

Ritter-type amination of C(sp³)-H bonds enabled by electrochemistry with SO₄²⁻

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By merging electricity with sulfate, the Ritter-type amination of C(sp³)-H bonds is developed in an undivided cell under room temperature. This method features broad substrate generality (71 examples, up to 93% yields), high functional-group compatibility, facile scalability, excellent site-selectivity and mild conditions. Common alkanes and electron-deficient alkylbenzenes are viable substrates. It also provides a straightforward protocol for incorporating C-deuterated acetylamino group into C(sp³)-H sites. Application in the synthesis or modification of pharmaceuticals or their derivatives and gram-scale synthesis demonstrate the practicability of this method. Mechanistic experiments show that sulfate radical anion, formed by electrolysis of sulfate, served as hydrogen atom transfer agent to provide alkyl radical intermediate. This method paves a convenient and flexible pathway for realizing various synthetically useful transformations of C(sp³)-H bonds mediated by sulfate radical anion generated via electrochemistry.

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Given the high prevalence of amines in natural products, agrochemicals, pharmaceuticals and organic materials¹, tremendous progress has been achieved for the construction of C-N bonds, including reductive amination², hydroamination³, and transition metal catalyzed cross coupling (e.g., Ullmann-Goldberg condensation, Chan-Lam coupling, Buchwald-Hartwig amination, etc)⁴⁻⁶. Among the various protocols reported, one of the most desirable strategies is the direct C-H amination in terms of high step- and atom-economy. Comparing with amination of C(sp²)-H bonds, direct incorporation of N-containing moieties into C(sp³)-H bonds is highly desirable but also challenging due to low reactivity and poor selectivity. To circumvent these limitations, many notable strategies were developed, including transition metal catalyzed C(sp³)-H activation⁷, C-H insertion catalysis⁸, and hydrogen atom transfer (HAT) process⁹. The functionalization of distinct C-H bonds via HAT process often proceeds in highly selective mode, thus avoiding the pre-incorporation of directing moiety into the substrate. Meanwhile, the selectivity and reactivity of HAT process can be rationally tuned by varying hydrogen acceptor and reaction additive. For instance, highly selective amination of C(sp³)-H bonds has been achieved by employing *N*-fluorobenzenesulfonimide^{10,11}, *N*-hydroxyimide derivatives¹²⁻¹⁴ and *di-tert*-butyl peroxide¹⁵⁻¹⁷ as HAT agents. Besides, 1,5-HAT enabled by nitrogen-centered radicals has also served as a robust and practical strategy in selective amination of remote unactivated C(sp³)-H bonds, especially the classic Hofmann-Löffler-Freytag reaction¹⁸⁻²⁰.

In recent years, the flourishing development of visible light induced photoredox catalysis enables a myriad of elegant C(sp³)-H functionalizations via HAT process under mild conditions. In particular, the decatungstate anion (W; [W₁₀O₃₂]⁴⁻)^{21,22}, in excited state, nitrogen radical²³⁻²⁵, oxygen radical²⁶⁻²⁹, and bromine radical³⁰ generated via photoredox have been employed as the efficient HAT agents for the selective amination of C(sp³)-H bonds. In addition, electrochemistry, which utilizes electron as oxidant or reductant, has accelerated clean, efficient and scalable transformation of C-H bonds into C-N bonds³¹⁻³⁶. Generally, these processes based on the direct or indirect anodic oxidation of substrates were highly limited to the relatively active C(sp³)-H bonds, including C(sp³)-H bonds adjacent to heteroatoms³⁷⁻⁴⁰, carbonyl⁴¹, allylic⁴², and benzylic groups⁴³⁻⁵⁰.

However, C-H amination through HAT process enabled by electrochemistry and electrophotocatalysis⁵¹⁻⁵⁴ could enlarge the substrate scope to unactivated alkanes. For instance, the remote inert C(sp³)-H bonds amination was developed to construct pyrrolidines through 1,5-HAT process, which was initiated by the electrochemical generated N radical⁵⁵⁻⁵⁷. Using DDQ and Mn(IV) diazide intermediate as HAT agents, Lei group⁵⁸ and Ackermann group⁵⁹ independently reported manganese-catalyzed photoelectrochemical and electrochemical oxidative azidation of C(sp³)-H bonds, respectively (Fig. 1a).

