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A remote C–C bond cleavage–enabled skeletal reorganization: Access to medium-/large-sized cyclic alkenes

Lei Li,* Zhong-Liang Li,* Qiang-Shuai Gu, Na Wang, Xin-Yuan Liu†

Although great success has been achieved in selective C–C bond cleavage via the intramolecular radical remote migration process of several carbon-based groups, the development of the radical-based remote vinyl migration process remains a formidable challenge because of the energetically unfavorable process. To address this problem, we report here, for the first time, a novel C–C bond reorganization strategy via an unprecedented radical 1,3-, 1,4-, or 1,5-vinyl migration triggered by various types of fluoroalkylation of alkenes for the efficient realization of 1,2-fluoroalkylalkenylation reaction. This strategy provides an expedient and broadly applicable platform to access skeletally and functionally diverse fluoroalkyl-containing medium- and large-sized cyclic alkenes with excellent chemo-, regio-, and stereoselectivity. The broad substrate scope, which covers distinctly electron-neutral or electron-deficient alkenyl migrating groups and various fluoroalkyl radical precursors, the excellent functional group tolerance, the remarkable selectivity, and the operational simplicity, as well as versatile transformations of the products, make this approach practical and attractive.

INTRODUCTION

Medium- and large-sized cyclic alkenes are one of the most prominent classes of structural motifs because they are not only prevalent in a wide range of biologically active natural products and therapeutic agents (*1*–*5*) but can also serve as a vital platform for diverse chemical functionalization given their unique and versatile chemical reactivity (*6*). Nevertheless, their elegant synthesis remains a formidable challenge with conventional cyclization or cycloaddition strategies, mainly due to unfavorable transannular interactions and entropic and/or enthalpic factors (*7*–*13*). To solve these problems, a revolutionary advancement in this field is the establishment of transition metal–catalyzed ring-closing metathesis, which has served as a reliable tool for the synthesis of otherwise hardly accessible complex medium- and large-sized cyclic alkenes (*14*–*22*). However, high-dilution and/or slow-addition operation has been frequently required to inhibit the undesired competitive oligomerization via intermolecular olefin metathesis. Therefore, developing a novel and operationally simple alternative strategy to construct these cyclic alkenes still remains a great need.

During the past few decades, selective C–C bond cleavage via the intramolecular radical remote migration process of carbon-based groups like aryl, cyano, or carbonyl groups has attracted much attention (Fig. 1A) (*23*–*31*). It is not only one of the most challenging themes at the intersection of both radical and rearrangement reactions but also represents an efficient tool for the preparation of complex organic molecules based on reorganization of the skeletons of readily available compounds (*23*–*31*). However, to the best of our knowledge, the radical-based remote vinyl migration process has rarely been approached, largely because of the energetically unfavorable β-scission process of intermediate **B** compared with that of other migration reactions aforementioned based on density functional theory calculations (Fig. 1A) (*32*). On the other hand, the increasing importance of fluoroalkyl-containing molecules in the development of pharmaceuticals and agrochemicals as well as materials has inspired considerable research efforts in discovering new practical perfluoroalkylation strategies for their synthesis (*33*–*38*). In particular, radical-mediated 1,2-difunctionalization of unactivated alkenes has emerged as one of the most powerful tools for the assembly of diverse fluoroalkyl-containing molecules (*39*–*50*). Despite these impressive advances, the fluoroalkylalkenylation of unactivated alkenes for the simultaneous incorporation of fluoroalkyl and alkenyl group into unactivated alkenes has never been reported. To achieve olefinic fluoroalkylalkenylation and efficiently attain the aforementioned synthetically formidable medium- and large-sized cyclic alkenes, we wondered whether a novel C–C bond reorganization strategy might be achieved via an unprecedented remote vinyl migration triggered by selective addition of fluoroalkyl radicals to one alkene in the substrate bearing two alkenyl groups (Fig. 1B). In this scenario, we expected that various in situ–generated fluoroalkyl radical species might selectively attack to the less sterically hindered terminal alkene to provide a transient alkyl radical **I.** Driven by the formation of a lower-energy neutral ketyl radical **III**, the subsequent exo cyclization and β-scission of intermediate **II** might lead to remote radical vinyl migration/ring expansion sequence to deliver the fluoroalkylated medium-/large-sized cyclic alkenes. However, several challenges would be associated with the development of such a process: (i) Because the initial radical Rf is inherently reactive and neutral (*51*, *52*), its addition to alkene could be complicated in both chemoselectivity and regioselectivity in the presence of two alkenyl groups of substrate. (ii) Several competitive pathways, such as common kinetically favorable β-scission to deliver intermediate **IV**, endo cyclization to generate intermediate **V**, and exo-cyclization–initiated other side reactions to provide **VI** and **VII**, should be overcome (*32*, *53*–*55*). (iii) A high degree of *E*/*Z* selectivity for the final alkene product should be achieved. Here, we describe the first successful development of a novel C–C bond reorganization strategy via an unprecedented radical 1,3-, 1,4-, or 1,5-vinyl migration. With such a strategy, 1,2-trifluoromethylalkenylation of unactivated alkenes has been successfully achieved with excellent chemo-, regio-,

