JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Manganese-Catalyzed Late-Stage Aliphatic C−H Azidation

Xiongyi Huang, Tova M. Bergsten, and John T. Groves*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544 United States

Supporting Information

ABSTRACT: We report a manganese-catalyzed aliphatic C−H azidation reaction that can efficiently convert secondary, tertiary, and benzylic C−H bonds to the corresponding azides. The method utilizes aqueous sodium azide solution as the azide source and can be performed under air. Besides its operational simplicity, the potential of this method for late-stage functionalization has been demonstrated by successful azidation of various bioactive molecules with yields up to 74%, including the important drugs pregabalin, memantine, and the anti-malarial artemisinin. Azidation of celestolide with a chiral manganese salen catalyst afforded the azide product in 70% ee, representing a Mn-catalyzed enantioselective aliphatic C−H azidation reaction. Considering the versatile roles of organic azides in modern chemistry and the ubiquity of aliphatic C−H bonds in organic molecules, we envision that this Mn-azidation method will find wide application in organic synthesis, drug discovery, and chemical biology.

Organic azides are of significant importance in organic synthesis, chemical biology, pharmaceutical discovery, and materials science. These versatile synthetic intermediates provide convenient access to a variety of functionalities such as amines, imines, amides, and triazoles.[1] Additionally, organic azides perform irreplaceable roles in chemical biology and drug discovery, due to the broad applications of azide−alkyne Huisgen cycloaddition and Staudinger ligation in "click" chemistry.[2] In materials science, azide-based transformations are widely used for surface modification, macromolecular engineering, and synthesis of novel polymeric materials.[3]

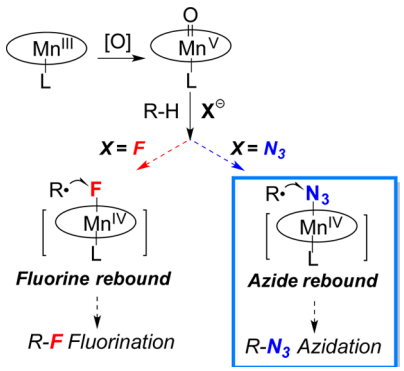
Since the preparation of the first organic azide, phenyl azide, in 1864, numerous azidation reactions have been developed, enabling the synthesis of organic azides from a variety of functionalities, including alkyl halides, amines, hydrazines, triazenes, alcohols, epoxides, aziridines, alkenes, diazonium ions, aldehydes, etc.[1] These advances have significantly expanded the synthetic availability of this functional group. More recently, direct aryl C−H azidation has been realized using transition-metal catalysis (Cu, Pd or Rh)[4] or with hypervalent iodine reagents through a Friedel−Crafts reaction process.[5] Moreover, recent developments in the field of catalytic amination and amidation have provided a plethora of methods for constructing aliphatic C−N bond through C−H activation.[6] In contrast, direct aliphatic C−H azidation reactions are noticeably lacking. Although hypervalent iodine reagents like IN_3 have been known to perform direct aliphatic C−H azidation,[7] the application of this reagent has been limited to simple hydrocarbons, primarily due to the harsh reaction conditions and/or instability.

Jiang et al. have reported an allylic, Pd-catalyzed C−H azidation method with NaN_3 as the azide source.[8] Gade et al. developed an enantioselective C−H azidation reaction of β-keto esters with an iron boxim catalyst and an azidoiodinane.[9] Bollinger et al. devised a variant of the SyrB2 halogenase enzyme that is capable of performing C−H azidation reaction on its preferred substrate.[10] The former two methods are restricted to allylic C−H bonds and β-keto ester α-positions, respectively. The enzymatic approach requires substrates to be bound to the carrier protein. Very recently, Hartwig et al. reported an elegant protocol for late-stage azidation of tertiary and benzylic C−H bonds using an iron catalyst and an azidoiodinane reagent.[11]

We report here a practical and complementary manganese-catalyzed C−H azidation reaction that is applicable to secondary, tertiary, and benzylic C−H bonds. The method uses easily handled aqueous sodium azide as the azide source. By harnessing the ubiquitous C−H bonds in organic molecules and the synthetic versatility of alkyl azides, this reaction provides a powerful chemical tool for late-stage diversification of drug-like molecules as well as for developing new biochemical reporters.

