Electrochemical C-C Bond Cleavage of Cyclopropanes towards the Synthesis of 1,3-Difunctionalized Molecules

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Abstract

Electrochemistry had a lot of inherent advantages in organic synthesis and many redox reactions have been achieved under electrochemical condition. However, the electrochemical C-C bond cleavage and functionalization reactions are less studied. Here we developed electrochemical C-C bond cleavage and 1,3-difunctionalization of arylcyclopropanes under catalyst-free and external-oxidant-free conditions. 1,3-difluorination, 1,3-oxyfluorination and 1,3-dioxygenation of arylcyclopropanes were achieved with a highly chemo- and regioselectivity by the strategic choice of nucleophiles. This protocol has good functional groups tolerance and can be scaled up. Mechanistic studies demonstrate that arylcyclopropane radical cation yielded from the anode oxidation and the following generated benzyl carbonium are the key intermediates in this transformation. This development provides a new scenario for constructing 1,3-difunctionalized molecules.

Introduction

C-C bonds are the basic skeleton of organic compounds and widely existed in nature, its deconstructive functionalization are meaningful.^[1-2] Cyclopropanes are important building blocks, ring strain release driven C-C bond cleavage and ring-opening of cyclopropanes have been widely applied in total synthesis and pharmacy.^[3-4] Donor-acceptor cyclopropanes (DACs) which are activated by vicinal electron-donating and electron-withdrawing groups, are predisposed to ring-opening under Lewis acid catalysis due to the inherent electronic bias.^[5-7] Although more common in nature, non-activated cyclopropanes are harder to ring-opening due to insufficient electronic bias. One ring-opening method relies on oxidative addition by transition metals. However, specific directing groups are normally needed for selective ring-opening functionalization and this kind of reaction is limited to ring-opening rearrangement and cycloaddition reactions.^[8] Another ring-opening method relies on electrophilic activation with Lewis acidic species. However, most of this kind of transformation is limited to electrophilic addition reactions.^[9-17] Ring-opening functionalization of arylcyclopropanes initiated through the single electron oxidation to yield the corresponding radical cations was discovered in the 1970s.^[18-19] In recent years, this strategy is further applied in 1,3-aminofunctionalization, 1,3-oxoamination and 1,3-oxochlorination of arylcyclopropanes in the presence of oxidants or light. However, in most cases large scalability application was not studied, and arylcyclopropanes with electron-withdrawing groups could not be well compatible due to high oxidative potential of electron-withdrawing groups substituted arylcyclopropanes (Figure 1a).^[20-24]

Organic electrochemistry is reviving due to the ease of scalability, the avoidance of stoichiometric oxidizers or reducing agents, and flexible reaction tunability.^[25] Various redox reactions have been achieved by the consumption of traceless electrons under constant potential or current conditions.^[26-38] As a main part of preparative electrosynthesis, anode processes such as C-H functionalization, oxidative coupling, decarboxylation and olefin functionalization had been developed.^[39-48] However, electrochemical oxidative C-C bond cleavage and functionalization are rarely developed due to the

inertness and weak electronic bias of C–C bonds, which are always encumbered by other bonds.^[8-49-50] Herein we developed the electrochemical C–C bond cleavage and 1,3-difunctionalization of arylcyclopropanes under constant current electrolysis based on the following mechanistic proposal (Figure 1b): Firstly, arylcyclopropane is oxidized to the radical cation by anode, which result in the weakness of the C_α–C_β bond, as the BDE of C_α–C_β bond decreases more than 30 kcal/mol from the neutral cyclopropane to the corresponding radical cation.^[51] Then the radical cation undergoes three-electron S_N2 reaction to give the benzyl radical.^[52] Different from thermochemical and photochemical conditions, benzyl radical can further lose one electron at anode and be converted to benzyl carbonium under electrochemical conditions.^[43] The following nucleophilic attack to the benzyl carbonium can yield the 1,3-difunctionalization product. 1,3-difluorination, 1,3-oxyfluorination and 1,3-dioxygenation of arylcyclopropanes could be accessible with a highly chemo- and regioselectivity by the strategic choice of nucleophiles, and fluorinated products could be prepared by employing Et₃N•3HF as nucleophilic fluorine source.^[53-58] A wide variety of arylcyclopropanes with electron-donating and electron-withdrawing groups could be converted to the 1,3-difunctionalized molecules.

