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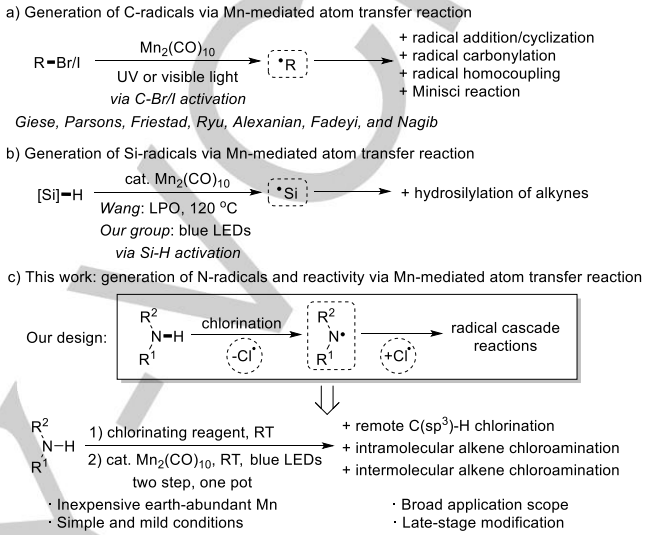
Generation and Reactivity of Amidyl Radicals: Manganese-Mediated Atom-Transfer Reaction

Run-Zhou Liu, Jinxia Li, Jun Sun, Xian-Guan Liu, Shuanglin Qu,* Ping Li,* and Bo Zhang*

Abstract: *A simple and efficient protocol to generate amidyl radicals from amine functionalities through a manganese-mediated atom transfer reaction has been developed. This approach employs an earth-abundant and inexpensive manganese complex, $Mn_2(CO)_{10}$, as the catalyst and visible light as the energy input. Using this strategy, site-selective chlorination of unactivated C(sp^3)-H bonds of aliphatic amines and intramolecular/intermolecular chloroaminations of unactivated alkenes were readily realized under mild reaction conditions, thus providing efficient access to a range of synthetically valuable alkyl chlorides, chlorinated pyrrolidines, and vicinal chloroamine derivatives. These practical reactions exhibit a broad substrate scope and tolerate a wide array of functional groups and complex molecules including various marketed drug derivatives.*

Introduction

As the twelfth most abundant element and the third most abundant transition metal after iron and titanium, manganese has been successfully exploited as a low-toxic and low-cost catalyst for a variety of practical transformations.[1] Manganese-catalyzed C-H oxidations,[2] halogenations,[1d] nitrogenations,[3] cross-couplings,[4] hydrosilylations,[1h] and C-H activations[1e,g,i] have been intensively investigated in the past decades. In stark contrast, manganese-catalyzed atom transfer reactions for generating radical species have received less attention. Prominently, several important precedents in photoinduced manganese-catalyzed/promoted atom transfer reactions have been reported by the groups of Giese,[5] Parsons,[6] Friestad,[7] Ryu,[8] Alexanian,[9] Fadeyi,[10] and Nagib[11]. However, all these reactions focus on the formation of carbon-centered radicals with alkyl halides as the C-radical precursors (Scheme 1a). Consequently, the exploitation of atom transfer reactions facilitated by earth-abundant manganese catalysis to generate other radicals, especially heteroatom-centered radicals, will be of high value to the synthetic chemistry field. In this context, Wang and co-workers[12], as well as our group[13] have recently realized the generation of silyl radicals from silanes through a manganese-catalyzed hydrogen atom transfer process, thereby enabling efficient construction of C-Si bonds (Scheme 1b). Inspired by these progresses and our ongoing research interest in developing sustainable radical transformations using inexpensive manganese as an atom transfer catalyst,[13,14] we reason that nitrogen-centered radicals (NCRs) could be produced by an atom transfer reaction catalyzed by manganese. NCRs are one of the most important classes of intermediates in radical chemistry and can be afforded by various methods.[15] However, the formation of NCRs by using simple and mild reaction conditions remains a challenge. To achieve our goal, a working hypothesis for generating NCRs by manganese-mediated atom transfer strategy is shown in Scheme 1c. We envisioned that by employing simple manganese complexes [e.g., $Mn_2(CO)_{10}$] as the catalysts, in situ formed stable *N*-Cl bonds from amines might be efficiently activated through a manganese-mediated halogen atom transfer process to furnish NCRs. Such a strategy would allow us to devise new radical cascade reactions in a simple and mild manner. Herein, we describe scenarios showing how this concept can be put into practice. The significant aspects of this work include the following: (1) This presents a novel approach to generate amidyl radicals, a highly important class of NCRs, starting from amine functionalities. (2) First examples for site-selective chlorination of unactivated C(sp^3)-H bonds of aliphatic amines as well as intramolecular and intermolecular chloroaminations of unactivated alkenes facilitated by manganese catalyst are reported. (3) These procedures proceed efficiently under very mild reaction conditions and are applicable for the late-stage modification of complex molecules.



Scheme 1. Generation of C-, Si-, and N-radicals and reactivity modes via Mn-mediated atom transfer reaction. LPO = dilauroyl peroxide.

