ACS Catalysis

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Direct S-Arylation of Unactivated Arylsulfoxides Using [Pd(IPr*)(cin)Cl]

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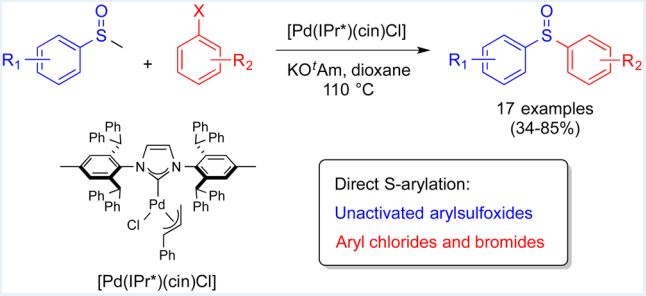
Supporting Information

ABSTRACT: The direct S-arylation of unactivated arylsulfoxides catalyzed by [Pd(IPr*)(cin)Cl] is described. Several arylmethylsulfoxides were coupled to various aryl halides in moderate to good yields (17 examples, 34−85%). Scope, limitations, and reaction mechanism are discussed.



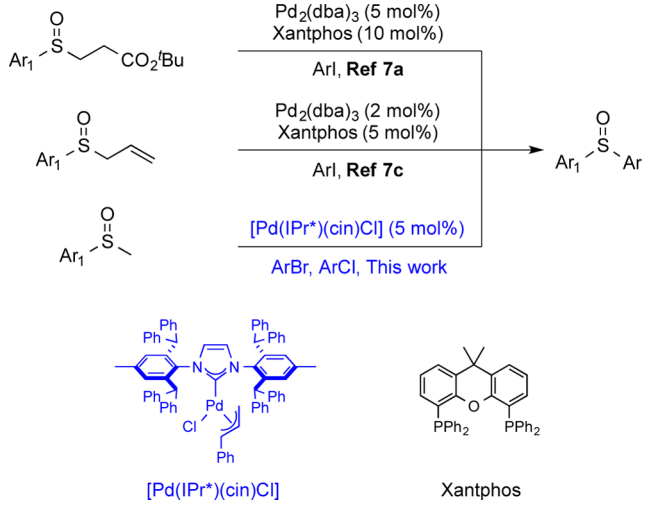
KEYWORDS: *palladium, N-heterocyclic carbenes (NHCs), arylation, sulfoxide, cross-coupling*

Palladium-catalyzed cross-coupling reactions are a popular means of assembling C−C bonds and are nowadays a subject of utmost importance in organic and organometallic chemistry.[1] Because of the general utility of palladium-catalyzed bond-forming protocols, the discovery of new reactivity involving these well-developed (and in numerous instances, well-defined) systems is important. Such findings are oftentimes achieved by introducing new ligands into metal-catalyzed reactions. Ongoing research in palladium chemistry focuses significantly on the development of bulky yet flexible as well as strong σ-donating ligands.[2] N-Heterocyclic carbenes (NHCs) have been shown as very efficient examples of such ligands, enabling original cross-coupling reactions.[3] We have developed a range of multipurpose well-defined palladium-NHC precatalysts useful in numerous cross-coupling reactions.[3,4]

Sulfoxides are important moieties as intermediates in organic synthesis and as ligands in catalysis.[5] Moreover, they are interesting because they are structural features of various biologically active compounds.[6] As a result of their wide range of utility, their functionalization using well-defined Pd-NHC complexes was investigated. In this Letter, the unprecedented S-arylation of unactivated arylsulfoxides is described using the [Pd(IPr*)(cin)Cl] precatalyst.

The reactivity of palladium complexes toward sulfoxides has been scarcely investigated in the literature.[7,8] Poli and Madec have notably reported the palladium catalyzed synthesis of bis-arylated sulfoxides via in situ-generated sulfenate anions.[7] The latter are formed from β-sulfinyl ester-[7a] or allylsulfoxides[7c] using $Pd_2(dba)_3$ as the palladium source and Xantphos as the ligand (Scheme 1). The system thus provides an interesting range of substituted biarylsulfoxides after cross-coupling with aryl halides. Nevertheless, despite its efficiency, the methodology is restricted to the use of aryl iodides. The use of aryl bromides leads to a decrease in the reactivity, and aryl chlorides are unreactive. Another drawback of this method is the need for activated sulfoxides that are not commercially available and must be prepared using a number of synthetic steps (generally two or three).[8a] More recently, Walsh and co-workers have reported on the α-arylation of sulfoxides.[8c] Although α-arylation of ketones is a well-known reaction,[9] the sulfoxide equivalent proved to be more challenging. The reaction makes use of 5−10 mol % of palladium, 20 mol % of the *N*-

