylamine **4bd** was further demonstrated by its transformation to a number of mixed ligands. Condensation of **4bd** with benzaldehyde in the presence of activated molecular sieve afforded the axially chiral imino sulfoxide **5**. The reduction of the sulfinyl group by treatment with trichlorosilane and triethylamine in toluene at reflux affords the corresponding electron-rich enantiopure thioether **6** in excellent yields. Recently, we and others have shown that mixed S/P ligands are excellent precursors for the synthesis of efficient catalysts with wide applicability.[13] Condensation of diphenylchlorophosphine with **6** afforded axially chiral mixed S/P ligand **7** in good yield, while the condensation of *o*-diphenylphosphine benzaldehyde with **6** in the presence of anhydrous copper sulfate gave the S/N/P ligand **8** in excellent yield (Scheme 3).

Scheme 2. Synthesis of Biarylamines **4ad** and **4bd**

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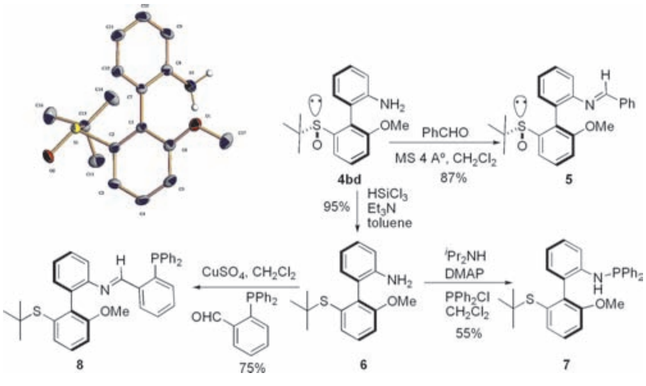
[12] Walker, S. D.; Barder, T. E.; Martinelli, J. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. These conditions were found to work well also for the coupling of iodide **1a.**

Scheme 3. ORTEP Diagram of Enantiopure Biarylamine **4bd** and the Synthesis of Some Useful Sulfur-Based Mixed Ligands Starting from **4bd**



Finally, to get better insight into the high diastereoselection observed with the *tert*-butylsulfinyl group, suitable crystals of the amine **4bd** were obtained as well as the structure ((R_S,aR)),[14] which was determined by X-ray analysis. Interestingly, there is a strong intramolecular hydrogen bond between the arylamine and the methyl ether, which may be important in the conformational stability of the molecule, and on its catalytic behavior. To explain the diastereoselectivity observed in the Suzuki−Miyaura coupling, we invoke as a first step an oxidative insertion of the palladium atom into the C1−I bond of the aryl iodide sulfoxide **1b** giving the five-member-ring palladacycle **1b′** (Figure 2).

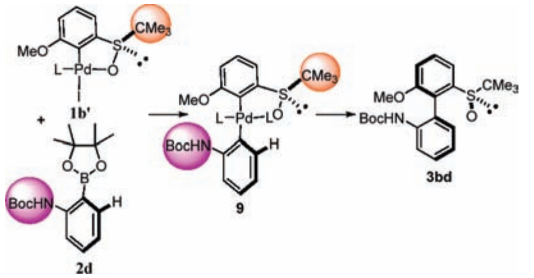


Figure 2. Model explaining the stereochemical outcome of the Suzuki−Miyaura coupling.

The proposed coordination of the ambidentate sulfoxide group to the palladium atom is through the oxygen atom, instead of the lone pair of sulfur in contrast to known S-bonding of the sulfoxide to soft metals. The main reasons of this change of coordination type are geometrical, steric, and mainly electronic due to the strong trans influence of the C-donor.[15] Under basic conditions, the approximation of the boronate **2d** to the complex **1b′** in the transmetalation step should take place with minimization of steric hindrance affording after reductive elimination compound **3bd**.

In conclusion, *tert*-butylsulfinyl groups in the ortho position of aryliodides allowed the highly atropo-diastereoselective synthesis of biaryls by a Suzuki−Miyaura cross-coupling reaction. This methodology showed the efficiency of the *tert*-butylsulfinyl group compared to the *p*-tolylsulfinyl group as a chiral controller. An access to various trisubstituted biaryl ligands in atropo-diastereomerically pure form is reported. We are currently investigating the use of these chiral biaryl ligands in asymmetric catalysis.

Acknowledgment. We thank the Dirección General de Investigación Científica y Técnica (grant No. CTQ2006-15515-CO2-01 and CTQ2007-61185), la Junta de Andalucía (grant P07-FQM-2774).

Supporting Information Available: Experimental procedures for the synthesis and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Crystallographic data (excluding structure factors) for structure **4bd** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-706230. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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