Conceptually, this azidation reaction derives from mechanistic analyses of the manganese-catalyzed C−H fluorination reported recently by our group (Scheme 1).[12] For C−H fluorination, the presence of fluoride as the axial ligand to manganese facilitates the fluorine transfer to incipient substrate radicals formed after a manganese(V)oxo-induced hydrogen abstraction step. Diversion of the reaction to afford the fluorination product rather than the usual hydroxylation product is made possible by the unusually

Scheme 1. Concept of Mn-Catalyzed C−H Azidation



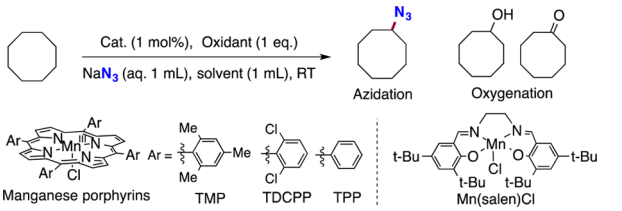
Received: February 23, 2015

DOI: 10.1021/jacs.5b01983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

low barrier to fluorine atom transfer from manganese(IV)-F species.[12a,13] Early results by Hill et al. and by us showed that manganese porphyrins were capable of mediating low-conversion C−H azidation of simple hydrocarbons along with oxygenation products.[13b,14] We considered that replacing fluoride with a suitable azide source might promote the more efficient formation of an analogous Mn^{IV}−N_3 intermediate, which would trap the substrate radical and form the desired C−N_3 bond.

Manganese-catalyzed azidation screening using exploratory conditions are shown in Table 1. A modest 3% yield of azidation

Table 1. Reaction Optimization with Cyclooctane



	catalyst	NaN_3 (M)	solvent	yield (%)	Az/Ox
1	Mn(TPP)Cl	6.3	CH_2Cl_2	3	1:1
2	Mn(TMP)Cl	6.3	CH_2Cl_2	26	5:1
3	Mn(TDCPP)Cl	6.3	CH_2Cl_2	18	2:1
4	Mn(TMP)Cl	6.3	$PhCF_3$	20	1.5:1
5	Mn(TMP)Cl	6.3	acetone	3	1:2
6	Mn(TMP)Cl	6.3	benzene	20	2:1
7	Mn(TMP)Cl	6.3	EtOAc	25	4:1
8	Mn(TMP)Cl	1.5	EtOAc	29	5.3:1
9	Mn(TMP)Cl	1.5	EtOAc	55[b]	3.9:1
10	Mn(salen)Cl	1.5	EtOAc	51[b,c]	3.7:1
11	Mn(TMP)Cl	1.5	EtOAc	53[b,d]	3.6:1

[a]Yields, based on starting substrate, and product distributions were determined by GC-MS. [b]4 equiv of PhIO were added sequentially. [c]5 mol % catalyst loading. [d]Reaction was carried out under air.

product with 1:1 azidation/oxygenation ratio (abbreviated as Az/Ox) was obtained with Mn(TPP)Cl as catalyst (Table 1, entry 1). The yield surged to 26% (Az/Ox = 5) by changing catalyst from Mn(TPP)Cl to Mn(TMP)Cl. Since CH_2Cl_2 solvent is not desirable for azidation due to the potential formation of explosive diazidomethane,[15] various solvents were screened and ethyl acetate was found to be optimal, affording a 25% yield (Az/Ox = 4). The effect of aqueous phase azide concentration on reaction yield and selectivity was investigated. Interestingly, decreasing the azide concentration from 6.3 to 1.5 M led to a slightly higher yield (29%, Az/Ox = 5.3). Serial addition of more oxidant further increased the yield. With 4 equiv of PhIO, the yield was increased to 55% (Az/Ox = 3.9) (Table 1, entry 9). Besides manganese porphyrins, manganese salen-type Jacobsen catalysts[16] were also found to be reactive for this C−H azidation reaction, albeit with higher catalyst loading (Table 1, entry 10). While most of the screening was performed under nitrogen atmosphere, carrying out the reaction under air led to only slightly decreased conversion and azidation selectivity (Table 1, entry 11), greatly simplifying the reaction setup. No azidation products were detected in control experiments in which the manganese catalysts were omitted.

