Organic LETTERS

Letter

pubs.acs.org/OrgLett

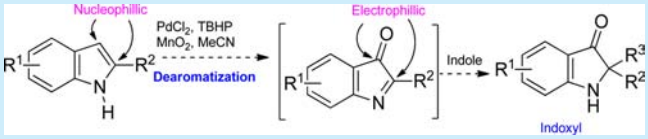
Oxidative Dearomatization of Indoles via Pd-Catalyzed C−H Oxygenation: An Entry to C2-Quaternary Indolin-3-ones

Sankar K. Guchhait,* Vikas Chaudhary, Vijay A. Rana, Garima Priyadarshani, Somnath Kandekar, and Maneesh Kashyap

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, SAS Nagar (Mohali), Punjab 160062, India

Supporting Information

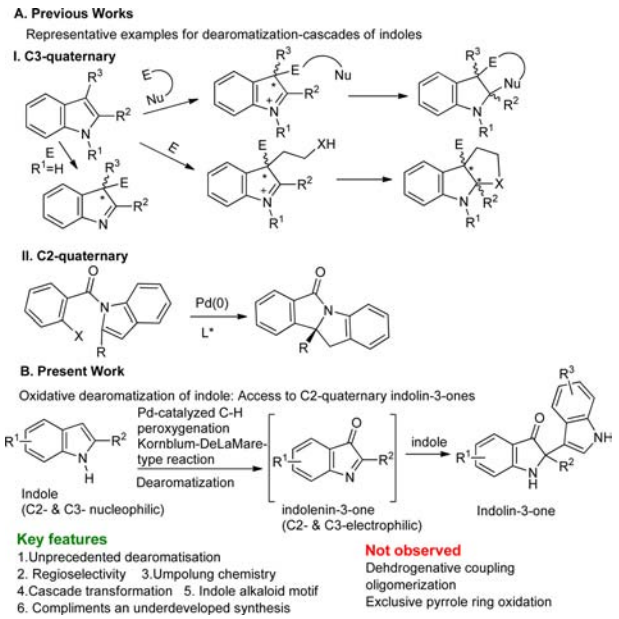
ABSTRACT: An oxidative dearomatization chemistry of 2-arylindole via a unique pathway involving Pd-catalyzed C−H peroxygenation is documented. Coupled with cascade transformation, it provides a new route to access indolin-3-ones bearing a C2-quaternary functionality, including a chiral center (indoxyls), a motif prevalent in indole alkaloids but synthetically underexplored. The method is chemo- and regioselective and compatible with versatile substrates. A mechanism has been outlined on the basis of results of control experiments, isolation/use of intermediates, and spectroscopic studies.



The chemistry of dearomatization generates reactive species that undergo versatile cascade reactions.[1] The strategy offers straightforward conversion of a planar (hetero)arene scaffold into a three-dimensional alicyclic molecular framework. In addition, the installation of quaternary sp^3-carbon provides structural novelty, enhanced topological complexity and diversity points, and improved druglike physical properties.[2] The dearomatization processes also exist in nature, which undergo via oxidation (oxygenases) or reduction (reductases).[3] In dearomatization chemistry, several electron-rich arenes and heteroarenes[4] and numerous inter- and intramolecular elegant strategies have been explored.[5] In recent years, the chemistry of dearomative cascade reactions of 3-substituted indoles constructing C3-quaternary indolines has literally flourished (Scheme 1A),[6] and the processes have been extensively applied to synthesis of indole alkaloids and bioactive products.[7] Toward synthesis of C2-quaternary indolines (Figure 1), which is relatively underexplored, intramolecular arylative dearomatization via a Pd-catalyzed reductive Heck or cyanation reaction[8] and an approach of chlorocyclization of indole-derived benzamides[9] are remarkable (Scheme 1A). In a method of synthesizing C3-quaternary indoline (oxindole) via oxidative rearrangement, the production of its isomeric C2-quaternary analogue (indoxyl) has also been reported.[10] The dearomatization−semipinacol rearrangement of indol-2-ylcyclobutanol provides indoxyl.[11]

