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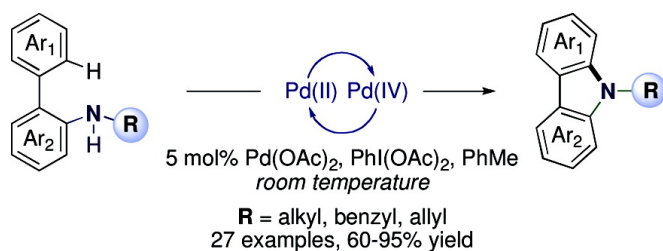
Oxidative Pd(II)-Catalyzed C#H Bond Amination to Carbazole at Ambient Temperature

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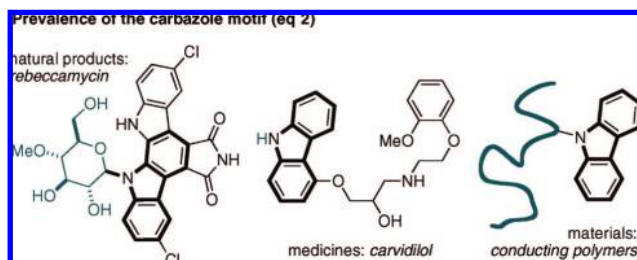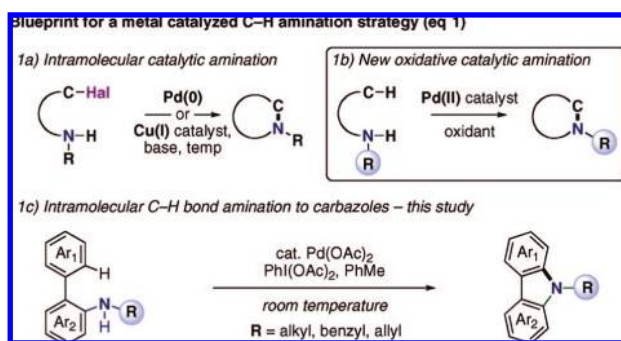
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Oxidative Pd(II)-Catalyzed C−H Bond Amination to Carbazole at Ambient Temperature

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The ubiquity of aromatic C−N bonds in organic molecules has made the development of novel amination methodologies an important objective for chemical synthesis. Until recently, traditional methods for diaryl−amine bond construction routinely focused on variations of Cu-mediated Ullmann coupling between an aryl halide and an aniline.[1] However, these processes can sometimes be problematic due to harsh conditions, therefore restricting their utility in complex molecule synthesis applications. The limitations of Ullmann-type amination reactions have now been marginalized through the pioneering studies carried out in the Buchwald and Hartwig laboratories.[2] The advances made through these modern day Pd(0) and Cu(I) catalyzed transformations mean that many classes of amine are now accessible.[2] Interestingly, the disconnection of the C−N bond in these processes, to an aryl halide and aniline, remains the same as in the case of Ullmann's seminal report (eq 1a).[1a] With this mind, we considered a direct catalytic C−H amination process could complement existing C−N bond forming strategies. Herein, we describe a Pd(II)-catalyzed intramolecular C−H bond amination strategy (eq 1b) and its application to direct carbazole formation (eq 1c);[3] this motif is common in bioactive natural products,[4a] has demonstrated importance in a range of therapeutics,[4b] and imparts novel properties in polymeric materials (eq 2).[4c] This Pd(II)-catalyzed amination process does not require prefunctionalization of the aryl group, operates under ambient conditions, and can be applied to the assembly of complex molecules.


Blueprint for a metal catalyzed C−H amination strategy (eq 1)

1a) Intramolecular catalytic amination

1b) New oxidative catalytic amination

1c) Intramolecular C−H bond amination to carbazoles – this study

Prevalence of the carbazole motif (eq 2)

natural products: rebeccamycin

medicines: carvidilol

materials: conducting polymers

In recent years, significant progress has been made in the area of metal-catalyzed amination of C−H bonds,[5,6] for example,

through highly reactive metallo-nitreneoids,[5a−f] and π-allyl-type species.[5g−i] More relevant to this study is the elegant Pd(II)-catalyzed intramolecular amination of acetanilide derivatives.[6] This Pd(II)/Pd(0) process is proposed to occur via coordination of the metal center to the amide, carbopalladation, and reductive elimination to form the C−N bond but requires rather forcing reaction conditions.

