Carbodefluorination via a carbene-initiated rearrangement strategy

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Abstract

The C–F bond cleavage and C–C bond formation (i.e., carbodefluorination) of readily accessible (per)fluoroalkyl groups constitutes an atom-economical and efficient route to partially fluorinated compounds. However, the selective mono-carbodefluorination of trifluoromethyl (CF_3) groups remains a formidable challenge, due to the notorious inertness of C–F bond and the risk of over-defluorination arising from C–F bond strength decrease as the defluorination proceeds. Herein, we report a carbene-initiated rearrangement strategy for the carbodefluorination of fluoroalkyl ketones with β,γ-unsaturated alcohols. The reaction starts with formation of a silver carbene from a fluoroalkyl ketone *N*-triftosylhydrazone, followed by nucleophilic addition of a β,γ-unsaturated alcohol to form a key oxonium ylide intermediate, which triggers selective C–F bond cleavage by HF elimination and C–C bond formation through Claisen rearrangement of *in situ* generated difluorovinyl ether. This method described here is versatile and enables the conversion of fluoroalkyl ketones into skeletally and functionally diverse α-mono- and α,α-difluoro-γ,δ-unsaturated ketones. The reaction mechanism and the origin of chemoselectivity were established by experimental and computational approaches. Collectively, current strategy integrates successive C–F bond cleavage and C–C bond formation on a single molecule entity by an intramolecular cascade process, thereby offering significant advances over existing stepwise strategies in term of selectivity, efficiency, functional group tolerance, etc.

Introduction

The construction of C–C bonds is fundamental to the art of organic synthesis as it provides access to the backbone of organic molecules, including pharmaceuticals, agrochemicals, and functional materials[1-5]. The development of new methods, that are advantageous in terms of selectivity, availability and affordability of starting materials, functional group tolerance, and environmental sustainability is a constant focus of organic chemistry. Among numerous C–C bond-forming reactions, dehalogenative cross-coupling reactions have long been regarded as the most reliable and efficient tactics for assembling carbon scaffolds [6-9]. However, in contrast to other C–X bonds (X = Cl, Br, I), the cleavage of a C–F bond and formation of a new C–C bond (so-called carbodefluorination) remain a formidable challenge in modern organic chemistry, especially in readily accessible trifluoromethyl (CF_3) groups[10-16]. The main challenge with this respect is the notorious inertness of C–F bonds, accompanied by a decrease in bond dissociation energy (BDE) as defluorination takes place[17], which often results in undesired over-defluorination (Fig. 1a)[10,18-20]. In this context, great efforts have been invested in achieving selective mono-carbodefluorination of the CF_3 group, especially in CF_3-substituted arenes and alkenes through the generation of difluoro-substituted carbanion (by low-valent metal or electrochemical reduction)[21-25], carbocation (using strong Lewis acids)[26,27] or radical (using excited state photocatalysts) intermediates by either heterolytic or homolytic cleavage of a C–F bond[28-35], where the

in situ generated difluoromethylene reactive intermediates can be stabilized through p–π conjugation (Fig. 1b). While the acyl-CF_3 compounds (CF_3C=O) are most abundant and easily available, only two classes of selective mono-defluorinative C–C bond-forming reactions of acyl-CF_3 derivatives have been disclosed, namely: (i) copper or low-valent magnesium promoted defluorinative coupling of trifluoromethyl ketones with aldehydes or ketones[23,36-38]; and (ii) radical defluorinative coupling of acyl-CF_3 with alkenes by spin-center shift (SCS) or photocatalysis[28,34,35], which can be ascribed to the incompatibility between the conditions required for the generation of reactive intermediates and high reactivity of the C=O bond. Nevertheless, these approaches to the carbodefluorination of CF_3-arenes, -alkenes, and -acyl compounds generally require a stepwise mechanism via reactive difluoromethylene intermediates, such as carbanions, carbocations, or radicals, which can generally lower the extent of selectivity, efficiency, substrate scope, and functional group tolerance. Hence, the development of a new strategy enabling the integration of successive C–F bond cleavage and C–C bond formation into an intramolecular cascade process would offer significant advantages over existing stepwise strategies.

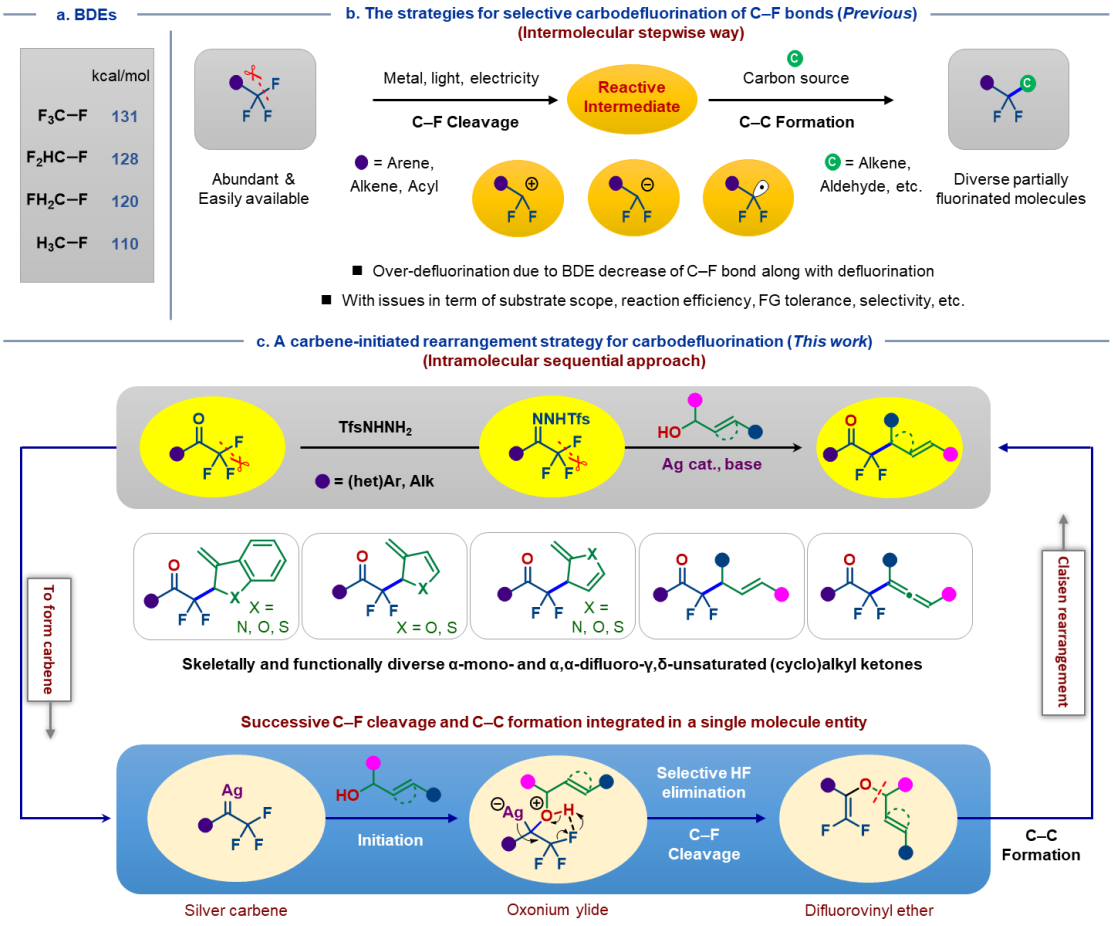


Fig. 1. Background and motivation for carbodefluorination of C–F bonds of trifluoromethyl groups.

Herein, we report a carbene-initiated rearrangement strategy for the carbodefluorination of fluoroalkyl ketones (Fig. 1c, up). Through the formation of *N*-sulfonylhydrazones, fluoroalkyl ketones have recently become versatile coupling partners, especially as a source of fluoroalkyl carbene in a range of C–C bond-forming reactions[39-47]. We envisaged that an intramolecular rearrangement strategy could provide an advantageous route for the efficient carbodefluorination of trifluoromethyl ketones, i.e., the formation of an oxonium ylide intermediate by nucleophilic addition of β,γ-unsaturated alcohols to a fluoroalkyl metal carbene might enable a sequential C–F bond cleavage / C–C bond formation through the Claisen rearrangement of an *in situ* generated difluorovinyl ether intermediate (Fig.

