Article

Electrocatalytic Radical Dichlorination of Alkenes with Nucleophilic Chlorine Sources

Niankai Fu, Gregory Stuart Sauer, and Song Lin

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b09388 • Publication Date (Web): 08 Oct 2017

Electrocatalytic Radical Dichlorination of Alkenes with Nucleophilic Chlorine Sources

Niankai Fu[†], Gregory S. Sauer[†], Song Lin*[†‡]

[†]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853
[‡]Atkinson Center for a Sustainable Future, Cornell University, Ithaca, NY 14853

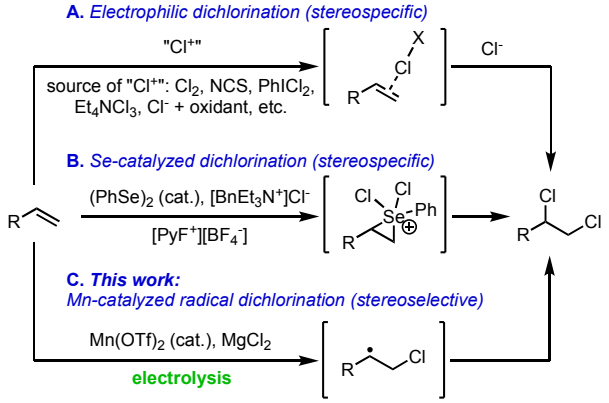
ABSTRACT: We report a Mn-catalyzed electrochemical dichlorination of alkenes with $MgCl_2$ as the chlorine source. This method provides operationally simple, sustainable, and efficient access to a variety of vicinally dichlorinated compounds. In particular, alkenes with oxidatively labile functional groups, such as alcohols, aldehydes, sulfides, and amines, were transformed into the desired vicinal dichlorides with high chemoselectivity. Mechanistic data are consistent with metal-mediated Cl atom transfer as the predominant pathway enabling dual C–Cl bond formation and contradict an alternative pathway involving electrochemical evolution of chlorine gas followed by Cl_2-mediated electrophilic dichlorination.

INTRODUCTION

Organochlorides are common structural motifs in many bioactive natural products[1] and polymers,[2] and are widely used as intermediates in organic synthesis. Among the earliest organic reactions discovered, the dichlorination of alkenes remains a highly prevalent method for incorporating chlorine atoms in organic molecules.[3] The ideal reagents for this transformation derive from nucleophilic chlorine sources because chlorine in nature exists almost exclusively as chloride equivalents. As such, the combination of Cl^- and a strong oxidant[4] has emerged as an attractive alternative to the traditional use of electrophilic chlorinating agents[5] such as Cl_2 and *N*-chlorosuccinamide (NCS) (Scheme 1A). In a particularly elegant example, a Se catalyst was used in conjunction with an electrophilic fluorine to engage alkenes in the formation *syn*-1,2-dichlorides in a stereospecific fashion (Scheme 1B).[6] However, current chlorination approaches are limited by the need for stoichiometric oxidants, which reduces functional group compatibility while generating wasteful and often environmentally hazardous byproducts.

Electrochemistry offers an efficient and sustainable alternative to conventional chemical approaches for redox organic transformations.[7] The application of a sufficient potential bias allows common organic molecules to lose or gain electrons at the electrode surface and produce highly reactive intermediates. Such electron-mediated redox processes inherently facilitate umpolung reactivity, mitigating the need for the activating agents used in traditional chemical syntheses. Indeed, recent studies have shown that electrochemistry can provide access to new reactivities challenging to achieve via canonical methods.[8]

Electrochemical chlorine formation via the chlor-alkali process is a commercialized protocol.[9] However, the high reactivity of this indiscriminate chlorinating agent, in addition to its toxicity and corrosive nature, has plagued the wide use of Cl_2 in the dichlorination of alkenes for synthetic applications.[6] Our previous success with the electrochemical diazidation of alkenes[10] demonstrated that reactive radical intermediates, such as N_3·, could be generated electrochemically under very mild conditions, and its downstream reactivity with the alkene substrate could be controlled by a redox-active metal with an excellent level of chemoselectivity. We envision that the combination of electrochemistry and metal catalysis may allow us to engage a radical pathway and bypass the intermediacy of Cl_2, thus achieving the dichorination of alkenes in a mild, selective, and sustainable fashion. Herein, we describe a chemo- and stereoselective protocol for the 1,2-dichloroalkane synthesis via catalyst-controlled anodic generation of chlorine radical from readily available chloride salts (Scheme 1C).

