

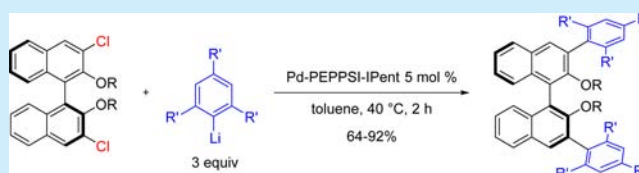
Pd-Catalyzed Cross-Coupling of Aryllithium Reagents with 2-Alkoxy-Substituted Aryl Chlorides: Mild and Efficient Synthesis of 3,3'-Diaryl BINOLs

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S Supporting Information

ABSTRACT: Palladium-catalyzed cross-coupling of aryllithium reagents with 2-alkoxy-substituted aryl chlorides is described. The reactions proceed under mild conditions with short reaction times and provide a wide range of 2-alkoxy-substituted biaryls. This new methodology is applied to the efficient preparation of 3,3'-diaryl BINOLs and represents the first synthesis of this important class of chiral compounds from the corresponding 3,3'-dichloro BINOLs.



The 2-alkoxy-substituted biaryl structure is found in a wide variety of pharmaceuticals¹ and natural products² and, in its deprotected form, provides the core unit of very efficient and highly selective chiral ligands³ and organocatalysts⁴ for asymmetric synthesis (Figure 1). As a consequence, its

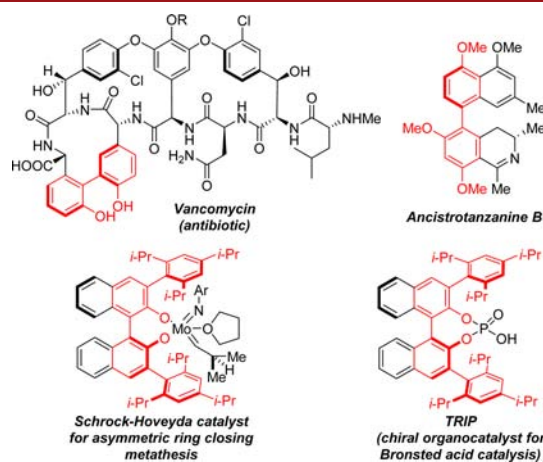


Figure 1. Examples of biologically active molecules, chiral ligand and organocatalyst containing the 2-alkoxy (or hydroxy) biaryl unit.

preparation has received considerable attention in organic chemistry. Among the available methods for the synthesis of these important structural motifs,⁵ the palladium-catalyzed cross-coupling of two aryl units is probably most frequently used.⁶ 2-Alkoxy-substituted biaryls can be accessed from a 2-alkoxy-aryllithium reagent as one of the coupling partners.

Alternatively, these compounds can be obtained by coupling of a 2-alkoxy-substituted aryl (pseudo)halide. However, these compounds are reluctant coupling partners due to their

combined electron-rich character and steric hindrance and their coupling usually requires harsh conditions.⁶

We have recently developed methodology to perform palladium-catalyzed direct cross-coupling of organolithium reagents with (hetero)aryl- and alkenyl bromides with high selectivity and broad scope.⁷ The reaction proceeds at rt in short reaction times. By coupling of different aryl bromides with 2-alkoxy-substituted aryllithium reagents, easily prepared via ortho-lithiation,⁸ a range of 2-alkoxy-substituted biaryls, including tri- and tetra-ortho-substituted ones,^{7b} can be obtained under our reported conditions. However, the use of 2-alkoxy-substituted bromoarenes revealed a limitation for the catalytic cross-coupling of aryllithium reagents as the homocoupled biaryl, resulting from Li–Br exchange, appeared as a major side product.^{7c} This limitation can represent a significant problem, especially if the synthesis of a hindered biaryl compound bearing an ortho-alkoxy moiety in both aryl groups is required. In this case, precomplexation of the organolithium with the Lewis basic ether moiety can facilitate the metal–halogen exchange while the stabilization by the alkoxy group in the ortho position makes the corresponding organolithium compound the most stable lithium species (Scheme 1).

