Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 1455

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 5th December 2024
Accepted 16th December 2024

DOI: 10.1039/d4sc08247h

rsc.li/chemical-science

General access to furan-substituted *gem*-difluoroalkenes enabled by PFTB-promoted cross-coupling of ene-yne-ketones and difluorocarbene†

Na Li,[a] Chenghui Li,[a] Qianying Zhou,[a] Xin Zhang,[a] Zhouming Deng,[b] Zhong-Xing Jiang[c] and Zhigang Yang *[a]

Replacement of a carbonyl group with fluorinated bioisostere (*e.g.*, CF_2=C) has been adopted as a key tactical strategy in drug design and development, which typically improves potency and modulates lipophilicity while maintaining biological activity. Consequently, new *gem*-difluoroalkenation reactions have undoubtedly accelerated this shift, and conceptually innovative practices would be of great benefit to medicinal chemists. Here we describe an expeditous protocol for the direct assembly of furan-substituted *gem*-difluoroalkenes *via* PFTB-promoted cross-coupling of ene-yne-ketones and difluorocarbene. In this multi-step tandem reaction process, the furan ring and the *gem*-difluorovinyl group are constructed simultaneously in an efficient manner. These products can serve as bioisosteres of the α-carbonyl furan core, which is an important scaffold present in natural products and drug candidates. The broad generality and practicality of this method for late-stage modification of bioactive molecules, gram-scale synthesis and versatile derivatisation of products has been described. Biological activity evaluation showed that the *gem*-difluoroalkene skeleton exhibited dramatic antitumor activity.

1 Introduction

Fluorinated compounds are commonly used in a wide range of applications, including pharmaceuticals, materials, agrochemicals, and ^{19}F MRI agents.[1] The fluorine atom contributes to the unique properties of these compounds, including strong electronegativity, a small atomic radius (comparable to that of hydrogen), and a high dissociation energy of the C–F bond.[2] Among the fluorinated functionalities, the *gem*-difluorovinyl group (CF_2=C) has attracted increasing interest in drug design and discovery, since CF_2=C can serve as a bioisostere of the carbonyl group, which is highly hydrophilic and electrophilic and susceptible to easy metabolic oxidation (Scheme 1B).[3] The direct incorporation of this motif onto organic molecules instead of carbonyl can significantly improve their metabolic stability, bioavailability and modulated lipophilicity compared to their non-fluorinated bioisostere counterpart.[4,5] Classically, the *gem*-difluorovinyl moiety has been acquired *via* Wittig,[6] Julia-Kocienski,[7] cross-coupling,[8] and dehalogenate functionalization[5] reactions (Scheme 1C).

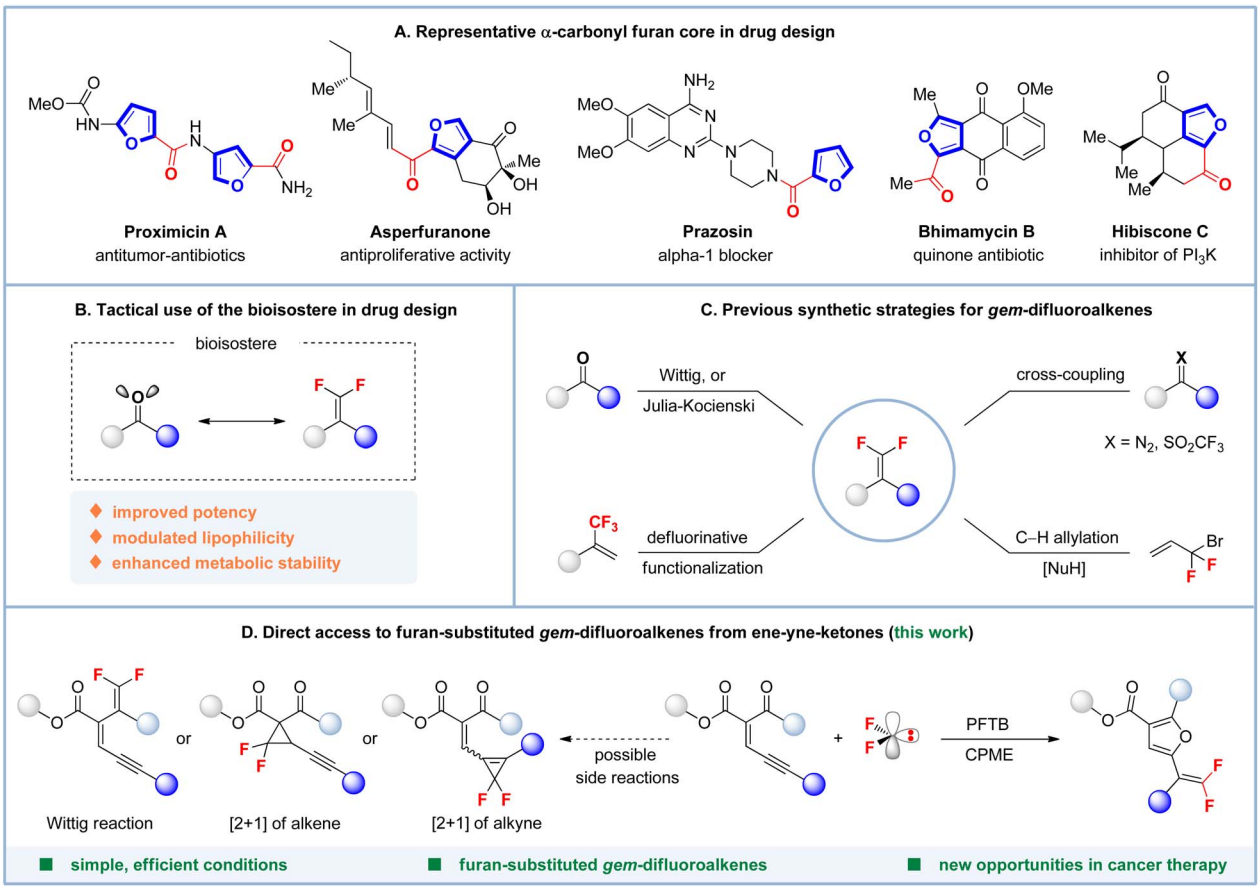
The α-carbonyl furan structure is particularly privileged, as it is found in a wide range of natural products and numerous pharmaceuticals (Scheme 1A).[9] There are still challenges to overcome to access furan-substituted *gem*-difluoroalkenes. Firsty, as an electron deficient singlet carbene species, difluorocarbene is more stable, although less reactive than other dihalocarbenes,[10] which readily react with carbonyl compounds and alkenes or alkynes and undergo typical carbene transformations such as the Wittig like reaction[6] or [2 + 1] cycloaddition.[11] Conjugated ene-yne-ketone[12b] bears ketone, alkenyl and alkynyl motifs, the present cyclized reaction needs to avoid the corresponding three potential side reactions (Scheme 1D). Secondly, most carbene reactions involving alkynes require associated transition metals (*e.g.*, Cu, Pd, Rh, *etc.*) to form metal carbene intermediates.[12] Moreover, the metal difluorocarbene strategy ([M]=CF_2) has also emerged as a powerful tool for the construction of direct difluoromethylation reactions since Zhang's pioneering work in 2015.[13] New reaction designs for the rapid assembly of furan-substituted *gem*-difluoroalkenes from readily available conjugated ene-yne-ketones with transition-metal-free conditions would be of considerable value in the development of pharmaceuticals and also represent