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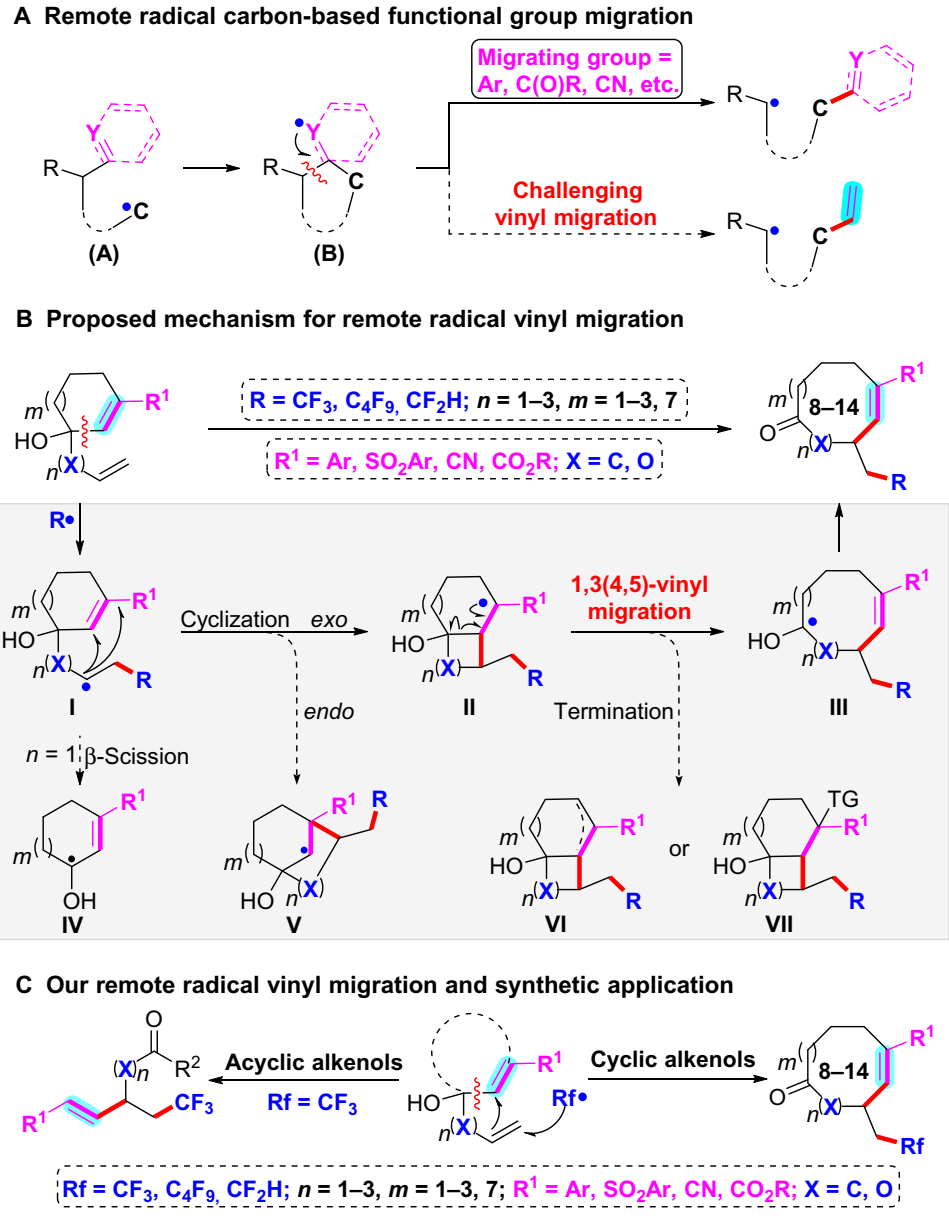


Fig. 1. Radical-initiated C–C bond cleavage via remote carbon-based functional group migration. (**A**) Reported remote radical aryl, carbonyl, and cyano migration and challenging vinyl migration process. (**B**) Proposed mechanism for remote radical vinyl migration process. (**C**) Our designed remote radical vinyl migration and synthetic application.

and stereoselectivity (Fig. 1C, left). This strategy has also provided a general and operationally simple approach for the synthesis of skeletally and functionally diverse fluoroalkylated medium-/large-sized cyclic alkenes or bridged ring systems, which constitute the core structures of many biologically active natural products, such as siamol (*1*), spartidienedione (*2*), tubercullariol D (*4*), longpene B (*5*), etc. (Figs. 1C, right, and 2).

