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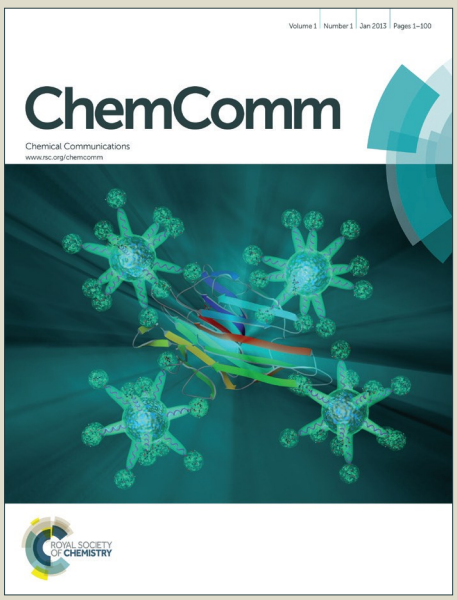

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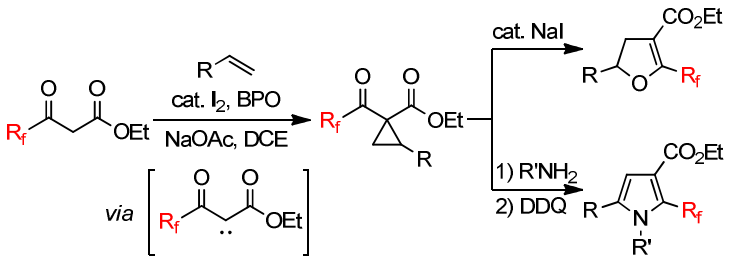
ABSTRACT

An efficient transition metal-free approach for the generation of acceptor/acceptor-carbene followed by trapping with alkenes to provide fluoroacetyl cyclopropanes has been described. The resulted cyclopropanes could be further converted into the fluoromethyl dihydrofurans or fluorodihydropyrroles through ring-expansion process.



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Transition Metal-Free Generation of the Acceptor/Acceptor-Carbene *via* α-Elimination: Synthesis of Fluoroacetyl Cyclopropanes†

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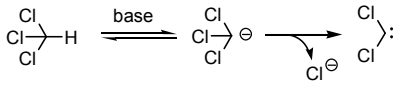
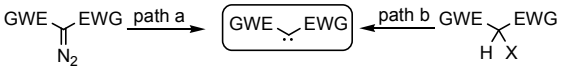
An efficient transition metal-free approach for the generation of acceptor/acceptor-carbene followed by trapping with alkenes to provide fluoroacetyl cyclopropanes has been described. The resulted cyclopropanes could be further converted into the fluoromethyl dihydrofurans or fluorodihydropyrroles through ring-expansion process.

Carbene chemistry has experienced tremendous growth in the past decades.[1] There are numerous ways for the generation of carbenes or carbenoids. Among them, α-elimination is one of the most important routes to generate carbenes.[2] In the α-elimination, both proton and leaving group are attached to the same carbon atom. This method is particularly useful in the synthesis of dihalocarbene (Scheme 1).[2a,3]



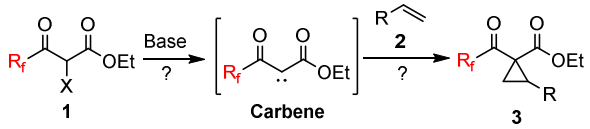
Scheme 1. α-Elimination for the Synthesis of Halocarbene.

Acceptor/acceptor carbene is very useful in the synthesis of functional cyclopropane, furan and pyrrole derivatives.[4] Decomposition of the corresponding diazo-compound is the common method to generate these carbene species.[1,4] However, such method generally suffered from potentially dangerous starting material (Scheme 2, path a). We anticipated that these important acceptor/acceptor carbenes might be generated through α-elimination from the corresponding halogenated precursors as well (Scheme 2, path b).