[a]*Department of Spine Surgery and Musculoskeletal Tumor, Zhongnan Hospital of Wuhan University, School of Pharmaceutical Sciences, Wuhan University, Wuhan, 430071, China. E-mail: zgyang@whu.edu.cn*

[b]*Department of Spine Surgery and Musculoskeletal Tumor, Zhongnan Hospital of Wuhan University, Wuhan, 430071, China*

[c]*State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, National Center for Magnetic Resonance in Wuhan, Wuhan Institute of Physics and Mathematics, Innovation Academy for Precision Measurement Science and Technology, Chinese Academy of Sciences-Wuhan National Laboratory for Optoelectronics, Wuhan 430071, China*

† Electronic supplementary information (ESI) available: Details on experimental procedures, screening of reaction conditions, characterization data, and copies of NMR. CCDC 2356931. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc08247h



Scheme 1 Background and synopsis of work. (A) Value of molecules containing an α-carbonyl furan core in pharmaceutical development. (B) Importance of *gem*-difluorovinyl moieties. (C) Traditional approaches to the synthesis of *gem*-difluoroalkenes. (D) This work: potential side reactions and the preparation of furan-substituted *gem*-difluoroalkenes *via* a one-pot, multistep process.

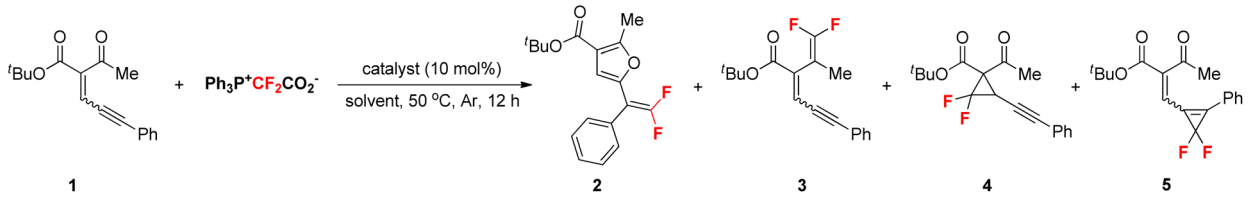
a significant challenge. Continuing our goal of increasing the adoption of fluorinated bioactive compounds in medicinal chemistry,[14] we set out our successful efforts to develop an expedient route to furan-substituted *gem*-difluoroalkenes. Several cyclized adducts were found to have excellent anti-proliferative activity against HeLa, 4T1 and HepG2 tumor cell lines.

2 Results and discussion

We commenced studies to optimize the tandem cyclization reaction conditions using conjugated ene-yne-ketone **1** as a model substrate. The reaction was conducted in 1,4-dioxane at 50 °C in the absence of transition metal. Initially, several classes of difluorocarbene reagents, such as $TMSCF_2Br$/TBAF, $BrCF_2COOEt/Cs_2CO_3$, $BrCF_2COOK/Cs_2CO_3$, HCF_2Cl/Cs_2CO_3, $TMSCF_3$/NaI and $Ph_3P^+CF_2CO_2^-$ were investigated, but no any fluorinated adducts were observed, except for the latter, which only gave the expected cyclized product **2** in 45% yield, and by-products **3–5** were not obtained (Table 1, entry 1). Encouraged by this result, common Lewis acids such as $AlCl_3$ or $BF_3 \cdot OEt_2$ was added individually as a catalyst, found to have no effect on reactivity, and the targeted product **2** was obtained in identical yield (Table 1, entries 2 and 3). For comparison, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which acts as an organocatalyst, was also investigated, taking advantage of its low acidity and hydrogen bond donating ability,[15] and the yield was slightly improved (Table 1, entry 4). In particular, switching the hydrogen bond donor catalyst from HFIP to perfluoro-*tert*-butanol (PFTB) gave the desired product **2** in a much better yield (Table 1, entry 5). These results indicate that the hydrogen bond can improve the reaction efficiency, which may be beneficial to facilitate the formation of a zwitterionic intermediate during the intramolecular cyclization process. Subsequently, other ether solvents such as THF, TBME and CPME were then examined, with the latter proving to be the most suitable, giving the expected cyclized adduct **2** in 84% yield (Table 1, entry 8). Finally, the reaction temperature and other Brønsted acids such as H_2O, PhOH, PhCOOH, CF_3COOH, *etc.* were also investigated and no superior results were observed (see SI for further optimization trials).

After the initial optimization, we investigated the generality of the tandem cyclization reaction by exploring a variety of conjugated ene-yne-ketones (Scheme 2). The influence of the ester group adjacent to the ketone moiety was first investigated. The ester moiety bearing a small hindered group such as methyl and long chain alkyl groups such as *n*-butyl, *n*-hexyl can slightly affect the efficiency of the cyclization reaction, the

Table 1 Optimization of the reaction conditions[a]