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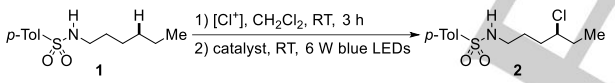
Results and Discussion

We first addressed remote C(sp^3)-H chlorination of amine substrates, since alkyl chlorides are very important and versatile synthetic intermediates for organic synthesis.[16] The groups of Studer,[17] Leonori,[18] and Yu[19] have recently achieved elegant amidyl radical directed remote C(sp^3)-H chlorinations by cleaving N-S, N-O, and N-Cl bonds with the help of LPO radical initiator and precious photoredox catalysts.[20,21] Obviously, developing alternative methods that feature a cheap catalytic system and operate under mild conditions to realize site-selective distal C(sp^3)-H chlorination would be very fascinating. Along this line, we began our endeavor by exploring the feasibility of manganese-catalyzed remote C(sp^3)-H chlorination of the alkylamine-derived sulfonamide **1**. This in situ activation is performed by simply reacting TCCA with **1** at room temperature. Then atom transfer catalyst $Mn_2(CO)_{10}$ was added, and the reaction mixture was irradiated with 6 W blue LEDs at room temperature for 12 h. To our delight, *δ*-C(sp^3)-H chlorination occurred, and the expected product **2** was isolated in 40% yield (Table 1, entry 1). Replacing TCCA with other electrophilic chlorinating reagents, such as NCS, NCP, and DCDMH, resulted in poor results (Table 1, entries 2-4). The yield was further improved by employing simple *t*BuOCl as the chlorine source (Table 1, entry 5). The catalysts $Mn(CO)_5Br$ and $Fe_2Cp_2(CO)_4$ led to significantly lower yields (Table 1, entries 6 and 7). Gratifyingly, a 80% yield of **2** was obtained when the reaction was irradiated for 1 h (Table 1, entry 8). Reducing the catalyst loading to 5 mol% led to a slight decrease in yield (entry 9). Control experiments were carried out and revealed that no chlorinated products were formed in the absence of $Mn_2(CO)_{10}$ or visible light irradiation (Table 1, entries 10 and 11).

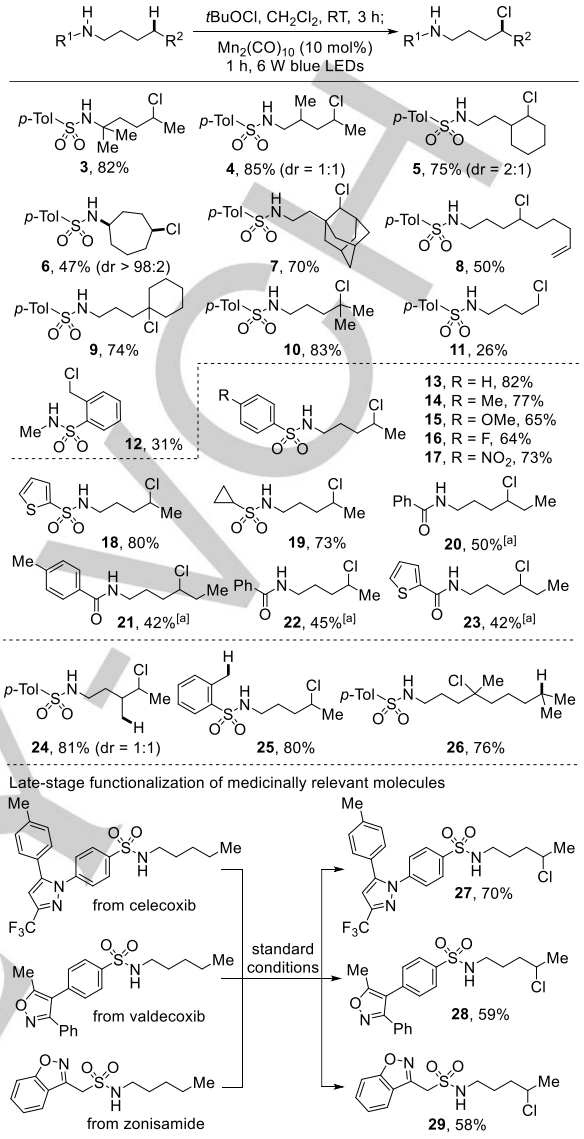
Table 1: Optimization of reaction conditions.[a]



Entry	[Cl$^+$]	Catalyst	Yield [%][b]
1	TCCA	$Mn_2(CO)_{10}$	40
2	NCS	$Mn_2(CO)_{10}$	0
3	NCP	$Mn_2(CO)_{10}$	0
4	DCDMH	$Mn_2(CO)_{10}$	trace
5	*t*BuOCl	$Mn_2(CO)_{10}$	50
6	*t*BuOCl	$Mn(CO)_5Br$	28
7	*t*BuOCl	$Fe_2Cp_2(CO)_4$	15
8[c]	*t*BuOCl	$Mn_2(CO)_{10}$	80
9[c,d]	*t*BuOCl	$Mn_2(CO)_{10}$	70
10[c,e]	*t*BuOCl	$Mn_2(CO)_{10}$	0
11[c]	*t*BuOCl	none	0

