ORGANIC LETTERS

2012
Vol. 14, No. 21
5534–5537

Efficient Pd-Catalyzed Direct Arylations of Heterocycles with Unreactive and Hindered Aryl Chlorides

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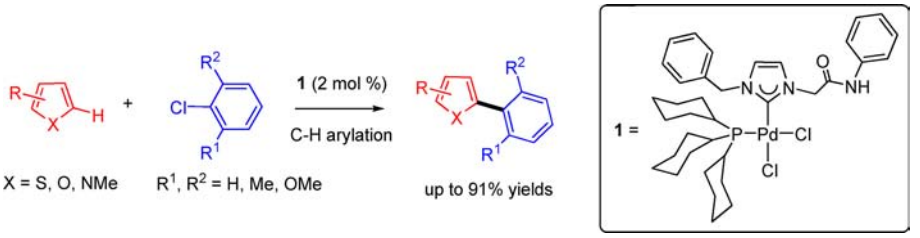
Received September 24, 2012

ABSTRACT



A highly electron-rich Pd complex can efficiently catalyze the direct arylation of heteroaromatics with unreactive and sterically congested aryl chlorides.

Heteroaromatic biaryls are important motifs in numerous products and pharmaceutical drugs.[1] The most commonly used synthetic route to these biaryls, metal-catalyzed Suzuki-type cross-coupling,[2] requires stoichiometric organometallic substrates, which give rise to problems of metal waste and extra synthetic steps. Recently, C−H arylation[3] has emerged as an effective approach for biaryl synthesis, and successive improvements allow for the use of this method to synthesize a broad range of heteroaromatic biaryls.[4] Nevertheless, one of the drawbacks of the existing procedures is that the aryl halides (coupling partners) used are limited to bromides and iodides; the less reactive but inexpensive aryl chlorides have come into use only recently.[5] Most of these recently developed strategies effectively aid the synthesis of heterocyclic biaryls from aryl chlorides, but the established reaction conditions are applicable only to certain heterocycle classes. In his impressive work, Daugulis demonstrated the Pd-catalyzed direct arylation of indoles, pyrroles, and furans with electron-rich and electron-deficient aryl chlorides using the Buchwald phosphine ligand.[5c] However, extensive efforts had to be devoted to optimize the reaction conditions for each substrate class, and high Pd (5 mol %) and phosphine loading (10 mol %) was required. More recently, Doucet reported that the use of a ferrocenyl diphosphine ligand allows for the direct arylation of numerous heteroaromatics, including oxazoles, benzofurans, indoles,

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(5) For selected examples, see: (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (c) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471. (d) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem.—Asian J.* **2007**, *2*, 1430. (e) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243. (f) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113. (g) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (h) Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279. (i) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (j) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332. (k) Kumar, P. V.; Lin, W.-S.; Shen, J.-S.; Nandi, D.; Lee, H. M. *Organometallics* **2011**, *30*, 5160.

10.1021/ol302635e
Published on Web 10/25/2012

and pyrazoles, with aryl chlorides.[6] While a low Pd loading of 0.5 mol % is sufficient for this reaction, only activated aryl chlorides can be used as coupling partners. The other notable drawback of the existing biaryl synthesis method based on direct arylation with aryl chlorides is that only a small amount of steric bulk is tolerated on the chlorides. That is, ortho-, meta- or 3,5-disubstituted chlorobenzenes were successfully utilized in several cases,[5a−f] but there is hardly any report on the use of highly hindered aryl chloride substrates as coupling partners, except for one case where 2,6-dimethylchlorobenzene was successfully made to react with a 1,2,3-triazole.[5d] Therefore, the search for a catalyst system that helps in addressing these problems would be advantageous for industrial applications of heteroaromatic biaryl synthesis.

Herein, we discuss the Pd-catalyzed direct arylation of heteroaromatics with aryl chlorides using a Pd(II) complex **1** bearing a functionalized N-heterocyclic carbene (NHC) and a tricyclohexylphosphine (Figure 1).