As part of our blueprint for an *ambient* and general catalytic C−H bond amination strategy, we reasoned that reductive elimination from a high oxidation state Pd(IV) center would more readily facilitate C−N bond formation.[8] To realize this process, an amine bearing an electron-donating group (**1**) should coordinate strongly to a Pd(II) catalyst, resulting in complex **I** that could then undergo cyclopalladation to form **II**. Next, oxidation of the Pd(II) complex **II** to a Pd(IV) species **III** would expedite C−N bond formation to form **2** (Scheme 1). Following this design strategy, we anticipated that both carbopalladation and oxidation, and hence the overall C−H amination process, could occur under ambient conditions.

Scheme 1. Proposed Mechanistic Hypothesis for C−H Amination
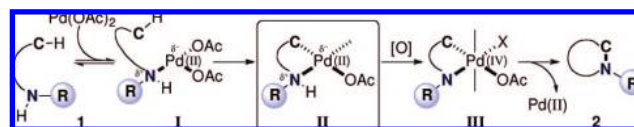
Guided by this, we began our studies by testing the reaction of *N*-Bn biphenyl **1a** to carbazole **2a** at *room temperature*, in the presence of catalytic amounts of Pd(OAc)$_2$ and an oxidant (Table 1).

Table 1. Optimization towards Catalytic C−H Bond Amination

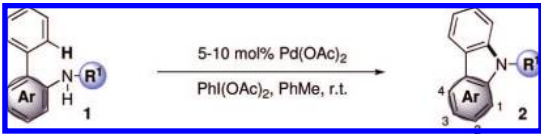| entry	catalyst loading, mol %	R	solvent	oxidant	yield, %[a]
1	10	Bn	DMF	t-BuOOBz	nr
2	10	Bn	DMF	PhI(OAc)$_2$	18 (**2a**)
3	10	Bn	CH$_2$Cl$_2$	PhI(OAc)$_2$	77 (**2a**)
4	10	H	DMF	t-BuOOBz	<10 (**2b**)
5	10	H	DMF	PhI(OAc)$_2$	34 (**2b**)
6	10	H	CH$_2$Cl$_2$	PhI(OAc)$_2$	<10 (**2b**)
7	10	Ac	DMF	t-BuOOBz	<10 (**2c**)
8	10	Ac	CH$_2$Cl$_2$	PhI(OAc)$_2$	<10 (**2c**)
9	5	Bn	PhMe	PhI(OAc)$_2$	96 (**2a**)

[a] Isolated yield after chromatography.

After screening a variety of conditions, we found that reaction of **1a** (R = Bn), with *t*-BuOOBz or phenyliodosyl diacetate

(PhI(OAc)$_2$) as oxidant and DMF as solvent, afforded carbazole **2a** in low yield (entries 1 and 2). However, changing the solvent to CH$_2$Cl$_2$, while maintaining PhI(OAc)$_2$ as oxidant, led to the formation of the desired product **2a** in 77% yield (entry 3). Interestingly, reaction of **1b** (R = H) under similar conditions afforded carbazole **2b** in poor yields (entries 4–6) that could not be improved on. Little reaction was observed with acetamide **1c** (R = Ac) at room temperature (entries 7 and 8), in contrast to related studies under more forcing conditions.[6a] Subsequent optimization on **1a** (R = Bn) revealed that reaction at room temperature with 5 mol % Pd(OAc)$_2$ as catalyst, 1.2 equiv of PhI(OAc)$_2$ as oxidant, and PhMe as solvent afforded 96% of the carbazole **2a** after 1 h (entry 9).[9a,b] These results clearly demonstrate that *N*-alkyl amines display enhanced reactivity in this Pd(II)-catalyzed C–H bond amination process, under ambient conditions. Furthermore, they suggest that key mechanistic differences exist between our Pd(II)-catalyzed amination and related transformations of acetanilides.[6a–d] No reaction was observed in the absence of the palladium catalyst.

