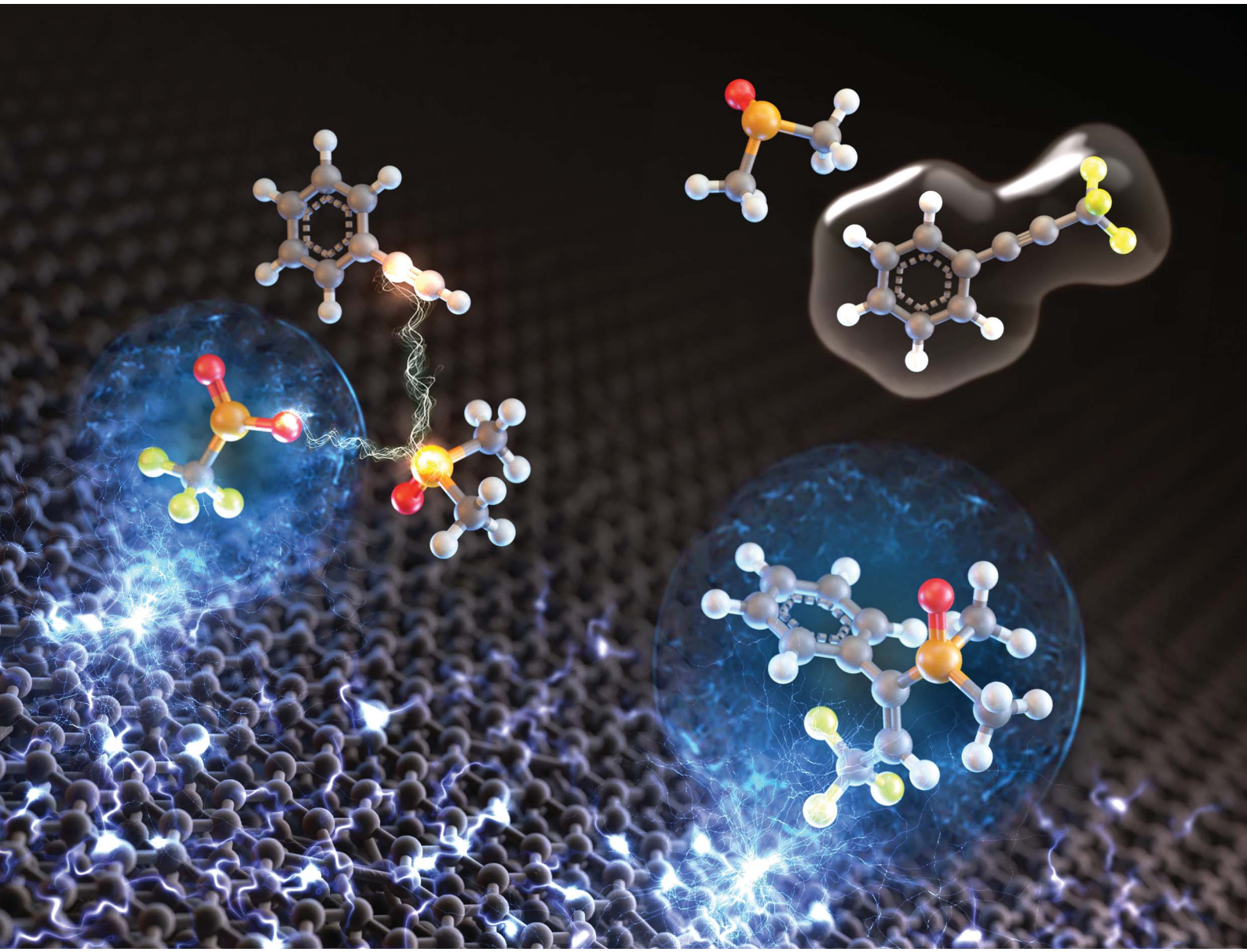
Volume 15
Number 47
21 December 2024
Pages 19637–20074

Chemical Science

rsc.li/chemical-science



ISSN 2041-6539

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

Eun Jin Cho *et al.*

Electrochemical trifluoromethylation of alkynes: the unique role of DMSO as a masking auxiliary

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2024, **15**, 19739

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 7th October 2024
Accepted 1st November 2024

DOI: 10.1039/d4sc06780k

rsc.li/chemical-science

Electrochemical trifluoromethylation of alkynes: the unique role of DMSO as a masking auxiliary†

