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$FeCl_3$-Mediated Radical Tandem Reactions of 3-Benzyl-2-oxindoles with Styrene Derivatives for the Stereoselective Synthesis of Spirocyclohexene Oxindoles

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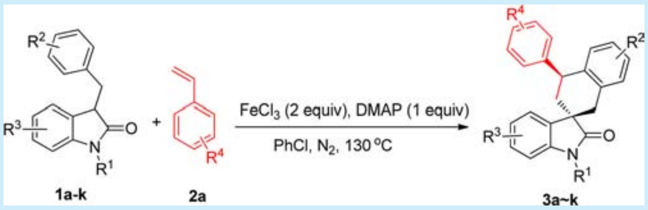
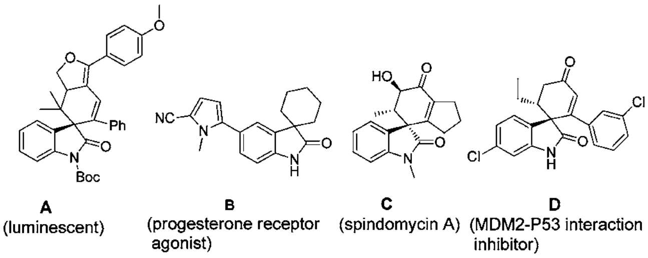
Supporting Information

ABSTRACT: A novel $FeCl_3$-mediated reaction of 3-benzyl-2-oxindoles with styrene derivatives was developed. The reaction provided spirocyclohexene oxindoles in good yields and excellent diastereoselectivities via a tandem radical addition/cyclization process.



As an important structural unit, spiro-oxindole motifs exist in a large number of natural products and clinical pharmaceuticals,[1] which often show a broad range of biological activities.[2] Among them, spirocyclohexene(-ane) oxindoles also show good photophysical and biological activities,[3] such as compound **A** (luminescent), compound **B** (progesterone receptor agonist), compound **C** (spindomycin A), and compound **D** (MDM2-P53 interaction inhibitor) (Figure 1) .



A (luminescent) **B** (progesterone receptor agonist) **C** (spindomycin A) **D** (MDM2-P53 interaction inhibitor)

Figure 1. Examples of biologically active spirooxindoles.

Several methods for the preparation of spirooxindoles have been developed, including cycloaddition, organocascade reactions, Prins cyclization, and multicomponent reactions.[4] However, there are relatively few reports about the application of C−H activation in the synthesis of spirooxindoles.[5] Over the past decades, selective C−H activation has provided increasingly important innovations for the construction of carbon−carbon and carbon−heteroatom bonds, as it is more environmentally benign and atom-economic than the conventional cross-coupling reactions.[6] In particular, difunctionalization of alkenes through selective C−H activation has emerged as a highly efficient approach to access natural products and biologically active molecules, because of their inherently mild conditions and high functional group compatibility.[7] Ruck et al. reported a novel palladium-catalyzed 5-exo-trig Heck cyclization with subsequent functionalization of an unactivated C−H bond for the synthesis of spirooxindoles.[5a] Zhu et al. reported an interesting synthesis of spirooxindoles through palladium-catalyzed domino carbopalladation/C(sp^3)−C(sp^3) bond-forming reactions.[5b] In 2012 Yuan et al. developed an efficient $FeCl_3$-catalyzed highly stereoselective intramolecular tandem 1,5-hydride transfer/ring closure reaction for the synthesis of a new class of spirocyclic oxindole tetrahydroquinolines.[5c] Later Duan et al. developed a metal-free oxidative spirocyclization of hydroxymethyl acrylamide with 1,3-dicarbonyl compounds via tandem sp^3 and sp^2 C−H functionalization followed by intramolecular dehydration.[5d] However, these approaches suffered from the use of noble-metal catalysts, commercially unavailable substrates, or pregeneration of organic halides; thereby, the method disclosed here complements previous methods.