1c, bottom). We eventually implement this carbene-initiated rearrangement strategy for selective carbodefluorination of fluoroalkyl ketones through the reaction between their *N*-triftosylhydrazones and β,γ-unsaturated alcohols by silver catalysis. The scope of this transformation includes five-membered (benzo-fused)heteroaryl carbinols, allyl and propargyl alcohols, thus providing access to skeletally and functionally diverse α-mono- and α,α-difluoro-γ,δ-unsaturated (cyclo)alkyl ketones (Fig. 1c, middle). Therefore, this chemistry offers a modular and highly general platform for selective mono-carbodefluorination of a wide variety of fluoroalkyl ketones.

Results and discussion

Transition-metal-catalyzed dearomative functionalization of (hetero)aromatics has recently emerged as a powerful method to access aliphatic cyclic compounds[48-54]. Dearomative functionalization of indoles to generate valuable indolines is particularly interesting due to the frequent occurrence of the latter substructures in natural products and other alkaloids[49]. Despite many advances, the formation of new carbon-carbon bonds via defluorinative dearomatization of indoles remains elusive[48,50,51]. The chemical inertness of the C–F bond, and the energetic barrier associated with the disruption of aromaticity are the main factors that prevent the success of the approach via indole defluorinative dearomatization. At the outset, we choose trifluoromethyl ketone-derived *N*-sulfonylhydrazones as diazo surrogates to verify the planned reaction hypothesis, with indole-3-carbinols serving as the nucleophile. A survey of various combinations of different fluoroalkyl *N*-sulfonylhydrazones, metal catalysts, solvents and temperature revealed that a mixture of phenyl trifluoromethyl ketone *N*-triftosylhydrazone (**1a**), indole-3-carbinol (**2aa**), K_2CO_3 (2.0 equiv) and $Tp^{Br3}Ag$ (10 mol%) in toluene at 80 °C achieved the desired defluorinative [3,3]-rearrangement product (**3**) in 84% yield (Fig. 2). With these optimized conditions in hand, we sought to examine the scope of this defluorinative dearomatization reaction with respect to various indole-3-carbinols. As shown in Fig. 2, all the primary indole-3-carbinols that were investigated afforded the desired rearrangement products **3**–**12** in high yield, regardless of the position and electronic effect of the substituents. A range of secondary indole-3-carbinols was also suitable for this reaction, forming 2-difluoroacylated indolines (**13**–**18**) in moderate to good yield with excellent stereoselectivity (*E/Z* up to >20:1). Again, the substitution patterns of the C2-substituted indoles did not affect significantly the reaction outcomes (**19–22**). This strategy thus provides a new opportunity for the construction of non-aromatic *N*-heterocycles containing a quaternary carbon center, which is the key precursor for the synthesis of polycyclic complex molecules[53-55]. Variation of the *N*-protecting group on the indole-3-carbinol was also well tolerated, including aryl and alkyl *N*-sulfonyl (**23–30**), *N*-Boc (**31**), *N*-Cbz (**32**) and *N*-acetyl (**33**) groups. In addition to indole-3-carbinols, indole-2-carbinols could also be employed without difficulty in this transformation, affording the corresponding products featuring an enamine motif (**34–38**), which are difficult to access with conventional methods[56,57]. Regarding the scope of *N*-triftosylhydrazones, an array of substrates reacted smoothly with indole-3-carbinol, affording the corresponding products (**39–56**) in high yield. Functional groups such as methyl (**39, 40**), *tert*-butyl (**41**), methoxy (**42, 53**), trifluoromethoxy (**43**), phenyl (**44**), halogen (**45–48, 51, 52**), trifluoromethyl (**49**), and vinyl (**50**) were well tolerated. The use of indole-2-carbinol in the reaction with a *p*-Br-phenyl trifluoromethyl ketone *N*-triftosylhydrazone also gave a similar reaction outcome (**57**).

We were pleased to find that a wide array of other heteroaryl carbinols are also suitable for this dearomatizing rearrangement. In addition to benzofurans and benzothiophenes, a variety of heterocyclic rings with a greater degree of aromaticity such as pyrrole, furan, and thiophene carbinols underwent the defluorinative dearomatization with phenyl trifluoromethyl *N*-triftosylhydrazone to generate the corresponding α,α-difluoro-γ,δ-unsaturated alkyl ketone products (**58–85**) in moderate to excellent yield, with good functional group tolerance. The formation of a quaternary center on a fused-ring furan (**80**) is particularly notable in view of the congested nature of this system. Collectively, these results demonstrate the first dearomative carbodefluorination of C(sp3)–F bonds, which constitutes a powerful method for the synthesis of a wide range of α-heterocyclic fluoroalkyl ketones.

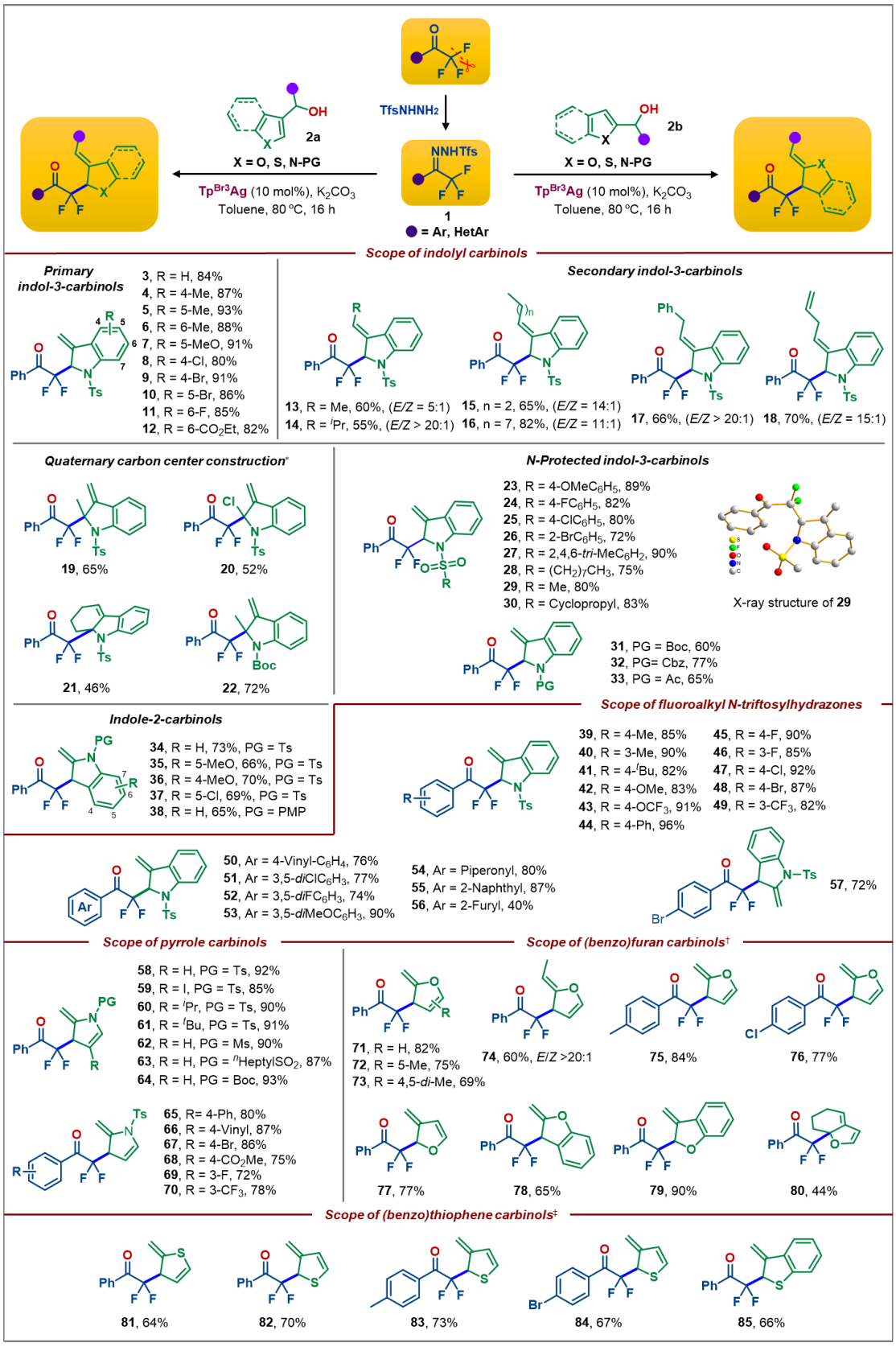
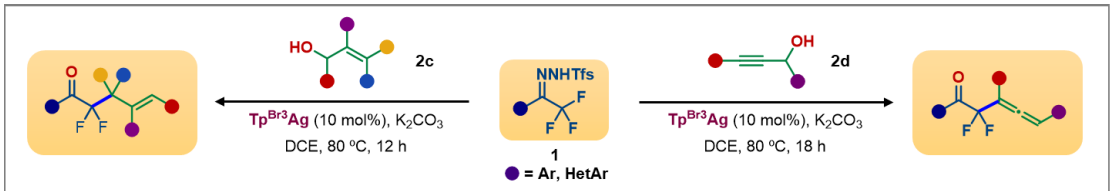


