Organic LETTERS

Letter

pubs.acs.org/OrgLett

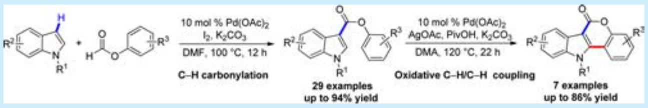
Pd-Catalyzed C−H Carbonylation of (Hetero)arenes with Formates and Intramolecular Dehydrogenative Coupling: A Shortcut to Indolo[3,2-*c*]coumarins

Jie Wu, Jingbo Lan,* Siyuan Guo, and Jingsong You*

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, PR China

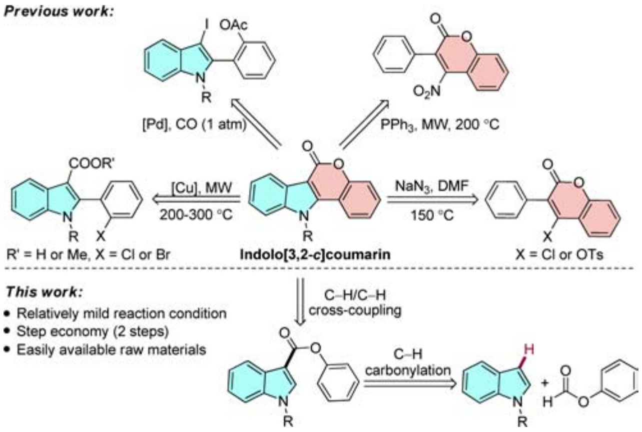
Supporting Information

ABSTRACT: An efficient protocol for the synthesis of (hetero)aryl carboxylic esters has been achieved by Pd-catalyzed C−H carbonylation of (hetero)arenes with aryl formates. A relatively wide range of functional groups can be tolerated in this transformation, and the corresponding esters are obtained in good yields. On this basis, an intramolecular oxidative C−H/C−H coupling has been developed to prepare indolo[3,2-*c*]coumarins.



Carboxylic ester and lactone derivatives (e.g., coumarins) are widely found in natural products, pharmaceuticals, and functional materials.[1−3] For example, indolo[3,2-*c*]-coumarins are an important class of fused coumarin derivatives that possess a variety of interesting biological activities, including antiangiogenesis, anticancer, and estrogenic activity.[4] The main methods to prepare the indolo[3,2-*c*]coumarins usually involve multistep condensation and cyclization to construct the indole scaffold and/or various traditional coupling and lactonization to forge the coumarin framework (Scheme 1).[5,6] These methods generally suffer from limitations such as substrate generality, harsh reaction conditions, and sometimes inaccessible or not easily accessible synthetic precursors. From the viewpoint of synthetic simplicity and step economy, the C−H carbonylation of (hetero)arenes and sequential intramolecular oxidative C−H/C−H coupling is doubtless one of the most ideal strategies to construct indolo[3,2-*c*]coumarins (Scheme 1).[7]

Scheme 1. Retrosynthesis of Indolo[3,2-*c*]coumarin

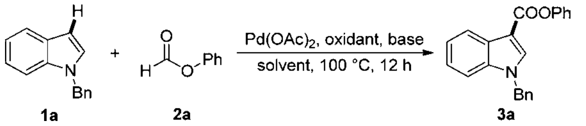


Although CO is a famous C1 building block and has been extensively used to synthesize aromatic carboxylic acids and ester derivatives in industry,[8] many chemists are slightly reluctant to employ it in academic laboratories.[9] Because of high toxicity, flammability, explosibility, and difficult handling of gaseous CO, a high-pressure reactor usually has to be employed. Therefore, formate esters have been widely used as alternative sources of CO in recent years because they are liquid or solid, which make them easy to handle.[9,10] Recently, considerable attention has been focused on the synthesis of aromatic carboxylic derivatives by using formate esters as the carboxyl source.[10] However, the C−H carbonylation of (hetero)arenes using aryl formate esters as a carboxyl source to form aromatic carboxylic esters remains unexplored. Following our continuing interest in C−H functionalization of heteroarenes,[11] we herein present an efficient synthesis of (hetero)aryl carboxylic esters via Pd-catalyzed C−H carbonylation of (hetero)arenes with aryl formate esters, which offers an opportunity to concisely prepare indolo[3,2-*c*]coumarins through an intramolecular oxidative C−H/C−H coupling between an indole ring and an arene (Scheme 1).