Styrene derivatives have been recognized as important starting materials in synthetic chemistry because of their low cost and easy availability. Recently we reported a direct olefination of 2-oxindole with styrene catalyzed by iodine providing cross-dehydrogenative-coupling (CDC) products (Scheme 1, eq 1).[8] Herein, we present an $FeCl_3$-mediated C(sp^3)−H activation of 3-benzyl-2-oxindoles by a sequential radical addition/cyclization with styrene derivatives for the direct construction of spirocyclohexene oxindoles (Scheme 1, eq 2).

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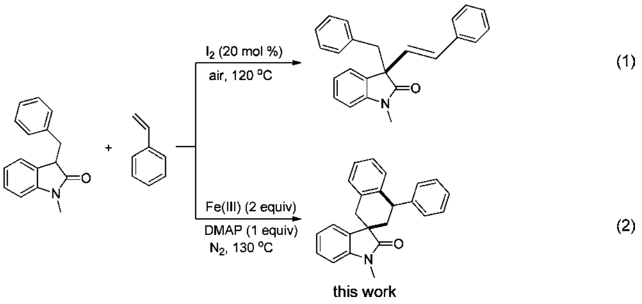
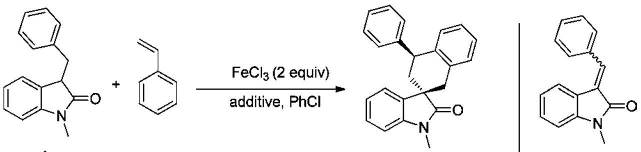
Scheme 1. Reactions between 2-Oxindoles and Styrene



Initially, the reaction of *N*-methyl-3-benzyl-2-oxindole **1a** and styrene **2a** was selected as a model reaction to produce the spirooxindole product **3a** (Table 1). $FeCl_3$ was selected as a promoter for this transformation, which was proven to be an effective catalyst in the radical arylation of 2-oxindole with arenes in air.[9] However, no desired spiro-oxindole product **3a** was obtained when $FeCl_3$ was used; only polymerization of styrene was observed (Table 1, entry 1).

Table 1. Condition Optimization[a]



1a **2a** **3a** **4**

entry	additive (equiv)	temp (°C)	yield of 3a (%)[b]
1	–	130	ND[j]
2	DMAP (1)	130	79
3	DBU (1)	130	66
4	DABCO (1)	130	40
5	Et_3N (1)	130	57
6	pyridine (1)	130	51
7	DMAP (1.5)	130	28
8	DMAP (0.5)	130	24
9[c]	DMAP (1)	130	77
10	DMAP (1)	100	75
11	DMAP (1)	120	70
12[d]	DMAP (1)	130	66
13[e]	DMAP (1)	130	77
14[f]	DMAP (1)	130	60
15[g]	DMAP (1)	130	59
16[h]	DMAP (1)	130	65
17[i]	DMAP (1)	130	60

[a] Reaction conditions: a mixture of oxindole **1a** (0.2 mmol), styrene **2a** (1 mmol), and $FeCl_3$ (0.4 mmol) in PhCl (8 mL) under N_2 for 7 h. [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] $FeCl_3 \cdot 6H_2O$ (0.4 mmol) was used. [d] 4 mL of PhCl were used. [e] 12 mL of PhCl were used. [f] Reaction in air. [g] **1a**:**2a** = 1:2. [h] 8 mL of toluene were used. [i] 8 mL of 1,2-dichlorobenzene were used. [j] ND: not detected.

