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Copper difluorocarbene-involved catalytic *gem*-difluoropropargylation

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The use of metal for catalytic difluorocarbene transfer reactions has long been hindered by the lack of understanding of metal difluorocarbene chemistry, despite the potential implications for medicinal chemistry and advanced materials science. Here, we report a copper-catalyzed difluorocarbene transfer reaction via 1,1-migration of copper difluorocarbene, in contrast to the previous nucleophilic addition of copper difluorocarbene pathway. This reaction enables the development of a modular catalytic *gem*-difluoropropargylation reaction using a variety of simple and widely available potassium propiolates, terminal alkynes, and allyl/propargyl electrophiles to couple difluorocarbene, opening an avenue to the precise synthesis of organofluorine compounds without tedious synthetic procedures. The impact of this protocol is demonstrated by the efficient synthesis of complex fluorinated skeletons and the rapid synthesis of key intermediates for pheromone derivatives and PGF2 agonists. Mechanistic studies reveal that the migratory insertion of difluorocarbene into the C-Cu bond of the alkynylcopper species is a key step in the reaction.

The precise fluorine editing of organic molecules has emerged as a powerful tool in modern drug discovery due to the beneficial effect of fluorine atom(s) that can significantly improve the metabolic stability, lipophilicity, and binding affinity of bioactive compounds[1–4]. Consequently, impressive achievements have been made in the fluoroalkylation reactions over the past decades[5–9]. However, most developed methods focus on the transformations of fluorinated carbanions, carbocations, and carbon-centered radicals[5–9]. Compared to these three active intermediates, difluorocarbene, the smallest fluorocarbon unit, has the advantage of forming two chemical bonds[10–12], providing a new dimension to expand the chemical space and create new fluorine structures for medicinal chemistry. Ideally, coupling difluorocarbene with two simple and readily available feedstocks would enable more efficient access to organofluorine compounds without the tedious synthesis of fluoroalkylating reagents (Fig. 1a). Nevertheless, this straightforward synthetic route is regulated by the high reactivity of difluorocarbene. As a result, only limited reaction types of difluorocarbene transfer reactions have been reported so far[13–16]. To overcome this limitation, the complexation of difluorocarbene with metal would be an attractive strategy, as the reactivity of difluorocarbene can be modulated by metal (Fig. 1b). However, due to the lack of catalytic activity in those isolated metal difluorocarbene complexes, the metal-catalyzed difluorocarbene transfer reaction remains a substantial challenge[17], in sharp contrast to the classic metal catalyzed carbene transfer reactions that have been proven to be a powerful transformation in organic synthesis[18–20]. This problem is further underscored by the lack of understanding of metal difluorocarbene chemistry, though investigating metal difluorocarbene complexes has been around for over 40 years[21].

We recently isolated palladium(0)[22] and copper(I)[23] difluorocarbene complexes ($[Pd^0]=CF_2$ and $[Cu^I]=CF_2$) and found they possess opposite reactivities ($[Pd^0]=CF_2$, nucleophilic; $[Cu^I]=CF_2$, electrophilic), though Pd^0 and Cu^I have the same d electron count. These findings have been applied in catalytic organic synthesis[24–27]. However, the initial step of these catalytic difluorocarbene transfer reactions requires the formation of the low valent metal

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difluorocarbene ([M] = CF_2, M = Pd^0, Cu^I) intermediates, followed by attacking the carbene carbon center with an electrophile or a nucleophile to generate a difluoroalkyl metal species ([M]-CF_2R) (Fig. 1c)[22,23]. We envision that the formation of the M-CF_2R species by migratory insertion of difluorocarbene into the C-M bond would open a new dimension to harness metal difluorocarbene chemistry for catalytic synthesis of organofluorine compounds, as the C-M bond can be easily constructed by transmetalation or oxidative addition[28], which would provide a more general pathway for catalytic difluorocarbene transfer reactions (Fig. 1d). To realize this hypothesis, one critical factor is the rapid formation of a metal difluorocarbene complex C-[M] = CF_2, followed by a facile migratory insertion pathway without the influence of coupling [M]-C with an electrophile or a nucleophile. Since copper is low-cost, earth-abundant, and easy to form a [Cu^I]-C species via transmetalation between [Cu^I] and a nucleophile[29], we assume that using copper as a catalyst under suitable conditions may address the above crucial issue and provide a cost-efficient route for modular construction of fluorinated structures (Fig. 1e), thus expanding copper difluorocarbene chemistry and opening an avenue to efficient, precise synthesis of organofluorine compounds.

Here, we disclose a copper-catalyzed *gem*-difluoropropargylation reaction via 1,1-migration of copper difluorocarbene (Fig. 1e). This reaction uses inexpensive and industrial feedstock potassium bromodifluoroacetate ($BrCF_2CO_2K$) as the difluorocarbene precursor[30,31], allowing various widely available potassium propiolates, terminal alkynes, and allyl/propargyl electrophiles to couple difluorocarbene, providing a facile route to accessing synthetically valuable *gem*-difluoropropargylated compounds. The distinct feature of this approach is its synthetic simplicity, eliminating the tedious synthesis of fluoroalkylating reagents or moisture-sensitive organometallic reagents. The diverse transformations of the resulting products, as well as the applications of the current protocol in the rapid synthesis of key intermediates for bioactive molecules, demonstrate the synthetic utility of this catalytic difluorocarbene transfer reaction, showing promise in modern drug discovery. Mechanistic studies reveal that the fast migratory insertion of difluorocarbene into the C-Cu bond of alkynylcopper(I) species is the key step for the catalytic difluorocarbene transfer.