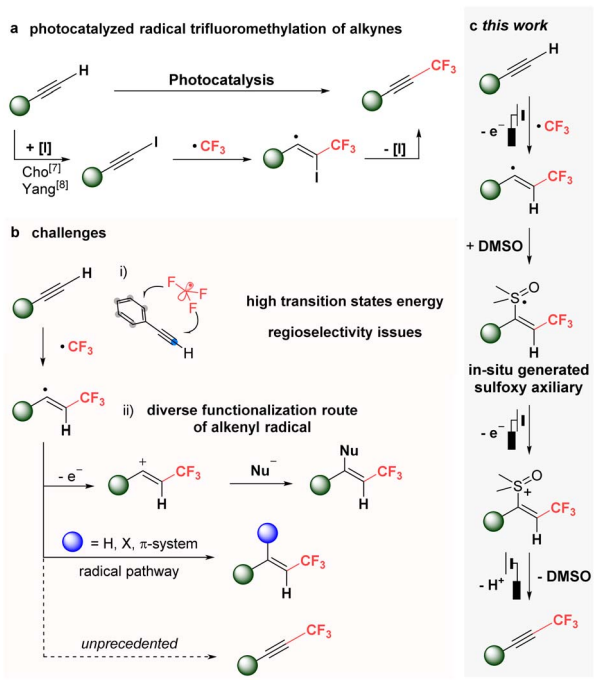
Jihoon Jang,‡ Ho Seong Hwang,‡ Haeryeong Jeong and Eun Jin Cho *

Recent advancements in eco-friendly radical fluoroalkylation have substituted traditional two-electron-based reactions. However, the radical trifluoromethylation of terminal alkynes remains a significant challenge, primarily due to the high reactivity of alkenyl radical intermediates, which predominantly engage in reactions other than the desired elimination. In this work, we have developed an electrochemical trifluoromethylation method for terminal alkynes, facilitating the efficient formation of CF_3-alkynes. The success of this method centers on the use of DMSO as a "masking auxiliary", which effectively stabilizes the alkenyl radical intermediate, allowing the reaction to proceed smoothly under mild conditions. This approach is supported by extensive experimental and computational studies, which elucidate the unique mechanism and expand the potential applications of radical trifluoromethylation across chemical synthesis.

Introduction

Recent advancements in eco-friendly radical chemistry, particularly through photochemistry[1] and electrochemistry,[1a,2] have led to the development of sustainable methods for generating radical intermediates using environmentally benign photons and electric energy, respectively. Among these methods, radical fluoroalkylations have emerged as particularly efficient due to their mild reaction conditions, offering a sustainable alternative to traditional fluoroalkylation processes.[3] Fluoroalkyl groups, especially the trifluoromethyl group, are crucial in enhancing the physical and biological properties of compounds, including metabolic stability, binding selectivity, bioavailability, and lipophilicity.[4] There has been significant progress in the radical trifluoromethylation of (hetero) aromatics, alkenes, and alkynes, which serve as substitutes and complements to traditional two-electron based processes.[3] However, the radical trifluoromethylation of terminal alkynes (C_{sp}–H) to form CF_3-alkynes remains a notable challenge.[5,6] Despite recent advances in photoredox-mediated trifluoromethylation of terminal alkynes by our group[7] and the Yang group,[8] these methods do not directly utilize terminal alkynes. Instead, they depend on *in situ* generated alkynyl-iodide as the actual substrate (Scheme 1a). Direct terminal C_{sp}–H functionalization using CF_3 radicals has necessitated the pre-functionalization of alkynes.

Several challenges arise in the radical alkynyl trifluoromethylation of aromatic alkynes. Selectivity issues can occur between the aromatic and alkyne moieties (Scheme 1b(i)).[9] More critically, the high reactivity of the alkenyl radical intermediate complicates the formation of alkynyl-CF_3 compounds (Scheme 1b(ii)). Due to its low oxidation potential, the vinyl radical is prone to oxidation into its cationic form,



Scheme 1 Alkynyl trifluoromethylations.

Department of Chemistry, Chung-Ang University, 84 Heukseok-ro, Dongjak-gu, Seoul 06974, Republic of Korea. E-mail: ejcho@cau.ac.kr

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4sc06780k

‡ These authors contributed equally.

making it susceptible to nucleophilic attack.[9,10] Additionally, the alkenyl radical intermediate can be captured easily by hydrogen, halogens, or pi-systems, leading to the formation of other trifluoromethylated products,[11] not CF_3-alkynes.