It was reported that the addition of base could prohibit the homopolymerization of styrene.[10] Thus, several organic bases, including DMAP, DBU, DABCO, Et_3N, and pyridine were examined as an additive (entries 2−6). DMAP exhibited the best ability for suppressing the homopolymerization of styrene, resulting in a high yield of **3a** (79%, entry 2). Further experiments demonstrated that the amount of DMAP had a significant influence on the yield. When 1.5 or 0.5 equiv of DMAP was used, the yields dramatically decreased to 28% and 24%, respectively (entries 7 and 8). Interestingly, $FeCl_3 \cdot 6H_2O$ with DMAP also displayed high activity for the reaction of **1a** with **2a**, giving **3a** in 77% yield (entry 9). X-ray single crystal analysis of **3a** clearly showed a spirooxindole structure and a chair conformation of the cyclohexene ring with the phenyl group in an equatorial position (Figure 2).[11] However, the use of a catalytic amount of $FeCl_3$ (20 mol %) with DMAP and DDQ (2 equiv) was not effective for the reaction, but only the oxidative product of **1a**, **4**, was obtained in 83% yield. Further studies revealed that conducting the reaction at 130 °C gave the best result (entry 2 vs entries 10 and 11). The amount of PhCl also influenced the yield: 4 and 12 mL of PhCl gave product in 66% and 77% yield, respectively (entries 12 and 13). If the reaction of **1a** with **2a** was carried out in air, the yield of **3a** was decreased to 60% (entry 14). Finally, when the amount of **2a** was decreased to 2.0 equiv, the yield of **3a** decreased to 59% (entry 15). Finally, different solvents, including toluene and 1,2-dichlorobenzene, were investigated (entries 16 and 17). However, no improvement in yield was gained by altering the solvent. The optimized conditions were employed as follows: a mixture of **1a** and **2a** (1:5) with $FeCl_3$ (2 equiv) and DMAP (1 equiv) in PhCl at 130 °C for 7 h.

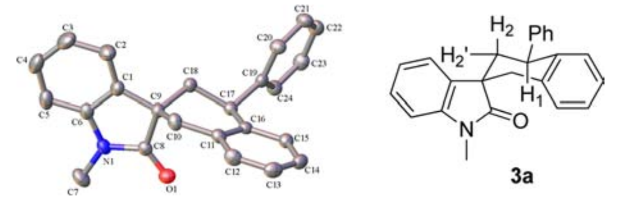


Figure 2. X-ray structure of **3a**.

With optimal reaction conditions in hand, various 3-benzyl-2-oxindoles were used to explore the substrate scope. It was shown in Scheme 2 that the *N*-substituent of 2-oxindole influenced the yield of the spirooxindole product slightly. For example, both the *N*-methyl- (**1a**) and *N*-benzyl-oxindoles (**1c**) gave the corresponding products **3a** and **3c** in 76% and 75% yield, respectively, as a single isomer. However, 3-benzyl-2-oxindole **1b** was less reactive, giving product **3b** in only 52% yield as a diastereomeric mixture (dr 13:1). The introduction of a chloro substituent to the 5- and 6-position of 2-oxindole afforded the products **3j** and **3k** in 67% and 72% yield, respectively. Next we investigated the effects of the substituents at the *meta*- and *para*-positions of the benzyl group. For example, introducing a methyl and methoxyl group at the *para*-position of the benzyl group gave the product **3d** in 55% yield and **3e** in 42% yield (dr 13:1). The introduction of chloro and bromo gave relatively high yields of the corresponding products **3f** and **3g** in 65% and 62% yield, respectively. 3-(3-Chlorobenzyl)-2-oxindole gave the product **3h** in 51% yield. Importantly, heterocyclic substituents, for example **1i**, also tolerated the reaction conditions, giving product **3i** in 62% yield as a mixture of two diastereomers (dr 4:1).

Various styrene derivatives were also employed in the reactions with **1a** under the optimized conditions. The spiro-oxindole products **3l−r** were listed in Scheme 3. Different substituents, either electron-withdrawing or electron-donating groups, could be used in the reactions with **1a**. For example, *para*-Me- and *para*-OAc-phenylethylene gave the product **3l**

