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Palladium-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones with Indoles: Synthesis of *N*-Vinylindoles

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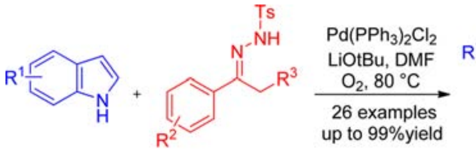
ABSTRACT



A general and efficient palladium-catalyzed oxidative cross-coupling reaction of *N*-tosylhydrazones with indoles providing *N*-vinylindoles has been developed. The reaction proceeds smoothly with various indoles and *N*-tosylhydrazones in a stereocontrolled manner, and a wide variety of *N*-vinylindoles were obtained up to 99% yields for 26 examples.

In recent years, intense efforts have been devoted to the direct functionalization of indole cores for the synthesis of active indole derivatives owing to their ubiquity in natural products, pharmaceuticals, and functional material.[1] In particular, *N*-vinylindoles are of increasing importance in material science as monomers for the synthesis of poly(*N*-vinylindoles),[2] which can be used as semiconductors and photosensitive materials.[2a,e] Among the various synthetic strategies to construct *N*-vinylindoles, the transition metal catalyzed cross-coupling reaction of indoles with prefunctionalized alkenes, such as vinyl triflates[3a] and vinyl halides,[3b,c] is a powerful and reliable method.[3] A straightforward and atom-efficient approach was developed by Li and co-workers via the gold(III)-catalyzed tandem reaction of *o*-alkynylanilines with terminal alkynes, affording 2-substituted *N*-vinylindole scaffolds in moderate yields.[4a] More recently, the hydroamination of alkynes was reported by Verma and co-workers and gave *N*-vinylindoles in a mixture of *Z*- and *E*-forms.[4b−d] Acid-promoted condensations of alkyl or aryl α-branched aldehydes with indole derivatives could provide *N*-vinylindoles.[5] Although these protocols provided access to *N*-vinylindoles, the narrow scope of substrates, high cost, and harsh reaction conditions have limited their applications. Considering the importance of *N*-vinylindoles and the drawbacks of the existing methods, the exploration and development of an alternative method to construct such a desirable framework is still attractive.

On the other hand, Barluenga's first employment of *N*-tosylhydrazones in the Pd-catalyzed cross-coupling reaction in 2007, which proceeded via the Bamford−Stevens intermediate,[6,7] has significantly reinvigorated the use of

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(1) For reviews on indole chemistry, see: (a) Sundberg, R. L. *Indoles*; Academic: London, 1996. (b) Hegedus, B. L. S. *Angew. Chem., Int. Ed.* **1988**, *27*, 1113. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673. (f) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (g) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 215. (h) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(2) (a) Brustolin, F.; Castelvetro, V.; Ciardelli, F.; Ruggeri, G.; Colligiani, A. *J. Polym. Sci., A: Polym. Chem.* **2001**, *39*, 253. (b) Oshiro, Y.; Shirota, Y.; Mikawa, H. *J. Polym. Sci. Polym. Chem. Ed.* **1974**, *12*, 2199. (c) Priola, A.; Gatti, G.; Cesca, S. *Makromol. Chem.* **1979**, *180*, 1. (d) Gipstein, E.; Hewett, W. A. *Macromolecules* **1969**, *2*, 82. (e) Maki, Y.; Mori, H.; Endo, T. *Macromolecules* **2007**, *40*, 6119.

(3) (a) Ondrus, M. M. A. E. *J. Org. Chem.* **2005**, *70*, 8638. (b) Liao, Q.; Wang, Y.; Zhang, L.; Xi, C. *J. Org. Chem.* **2009**, *74*, 6371. (c) Artyom, Y.; Lebedev, V. V. I; Denis, N.; Kazyul'kin; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, No. 4, 623. (d) Bogdal, D.; Jaskot, K. *Synth. Commun.* **2000**, *30*, 3341. (e) Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2007**, *8*, 1318.

(4) (a) Zhang, Y. H.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627. (b) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *13*, 1630. (c) Joshi, M.; Tiwari, R.; Verma, A. K. *Org. Lett.* **2012**, *14*, 1106. (d) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 5633.