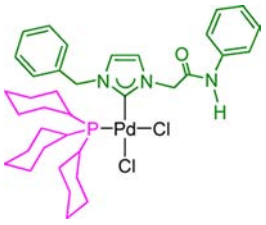


Figure 1. Pd(II) Complex **1** for C−H arylation.

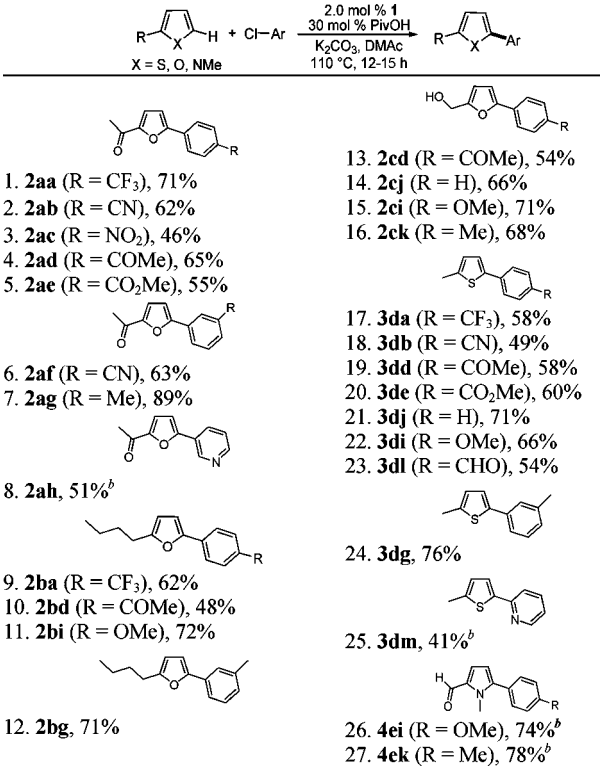
We chose **1** as the precatalyst because this robust and highly electron-rich Pd(II) complex actively promotes aryl C−Cl bond cleavage, thus showing excellent catalytic activity in traditional C−C cross-coupling reactions.[7] For aryl C−H bond activation, we employed catalytic amounts of pivalic acid, which has been shown to function as a proton shuttle in the bond cleavage step.[8] In the presence of the aforementioned catalyst system and at a mild 2% Pd loading, the reaction has broad substrate scope and most notably, highly hindered aryl chlorides can furnish the desired heteroaromatic biaryls in moderate-to-excellent yields.

By considering Fagnou's direct arylation procedure[8] and screening the reaction parameters, we decided the optimum reaction conditions: **1**, 2 mol %; PivOH, 30 mol %; K_2CO_3, 1.5 equiv; aryl chloride, 1.0 equiv; heterocycle, 1.2 equiv; solvent, DMAc; reaction temperature, 110 °C; reaction time, 12−15 h. Under the optimized conditions, a series of heterocyclic substrates reacted with aryl chlorides having different electronic properties to furnish the biaryl products in moderate-to-excellent yields (Scheme 1). The coupling reactions were highly regioselective, and in almost all the cases, only C5 arylated products were formed. Hardly any modification of the reaction conditions was required for different classes of heterocyclic substrates.

2-Acetylfuran bearing a C2 electron-withdrawing group reacted with various aryl chlorides to afford the corresponding 2-arylfurans in moderate-to-good yields (entries 1−7). In general, electron-rich aryl chlorides give higher yields than do electron-deficient chlorides. Further, highly electron deficient haloarenes bearing a nitro, cyano, or acetyl group typically give low product yields.[9] As shown in entries 1−6, even such haloarenes readily reacted with 2-acetylfuran to afford the corresponding products in synthetically useful yields. When using the electron-rich 3-chlorotoluene as the coupling partner, **2ag** was obtained in very good yield (89%, entry 7).