RESULTS

Reaction condition optimization

First, substrate **1A** was easily obtained by adding allylzinc chloride to (*E*)-4-phenylbut-3-en-2-one at −78°C. We then initiated our investigation for radical remote vinyl migration on linear substrate **1A** with commercially available Togni's reagent **2** (*56*) as a CF_3 radical source. We were delighted to find that the desired 1,2-trifluoromethylalkenylation product **3A** was obtained in 55% yield with excellent *E*/*Z* selectivity in the presence of CuI [10 mole percent (mol %)] at 80°C in 24 hours via an unprecedented 1,3-vinyl migration process (Table 1, entry 1). Further screening of reaction parameters (Table 1, entries 2 to 15), through variation of the copper catalysts, the molar ratio of the reactants, organic solvents, reaction temperature, and time, has led to the identification of the optimal reaction conditions as follows: The reaction of **1A** and **2** with a molar ratio of 1.0:2.4 (**2** was added in two portions with a time interval of 10 hours) in the presence of CuCN (10 mol %) in 1,4-dioxane at 80°C for 20 hours to afford **3A** in 69% yield (entry 15). Note that the

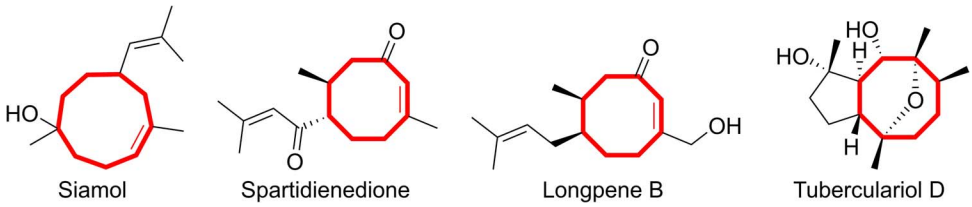
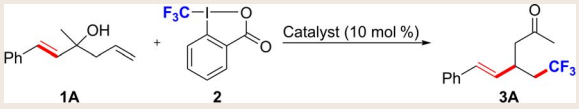


Fig. 2. Representative natural products containing medium-sized cyclic alkenes and bridged rings. Several natural products of eight- and nine-membered cyclic alkenes and bridged ring are shown.

Table 1. Screening of the reaction conditions. Reaction conditions: **1A** (0.2 mmol), **2** (1.5 equiv.), and Cu(I) (10 mol %) under argon atmosphere. Conversion (*c*) and yield (*y*) were determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy using CH_2Br_2 as an internal standard. **2** (1.2 equiv.) was added for entry 6. **2** (1.8 equiv.) was added for entry 7. **2** (2.4 equiv.) was added in two portions with a time interval of 10 hours for entry 15. EtOAc, ethyl acetate; DCE, 1,2-dichloroethane; THF, tetrahydrofuran.



Entry	[Cu]	Solvent	*T* (°C)	Time (hours)	*c* (%)	*y* (%)
1	CuI	EtOAc	80	24	90	55
2	CuBr	EtOAc	80	24	95	46
3	CuCl	EtOAc	80	24	90	54
4	CuOAc	EtOAc	80	24	100	55
5	CuCN	EtOAc	80	24	90	58
6	CuCN	EtOAc	80	24	70	34
7	CuCN	EtOAc	80	24	100	52
8	CuCN	EtOAc	60	24	30	20
9	CuCN	EtOAc	80	18	85	61
10	CuCN	EtOAc	100	24	100	40
11	CuCN	DCE	80	18	100	32
12	CuCN	CH_3CN	80	18	100	38
13	CuCN	THF	80	18	40	30
14	CuCN	1,4-Dioxane	80	18	70	58
15	CuCN	1,4-Dioxane	80	20	95	69

intramolecular radical 1,3-migration process of other carbon-based groups has rarely been achieved in previously reported processes, probably due to the strained four-membered cyclic transition state involved in this process (*26*, *31*). In sharp contrast, the present radical vinyl migration process was surprisingly viable enough to accommodate such an unfavorable pathway, thus substantially expanding the scope of carbon-based functional group migration process. The reason might be that the activation energy is low for the formation of intermediate **II** in vinyl migration compared with that for carbonyl and aryl migration, which involves breaking a relatively high-energy C=O bond and dearomatization (see fig. S1 and the detailed discussion in the Supplementary Materials).

