Organic LETTERS

Letter

pubs.acs.org/OrgLett

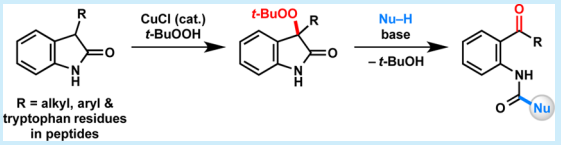
Oxidative Fragmentations and Skeletal Rearrangements of Oxindole Derivatives

Hendrik F. T. Klare, Alexander F. G. Goldberg, Douglas C. Duquette, and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

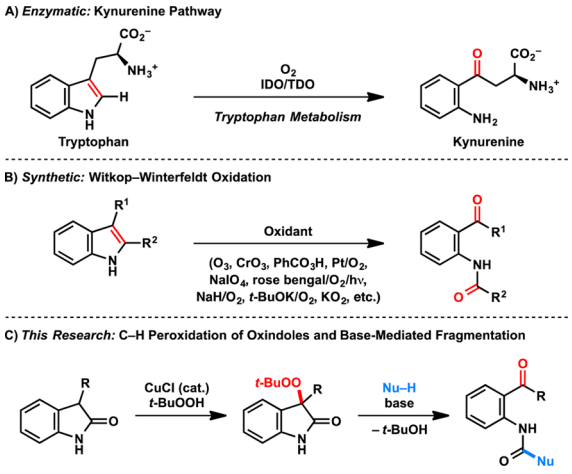
Supporting Information

ABSTRACT: An oxidative sequence for the conversion of oxindoles to structurally distinct heterocyclic scaffolds and aniline derivatives is disclosed by the combination of a copper-catalyzed C−H peroxidation and subsequent base-mediated fragmentation reaction. In contrast to classic enzymatic (i.e., kynurenine pathway) and biomimetic methods (i.e., Witkop−Winterfeldt oxidation) for oxidative indole cleavage, this protocol allows for the incorporation of external nucleophiles. The new transformation displays broad functional group tolerance and is applicable to tryptophan derivatives, opening potential new avenues for postsynthetic modification of polypeptides, bioconjugation, and unnatural amino acid synthesis.



The chemistry of indoles and their derivatives is diverse and well-studied owing to their ubiquity in natural products, pharmaceuticals, agrochemicals, fragrances, and organic dyes and pigments.[1] Importantly, indole serves as part of the side-chain of tryptophan, an essential amino acid and a precursor to an array of bioactive small molecules and complex natural products. For instance, dietary tryptophan that is not incorporated into proteins is predominately metabolized along the kynurenine pathway to several nonindole, bioactive metabolites (Scheme 1A).[2] Similarly, complex indole-containing natural products are often observed alongside oxidized derivatives.[3] The biomimetic variant of this transformation, known as the Witkop−Winterfeldt oxidation,[4] has been accomplished under a variety of conditions[5] and is one of the few methods available for the conversion of indoles to structurally distinct scaffolds (Scheme 1B).[6]

Scheme 1. Oxidative Fragmentations of the Indole Core[a]



[a]IDO = indoleamine 2,3-dioxygenase; TDO = tryptophan 2,3-dioxygenase.

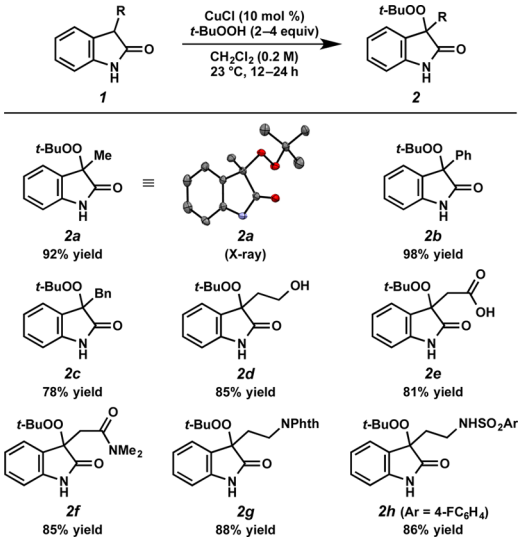
The discovery of new indole fragmentation and ring-expansion methods is particularly appealing given the numerous methods for the preparation[7] and functionalization[8] of indoles. The utility of methods for indole synthesis could be broadened by considering them not only as synthetic targets, but as intermediates toward other heterocycles as well. Furthermore, mild and selective transformations of indoles may be applied to tryptophan fragments in applications such as bioconjugation.[9,10] As part of our research on new indole-related methodologies[11] and on indole-containing natural products,[12] we have discovered a mechanistically different sequence for oxidative fragmentation of indole and oxindole derivatives that is complementary to the prevailing synthetic and enzymatic pathways (Scheme 1C). This method facilitates C2−C3 bond cleavage of the oxindole ring with concomitant reaction with a nucleophile, thereby offering access to diverse heterocycles and aniline derivatives, which are unattainable by conventional biomimetic oxidations.