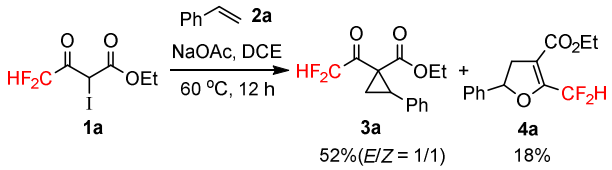
Scheme 2. Generation of Acceptor/acceptor Carbene.

It's well known that the introduction of fluorine atom(s) into organic molecules allows the simultaneous modulation of electronic, lipophilic, and steric parameters, all of which can profoundly influence both the physical and biological properties due to the unique physical properties of the fluorine atom.[5] Cyclopropane derivatives are a unique class of compounds with fundamental importance of being the smallest all-carbon cyclic molecules as well as having practical significance as recurring units in numerous natural products and as valuable synthons for many chemical transformations.[6] We then envisioned that fluorinated cyclopropane derivatives **3** might be synthesized through α-elimination of the halogen-precursor **1** (Scheme 3).



Scheme 3. Synthesis of Fluoroacetyl Cyclopropane Derivatives through α-Elimination.

As iodine having the best leaving ability among four halogen atoms, 2-iodo-difluoroacetyl ethyl acetate **1a** was then initially used as model substrate to test the above hypothesis (Scheme 4). When the reaction was conducted in DCE at 60 °C for 12 h with NaOAc as base, the desired product **3a** could be formed in 52% yield, accompanied with 18% dihydrofuran **4a**.



Scheme 4. The Reaction of 2-Iodo-difluoroacetyl Ethyl Acetate with Styrene.

Although 2-iodo-difluoroacetyl ethyl acetate **1a** could be used as efficient carbene source through α-elimination, however, compound **1a** is unstable to light and heat. It decomposed slowly even in the refrigerator in dark. For this reason, we then turned our

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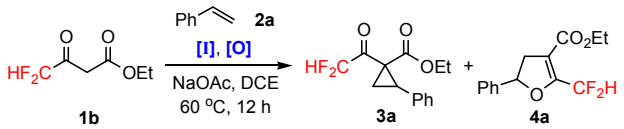
attention to generate 2-iodo-difluoroacetyl ethyl acetate **1a** *in situ*. Ethyl 4,4-difluoro-3-oxobutanoate **1b** was then used as model substrate to investigated various iodinating conditions (Table 1). When 1.0 equiv. of I_2 was used as iodinating reagent for this transformation, neither cyclopropane **3a** nor dihydrofuran **4a** could be detected (Table 1, entry 1). Presumably because the sole I_2 was not a good iodinating reagent. It is well known that I_2/oxidant or I^-/oxidant was the most commonly used iodinating reagent.[7] Furthermore, iodine ion would be regenerated in every catalytic cycle; and catalytic amount of iodine source (I_2 or I^-) should be enough for this transformation. Therefore, three different oxidants, TBPB (*tert*-butyl peroxybenzoate), TBHP (*tert*-butyl hydroperoxide), and BPO (benzoyl peroxide), were then investigated for the combination of I_2/oxidant to tested for this reaction (entries 2-4). When I_2/TBPB and I_2/TBHP were applied for this system, the desired product **3a** could be detected in 37% and 31% yields, respectively (entries 2-3). Gratifyingly, the combination of I_2/BPO significantly enhanced the yield of **3a** (entry 4, 82%). Interestingly, no dihydrofuran **4a** was detected for the I_2/oxidant system. The reaction did not occur without addition of NaOAc. KI and NIS were proved to be inferior iodine source for this reaction, giving the yield in 67% and 16%, respectively (entries 6-7).

