Synthesis of difluoromethylated allenes through trifunctionalization of 1,3-enynes

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Organofluorine compounds have shown their great value in many aspects. Moreover, allenes are also a class of important compounds. Fluorinated or fluoroalkylated allenes might provide an option as candidates for drug and material developments, as allenes allow a great number of valuable transformations. Herein, we report a metal-free synthesis of difluoromethylated allenes via regioselective trifunctionalization of 1,3-enynes. This method proceeds through double C–F bond formation with concomitant introduction of an amino group to the allene. Synthetic applications are conducted and preliminary mechanistic studies suggest that a two-step pathway is involved. DFT calculations revealed an unusual dibenzenesulfonimide-assisted fluorination/fluoroamination with NFSI. In addition, kinetic reaction study revealed the induction period of both major and side products to support the proposed reaction mechanism. This work offers a convenient approach for the synthesis of a range of difluoromethylated allenes and is also a rare example of trifunctionalization of 1,3-enynes.
Organofluorine compounds have shown great importance over the years in the fields such as medicinal chemistry and agrochemistry, as the introduction of fluorine atom(s) onto molecules would modify considerably their chemical and physicochemical properties1–6. Thus, methods for the synthesis of organofluorine compounds have been flourished in both profundity and scope7–13. The difluoromethyl group (CF₂H), as an analogue of the well-known trifluoromethyl group (CF₃), has recently received increasing attentions and many powerful methods for its introduction into organic compounds have been developed14–19. On the other hand, allenes are key intermediates in organic synthesis and are important structural motifs that can also be found in natural products20–24. For the purpose of providing diverse fluorinated molecules to meet the increasing demand for drug discovery and new materials development, methods for efficient synthesis of various fluorinated or fluorooalkylated allenes are evidently of great value, as such allenes allow a great number of valuable skeletal and stereochemical transformations25.

Over the past few decades, many difluoromethylation reactions have been successfully developed, enabling facile synthesis of different types of difluoromethylated compounds. Most commonly, the CF₂H group (or CF₂R group) is accessed from a CF₂-containing building block or agent26–29. For example, the syntheses of difluoromethylated allenes typically require the use of difluoromethyl metal compounds30–34. Recently, Wang et al. developed the nickel-catalyzed carbofluoromethylation affording difluorooalkylated allenes using ethyl bromodifluoroacetate35. Notwithstanding these significant breakthroughs, the development of efficient and diversified approaches for the facile construction of difluoromethylated allenes is still challenging especially from non-CF₂-containing building blocks and methods for the synthesis of difluorooalkylated allenes are still demanded.

Inspired by earlier reports on gem-difluorination (Fig. 1a)37–40 and fluorooamination of styrenes (Fig. 1b)41–44, also as one part of our continuous efforts on functionalization of unsaturated compounds45–48 herein, we report a metal-free consecutive trifluoromethylation of 1,3-enynes for the assembly of various difluoromethylated allenyl amines (Fig. 1c) using NFSI as the fluorination and amination source49,50–59. The synthetic potential of difluoromethylated allenes is demonstrated by transformations to a variety of difluoromethylated compounds51.