In the course of our studies on oxidative transformations of oxindoles, we observed that 3-methyloxindole (**1a**) undergoes a Kharasch−Sosnovsky-type C−H peroxidation[13] by *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of numerous metal salts (Scheme 2).[14] Notably, Cheng, Liu, and co-workers independently reported that the same reaction is also catalyzed by cobalt(II) salen complexes in aqueous solution, requiring slightly elevated temperatures of 55 °C for efficient turnover.[15] While the Schiff base ligand proved to be crucial in their protocol, we found that catalytic amounts of simple base metal salts alone promote the C−H peroxidation of oxindoles already at room temperature in various organic solvents such as CH_2Cl_2, CH_3CN, or MeOH (see Tables S1−S3 in the Supporting

Received: December 20, 2016

DOI: 10.1021/acs.orglett.6b03789
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. C−H Peroxidation of 3-Substituted Oxindoles

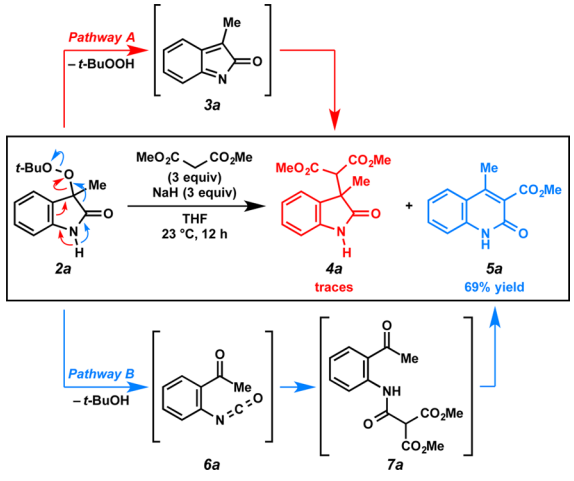


Information). Copper(I) chloride provided optimal results, and peroxidation proceeded exclusively at the benzylic position of the oxindole core; the structure of 3-peroxyoxindole **2a** was unambiguously confirmed by single-crystal X-ray diffraction analysis. The reaction also performed well in the presence of water, thereby allowing the use of aqueous solutions of *t*-BuOOH. However, no desired reaction was observed with any other peroxide besides *t*-BuOOH. While exploring the substrate scope, we found that this selective peroxidation reaction tolerates a variety of functional groups, including alcohols (**2d**), carboxylic acids (**2e**), amides (**2f**), and protected amines (**2g** and **2h**).

Although a number of approaches to access various organic peroxides have been developed,[16] methods to prepare peroxides bearing an oxindolyl functionality are still scarce.[17] The catalytic direct C−H peroxidation provides straightforward access to N-unsubstituted 3-peroxyoxindoles,[15] which represent an unusual class of previously unexplored oxindole derivatives.[18] We therefore set out to study the reactivity profile of these compounds in the context of new reaction discovery.