Table 1. Optimization of Reaction Conditions.[a]

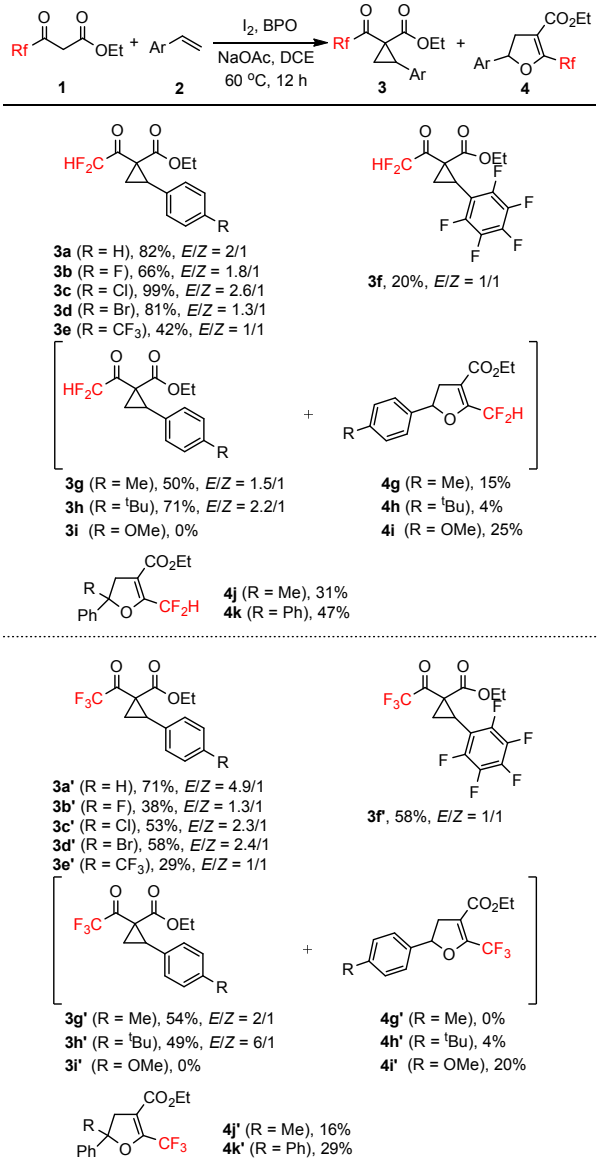


Entry	[I]	[O]	Yield[b]	
			3a (*E*/*Z*)[c]	**4a**
1	I_2 (100 mol%)	-	-	-
2	I_2 (10 mol%)	TBPB (1.5 eq.)	37% (1/2)	-
3	I_2 (10 mol%)	TBHP (1.5 eq.)	31% (5/1)	-
4	I_2 (10 mol%)	BPO (1.5 eq.)	82% (1.8/1)[d]	-
5[e]	I_2 (10 mol%)	BPO (1.5 eq.)	-	-
6	KI (20 mol%)	BPO (1.5 eq.)	67% (1.8/1)	trace
7	NIS (10 mol%)	BPO (1.5 eq.)	16% (1.8/1)	-

[a] The reaction was set using **1b** (0.5 mmol), styrene **2a** (1.0 mmol), NaOAc (0.5 mmol), DCE (2.0 mL), TBPB: *tert*-butyl peroxybenzoate, TBHP: *tert*-Butyl hydroperoxide, BPO: benzoyl peroxide; [b] The yields were determined by ^{19}F NMR with $PhCF_3$ as internal standard; [c] *E*/*Z* ratio were determined by ^{19}F NMR; [d] Isolated yield; [e] Without NaOAc.