The coupling reactions also proceeded smoothly when an electron-rich furan was used as the substrate (entries 9−12). The reaction of 2-*n*-butylfuran with the electron-deficient 4-chlorotrifluoromethylbenzene and 4-chloroacetophenone afforded the coupled products **2ba** and **2bd** in 62 and 48% yield, respectively (entries 9 and 10). These yields, however, were markedly lower than those of **2aa**

Scheme 1. Direct Arylation of Heterocycles with Aryl Chlorides[a]



[a] Conditions (unless otherwise specified): heterocycle (1.2 mmol), ArCl (1.0 mmol), K_2CO_3 (1.5 equiv), DMAc (2.5 mL), cat. (2.0 mol %), PivOH (30 mol %), 110 °C, 12 h, isolated yield. [b] 15 h.

(6) Roy, D.; Mom, S.; Royer, S.; Lucas, D.; Hierso, J.-C.; Doucet, H. *ACS Catal*. **2012**, *2*, 1033.

(7) Liao, C.-Y.; Chan, K.-T.; Tu, C.-Y.; Chang, Y.-W.; Hu, C.-H.; Lee, H. M. *Chem.—Eur. J*. **2009**, *15*, 405.

(8) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 16496. (b) Lapointe, D.; Fagnou, K. *Chem. Lett*. **2010**, *39*, 1118. (c) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315.

(9) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem*. **2009**, *74*, 1826.

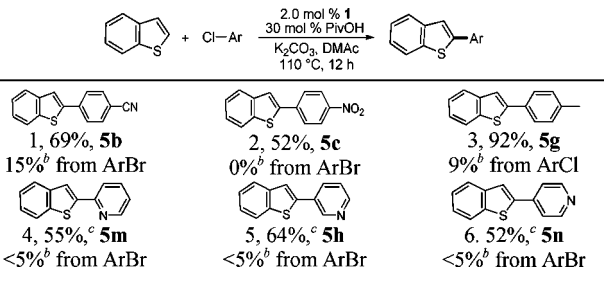
(71%, entry 1) and **2ad** (65%, entry 5) obtained from 2-acetylfuran. Entries 13−16 demonstrated that when using the present catalyst system, protection/deprotection of the hydroxyl group on the furan moiety can be avoided.[10] Thus, **2ci** and **2ck** could be obtained from the corresponding hydroxy furans in much higher yields (71 and 68%, respectively) than those reported by Doucet (10 and 15%), who used simple $Pd(OAc)_2$ and aryl bromides as substrates.[10]

Direct arylation of 2-methylthiophene bearing a C2 electron-donating group followed essentially the same trend. Both electron-rich and electron-deficient aryl chlorides could be employed as coupling partners to furnish 2-arylthiophene in moderate-to-excellent yields (entries 17−24).

In the direct arylation of 1-methyl-2-formylpyrrole with aryl chlorides, the aldehyde group was well tolerated, and the coupled products **4ei** and **4ek** were obtained in good yields (entries 26 and 27). The coupling procedure could also be applied to produce biheteroaryl motifs. Thus, the reaction between 2-acetylfuran and the heterocyclic aryl chloride, 3-chloropyridine, proceeded smoothly to afford **2ah** in 51% (entry 7). Similarly, coupling of 2-methylthiophene with 2-chloropyridine afforded **3dm** in reasonable yield (41%, entry 25).