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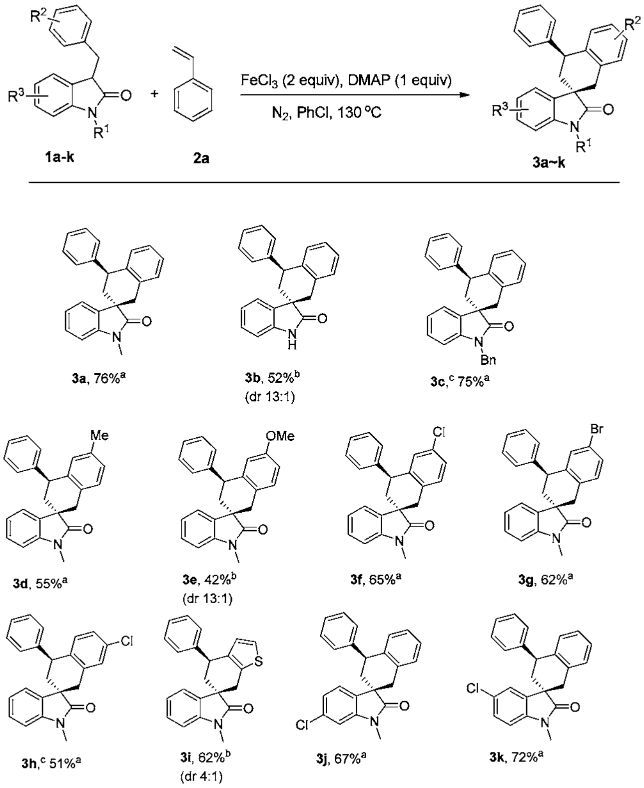
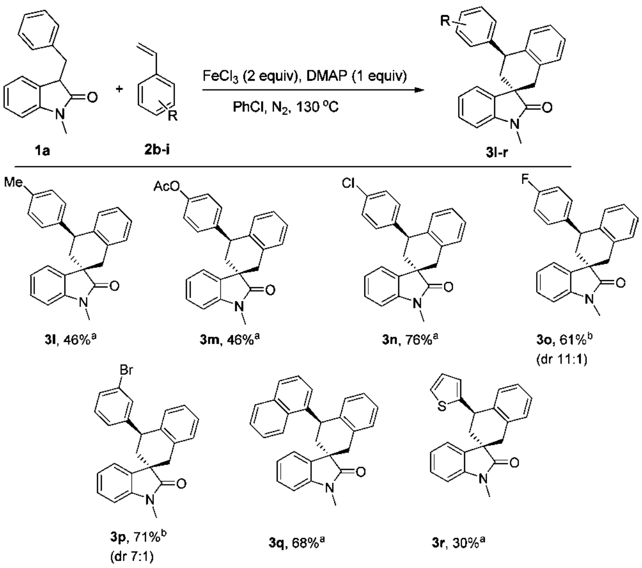
Scheme 2. Substrate Scope of 3-Benzyl-2-oxindoles



[a]Isolated yields. [b]Diastereomeric mixtures. [c]$FeCl_3·6H_2O$ (2.0 equiv) was used.

Scheme 3. Substrate Scope of Styrene Derivatives

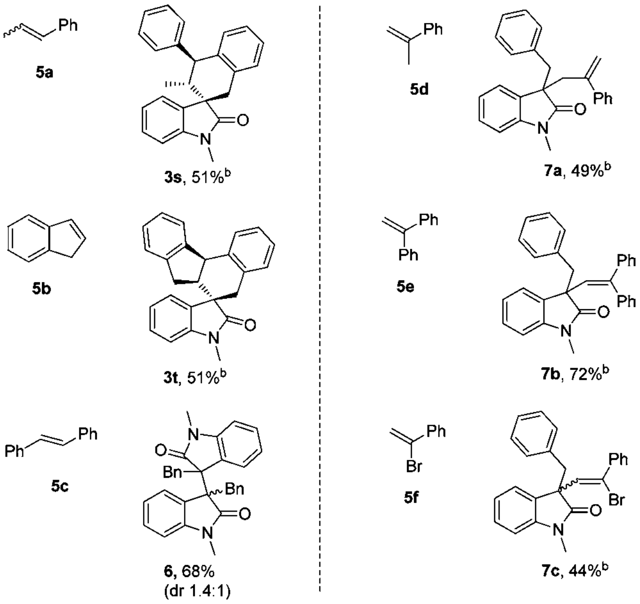


[a]Isolated yields. [b]Diastereomeric mixtures.