Results

Investigation of reaction conditions. We began our investigation by exploring the selective synthesis of 1,3-difluorination, 1,3-oxyfluorination and 1,3-dioxygenation products from phenylcyclopropane. After extensive screening of various conditions (for more details, see SI), 1,3-difluorination product **2** was obtained in 77% yield using Et₃N•3HF as fluorine source by conducting the electrolysis under constant current of 16 mA in an undivided cell equipped with platinum plate as both anode and cathode (Table 1, Entry 1). 1,3-oxyfluorination product **3** was obtained in 47% yield with the concomitant formation of other three 1,3-difunctionalization products under the existence of both Et₃N•3HF and MeOH (Table 1, Entry 2). The yield of 1,3-oxyfluorination product **3** increased slightly when decreasing the reaction temperature to 0°C (Table 1, Entry 3). An obviously improved yield was observed by using carbon cloth as anode materials (Table 1, Entry 4). The influence of the concentration of phenylcyclopropane to the reaction could be neglected (Table 1, Entry 5). 1,3-oxyfluorination product **3** was finally observed in 76% yield by adjusting the ratio of Et₃N•3HF/MeOH (Table 1, Entry 6). The good selectivity of the 1,3-oxyfluorination product **3** was speculated to be controlled by kinetics. At the first step, the reaction rate between MeOH and arylcyclopropane radical cation is larger than reaction rate between Et₃N•3HF and arylcyclopropane radical cation, which possibly due to lower nucleophilicity of Et₃N•3HF than MeOH.^[57] So arylcyclopropane radical cation mainly reacts with MeOH instead of Et₃N•3HF. According to the rate constant equation proposed by Mayr et al, the reaction rate of benzyl carbonium with MeOH or Et₃N•3HF are both very fast and determined by diffusion rate,^[59-60] so fluorination is the major process in the second step because of the excess amount of fluorine source compared with methanol in the reaction system. Further condition screening demonstrated that 1,3-dioxygenation products could be obtained in 95% yield under the electrolysis in MeOH with Bu₄NBF₄ as supporting electrolyte (Table 1, Entry 7).

Table 1. Optimization of the reaction conditions.^a

Entry	Temp. (°C)	Et ₃ N·3HF/ CH ₃ OH (mL)	Electrode	Yield (%) ^b			
				2	3	4	5
1	25	1.2/0	Pt(+) Pt(-)	77	0	0	0
2	25	1.2/0.5	Pt(+) Pt(-)	7	47	4	19
3	0	1.2/0.5	Pt(+) Pt(-)	7	50	4	20
4	0	1.2/0.5	CC(+) Pt(-)	3	63	2	25
5 ^c	0	1.2/0.5	CC(+) Pt(-)	2	64	2	27
6 ^c	0	0.8/0.2	CC(+) Pt(-)	5	76	2	16
7 ^{c,d}	25	0/6	CC(+) Pt(-)	0	0	0	95

^a Reaction conditions: electrode surface (1.5*1.5 cm², $J = 7.1$ mA/cm²), 16 mA, undivided cell, **1** (0.5 mmol), PhCF₃ (4.8 mL), 2 h, 2.4 F mol⁻¹ (based on **1**). ^b GC Yield using biphenyl as internal standard. ^c **1** (0.25 mmol), 1 h. ^d Without PhCF₃, Bu₄NBF₄ (0.25 mmol) was added as supporting electrolyte. CC: Carbon cloth.

Substrate scope. To investigate the substrate scope of the 1,3-difluorination reaction, we tested diverse range of arylcyclopropanes under the optimized condition (Figure 2). Phenylcyclopropane gave 75% NMR yield (**2**). Methanesulfonyl group no matter at *para* or *meta* position was well amenable to this protocol to give the desired products in good yields (**6** and **7**). Halogen groups such as F, Cl, Br and I were also compatible with this transformation (**8-12**), these groups could supply potential reactive sites for further transformation through coupling reactions. *Ortho* substituted arylcyclopropane was also suitable reaction partner, furnishing the desired 1,3-difluorination product with 58% yield (**13**). Arylcyclopropanes with electron-withdrawing groups (such as ester, amide, acetyl, cyano, nitro and aldehyde groups) were also amenable, furnishing the desired products in 42-56% yields by prolonging the reaction time (**14-20**), although these substrates have higher oxidative potential. Trifluoromethyl and oxytrifluoromethyl substituted arylcyclopropanes gave the corresponding products in 49% and 53% yields, respectively (**21-22**). TMS group was retained in this transformation with 52% yield (**23**). Alkyl group such as tert-butyl group underwent the reaction in lower yield of 40% (**24**). 3-Methyl-4-ester substituted arylcyclopropane provided the desired product with 54% yield (**25**). Moreover, heterocyclic arylcyclopropane such as thienyl cyclopropane was also suitable for this reaction (**26**). Then, the feasibility of 1,1-disubstituted cyclopropanes and 1,2-disubstituted cyclopropanes were also tested. 1,1-disubstituted cyclopropanes were good reaction partners to this reaction, giving the 1,3-difluorination products with tertiary-carbon-fluorine bonds formation in good yields (**27-29**). Trans 1,2-diphenylcyclopropane provided 1,3-difluorination products with 61% yield and 1.3:1 diastereoselectivity (**30**). 1,2-diphenylcyclopropane radical cation had been determined to be open geometries.^[51] Tri-substituted cyclopropane was also