The generality of the catalyst system for the coupling of different heterocyclic substrates with aryl chlorides was further manifested by its efficiency in the production of challenging coupled products reported in the literature. Preparation of several heteroaromatic biaryls by Fagnou's direct arylation protocol is well-known to be difficult.[9] Scheme 2 shows some benzothiophene-based biaryls

Scheme 2. Direct Arylation of Benzothiophene with Aryl Halides[a]

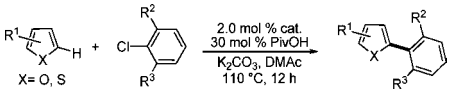


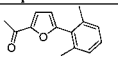
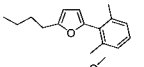
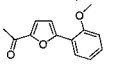
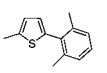
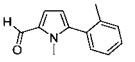
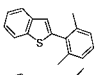
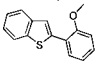
[a] Conditions (unless otherwise specified): same as Scheme 1. [b] Conversion of the limiting starting material, ref 9. [c] 15 h.

produced in low yields in previous studies but in reasonable yields in the present study. Kappe recently reported the successful arylation of some of these unreactive heterocyclic substrates with aryl bromides and heteroaryl bromides.[11] However our catalyst system allows for the use of aryl chlorides as coupling partners in place of bromide substrates. Fagnou reported that coupling between benzothiophene with 4-bromobenzonitrile resulted in poor yield with only a 15% conversion of the starting material (entry 1). Under our optimized reaction conditions and with the chloride analogue as the coupling partner, the desired product **5b** was obtained in 69% isolated yield. Similarly, **5c** and **5g** were successfully produced from aryl chlorides (entries 2 and 3). The present catalyst system was much more effective for the preparation of biheteroaryl motifs from chloropyridines than was Fagnou's protocol (entries 4−6). It should be noted that equally effective catalyst systems for the Pd-catalyzed direct arylation of heterocycles with nonsterically hindered aryl chlorides have also been reported by Mori[5i] and Daugulis.[5b] For example, Mori reported the same yield of **5g** using 2 mol % $Pd(Pt\text{-}Bu)_3$ as catalyst. A biheteroaryl compound similar to **5m** was obtained in 72% yield from the catalyst system reported by Daugulis using 5 mol % $Pd(OAc)_2/P(Ad)_2Bu$ (1:2) as catalyst.[5b]

The catalyst system was also highly effective for the coupling reaction of sterically hindered aryl chlorides (Table 1). 2-Acetylfuran, 2-*n*-butylfuran, 2-methyl thiophene and benzothiophene reacted smoothly with 2,6-dimethylchlorobenzene to afford the biaryl products in good-to-excellent yields (77−91%, entries 1, 2, 4, 8). Under our optimized reaction conditions, **2bo**, which was previously prepared in relatively low yield (40%) by Doucet via the Pd-catalyzed direct arylation with the more reactive bromo analogue, was obtained in 84% yield.[12] As opposed to this, under our conditions, 2-methylthiophene and 2-chloro-1,3-dimethylbenzene, which bears two ortho

Table 1. Direct Arylation of Heterocycles with Hindered Aryl Chlorides[a]



entry	cat.	product		yield (%)
1	**1**		**2ao**	77
2	**1**		**2bo**	84
3	**1**		**2ap**	63
4	**1**			91
5	$Pd(OAc)_2$/IMesHCl (1:1)		**3do**	<5
6	IMesPd(OAc)(κ^2-OAc)			48
7	**1**		**4eg**	68[b]
8	**1**			88
9	IMesPd(OAc)(κ^2-OAc)		**5o**	21
10	**1**		**5p**	62

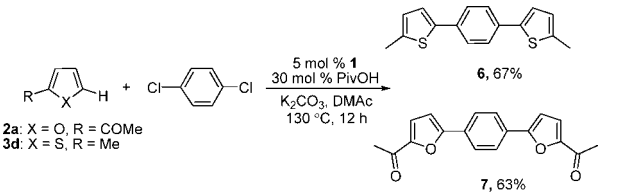
[a] Conditions (unless otherwise specified): same as Scheme 1. [b] 15 h.

(10) Roger, J.; Požgan, F.; Doucet, H. *Adv. Synth. Catal.* **2010**, *352*, 696.

(11) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 8138.

(12) Roy, D.; Mom, S.; Lucas, D.; Cattey, H.; Hierso, J.-C.; Doucet, H. *Chem.—Eur. J.* **2011**, *17*, 6453.