[a] Reaction conditions: **1** (0.2 mmol) and chlorinating reagent (0.2 mmol) in CH_2Cl_2 (1.0 mL) were stirred at room temperature under N_2 for 3 h. After that catalyst (10 mol%) and CH_2Cl_2 (1.0 mL) were added, and the reaction mixture was irradiated with 6 W blue LEDs at room temperature under N_2 for 12 h. [b] Isolated yields. [c] The reaction was irradiated for 1 h. [d] Using 5 mol% $Mn_2(CO)_{10}$. [e] The reaction was conducted in the dark. Tol = tolyl, TCCA = trichloroisocyanuric acid, NCS = N-chlorosuccinimide, NCP = N-chlorophthalimide, DCDMH = 1,3-dichloro-5,5-dimethylhydantoin.

Under the optimized reaction conditions, we explored the scope of this remote C(sp^3)-H chlorination (Scheme 2). Sulfonamides bearing *α* or *β*-substituents to nitrogen were smoothly transformed into the desired products in good yields (**3**, **4**). Ring chlorination can be realized, as exemplified by the efficient preparation of **5** and **6**. An adamantyl substrate underwent successful chlorination



Scheme 2. Scope of the remote C(sp^3)-H chlorination. Reaction conditions: see entry 8, Table 1. [a] TCCA (0.5 equiv) was used instead of *t*BuOCl, and the reaction was irradiated for 12 h. Yields of isolated products are given.

to furnish **7** in 70% yield. Notably, a substrate carrying a pending alkene group also participated in this transformation to give **8** in 50% yield. In this case, no cyclized product was observed, indicating that recombination of the translocated C-radical with Cl is rapid. As expected, unactivated tertiary C-H bonds in cyclic and acyclic systems could be selectively chlorinated (**9**, **10**). Likewise, site-specific chlorination of primary C(sp^3)-H bonds is successful (**11**). This method can be broadened to benzylic C-H chlorination, as supported by the synthesis of **12**. Furthermore, a range of sulfonamides bearing electron-donating and electron-withdrawing substituents on the aromatic ring all proceeded efficiently to afford products **13**-**17** in 64-82% yields. A heteroarene such as thiophene was compatible (**18**). Alkyl-substituted sulfonamides proved to be viable substrates (**19**). Apart from sulfonamides, we found that site-selective C(sp^3)-H chlorination of carboxamides could be achieved by switching to TCCA as the chlorine source (**20**-**23**). We further interrogated the selectivity of this chlorination

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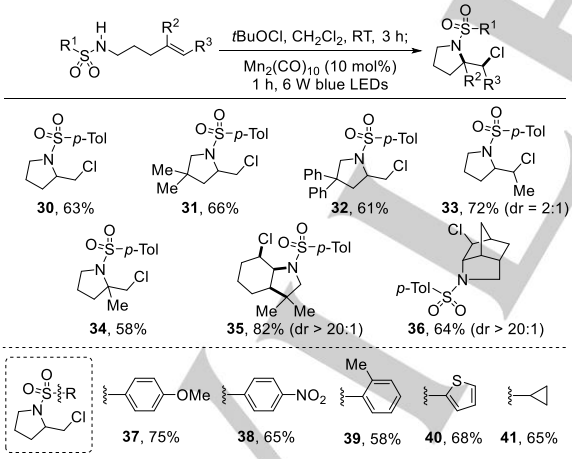
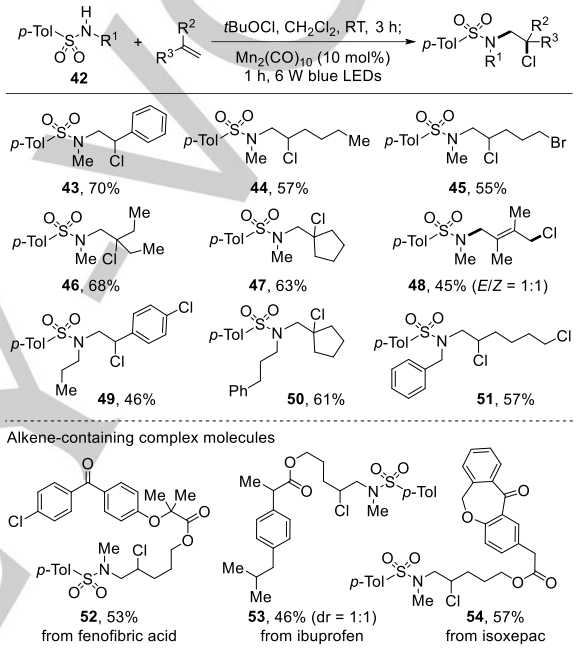
when substrates have two reactive sites. As shown in **24**, chlorination of secondary C(sp^3)-H bond predominated over that of primary C(sp^3)-H bond. When simultaneously presented with aliphatic and benzylic C-H bonds, only chlorination of aliphatic C-H bond was observed (**25**). With a substrate containing two electronically similar tertiary C-H bonds, the chlorination event occurs exclusively at the position proximal to the nitrogen (**26**). To illustrate the utility of this method, a series of more complex medicinally relevant compounds were examined. Substrates derived from celecoxib, valdecoxib, and zonisamide were readily converted to their corresponding products **27**-**29** in synthetically useful yields with complete site selectivity.