Results

Mechanistic investigation

To test our hypothesis, we chose terminal alkynes as the nucleophiles, as the resulting *gem*-difluoropropargyl structure is a synthetically versatile synthon for diverse transformations. Notably, it has been widely used in copper-free click chemistry[32,33] due to the unique properties of the difluoromethylene (CF_2) group, which can lower the lowest unoccupied molecular orbital (LUMO) of the alkynes[32,34]. Furthermore, the CF_2 group is a bioisostere of the oxygen atom and the carbonyl group (Fig. 1f)[2,35]. Incorporating the CF_2 group at the metabolically labile position can enhance the metabolic stability of bioactive molecules[1–4]. It has been one of the valuable strategies for discovering new bioactive molecules by tactically site-selective difluoromethylenation (Fig. 1f)[1–4,35,36]. However, efficient methods for such a *gem*-difluoropropargyl structure are limited. The developed methods either rely on the deoxyfluorination of alkynyl ketones with sulfur fluorides[37] or coupling *gem*-difluoropropargyl bromides with organometallic reagents[38,39], aldehydes[40], or imines[41]. However, the requirement of multiple steps to prepare the substrates, such as alkynyl ketones and organometallic reagents, as well as the poor functional group compatibility of sulfur fluorides, and the use of strong base *n*-butyllithium to prepare *gem*-difluoropropargyl bromides[42] regulate the widespread applications of these methods. Yet, the current catalytic modular synthesis harnessing copper difluorocarbene chemistry would overcome these limitations and provide straightforward access to the *gem*-difluoropropargyl structure.

Initially, to ascertain the feasibility of the migratory insertion of difluorocarbene into the C-Cu bond, we prepared the 1,10-phenanthroline-supported alkynyl complex **A1**[43]. Unexpectedly, treatment of **A1** with inexpensive and widely available difluorocarbene precursor $BrCF_2CO_2K$ **1** in CH_3CN at 50 °C afforded a trifluoroalkene **3** instead of *gem*-difluoropropargyl copper complex **C1** (Fig. 2a). A similar result was also observed in DMF. Although low yields of **3** were obtained due to the decomposition of **A1**, these results demonstrate the feasibility of the migratory insertion pathway. Once **C1** was formed via the copper difluorocarbene complex **B1**, it underwent another difluorocarbene insertion to generate a tetrafluoroalkylcopper **E1** (ref 23). Finally, the β-fluoride (β-F) elimination of **E1** produced **3**. This possible pathway indicates that the difluorocarbene elongation in the alkynyl copper complex **C1** is favorable, and the tetrafluoroalkyl copper **E1** is prone to β-F elimination due to its instability. Complex **A1** could also be used as a nucleophile to react with **1** and allyl chloride **2a** in CH_3CN, providing the three-component coupling product **4** in 38% yield along with a side product **5** (13%) generated between **A1** and **2a** (Fig. 2b). Replacing CH_3CN with DMF led to a lower yield of **4**. No **4** was observed using DMSO. These results suggest that the formation of **C1** via an alkynylcopper difluorocarbene complex **B1** through 1,1-migration is reasonable, which should be faster than the cross-coupling of **A1** with **2a** in a suitable reaction media, such as CH_3CN and DMF, thereby facilitating the formation of *gem*-difluoropropargyl structure in the catalytic reaction. Given the difficulty in obtaining **C1** through the current difluorocarbene pathway, we prepared *gem*-difluoropropargyl cadmium species **F1** and **F2** by reaction of *gem*-difluoropropargyl bromide **6** with cadmium in DMF[44]. These two organocadmium reagents were assigned according to the literature[45]. Transmetalation of the mixture of **F1** and **F2** with CuI at −40 °C afforded the *gem*-difluoropropargyl copper **C2** and bis(*gem*-difluoropropargyl)copper species **C3** in 41% yield and 8% yield, respectively. Since it is hard to isolate these two species, they were directly used to react with allyl chloride **2a**, providing **7** in 95% yield, thus demonstrating the feasibility of coupling *gem*-difluoroproparyl copper with an electrophile (Fig. 2c). To investigate the possibility of nucleophilic addition of alkynyl species to the carbene carbon center, we prepared copper difluorocarbene complex **G**[23]. However, no desired product **4** was obtained when **G** was treated with **2a** and alkynyl nucleophiles, including alkynyl lithium/zinc reagents (**8a, 8b**) and potassium propiolate **9a** (Fig. 2d). Thus, the pathway beginning with the formation of [Cu^I]=CF_2, followed by a reaction with an alkynyl nucleophile, is less likely.

Based on the above results, a copper-catalyzed difluorocarbene transfer reaction should be feasible for the catalytic modular synthesis of *gem*-difluoropropargylated compounds. In this copper-catalyzed process, the reaction is initiated by the formation of an alkynylcopper species **A**, which subsequently undergoes complexation with a difluorocarbene to generate an alkynylcopper difluorocarbene intermediate **B**. This key intermediate undergoes 1,1-difluorocarbene migratory insertion to produce the *gem*-difluoropropargyl copper species **C**. Finally, **C** reacts with an electrophile to produce the *gem*-difluoropropargylated compound and releases copper catalyst simultaneously (Fig. 2e).