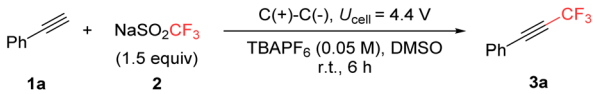
Herein, an unprecedented radical electrochemical approach is presented for the direct synthesis of alkynyl-CF_3 compounds from terminal alkynes, effectively overcoming these challenges (Scheme 1c). To address the issues mentioned above, DMSO was employed as a "masking auxiliary", leveraging its ability to stabilize the free alkenyl radical intermediate. Although DMSO is typically limited in electrochemistry due to its redox active character,[12] this characteristic was utilized to enable the crucial final step of regenerating the alkyne moiety.

Results and discussion

Electrochemical trifluoromethylation of alkynes

The investigation was initiated using phenylacetylene (**1a**) as a model substrate, with $NaSO_2CF_3$ (**2**) as the CF_3 radical source in DMSO (Table 1). The reaction was conducted under constant voltage electrolysis in an undivided cell, utilizing tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as the electrolyte, and graphite [C(+)/C(−)] as both the working and counter electrodes. The cell potential was optimized within the range of 3.5 V to 5.0 V, ultimately determining that 4.4 V was optimal, yielding **3a** in 79% yield. However, when the cell voltage exceeded 4.4 V, the formation of the reduced byproduct, ethylbenzene, increased (see Fig. S1† in the ESI for detailed experimental data†). Despite the inherent electrochemical challenges, DMSO facilitated notably high yields, suggesting a unique role in this transformation. In contrast, other solvents, such as MeCN and DMF, resulted in lower yields (entries 2 and 3). Substituting $TBAPF_6$ with other tetra-*n*-butylammonium salts, such as $TBABF_4$ and $TBANO_3$, produced comparable yields (entries 4 and 5), whereas the use of inorganic electrolytes like KPF_6 led to a reduced yield (entry 6). $Zn(SO_2CF_3)_2$ can also serve as a CF_3 radical source in place of $NaSO_2CF_3$, albeit with a slightly lower yield (entry 7). Further optimization of electrolyte concentration, ranging from 0.02 M to 0.06 M, did not increase the reactivity (entries 11–13). As a control, no reaction occurred in the absence of electrical input, supporting the necessity of the electrochemical redox process (entry 14).

Table 1 Optimization process[a]

