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Copper-Catalyzed Cascade Double C3-Indolations of 3-Diazoindolin-2-imines with Indoles: Convenient Access to 3,3-Diaryl-2-iminoindoles

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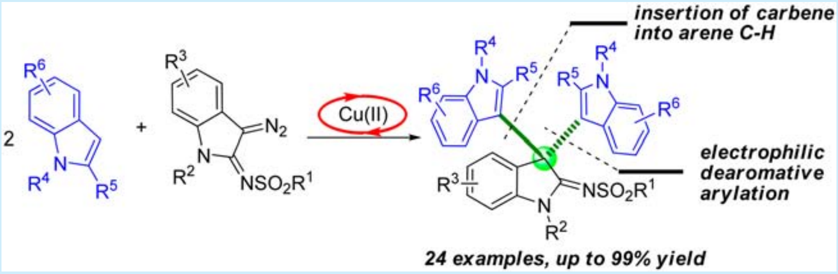
S *Supporting Information*



ABSTRACT: Symmetrical 3,3-diaryl-2-iminoindoles were prepared from 3-diazoindolin-2-imines and indoles via a copper-catalyzed cascade arylation/dehydrogenative cross-coupling process. By controlling the molar ratio of reactants and the operation procedure, 3-aryl-2-aminoindoles and asymmetrical 3,3-diaryl-2-iminoindoles could be approached.

Indole and its derivatives are privileged structures in natural products, bioactive pharmaceutics, and organic optoelectronic materials. Integration of three indoles in a single molecule is of interest to scientists not only because of the interesting architecture but also due to the indole's unique property (Figure 1). For example, trisindoline, isolated from the culture of *Vibrio sp.* that is a bacteria separated from the fresh marine sponge Hyrtiosaltum, presents antibiotic activity.[1] Idiospermuline, a representative of many biologically active cyclotryptamine alkaloids, is a highly toxic component of idiospermum seeds, preventing animals from eating them.[2] Structures of these bioactive compounds all share a similar structure of 3,3′-diaryloxindole or 3-arylindole substructure with an all-carbon quaternary stereocenter. With regard to the preparation of such privileged structures, many efficient methodologies have been developed.

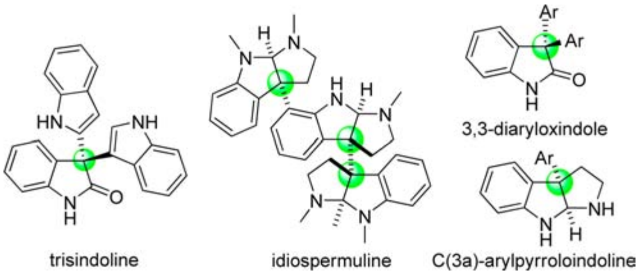


Figure 1. Privileged structures of 3,3′-diaryloxindole and C(3a)-arylpyrroloindoline.

The traditional synthetic route to symmetrical 3,3′-diaryloxindole is the Friedel−Crafts approach (Scheme 1, route a), starting from isatin and electron-rich arenes through iterative electrophilic aromatic substitutions, which was created by Baeyer and Lazarus at the end of the 19th century.[3] Klumpp and Olah investigated the influence of the acid strength on this process and also produced asymmetrical 3,3-diaryloxindoles by the reaction of isatin with a mixture of aromatics.[4] This approach was modified by Nicolaou et al. and applied in the total synthesis of diazonamide **A**, in which the construction of a C3 quaternary stereocenter of indole with two different aryls was a challenging task.[5]

Transition-metal-catalyzed direct C3-arylation of indole was developed for the preparation of 3-arylindole (Scheme 1, route b).[6] Sammakiain employed this method for the synthesis of asymmetrical 3,3-diaryloxindoles[7] and natural product diazonamide **A**.[8] Palladium-catalyzed dearomative C3-arylation of indole, which furnished spiroindolenine derivatives with an all-carbon quaternary stereocenter at C3 of the indole ring, was reported by You's group.[9]