**Results**

**Reaction optimization.** We commenced reaction condition optimization using CuTC as the catalyst and 1,10-phenanthroline as the ligand. As shown in Table 1, the reaction between 1,3-enyne 1a and NFSI was originally thought to involve intermolecular 1,4-fluorooamination, providing the mono-fluoromethylated allene 3a as the desired product50. However, only a trace amount of 3a was detected, and a new compound, the difluoromethylated allene 4a, was obtained as major product albeit in a low yield (Table 1, entry 1). Formation of the product 4a alluded to a previously unknown reaction, and we therefore decided to optimize the conditions towards formation of 4a. With the Pd(OAc)₂/BC catalyst system52, product 4a was obtained in 34% yield (Table 1, entry 2). Use of a CoCl₂ catalyst failed to provide any targeted 4a (Table 1, entry 4), while Pt(COD)Cl₂ and NiCl₂ showed a better performance than the Pd(OAc)₂/BC catalyst system (Table 1, entry 5 v. entry 6 v. entry 2). After extensive screening experiments, it was found that the reaction of the 1,3-enyne 1a with NFSI afforded 4a in 28% yield, even in the absence of catalyst and ligand (Table 1, entry 7). The yield of 4a was further improved to 44% upon running the reaction at an elevated temperature (Table 1, entry 8). Other solvents were screened and it was found that toluene and chloroform provide the product 4a in 66 and 61% yield (Table 1, entries 9 and 10), while acetonitrile, a polar solvent, afforded the targeted product in only 12% yield (Table 1, entry 11). Furthermore, the yield of 4a dropped when the reaction was carried out in toluene at 100 °C (Table 1, entry 12). Notably, a small amount of the monofluoromethylated allene 3a was observed in all these reactions.

**Substrate scope.** With the optimal reaction conditions in hand, the substrate scope was studied and various difluoromethylation allenes were successfully prepared in moderate to good yields. As shown in Fig. 2, the phenyl group at position 2 can be replaced by a substituted phenyl group (4b–4v). Electron-donating groups on the benzene ring, such as a methyl group, an iso-butyl group, or a tert-butyl group, and electron-withdrawing substituents such as Br, F, and CN on the benzene ring are tolerated. Enynes with primary, secondary, or tertiary alkyl groups linked with the C–C triple bond could also be diversified. As examples, 1,3-enynes with a n-hexyl group (1b–1l), a cyclopropyl group (1k, 1l, and 1n), a chloroalkyl group (1m), or a tert-butyl group (1o) are suitable substrates for the direct difluoromethylation reaction. 1,3-Enynes bearing a silyl group (1r), a silyl ether moiety (1s), or an ester group (1t) also engage in this reaction. Moreover, 2,4-diaryl substituted 1,3-enynes can be used as the substrates to afford the corresponding products in moderate yields (see 4u and 4v). However, (3-methylbut-3-en-1-yn-1-yl)benzene (1w), as an example for non-styrene systems, only provided the desired product 4w in 24% yield, which might be due to the less stability of the intermediate compared to that of 1-alkynyl styrenes. The structures of the difluoromethylated allenes 4k and 4l were unambiguously confirmed by single crystal X-ray diffraction.

Encouraged by the results using terminal 1,3-enynes, we next investigated difluoromethylation of internal 1,3-enynes aiming at the preparation of difluoroalkylated allenes. With 1,3-enyne 1x, bearing a primary alkyl group linked with the C–C triple bond, only a 28% yield of the product 4x was obtained, and the accompanying monofluoromethylation product 3x was produced in 46% yield as major compound. However, it was found that the substrates bearing a bulky group at the triple bond deliver the corresponding products 4y–4ae in higher yields and functionalities such as the ester group (4ac) and silyl groups (4ad and 4ae) are tolerated.

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**Fig. 1 Fluorination or difluorination of C–C bonds.** a Gem-difluorination of styrenes. b Fluorooamination of styrenes. c This work: facile synthesis of difluoromethylated allenes.
Synthetic applications. Synthetic applications of this consecutive difluoroamination of 1,3-enynes have been demonstrated and are shown in Fig. 3. In the presence of N-iodosuccinimide (NIS), the difluoromethylated allene 4m was regioselectively transformed into the (Z,Z)-diene 5 in 54% yield. Note that during iodination one of the sulfonyl groups of the -N(SO2Ph)2 functionality was removed. Interestingly, when the allene 4u bearing two phenyl groups was subjected to the reaction with NIS, the difluoromethylated vinyl imine 6 was formed. Such vinyl iodides, 5 and 6, are also pivotal building blocks for further transformations60. Moreover, the silyl group of the allene 4s could be readily removed to afford the allene 7 with a free alcohol group (81%), which could be further cyclized in 57% yield to the multi-substituted 3,6-dihydro-2H-pyran 8.

