Organic LETTERS

Letter

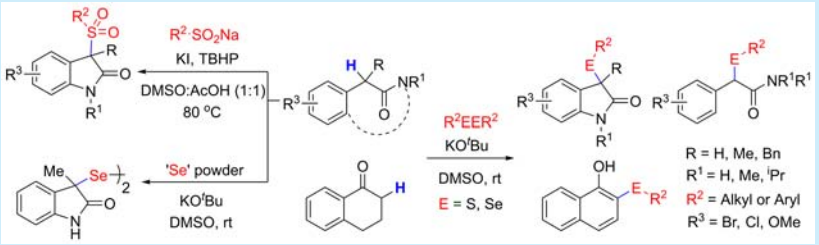
pubs.acs.org/OrgLett

Transition-Metal-Free Selective Oxidative C(sp^3)−S/Se Coupling of Oxindoles, Tetralone, and Arylacetamides: Synthesis of Unsymmetrical Organochalcogenides

Ch. Durga Prasad, Moh. Sattar, and Sangit Kumar*

Department of Chemistry, Indian Institute of Science Education and Research (IISER), Bhopal, MP 462 066, India

Supporting Information



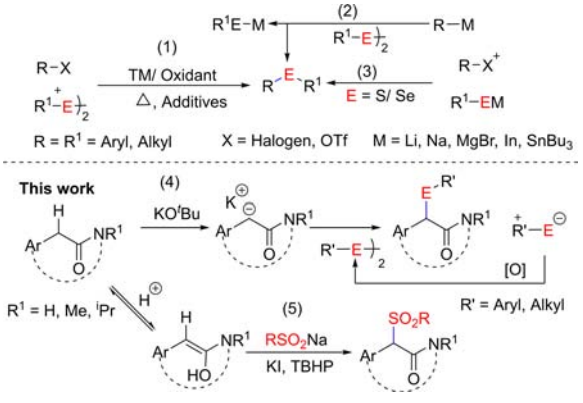
ABSTRACT: Transition-metal-free synthetic methods have been developed for the preparation of unsymmetrical diaryl and aryl alkyl chalcogenides: sulfones, sulfides, and selenides from the sp^3-C−H bond of oxindole, tetralone, arylacetamide, and aryl chalcogenide precursors. Sulfones were obtained from sodium sulfinates using potassium iodide, *tert*-butyl hydroperoxide in DMSO, and acetic acid. Sulfides and selenides were prepared from diaryl disulfides or diselenides employing potassium *tert*-butoxide in DMSO. α-Tetralone underwent concomitant chalcogenation and aromatization resulting in 2-chalcogenyl-1-naphthols in one pot.

The formation of the aryl C−E (S/Se) bond is one of the fundamental reactions in synthetic chemistry, and it constitutes a key step toward accessing a broad range of organic molecules, which are prevalent in drugs, antioxidants, and metal complexes.[1−3] 3-Chalcogenated, particularly thiolated and sulfonated oxindoles are known to have promising anticancer, antifungal, and antitubercular activities.[4] For example, 3-spirothiazolidinones are potent and selective inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B.[4d] 2-Phenylchalcogenyl-l-naphthols have been proven to be potent 5-lipoxygenase inhibitors and promising antioxidants.[2c]

The carbon−chalcogen coupling reactions were mainly achieved in the following modes: (a) TM-catalyzed coupling of aryl/alkyl halides with organochalcogenides (eq 1, Scheme 1)[5] and (b) a conventional route in which aryl/alkyl dichalcogenides were reacted with organolithium/Grignard reagents (eq 2) or in another approach where lithium or magnesium organochalcogenolates were treated with organic halides (eq 3).[6] The preparation of organolithium and Grignard reagents involves strict inert conditions and often requires organohalide substrates. Moreover, an excess of aryl dichalcogenide is required as the reaction provides unsymmetrical diorganochalcogenide and lithium or magnesium organochalcogenolate as the byproduct (eq 2). In fact, sulfonylation[7] and chalcogenation[8] of the sp^2 or sp^3 C−H bond of aromatic/aliphatic functionalities via direct C−H functionalization were reported in the literature, while that of the oxindole framework has not been reported to date.

