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Single-carbon-atom transfer to *para*-quinone methides from TMSCF$_2$Br†

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Single-carbon-atom transfer reactions offer a powerful strategy for constructing complex molecular architectures by sequential assembly of substituents around the atomic carbon core. However, the limited availability of atomic carbon sources has significantly hindered progress in this field. Herein, we demonstrate a single-carbon atom transfer reaction utilizing commercially available TMSCF$_2$Br as an atomic carbon equivalent. Through a cascade of 1,6-addition and TBAF-catalyzed intramolecular cyclization with *para*-quinone methides (*p*-QMs), *gem*-difluorinated spiro[2.5]octa-4,7-dien-6-ones were efficiently formed. These spirocyclic intermediates exhibit remarkable electrophilicity, enabling stereoselective capture of diverse nucleophiles to access fluorinated alkenes with excellent stereocontrol. The resulting fluoroalkenes serve as versatile platforms for constructing tetrasubstituted alkenes *via* nucleophilic vinylic substitution (S$_N$V), achieving excellent stereoselectivities. In the presence of a 1,3-bisnucleophile, for example a C2-substituted acetoacetate ester, cyclic 2-methylene-2,3-dihydrofuran was generated *via* a sequential S$_N$V reaction with excellent stereoselectivities. Moreover, a computational study and a control experiment provide insight into the mechanism of the reaction.

Introduction

Molecular skeleton editing has emerged as a transformative strategy for diversifying molecular complexity in synthetic chemistry.[1] While advancements in late-stage functionalization have enabled precise modifications of (hetero)aromatic backbones,[2] the incorporation of a single carbon atom into molecular frameworks with simultaneous formation of four bonds provides a fascinating platform to enhance molecular complexity beyond aromatic compounds (Scheme 1(1)).[3–10] Wherein, single C(sp)-atom transfer reactions have been well-developed to construct alkynes and allenes, including several textbook reactions.[4] In contrast, single C(sp^2)- and C(sp^3)-atom transfer reactions are still largely underdeveloped due to the limited types of atomic carbon sources. With the development of novel atomic carbon sources from the Tobisu,[5] Hansmann,[6] Glorius[7] and Suero[8] groups, especially the carbene precursors, significant breakthrough has been made over the past few years

(Scheme 1(2)). For example, using N-heterocyclic carbene (NHC) and diazosulfur ylide (Ph$_2$S=C=N$_2$) reagents as single C(sp^3)-atomic sources, γ-lactams and highly strained carbon spirocenters were constructed by the Tobisu and Hansmann groups, respectively (Scheme 1(3)).[4,5] Shevlin and colleagues made seminal contributions to the development of C(sp^2)-atom transfer reactions with arc-discharge-generated carbon atoms and *tert*-butylbenzene systems.[9] However, the synthetic utility of this method remains limited due to its remarkably low efficiency (Scheme 1(4a)). In 2010, Baceiredo and Kato reported another example with mixed *P,S*-bis(ylide) as a carbon atom source, allowing the creation of vinyl phenyl sulfide in quantitative yield *via* sequential elimination of phosphine oxide and Ph$_2$S (Scheme 1(4b)).[10] Very recently, Glorius's group developed a new reagent, chloro-diazoacetyl diarylmethanone oxime (Cl-DADO), enabling access to C3-functionalized quinolines *via* stepwise Rh-catalyzed carbyne insertion/functionalization of the oxime ester (Scheme 1(4c)).[7] Despite these advances, further exploration of novel single-carbon-atom transfer reaction remains highly desirable yet challenging.

Commercially available TMSCF$_2$Br presents an attractive yet underexploited reagent, offering triple functionality as a TMSCF$_2$ radical donor, a difluorocarbene precursor and an atomic carbon equivalent (Scheme 1(5)).[11] While the efficacy of the first two variants has been empirically validated,[12] its implementation potential in single-carbon-atom transfer reactions remains elusive.[13] Concurrently, *para*-quinone methides (*p*-QMs) have gained prominence as versatile synthons due to