To further explore the potential of this protocol, we attempted to apply this manganese-mediated atom transfer strategy to the intramolecular chloroamination of alkenes, which would create a chlorinated pyrrolidine core that is an important substructure present in many natural products and biological active molecules.[22] Although great progress has been made in the development of intramolecular alkene chloroamination,[23] these reactions require the use of an expensive palladium catalyst or stoichiometric strong oxidant. On the contrary, our complementary strategy described in Scheme 3 uses inexpensive manganese as the catalyst, and these chloroamination reactions work well under very mild reaction conditions. Remarkably, sulfonamides possessing diverse alkene substituent patterns, including terminal (**30**-**32**), 1,2-disubstituted (**33**), and 1,1-disubstituted alkenes (**34**), reacted under slightly modified reaction conditions to afford the desired products in good yields. We could show that formation of bicyclic and bridged ring systems is possible using this novel method (**35**, **36**). Intriguingly, high diastereoselectivity was observed in both cases. Moreover, a variety of aryl- and alkyl-substituted sulfonamides were well-tolerated, leading to products **37**-**41** in good yields.



Scheme 3. Scope of the intramolecular chloroamination of alkenes. Reaction conditions: sulfonamide (0.2 mmol) and *t*BuOCl (0.4 mmol) in CH_2Cl_2 (1.0 mL) were stirred at room temperature under N_2 for 3 h. After that $Mn_2(CO)_{10}$ (10 mol%) and CH_2Cl_2 (1.0 mL) were added, and the reaction mixture was irradiated with 6 W blue LEDs at room temperature under N_2 for 1 h. Yields of isolated products are given. The relative configuration of **35** and **36** was determined by ROESY analysis.

Encouraged by these results, we next evaluated the viability of this strategy for intermolecular chloroamination of unactivated alkenes (Scheme 4).[24] We are pleased to find that a diverse set of simple olefins, including terminal (**43**-**45**) and 1,1-disubstituted olefins (**46**, **47**), are suitable reaction partners that can efficiently react with sulfonamide **42** to produce the targeted products with yields ranging from 55% to 70%. 2,3-Dimethylbutadiene provided product **48** in 45% yield, but with low stereoselectivity. We also observed that a portfolio of N-alkyl sulfonamides are eligible for this transformation with products **49**-**51** being formed in good yields. It is important to note that several substrates with more elaborate molecular architectures, such as fenofibric acid, ibuprofen, and isoxepac, were readily functionalized, affording products **52**-**54** in good yields. These results further highlight the potential of this chloroamination reaction for the late-stage functionalization of complex molecules.



Scheme 4. Scope of the intermolecular chloroamination of alkenes. Reaction conditions: sulfonamide (0.3 mmol) and *t*BuOCl (0.3 mmol) in CH_2Cl_2 (1.0 mL) were stirred at room temperature under N_2 for 3 h. After that $Mn_2(CO)_{10}$ (10 mol%), alkene (0.2 mmol), and CH_2Cl_2 (1.0 mL) were added, and the reaction mixture was irradiated with 6 W blue LEDs at room temperature under N_2 for 1 h. Yields of isolated products are given.

To demonstrate the practical usefulness of this methodology, we performed one reaction at larger scale (3.0 mmol) and isolated **27** in 73% yield (1.085 g) (Scheme 5). Moreover, follow-up chemistry on model compound **27** was investigated. Treatment of **27** with NaN_3 afforded azide **55** in 83% yield. **55** underwent a Cu-catalyzed [3+2] alkyne/azide cycloaddition to furnish triazole **56** in 95% yield. The construction of C-S bond could be implemented through nucleophilic substitution with sodium benzenethiolate, delivering product **57** in 42% yield. The pyrrolidine derivative **58** was readily prepared in 98% yield through intramolecular cyclization.

To gain insights into the mechanism, we performed several mechanistic experiments with the model substrate **1**. When **1** was treated with *t*BuOCl in CH_2Cl_2 at room temperature for 3 h, *N*-chlorosulfonamide **59** was obtained in 97% yield. Further, **59** was used as the starting material and underwent smooth photochemical reaction to produce **2** in 90% yield (Scheme 6a).