and **3m** in the same yield (46%). While *p*-chloro and *p*-fluorophenylethylene gave the products in 76% (**3n**) and 61% (**3o**, dr 11:1) yields, respectively. The reaction of *meta*-bromophenylethylene with **1a** provided the product **3p** in 71% yield as a diastereomeric mixture (dr 7:1). 1-Vinylnaphthalene was compatible under the reaction conditions, giving the product **3q** in 68% yield, while 2-vinylthiophene was less effective to give product **3r** in a lower yield (30%).

The reaction of disubstituted ethylenes with **1a** exhibited different reactivities (Scheme 4). When 1-phenyl-2-methylethylene **5a** and indene **5b** were used, spiro-oxindole product **3s** and **3t** were obtained in the same yield (51%). However, when 1,2-diphenylethylene **5c** was used, compound **6** as the dimer of **1a** was obtained in 68% yield, and **5c** did not participate in the reaction at all. For 1,1-disubstituted ethylenes, the products of carbon−carbon cross-coupling were obtained. 1,1-Diphenyl ethylene **5e** and 1-phenyl-1-bromoethylene **5f** afforded Heck-type product **7b** and **7c** in 72% and 44% yields, respectively. 1-Phenyl-1-methyl ethylene **5d** gave the product **7a** with the double bond migration.

Scheme 4. Scope of Disubstituted Ethylenes

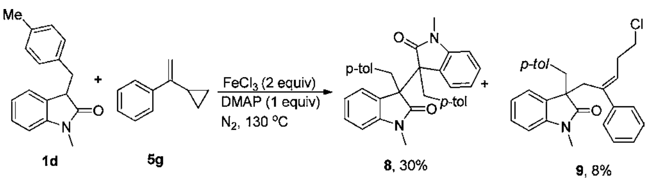


[a]Reaction conditions: a mixture of oxindole **1** (1 equiv), disubstituted ethylene **5** (5 equiv) in the presence of $FeCl_3$ (2 equiv) and DMAP (1 equiv) at 130 °C under N_2 atmosphere was stirred for 7 h. [b]Isolated yields.

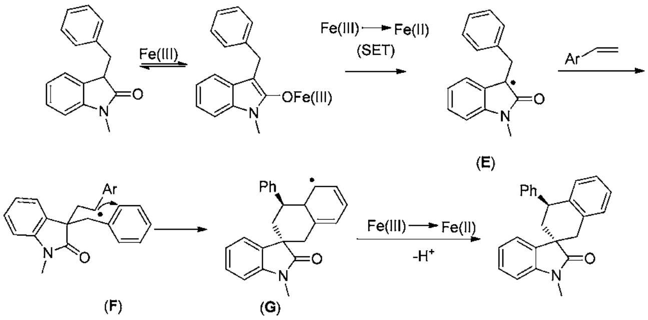
The thermal ring-opening and rearrangement reaction of vinylcyclopropane is often used to demonstrate the reaction trapping through a radical process.[12] The reaction of 3-(4-methylcbenzyl)-2-oxindole **1d** with 1-phenylvinylcyclopropane **5g** (**1d**/**5g** = 1:3) under the same reaction conditions provided the product **8** as the dimer of **1d** in 30% yield and the cyclopropane ring-opening and rearrangement product **9** in 8% yield (Scheme 5).

On the basis of the above-mentioned results, a mechanism is tentatively proposed (Scheme 6). First, 3-benzyl-2-oxindole could tautomerize to its enol form, which is easily oxidized in the presence of $FeCl_3$ to give the corresponding radical **E** via a single-electron transfer (SET), while at the same time Fe(II)

Scheme 5. Reaction of 1d with 5g



Scheme 6. Proposed Mechanism



was formed.[13] Second the attack of radical **E** to styrene provided radical intermediate **F**. The intermediate **F** exhibited a chairlike transition state with the phenyl group in an equatorial position and then underwent an intramolecular cyclization to generate radical **G** with high diastereoselectivity. Finally, an Fe(III)-mediated oxidation of the radical intermediate **G** into the corresponding carbocation, followed by the loss of H^+, affords the desired spiro-oxindole products.