Here, we report a new class of oxidative dearomatization of C2-substituted indoles via Pd-catalyzed C−H peroxygenation and Kornblum−DeLaMare-type reactions,[12] producing a reactive intermediate 2-aryl-3*H*-indol-3-one. Its cascade condensation with a dissimilar indole yielded the indoline bearing C2-quaternary and 3-keto functionality (Scheme 1B). There are few literature reports for the synthesis of 2,2-diarylindolin-3-one,[13] one of which describes a Brønsted acid catalyzed reaction of 2-aryl-3*H*-indol-3-one with indole.[14a] However, 2-aryl-3*H*-indol-3-ones are not easily accessible and require multistep synthesis.[14b] It is worth mentioning that the oxidation of indole via singlet oxygenation[15] or using Mo-based oxidants,[16] which forms 2-methoxy/hydroxyl-substituted 1,2-dihydro-3*H*-indol-3-one, and the subsequent acid-catalyzed substitution produces an indolin-3-one bearing a C2-quaternary chiral center. The oxidative self-di-/trimerization of indoles

Scheme 1. Dearomatization of Indoles: Previous and Present Work



Received: January 25, 2016
Published: March 17, 2016

DOI: 10.1021/acs.orglett.6b00244
Org. Lett. 2016, 18, 1534−1537

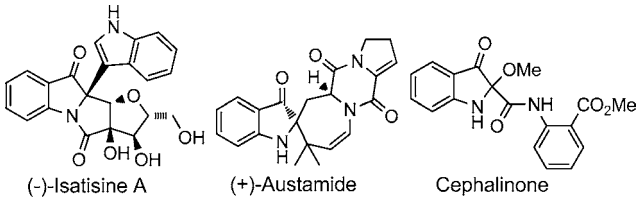
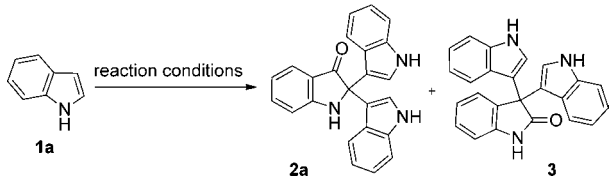


Figure 1. Representative examples of NPs containing C2-quaternary indolin-3-ones (indoxyls).[17]

using different oxidants and mechanistic aspects is also known.[18]

At the outset, we envisaged that a high energy barrier associated with dearomatization and the chemoselectivity control in this new reaction could be of concern for its development. For a proof of the concept, a reaction of cascade oxidative dearomatization and condensation of indole toward production of 2,2-bis(indol-3-yl)indolin-3-one, as a rapid and simpler mode of investigation, was first considered. We commenced our study for the reaction of indole using $Pd(OAc)_2$ catalyst and ^tBuOOH (entry 1, Table 1). Gratifyingly, the desired product was obtained, although in 35% yield. To our surprise, formation of a regioisomeric product, 3,3-bis(indol-3-yl)indolin-2-one, in considerable quantity (10%) was also observed. This isomer formed obviously due to C2-H peroxygenation of indole, indicating an additional concern of regiocontrol in the reaction. After various experiments, pleasingly, a good yield (62%) of the desired product as well as improved regioselectivity were obtained using an optimum quantity (2.2 equiv) of TBHP along with MnO_2 as a co-oxidant (entry 3). The reaction did not proceed in the absence of TBHP (entry 6). The reaction without MnO_2 provided a lower yield (entry 7). The regioselectivity was further improved by lowering the reaction temperature to an optimum (60 °C). Next, we evaluated the role of solvent. Use of polar aprotic solvents such as THF, acetonitrile, and DMSO improved the regioselectivity as well as yield, and acetonitrile was found to be best. The use of polar protic solvents EtOH, PEG-400, and H_2O was found to be detrimental for conversion and regioselectivity. The reaction performed without Pd catalyst did not proceed. Among various Pd catalysts tested, to our delight, $PdCl_2$ gave the desired product in 90% yield. The other isomeric product virtually did not form. Reaction under O_2 as oxidant in place of TBHP did not proceed, while Oxone reduced the yield of **2a**. Cu catalysts such as CuI, $CuCl_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$ were ineffective. The addition of 1 equiv of a base (Et_3N)/ or an acid (AcOH) prevented the reaction from proceeding.

