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COMMUNICATION

Mn-catalyzed paired electrochemical facile oxychlorination of styrenes via oxygen reduction reaction

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Accepted 00th January 20xxSiyu Tian^a, Xiaofei Jia^b, Ling Wang^a, Baoying Li^a, Siyuan Liu^a, Li Ma^a, Wei Gao^a, Yingqin Wei^a, and Jianbin Chen^{a*}

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Reported herein is electrochemical engendering chlorine radical by manganese catalyst at a controllable pattern with cheap commodity MgCl₂ as chlorine source. In combination with oxygen reduction reaction, chloroacetophenones were synthesized with abundant styrene as the feedstock in good to excellent yields.

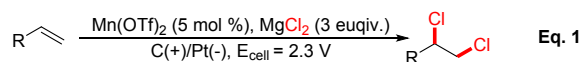
Organic electrochemistry offers a mild and efficient alternative to conventional chemical approaches, particularly for redox transformations. Remarkably, the absence of exogenous chemical oxidants in combination of the easily scalable nature of electrochemistry reduces the costs, especially for large-scale synthesis.¹ However, in this research area, most of the attention has been focused on one side half-reaction. The other side complementary half-reaction was used to avoid interference with the desired process and/or to match the fast kinetics. In sharp contrast, paired electrolysis can take the advantage of both side half-reaction into one target transformation.² Nevertheless, this subject of paired electrolysis is underdeveloped compared to the fast increasing one side electrolysis.

Because of the highly reactive intermediate such as superoxide ion O₂⁻,³ application of oxygen reduction reaction (ORR) in electroorganic synthesis represents one of the fascinating research topics. Significantly, the long half-life time of the electrogenerated superoxide ion (approximately 30 minutes at ambient temperature) makes it to be an outstanding persistent radical⁴ and allows the subsequent chemical reactions to occur in a catholyte solution.⁵ Although the advantages are noticeable, successful examples of ORR that have been devoted to organic transformations are very elusive.⁶ Due to the highly reactive chlorine radical (BDE_{HCl} =

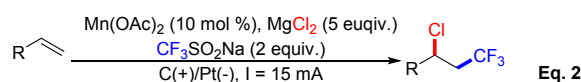
103 kcal/mol), direct harnessing of this notorious radical is a challenging task (E_{Cl[•]/Cl⁻} = 1.56 V).⁷ In order to overcome this challenge, Lin and co-workers elegantly described Mn-electrocatalyzed dichlorination, trifluoro-chlorination and chloroalkylation of activated and unactivated olefins with nucleophilic chloride salts.⁸ In these cases, the catalytic species was generated *in situ* as a form of chlorine bound [Cl-Mn(II)] complexes. Oxidation of [Cl-Mn(II)] to [Cl-Mn(III)] at the surface of anode generates the chlorine radical in a controlled manner (Eq. 1 to Eq. 3, **Scheme 1**).

Considering the pivotal role of chloroacetophenones in pharmaceutical and agrochemical synthesis⁹ and the drawbacks of previous approaches (expensive feedstocks,¹⁰ multi-step reactions,¹¹ stoichiometric oxidants¹² and low atom-efficient¹³), we envision that utilizing anodic controllable generating chlorine radical and cathodic forming superoxide ion can cross-coupled in a paired manner. Thus, we herein report the electrochemical Mn-catalyzed oxychlorination with a variety of alkenes in order to produce the corresponding chloroacetophenones (Eq. 4, **Scheme 1**).

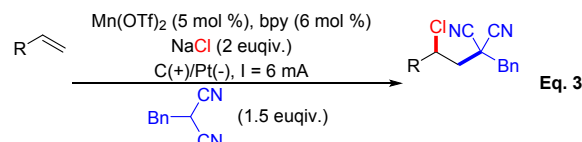
J. Am. Chem. Soc. 2017, 139, 15548-15553 ref. 8a



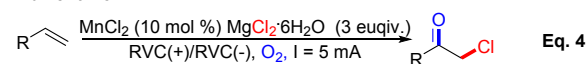
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Current work



Scheme 1. Representative procedures for Mn-catalyzed electrochemical chlorination.