As one of the important intermediates in modern organic synthesis, diazo compounds could be directly arylated through C−H insertion. The acid or transition-metal-catalyzed arylation of 3-diazooxindoles with electron-rich arenes took place on the C-3 position of indoles to give 3-aryloxindoles with high regioselectivity (Scheme 1, route c).[10] Based on this kind of metal carbene intermediates, Hu's[11] and Gong's groups[12] also synthesized various 3,3′-bisindoles with an all-carbon quater-

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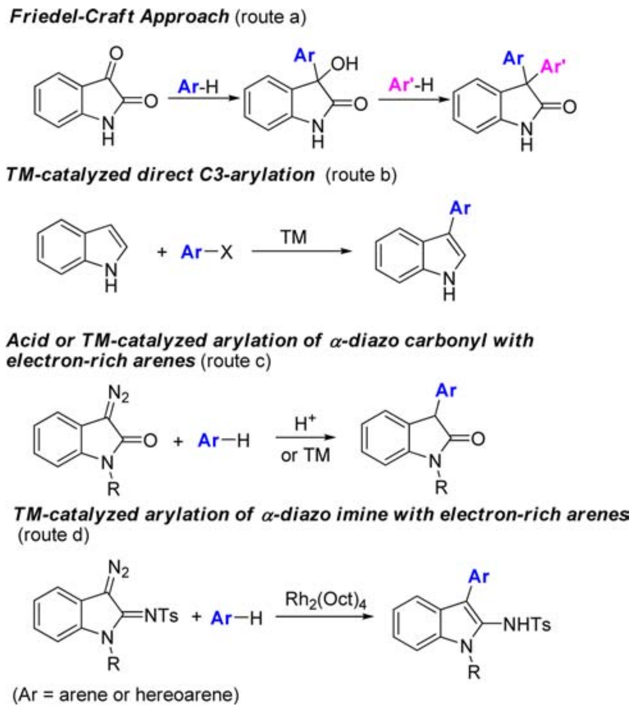
Scheme 1. Literature Reported Methods in the Preparation of 3,3′-Diarylindole and 3-Arylindole

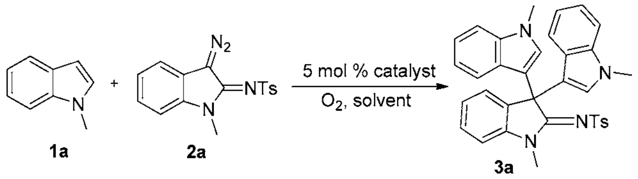


nary center though a rhodium- or ruthenium-catalyzed three-component reaction of 3-diazooxindoles with indole, and electrophiles. More recently, we developed a convenient and economic method to construct 3,3′-bisindoles through Ar–H insertion of α-imino rhodium carbenes derived from 3-diazoindolin-2-imines (Scheme 1, route d).[13a] As part of our ongoing commitment to α-imino metal carbenes,[13] here we would like to report a copper-catalyzed cascade double arylation of 3-diazoindolin-2-imines, furnishing symmetrical and asymmetrical 3,3-diaryl-2-imino-indoles.

To begin with, the reaction between 1-methyl-1*H*-indole (**1a**) and 3-diazoindolin-2-imine (**2a**) was carried out in the presence of $Cu(OTf)_2$ in dichloroethane (DCE) at 50 °C for 8 h under an oxygen atmosphere. Fortunately, 3,3-diarylindolin-2-imine (**3a**) was isolated in 81% yield. The reaction regioselectively occurred on the 3-position of 1-methyl-1*H*-indole (**1a**) without the contaminant of that on the 2-position. The structure of **3a** was confirmed by the single crystal analysis of its analog (**3s**).[14] By screening other Cu(II) catalysts, $Cu(OTf)_2$ was found to be optimal (Table 1, entries 1–6). Meanwhile Cu(I) also catalyzed the reaction to some extent, with CuOTf giving a comparable yield (Table 1, entries 7 and 8). As to the solvent used, polar aprotic solvents (CH_3CN, DMF, and DMSO) were not suitable in comparison with DCE, toluene, and THF. Among these, DCE provided the highest yield (Table 1, entries 1, 9–13). By screening the reaction temperature and reaction time (Table 1, 14–19), the optimal reaction temperature and reaction time were found to be 35 °C and 24 h, respectively (Table 1, entry 16). When the reaction was conducted under an air atmosphere, a dramatically decreased yield was observed (Table 1, entry 20).