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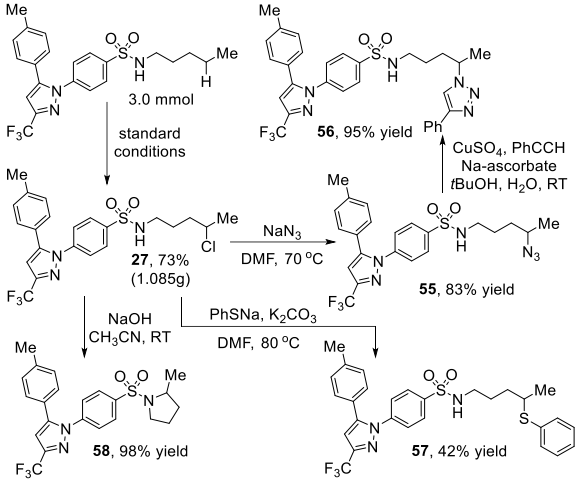
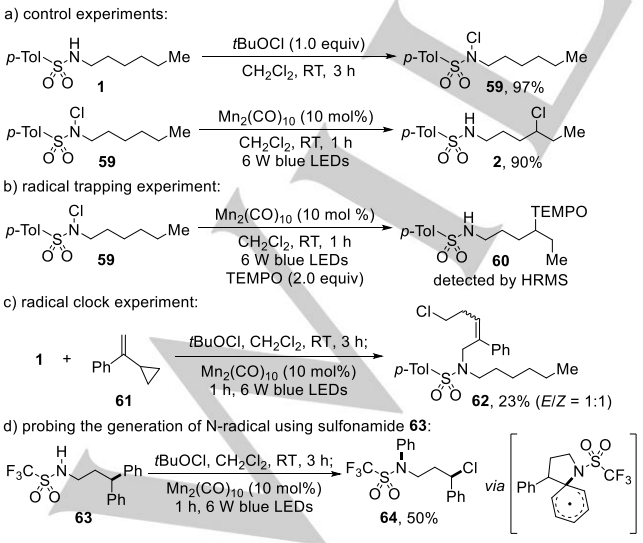


Scheme 5. Gram-scale reaction and diversification of **27**.

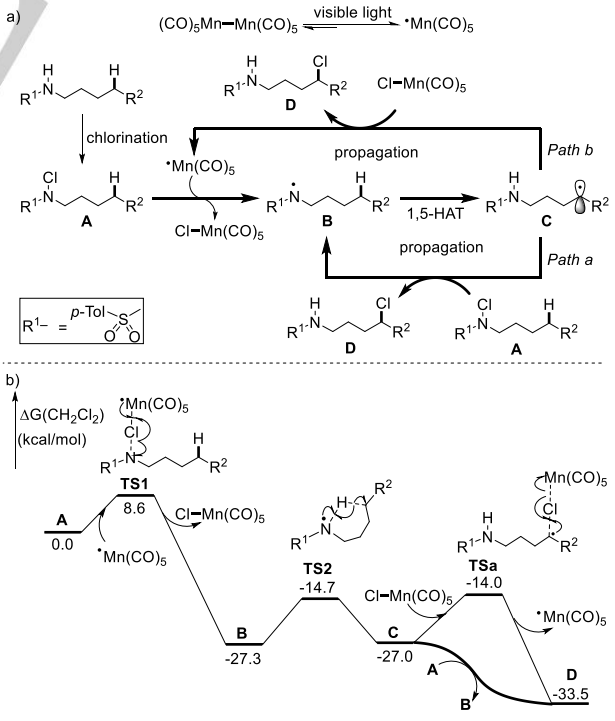
These observations indicate that the *N*-chlorinated species is a competent intermediate in this reaction. Next, radical trapping experiment and radical clock experiment were performed. When 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added, this reaction was completely suppressed. Meanwhile, the TEMPO-trapped product **60** could be identified by high-resolution mass spectrometry (HRMS) (Scheme 6b). Subjecting of **1** and radical clock substrate **61** to our standard reaction conditions afforded the ring-opened product **62** in 23% yield (Scheme 6c). When sulfonamide **63** was subjected to the optimized reaction conditions, 1,4-aryl migration product **64** was isolated in 50% yield (Scheme 6d). These results suggest that a C-radical and N-radical are generated in this transformation. To probe whether a cationic intermediate is involved in chlorine atom transfer process, some nucleophiles such as MeOH and H_2O were added to the reaction. As anticipated, the addition of MeOH or H_2O resulted in no adduct product. These experiments along with the lack of pyrrolidine formation show that chlorine atom transfer to a C-radical intermediate rather than carbocation is operative. Finally, we studied the remote C(sp^3)-H chlorination of **59** in the absence of manganese using azobisisobutyronitrile (AIBN) or Et_3B as a



Scheme 6. Mechanistic studies.

representative radical initiator. Under these radical conditions, **2** could be obtained in low yields, suggesting that $Mn_2(CO)_{10}$ might serve as both an atom transfer catalyst and a radical initiator.