Fig. 2. Scope of defluorinative dearomatization of indole carbinols with fluoroalkyl *N*-triftosylhydrazones. Reaction conditions: all reactions were carried out with **1** (0.3 mmol, 1.0 equiv), **2a** or **2b** (0.6 mmol, 2.0 equiv), K_2CO_3 (0.6 mmol, 2 equiv) and $Tp^{Br3}Ag$ (10 mol%) in toluene (4 mL) at 80 °C for 16 h. ∗Reaction were carried out

at 80 °C for 8 h, then 120 °C for 24 h. †DCM was used instead of toluene. ‡Cs_2CO_3 was used instead of K_2CO_3 under 100 °C. All yield refers to isolated yield.

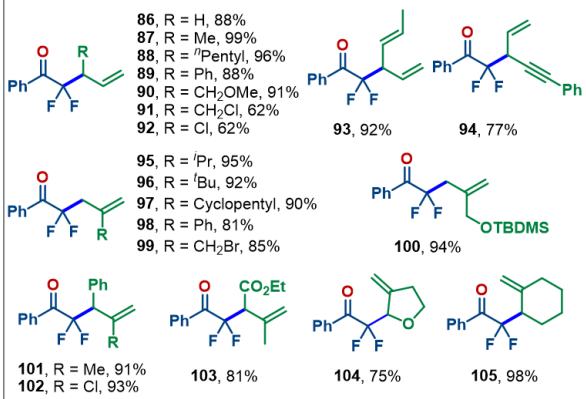
Having established a strategy for the highly selective defluorinative functionalization of C–F bonds in the acyl CF_3 group with heteroaromatic carbinols, we speculated whether the scope of this transformation could be expanded to other β,γ-unsaturated alcohols. In the event, this chemistry indeed proved suitable for application with these other substrates, with optimization of the carbodefluorination reaction between **1a** and allyl alcohol (**2c**) summarized in Supplementary Table S2 and Table S3. Under these optimized conditions (Fig. 3), a broad range of 1,1- and 1,2-disubstituted primary allyl alcohols bearing different (cyclo)alkyl and aryl substituents were found to give good to excellent yield of the desired products (**86–100**). Functionalities such as halogens (**91**, **92**, **99**), alkene (**93**) and alkyne (**94**) motifs remain intact, allowing for further derivatizations. Trisubstituted allyl alcohols possessing styryl (**101**), alkenyl chloride (**102**), alkenyl ester (**103**), and (hetero)cyclic alkene (**104**, **105**) also performed well. Similar to primary allyl alcohols, secondary alcohols bearing functionalities such as cycloalkyl (**106**, **115**), phenyl (**107**), ester (**108**), piperidine (**109**), alkenyl (**110**, **113**), allyl ether (**111**), ketal (**112**) and methyl (**114**, **117**) groups at the α-position were suitable for this transformation, affording a range of disubstituted homoallylic α,α-difluoroketones (**106–117**) in 53–94% yield. α,α-Difluoro-γ,δ-enones with a fluoroalkyl all-carbon quaternary center could be prepared (**118–122**) in moderate to excellent yield using 1,1-disubstituted allyl alcohols; such α-difluoroalkyl quaternary carbons, which cannot be easily prepared by conventional methods[58,59]. This protocol was also applicable for the late-stage modification of natural products, such as myrtenol (**123**), geraniol (**124**) and insect repellent cyclocitral (**125**) with high selectivity and high yield.

The propargylic Claisen rearrangement is a powerful method for the synthesis of allenes[60-62]. With this in mind, we next examined the carbodefluorination of trifluoromethyl ketones with propargyl alcohols, with a view to accessing difluoroalkyl-subsituted allenes, which are gaining importance in drug discovery. We were delighted to find that a variety of propargyl alcohols provided the desired α-CF_2 allenyl products in good yield and selectivity (**126**–**154**). To our knowledge, this is the first example of selective C–F allenylation of CF_3 groups[10–16]. This chemistry proved most effective using propargyl alcohol itself, which exhibited high reactivity and gave the desired product (**126**) in near quantitative yield. However, also both acylic (linear or branched) and cycloalkyl-substituted propargyl alcohols smoothly afforded the corresponding allenes in 78–97% yield (**127**–**130**). Pleasingly, propargyl alcohols bearing phenyl (**131**), naphthyl (**132**), thienyl (**133**), TMS (**134**) and halogen (**135, 136**) groups on the alkyne terminus proved suitable substrates, providing the corresponding products in good yield in almost all cases. TMS, Cl or Br functionalities could be retained in the products, which allows for further orthogonal functionalization of the thus obtained products. Alkyl propargyl alcohols containing various functionalities on the alkyl sidechain, such as phenyl (**137**), chloro (**138**), ether (**139**), ester (**140**), pyran (**141**), alkenyl (**142**), and alkynyl (**143**) groups, were all amenable in this reaction. Notably, the free alkenyl and alkynyl units in **142** and **143** were untouched, which demonstrates the high selectivity of the alcohol hydroxyl (-OH) group toward metal carbene trapping to form the proposed intermediate oxonium ylides[42]. Polyfunctionalized allenes were found to be hard to prepare by existing methods[62-66]. Furthermore, a cyclohexene-conjugated difluoroalkyl allene (**144**), a useful synthon in cycloaddition reaction to access polycyclic fluorinated molecules, was also obtained in 80% yield from the corresponding enyne. Secondary propargyl alcohols proved to be similarly suitable substrates, providing diverse disubstituted and trisubstituted allenes (**145**–**152**). Notably, this strategy enables access to structures bearing pharmaceutically relevant sidechains, such as floramelon (**153**) and citronellal (**154**).



Scope of allyl alcohols

Primary allyl alcohols



86, R = H, 88%
87, R = Me, 99%
88, R = ^{n}Pentyl, 96%
89, R = Ph, 88%
90, R = CH_2OMe, 91%
91, R = CH_2Cl, 62%
92, R = Cl, 62%

93, 92%

94, 77%

95, R = ^{i}Pr, 95%
96, R = ^{t}Bu, 92%
97, R = Cyclopentyl, 90%
98, R = Ph, 81%
99, R = CH_2Br, 85%