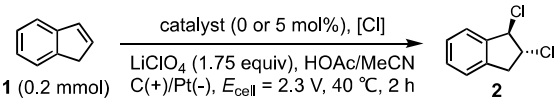


Scheme 1. Dichlorination of alkenes: chemical vs electrocatalytic approaches

RESULTS AND DISCUSSION

We chose indene (**1**) as the model substrate for this study because (1) it contains a relatively reactive C=C π-bond, and (2) its alkene substitution pattern allowed for an investigation of the stereochemistry of the dichlorination process. Our initial attempt to drive dichlorination with electricity suggested that this transformation would take place at a cell potential (E_{cell}) of 2.3 V [corresponding to an anodic potential of ca. 0.94 V vs ferrocenium/ferrocene ($Fc^{+/0}$)]. At 40 °C with LiCl as the chlorine source, $LiClO_4$ as the electrolyte, HOAc as the sacrificial oxidant, and MeCN as the solvent, 1,2-dichloroindane (**2**) was formed in 16% yield in a 1:1 diastereomeric ratio (dr) with ~80% starting material recovered (Table 1, entry 1). Despite a promising lead result, this direct electrolysis protocol showed poor reactivity and stereoselectivity. The observed stereochemical infidelity demonstrated that the chlorination reactivity could be attributed primarily to a radical pathway, although the contribution of a stereospecific, chloronium-ion-mediated process could not be conclusively ruled out. We reasoned that the low yield was a result of the sluggish generation of Cl· [$E(Cl\cdot/Cl^-)$ = 1.56 V][11] under direct electrolysis. Indeed, when the applied potential was increased to 2.8 V, the desired product was detected in marginally enhanced yield (32%). However, the chemoselectivity was substantially diminished, as a mere <15% indene was recovered and the remainder was converted to unidentified byproducts.

Table 1. Reaction discovery and optimization



1 (0.2 mmol) **2**

Entry	Cl source	Catalyst	Yield (%)[a]	dr
1	LiCl (4 equiv)	None	16 (32[b])	1:1
2	LiCl (4 equiv)	$Cu(OTf)_2$	14	1:2
3	LiCl (4 equiv)	$Mn(OTf)_2$	63	>19:1
4	$MgCl_2$ (2 equiv)	$Mn(OTf)_2$	89	>19:1
5	$CaCl_2$ (2 equiv)	$Mn(OTf)_2$	<5	ND
6	NaCl (4 equiv)	$Mn(OTf)_2$	8	>19:1
7	$MgCl_2$ (2 equiv)	$Mn(OAc)_2{\cdot}4H_2O$	86	>19:1
8[c]	$MgCl_2$ (2 equiv)	$Mn(OTf)_2$	98	17:1
9	$MgCl_2$ (1 equiv)	$Mn(OTf)_2$	63	>19:1
10	**$MgCl_2$ (3 equiv)**	**$Mn(OTf)_2$**	**92 (90[d])**	**>19:1**
11[e]	$MgCl_2$ (2 equiv)	$Mn(OTf)_2$	54	>19:1