Substrate scope

With the optimal reaction conditions established, the generality of the current system for the 1,2-trifluoromethylalkenylation of linear substrates was next investigated (Fig. 3). First, the radical 1,3-vinyl migration was surveyed and a variety of substrates bearing electron-donating or electron-withdrawing groups on the aryl ring attached to the internal alkenyl group afforded **3A** to **3H** in 63 to 81% yields with excellent *E*/*Z* selectivity. Further studies showed that the geminal-disubstituted alkene **1I** also underwent this reaction to furnish the desired product **3I** bearing a quaternary carbon center in 65% yield. Note that the reaction with **1J** and **1K** exhibited excellent chemoselectivity for the radical vinyl migration over other potential phenyl or hydrogen migration process to selectively afford **3J** and **3K**, respectively. Next, 1,4- and 1,5-vinyl migration were examined to expand the synthetic utility of this methodology. Gratifyingly, under the reaction conditions similar to those of the 1,3-vinyl migration process, a wide range of linear alkenols **1L** and **1Q** and aryl-tethered alkenols **1M** to **1P** having different electronic and geometric features were all found to be suitable substrates to afford expected products **3L** to **3Q** in 30 to 78% yields. The excellent chemoselectivity for vinyl migration over phenyl migration was also observed for 1,4- and 1,5-vinyl migration, as proven by the exclusive formation of **3L**, **3P**, and **3Q** from the corresponding substrates. To further evaluate the utility of the vinyl migration, we carried out the preparative-scale synthesis of **3A.** As demonstrated in Fig. 3, there was almost no change on the chemical yield (63%), indicating that this protocol should be potentially useful in large-scale chemical production. Overall, the 1,2-trifluoromethylalkenylation of alkenols features a broad compatibility for a diverse range of substrates through an unprecedented radical 1,3-, 1,4-, or 1,5-vinyl migration with excellent selectivity, thus providing the first straightforward and attractive strategy for concomitant efficient installation of valuable trifluoromethyl and diversely functionalizable alkenyl groups into alkenes.

Encouraged by the above success, we thus switched our efforts toward the synthetically challenging medium- and large-sized cyclic alkenes. To this end, we rationally designed the cyclic styrene-type alkenols, which are easily prepared by adding the organolithium reagent or organozinc reagent to the corresponding α,β-unsaturated ketones. The selective addition of CF_3 radical to the terminal alkenyl moiety would trigger ring expansion by a similar remote vinyl migration process (Fig. 4). Under the reaction conditions analogous to those for linear substrates, a variety of six-membered ring substrates containing electron-donating, electron-withdrawing, or electron-neutral groups on the alkenyl aryl ring were all applicable for the radical 1,3-vinyl migration process to generate the expected eight-membered alkenes **5A** to **5C** in 60 to 70% yields. The reaction of **4D** featuring a seven-membered ring also worked well to afford the corresponding nine-membered alkene **5D** in 54% yield. The high efficiency of the present protocol in