Mechanistic studies. Finally, preliminary experiments to probe the mechanism of the difluoromethylated allene formation reaction were performed. Since the difluoroamination product 3a was found as a side product (see Table 1), 3a was supposed to be the reaction intermediate and was therefore subjected to the standard conditions. However, the desired product 4a was not detected (Fig. 4a). Notably, during reaction optimization the fluorinated 1,3-enyne 61–68 9a was observed. In addition, treatment of the 1,3-enyne 1a with a reduced amount of NFSI afforded compound 9a along with targeted 4a. Therefore, we suspected that 9a might be a key intermediate in this cascade. Indeed, when compound 9a was subjected to the reaction with NFSI, product 4a was isolated in 74% yield (Fig. 4b), suggesting that 9a, rather than 3a, is a possible intermediate for the difluoroamination and this reaction probably relies on a two-step process.

DFT study. On the other hand, DFT study was also performed according to the experiments of mechanism studies. Initially, three kinds of 1,3-enyne radical cation species oxidized by NFSI were considered, but the enthalpies were too high (ΔH > 57 kcal/mol) to support the cation radical process (Supplementary Fig. 1)44. We then focus on the allenyl cation pathways. Two-component reactions of an 1,3-enyne with NFSI were investigated in different orientations of NFSI to transfer the fluoride to 1,3-enyne, 1. Two transition states, TS1 and TS1′, were located leading to the reactive intermediate 9 with a dibenzenesulfonimide (DBSI) moiety synchronously and the 1,2-adduct N-(1-fluoro-2-phenylhept-3-yn-2-yl)-N-(phenylsulfonyl)benzenesulfonamide (10), with activation free energy of 25.1 and 31.1 kcal/mol, respectively (Supplementary Fig. 2), in which producing DBSI via TS1 is a concerted process after fluorine transfer. Intrinsic reaction coordinate (IRC) calculations have been conducted for the validity of concerted proton transfer and 1,2-addition from TS1 and TS1′, respectively (Supplementary Figs. 3 and 4). In addition, TS6, the transition state corresponding to the bisphenylsulfonyl imide moiety of NFSI directly addition to the 4C atom of 1, was calculated as well. However, the activation energy of TS6 is so much higher (59.4 kcal/mol), and it results in a 3,4-addition compound N-(3-fluoro-2-phenylhepta-1,3-dien-4-yl)-N-(phenylsulfonyl)benzenesulfonamide (11) (Supplementary Fig. 2) which was confirmed by ICR calculation as well as the calculations from TS1 and TS1′. It is worth noting that no transition state corresponding to 1,4-addition to form desired product 4 can be located. This is reasonable because the bond distance of N-F of the optimized NFSI molecule is 1.40 Å much less than the distance between 1 C and 4 C in the optimized structure of 1 (d(1C-4C) = 3.54 Å).

Since the product (N-(1,1-difluoro-2-phenyleca-2,3-dien-4-yl)-4-methyl-N-tosylbenzenesulfonamide, 12) adducted by N (Ts)2 can be observed in presence of the HN(Ts)2 (see crossover reaction in Supplementary Methods), three-component reactions of 1,3-enyne with NFSI and DBSI were further considered and discussed. Figure 5 shows the overall potential energy surface from 1 to produce the 1,4-addition major product 4 and minor product 3. As described above, 1 reacts with NFSI first to form

Table 1 Reaction condition optimization.

| Entry | Cat. | Ligand | Solvent | Yield of 4a (%) |
|-------|------|--------|---------|----------------|
| 1     | CuTC | 1,10-Phen | DCM | <5 |
| 2     | Pd(OAc)2 | BC | DCM | 34 |
| 3     | PdCl2 | 1,10-Phen | DCM | 24 |
| 4     | CoCl2 | 1,10-Phen | DCM | trace |
| 5     | Pt(COD)Cl2 | 1,10-Phen | DCM | 40 |
| 6     | NiCl2 | 1,10-Phen | DCM | 48 |
| 7     | -    | -      | DCM | 28b |
| 8     | -    | -      | DCM | 44c |
| 9     | -    | -      | toluene | 66c (65)d, e |
| 10    | -    | -      | CHCl3 | 61c |
| 11    | -    | -      | CH3CN | 12c |
| 12    | -    | -      | toluene | 51f |

