Carbodefluorination of fluoroalkyl ketones via a carbene-initiated rearrangement strategy

Received: 1 February 2022
Accepted: 12 July 2022
Published online: 25 July 2022

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 (CF₃) groups remains a 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 to provide skeletally and functionally diverse α-mono- and α,α-difluoro-γ,δ-unsaturated ketones. The reaction starts with the formation of silver carbenes from fluoroalkyl N-triftosylhydrazones, followed by nucleophilic attack of a β,γ-unsaturated alcohol to form key silver-coordinated oxonium ylide intermediates, which triggers selective C–F bond cleavage by HF elimination and C–C bond formation through Claisen rearrangement of in situ generated difluorovinyl ether. The origin of chemoselectivity and the reaction mechanism are determined by experimental and DFT calculations. Collectively, this strategy by an intramolecular cascade process offers significant advances over existing stepwise strategies in terms of selectivity, efficiency, functional group tolerance, etc.

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. 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. 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 (CF₃) groups. 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, which often results in undesired over-defluorination (Fig. 1a). In this context, great efforts have been invested in achieving selective mono-
carbodefluorination of the CF₃ group, especially in CF₃-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 bond²⁸–³⁵, where the in situ generated difluoromethylene reactive intermediates can be stabilized through p–π conjugation (Fig. 1b). While the acyl-CF₃ compounds (CF₃C=O) are most abundant and easily available, only two classes of selective mono-defluorinative C–C bond-forming reactions of acyl-CF₃ derivatives have been disclosed, namely: (i) copper or low-valent magnesium promoted defluorinative coupling of trifluoromethyl ketones with aldehydes or ketones²³,³⁶–³⁸; and (ii) radical defluorinative coupling of acyl-CF₃ with alkenes by spin-center shift (SCS) or photocatalysis²⁸,³⁴,³⁵, 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 CF₃-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. 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 reactions³⁹–⁴⁷. Moreover, the rearrangement reaction of fluorne-containing molecules can provide various fluorne-containing molecular frameworks⁴⁸–⁵³. Hence, the development of a 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.

Here, we report a carbene-initiated rearrangement strategy for the carbodefluorination of fluoroalkyl ketones (Fig. 1c, up). We envisage that an intramolecular rearrangement strategy could provide an advantageous route for the efficient carbodefluorination of trifluoromethyl ketones, i.e., the formation of a metal-coordinated ylide intermediate by nucleophilic attack 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).

Results and discussion

Substrate scope

Transition-metal-catalyzed dearomative functionalization of (hetero)aromatics has recently emerged as a powerful method to access allphatic cyclic compounds⁵⁴–⁶⁰. 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. Despite many advances, the formation of new carbon-carbon bonds via defluorinative dearomatization of indoles remains elusive. 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 for 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 nucophile. A survey of various combinations of different fluoroalkyl N-sulfonylhydrazones, metal catalysts, solvents and temperature revealed that a mixture of phenyl trifluoromethyl ketone N'-trifosetylhydrazone (1a), indole-3-carbinol (2aa), K$_2$CO$_3$ (2.0 equiv) and Tf$_2$N$_2$Ag (10 mol%) in toluene at 80 °C achieved the desired defluorinative [3,3]-rearrangement product (3) in 84% yield (Fig. 2). The driving force to destroy the aromaticity of the substrate comes from the flow of electrons during the opening of the six-membered ring transition state during the [3,3]-rearrangement. 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 product (3) 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-defluorocycloated indolines (13–15) in moderate to good yield with excellent stereoselectivity (E/Z up to >20:1). However, we observed that tertiary alcohols are not suitable for this transformation, possibly because the structures of tertiary alcohols are not suitable for deamination due to the presence of the keto group in high yield. Despite many advances, the formation of new carbon-carbon bonds via defluorinative dearomatization of indoles remains elusive. 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 for 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 nucophile. 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Trisubstituted allyl alcohols possessing styryl (101), alkyl chloride (102), alkyl 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), alky 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-difuoroalkenes (106–117) in 53–94% yields. α,α-Difuoro-γ,δ-alkenes with fluoroalkyl all-carbon quaternary center could be prepared (118–122) in moderate to excellent yield using 1,1-disubstituted allyl alcohols; such α-difuoroalkyl quaternary carbons, which cannot be easily prepared by conventional methods. This protocol was also applicable for the late-stage modification of natural products, such as myrtanol (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. With this in mind, we next examined the carbodifluorination of trifluoromethyl ketones with propargyl alcohols, with a view to accessing difluoroalkyl-substituted 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. To our knowledge, this is the first example of selective C–F allenolysis of CF$_3$ groups. This chemistry proved most effective using propargyl alcohol itself, which exhibited high reactivity and gave the desired product in near quantitative yield. However, both acyclic 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), alk enyl (142), and alkynyl (143) groups, were all amenable in this reaction. Notably, the free alkyl 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 silver-coordinated oxonium ylides. Polyfunctionalized allenes were found to be hard to prepare by existing methods. Furthermore, a cy clohexene-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).
**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), K2CO3 (0.6 mmol, 2 equiv) and Tp3Ag (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. †Cs2CO3 was used instead of K2CO3 under 100 °C. All yield refers to isolated yield.