Scheme 1. S-Arylation of Activated and Unactivated Arylsulfoxides via the Generation of Sulfenate Anions



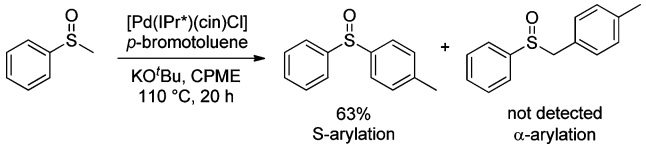
Received: July 9, 2013
Revised: August 17, 2013
Published: August 20, 2013

   dx.doi.org/10.1021/cs400533e | *ACS Catal.* 2013, 3, 2190−2193

(dicyclohexylphosphino)-2-(2′-tolyl)indole ligand and is performed in CPME at 110 °C in the presence of an excess of LiO^{t}Bu as the base. Of note, the sequence uses a specific phosphine to promote the reaction, illustrating once more that the nature of the ligand is vital in cross-coupling catalysis. Well-defined Pd-NHC complexes, especially the [Pd(NHC)(cin)Cl] family, have already proven to be very efficient precatalysts in numerous cross-coupling reactions.[2b,c,4b,10] As a consequence, their reactivity toward arylsulfoxides was examined.

The reaction between methylphenylsulfoxide and *p*-bromotoluene was first examined employing the Walsh conditions[8c] and a range of [Pd(NHC)(cin)Cl] precatalysts. KO^{t}Bu was initially chosen rather than LiO^{t}Bu because of the beneficial role of this base with the Pd-NHC systems in various other couplings.[4b] The reactivity of different palladium precatalysts was evaluated (see Supporting Information). Among them, only [Pd(IPr*)(cin)Cl)] allowed conversion of the starting materials. The product was isolated in 63% yield and was found to result from the direct and selective S-arylation of the sulfoxide (Scheme 2).

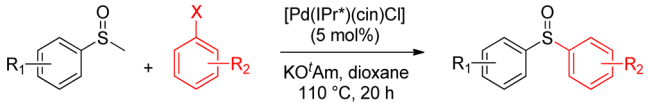
Scheme 2. Initial Lead for S-Arylation of Methylphenylsulfoxide

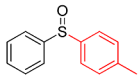
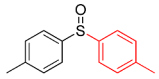
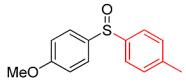
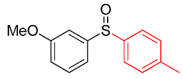
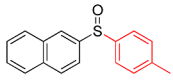
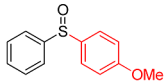
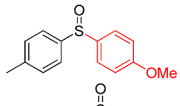
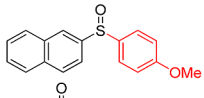
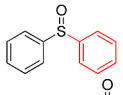
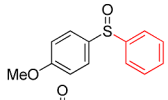
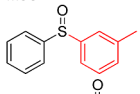
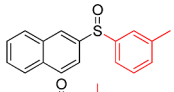
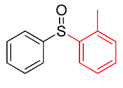
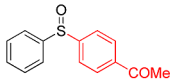


Interestingly, no α-arylated product was detected in the reaction mixture. With this promising result in hand, optimization was carried out (see Supporting Information). The reaction reached complete conversion using *p*-bromotoluene (2 equiv), KO^{t}Am (3 equiv) as the base, and [Pd(IPr*)(cin)Cl] (5 mol %) in dioxane (1M) at 110 °C for 20 h, and the desired compound was isolated in an excellent yield (82%, Table 1, entry 1). In contrast to the other Pd-NHC precatalysts, only [Pd(IPr*)(cin)Cl)] was able to promote the reaction. This result was attributed to the *flexible steric bulk* of the IPr* ligand.[2c,11] Compared with the work of Poli,[7] the use of activated sulfoxides is not required, and the reaction occurred directly using commercially available substrates. This new sequence appears to provide a straightforward access to sulfenate anions.

With the optimized reaction conditions in hand, the scope and limitations of the transformation were next studied (Table 1). At first, various arylmethylsulfoxides were coupled to *p*-bromotoluene. The use of sulfoxides bearing methyl or methoxy groups in the para or meta position afforded the expected biarylsulfoxides in good yields (67−85%; entries 4, 6, 8). Methyl(naphtalen-2-yl)sulfoxide was also successfully used, yielding the desired product in a 77% yield (entry 9). Because aryl chlorides are known to be more challenging substrates in cross-coupling reactions, their reactivity was next explored. Interestingly, using *p*-chlorotoluene instead of *p*-bromotoluene did not significantly affect the reaction. A slight decrease in the yield of about 10% was observed, but the desired compounds were still obtained in good yields (55−71%; entries 2, 5, 7, 10). On the other hand, *p*-iodotoluene exhibited much lower catalytic activity. In this case, the reaction did not reach completion and the formation of a complex mixture of products was observed by GC (entry 3).