With the optimized reaction conditions (Table 1, entry 16), we tested the substrate diversity (Table 2). Beginning with the alternation of substituents on indole, the R^1 group on the nitrogen of indole could be alkyl, aryl, benzyl, and allyl. The corresponding products **3a–f** were obtained in 57%–98%yields (Table 2, entries 1–6). When the R^1 was an electron-withdrawing group, such as Boc (**1g**) or Ts (**1h**), the desired product was not detected although **2a** was completely consumed in each case (Table 2, entries 7 and 8). Substituted groups on 5-, 6-, 7-positions of indoles could be either electron-donating or -withdrawing. Thus, 3,3-diarylindolin-2-imines **3g–m** were prepared in yields between 60% and 93% (Table 2, entries 9–15). 1,2-Dimethyl-1*H*-indole (**1p**), with methyl blocked at the 2-position of indole, provided the desired product **3n** in excellent yield (Table 2, entry 16). 1-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (**1q**) could react at higher temperature to give **3o** (Table 2, entry 17).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Cu(OTf)_2$	DCE	50	8	81
2	$Cu(acac)_2$	DCE	50	8	64
3	$Cu(NO_3)_2{\cdot}3H_2O$	DCE	50	8	66
4	$CuCl_2{\cdot}2H_2O$	DCE	50	8	54
5	$Cu(OAC)_2{\cdot}H_2O$	DCE	50	8	63
6	$CuBr_2$	DCE	50	36	18
7	Cu_2O	DCE	50	36	40
8	CuOTf	DCE	50	8	78
9	$Cu(OTf)_2$	toluene	50	8	76
10	$Cu(OTf)_2$	THF	50	8	64
11	$Cu(OTf)_2$	CH_3CN	50	8	trace
12	$Cu(OTf)_2$	DMF	50	8	trace
13	$Cu(OTf)_2$	DMSO	50	8	trace
14	$Cu(OTf)_2$	DCE	80	8	60
15	$Cu(OTf)_2$	DCE	50	24	86
16	$Cu(OTf)_2$	DCE	35	24	98
17	$Cu(OTf)_2$	DCE	35	16	65
18	$Cu(OTf)_2$	DCE	35	8	32
19	$Cu(OTf)_2$	DCE	rt	36	79
20	$Cu(OTf)_2$	DCE	35	24	58[c]

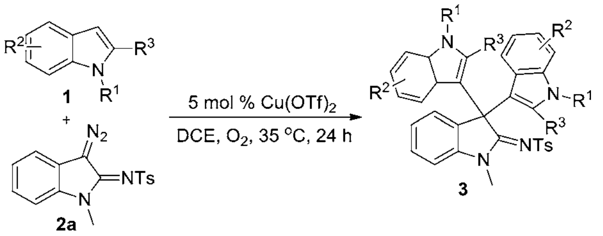
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), catalyst (0.005 mmol), solvent (1 mL), O_2. [b]Isolated yield. [c]In air.

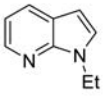
As shown in Table 3, the R^4 group in the benzene ring of 3-diazoindolin-2-imines **2** could be altered from hydrogen, methyl, methoxy, to nitro. In these cases, the substituent effect is not apparent in comparison with that on indoles **1**. The R^6 group in sulfonyl could be either aliphatic or aromatic, such as methyl, phenyl, *p*-methylphenyl, *p*-methoxyphenyl, *p*-chlorophenyl, and *p*-nitrophenyl.

