ORGANIC
LETTERS

2010
Vol. 12, No. 1
156−158

Selective Unusual Pd-Mediated Biaryl Coupling Reactions: Solvent Effects with Carbonate Bases

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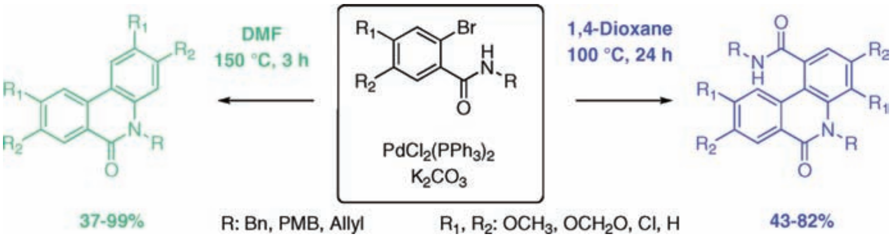
Received November 5, 2009

ABSTRACT



A one-step Pd-catalyzed reaction performed on an *o*-bromobenzamide permitted the selective formation of either phenanthridinones 2 via an ipso substitution or new phenanthridinone-1-carboxamides 3 through a direct N-arylation. A direct correlation between the solvent polarity and the carbonate base on the selectivity has been observed. The proposed catalytic cycle involves the initial formation of a common intermediate and depends on the base assistance.

o-Bromobenzamide units such as **1** are of particular interest in the Pd-mediated synthesis of natural products, as well as CNS and anticancer candidates.[1] It was recently shown that Pd-catalyzed coupling of two molecules of **1a** furnished phenanthridinone **2a**, when treated by $Pd(OAc)_2$, a triaryl phosphine ligand, and a carbonate base.[2] In our hands, compound **2a** was also selectively obtained with the system $PdCl_2(PPh_3)_2$ and K_2CO_3 in DMF (Table 1). Surprisingly, when 1,4-dioxane was used instead of DMF, the coupling reaction followed a completely different pathway, leading to the selective formation of the unexpected 1-carboxamide phenanthridinone **3a**.

We investigated these reactions to understand the origin of the difference of selectivity observed. The results are presented in this communication.

A large variety of *o*-bromobenzamides **1a−k** differing by the N-protecting groups (R: benzyl, PMB, allyl) and the substituents on the aromatic ring (R_1 and R_2: OCH_3, OCH_2O, Cl) were selected. The scope of these coupling processes was first studied, and the results are listed in Table 1.

In all conditions, a single product was obtained in moderate to excellent yield, but its structure depended upon the solvent used. Indeed, only phenanthridinones **2** were formed in DMF, whereas 1-carboxamide phenanthridinones **3** were exclusively obtained in dioxane. Moreover, the coupling is faster in DMF than in dioxane (3 h versus 24 h). The variations observed are similar in both series. Thus, the nature of the N-protecting group does not influence the outcome of the reactions. In addition, a Pd(II)-mediated *E*/*Z* isomerization of the allyl double bond was observed in dioxane for **1g**,

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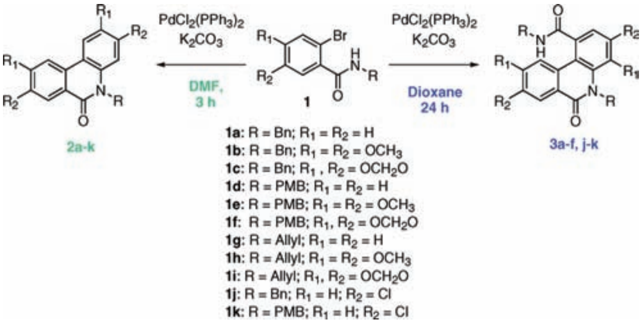
(1) Dewick, P. W. *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; Wiley-Blackwell: Oxford, 2009; p 311. Bastida, J.; Lavilla, R.; Viladomat, F. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2006; Vol. 63, p 87. Wermuth, C. G. *The Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: London, 2003.

(2) (a) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722. (b) Furata, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183. First example of this reaction, see: Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347. See also: Thansandote, P.; Hulcoop, D. G.; Langer, M.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1673. For a review on transition-metal catalyzed direct arylation, see: Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. Thansandote, P.; Lautens, M. *Chem.−Eur. J.* **2009**, *15*, 5874.

