C–C Activation

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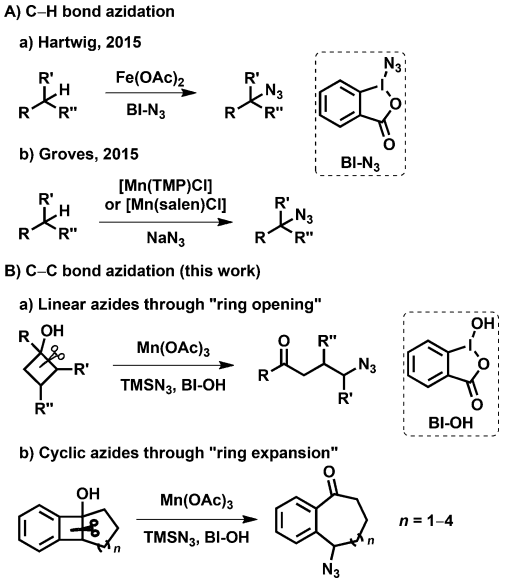
Manganese-Catalyzed Oxidative Azidation of Cyclobutanols: Regiospecific Synthesis of Alkyl Azides by C–C Bond Cleavage

*Rongguo Ren, Huijun Zhao, Leitao Huan, and Chen Zhu**

Abstract: *A novel, manganese-catalyzed oxidative azidation of cyclobutanols is described. A wide range of primary, secondary, and tertiary alkyl azides were generated in synthetically useful yields and exclusive regioselectivity. Aside from linear alkyl azides, otherwise elusive medium-sized cyclic azides were also readily prepared. Preliminary mechanistic studies reveal that the reaction likely proceeds by a radical-mediated C–C bond cleavage/C–N_3 bond formation pathway.*

Organoazides, in particular alkyl azides, are widely used as versatile synthetic intermediates to construct nitrogen-containing molecules owing to their unique reactivity.[1] The synthetic utility of alkyl azides has been explicitly demonstrated by their employment in many powerful organic and bioorthogonal transformations.[2–5] Moreover, the incorporation of an azide moiety into a molecule usually leads to a remarkable improvement in the biological activities.[6] Therefore, the development of mild and efficient azidation methods is of great significance for multiple fields of chemistry, medicine, biology, and materials sciences.

The most common route to alkyl azides relies on the nucleophilic substitution of alkyl halides by inorganic azides.[7] However, the halide precursors are sometimes difficult to obtain. During the past decade, widespread interest in the azidation of olefins has provided another solution for the formation of alkyl azides.[8] Alkyl C–H and C–C bonds are inert but abundant in organic compounds; therefore, the direct elaboration of C–H and C–C bonds into target functional groups represents the ideal and most straightforward way for the introduction of functional groups. Very recently, the groups of Hartwig[9a] and Groves[9b] independently developed elegant C–H bond azidation processes by means of iron and manganese catalysis to produce alkyl azides in modest chemical yields (Scheme 1 A).[9,10] Although these azidation processes are robust, they primarily occurred at tertiary and benzylic carbon atoms. We herein disclose a novel, manganese-catalyzed azidation of cyclobutanols to efficiently generate alkyl azides by C–C bond cleavage. A wide range of γ-carbonyl-containing primary, secondary, and tertiary alkyl azides were readily furnished in synthetically useful yields (Scheme 1 B).



Scheme 1. Transition-metal-catalyzed synthesis of alkyl azides by cleaving inert chemical bonds. TMS = trimethylsilyl.

Cyclopropanols and cyclobutanols can be regarded as readily available precursors for the synthesis of β- and γ-substituted ketones by radical-clock strategies.[11] Reactions of cyclopropanols that proceed by single-electron oxidation can be easily realized owing to the high reactivity that is induced by the notable ring strain of the three-membered ring, and have attracted much interest.[12] In contrast, radical-mediated transformations of cyclobutanols have rarely been reported,[13,14] even though cyclobutane has a strain energy (26.3 kcal mol^{-1}) similar to that of cyclopropane (29.0 kcal mol^{-1}).[15] This surprising finding could be rationalized by the fact that the ring strain of *gem*-disubstituted cyclobutanes is significantly lower owing to the Thorpe–Ingold effect, which thus stabilizes cyclobutanols.[16] On the other hand, in situ formed γ-benzoylpropyl radicals, as the open-chain tautomers of the cyclobutoxy radicals, rapidly undergo intramolecular cyclization to generate 1-tetralones rather than intermolecular trapping processes with extrinsic radical scavengers.[17] Therefore, the efficient capture of open-chain alkyl radicals remains to be a significant challenge.