(5) Fridkin, G.; Boutard, N.; D. Lubell, W. *J. Org. Chem.* **2009**, *74*, 5603.

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readily available *N*-tosylhydrazones, which were derived from the corresponding aldehydes or ketones, as the precursors of *in situ*-generated nonstabilized diazo compounds in the formation of C−C,[8] C−O,[9] C−P,[10] C−S,[11] C−B,[12] and C−N[13] bonds through both metal-catalyzed and metal-free processes.[14] Migratory insertion involving a palladium carbene was proposed to constitute the key step in these processes.[15] Although impressive progress has been achieved, however, to the best of our knowledge, C−N bond formation using *N*-tosylhydrazone as a carbonyl surrogate has been rarely reported.[13] Based on that, we report herein a novel approach to *N*-vinylindoles via Pd-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with indoles.

The condensation of indole **1a** with *N*-tosylhydrazone **2a** was initially chosen as a model reaction to screen the reaction parameters. The desired product **3a** was obtained in 56% yield using 10 mol % $Pd(OAc)_2/PPh_3$ as a catalyst, 3.0 equiv of LiOtBu as a base, in toluene at 110 °C (Table 1, entry 1). Inspired by the preliminary results, the solvents were examined first (entries 1−4). *N,N*-Dimethyl formamide (DMF) gave unparalleled performance in this reaction, providing the desired product in 82% yield (entry 3). When the loading of catalyst was reduced to 5 mol %, the product **3a** was afforded in 80% yield (entry 5). While, complete inactivity of this reaction system was observed in the absence of the palladium acetate (entry 6). The base and the reaction temperature are critical for this transformation. Of the temperature tested, 80 °C appeared to be the most favorable (entry 5 vs 7). Whereas, the yield was decreased to 75% by continuous lowering of the temperature to 60 °C (entry 7 vs 8). Further fine-tuning of the reaction conditions has revealed that LiOtBu was superior to other inorganic bases, such as K_2CO_3, NaOAc, and KOtBu (entries 7, 10−13). The yield was not improved significantly by using $Pd(PPh_3)_2Cl_2$ as a catalyst instead of $Pd(OAc)_2$ in the presence of 10 mol % PPh_3 (entry 13 vs 14). However, the yield of **3a** could reach 94% without adding PPh_3 (entry 15). Interestingly, the reaction proceeded to completion within 36 h when 2.5 mol % of $Pd(PPh_3)_2Cl_2$ was loaded and gave a 92% isolated yield (entry 17). The controlled experiments were carried out under air or N_2, which led to lower yields of **3a** (entries 19, 20). After additional evaluations of palladium catalysts, bases, temperatures, and catalyst loadings, a combination of **1a**:**2a** = 1:1.5, 5 mol % $Pd(PPh_3)_2Cl_2$, and 2.0 equiv of LiOtBu in DMF at 80 °C were found to be optimal, and **3a** was isolated in 99% yield within 4 h (entry 16).

With the optimized reaction conditions established (Table 1, entry 16), the scope of the substrates for this reaction was investigated. As shown in Scheme 1, this catalytic system exhibited highly catalytic activity for a large range of *N*-tosylhydrazones and indoles and afforded the main products **3** in up to 99% yields for 26 examples. A wide variety of functional groups including nitro, halogens, ether, aryl, and trifloromethyl groups were tolerated under the optimal reaction conditions. *N*-Tosylhydrazones with both electron-donating and -withdrawing substituents were compatible with this reaction system, providing the corresponding coupling products in good to excellent yields (87−99%, Scheme 1, **3a**−**g**). This reaction was not affected significantly by the steric hindrance in *N*-tosylhydrazones. The variation of substituents at the *ortho*, *meta*, and *para* position in *N*-tosylhydrazones could afford the desired products in 92−96% yields (**3b**, **3h**, **3i**). Tosylhydrazones derived from 1-(naphthalen-2-yl) ethanone and dihydronaphthalen-1(2*H*)-one were also good partners for this transformation. The desired products **3k** and **3l** were obtained in 92% and 91% yields, respectively.