With an optimized set of reaction conditions, attention was turned to the exploration of the scope of this Pd(II)-catalyzed C–H amination process. We first examined the effect of the nitrogen substituent; mindful of the fact that we needed to demonstrate a range of tolerant groups, we also need to be able to remove the *N*-substituent if necessary. Simple alkyl, benzyl, and allyl motifs all worked well in the reaction, providing the carbazoles **2a–g** in good yields (Table 2, entries 1–5).

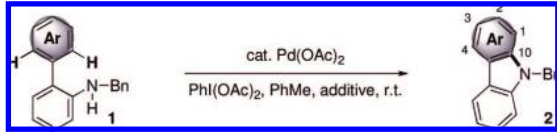**Table 2.** Scope of C–H Bond Amination: Aniline Substituents

entry	catalyst loading, mol %	R^1	Ar (in 2)[a]	time h	yield, %[b]
1	5	Bn	(C$_6$H$_4$)	1	96 (**2a**)
2	5	*i*-Pr	(C$_6$H$_4$)	4	96 (**2a**)
3	5	Me	(C$_6$H$_4$)	2	80 (**2d**)
4	10	allyl	(C$_6$H$_4$)	2	79 (**2e**)
5	5	*t*-bu	(C$_6$H$_4$)	1.5	80 (**2f**)
6	5	Bn	1-Me-(C$_6$H$_3$)	5	81 (**2g**)
7	5	Bn	2-OMe-(C$_6$H$_3$)	3	89 (**2h**)
8[c]	10	Bn	2-CF$_3$-(C$_6$H$_3$)	1.5	85 (**2i**)
9	5	Bn	3-Cl-(C$_6$H$_3$)	2	64 (**2j**)
10[c]	5	Bn	3-Me-(C$_6$H$_3$)	1	89 (**2k**)
11	5	Bn	3-F-(C$_6$H$_3$)	3	70 (**2l**)
12	10	Bn	3-CO$_2$Me-(C$_6$H$_3$)	24	60 (**2n**)
13	10	*i*-Pr	3-I-(C$_6$H$_3$)	12	71 (**2o**)
14[c]	10	Bn	4-Me-(C$_6$H$_3$)	3	83 (**2p**)

[a] Standard carbazole numbering. [b] Reaction with 1 equiv of AcOH. [c] Isolated yield after chromatography.

The reaction was also amenable to a range of groups on the aniline ring with varied electronic and steric properties (Table 2, entries 6–13). Importantly, the 3-iodo derivative (entry 13) smoothly forms the carbazole **2o** in good yield without compromising the C–I bond, highlighting the compatibility of this reaction with the functionality used in other metal-catalyzed coupling processes. Substitution on the aryl donor portion of the molecule was next tested (Table 3), and again it was found that the reaction tolerated a range of electronic and steric groups, providing the carbazoles in good to excellent yields under mild conditions.[9c]

During our scope studies we had noticed that electron-rich substrates reacted faster than electron-deficient molecules. Accord-

**Table 3.** Scope of C–H Bond Amination: Aryl-Ring Substituents

entry	catalyst loading, mol %	Ar (in 2)[a]	additive	time, h	yield, %[b]
1[c]	5	3-(OMe)-C$_6$H$_4$	–	4	85 (**2q**)
2	5	3-(Me)-C$_6$H$_4$	1 equiv of AcOH	1	86 (**2l**)[d]
3	10	3-(F)-C$_6$H$_4$	–	3	72 (**2m**)[e]
4	10	3-(Cl)-C$_6$H$_4$	1 equiv of AcOH	2	80 (**2k**)
5	10	3-(CO$_2$Me)-C$_6$H$_4$	1 equiv of AcOH	5	95 (**2n**)
6[f]	10	3-(NO$_2$)-C$_6$H$_4$	1 equiv of AcOH	36	72 (**2r**)
7	5	2-(OMe)-C$_6$H$_4$	–	4	81 (**2i**)
8	5	2-(CO$_2$Me)-C$_6$H$_4$	–	5	94 (**2s**)
9	5	4-(Me)-C$_6$H$_4$	1 equiv of AcOH	3	56 (**2o**)
10	5	4-(OMe)-C$_6$H$_4$	–	4	75 (**2f**)
11	20	α-C$_{10}$H$_6$	1 equiv of AcOH	3	63 (**2u**)