The Pd-catalyzed C−H carbonylation of (hetero)arenes with aryl formates to produce carboxylic esters was first investigated. 1-Benzyl-1*H*-indole (**1a**) and phenyl formate (**2a**) were chosen as model substrates to optimize the reaction conditions (Table 1). Using palladium acetate as a catalyst, various common inorganic oxidants (e.g., $Cu(OAc)_2$, Ag_2CO_3, and $K_2S_2O_8$) or organic oxidants (e.g., DDQ and $PhI(OAc)_2$) were screened, but all failed to give the desired product (Table 1, entries 1−5). Fortunately, when iodine was tested as an oxidant, product **3a** was obtained in 52% yield (Table 1, entry 6). It was speculated that the Pd-catalyzed C−H carbonylation might involve an in situ iodination process.[12] The structure of **3a** was confirmed by

Received: September 17, 2014
Published: November 3, 2014

Table 1. Optimization of the Pd-Catalyzed C−H Carbonylation[a]



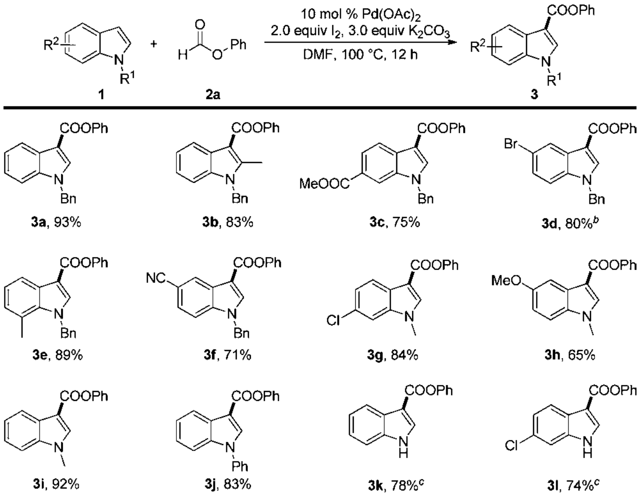
entry	oxidant	base	solvent	yield (%)[b]
1	Cu(OAc)$_2$	K$_2$CO$_3$	DMF	NR
2	Ag$_2$CO$_3$	K$_2$CO$_3$	DMF	NR
3	K$_2$S$_2$O$_8$	K$_2$CO$_3$	DMF	NR
4	DDQ	K$_2$CO$_3$	DMF	ND
5	PhI(OAc)$_2$	K$_2$CO$_3$	DMF	NR
6	I$_2$	K$_2$CO$_3$	DMF	52
7	I$_2$	Na$_2$CO$_3$	DMF	30
8	I$_2$	K$_3$PO$_4$	DMF	trace
9	I$_2$	KHCO$_3$	DMF	trace
10	I$_2$	Et$_3$N	DMF	trace
11	I$_2$	K$_2$CO$_3$	toluene	ND
12	I$_2$	K$_2$CO$_3$	1,4-dioxane	trace
13	I$_2$	K$_2$CO$_3$	DMSO	50
14[c]	I$_2$	K$_2$CO$_3$	DMF	78
15[c,d]	I$_2$	K$_2$CO$_3$	DMF	93

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mmol, 2.0 equiv), Pd(OAc)$_2$ (5 mol %), oxidant (2.0 equiv), base (3.0 equiv) and solvent (1.0 mL) at 100 °C for 12 h under N$_2$. [b]Isolated yield. [c]Phenyl formate (2.0 mmol, 4.0 equiv). [d]Pd(OAc)$_2$ (10 mol %). DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone. ND = no detection. NR = no reaction.

single-crystal X-ray diffraction (Figure S1). Next, other parameters were screened. After screening a variety of bases (e.g., Na$_2$CO$_3$, K$_2$CO$_3$, KHCO$_3$, K$_3$PO$_4$, and Et$_3$N), K$_2$CO$_3$ was clearly the most effective (Table 1, entries 6−10). Among the solvents investigated, DMF was found to be the best choice (Table 1, entries 11−13). Finally, the best result was obtained by using iodine as the oxidant in the presence of Pd(OAc)$_2$ (10 mol %) and K$_2$CO$_3$ (3.0 equiv) in DMF at 100 °C for 12 h.

