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Efficient Stereochemical Controllers in Biaryl Suzuki Coupling Reactions: Benzylic Carbinols Bearing in β-Position Thioether, Dimethylamino, or Sulfoxide Groups

Pierre-Emmanuel Broutin and Françoise Colobert*

Laboratoire de stéréochimie associé au CNRS, UMR 7509 Université Louis Pasteur, ECPM 25 rue Becquerel, 67087 Strasbourg Cedex 2, France

fcolober@chimie.u-strasbg.fr

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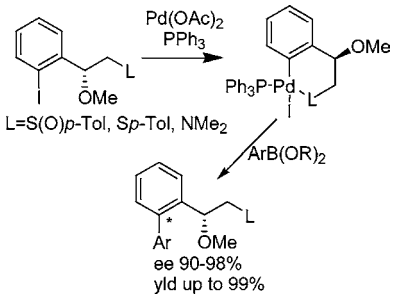
ABSTRACT



Highly atropo-diastereoselective Suzuki coupling between aryl halides bearing stereogenic benzylic carbinols with sulfoxide, thioether, or dimethylamino groups as efficient internal chelating ligands and 2-methoxy-1-naphthylboronic acid were performed with high yields; a palladacycle is proposed as a potential transition state.

Axially chiral biaryls are common structural motifs in natural products and chiral ligands, and they constitute attractive synthetic targets because of their interesting properties.[1] The key step in such syntheses is always the coupling reaction between the two aromatic units. A high number of synthetic approaches have been reported.[2] However, efficient examples of asymmetric Suzuki reactions are quite rare and have been reported only in the past few years. The use of chiral ligands was first explored by Nicolaou[3] in the total synthesis of vancomycin. Cammidge,[4] Buchwald,[5] Baudoin,[6] Johannsen,[7] and very recently Mikami[8] reported atropo-enantioselective

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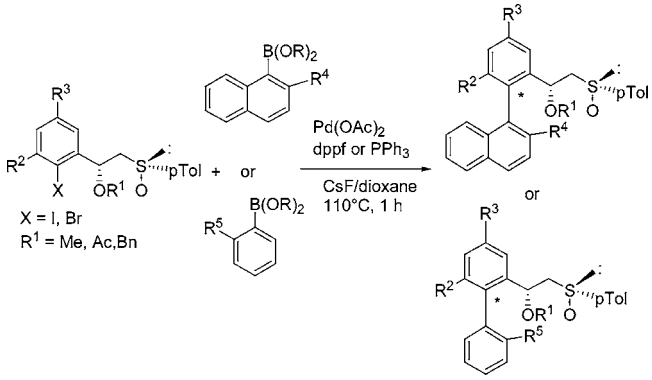
Suzuki couplings induced by chiral ligands for the synthesis of binaphthyl or phenylnaphthyl compounds. We recently communicated the asymmetric Suzuki coupling with chiral phosphine ligands: BINAP and Tol-BINAP with $Pd(OAc)_2$ or $(\eta^3\text{-allylPdCl})_2$ in the synthesis of 2,2′-dimethoxy-1,1′-dinaphthalene.[9] Only two atropo-diastereoselective Suzuki couplings were reported by Uemura[10] using chiral arene-(chromium) halide complexes and by Lipshutz using as a chiral auxiliary a stereocenter attached to a phosphine ligand.[11]

Recently, we reported the use of a stereogenic benzylic carbinol substituent as an efficient stereochemical controller in the biaryl Suzuki coupling reaction.[12] This stereogenic benzylic group was introduced by the reduction of a β-ketosulfoxide[13] ortho to the aryl halide unit (Scheme 1).

Scheme 1. Asymmetric Biaryl Suzuki Coupling Using Stereogenic Benzyloxy Groups



This new atropo-diastereoselective Suzuki coupling reaction allows the synthesis of biphenyl, binaphthyl, and phenylnaphthyl derivatives with excellent control of the axial chirality up to 98% de and excellent yield up to 99%.