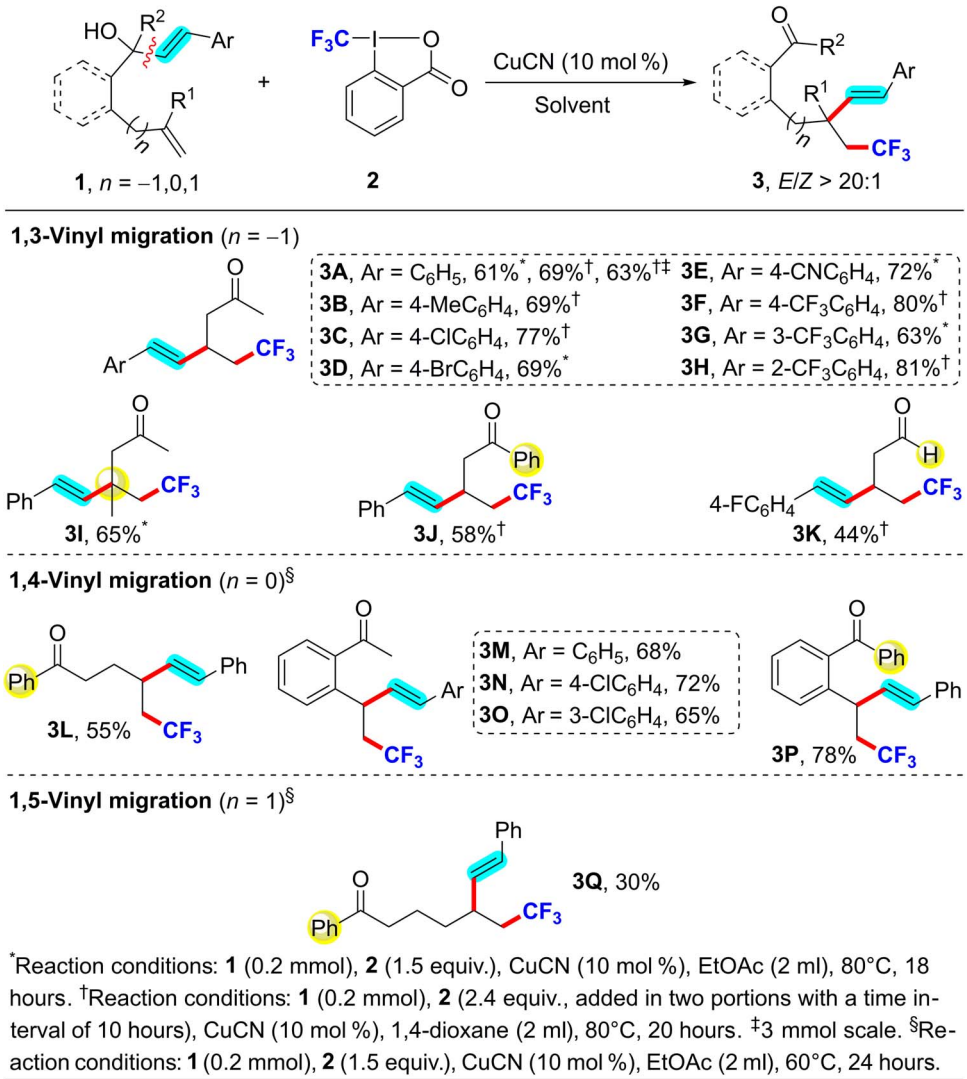


Fig. 3. Substrate scope of linear substrates. 1,3-, 1,4-, and 1,5-vinyl migration processes all provided desired products in moderate to good yields.

preparing macrocyclic alkenes was demonstrated by the isolation of the 14-membered alkene **5E** in 46% yield. To increase the diversity of products, we then investigated the construction of benzannulated medium-sized cyclic alkenes via radical 1,4-vinyl migration (Fig. 4B). Under the standard reaction conditions, the expected benzannulated 9- and 10-membered alkenes **5F** to **5J** were obtained in 41 to 52% yields from the corresponding substrates bearing different opening-ring sizes and distinctly electronic groups at different positions on the aryl ring directly connected with the migrating alkene. The structure of product **5I** was firmly established by x-ray crystallographic analysis (fig. S2). Furthermore, the reaction of the eight-membered substrate **4K** proceeded smoothly to deliver the benzannulated 11-membered alkene **5K** in 31% yield as a 4:1 mixture of *E*/*Z* isomers under the standard reaction conditions. Note that the external alkenol **4L** was also suitable for the vinyl migration reaction to deliver the nine-membered product **5L** with an external C=C double bond in 60% yield as a 5:1 mixture of *E*/*Z* isomers (Fig. 4C). To demonstrate the practicality of this process, we performed the preparative-scale synthesis of **5A**, as depicted in Fig. 4. The chemical yield of **5A** was not significantly influenced (59%), suggesting that this protocol should be potentially useful in large-scale production of medium-sized cyclic alkenes.

To further enrich the functional group diversity at the alkenyl positions, we subsequently examined substrates bearing polar olefin moieties. Much to our surprise, a phenylsulfonyl-substituted vinyl group successfully migrated under the standard reaction conditions to provide the eight-membered product **6** in 79% yield (Fig. 4D). The structure of **6** was carefully confirmed by x-ray crystallographic analysis (fig. S2). More encouragingly, electron-deficient alkenes conjugated with much more synthetically valuable cyano and ester groups both proved to be viable for migration, thus furnishing the corresponding products **7** and **8** in 58 and 60% yields, respectively.