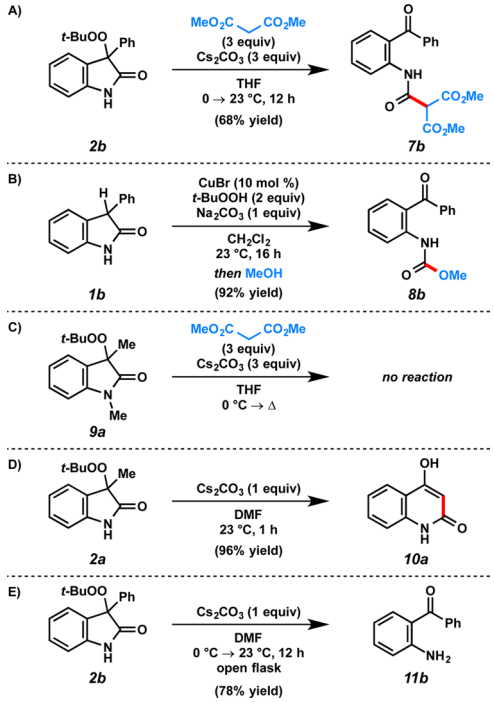
Aside from well-established reductive O−O bond cleavage of the peroxide, we reasoned that the *tert*-butylperoxy substituent could serve as a leaving group for the purpose of oxindole alkylation. Akin to our previous studies on this topic,[11c−e] we considered that basic elimination of *t*-BuOOH from oxindole **2a** would lead to reactive *o*-azaxylylene intermediate **3a**. This species could then react with a malonate nucleophile to afford C3 alkylated product **4a** (Scheme 3, pathway A). In the event, we observed only traces of the expected alkylated oxindole **4a**, and we were surprised to discover that quinolone **5a** was formed as the major product in 69% yield. We proposed that the peroxyoxindole **2a** reacts by a 4-oxa-Grob fragmentation,[19] alternatively, this may be considered a homologous Kornblum−DeLaMare rearrangement,[20] involving a C2−C3 bond cleavage and elimination of *tert*-butyl alcohol (Scheme 3, pathway B). This fragmentation would result in the simultaneous generation of a benzylic ketone at C3 and an isocyanate moiety (cf. **6a**), which then suffers nucleophilic attack by dimethyl malonate. Finally, the proposed intermediate **7a** could convert to the observed quinolone **5a** by net condensative decarboxymethylation with the benzylic ketone, a process presumably driven by the formation of extended conjugation.

Scheme 3. Competing Pathways for Base-Mediated Peroxyoxindole Fragmentation



To confirm this mechanistic hypothesis, we designed several control experiments with alternative nucleophiles and substrates (Scheme 4). First, phenyl-substituted peroxyoxindole **2b** was

Scheme 4. Mechanistic Control Experiments



treated under similar conditions, and we observed malonate adduct **7b**, analogous to the proposed intermediate **7a** (Scheme 3, pathway B). Second, the presumed isocyanate intermediate could be trapped by methanol to afford carbamate **8b**. In this example, both the peroxidation and the fragmentation were performed in a single flask. Third, *N*-methylated analogue **9a** proved to be unreactive, regardless of whether a malonate nucleophile was present or not, suggesting that deprotonation of the oxindole nitrogen is critical for reactivity; this experiment reasonably excludes the possibility of fragmentation occurring by nucleophilic attack at the oxindole carbonyl. Fourth, in the absence of an external nucleophile, 3-methyl-substituted peroxyoxindole **2a** undergoes intramolecular cyclization to

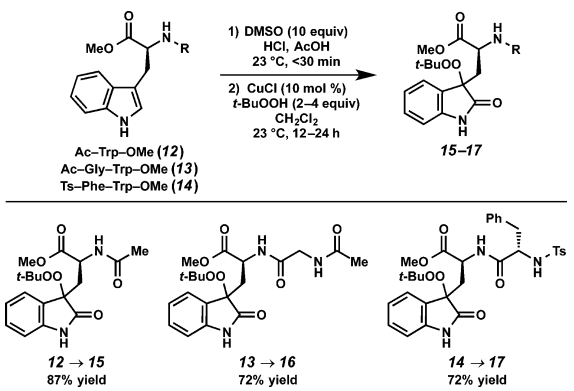
DOI: 10.1021/acs.orglett.6b03789
Org. Lett. XXXX, XXX, XXX−XXX

form 4-hydroxyquinolinone **10a**. Finally, hydrolysis occurs in the presence of water to generate the corresponding aniline (e.g., **11b**). Overall, the peroxide fragmentation is rapid at ambient temperature, and the starting materials are typically consumed within seconds. The nascent 2-acylphenylisocyanate, which has also been observed directly by in situ ReactIR spectroscopy (see Figure S1), is then transformed into different heterocycles and aniline derivatives by intra- or intermolecular nucleophilic attack.

The oxindole fragmentation reaction is noteworthy in the context of the kynurenine pathway[2] and the Witkop oxidation.[4] In biological systems, catabolism of tryptophan is accomplished primarily by two heme enzymes, indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase (cf. Scheme 1A). The mechanism of this enzymatic reaction is believed to proceed by initial epoxidation of the indole, followed by ring opening and oxidative cleavage by an iron oxo intermediate to afford *N*-formylkynurenine, which decomposes under aqueous conditions to the corresponding aniline, namely kynurenine.[2] The biomimetic Witkop oxidation can be performed under a variety of conditions (cf. Scheme 1B), and may proceed by several mechanisms.[4,5] Notably, in all of these cases, the indole substituents at C2 and C3 remain unchanged in the course of the oxidative transformation. In contrast, we have demonstrated a complementary oxidative sequence, which occurs by a distinct mechanistic pathway, allowing for installation of new functionality in the oxidized derivative with oxygen-, carbon-, and nitrogen-based nucleophiles.