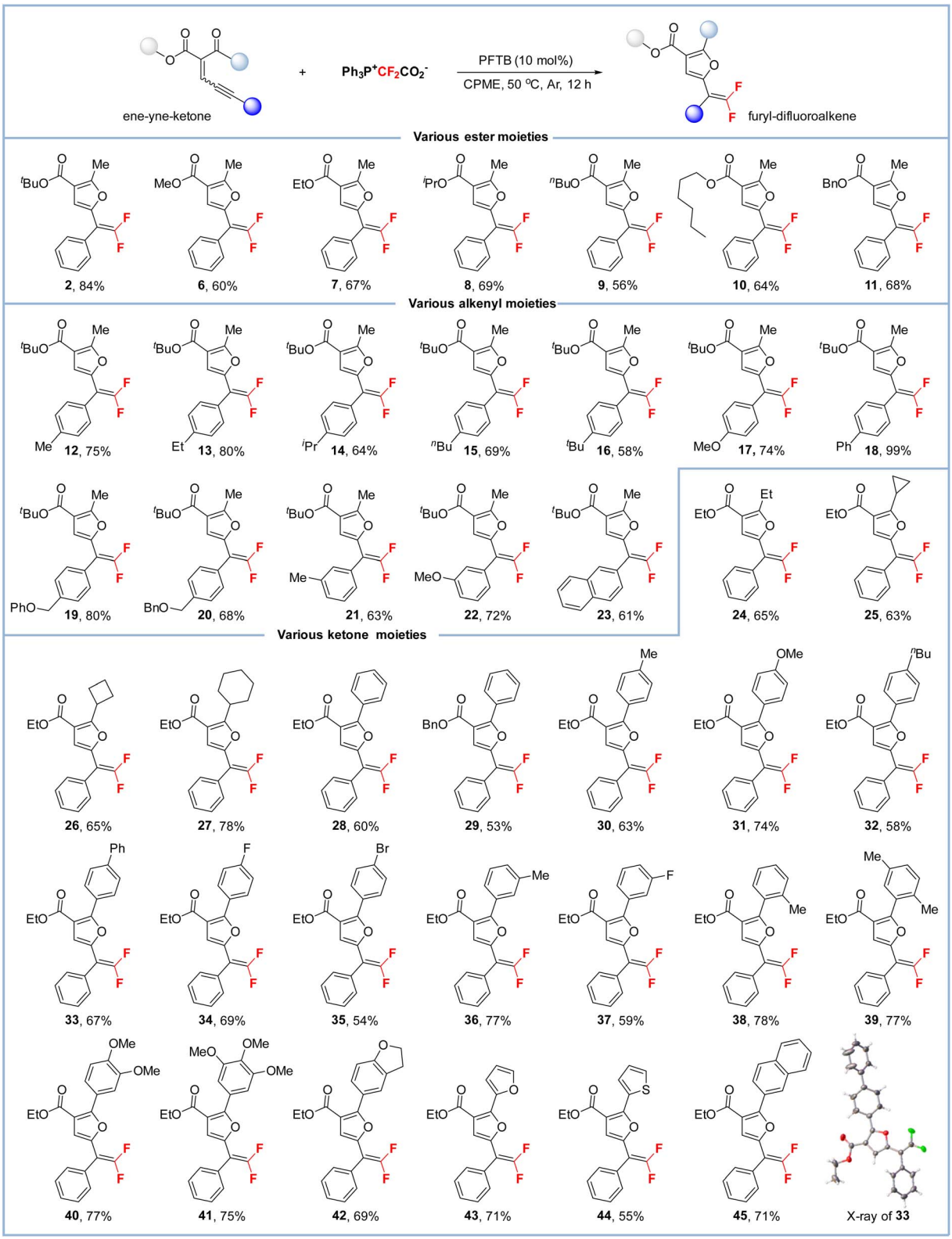
Entry	Catalyst	Solvent	Yield of **2** (%)
1	None	1,4-Dioxane	45
2	$AlCl_3$	1,4-Dioxane	45
3	BF_3 OEt_2	1,4-Dioxane	45
4	HFIP	1,4-Dioxane	51
5	PFTB	1,4-Dioxane	63
6	PFTB	THF	51
7	PFTB	TBME	63
8	PFTB	CPME	84

[a] Reaction conditions: **1** (E/Z = 1 : 1, 0.1 mmol), $Ph_3P^+CF_2CO_2^-$ (2.0 equiv.), catalyst (10 mol%) in solvent (1.0 mL) at 50 °C under Ar for 12 h. ^{19}F NMR yields with $PhCF_3$ as internal standard. **3–5** were not found. PFTB = Perfluoro-*tert*-butanol; CPME = Cyclopentyl methyl ether; HFIP = 1,1,1,3,3,3-Hexafluoroisopropanol.

corresponding products **6**, **9**, **10** were afforded in 60%, 56% and 64% yields respectively. This may be due to the fact that ester groups with little hindrance are more easily hydrolysed in acidic environments. The compatibility of the alkynyl moiety of the conjugated ene-yne-ketone was also further investigated by examining the electronic features and the positional change (*para* or *meta*) of the phenyl ring, which provided the expected cyclized adducts **12–22** in 58–99% yields. However, the phenyl ring with electron-deficient substituents or the *ortho* position of the phenyl ring was substituted and aliphatic alkynyl had a significant effect on the cyclization efficiency, resulting in the failure to form the desired product.

