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Electrocatalysis

Synthesis of Chlorotrifluoromethylated Pyrrolidines by Electrocatalytic Radical Ene-Yne Cyclization

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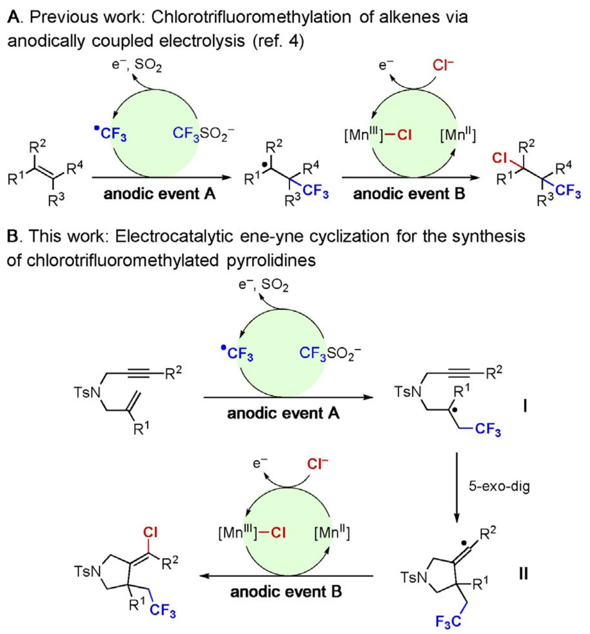
Abstract: The stereoselective synthesis of chlorotrifluoromethylated pyrrolidines was achieved using anodically coupled electrolysis, an electrochemical process that combines two parallel oxidative events in a convergent and productive manner. The bench-stable and commercially available solids CF_3SO_2Na and $MgCl_2$ were used as the functional group sources to generate $CF_3^{\bullet}$ and $Cl^{\bullet}$, respectively, via electrochemical oxidation, and the subsequent reaction of these radicals with the 1,6-enyne substrate was controlled with an earth-abundant Mn catalyst. In particular, the introduction of a chelating ligand allowed for the ene–yne cyclization to take place with high stereochemical control over the geometry of the alkene group in the pyrrolidine product.

Synthetic electrochemistry, which uses electrons as oxidizing or reducing "reagents," has emerged as a powerful tool for the efficient and sustainable synthesis of complex organic compounds.[1] Compared with conventional methods for organic synthesis, electrochemistry offers the unique capacity to precisely control the redox potential input, generate reactive intermediates cleanly via direct electron transfer, and integrate multiple redox events into single reaction systems in a concerted and productive manner. These characteristics make electrochemistry an attractive approach for meeting the prevailing trends in organic chemistry[2] and providing new bond-forming strategies to innovate the synthesis of complex targets.[3]

Using an electrochemical approach, we recently developed a method for the chlorotrifluoromethylation of alkenes using commercially available Langlois reagent (CF_3SO_2Na) and $MgCl_2$ as functional group donors and $Mn(OAc)_2$ as a catalyst (Scheme 1 A).[4] The proposed mechanism entails the parallel oxidative generation of two open-shell intermediates, $CF_3^{\bullet}$ and $[Mn^{III}]$–Cl, via anodically coupled electrolysis, followed by their selective additions across the C=C π-bond.[5] Distinct from existing methods for the same transformation, the radical-mediated mechanism and mild reaction conditions enabled by electrocatalysis allow for broader substrate scope and excellent functional group compatibility. In particular, preliminary data showed that a 1,6-enyne substrate undergoes a cascade of selective alkene trifluoromethylation, radical ene-yne cyclization,[6,7] and chlorination to furnish substituted pyrrolidine derivatives (Scheme 1 B), albeit with moderate efficiency and low stereoselectivity.[4] Such highly functionalized heterocycles are particularly compelling structures for medicinal chemistry research, as they contain a substituted pyrrolidine[8] and a CF_3 group,[9] both prevalent functionalities in numerous bioactive compounds. In addition, the alkenyl chloride motif provides opportunities for further synthetic elaboration.[10] In this work, we report detailed reaction development based on our initial result that leads to the highly regio- and stereoselective ene-



Scheme 1. Anodically coupled electrolysis for the chlorotrifluoromethylation of alkenes (**A**) and its application in the radical cyclization of 1,6-enynes for the synthesis of chlorotrifluoromethylated pyrrolidines (**B**).