Having developed a selective oxindole peroxidation/fragmentation sequence, we envisioned the implementation of our protocol on tryptophan derivatives, paving the way toward relevant applications such as unnatural amino acid synthesis and bioconjugation. In this context, it is relevant to note that methods have been established for the incorporation of oxidized tryptophan units on polypeptides and complex natural products.[21] We therefore prepared *N*-acetyl-L-tryptophan methyl ester (**12**), as well as the two dipeptides **13** and **14**, as model substrates to this end. These tryptophan derivatives were converted to the corresponding peroxyoxindoles **15**, **16**, and **17** using a two-step sequence combining the known acidic DMSO oxidation to oxindolylalanine derivatives[22] with our newly developed peroxidation reaction (Scheme 5). The initial DMSO oxidation was typically high yielding, although the C2-chlorinated indole was routinely observed as a minor side product. In all three cases, the peroxidation reaction proceeded smoothly, despite the presence of several potential sites of reactivity, including the benzylic center on phenylalanine, and

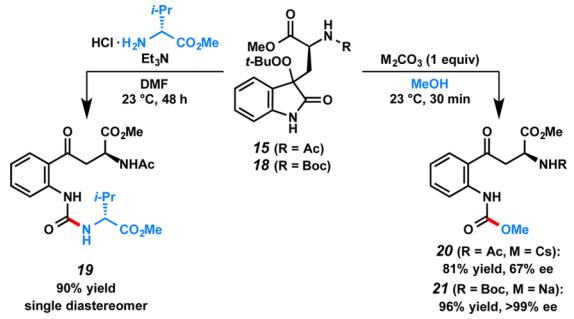
Scheme 5. C−H Peroxidation of Tryptophan Derivatives



the α-carbon on each amino acid. Although this sequence is unselective with regard to the stereochemistry at the indole 3-position, this is inconsequential in the context of the fragmentation reaction since that center is planarized in the final products.

The reactivity of the tryptophan-derived peroxide **15** was akin to that observed with simpler substrates, affording skeletally rearranged kynurenine derivatives, including valine-derived urea **19** and methyl carbamate **20** (Scheme 6). Interestingly, *N*-

Scheme 6. Tryptophan-Derived Peroxide Fragmentation



acetylkynurenine methyl carbamate **20** was obtained in diminished enantiomeric excess. While the two-step oxidation sequence furnished peroxyoxindole **15** as an enantiomerically pure mixture of diastereomers, treatment with cesium carbonate in methanol led to partial racemization. Attempts to optimize the methanolysis reaction using a wide array of organic and inorganic bases, cosolvents, and reduced temperatures did not assist in preserving enantiomeric excess. Consequently, we synthesized the *N*-Boc protected peroxyoxindole **18**. Gratifyingly, this substrate furnished the corresponding *N*-Boc-kynurenine methyl carbamate **21** in excellent yield with perfect stereochemical fidelity when treated with sodium carbonate in methanol. Preliminary findings have also shown that these peroxides react selectively with amines in DMSO/H_2O mixtures at pH $\geq$ 9 to afford coupled derivatives. These experiments suggest that the oxindole fragmentation reaction may potentially be applied in the context of bioconjugation and unnatural amino acid synthesis.

In summary, we have discovered a mild, selective, and biocomplementary sequence for oxidative indole fragmentation that hinges on a copper-catalyzed C−H peroxidation of oxindoles followed by a base-mediated rearrangement. In contrast to known biomimetic indole oxidations, this method provides access to diverse heterocycles and aniline derivatives from a single precursor and constitutes an exquisite opportunity for tryptophan modification. Applications of this method toward bioconjugation, unnatural amino acid synthesis, and postsynthetic peptide modification are the subject of ongoing investigations 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.6b03789.

X-ray data for **2a** (CIF)

Experimental procedures, characterization, optimization, and crystallographic data as well as NMR and IR spectra (PDF)

DOI: 10.1021/acs.orglett.6b03789
Org. Lett. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Author

*E-mail: stoltz@caltech.edu.