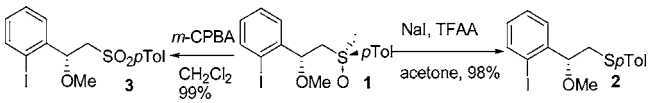
Simultaneously to our first communication,[12] diastereoselective Suzuki coupling between a chiral benzylic alcohol and sterically hindered arylboronic esters was reported in the approach to cyclooctadiene lignans.[14]

The presence of a chiral center such as a chiral benzylic alcohol in the ortho position of the aryl halide could be very useful in the total synthesis of biologically active compounds such as (−)-steganacin,[15] korupensamine A,[16] and the biaryl unit of vancomycin [17] which could arise from precursors bearing a benzylic stereocenter. We postulated that the diastereoselectivity of the coupling reaction is mainly controlled by the stereogenic carbon atom closer to the biaryl C−C-bond formed.

To generalize the use of benzylic carbinols as efficient precursors to asymmetric biaryl moieties, we proposed to understand the exact role of the stereogenic sulfur atom: the sulfoxide group. We report herein the biaryl Suzuki coupling between 2-methoxy-1-naphthylboronic acid and aryl iodide with a stereogenic benzylic hydroxy group in the ortho position, bearing in the β position, instead of a *p*-tolylsulfoxide group as in **1,** a *p*-tolyl thioether (compound **2**)**,** a *p*-tolyl sulfone (compound **3**), no substituent (compound **4**), a methoxy as in **6**, benzyloxy as in **7**, *p*-tolyloxy group in **8**, or a *N*,*N*-dimethylamino group in **9**.

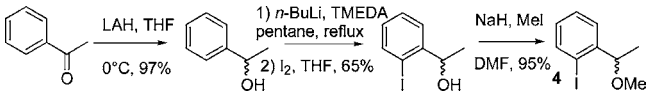
Syntheses of these aryl iodides were performed using known methods. Starting from the sulfoxide derivative **1**, reduction by treatment with trifluoroacetic anhydride and sodium hydride in acetone afforded the corresponding *p*-tolylthioether **2** in quantitative yield.[18] On the other hand, oxidation of **1** with *m*-CPBA in CH_2Cl_2 led to the corresponding sulfone **3** in 99% yield (Scheme 2).

Scheme 2. Reduction and Oxidation of the Sulfoxide Group



The synthetic sequence leading to the aryl iodide bearing in the ortho position the stereogenic methylcarbinol **4** without a subtituent in β position is outlined in Scheme 3.[19]

Scheme 3. Synthesis of Benzylic Carbinol without a Substituent in the β Position



Treatment of the sulfoxide **1** under typical Pummerer conditions[20] [(i) trifluoroacetic anhydride (TFAA), 2,6-lutidine; (ii) K_2CO_3; (iii) $NaBH_4$] gave in excellent yield the corresponding alcohol **5** which was converted to the methyl ether and benzyl ether by treatment with sodium hydride and

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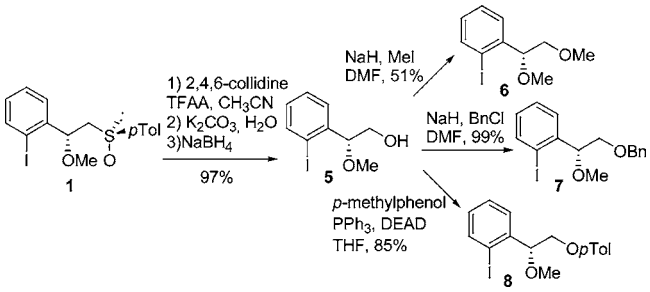
methyl iodide or benzyl chloride in DMF affording **6** and **7**, respectively[21] (Scheme 4).