Here, we report the organochalcogenation of an sp^3-C−H bond of oxindole, phenylacetamide, and tetralone substrates by using potassium *tert*-butoxide (KO^{t}Bu) as a base in dimethyl sulfoxide (DMSO) for the synthesis of biologically important organochalcogenides and also generated organothiolate or selenolate oxidized in situ into the respective disulfide or diselenide (eq 4). On the other hand, organosulfones were obtained by enolization of amide followed by the addition of sulfonyl radical, which was generated from the reaction of *tert*-butyl hydroperoxide (TBHP) and potassium iodide (KI) with sodium sulfinate (eq 5).

Scheme 1. Chalcogenation and Sulfonylation of Amides

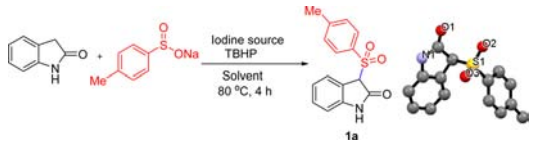


Received: December 15, 2016
Published: February 9, 2017

DOI: 10.1021/acs.orglett.6b03735
Org. Lett. 2017, 19, 774−777

Owing to our continued interest in organochalcogen chemistry[9] and TM-free C−H functionalization,[10] we attempted the synthesis of 3-sulfonated oxindole using KO^{t}Bu by direct sp^3 C−H functionalization of oxindole employing sodium sulfinate as the sulfonylating agent. However, the reaction failed to yield the desired 3-sulfonated oxindole **1a** despite several attempts (Table 1, entry 1). Next, we envisioned that an oxidant in the presence of acidic conditions would accomplish the sulfonylation reaction.

Table 1. Survey of Reaction Conditions[a]



entry	iodine source	solvent	yield (%)
1	−/KO^{t}Bu	DMSO	ND
2	−	DMSO/AcOH (1:1)	ND
3[b]	KI	DMSO/AcOH (1:1)	32
4	KI	DMSO/AcOH (1:1)	70

[a]Reaction was carried out using oxindole (0.2 mmol), sodium *p*-toluene sulfinate (0.4 mmol), iodine source (1 equiv), and TBHP (1 equiv) in solvent (1 mL) at 80 °C for 4 h. [b]TBHP was not added. ND = not detected.

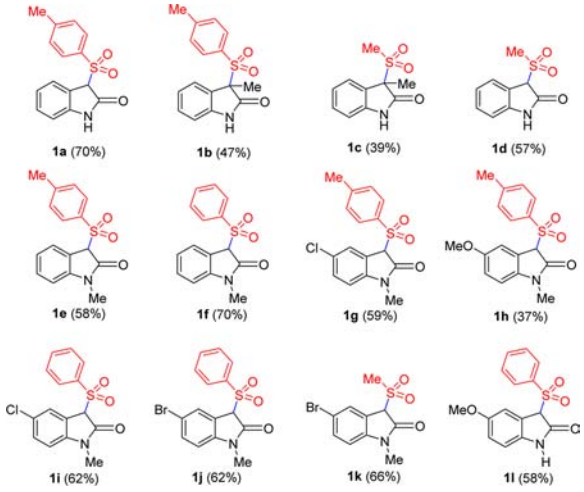
Unfortunately, with TBHP alone as an oxidant, the reaction did not occur (entry 2, Table 1). The addition of 1 equiv of KI along with TBHP gave 70% yield of the desired product **1a** (entry 4, Table 1; for details on optimization of reaction conditions, see the SI). The structure of **1a** was also confirmed by single-crystal X-ray diffraction study (CCDC No. 1474948).

With the optimized reaction conditions in hand, we investigated the scope of oxindoles in the reaction system (Scheme 2). In most cases, oxindoles were smoothly converted to the corresponding sulfonated oxindoles in moderate to good yields. Oxindoles with a free *N*-H group as well as *N*-protected groups reacted well, and the respective sulfonated products **1a**−**1l** were obtained. For example, the reaction of 3-methyloxindole with sodium *p*-toluenesulfinate gave 3-methyl-3-tosylindolin-2-one **1b** in 47% yield, whereas the reaction with methanesulfinate gave 3-methyl-3-(methylsulfonyl)indolin-2-one **1c** in 39% yield. The reaction of oxindole with methanesulfinate afforded 3-(methylsulfonyl)indolin-2-one **1d** in 57% yield. Next, the reaction of *N*-methyloxindole with sodium *p*-toluenesulfinate gave 1-methyl-3-tosylindolin-2-one **1e** in 58% yield, while the reaction with sodium benzenesulfinate provided 1-methyl-3-(phenylsulfonyl)indolin-2-one **1f** in 70% yield.