Table 1. Optimization Studies[a]



no.	catalyst (mol %)	TBHP (equiv), MnO_2 (equiv)	temp (°C), time (h)	solvent	yield[b] (%) of **2a, 3**
1	$Pd(OAc)_2$ (5)	4, 2	80, 4	toluene	35, 10
2	$Pd(OAc)_2$ (5)	3, 2	80, 4	toluene	43, 10
3	$Pd(OAc)_2$ (5)	2.2, 2	80, 5	toluene	62, 10
4	$Pd(OAc)_2$ (5)	2, 2	80, 5	toluene	55, 8
5	$Pd(OAc)_2$ (5)	1.2, 2	80, 8	toluene	42, 5
6	$Pd(OAc)_2$ (5)	0, 2	80, 24	toluene	NR[c]
7	$Pd(OAc)_2$ (5)	2.2, 0	80, 4	toluene	45, 5
8	$Pd(OAc)_2$ (5)	2.2, 0	60, 6	toluene	65, 12
9	$Pd(OAc)_2$ (5)	2.2, 2	60, 12	THF	53, 12
10	$Pd(OAc)_2$ (5)	2.2, 2	60, 12	MeCN	79, trace
11	$Pd(OAc)_2$ (5)	2.2, 2	60, 12	DMSO	70, trace
12	$Pd(OAc)_2$ (5)	2.2, 2	60, 12	EtOH	45, 20
13	$Pd(OAc)_2$ (5)	2.2, 2	60, 12	PEG-400	27, 12
14	$Pd(OAc)_2$ (5)	2.2, 2	60, 9	H_2O	23, 30
15	Nil	2.2, 2	60, 24	MeCN	trace
16	$Pd(PPh_3)_2Cl_2$ (5)	2.2, 2	60, 6	MeCN	75, trace
17	$PdCl_2$ (5)	2.2, 2	60, 6	MeCN	90, trace
18	$PdCl_2$ (2.5)	2.2, 2	60, 6	MeCN	58, trace

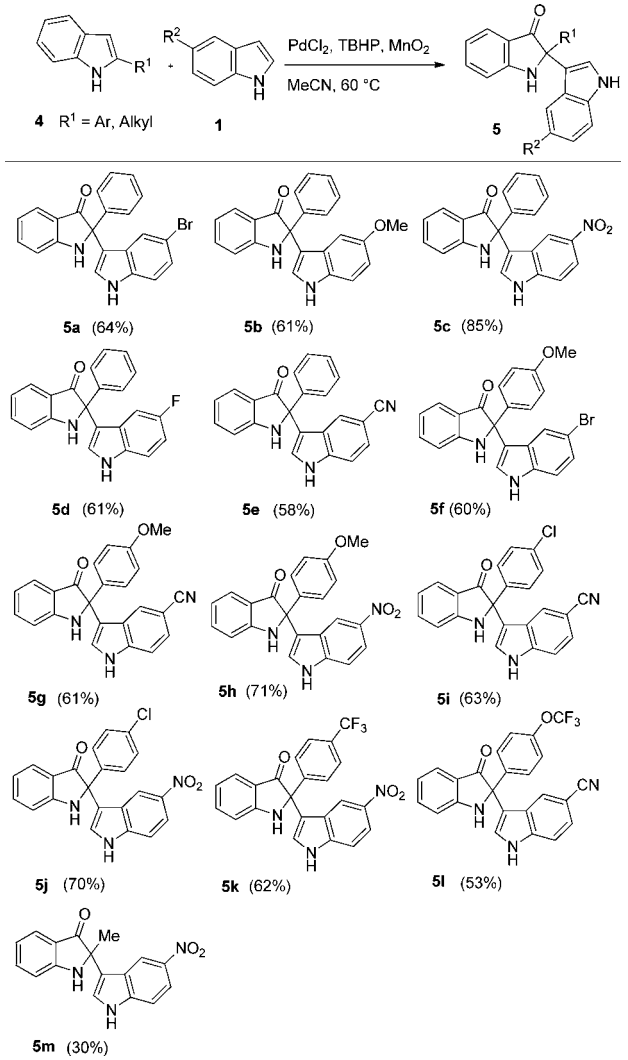
[a]Indole (1 mmol); solvents were utilized as received from commercial sources. [b]Isolated yield for maximum conversion in optimum time. [c]No reaction.