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3 PdCl2 1,10-Phen DCM 24
4 CoCl2 1,10-Phen DCM trace
5 Pt(COD)Cl2 1,10-Phen DCM 40
6 NiCl2 1,10-Phen DCM 48
7 - - DCM 28b
8 - - DCM 44c
9 - - toluene 66c (65)d, e
10 - - CHCl3 61c
11 - - CH3CN 12c
12 - - toluene 51f

Reaction conditions: 1,3-enyne (3a, 0.25 mmol), NFSI (0.75 mmol), cat (10 mol%), ligand (10 mol%), solvent (0.5 mL), 65°C, under a N2 atmosphere.

a1H NMR yield
bThe reaction was performed at 60°C
cThe reaction was performed at 80°C
dIsolated yield in parentheses
eThe 1H NMR yield of 1a
fIsolated yield in parentheses

TS1 is so much lower (25.1 kcal/mol) compared with TS6 (31.1 kcal/mol) that 1,2-addition from TS1 is considered, but the enthalpies were too high (ΔH > 57 kcal/mol) to support the cation radical process (Supplementary Fig. 1)44. We then focus on the allenyl cation pathways. Two-component reactions of an 1,3-enyne with NFSI were investigated in different orientations of NFSI to transfer the fluoride to 1,3-enyne, 1. Two transition states, TS1 and TS1′, were located leading to the reactive intermediate 9 with a dibenzenesulfonimide (DBSI) moiety synchronously and the 1,2-adduct N-(1-fluoro-2-phenylhept-3-yn-2-yl)-N-(phenylsulfonyl)benzenesulfonamide (10), with activation free energy of 25.1 and 31.1 kcal/mol, respectively (Supplementary Fig. 2), in which producing DBSI via TS1 is a concerted process after fluorine transfer. Intrinsic reaction coordinate (IRC) calculations have been conducted for the validity of concerted proton transfer and 1,2-addition from TS1 and TS1′, respectively (Supplementary Figs. 3 and 4). In addition, TS6, the transition state corresponding to the bisphenylsulfonyl imide moiety of NFSI directly addition to the 4 C atom of 1, was calculated as well. However, the activation energy of TS6 is so much higher (59.4 kcal/mol), and it results in a 3,4-addition compound N-(3-fluoro-2-phenylhepta-1,3-dien-4-yl)-N-(phenylsulfonyl)benzenesulfonamide (11) (Supplementary Fig. 2) which was confirmed by ICR calculation as well as the calculations from TS1 and TS1′. It is worth noting that no transition state corresponding to 1,4-addition to form desired product 4 can be located. This is reasonable because the bond distance of N-F of the optimized NFSI molecule is 1.40 Å much less than the distance between 1 C and 4 C in the optimized structure of 1 (d(1C-4C) = 3.54 Å).

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Fig. 2 Substrate scope of 1,3-enynes. Reaction conditions: 1,3-enyne (1, 0.5 mmol), NFSI (1.5 mmol), toluene (1 mL), 80-100 °C, N₂ atmosphere, Isolated yield. aWith CHCl₃ (1 mL) as the solvent. bThe reaction was performed in cyclohexane and the monofluoromethylated allene 3x was obtained in 46% yield.
the reactive intermediate 9 with the DBSI through the lowest energetic transition state TS1. Then, the reactive intermediate 9 reacts with a second NFSI to form an ion pair of difluoromethylallenyl cation and bisphenylsulfonyl imide anion (int1) through TS2 with the energy barrier of 25.5 kcal/mol. Subsequently, an adjacent DBSI, generated from the first step, participates in the reaction to suspend the 2-addition of bisphenylsulfonyl imide anion to difluoromethylallenyl cation. A low barrier transition state TS3 (13.9 kcal/mol) corresponding to simultaneous imide generation due to the arti-