100, 94%

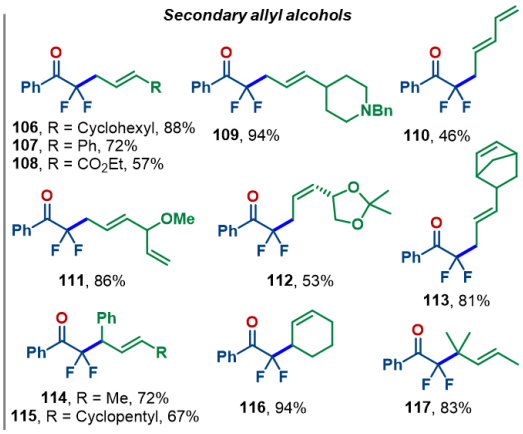
101, R = Me, 91%
102, R = Cl, 93%

103, 81%

104, 75%

105, 98%

Secondary allyl alcohols



106, R = Cyclohexyl, 88%
107, R = Ph, 72%
108, R = CO_2Et, 57%

109, 94%

110, 46%

111, 86%

112, 53%

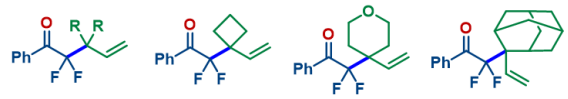
113, 81%

114, R = Me, 72%
115, R = Cyclopentyl, 67%

116, 94%

117, 83%

Quaternary carbon center construction



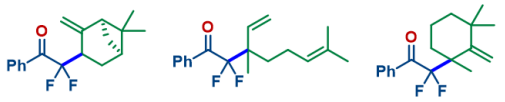
118, R = Me, 98%
119, R = Ph, 53%

120, 95%

121, 94%

122, 96%

Late stage modification of bioactive molecules

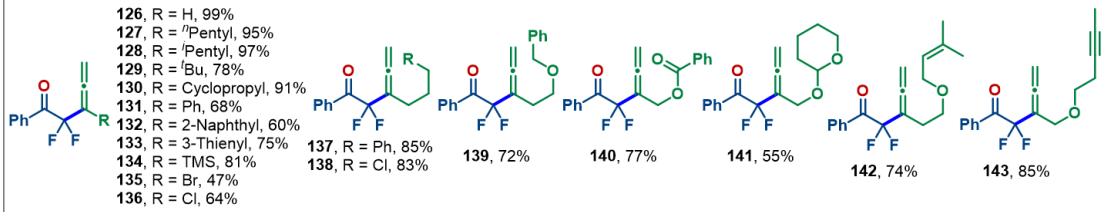


123, 99%
from Myrtenol

124, 81%
from Geraniol

125, 98%
from Cyclocitral

Scope of propargyl alcohols



126, R = H, 99%
127, R = ^{n}Pentyl, 95%
128, R = ^{i}Pentyl, 97%
129, R = ^{t}Bu, 78%
130, R = Cyclopropyl, 91%
131, R = Ph, 68%
132, R = 2-Naphthyl, 60%
133, R = 3-Thienyl, 75%
134, R = TMS, 81%
135, R = Br, 47%
136, R = Cl, 64%

137, R = Ph, 85%
138, R = Cl, 83%

139, 72%

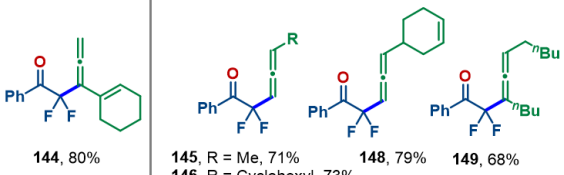
140, 77%

141, 55%

142, 74%

143, 85%

Secondary propargyl alcohols



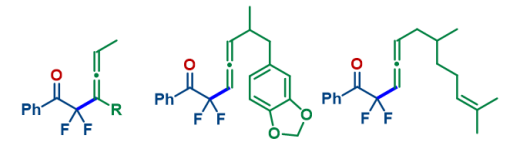
144, 80%

145, R = Me, 71%
146, R = Cyclohexyl, 73%
147, R = Phenylethyl, 81%

148, 79%

149, 68%

Late stage modification of bioactive molecules



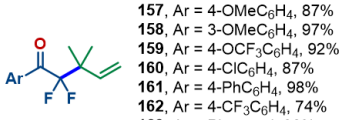
150, R = TMS, 81%
151, R = *p*-Tolyl, 83%
152, R = 3-Thienyl, 52%

153, 54%, dr = 5:1
from *Floramelon*

154, 75%, dr > 20:1
from *Citronellal*

Scope of N-triftosylhydrazones

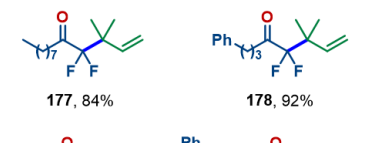
Aryl-N-triftosylhydrazones



155, Ar = 4-MeC_6H_4, 99%
156, Ar = 4-^{t}BuC_6H_4, 83%
157, Ar = 4-$OMeC_6H_4$, 87%
158, Ar = 3-$OMeC_6H_4$, 97%
159, Ar = 4-$OCF_3C_6H_4$, 92%
160, Ar = 4-ClC_6H_4, 87%
161, Ar = 4-PhC_6H_4, 98%
162, Ar = 4-$CF_3C_6H_4$, 74%
163, Ar = Piperonyl, 96%
164, Ar = Naphthyl, 90%
165, Ar = 2-Furyl, 48%

166, Ar = 4-MeC_6H_4, 95%
167, Ar = 3-MeC_6H_4, 97%
168, Ar = 3-$OMeC_6H_4$, 98%
169, Ar = 4-$OCF_3C_6H_4$, 93%
170, Ar = 3-FC_6H_4, 97%
171, Ar = 4-BrC_6H_4, 96%
172, Ar = 4-$CF_3C_6H_4$, 89%
173, Ar = 2,4-*di*ClC_6H_3, 93%
174, Ar = 2-Naphthyl, 91%
175, Ar = 2-Fluorenyl, 94%
176, Ar = Piperonyl, 90%

Alkyl-N-triftosylhydrazones[a]



177, 84%

178, 92%

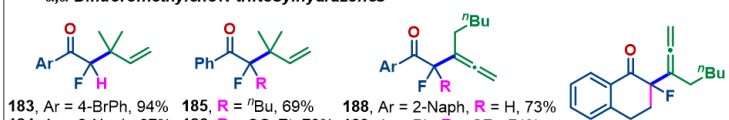
179, 78%

180, 62%

181, 51%

182, 47%

α,α-Difluoromethylene N-triftosylhydrazones



183, Ar = 4-BrPh, 94%
184, Ar = 2-Naph, 87%

185, R = ^{n}Bu, 69%
186, R = CO_2Et, 70%
187, R = CF_3, 92%

188, Ar = 2-Naph, R = H, 73%
189, Ar = Ph, R = CF_3, 71%
190, Ar = Ph, R = CO_2Et, 60%

191, 61%

Fig. 3. **Scope of Defluorinative Allylation.** Reaction conditions: all reactions were carried out with **1** (0.3 mmol, 1.0 equiv), **2c**/**2d** (0.6 mmol, 2.0 equiv), K_2CO_3 (0.6 mmol, 2 equiv) and $Tp^{Br3}Ag$ (10 mol%) in 1,2-dichloroethane (DCE) (4 mL) at 80 °C. Isolated yields. ***1** (0.3 mmol, 1.0 equiv), **2** (0.6 mmol, 2.0 equiv), *N*,*N*-diisopropylethylamine (DIPEA) (0.6 mmol, 2 equiv) and $Rh_2(esp)_2$ (2 mol%) in DCE (4 mL) at 80 °C.

Finally, we turned our attention to fluoroalkyl ketone *N*-triftosylhydrazones. Both electron-withdrawing and -donating groups on the phenyl ring of the *N*-triftosylhydrazones showed little influence on the reaction outcome and in all instances the desired C–F allylated (**155–162**) and C–F allenylated (**166–173**) products were obtained in good to excellent yield. Piperonyl (**163, 176**), naphthyl (**164, 174**), furyl (**165**), and fluorenyl **(175**) *N*-triftosylhydrazones were also found to be suitable starting materials. We note that superior efficiency was observed using ($Rh_2(esp)_2$ as catalyst instead of $Tp^{Br3}Ag$ in the reaction of *N*-triftosylhydrazones derived from alkyl trifluoromethyl ketones (**177–182**). Remarkably, the reaction was not restricted to α-trifluoromethyl *N*-triftosylhydrazones. In fact, hydrazones derived from α,α-difluoromethyl (**183**, **184, 188**) and α,α-difluoropentyl (**185**) ketones, a α,α-difluoroketoester (**186, 190**) and a difluorocycloalkyl (**191**) ketone were also capable of undergoing this coupling / rearrangement reaction, providing unprecedented opportunities to access a broad array of chemical diversity under a single reactivity platform. In the case of pentafluoroethyl ketone-derived *N*-triftosylhydrazones, the α-C–F bond could be converted to the corresponding allylated (**187**) and allenylated products (**189**) in 92% and 71% yield, respectively, featuring α-fluoro-β-trifluoromethyl functionality.