The scope of the reaction was further expanded to other radical precursors. A variety of electronically distinct fluoroalkyl sulfonyl chlorides (*57*), such as trifluoromethyl, difluoromethyl, and even perfluorobutyl ones, were found to be suitable precursors via extrusion of sulfur dioxide in the presence of CuI (10 mol %) and Ag_2CO_3 (0.75 equiv.) to afford the expected products **6**, **10**, and **11** in 45 to 65% yields (Fig. 5A). Thus, the functional diversity of the synthesized medium-sized cyclic

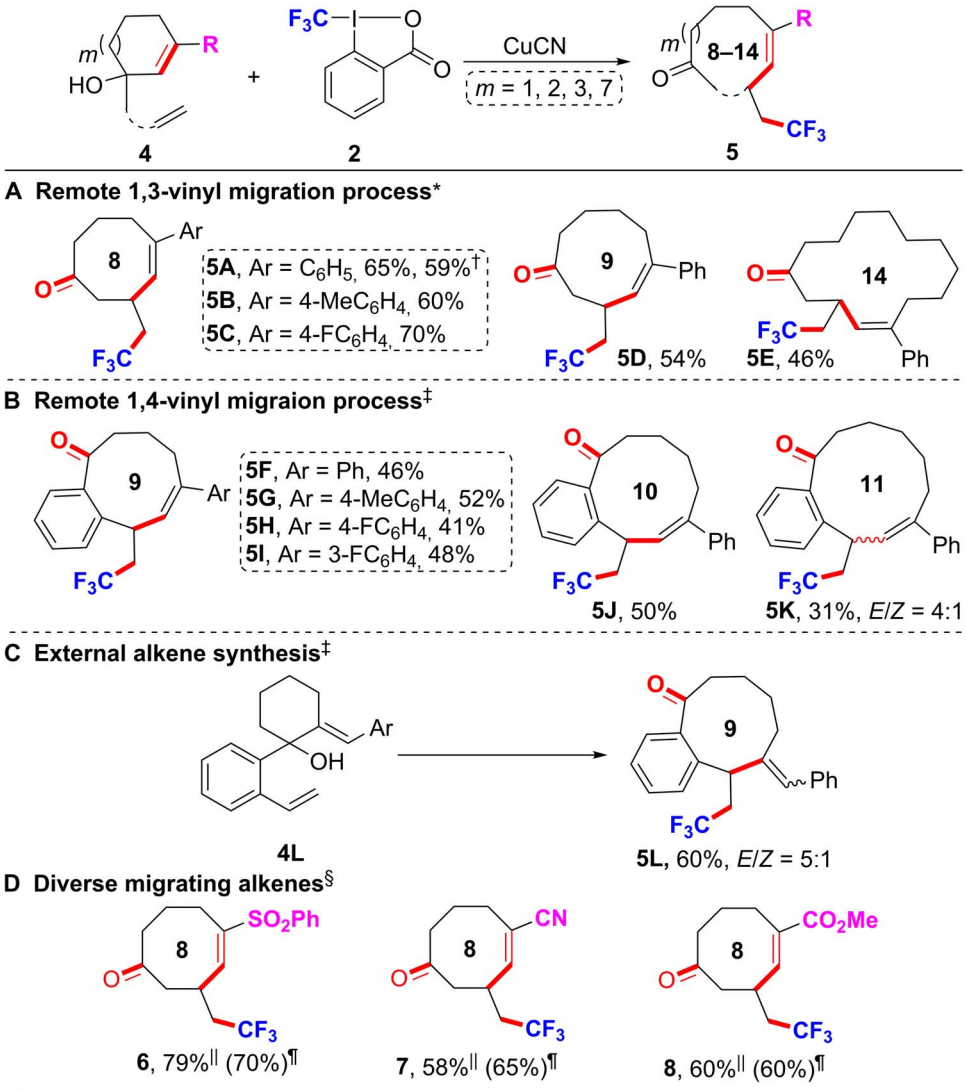


Fig. 4. Scope for medium- and large-sized cyclic alkenes. Diverse medium- and large-sized cyclic alkenes are constructed. (**A**) Remote 1,3-vinyl migration process. (**B**) Remote 1,4-vinyl migration process. (**C**) Synthesis of external cyclic alkenes. (**D**) Functional group diversity at alkenyl position.

alkenes was further increased. On the other hand, substrate **4P** bearing an electron-rich vinyl ether group underwent radical remote 1,5-vinyl migration to give the expected product **12**, albeit in 12% yield along with the exo-cyclization product **13** in 43% yield (Fig. 5B), which is currently under further optimization in our laboratory. In addition, the formation of **13** also provided some indirect support for a stepwise remote vinyl migration pathway, as described in Fig. 1B.

Versatile transformations

The alkenyl and carbonyl moieties in the constructed medium-sized cyclic alkenes provide great potential for further transformations to deliver additional bonding and valuable functional groups, thus enhancing the complexity and diversity of products. In addition, the conformational preference of medium-sized cyclic alkenes may result in excellent stereocontrol for remote functional group manipulation (*58*). In this scenario, the dihydroxylation of **5A** provided a bridged hemiketal **14** in 62% yield with excellent diastereoselectivity (Fig. 6A), which is quite similar to the core structure of tubercullariol D. The selective reduction of the carbonyl group of **5A** by $LiAlH_4$ delivered the alcohol **15** in 82% yield with a high diastereoselectivity of 15:1 (Fig. 6B). Furthermore, the epoxidation of **5A**, **5C**, and **5D** with *m*CPBA (*m*-chloroperbenzoic acid) all efficiently afforded the corresponding medium-sized cyclic epoxides **16**, **17**, and **18**, respectively, with excellent diastereoselectivity (>20:1) (Fig. 6C).