Several Ritter-type reactions have been disclosed by Baran⁶⁰, Liu & Chen⁶¹, providing elegant methods for the amination of inert C(sp³)-H bonds (Fig. 1b). In these works, stoichiometric amounts of expensive oxidants (Selectfluor and hypervalent iodine) were employed to promote the conversion of C(sp³)-H to carbon cation. Lambert and coworkers developed the Ritter type C(sp³)-H amination of benzylic sites⁴⁷ and the diamination of vicinal C-H bonds via Ritter-type step⁶² by virtue of trisaminocyclopropenium ion (TAC) as the notable electrophotocatalyst (Fig. 1b). König group²⁹ and Hartwig group¹⁷ reported the reactions of alkanes with simple amides to form the corresponding *N*-alkyl products using *t*BuOO*t*Bu as HAT agent (Fig. 1c). In order to enrich the application of Ritter-type C(sp³)-H amination reaction, we conceived to develop an economic manifold that avoids the use of expensive or unstable oxidants, through electrochemical approach.

Generally, thermal, photolysis, electrolysis and metal activated decomposition of peroxodisulfate, which is prepared by the electrolysis of sulfate in industrial process^{63,64}, can provide a powerful HAT species, sulfate radical anion, thus initiating the C-H bonds functionalization⁶⁵⁻⁶⁹. As a consequence, we envisaged that S₂O₈²⁻ could be prepared by the anodic oxidation of H₂SO₄ and then would undergo cathodic reduction to yield sulfate radical anion, similar to the protocol reported by Xu group, in which chloride radical was generated by irradiating the anodically formed Cl₂ from Cl⁻ and served as robust HAT agent to form alkyl radical under photoelectrochemical systems⁷⁰.

Here, we report a broadly applicable electrochemical strategy for Ritter type C(sp³)-H amination where aliphatic carbon cation is generated via sulfate radical anion mediated HAT followed by further oxidation under electrolysis (Fig. 1d).

Results and discussion

Reaction optimization. Since the product from direct C-H amination of 1,3-dimethyladamantane is used as prodrug for the treatment of Alzheimer's disease, 1,3-dimethyladamantane was chosen as the model reactant to investigate the reaction conditions (Table 1). All the electrolysis reactions were conducted in undivided cells. Based on the conditions screening, the optimal conditions comprised Pt plates as anode and cathode, H₂SO₄ as pre-oxidant, *n*Bu₄NBF₄ as electrolyte, CH₃CN as solvent and nitrogen source. Under the standard conditions, 93% yield was obtained under 5 mA constant current for 20 h. The reaction did not proceed at room temperature in the absence of electricity (Table 1, entry 2) until the temperature was increased to 65 °C with a low yield of 14% (Table 1, entry 3). Among all the tested acids, H₂SO₄ gave the optimal yield. Decreasing the amount of H₂SO₄ was detrimental to the reaction yield (Table 1, entries 5-7). Performing the electrolysis without H₂SO₄ only gave trace amount of product, demonstrating the pivotal role of H₂SO₄ in the C(sp³)-H amination. Notably, the yield was also obviously diminished when the Pt anode was replaced by carbon materials (Table 1, entries 8-10). Either lower or higher current (e.g., 3.0 mA, 7 mA, 10 mA) was not conducive to this reaction (Table 1, entries 11-13). Replacing H₂SO₄ with equivalent amounts of K₂S₂O₈ could also provide product **1** with 84% yield (Table 1, entry 14). Therefore, peroxodisulfate probably formed by electrolyzing sulfate assisted the rupture of C-H bonds. Besides, the yield could also reach 76% by using Na₂SO₄ as sulfate source (Table 1, entry 15). The methanesulfonic acid also showed good performance (Table 1, entry 16) due to the generation of permethanesulfonic acid by the anodic oxidation of methanesulfonic acid, which is similar to peroxydisulfate⁷¹. Other more detailed conditions were presented in the Supplementary Information (Supplementary Table 1).