Parallel to our work with bromides,⁷ we also developed catalytic cross-coupling of aryllithium reagents with less reactive

Scheme 1. Metal–Halogen Exchange and Stabilization of Aryllithium



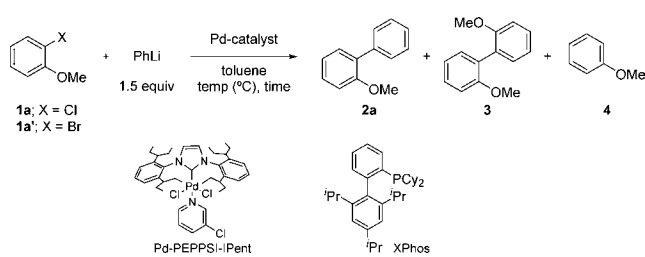
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aryl chlorides.^{9,10} As aromatic chlorides are less prone to undergo halogen–lithium exchange,¹¹ and taking advantage of the high reactivity of RLi reagents in cross-coupling, we envisioned that 2-alkoxy-substituted aryl chlorides might be suitable substrates for the synthesis of 2-alkoxy-substituted biaryls through palladium-catalyzed cross-coupling with aryllithium reagents. Building on our recent findings,⁹ we present herein a highly efficient and selective cross-coupling of aryllithium reagents with 2-alkoxy-substituted aryl chlorides. Furthermore, we report a mild and fast synthesis of 3,3'-diaryl-1,1'-bi-2-naphthols (BINOLs) as an example of the versatility of the present method.

As an initial experiment, we performed the reaction between 2-bromoanisole and phenyllithium under the optimized conditions for the palladium-catalyzed cross-coupling of aryl bromides with organolithium reagents (Pd₂(dba)₃/P^tBu₃).^{7a} Although the desired cross-coupled product **2a** was the major product, considerable amounts of the homocoupling product **3** and dehalogenated product **4** were obtained (Table 1, entry 1). In

Table 1. Screening of Reaction Conditions



entry ^a	X	[Pd]/ligand (mol %)	temp (°C)	time (h) ^b	conv (%) ^c	2a:3:4 ^c
1 ^d	Br	Pd ₂ (dba) ₃ (2.5) P ^t Bu ₃ (7.5)	rt	1	full	74:23:3
2	Cl	Pd-PEPPSI-IPent (5)	35	3.5	97	86:5:6
3	Cl	Pd ₂ (dba) ₃ (2.5) XPhos (10)	40	3.5	90	61:27:2
4	Cl	Pd-PEPPSI-IPent (5)	40	2	full	91:5:4
5 ^e	Cl	Pd-PEPPSI-IPent (5)	40	2	full (78%) ^f	92:4:4
6 ^e	Br	Pd-PEPPSI-IPent (5)	40	2	Full	63:28:9

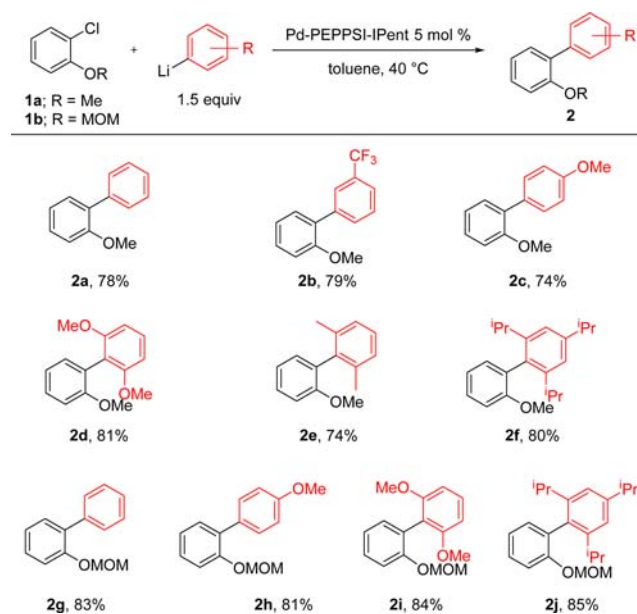
^aConditions: PhLi (1.8 M solution in dibutyl ether diluted with THF to a final concentration of 0.6 M) added slowly to a solution of **1** (0.3 mmol) in toluene (1 mL unless otherwise noted). ^bAddition time. Reaction was stopped once addition of PhLi was finished. ^cDetermined by GC analysis. ^dIn 2 mL of toluene. ^eIn 0.5 mL of toluene. ^fValue in brackets refers to yield of isolated product **2a**. dba = dibenzylideneacetone.