The optimized reaction conditions were established based on these reaction screening results (Figure 1). A wide range of substrates was efficiently converted to the corresponding azides. Reaction times were generally 3−12 h with no need of a phase-

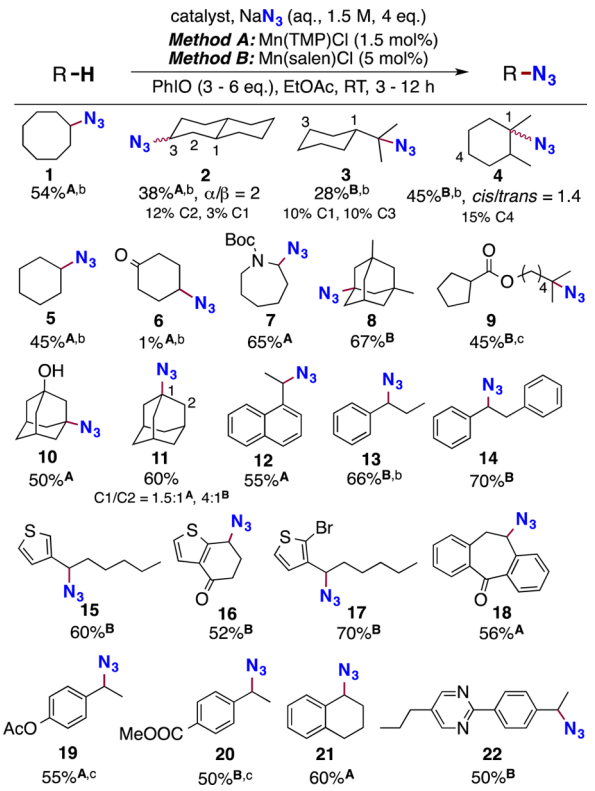


Figure 1. Substrate scope of Mn-catalyzed C−H azidation. (a) Conditions: catalyst (method A: 1.5 mol % Mn(TMP)Cl; method B: 5 mol % Mn(salen)Cl), substrate (0.6 mmol), 1.5 mL of NaN_3 (aq., 1.5 M, 4 equiv), 1 mL of EtOAc, 23 °C. PhIO (3−6 equiv) was added in portions (0.8−1.0 equiv PhIO each portion). The reaction was monitored by TLC, GC-MS or LC-MS. Isolated yields of major products are reported unless notified otherwise. A and B superscripts refer to methods A and B, respectively. Azide to oxygenated product ratios were 2−4:1. (b) Yields were determined relative to starting material by GC-MS. (c) Methyl acetate was used as solvent.

transfer catalyst. Functionalities including amide, ester, ketone, carbamate, tertiary alcohol, terminal alkyne, and heteroaryl groups including pyridine, thiophene, and pyrimidine were well tolerated. Secondary alcohols were oxidized to ketones and cyclohexene afforded a 1:1 ratio of allylic azide and epoxide. The regio-selectivity of C−H activation could be regulated by the electronic and steric properties of the ligand, as we have previously shown for C−H halogenations.[12a,13c] For example, azidation of adamantane with Mn(TMP)Cl led to a 1.5:1 ratio of tertiary to secondary products compared to 4:1 tertiary/secondary ratio with the manganese salen catalyst (Figure 1, **11**). The reaction of *trans*-decalin with the bulky Mn(TMP)Cl catalyst afforded mostly secondary azidation products with a 3.2-to-1 ratio of C3 over C2 (Figure 1, **2**). The efficiency of C−H activation was significantly affected by the electronic properties of the substrate. While a 45% yield (based on the substrate) was observed for azidation of cyclohexane, the more electron-deficient cyclohexanone only yielded 2% azidation product under the same conditions. The potential synthetic application of this Mn-azide method was demonstrated by the successful azidation of common structural motifs in bioactive molecules such as tetrahydronaphthalene, dibenzocycloheptane, and adamantane.