Evaluation of substrate scope. With the optimized conditions in hand, we next evaluated the substrates scope of alkanes in this protocol (Fig. 2). First, tertiary alkanes were well tolerated and afforded amination products in 44-93% yields with excellent regioselectivity (Fig. 2, 1-8). Of note, the reaction with deuterated acetonitrile as nitrogen source gave C-deuterated acetamination products **2** and **6** with 85 and 78% yields, respectively. Generally, the amination of secondary C(sp³)-H bond is more challenging than that of tertiary C(sp³)-H bond, so 16.0 equivalents of H₂SO₄ is required. A variety of cyclic, secondary hydrocarbons were smoothly transformed into aliphatic amide products (Fig. 2, 9-12) in moderate to good yields, while the reaction with cyclododecane furnished the product **13** in 32% yield due to the poor solubility in acetonitrile. However, when using different types of linear alkanes, two isomers were obtained with different ratios. The electrolysis of *n*-hexane provided 1:1 ratio of isomers

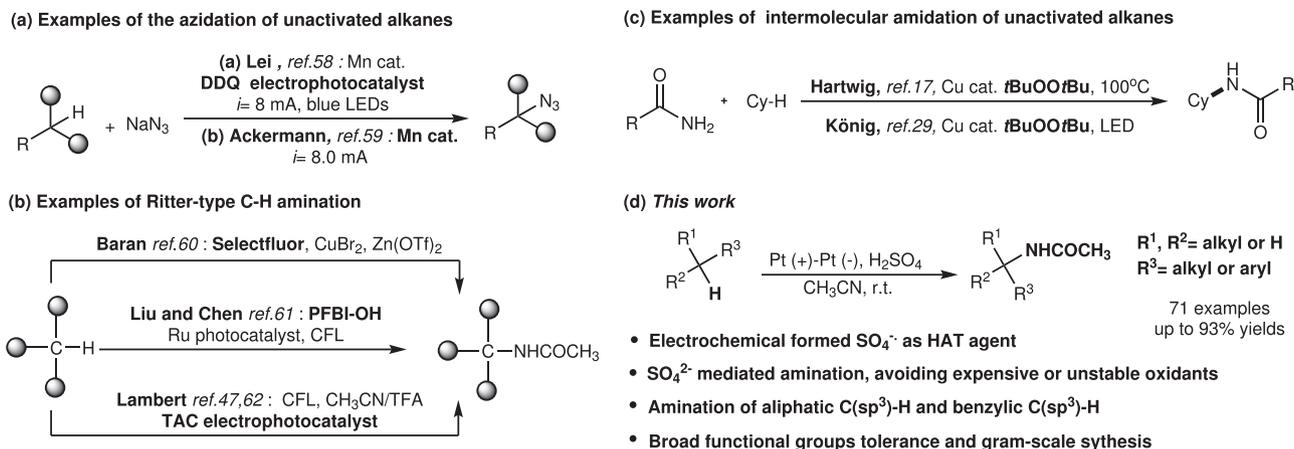


Fig. 1 Examples of C(sp³)-H amination reactions. **a** Examples of the azide reaction of unactivated alkanes via (photo)electrocatalysis. **b** Examples of Ritter-type C-H amination via Selectfluor, hypervalent iodine reagent and TAC electrophotocatalyst. **c** Examples of intermolecular amidation of unactivated alkanes via *t*BuOO*t*Bu and Cu cat. **d** This work: Ritter-Type amination of C(sp³)-H bonds enabled by the electrochemistry with SO₄²⁻.

Table 1 Optimization of reaction conditions.

Entry	Deviation from standard conditions	Yield ^a	Entry	Deviation from standard conditions	Yield ^a
1	None	93%	9	CF ^c as anode	23%
2	No current	0	10	Graphite as anode	22%
3	No current, 65°C	14%	11	3 mA	88%
4	No H ₂ SO ₄	5%	12	7 mA	83%
5	H ₂ SO ₄ (0.17 M, 1 eq.)	51%	13	10 mA	82%
6	H ₂ SO ₄ (0.33 M, 2 eq.)	79%	14	4 eq. K ₂ S ₂ O ₈	84%
7	H ₂ SO ₄ (0.5 M, 3 eq.)	82%	15	4 eq. Na ₂ SO ₄	76%
8	RVC ^b as anode	21%	16	CH ₃ SO ₃ H	89%

Standard conditions: **1a** (82 mg, 0.5 mmol), 98% H₂SO₄ (108 μ L, 2 mmol, 0.67 M), *n*Bu₄NBF₄ (0.1 M) as electrolyte, Pt (+), Pt (-), CH₃CN 3 mL, at r.t. for 20 h.

^aIsolated yield.
^bRVC means reticulated vitreous carbon foam.
^cCF means carbon fiber.

with 54% yield. For linear alkanes containing electron-deficient moieties, such as ester, bromine, and chlorine, the aminations were apt to take place at the secondary C-H bonds far away from these functional groups, leading to the mixture of acetamination products **17–19** with different ratios about 2.3:1, 1.5:1, and 1.3:1, respectively. To our delight, the amination of 1-bromopentane and 1-chloropentane occurred preferentially at C-H bond away from halogens with high regioselectivity and provided single products in good yields (Fig. 2, **15**, **16**).