Later, the scope of *N*-methyloxindoles having substituents on the phenyl ring was investigated under the optimized reaction conditions of the sulfonylation reaction. Irrespective of the electronic effect of the substituent attached to the phenyl ring, the corresponding sulfonated products were formed in decent yields. The reaction of *N*-methyloxindoles with electron-deficient substituents such as bromo and chloro resulted in 59−66% yields of the respective sulfonated products **1g**, **1i**−**1k**. In the case of the reaction with an electron-rich methoxy group substituted *N*-methyloxindole, a poor yield of the product **1h** was obtained. The same reaction of oxindole with a free *N*-H group gave a 58% yield of the sulfonated indole **1l**. 3-Benzyl-substituted oxindole was not compatible in the sulfonylation reaction to form quaternary-centered 3-sulfonated oxindole.

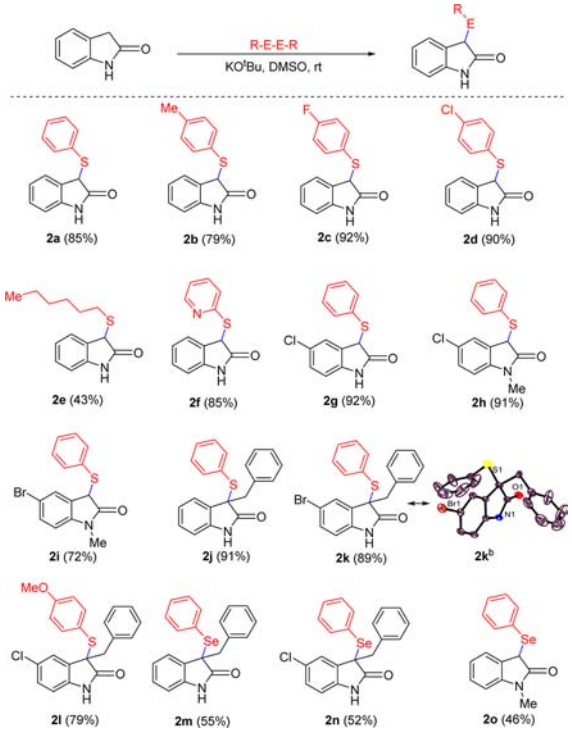
Next, we turned our attention to the synthesis of another class of biologically important 3-chalcogenyl oxindoles (Scheme 3).

Scheme 2. Scope of 3-Sulfonated Oxindoles[a]



[a]Reaction was performed using oxindole (0.5 mmol), sulfinate salt (1 mmol), KI (1 equiv), and TBHP (1 equiv) in AcOH/DMSO = 1:1 (1 mL) at 80 °C for 4 h unless otherwise mentioned.

Scheme 3. Synthesis of 3-Chalcogenyloxindoles[a]



[a]Reaction was performed using aryl disulfide (0.3 mmol), oxindole (0.6 mmol), and KOtBu (0.66 mmol) in DMSO (1 mL) at rt for 6 h unless otherwise mentioned. [b]Crystal structure of **2k** (CCDC No. 1500696).

We attempted the sulfenylation reaction with phenyl disulfide under the optimized KI-mediated conditions. Unfortunately, the sulfenylation reaction was not clean, and formation of the complex reaction mixture was observed. Next, we thought a base could promote the sulfenylation reaction by a nucleophilic attack

DOI: 10.1021/acs.orglett.6b03735
Org. Lett. 2017, 19, 774−777

of in situ generated carbanion from oxindole to disulfides or thiols (Scheme 1, eq 4).