ORCID

Hendrik F. T. Klare: 0000-0003-3748-6609

Brian M. Stoltz: 0000-0001-9837-1528

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSF under the CCI Center for Selective C−H Functionalization (CHE-1205646). We thank DAAD (postdoctoral fellowship to H.F.T.K.), NSERC (graduate scholarship to A.F.G.G.), NSF (predoctoral research fellowship to D.C.D., No. DGE-1144469), the Gordon and Betty Moore Foundation, Amgen, Abbott, Boehringer Ingelheim, and Caltech for financial support. Larry Henling (Caltech) is acknowledged for X-ray analysis, and Dr. Robert Craig and Dr. Guillaume Lapointe (both Caltech) are thanked for helpful discussions.

REFERENCES

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: London, 1970. (b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (c) *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; Gribble, G. W., Ed.; Springer: Berlin, 2010.

(2) For reviews of the kynurenine pathway, see: (a) Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. *Chem. Rev.* **1996**, *96*, 2841−2887. (b) Stone, T. W.; Darlington, L. G. *Nat. Rev. Drug Discovery* **2002**, *1*, 609−620. (c) Millett, E. S.; Efimov, I.; Basran, J.; Handa, S.; Mowat, C. G.; Raven, E. L. *Curr. Opin. Chem. Biol.* **2012**, *16*, 60−66. (d) Naismith, J. H. *Biochem. Soc. Trans.* **2012**, *40*, 509−514. (e) Davis, I.; Liu, A. *Expert Rev. Neurother.* **2015**, *15*, 719−721.

(3) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532−547.

(4) (a) Witkop, B. *Justus Liebigs Ann. Chem.* **1944**, *556*, 103−114. For a review, see: (b) Mentel, M.; Breinbauer, R. *Curr. Org. Chem.* **2007**, *11*, 159−176.

(5) For selected examples, see: (a) Warnell, J. L.; Berg, C. P. *J. Am. Chem. Soc.* **1954**, *76*, 1708−1709. (b) Brown, R. R.; Price, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 4158−4159. (c) Nakagawa, M.; Kato, S.; Fukazawa, H.; Hasegawa, Y.; Miyazawa, J.; Hino, T. *Tetrahedron Lett.* **1985**, *26*, 5871−5874. (d) Ross, F. C.; Botting, N. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 875−878. (e) Hamdy, M. S.; Scott, E. L.; Carr, R. H.; Sanders, J. P. M. *Catal. Lett.* **2012**, *142*, 338−344. (f) Maitrani, C.; Heyes, D. J.; Hay, S.; Arumugam, S.; Popik, V. V.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2734−2737. (g) Kleijn, L. H. J.; Müskens, F. M.; Oppedijk, S. F.; de Bruin, G.; Martin, N. I. *Tetrahedron Lett.* **2012**, *53*, 6430−6432.

(6) For other examples of indole fragmentation methods, see: (a) Closs, G.; Schwartz, G. *J. Org. Chem.* **1961**, *26*, 2609. (b) Ihara, M.; Noguchi, K.; Fukumoto, K. *Tetrahedron* **1985**, *41*, 2109−2114. (c) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036−4041. (d) Liu, M.; Shu, M.; Yao, C.; Yin, G.; Wang, D.; Huang, J. *Org. Lett.* **2016**, *18*, 824−827.

(7) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469−6480. (c) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195−7210.

(8) (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9664. (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449−4465. (c) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508−3549.

(9) For reviews of bioconjugation, see: (a) Hackenberger, C. P. R.; Schwarzer, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 10030−10074. (b) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974−6998. (c) Spicer, C. D.; Davis, B. G. *Nat. Commun.* **2014**, *5*, 4740. (d) Koniev, O.; Wagner, A. *Chem. Soc. Rev.* **2015**, *44*, 5495−5551. (e) Krall, N.; da Cruz, F. P.; Boutureira, O.; Bernardes, G. J. L. *Nat. Chem.* **2016**, *8*, 103−113.