Next, the scope of alkylbenzenes was assessed (Fig. 3). The amination reaction of alkylbenzenes bearing different functional groups at aliphatic chain, such as carbonyl, alkenyl and cyano group, underwent smoothly to deliver **20–30** in 41–76% yields, with less amount of H₂SO₄ and shorter reaction times. Product **24** was afforded with excellent regioselectivity, illustrating that C(sp³)-H amination preferentially reacted at benzylic over tertiary C-H bond. Besides, the phenylpropene underwent isomerization to form **28** in 41% yield. Furthermore, derivatives of toluene and ethylbenzene containing various functional groups on the benzene ring, including halogen, cyano, ester, carbonyl, nitro, amino, methoxyl, and alkyl groups, were well accommodated (Fig. 3, **31–41**). Mono-acetamination product

were provided for the alkylbenzenes with multiple benzylic sites. Commonly, nitro group and iodine atom are prone to be reduced under electrolysis^{72–75}, but remained intact under our reaction conditions. In particular, this reaction system was tolerated to unprotected amine groups, furnished products **39** and **41** in 25 and 54% yields, respectively, likely as a result of the acidification of amines. It is worth noting that previous electrochemical methods did not work for the amination of alkylbenzenes bearing strong electron-withdrawing groups^{43–46,48–50}, which are viable reactants under our reaction systems. In addition, the α -amino acid precursors and β -amino acid precursors (Fig. 3, **58–62**) were also obtained in good yields.

With the replacement of acetonitrile by ethyl cyanoacetate, butyronitrile, isobutyronitrile and adiponitrile, the reaction could also take place to yield products **63–68** in moderate to good yields. (Fig. 4a) To further explore the synthetic utility of the methodology, the modification of natural products and pharmaceuticals (Fig. 4b) and scaled-up experiments (see the Supplementary Methods for details) were carried out. The amination of esterified ibuprofen was site-selectively occurred at the less hindered benzyl position in 77% yield. The natural deoxyfenisin and fragrance celestolide were functionalized to give product **70** and

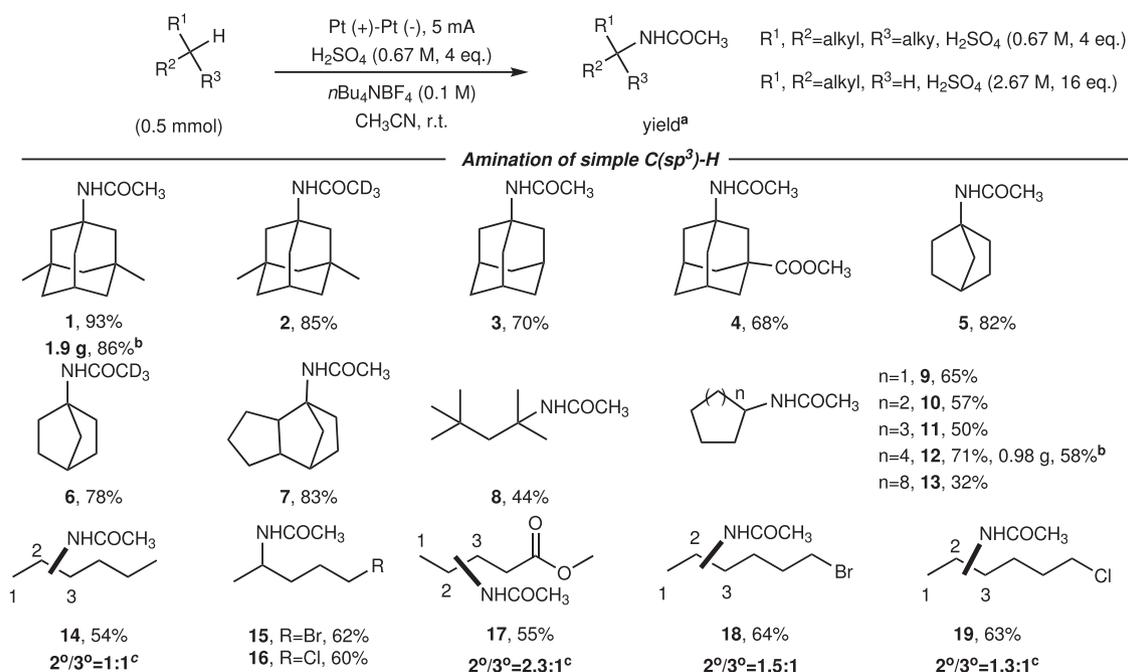


Fig. 2 Reaction scope of alkyl substrates. ^aIsolated yield; ^bElectrolysis performed on 10 mmol scale; ^cRegio isomeric ratios were determined by ¹H NMR.