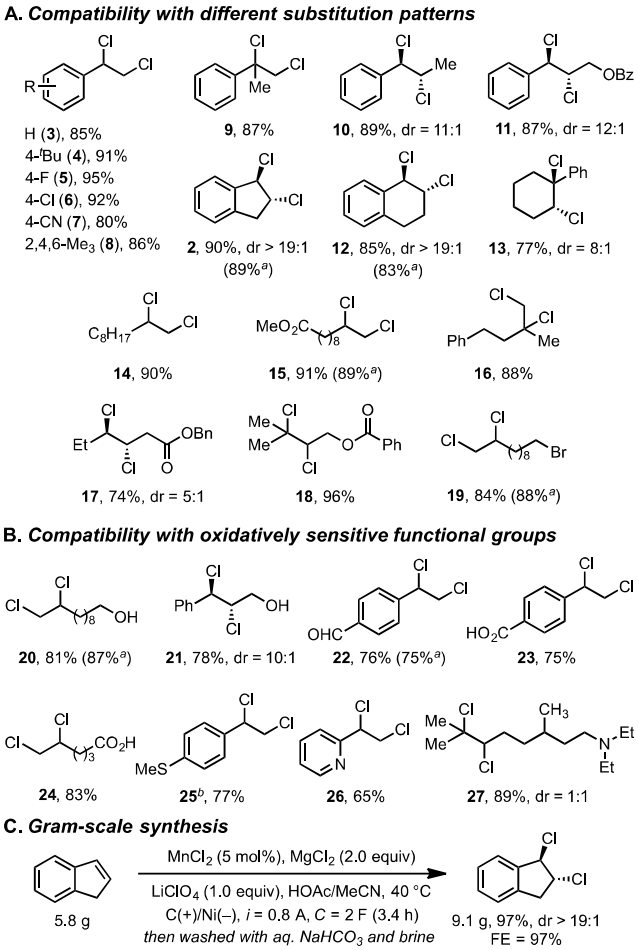
[a]Yields determined with ^1H NMR. [b]E_{cell} = 2.8 V. [c]$TBAPF_6$ instead of $LiClO_4$ as electrolyte. [d]Isolated yield. [e]E_{cell} = 2.1 V.

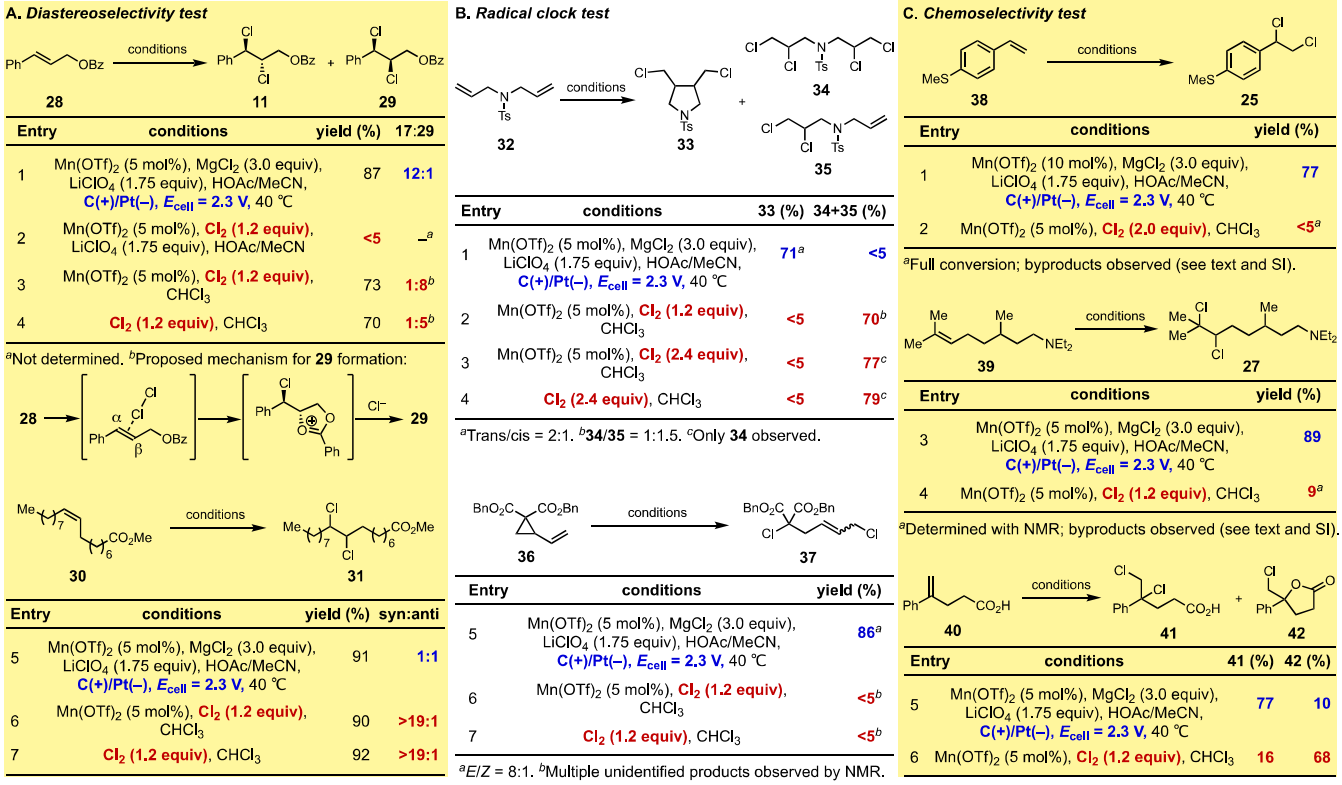
We then sought to employ a redox-active metal to impart kinetic control over the dichlorination reactivity and obtained encouraging results. Although the addition of Cu^{II}, a transition metal used frequently in atom-transfer radical reactions for carbon–halogen bond formation,[12] failed to improved reactivity (see Table 1, entry 2), the introduction of Mn^{II} created a highly reactive system in which the 1,2-*trans*-dichloroindane was isolated as the sole diastereomeric product in 63% yield (entry 3). The high diastereoselectivity likely arises from a combination of the steric and electronic properties of the putative chlorine transfer agent ($[Mn]^{III}$–Cl). This Mn-bound complex not only has a bulkier steric profile, but its Cl motif also bears a partial charge more negative than that of its free radical counterpart, plausibly leading to electrostatic repulsion with the previously installed Cl substituent if approaching from the same side.