[a] Standard carbazole numbering. [b] Isolated yield after chromatography. [c] Reaction at 5 °C. [d] 6:1 mixture of C10 and C4 carbazole isomers. [e] 3:1 mixture of C10 and C4 carbazole isomers. [f] Reaction at 100 °C.

ingly, competition experiments between **1n** (R = CO$_2$Me) and **1q** (R = OMe) showed a preference for the formation of **2q** (R = OMe). This could support an electrophilic mechanism,[10] but it is possible that it could be the result of a stronger interaction of the more electron-rich C–H bond with the metal.[11,12]

To probe the structure of the carbopalladation complex, we prepared palladacycle **IIa** from amine **1a** and Pd(OAc)$_2$ in PhMe at room temperature. We anticipated that the palladacycle **IIa** would be dimeric;[7] however, X-ray diffraction revealed that the palladacycle **IIa** was a trinuclear complex, comprising two cyclopalladated aminobiphenyl **1a** units linked through bridging acetates to a third Pd(II) center (Scheme 2).[13]

Scheme 2. Isolation of a Trinuclear Carbopalladation Complex
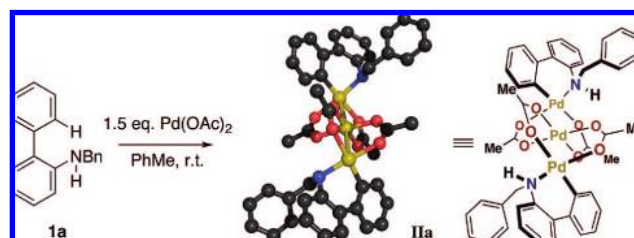
The existence and stability of **IIa** suggests that oxidation to Pd(IV) must promote reductive elimination; this is a rare example of C/N reductive elimination from a high oxidation state transition metal complex.[8] In confirming this, we found **IIa** can be smoothly converted to carbazole **2a** on treatment with PhI(OAc)$_2$ in PhMe. It is also possible that **IIa** breaks down to a monomeric species prior to oxidation. However, we observed that the complex **IIa** shows no crossover when mixed with 5 equiv of a different amine, suggesting that the complex is stable under *pseudo*-catalytic conditions. Furthermore, the oxidation of **IIa** does not proceed in highly coordinating solvents, such as DMSO, or in the presence of coordinating additives (pyridine). These solvents are known to break di- and trinuclear palladacycles to monomeric species. Taken together, these results indicate that the reaction does not proceed through a monomeric palladacycle and, more importantly, that a higher order complex is essential for catalytic activity and amination under such mild conditions.

Finally, we sought to test the amination reaction in more complex systems (Scheme 3). In particular, we were attracted to *N*-glycosyl carbazoles, due to the prevalence of this motif in a range of natural products.[4a] We were pleased to find that **1v** underwent smooth C−H bond amination to form carbazole **2v** in good yield. Despite the sensitivity and the steric encumbrance at the *N*-glycosyl linkage, the successful outcome demonstrates the potential for this C−H bond amination process in more challenging situations.

Scheme 3. Formation of *N*-Glycosyl Carbazoles
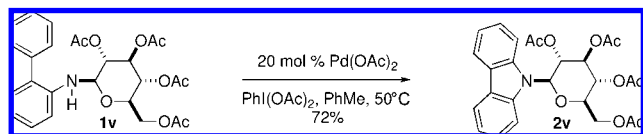
We also found that if we changed the oxidation system to I₂−PhI(OAc)₂,[8e] we were able to affect a tandem reaction wherein **1a** is first iodinated in the *para*-position to the electron-donating amino group, before undergoing C−H bond amination giving **2o**.[14] The product of this reaction can be further elaborated to **3** using a Suzuki cross coupling reaction allowing a facile method for the generation of highly functionalized carbazoles (Scheme 4).