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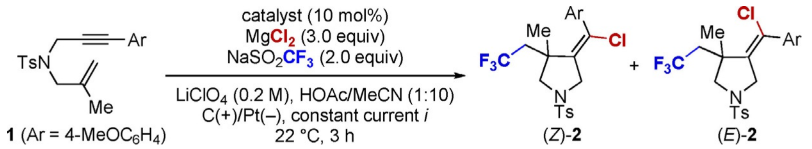
Table 1. Reaction optimization.[a]



Entry	Catalyst	Ligand	[1] [M]	i [mA]	Yield[b,c] [%]	Z/E[c]
1	$Mn(OAc)_2$	–	0.02	8	62	3.4:1
2	$Mn(OTf)_2$	–	0.02	8	61	5.1:1
3	$Mn(OTf)_2$	bpy[d]	0.02	8	67	$>$19:1
4	$Mn(OTf)_2$	bpy[d]	0.03	10	82 (80)[e]	$>$19:1
5	$Mn(OTf)_2$	bpy[d]	0.03	–[f]	$<$5	–[g]
6	–	–	0.03	10	$<$5	–[g]

[a] Reactions conducted on a 0.1 mmol scale. [b] Combined yield of (*E*)- and (*Z*)-**2**. [c] Determined with ^{19}F NMR. [d] 20 mol%. [e] Isolated yield in parentheses. [f] No external current applied. [g] Not determined.

yne cyclization for the synthesis of chlorotrifluoromethylated pyrrolidines.

Our hypothesized reaction mechanism entails the simultaneous anodic oxidation of CF_3SO_2Na[11] and $[Mn^{II}]$–Cl, the latter of which is formed upon mixing the Mn catalyst and $MgCl_2$. The reduction potentials of CF_3SO_2Na and $[Mn^{II}]$–Cl are 0.81 and 0.75 V, respectively (vs. ferrocenium/ferrocene redox couple $Fc^{+/0}$; Figure 1).[12] As such, with sufficient anodic potential, both species can be oxidized on the electrode surface at comparable rates, paving the way for the subsequent radical functionalization of the substrate. Notably, cyclic voltammetry shows that the redox wave corresponding to $[Mn^{III}]$–Cl/$[Mn^{II}]$–Cl couple is apparently reversible, which indicates that $[Mn^{II}]$–Cl is highly persistent in the reaction system. In the presence of the 1,6-enyne substrate, the addition of $CF_3^{\bullet}$ to the alkene takes place preferentially owing to the higher reactivity of $CF_3^{\bullet}$ (a transient free radical) compared with that of $[Mn^{III}]$–Cl (a persistent radical) and the higher reactivity of an alkene relative to that of an alkyne. The resultant intermediate **I** then undergoes 5-*exo*-dig cyclization onto the alkyne, leading to alkenyl radical **II**. This radical is highly unstable (bond dissociation energy of an alkenyl C–H bond is approximately 110 kcal mol^{-1})[13] and can in principle participate in a variety of side reactions. In our previous studies, we demonstrated that an sp^3 carbon-centered radical can be efficiently captured by $[Mn^{III}]$–Cl to form a C–Cl bond.[4,14] We reasoned that this Mn-bound latent Cl radical would also react with an alkenyl radical and that the efficiency and selectivity of this atom transfer process could be controlled by tuning the ligand on the metal center.