accordance with our hypothesis, the use of 2-chloroanisole as the substrate under the optimized conditions for the coupling of deactivated aryl chlorides with organolithium reagents⁹ (Pd-PEPPSI-IPent¹² as catalyst) gave rise to 2-methoxy-1,1'-biaryl **2a** with higher selectivity (entry 2). Surprisingly, the use of the catalyst comprising Pd₂(dba)₃ and XPhos¹³ as the ligand, which proved to be very efficient for the coupling of a range of aryl chlorides with organolithium reagents,⁹ led to disappointing selectivity in this case (entry 3). Fine tuning of the reaction conditions, comprising faster addition of the organolithium reagent, a slightly higher temperature (40 °C), and a higher substrate concentration, allowed **2a** to be obtained with high selectivity (92%) and in very good yield (entries 4 and 5). In

contrast, the use of 2-bromoanisole under these conditions led to considerable amounts of side products **3** and **4** (entry 6).

Having established conditions for the palladium-catalyzed cross-coupling of 2-chloroanisole with phenyllithium (Table 1, entry 5) we investigated the coupling of different aryllithium reagents and 2-alkoxy-substituted aryl chlorides (Scheme 2). 2-

Scheme 2. Pd-Catalyzed Cross-Coupling of Aryllithium Reagents with 2-Alkoxy-Substituted Aryl Chlorides^a



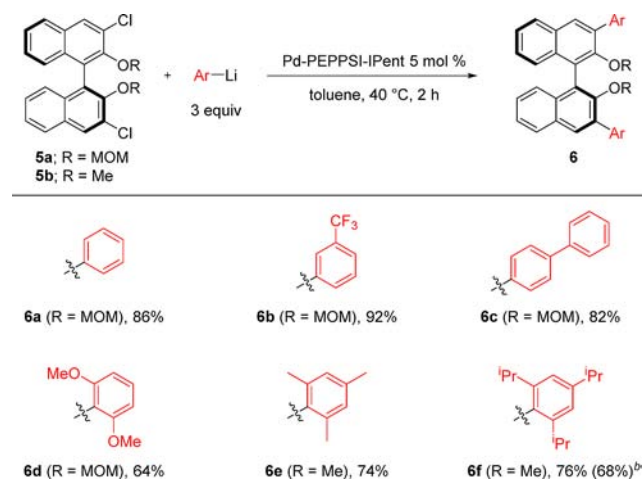
^aConditions: see Table 1, entry 5. Selectivity >90% in all cases. Yield values refer to isolated products after purification.

Chloroanisole could also be efficiently coupled with meta- and para-substituted aryllithium reagents affording the corresponding 2-methoxy biaryls **2b** and **2c** in good yields under the standard conditions. A challenging problem in cross-coupling processes is the combination of two sterically hindered coupling partners which both bear large ortho substituents. To our delight, the coupling with 2,6-dimethoxyphenyllithium, easily generated by direct ortho-lithiation of 1,3-dimethoxybenzene, proceeded smoothly and triortho-methoxy-substituted biaryl **2d** was obtained in good yield with total selectivity. Also alkyl substituents in the organolithium reagent are well tolerated as illustrated by the synthesis of biaryl **2e**. Remarkably, the highly hindered 2,4,6-triisopropylphenyllithium¹⁴ could be coupled under these mild conditions (40 °C, 2 h) affording the corresponding trisubstituted biaryl **2f** in 80% yield. To the best of our knowledge, only one example for the synthesis of biaryl **2f** from 2-chloroanisole has been reported using 2,4,6-triisopropylphenylzinc chloride at 70 °C.¹⁵ Importantly, 1-chloro-2-(methoxymethoxy)benzene **1b** was also a suitable substrate for this palladium-catalyzed cross-coupling with organolithium reagents. As far as we know, this substrate has never been used before in cross-coupling reactions. In addition to its electron-rich character and large steric hindrance, the presence of the MOM group in the ortho position represents an extra challenge for the cross-coupling of organolithium reagents due to its great ability as a directing group for the ortho-lithiation of this substrate.¹⁶ However, to our delight, the palladium-catalyzed cross-coupling of different aryllithium reagents with **1b** worked very well, and the corresponding 2-methoxymethoxy-substituted biaryls **2g–j**

were obtained in high yields and with excellent selectivity in all cases, even when the highly hindered 2,4,6-triisopropylphenyllithium was used (**2j**).