Density functional theory (DFT) calculations were carried out to further understand the mechanism of this reaction.[25] A plausible reaction mechanism is depicted in Scheme 7a [with the remote C(sp^3)-H chlorination of aliphatic amines as an example], and the DFT-calculated free energy profile is shown in Scheme 7b. First, $Mn_2(CO)_{10}$ is converted to $^{\bullet}Mn(CO)_5$ by visible-light-induced Mn-Mn bond homolysis (bond dissociation energy, BDE of Mn-Mn bond = 15 kcal/mol).[13,14,26] The resulting $^{\bullet}Mn(CO)_5$ abstracts the Cl atom from N-Cl bond of in situ formed *N*-chlorosulfonamide **A** via **TS1** (with a free energy activation barrier of 8.6 kcal/mol), generating the amidyl radical **B** and $ClMn(CO)_5$ with energy decreased by 27.3 kcal/mol. Then, the 1,5-hydrogen atom transfer (HAT) occurs through **TS2**, crossing a free energy activation barrier of 12.6 kcal/mol, leading to the C-radical **C**. Next, the Cl atom transfer could proceed through two possible pathways. Along *Path a*, **C** accepts the Cl atom from **A** to produce **B** and product **D**. Interestingly, the Cl atom is directly transferred from **A** to **C** without an energetic barrier. The potential energy surface (PES) scanning also supports that this process is barrierless (see Figure S3 in SI). Following *Path b*, $ClMn(CO)_5$ provides the Cl atom via **TSa** with a free energy activation barrier of 13 kcal/mol (**TSa** relative to **C**). Overall, **A** is more effective than $ClMn(CO)_5$ to provide the Cl atom. We determined the quantum yield of the reaction of **59** to be 22 (λ = 420 nm). The barrierless process for radical chain propagation (of **A** to **B**) also explains the observed high quantum yield [see the Supporting Information (SI) for details].[27] Although *Path a* is more favorable than *Path b*, we could not completely exclude *Path b* because the corresponding activation barrier is not high (13.0 kcal/mol), which is accessible



Scheme 7. a) Proposed reaction mechanism. b) Calculated free energy profile for the formation of product.

under the reaction conditions. During the late reaction stage when the concentration of **A** is low in the system, $ClMn(CO)_5$ can effectively provide the chlorine atom (on the basis of the predicted accessible activation barrier), which supports our experimental observations that $Mn_2(CO)_{10}$ not only acts as a radical initiator but also an atom transfer catalyst.

Conclusion

In summary, we have presented a novel strategy for generation of amidyl radicals from amines through an atom transfer reaction facilitated by an inexpensive earth-abundant manganese complex, $Mn_2(CO)_{10}$. This procedure enables site-selective chlorination of unactivated $C(sp^3)$-H bonds of aliphatic amines and intramolecular/intermolecular chloroaminations of unactivated alkenes, thereby providing a mild and efficient approach to a wide array of synthetically versatile alkyl chlorides, chlorinated pyrrolidines, and vicinal chloroamine derivatives. These reactions operate under visible-light irradiation and display good functional-group compatibility and wide substrate scope and are amenable to gram-scale preparation. Additionally, the practicality of this chemistry is demonstrated on the late-stage functionalization of complex drug derivatives. Efforts to extend this methodology to other NCR-mediated radical cascade reactions are currently underway in our laboratory.

Acknowledgements

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Keywords: radicals • chlorination • manganese • visible light • synthetic methods

[1] For selected reviews, see: a) B. B. Snider, *Chem. Rev.* **1996**, *96,* 339; b) G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109,* 1434; c) M. Mondal, U. Bora, *RSC Adv.* **2013**, *3,* 18716; d) W. Liu, J. T. Groves, *Acc. Chem. Res.* **2015**, *48,* 1727; e) W. Liu, L. Ackermann, *ACS Catal.* **2016**, *6,* 3743; f) J. R. Carney, B. R. Dillon, S. P. Thomas, *Eur. J. Org. Chem.* **2016**, 3912; g) Y. Hu, B. Zhou, C. Wang, *Acc. Chem. Res.* **2018**, *51,* 816; h) X. Yang, C. Wang, *Chem. Asian J.* **2018**, *13,* 2307; i) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119,* 2192.

[2] For selected examples, see: a) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312,* 1941; b) X. Wu, M. S. Seo, K. M. Davis, Y.-M. Lee, J. Chen, K.-B. Cho, Y. N. Pushkar, W. Nam, *J. Am. Chem. Soc.* **2011**, *133,* 20088; c) R. V. Ottenbacher, D. G. Samsonenko, E. P. Talsi, K. P. Bryliakov, *Org. Lett.* **2012**, *14,* 4310; d) L. Ma, Y. Pan, W.-L. Man, H.-K. Kwong, W. W. Y. Lam, G. Chen, K.-C. Lau, T.-C. Lau, *J. Am. Chem. Soc.* **2014**, *136,* 7680; e) D. Shen, C. Miao, S. Wang, C. Xia, W. Sun, *Org. Lett.* **2014**, *16,* 1108; f) A. M. Adams, J. D. Bois, H. A. Malik, *Org. Lett.* **2015**, *17,* 6066.

[3] For selected examples, see: a) X.-Q. Yu, J.-S. Huang, X.-G. Zhou, C.-M. Che, *Org. Lett.* **2000**, *2,* 2233; b) J.-L. Liang, J.-S. Huang, X.-Q. Yu, N. Zhu, C.-M. Che, *Chem. Eur. J.* **2002**, *8,* 1563; c) X. Huang, T. M. Bergsten, J. T. Groves, *J. Am. Chem. Soc.* **2015**, *137,* 5300; d) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem.* **2015**, *7,* 987; e) X. Huang, T. Zhuang, P. A. Kates, H. Gao, X. Chen, J. T. Groves, *J. Am. Chem. Soc.* **2017**, *139,* 15407; f) J. R. Clark, K. Feng, A. Sookezian, M. C. White, *Nat. Chem.* **2018**, *10,* 583.