With the best conditions in hand (Table 1, entry 4), the substrate scope was then examined. As summarized in Table 2, the base-promoted cyclopropanation process could be successfully applied to a variety of styrene derivative **2**. The reaction was sensitive to the electronic properties of the styrene derivatives. For example, styrene derivatives substituted with electron-withdrawing groups on the phenyl ring could be selectively converted into the desired cycloproanes (**3b**-**3f**), without detecting the side product dihydrofuran **4**. Those substrates with strong electron-withdrawing group, 4-trifluoromethyl styrene and 2,3,4,5,6-pentafluoro styrene, giving the corresponding product **3e** and **3f** in much lower yields. In contrast, when styrene derivatives substituted with alkyl groups (methyl or *t*-butyl) were used as substrates, mixture products of cyclopropane (**3g**, **3h**) and dihydrofurans (**4g**, **4h**) could be obtained. 4-MeO-styrene transferred to dihydrofuran **4i** solely in 25% yield. Similarly, both α-methyl styrene and α-phenyl styrene furnished the dihydrofurans products as well, with the yields being 31% and 47%, respectively. In addition to ethyl 4,4-difluoro-3-oxobutanoate **1b**, ethyl 4,4,4-trifluoro-3-oxobutanoate **1c** could be used as the carbene source for this reaction as well, providing trifluoroacetyl substituted **3'** and dihydrofuran **4'**. As shown in Table 2, it has the similar products selectivities with the difluoro

Table 2. Substrate Scopes[a]



[a] The reaction was set using **1** (0.5 mmol), **2** (1.0 mmol), I_2 (0.05 mmol), BPO (0.75 mmol), NaOAc (0.5 mmol), DCE (2.0 mL); Isolated yield.

counterpart. For example, electron-neutral or electron-deficient styrene derivatives selectively led to the cyclopropanes (**3a'**-**3g'**). Electron-rich or disubstituted styrenes preferred the formation of dihydrofuran (**4i'**-**4k'**).

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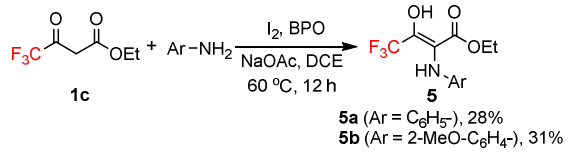
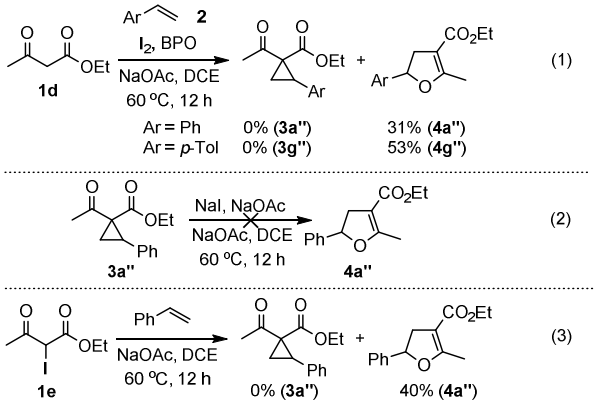
In addition to the cyclopropanation reaction, N-H insertion, which presents another carbene-transfer reaction, was also tested for this system. For example, when aromatic amine was subjected to the same reaction conditions with ethyl 4,4,4-trifluoro-3-oxobutanoate **1c** as carbene source, the desired N-H insertion products **5** could be produced, albeit in only about 30% yields (Scheme 5).



[a] **1a** (0.25 mmol), DCE (1.0 mL).

Scheme 5. Iodine-promoted Amination.[a]