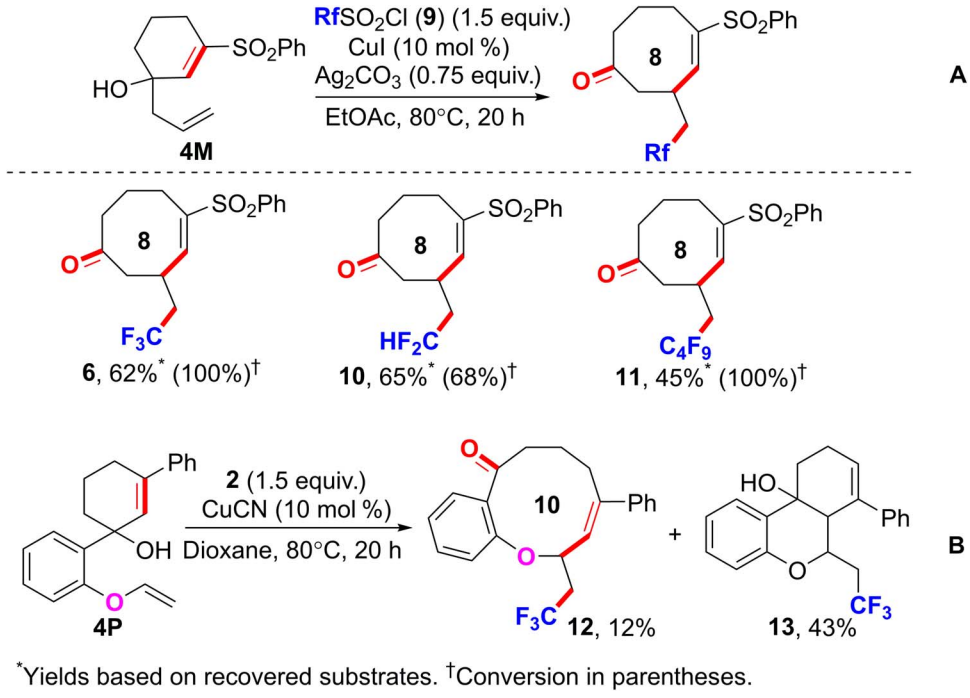


Fig. 5. Scope for other radical precursors and polar alkenes. More fluoroalkyl-containing eight-membered cyclic alkenes are formed. (**A**) Applicability of other radical precursors. (**B**) Applicability of electron-rich vinyl ether substrate.

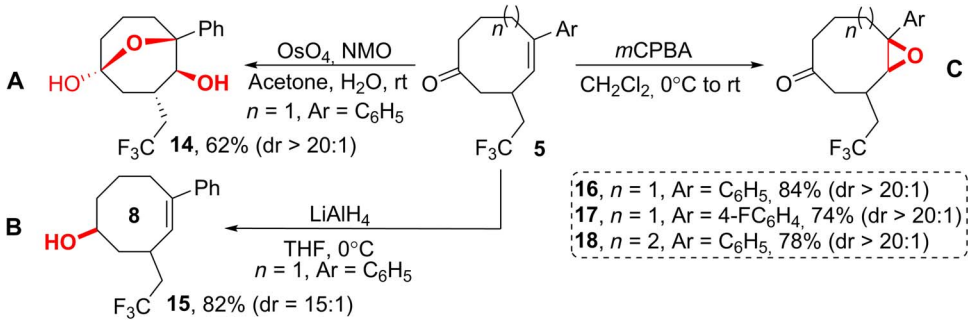


Fig. 6. Versatile transformations. The medium-sized cyclic alkenes are applicable for diverse transformation. (**A**) Dihydroxylation of cyclic alkene. (**B**) Epoxidation of cyclic alkenes. (**C**) Reduction of carbonyl group. NMO, *N*-methylmorpholine *N*-oxide; rt, room temperature; dr, diastereomeric ratio.

DISCUSSION

To gain some insights into the reaction mechanism, we conducted radical-trapping experiments conducted by using 2,2,6,6-tetramethyl-1-piperidinyloxy or benzoquinone as the radical scavengers under the standard conditions. The reactions were significantly inhibited by these reagents, suggesting that a radical process is involved under the current conditions (scheme S1). These experimental results, together with the observed exo-cyclization product for the substrate **4P** (Fig. 5B), are in support of our initial proposal, as shown in Fig. 1B.