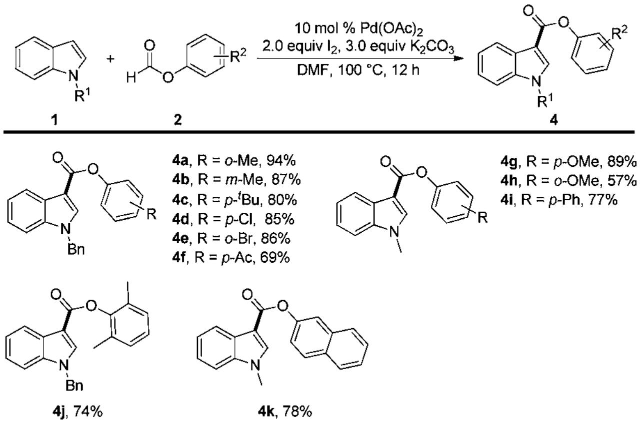
Utilizing the optimal conditions, the reaction scope of indole derivatives was first investigated, and the results are summarized in Scheme 2. To our delight, a relatively broad range of indole derivatives with a substituent at C2, C5, C6, or C7 position of the indole ring were successfully transformed to desired products in good to excellent yields. It was gratifying that chloride and bromide were tolerated, although they were sometimes highly reactive under palladium catalysis. The reaction condition was also compatible with other functional groups on indoles (e.g., ester, nitrile, and methoxy groups) (Scheme 2, **3c**−**3h**), which could be subjected to further synthetic transformations. Indoles with other N-protecting groups such as methyl and phenyl could also give the corresponding products in satisfactory yields, and free (N−H) indoles could even couple with **2a** in good yields (Scheme 2, **3k** and **3l**).

Scheme 2. Pd-Catalyzed C−H Carbonylation of Various Indole Derivatives with 2a[a]



[a]Reactions were carried out using Pd(OAc)$_2$ (10 mol %), K$_2$CO$_3$ (3.0 equiv), I$_2$ (2.0 equiv), indole derivative (0.50 mmol), and **2a** (2.0 mmol, 4.0 equiv) in DMF (1.0 mL) under N$_2$ at 100 °C for 12 h. Isolated yields. [b]80 °C. [c]Pd(OAc)$_2$ (5 mol %).

Scheme 3. Pd-Catalyzed C−H Carbonylation of Indoles with Various Aryl Formates[a]



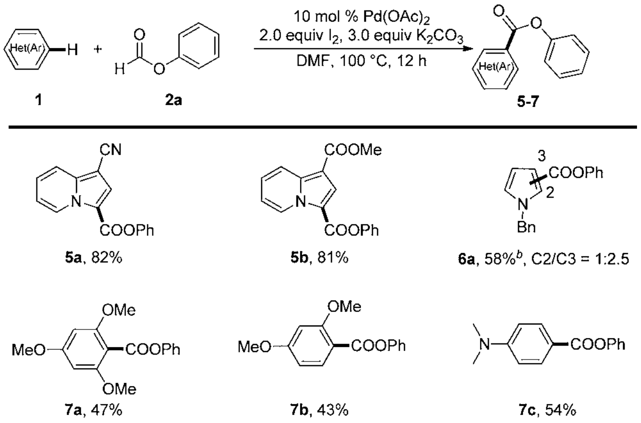
[a]Reactions were carried out using Pd(OAc)$_2$ (10 mol %), K$_2$CO$_3$ (3.0 equiv), I$_2$ (2.0 equiv), indole (0.50 mmol), and **2** (2.0 mmol, 4.0 equiv) in DMF (1.0 mL) under N$_2$ at 100 °C for 12 h. Isolated yields.