Further improvements were observed when LiCl was replaced with $MgCl_2$, which furnished the product in 89% yield and >19:1 dr with only a trace amount of indene recovered (entry 4). Attempts to use NaCl or $CaCl_2$ as the chlorine source proved unsuccessful, primarily due to the low solubility of these salts in the reaction medium (entries 5 and 6). Other Mn salts, such as $Mn(OAc)_2$, also proved to be competent catalyst precursors in this system (entry 7). The electrolyte $LiClO_4$ did not play an explicit role in the dichlorination reactivity; replacing it with tetrabutylammonium hexafluorophosphate ($TBAPF_6$) resulted in similar reactivity (98% yield, dr = 17:1, entry 8). The quantity of $MgCl_2$ could be reduced to 1 equiv while still achieving synthetically useful product yield (entry 9). Complete consumption of **1** and near quantitative formation of **2** were accomplished by increasing $MgCl_2$ loading to 3 equiv (entry 10). Under these conditions, simply passing the reaction mixture through a short silica plug was sufficient to remove polar components and obtain spectroscopically pure product. Finally, the dichlorination could also take place at a decreased cell potential of 2.1 V albeit at a slower rate (entry 11). Notably, H_2 generated via cathodic proton reduction and $Mg(OAc)_2$ constituted the only byproducts, which renders our dichlorination system highly sustainable compared with existing protocols.

We found that under the optimal conditions, a variety of styrene-derived alkenes proved suitable as substrates, providing vicinal dichloroalkanes in generally excellent yields (Scheme 2A). In particular, cyclic alkenes and β-alkylstyrenes were converted to their corresponding dichlorides in high diastereoselectivity. This protocol was also applicable to aliphatic alkenes with various substitution patterns. Terminal, 1,1- and 1,2-disubstituted, and trisubstituted alkenes all readily underwent the desired dichlorination. Tetrasubstituted alkenes were also reactive; however, we were unable to isolate the desired products in appreciable yields. We attribute this outcome to the greater susceptibility of vicinal bis-*tert*-alkylchlorides to solvolysis via the corresponding highly stabilized chloronium ions.