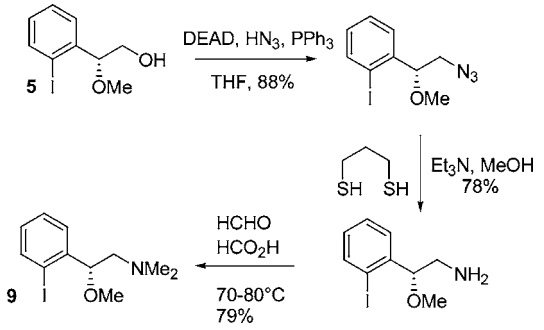
Scheme 4. Synthesis of Benzylic Carbinol with an Ether in the β Position



A Mitsunobu-type reaction[22] performed on **5** with *p*-methylphenol, PPh_3, and DEAD in THF led to the *p*-tolyl ether **8** in good yield (Scheme 4).

To obtain the aryl iodide with the *N*,*N*-dimethylamino group **9**, alcohol **5** was submitted to a Mitsunobu-type reaction with HN_3, PPh_3, and DEAD in THF[23] followed by reduction of the formed azo group with 1,3-propanedithiol and Et_3N in MeOH.[24] Methylation of the primary amine with formaldehyde and formic acid[25] gave **9** in 54% overall yield (Scheme 5).

Scheme 5. Synthesis of Benzylic Carbinol with a Dimethylamino Group in the β Position



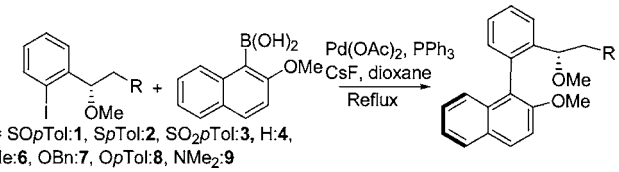
With the desired aryl iodides in hand, we began the study of their Suzuki coupling reactions with 2-methoxy-1-naphthylboronic acid (Table 1). The reactions were conducted using as catalyst $Pd(OAc)_2$ with PPh_3 and cesium fluoride as a base in dioxane at reflux.

With the *p*-tolyl thioether instead of the *p*-tolyl sulfoxide, the coupling reaction was still very efficient, proceeding with high yield and diastereoselectivity (Table 1, entry 2). Similarly, with the dimethylamino group excellent selectivity was obtained (Table 1, entry 8). These results indicate that the presence of coordinating atoms, with a high affinity to palladium, is essential for a total control of the selectivity. With a methoxy, benzyloxy, or *p*-tolyloxy group, diastereoselectivity is much lower (30−40%), probably due to the steric hindrance without coordination of the oxygen atom to the palladium (Table 1, entries 5−7). In the coupling reaction with the sulfone,[12] 70% diastereomeric excess was obtained (Table 1, entry 3).

Finally, weak selectivity was observed in the coupling with iodide **3** bearing the stereogenic methoxy with no substituent in the β position (Table 1, entry 4).

In conclusion, a plausible mechanism responsible for the high selectivity might reasonably invoke the formation of a palladacycle during oxidative addition in which palladium is coordinated to the internal chelating ligand such as a *p*-tolyl sulfoxide,[26] a *p*-tolyl thioether (coordination by the sulfur atom), or a dimethylamino group (coordination by the nitrogen atom) (Scheme 6).

Table 1. Suzuki Couplings between Aryl Iodides **1**−**4** and **6**−**9** and 2-Methoxy-1-naphthylboronic Acid[a]

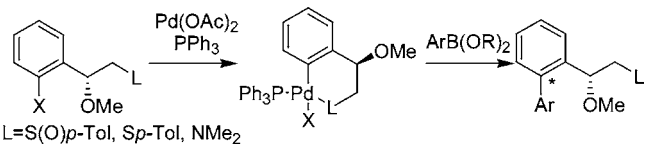


R = SO*p*Tol:**1**, S*p*Tol:**2**, SO_2*p*Tol:**3**, H:**4**, OMe:**6**, OBn:**7**, O*p*Tol:**8**, NMe_2:**9**

entry	aryl iodide	R	time (h)	yield (%)	dr[b]	axial chirality[c]
1	**1**	SO-*p*-Tol	1	99	>99/1	a*R*
2	**2**	S-*p*-Tol	1	99	>99/1	a*R*
3	**3**	SO_2-*p*-Tol	2	94	85/15	a*R*
4	**4**	H	20	77	60/40	a*R*
5	**6**	OMe	2	91	70/30	a*R*
6	**7**	OBn	1	91	70/30	a*R*
7	**8**	O-*p*-Tol	4	79	65/35	a*R*
8	**9**	NMe_2	2	73[d]	>95/5	a*R*