Table 1. Scope of the S-Arylation Reaction[a]



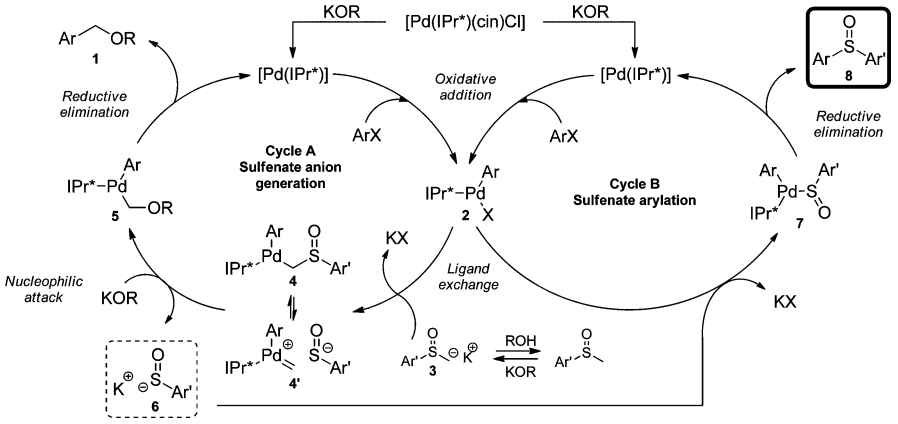
Entry	X	Product	Yield (%)[b]
1	Br		82
2	Cl		71
3	I		nd[c]
4	Br		85
5	Cl		71
6	Br		73
7	Cl		55
8	Br		67
9	Br		77
10	Cl		66
11	Br		47
12	Cl		39
13	Br		39
14	Br		50
15	Br		62
16	Br		34
17	Br		42
18	Br		50
19	Br		nd[c]
20	Br		0[d]
21	Cl		0[d]
22	I		0[d]

[a]Reagents and conditions: arylsulfoxide (0.5 mmol), aryl halide (1.0 mmol), KO^{t}Am (1.5 mmol), [Pd(IPr*)(cin)Cl] (5 mol %), dioxane (0.5 mL, 1 M), 110 °C, 20 h. [b]Isolated yield after chromatography on silica gel. [c]nd = not determined. An inseparable mixture of coupling product, starting materials, and unidentified compounds was observed by GC. [d]No conversion of the methylphenylsulfoxide was observed.

The reactivity of the deactivated *p*-bromo and *p*-chloroanisoles was next studied (entries 11−14). The catalytic system proved to be less efficient in these cases. The reactions did not reach completion, and the formation of several unidentified byproducts was observed by GC; however the expected compounds were still isolated in modest to moderate yields (39−50%). The effect of the sterics of the bromide was next investigated, and the coupling was found to be highly sensitive to subtle modifications. Moving the methyl group of the

dx.doi.org/10.1021/cs400533e | ACS Catal. 2013, 3, 2190−2193

Scheme 3. Proposed Catalytic Cycle for the Direct S-Arylation Reaction



bromide partner from the para to the meta position resulted in a drop in the yield (entries 17 and 18 vs 1 and 9; 42% and 50% vs 82% and 77%, respectively). On the other hand, ortho-substituted bromides were not found to be suitable coupling partners. Indeed, the reaction led to the formation of an inseparable mixture of products (entry 19). It is noteworthy that Poli and co-workers observed a similar decrease in reactivity using allylsulfoxides.[7c]

Finally, when activated halides were used, no conversion of the methylphenylsulfoxide was observed (entries 20–22).[12] The new catalytic system was found to be complementary to the ones reported in the literature.[7] Indeed, using the Poli protocol, the coupling was limited mainly to the use of aryl iodides. Using our protocol, we were able to promote the coupling using aryl bromides and chlorides. In terms of efficiency (range of isolated yields), our system proved to be globally as good (33–96% using the β-sulfinyl ester sulfoxides[7a]) or more efficient (15–60% using the allyl sulfoxides[7c]). Moreover, the starting sulfoxides used here were either commercially available or prepared in only one step.

Our attention finally focused on the mechanism of this transformation to understand how the methylsulfoxide bond was deconstructed. The proposed mechanism (Scheme 3) consists of two different manifolds: cycles A and B. During the course of our optimization experiments, we isolated and characterized **1** as a byproduct of the reaction. At first (cycles A and B), the palladium(0) active species was formed in situ by activation of the precatalyst in the presence of the base (KOR = KO^{t}Am or KO^{t}Bu). Then, the oxidative addition takes place, leading to the formation of complex **2**. In the meantime, as postulated by Walsh and co-workers,[8c] a reversible deprotonation of the weakly acidic α-protons of the arylmethylsulfoxide by KOR affords the α-sulfinyl anion **3**. After ligand exchange (cycle A), complex **4** is subsequently formed, which may be in equilibrium with the cleaved ionized carbenic form **4′**. At this stage, no reductive elimination was observed; the formation of the α-arylated product was never detected in the reaction medium.