With these promising results in hand, we set out to apply the method to more complex bioactive molecules (or their protected

DOI: 10.1021/jacs.5b01983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

analogs), encompassing the important drugs memantine (Namenda) and pregabalin (Lyrica), the Parkinson's disease drug rasagiline (Azilect), the opium alkaloid antispasmodic drug papaverine (Pavabid), ibuprofen, the terpenoid sclareolide, the antimalarial artemisinin, and the estrogenic hormone estrone. Gratifyingly, subjecting these molecules to the Mn-azide method afforded corresponding azides with yield up to 74% yield. Pregabalin was selectively functionalized at the C−H bond adjacent to the NHBoc protecting group, as a result of the radical-stabilizing ability and weak electron-withdrawing property of the carbamate nitrogen (Figure 2, **24**). Sclareolide

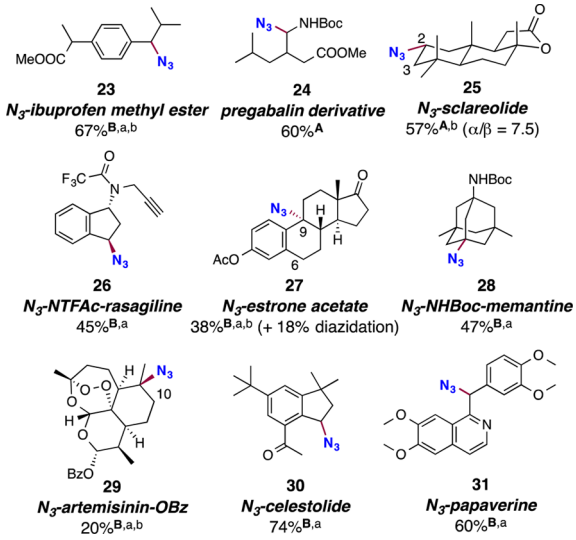


Figure 2. Late-stage azidation of bioactive molecules. A and B superscripts refer to methods A and B, respectively. Azide to oxygenated product ratios were 2−4:1. (a) Manganese salen catalyst was used. (b) Methyl acetate was used as solvent.

afforded C2 azidation as the major product in 57% yield and a high α/β ratio of 7.5 (Figure 2, **25**). Although estrone acetate has several possible reactive sites, the C9-α azide was obtained as the major product in 38% yield. Interestingly, the major side product was determined to be a diazidation product with both C9 and C6 being activated (Figure 2, **27**). The method is also applicable to fragile molecules like artemisinin. With the manganese salen catalyst, the C10 tertiary azide was found to be the exclusive azidation product (Figure 2, **29**). These results highlight the enabling power of this method to late-stage functionalization.

We conducted a number of experiments to elucidate the reaction mechanism. Stirring the Mn(TMP)Cl ethyl acetate solution with an aqueous solution of NaN_3 led to facile ligand exchange to form Mn(TMP)N_3, as observed by UV−vis spectroscopy (479−485 nm, Figure S1). The dependence of the regioselectivity on the catalyst ligand architecture suggests a catalyst-based intermediate for the hydrogen abstraction step, presumably an oxomanganese(V) species, rather than the azide radical observed for C−H activation with azidoiodinane reagents. This conclusion was further supported by measurement of the deuterium kinetic isotope effect (KIE). Reaction of a 1:1 mixture of toluene and toluene-d_8 produced competitive intermolecular KIEs of 7.8 and 9.3, respectively, for Mn(TMP)Cl and Mn(salen)Cl (Figure 3a). The values are significantly larger than the KIE value observed for hydrogen abstraction by the azide radical (~5).[11,17] The radical nature of the reaction was demonstrated by using norcarane as a probe substrate (Figure