*PG protecting group, Ts tosly, Boc t-butoxycarbonyl, Cbz carbobenzyloxy, Ac acetyl, PMP p-methoxyphenyl, Ms methanesulfonyl.*

### Primary indol-3-carbinols

| R          | Yield (%) |
|------------|-----------|
| H          | 84%       |
| 4-Me       | 87%       |
| 5-Me       | 93%       |
| 6-Me       | 88%       |
| 7-MeO      | 91%       |
| 4-Cl       | 80%       |
| 4-Br       | 91%       |
| 5-Br       | 86%       |
| 6-F        | 85%       |
| 6-CO2Et    | 82%       |

### Secondary indol-3-carbinols

| R          | Yield (%) | Configuration |
|------------|-----------|---------------|
| Me         | 65%       | (E/Z = 5:1)   |
| Pr         | 55%       | (E/Z > 20:1)  |
| Br         | 66%       | (E/Z = 20:1)  |
| n          | 70%       | (E/Z = 15:1)  |

### Quaternary carbon center construction

| PG          | Yield (%) |
|-------------|-----------|
| Ts          | 65%       |
| Boc         | 72%       |

### N-Protected indol-3-carbinols

| R          | Yield (%) |
|------------|-----------|
| 4-OMePh   | 89%       |
| 4-F        | 82%       |
| 4-Cl       | 80%       |
| 2-Br       | 72%       |
| 2,4,6-Tr-MePh2 | 80%     |
| 2(2H)-CH2Ph | 75%       |
| Me         | 80%       |
| Cyclopropyl | 83%       |

### Scope of fluoroalkyl N-triftosylhydrazones

| R          | Yield (%) |
|------------|-----------|
| 4-Me       | 85%       |
| 3-Me       | 90%       |
| 4-Br       | 82%       |
| 4-OMe      | 83%       |
| 4-OCF3     | 91%       |
| 4-F        | 86%       |
| 3-F        | 90%       |
| 3-CF3      | 62%       |

### Scope of pyrrole carbinols

| R          | Yield (%) |
|------------|-----------|
| Ph         | 92%       |
| I          | 85%       |
| Ph         | 90%       |
| 3-Me       | 81%       |
| H          | 90%       |
| PG         | 87%       |
| H          | 83%       |

### Scope of (benzofuran) carbinols

| R          | Yield (%) |
|------------|-----------|
| H          | 82%       |
| 5-Me       | 75%       |
| 4,5-di-Me  | 69%       |
| 4-Ph       | 80%       |
| 4-Vinyl    | 87%       |
| 4-Br       | 95%       |
| 4-CO2Me    | 75%       |
| 3-F        | 72%       |
| 3-CF3      | 78%       |

### Scope of (benzo)thiophene carbinols

| R          | Yield (%) |
|------------|-----------|
| Ph         | 64%       |
| 3-Me       | 70%       |
| 5-Me       | 73%       |
| Br         | 67%       |
| 4-Me       | 67%       |
| 4-F        | 69%       |

[Article](https://doi.org/10.1038/s41467-022-31976-z)
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), K₂CO₃ (0.6 mmol, 2 equiv) and TpBr₂Ag (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-dipropylpropylamine (DPEA) (0.6 mmol, 2 equiv) and Rh₂(esp)₂ (2 mol%) in DCE (4 mL) at 80 °C. Ar arecyl, HetAr heteroaryl, TBDMS tert-butyldimethylsilyl, Bn benzyl, TMS trimethylsilyl, nBu n-butyl, dr diastereomeric ratio.
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 (Rh2(esp)2 as catalyst instead of TpBr3Ag 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-difluoropropyl (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.

**Gram-scale reaction and further transformations**

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 methods74–76. 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...
allenyloieties, these products could be easily transformed into a broad range of fluorinated building blocks of medicinal relevance. For example, the terminal alkenic 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 effcienct (194–197), while combining olefination with aromatizing (3,3)-sigmatropic rearrangement offers an attractive entry to 1,1-difluoroalkane products (198). The selective nucelophilic gem-difluorolysis 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 NaBH4, 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 multivinicial fluorination20–29. 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 molecules30. Carbonyl alkenylation of 86 and 127 gave the desired products 202 and 207 in 85% and 90% 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.

Mechanistic investigations

Mechanistic experiments and computational studies were conducted to explore the mechanism of this cascade carbodifluorination process. The progress of the reaction depicted in Fig. 5a was first examined by 1H 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 in formation of the difluoroalkene intermediate, and also facilitates the rearrangement process. A control experiment showed that exposing pre-prepared ether 210 to the standard conditions failed to give the defluorinating rearrangement product 44 (Fig. 5b, eq. 3). This result excluded the possibility of forming an ether intermediate through O-H carbone insertion31. 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 metal ylide to give an ether.

Density functional theory (DFT) calculations at the SMD(toluene)//B3LYP-D3/def2svp 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 nucleophilic attack, 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 Tf2Ag catalyst to give a silver carbone. The energy barrier for generation of a silver-coordinated oxonium ylide Int2 by reaction of indole-3-carbinol with this silver carbone is low (2.6 kcal mol−1). The NPA 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 3-membered ring transition state TS2 to generate the gem-difluorovinyl ether intermediate Int4 by single bond rotation of initially silver-associated gem-difluorovinyl ether intermediate Int3. Notably, the energy barrier for the HF elimination is lower (ΔAG‡ = 11.8 kcal mol−1) than proton transfer to form an O-H insertion product (ΔAG‡ = 20.8 kcal mol−1) (see Supplementary Fig. 7 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 ΔAG‡ = 15.5 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 20.7 kcal mol−1. To explain this reactivity difference, the NPA charge analysis of Int4 and Int4 was carried out. We found that the O–Ag weak coordination in Int4, which is absent in Int4, enhances the C–O bond polarity (NPA charge differences: 0.46 in Int4 vs 0.39 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 analysis32 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 Supplementary Fig. 8). In a word, all of these factors facilitate the silver-catalyzed [3,3] rearrangement.

In summary, we have established a carbene-initiated rearrangement strategy for the carbodifluorination of fluoroalkyl ketones by the merger of silver catalysis and fluoroalkyl trifluorohydrizones. 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, nucleophilic attack, C–F bond cleavage, and eventual C–C bond formation through Claisen rearrangement of resultant difluoroalkyl ethers. A broad range of (hetero)aryl/alkyl fluoroalkyl ketones and β,γ-unsaturated alcohols (heteroaryl (indole, pyrrole, benzofuran, benzothiophene) carbonyls, allyl alcohols and propargyl alcohols) were all found to be amenable to this silver-catalyzed protocol, thereby allowing single-step access to selectively and functionally diverse α-monofluoro-β,γ-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 an avenue to exploit the carbodifluorination of C(sp3)–F bonds.