Scheme 2. Substrate scope. Isolated yields are reported. [a]Faradaic efficiency under a controlled current of 8 mA after passing 2 F charge. [b]With 10 mol% catalyst.





Scheme 3. Control experiments: electrocatalytic radical dichlorination vs Cl_2-mediated dichlorination of alkenes.

The ability to control the applied potential gives electrosynthesis an innate advantage over conventional protocols that use indiscriminate chemical redox agents. As an illustrative example, we conducted the electrochemical dichlorination at a potential close to the minimum needed for catalyst turnover, which is well below that of many oxidation-sensitive functionalities, and employed HOAc as the terminal oxidant. As a result, an array of compounds containing oxidatively labile functionalities, such as alcohol, aldehyde, *N*-heterocycle, sulfide, carboxylic acid, and amine groups, proved viable as substrates, leading to the desired products in high yields while leaving vulnerable functional groups intact (Scheme 2B). A representative set of substrates was also investigated under constant current electrolysis and recorded excellent Faradeic efficiency (see Supporting Information). These results are a significant improvement over the state-of-the-art for alkene dichlorination, as no existing methods using either electrophilic chlorine or Cl^- in combination with stoichiometric oxidants are shown compatible with a majority of the aforementioned substrates. As such, this electrochemical protocol provides convenient access to a substantially wider variety of vicinally dichlorinated compounds from readily available alkenes.

Finally, we conducted the dichlorination of indene on a multi-gram scale and obtained pure product with nearly quantitative yield and current efficiency after simple aqueous workup of the reaction (Scheme 2C).

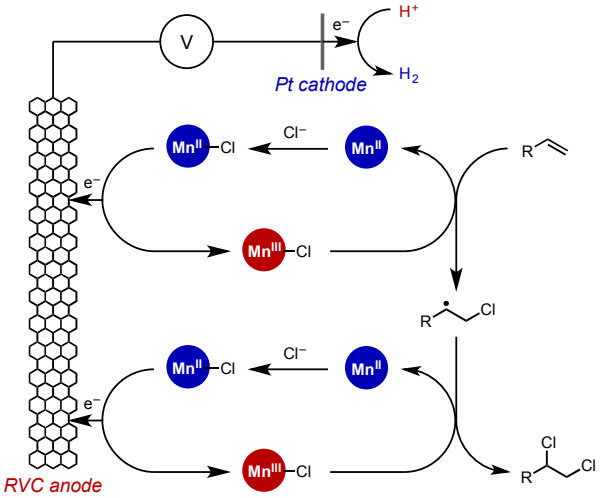
The engagement of a Cl· equivalent and formation of a carbon-centered radical in the electrochemical dichlorination was supported by several control experiments (Scheme 3). These results are also contradictory to an alternative mechanistic pathway mediated by electrochemically generated Cl_2. First, reaction with several substrates using Cl_2 in lieu of $MgCl_2$ and electricity proved that the medium for our electrocatalytic protocol was unsuitable for electrophilic alkene dichlorination (for an example, see Scheme 3A, entry 2). We attribute this finding to the presence of other nucleophilic species in the reaction medium, including MeCN and acetate, which compete with Cl^- for addition to the alkene-Cl_2 complex or chloronium ion intermediates. As such, we conducted control experiments with Cl_2 under modified reaction conditions[6] with or without the Mn catalyst.

With cinnamyl benzoate (**28**), our electrocatalytic protocol furnished *anti*-1,2-dichloride **11** as the predominant diastereomeric product (dr = 12:1, see Scheme 3A, entry 1). In stark contrast, the Cl_2-mediated reactions produced *syn*-1,2-dichloride **29** as the major product in ≥5:1 dr. This product likely arose from electrophilic activation of the alkene by Cl_2 followed by anchimeric assistance from the neighboring benzoyl group. Cl^- addition to the resultant 1,3-dioxolium intermediate then yielded **29** with net retention of the stereochemistry at the β-carbon. In addition, methyl oleate (**30**) was also investigated in the electrocatalyzed and Cl_2-mediated dichlorination reactions to form **31** with markedly different product dr (entries 5 vs 6 & 7).