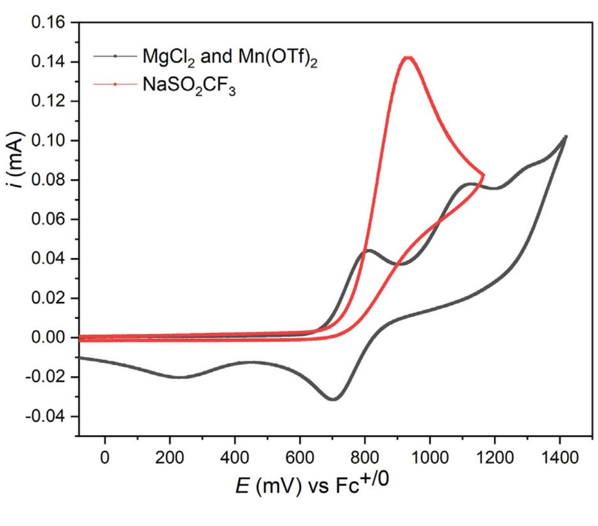
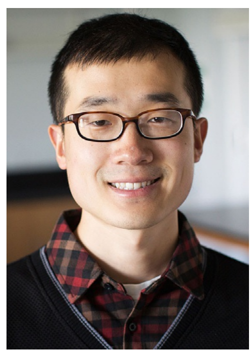


Figure 1. Cyclic voltammograms of CF_3SO_2Na and a mixture of $Mn(OTf)_2$ and $MgCl_2$. Conditions: $LiClO_4$ (0.10 M in MeCN) and HOAc (60 mM) with a) CF_3SO_2Na (8.0 mM) (red) or b) $Mn(OTf)_2$ (2.0 mM) and $MgCl_2$ (8.0 mM) (black). Scan rate: 100 mV s^{-1}.

In our initial experiment using 1,6-enyne **1** as the model substrate, $Mn(OAc)_2$ as the catalyst, HOAc as the sacrificial oxidant, and $LiClO_4$ as the electrolyte in MeCN at room temperature, the application of a constant current of 8 mA led to the formation of pyrrolidine product **2** as a pair of alkene geometric isomers in 62% overall yield and moderate selectivity (Z/E = 3.4:1; Table 1, entry 1). Changing the catalyst to $Mn(OTf)_2$ marginally increased the stereoselectivity to 5.1:1 while maintaining the same level of reactivity (entry 2).

We hypothesized that the product stereochemistry was sterically controlled (Figure 2). α-Aryl alkenyl radicals (e.g., **III**) are sp-hybridized owing to the conjugation between the aryl π orbitals and the singly occupied molecular orbital.[15] This orbital is perpendicular to the alkene π orbitals, and one side is



Song Lin grew up in Tianjin, China and received his B.S. degree from Peking University in 2008. After completing his PhD at Harvard University with Prof. Eric Jacobsen, he joined Prof. Christopher Chang at UC Berkeley to carry out his postdoctoral studies. In July 2016, he moved to Cornell University to start his independent research career. The Lin Lab is interested in developing new catalytic strategies to solve challenging problems in organic synthesis with a particular emphasis on electrochemistry and radical redox catalysis. Dr. Lin is a recent recipient of the Thieme Chemistry Journal Award, the 3M Nontenured Faculty Award, and the NSF CAREER Award.