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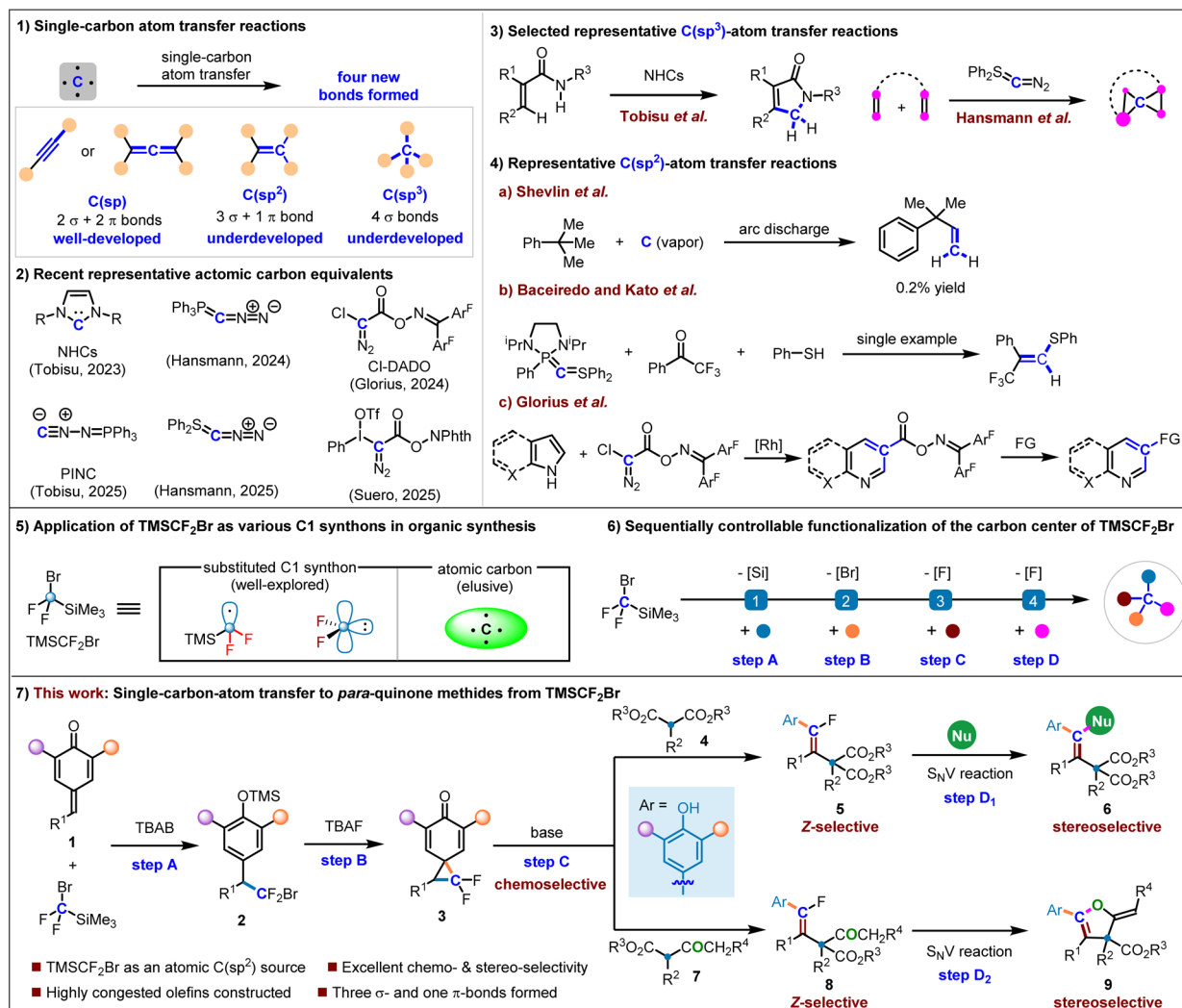
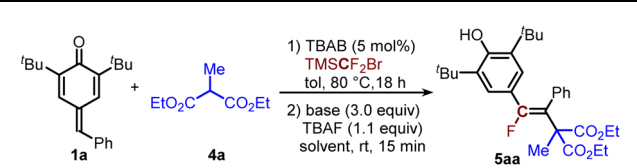**Scheme 1** The chemistry of single-carbon atom transfer reaction.