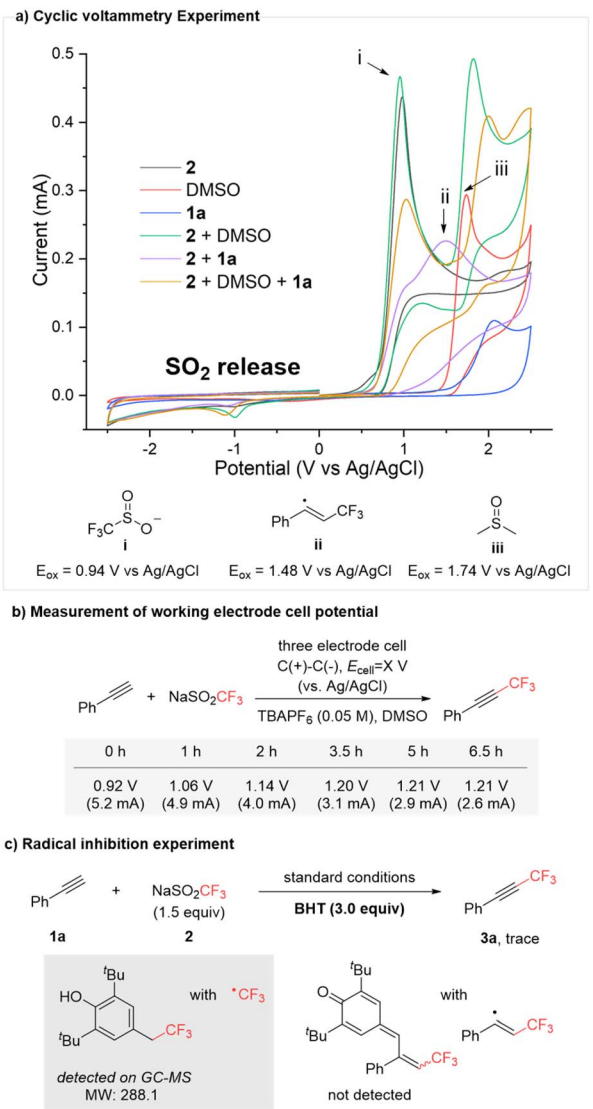


Entry	Variations	Yield[b] (%)
1	None	79
2	MeCN instead of DMSO	9
3	DMF instead of DMSO	46
4	$TBABF_4$ instead of $TBAPF_6$	72
5	$TBANO_3$ instead of $TBAPF_6$	77
6	KPF_6 instead of $TBAPF_6$	35
7	$Zn(SO_2CF_3)_2$ instead of $NaSO_2CF_3$	60
8	$NaSO_2CF_3$ 1.0 equiv.	32
9	$NaSO_2CF_3$ 2.0 equiv.	76
10	$NaSO_2CF_3$ 3.0 equiv.	46
11	$TBAPF_6$ (0.02 M)	44
12	$TBAPF_6$ (0.04 M)	70
13	$TBAPF_6$ (0.06 M)	76
14	No electricity	N.R

[a] 0.3 mmol scale. [b] Yields were determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard.

Mechanistic investigations of electrochemical trifluoromethylation of alkynes

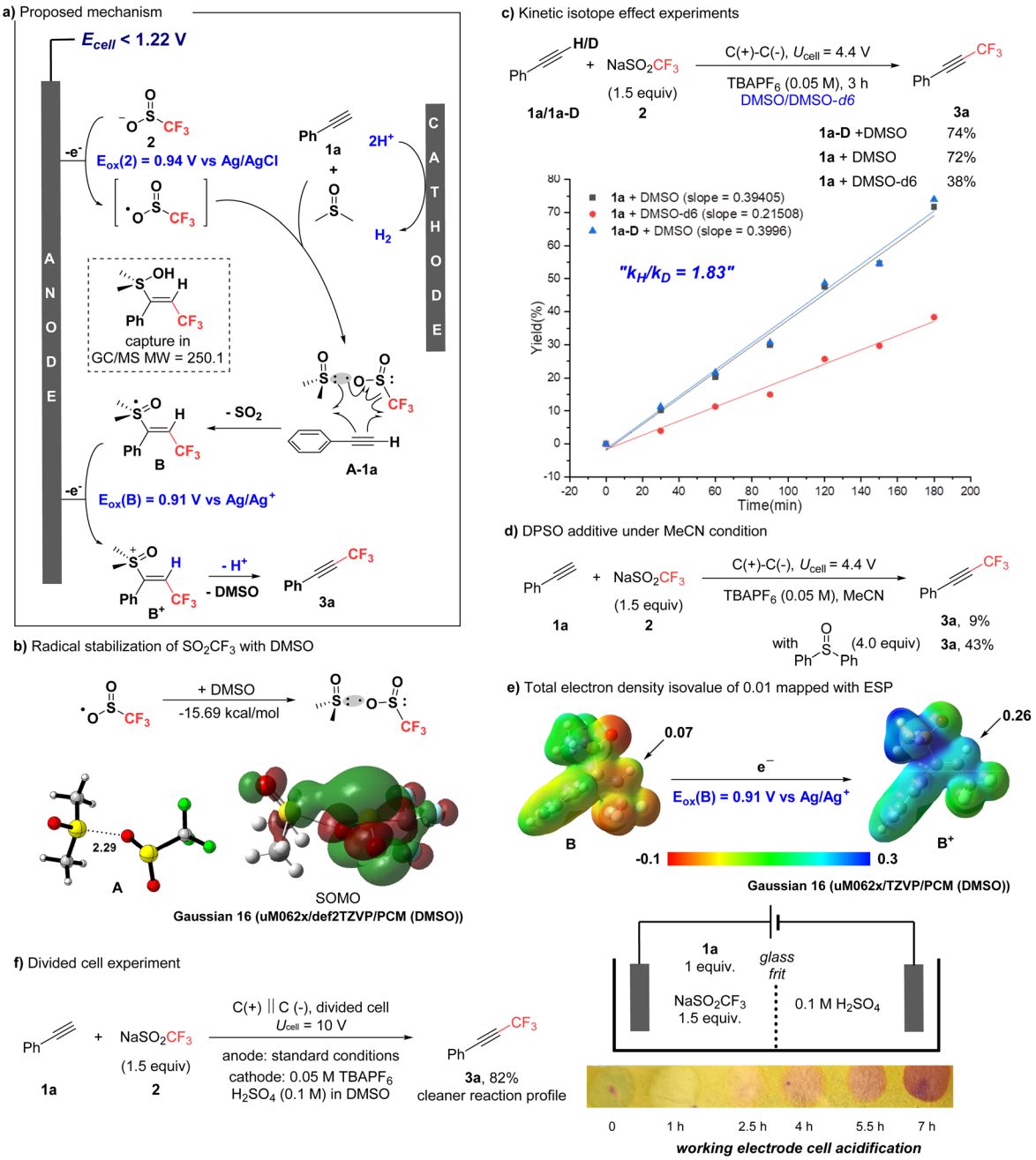
To gain deeper insight into the reaction mechanism, particularly the role of DMSO, a series of mechanistic investigations were conducted. Initially, cyclic voltammetry experiments were performed (Scheme 2a). In MeCN with $TBAPF_6$ as the electrolyte, $NaSO_2CF_3$ (**2**, black), DMSO (red), and phenylacetylene (**1a**, blue) exhibited irreversible oxidation peaks at 0.94 V, 1.74 V,