Optimizations for catalytic reactions

Inspired by the above observations and the possible pathway illustrated in Fig. 1e, we explored a catalytic coupling reaction between terminal alkyne **8c** and allyl chloride **2a** to couple with difluorocarbene (Table 1). When **8c** (1.0 equiv) was treated with **2a** (1.5 equiv) and difluorocarbene precursor **1** (2.0 equiv) in the presence of CuCl (10 mol%) and 1,10-phenanthroline **L1** (10 mol%) in CH_3CN at 50 °C using K_2CO_3 as the base, 10% yield of the desired product **4** was obtained along with 5% yield of side product **5** (entry 1). The use of CH_3CN as the solvent is due to its good solubility for $BrCF_2CO_2K$. A survey of the ligands showed that ligand **L4** could suppress the

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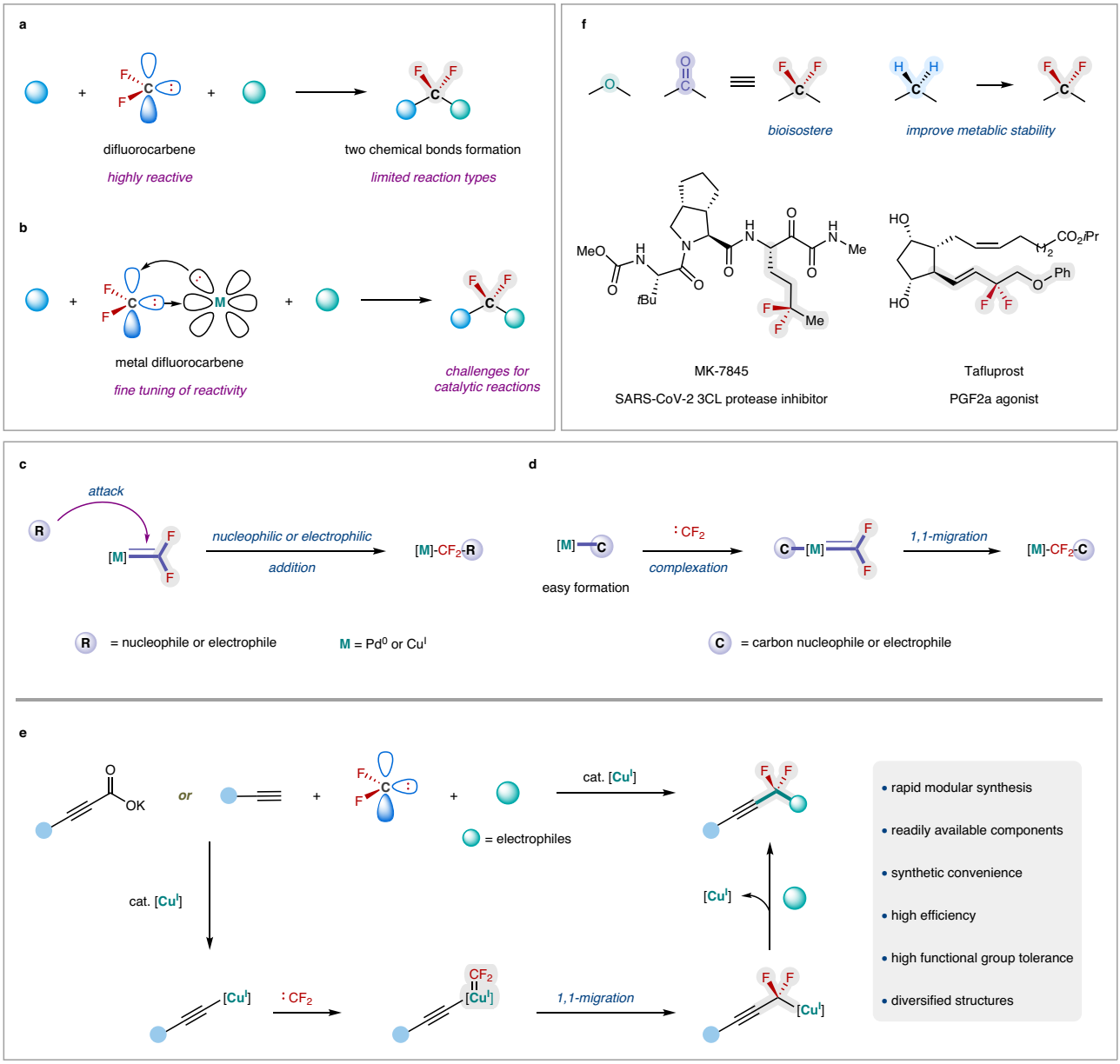

Fig. 1 | Metal difluorocarbene-involved catalytic coupling. a Coupling free difluorocarbene. **b** Metal difluorocarbene-involved catalytic coupling. **c** Previous nucleophilic or electrophilic addition of metal difluorocarbene. **d** Catalytic difluorocarbene transfer via 1,1-migration. **e** Our report on the copper difluorocarbene-involved catalytic *gem*-difluoropropargylation. **f** Unique properties of the CF_2 group and representative CF_2-containing bioactive molecules.