[4] For selected examples, see: a) S.-K. Kang, J.-S. Kim, S.-C. Choi, *J. Org. Chem.* **1997**, *62,* 4208; b) G. Cahiez, D. Luart, F. Lecomte, *Org. Lett.* **2004**, *6,* 4395; c) G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.* **2007**, *129,* 13788; d) G. Cahiez, O. Gager, F. Lecomte, *Org. Lett.* **2008**, *10,* 5255; e) Y.-C. Teo, F.-F. Yong, C.-Y. Poh, Y.-K. Yan, G.-L. Chua, *Chem. Commun.* **2009**, 6258; f) G. Cahiez, C. Duplais, J. Buendia, *Angew. Chem. Int. Ed.* **2009**, *48*, 6731; *Angew. Chem.* **2009**, *121*, 6859.

[5] B. Giese, G. Thoma, *Helv. Chim. Acta.* **1991**, *74*, 1135.

[6] a) B. C. Gilbert, W. Kalz, C. I. Lindsay, P. T. McGrail, A. F. Parsons, D. T. E. Whittaker, *Tetrahedron Lett.* **1999**, *40*, 6095; b) B. C. Gilbert, W. Kalz, C. I. Lindsay, P. T. McGrail, A. F. Parsons, D. T. E. Whittaker, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1187; c) N. Huther, P. T. McGrail, A. F. Parsons, *Tetrahedron Lett.* **2002**, *43*, 2535.

[7] a) G. K. Friestad, J. Qin, *J. Am. Chem. Soc.* **2001**, *123,* 9922; b) G. K. Friestad, A. Ji, *Org. Lett.* **2008**, *10*, 2311; c) G. K. Friestad, K. Banerjee, *Org. Lett.* **2009**, *11*, 1095; d) K. A. Slater, G. K. Friestad, *J. Org. Chem.* **2015**, *80*, 6432.

[8] T. Fukuyama, S. Nishitani, T. Inouye, K. Morimoto, I. Ryu, *Org. Lett.* **2006**, *8,* 1383.

[9] C. M. McMahon, M. S. Renn, E. J. Alexanian, *Org. Lett.* **2016**, *18*, 4148.

[10] P. Nuhant, M. S. Oderinde, J. Genovino, A. Juneau, Y. Gagné, C. Allais, G. M. Chinigo, C. Choi, N. W. Sach, L. Bernier, Y. M. Fobian, M. W. Bundesmann, B. Khunte, M. Frenette, O. O. Fadeyi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15309; *Angew. Chem.* **2017**, *129*, 15511.

[11] L. Wang, J. M. Lear, S. M. Rafferty, S. C. Fosu, D. A. Nagib, *Science* **2018**, *362*, 225.

[12] X. Yang, C. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 923; *Angew. Chem.* **2018**, *130*, 935.

[13] H. Liang, Y.-X. Ji, R.-H. Wang, Z.-H. Zhang, B. Zhang, *Org. Lett.* **2019**, *21*, 2750.

[14] W.-Z. Weng, H. Liang, R.-Z. Liu, Y.-X. Ji, B. Zhang, *Org. Lett.* **2019**, *21*, 5586.

[15] For selected reviews, see: a) Z. B. Alsfassi, *N-Centered Radicals*, Wiley: New York, 1998; b) S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603; c) M. Minozzi, D. Nanni, P. Spagnolo, *Chem. Eur. J.* **2009**, *15*, 7830; d) S. B. Höfling, M. R. Heinrich, *Synthesis* **2011**, 173; e) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Soc. Rev.* **2016**, *45*, 2044; f) T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069; g) M. D. Kärkäs, *ACS Catal.* **2017**, *7,* 4999; h) J. Davies, S. P. Morcillo, J. J. Douglas, D. Leonori, *Chem. Eur. J.* **2018**, *24*, 12154.

[16] For selected reviews, see: a) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346,* 1525; b) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656; *Angew. Chem.* **2009**, *121*, 2694; c) N. Kambe, T. Iwasaki, J. Terao, *Chem. Soc. Rev.* **2011**, *40*, 4937; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417; e) X. Hu, *Chem. Sci.* **2011**, *2*, 1867; f) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767; g) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587.

[17] Y. Xia, L. Wang, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 12940; *Angew. Chem.* **2018**, *130*, 13122.

[18] S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 12945; *Angew. Chem.* **2018**, *130*, 13127.

[19] Q. Qin, S. Yu, *Org. Lett.* **2015**, *17,* 1894.