their inherent aromaticity-driven reactivity, particularly in 1,6-addition cascades.[14] We envisioned that merging the *p*-QMs' reactivity with TMSCF₂Br's latent single atomic carbon-donating capability would provide unprecedented opportunities for advancing single-carbon-atom transfer reactions. Several challenges are apparent for this transformation: (1) functionalization of TMSCF₂Br in a sequentially controllable manner is essential to generate single atomic carbon doped products in synthetically useful yields (Scheme 1(6)). (2) The regioselectivity of the ring-opening of 1,1-difluoro-spiro[2.5] octa-4,7-dien-6-one **3** is not clear for different nucleophiles (Scheme 1(7)). (3) It is challenging to construct the highly congested tetra-substituted olefins **5**, **6** and **8**. (4) The control of the stereoselectivities for the formation of fully substituted olefin **6** and the chemoselectivities for the intramolecular SₙV reaction of intermediate **8** to generate **9** is another challenge.[15] With our continuing interest in the construction of stereodefined alkenes and the chemistry of *p*-QMs,[16] we herein report a skeleton editing of *p*-QMs *via* a single-carbon atom transfer reaction, enabling the stereoselective construction of sterically hindered

tetra-substituted fluoroalkenes and 2-methylene-2,3-dihydrofurans. The fluoroalkenes could serve as a platform to undergo diversity-oriented synthesis, giving sterically hindered tetra-substituted alkenes *via* a formal SₙV reaction with good retention of the olefinic configuration. The *exo*-alkene motif of 2-methylene-2,3-dihydrofurans could undergo a series of late-stage transformations to enrich the structural diversity of the products. Of note is that the TMSCF₂Br works as an atomic sp²-hybridized carbon.

Results and discussion

To probe our hypothesis, we initiated our studies with *para*-quinone methide **1a** and diethyl 2-methylmalonate **4a** as the model substrates to construct fluoroalkene **5aa**. Substrate **1a** was first treated with TBAB in the presence of TMSCF₂Br in toluene at 80 °C for 18 h,[17] followed by the addition of TBAF, **4a** and ᵗBuOK in THF. The tetra-substituted fluoroalkene **5aa** was isolated in 42% yield with >20 : 1 *Z*-selectivity (Table 1, entry 1). Screening of bases indicated that the base had a great impact on

Table 1 Optimization of reaction conditions (steps A–C)^{a,b,c}

Entry	Base	Solvent	Yield (%)	Z/E
1	^{t}BuOK	THF	42	>20 : 1
2	K_2CO_3	THF	ND	—
3	$KHCO_3$	THF	ND	—
4	$PhCO_2Na$	THF	Trace	—
5	NaH	THF	75	>20 : 1
6	NaH	MTBE	Trace	—
7	NaH	DMF	38	>20 : 1
8	NaH	MeCN	36	>20 : 1
9	NaH	Toluene	33	>20 : 1
10	NaH	DCM	ND	—
11^d	NaH	THF	87	>20 : 1
12^e	NaH	THF	68	>20 : 1

^{a} Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), TMSCF$_2$Br (2.0 equiv.), TBAB (5 mol%) and toluene (1.0 mL) in a sealed tube, 80 °C, 18 h, then **4a** (1.0 mmol, 2.0 equiv.), TBAF (1.1 equiv.) and base (1.1 equiv.) in solvent (2.0 mL) was added. The reaction mixture was stirred at rt for 15 minutes. ^{b} Isolated yields. ^{c} The Z/E ratio was determined by ^{1}H NMR. ^{d} 0.4 equiv. of TBAF was used. ^{e} 0.2 equiv. of TBAF was used.

the yield (entries 2–5). While the yield of **5aa** could be further promoted to 75% in the presence of NaH, only trace product was detected when PhCO$_2$Na was used; no product was detected using K$_2$CO$_3$ or KHCO$_3$. Subsequent solvent optimization (entries 6–10) failed to improve outcomes. The yield of **5aa** could be further improved to 87% after reducing the loading of TBAF to 0.4 equivalent (entry 11). Further decreasing the equivalent of TBAF did not improve the yield of **5aa** (entry 12).

With the optimized conditions for the steps A-C established, we next evaluated the substrate scope of p-QMs and substituted malonates. As shown in Table 2a, p-QMs containing various electron-withdrawing or electron-donating groups at the para-, meta- or ortho-position of the phenyl ring are suitable substrates for this transformation, producing **5ba–5ia** in 51–82% yields. Substrates bearing multiple substituents on the phenyl ring were also amenable to this reaction, and products **5ja** and **5ka** were isolated in 69% and 71% yields, respectively. When the tert-butyl groups were replaced with isopropyl groups, **5la** was obtained in 76% yield. When unsymmetrical para-quinone methide **1m** was used, the corresponding product **5ma** was isolated in 80% yield. Diethyl 2-methylmalonate containing a phenyl or allyl group at the C2-position is also a suitable substrates for this transformation, delivering **5ab** and **5ac** in 52% yields. When dimethyl 2-methylmalonate was used, the product **5ad** could be obtained in 70% yield. All transformations proceeded with exceptional stereocontrol (>20 : 1 Z-selectivity), underscoring the robustness of this platform for constructing congested alkenes. To complete the C(sp^2)-atomic transfer reaction, **5aa** was further subjected to intermolecular functionalization with various nucleophiles, aiming to enrich the