In a set of radical clock experiments, *N*-tosyl diallylamine **32** and vinyl cyclopropane derivative **36** underwent cyclization and rupture of the three-membered ring, respectively, upon subjection to the electrocatalytic dichlorination conditions (Scheme 3B, entries 1 and 5). In contrary, Cl_2-mediated dichlorination conditions tested negative in the radical clock experiments. Starting from **32**, direct dichlorination of one or both of the terminal C=C bonds occurred, depending on the amount of Cl_2 added, while no pyrrolidine **33** was observed (entries 2 & 3). Electrophilic chlorination of **36** led to an intractable mixture of products[13] with no evidence of **37** formation (entries 6 & 7).

Finally, we investigated the chemoselectivity of electrophilic dichlorination reaction in comparison to the electrocatalytic method (Scheme 3C). Alkenes containing oxidatively labile groups, such as **38** and **39**, failed to produce the desired 1,2-dichlorides **25** and **27**, respectively, in the presence of Cl_2 (entries 2 & 4). Instead, oxidation and/or chlorination of the methylsulfide and tertiary amine groups, respectively, were evident from NMR and MS analyses of the reaction mixture.[14] When 4-pentenoic acid **40** was employed as the substrate, electrocatalytic (entry 5) and Cl_2-mediated processes (entry 6) displayed opposite chemoselectivity. When Cl_2 was used, instead of direct dichlorination of the C=C bond, chlorolactonization took place predominantly to furnish **42**. Taken together with other data from the aforementioned control experiments, we ruled out the mechanistic possibility involving electrochemical generation of Cl_2 followed by its electrophilic addition to the alkene.

Chlorine radicals are notoriously reactive species that can activate virtually any $C(sp^3)$–H bond via hydrogen atom abstraction (BDE_{HCl} = 103 kcal/mol). The generation of Cl· usually relies on the decomposition of highly electrophilic Cl precursors[5b] such as Cl_2 and NCS. Recent advances in organometallic catalysis have opened new avenues to Cl· formation under much milder conditions. For instance, chloride and hypochlorite complexes of high-valent transition metals (e.g., Ni^{III}, Mn^{IV}) are competent Cl· surrogates under photochemical or conventional chemical conditions.[15,16] We hypothesize that in our electrochemical system, the chlorine radical takes the form of anodically generated $Mn^{III}ClX_2$ (X = Cl or OAc),[17,18] which then serves as the atom-transfer agent to deliver both equivalents of chlorine to the alkene and thus implement vicinal dichlorination (Scheme 4).



Scheme 4. Proposed catalytic cycles.

The results of cyclic voltammetry studies provided evidence that a Cl-bound Mn^{III} complex can indeed be produced upon applying a sufficient potential bias (Figure 1). A $MgCl_2$ solution in HOAc/MeCN displayed an irreversible anodic wave of Cl^- oxidation with a peak potential of 1.1 V (blue line). $Mn(OTf)_2$ alone showed no oxidation event within the potential range of 0 to 1.4 V (red line). However, the addition of $MgCl_2$ resulted in the appearance of a quasi-reversible feature at 0.75 V (yellow line), which we attributed to the Mn^{II}/Mn^{III} redox couple of the chloride-bound complex. A few additional oxidative waves were also observed at more positive potentials and may arise from the direct oxidation of free Cl^- and overoxidation of Mn^{III} to Mn^{IV}. Further addition of 4-*t*-butylstyrene led to the desymmetrization of the Mn^{II}/Mn^{III} redox couple in addition to a small but consistently recorded current enhancement (green line). This catalytic current became more apparent at lower scan rates (see Supporting Information). These data are consistent with the catalytic activity of the putative $Mn^{III}ClX_2$ agent in Cl· transfer toward vicinal dichlorination. This radical addition occurs at a rate slower than that of the electrochemical turnover of the catalyst. In a manner reminiscent of metal-oxo radical chemistry, the association of Cl· with a high valent Mn center preserves its open-shell character toward inducing C=C homolysis and subsequent reaction with the incipient carbon-centered radical. Meanwhile, Mn allows these radical transformations to occur in a manner that is much more controlled than those involving promiscuous free Cl·, leading to the observed high chemoselectivity.