Scheme 2 Mechanistic investigations.

and 2.08 V *vs.* Ag/AgCl, respectively. Notably, the oxidation peak at 2.08 V disappeared when $NaSO_2CF_3$ **2** and phenylacetylene **1a** were combined (purple), and a new oxidation peak emerged at 1.48 V, attributed to the oxidation of the alkenyl-CF_3 radical (**ii**). Interestingly, upon the addition of DMSO (light brown), the oxidation peak corresponding to the alkenyl-CF_3 radical (**ii**) vanished, while the oxidation peak for **1a** reappeared. Additionally, a reduction peak for SO_2 at −0.98 V *vs.* Ag/AgCl was observed, which was only detected in the presence of DMSO (green and light brown).[13] These observations, along with previous report,[13] suggest that in the presence of DMSO, the SO_2CF_3 radical decomposes into CF_3 radical and SO_2 more slowly than in its absence, indicating DMSO's involvement in this electrochemical trifluoromethylation.

Further investigation revealed that under optimized conditions (U_{cell} = 4.4 V), the working electrode cell potential in a three-electrode setup did not exceed 1.22 V *vs.* Ag/AgCl (Scheme 2b). According to the cyclic voltammetry data in Scheme 2a, only the trifluoromethylsulfinate ($-SO_2CF_3$) could be oxidized under these conditions. This suggests that the oxidation of the free alkenyl radical intermediate (**ii**) (1.48 V) does not occur during the transformation, indicating the presence of a more reactive intermediate. This hypothesis was supported by experiments involving the radical quencher butylated hydroxy



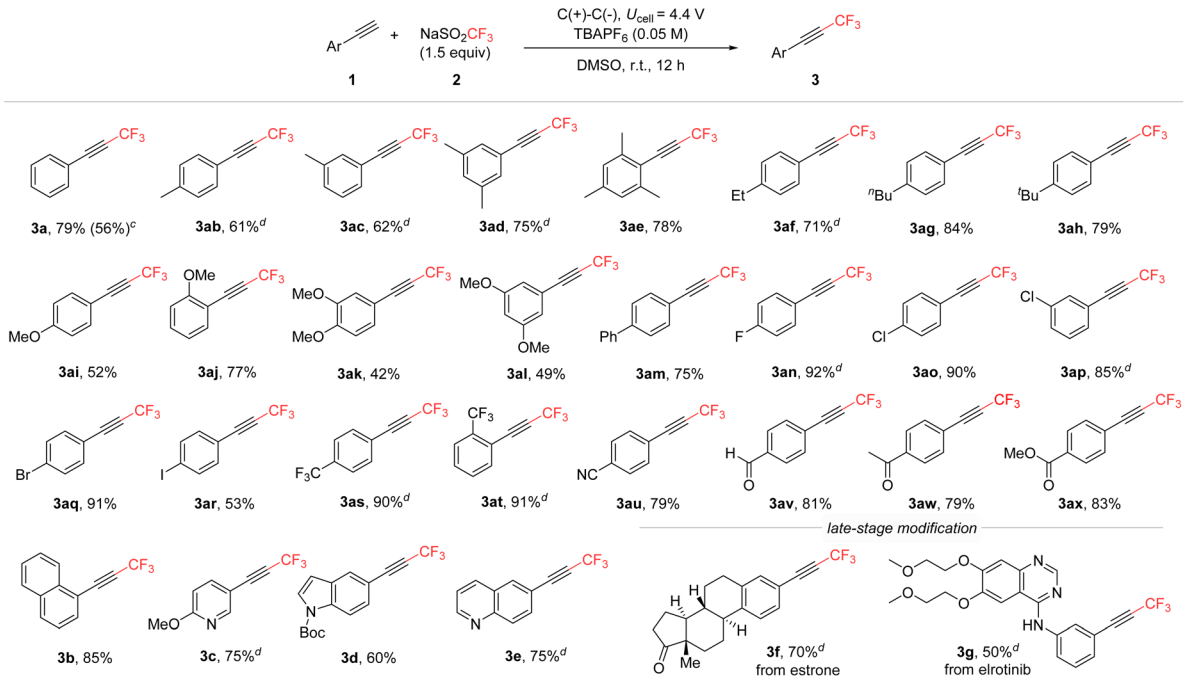
Scheme 3 Proposed mechanism with supporting experimental evidence.