The above results demonstrate that readily available α-fluoroalkyl ketones can be converted into a wide variety of valuable α,α-difluoro-γ,δ-unsaturated (cyclo)alkyl ketones with diverse substitution patterns through a silver carbene-initiated defluorination and rearrangement cascade of the corresponding sulfonyl hydrazones. Most of these compounds are newly synthesized and inaccessible by other conventional methods[67-69]. To test the scalability and practicality of this protocol, the gram-scale synthesis of **3**, **86**, and **127** were carried out with the standard set of conditions that we have developed, providing the corresponding products with synthetic efficiency equivalent to the smaller-scale reactions (Fig. 4). Given the importance of α,α-difluoroketones as privileged substructures in medicinal chemistry and the versatile reactivity of carbonyl, heterocyclic, vinyl, and allenyl moieties, these products could be easily transformed into a broad range of fluorinated building blocks of medicinal relevance. For example, the terminal alkene unit of dearomatization product **3** could be readily cyclopropanated with formyl or trifluoromethyl diazomethanes, affording the corresponding spiroindolines (**192**, **193**) in excellent yield. Furthermore, carbonyl reduction, alkene hydrogenation, alkene bromination, and carbonyl olefination of **3** were achieved with good efficiency (**194–197**), while combining olefination with aromatizing (3,3)-sigmatropic rearrangement offers an attractive entry to 1,1-difluoroalkene products (**198**). The selective nucleophilic *gem*-difluorination of the carbonyl group of **86** and **127** with DAST provided the corresponding tetrafluoro products (**199**, **204**) in 77% and 97% yield, respectively. Compounds **86** and **127** were readily reduced to alcohols in the presence of $NaBH_4$, which enabled monofluorination of products **200** and **205** with DAST to afford the trifluoroalkylated products **201** and **206** in high yield. These conversions enable the synthesis of products with tuneable multivicinal fluorination[70-72]. This platform is attractive for the site-specific introduction of fluorine in aliphatic chains. Notably, the secondary fluoroalkyl alcohol units in compounds **194**, **200**, and **215** are important motifs in bioactive molecules[73]. Carbonyl alkenylation of **86** and **127** gave the desired products **202** and **207** in 85% and 80% yield, respectively. Finally, the radical difunctionalization of olefins (**86**) and allenes (**127**) reliably provided products **203** (69% yield, dr = 5:4) and **208** (76%, stereoselectivity 2:1), respectively.

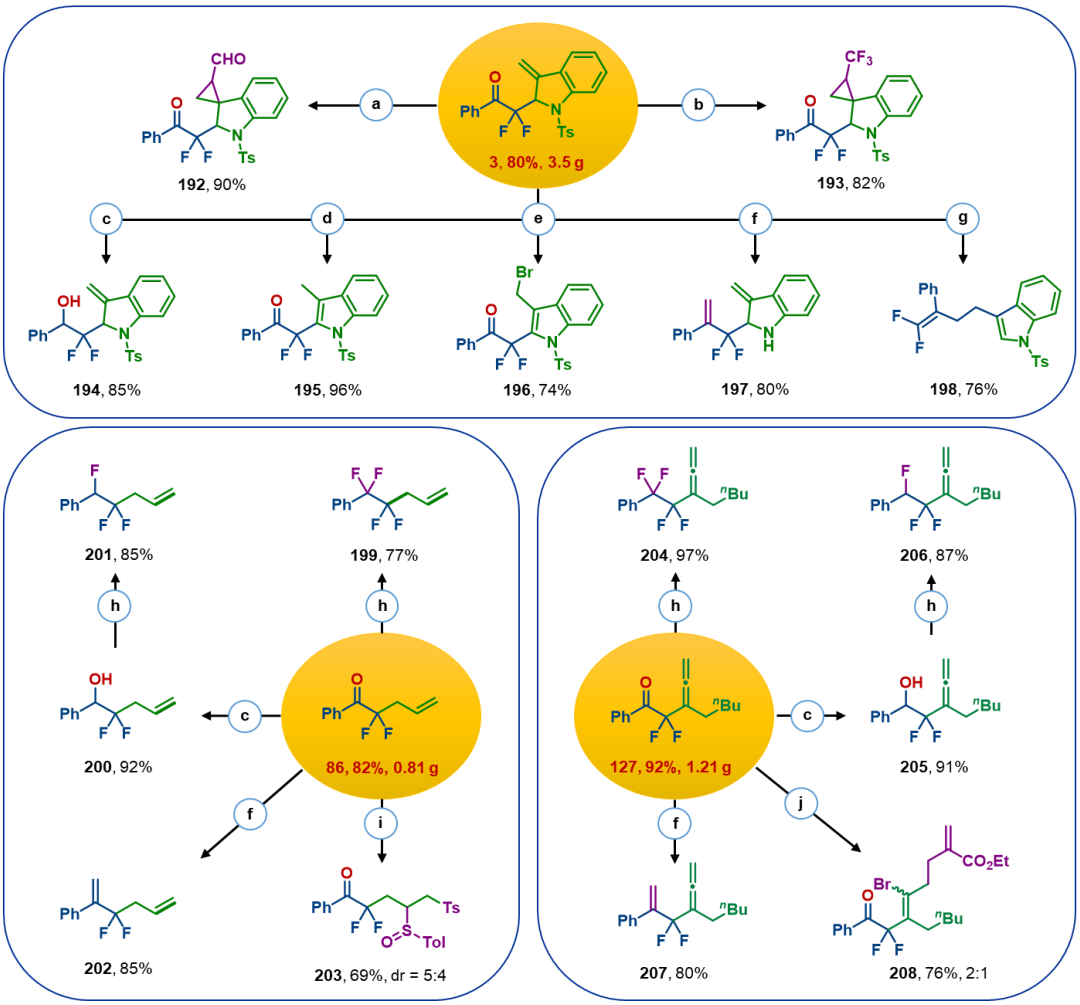


Fig. 4. **Gram-scale synthesis and further transformation.** Reaction conditions: a. **3** (0.2 mmol), DFHZ-Tfs (0.4 mmol), FeTPPCl (3 mol%), aqueous NaOH (5.0 wt%)/toluene, 60 °C; b. **3** (0.2 mmol), TFHZ-Tfs (0.4 mmol), FeTPPCl (3 mol%), K_2CO_3 (0.6 mmol), 1,4-dioxane (3 mL), 40 °C; c. **3**/**86**/**127** (0.2 mmol), $NaBH_4$ (0.24 mmol) in CH_3OH (2 mL) at 25 °C; d. NaI (0.32 mmol), TMSCl (0.32 mmol), H_2O (0.16 mmol), CH_3CN (2 mL), room temperature; e. **3** (0.3 mmol), NBS (1.1 equiv), DCM (2 mL), 0 °C ~ rt; f. **3**/**86**/**127** (0.2 mmol), Ph_3PCH_3Br (0.4 mmol), ^{t}BuOK (0.4 mmol), THF (2 mL), 25 °C; g. **3** (0.2 mmol), Ph_3PCH_3Br (0.3 mmol), ^{t}BuOK (0.3 mmol), THF (2 mL), 25 °C ~ 60 °C; h. **86**/**127**/**200**/**205** (0.2 mmol), DAST (0.2 mmol) in DCM (2 mL) at -78 °C ~ rt; i. **86** (0.2 mmol), $TolSO_2Na$ (1.8 mmol), CH_3COCl (1.2 mmol), $CHCl_3$ (2 mL), 10 °C; j. **127** (0.2 mmol), AIBN (0.04 mmol), ethyl bromomethacrylate (0.4 mmol), toluene (2 mL), 80 °C.