In the case where R^5 is *tert*-butyl (**2i**), the diarylation reaction generated the deprotected product **3y** in 78% yield (Scheme 2). It is noticeable that **3y** could not be directly prepared from the unprotected 3-diazoindolin-2-imine and 1-methylindole (**1a**).

In order to understand the reaction mechanism, a condition-controlled reaction between indoles **1** and 3-diazoindolin-2-imine (**2a**) in an equivalent molar ratio was performed under nitrogen at room temperature for 3 h. As shown in Table 4, 3-arylindolin-2-amines **4a–g** were isolated in 65%–95% yields. Further arylation of the monoarylated compounds **4c** and **4g** with indoles was achieved under oxygen conditions, furnishing

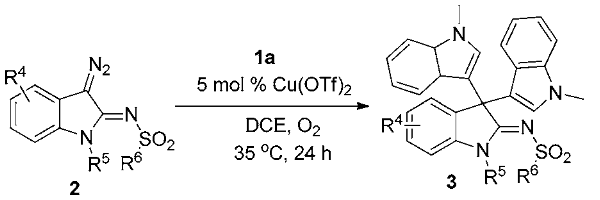
Table 2. Scope of Indoles[a]



entry	**1** (R^1/R^2/R^3)	product	yield (%)[b]
1	**1a** (Me/H/H)	**3a**	98
2	**1b** (Et/H/H)	**3b**	91
3	**1c**(Ph/H/H)	**3c**	87
4	**1d** (p-MeOC$_6$H$_4$/H/H)	**3d**	83
5	**1e** (Bn/H/H)	**3e**	57
6	**1f** (Allyl/H/H)	**3f**	60
7	**1g** (Boc/H/H)	-	ND[c]
8	**1h** (Ts/H/H)	-	ND[c]
9	**1i** (Me/5-Cl/H)	**3g**	80[c]
10	**1j** (Me/5-MeO/H)	**3h**	93[d]
11	**1k** (Me/7-Br/H)	**3i**	60[c]
12	**1l** (Me/5-NO$_2$/H)	**3j**	71[c]
13	**1m** (Me/6-Cl/H)	**3k**	82[c]
14	**1n** (Et/6-Cl/H)	**3l**	83[c]
15	**1o** (Et/5-MeO/H)	**3m**	85[d]
16	**1p** (Me/H/Me)	**3n**	92
17	 **1q**	**3o**	57[e]

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), DCE (2 mL), Cu(OTf)$_2$ (0.01 mmol), O$_2$, 35 °C, 24 h. [b] Isolated yields refer to **2**. [c] 50 °C. [d] rt. [e] 70 °C, 6 h.

Table 3. Scope of 3-Diazoindolin-2-imines[a]



entry	**2** (R^4/R^5/R^6)	product	yield (%)[b]
1	**2b** (H/Me/Me)	**3p**	90
2	**2c** (H/Me/Ph)	**3q**	84
3	**2d** (H/PhCH=CH/Tol)	**3r**	95
4	**2e** (5-NO$_2$/Me/Tol)	**3s**	80[c]
5	**2f** (H/Me/*p*-MeOC$_6$H$_4$)	**3t**	80
6	**2g** (6-MeO/Bn/Tol)	**3u**	98
7	**2h** (5-Me/Bn/Tol)	**3v**	98
8	**2i** (H/Me/*p*-ClC$_6$H$_4$)	**3w**	95
9	**2j** (H/Me/*p*-NO$_2$C$_6$H$_4$)	**3x**	99

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), DCE (2 mL), Cu(OTf)$_2$ (0.01 mmol), O$_2$, 35 °C, 24 h. [b] Isolated yields refer to **2**. [c] 50 °C.