In light of our recent success with the silver-catalyzed synthesis of γ-fluorinated ketones,[18] we wondered whether a similar ring-opening strategy could be applied to the

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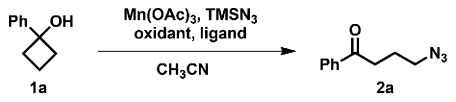
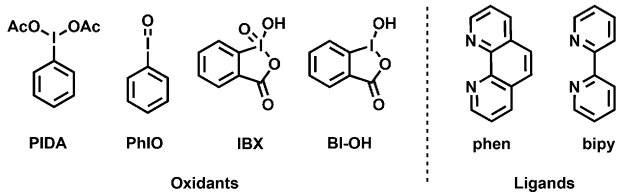
Table 1: Variation of oxidant and ligand.[a]



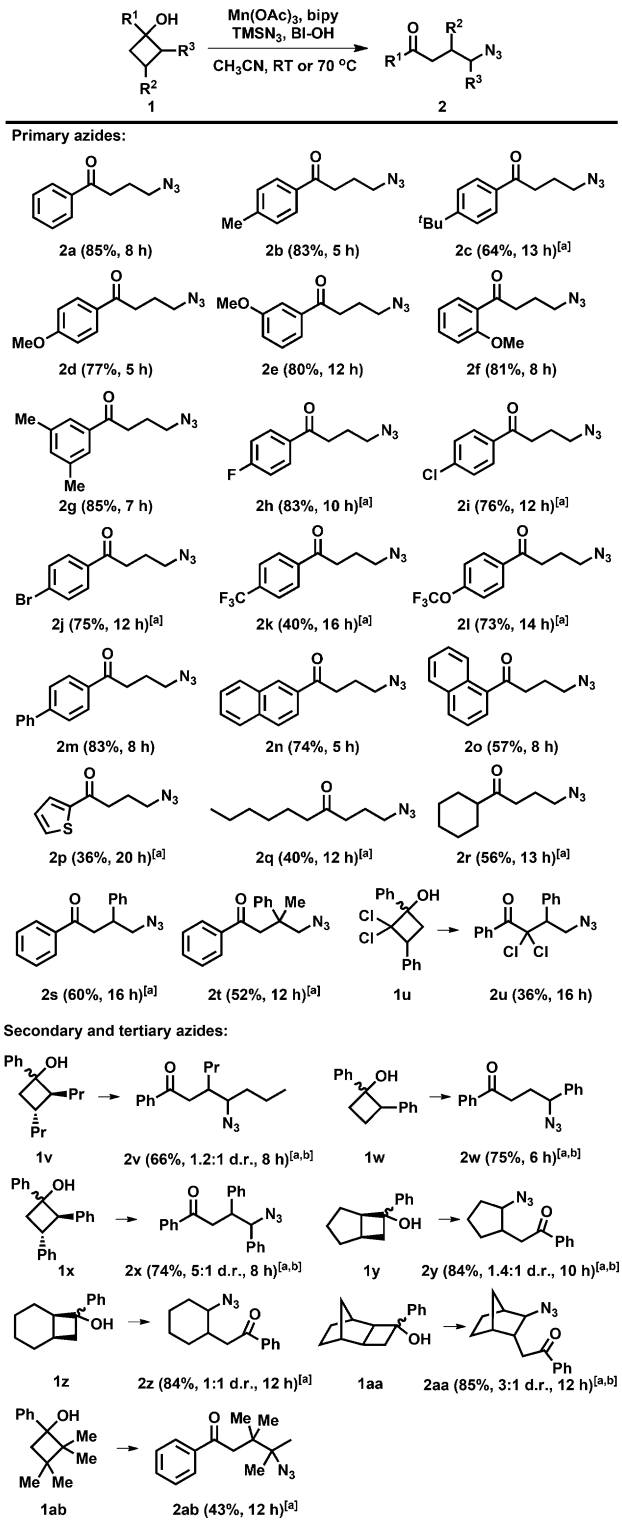


Entry	Oxidant	Ligand	Yield[b] [%]
1	H_2O_2	–	0
2	TBHP	–	< 5
3	$K_2S_2O_8$	–	< 5
4	O_2	–	16
5	PIDA	–	32
6	PhIO	–	30
7	IBX	–	66
8	BI-OH	–	61
9	BI-OH	phen	82
10	BI-OH	bipy	85
11	IBX	bipy	37