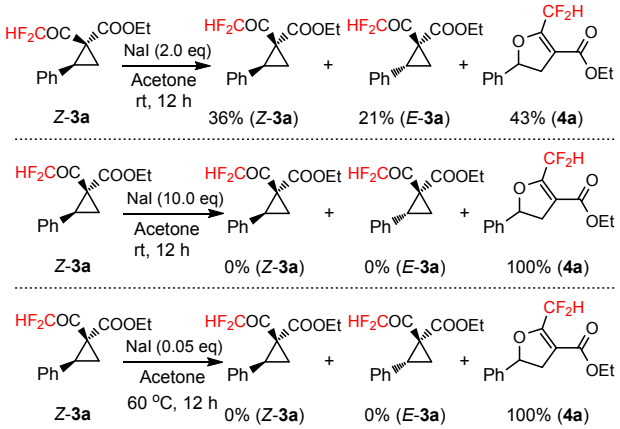
Interestingly, when non-fluorinated substrate, ethyl acetoacetate **1d**, was subjected to the same cyclopropanation reaction conditions, only dihydrofurans **4"** were formed instead in moderated yields (Scheme 6, eq. 1). The control reaction showed **3a"** could not be transferred to dihydrofuran **4a"** (eq. 2). Furthermore, the reaction of 2-iodo-acetyl ethyl acetate **1e** and styrene furnished dihydrofurans **4a"** (eq. 3). These results indicated that non-fluorinated substrate **1d** might undergo the carbene-involved [3+2]-cycloaddition reaction,[8] not the cyclopropanation reaction.



[a] The reaction was set using **1d** (0.5 mmol), **2** (1.0 mmol), I_2 (0.05 mmol), BPO (0.75 mmol), NaOAc (0.5 mmol), DCE (2.0 mL); Isolated yield; Cyclopropane **3a"** in eq. 2 was prepared following published literature procedure.[9]

Scheme 6. The Reaction of Non-fluorinated Substrate.[a]

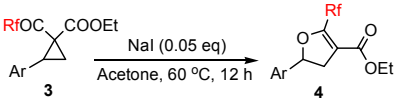
Different from nonfluorinated cyclopropane **3a"**, fluoroacetyl cyclopropane **3** could be easily converted into the corresponding dihydrofuran **4** under the catalysis of iodide ion. As shown in Scheme 7, cyclopropane *Z*-**3a** could be converted into mixtures of cyclopropanes *Z*-**3a** (36%), *E*-**3a** (21%), and dihydrofuran **4a** (43%) in the presence of 2.0 equiv. of NaI in acetone for 12 h. Increase the amount of NaI to 10.0 equivalents, cyclopropane *Z*-**3a** was completely converted into dihydrofuran **4a**. Actually, when the temperature was elevated to 60 °C, only 5 mol% NaI could catalyzed the transformation of cyclopropane *Z*-**3a** into dihydrofuran **4a** (Scheme 7) within 12 h.

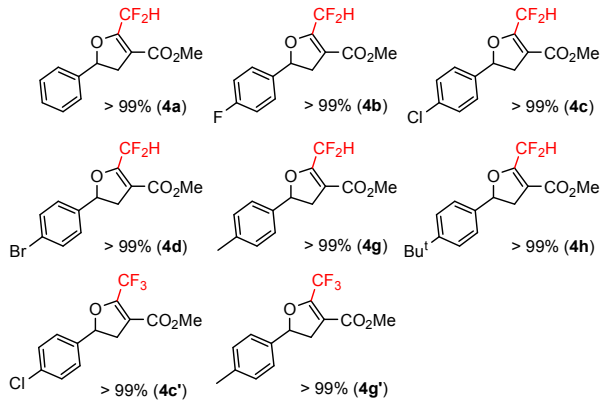


[a] **3** (0.25 mmol), acetone (1.0 mL). NMR yield.

Scheme 7. Iodine-promoted Isomerization of Cyclopropane.[a]

Such iodide-catalyzed ring expansion process is very efficient for different substrates. As shown in Scheme 8, all cyclopropanes **3** were coverted into the corresponding dihydrofurans **4** in quantitive yields within 12 h at 60 °C.





[a] **3** (0.25 mmol), acetone (1.0 mL).