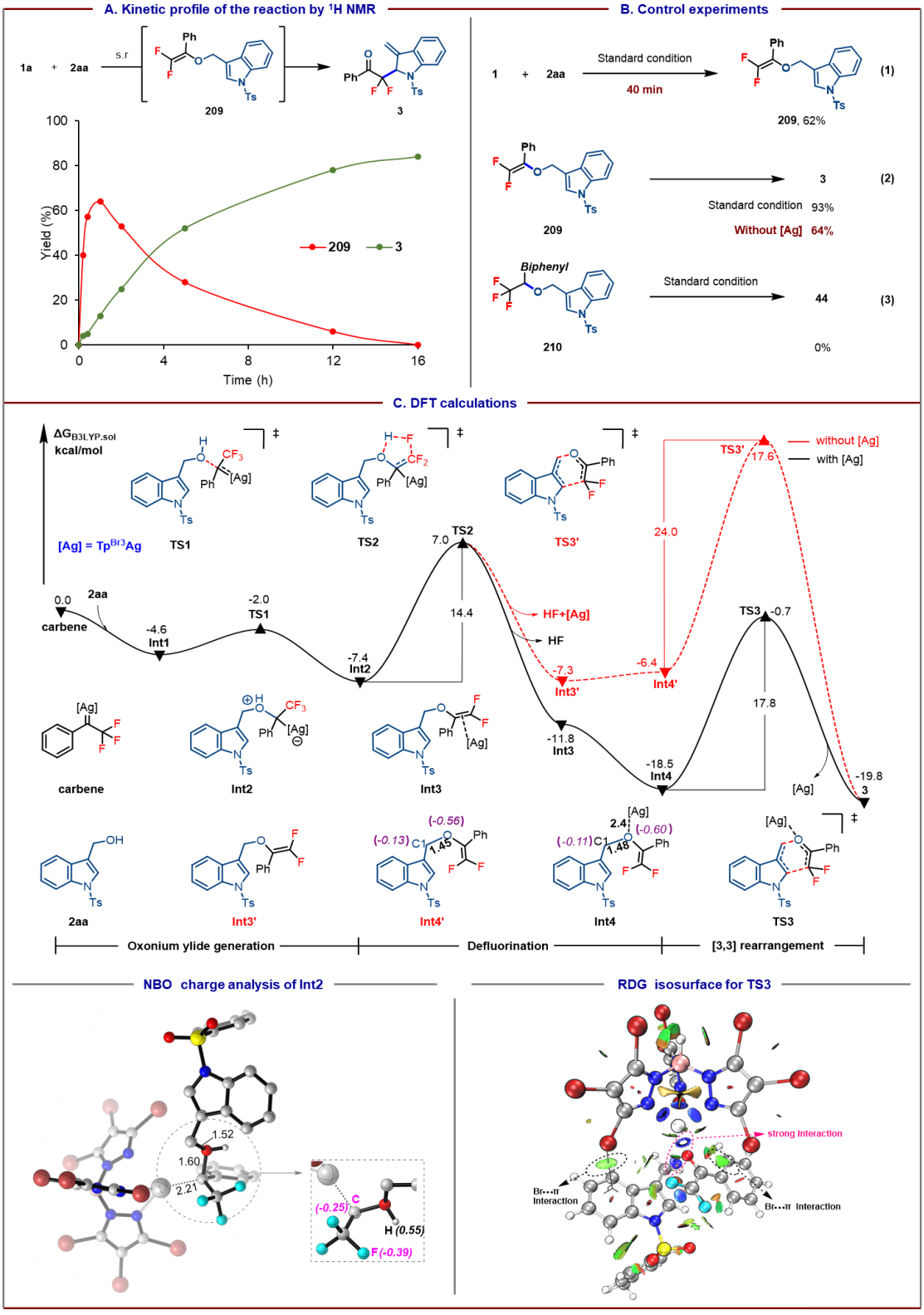


Fig. 5. (**A**) Reaction kinetics study; (**B**) Control experiments; (**C**) A plausible mechanism based on DFT-computed free-energy profile (ΔG, in kcal·mol^{-1}). Standard condition: **1a** (0.3 mmol, 1.0 equiv), **2aa** (0.6 mmol, 2.0 equiv), K_2CO_3 (0.6 mmol, 2 equiv) and $Tp^{Br3}Ag$ (10 mol%) in toluene (4 mL) at 80 °C.

Mechanistic experiments and computational studies were conducted to explore the mechanism of this cascade carbodefluorination process. The progress of the reaction depicted in Fig. 5a was first examined by ^{1}H NMR. This

showed initial formation of intermediate **209**, which reached maximum intensity within an hour. This was transformed to give product **3**, the latter being the near sole reaction component by 16 h. This result suggests that rapid *gem*-difluoroalkenylation is a critical step for the success of this reaction, with this reactive intermediate **209** readily undergoing Claisen rearrangement to afford the final product. Indeed, the subjection of isolated **209** (62% yield (after 40 min), Fig. 5b, eq. 1) to the reaction conditions resulted in 91% yield of product **3**, while the reaction of this intermediate in the absence of silver catalyst afforded **3** in 64% yield (Fig. 5b, eq. 2). These results suggest that the Ag catalyst plays a critical role not only in the formation of the difluoroalkene intermediate, but also in the rearrangement process. A control experiment showed that exposing pre-prepared ether **210** to the standard conditions failed to give the defluorinative rearrangement product **44** (Fig. 5b, eq. 3). This result excluded the possibility of forming an ether intermediate through O–H carbene insertion[74]. Overall, these results suggest that HF elimination to form a *gem*-difluorinated vinyl ether is more favorable than the 1,2-H transfer process of ylides to give an ether.

Density functional theory (DFT) calculations at the SMD(toluene)//B3LYP/6-31G(d,p)-SDD(Ag,Br) level of theory were carried out to rationalize the proposed pathway, with the reaction between **1a** and indole-3-carbinol **2aa** selected as a model. As summarized in Fig. 5c, this pathway involves onium ylide generation, C–F bond cleavage, and [3,3] rearrangement. Compound **1a** is known to undergoes easily a base-mediated decomposition to form a diazo species, which then reacts with $Tp^{Br3}Ag$ catalyst to give a silver carbene[44]. The energy barrier for generation of an oxonium ylide **Int2** by reaction of indole-3-carbinol with this silver carbene is low (2.6 kcal mol^{-1}). The NBO charge analysis of **Int2** shows the F atoms carry more negative charge than the carbene carbon atom, which facilitates abstraction of the hydroxyl proton to form HF. This occurs via a 5-membered ring transition state **TS2** to generate the *gem*-difluorovinyl ether intermediate **Int4** by single bond rotation of initially formed silver-associated *gem*-difluorovinyl ether intermediate **Int3**. Notably, the energy barrier for the HF elimination is lower ($\Delta\Delta G^{\ddagger}$ = 14.4 kcal mol^{-1}) than proton transfer to form an O–H insertion product ($\Delta\Delta G^{\ddagger}$ = 18.6 kcal mol^{-1}) (see Fig. S6 for details), which is in good agreement with the experimental observations above. Eventually, formation of product **3** takes place by silver-promoted [3,3] rearrangement from **Int4** via **TS3**, which possesses an energy barrier of $\Delta G^{\ddagger}$ = 17.8 kcal mol^{-1} and constitutes the rate-determining step. However, in the absence of silver catalysis, the energy barrier for this step is as high as 24.0 kcal mol^{-1}. To explain this reactivity difference, the NBO charge analysis of **Int4** and **Int4'** were carried out. We found that the O–Ag weak coordination in **Int4**, which is absent in **Int4'**, enhances the C_1–O bond polarity (NBO charge differences: 0.49 in **Int4** *vs* 0.43 in **Int4'**), thus weakens this bond in **Int4** and makes it easier to break (1.48 Å *vs* 1.45 Å). Furthermore, the color-filled reduced density gradient (RDG) isosurface analysis[75,76] indicate the presence of a strong stabilizing interaction between Ag and O atoms, and also a weak Br···π interaction between the ligand and the benzene ring, both can stabilize the transition state **TS3** (Fig. 5C) (for **TS3'** RDG isosurface, see Fig. S7). In a word, all of these factors facilitate the silver-catalyzed [3,3] rearrangement. Silver catalysis of a [3,3] rearrangement is, to our knowledge, without precedent and provides a valuable template for further catalysis of such pericyclic processes[77].

Conclusion

We have established a conceptually novel carbene-initiated rearrangement strategy for the carbodefluorination of fluoroalkyl ketones by the merger of silver catalysis and fluoroalkyl *N*-triftosylhydrazones. This method enables the integration of successive C–F bond cleavage and C–C bond formation on a single molecule entity through a silver carbene-triggered defluorination and rearrangement cascade, including sequential carbene generation, oxonium ylide formation, C–F bond cleavage, and eventual C–C bond formation through Claisen rearrangement of resultant difluorovinyl ethers. A broad range of (hetero)aryl/alkyl fluoroalkyl ketones and β,γ-unsaturated alcohols (heteroaryl (indole, pyrrole, (benzo)furan, (benzo)thiophene) carbinols, allyl alcohols and propargyl alcohols) were all found to be amenable to this silver-catalyzed protocol, thereby allowing single-step access to skeletally and functionally

diverse α-mono- and α,α-difluoro-γ,δ-unsaturated ketones. These highly functionalized fluorinated molecules will be of great interest as building blocks in drug discovery and materials science. Overall, we believe that this work has opened a new avenue to exploit the carbodefluorination of C(sp^3)–F bonds.