[a] **1a** (0.20 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.04 mmol, 20 mol%), ligand (0.044 mmol, 22 mol% when added), $TMSN_3$ (0.40 mmol, 2.0 equiv), and oxidant (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at room temperature for 5 min, then 70°C for 8 h. [b] Yields of isolated products. TBHP = *tert*-butyl hydroperoxide.

construction of alkyl azides. However, to our disappointment, all attempts with silver catalysts gave rise to the undesired 1-tetralone.[17] These negative results prompted us to re-investigate various transition-metal catalysts. After considerable efforts, we found that the use of $Mn(OAc)_3$ enabled the conversion of cyclobutanol **1a** into the desired azide **2a**. The nature of the oxidant was crucial to the reaction outcome (Table 1). Whereas commonly used oxidants, such as H_2O_2, TBHP, $K_2S_2O_8$, and O_2, gave poor chemical yields (entries 1–4), hypervalent iodine reagents were promising candidates to promote the redox cycle (entries 5–8). The lower yields obtained with PIDA and PhIO could be attributed to the consumption of $TMSN_3$ through the generation of highly unstable acyclic azido hypoiodite, which rapidly decomposed at room temperature.[19] The use of IBX and BI-OH gave comparable, modest yields (entries 7 and 8). Remarkably, the addition of N,N-bidentate ligands, such as phen and bipy, significantly improved the yield; the latter ligand performed slightly better (entries 9 and 10). The incompatibility of IBX and bipy was probably caused by oxidation processes (entry 11).

With the optimized reaction conditions in hand, we set out to evaluate the generality of the method. The reaction displayed a superb functional-group tolerance; a wide array of substituted tertiary cyclobutanols were readily converted into the corresponding alkyl azides (Scheme 2). Electron-rich substrates consistently afforded the corresponding products in good yields regardless of their steric properties (**2a**–**2g**). Various halides were compatible with the reaction conditions (**2h**–**2j**), providing a platform for later manipulations. Substrates with strongly electron-withdrawing groups, such as CF_3 and CF_3O, were also readily converted into the desired alkyl azides (**2k**, **2l**). Remarkably, heteroaryl and alkyl cyclo-

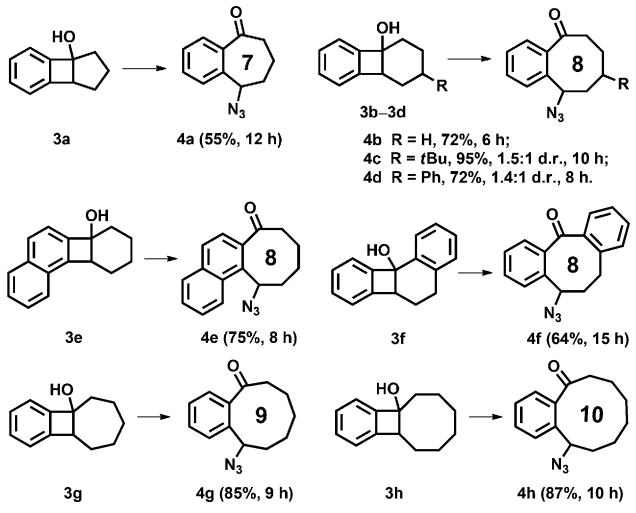


Scheme 2. Ring-opening strategy for the synthesis of alkyl azides. Reaction conditions: **1** (0.20 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.04 mmol, 20 mol%), bipy (0.044 mmol, 22 mol%), $TMSN_3$ (0.40 mmol, 2.0 equiv), and BI-OH (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL), 70°C. Yields of isolated products are given. [a] $TMSN_3$ (3.0 equiv) and BI-OH (3.0 equiv). [b] At room temperature.

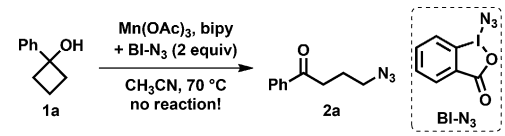
butanols were suitable substrates to deliver **2p**–**2r** in synthetically useful yields. Challenging substrates such as **2s** and **2t**, which may experience appreciable Thorpe–Ingold effects owing to the multisubstituted cyclobutyl ring, furnished the products in moderate yields. The reaction of **2u** was interesting as the azidation regioselectively occurred at the non-chlorinated carbon atom. Apart from primary azides, secondary and tertiary alkyl azides were also efficiently generated under these reaction conditions. With cyclobutanols bearing either alkyl or aryl substituents adjacent to the hydroxy group (**1v**–**1x**), the azide was regioselectively introduced to the methine position, affording secondary azides as the sole products. Likewise, the azidation only took place on the ring to afford cyclic azides when bicyclic substrates were employed (**1y**–**1aa**). Starting from the highly substituted and sterically crowded substrate **1ab**, tertiary azide **2ab** was produced in useful yield. Secondary cyclobutanols were not compatible with the reaction conditions as they were oxidized into the corresponding cyclobutanones.