toluene (BHT). The reaction was inhibited, confirming that the process is radical-mediated (Scheme 2c). GC-MS analysis detected a BHT-CF_3 adduct, while no BHT-alkenyl-CF_3 adduct was observed.[14] This suggests that the free alkenyl-CF_3 radical (**ii**) is short-lived and, rather than undergoing oxidation, is converted to another intermediate that plays a key role in this electrochemical redox process.

Based on our results, we propose a mechanism (Scheme 3a), supported by a series of further experimental and computational studies (Scheme 3b–f). The $-SO_2CF_3$ (**2**) undergoes single-electron oxidation, generating $\cdot SO_2CF_3$. This radical can be stabilized by DMSO, as confirmed by DFT calculations (uM062X/def2TZVP/PCM in DMSO), which showed a strong interaction between DMSO and the SO_2CF_3 radical (-15.69 kcal mol^{-1} and O–S distance 2.29 Å) (Scheme 3b).[15] In the presence of phenylacetylene **1a**, the CF_3 radical adds to the alkyne moiety, and then reacts with DMSO. Crucially, DMSO functions as an electroauxiliary,[16] effectively masking the free alkenyl radical intermediate. The involvement of DMSO was further supported by kinetic isotope effect (KIE) experiments (Scheme 3c and Fig. S3 in the ESI†). While the reaction with deuterium-exchanged terminal alkyne showed no significant KIE, the use of DMSO-d6 resulted in reduced reactivity, with a KIE value of 1.83, indicating DMSO's role in the process. Although the reaction did not proceed well in MeCN, the addition of another sulfoxide—4 equivalents of diphenylsulfoxide (DPSO)—improved the reaction yield, further supporting the involvement of sulfoxide in promoting the transformation (Scheme 3d). The rapid formation of an intermediate (**B**) between the alkenyl radical and DMSO leads to a masked species with an oxidation potential of 0.91 V *vs.* Ag/AgCl (uM062X/TZVP/PCM (DMSO)), which is easily oxidized under the applied cell conditions (<1.22 V). The presence of **B** was additionally confirmed by GC-MS and LC-MS analysis. The oxidation of **B** to $\mathbf{B}^+$ increases the acidity of the vinyl hydrogen atom, as demonstrated by the electrostatic potential map in Scheme 3e, where the ESP value shifts from 0.07 in **B** to 0.26 in $\mathbf{B}^+$, facilitating the key deprotonation step that results in the formation of the trifluoromethylated alkyne **3a**. Further evidence supporting this deprotonation step was obtained from the reaction conducted in a divided cell (Scheme 3f and Fig. S4 in the ESI†). During the reaction, the anodic cell becomes increasingly acidic due to ongoing deprotonation. Additionally, performing the reaction in a divided cell resulted in a cleaner reaction profile, further validating the proposed mechanism.