Methods

General procedure for the synthesis of Tf2Ag

Pre-sublimated HF–3,4,5-tribromopyrazole (40 mmol, 4.0 equiv) and TIBH4 (10 mmol, 1.0 equiv) were added to a 250 mL Schlenk tube and mix well (no magnetic stir required). The tube was fitted with a reflux condenser and a nitrogen balloon (to balance the increased pressure of hydrogen production during the reaction), and three vacuum/nitrogen cycles were made. The reaction was heated at 180 °C for 2 h, then the temperature was raised to 200 °C and the reaction was continued for 2 h. After cooling to room temperature, unreacted pyrazole was removed by vacuum sublimation (150 °C, 2 mbar) to give TfTfBP as a white solid. AgOTf (10 mmol, 1.0 equiv) and TITP (10 mmol, 1.0 equiv) were added to the acetone solution to dissolve. After stirring in the dark for 20 h, a white solid precipitated from the initially colorless solution. The solid was filtered off and dried under vacuum for 12 h to give the complex [Tf2AgCl3]3Cl (38% yield). Tf2AgCl3 was carried out in freshly distilled tetrahydrofuran (100 mL) for 30 min in the dark. The solvent was removed under reduced pressure, and white solid Tf2Ag was quantitatively obtained after vacuum drying.

General procedure carbodifluorination reaction of indole-3-carbinols

To a dried sealed tube was charged with N-tfsylhydrazone (0.3 mmol, 1.0 equiv), indole-3-carbinol (0.6 mmol, 2.0 equiv), Tf2Ag (10 mol%), K2CO3 (0.6 mmol, 2.0 equiv) in an argon-filled glovebox. Anhydrous
Fig. 5 | Mechanistic experiments and computational studies. 
a Reaction kinetics study; b Control experiments; c A plausible mechanism based on DFT-computed free-energy profile ($\Delta G$, in kcal·mol$^{-1}$). Standard condition: 2aa (0.6 mmol, 2.0 equiv), K$_2$CO$_3$ (0.6 mmol, 2 equiv) and Tp$^{33}$Ag (10 mol%) in toluene (4 mL) at 80 °C. Ts tosyl.
toluene (4 mL) was added. The resulting mixture was stirred at 80 °C for 16 h. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, and filtered through a short pad of diatomite with ethyl acetate (EtOAc) as an eluent. The filtrate was concentrated in vacuo and then the resulting crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:25; v:v) to obtain the product.

General procedure carbodefluorination reaction of 2-substituted indole-3-carbinols

To a dried sealed tube was charged with N-tfisyldihydrazone (0.3 mmol, 1.0 equiv), TPAAg (10 mol%), K₂CO₃ (0.6 mmol, 2.0 equiv) in an argon-filled glovebox. Anhydrous toluene (4 mL) was added. The resulting mixture was stirred at 80 °C for 8 h, then the temperature was increased to 120 °C and stirring was continued for 24 h. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, and filtered through a short pad of diatomite with ethyl acetate (EtOAc) as an eluent. The filtrate was concentrated in vacuo and then the resulting crude product was purified by column chromatography using ethyl acetate/petroleum ether as eluent to obtain the product.

Data availability

The data that support the findings of this study are available within the paper and its Supplementary Information and Supplementary Data files. Raw data are available from the corresponding author on request.

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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). X.B. and E.A. thank the Newton Trust for support (NAF\R1\191210).

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LL., X-Y.Z., Y.N. and X-L.Z. contributed equally to this work. L.L., X-Y.Z., Y.N., X-L.Z., B.L., Z.S., P.S. and S.L. performed the experimental investigations and theoretical calculations. L.L., X-Y.Z., Y.N., X-L.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.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-022-31976-z.

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Peer review information Nature Communications thanks Chao Feng and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

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