Subsequently, a variety of substituted aryl formates were investigated under the optimized reaction conditions, and the results are shown in Scheme 3. Aryl formates bearing either electron-donating groups or electron-withdrawing groups gave the desired products in good to excellent yields. In addition, 2,6-dimethylphenyl formate with steric hindrance was also compatible in the transformation, delivering **4j** in 74% yield. Naphthyl formate was also tested, affording 2-naphthyl indole-3-carboxylate (**4k**) in 78% yield. However, alkyl formates such as methyl formate did not afford the corresponding product.[10c,d]

To further expand the scope of this methodology, we applied this catalytic system to other (hetero)arenes (Scheme 4). The reaction of indolizines afforded the corresponding esters in good yields (Scheme 4, **5a** and **5b**). When pyrrole was employed as the substrate, the carbonylation reaction occurred at both C2 and C3 positions with a 1:2.5 ratio of C2/C3 (Scheme 4, **6a**). Moreover, the C2- and C3-carbonylated products could be isolated by column chromatography. It is worth noting that the benzene rings could also work to provide the benzoate derivatives in moderate yields (Scheme 4, **7a**−**7c**).

After the C−H carbonylation was implemented, the cyclization reaction via the intramolecular oxidative C−H/C−H coupling to build up indolo[3,2-*c*]coumarins was investigated. Although numerous transition-metal-catalyzed intramolecular oxidative C−H/C−H coupling reactions between

Scheme 4. Pd-Catalyzed C−H Carbonylation of Other (Hetero)arenes with 2a[a]

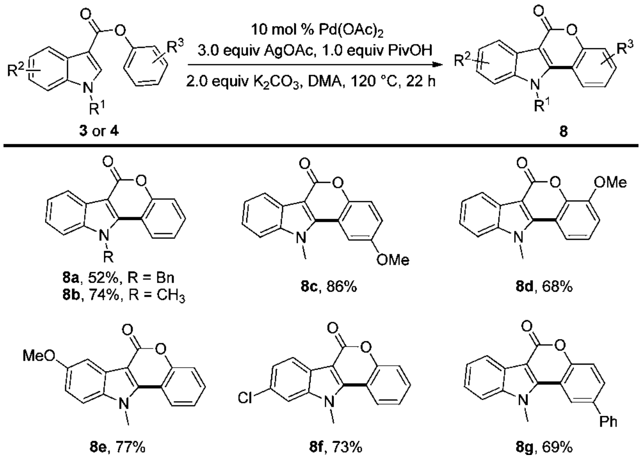


[a] Reactions were carried out using $Pd(OAc)_2$ (10 mol %), K_2CO_3 (3.0 equiv), I_2 (2.0 equiv), (hetero)arene (0.50 mmol), and **2a** (2.0 mmol, 4.0 equiv) in DMF (1.0 mL) under N_2 at 100 °C for 12 h. Isolated yields. [b] The ratio was determined by isolated yield. $Pd(OAc)_2$ (5 mol %).

two (hetero)arenes have been reported,[13] the intramolecular oxidative C−H/C−H coupling of aryl esters of aromatic carboxylic acids to form lactones still remains underrepresented. Thus, the resulting phenyl 1-benzyl-1*H*-indole-3-carboxylate (**3a**) was chosen as a model substrate to optimize the reaction condition. After screening several parameters (see Table S2), the best result was obtained by using AgOAc as the oxidant, pivalic acid (PivOH) as the additive, and K_2CO_3 as the base in the presence of $Pd(OAc)_2$ (10 mol %) in DMA at 120 °C for 22 h. Next, the scope of this oxidative cyclization was investigated, and indolo[3,2-*c*]coumarins with different substituents were obtained in moderate to good yields (Scheme 5). The structure of product **8a** was confirmed by X-ray analysis of single crystals (Figure S2).

In conclusion, we have developed an efficient palladium-catalyzed C−H carbonylation of (hetero)arenes with formate esters to prepare (hetero)aryl carboxylic esters with good functional group tolerance. Both N-protected and unprotected indoles can readily react with a variety of phenyl formates. Other (hetero)arenes such as indolizines, pyrroles, and electron-rich benzene rings are capable of coupling with phenyl formates. An intramolecular oxidative C−H/C−H coupling of the resulting esters has been developed to synthesize indole-fused coumarins. A series of indolo[3,2-*c*]coumarin derivatives are obtained in good yields. Further studies to apply this strategy are currently in process.