As we have already explored KO^{t}Bu as a promoter in carbon−carbon coupling reactions,[10] we attempted the sulfenylation reaction of oxindole with benzenethiol using the same conditions. Benzenethiol gave the 3-sulfenylated oxindole **2a** in low yield (20%). However, the complete conversion of benzenethiol into disulfide was noticed. Hence, phenyl disulfide was used as the source of sulfur. Indeed, a considerable increase in the yield of **2a** was observed. Tuning the stoichiometry to 0.3 mmol of phenyl disulfide, 0.6 mmol of oxindole, and 1.1 equiv of KO^{t}Bu in DMSO at room temperature resulted in the respective 3-sulfenyloxindole **2a** in 85% yield.

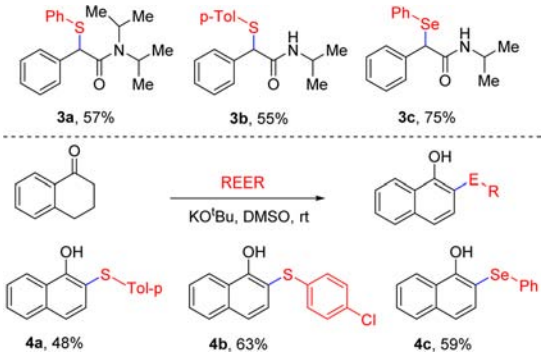
With these conditions in hand, we then explored the scope of this method utilizing various disulfides. It was found that different substituted disulfides are compatible in this reaction and afforded structurally diverse 3-sulfenyloxindoles in 43−92% yields (Scheme 3). At first, various aromatic disulfides were tested under our reaction conditions. For example, the reaction of 2-oxindole with *p*-tolyl disulfide provided 3-(*p*-tolylthio)indolin-2-one **2b** in 79% yield. The reaction of substituted phenyl disulfides, especially with electron-poor substituents such as chloro and fluoro groups, resulted in an excellent outcome of the corresponding 3-sulfenylindoles **2c** and **2d**. An attempted reaction of oxindole with an aliphatic substrate, *n*-hexyl disulfide, was also successful to afford 3-(hexylthio)indolin-2-one **2e**, albeit in low yield. Likewise, a reaction of oxindole with a heteroaromatic substrate, 2-pyridyl disulfide, gave 3-(pyridin-2-ylthio)indolin-2-one **2f** in 85% yield. Then the scope of the phenyl ring substituted oxindoles were tested to check the viability of the reaction system. The reaction of oxindoles with electron-deficient substituents such as bromo and chloro resulted in 72−92% yields of the respective sulfenylated products **2g−2i**.

The beauty of this method lies in the successful extension to prepare the quaternary-centered 3-sulfenyloxindoles. 3-Benzyloxindole, on reaction with phenyl disulfide, provided 3-benzyl-3-(phenylthio)indolin-2-one **2j** in 91% yield. The substituents on either phenyl ring of oxindole or that of aryl disulfide did not affect the elegance of the current reaction system in affording the corresponding 3,3-disubstituted sulfenyloxindoles **2k**, **2l**. Gratifyingly, phenyl diselenide was also compatible with the reaction system (Scheme 3). 3-Benzyloxindoles, on reaction with phenyl diselenide, gave the respective selenenyl products **2m−2o** in modest yields. Unfortunately, phenyl ditelluride could not afford the respective tellurated oxindole; instead, 3-hydroxyoxindole was formed as the major product.

To check the versatility of the present reaction, we attempted a reaction of linear amide (2-phenylacetamide) with phenyl dichalcogenide (Scheme 4). Indeed, chalcogenated phenylacetamides **3a−c** were obtained in moderate to good (55−75%) yields.