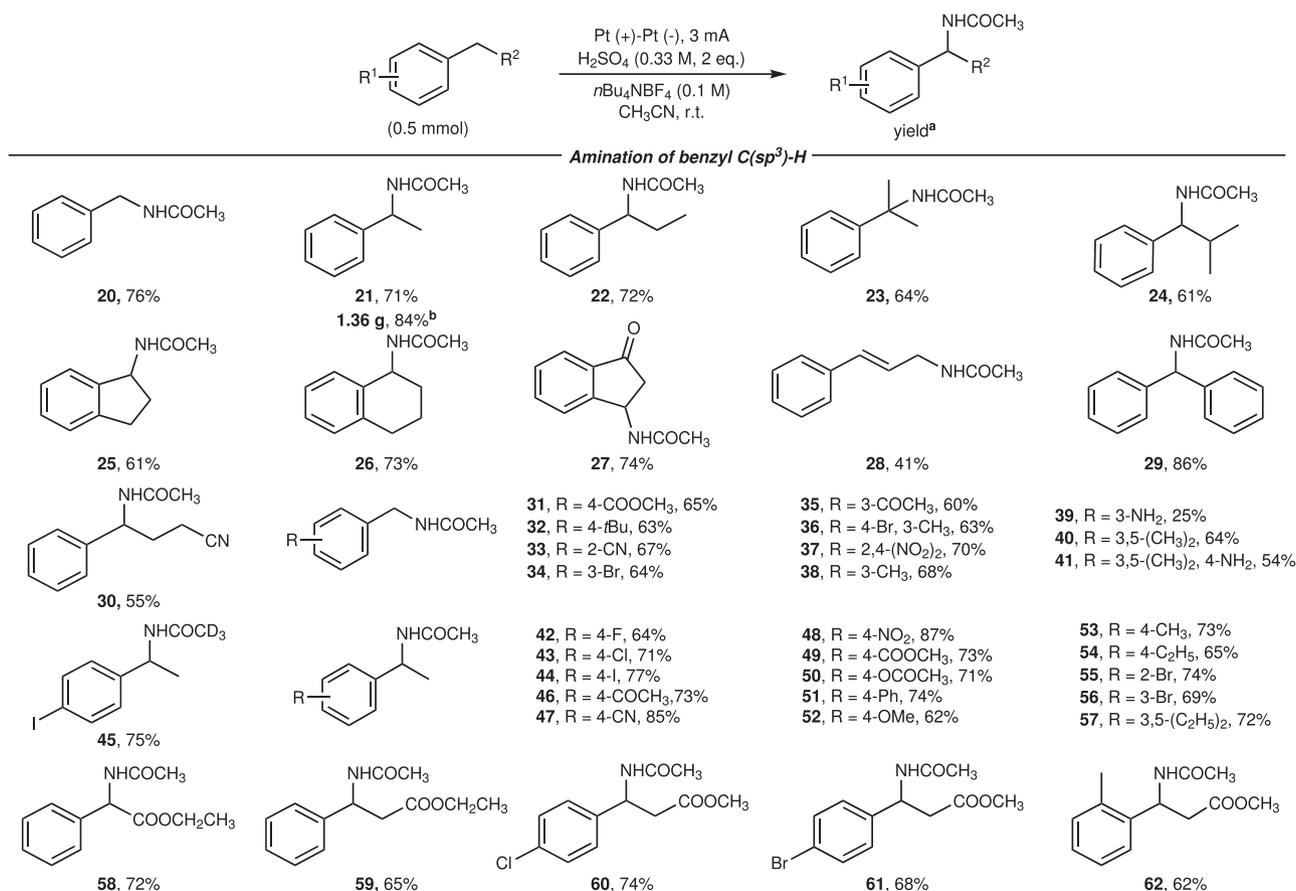


Fig. 3 Reaction scope of arene-containing substrates. ^aIsolated yield; ^bElectrolysis performed on 10 mmol scale.