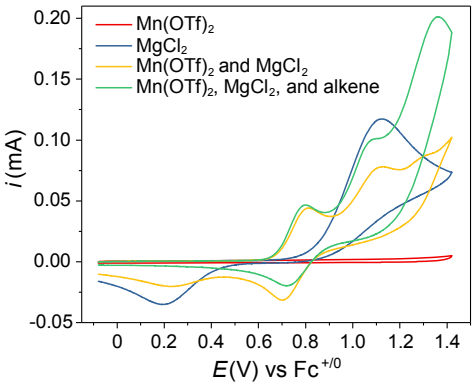


Figure 1. Cyclic voltammetry studies.

CONCLUSION

In sum, we developed a metal-catalyzed electrochemical dichlorination of alkenes with electricity as the primary energy input and H_2 and $Mg(OAc)_2$ as the sole byproducts. We anticipate that the development of this operationally simple, sustainable, efficient, and selective chlorination protocol combined with its mechanistic characterization will guide the future design and application of electrocatalysis in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

songlin@cornell.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support was provided by Cornell University and the Atkinson Center for a Sustainable Future. This study made use of the Cornell Center for Materials Research Shared Facilities (DMR-1120296) and the NMR facility (CHE-1531632) supported by the NSF. G.S.S is grateful for the NSF Graduate Fellowship (DGE-1650441).

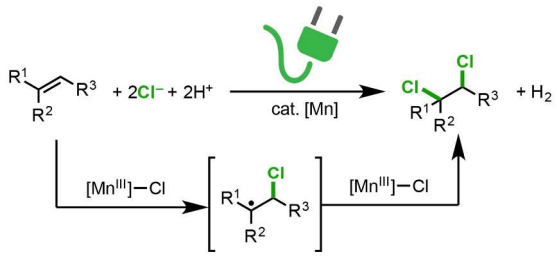
REFERENCES

1. (a) Gribble, G. W. *J. Nat. Prod.* **1992**, 55, 1353–1395. (b) Gál, B.; Bucher, C.; Burns, N. Z. *Mar. Drugs* **2016**, *14*, 206.
2. Sawada, H. In *Encyclopedia of Polymeric Nanomaterials*; Kobayashi, S., Müllen, K., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2015; pp 1–10.
3. (a) Cresswell, A. J.; Eey, S. T. C.; Denmark, S. E. *Angew. Chem., Int. Ed.* **2015**, *54*, 15642–15682. (b) Chung, W. J.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2016**, 55, 4396–4434.
4. For examples, see: (a) Uemura, S.; Onoe, A.; Okano, M. *Bull. Chem. Soc. Jpn.* **1974**, 3121–3124. (b) Ho, T.-L.; Gupta, B. G. B.; Olah, G. A. *Synthesis* **1977**, 676–677. (c) Nugent, W. A. *Tetrahedron Lett.* **1978**, *19*, 3427–3430. (d) Donnelly, K. D.; Fristad,

W. E.; Gellerman, B. J.; Peterson, J. R.; Selle, B. J. *Tetrahedron Lett.* **1984**, *25*, 607–610. (e) Markó, I. E.; Richardson, P. R.; Bailey, M.; Maguire, A. R.; Coughlan, N. *Tetrahedron Lett.* **1997**, *38*, 2339–2342.