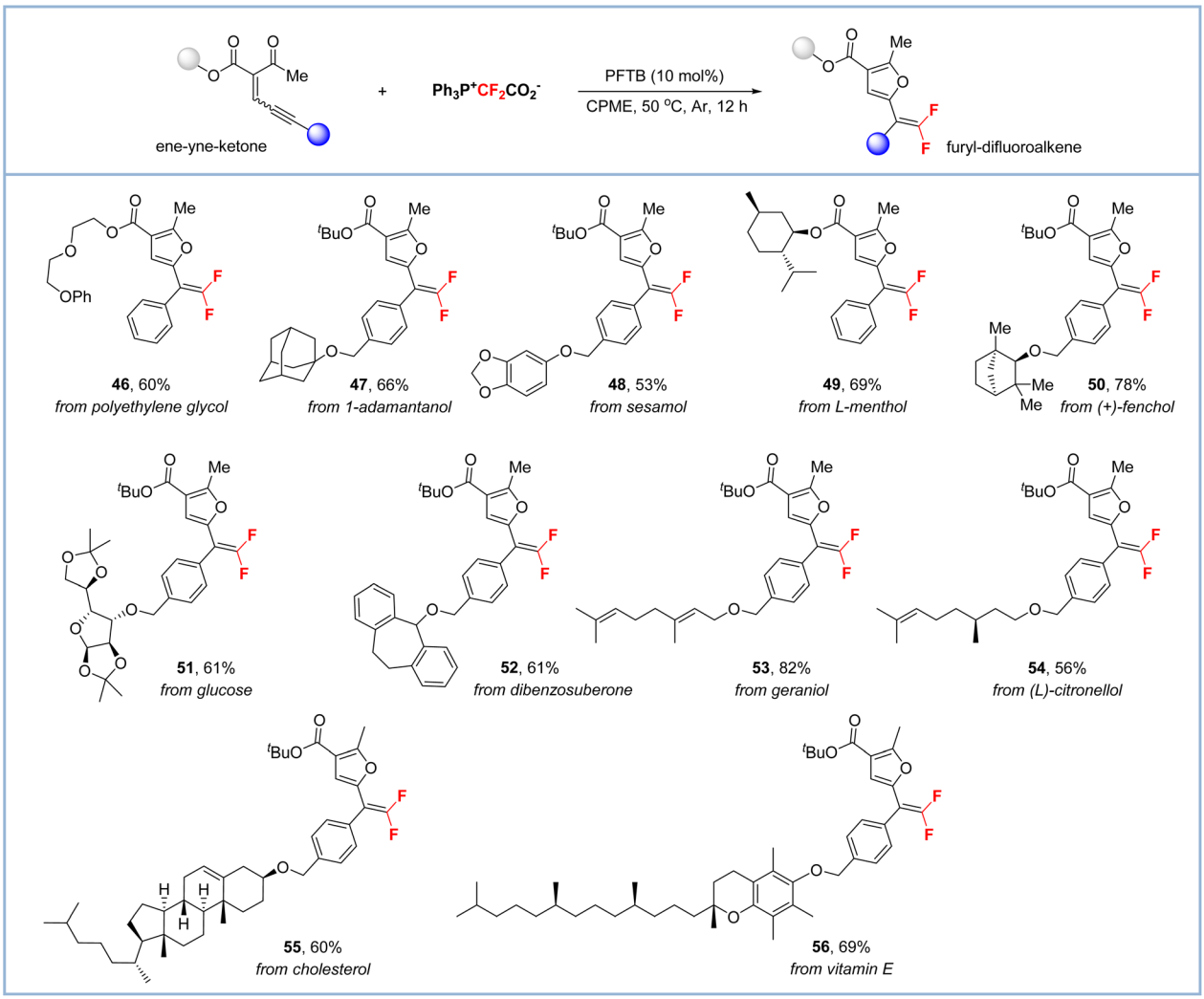
Fortunately, when the β-naphthylacetylene-derived substrate was subjected to this transformation, the reaction proceeded smoothly and delivered the desired product **23** in good yield. Subsequently, our attention was directed towards the evaluation of the scope of different substituents on the ketone skeleton. The synthesis of conjugated ene-yne-ketones can be achieved through the condensation of alkyne aldehydes and β-keto ethyl esters, which are commercially available in numerous candidate structures. Therefore, ethyl was chosen as the ester group for our next investigation. In general, the cyclization reactions of a wide range of aliphatic and aromatic ketone-containing substrates with $Ph_3P^+CF_2CO_2^-$ proceeded smoothly, enabling the furyl-difluoroalkenes with good yields (products **24–45**). For example, ketone moieties containing aliphatic groups such as ethyl, cyclopropyl, cyclobutyl and cyclohexyl were found to be well compatible and provided the desired products **24–27** in 63–78% yields. For the aromatic ketones, the steric hindrance (*ortho*) and the different electron properties at the *para* and *meta* positions had little effect on the reaction efficiency under the present conditions, giving the desired adducts **28–38** in good yields. Incorporating multiple substituents such as 2,5-dimethyl, 3,4-dimethoxy, 3,4,5-trimethoxy into the benzene ring could slightly improve the reaction efficiency (products **39–41**). Gratifyingly, the present protocol has also been successfully applied to medically relevant heteroaromatic ring (*e.g.*, dihydrobenzofuryl, furyl, and thienyl) and fused ring (2-naphthyl) substrates with no loss of efficiency (products **42–45**). Finally, the structure of **33** was unambiguously confirmed by X-ray crystallography analysis (CCDC 2356931).

The excellent functional group compatibility mentioned above further encourages us to apply this approach to the late-stage modification of bioactive molecules, natural products and therapeutic agents. To our delight, furyl-difluoroalkene analogues of polyethylene glycol and 2-adamantanol were successfully synthesized in satisfactory yields (products **46–47**). Conjugated ene-yne-ketones derived from small molecules such as sesamol, L-menthol and (+)-fenchol were suitable substrates, although the former gave a relatively low yield (products **48–50**). Similarly, substrates derived from glucose and dibenzosuberone were readily converted to the corresponding adducts **51** and **52** in identical yields (61%). Geraniol and citronellol,[16] which have similar structures, were isolated from plants of the genus Geranium and derivatised on the substrates, the former delivering the corresponding product **53** in excellent yields, while the latter was moderate (**54**). Vitamin E, a plant-based antioxidant essential for human health,[17] and cholesterol are both crucial for cell membrane structure, signal transduction, and overall human health.[18] Conjugated ene-yne ketones derived from them as complex natural products could also be readily subjected to cyclized *gem*-difluorovinylation reactions despite unprecedentedly high molecular weights (products **55–56**). All these results show that this current protocol opens a new door for the direct modification of biologically active molecules and drugs without the need for multi-step parallel synthesis, which could facilitate new drug design in the future (Scheme 3).



Scheme 2 Substrate scope.[a] Standard reaction conditions: conjugated ene-yne-ketone ($E/Z = 1:1$, 0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (2.0 equiv.), and PFTB (10 mol%) in CPME (5.0 mL) at 50 °C under Ar for 12 h. Isolated yields are shown.

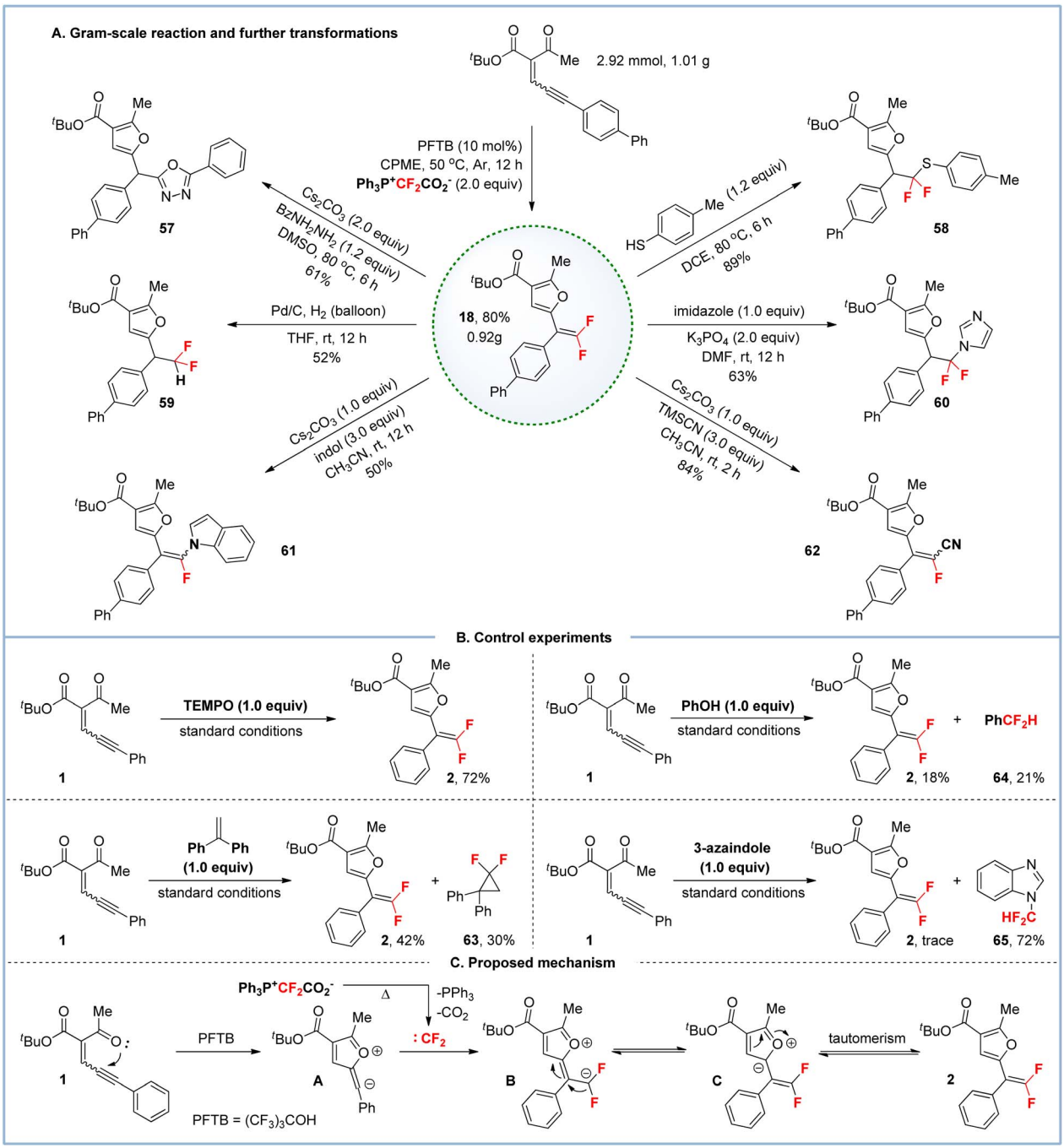
To demonstrate the applicability of the cyclized *gem*-difluorovinylation reaction, a gram-scale reaction was carried out with 1.01 g of conjugated ene-yne-ketone and $Ph_3P^+CF_2CO_2^-$ (2.0 equiv.), delivering the corresponding adduct **18** (0.92 g) in 80% isolated yield, with a slight decrease in efficiency compared to the small-scale reaction (Scheme 4A).