71, respectively. Next, we carried out gram-scale amplification experiments, in which aminated products (**1**, **12**, **21**) were obtained with satisfying yields.

Compounds **1b** and **3b** are the precursors of the drug memantine hydrochloride for the treatment of Alzheimer's disease

and the antiviral drug amantadine hydrochloride, respectively. Therefore, further hydrolysis of compounds **1** and **3** were shown in Fig. 5. Our methodology could be applied for preparing the precursors of memantine hydrochloride **1b** and amantadine hydrochloride **3b** in two steps from simple materials, avoiding

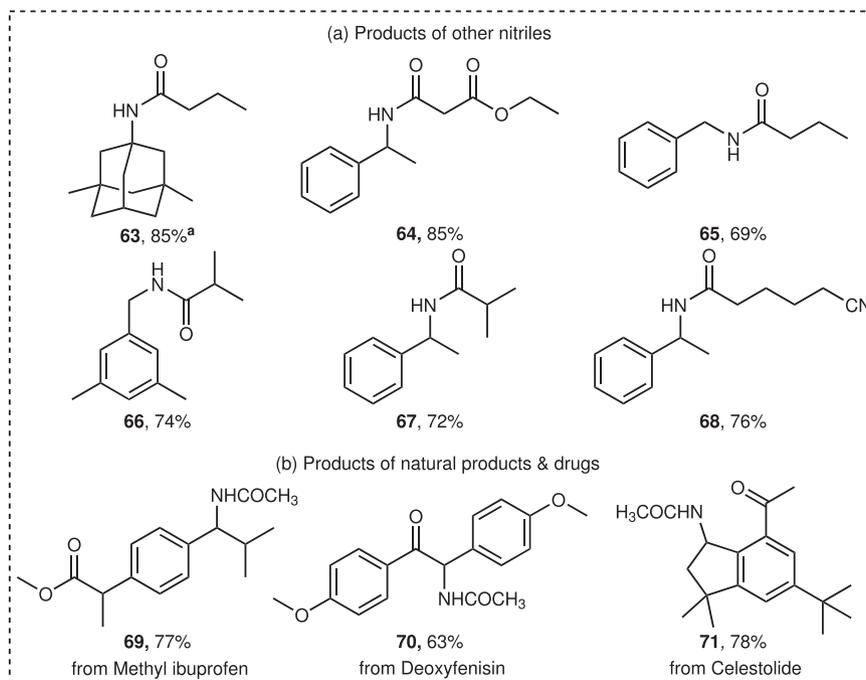


Fig. 4 Reaction scope other nitriles and the modification of natural products and drug molecules. **a** Products of other nitriles. **b** Products of natural products & drugs. Conditions: substrate (0.5 mmol), H_2SO_4 (54 μL , 1 mmol, 0.33 M), $n\text{Bu}_4\text{NBF}_4$ (0.1 M), CH_3CN (3 mL), 5 mA; ^aConditions: substrate (0.5 mmol), H_2SO_4 (108 μL , 2 mmol, 0.67 M), $n\text{Bu}_4\text{NBF}_4$ (0.1 M), CH_3CN (3 mL), 5 mA.

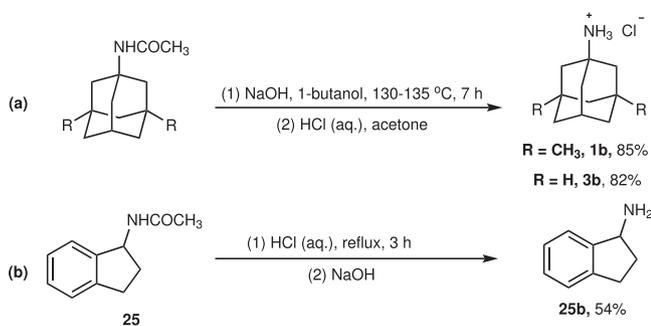


Fig. 5 Hydrolysis of amide products. **a** Conditions: Amide compound (3.0 mmol, 1 eq.), NaOH (24 mmol, 8 eq.), 1-butanol as solvent, 130–135 °C for 7 h. Then, the free base was added 5 M aq. HCl (3 mL) to give hydrochloride. **b** Conditions: **25** (3.0 mmol, 1 eq.), HCl (3 M, 10 eq.), reflux for 3 h.

the use of bromine and the large amount of H_2SO_4 while maintaining high yields (79 and 57% total yields). The hydrolysis of **25** also yielded **25b**, a key intermediate for the synthesis of rasagiline (see the Supplementary Methods for details).