The key step of the catalytic cycle next highlights a nucleophilic attack of the base on the carbon, linking the sulfoxide moiety to the palladium center in complex **4** or **4′**. For steric reasons, this might be favored with complex **4′**. This has the effect of releasing complex **5** and sulfenate anion **6**, which is necessary for the reaction to proceed. After reductive elimination, complex **5** yields byproduct **1** and regenerates the palladium(0) active species. In cycle B, the sulfenate anion **6** reacts with complex **2** to form **7**. Finally, the desired biarylsulfoxide **8** is formed after reductive elimination, and the palladium(0) active species is regenerated. As presented here, cycle A is necessary for cycle B to take place. This explains why 2 equiv of halide are required for the success of the reaction. One is sacrificed to generate the sulfenate anion while the second one is used to arylate the sulfoxide.

In summary, we have developed a direct S-arylation of unactivated arylsulfoxides using bromides and chlorides. [Pd(IPr*)(cin)Cl] was shown to be the precatalyst of choice to promote the reaction, the use of other [Pd(NHC)(cin)Cl] congeners being inefficient in this transformation. The reaction proved to be sensitive to small modifications in the nature of the halide. Especially, deactivated and sterically hindered halides were not efficiently converted. However, several differently substituted biarylsulfoxides were efficiently prepared (17 examples, 34–85%). Interestingly, the reaction is complementary with other procedures described in the literature, and chlorides were efficiently used for the first time in such a coupling reaction.

■ ASSOCIATED CONTENT

Supporting Information

Optimization tables, spectroscopic data, and copies of spectra for all compounds. 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the EC for funding through the seventh framework program SYNFLOW. Umicore is thanked for its generous gifts of materials. S.P.N. is a Royal Society Wolfson Research Merit Award holder.

■ ABBREVIATIONS

NHCs, N-heterocyclic carbenes; IPr*, 1,3-bis(2,6-bis-(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene; cin, cinnamyl = phenylallyl

REFERENCES

(1) *Metal-Catalyzed Cross-Coupling Reactions*; de Mejeire, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
(2) (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (b) Chartoire, A.; Frogneux, X.; Nolan, S. P. *Adv. Synth. Catal.* **2012**, *354*, 1897−1901. (c) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 4517−4521. (d) Valente, C.; Calimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332. (e) Berthon-Gelloz, G.; Siegler, M. A.; Spek, A. L.; Tinant, B.; Reek, J. N. H.; Marko, I. E. *Dalton Trans.* **2010**, *39*, 1444−1446.
(3) (a) Marion, N.; Nolan Steven, P. *Acc. Chem. Res.* **2008**, *41*, 1440−1449. (b) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169.
(4) (a) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816−3821. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111.
(5) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133−5209. (b) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172−2173. (c) Jiang, C.; Covell, D. J.; Stepan, A. F.; Plummer, M. S.; White, M. C. *Org. Lett.* **2012**, *14*, 1386−1389.
(6) (a) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609−624. (c) Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19−31.
(7) (a) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951−5954. (b) Maitro, G.; Vogel, S.; Sadaoui, M.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2007**, *9*, 5493−5496. (c) Bernoud, E.; Le Duc, G.; Bantreil, X.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2010**, *12*, 320−323.
(8) (a) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *J. Org. Chem.* **2006**, *71*, 7449−7454. (b) Colobert, F.; Ballesteros-Garrido, R.; Leroux, F. R.; Ballesteros, R.; Abarca, B. *Tetrahedron Lett.* **2007**, *48*, 6896−6899. (c) Jia, T.; Bellomo, A.; Baina, K. E. L.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 3740−3743.
(9) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053−4056. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.
(10) (a) Martin, A. R.; Chartoire, A.; Slawin, A. M. Z.; Nolan, S. P. *Beilstein J. Org. Chem.* **2012**, *8*, 1637−1643. (b) Chartoire, A.; Boreux, A.; Martin, A. R.; Nolan, S. P. *RSC Adv.* **2013**, *3*, 3840−3843.
(11) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690−3693.
(12) Reactions between methylphenylsulfoxide and other activated halides, such as 1-bromo-4-nitrobenzene, 1-bromo-4-(trifluoromethyl) benzene, and 1-chloro-4-fluorobenzene, were attempted but failed to give the desired products.