generation of **5** and increase the yield of **4** to 34% (entries 2-4, Supplementary Table 2). This finding is likely attributed to the preferential complexation between the electron-rich alkynyl copper species, stabilized by ligand **L4**, and the electron-deficient difluorocarbene. This interaction is more favorable than the complexation of alkynyl copper species with the carbon-carbon double bond of the electrophile **2a**. Consequently, the formation of the *gem*-difluoropropargyl copper complex occurs more rapidly via migratory insertion of difluorocarbene into the Cu-C bond than through the oxidative addition of the alkynyl copper to the electrophile. This kinetic preference effectively suppresses the formation of byproduct **5**. Replacing K_2CO_3 with Na_2CO_3 slightly improved the reaction efficiency (entry 5, Supplementary Table 3). However, the undesired defluorination of **8c** and the sensitivity of $[Cu^I]=CF_2$ to base make it challenging to further increase the yield. To circumvent these limitations, we chose readily available potassium propiolate **9b** as an alternative substrate. We envisioned that the relatively faster release of the alkynyl nucleophile through decarboxylation of **9b**, without the need for a base, would benefit the reaction efficiency. Similar to terminal alkyne **8c**, the ligand is critical for the reaction (entries 6-8, Supplementary Table 5), and **L4** remained the optimal ligand, providing **7** in 73% yield at 80 °C (entry 6). Decreasing the reaction temperature to 70 °C increased the yield to 85% (entry 9). To further optimize the reaction conditions, we examined a series of reaction parameters, including copper catalysts, solvents, catalyst loading amounts, reactant ratios, and reaction times (entries 10, 11, Supplementary Tables 6–11). Finally, the optimized reaction conditions were identified by shortening the reaction time to 30 min with 7.5% mol CuCl/**L4** as the catalyst (entry 12). Under these conditions, 1.5 equiv of **1** and 1.2 equiv of **2a** could provide **7** in 80% isolated yield. Notably, this reaction proceeded smoothly, even shortening the reaction time to 10 min (entry 13). This distinct feature is in sharp contrast to conventional copper-catalyzed fluoroalkylation reactions, which typically require a long time, thereby underscoring the advancement of the current copper-catalyzed difluorocarbene

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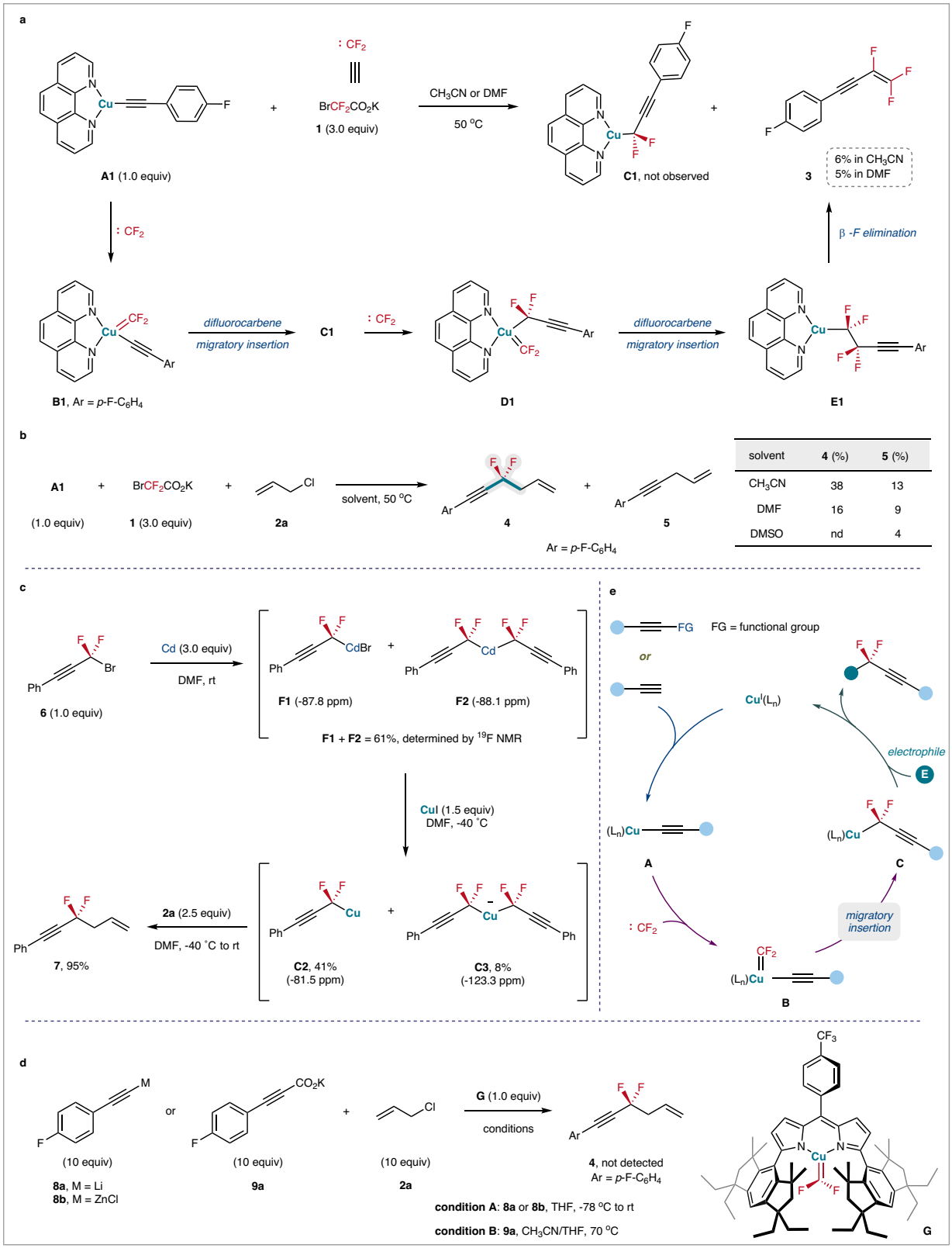

Fig. 2 | Mechanistic studies of *gem*-difluoropropargylation via 1,1-migration of copper difluorocarbene. a Stoichiometric reaction of alkynylcopper complex **A1** with difluorocarbene. **b** Stoichiometric reaction of **A1** with difluorocarbene and allyl chloride **2a**. **c** Preparation of alkynylcopper species and their reactions with **2a**. The number in parentheses is the ^{19}F NMR chemical shift. **d** Reaction of alkynyl nucleophiles with **2a** and copper difluorocarbene **G**. **e** Possible pathway for the copper difluorocarbene-involved catalytic *gem*-difluoropropargylation.