Scheme 3. Twofold C−H Bond Arylation



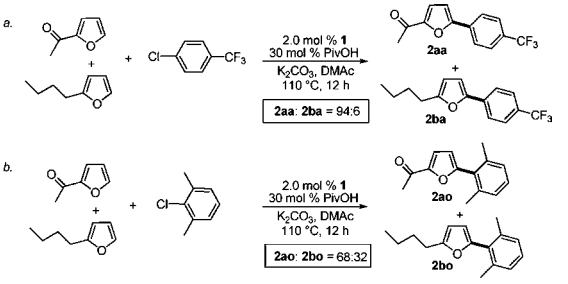
methyl groups, could be coupled in the presence of **1** to afford **3do** in excellent yield (91%). To the best of our knowledge, this is the first report on the use of 2,6-dimethylchlorobenzene for the preparation of biaryls with furan and thiophene. Entries 4−6 and 8−9 also indicated that **1** was more effective than the preformed [IMesPd(OAc)(κ^2-OAc)] or in situ $Pd(OAc)_2$/IMesHCl catalyst systems derived from the typical NHC ligand of IMes.[3h,i] Other hindered aryl chloride substrates such as 2-chloroanisole and 2-chlorotoluene could also be employed in the coupling reaction (entries 3, 7, 10).

The new protocol could be extended to the synthesis of triaryl compounds **6** and **7** from the unreactive 1,4-dichlorobenzene (Scheme 3) as well. However, a higher Pd loading of 5 mol % and higher reaction temperature (130 °C) were required, and **6** and **7** were furnished in 67 and 63% yields, respectively. This result was definitely encouraging since previously, the extended system of **6** could be obtained from only the expensive 1,4-diiodobenzene by Ir-catalyzed direct arylation.[13]

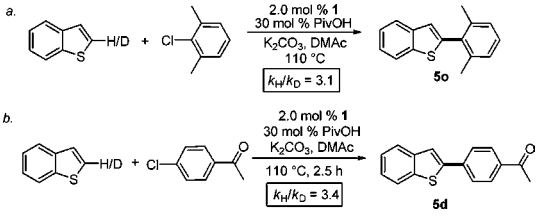
Mechanistic investigations were performed to shed light on the catalytic pathway. Although both **2aa** and **2ba** can be obtained in good yields in individual reactions (vide supra), the competitive experiment reveals that electron-deficient heterocycle reacts preferentially over electron-rich substrate, affording **2aa** and **2ba** in the ratio of 94:6 (Scheme 4a). Similarly, a product ratio of 68:32 in favor of the electron-deficient heterocycle was obtained with the sterically hindered 2-chloro-1,3-dimethylbenzene as coupling partner (Scheme 4b). Using chloride substrates with different electronic and steric properties, the kinetic isotope experiments reveal similar k_H/k_D values of 3.1 and 3.4 (Scheme 5). These results support the possible involvement of a concerted metalation−deprotonation (CMD) pathway rather than electrophilic aromatic substitution or

(13) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644.

Scheme 4. Competitive Experiments



Scheme 5. Kinetic Isotope Experiments



radical process and the C−H bond cleavage being the rate-determining step.[8]

In summary, the catalyst system based on complex **1** was highly effective for the regioselective C−H arylation of heteroaromatics by aryl chlorides. The general reaction conditions developed allowed for the use of a wide range of heterocycles, including thiophene, furan, and pyrrole, as substrates and aryl halides with different electronic properties as coupling partners. In almost all the cases, the desired coupled products could be obtained in moderate-to-excellent yields. The catalyst system allows the general use of nonactivated and highly congested aryl chlorides in heteroaromatic biaryl synthesis via direct arylation.

Acknowledgment. We thank the National Science Council of Taiwan for supporting this work.

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

The authors declare no competing financial interest.