Scheme 3 Late-stage functionalization of bioactive molecules.[a] Standard reaction conditions: conjugated ene-yne-ketone (E/Z = 1 : 1, 0.3 mmol), $Ph_3P^+CF_2CO_2^-$ (2.0 equiv.), and PFTB (10 mol%) in CPME (3.0 mL) at 50 °C under Ar for 12 h. Isolated yields are shown.

Furans and their derivatives are important scaffolds and are routinely used in drug discovery, while the *gem*-difluorovinyl group, which serves as a fluorinated synthon, has recently attracted considerable attention from chemists, such as its use for nucleophilic additions,[19] defluorinative functionalization,[5e] *etc.* Therefore, we expected the resulting furan-substituted *gem*-difluoroalkenes to undergo various synthetic transformations. As shown in Scheme 4A, the treatment of product **18** with benzoyl hydrazine in DMSO at 80 °C resulted in the observation of a disubstituted 1,3,4-oxadiazole **57** in a yield of 61% by a cyclization process in the presence of an excess amount of Cs_2CO_3. Interestingly, the nucleophilic addition reactions of *gem*-difluoroalkenation were observed when heteroatomic nucleophiles, such as 4-methylbenzenethiol and imidazole, were employed, resulting in the corresponding products **58** and **60** with satisfactory yields. As anticipated, the *gem*-difluorovinyl moiety was also readily hydrogenated in THF in the presence of hydrogen (balloon) and catalytic palladium on activated carbon (Pd/C), resulting in the formation of CF_2H **59** in a moderate yield. Defluorinating substitutions can be achieved by treating product **18** with strong nucleophiles such as indole or TMSCN at room temperature in the presence of Cs_2CO_3, and the trisubstituted α-monofluoroalkenes **61–62** were obtained in good yields.

In order to elucidate the possible reaction mechanism, a series of control experiments were conducted (Scheme 4B). The addition of TEMPO, a free radical inhibitor, under standard conditions resulted in a slight effect on the reaction efficiency, indicating that the free radical pathway could be excluded. As a common carbene scavenger, 1,1-diphenylethylene was then subjected to the cyclized *gem*-difluorovinylation reaction, the reaction was significantly blocked and accompanied by the formation of a *gem*-difluorinated cyclopropane **63** in 30% yield. Furthermore, the reactions were almost completely suppressed when phenol and 3-azaindole were added individually to the reaction system. The accompanying difluorocarbene-trapped products **64** and **65** were identified by ^{19}F NMR in 21% and 72% yields, respectively. The above results indicated that the



Scheme 4 Gram-scale synthesis, synthetic transformations, and mechanistic studies.

present cyclized reaction proceeded through a difluorocarbene route.

Based on the results of the above control experiments and related literature studies,[10] a hypothetical reaction pathway is illustrated as shown in Scheme 4C. Initially, the conjugated ene-yne ketone **1** was activated by the $(CF_3)_3COH$ (PFTB), which can take advantage of its low acidity and hydrogen bonding ability, similar to $(CF_3)_2CHOH$ (HFIP),[15] followed by an intramolecular nucleophilic attack of carbonyl oxygen, forming the zwitterionic intermediate **A**, which could be further stabilized by PFTB. Subsequently, the vinyl anion of intermediate **A** rapidly captured a difluorocarbene species ($:CF_2$) generated by the thermal dissociation of $Ph_3P^+CF_2CO_2^-$ to form a new zwitterionic intermediate **B/C**. Finally, the expected furan-substituted *gem*-difluoroalkene **2** was obtained *via* the tautomerism equilibrium of intermediate **B/C**.

Given the prevalence of the α-carbonyl furan core in medicinal design, we are particularly interested in exploring the antitumor activities of the synthesized furan-substituted *gem*-difluoroalkene, which serve as its bioisostere. After initial

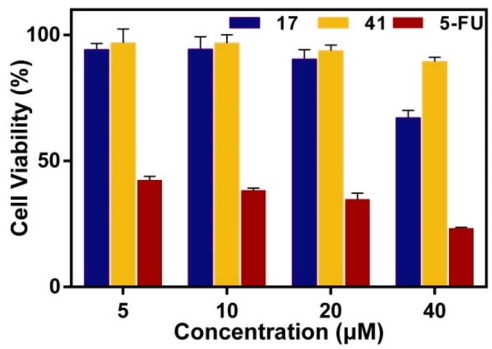
evaluation in HeLa human cervical cancer cells using a CCK-8 assay, compounds **11**, **17**, **38**, **41**, **42**, and **44** were found to exhibit high activities (see SI for details). These compounds were then selected for further testing against cancer cell lines using the well-known fluorinated anticancer drug 5-fluorouracil (5-FU) as a positive control. Besides HeLa cells, the other two cancer cell lines are murine breast cancer cells (4T1) and human hepatoma cells (HepG2). As shown in Fig. 1A, the results of the structure–activity relationship (SAR) studies indicated that compounds bearing three methoxy groups at the 3,4,5 positions of the phenyl ring in vicinity to the ester moiety, or one methoxy at the *para* position of the phenyl ring in vicinity to the *gem*-difluorovinyl moiety, exhibited enhanced activity. The compounds **17** and **41** exhibited potent inhibitory potency in the 4T1 cell line, with IC_{50} values of 21.01 and 24.27 μM, respectively.