Medium-sized all-carbon rings are important and ubiquitous in organic compounds, but usually difficult to obtain. A series of benzocyclic azides (**4a**–**4h**) with seven- to ten-membered rings were furnished in good yields by making use of the manganese-catalyzed ring-expansion strategy (Scheme 3). Remarkably, the transformations proceeded in the absence of bipy ligand even at room temperature. The complexity of the products could be easily increased by installing substituents on either the arene or the cycloalkanol moiety (**4c**–**4f**).

To gain further insights into the azidation reaction, several mechanistic experiments were performed. First, under the standard reaction conditions, TEMPO or BHT was added as a radical probe. The resulting suppression of the formation of **2a** (< 10% yield) might suggest a radical-mediated pathway. This possibility was corroborated by the reactions of **1v**, **1x**–**1z**, and **1aa**, which yielded the azidation products as mixtures of diastereomers, whereas the formation of single diastereomers would be expected if the reaction proceeded through an ionic pathway. Then, the electrophilic azidation agent BI-N_3 was used instead of BI-OH and $TMSN_3$ under otherwise identical conditions (Scheme 4). The azidation of **1a** did not take place, explicitly illustrating a) that BI-N_3 was not generated as the actual azidation reagent in the reaction mixture, and b) that the ionic pathway could be ruled out.



Scheme 3. Ring-expansion strategy for the synthesis of medium-sized cyclic azides. Reaction conditions: **3** (0.20 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (0.04 mmol, 20 mol%), $TMSN_3$ (0.60 mmol, 3.0 equiv), and BI-OH (0.60 mmol, 3.0 equiv) in CH_3CN (1.5 mL), room temperature. Yields of isolated products are given.



Scheme 4. Control experiment: employing BI-N_3 instead of BI-OH and $TMSN_3$.

Based on these experimental observations, a reaction mechanism was postulated (Figure 1). Initially, $Mn(OAc)_3$, $TMSN_3$, and BI-OH generate the high-valent Mn^V–N_3 species **A**.[20] The reaction of **A** with cyclobutanol **1** leads to the formation of complex **B**, which undergoes simultaneous SET to generate Mn^{IV}–N_3 species **C** and cyclobutyloxy radical **D**. The open-chain tautomer of **D**, alkyl radical **E**, is then intercepted by the azidation reagent **C**, eventually leading to alkyl azide **2**. It is likely that once formed, the intermediates **C**, **D**, and **E** are confined within a solvent cage, which promotes the azidation. Otherwise, the free alkyl radical **E** would instantly cyclize to generate 1-tetralone.[17]

In summary, we have described a novel and efficient method for the manganese-catalyzed synthesis of alkyl azides by the C–C bond cleavage of cyclobutanols that tolerated a broad range of functional groups and proceeded with unique regioselectivity. A wide range of primary, secondary, and tertiary alkyl azides were generated in synthetically useful yields. Moreover, a series of medium-sized cyclic azides were also obtained in good yields. Preliminary mechanistic studies indicate the involvement of a radical pathway. Further mechanistic studies and investigations towards the application of the manganese-catalyzed cyclobutanol ring-opening

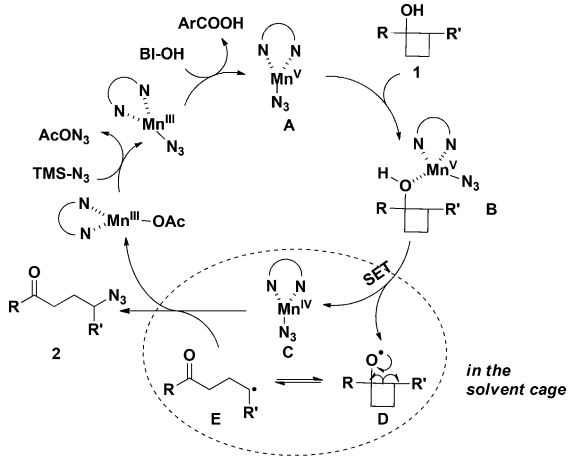


Figure 1. Proposed reaction mechanism.

for the construction of γ-functionalized ketones are ongoing in our laboratory.