complexity and diversity of tetra-substituted alkenes (Table 2b, step D). Generally, in the presence of ^{t}BuOK, various O-, N-, P-, and C-nucleophiles could participate in intermolecular nucleophilic vinylic substitution (S$_N$V) reactions[18] under mild conditions, giving **6a–6e** in 70–86% yields with 13–20:1 Z-selectivity and **6f** in 66% yield with > 20:1 E-selectivity. In addition, as a proof of concept, this reaction was run in one pot, and the corresponding product **6b** was isolated in 60% yield with > 20:1 Z-selectivity (Table 2c).

Encouraged by the above-mentioned single-carbon-atom transfer to p-QMs from TMSCF$_2$Br with two different nucleophiles via stepwise functionalization, we next turned our attention to bisnucleophiles to examine the ability of this single-carbon-atom transfer reaction to construct cyclic compounds. First, ethyl 2-methyl-3-oxobutanoate **7a** was tested. It's noteworthy that **7a** contains three potential nucleophilic sites, and the chemoselectivity for the intramolecular S$_N$V reaction of **8aa** is another challenge. Under our previous standard conditions, the intramolecular O-substituted S$_N$V product **9aa** was successfully obtained in 17% yield, accompanied by the formation of **8aa** in 47% yield, while the intramolecular C-substituted S$_N$V product **9aa'** was not detected (Scheme 2(1)). At this stage, initiating condition screening with compound **2a** as the precursor presented an enhanced efficiency profile for subsequent development. To our delight, the yield of **8aa** could be further improved to 79% with ^{t}BuOK as the base (Scheme 2(2), see the ESI† for details of the condition screening).

Dihydrofuran skeletons and derivatives are important skeletons widely found in natural products and bioactive molecules (Scheme 2(3)).[19] For example, Tunicamycin V is an N-glycosylation inhibitor, and has been used as a pharmacological inducer of endoplasmic reticulum (ER) stress.[19f] Acortatarins A and B are two spirocyclic alkaloids that significantly inhibit reactive oxygen species production in high-glucose-stimulated mesangial cells.[19g] In this context, we further explored the substrate scope of p-QMs for the construction of 2-methylene-2,3-dihydrofurans via single-carbon-atom transfer reactions. As shown in Table 3, substrates **2** containing various electron-donating groups and electron-withdrawing groups at the ortho-, meta- and para-positions are all compatible with this reaction, delivering products **9ab–9am** in 46–82% yields. When the R^1 group was a heterocycle such as indole and thiophene, the corresponding products **9an** and **9ao** were obtained in moderate yields. Cyclopropyl (R^1) substituted p-QM could also deliver **9ap** in 42% yield accompanied by some unknown byproducts detected. Other alkyl groups such as cyclohexyl, phenylethyl could not give the corresponding products (not shown in Table 3). The unsymmetric p-QM derived adduct **2q** generated **9aq** smoothly in 64% yield. When the reaction was run on a 4 mmol scale, the product **9aa** could still be isolated in 75% yield (1.34 g) without loss of efficiency.