Methods

Supporting Information

Detailed information about the experimental procedures as well as analytical data is provided in the Supplementary Information.

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L.L., X.Z., Y.N. and X.Z. contributed equally to this work. L.L., X.Z., Y.N., X.Z., B.L., Z.Z., P.S. and S.L. performed the experimental investigations and theoretical calculations. L.L., X.Z., Y.N., X.Z. and X.B. conceived the concept, designed the project, analyzed the data, and together with P.S., G.Z. and E.A. discussed the results and prepared this manuscript.

Competing interests

The authors declare no competing interests.

Acknowledgements

This work was supported by NSFC (21871043, 21961130376, 22101044), Postdoctoral Innovation Talent Support Program (BX20200079), Department of Science and Technology of Jilin Province (20190701012GH, 20200801065GH), Fundamental Research Funds for the Central Universities (2412020FZ006). XB and EA thank the Newton Trust for support (NAF\R1\191210).

References

1. Kumara, R. & Van der Eycken, E. V. Recent approaches for C–C bond formation via direct dehydrative coupling strategies. *Chem. Soc. Rev.* **42**, 1121–1146 (2013).
2. Zetzsche, L. E. & Narayan, A. R. H. Broadening the scope of biocatalytic C–C bond formation. *Nat. Rev. Chem.* **4**, 334–346 (2020).
3. Wang, C.-S., Dixneuf, P. H. & Soulé, J.-F. Photoredox catalysis for building C–C bonds from C(sp^2)–H bonds. *Chem. Rev.* **118**, 7532–7585 (2018).
4. Zhao, B. L., Rogge, T., Ackermann, L. & Shi, Z. Z. Metal-catalysed C–Het (F, O, S, N) and C–C bond arylation. *Chem. Soc. Rev.* **50**, 8903–8953 (2021).
5. Balanta, A., Godard, C. & Claver, C. Pdnanoparticles for C–C coupling reactions. *Chem. Soc. Rev.* **40**, 4973–4985 (2011).
6. Negishi, E. A. Handbook of organopalladium chemistry for organic synthesis; Wiley-Interscience: New York, 2002.
7. Miyaura, N. Cross-coupling reactions: A practical guide; Springer: New York, 2002.
8. Espinet, P. & Echavarren, A. M. The mechanisms of the Stille reaction. *Angew. Chem. Int. Ed.* **43**, 4704–4734 (2004).

9. Beletskaya, I. P. & Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **100**, 3009–3066 (2000).
10. Amii, H. & Uneyama, K. C–F Bond activation in organic synthesis. *Chem. Rev.* **109**, 2119–2183 (2009).
11. Ahrens, T., Kohlmann, J., Ahrens, M. & Braun, T. Functionalization of fluorinated molecules by transition-metal-mediated C–F bond activation to access fluorinated building blocks. *Chem. Rev.* **115**, 931–972 (2015).
12. Ma, X. & Song, Q. Recent progress on selective deconstructive modes of halodifluoromethyl and trifluoromethyl-containing reagents. *Chem. Soc. Rev.* **49**, 9197–9219 (2020).
13. Jaroschik, F. Picking one out of three: Selective single C−F activation in trifluoromethyl groups. *Chem. Eur. J.* **24**, 14572–14582 (2018).
14. Uneyama, K. & Amii, H. A review of Mg metal-promoted C−F bond activation; a reliable synthetic approach to difluorinated organic compounds. *J. Fluor. Chem.* **114**, 127–131 (2002).
15. Stahl, T., Klare, H. F. T. & Oestreich, M. Main-group Lewis acids for C–F bond activation. *ACS Catal.* **3**, 1578–1587 (2013).
16. Pattison, G. Methods for the synthesis of α,α-difluoroketones. *Eur. J. Org. Chem.* **2018**, 3520–3540 (2018).
17. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **37**, 308–319 (2008).
18. Shen, Q. et al. Review of recent advances in C–F bond activation of aliphatic fluorides. *J. Fluor. Chem.* **179**, 14–22 (2015).
19. Wettergren, J., Ankner, T. & Hilmersson, G. Selective α-defluorination of polyfluorinated esters and amides using $SmI_2/Et_3N/H_2O$. *Chem. Commun.* **46**, 7596–7598 (2010).
20. Iwamoto, H., Imiya, H., Ohashi, M. & Ogoshi, S. Cleavage of C(sp^3)–F bonds in trifluoromethylarenes using a bis(NHC)nickel(0) complex. *J. Am. Chem. Soc.* **142**, 19360–19367 (2020).
21. Uneyama, K., Maeda, K., Kato, T. & Katagiri, T. Preparation of 2,2-difluoroenol silyl ethers by electroreductive defluorination of trifluoromethyl ketones. *Tetrahedron Lett.* **39**, 3741–3744 (1998).
22. Yamauchi, Y., Fukuhara, T., Hara, S. & Senboku, H. Electrochemical carboxylation of α,α-difluorotoluene derivatives and its application to the synthesis of a-fluorinated nonsteroidal anti-inflammatory drugs. *Synlett* **3**, 438–442 (2008).
23. Amii, H., Kobayashi, T., Hatamoto, Y. & Uneyama, K. Mg^0-Promoted selective C–F bond cleavage of trifluoromethyl ketones: A convenient method for the synthesis of 2,2-difluoro enol silanes. *Chem. Commun.* **1999**, 1323–1324 (1999).
24. Hata, H., Kobayashi, T., Amii, H., Uneyama, K. & Welch, J. T. A new sequential defluorination route to α-fluoro-α,β-unsaturated ketones from trifluoromethyl ketones. *Tetrahedron Lett.* **43**, 6099–6102 (2002).
25. Amii, H., Hatamoto, Y., Seo, M. & Uneyama, K. A new C–F bond-cleavage route for the synthesis of octafluoro[2.2]paracyclophane. *J. Org. Chem.* **66**, 7216–7218 (2001).
26. Mandal, D., Gupta, R., Jaiswal, A. K. & Young, R. D. Frustrated Lewis-pair-meditated selective single fluoride substitution in trifluoromethyl groups. *J. Am. Chem. Soc.* **142**, 2572–2578 (2020).
27. Briceno-Strocchia, A. I., Johnstone T. C. & Stephan, D. W. Using frustrated Lewis pairs to explore C–F bond activation. *Dalton Trans.* **49**, 1319–1324 (2020).
28. Yu, Y. J. et al. Sequential C–F bond functionalizations of trifluoroacetamides and acetates via spin-center shifts. *Science* **371**, 1232–1240 (2021).
29. Chen, K., Berg, N., Gschwind, R. & König, B. Selective single C(sp^3)–F bond cleavage in trifluoromethylarenes: Merging visible-light catalysis with Lewis acid activation. *J. Am. Chem. Soc.* **139**, 18444–18447 (2017).
30. Vogt, D. B., Seath, C. P., Wang, H., Jui, N. T. Catalytic defluoroalkylation of trifluoromethylaromatics with

unactivated alkenes. *J. Am. Chem. Soc.* **141**, 13203–13211 (2019).