Scheme 8. Scope for the Iodine-promoted Isomerization of Cyclopropane.[a]

To further demonstrate the applicability of this iodine catalysis system, we then explored the further chemical transformations of fluoroacetyl cyclopropane **3**. Pyrrole is an important class of heterocycle that is widely distributed in various natural products and biologically important molecules.[10] Similar to dihydrofuran, it is supposed that fluorodihydropyrrole would be formed when amine was added in the ring expansion process. Followed by the addition of oxidants would provide the corresponding fluoropyrrole derivatives. Interestingly, dihydrofuran **4** could not be oxidized into the corresponding furan by DDQ, presumably due to the unique fluorine effects. As shown in Scheme 9, such ring expansion/ oxidation process was very efficient for both aliphatic and aromatic amines. It is interesting to note that a mixture of the desired difluoromethyl pyrrole **6a** and aldehyde **6a'** were formed when

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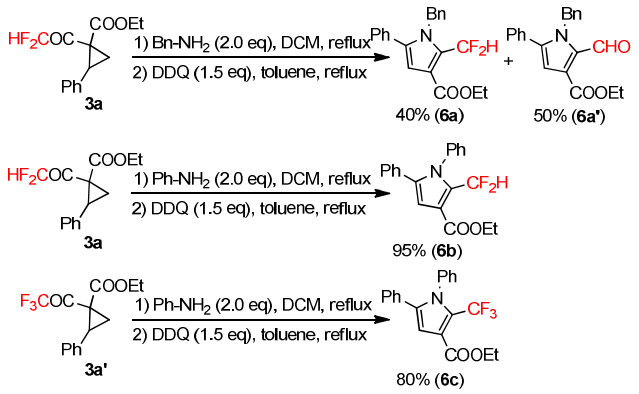
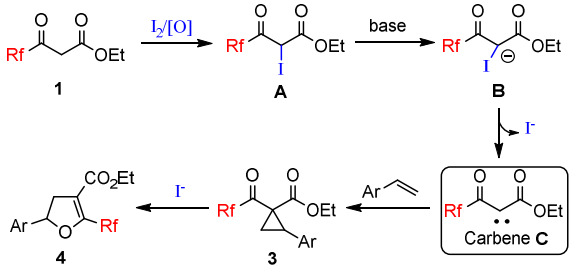
$BnNH_2$ was used as nitrogen source. Aromatic amine, $PhNH_2$, could furnish the desired pyrroles **6b** and **6c** in excellent yields when reacted with fluoroacetyl cyclopropanes **3a** and **3a'**.



Scheme 9. Further Transformations of Cyclopropanes

A tentative reaction mechanism for this iodine-promoted cyclopropanation reaction was then proposed in Scheme 10. Initially fluoroacetyl acetate **1** was converted into 2-iodo-fluoroacetyl acetate **A** under the conditions of I_2/oxidant. In the presence of base, 2-iodo-fluoroacetyl acetate **A** underwent α-elimination to lead free carbene intermediate **C**, which then was cyclopropanated with aromatic alkenes to lead the corresponding cyclopropane **3**. The control reactions indicated that iodide ion (I^-) could promote the transformation of cyclopropane **3** into dihydrofuran **4**.



Scheme 10. Proposed Reaction Mechanism.

In conclusion, we have developed a mild iodine-catalyzed and transition metal-free method to generate acceptor/ acceptor-carbene *via* base-promoted α-elimination of 2-iodo-fluoroacetyl acetate, which was generated *in situ* from fluoroacetyl acetate **1** with I_2/oxidant. The control reactions revealed that iodide ion could promote the transformation of cyclopropane **3** into fluoromethyl dihydrofuran **4** efficiently. Furthermore, the product fluoroacetyl cyclopropane **3** could be further converted into fluoromethyl pyrrole **6** through the ring-expansion with amine and followed by oxidation with DDQ. We believed such process would provide some useful insights for the carbene chemistry. Furthermore, owing to the excellent substrate scopes and mild reaction conditions, this transition metal-free system may hold considerable potential for the construction of useful heterocylic molecules. Investigations on the detailed reaction mechanism, and additional applications of this reaction are underway in our laboratory.

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedure, spectral data, and copies of the NMR spectra of products. See DOI: 10.1039/c0ccxxxxxx

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