Next, the scope of substituted acetoacetic esters was examined. As shown in Table 4, acetoacetic esters containing various alkyl groups at the C2-position were all compatible with this reaction, giving products **9ba–9da** in 45–83% yields. Notably, the generation of some uncertain byproducts led to a moderate yield for product **9ca** while the conversion of **2a** was complete.
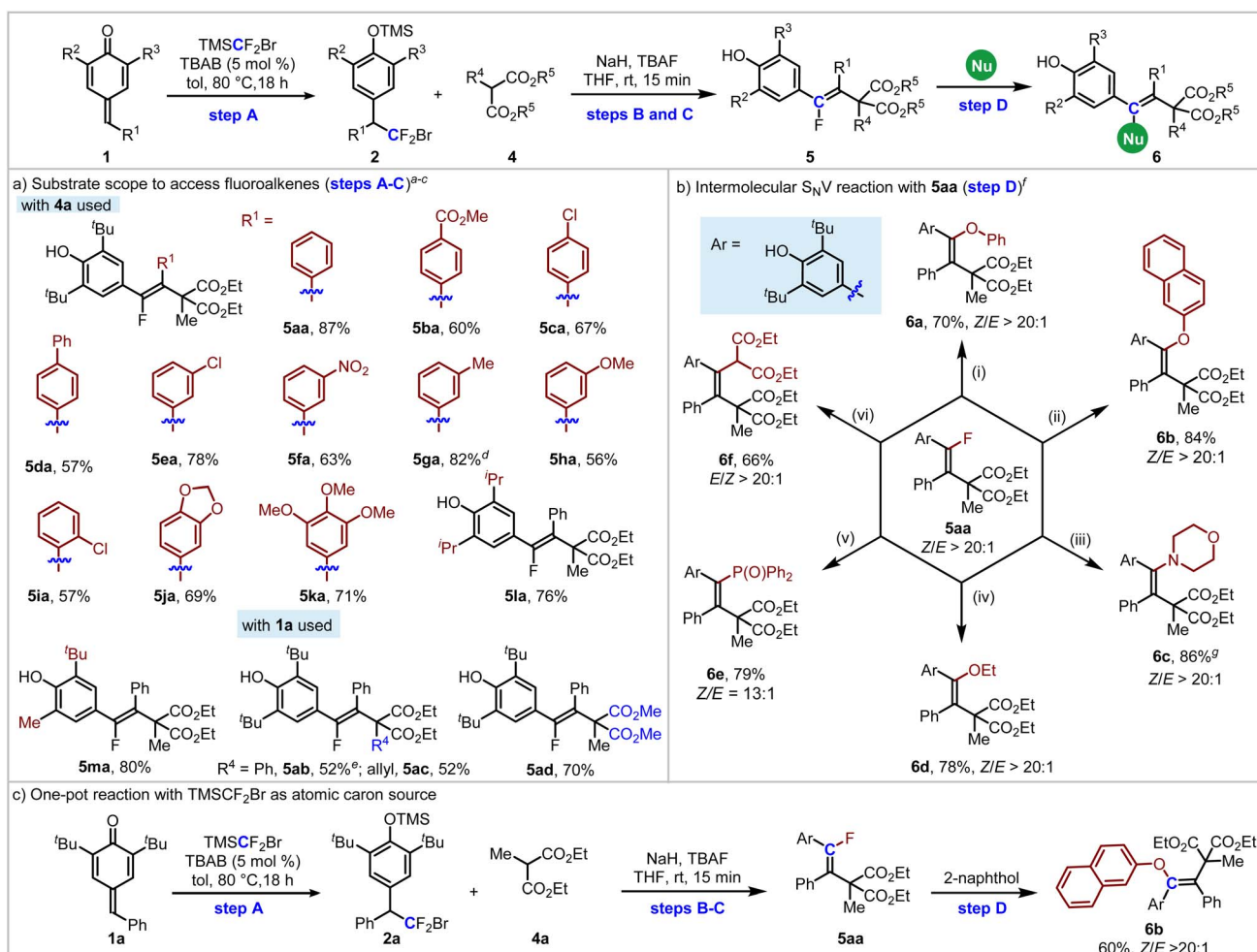
Table 2 Single-carbon-atom transfer to *p*-QMs from TMSCF$_2$Br with two different nucleophiles[a,b,c]

a) Substrate scope to access fluoroalkenes (steps A–C)[a–c]

with **4a** used

5aa, 87%
5ba, 60%
5ca, 67%
5da, 57%
5ea, 78%
5fa, 63%
5ga, 82%[d]
5ha, 56%
5ia, 57%
5ja, 69%
5ka, 71%
5la, 76%

with **1a** used

5ma, 80%
R^4 = Ph, **5ab**, 52%[e]; allyl, **5ac**, 52%
5ad, 70%

b) Intermolecular S$_N$V reaction with **5aa** (step D)[f]

6a, 70%, Z/E > 20:1
6b, 84% Z/E > 20:1
6c, 86%[g] Z/E > 20:1
6d, 78%, Z/E > 20:1
6e, 79% Z/E = 13:1
6f, 66% E/Z > 20:1
5aa Z/E > 20:1

c) One-pot reaction with TMSCF$_2$Br as atomic caron source

1a → **2a** → **5aa** → **6b**, 60%, Z/E >20:1

[a] **1** (0.5 mmol, 1.0 equiv.), TMSCF$_2$Br (1.0 mmol, 2.0 equiv.), TBAB (5 mol%) and toluene (1.0 mL) in a sealed tube, 80 °C, 18 h, and then **4** (1.0 mmol, 2.0 equiv.), TBAF (0.4 equiv.) and NaH (3.0 equiv.) were added. The reaction mixture was stirred at rt for 15 minutes. [b] Isolated yields. [c] The Z/E ratio was determined by ^{1}H NMR. [d] The reaction time for steps B and C was further prolonged to 30 min. [e] NaH (5.0 equiv.) was used. [f] Nucleophiles (0.4 mmol, 2.0 equiv.), **5aa** (0.2 mmol, 1.0 equiv.) and ^{t}Bu (4.0 equiv.) in DCM were stirred at rt to 60 °C for 12 h. [g] K$_3$PO$_4$ (0.4 mmol, 2.0 equiv.) and DMF were used.