Scheme 2. Formation of the Deprotected Product 3y

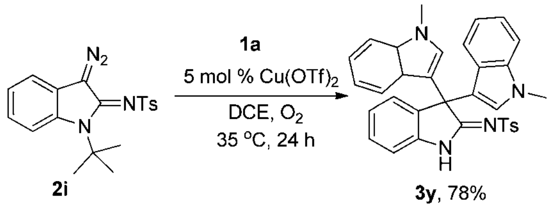
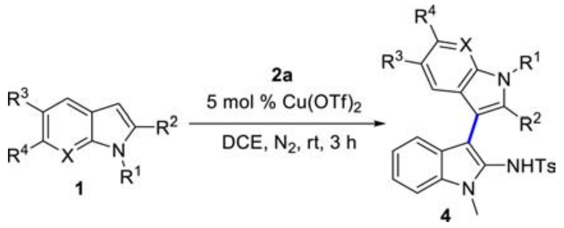


Table 4. Formation of 3-Arylindolin-2-amines 4[a]

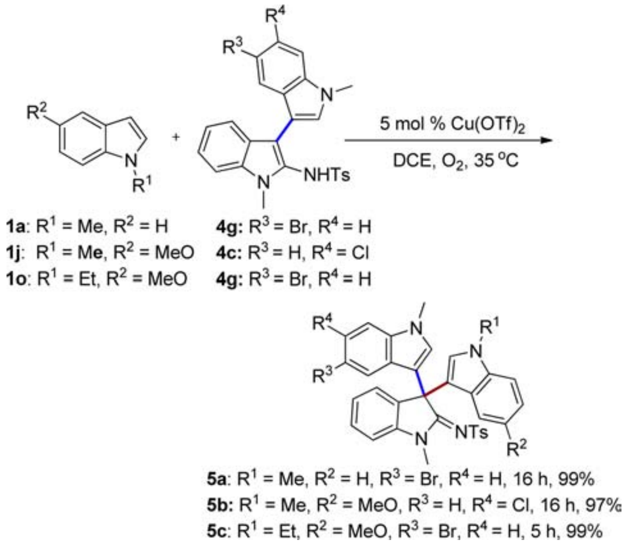


entry	**1** (X/R^1/R^2/R^3/R^4)	product	yield (%)[b]
1	**1a** (CH/Me/H/H/H)	**4a**	73
2	**1j** (CH/Me/H/MeO/H)	**4b**	71
3	**1m** (CH/Me/H/H/Cl)	**4c**	87
4	**1o** (CH/Et/H/MeO/H)	**4d**	70
5	**1p** (CH/Me/Me/H/H)	**4e**	86
6	**1q** (N/Et/H/H/H)	**4f**	65[c]
7	**1r** (CH/Me/H/Br/H)	**4g**	95

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), DCE (2 mL), Cu(OTf)$_2$ (0.01 mmol), N$_2$, room temperature, 3 h. [b] Isolated yields. [c] 50 °C, 24 h.

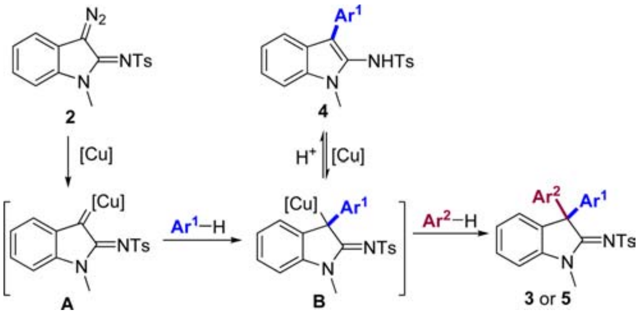
asymmetrical 3,3-diarylindolin-2-imines **5a–c** in excellent yields (Scheme 3).