α-Tetralone, a cyclic ketone, was also tested under the reaction conditions (Scheme 4). Unexpectedly, it resulted in the formation of 2-chalcogenyl-1-naphthols **4a−4c** by concomitant chalcogenation and aromatization (Scheme 4). 2-Hydroxyaryl chalcogenides were proven to be good antioxidants.[2c] The previous routes for the synthesis of these compounds involve two steps: lithiation of 2-bromoaryl alcohol followed by addition of diaryl dichalcogenide to the resulting dianion.[2e] In another approach, electrophilic selenation of phenol provided 2-hydroxyaryl selenide.[9a] Nonetheless, the *para*-position needs to be blocked in order to obtain *ortho* as a major product, and harsh reaction

Scheme 4. Chalcogenation of Acetamides and *α*-Tetralone[a]

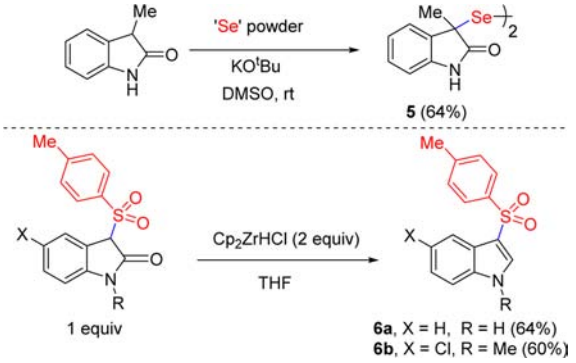


[a]Aryl dichalcogenide (0.5 mmol), substrates (1 mmol), and KOtBu (1.1 mmol for **3a−3c** and 2.2 mmol for **4a−4c**) were used unless otherwise mentioned.

conditions are also required to generate the aryl chalcogenenium ion (ArS$^+$/ArSe$^+$).

Here, we could access 2-chalcogenyl-1-naphthols **4a−4c** using this method in decent yields. Moreover, the addition of selenium powder to 3-methyloxindole under the present reaction conditions provided 3,3′-diselanediylbis(3-methylindolin-2-one) **5** in 64% yield (Scheme 5).

Scheme 5. Formation of Diselenide 5 and 3-Sulfonylindoles



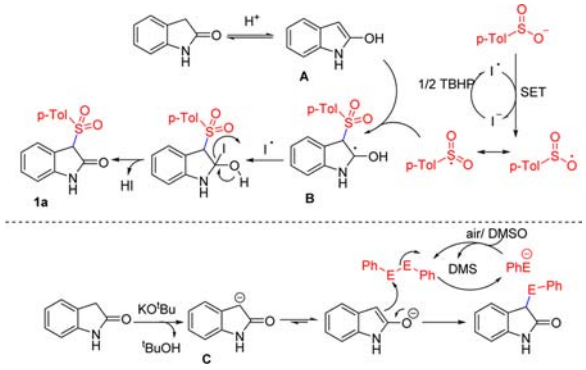
The synthetic utility of the synthesized 3-sulfonyloxindoles was then explored by using Schwartz reagent to obtain the respective 3-sulfonylindoles (Scheme 5). 3-Tosylindolin-2-ones **1a** and **1g**, on reaction with Schwartz reagent, provided 3-tosyl-1*H*-indoles **6a** and **6b** in 64 and 60% yields, respectively.

A plausible mechanism for the sulfonylation reaction is depicted in Scheme 6 based on the obtained results and control experiments. Oxindole can reversibly exist in an enol form **A** in the presence of acetic acid. TBHP converts iodide into iodine radical. Aryl sulfinate ion could be transformed by a single-electron transfer (SET) to a sulfinate radical at the expense of the iodine radical. Sulfinate radicals exhibit reactivity by way of sulfur to form a sulfonate radical, which then added to the C═C bond of enol **A** to form radical intermediate **B**, which would undergo the transfer of electron followed by proton transfer to the iodine radical leading an elimination of HI and concomitant generation of 3-arylsulfonated indole (**1a**).

In an aryl chalcogenation reaction, oxindole undergoes deprotonation in the presence of KO^{t}Bu to form *α*-carbanion **C** that can reversibly exist in an oxy anion, which on reaction with dichalcogenide forms 3-chalcogenyloxindole. On the other hand, phenyl chalcogenolate anion would oxidize back to the aryl

DOI: 10.1021/acs.orglett.6b03735
Org. Lett. 2017, 19, 774−777

Scheme 6. Mechanism for the Sulfonylation and Chalcogenation



dichalcogenide by DMSO or air in basic conditions.[10c] Similarly, the formation of 2-chalcogenyl-1-naphthols **4a−4c** and diselenide **5** may be rationalized (see the SI for details). It is worth noting that 1 equiv of dichalcogenide was enough to compensate for 2 equiv of amide precursor, which was not likewise in the case of conventional coupling of chalcogenide precursors with aryllithium/aryl Grignard reagents (vide supra).