cial catalysis of DBSI, can be detected with 11.7 kcal/mol of barrier resulting in the monofluoromination product 3 and regenerating a DBSI. It is noteworthy that the barrier of TS3, 3.9 kcal/mol higher than that of TS1, may be somewhat too high to compete with the path of 9 generation due to the artificial overestimation of unfavorable DBSI association entropy, as seen in comparison with the energy difference between int1 and int2. Nevertheless, according to the crossover reaction, the proposed trimolecular pathway with higher barrier to form the side product 3 is believed to take place in the reactions.

**Kinetic studies.** For further supporting this hypothesis, kinetic studies of the reaction was therefore conducted to track the formations of side product 3, major product 4 and active intermediate 9 (Supplementary Fig. 5). Because of lacking 9 and DBSI, the induction period of formation of 3 and 4 should thus be seen if the trimolecular pathway is the favorable one. Figure 6 presents the kinetic profiles for the formations of 3a, 4a and 9a. As expected, the reaction rate of 9a is faster than that of 3a, and the induction period of 3a and 4a can be observed. Initially, even no trace amount of 3a and 4a can be detected in the first 6 minutes. After that, trace amounts of 3a can be observed, but the rate of generation is very slow; nevertheless, the yield of 9a has been over 10% at the 20 minute. Although the yields of 3a and 4a are almost the same in the first one hour, the generation rate of 4a seems to accelerate probably due to the increase of concentration of 9a. Finally, the active intermediate 9a is consumed to deliver the major product 4a at the end of reaction, and the amounts of 3a should stop to grow after expending all of the reactant 1a. The fast generation rate of 9 and the induction periods of formations of 3 and 4 are well consistent with the proposed reaction mechanism.

**Proposed mechanism.** Based on our mechanistic experiments, theoretical studies and published work, the proposed mechanism for the synthesis of difluoromethylated allenes from trifunctionalization of 1,3-enynes is depicted in Fig. 7. Initially, electrophilic fluorination of the 1,3-enyne 1 by NFSI synchronously generates the dibenzensulfonimide and the fluorinated enyne 9 as the reactive intermediate. The second NFSI then reacts with 9 to afford the major product 4 assisted by the DBSI, adjacent to 9. On the other hand, accumulation of DBSI will aid the formation of fluorination product 3, which is observed as a
In conclusion, a metal-free synthesis of various difluoromethylated allenes through difluoroamination of 1,3-enynes has been developed. NFSI was used as the reactant and a broad substrate scope was obtained. The synthetic potential of difluoromethylated allenes has been demonstrated by transformations of them to a variety of useful difluoromethylated compounds. Moreover, this reaction is also a rare example of trifunctionalization of 1,3-enynes. Preliminary mechanistic studies suggest that a two-step pathway is involved and DFT studies revealed a dibenzenesulfonimide-assisted fluorination/difluoroamination with NFSI.

**Methods**

**General procedure.** In a flame-dried Schlenk tube, NFSI (1.5 mmol, 3.0 equiv.) was dissolved in toluene (1 mL) under a nitrogen atmosphere. Then, 1,3-enyne (0.5 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at 80 °C for 12 h. After the reaction completion as detected by TLC, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EA or PE/DCM) to afford the allene product.
Data availability
Detailed experimental procedures and characterization of compounds can be found in the Supplementary Information. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (4k: CCDC 1891507; 4f: CCDC 1891508; 8: CCDC 1891506). These data could be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. All data are available from the authors upon request.

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Author contributions

M.T.M. and H.B. conceived the idea. M.T.M., Y.J., and C.Y. conducted the experiments and they contribute equally to this paper. M.-F.C. conducted the DFT calculation. M.J. and X.Z. synthesized the substrates and repeated the reactions. M.T.M., Y.J., C.Y., Y.L. and H.B. analyzed the data. Y.L., Z.W., A.S. and H.B. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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