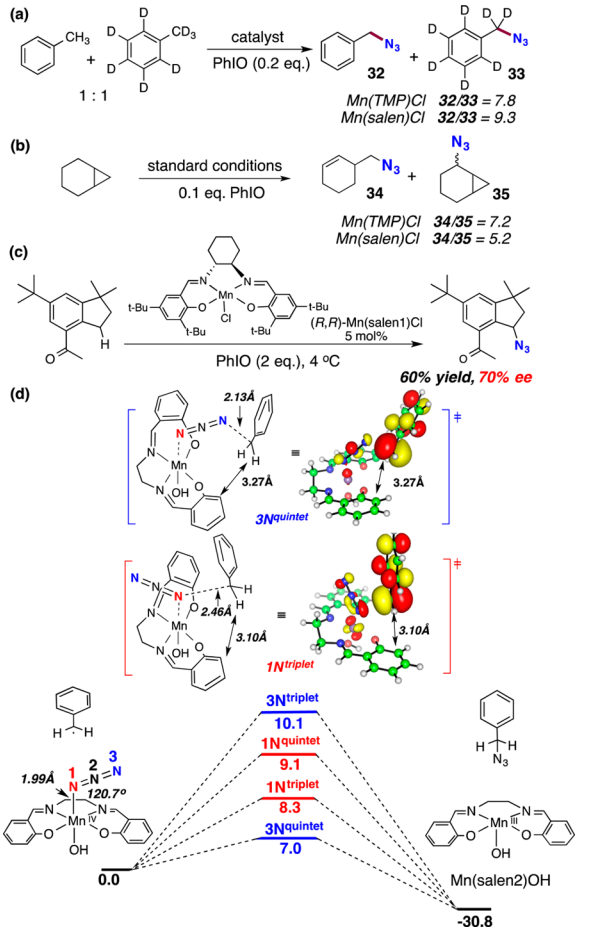


Figure 3. (a) KIE studies of Mn-catalyzed C−H azidation. (b) Azidation with norcarane substrate. (c) Enantioselective C−H azidation with a chiral manganese salen catalyst. (d) DFT calculations of the azide-transfer step (kcal/mol at 298 K). $3N^{quintet}$ refers to azide transfer through nitrogen N3 on quintet surface and other pathways are labeled accordingly.

3b).[18] The ratios of rearranged product, 3-azidomethylcyclohexane (**34**) to unrearranged product, 2-azidonorcaranes (**35**) are 7.2 and 5.2 for Mn(TMP)Cl and Mn(salen)Cl, respectively. Given that ring-opening rate constant of 2-norcaranyl radical is 2×10^8 M^{-1} s^{-1}, the obtained ratios indicate rather long radical lifetimes of 36 and 26 ns.

To study the azido-transfer step, the chiral manganese salen Jacobsen catalyst was used.[16] Surprisingly, azidation of celestolide with this catalyst afforded a 63% ee at 25 °C and 70% ee at 4 °C (Figure 3c), representing a Mn-catalyzed enantioselective aliphatic C−H azidation. The enantioselectivity was reversed when changing from (*R*,*R*)-Mn(salen1)Cl to (*S*,*S*)-Mn(salen1)Cl. This high ee clearly demonstrates the involvement of a manganese-bound azide intermediate in the azido-transfer step.

DFT calculations with an unsubstituted azidomanganese(IV) salen model and a tolyl radical were employed to probe the facile azide ligand transfer from Mn^{IV}−N_3 to the substrate radicals (B3LYP/6-31G(d) (SDD for Mn), see computational details in the SI). The calculated bond lengths for Mn^{IV}−N_3 and the Mn−N_1−N_2 bond angle were very similar to the previous reported X-ray crystal structures of Mn^{IV}−N_3 salen complexes, 1.99 Å and 120.7°, respectively (Figure 3d).[16] We considered four reasonable pathways by which a substrate radical could interact

DOI: 10.1021/jacs.5b01983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

with $Mn^{IV}-N_3$: approach to either the manganese-bound (N1) or terminal (N3) azido-nitrogen on either the triplet or quintet energy surfaces. All of these trajectories had low barriers, with the lowest energy transition state obtained for azido-transfer through N3 on the quintet surface, which had an energy barrier of only 7.0 kcal/mol. The azido-transfer transition state at the N1 nitrogen was found just above at 8.3 kcal/mol on the triplet energy surface. Closer inspection of the structures of these transition states revealed that the benzylic carbon of the tolyl radical is in close proximity to the aryl group of the salen ligand in both structures (3.27 and 3.10 Å), consistent with the observed enantioselectivity. Based on these mechanistic considerations, we propose a reaction mechanism similar to that of Mn−F C-H fluorination,[12a] wherein PhIO first oxidizes the resting Mn(III) catalyst to the hydrogen-abstracting oxoMn(V) intermediate (Figure 4). The

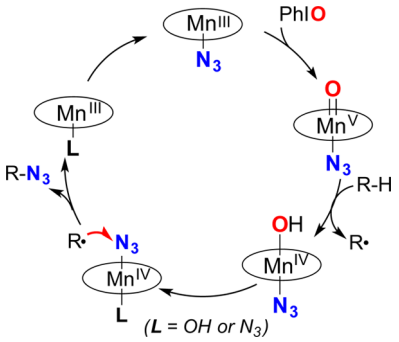


Figure 4. Proposed Mn-azide reaction mechanism.

substrate radical formed after hydrogen abstraction is then captured by $Mn^{IV}-N_3$ intermediate to form $C-N_3$ bond and regenerate the catalyst in accordance with the energy landscape in Figure 3d.