With the developed protocol, we next investigated its flexibility for the reaction of 2-substituted indoles with C2-H-free indoles toward preparation of indoxyls bearing a C2-quaternary chiral center (Scheme 2). Various 2-arylindoles and C2-unsubstituted indoles were used as substrates. We were pleased to find that the protocol was adaptable for accommodating varied substrates. The reaction was found to be nonsignificantly sensitive to electronic effects, as the substrates possessing electron-withdrawing as well as electron-donating functionalities (Cl/OMe/CF_3/OCF_3 in 2-aryl or Br/OMe/NO_2/F/CN in indole ring) were compatible in the method. The tolerance of various functionalities including bromo/chloro groups in the reaction provides an opportunity for further derivatization of products. C2-Alkyl-substituted indole also underwent reaction, although the product was obtained in low yield and several nonisolable side products formed plausibly due to benzylic oxidation. Importantly, no cross/self-dehydrogenative couplings of indoles, which are known to undergo under Pd(II)-catalyzed oxidative conditions, were observed, as indicated by mass spectrometry of crude mixtures of several reactions. Furthermore, despite the acidic conditions, the indole oligomerization did not proceed. The generality of the developed method was further explored in the formation of 2,2-bis(indol-3-yl)indolin-3-ones (Table 2). Delightfully, indoles possessing various substitutions at benzene ring underwent the reaction smoothly and the desired indoxyls were obtained in high-to-excellent yields. Both electon-donating and electron withdrawing functionalities (OMe/F/NO_2/CN) did not cause any significant effect in the reaction. The oxidative dearomatization was found to be extremely regioselective, as the other isomeric product 3,3-bis(indol-3-yl)indolin-2-one virtually did not form in each example. Despite the challenges of overcoming high energy barrier and selectivity issues, the reaction method was chemo- as well as regioselective and viable under mild conditions and provided products with up to 90% yield. Besides, the additional C3-keto functionality in the indoline framework is useful for a variety of structural elaborations.

Next, we were interested in gaining insight to the possible mechanism. The reactions performed in the presence of TEMPO or BHT reduced the reaction rates and resulted in trace/no formation of desired products, indicating involvement of radical-based transformation. Under optimized conditions,

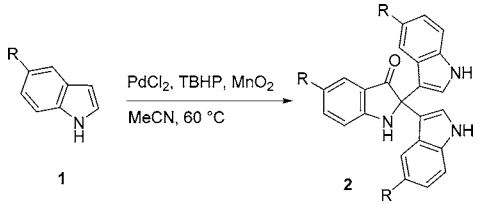
DOI: 10.1021/acs.orglett.6b00244
Org. Lett. 2016, 18, 1534−1537

Scheme 2. Substrate Scope: Synthesis of Indolin-3-ones Bearing C2-Quaternary Chiral Center[a,b]



[a]Substrates, reagents, and conditions: 2-substituted indole (1 mmol), C2-H free indole (1 equiv), $PdCl_2$ (5 mol %), TBHP (70% aq, 2.2 equiv), MnO_2 (2 equiv), MeCN (1 mL), 60 °C; [b]Isolated yield for maximum conversion in optimum time (3−6 h).