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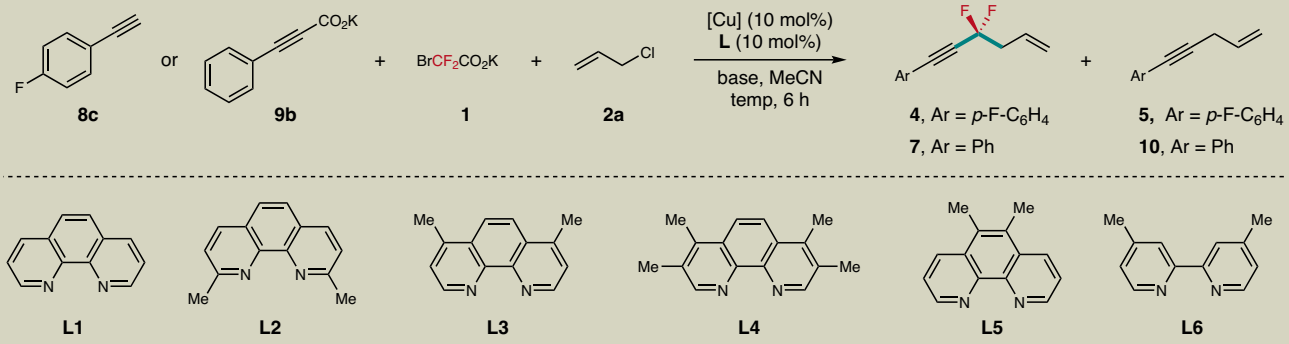
Table 1 | Representative results for the optimization of the reaction conditions[a]



Entry	[Cu]	L	Base	Temp (°C)	4 or 7, yield (%)[b]	5 or 10, yield (%)[b]
1[c]	CuCl	**L1**	K_2CO_3	50	**4**, 10	**5**, 5
2[c]	CuCl	**L2**	K_2CO_3	50	**4**, 25	**5**, 30
3[c]	CuCl	**L3**	K_2CO_3	50	**4**, 2	**5**, 37
4[c]	CuCl	**L4**	K_2CO_3	50	**4**, 34	**5**, nd
5[c]	CuCl	**L4**	Na_2CO_3	50	**4**, 38	**5**, nd
6[d]	CuCl	**L4**	--	80	**7**, 73	**10**, --
7[d]	CuCl	**L5**	--	80	**7**, 48	**10**, --
8[d]	CuCl	**L6**	--	80	**7**, 27	**10**, --
9[d]	CuCl	**L4**	--	70	**7**, 85	**10**, --
10[d]	CuBr	**L4**	--	70	**7**, 80	**10**, --
11[d]	CuI	**L4**	--	70	**7**, 55	**10**, --
12[d,e]	CuCl	**L4**	--	70	**7**, 82 (80)	**10**, --
13[d,e,f]	CuCl	**L4**	--	70	**7**, 83	**10**, --
14[d]	none	**L4**	--	70	**7**, nd	**10**, --
15[d]	CuCl	none	--	80	**7**, 3	**10**, --

[a]Reaction conditions (unless otherwise specified): **8c** or **9a** (0.2 mmol, 1.0 equiv), **1** (2.0 equiv), **2a** (1.5 equiv), MeCN (2 mL), 6 h.
[b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard; nd, not detected.
[c]Using **8c** as the substrate.
[d]Using **9b** as the substrate.
[e]**9b** (0.5 mmol, 1.0 equiv), **1** (1.5 equiv), **2a** (1.2 equiv), CuCl/**L4** (7.5 mol%), 30 min. The data in the parentheses is the isolated yield.
[f]The reaction was run in 10 min.

transfer reaction. No product was observed without copper salt or ligand (entries 14, 15), demonstrating the essential role of Cu/**L** in promoting the reaction. It should be mentioned that we did not observe the formation of the tetrafluorohomoproargylated byproduct during the reaction process. This result suggests that the oxidative addition of the *gem*-difluoropropargyl copper complex with the allyl electrophile is faster than the difluorocarbene elongation process. This preference is likely attributed to the relatively stronger Cu-CF_2 alkynyl bond, which results in a slower migratory insertion of the difluorocarbene compared to the oxidative addition of the *gem*-difluoropropargyl copper complex.