Subsequently, the cytotoxicity of *gem*-difluoroalkene analogs **17** and **41** was evaluated in human normal mammary epithelial cells (MCF-10A) to ascertain their potential as therapeutic agents, with 5-FU serving as the positive control. As illustrated

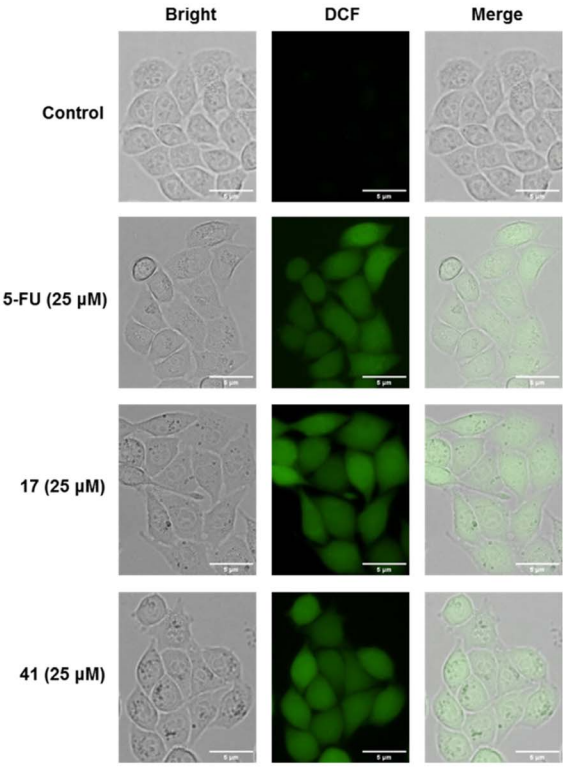
A. Antitumor activities of furan-substituted *gem*-difluoroalkenes

Compounds	IC_{50} (μM) ± SD		
	HeLa	4T1	HepG2
11	> 50	34.49 ± 0.56	> 50
17	47.25 ± 0.13	21.01 ± 0.46	> 50
38	> 50	27.71 ± 1.11	> 50
41	27.28 ± 0.89	24.27 ± 0.76	41.51 ± 0.74
42	> 50	33.05 ± 0.58	> 50
44	> 50	39.42 ± 0.64	> 50
5-FU	9.79 ± 0.37	0.15 ± 0.04	4.96 ± 0.20

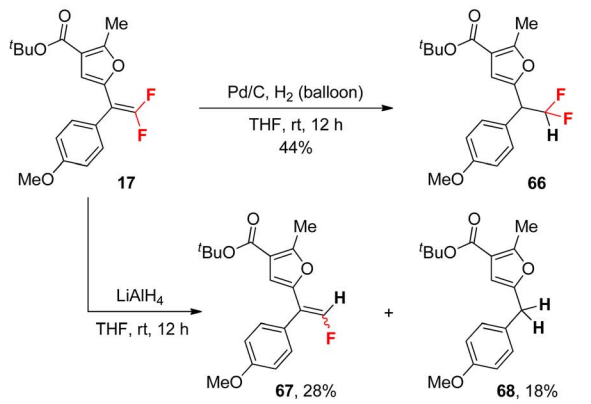
B. Toxicity of compounds **17** and **41** on MCF-10A



C. Quantification of intracellular ROS levels using DCFH-DA



D. Elaboration of the *gem*-difluorovinyl motif of compound **17**



E. Comparison of antitumor activity (**66**, **67**, **68** vs. **5-FU**)

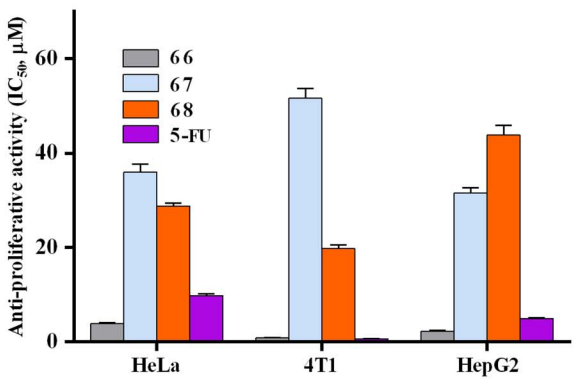


Fig. 1 Biological activity evaluation. (A) Cells were incubated with compounds for 48 h and cell viability was measured by CCK-8 assay; IC_{50} is the concentration of compound required to inhibit cell growth by 50%; SD (standard deviation) of three independent experiments. (B) Toxicity of compounds **17**, **41** and 5-FU on normal cell (MCF-10A). (C) ROS levels in HeLa cells were detected by DCFH-DA staining after incubation with compounds **17**, **41** and 5-FU at 25 μM for 24 h. (D) Diversification of *gem*-difluorovinyl-containing product **17**. (E) Anti-proliferative activities on HeLa, 4T1 and HepG2 cell lines for compound **17** and its derivatives (IC_{50}, μM).

in Fig. 1B, at concentrations of 5, 10, 20 and 40 μM, the cytotoxicity of compounds **17** and **41** to MCF-10A cells was found to be significantly lower than that of 5-FU. The results indicate that furan-substituted *gem*-difluoroalkenes **17** and **41** may be relatively safe *in vitro* and feasible as effective agents for cancer therapy, which deserves further focus in the future.

Typically, the level of intracellular reactive oxygen species (ROS) is often associated with apoptosis of tumor cells.[20] DCFH-DA is an oxidation-sensitive fluorescent probe that can penetrate cell membranes and be enzymatically hydrolyzed into free DCFH, which is then oxidized by intracellular ROS to form DCF with green fluorescence. As shown in Fig. 1C, after 24 hours of incubation of 4T1 cells with 25 μM of **17** and **41**, the green fluorescence was significantly increased compared to the control group as observed by fluorescence microscopy. These results suggest that both compounds are capable of inducing ROS production in 4T1 cells, thereby increasing intracellular ROS levels.