[20] For recent examples on the Hofmann-Löffler-Freytag (HLF) reaction, see: a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287; *Angew. Chem.* **2015**, *127*, 8405; b) E. A. Wappes, S. C. Fosu, T. C. Chopko, D. A. Nagib, *Angew. Chem. Int. Ed.* **2016**, *55*, 9974; *Angew. Chem.* **2016**, *128*, 10128; c) C. Q. O'Broin, P. Fernández, C. Martínez, K. Muñiz, *Org. Lett.* **2016**, *18*, 436; d) E. A. Wappes, K. M. Nakafuku, D. A. Nagib, *J. Am. Chem. Soc.* **2017**, *139*, 10204; e) P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñiz, *Angew. Chem. Int. Ed.* **2017**, *56*, 8004; *Angew.*

Chem. **2017**, *129*, 8117; f) D. Zhang, H. Wang, H. Cheng, J. G. Hernández, C. Bolm, *Adv. Synth. Catal.* **2017**, *359*, 4274; g) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher, K. Muñiz, *ACS Catal.* **2018**, *8*, 3918; h) X. Hu, G. Zhang, F. Bu, L. Nie, A. Lei, *ACS Catal.* **2018**, *8*, 9370; i) X.-Q. Mou, X.-Y. Chen, G. Chen, G. He, *Chem. Commun.* **2018**, *54*, 515; j) Y. Kumar, Y. Jaiswal, A. Kumar, *Org. Lett.* **2018**, *20*, 4964; k) F. Wang, S. S. Stahl, *Angew. Chem. Int. Ed.* **2019**, *58*, 6385; *Angew. Chem.* **2019**, *131*, 6451; l) K. Kiyokawa, S. Nakamura, K. Jou, K. Iwaida, S. Minakata, *Chem. Commun.* **2019**, *55*, 11782.

[21] For recent examples on N-radical directed remote C(sp^3)-H halogenations, see: a) B. J. Groendyke, D. I. AbuSalim, S. P. Cook, *J. Am. Chem. Soc.* **2016**, *138*, 12771; b) T. Liu, M. C. Myers, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 306; *Angew. Chem.* **2017**, *129*, 312; c) M. A. Short, J. M. Blackburn, J. L. Roizen, *Angew. Chem. Int. Ed.* **2018**, *57*, 296; *Angew. Chem.* **2018**, *130*, 302. For an example on N-radical directed benzylic C-H difluoromethylation, see: X. Zeng, W. Yan, M. Paeth, S. B. Zacate, P.-H. Hong, Y. Wang, D. Yang, K. Yang, T. Yan, C. Song, Z. Cao, M-J. Cheng, W. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 19941.

[22] For selected examples, see: a) A. J. Blackman, C. Li, D. C. R. Hockless, B. W. Skelton, A. H. White, *Tetrahedron* **1993**, *49,* 8645; b) L. Rahbæk, C. Christophersen, *J. Nat. Prod.* **1997**, *60,* 175; c) K. Pors, S. D. Shnyder, P. H. Teesdale-Spittle, J. A. Hartley, M. Zloh, M. Searcey, L. H. Patterson, *J. Med. Chem.* **2006**, *49,* 7013.

[23] For selected examples, see: a) A. Lei, X. Lu, G. Liu, *Tetrahedron Lett.* **2004**, *45*, 1785; b) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23,* 5618; c) F. E. Michael, P. A. Sibbald, B. M. Cochran, *Org. Lett.* **2008**, *10,* 793; d) G.-Q. Liu, Y.-M. Li, *J. Org. Chem.* **2014**, *79,* 10094.

[24] For recent examples on intermolecular chloroamination reactions of alkenes, see: a) L. Legnani, G. Prina-Cerai, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**, *362*, 434; b) N. Zhu, Y. Li, H. Bao, *Org. Chem. Front.* **2018**, *5,* 1303.

[25] DFT calculations were performed by Gaussian program under the level of M06-L/6-311++G(d,p)-SMD(CH_2Cl_2)//M06-L/6-31G(d,p)-SMD (CH_2Cl_2) and SDD for Mn atom. See SI for computational details.

[26] Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca, Raton, 2007.

[27] M. A. Cismesia, T. P. Yoon, *Chem. Sci.* **2015**, *6*, 5426.

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RESEARCH ARTICLE

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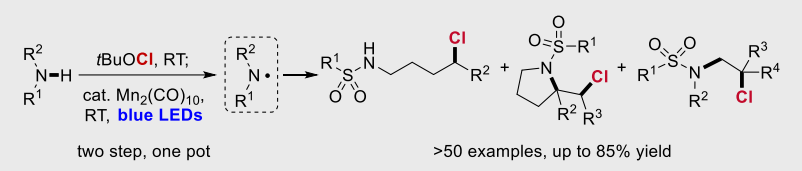
Generation and Reactivity of Amidyl Radicals: Manganese-Mediated Atom-Transfer Reaction



A visible-light-driven manganese-mediated protocol for generation of amidyl radicals from amines is described. This novel strategy enables site-selective chlorination of unactivated C(sp^3)-H bonds of aliphatic amines and intramolecular/intermolecular chloroaminations of unactivated alkenes. These reactions feature a broad substrate scope, good functional-group tolerance, scalability, and excellent practicality.