In summary, we have developed an accessible TM-free synthetic method for the synthesis of 3-sulfonyloxindoles using KI, TBHP as an oxidant in DMSO, and acetic acid. The reaction system is compatible to make a library of sulfonated oxindoles. Similarly, we have also presented a TM-free method for the sulfenation and selenation of C−H bond of oxindoles, phenylacetamides, and α-tetralone using KO^{t}Bu in DMSO at room temperature. We believe that these developed methods are significant, owing to their potentially simple operational procedures. Synthesis of densely substituted organochalcogenides and their antioxidant studies is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03735.

Experimental details, NMR spectra, and X-ray crystallographic data (PDF)

X-ray data for compound **1a** (CIF)

X-ray data for compound **2k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sangitkumar@iiserb.ac.in.

ORCID

Ch. Durga Prasad: 0000-0002-6473-8405

Sangit Kumar: 0000-0003-0658-8709

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.K. thanks DST-SERB (EMR/2015/000061), New Delhi, and IISER Bhopal for generous funding. C.D.P. and M.S. thank UGC, CSIR, New Delhi, for their fellowships.

■ REFERENCES

(1) (a) Mugesh, G.; du Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (b) Nogueira, C. W.; Zeni, G.; Rocha, B. T. *Chem. Rev.* **2004**, *104*, 6255. (c) Shahzad, S. A.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2588. (d) Wirth, T. Organoselenium Chemistry: Modern Developments in Organic Synthesis. *Top. Curr. Chem.* **2000**, *208*, 1. (e) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504. (f) Shahzad, S. A.; Vivant, C.; Wirth, T. *Org. Lett.* **2010**, *12*, 1364. (g) Wirth, T. *Organoselenium Chemistry: Synthesis and Reactions*; Wiley-VCH: Weinheim, 2012; pp 1−65 and 321−356. (h) Wirth, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 10074.

(2) (a) Cotgreave, I. A.; Moldéus, P.; Brattsand, R.; Hallberg, A.; Andersson, C.-M.; Engman, L. *Biochem. Pharmacol.* **1992**, *43*, 793. (b) Engman, L.; Andersson, C.; Morgenstern, R.; Cotgreave, I. A.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 2929. (c) Engman, L.; Stern, D.; Frisell, H.; Vessman, K.; Berglund, M.; Ek, B.; Andersson, C.-M. *Bioorg. Med. Chem.* **1995**, *3*, 1255. (d) Johansson, H.; Shanks, D.; Engman, L.; Amorati, R.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2010**, *75*, 7535. (e) Poon, J.-F.; Singh, V. P.; Engman, L. *J. Org. Chem.* **2013**, *78*, 6008. (f) Singh, V. P.; Poon, J.-F.; Butcher, R. J.; Engman, L. *Chem. - Eur. J.* **2014**, *20*, 12563. (g) Poon, J.-F.; Singh, V. P.; Yan, J.; Engman, L. *Chem. - Eur. J.* **2015**, *21*, 2447.

(3) (a) Apte, S. D.; Zade, S. S.; Singh, H. B.; Butcher, R. J. *Organometallics* **2003**, *22*, 5473. (b) Chakraborty, T.; Sharma, S.; Singh, H. B.; Butcher, R. J. *Organometallics* **2011**, *30*, 2525.

(4) (a) Mehta, R. G.; Liu, J.; Constantinou, A.; Hawthorne, M.; Pezzuto, J. M.; Moon, R. C.; Moriarty, R. M. *Anticancer Res.* **1994**, *14*, 1209. (b) Dandia, A.; Sati, M.; Arya, K.; Sharma, R.; Loupy, A. *Chem. Pharm. Bull.* **2003**, *51*, 1137. (c) Pedras, M. S. C.; Hossain, M. *Org. Biomol. Chem.* **2006**, *4*, 2581. (d) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hubel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902.

(5) (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291.