In conclusion, we have developed a facile and convenient manganese-catalyzed aliphatic C−H azidation reaction. The reported reaction uses easily handled aqueous NaN_3 solutions as the azide source and is operationally simple. The potential of this method for applications in organic synthesis, chemical biology and drug discovery has been demonstrated by the successful late stage azidation of several bioactive molecules. With an initial high enatioselectivity with chiral manganese salen catalyst, we are now working to further improve the enantioselectivity of this reaction and expanding its substrate scope. Furthermore, efforts are being undertaken to extend the concept illustrated in this paper to the installation of other pseudohalogen functional groups to molecules via manganese-catalyzed C−H activation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic data for all new compounds, and details for the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*jtgroves@princeton.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the US National Science Foundation award CHE-1148597. X.H. thanks the Howard Hughes Medical Institute for fellowship support. The authors thank Prof. A. G. Doyle for access to chiral HPLC.

■ REFERENCES

(1) (a) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) *Organic Azides: Syntheses and Applications*; John Wiley & Sons, Ltd: Chichester, U.K., 2010.

(2) (a) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (b) Grammel, M.; Hang, H. C. *Nat. Chem. Biol.* **2014**, *10*, 239.

(3) (a) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791. (b) Xi, W.; Scott, T. F.; Kloxin, C. J.; Bowman, C. N. *Adv. Funct. Mater.* **2014**, *24*, 2572.

(4) (a) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924. (b) Xie, F.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 11862. (c) Zheng, Q.-Z.; Feng, P.; Liang, Y.-F.; Jiao, N. *Org. Lett.* **2013**, *15*, 4262. (d) Fan, Y.; Wan, W.; Ma, G.; Gao, W.; Jiang, H.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 5733. (e) Yao, B.; Liu, Y.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *J. Org. Chem.* **2014**, *79*, 11139.

(5) (a) Lubriks, D.; Sokolovs, I.; Suna, E. *J. Am. Chem. Soc.* **2012**, *134*, 15436. (b) Telvekar, V. N.; Sasane, K. A. *Synth. Commun.* **2012**, *42*, 1085.

(6) (a) Lescot, C.; Darses, B.; Collet, F.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2012**, *77*, 7232. (b) Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodriguez, A. D.; Cravatt, B. F.; Romo, D. *Nat. Chem.* **2013**, *5*, 510. (c) Yu, X. Q.; Huang, J. S.; Zhou, X. G.; Che, C. M. *Org. Lett.* **2000**, *2*, 2233. (d) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (e) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (f) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (g) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. *Science* **2011**, *332*, 448. (h) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (i) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (j) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036. (k) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. (l) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384. (m) Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092. (n) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591. (o) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901.

(7) (a) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192. (b) Viuf, C.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 623.

(8) Chen, H.; Yang, W.; Wu, W.; Jiang, H. *Org. Biomol. Chem.* **2014**, *12*, 3340.

(9) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

(10) Matthews, M. L.; Chang, W.-c.; Layne, A. P.; Miles, L. A.; Krebs, C.; Bollinger, J. M., Jr. *Nat. Chem. Biol.* **2014**, *10*, 209.

(11) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600.

(12) (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (b) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

(13) (a) Groves, J. T.; Kruper, W. J.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375. (b) Kruper, W. J., Jr. Ph.D. Dissertation, University of Michigan, 1982. (c) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847.

(14) Hill, C. L.; Smegal, J. A.; Henly, T. J. *J. Org. Chem.* **1983**, *48*, 3277.

(15) Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285.

(16) (a) Kurahashi, T.; Fujii, H. *Inorg. Chem.* **2008**, *47*, 7556. (b) Kurahashi, T.; Hada, M.; Fujii, H. *J. Am. Chem. Soc.* **2009**, *131*, 12394.

(17) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Org. Biomol. Chem.* **2005**, *3*, 816.

(18) Groves, J. T. *J. Inorg. Biochem.* **2006**, *100*, 434.

DOI: 10.1021/jacs.5b01983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX