Defluorinative Carboimination of Trifluoromethyl Ketones

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Abstract:

The monofunctionalized carbodefluorination of readily accessible CF_3 groups is acknowledged as an attractive approach to the preparation of partially fluorinated molecules. However, their defluorinative difunctionalization remains a challenging and unmet goal. Herein, we report an unprecedented defluorinative carboimination of trifluoromethyl ketones via a strategy of silver carbene-initiated rearrangement, in which both C–F bond and carbonyl group of the trifluoromethyl ketones were functionalized simultaneously, thus providing a straightforward synthetic method for medicinally relevant α,α-difluoroimines. The current approach involves a silver carbene-initiated intramolecular cascade process by integrating successive cleavage of C–F bond and formation of C–C and C=N bonds on a single molecule entity, which differs relevantly from the stepwise mechanism of reported carbodefluorination of CF_3 groups. Mechanistic studies disclose that silver catalysis plays a critical role, particularly in the stages of C–F bond cleavage and aza-Claisen rearrangement.

Main Text:

The unique physical and biological properties of fluorine atoms led to their ubiquity in pharmaceuticals (*1-4*), agrochemicals (*5*), and polymetric materials (*6*). Among these organic fluorine compounds, CF_2-containing molecules have received an increasing attention because of the advantageous effects stemming from the presence of germinal fluorine atoms (*7-8*) and of acting as more-lipophilic bioisosteres for alcohols and thiols (Fig. 1A) (*9-10*). Over the past decade, considerable efforts have been devoted to the development of flexible synthetic methods to access these fluorine molecules. Most of the approaches reported so far, however, feature site-selective difluorination and transformations of the pre-installed CF_2-groups (*11-21*). The carbodefluorination of CF_3 group has been recognized as one of the most ideal strategies for the synthesis of CF_2-containing compounds in view of the abundant amount and low cost of CF_3 sources (*22-23*), despite the challenges posed by the selective cleavage of C–F bond of CF_3 group, because of the high bond dissociation energy (BDE) and of over-defluorination which is often observed (*24-27*). In the past decade, impressive advances in the controllable carbodefluorination of CF_3 groups have been achieved (Fig. 1B). These strategies generally involve a stepwise mechanism including, after cleaving the C–F bond, the generation of reactive intermediates, such as (i) electrophilic carbocation using strong Lewis acids (*28-29*), (ii) nucleophilic carbanion by low-valent metal or electrochemical reduction (*30-32*), and (iii) radical generated by single-electron reduction (*33-41*). A π-system (*i.e.*, arene, alkene, and carbonyl groups) is often required to accelerate the elimination of fluorine and/or to stabilize, by the p–π conjugation effect, the *in situ* generated difluoromethylene intermediates. Nevertheless, only one C–F bond could be efficiently carbofunctionalized in such reactions. Very recently, Wang, Houk, and colleagues reported an elegant carbofunctionalization of CF_3 groups capable of affording 1,1-dialkylation products by a two-stage iterative defluorinative alkylation of α-trifluoromethyl carbonyl compounds via radical spin-center shift, while the π-system remains unaltered (*42*). Simultaneous 1,2-difunctionalization of both C–F bond and π-system of π-CF_3 molecules would be suitable to achieve more complex partially fluorinated molecules in a single step, however, such a strategy remains unexplored so far (Fig. 1C).

We report herein an unprecedented carboimination of trifluoromethyl ketones via a strategy of carbene-initiated rearrangement, which therefore constitutes the first method of defluorinative 1,2-difunctionalization of π-CF_3 molecules (Fig. 1D) (*43-44*). Distinct from the stepwise mechanism of previous carbodefluorinations (Fig. 1B), the carboimination reaction proceeds through intramolecular cascade process, involving the initial formation of silver carbene (*45-48*) followed by the attack of an allylamine to provide the key ammonium ylide; C–F bond cleavage is then triggered by selective HF elimination to form a rearrangeable *N*-allyl difluoroenamine intermediate and formation of C–C and C=N bonds is eventually achieved through a rare *aza*-Claisen rearrangement. Notably, the *aza*-Claisen rearrangement typically requires harsh reaction conditions (*49*). Herein, the silver catalyst plays a critical role in the generation of the difluoroalkene intermediate as well as in facilitating the *aza*-Claisen rearrangement under mild conditions. In addition to the mechanistic novelty, this carbene-initiated rearrangement approach offers a straightforward method for the synthesis of multi-functional CF_2-containing compounds from easily accessible CF_3 sources (Fig. 1A).

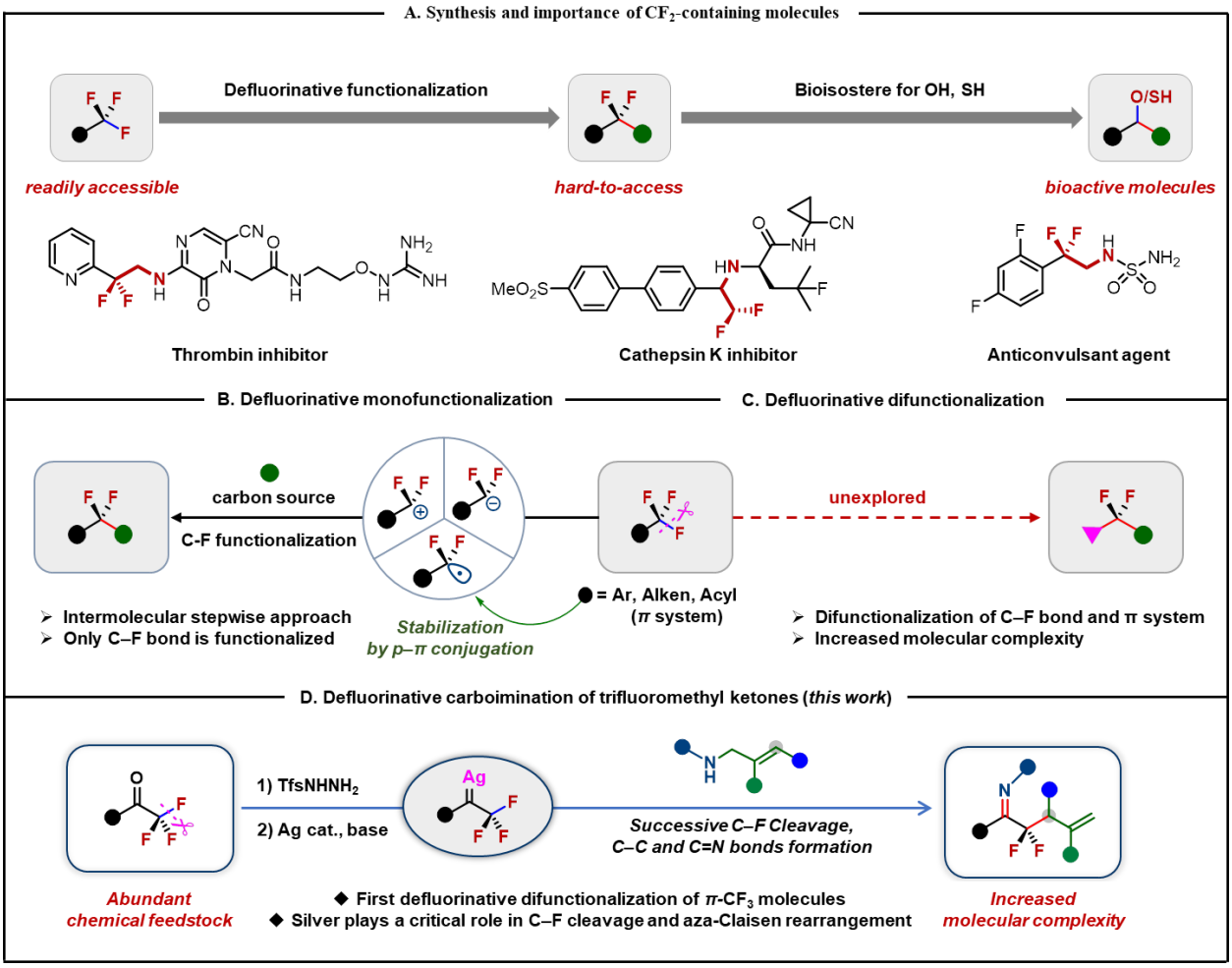


Fig. 1. Strategies for selective defluorinative carbofunctionalization of π-CF_3 molecules. (A) Synthesis and importance of CF_2-containing molecules. **(B)** Defluorinative monofunctionalization. **(C)** Defluorinative difunctionalization. **(D)** Approach described herein: Defluorinative carboimination of trifluoromethyl ketones. Tfs: 2-(trifluoromethyl)benzenesulfonyl.

Results and discussion

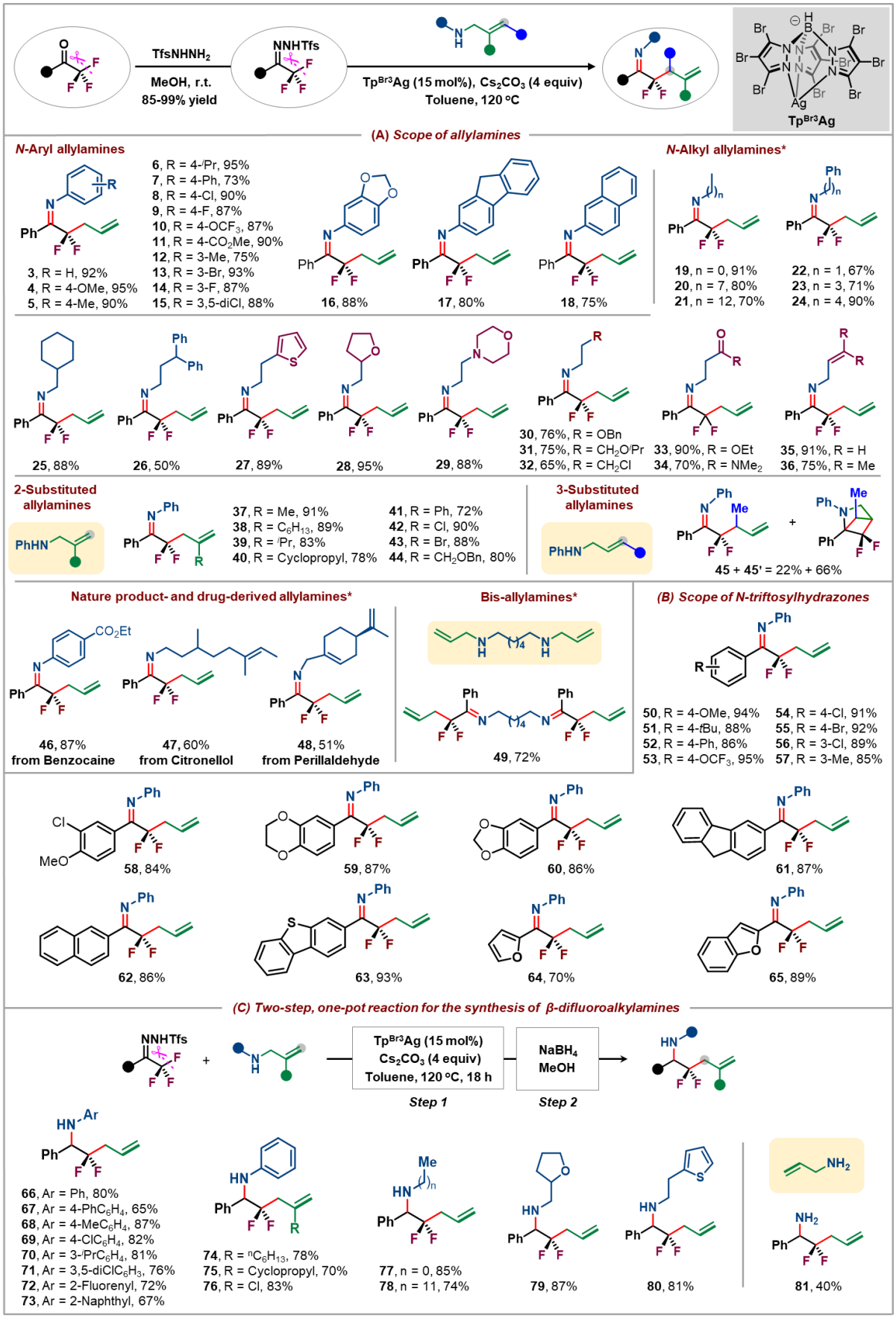
The reaction conditions were initially investigated by employing the reaction of *N*-triftosylhydrazone (**1a**) and *N*-allylaniline (**2**) as a model and varying the transition-metal catalysts. The results showed that only $Tp^{Br3}Ag$ proved to be effective for this tandem reaction, using Cs_2CO_3 as a base in toluene at 120 ºC, obtaining the desired imine product (**3**) in 92% yield (For details, see Supporting Information, Table S1). With the optimal reaction conditions in hand, we first examined the scope of this defluorinative carboimination reaction using a variety of allylamines (Scheme 1A). The carboimination reaction proceeds in high yield with various *N*-aryl allylamines bearing electron-donating, electron-neutral, and electron-withdrawing substituents on the aromatic ring (**3**-**18**). Furthermore, we were pleased to find that a wide range of *N*-alkyl allylamines also proved to be effective reaction partners, and the length or bulkiness of the alkyl chain had no significantly effect on efficiency (**19**-**36**). Notably, the reaction was well compatible with a range of functional groups (*e.g.*, Cl, Br, ether, OBn, alkylamine, ester, C=C double bond) commonly encountered in organic synthesis. When *N*-allylbut-2-en-1-amine was used, the aza-Claisen rearrangement selectively occurred in the less hindered terminal double bond, providing the

product **36** in 75% yield. The position of substituents on the double bond of allylamines has a remarkable effect on their reactivity. For example, *N*-phenyl allylanilines, having alkyl, aryl, halogens or -CH_2OBn α to amine, all reacted efficiently with **1a** to afford the corresponding α,α-difluoroimines (**37**-**44**) in good to excellent yield. In contrast, the substrate with internal double bond produced the desired product **45** in 22% yield only, while an azabicyclo[2.1.1]hexane **45'** was obtained in 66% yield. The formation of **45'** may be explained via an intramolecular [2+2]-cycloaddition pathway, probably because the increased steric hindrance has influenced the outcome of the [3,3]-sigmatropic reaction of *N*-allyl difluoroenamines.(*50*) To further examine the practicality of this method, the applications to a local anesthetic Benzocaine and natural products Perillaldehyde and Citronellol derived allylamines were performed under the standard conditions, which all smoothly afforded the corresponding products **46**-**48** in 51-87% yield. This difunctionalization methodology can also be used to perform the synthesis of more complex compounds containing the CF_2 unit, as exemplified by compound **49** which was obtained in one step by double carboimination of a bis-allylaniline substrate.

We next turned our attention to the reaction component of *N*-triftosylhydrazones, which were readily prepared in high yield by the condensation of trifluoromethyl ketones with $TfsNHNH_2$. As shown in Scheme 1B, a wide variety of trifluoromethyl *N*-triftosylhydrazones reacted smoothly with *N*-allylaniline **2a**, affording the corresponding α,α- difluoroimines (**50**-**65**) in good to high yield. The substituents such as alkyl (**51** and **57**), alkoxy (**50** and **58**-**60),** phenyl (**52** and **61**), trifluoromethoxy (**53**), and halogen (**54**-**56**, **58**) were well tolerated. Furthermore, a range of *O*- and *S*-containing heteroaromatics of interest for medicinal chemistry were tolerated and usually obtained in good yield (**63**-**65**).

In view of the increasing applications of β-difluoroalkylamines in drug discovery (*2*), we questioned whether it would be possible to ccess β-difluoroalkylamines products directly from trifluoromethyl ketones in a two-step, one-pot process consisting of carboimination of trifluoromethyl ketones, followed by reduction of α,α-difluoroimines. We were pleased to find that using phenyl trifluoromethyl ketone *N*-triftosylhydrazone (**1a**) as the CF_2 source, a variety of allylamines efficiently underwent the carboimination and subsequent reduction of the resulted imines with $NaBH_4$ simply in one-pot operation, affording the desired β-difluoroalkylamines products **66**-**80** in 65-87% yield. Moreover, the *N*-unprotected allylamine also proved to be a suitable substrate and resulted in the corresponding primary amine product **81**, despite of a low yield (40%) observed. Taken together, these results have demonstrated the usefulness of such a step-economic and operationally simple method for the synthesis of medicinally relevant β-difluoroalkylamines (*2*), from readily available trifluoromethyl ketones and allylamines.

All these compounds summarized in Scheme 1 are newly synthesized and hard to be accessed by other conventional methods. To explore the synthetic utility of this method, we carried out the gram-scale syntheses and further transformations, using the compounds **3** and **68** as the typical examples (Fig. 2). The reaction of *N*-triftosylhydrazone (**1a**) and *N*-allylaniline (**2**) was carried out at a 5 mmol scale and produced α,α-difluoroimine **3** in 87% yield and β-difluoroalkylamine **68** in 80% yield, respectively, under the standard carboimination and carboamination conditions. These two multi-functional products could act as versatile building blocks for the synthesis of a variety of CF_2-containing organic molecules. For instance, the rhenium-catalyzed [3+2] annulation of imine **3** and benzyl isocyanate gave an iminoisoindolinone **82** in 73% yield, which represents a class of biologically interesting CF_2-


TfsNHNH2
MeOH, r.t.
85-99% yield
NNHTfs
TpBr3Ag (15 mol%), Cs2CO3 (4 equiv)
Toluene, 120 °C
TpBr3Ag
(A) Scope of allylamines
N-Aryl allylamines
3, R = H, 92%
4, R = 4-OMe, 95%
5, R = 4-Me, 90%
6, R = 4-iPr, 95%
7, R = 4-Ph, 73%
8, R = 4-Cl, 90%
9, R = 4-F, 87%
10, R = 4-OCF3, 87%
11, R = 4-CO2Me, 90%
12, R = 3-Me, 75%
13, R = 3-Br, 93%
14, R = 3-F, 87%
15, R = 3,5-diCl, 88%
16, 88%
17, 80%
18, 75%
N-Alkyl allylamines*
19, n = 0, 91%
20, n = 7, 80%
21, n = 12, 70%
22, n = 1, 67%
23, n = 3, 71%
24, n = 4, 90%
25, 88%
26, 50%
27, 89%
28, 95%
29, 88%
30, 76%, R = OBn
31, 75%, R = CH2OiPr
32, 65%, R = CH2Cl
33, 90%, R = OEt
34, 70%, R = NMe2
35, 91%, R = H
36, 75%, R = Me
2-Substituted allylamines
PhHN
37, R = Me, 91%
38, R = C6H13, 89%
39, R = iPr, 83%
40, R = Cyclopropyl, 78%
41, R = Ph, 72%
42, R = Cl, 90%
43, R = Br, 88%
44, R = CH2OBn, 80%
3-Substituted allylamines
PhHN
45 + 45' = 22% + 66%
Nature product- and drug-derived allylamines*
46, 87%
from Benzocaine
47, 60%
from Citronellol
48, 51%
from Perillaldehyde
Bis-allylamines*
49, 72%
(B) Scope of N-triftosylhydrazones
50, R = 4-OMe, 94%
51, R = 4-tBu, 88%
52, R = 4-Ph, 86%
53, R = 4-OCF3, 95%
54, R = 4-Cl, 91%
55, R = 4-Br, 92%
56, R = 3-Cl, 89%
57, R = 3-Me, 85%
58, 84%
59, 87%
60, 86%
61, 87%
62, 86%
63, 93%
64, 70%
65, 89%
(C) Two-step, one-pot reaction for the synthesis of β-difluoroalkylamines
NNHTfs
TpBr3Ag (15 mol%)
Cs2CO3 (4 equiv)
Toluene, 120 °C, 18 h
Step 1
NaBH4
MeOH
Step 2
66, Ar = Ph, 80%
67, Ar = 4-PhC6H4, 65%
68, Ar = 4-MeC6H4, 87%
69, Ar = 4-ClC6H4, 82%
70, Ar = 3-iPrC6H4, 81%
71, Ar = 3,5-diClC6H3, 76%
72, Ar = 2-Fluorenyl, 72%
73, Ar = 2-Naphthyl, 67%
74, R = nC6H13, 78%
75, R = Cyclopropyl, 70%
76, R = Cl, 83%
77, n = 0, 85%
78, n = 11, 74%
79, 87%
80, 81%
81, 40%

Scheme 1. A) Reaction conditions for step 1: all reactions were carried out with allylamine (0.2 mmol, 1.0 equiv), *N*-triftosylhydrazone (0.4 mmol, 2.0 equiv), Cs_2CO_3 (0.8 mmol, 4.0 equiv), $Tp^{Br3}Ag$ (15 mol%) in toluene (5 mL) at 120 °C for 18 h. *Reactions were carried out with $Tp^{Br3}Ag$ (25 mol%) at 80 °C for 8 h, then 120 °C for 12 h. All yield refers to isolated yield. **B) Reaction conditions for step 2:** step 1 was complete, then removal of Ag catalyst and toluene from the residue were added $NaBH_4$ (2.5 equiv) and CH_3OH (2 mL).

containing azaheterocycles containing a quaternary carbon center (*51*). Moreover, the difluoromethyl ketone **83** and the dibromide **84** were obtained in high yield by the treatment of **3** with silica gel and hydrobromic acid, respectively (*52*). On the other hand, a number of azaheterocycles containing a CF_2 unit in the skeleton were prepared in high yield through the intramolecular aminofunctionalization of **68**. For example, the treatment of **68** with NIS produced a thermodynamic product 5-iodopiperidine **85** in 90% yield (*53*), while a kinetically favored pyrrolidine **86** was obtained when using NBS instead of NIS, in which the phenyl ring was also brominated at the *para*-position simultaneously. Moreover, a SCN-containing pyrrolidine **87**, a key precursor for the synthesis of diverse organosulfur compounds (*54-55*), could be prepared by intramolecular aminothiocyanation of **68** (*56*).

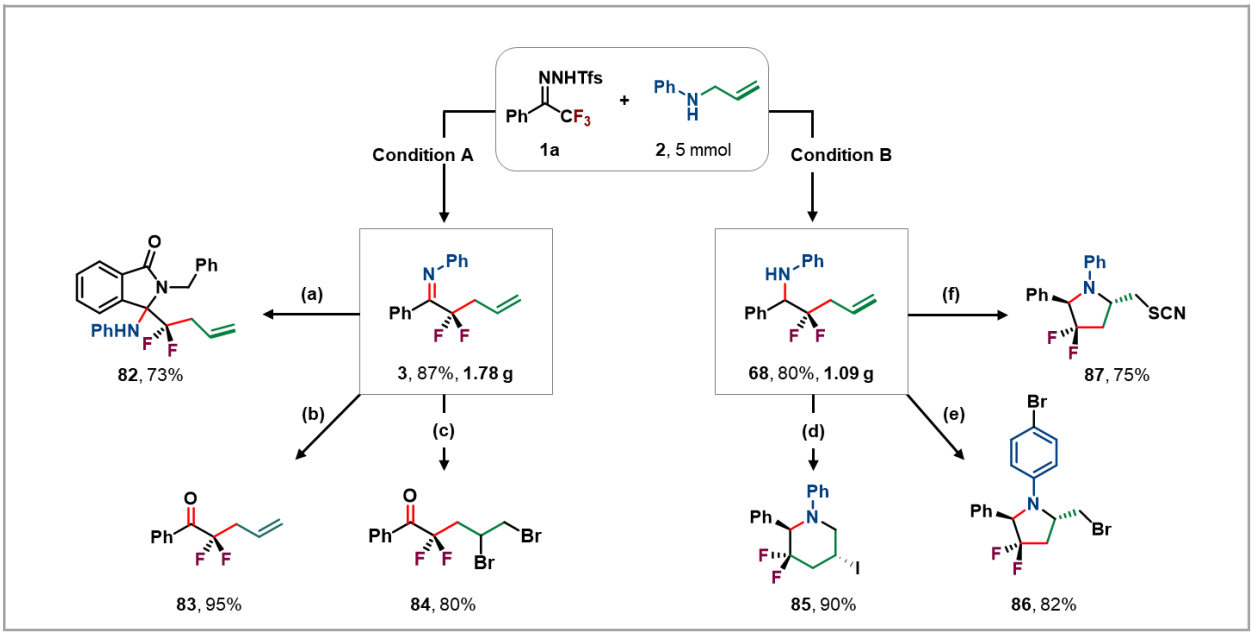


Fig. 2. Conditions A: **1a** (10 mmol, 2.0 equiv), **2** (5 mmol, 1.0 equiv), Cs_2CO_3 (20 mmol, 4.0 equiv) and $Tp^{Br3}Ag$ (15 mol%) in toluene (40 mL) at 120 °C for 18 h. **Conditions B**: **1a** (10 mmol, 2.0 equiv), **2** (5 mmol, 1.0 equiv), Cs_2CO_3 (20 mmol, 4.0 equiv) and $Tp^{Br3}Ag$ (15 mol%) in toluene (40 mL) at 120 °C for 18 h; then removal of Ag catalyst and toluene from the residue were added $NaBH_4$ (2.5 equiv), CH_3OH (20 mL). (a) **3** (0.3 mmol), 4-methylbenzyl isocyanate (0.6 mmol, 2.0 equiv), Re_2CO_{10} (0.03 mmol, 0.1 equiv), *o*-xylene (3 mL), under Ar at 150 °C for 60 h. (b) **3** (0.3 mmol), HBr (48% aq, 5.0 equiv), DMSO (1 mL), $CHCl_3$ (1 mL), 25 °C. (c) Stirred in CH_2Cl_2 (2 mL) with silica gel at room temperature, overnight. (d) **68** (0.3 mmol, 1.0 equiv), NIS (0.6 mmol, 2.0 equiv), CH_2Cl_2 (2 ml), 25 °C, 10 min. (e) **68** (0.3 mmol, 1.0 equiv), L-Proline (30 mol%), NBS

(0.6 mmol, 2.0 equiv), THF (3 mL) at 0 °C. (f) **68** (0.2 mmol, 1.0 equiv), NaSCN (0.6 mmol, 3.0 equiv) and I_2 (0.6 mmol, 3.0 equiv) in EtOAc (3 mL).

Mechanistic investigations

To gain more insights into the proposed mechanism in Figure 1D and the origin of chemoselectivity, experimental studies and DFT calculations were conducted. First, the key *N*-allyl difluoroenamine intermediate **88** was successfully isolated in 75% yield by ceasing the reaction at 40 min (Fig. 3A, left). Subjection of **88** to the standard reaction conditions resulted in product **3** in 92% yield, whereas in the absence of silver catalyst only 60% yield was obtained. These results indicate that the silver catalyst facilitates the aza-Claisen rearrangement of **88** that typically requires harsh reaction conditions (*49*). Moreover, the possibility that the reaction proceeds through the sequential formation of an amine intermediate by N–H carbene insertion (*57-60*) and then the elimination of HF to give intermediate **88** was excluded by the designed experiment of separately synthesized amine **89**, because no reaction was observed under the standard conditions (Fig. 3A, right).

More mechanistic information was obtained by density functional theory (DFT) calculations that were partly displayed in Figure 3B with an ammonium ylide **Int2** as the starting point, which was readily generated *in situ* from silver carbene and *N*-allylaniline **2** with an energy barrier of 3.6 kcal mol^{-1} (For details, see Supporting Information, Fig. S1). The results indicate that **Int2** could undergo selective HF elimination to form Ag-coordinated *gem*-difluorovinylamine **Int3** via a five-membered ring transition state **TS2** ($\Delta\Delta G^{\ddagger}$ = 20.8 kcal mol^{-1}), rather than proton transfer to give an N–H insertion product **89** via **TS2′** ($\Delta\Delta G^{\ddagger}$ = 31.5 kcal mol^{-1}. For details, see Supporting Information, Fig. S2), which is consistent with above experimental observation. To clarify the origin of the chemoselectivity, HOMO analysis of **Int2** was performed and showed that the symmetry matching of F and H atoms favors the elimination of HF, while the symmetry of carbene carbon and H does not match. The single bond rotation of **Int3** leads to an intermediate **Int4**, which then converts to product **3** via **TS3** by aza-Claisen rearrangement with an energy barrier of 23.2 kcal mol^{-1}, clearly being the rate-determining step. Alternatively, *gem*-difluorovinylamine **Int3'** (compound **88**), without coordinated Ag catalyst, could undergo a thermal aza-Claisen rearrangement, albeit with much higher energy barrier (**TS3',** $\Delta\Delta G^{\ddagger}$ = 28.9 kcal mol^{-1}), thus highlighting the role of silver catalyst capable of facilitating the aza-Claisen rearrangement. The effect of silver was further analyzed with the help of NBO charge analysis of **Int4** and **Int4′**, respectively. It was found that the weak coordination of Ag to N in **Int4** enhances the C–N bond polarity and renders it more easy to cleave, as indicated by the facts that the NBO charge difference increased from 0.17 of **Int4'** to 0.24 of **Int4** and the C–N bond length increased from 1.47 Å in **Int4'** to 1.50 Å in **Int4**. Furthermore, the color-filled reduced density gradient (RDG) isosurface analysis shows a strong interaction between Ag and N atoms and a weak Br···π interaction between the Tp^{Br3} ligand and the benzene ring, both of which could stabilize the transition state **TS3** (for RDG of **TS3′**, see Supporting Information, Fig. S3). Collectively, the reaction mechanism involves the initial formation of a silver carbene, followed by nucleophilic addition of an allylamine to give a key ammonium ylide intermediate, which then triggers the selective C–F bond cleavage by HF elimination and subsequent formation of C–C and C=N bonds by aza-Claisen rearrangement of *in situ* generated *gem*-difluorovinylamine. During this process, $Tp^{Br3}Ag$ plays a critical role, especially in the stages of C–F bond cleavage and aza-Claisen rearrangement.

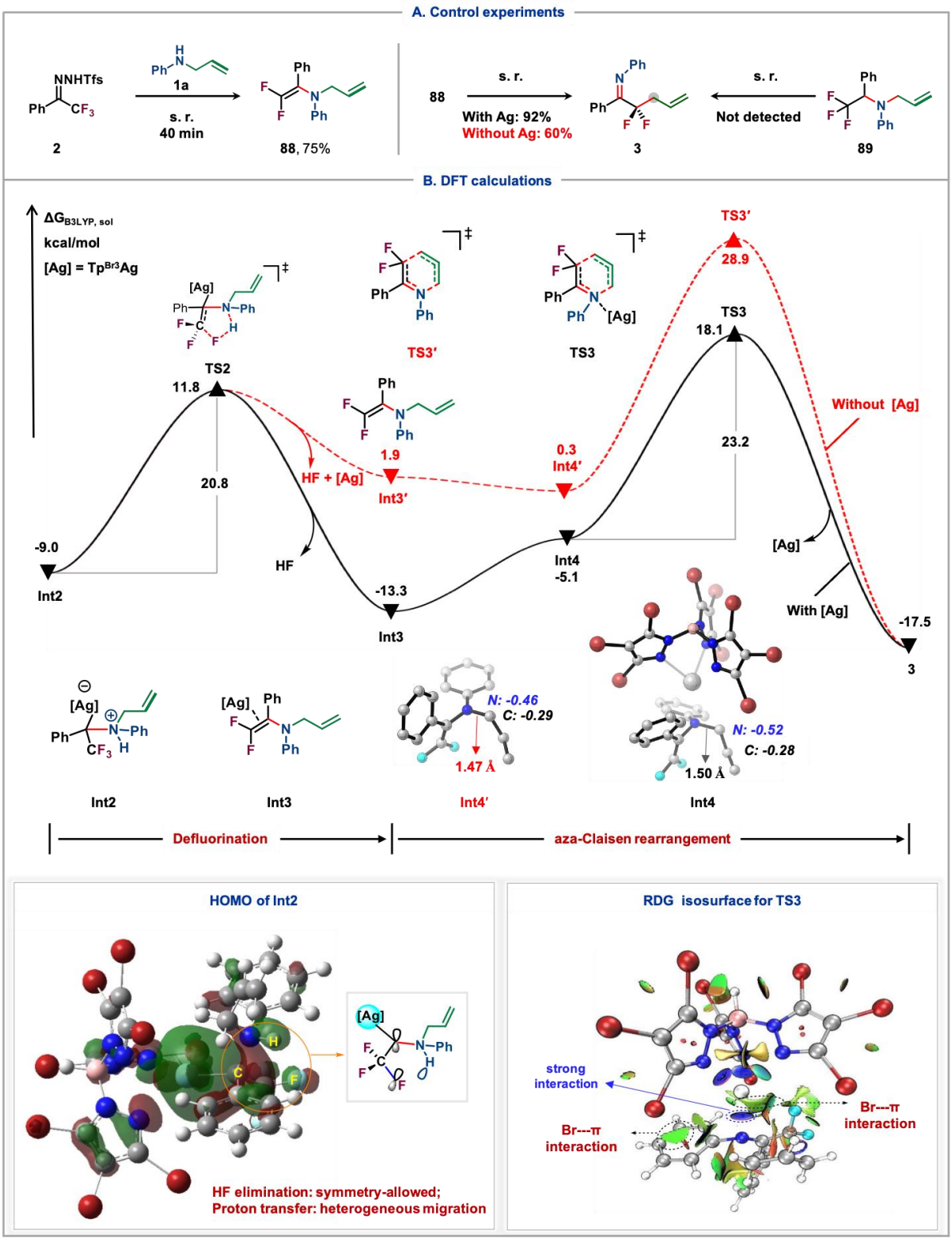


Fig. 3. Mechanistic studies. (A) Control experiments. **(B)** A plausible mechanism based on DFT-computed free-energy profile at the SMD (toluene)//B3LYP/6-31G(d,p)-SDD(Ag,Br) level of theory (ΔG, in kcal·mol^{-1})**.**

Conclusion

In summary, we have developed a defluorinative carboimination reaction of trifluoromethyl ketones through a conceptually distinct strategy of carbene-initiated rearrangement, which affords a variety of otherwise hardly accessible α,α-difluoroimines. This report, which represents the first example of simultaneous difunctionalization of C–F bond and π-system of π-CF_3 molecules, provides a new approach to the functionalization of C(sp^3)–F bonds via merging of silver carbene and classical σ-rearrangement.

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Competing interests:

Authors declare that they have no competing interests.

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