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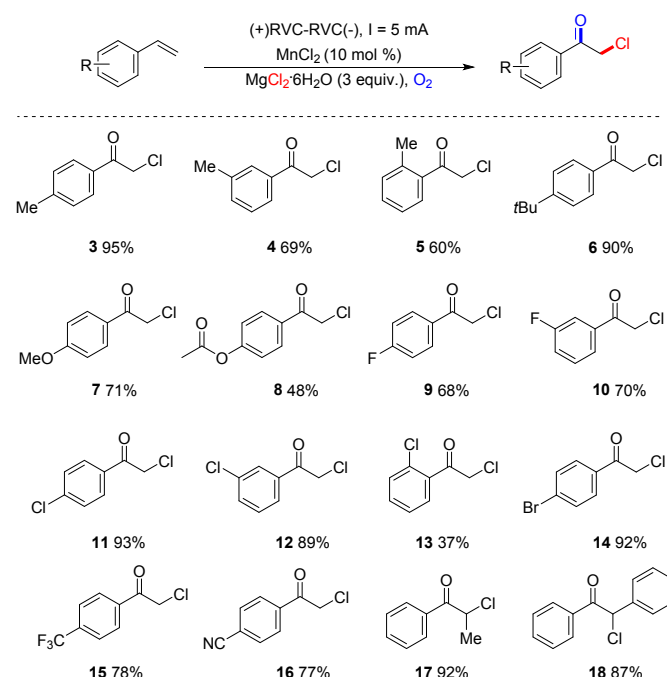
The optimal system was obtained as following: manganese chloride (MnCl_2 , 10 mol %), magnesium chloride hexahydrate ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 3 equivalents), reticulated vitreous carbon (RVC) as both anode and cathode in solvent mixtures of acetone and dichloromethane (DCM), with electrostatic mode ($I = 5 \text{ mA}$) under oxygen atmosphere at 40°C . Significantly, acetone and acetonitrile (MeCN) resulted in a decrease of the yield while DCM totally shut down the reaction (entries 2-4, **Table 1**). The solvent effect can be explained by the conductivity of the system: DCM (1.36 ms/cm) < Acetone (3.53 ms/cm) < Acetone-DCM (4.43 ms/cm) < MeCN (5.87 ms/cm).¹⁴ Those results indicated that the cell potential was the key parameter. Replacing of the RVC with platinum (Pt) plate as the anode or cathode gave moderate efficiency (entries 5 & 6, **Table 1**). Reducing the reaction time to 6 h resulted in 67 % yield (entry 7, **Table 1**). Notably, electrolytes played a key role for this transformation as inferior yields were observed when tetrabutylammonium tetrafluoroborate ($n\text{Bu}_4\text{NBF}_4$) and potassium hexafluorophosphate (KPF_6) were employed (entries 8 & 9, **Table 1**). Increasing or decreasing the electric current showed detrimental effect (entries 10 & 11, **Table 1**). Good efficiency was still obtained when the reaction was setup at room temperature (r. t.) (entry 12, **Table 1**). Electricity, manganese and dioxygen were indispensable for the transformation (entries 13 & 15, **Table 1**).

Table 1. Screening the optimal condition.

Entry	Variation from the standard conditions	Yield
1	None	93%
2	Acetone instead of Acetone/DCM	65%
3	DCM instead of Acetone/DCM	n.d.
4	MeCN instead of Acetone/DCM	43%
5	(+)RVC(-)Pt	63%
6	(+)Pt-RVC(-)	55%
7	6 h	67%
8	Bu_4NBF_4 instead of LiClO_4	10%
9	KPF_6 instead of LiClO_4	32%
10	2.5 mA	42%
11	10 mA	69%
12	r. t. instead of 40°C	85%
13	No electricity	n.d.
14	No MnCl_2	n.d.
15	N_2	trace

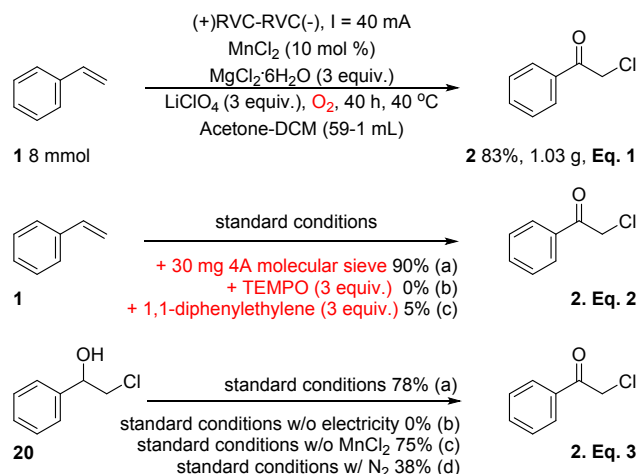
With the optimal conditions in hand, then we focused on the substrate scope (**Table 2**). First, we examined the electronic effect of a variety of olefins. Not only the electron-releasing groups such as methyl (**3-5**), tertiary butyl (**6**), methoxyl (**7**), phenolic ester (**8**), but also the electron-withdrawing substitutes for instance, fluoro (**9-10**), chloro (**11-13**), bromo (**14**), trifluoromethyl (**15**) and cyano (**16**) worked smoothly under our conditions. Moreover, 1,2-substituted olefins were successfully transformed into the targeted products in good to excellent yields (**17-18**). Next, we analyzed the steric hindrance effect, clearly, *para*-substituted analogues displayed superior efficiency than *meta*- and *ortho*-ones originating from the steric hindrance (**3 vs 4 & 5**; **11 vs 12 & 13**).

Table 2. Substrate scope.