(1) **1a** → **2a** → **3a** → **8aa**, 47% yield → **9aa**, 17% yield (O-sub.) / **9aa'**, ND (C-sub.)

(2) **2a** + **7a** → 1) ^{t}BuOK, 30 min 2) TBAF, 15 min → **9aa**, 79% yield

Challenges:
♦ Three potential nucleophilic sites of **7a**
♦ Chemoselectivities for the intramolecular S$_N$V reaction (O-substitution vs Me-substitution)

(3) Selected natural products, bioactive molecules containing dihydrofuran and derivatives

tunicamycin V
R = H, **acortatarin A**; R = OH, **acortatarin B**
(-)-funebral
chromophore
antibacterial agent

Scheme 2 Single-carbon-atom transfer to *p*-QMs from TMSCF$_2$Br with bisnucleophile **7a**.

Table 3 Substrate scope of *p*-QMs with bisnucleophile **7a**[a,b]
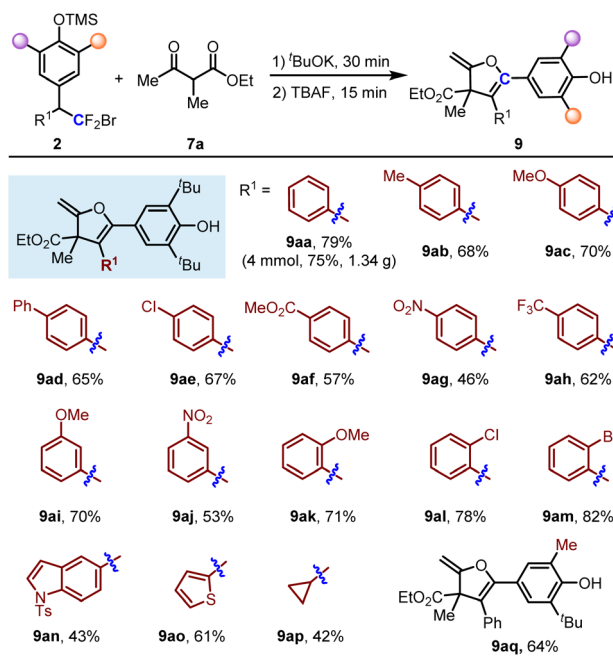
[a] Reaction conditions: **2** (0.2 mmol, 1.0 equiv.), **7a** (0.4 mmol, 2.0 equiv.), TBAF (0.08 mmol, 0.4 equiv.) and [t]BuOK (0.8 mmol, 4.0 equiv.) in DCM at 60 °C. [b] Isolated yield.
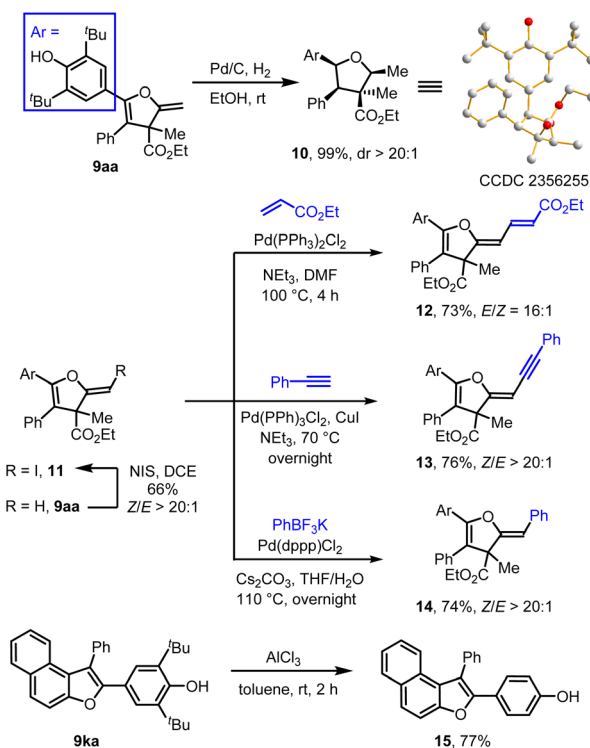
Table 4 Substrate scope of bisnucleophile with **2a**[a,b]
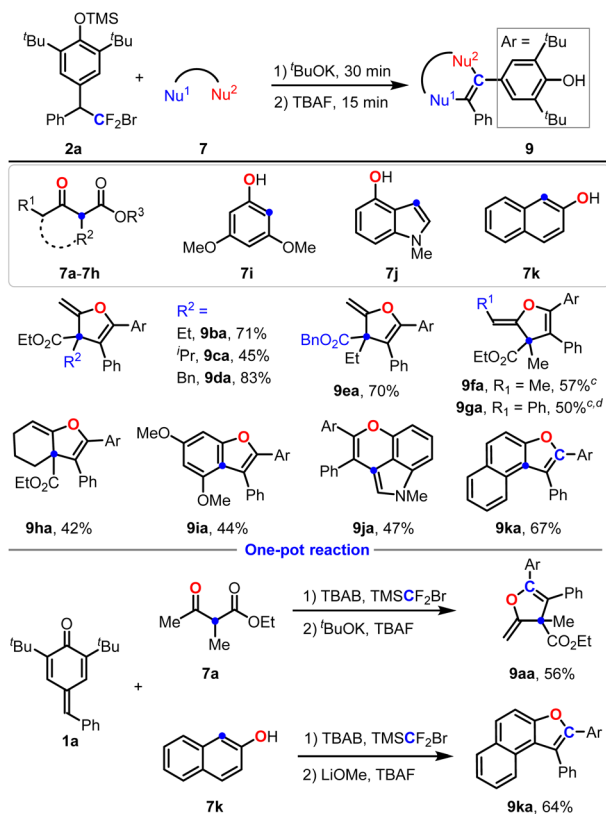
[a] Reaction conditions: **2a** (0.2 mmol, 1.0 equiv.), **7** (0.4 mmol, 2.0 equiv.), TBAF (0.08 mmol, 0.4 equiv.) and [t]BuOK (0.8 mmol, 4.0 equiv.) in DCM at 60 °C. [b] Isolated yield. [c] The *Z/E* ratio (>20 : 1) was determined by ^{1}H NMR. [d] Room temperature.