(6) (a) Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* **2001**, *123*, 30. (b) Mugesh, G.; Singh, H. B. *Acc. Chem. Res.* **2002**, *35*, 226. (c) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236.

(7) (a) Reddy, M. A.; Reddy, P. S.; Sreedhar, B. *Adv. Synth. Catal.* **2010**, *352*, 1861. (b) Zuo, J.; Wu, Z.-J.; Zhao, J.-Q.; Zhou, M.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 634. (c) Lan, X.-W.; Wang, N.-X.; Bai, C.-B.; Zhang, W.; Xing, Y.; Wen, J.-L.; Wang, Y.-J.; Li, Y.-H. *Sci. Rep.* **2015**, *5*, 18391. (d) Yang, Y.; Li, W.; Xia, C.; Ying, B.; Shen, C.; Zhang, P. *ChemCatChem* **2016**, *8*, 304.

(8) (a) Taniguchi, N. *J. Org. Chem.* **2004**, *69*, 6904. (b) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241. (c) Tang, R.-Y.; Xie, Y.-X.; Xie, Y.-L.; Xiang, J.-N.; Li, J.-H. *Chem. Commun.* **2011**, *47*, 12867. (d) Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2012**, *14*, 2726. (e) Zeng, J.-W.; Liu, Y.-C.; Hsieh, P.-A.; Huang, Y.-T.; Yi, C.-L.; Badsara, S. S.; Lee, C.-F. *Green Chem.* **2014**, *16*, 2644. (f) Badsara, S. S.; Liu, Y.-C.; Hsieh, P.-A.; Zeng, J.-W.; Lu, S.-Y.; Liu, Y.-W.; Lee, C.-F. *Chem. Commun.* **2014**, *50*, 11374. (g) Liu, X.-W.; Han, W.-Y.; Liu, X.-L.; Zhou, Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2014**, *70*, 9191. (h) Azeredo, J. B.; Godoi, M.; Martins, G. M.; Silveira, C. C.; Braga, A. L. *J. Org. Chem.* **2014**, *79*, 4125. (i) You, Y.; Wu, Z.-J.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 8470. (j) Qian, P.-C.; Liu, Y.; Song, R.-J.; Hu, M.; Yang, X.-H.; Xiang, J.-N.; Li, J.-H. *Eur. J. Org. Chem.* **2015**, *2015*, 1680. (k) Taniguchi, N. *J. Org. Chem.* **2015**, *80*, 1764. (l) Yang, Y.; Li, W.; Ying, B.; Liao, H.; Shen, C.; Zhang, P. *ChemCatChem* **2016**, *8*, 2916. (m) Saba, S.; Rafique, J.; Braga, A. L. *Catal. Sci. Technol.* **2016**, *6*, 3087. (n) Rafique, J.; Saba, S.; Rosario, A. R.; Braga, A. L. *Chem. - Eur. J.* **2016**, *22*, 11854. (o) Itoh, T.; Nagata, K.; Sano, D.; Aoyama, O.; Kanemitsu, T.; Miyazaki, M.; Odanaka, Y.; Machida, A. *Heterocycles* **2016**, *92*, 631. (p) Khanal, H. D.; Kim, S. H.; Lee, Y. R. *RSC Adv.* **2016**, *6*, 58501.

(9) (a) Prasad, C. D.; Balkrishna, S. J.; Kumar, A.; Bhakuni, B. S.; Shrimali, K.; Biswas, S.; Kumar, S. *J. Org. Chem.* **2013**, *78*, 1434. (b) Kumar, A.; Kumar, S. *Tetrahedron* **2014**, *70*, 1763. (c) Prasad, C. D.; Verma, A.; Sattar, M.; Kumar, S. *RSC Adv.* **2015**, *5*, 75881.

(10) (a) Kumar, S.; et al. *Org. Lett.* **2015**, *17*, 82. (b) Rathore, V.; Sattar, M.; Kumar, R.; Kumar, S. *J. Org. Chem.* **2016**, *81*, 9206. (c) Kumar, S.; Kadu, R.; Kumar, S. *Org. Biomol. Chem.* **2016**, *14*, 9210.

DOI: 10.1021/acs.orglett.6b03735
Org. Lett. 2017, 19, 774−777