Finally, to determine whether the fluorine-containing group on the product is beneficial to its antitumor activity, several transformations were performed focusing on the *gem*-difluorovinyl motif of compound **17** (Fig. 1D). The *gem*-difluoroalkene **17** is readily converted to the CF_2H-containing product **66** in the presence of Pd/C and hydrogen. In addition, the monofluoroalkene **67** was readily accessible by further hydrodefluorination of the *gem*-difluorovinyl motif with $LiAlH_4$ as reductant, accompanied by the formation of the defluorinated product **68**, which is difficult to obtain by conventional strategies. With these derivatives of *gem*-difluoroalkene **17**, we then evaluated their biological activity in cells, focusing on their fluorinated units for comparison. As shown in Fig. 1E, fluorinated compounds **66** and **67** as well as non-fluorinated furan core compound **68** showed good anticancer activities against all the above three cancer cell lines. In particular, compound **66**, in which the *gem*-difluorovinyl group is hydrogenated, was found to exhibit the most excellent inhibitory activity against HeLa and HepG2 cancer cell lines, significantly exceeding that of the classical fluorine-containing anticancer drug 5-FU, with IC_{50} values of 3.92 and 2.31 μM, respectively. These results clearly demonstrated the potential of the fluorine-containing scaffold as a favorable motif for enhancing the biological properties of drug candidates containing a furan core.

3 Conclusions

In conclusion, we have developed a general PFTB-promoted cyclized *gem*-difluorovinylation approach by using conjugated ene-yne-ketones as the furan source and $Ph_3P^+CF_2CO_2^-$ as an efficient $:CF_2$ agent to access furan-substituted *gem*-difluoroalkenes that serve as bioisosteres of the α-carbonyl furan core. Three potential side reactions based on the ketone, alkenyl, and alkynyl moieties of conjugated ene-yne-ketones with difluorocarbene were not been identified. The late-stage functionalization of naturally occurring biomolecules and drug-derived complex molecules, as well as the synthetic conversion of the resulting furyl-difluoroalkenes to high-value fluorinated compounds, were demonstrated to highlight the synthetic value of this protocol. Many products showed dramatic antiproliferative activity in HeLa, 4T1 and HepG2 tumor cell lines. Among them, the derivative with hydrogenated *gem*-difluorovinyl moiety (**66**) showed the most potent effect against the HeLa and HepG2 cells with IC_{50} values of 3.92 and 2.31 μM, respectively, exceeding that of the positive control 5-fluorouracil (5-FU), opening new opportunities in cancer therapy.

Data availability

Details on experimental procedures and characterization data, as well as X-ray data of **33**, are available in the ESI.†

Author contributions

Z. Yang conceived the idea, designed the research project, and drafted the manuscript. N. Li performed the chemical experiments, conducted cell-based assays and was responsible for compiling the ESI.† C. Li, Q. Zhou and X. Zhang helped with the chemical experiments. Z. Deng and Z.-X. Jiang assisted in the design of the research project. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are thankful for financial support from the National Key Research and Development Program of China (grant no. 2018YFA0704000), the National Natural Science Foundation of China (grant no. 22077098), and the Natural Science Foundation of Hubei Province (2022CFB204). We also thank Ran Zhang from the Core Facility of Wuhan University for his assistance with NMR and X-ray crystallographic analysis.

Notes and references

1 For selected reviews and book, see:(*a*) K. Uneyama, *Organofluorine Chemistry*, Wiley-Blackwell, New Delhi, 2006; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (*c*) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496–3508; (*d*) T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16–29; (*e*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518; (*f*) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksch, *Chem. Rev.*, 2019, **119**, 10718–10801; (*g*) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467; (*h*) P. T. Lowe and D. O'Hagan, *Chem. Soc. Rev.*, 2023, **52**, 248–276.

2 (*a*) J. Wahsner, E. M. Gale, A. Rodríguez-Rodríguez and P. Caravan, *Chem. Rev.*, 2019, **119**, 957–1057; (*b*) T. Wu, A. Li, K. Chen, X. Peng, J. Zhang, M. Jiang, S. Chen,

X. Zheng, X. Zhou and Z.-X. Jiang, *Chem. Commun.*, 2021, **57**, 7743–7757.

3 (*a*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (*b*) H. Yanai and T. Taguchi, *Eur. J. Org Chem.*, 2011, **2011**, 5939–5954; (*c*) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.

4 (*a*) C. Leriche, X. He, C.-W. T. Chang and H.-W. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 6348–6349; (*b*) G. Magueur, B. Crousse, M. Ourévitch, D. Bonnet-Delpon and J.-P. Bégué, *J. Fluorine Chem.*, 2006, **127**, 637–642.

5 For selected reviews, see:(*a*) G. Chelucci, *Chem. Rev.*, 2012, **112**, 1344–1462; (*b*) M. Decostanzi, J.-M. Campagne and E. Leclerc, *Org. Biomol. Chem.*, 2015, **13**, 7351–7380; (*c*) X. Zhang and S. Cao, *Tetrahedron Lett.*, 2017, **58**, 375–392; (*d*) X.-J. Zhang, Y.-M. Cheng, X.-W. Zhao, Z.-Y. Cao, X. Xiao and Y. Xu, *Org. Chem. Front.*, 2021, **8**, 2315–2327; (*e*) P. H. S. Paioti, S. A. Gonsales, S. Xu, A. Nikbakht, D. C. Fager, Q. Liu and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208742; (*f*) K. Wang and W. Kong, *ACS Catal.*, 2023, **13**, 12238–12268.

6 (*a*) D. G. Cox, N. Gurusamy and D. J. Burton, *J. Am. Chem. Soc.*, 1985, **107**, 2811–2812; (*b*) I. Nowak and M. J. Robins, *Org. Lett.*, 2005, **7**, 721–724; (*c*) J. Zheng, J. Cai, J.-H. Lin, Y. Guo and J.-C. Xiao, *Chem. Commun.*, 2013, **49**, 7513–7515; (*d*) J. Zheng, J.-H. Lin, J. Cai and J.-C. Xiao, *Chem.–Eur. J.*, 2013, **19**, 15261–15266; (*e*) K. Aikawa, W. Toya, Y. Nakamura and K. Mikami, *Org. Lett.*, 2015, **17**, 4996–4999.

7 (*a*) Y. Zhao, W. Huang, L. Zhu and J. Hu, *Org. Lett.*, 2010, **12**, 1444–1447; (*b*) B. Gao, Y. Zhao, M. Hu, C. Ni and J. Hu, *Chem.–Eur. J.*, 2014, **20**, 7803–7810; (*c*) X.-P. Wang, J.-H. Lin, J.-C. Xiao and X. Zheng, *Eur. J. Org Chem.*, 2014, **2014**, 928–932; (*d*) Q. Luo, X. Wang and J. Hu, *Tetrahedron*, 2022, **113**, 132694.

8 (*a*) M. Hu, C. Ni, L. Li, Y. Han and J. Hu, *J. Am. Chem. Soc.*, 2015, **137**, 14496–14501; (*b*) Z. Zhang, W. Yu, C. Wu, C. Wang, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 273–277; (*c*) R.-Y. Yang, H. Wang and B. Xu, *Chem. Commun.*, 2021, **57**, 4831–4834; (*d*) G. Wang, W. Li, T. Liu, Y. Zhang, B. Wang, F. Xue, W. Jin, C. Ma, Y. Xia and C. Liu, *Chem. Sci.*, 2022, **13**, 11594–11599.