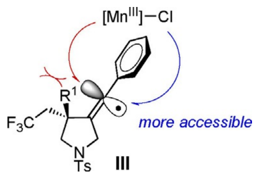
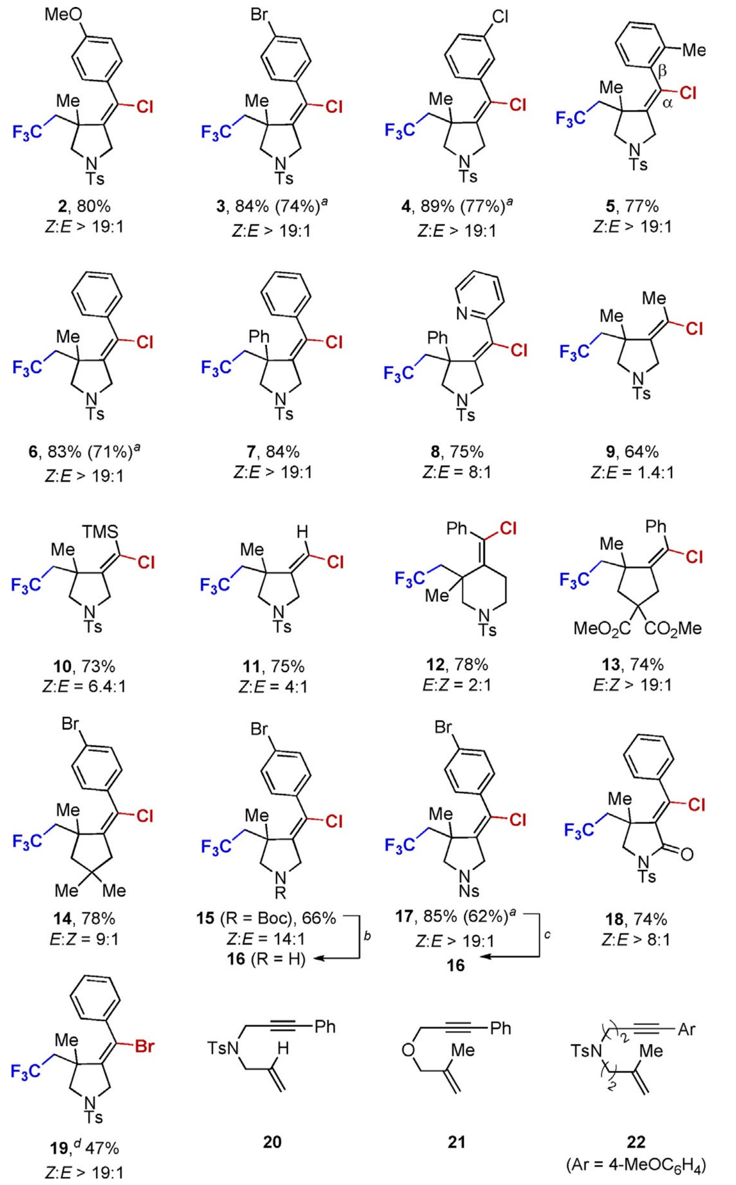


Figure 2. Graphical rationale for the observed alkene *Z*/*E* stereoselectivity.

shielded by the substituents at the quaternary carbon α to the alkene. This steric hindrance drives the [Mn^{III}]–Cl to approach **III** from the less congested side, resulting in the observed stereoselectivity favoring the *Z* isomer product. This hypothesis led us to reason that the addition of a ligand might increase the steric profile of [Mn^{III}]–Cl and further augment the stereochemical differentiation. Indeed, when 20 mol% 2,2′-bipyridine (bpy) was added to the reaction system, (*Z*)-**2** was observed as practically a single isomeric product (*Z*/*E* > 19:1) in 67% yield (entry 3).[16] The yield increased to 82% (while maintaining high stereoselectivity) by increasing the applied current to 10 mA and the substrate concentration to 0.03 M (entry 4). Controlled experiments showed that in the absence of the Mn catalyst or electrical input, no desired pyrrolidine product was formed (entries 5 and 6, respectively),[17] which demonstrates the critical role of the Mn catalyst and current in promoting the ene-yne cyclization reaction.