10.1021/ol902570s

Table 1. Scope of the Coupling Reactions[a]



entry	substrate	product (yield) - solvent	
		DMF	dioxane
1	**1a**	**2a**, 55%	**3a**, 49%
2	**1b**	**2b**, 88%	**3b**, 63%
3	**1c**	**2c**, 91%	**3c**, 80%
4	**1d**	**2d**, 71%	**3d**, 48%
5	**1e**	**2e**, 80%	**3e**, 82%
6	**1f**	**2f**, 99%	**3f**, 80%
7	**1g**	**2g**, 55%	*E*/*Z* isomerization
8	**1h**	**2h**, 80%	*E*/*Z* isomerization
9	**1i**	**2i**, 95%	*E*/*Z* isomerization
10	**1j**	**2j**, 54%	**3j**, 43%
11	**1k**	**2k**, 46%	**3k**, 61%

[a] Reaction conditions: $PdCl_2(PPh_3)_2$ (5 mol %), K_2CO_3 (3 equiv), *o*-bromobenzamide (1 equiv), dioxane or DMF (20 mL) at 100 or 150 °C, respectively.

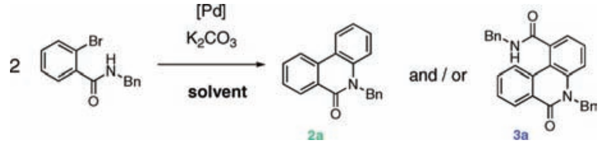
1h, and **1i**, in which case no coupling process occurred (entries 7−9).[3] The presence of electron-donating substituents, such as OCH_3 and OCH_2O, dramatically increased the yields of the reactions (entries 2, 3, 5, 6, 8, and 9). In contrast, substitution by a deactivating chlorine led to moderate yields, close to those observed with an unsubstituted aromatic ring (entries 10 and 11 vs entries 1, 4, and 7).

To understand the selectivity observed, the role of the solvent was studied more precisely with different Pd(II) and Pd(0) complexes (Table 2). THF, a usual solvent in Pd chemistry, was chosen for its intermediate polarity between dioxane and DMF. Remarkably, results are very homogeneous. In less polar dioxane, only compound **3a** was obtained, whereas tricycle **2a** was selectively formed in DMF, independently of the Pd source (entries 1 and 3, respectively).[4] In THF, a mixture of **2a** and **3a** was observed, suggesting that the solvent polarity could be directly involved in the selectivity (entry 2).

The fact that Furata and co-workers only reported the formation of **2a** in dioxane when using Cs_2CO_3 as a base prompted us to investigate the influence of the solvent/base association on the reaction.[2b] Thus, the effect of Na_2CO_3, K_2CO_3, and Cs_2CO_3 was studied in dioxane, THF, and DMF. As shown in Table 3, the selectivity of the reactions directly depends upon the solvent polarity and the base dissociation. Without base, no reaction was observed, outlining the importance of the alkaline agent in these reactions (entry 1). For example, in moderately polar THF, compound **3a** was obtained with weakly dissociated sodium carbonate, whereas the use of easily dissociated cesium carbonate led to phenanthridinone **2a** (entries 2 and 4). Interestingly, the use of THF as solvent also resulted in a significant increase in the yields of **2a** or **3a** (see Table 1, entry 1 for comparison). Potassium carbonate led to a mixture of **2a** and **3a** (entry 3). Consequently, these results show a direct correlation between the base dissociation and the formation of **2a**, suggesting that the base is directly involved in the reaction mechanism.[5]

To account for these results, a plausible catalytic cycle is proposed in Scheme 1. Both reactions involve an aryl−aryl

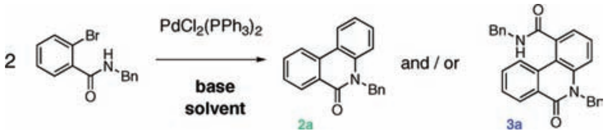
Table 2. Solvent Effect and Pd Source[a]



entry	solvent	product (selectivity) - Pd complex		
		$PdCl_2(PPh_3)_2$	$PdCl_2(dppf)$	$Pd(PPh_3)_4$
1	dioxane	**3a**	**3a**	**3a**
2	THF	**3a/2a** (1:1.4)	**3a/2a** (2:1)	**3a/2a** (3:1)
3	DMF	**2a**	**2a**	**2a**

[a] Reaction conditions: Pd complex (5 mol %), K_2CO_3 (3 equiv), *o*-bromobenzamide **1a** (1 equiv), dioxane, THF, or DMF (20 mL) at 100, 60, or 150 °C, respectively.

Table 3. Nature of the Base and Solvent Effect[a]



entry	base	product (global yields, selectivity) - solvent		
		dioxane	THF	DMF
1	no base	no reaction	no reaction	no reaction
2	Na_2CO_3	**3a** (traces)	**3a** (86%)	**3a/2a** (64%, 1:3.3)
3	K_2CO_3	**3a** (49%)	**3a/2a** (56%, 1:1.4)	**2a** (55%)
4	Cs_2CO_3	**3a/2a** (69%, 1.5:1)	**2a** (90%)	**2a** (80%)

[a] Reaction conditions: $PdCl_2(PPh_3)_2$ (5 mol %), base (3 equiv), *o*-bromo arylcarboxamide **1a** (1 equiv), dioxane, THF, or DMF (20 mL) at 100, 60, or 150 °C, respectively.