Substrates scope

With the viable reaction conditions in hand, we examined the scope of this copper difluorocarbene-involved catalytic *gem*-difluoropropargylation reaction (Fig. 3). Various potassium arylpropiolates were applied to this transformation (Fig. 3a), providing the corresponding *gem*-difluoropropargylated products efficiently (**4, 7, 12-33**). Generally, aromatic propiolates bearing an electron-donating substituent provided higher yields than electron-deficient substrates. The reaction exhibited high functional group tolerance. Base and nucleophile sensitive functional groups, such as ketone (**13**), ester (**14**), and nitrile (**16**), were compatible with the reaction; aryl fluoride (**4**), chloride (**21**), bromide (**17, 19-21**), and iodide (**18**) moieties underwent the current copper-catalyzed process smoothly. Additionally, the position of bromide in the aromatic ring did not affect the reaction efficiency. Para-, meta-, and ortho-aryl bromides efficiently delivered the corresponding *gem*-difluoropropargylated products (**17, 19, 20**). The high compatibility of the chlorobromoaryl moiety (**21**) offers a good opportunity for diversified transformations by sequential aryl bromide and chloride functionalization. Ferrocene- and thiophene-containing substrates were also employed in the reaction, yielding moderate to good yields (**22-24**). However, low yield was obtained with the pyridine-containing substrate (**25**). The reaction was not restricted to allyl chloride **2a**, as substituted allyl chlorides, including linear, branched, and cyclic allyl chlorides (**26-33**), underwent smooth coupling. Even highly reactive allyl chlorides bearing vinyl chloride (**31**) or unsaturated ester (**32**) were still amenable to the reaction. In the case of linear allyl chloride (**26**), no branched product was observed. The observed regioselectivity is likely due to the steric effect that influences the reductive elimination of the Cu(III) species, generated between the *gem*-difluoropropargyl copper complex and the allyl electrophile. Specifically, steric interactions between the *gem*-difluoropropargyl group and the substituent on the allyl moiety favor reductive elimination at the less hindered position, thereby yielding a linear product.

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In addition to arylpropiolates, alkyl- and silyl-substituted propiolates were competent coupling partners (**34**-**39**). The aliphatic side chain bearing a benzyloxy (**35**), chloride (**36**), sulfamide (**37**), or cyclopropyl (**38**) group did not interfere with the reaction efficiency. This approach could also be extended to propargyl electrophiles (Fig. 3b). One problem with this type of substrate is the formation of a

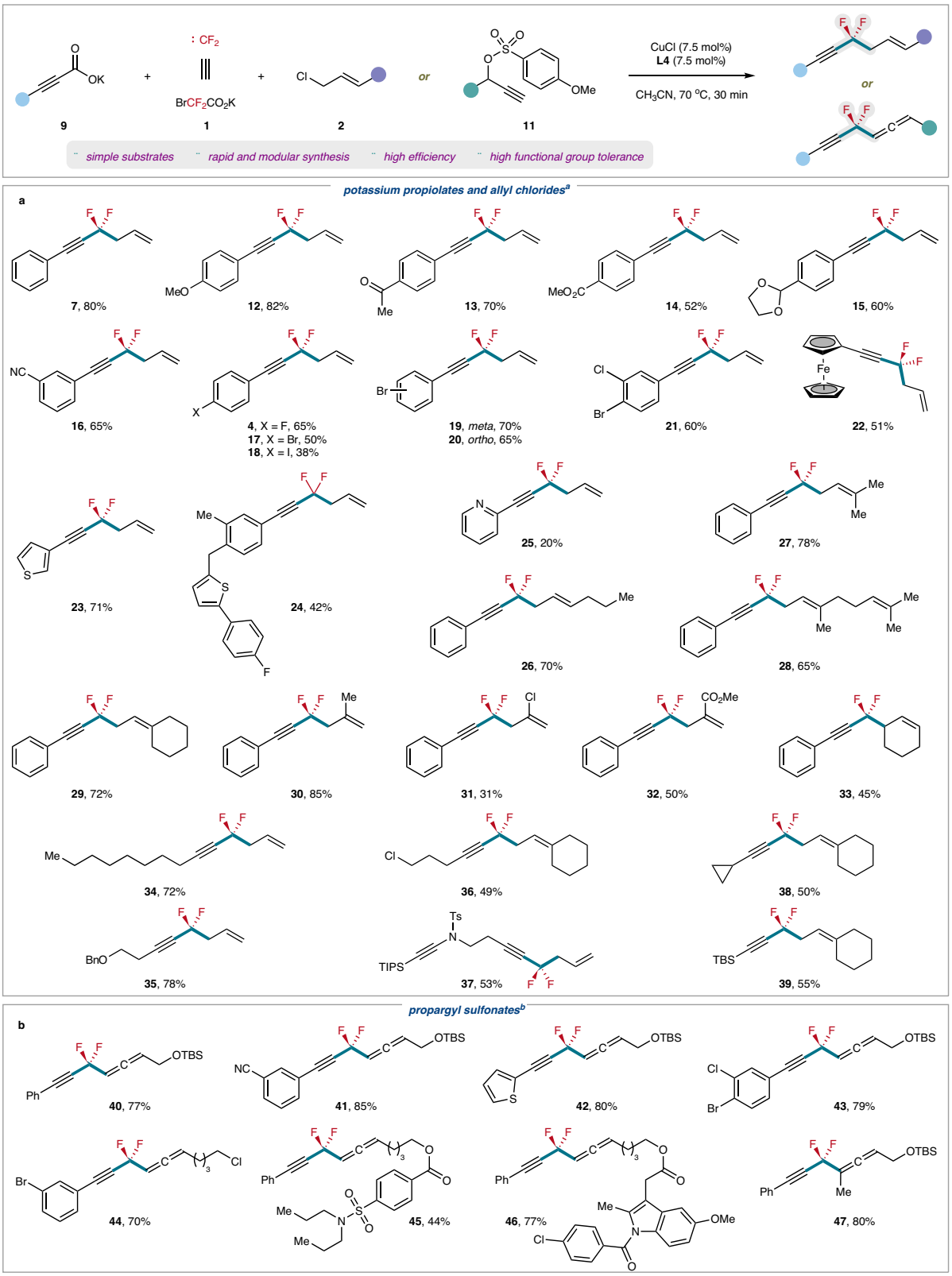

Fig. 3 | Copper difluorocarbene involved catalytic *gem*-difluoropropargylation. **a** Substrate scope of potassium propiolates and allyl chlorides. **b** Substrate scope of propargyl sulfonates. [a]**9** (0.5 mmol, 1.0 equiv), **1** (1.5 equiv), **2** (1.2 equiv), MeCN (5 mL). [b]**11** (0.5 mmol, 1.0 equiv), **1** (1.5 equiv), **9** (1.2 equiv). All reported yields are isolated yields.