(10) For examples of tryptophan modification, see: (a) Antos, J. M.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 10256−10257. (b) Foettinger, A.; Melmer, M.; Leitner, A.; Lindner, W. *Bioconjugate Chem.* **2007**, *18*, 1678−1683. (c) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 6301−6308. (d) Ruiz-Rodríguez, J.; Albericio, F.; Lavilla, R. *Chem. - Eur. J.* **2010**, *16*, 1124−1127. (e) Popp, B. V.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 6660−6662. (f) Chen, Z.; Popp, B. V.; Bovet, C. L.; Ball, Z. T. *ACS Chem. Biol.* **2011**, *6*, 920−925. (g) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014**, *50*, 3052−3054. (h) Zhu, Y.; Bauer, M.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 9980−9983. (i) Seki, Y.; Ishiyama, T.; Sasaki, D.; Abe, J.; Sohma, Y.; Oisaki, K.; Kanai, M. *J. Am. Chem. Soc.* **2016**, *138*, 10798−10801.

(11) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (c) Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 7571−7573. (d) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037−8041. (e) Lee, C. W.; Han, S.-J.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron* **2015**, *71*, 3666−3670.

(12) (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203−1205. (b) Han, S.-J.; Vogt, F.; Krishnan, S.; May, J. A.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 3316−3319. (c) Han, S.-J.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *J. Org. Chem.* **2015**, *80*, 528−547. (d) Li, Z.; Geng, Q.; Lv, Z.; Pritchett, B. P.; Baba, K.; Numajiri, Y.; Stoltz, B. M.; Liang, G. *Org. Chem. Front.* **2015**, *2*, 236−240.

(13) (a) Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 756. (b) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1958**, *23*, 324−325. (c) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72−78.

(14) Wang and co-workers reported the direct chlorooxidation of indoles using $CuCl_2$ and *t*-BuOOH to yield 3,3-disubstituted 3-chlorooxindoles. The formation of a 3-peroxyoxindole was observed as a byproduct in this reaction: Wang, H.; Liu, D.; Chen, H.; Li, J.; Wang, D. Z. *Tetrahedron* **2015**, *71*, 7073−7076.

(15) Kong, D.-L.; Cheng, L.; Yue, T.; Wu, H.-R.; Feng, W.-C.; Wang, D.; Liu, L. *J. Org. Chem.* **2016**, *81*, 5337−5344.

(16) Krylov, I. B.; Vil', V. A.; Terent'ev, A. *Beilstein J. Org. Chem.* **2015**, *11*, 92−146.

(17) (a) An, G.; Zhou, W.; Zhang, G.; Sun, H.; Han, J.; Pan, Y. *Org. Lett.* **2010**, *12*, 4482−4485. (b) Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* **2012**, *14*, 4762−4765. (c) Arai, A.; Tsuchiya, K.; Matsumura, E. *Org. Lett.* **2015**, *17*, 2416−2419. (d) Nakamura, S.; Takahashi, S. *Org. Lett.* **2015**, *17*, 2590−2593. (e) Liu, J.; Zhu, F.-M.; Chu, Y.-B.; Huang, L.-H.; Zhou, Y.-F. *Tetrahedron: Asymmetry* **2015**, *26*, 1130−1137. (f) Kischkewitz, M.; Daniliuc, C.-G.; Studer, A. *Org. Lett.* **2016**, *18*, 1206−1209.

(18) For a sequential Michael addition/oxidation/ring-cleavage process of oxindoles, see: Miao, C.-B.; Zeng, Y.-M.; Shi, T.; Liu, R.; Wei, P.-F.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2016**, *81*, 43−50.

(19) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1−15. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535−546. (c) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741−3766.

(20) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880−881.

(21) (a) Todorovski, T.; Fedorova, M.; Hennig, L.; Hoffmann, R. *J. Pept. Sci.* **2011**, *17*, 256−262. (b) Lam, H. Y.; Zhang, Y.; Liu, H.; Xu, J.; Wong, C. T. T.; Xu, C.; Li, X. *J. Am. Chem. Soc.* **2013**, *135*, 6272−6279. (c) Wong, C. T. T.; Lam, H. Y.; Li, X. *Org. Biomol. Chem.* **2013**, *11*, 7616−7620.

(22) (a) Savige, W. E.; Fontana, A. *J. Chem. Soc., Chem. Commun.* **1976**, 599−600. (b) Savige, W. E.; Fontana, A. *Methods Enzymol.* **1977**, *47*, 442−453. (c) Szabó-Pusztay, K.; Szabó, L. *Synthesis* **1979**, *1979*, 276−277. (d) Savige, W. E.; Fontana, A. *Int. J. Pept. Protein Res.* **1980**, *15*, 285−297.

DOI: 10.1021/acs.orglett.6b03789
Org. Lett. XXXX, XXX, XXX−XXX