Table 2. Substrate Scope: Synthesis of 2,2-Bis(indol-3-yl)indolin-3-ones[a]

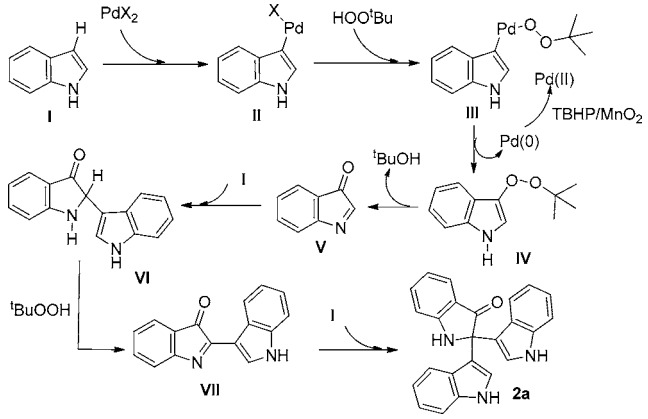


no.	R	product	yield[b] (%)	no.	R	product	yield[b] (%)
1	H	**2a**	90	4	NO_2	**2d**	81
2	OMe	**2b**	86	5	Ph	**2e**	84
3	F	**2c**	83	6	CN	**2f**	80

[a]Substrate, reagents, and conditions: substituted indole (1 mmol), $PdCl_2$ (5 mol %), TBHP (70% aq, 2.2 equiv), MnO_2 (2 equiv), MeCN (1 mL), 60 °C; [b]Isolated yield for maximum conversion in optimum time (4−5 h).

none of the intermediate formed in isolable quantities. Reaction of 2-(4-methoxyphenyl)-1*H*-indole in the absence of C2-H-free indole under the optimized conditions produced 2-(4-methoxyphenyl)benzo[*d*][1,3]oxazin-4-one (**6**) and 2,2′-bis(4-methoxyphenyl)-2,3-biindolin-3-one (**7**), which might be generated from a common intermediate 2-(4-methoxy)-3*H*-indol-3-one by Baeyer−Villiger oxidation and oligomerization, respectively (see the Supporting Information). The mass spectra of crude mixtures withdrawn at intermediate time intervals also indicated formation of 3*H*-indol-3-ones. 2-Phenyl-3*H*-indol-3-one (**8**), prepared by the reported method[14b] (see the SI), when utilized in the reaction with 5-nitroindole under optimized conditions provided product **5c** in similar yield. All of these suggest the formation of the 3*H*-indol-3-one motif as an intermediate in the reaction. The NMR spectra of the reaction mixture at intermediate times suggested the presence of a *tert*-butylperoxy motif in the intermediates (see the SI). The control reactions of indole + TBHP and indole + TBHP + MnO_2 under otherwise indentical conditions produced indole-oxidation products in trace quantities, indicating poor susceptibility of indole toward direct oxidation by TBHP−MnO_2. The absence of indole C3-H in the NMR spectra of a mixture obtained after the reaction of indole, $PdCl_2$ (1 equiv) and TBHP (2.2 equiv) in MeCN at 60 °C for 1 h[19] suggested the involvement of C3-electrophilic palladation.[20] Based on these observations, a plausible mechanism is outlined (Scheme 3). The electrophilic palladation of indole,[20] reaction with

Scheme 3. Plausible Mechanism



TBHP, and reductive elimination constructs indole 3-*tert*-butylperoxide (**IV**). Its conversion via a pathway similar to the Kornblum−DeLaMare reaction produces key intermediate 3*H*-indol-3-one (**V**). Electrophilic trapping with indole leads to formation of **VI**. Dehydrogenation followed by trapping with second indole gives the final product. Oxidation of Pd(0) to Pd(II) occurs by TBHP/MnO_2. Importantly, the present dearomatization chemistry generating 3*H*-indol-3-one skeleton from indole represents a unique class of umpolung chemistry and can now enable indole's versatile chemical modifications that are otherwise not possible.

In conclusion, we have developed a new reaction of oxidative dearomatization of indole and cascade electrohilic indolylation. The dearomatization involves the Pd-catalyzed C-3 peroxygenation with TBHP and a Kornblum−DeLaMare-type reaction generating a reactive 3*H*-indol-3-one motif from indole. The developed reaction has for the first time installed simultaneously the C2-quaternary, including the chiral center and the

DOI: 10.1021/acs.orglett.6b00244
Org. Lett. 2016, 18, 1534−1537

3-keto functionality in indolines, providing access to various indoxyls. The approach has potential to pave the way for preparation of C2-quaternary indoline skeleton which is synthetically underexplored compared to C3-quaternary analogs (oxyindoles) and prevalent in indole alkaloids as well as biologically relevant products. More importantly, given the rich combination of C2-quaternary and C3-keto functionality in the skeleton, the reaction is useful in synthesizing versatile indoline derivatives including the analogues with a new fused ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00244.