We subsequently investigated the substrate scope (Scheme 2) of the electrocatalytic radical ene-yne cyclization reaction under the optimized conditions (Table 1, entry 4). A set of 1,6-enynes with electron-rich, electron-deficient, and electron-neutral aryl groups on the alkyne all proved suitable substrates, providing the chlorotrifluoromethylated pyrrolidines in high yield and excellent stereoselectivity (**2**–**6**). Compound **5** was isolated as two diastereomers in about 1:1 ratio with respect to the stereochemistry of the C_α–C_β bond, as the highly substituted C=C bond in **5** restricts the free rotation of C_α–C_β. Styrene-derived substrates were smoothly converted to the corresponding products (**7** and **8**). Single crystals of pyrrolidine **7** were obtained from dichloromethane/*n*-pentane solution at room temperature, and X-ray diffraction data confirmed our structural assignment, including the configuration of the newly formed C=C bond (Figure 3). When pyridine was added to the alkyne unit, the cyclization product (**8**) was obtained with decreased stereoselectivity (*Z*/*E* = 8:1). Alkyl- and silyl-substituted alkynes (**9** and **10**) as well as terminal alkynes (**11**) proved compatible with the electrocatalytic reaction, providing the cyclization products in good yield. The stereoselectivity of these substrates was substantially lower than that of the aryl-substituted examples, however. This decrease in the product *Z*/*E* ratio stems from the sp^2 hybridization of α-alkyl alkenyl radicals (e.g., **IV**).[15] In the Curtin–Hammett scenario depicted in Figure 4, owing to the steric effect, less stable pro-(*Z*)-**IV** reacts faster with [Mn^{II}]–Cl, whereas more stable pro-(*E*)-**IV** reacts slower. As such, the destructive interplay between thermodynamics and kinetics resulted in decreased product stereoselectivity.[18]



Scheme 2. Substrate scope. Reactions were conducted on a 0.1 mmol scale. See Table 1, entry 4 for reaction conditions. a) Yield of reaction on a 1.0 mmol scale; $TBAClO_4$ was used as the electrolyte instead of $LiClO_4$; reaction time: 8 h. b) Reaction conditions: CF_3CO_2H, CH_2Cl_2, 0 °C; 79% yield. c) Reaction conditions: PhSH, KOH, MeCN, 50 °C; 82% yield. d) Using KBr instead of $MgCl_2$ under a constant cell potential of 2.3 V for 5 h.

The scope of this radical cyclization reaction was successfully extended to piperidine formation (**12**) using a structurally analogous 1,7-enyne substrate. The conformational flexibility of the six-membered heterocycle likely weakened the capacity of the Mn catalyst for stereochemical control in the last Cl$^\bullet$ transfer step, which led to the low *E*/*Z* selectivity (2:1) observed. Furthermore, highly substituted cyclopentane **13** could also be synthesized in high yield and stereochemically pure form using carbon-tethered 1,6-enynes with *gem*-diester groups. To further explore the Thorpe–Ingold effect in our radical cyclization reaction, we synthesized a structurally analogous enyne with *gem*-

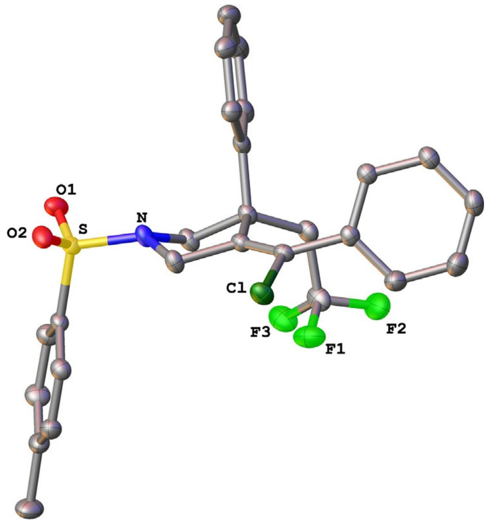


Figure 3. ORTEP drawing of compound **7** showing thermal ellipsoids with 30 % probability. Hydrogen atoms have been omitted for clarity.