tolerated in this transformation (**31**). Moreover, arylcyclopropanes containing complex nature product scaffolds were also compatible in this transformation. L-menthol scaffold substrate provided the desired product in 86% yield (**32**). 5 α -cholestan-3 β -ol scaffold substrate provided the corresponding product in 65% yield with 10% starting material recovered (**33**). Protected sugar group was also tolerated, and 82% yield was obtained (**34**). Androsterone scaffold substrate gave the desired product in 33% yield with 36% starting material recovered (**35**). The compatibility of these complex substrates further confirm the practicality of this transformation.

The scope of the 1,3-oxyfluorination reaction was also explored, as shown in Figure 3. *Para*-bromine substituted phenylcyclopropane was compatible to give the target product in moderate yield (**36**). Both electro-donating group and electro-withdrawing groups could be tolerated in this transformation (**37-39**). Subsequently, the scope of the alcohols was examined. Alcohols such as EtOH, *n*-BuOH and long-chain primary alcohols (*n*-C₆H₁₃OH and *n*-C₈H₁₇OH) were transformed into desired products with good efficiency (**40-43**). 2-Chloro-1-ethanol afforded the desired product in 40% yield (**44**). Secondary alcohols (*i*-PrOH and cyclohexanol) were suitable substrates (**45-46**). Sterically hindered tertiary alcohol was also tolerant (**47**). Besides alcohols, ethers could also participate in this reaction as oxygen nucleophiles (Figure 3). 1,3-Oxyfluorination could proceed smoothly when using ether as both reactant and solvent (**48-50**). Cyclic ether such as tetrahydrofuran gave interesting product **48** in 43% yields with etheric ring-opening, accompanying with 14% 1,3-difluorination product. 1,2-Dimethoxyethane gave 1,3-oxyfluorination product **49** in 44% yield. The reaction system was separated into two phases and not conductive when using tetrahydropyran as both reactant and solvent. To solve the problem of solubility and conductivity, DCE was added to enhance the solubility and 1,3-oxyfluorination product **50** was obtained in 36% yield. Notably, C-O etheric bond was broken in these transformations. It is proposed that oxonium is the key intermediate for cleavage of C-O etheric bond (for more details, see SI).^[61-62]

Finally, the scope of the 1,3-dioxygenation reaction was investigated (Figure 4). Arylcyclopropanes with electron-donating groups (-OMe, -OPh) gave 74% and 93% yields, respectively (**51-52**). *Para* tert-butyl substituted arylcyclopropane underwent the reaction in 85% yield (**53**). Both TMS and halogen groups could be tolerated (**54-55**). The electronically deficient arylcyclopropane could also give 1,3-dioxygenation products with high yields (**56-57**).

The scalability of the method was demonstrated by using carbon cloth as anode and nickel foam as cathode instead of expensive platinum electrode with equivalent amount of Et₃N•3HF (Figure 5). The yields increased for most of the tested substrates when operated at gram scale. The yields increased from 75% to 90% for *para*-methanesulfonyl substituted phenylcyclopropane (**6**). The yields increased to 65% and 63% for ester (**14**) and oxytrifluoromethyl (**22**) substituted arylcyclopropanes. Only for 4-bromocyclopropylbenzene (**10**), the yields decreased slightly from 67% to 63%.

Discussion

To gain more insight into the aforementioned transformation, mechanistic studies were conducted. Redox potential of the cyclopropanes was tested by cyclic voltammetry experiments (Figure 6a). The alkyl substituted cyclopropane **1c** has high oxidation potential and no oxidation peak can be observed under 3V. In contrast, arylcyclopropanes even with strong electron withdrawing group ($-\text{NO}_2$) have relatively lower oxidative potential ($E_{\text{onset}}=1.68$ V for **1** and $E_{\text{onset}}=1.99$ V for **1a**). These results illustrate that aryl group is important for the oxidation of the cyclopropane substrates. The charge distribution of phenylcyclopropane radical cation has been studied by DFT calculation (Figure 6b). The results show that distal C atom in cyclopropane motif possess partial positive charge and are the potential nucleophilic attack sites. Considering the reaction between benzyl radical and dioxygen was very fast (rate constant $2.8 \times 10^9 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$),^[63] the reaction was run in the presence of dioxygen instead of nitrogen in order to trap the possible benzyl radical intermediate. The detection of the oxygenation products highly proposed the formation of the benzyl radical during the reaction (Figure 6c). In addition, the existence of benzyl radical was also evidenced by the trapping experiment using BrCCl_3 .^[64-65] Furthermore, the electrolysis of phenylcyclopropane and $\text{Et}_3\text{N} \cdot 3\text{HF}$ in CH_3CN resulted in isolation of amidation product, which suggest the involvement of benzyl carbonium intermediate during the reaction (Figure 6d).^[66-67]