31. Luo, C. S. & Bandar, J. S. Selective defluoroallylation of trifluoromethyl. *J. Am. Chem. Soc.* **141**, 14120–14125 (2019).
32. Luo, Y.-C., Tong, F.-F., Zhang Y., He, C.-Y. & Zhang, X. G. Visible-light-induced palladium-catalyzed selective defluoroarylation of trifluoromethylarenes with arylboronic acids. *J. Am. Chem. Soc.* **143**, 13971–13979 (2021).
33. Yan, S.-S. et al. Visible-light photoredox-catalyzed selective carboxylation of $C(sp^3)$–F bonds with CO_2. *Chem* **7**, 3099–3113 (2021).
34. Ghosh, S. et al. HFIP-assisted single C–F bond activation of trifluoromethyl ketones using visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **2021**, DOI: 10.1002/anie.202115272.
35. Campbell, M. W. et al. Photochemical C–F activation enables defluorinative alkylation of trifluoroacetates and -acetamides. *J. Am. Chem. Soc.* **143**, 19648–19654 (2021).
36. Amii, H., Kobayashi, T., Terasawa, H. & Uneyama, K. Difluorinated danishefsky's diene: A versatile C4 building block for the fluorinated six-membered rings. *Org. Lett.* **3**, 3103–3105 (2001).
37. Doi, R., Ohashi, M. & Ogoshi, S. Copper-catalyzed reaction of trifluoromethylketones with aldehydes via a copper difluoroenolate. *Angew. Chem. Int. Ed.* **55**, 341–344 (2016).
38. Uneyama, K., Mizutani, G., Maeda, K. & Kato, T. Electroreductive defluorination of trifluoromethyl ketones and trifluoroacetic acid derivatives. *J. Org. Chem.* **64**, 6717–6723 (1999).
39. Xia, Y., Qiu, D. & Wang, J. Transition-metal-catalyzed cross-couplings through carbene migratory insertion. *Chem. Rev.* **117**, 13810–13889 (2017).
40. Xia, Y. & Wang, J. *N*-tosylhydrazones: Versatile synthons in the construction of cyclic compounds. *Chem. Soc. Rev.* **46**, 2306–2362 (2017).
41. Sivaguru, P. & Bi, X. Fluoroalkyl *N*-sulfonylhydrazones: An efficient reagent for the synthesis of fluoroalkylated compounds. *Sci. China Chem*. **64**, 1614–1629 (2021).
42. Zhang, X. Y. et al. Fluoroalkyl *N*-triftosylhydrazones as easily decomposable diazo surrogates for asymmetric [2 + 1] cycloaddition: Synthesis of chiral fluoroalkyl cyclopropenes and cyclopropanes. *ACS Catal*. **11**, 8527–8537 (2021).
43. Zhang, X. Y. et al. Use of trifluoroacetaldehyde *N*-tfsylhydrazone as a trifluorodiazoethane surrogate and its synthetic applications. *Nat. Commun*. **10**, 284–292 (2019).
44. Liu, Z. et al. Site-selective C–H benzylation of alkanes with *N*-triftosylhydrazones leading to alkyl aromatics. *Chem* **6**, 2110–2124 (2020)
45. Ning, Y. et al. Difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs) as a bench-stable crystalline diazo surrogate for diazoacetaldehyde and difluorodiazoethane. *Angew. Chem. Int. Ed.* **59**, 6473–6481 (2020).
46. Wang, H., Ning, Y., Sun, Y., Sivaguru, P. & Bi, X. Cycloaddition of trifluoroacetaldehyde *N*-triftosylhydrazone (TFHZ-Tfs) with alkynes for synthesizing 3-trifluoromethylpyrazoles. *Org. Lett*. **22**, 2012–2016 (2020).
47. Ma, Y., Reddy, B. R. P. & Bi, X. Coupling of trifluoroacetaldehyde *N*-triftosylhydrazone with organoboronic acids for the synthesis of *gem*-difluoroalkenes. *Org. Lett*. **21**, 9860–9863 (2019).
48. Pape, A. R., Kaliappan, K. P. & Kündig, E. P. Transition-metal-mediated dearomatization reactions *Chem. Rev.* **100**, 2917–2940 (2000).
49. Roche, S. P. & Porco Jr, J. A. Dearomatization strategies in the synthesis of complex natural products. *Angew. Chem. Int. Ed.* **50**, 4068–4093 (2011).
50. Zheng, C. & You, S.-L. Advances in catalytic asymmetric dearomatization. *ACS Cent. Sci.* **7**, 432–444 (2021).
51. Liang, X.-W., Zheng, C. & You, S.-L. Dearomatization through halofunctionalization reactions. *Chem. Eur. J.*

22, 11918–11933 (2016).

52. Nair, V. N. et al. Catalyst-controlled regiodivergence in rearrangements of indole-based onium ylides. *J. Am. Chem. Soc.* **143**, 9016–9025 (2021).
53. Boyarskikh, V., Nyong, A. & Rainier, J. D. Highly diastereoselective sulfonium ylide rearrangements to quaternary substituted indolines. *Angew. Chem. Int. Ed.* **47**, 5374–5377 (2008).
54. Novikov, A. V., Kennedy, A. R. & Rainier, J. D. Sulfur ylide-initiated thio-Claisen rearrangements. The synthesis of highly substituted indolines. *J. Org. Chem.* **68**, 993–996 (2003).
55. James, M. J., O'Brien, P., Taylor, R. J. K. & Unsworth, W. P. Synthesis of spirocyclic indolenines. *Chem. Eur. J.* **22**, 2856–2881 (2016).
56. Kida, N. et al. Control of charge transfer phase transition and ferromagnetism by photoisomerization of spiropyran for an organic-inorganic hybrid system, (SP)[FeIIFeIII(dto)$_3$] (SP = spiropyran, dto = $C_2O_2S_2$). *J. Am. Chem. Soc.* **131**, 212–220 (2009).
57. Hammarson, M., Nilsson, J. R., Li, S. M., Lincoln, P. & Andréasson, J. DNA-Binding properties of amidine-substituted spiropyran photoswitches. *Chem. Eur. J.* **20**, 15855–15862 (2014).
58. Yu, J. et al. Highly efficient "On water" catalyst-free nucleophilic addition reactions using difluoroenoxysilanes: Dramatic fluorine effects. *Angew. Chem. Int. Ed.* **53**, 9512–9516 (2014).
59. Hu, X. et al. Regioselective markovnikov hydrodifluoroalkylation of alkenes using difluoroenoxysilanes. *Nat. Commun.* **11**, 5500–5508 (2020).
60. Purser, S., Moore, P. R., Swallow, S. & Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).
61. Yu, S. & Ma, S. Allenes in catalytic asymmetric synthesis and natural product syntheses. *Angew. Chem. Int. Ed.* **51**, 3074–3112 (2012).
62. Bäckvall, J.-E., Posevins, D. & Bermejo-López, A. Iron-catalyzed cross-coupling of propargyl ethers with grignard reagents for the synthesis of functionalized allenes and allenols. *Angew. Chem. Int. Ed.* **60**, 22178–22183 (2021).
63. Song, T. et al. Kinetically controlled radical addition/elimination cascade: From alkynyl aziridine to fluorinated allenes. *Org. Lett.* **22**, 2419–2424 (2020).
64. Jaye, J. A. & Sletten, E. M. Simple synthesis of fluorinated ene-ynes via in situ generation of allenes. *Synthesis* **53**, 4297–4307 (2021).
65. Hoffmann-Röder, A. & Krause, N. Enantioselective synthesis of and with allenes. *Angew. Chem. Int. Ed.* **41**, 2933–2935 (2002).
66. Brummond, K. M. & DeForest, J. E. Synthesizing allenes today (1982–2006). *Synthesis* **6**, 795–818 (2007).
67. Furuya, T., Kamlet, A. & Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **473,** 470–477 (2011).
68. Campbell, M. G. & Ritter, T. Modern carbon-fluorine bond forming reactions for aryl fluoride synthesis. *Chem. Rev.* **115**, 612–633 (2015).
69. Yang, X., Wu, T., Phipps, R. J. & Toste, F. D. Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. *Chem. Rev.* **115**, 826–870 (2015).
70. Hunter, L. & O'Hagan, D. Multivicinal fluoroalkanes: A new class of organofluorine compounds. *Org. Biomol. Chem.* **6**, 2843–2848 (2008).
71. O'Hagan, D. Organofluorine chemistry: Synthesis and characterisation of vicinal fluoromethylene motifs. *J. Org. Chem.* **77**, 3689–3699 (2012).
72. Meyer, S., Häfliger, J. & Gilmour, R. Expanding organofluorine chemical space: the design of chiral fluorinated isosteres enabled by I(I)/I(III) catalysis. *Chem. Sci.* **12**, 10686–10695 (2021).

73. Wouters, J. et al. A reversible monoamine oxidase an inhibitor, befloxatone: structural approach of its mechanism of action. *Bioorg. Med. Chem.* **7**, 1683–1693 (1999).
74. Ren, Y. Y., Zhu, S. F. & Zhou, Q. L. Chiral proton-transfer shuttle catalysts for carbene insertion reactions. *Org. Biomol. Chem.* **16**, 3087–3094 (2018).
75. Johnson, E. R. et al. Revealing noncovalent interactions. *J. Am. Chem. Soc.* **132**, 6498–6506 (2010).
76. Lu, T. & Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* **33**, 580–592 (2012).
77. Li, C.-J. & Bi, X. *Silver Catalysis in Organic Synthesis* (Wiley-VCH, Verlag GmbH & Co. KGaA, **2019**).