[a] Reaction conditions: **1**−**4**, **6**−**9** (1 equiv), 2-methoxy-1-naphthylboronic acid (2 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (30 mol %), CsF (4 equiv), dioxane, reflux. [b] Determined by ^1H NMR on the crude mixture. [c] Determined by X-ray crystallography and ^1H NMR NOESY experiments.[12] [d] Yield nonoptimized.

Scheme 6. Palladacycle Transition State with Sulfoxide



Considering the case of the sulfoxide, coordination of the sulfur atom to the palladium should give a rigid six-membered palladacycle **I**. At this point, the transmetalation

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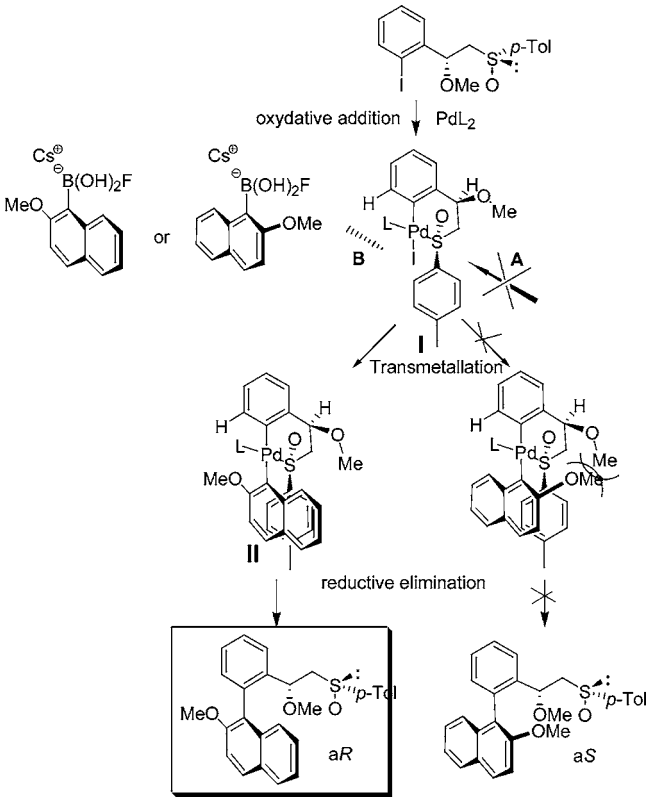
Scheme 7. Mechanistic Study



would take place on the opposite side of the stereogenic carbinol (pathway B). Isomerization of the *trans*-palladium complex **II** to the *cis*-complex would occur giving preferentially after reductive elimination one atropo-diastereomer a*R* with the naphthylic methoxy group in the back. Approach of the naphthyl moiety with the methoxy group in front would lead to a nonbinding interaction between the stereogenic methoxy and the naphthylmethoxy groups (Scheme 7).

To explain the diastereoselectivity obtained in the coupling reaction with the sulfone, we propose a coordination of one of the oxygen atoms to the palladium giving a seven-membered transition state which is less rigid than the six-membered transition state and would lead to a less selective approach (Figure 1).

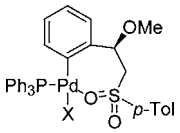


Figure 1. Palladacycle transition state with sulfone.

In summary, we have shown that the high atropo-diastereoselectivity obtained in the Suzuki cross-coupling reaction between aryl halides bearing stereogenic benzylic carbinols and boronic acids is essentially due to the presence of an internal chelating ligand β to the stereogenic carbinol giving a rigid palladacycle as an intermediate. Further applications of this method to the asymmetric synthesis of biologically active compounds containing biaryl units are now in progress.

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

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