Experimental Section

Cyclobutanol **1** (0.2 mmol, 1.0 equiv), $Mn(OAc)_3{\cdot}2H_2O$ (0.04 mmol, 0.2 equiv), bipy (0.044 mmol, 0.22 equiv), and BI-OH (0.4 mmol, 2.0 equiv) were added to a flask, which was evacuated and flushed with nitrogen three times. CH_3CN (1.5 mL) was added to the mixture with a syringe, and the mixture was then stirred at 25 °C for 5 min. Subsequently, $TMSN_3$ (0.4 mmol, 2.0 equiv) was added to the reaction mixture, which was left to stir at 70 °C until the starting materials had been completely consumed (determined by TLC analysis). The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to give product **2**.

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[1] a) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240; *Angew. Chem.* **2005**, *117*, 5320–5374; b) *Organic Azides: Syntheses and Applications*, Wiley, Chichester, **2010**; c) G. Lapointe, A. Kapat, K. Weidner, P. Renaud, *Pure Appl. Chem.* **2012**, *84*, 1633–1641.

[2] For a review on the Curtius rearrangement, see: H. Lebel, O. Leogane, K. Huard, S. Lectard, *Pure Appl. Chem.* **2006**, *78*, 363–375.

[3] For a review on the Schmidt reaction, see: S. Lang, J. A. Murphy, *Chem. Soc. Rev.* **2006**, *35*, 146–156.

[4] For reviews on the Staudinger reaction, see: a) M. Köhn, R. Breinbauer, *Angew. Chem. Int. Ed.* **2004**, *43*, 3106–3116; *Angew. Chem.* **2004**, *116*, 3168–3178; b) E. M. Sletten, C. R. Bertozzi, *Acc. Chem. Res.* **2011**, *44*, 666–676.

[5] For reviews on the click reaction, see: a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128–1137; c) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952–3015.

[6] a) D. M. Huryn, M. Okabe, *Chem. Rev.* **1992**, *92*, 1745–1768; b) R. Kumar, L. I. Wiebe, E. E. Knaus, *J. Med. Chem.* **1993**, *36*, 2470–2474.

[7] E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297–368.

[8] For recent examples, see: a) M. Tiecco, L. Testaferri, C. Sand, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Angew. Chem. Int. Ed.* **2003**, *42*, 3131–3133; *Angew. Chem.* **2003**, *115*, 3239–3241; b) J. Waser, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 8294–8295; c) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712; d) F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, *Angew. Chem. Int. Ed.* **2010**, *49*, 6365–6368; *Angew. Chem.* **2010**, *122*, 6509–6512; e) K. Weidner, A. Giroult, P. Panchaud, P. Renaud, *J. Am. Chem. Soc.* **2010**, *132*, 17511–17515; f) A. Kapat, A. König, F. Montermini, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133*, 13890–13893; g) E. K. Leggans, T. J. Barker, K. K. Duncan, D. L. Boger, *Org. Lett.* **2012**, *14*, 1428–1431; h) F. C. Sequeira, S. R. Chemler, *Org. Lett.* **2012**, *14*, 4482–4485; i) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 7985–7989; *Angew. Chem.* **2013**, *125*, 8143–8147; j) B. Zhang, A. Studer, *Org. Lett.* **2013**, *15*, 4548–4551; k) Y. Yuan, T. Shen, K. Wang, N. Jiao, *Chem. Asian J.* **2013**, *8*, 2932–2935; l) F. Wang, X. Qi, Z. Liang, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1881–1886; *Angew. Chem.* **2014**, *126*, 1912–1917; m) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790–1793; n) X. Sun, X. Li, S. Song, Y. Zhu, Y. Liang, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 6059–6066; o) F. Wang, N. Zhu, P. Chen, J. Ye, G. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 9356–9360; *Angew. Chem.* **2015**, *127*, 9488–9492.

[9] a) A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600–604; b) X. Huang, T. M. Bergsten, J. T. Groves, *J. Am. Chem. Soc.* **2015**, *137*, 5300–5303.