Switching the R^3 group from an ethyl group to a benzyl group could still deliver product **9ea** in 70% yield. Intriguingly, introducing an alkyl or aryl group at the α-position of the ketone (R^1 = Me or Ph) could also afford the cyclic products **9fa** and **9ga** in moderate yields with excellent *Z*-selectivities. Ethyl 2-oxocyclohexane-1-carboxylate **7h** could also deliver the corresponding product **7ha** in 42% yield. Next, electron-rich phenolic substrates **7i–7k** were tested, generating **9ia–9ka** in 44–67% yields. Again, a one pot reaction was performed to probe the efficacy of this single-carbon-atom transfer reaction, giving **9aa** in 56% yield and **9ka** in 64% yield.

To demonstrate the synthetic utility of this single-carbon-atom transfer reaction, a series of transformations of the products were conducted. As shown in Scheme 3, Pd/C-catalyzed hydrogenation of 2-methylene-2,3-dihydrofuran **9aa** proceeded smoothly, and the product **10** containing four contiguous chiral centres was isolated in 99% yield with > 20 : 1 dr. The relative configuration of **10** was determined by X-ray analysis. In the presence of *N*-iodosuccinimide (NIS), the terminal alkene **9aa** was iodinated to afford **11** in 66% yield with > 20 : 1 *Z*-selectivity. The vinyl iodide motif of compound **11** provided a handle for further functionalization, enriching the structural diversity of 2-methylene-2,3-dihydrofurans. For example, vinyl iodide could participate to a series of palladium-catalyzed stereoretentive cross-coupling reactions, including Heck, Sonogashira and Suzuki reaction, generating products **12–14** in 73–76% yields. The *tert*-butyl groups of **9ka** were removed *via* AlCl₃-catalyzed retro-Friedel–Crafts alkylation, yielding product **15** in 77% yield.