In conclusion, we have developed a electrochemical C-C bond cleavage of arylcyclopropanes, enabling 1,3-difunctionalization of arylcyclopropanes to yield 1,3-difluorination, 1,3-oxyfluorination and 1,3-dioxygenation products. Neither additional oxidant and catalyst were needed in this transformation. Productive gram-scale 1,3-difluorination reaction was running by using stoichiometric amount of commercial available $\text{Et}_3\text{N} \cdot 3\text{HF}$ as fluorine source. Mechanistic studies show that arylcyclopropane radical cation and benzyl carbonium play paramount role in this reaction. This study provides a new and simple strategy for constructing 1,3-difunctionalized molecules.

Methods

General procedure (2). An oven-dried undivided three-necked bottle equipped with a stir bar. The bottle was equipped platinum plate (15 mm×15mm×0.3 mm) as both the anode and cathode and then charged with argon gas in glove box. Phenylcyclopropane (0.5 mmol), $\text{Et}_3\text{N} \cdot 3\text{HF}$ (1.2 mL) and PhCF_3 (4.8 mL) were added. The reaction mixture was stirred and electrolyzed at a constant current of 16 mA at 25 °C for 2 h. The reaction was diluted with water. The organic layer was extracted with CH_2Cl_2 , dried with anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The pure product was obtained by flash column chromatography on silica gel. Full experimental details can be found in the Supplementary Methods.

Declarations

Data availability. The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

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Author Contributions

A.L. and P.P. conceived the project and designed the experiments. P.P. developed the reactions, and contributed to the reaction scope and mechanistic studies. X.Y., K.Z., Z.L. and Y.C. contributed to the reaction scope and participated in the substrates synthesis. L.Z. and H.Z. discussed the results. H.Z. performed the theoretical calculation. P.P., H.Z. and A.L. wrote the paper, Supplementary methods, and related materials.

Additional Information

Supplementary Information: Experimental procedure, characterization data, and copies of ^1H , ^{13}C and ^{19}F spectra. This material is available free of charge via the Internet at <http://www.nature.com/naturecommunications>.

Competing financial interests: The authors declare no competing financial interests.

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Figures

a, Thermochemical and photochemical strategy

b, This work: Electrochemical strategy

Figure 1

1,3-difunctionalization of cyclopropanes based on radical cation mechanism. (a) Thermochemical and photo-chemical strategy. (b) This work: Electrochemical strategy.

Figure 2

Substrate scope of 1,3-difluorination reaction. Reaction condition: Cyclopropanes (0.25 or 0.5 mmol), Et₃N·3HF (1.2 mL), PhCF₃ (4.8 mL), 16 mA, 40 min–20 h, isolated yields, electrode surface (1.5*1.5 cm², J = 7.1 mA/cm²), undivided cell. a NMR yield using 1-fluoronaphthalene as internal standard. b 0.1 mmol scale, 2-6 h. c 0.5 mL DCE was added. s.m., starting material. For more details, see SI.

Figure 3

Substrate scope of 1,3-oxyfluorination reaction. Reaction condition: Cyclopropanes (0.25 mmol), Et₃N•3HF (0.8 mL), ROH (0.2-0.75 mL), PhCF₃ (4.8 mL), 16 mA, 1 h, isolated yields. a Reaction condition: Cyclopropanes (0.5 mmol), Et₃N•3HF (1.2 mL), ether (4.8 mL), isolated yields. b 1 mL DCE was added. For more details, see SI.

Figure 4

Substrate scope of 1,3-dioxygenation reaction. Reaction condition: Cyclopropanes (0.25 mmol), Bu₄NBF₄ (0.25 mmol), MeOH (6 mL), 16 mA, 50 min-1 h, isolated yields. For more details, see SI.

Figure 5

Large-scale synthesis. Reaction condition: Cyclopropanes (6 or 8 mmol), Et₃N·3HF (2.4 mL), PhCF₃ (9.6 mL), 25-75 h, isolated yields. NF: nickel foam. For more details, see SI.

a, Cyclic voltammetry Studies

b, Electrostatic potential surface and charge of 1⁺⁺

c, Trap of benzyl radical intermediate

d, Trap of benzyl carbonium intermediate

Figure 6

Mechanistic studies. (a) Cyclic voltammetry studies. (b) Electrostatic potential surface and charge of phenylcyclopropane radical cation ($1\cdot^+$). (c) Trap of benzyl radical intermediate. (d) Trap of benzyl carbonium intermediate.

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