Mechanistic studies. To obtain more insights into the Ritter-type amination reaction mechanism, a series of mechanistic studies were conducted. First, replacing sulfuric acid with sodium sulfate, potassium persulfate and methanesulfonic acid, which are unlikely to facilitate the Ritter-type step, 76–89% yields of desired product were provided (Fig. 6a). Besides, the formation of persulfate via the electrolysis of sulfuric acid under standard conditions was also proved by UV absorption spectra experiment (Supplementary Fig. 6). So, sulfuric acid was proved to promote the activation of $\text{C}(\text{sp}^3)\text{-H}$ rather than as an additive to facilitate the Ritter-type step. 65% yield of product **1** was delivered by electrolyzing **1a** at anodic chamber under standard conditions, demonstrating the generation of sulfate radical cation through the direct anodic oxidation (Fig. 6a).

By comparing the oxidation potentials of sulfate ($E^0 = 2.6\text{ V}$ vs NHE) and some alkanes in literatures^{76–80}, sulfates are likely to be oxidized by anode in prior to alkanes. However, heating or irradiating $\text{K}_2\text{S}_2\text{O}_8$ with **1a** did not afford the product **1** (Fig. 6a). We envisaged that the conversion of carbon radical to carbon cation could be accomplished by anode oxidation rather than the single electron transfer of $\text{SO}_4^{\cdot-}$. Radical clock experiment confirmed that radical intermediate **72b** was generated and underwent ring opening and further oxidation, furnishing carbon cation intermediate (Fig. 6b).

Based on the studies mentioned above, a possible mechanism for this reaction process was shown in Fig. 6c. Initially, sulfate anion SO_4^{2-} underwent a single electron oxidation process at the anode to afford $\text{SO}_4^{\cdot-}$. As a powerful HAT agent, $\text{SO}_4^{\cdot-}$ abstracted hydrogen atom from the substrate **1a** to generate carbon radical **73**, which was oxidized at the anode to the carbocation intermediate **74**. Subsequently, nucleophilic attack of acetonitrile to **74** through classic Ritter reaction process provided final product **1**. At the same time, the dimerization of $\text{SO}_4^{\cdot-}$ generated $\text{S}_2\text{O}_8^{2-}$, which was then transferred to the cathode area and reduced back to SO_4^{2-} .

In summary, we have developed an electrochemical approach that can be applied for the Ritter-type amination reaction of aliphatic $\text{C}(\text{sp}^3)\text{-H}$ and benzylic $\text{C}(\text{sp}^3)\text{-H}$ under mild conditions. By electrolyzing sulfate, $\text{SO}_4^{\cdot-}$ was generated and abstracted hydrogen atom from $\text{C}(\text{sp}^3)\text{-H}$ bonds. This electrochemical method also exhibited excellent regioselectivity and functional groups tolerance, rendering the reaction simple, safe, widely applicable. It is anticipated that this method would provide a convenient and alternative entry for the synthesis of amines derivatives.

Methods

Representative procedure for amination. An oven-dried undivided cell was equipped with a stir bar, 1,3-dimethyladamantane (82 mg, 0.5 mmol, 1 eq.), 98% H_2SO_4 (108 μL , 2 mmol, 0.67 M, 4 eq.), $n\text{Bu}_4\text{NBF}_4$ (98 mg, 0.3 mmol, 0.1 M), CH_3CN (3 mL). Air has little effect on this reaction. The assembled electrodes were placed into the solution. The silica gel plug was sealed with film. The mixture was