The gram-scale reaction was demonstrated providing satisfied yield highlighting the readily scalable nature of electrosynthesis. (**Eq. 1, Scheme 2**). In order to gain insights into the reaction mechanism, a variety of control experiments were conducted. The addition of radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 1,1-diphenylethylene resulted in a significant decrease of the product formation which strongly indicated a radical pathway (**Eq. 2, Scheme 2**). The influence of residual water was excluded because comparable yield was still obtained with freshly dried acetone and DCM as solvent mixture in the presence of 30 mg activated molecular sieve (**Eq. 2a, Scheme 2**). Moreover, the chlorohydroxylated intermediate **20** was transformed into the desired molecule under standard conditions. In sharp contrast, no conversion was observed in the absence of electricity (**Eq. 3, Scheme 2**). These phenomena implied structure **20** can function as one of the intermediates en route to the desired scaffold **2**.

To gain further information of the reaction mechanism, cyclic voltammetry (CV) analyses of the components of the catalytic system were performed (see



Scheme 2. Gram-scale synthesis and control experiments.

supporting information). The distinct oxidative potential of each component ($E_p = 0.9$ V vs Ag/Ag⁺ for MnCl₂; $E_p = 1.1$ V vs Ag/Ag⁺ for Cl⁻; $E_p = 1.78$ V vs Ag/Ag⁺ for styrene) was obtained. Thus, it's believable to initiate the reaction via anodic oxidation of Mn(II)Cl₂ to Mn(III)Cl₂ releasing chlorine radical in a controlled manner (**Scheme 3**). Notably, the reduction peak of the reversible redox-couple of MnCl₂ was completely disappeared during the backward scanning when styrene was added to MnCl₂ solution (**Figure 1**). Evidently, this result demonstrated a fast interaction between electrogenerated Mn(III)Cl₂ and styrene delivering radical **A** and Mn(II) intermediates. Coordination of chloride with Mn(II) form [Mn(II)Cl] and closed the anodic catalytic ring. At the same time, oxygen reduction reaction took place at cathode generating persistent radical - superoxide ion. Generally, quasi-reversible one-electron reduction of oxygen at -0.85 V versus SCE delivers superoxide ion O₂^{-•} in aprotic environments. Further reduction of the electrochemically generated radical anion at cathode can be observed at more negative potential in protic conditions which finally can be regarded as two-electron reduction process.¹⁵ Cross-coupling of the nascent transient radical **A** with superoxide ion furnished intermediate **C** which decomposed to compound **20**. Then further oxidation of **20** by electricity and/or superoxide ion led to product **2** (**Scheme 3**). This proposal was corroborated by the control experiments (entry 15, **Table 1** & **Eq. 3**, **Scheme 2**) as electricity and dioxygen were necessary under our standard conditions for effective transformation of **20** whereas manganese was not. Overall, these findings fulfill the concept of paired electrolysis.

Conclusions

In summary, we developed a facile electrochemical manganese-catalyzed difunctionalization of alkenes with

inorganic nucleophilic chloride salts and dioxygen as the cost-effective and abundant feedstock. Thus, a diverse array of

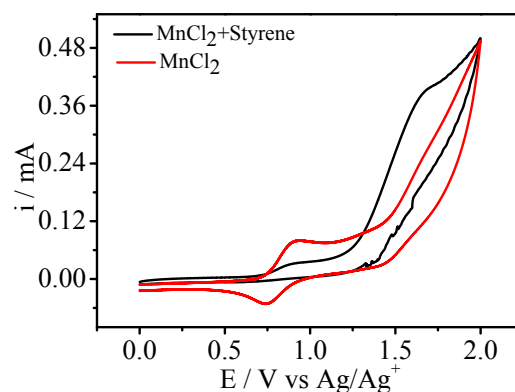
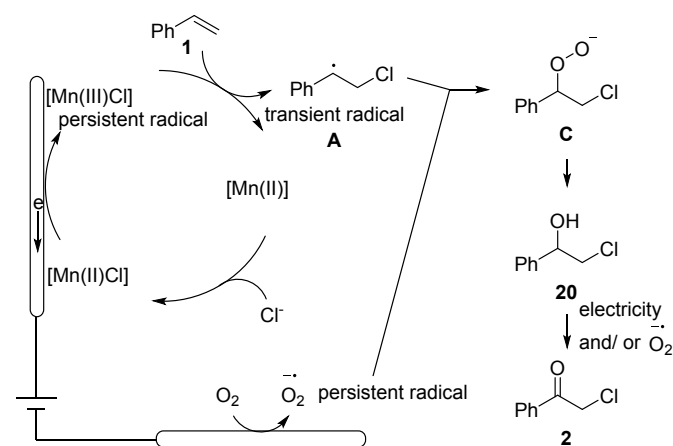


Figure 1. Cyclic voltammogram of MnCl₂ and/or styrene. Conditions: the glassy carbon, Ag/AgNO₃ and platinum wire were used as working electrode, Ag/AgNO₃ reference electrode, and counter electrode respectively. Electrolyte: LiClO₄ (1.2 mM), MnCl₂ (0.12 mM), styrene (0.12 mM) in acetone-DCM. Scan rate: 100 mV/s.



Scheme 3. Proposed mechanism.

chloroacetophenones was generated in good to excellent yields by this eco-friendly protocol. Nevertheless, the low conversion and yield of electronic unbiased alkyl olefins is the major drawback of this new catalytic system. Investigations are undergoing on this topic in our lab, and the related results will be reported in due time.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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