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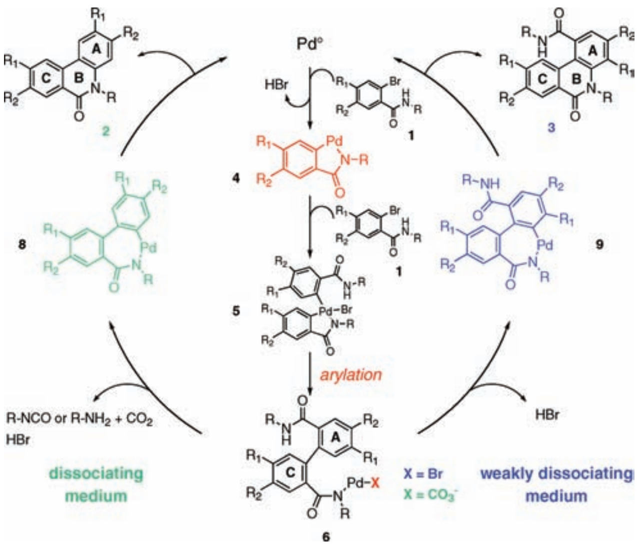
(3) Pd(II)-mediated isomerization of heteroatom-allyl is known, see: Negishi, E.-i. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijeire A., Eds.; Wiley: New York, 2002; p 2783.

(4) In a similar polar solvent, CH_3CN, compound **2a** was also obtained selectively.

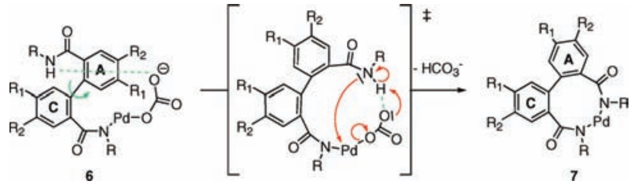
Scheme 1. Plausible Mechanistic Pathways



connection followed by an *N*-aryl coupling step.[6] Starting from in situ generated Pd(0), insertion into the C−Br bond gives rise to five-membered Pd(II) palladacycle **4**. Then insertion into a second arylcarboxamide unit occurs, producing Pd(IV) intermediate **5**, which can undergo an aryl−aryl bond reaction to give Pd(II) intermediate **6**.

At this point, two different intramolecular pathways can proceed. In dissociating medium, carbonate may exchange with bromide on Pd(II) complex **6** (Scheme 2). Then a concerted mechanism proceeds including a carbonate-induced amide deprotonation with concomitant rotation of the aryl unit A around the aryl−aryl bond, followed by a nucleophilic attack of the nitrogen with departure of HCO_3^-.[7] An ipso substitution on the resulting Pd(II) intermediate **7** with elimination of an RNCO unit (or $RNH_2 + CO_2$) gives complex **8**, which releases tricycle **2** after reductive elimination.[8]

Scheme 2. Proposed Role of the Carbonate Base



In weakly dissociating medium, no carbonate−bromide exchange occurs. A Pd(II)-mediated *N*-arylation can occur to release compound **3** after reductive elimination. To the best of our knowledge, this is one of the first examples of an *N*-Pd(II) species insertion into a C−H bond.[9]

In summary, we describe here simple and efficient reaction conditions to access selectively two differently substituted phenanthridinone skeletons from a common precursor in a one-step sequence. The reaction pathway proposed involves the formation of a common aryl−aryl Pd(II) intermediate which can undergo either an ipso substitution or an N-arylation depending on the medium. This selectivity is governed by the base dissociation which, in dissociating medium, can directly participate in the reaction pathway. The scope of the *N*-Pd(II) species insertion into a C−H bond in other (hetero)polycyclic series is currently under investigation.

Acknowledgment. E. Prost and P. Leproux (Université Paris Descartes UMR CNRS 8638) are gratefully acknowledged for their technical assistance (NMR and Mass spectra). Dr. L. Micouin (Université Paris Descartes UMR CNRS 8638) is acknowledged for fruitful discussions. We are grateful to Dr. A. Jutand (École Normale Supérieure, Département de Chimie UMR CNRS-ENS-UPMC 8640) for helpful discussions during the preparation of the manuscript.

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

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(5) A possible base counterion effect is conceivable. A study of base effects in intramolecular direct N-arylation was conducted by Fagnou and co-workers, but the conclusion remained elusive. See: Campeau, L.-C.; Parisien, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. See also: Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

(6) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512, and references cited.

(7) For an example of amide deprotonation induced by a carbonate base in a Pd process, see: Erb., W.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 3109.

(8) Example of Pd-catalyzed arylation with concomitant decarbamoylation, see: Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(9) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603.