Substrate scope

Next, under the optimized conditions, the substrate scope was explored by using various alkyne derivatives to synthesize the corresponding CF_3-alkynes (Scheme 4). The reactions were successful across a broad range of phenylacetylene derivatives, regardless of the electron density or positional variation of the substituents. Both electron-donating (**3ab–3al**) and electron-withdrawing (**3an–3ax**) groups on the phenyl ring yielded the desired CF_3-alkynes. Additionally, this method was effectively applied to extended conjugated systems, such as biphenyl (**3am**) and naphthalene (**3b**). Substituents at the *ortho*-, *meta*-, and *para*-positions of phenylacetylene were all compatible, demonstrating the versatility of the reaction conditions. Moreover, heterocyclic alkynes containing pyridine, indole, and quinoline moieties also proved to be suitable substrates (**3c**, **3d**, **3e**). The



Scheme 4 Substrate scope[a,b]; [a]0.3 mmol scale. [b]Isolated yields, [c]20 mmol scale with 136 h reaction time. [d]Yields were determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard.

mild electrochemical conditions tolerated various functional groups, including reactive halides (**3ao–3ar**) and carbonyl substrates like aldehydes (**3av**), which are often incompatible with photoredox- or basic conditions. To further demonstrate the broad applicability of this methodology, its use was extended to the late-stage modification of pharmaceutical molecules. Structurally complex alkyne derivatives, such as those based on estrone and the anti-cancer drug erlotinib, were efficiently trifluoromethylated in a divided cell under standard conditions (**3f** and **3g**). However, under the conditions, reactions involving aliphatic alkynes did not yield CF_3-alkynes; instead, they produced CF_3-alkenes, reduced alkanes, and some unidentified compounds.

Conclusions

In conclusion, we successfully developed an electrochemical trifluoromethylation method for terminal alkynes, achieving the efficient formation of CF_3-alkynes—a transformation that has posed significant challenges in radical chemistry. The success of this method is attributed to the strategic use of DMSO as an electroauxiliary, which effectively stabilizes the alkenyl radical intermediate, thereby enabling the reaction to proceed under mild conditions. Comprehensive experimental and computational studies strongly supported this approach, elucidating the unique mechanism and expanding the scope of radical trifluoromethylation for diverse applications in chemical synthesis.

Data availability

The data underlying this study are available in the published article and its ESI.†

Author contributions

J. Jang, H. S. Hwang and H. Jeong performed synthetic experiments and mechanistic studies. E. J. Cho coordinated all of the experiments, analyses, and co-wrote the manuscript. All authors contributed to the discussion on the study and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Research Foundation of Korea (NRF-2020R1A2C2009636 and RS-2024-00409659) and the Ministry of Trade, Industry and Energy, Korea (Technology Innovation Program, RS-2023-00266039).

References

1 (*a*) R. Shaw, N. Sihag, H. Bhartiya and M. R. Yadav, *Org. Chem. Front.*, 2024, **11**, 954; (*b*) Y. Ouyang and F.-L. Qing, *J. Org. Chem.*, 2024, **89**, 2815; (*c*) C. H. Ka, S. Kim and E. J. Cho, *Chem. Rec.*, 2023, **23**, e202300036; (*d*) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot and T. Ritter, *Angew. Chem., Int. Ed.*, 2019, **58**, 14615; (*e*) E. H. Oh, H. J. Kim and S. B. Han, *Synthesis*, 2018, **50**, 3346; (*f*) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (*g*) E. J. Cho, *Chem. Rec.*, 2016, **16**, 47.

2 (*a*) S. Kim and H. Kim, *J. Am. Chem. Soc.*, 2024, **146**, 22498; (*b*) Z. Zou, W. Zhang, Y. Wang and Y. Pan, *Org. Chem. Front.*, 2021, **8**, 2786; (*c*) R. P. Bhaskaran and B. P. Babu, *Adv. Synth. Catal.*, 2020, **362**, 5219.

3 (*a*) C. Urban, F. Cadoret, J.-C. Blazejewski and E. Magnier, *Eur. J. Org Chem.*, 2011, 4862; (*b*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156.

4 (*a*) A. Abula, Z. Xu, Z. Zhu, C. Peng, Z. Chen, W. Zhuan and H. A. Aisa, *J. Chem. Inf. Model.*, 2020, **60**, 6242; (*b*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.

5 (*a*) D. Mandal, S. Maji, T. Pal, S. K. Sinha and D. Maiti, *Chem. Commun.*, 2022, **58**, 10442; (*b*) A. Hassanpour, M. R. P. Heravi, A. Ebadi, A. Hosseinian and E. Vessally, *J. Fluorine Chem.*, 2021, **245**, 109762; (*c*) G. Li, C. Zhang, C. Song and Y. Ma, *Beilstein J. Org. Chem.*, 2018, **14**, 155.