Scheme 5. Synthesis of Indolo[3,2-*c*]coumarins through Intramolecular Oxidative C−H/C−H Coupling[a]



[a] Reactions were carried out using $Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), PivOH (1.0 equiv), K_2CO_3 (2.0 equiv), and **3** or **4** (0.20 mmol) in DMA (1.0 mL) under N_2 at 120 °C for 22 h. Isolated yields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, X-ray crystal structures (CIF) of **3a** (CCDC-1027233) and **8a** (CCDC-1015167), and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jingbolan@scu.edu.cn.
*E-mail: jsyou@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from 973 Program (2011CB808601), 863 Program (2013AA031901), the National NSF of China (Nos. 21372164, 21172155, 21025205, 21272160, 21321061, 21432005, and J1103315), and Sichuan Provincial Foundation (2012JQ0002). We thank the Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University, for NMR measurements and X-ray measurements.

■ REFERENCES

(1) (a) Ogliaruso, M. A.; Wolfe, J. F. *Synthesis of Carboxylic Acids, Esters and Their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991. (b) Otera, J.; Nishikido, J. *Esterification: Methods, Reactions, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2010. (c) Janecki, T. *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; Wiley-VCH: Weinheim, Germany, 2013.

(2) For functional coumarins, see: (a) Hara, K.; Tachibana, Y.; Ohga, Y.; Shinpo, A.; Suga, S.; Sayama, K.; Sugihara, H.; Arakawa, H. *Sol. Energy Mater. Sol. Cells* **2003**, *77*, 89. (b) Lee, M.-T.; Yen, C.-K.; Yang, W.-P.; Chen, H.-H.; Liao, C.-H.; Tsai, C.-H.; Chen, C. H. *Org. Lett.* **2004**, *6*, 1241. (c) Patil, P. O.; Bari, S. B.; Firke, S. D.; Deshmukh, P. K.; Donda, S. T.; Patil, D. A. *Bioorg. Med. Chem. Lett.* **2013**, *21*, 2434.

(3) For selected examples on bioactive molecules, see: (a) Gale, J. D.; Grossman, C. J.; Whitehead, J. W. F.; Oxford, A. W.; Bunce, K. T.; Humphrey, P. P. A. *Br. J. Pharmacol.* **1994**, *111*, 332. (b) Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao, M. *J. Nat. Prod.* **2002**, *65*, 500. (c) Tao, H.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979. (d) Leneva, I. A.; Russell, R. J.; Boriskin, Y. S.; Hay, A. J. *Antiviral Res.* **2009**, *81*, 132.

(4) (a) Dakshanamurthy, S.; Kim, M.; Browna, M. L.; Byers, S. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4551. (b) Iwao, M.; Ishibashi, F.; Fukuda, T.; Hasegawa, H. Patent Appl. WO 2012099129, 2012.

(5) For selected examples on construction of the indole structure by using coumarin derivatives, see: (a) Stadlbauer, W.; Laschober, R.; Kappe, T. *Monatsh. Chem.* **1991**, *122*, 853. (b) Irgashev, R. A.; Karmatsky, A. A.; Slepukhin, P. A.; Rusinov, G. L.; Charushin, V. N. *Tetrahedron Lett.* **2013**, *54*, 5734.

(6) For selected examples on construction of the coumarin structure using indole derivatives, see: (a) Yao, T.; Yue, D.; Larock, R. C. *J. Org.*

Chem. **2005**, *70*, 9985. (b) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379. (c) Nealmongkol, P.; Tangdenpaisal, K.; Sitthimonchai, S.; Ruchirawat, S.; Thasana, N. *Tetrahedron* **2013**, *69*, 9277.

(7) For selected recent reviews, see: (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452. (d) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.

(8) For recent reviews on carbonylation reactions, see: (a) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (d) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788. (e) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1.

(9) For review on carbonylation without the direct use of CO, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(10) For recent examples, see: (a) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (b) Schareina, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205. (c) Fujihara, T.; Hosoki, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *Chem. Commun.* **2012**, *48*, 8012. (d) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100. (e) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 5370. (f) Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 3183.

(11) (a) Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466. (b) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (c) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365. (d) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 580. (e) Li, G.; Qian, S.; Wang, C.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7837.

(12) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577.

(13) For selected examples, see: (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (b) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (c) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2011**, *133*, 1209. (d) Li, H.; Zhu, R.-Y.; Shi, W.-J.; He, K.-H.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4850. (e) Gandeepan, P.; Hung, C.-H.; Cheng, C.-H. *Chem. Commun.* **2012**, *48*, 9379.