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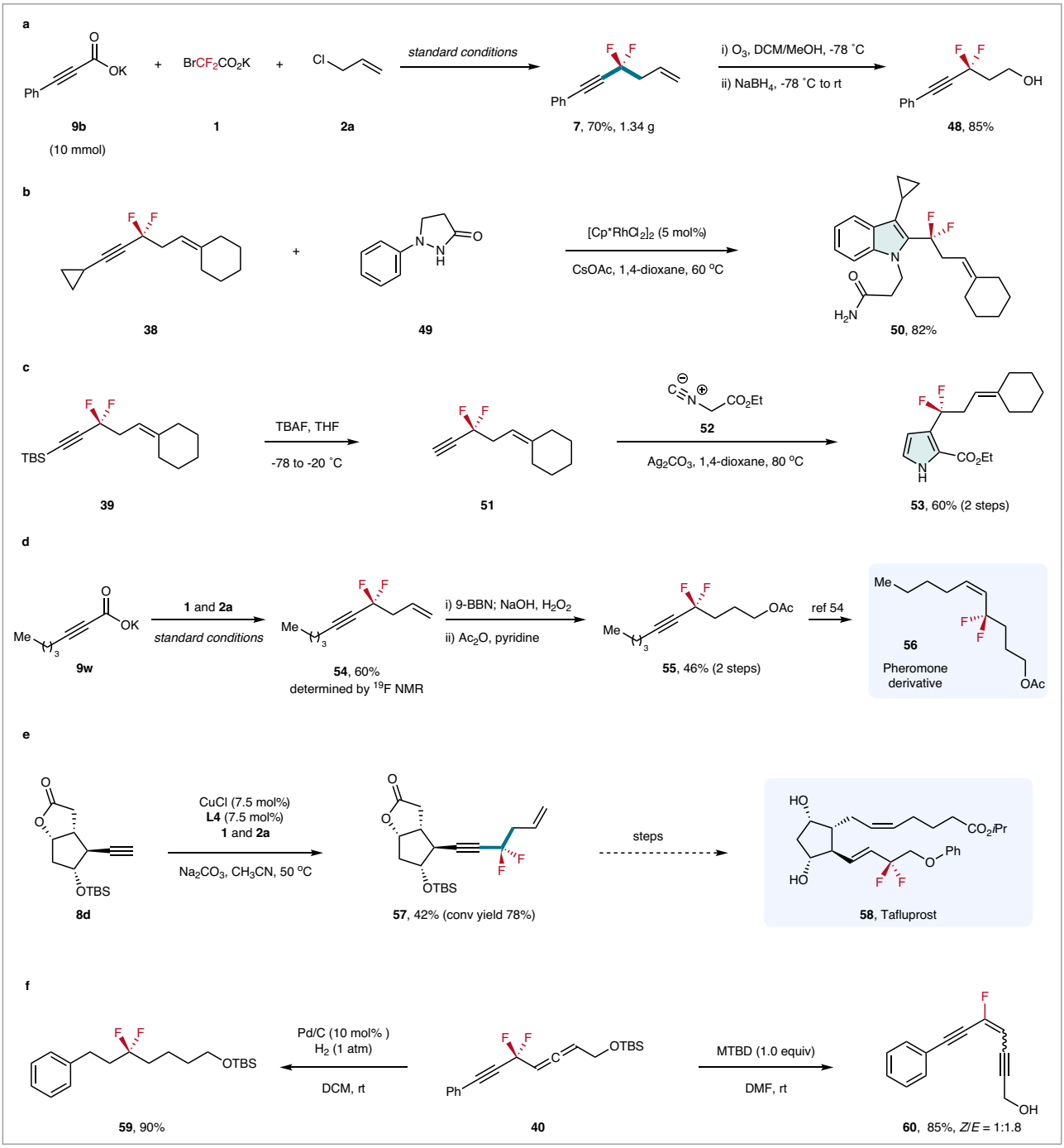

Fig. 4 | Diverse transformations of the *gem*-difluoropropargylated products. **a** Gram-scale synthesis of **7** and its transformation. **b** Synthesis of difluoroalkylated indole **46**. **c** Synthesis of difluoroalkylated pyrrole **49**. **d** Synthesis of the key intermediate **51** for pheromone derivative **52**. **e** Synthesis of the key intermediate **53** for PGF_{2a} analogue **54**. **f** Transformations of compound **40**.