In summary, we have developed an efficient approach for the stereoselective synthesis of spirocyclohexene oxindoles by $FeCl_3$-mediated reactions of 3-benzyl-2-oxindoles with styrene derivatives through a radical addition/cyclization process. $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ bonds are formed in tandem reactions with excellent diastereoselectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00234.

Experimental details, characterizations, and NMR spectra of all products and X-ray data for **3a** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369. (f) Wu, H.-R.; He, X.-F.; Jin, X.-J.; Pan, H.; Shi, Z.-N; Xu, D.-D; Yao, X.-J; Zhu, Y. *Fitoterapia* **2015**, *106*, 175. (g) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127.

(2) (a) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, *2009*, 165. (b) Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2009**, *44*, 3821. (c) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573. (d) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (e) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653. (f) Damera, K.; Yu, B.; Wang, B. *J. Org. Chem.* **2015**, *80*, 5457.

(3) (a) Badillo, J.-J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758. (b) Xie, D.; Yang, L.; Lin, Y.; Zhang, Z.; Chen, D.; Zeng, X.; Zhong, G. *Org. Lett.* **2015**, *17*, 2318. (c) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861. (d) Guo, K.; Fang, T.; Wang, J.; Wu, A.-A.; Wang, Y.; Jiang, J.; Wu, X.; Song, S.; Su, W.; Xu, Q.; Deng, X. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4995. (e) Schö nhaber, J.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 6196.

(4) For selected examples, see: (a) Subba Reddy, B. V.; Swathi, V.; Swain, M.; Bhadra, M. P.; Sridhar, B.; Satyanarayana, D.; Jagadeesh, D. *Org. Lett.* **2014**, *16*, 6267. (b) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 16720. (c) Piou, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11561. (d) Bergonzini, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 971. (e) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (f) Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418. (g) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584. (h) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (i) Cheng, D.-J.; Ishihara, Y.; Tan, B.; Barbas, C.-F. *ACS Catal.* **2014**, *4*, 743. (j) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (k) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160. (l) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821.

(5) (a) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711. (b) Piou, T.; Neu-ville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11561. (c) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054. (d) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2013**, *15*, 5254.

(6) (a) *Topics in Current Chemistry, C−H Activation*; Yu, J.-Q., Shi, Z.-J., Eds.; Springer: Berlin, 2010; Vol. 292. (b) Du, W.; Tian, L.; Lai, J.; Huo, X.; Xie, X.; She, X.; Tang, S. *Org. Lett.* **2014**, *16*, 2470. (c) Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13871. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (f) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (g) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061.

(7) (a) Beccalli, E. M.; Broggini, G. M.; Martinelli, S.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (c) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (e) Xie, Y.-X.; Song, R.-J.; Xiang, J.-N.; Li, J.-H. *Youji Huaxue* **2012**, *32*, 1555. (f) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(8) Huang, H.-Y.; Wu, H.-R.; Wei, F.; Wang, D.; Liu, L. *Org. Lett.* **2015**, *17*, 3702.

(9) Wu, H.-R.; Huang, H.-Y.; Ren, C.-L.; Liu, L.; Wang, D.; Li, C.-J. *Chem. - Eur. J.* **2015**, *21*, 16744.

(10) Lv, J.; Zhong, X. R.; Luo, S. Z. *Chem. - Eur. J.* **2014**, *20*, 8293.

(11) Crystallographic data for spiro-oxindoles **3a** have been deposited at the Cambridge Crystallographic Date Centre (CCDC 1060529).

(12) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

(13) (a) Niwa, T.; Ishii, S.; Hiramatsu, A.; Osawa; Biosci, T. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 1870. (b) Schmittel, M.; Baumann, U. *Angew. Chem., Int. Ed.* **1990**, *29*, 541.