Experimental procedure, intermediate-trapped products, ^{1}H NMR and ESI-MS spectra of crude mixtures, full characterization of new products, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: skguchhait@niper.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from CSIR, New Delhi, for this investigation. V.C. is thankful to CSIR, New Delhi, for his fellowship. G.P. is thankful to NIPER for her fellowship.

■ REFERENCES

(1) (a) López Ortiz, F.; Iglesias, M. J.; Fernndez, I.; Snchez, C. M. A.; Gmez, G. R. *Chem. Rev.* **2007**, *107*, 1580. (b) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (c) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

(2) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14740.

(3) (a) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, *2009*, 685. (b) Schätzle, M. A.; Flemming, S.; Husain, S. M.; Richter, M.; Gnther, S.; Mller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2643.

(4) (a) Zhang, S.; Yu, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Chem. Commun.* **2015**, *51*, 3842. (b) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci.* **2012**, *3*, 205.

(5) (a) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327.

(6) For selected examples, see: (a) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46. (b) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *Chem. Sci.* **2012**, *3*, 3170. (c) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (d) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L *J. Am. Chem. Soc.* **2010**, *132*, 11418. (e) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350. (f) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111. (g) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238. (h) Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140. (i) Roche, S. P.; Tendoung, J. J. Y.; Tréguier, B. *Tetrahedron* **2015**, *71*, 3549.

(7) (a) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964. (c) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5482. (d) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (e) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (f) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485. (g) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716. (h) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052. (i) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557.

(8) (a) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. *J. Am. Chem. Soc.* **2015**, *137*, 4936. (b) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett.* **2015**, *17*, 4838.

(9) Yin, Q.; You, S.-L. *Org. Lett.* **2013**, *15*, 4266.

(10) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009.

(11) Peng, J.-B.; Qi, Y.; Ma, A.-J.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H.; Zhang, S.-Y. *Chem. - Asian J.* **2013**, *8*, 883.

(12) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(13) Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Zhuang, G.-L.; Gao, J. -R.; Jia, Y.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 11205.

(14) (a) Rueping, M.; Raja, S.; Nunez, A. *Adv. Synth. Catal.* **2011**, *353*, 563. (b) Najahi, E.; Valentin, A.; Fabre, P. − L.; Reybier, K.; Nepveu, F. *Eur. J. Med. Chem.* **2014**, *78*, 269.

(15) Ke-Qing, L. *Synth. Commun.* **1996**, *26*, 149.

(16) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830.

(17) (a) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127. (b) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (c) Wu, P.-L.; Hsu, Y.-L.; Jao, C.-W. *J. Nat. Prod.* **2006**, *69*, 1467.

(18) (a) Chien, C. S.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 1843. (b) Altinis Kiraz, C. I. A.; Emge, T. J.; Jimenez, L. S. *J. Org. Chem.* **2004**, *69*, 2200. (c) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Adv. Synth. Catal.* **2012**, *354*, 1873. (d) Kong, Y. − B.; Zhu, J. − Y.; Chen, Z. − W.; Liu, L. − X. *Can. J. Chem.* **2014**, *92*, 269. (e) Rebelo, S. L. H.; Linhares, M.; Simões, M. M. Q.; Silva, A. M. S.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Freire, C. *J. Catal.* **2014**, *315*, 33. (f) Ganachaud, C.; Garfagnoli, V.; Tron, T.; Iacazio, G. *Tetrahedron Lett.* **2008**, *49*, 2476. (g) Young, T. E.; Auld, D. S. *J. Org. Chem.* **1963**, *28*, 418. (h) Qin, W.-B.; Chang, Q.; Bao, Y.-H.; Wang, N.; Chen, Z.-W.; Liu, L.-X. *Org. Biomol. Chem.* **2012**, *10*, 8814.

(19) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

(20) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

DOI: 10.1021/acs.orglett.6b00244
Org. Lett. 2016, 18, 1534−1537