6 (*a*) S. T. Shreiber and D. A. Vicic, *Angew. Chem., Int. Ed.*, 2021, **60**, 18162; (*b*) J. Li, K. Liu, K. Zheng, C. Zheng, H. Xiao and S. Fan, *J. Org. Chem.*, 2020, **85**, 8723; (*c*) H.-S. M. Siah and A. Fiksdahl, *J. Fluorine Chem.*, 2017, **197**, 24; (*d*) L. He and G. C. Tsui, *Org. Lett.*, 2016, **18**, 2800.

7 N. Iqbal, J. Jung, S. Park and E. J. Cho, *Angew. Chem., Int. Ed.*, 2014, **53**, 539.

8 (*a*) X. Shi, B. Yu, X. Zhou and Y. Yang, *Chem. Commun.*, 2024, **60**, 2532; (*b*) X. Shi, T. Song, Q. Li, X. Guo and Y. Yang, *Org. Lett.*, 2022, **24**, 8724.

9 W. Jud, C. O. Kappe and D. Cantillo, *Org. Biomol. Chem.*, 2019, **17**, 3529.

10 (*a*) S. Tanaka, Y. Nakayama, Y. Konishi, T. Koike and M. Akita, *Org. Lett.*, 2020, **22**, 2801; (*b*) W. Lee, Y. Lee, M. Yoo, S. B. Han and H. J. Kim, *Org. Chem. Front.*, 2020, **7**, 3209; (*c*) A.-L. Barthelemy, G. Dagousset and E. Magnier, *Eur. J. Org Chem.*, 2020, 1429; (*d*) Y. R. Malpani, B. K. Biswas, H. S. Han, Y.-S. Jung and S. B. Han, *Org. Lett.*, 2018, **20**, 1693; (*e*) H. S. Han, Y. J. Lee, Y.-S. Jung and S. B. Han, *Org. Lett.*, 2017, **19**, 1962; (*f*) R. Tomita, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2015, **54**, 12923.

11 (*a*) F. Xiang, D. Wang, K. Xu and C.-C. Zeng, *Org. Lett.*, 2024, **26**, 411; (*b*) X. Wang, W. Zhou, W. Xie, Q. Chen and J. Wu, *Chin. Chem. Lett.*, 2023, **34**, 107984; (*c*) N. Petek, H. Brodnik, O. Reiser and B. Štefane, *J. Org. Chem.*, 2023, **88**, 6538; (*d*) Z.-H. Yan, W.-C. Li, Y.-H. Wu, Q.-B. Yan, Z.-L. Wei and W.-W. Liao, *Org. Chem. Front.*, 2022, **9**, 5912; (*e*) H. Wang, S. Li, Y. Cui, M. Liu, X. Bu, H. Tian and X. Yang, *New J. Chem.*, 2022, **46**, 20412; (*f*) W. Zhang, Z. Zou, W. Zhao, S. Lu, Z. Wu, M. Huang, X. Wang, Y. Wang, Y. Liang, Y. Zhu and Y. Pan, *Nat. Commun.*, 2020, **11**, 2572; (*g*) T. Shang, J. Zhang, Y. Zhang, F. Zhang, X.-S. Li and G. Zhu, *Org. Lett.*, 2020, **22**, 3667.

12 O. Hammerich, *Organic Electrochemistry*, Taylor & Francis Group, CRC Press, 2016.
13 A. G. O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran and D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2014, **53**, 11868.
14 In our previous work using $NaSO_2CF_3$ and phenylacetylene in MeCN solvent, BHT-alkenyl-CF_3 adduct was observed, see: J. Jang and E. J. Cho, *Adv. Synth. Catal.*, 2024, **366**, 3450.
15 Regarding two-center/three-electron bond structure, see: (*a*) S.-Q. Cai, K.-F. Zhang and X.-H. Cai, *Curr. Org. Chem.*, 2022, **26**, 91; (*b*) R. Gleiter and G. Haberhauer, *Coord. Chem. Rev.*, 2017, **344**, 263; (*c*) M. M. D. Pramanik and N. Rastogi, *Chem. Commun.*, 2016, **52**, 8557.
16 J. Yoshida, K. Nishiwaki, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265.