Scheme 3. Formation of 3,3-Diarylindolin-2-imines 5



Based on these results and our previous finding in 3-diazoindolin-2-imine chemistry,[11,15] we postulated a working mechanism for this transformation (Scheme 4). In the presence of the copper catalyst, copper-carbene **A**[16] is formed in situ from 3-diazoindolin-2-imine during the process. Addition of electron-rich indole on electrophilic copper-carbene species leads to the formation of intermediate **B**. If one more

Scheme 4. Proposed Mechanism for the Formation of 3,3-Diarylindolin-2-imines 3 and 5



equivalent electron-rich arene existed in the reaction media, the intermediate **B** provided an electrophilic site and reacted. Thus, 3,3-diarylindolin-2-imines **3** were afforded. If the reaction between **2** and **1** preformed stoichimetrically, the intermediate **B** underwent metal–H exchange to result in the formation of the monoarylated products **4**. The monoarylated compounds **4** could react with the copper catalyst to generate **B** via an electrophilic metalation pathway and provide asymmetrical 3,3-diarylindolin-2-imines **5** when a different arene was used.

In conclusion, we developed a novel and efficient synthesis of 3,3-diaryl-2-iminoindoles via copper-catalyzed reactions of 3-diazoindolin-2-imines and indoles. The cascade process involves a C–H insertion of arene on the electron-deficient α-imino copper carbene which was derived from the copper-catalyzed decomposition of 3-diazoindolin-2-imine and a copper-catalyzed dehydrogenative cross-coupling. When the reaction was carried out step-by-step, asymmetrical 3,3-diaryl-2-iminoindoles could be prepared by sequentially feeding different arenes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds, and crystallographic information file (CIF) for compound **3s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449.

(2) Kinthada, L. K.; Ghosh, S.; De, S.; Bhunia, S.; Dey, D.; Bisai, A. *Org. Biomol. Chem.* **2013**, *11*, 6984.

(3) Baeyer, A.; Lazarus, M. J. *Chem. Ber.* **1885**, *18*, 2637.

(4) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481.

(5) Nicolaou, K. C.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.

(6) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (c) Cornella, J.; Lu, P. F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (e) Zhang, Z. Q.; Hu, Z. Z.; Yu, Z. X.; Lei, P.; Chi, H. J.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415.

(7) Mai, C. K.; Sammons, M. F.; Sammakia, T. *Org. Lett.* **2010**, *12*, 2306.

(8) Mai, C. K.; Sammons, M. F.; Sammakia, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 2397.

(9) Wu, K. J.; Dai, L. X.; You, S. L. *Org. Lett.* **2012**, *14*, 3772.

(10) (a) Zhai, C. W.; Xing, D.; Jing, C. C.; Zhou, J.; Wang, C. J.; Wang, D. W.; Hu, W. H. *Org. Lett.* **2014**, *16*, 2934. (b) Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *Chem. Common.* **2002**, 824. (c) Muthusamy, S.; Gunanathan, C. *Synlett* **2002**, *11*, 1783. (d) Yu, Z. Z.; Ma, B.; Chen, M. J.; Wu, H. L.; Liu, L.; Zhang, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 6904.

(11) Xing, D.; Jing, C. C.; Li, X. F.; Qiu, H.; Hu, W. H. *Org. Lett.* **2013**, *15*, 3578.

(12) Chen, D. F.; Zhao, F.; Hu, Y.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 10763.

(13) (a) Xing, Y. P.; Sheng, G. R.; Wang, J.; Lu, P.; Wang, Y. G. *Org. Lett.* **2014**, *16*, 1244. (b) Sheng, G. R.; Huang, K.; Chi, Z. H.; Ding, H. L.; Xing, Y. P.; Lu, P.; Wang, Y. G. *Org. Lett.* **2014**, *16*, 5096.

(14) CCDC 1023440 contains the supplementary crystallographic data for **3s**.

(15) Sheng, G. R.; Huang, K.; Chi, Z. H.; Ding, H. L.; Xing, Y. P.; Lu, P.; Wang, Y. G. *Org. Lett.* **2014**, *16*, 5096.

(16) (a) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, DOI: 10.1039/C4SC03358B. (b) Zhao, X.; Zhang, Y.; Wang, J. B. *Chem. Commun.* **2012**, *48*, 10162.