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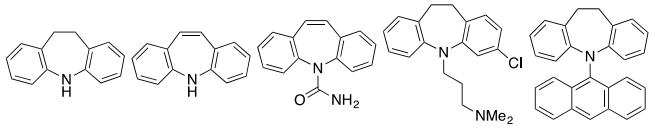
Palladium catalyzed *N*-Arylation of Iminodibenzyls and Iminostilbenes with Aryl and Hetero-Aryl Halides

Wenliang Huang,[a] and Stephen L. Buchwald*[a]

Abstract: Compounds containing the iminodibenzyl and iminostilbene ring systems are prevalent in medicinal targets and functional materials. Herein we report palladium catalyzed conditions for the *N*-arylation of these ring systems. This protocol could be applied to a variety of (hetero)aryl chloride and bromide substrates, including ones which are sterically hindered or those containing a variety of functional groups. Use of the fourth generation palladacycle precatalyst allowed good to excellent yields to be obtained using low palladium catalyst loadings (0.1 to 1 mol%).

Nitrogen-containing heterocyclic compounds are widespread substructures in compounds of interest to the biological and materials sciences.[1] As prevalent subclasses of these compounds, iminodibenzyls and iminostilbenes (dibenzo fused azepanes and azepines, respectively) occur in a variety of pharmaceutical agents, including those with antihistamine, analgesic, and antipsychotic properties.[2] Recently, their derivatives have also emerged as promising alternatives to diphenylamine, carbazole, and acridine-based compounds for use as emissive or host materials for organic light emitting diodes (OLEDs).[3] In some cases, the iminodibenzyl and iminostilbene analogues showed enhanced thermostability or photophysical properties relative to other diarylamino based materials.[3a, 3b] Hence, general methods for the preparation of these functionalized ring systems would be of considerable value to investigators in these fields.



Several palladium-catalyzed methods to construct the iminodibenzyl or iminostilbene core have been reported, including two-component cyclizations of amines[4] or anilines[5] with 2,2'-dihalostilbene or dihalodibenzyl precursors, and one-pot cascade reactions using single or dual-catalyst systems.[6] However, two component cyclization approaches require starting materials whose preparation are often nontrivial, while cascade processes are generally narrower in scope and functional group tolerance, or furnish the desired product in only moderate yield, limiting the applicability of these methods. On the other hand, only a handful of methods for the functionalization of the preexisting ring system have been reported. A few examples of the palladium catalyzed *N*-arylation of iminodibenzyl and iminostilbene have appeared sporadically in the literature, generally with unfunctionalized aryl halide substrates, and high catalyst loadings are frequently employed (2-5 mol% Pd).[3a, 3e, 3i, 7] Alternatively, Ullmann-type conditions for *N*-arylation requiring a stoichiometric copper promoter and high temperatures have also been utilized.[3a]

In the course of investigating the photophysical properties of iminodibenzyls and iminostilbenes as candidates for electroluminescent materials, we required the preparation of a series of *N*-arylated analogues that covered a range of steric and electronic profiles. We therefore pursued the development of a general palladium-catalyzed method for the *N*-arylation of these heterocyclic compounds. Here, we present general conditions for the *N*-arylation of iminodibenzyls and iminostilbenes resulting from these studies. Notably, heteroaryl halides and sterically hindered aryl halides, including ones that are 2,6-disubstituted, are readily tolerated by this protocol, and catalyst loadings of 0.1 mol% are sufficient in most cases.