[10] For a highlight, see: a) M. V. Vita, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 5290–5292; *Angew. Chem.* **2015**, *127*, 5380–5382; for seminal examples of C–H azidation, see: b) C. L. Hill, J. A. Smegal, T. J. Henly, *J. Org. Chem.* **1983**, *48*, 3277–3281; c) T. Kojima, R. A. Leising, S. Yan, L. Que, Jr., *J. Am. Chem. Soc.* **1993**, *115*, 11328–11335; d) V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash, J. T. Bolz, *J. Am. Chem. Soc.* **1996**, *118*, 5192–5197; for examples of $C(sp^2)$–H azidation, see: e) C. Tang, N. Jiao, *J. Am. Chem. Soc.* **2012**, *134*, 18924–18927; f) D. Lubriks, L. Sokolovs, E. Suna, *J. Am. Chem. Soc.* **2012**, *134*, 15436–15442; g) Q. Zheng, P. Feng, Y. Liang, N. Jiao, *Org. Lett.* **2013**, *15*, 4262–4265; h) H. Yin, T. Wang, N. Jiao, *Org. Lett.* **2014**, *16*, 2302–2305.

[11] a) D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317–323; b) K. E. Liu, C. C. Johnson, M. Newcomb, S. J. Lippard, *J. Am. Chem. Soc.* **1993**, *115*, 939–947.

[12] For recent examples, see: a) J. Jiao, L. X. Nguyen, D. R. Patterson, R. A. Flowers II, *Org. Lett.* **2007**, *9*, 1323–1326; b) Y.-F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570–12572; c) Y.-F. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 6411–6421; d) A. Ilangovan, S. Saravanakumar, S. Malayappasamy, *Org. Lett.* **2013**, *15*, 4968–4971; e) S. Bloom, D. D. Bume, C. R. Pitts, T. Lectka, *Chem. Eur. J.* **2015**, *21*, 8060–8063; f) S. Ren, C. Feng, T.-P. Loh, *Org. Biomol. Chem.* **2015**, *13*, 5105–5109; g) D. G. Kananovich, Y. A. Konik, D. M. Zubrytski, I. Järving, M. Lopp, *Chem. Commun.* **2015**, *51*, 8349–8352; h) Y. Li, Z. Ye, T. M. Bellman, T. Chi, M. Dai, *Org. Lett.* **2015**, *17*, 2186–2189; i) Z. Ye, M. Dai, *Org. Lett.* **2015**, *17*, 2190–2193.

[13] For early examples of using stoichiometric amounts of metal reagent, see: a) K. Meyer, J. Rocek, *J. Am. Chem. Soc.* **1972**, *94*, 1209–1214; b) S. Tsunoi, I. Ryu, Y. Tamura, S. Yamasaki, N. Sonoda, *Synlett* **1994**, 1009–1011; c) B. M. Casey, C. A. Eakin, R. A. Flowers II, *Tetrahedron Lett.* **2009**, *50*, 1264–1266.

[14] For pioneering examples based on the use of transition-metal complexes, see: a) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *Chem. Commun.* **2002**, 50–51; b) S. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869; c) M. Ethirajan, H. Oh, J. K. Cha, *Org. Lett.* **2007**, *9*, 2693–2696; d) A. Ziadi, R. Martin, *Org. Lett.* **2012**, *14*, 1266–1269; e) N. Ishida, Y. Nakanishi, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 11875–11878; *Angew. Chem.* **2013**, *125*, 12091–12094.

[15] P. R. Khoury, J. D. Goddard, W. Tam, *Tetrahedron* **2004**, *60*, 8103–8112.

[16] A. L. Ringer, D. H. Magers, *J. Org. Chem.* **2007**, *72*, 2533–2537.

[17] J. Yu, H. Zhao, S. Liang, X. Bao, C. Zhu, *Org. Biomol. Chem.* **2015**, *13*, 7924 – 7927.
[18] H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490 – 3493.
[19] a) R. M. Moriarty, R. K. Vaid, V. T. Ravikumar, B. K. Vaid, T. E. Hopkins, *Tetrahedron* **1988**, *44*, 1603 – 1607; b) P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406 – 3418.
[20] For examples of oxidizing Mn^{III} to Mn^{V} with hypervalent iodine reagents, see: a) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III, J. T. Groves, *Science* **2012**, *337*, 1322 – 1325; b) W. Liu, J. T. Groves, *Angew. Chem. Int. Ed.* **2013**, *52*, 6024 – 6027; *Angew. Chem.* **2013**, *125*, 6140 – 6143; c) X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842 – 6845.

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