Additionally, nonterminal olefins **3m**, **3n**, and **3r** could be obtained in 99%, 94%, and 83% yields, respectively. Normally, the substrates with a halogen easily undergo the arylation reaction with *N*-tosylhydrazones to afford biaryl derivatives.[6,8g−j] To our delight, the presence of halides on the aromatic ring of *N*-tosylhydrazones did not interfere with the formation of the desired products (**3b**−**d**, **3h**−**i**, **3o**), which provided opportunities for further synthetic elaboration. The substrate scope could be extended to *N*-tosylhydrazone derived from 1-(2,4-dichlorophenyl) ethanone to

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(6) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587.

(7) (a) Adlingto, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55. (b) Bamford, W. R.; Stevens, T. S. *J. Am. Chem. Soc.* **1952**, 4735. (c) Fulton, J. R.; Aggarwal, V. K.; Vicente, J. de. *Eur. J. Org. Chem.* **2005**, *8*, 1479.

(8) For seleted examples, see: (a) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856. (b) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494. (c) Zhou, L.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 922. (d) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5953. (e) Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2012**, *134*, 5742. (f) Zhao, X.; Wu, G. J.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (g) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2008**, *14*, 4792. (h) Brachet, E.; Hamze, A.; Peyrat, J.-F.; Brion, J.-D.; Alami., M. *Org. Lett.* **2010**, *12*, 4042. (i) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (j) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (k) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931.

(9) (a) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4993. (b) Aggarwal, V. K.; Patel, M.; Studley, J. *Chem. Commun.* **2002**, *14*, 1514. (c) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430. (d) Zhou, A.; Wu, L.; Li, D.; Chen, Q.; Zhang, X.; Xia, W. *Chin. J. Chem.* **2012**, *30*, 1862.

(10) (a) Wu, L.; Zhang, X.; Chen, Q. Q.; Zhou, A. K. *Org. Biomol. Chem.* **2012**, *10*, 7859. (b) Miao, W.; Gao, Y.; Li, X.; Gao, Y.; Tang, G.; Zhao, Y. *Adv. Synth. Catal.* **2012**, *354*, 2659. (c) Chen, Z.-S.; Zhou, Z.-Z.; Hua, H.-L.; Duan, X.-H.; Luo, J.-Y.; Wang, J.; Zhou, P.-X.; Liang, Y.-M. *Tetrahedron* **2013**, *69*, 1065.

(11) (a) Ding, Q.; Cao, B.; Yuan, J.; Liu, X.; Peng, Y. *Org. Biomol. Chem.* **2011**, *9*, 748. (b) Li, Y.; Huang, Z.; Wu, X.; Xu, P.-F.; Jin, J.; Zhang, Y.; Wang, J. *Tetrahedron* **2012**, *68*, 5234. (c) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Eur. J. Org. Chem.* **2011**, *8*, 1520. (d) Feng, X. W.; Wang, J.; Zhang, J.; Yang, J.; Wang, N.; Yu, X. Q. *Org. Lett.* **2010**, *12*, 4408.

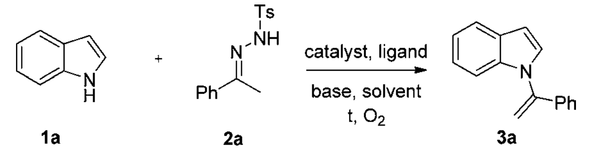
(12) Li, H.; Wang, L.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2943.

(13) (a) Hamze, A.; Tréguier, B.; Brion, J. D.; Alami, M. *Org. Biomol. Chem.* **2011**, *9*, 6200. (b) Barluenga, J.; Tomás-Gamasa, M.; Valdés, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5950.

(14) For recent reviews on the use of *N*-tosylhydrazones, see: (a) Shao, Z. H.; Zhang, H. B. *Chem. Soc. Rev.* **2012**, *41*, 560. (b) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (c) Zhang, Y.; Wang, J. *Top. Curr. Chem.* **2012**, *327*, 239. (d) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486.

(15) (a) Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2363. (b) Albeniz, A. C.; Espinet, P.; Manrique, R.; Perez-Mateo, A. *Chem.—Eur. J.* **2005**, *11*, 1565. (c) Albéniz, A. C.; Espinet, P.; Pérez-Mateo, A.; Nova, A.; Ujaque, G. *Organometallics* **2006**, *25*, 1293.

Table 1. Optimization of Reaction Conditions[a]



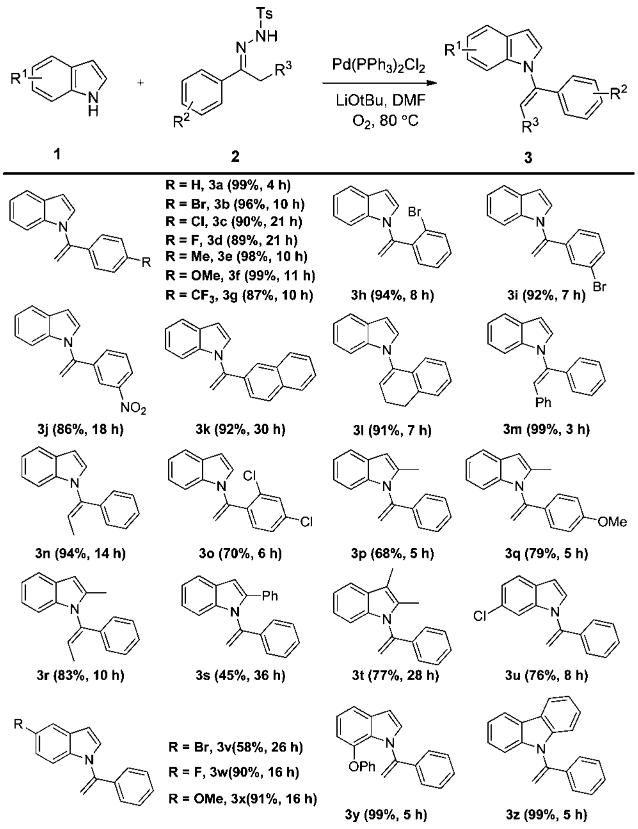
entry	catalyst (mol %)	solvent	*t* (°C)	base (equiv)	yield (%)[c]
1	$Pd(OAc)_2$ (10)	toluene	110	LiOtBu (3.0)	56
2	$Pd(OAc)_2$ (10)	1,4-dioxane	110	LiOtBu (3.0)	58
3	$Pd(OAc)_2$ (10)	DMF	110	LiOtBu (3.0)	82
4	$Pd(OAc)_2$ (10)	DMSO	110	LiOtBu (3.0)	20
5	$Pd(OAc)_2$ (5)	DMF	110	LiOtBu (3.0)	80
6	–	DMF	110	LiOtBu (3.0)	0
7	$Pd(OAc)_2$ (5)	DMF	80	LiOtBu (3.0)	91
8	$Pd(OAc)_2$ (5)	DMF	60	LiOtBu (3.0)	75
9[b]	$Pd(OAc)_2$ (5)	DMF	80	LiOtBu (3.0)	77
10	$Pd(OAc)_2$ (5)	DMF	80	KOtBu (3.0)	78
11	$Pd(OAc)_2$ (5)	DMF	80	NaOtBu (3.0)	72
12	$Pd(OAc)_2$ (5)	DMF	80	K_2CO_3 (3.0)	70
13	$Pd(OAc)_2$ (5)	DMF	80	NaOAc (3.0)	89
14	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	LiOtBu (3.0)	86
15[b]	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	LiOtBu (3.0)	94
16[b]	**$Pd(PPh_3)_2Cl_2$ (5)**	**DMF**	**80**	**LiOtBu (2.0)**	**99**
17[b]	$Pd(PPh_3)_2Cl_2$ (2.5)	DMF	80	LiOtBu (2.0)	92
18[b,d]	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	LiOtBu (2.0)	93
19[b,e]	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	LiOtBu (2.0)	85
20[b,f]	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	LiOtBu (2.0)	42

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), solvent (2 mL), PPh_3 (10 mol %), under O_2. [b] Without ligand. [c] Isolated yields based on **1a**. [d] **1a**:**2a** = 1:1.2. [e] Under air atmosphere. [f] Under N_2. DMSO = Dimethyl sulfoxide.

deliver **3o** with reasonable yields (70%). As a limitation of this transformation, we found that *N*-tosylhydrazones derived from cyclohexanone, 1-methylpiperidin-4-one, and tetrahydropyran-4-one failed to yield the desired products, probably due to the relative less stability of the corresponding carbene intermediates derived from aliphatic ketones.