At the outset of our study, we selected 2,6-dimethylbromobenzene and iminodibenzyl as model substrates because of the potential challenges in forming a bond between sterically hindered starting materials of this nature.[5,8] The reaction optimization process is summarized in Table 1. We first evaluated a series of dialkylbiarylphosphine ligands,[9] **L1** to **L5** using $Pd_2(dba)_3$ as the palladium source and NaO*t*Bu as the base (Entry 1-5). Out of the ligands explored, RuPhos (**L5**) afforded the best result. This is consistent with our previous finding that RuPhos is a suitable ligand for the arylation of secondary anilines.[10] We then examined the effect of different bases on the reaction outcome (see the Supporting Information for the complete tabulation of results) and found that use of $Li(NSiMe_3)_2$ resulted in improved reactivity (Entry 6). Finally, we studied the impact of palladium sources. The use of the fourth generation palladacycle precatalyst (**Pd-L5-G4**), which provides efficient entry into LPd(0), was found to be most effective and allowed a low catalyst loading of 0.1 mol% with no need for additional ligand (Entry 9). In comparison, the third generation precatalyst (**Pd-L5-G3**) provided significantly lower yield (Entry 8). This finding could be rationalized by the generation of carbazole as a byproduct in the activation of the **Pd-L5-G3**,[11] which could competitively bind to palladium when a weakly nucleophilic amine like iminodibenzyl is used as a coupling partner. The fourth generation precatalyst that our lab has developed avoids this problem, since *N*-methylcarbazole is generated instead.[12]

Table 1. Optimization of N-arylation of iminodibenzyl (**1**) and iminostilbene (**2**).[a]

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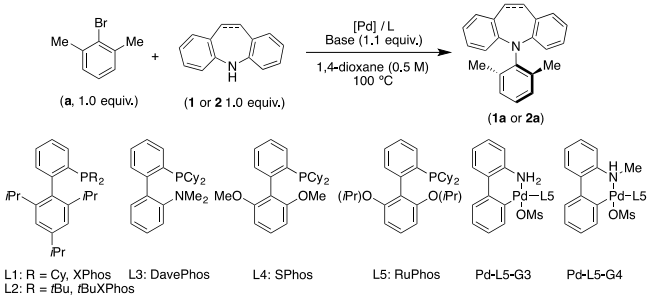


Entry	[Pd] (mol%)	L (mol%)	Base	GC Yield
1	$Pd_2(dba)_3$ (1%)	L1 (2%)	NaO*t*Bu	56%
2	$Pd_2(dba)_3$ (1%)	L2 (2%)	NaO*t*Bu	2%
3	$Pd_2(dba)_3$ (1%)	L3 (2%)	NaO*t*Bu	10%
4	$Pd_2(dba)_3$ (0.5%)	L4 (1%)	NaO*t*Bu	52%
5	$Pd_2(dba)_3$ (0.5%)	L5 (1%)	NaO*t*Bu	64%
6	$Pd_2(dba)_3$ (0.5%)	L5 (1%)	$Li(NSiMe_3)_2$	96%
7	$Pd_2(dba)_3$ (0.1%)	L5 (0.2%)	$Li(NSiMe_3)_2$	88%
8	Pd-L5-G3 (0.1%)	--	$LiN(SiMe_3)_2$	82%
9	Pd-L5-G4 (0.1%)	--	$Li(NSiMe_3)_2$	96%
10[b]	Pd-L5-G4 (0.1%)	--	$Li(NSiMe_3)_2$	92%

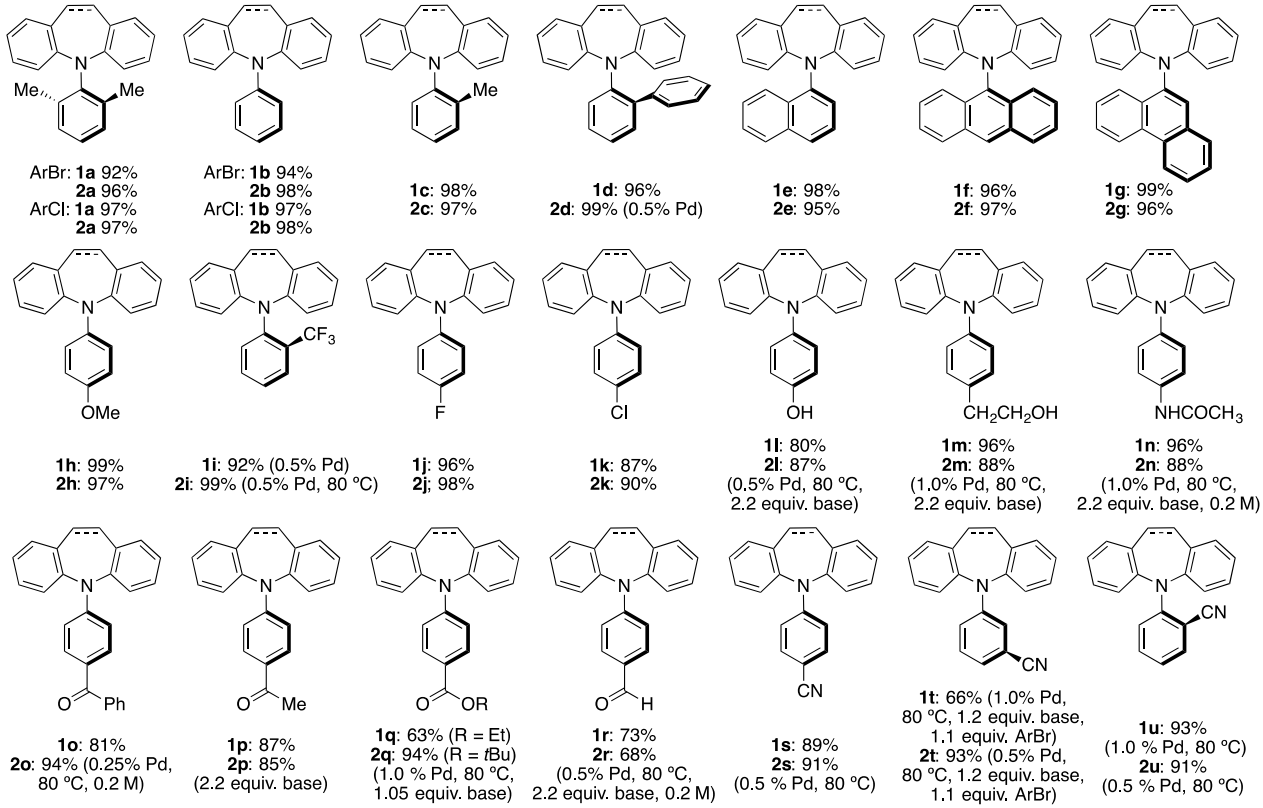
[a] Reaction conditions: 2-bromo-*m*-xylene and iminodibenzyl (1 mmol each), base (1.1 mmol), 1,4-dioxane (2 mL), 100 ºC, 16 h. [b] Using iminostilbene as nucleophile.

The conditions shown in Entries 9 and 10 of Table 1 were adopted as the standard reaction conditions for exploration of the substrate scope of this process. The scope of the transformation with respect to aryl halide was found to be broad (Table 2). In most cases, the reactivity of iminodibenzyl (**1**, products labeled as **1a**-**u**) and iminostilbene (**2**, products labeled as **2a**-**u**) were comparable. For the sake of brevity, we will only mention the iminodibenzyl product in the following discussion unless a substantial difference was observed. Both electron rich (**1h**) and electron poor (**1i**) aryl bromides underwent cross coupling in excellent yield. Aryl bromides containing a variety of *ortho* substituents, including methyl (**1a**, **1c**), phenyl (**1d**), trifluoromethyl (**1i**) and cyano (**1u**), also represented excellent substrates. Furthermore, high yields were maintained when aryl chloride was used in place of the aryl bromide under otherwise identical reaction conditions (**1a**, **1b**). However, when 1-chloro-4-bromobenzene was used as the substrate, *N*-arylation took place exclusively at the aryl bromide substituent (**1k**). Polycyclic aryl bromides also provided high yields under standard conditions (**1e**-**g**). Compound **1f**, prepared in excellent yield (96%) employing the current method, has been shown to exhibit interesting photoluminescent properties as a consequence of its distorted framework.[3i] In comparison, its previous synthesis from identical starting materials using **PEPPSI-IPr** as the Pd precatalyst (5 mol%) provided the coupling product in only 47% yield. Preliminary results showed that compounds **1e**-**f** and **2e**-**f** emitted blue light under UV-light excitation and could be potential luminescent materials.

Subsequently, we investigated the functional group tolerance of this process. Although moderate to excellent yields could be achieved for functionalized substrates, higher catalyst loadings (up to 1 mol%) were sometimes required. In addition, a lower temperature (80 ºC) was sometimes optimal for substrates containing sensitive functional groups (**1l**-**1n**, **1q**-**1u**). In some cases, this protocol was found to be applicable to unprotected substrates bearing acidic protons, such as those containing phenol, alcohol, or amide functional groups, as long as an additional equivalent of base was added (2.2 equiv. $Li(NSiMe_3)_2$ for **1l**-**1n**). Several additional carbonyl functional groups, including a diaryl ketone, a methyl ketone, an ester, and an aldehyde, could also be handled, affording the coupled product in moderate to excellent yield (63-94% yield). For aryl bromides bearing an ester group, transformation of the ester to an amide could compete with palladium catalyzed C-N cross coupling. When iminodibenzyl is used as the amine coupling partner, the reaction rate of C-N cross coupling is significant faster than amide formation and thus an ethyl ester could be tolerated (**1q**). For iminostilbene, it was necessary to use a *t*-butyl ester to obtain a high yield of the desired C-N coupled product (**2q**). When an aldehyde was present, additional base (2.2 equiv. $Li(NSiMe_3)_2$) was likewise necessary to achieve good yield (**1r**). Although no acidic proton is present, it is possible that the first equivalent of base is consumed through addition into the aldehyde to form a hemiaminal. In addition to its versatility in organic synthesis, the nitrile group has been incorporated in many OLED materials[13] because of its electron withdrawing character and ability to extend the π-system of the molecule.[14] Thus, aryl bromides bearing *ortho*-, *meta*-, and *para*-nitrile substituents were explored and were all found to be competent substrates, providing the respective product in moderate to excellent yield (66-93%).

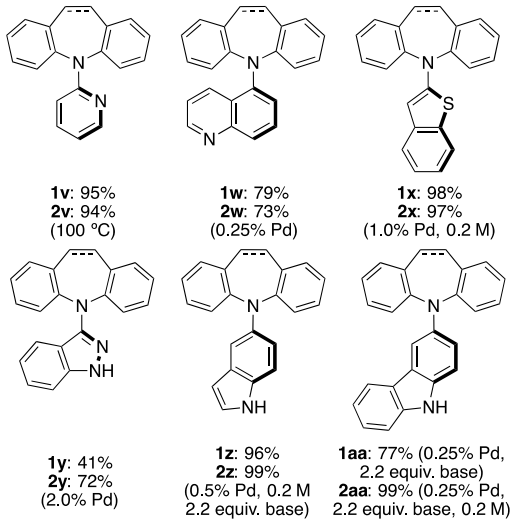
Heteroaryl groups are common structures in both pharmaceutical drugs and organic luminescent materials.[1, 15] and were thus explored as coupling partners (Table 3). Heteroaryl bromides, such as 2-bromopyridine and 5-bromoquinoline, were both excellent substrates, affording the desired products in high yield under low catalyst loading (**1v**, **1w**). In addition, the coupling of 5-membered heteroaryl bromides, including 2-bromobenzo[*b*]thiophene and 3-bromo-1*H*-indazole, was also possible and afforded the arylation products (**1x**, **1y**) in high and moderate yields, respectively. Unprotected 5-bromoindole and 3-bromocarbazole similarly provided high yield of the *N*-arylated product (**1z**, **1aa**) with relatively low catalyst loading (0.25 to 0.5 mol% Pd) when additional base (2.2 equiv. $LiN(SiMe_3)_2$) was used. The selective *N*-arylation of iminodibenzyl and iminostilbene in the presence of indole or carbazole suggests that the seven-membered *N*-heterocycles are better nucleophiles compared to the five-membered ones under current reaction conditions. The amination at the 3-position of carbazole provides access to another potentially useful scaffold for the synthesis of OLED materials.[16]

Table 2. Substrate scope of aryl halide for the N-arylation of iminodibenzyl (**1**) and iminostilbene (**2**).[a]



[a] Reaction conditions (unless specified in parenthesis): aryl halide (1 mmol) and iminodibenzyl (**1**) or iminostilbene (**2**) (1 mmol), $Li(NSiMe_3)_2$ (1.1 mmol), 0.1 mol% **Pd-L5-G4**, 1,4-dioxane (2.0 mL), 100 ºC, 16 h. Yields are isolated yields after column chromatography, average of two runs (same for Table 3 and 4).

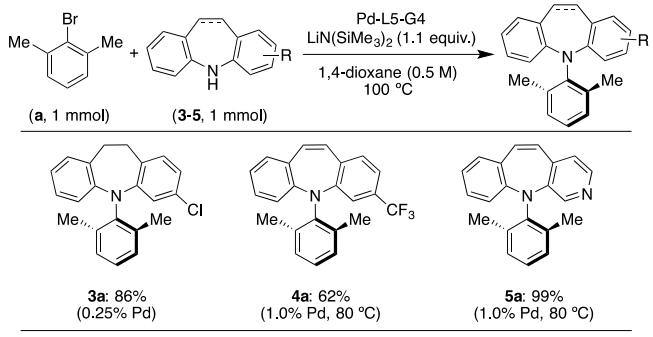
Table 3. Substrate scope of hetero-aryl bromide.[a]



[a] Reaction conditions (unless specified in parenthesis): hetero-aryl halide (1 mmol) and iminodibenzyl (**1**) or iminostilbene (**2**) (1 mmol), $Li(NSiMe_3)_2$ (1.1 mmol), 0.1 mol% **Pd-L5-G4**, 1,4-dioxane (2.0 mL), 80 ºC, 16 h.

In addition, we briefly studied the reactivity of functionalized iminodibenzyl and iminostilbene starting materials, which are present in a number of pharmaceutical products (Table 4).[2f, 4a, 6c] *N*-arylation of 3-chloroiminodibenzyl (**3**) with 2,6-dimethylbromobenzene provided the C-N coupled product in high yield (86%) at low palladium loading (0.25 mol%) without competitive amination of the aryl chloride (**3a**). The coupling of 3-trifluoromethyliminostilbene required a higher catalyst loading (1 mol%) to give moderate yield (62%) presumably due to its reduced nucleophilicity (**4a**). Notably, 3-azaiminostilbene (**5**) underwent coupling to deliver the *N*-arylation product in quantitative yield (**5a**). These results suggest that this protocol may be applicable to the *N*-arylation of other functionalized benzo-fused ring systems of interest in organic luminescent materials and pharmaceutical drugs.

Table 4. Substrate scope of nucleophiles.[a]



[a] Reaction conditions (unless specified in parenthesis): 2-bromo-*m*-xylene and nucleophile (**3**, **4**, or **5**) (1 mmol each), $Li(NSiMe_3)_2$ (1.1 mmol), 0.1 mol% **Pd-L5-G4**, 1,4-dioxane (2.0 mL), 100 ºC, 16 h.

In summary, we have developed an efficient *N*-arylation method for iminodibenzyls and iminostilbenes by employing a RuPhos-based fourth generation palladacycle precatalyst. Due to the importance of these two heterocyclic systems to researchers in medicinal chemistry and organic materials, this new general protocol should serve as a versatile synthetic tool that complements currently available methods. Furthermore, the operational simplicity of the protocol, in addition to the commercial availability of the precatalyst and low catalyst loadings required, are features that render the method reported here practical for researchers in academic and industrial settings.

Experimental Section

Experimental procedures and characterization data including NMR spectra are included in supporting information.

Acknowledgements

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References

[1] a) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874; b) D. Chen, S.-J. Su, Y. Cao, *J. Mater. Chem. C* **2014**, *2*, 9565.
[2] a) F. Albani, R. Riva, A. Baruzzi, *Pharmacopsychiat.* **1995**, *28*, 235; b) T. Okuma, A. Kishimoto, *Psychiatry Clin. Neurosci.* **1998**, *52*, 3; c) A. F. Ambrosio, P. Soares-da-Silva, *Neurochem. Res.* **2002**, *27*, 121; d) R. M. A. Hirschfeld, S. Kasper, *Int. J. Neuropsychoph.* **2004**, *7*, 507; e) N. M. Tsankova, O. Berton, W. Renthal, A. Kumar, R. L. Neve, E. J. Nestler, *Nat. Neurosci.* **2006**, *9*, 519; f) P. K. Gillman, *Br. J. Pharmacol.* **2007**, *151*, 737; g) J. M. Gomez-Arguelles, R. Dorado, J. M. Sepulveda, R. Huet, F. G. Arrojo, E. Aragon, A. Herrera, C. Trron, B. Anciones, *J. Clin. Neurosci.* **2008**, *15*, 516; h) V. Krishnan, E. J. Nestler, *Nature* **2008**, *455*, 894; i) D. Lednicer, *Strategies for Organic Drugs Synthesis and Design*, 2nd ed., Wiley, Hoboken, NJ, **2009**; j) H. Singh, N. Gupta, P. Kumar, S. K. Dubey, P. K. Sharma, *Org. Process Res. Dev.* **2009**, *13*, 870; k) M. Tian, A. Abdelrahman, S. Weinhausen, S. Hinz, S. Weyer, S. Dosa, A. El-Tayeb, C. E. Müller, *Bioorg. Med. Chem.* **2014**, *22*, 1077.
[3] a) B. E. Koene, D. E. Loy, M. E. Thompson, *Chem. Mater.* **1998**, *10*, 2235; b) D. F. O'Brien, P. E. Burrows, S. R. Forrest, B. E. Koene, D. E. Loy, M. E. Thompson, *Adv. Mater.* **1998**, *10*, 1108; c) T.-Y. Wu, Y. Chen, *J. Polym. Sci. A Polym. Chem.* **2002**, *40*, 3847; d) M.-X. Yu, J.-P. Duan, C.-H. Lin, C.-H. Cheng, Y.-T. Tao, *Chem. Mater.* **2002**, *14*, 3958; e) C.-T. Chen, J.-S. Lin, M. V. R. K. Moturu, Y.-W. Lin, W. Yi, Y.-T. Tao, C.-H. Chien, *Chem. Commun.* **2005**, 3980; f) T.-Y. Wu, M.-H. Tsao, F.-L. Chen, S.-G. Su, C.-W. Chang, H.-P. Wang, Y.-C. Lin, W.-C. Ou-Yang, I.-W. Sun, *Int. J. Mol. Sci.* **2010**, *11*, 329; g) Y.-H. Yu, C.-H. Huang, J.-M. Yeh, P.-T. Huang, *Org. Electron.* **2011**, *12*, 694; h) Y. Suzuki, N. Fukui, K. Murakami, H. Yorimitsu, A. Osuka, *Asian J. Org. Chem.* **2013**, *2*, 1066; i) S. Sasaki, K. Hattori, K. Igawa, G.-i. Konishi, *J. Phys. Chem. A* **2015**, *119*, 4898; j) S. Sasaki, G. P. C. Drummen, G.-i. Konishi, *J. Mater. Chem. C* **2016**, *4*, 2731.
[4] a) N. Božinović, I. Opsenica, B. A. Šolaja, *Synlett* **2013**, *24*, 49; b) H. Christensen, C. Schjøth-Eskesen, M. Jensen, S. Sinning, H. H. Jensen, *Chem. Eur. J.* **2011**, *17*, 10618.
[5] X. Zhang, Y. Yang, Y. Liang, *Tetrahedron Lett.* **2012**, *53*, 6406.
[6] a) D. Tsvelikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14048; b) N. Della Ca, G. Maestri, M. Malacria, E. Derat, M. Catellani, *Angew. Chem.* **2011**, *123*, 12465; *Angew. Chem. Int. Ed.* **2011**, *50*, 12257; c) J. Tsoung, J. Panteleev, M. Tesch, M. Lautens, *Org. Lett.* **2014**, *16*, 110.
[7] a) P. D. Thornton, N. Brown, D. Hill, B. Neuenswander, G. H. Lushington, C. Santini, K. R. Buszek, *ACS Combinatorial Science* **2011**, *13*, 443; b) K. H. Chung, C. M. So, S. M. Wong, C. H. Luk, Z. Zhou, C. P. Lau, F. Y. Kwong, *Synlett* **2012**, *2012*, 1181.
[8] Y. Nakayama, N. Yokoyama, H. Nara, T. Kobayashi, M. Fujiwhara, *Adv. Synth. Catal.* **2015**, *357*, 2322.
[9] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
[10] a) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.
[11] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916.
[12] N. C. Bruno, N. Niljianskul, S. L. Buchwald, *J. Org. Chem.* **2014**, *79*, 4161.
[13] a) T. Nakagawa, S.-Y. Ku, K.-T. Wong, C. Adachi, *Chem. Commun.* **2012**, *48*, 9580; b) G. Méhes, H. Nomura, Q. Zhang, T. Nakagawa, C. Adachi, *Angew. Chem.*, **2011**, *124*, 11473; *Angew. Chem. Int. Ed.* **2012**, *51*, 11311; c) H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, *492*, 234; d) Y. Tao, K. Yuan, T. Chen, P. Xu, H. Li, R. Chen, C. Zheng, L. Zhang, W. Huang, *Adv. Mater.* **2014**, *26*, 7931; e) A. Chihaya, *Jpn. J. Appl. Phys.* **2014**, *53*, 060101; f) T. Nishimoto, T. Yasuda, S. Y. Lee, R. Kondo, C. Adachi, *Mater. Horiz.* **2014**, *1*, 264; g) B. Li, H. Nomura, H. Miyazaki, Q. Zhang, K. Yoshida, Y. Suzuma, A. Orita, J. Otera, C. Adachi, *Chem. Lett.* **2014**, *43*, 319.
[14] a) N. Akai, S. Kudoh, M. Nakata, *Chem. Phys. Lett.* **2003**, *371*, 655; b) A. Yassar, F. Demanze, A. Jaafari, M. El Idrissi, C. Coupry, *Adv. Funct. Mater.* **2002**, *12*, 699; c) K. R. Justin Thomas, M. Velusamy, J. T. Lin, Y. T. Tao, C. H. Chuen, *Adv. Funct. Mater.* **2004**, *14*, 387.
[15] a) S. Hotta, in *Handbook of Thiophene-Based Materials*, John Wiley & Sons, Ltd, **2009**, pp. 477; b) I. F. Perepichka, D. F. Perepichka, H. Meng, in *Handbook of Thiophene-Based Materials*, John Wiley & Sons, Ltd, **2009**, pp. 695.
[16] S. Hirata, Y. Sakai, K. Masui, H. Tanaka, S. Y. Lee, H. Nomura, N. Nakamura, M. Yasumatsu, H. Nakanotani, Q. Zhang, K. Shizu, H. Miyazaki, C. Adachi, *Nat. Mater.* **2015**, *14*, 330.

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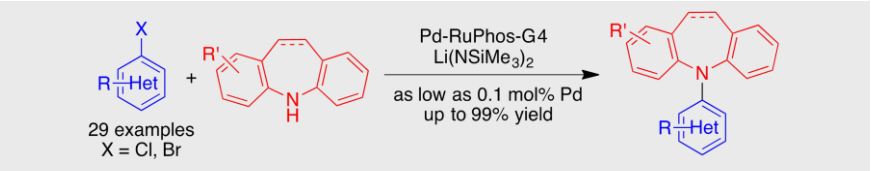

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Palladium catalyzed *N*-Arylation of Iminodibenzyls and Iminostilbenes with Aryl and Hetero-Aryl Halides

Crowded but Coupled! A general protocol of *N*-arylation of iminodibenzyls and iminostilbenes is reported for a variety of hindered and heterocyclic aryl halide substrates at low loadings of palladacycle precatalyst. This methodology has wide substrate scope and excellent functional group tolerance and allows access to products of relevance to the medicinal and materials sciences.

Keywords: Buchwald-Hartwig Amination • Palladium Pre-catalyst • Steric-Hindered Aryl Halide • Iminodibenzyl and iminostilbene • OLED