copper-allenylidene complex between the copper catalyst and the propargyl electrophile[46]. This competitive side reaction significantly influences the current copper-catalyzed difluorocarbene transfer process. After extensive efforts (Supplementary Table 12), we found that using propargyl sulfonates as the limiting substrates could suppress this undesired side reaction, producing various *gem*-difluoropropargylated allenes with high efficiency. Although the synthesis of allenes has been well established[47–50], efficient methods for such fluoroalkylated allenes have yet to be reported. Given the synthetic versatility of allene and alkyne, the resulting *gem*-difluoropargylated allenes should be a valuable structure for diverse transformations. As depicted in Fig. 3b, arylpropiolates underwent smooth coupling with good functional group tolerance (**40**-**44**). Versatile synthetic handles, such as nitrile (**41**), thiophene (**42**), aryl bromide (**43**,**44**), and alkyl chloride (**44**) moieties, tolerate the reaction well. In contrast to the allyl electrophiles, arylpropiolate bearing an electron-withdrawing group provided a higher yield (**41**). The reaction is also compatible with complex molecule-containing substrates, as demonstrated by the efficient synthesis of *gem*-difluoropropargylated allenes **45** and **46**. Furthermore, trisubstituted allene **47** could also be achieved with high efficiency. However, alkylpropiolates yielded only 20–30% of the products, and using benzyl bromide as the electrophile

resulted in a 13% yield (for details, see the Supplementary Information). Notably, for all the coupling reactions described above, no [2 + 1] cycloaddition side products were generated between difluorocarbene and the unsaturated carbon-carbon bond[15], thereby further advancing this copper catalytic system.

Gram-scale reaction and applications

The reaction is readily scalable, as demonstrated by the gram-scale synthesis of **7** with high yield (Fig. 4a). The resulting *gem*-difluoropropargyl products can be elaborated through a myriad of transformations to create a diverse range of new organofluorine compounds. Selective oxidative cleavage of the carbon-carbon double bond of **7** with ozone, followed by reduction with $NaBH_4$, afforded alcohol **48** efficiently. Cyclization of **38** with phenidone **49** via rhodium catalysis produced difluoroalkylated indole **50** with high efficiency (Fig. 4b)[51]. The *gem*-difluoropropargyl structure could also be used to construct the difluoroalkylated pyrrole **53** through deprotection of **39**, followed by silver-catalyzed [3 + 2] reaction with ethyl isocyanoacetate **52** (Fig. 4c)[52]. Given the unique properties of the CF_2 group and critical applications of indole and pyrrole in medicinal chemistry, the rapid access to these complex fluorinated molecules that otherwise require tedious steps to prepare through conventional methods provides a good opportunity to discover new interesting bioactive molecules. Remarkably, this copper-catalyzed difluorocarbene transfer reaction could be used as a key step to introduce the CF_2 group at the metabolically labile allylic position of bioactive molecules. As shown in Fig. 4d, pheromone derivative **56**, a probe used to study hydrophobic interaction in pheromone reception, was rapidly accessed from **54** via two steps, followed by a reported procedure[53]. Since the *Z*-difluoroalkylated alkenes have been found in a series of pheromone analogs[53], this copper difluorocarbene-involved catalytic *gem*-difluoropropargylation should have applications in such compounds. Furthermore, using the (-)-corey lactone diol-derived terminal alkyne **8d** as the substrate could directly afford **53** by harnessing the current copper difluorocarbene chemistry (Fig. 4e). Although a 42% yield of **57** was obtained, 46% of **8d** could be recovered. Notably, compound **57** could be used as a potential key intermediate for synthesizing tafluprost **58**, a $PGF_{2\alpha}$ agonist for treating glaucoma[36], thus underscoring the synthetic utility of this transformation. The transformations of *gem*-difluoropropargylated allene **40** were also performed. Hydrogenation of **40** efficiently produced difluoroalkylated compound **59**. Treatment of **40** with MTBD (7-Methyl-1,5,7-triazabicyclo[4.4.0]decene-5) at room temperature selectively cleaved one of its C-F bonds, yielding a medicinally interesting enediyne **60** in good yield.

In summary, a copper difluorocarbene-involved catalytic coupling reaction has been developed. The stoichiometric reactions reveal that a difluorocarbene migratory insertion into the C-Cu bond is a key step in the catalytic cycle. This approach enables the rapid, modular synthesis of valuable *gem*-difluoropropargyl structures using a wide range of readily available, simple components, including potassium propiolates, terminal alkynes, and allyl/propargyl electrophiles. This reaction opens an avenue for the efficient and precise synthesis of organofluorine compounds. Most importantly, this work should also prompt the development of new metal difluorocarbene-involved catalytic coupling reactions in methodology development.

Methods

General procedure of the *gem*-difluoropropargylation

To a 25 mL Schlenk tube, CuCl (7.5 mol%), **L4** (7.5 mol%), potassium propiolate **9** (0.5 mmol, 1.0 equiv), and $BrCF_2CO_2K$ (1.5 equiv) were added under Ar. Anhydrous MeCN (5 mL) was added, and the mixture was stirred for 2 min before adding the corresponding allyl chloride **2** (1.2 equiv). The tube was screw-capped and heated at 70 °C (oil bath). After stirring for 30 min, the reaction was cooled to room temperature and concentrated in *vacuo*. The residue was purified by silica gel column chromatography and reverse-phase column chromatography to provide the desired product.

Data availability

Experimental procedures, characterization of new compounds, and all other data generated in this study are available in the Supplementary Information. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

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Author contributions

X. Zhang conceived the research concept. X. Zhang directed the project. X. Zeng conducted the experiments. S.-P. S. examined some substrates. X. Zeng and H.-Y. Z. analyzed the data. X. Zhang wrote the manuscript. All authors reviewed and edited the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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