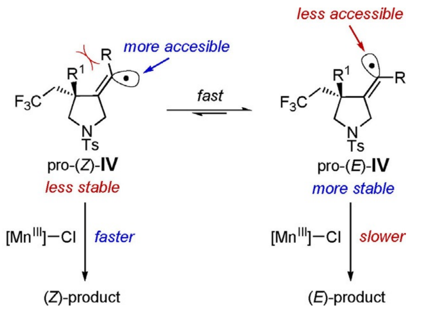


Figure 4. Rationale for the observed alkene *Z*/*E* stereoselectivity in products **9**–**11**.

dimethyl substituents, which was smoothly converted to product **14** in satisfying yield and selectivity.

Our initial attempts to synthesize unprotected pyrrolidine **16** via direct electrochemical cyclization of the corresponding enyne or removal of the Ts group in product **3** proved unsuccessful. To access **16**, we explored substrates with different N-protecting groups in our electrochemical reaction. When Boc was employed as the protecting group, the cyclization product (**15**) was formed in good yield and a *Z*/*E* ratio of 14:1. The carbamate group could subsequently be removed under acid-promoted conditions, furnishing the unprotected pyrrolidine (**16**) in high efficiency. When an enyne with *N*-2-nitrophenylsulfonyl (Ns) group was subjected to the electrochemical cyclization, desired product **17** was obtained in 85 % yield as a single stereoisomer. This product could also be converted to **16** in 82 % yield via thiophenol-promoted Ns deprotection.

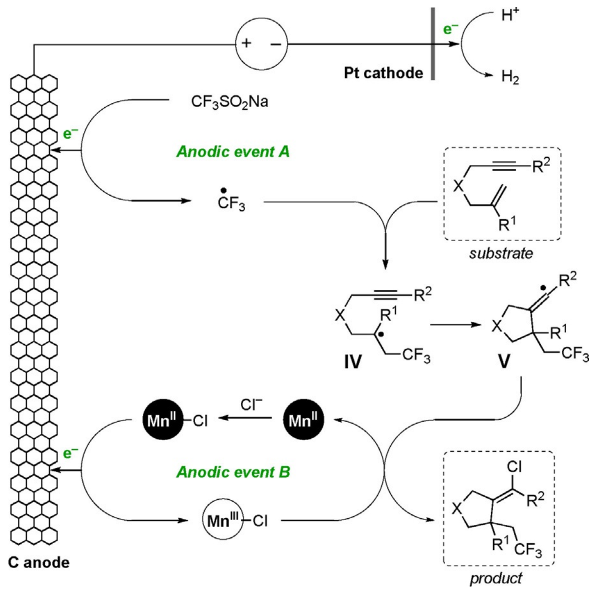
Pyrrolidone product **18** could also be obtained from the corresponding enyne substrate in high efficiency and selectivity. Finally, when $MgCl_2$ in the reaction system was replaced by KBr, the bromotrifluoromethylated pyrrolidine (**19**) was observed as the major product in synthetically useful yield as a single alkene geometric isomer.

At its current stage of development, our method cannot be applied to substrates **20** and **21**. Reactions with these enynes under the standard conditions furnished the desired products in low yield along with several side products. Although these side products have not been definitely identified, we hypothesize that competing direct difunctionalization of the alkene or alkyne groups in **20** and reactions involving the labile H atom α to the O in **21** complicated the desired transformation. Indeed, in our previously reported alkene chlorotrifluoromethylation reaction,[4] hydrogen atom abstraction was often observed with substrates bearing labile C—H bonds as evident from the formation of CF_3H. Attempts to adopt our method in the synthesis of azapane type structures from 1,8-enynes (e.g., **21**) proved unsuccessful. Although the cyclization product was detected with NMR and mass spectrometry, the slow kinetics of the ring-closure process allowed various side reactions including direct alkene difunctionalization and aromatic trifluoromethylation to plague the desired reactivity.