5. For examples, see: (a) Atterberg, A., Widman, O. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1841–1844. (b) Poutsma, M. L. *Science* **1967**, *157*, 997–1005. (c) Tanner, D. D.; Gidley, G. C. *J. Org. Chem.* **1968**, *33*, 38–43. (d) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4204–4208. (e) Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2342–2344. (f) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518. (g) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–576. (h) Snyder, S. A.; Tang, Z. Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745. (i) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134–8137. (j) Kamada, Y.; Kitamura, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Biomol. Chem.* **2013**, *11*, 1598–1601. (k) Landry, M. L.; Hu, D. X.; McKenna, G. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 5150–5158.
6. Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Nature Chem.* **2015**, *7*, 146–152.
7. (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554. (b) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265–2299. (c) Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492–2521. (d) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2*, 302–308. (e) Yan, M.; Kawamata, Y.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, accepted article, DOI 10.1002/anie.201707584.
8. (a) Moeller, K. D.; Marzabadi, M. R.; New, D. G.; Chiang, M. Y.; Keith, S. *J. Am. Chem. Soc.* **1990**, *112*, 6123–6124. (b) Sowell, C. G.; Wolin, R. L.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 485–488. (c) Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc.* **2001**, *123*, 11314–11315. (d) Ischay, M. A.; Mubarak, M. S.; Peters, D. G. *J. Org. Chem.* **2006**, *71*, 623-628. (e) Kirste, A.; Schnakenburg, G.; Stecker, F.; Fischer, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 971–975. (f) Sawamura, T.; Takahashi, K.; Inagi, S.; Fuchigami, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 4413–4416. (g) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000–5003. (h) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5571–5574. (j) Hickey, D. P.; Schiedler, D. A.; Matanovic, I.; Doan, P. V.; Atanassov, P.; Minteer, S. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 16179–16186. (k) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Nature* **2016**, *533*, 77–81. (l) Badalyan, A.; Stahl, S. S. *Nature* **2016**, *535*, 406–410. (m) Xiong, P.; Xu H.-H.; Xu, H.-C. *J. Am. Chem. Soc.* **2017**, *139*, 2956–2959. (n) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Yan, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13088–13093. (o) Gieshoff, T.; Kehl, A.; Schollmeyer, D.; Moeller, K. D.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2017**, *139*, 12317–12324.
9. Karlsson, R. K. B.; Cornell, A. *Chem. Rev.* **2016**, *116*, 2982–3028.
10. Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. *Science* **2017**, *357*, 575–579.
11. Wardman, P. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1637.
12. Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11.
13. See Supporting Information for the ^{1}H NMR spectrum of the crude reaction mixture.
14. With **38**, at least three products resulting from oxidative *S*-demethylation were observed by NMR. Presumably, this process arose from *S*-chlorination followed by HCl elimination to form the corresponding thionium ion in a manner analogous to the Pummerer rearrangement. For a reference, see: Truce, W. E.; Birum, G. H.; McBee, E. T. *J. Am. Chem. Soc.* **1952**, *74*, 3594–3599. With **39**, products resulting from oxidative chlorination of the tertiary amine group were observed by MS. These byproducts have not been definitively identified. See Supporting Information for the ^{1}H NMR spectra of the isolated form of some of these byproducts.
15. (a) Hwang, S. J.; Powers, D. C.; Maher, A. G.; Anderson, B. L.; Hadt, R. G.; Zheng, S. L.; Chen, S.; Nocera, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 6472–6475. (b) Shields, B. J.; Doyle, A. G. *J. Am. Chem. Soc.* **2016**, *138*, 12719–12722.
16. Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847–12849.
17. Stoichiometric $Mn(OAc)_3$ in combination with $MgCl_2$ (2 equiv) gives dichloride **2** from **1** in 35% yield with >19:1 dr.
18. (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363. (b) Snider, B. B. *Tetrahedron* **2009**, *65*, 10738–10744.

Insert Table of Contents artwork here



26 examples, up to 9 gram scale, 65–97% yield

operationally simple, energy efficient, environmentally friendly, broad substrate scope, compatible with oxidatively sensitive groups