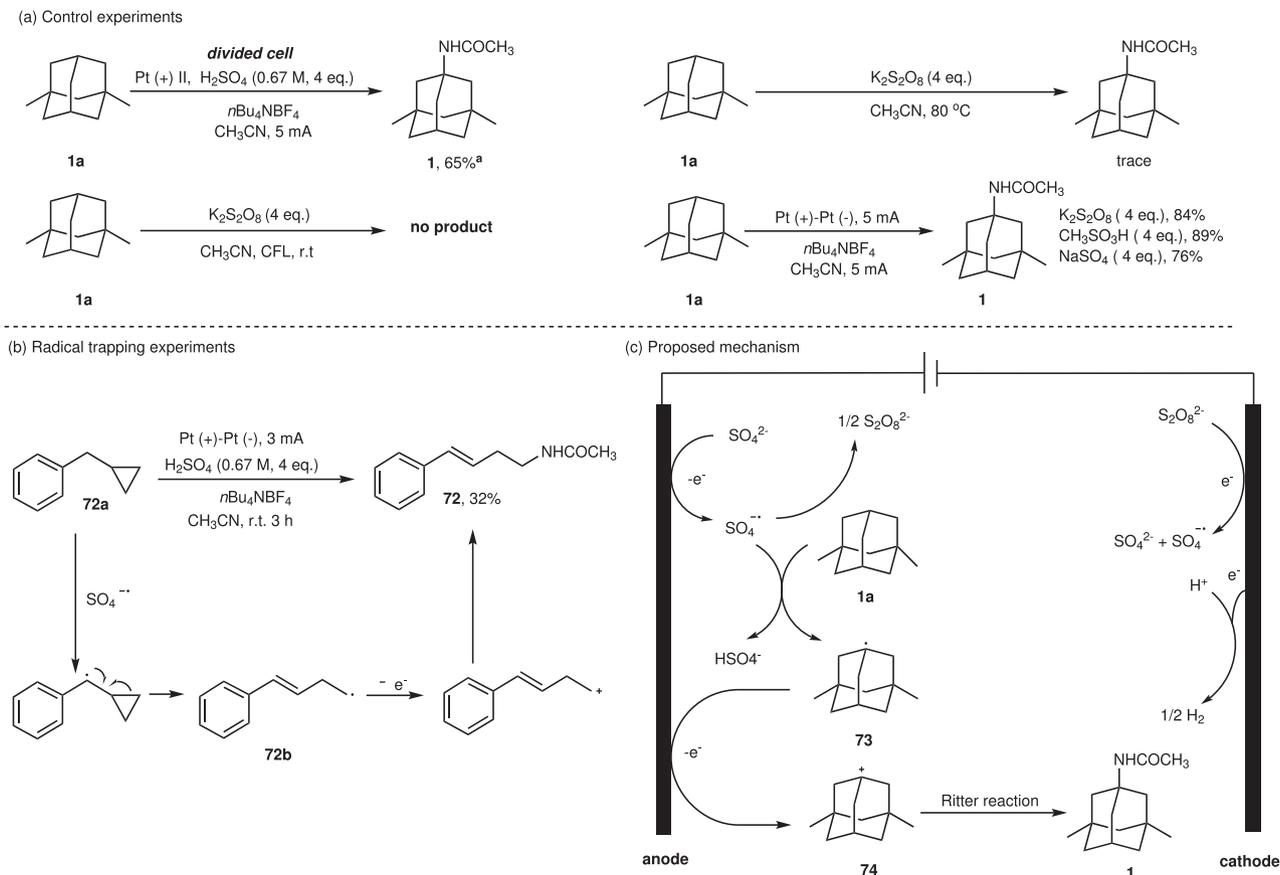


Fig. 6 Mechanistic studies. **a** Control experiments. ^aFor the reaction, to the anodic chamber was added **1a** (0.5 mmol), H₂SO₄ (108 μ L, 2 mmol, 0.67 M), *n*Bu₄NBF₄ (0.1 M) and CH₃CN (3 mL), the cathodic chamber was added *n*Bu₄NBF₄ (0.1 M) and CH₃CN (3 mL). **b** Radical trapping experiments. **c** Proposed mechanism.

electrolyzed at a constant current of 5 mA until the tertiary alkane was completely consumed (See Supplementary Fig. 3). The Pt electrodes were washed by water, ethanol, and DCM in turn. After the reaction is over, drop NaHCO₃ saturated solution into the reaction system slowly until no bubbles were observed. The aqueous layer was separated and extracted with EtOAc (3 \times 10 mL), and the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Following concentration *in vacuo*, the crude product was purified by column chromatography on silica gel to give pure product **1** (103 mg, 93%; see the Supplementary Methods for details).

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information file. For experimental details and compound characterization data see Supplementary Methods. For ¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra see Supplementary Figs. 7–82.

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L.Z. and Y.F. contributed equally to this work. L.Z., Y.F., and Y.S. performed the experiments, analyzed the data. C.L. and M.S. assisted the purification of compounds and analysis of data. R.C., W.Z., and X.Q. contributed to mechanistic studies. L.Z., Y.F., Y.M., and J.Y. wrote the manuscript, supplementary methods, and related materials. Y.M. and J.Y. designed and directed the project. L.Z., Y.F., R.C., W.Z., X.Q., Y.M., and J.Y. revised the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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