To gain insight into the reaction mechanism, a control experiment was conducted. As shown in Scheme 4(a), vinyl fluoride **8aa** could be converted to **9aa** smoothly in 96% yield in the presence of KO*t*Bu, while no cyclic product **17** could be detected when compound **16** was used. Collectively, these results suggest that **8aa** serves as the intermediate for the cyclic process and the hydroxyl group is essential for the intramolecular S_NV reaction. Combined with previous studies,[16g,17] a plausible mechanism for the formation of 2-methylene-2,3-dihydrofuran **9aa** was proposed as shown in Scheme 4(b). In the presence of TBAF, **2a** could be transformed to spiro **INT-I** *via* sequential desilylation/cyclization. Then the enolate **II** generated from **7a** and basic KO*t*Bu underwent regioselective nucleophilic substitution with **INT-I** to give **INT-III**. Dearomatization of **INT-III** *via* the elimination of fluoride and base promoted enolization generated **INT-IV**, which then underwent intramolecular 1,6-addition to yield **INT-V**. Phenolic anion or enol ether assisted elimination of the fluoride anion from **INT-V** would give **INT-VI-1(2)**, and then proton transfer (P.T.) would produce the product **9aa**. To probe the origin of the regioselectivity for the ring-opening step of **INT-I**, a computational study was conducted. As shown in Scheme 4(c), the computational study of **INT-I** showed that the C₂–C₃ bond possesses the smallest bond order in the cyclopropane unit.[20] In other words, the C₂–C₃ bond is the weakest bond in the cyclopropane unit.

Scheme 3 Transformations of the products.
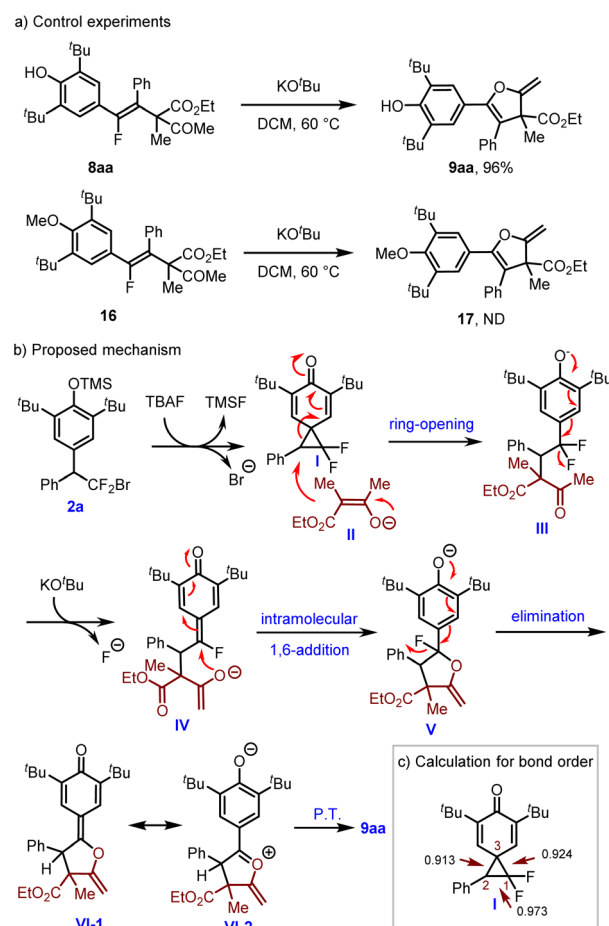
Scheme 4 Control experiment and the proposed mechanism.

Conclusions

In summary, we have developed a single-carbon atom transfer reaction of the alkene motifs of *p*-QMs. In the presence of a nucleophile such as malonic acid ester, tetra-substituted fluoroalkenes were constructed with excellent stereoselectivities. The fluoroalkenes could further react with another nucleophile *via* formal $S_N V$ reaction to generate highly congested tetra-substituted olefins with good to excellent stereoselectivities. When 1,3-bisnucleophiles were used, cyclic products such as 2-methylene-2,3-dihydrofurans were obtained with excellent chemo- and stereo-selectivities. Sequentially controllable functionalization of $TMSCF_2Br$ enables it to act as an atomic carbon equivalent. More importantly, this reaction features with mild conditions, a broad substrate scope and the ability to enable diversity-directed synthesis. Further applications of $TMSCF_2Br$ as an atomic carbon source are currently ongoing in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI,† including detailed experimental procedures and characterization data for new compounds. Crystallographic data have been deposited with the CCDC with deposition numbers 2356255 (10).

Author contributions

H. Y. and S. G. directed the project and revised the manuscript. R. S. and P. Z. performed the experiments, and analysed and interpreted the results; they contributed equally to this work. Y. Y., J. Z., Q. C. and C. Y. were involved in the preparation of the substrates. X. L. performed the computational studies. C. Y. and A. L. revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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