Chiral 3,3'-diaryl-1,1'-bi-2-naphthols (BINOLs) represent a very important class of 2-alkoxy substituted biaryls. These compounds,³ and the corresponding phosphorus derivatives, such as phosphoramidites¹⁷ and phosphoric acids,¹⁸ have been successfully used as ligands or catalysts in a variety of catalytic asymmetric reactions. The importance of the aryl substituents at the 3,3'-positions is due to the fact that their electronic and steric properties play a crucial role in the performance of the catalyst resulting from their proximity to the catalytic center. The development of new, simple, and versatile complementary methods for the introduction of different aryl groups in the 3,3'-positions of the binaphthol backbone is highly desirable. Methods for the synthesis of 3,3'-diaryl BINOLs include Kumada coupling,¹⁹ Suzuki coupling,²⁰ and Negishi coupling.²¹ However, these protocols involve either reactive aryl iodides or bromides and frequently require high temperatures and/or long reaction times. We envisioned that the palladium-catalyzed cross-coupling of organolithium reagents and 2-alkoxy-substituted aryl chlorides might be applied to the synthesis of 3,3'-diaryl BINOLs providing a useful alternative. This would represent a fast and mild protocol and the first example of the use of an aryl chloride for the synthesis of these important compounds. To our delight, this new methodology proved to be very efficient for this coupling, and a range of different 3,3'-diaryl BINOLs could be obtained in very good yield and selectivity from the corresponding aryllithium reagents and 3,3'-dichloro BINOLs (Scheme 3).

Scheme 3. Synthesis of 3,3'-diaryl BINOLs by Pd-Catalyzed Cross-Coupling with Aryllithium Reagents^a



^aConditions: ArLi (0.6 mmol) added over 2 h to a solution of **5** (0.2 mmol) in toluene (1 mL). Yield values refer to isolated products after purification. ^bYield in brackets refers to the reaction run on a 1.6 mmol (613 mg) scale.

The coupling between phenyllithium and (S)-3,3'-dichloro-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **5a** could be performed in high selectivity using the optimized catalytic system and afforded BINOL **6a** in 86% yield. Similarly, the use of 3-trifluoromethylphenyllithium and [1,1'-biphenyl]-4-ylolithium gave rise to the corresponding 3,3'-diaryl BINOLs **6b** and **6c** in excellent yields. Diortho-substituted aryllithium reagents were also efficient coupling partners for this transformation.

Importantly, substrate **5a** could be efficiently arylated with 2,6-dimethoxyphenyllithium. To the best of our knowledge, the synthesis of the corresponding 3,3'-diaryl BINOL **6d** has no precedent in the literature. Besides the bulkiness given by the two ortho-substituents in the aryl groups, this BINOL offers the possibility of an additional coordination of the methoxy groups to e.g. a metallic center.²² A bulky trisubstituted aryllithium reagent such as mesityllithium was also readily coupled under these conditions. In this case substrate **5a** gave rise to poor yield and it was necessary to use (S)-3,3'-dichloro-2,2'-bis(methoxy)-1,1'-binaphthalene **5b** as a coupling partner in order to obtain 3,3'-dimesityl BINOL **6e** in high yield. Remarkably, 3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-binaphthalene **6f** could be synthesized by the Pd-catalyzed cross-coupling of 2,4,6-triisopropylphenyllithium. Despite the large steric hindrance of both coupling partners, the reaction could be successfully carried out under these mild conditions (40 °C, 2 h) achieving high yield (76%) and selectivity. Importantly, the reaction could be also performed on a larger scale (1.6 mmol) with a similar result. It is important to note that binaphthalene **6f** is the precursor of 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP) which has emerged as a very powerful catalyst in terms of activity and enantioselectivity for several asymmetric transformations.²³ The present methodology gives straightforward access to this precursor with high efficiency in a very short reaction time.

In summary, we have developed a palladium-catalyzed cross-coupling of aryllithium reagents with 2-alkoxy-substituted aryl chlorides. The reaction proceeds under mild conditions in short reaction times and affords 2-alkoxy-substituted biaryls in very good yields with high selectivity. The use of a chloride as a substrate is key to avoiding the undesired formation of side products as the competing lithium-halogen exchange is suppressed. In addition, this highly practical methodology gives ready access to chiral 3,3'-diaryl 1,1'-bi-2-naphthols which are key compounds for asymmetric catalysis. As far as we know, this methodology represents the first example of the synthesis of these compounds from the corresponding 3,3'-dichloro 1,1'-bi-2-naphthols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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