In conclusion, we have successfully achieved a novel C–C bond reorganization strategy via an unprecedented radical 1,3-, 1,4-, and 1,5-vinyl migration triggered by various types of fluoroalkylation of alkenes. This approach not only embodies a valuable 1,2-fluoroalkylalkenylation reaction of alkenes but also offers an attractive and broadly applicable platform to access skeletally and functionally diverse perfluoroalkyl-containing 8- to 14-membered cyclic alkenes with excellent chemo-, regio-, and stereoselectivity. In particular, this protocol features a broad substrate scope, including distinctly electron-neutral or electron-deficient alkenyl migrating groups and diverse perfluoroalkyl radical precursors, wide functional group compatibility, and operational simplicity. Furthermore, the high synthetic utility of the current process in organic and medicinal chemistry was showcased by straightforward manipulation of the alkene and carbonyl groups in thus obtained medium-sized cyclic alkene products with high diastereoselectivity. Detailed mechanistic studies and further expansion of this methodology are currently ongoing in our laboratory.

MATERIALS AND METHODS

Experimental design

All reactions were carried out under argon atmosphere using Schlenk techniques. Reagents were purchased from commercial sources and used as received. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 GF_{254} plates. Flash column chromatography was performed using Tsingdao silica gel (60; particle

size, 0.040 to 0.063 mm). Visualization on TLC was achieved by using ultraviolet light (254 nm) or iodine. NMR spectra were recorded on a Bruker DPX 400 or a Bruker DPX 500 spectrometer at 400 or 500 MHz (^{1}H NMR), 100 or 125 MHz (^{13}C NMR), 376 MHz (^{19}F NMR), and 162 MHz (^{31}P NMR) in $CDCl_3$ with tetramethylsilane as an internal standard [$CFCl_3$ as an external reference (0 parts per million) for ^{19}F NMR]. The chemical shifts are expressed in parts per million, and coupling constants are given in hertz. Data for ^{1}H NMR were recorded as follows: chemical shift (in parts per million), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant (hertz), and integration. Data for ^{13}C NMR were reported in terms of chemical shift (δ, parts per million). Mass spectrometric data were obtained using Bruker Apex IV RTMS.

General procedure for trifluoromethylation reactions

Method A

A 25-ml Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv.), **2** (94.5 mg, 0.3 mmol, 1.5 equiv.), CuCN (1.8 mg, 0.02 mmol, 0.1 equiv.), and EtOAc (2.0 ml) under argon atmosphere. The sealed tube was then stirred at 80°C for 18 hours. After completion of the reaction as monitored by TLC, EtOAc (30 ml) was added, and the reaction mixture was washed with saturated $NaHCO_3$ (2 × 5 ml) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude product, which was purified by flash column chromatography to afford products **3A**, **3D**, **3E**, **3G**, and **3I.**

Method B

A 25-ml Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv.), **2** (76 mg, 0.24 mmol, 1.2 equiv.), CuCN (1.8 mg, 0.02 mmol, 0.1 equiv.), and 1,4-dioxane (2.0 ml) under argon atmosphere. The sealed tube was then stirred at 80°C for 10 hours. Then, a second portion of **2** (76 mg, 0.24 mmol, 1.2 equiv.) was added, and the tube was stirred for another 10 hours. After completion of the reaction as monitored by TLC, EtOAc (30 ml) was added, and the reaction mixture was washed with saturated $NaHCO_3$ (2 × 5 ml) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude product, which was purified by flash column chromatography to afford products **3A** to **3C**, **3F**, **3H**, **3J**, and **3K.**

Method C

A 25-ml Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv.), **2** (94.5 mg, 0.3 mmol, 1.5 equiv.), CuCN (1.8 mg, 0.02 mmol, 0.1 equiv.), and EtOAc (2.0 ml) under argon atmosphere. The sealed tube was then stirred at 60°C for 24 hours. After completion of the reaction as monitored by TLC, EtOAc (30 ml) was added, and the reaction mixture was washed with saturated $NaHCO_3$ (2 × 5 ml) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude product, which was purified by flash column chromatography to afford products **3L** to **3Q.**

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/11/e1701487/DC1

scheme S1. Control experiments.

fig. S1. Speculated energy profiles for carbonyl, aryl, and vinyl migration process.

fig. S2. X-ray structures of **5I** and **6.**

Experimental procedure

Mechanistic study

NMR spectra

CIF Files 1 and 2

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