Scheme 4. Applications of Pd(II)-Catalyzed C−H Bond Amination
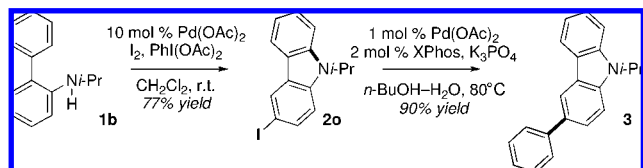
In summary, we have developed a new Pd(II)-catalyzed C−H bond amination reaction to form carbazoles, an important motif that is prevalent in a range of systems. The catalytic amination process operates under extremely mild conditions, has a broad substrate scope, and forms the carbazole products in good to excellent yields. Carbazoles possessing complex molecular architecture can also be formed using this reaction, highlighting its potential in natural product synthesis applications. Isolation of a trinuclear cyclopalladation complex suggests that the mechanism of the reaction proceeds through a Pd(II)/Pd(IV) manifold. More detailed mechanistic investigations are ongoing, and these results will be reported in due course. We are also investigating the development of an intermolecular C−H bond amination process using this concept.

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

References

(1) (a) Ullmann, F. *Ber.* **1903**, *36*, 2382. For reviews, see: (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett.* **2003**, *15*, 2428. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1043.

(2) For seminal reports, see: (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. (b) Guram, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (c) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215 For reviews, see: (e) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 699. (f) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (g) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(3) For recent examples, see: (a) Liegault, Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (b) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413. For review, see: (c) Knolker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4304.

(4) (a) Sànchez, C.; Mèndez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007. (b) Cheng, J.; Kamiya, K.; Kodama, I. *Cardiovasc. Drug Rev.* **2001**, *19*, 152. For a recent example, see: (c) Blouin, N; Michaud, A.; Gendron, D.; Wakim, D.; Blair, B.; Neagu-Plesu, R.; Belletete, M.; Durocher, G.; Tao, Y.; Leclerc, M. *J. Am. Chem. Soc.* **2008**, *130*, 732.

(5) C−H amination via nitrenes: (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378, and references therein. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (c) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (d) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (f) Smitrovitch, J. H.; Davies, I. W *Org. Lett.* **2004**, *6*, 533. For examples of allylic C−H aminations see: (g) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (h) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (i) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. For Cu-catalyzed aminations, see: (j) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (k) Hamada, T.; Ye, X; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(6) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Li, B.-J.; Tian, S.-L.; Fang, F.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1. (c) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (d) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603.

(7) For a recent review on palladacycles see Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527, and references therein.

(8) (a) For selected examples of reductive elimination of C-heteroatom bonds from Pd(IV), see: (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (b) Fu, Y.; Li, Z.; Liang, S.; Guo, Q.-X.; Liu, L. *Organometallics* **2008**, *27*, 3736. (c) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (d) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *27*, 1365. (e) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. For reductive elimination from Pt(IV), see: (f) Pawlikowski, A. V.; Getty, A. D.; Goldberg, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 10382.

(9) (a) See Supporting Information for more details. (b) No reaction is observed in the absence of Pd(OAc)₂. (c) AcOH improved yield of **2**.

(10) For electrophilic mechanism examples, see: (a) Parshall, G. W. *Acc. Chem. Res.* **1970**, *3*, 139. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. For C−H abstraction mechanism examples, see: (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (e) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

(11) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403. (b) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A *J. Am. Chem. Soc.* **2005**, *127*, 13754.

(12) For the monodeuterioamine *d*-**1a** we observed a kinetic isotope effect of 2.27; see Supporting Information for details.

(13) (a) Friedlein, F. K.; Kromm, K.; Hampel, F.; Gladysz, J. A. *Chem.−Eur. J.* **2006**, *12*, 5267. (b) Giri, R.; Liang, J.; Lei, J.; Li, J.; Wang, D.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Moyano, A.; Rosol, M.; Moreno, R. M.; Lopez, C.; Maestro, M. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1865. (d) Ukhin, L. Y.; Dolgopolova, N. A.; Kuz'mina, L. G.; Struchkov, Y. T. *J. Organomet. Chem.* **1981**, *210*, 263.

(14) We do not believe that this reaction proceeds through a directed Pd(II)-catalyzed iodination, followed by amination of the C−I bond. See : Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. Treatment of the corresponding iodo-biphenyl amine (**1o**) under the oxidative Pd(II) conditions affords the same product, **2o**, as seen in the tandem reaction.

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