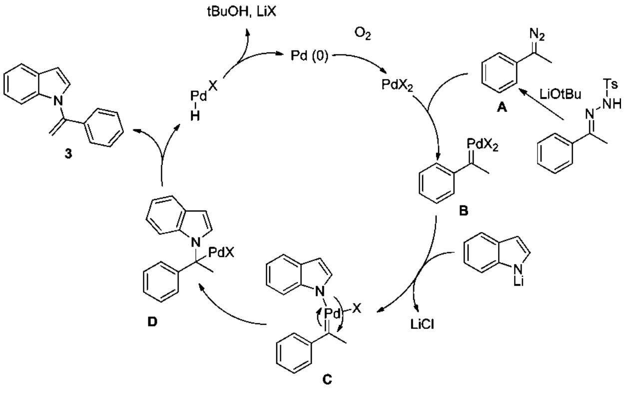
Moreover, the reaction tolerated electronically and sterically diverse substituents at the indole moiety. Both mono- and disubstituted indoles effectively participated in this reaction (**3p**−**y**). More sterically congested substrates delivered the target products with moderate yields (**3p**−**t**). A series of 5-substituted-1-(1-phenylvinyl)-1*H*-indole scaffolds could be readily prepared under the standard reaction conditions (**3v**−**x**). Notably, the halide moieties on the aromatic ring of indoles also remained intact under the present Pd^{II}/Pd^0 catalytic cycle (**3u**−**w**). Encouraged by the success with various substituted indoles, we were pleased to observe that carbazole could also be employed as a substrate to furnish the corresponding product in 99% yield (**3z**).[16] 1*H*-Imidazole, 1*H*-benzo[*d*]imidazole, 1*H*-pyrrole, and 1*H*-indazole were also probed, and the corresponding products were not observed. The stereochemistry of **3r** was further confirmed by ^1H NMR and NOESY spectra and assigned as the *E* isomer (for details, see the Supporting Information).

Scheme 1. *N*-Vinylation of Indoles with *N*-Tosylhydrazones[a]



[a] Reaction conditions: Indole (0.5 mmol), *N*-tosylhydrazone derivatives (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), LiOtBu (2.0 equiv), DMF (2 mL) under O_2, 80 °C. Isolated yields based on indoles.

Scheme 2. Proposed Mechanistic Pathway



Based on the experimental results obtained and in the literature on transition metal catalyzed cross-coupling reactions of *N*-tosylhydrazones,[3c,6,17] a plausible mechanism was proposed (shown in Scheme 2). An initial reaction

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(16) During our preparation of the manuscript, the synthesis of *N*-vinyl carbazole was reported by: Takeda, D.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 1242.

of the diazocompound **A** (generated *in situ* from *N*-tosylhydrazones in the presence of base) with palladium gave a palladium-carbene **B** species. Then base-assisted ligand exchange of palladium-carbene **B** with lithated indole provided an indolyl palladium **C** species. Next, the indolyl palladium **C** species underwent a migratory insertion process to give intermediate **D**. Finally, *syn* β-hydrogen elimination of **D** produced the olefin **3** and Pd(0) species in the presence of base. Oxidation of the Pd(0) species by O_2 regenerated the active Pd(II) species.

In conclusion, we have developed a novel type of Pd-catalyzed oxidative cross-coupling reaction to access *N*-vinylindoles using cheap and readily available starting materials as well as the environmentally benign oxidant via a sequential palladium carbene migratory insertion and β-H elimination process, which formed a C−N and a C=C bond spontaneously. This transformation provided an easy and efficient method for the synthesis of *N*-vinylindoles derivatives and exhibited good functional group tolerance and a remarkably wide scope. Further investigations to gain detailed mechanistic insight into this reaction and extension of the coupling reaction to other types of C−N bond-forming reactions are currently underway in our group.

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Supporting Information Available. Synthesis procedure, characterization, ^{1}H and ^{13}C NMR spectra of products **3a**−**z**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript was published ASAP on June 4, 2013. Table 1 footnotes have been updated. The corrected version was reposted on June 7, 2013.

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(17) Satoh, J.; Sakurada, J. *Tetrahedron* **2007**, *63*, 3806.

The authors declare no competing financial interest.