Finally, we demonstrated our electrochemical synthesis of substituted pyrrolidines on preparative scales. Direct adoption of our previous conditions optimized for the 0.1 mmol scale electrolysis (see entry 4, Table 1) proved unsuccessful on a 1 mmol scale, resulting in a much more sluggish reaction. Attempts to improve the reaction rate by increasing the current input led to unproductive consumption of the enyne and CF_3SO_2Na. We noticed that under our electrolysis conditions, the Pt cathode surface darkened during the course of the electrolysis. The surface passivation presumably caused the cell resistance to increase thereby reducing the reaction rate substantially, leading to low conversion. This issue was addressed by the introduction of an organic electrolyte, tetrabutylammonium perchlorate ($TBAClO_4$), instead of $LiClO_4$. The cathode color change was not observed under these modified conditions and the 1 mmol scale synthesis of **3**, **4**, **6**, and **17** proceeded smoothly with high efficiency (see Scheme 2).

A catalytic cycle was proposed for the electrochemical ene-yne cyclization (Scheme 3). Anodically coupled electrolysis enables the formation of electrophilic radicals, $CF_3^{\bullet}$ (anodic event A) and $[Mn^{III}]$—Cl (anodic event B), from the catalyst and functional group donors. The addition of the transient and highly reactive $CF_3^{\bullet}$ to the trisubstituted alkene leads to the formation of an sp^3 carbon-centered radical. This intermediate undergoes subsequent intramolecular addition to the alkyne to form an alkenyl radical intermediate. In the presence of $[Mn^{III}]$—Cl, a persistent open-shell metal complex, this highly reactive carbon-centered radical is harnessed and converted to an alkenyl chloride via radical atom transfer.[19] The catalyst returns to the Mn^{II} oxidation state in this process and is turned over on the electrode via single-electron oxidation.

In summary, we report an electrocatalytic protocol for the synthesis of chlorotrifluoromethylated pyrrolidine derivatives. This reaction is enabled by anodically coupled electrolysis in which the parallel anodic generation of a pair of reactive radical species and their subsequent reaction take place in a convergent and productive manner. The addition of these intermediates to the alkene is controlled by a redox-active Mn catalyst. The introduction of 2,2′-bipyridine as the ligand allows the



Scheme 3. Proposed catalytic cycle entailing anodically coupled electrolysis.

ene-yne cyclization products to be formed in high stereoselectivity with respect to the alkene geometry. We anticipate that the extension of our electrocatalytic strategy to the synthesis of highly functionalized pyrrolidines will encourage the broader application of the approach in the preparation of complex targets pertinent to the pharmaceutical industry.

Experimental Section

General procedure for the electrocatalytic ene-yne cyclization: An oven-dried, one-compartment electrochemical cell was equipped with a magnetic stir bar, a carbon felt anode ($1\times0.5\times0.3\ cm^3$ connected to a 2B pencil lead), and a platinum plate cathode ($0.5\times1.0\ cm^2$). To this setup was added $Mn(OTf)_2$ (3.5 mg, 10 mol%), bpy (3.1 mg, 20 mol%), $MgCl_2$ (28.2 mg, 0.3 mmol, 3.0 equiv), and CF_3SO_2Na (31.2 mg, 0.2 mmol, 2.0 equiv). The cell was sealed using a rubber septum and flushed with nitrogen gas for 5 min. Then, the electrolyte solution (0.2 M $LiClO_4$ in MeCN, 3.0 mL) and substrate (0.1 mmol, 1 equiv) were added sequentially via syringe. The reaction mixture was then purged with nitrogen gas and stirred for an additional 5 min. Acetic acid (0.3 mL) was then added via syringe. After piercing the septum with a nitrogen-filled balloon to sustain the nitrogen atmosphere, electrolysis was initiated at a constant current of 10 mA at room temperature. The current input was removed after 3 h. The reaction mixture was subsequently poured into a saturated sodium bicarbonate solution (ca. 15 mL). The aqueous layer was separated and extracted with dichloromethane (3×5 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. After concentration in vacuo, the crude residue was subjected to flash column chromatography on silica gel to yield the desired cyclization product.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anodically coupled electrolysis · electrocatalysis · ene-yne cyclization · pyrrolidine · trifluoromethylation

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