9 (*a*) H.-P. Fiedler, C. Bruntner, J. Riedlinger, A. T. Bull, G. Knutsen, M. Goodfellow, A. Jones, L. Maldonado, W. Pathom-aree, W. Beil, K. Schneider, S. Keller and R. D. Sussmuth, *J. Antibiot.*, 2008, **61**, 158–163; (*b*) C. C. C. Wang, Y.-M. Chiang, M. B. Praseuth, P.-L. Kuo, H.-L. Liang and Y.-L. Hsu, *Basic Clin. Pharmacol. Toxicol.*, 2010, **107**, 583–589; (*c*) S. K. Manna, S. Giri, S. Mondal, R. N. Sana, A. K. Samal and A. Mandal, *ChemistrySelect*, 2023, **8**, e202203150; (*d*) C. Besley, D. P. Rhinehart, T. Ammons, B. C. Goess and J. S. Rawlings, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 3087–3091.

10 For selected reviews, see:(*a*) P. J. Brothers and W. R. Roper, *Chem. Rev.*, 1988, **88**, 1293–1326; (*b*) C. Ni and J. Hu, *Synthesis*, 2014, **46**, 842–863; (*c*) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278; (*d*) J. W. Lee, K. N. Lee and M.-Y. Ngai, *Angew. Chem., Int. Ed.*, 2019, **58**, 11171–11181; (*e*) J.-H. Lin and J.-C. Xiao, *Acc. Chem. Res.*, 2020, **53**, 1498–1510; (*f*) J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco and V. Gouverneur, *Chem. Soc. Rev.*, 2021, **50**, 8214–8247; (*g*) F.-L. Qing, X.-Y. Liu, J.-A. Ma, Q. Shen, Q. Song and P. Tang, *CCS Chem.*, 2022, **4**, 2518–2549; (*h*) X. Ma, J. Su and Q. Song, *Acc. Chem. Res.*, 2023, **56**, 592–607.

11 (*a*) F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash and G. A. Olah, *Angew. Chem., Int. Ed.*, 2011, **50**, 7153–7157; (*b*) L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2013, **52**, 12390–12394; (*c*) X.-Y. Deng, J.-H. Lin, J. Zheng and J.-C. Xiao, *Chem. Commun.*, 2015, **51**, 8805–8808; (*d*) A. García-Domínguez, T. H. West, J. J. Primozic, K. M. Grant, C. P. Johnston, G. G. Cumming, A. G. Leach and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2020, **142**, 14649–14663.

12 For selected reviews on metal carbenes and conjugated ene-yne-ketones, see:(*a*) L. D. Shirtcliff, S. P. McClintock and M. M. Haley, *Chem. Soc. Rev.*, 2008, **37**, 343–364; (*b*) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810–13889; (*c*) S. Teng and J. Zhou, *Chem. Soc. Rev.*, 2022, **51**, 1592–1607. For selected recent examples on conjugated ene-yne-ketones, see: (*d*) S. Mao, L. Tang, C. Wu, X. Tu, Q. Gao and G. Deng, *Org. Lett.*, 2019, **21**, 2416–2420; (*e*) T. Chen, W. Wu and Z. Weng, *Tetrahedron*, 2019, **75**, 130751; (*f*) J. Huang, F. Li, L. Cui, S. Su, X. Jia and J. Li, *Chem. Commun.*, 2020, **56**, 4555–4558; (*g*) H. Peng, Y. Wan, Y. Zhang and G. Deng, *Chem. Commun.*, 2020, **56**, 1417–1420; (*h*) L. Tang, Y. Zhang and G. Deng, *J. Org. Chem.*, 2021, **86**, 13245–13251; (*i*) Y. Wan, Y. Zhu, H. Peng and G. Deng, *J. Org. Chem.*, 2022, **87**, 281–293; (*j*) Q. Jiang, A. Li, X. Liu, Y. Yu, B. Zhu and H. Cao, *J. Org. Chem.*, 2022, **87**, 7056–7063; (*k*) H.-J. Cho, Y. L. Kim and J. H. Kim, *J. Org. Chem.*, 2022, **87**, 16424–16435; (*l*) M. Zhang, M. Liu, Y. Qiu, M. Peng, Z. Zhang, S. Song, X.-B. Chen and F. Yu, *Adv. Synth. Catal.*, 2024, **366**, 2363–2369; (*m*) G. Zhang, X. Cai, J. Jia, B. Feng, K. Yang and Q. Song, *ACS Catal.*, 2023, **13**, 9502–9508; (*n*) H. Peng, Y. Zhang and G. Deng, *J. Org. Chem.*, 2023, **88**, 7038–7045; (*o*) J. Wang, Z. Li, S. Bai, Q. Zhou, T. Wu, Z. Hu and X. Xu, *Chin. Chem. Lett.*, 2023, **34**, 107823; (*p*) S.-Y. Zou, F. Yang, X. Zhao, X.-G. Ren, Z.-S. Chen and K. Ji, *Org. Chem. Front.*, 2023, **10**, 767–773.

13 (*a*) Z. Feng, Q.-Q. Min and X. Zhang, *Org. Lett.*, 2016, **18**, 44–47; (*b*) X. Zeng, Y. Li, Q.-Q. Min, X.-S. Xue and X. Zhang, *Nat. Chem.*, 2023, **15**, 1064–1073.

14 (*a*) H. Zhang, X. Li, Q. Shi, Y. Li, G. Xia, L. Chen, Z. Yang and Z.-X. Jiang, *Angew. Chem., Int. Ed.*, 2015, **54**, 3763–3767; (*b*) X. Li, N. Li, L. Yang, R. Jiang, Y. He, J. Shi, Z.-X. Jiang and Z. Yang, *ACS Catal.*, 2023, **13**, 12755–12765; (*c*) Y. Mao, N. Li, J. Liu, Z.-X. Jiang and Z. Yang, *Org. Lett.*, 2023, **25**, 7567–7572; (*d*) Q. Zhou, M. Huang, Y. Shen, Z. Chen, L. Xu and Z. Yang, *Org. Lett.*, 2024, **26**, 1212–1217.

15 H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood IV and J. Aubé, *Chem. Rev.*, 2022, **122**, 12544–12747.

16 M. E. Bergman, M. Bhardwaj and M. A. Phillips, *Plant J.*, 2021, **107**, 493–510.

17 L. M. Ulatowski and D. Manor, *Neurobiol. Dis.*, 2015, **84**, 78–83.
18 E. J. Westover and D. F. Covey, *J. Membr. Biol.*, 2004, **202**, 61–72.
19 (*a*) P. Tian, C.-Q. Wang, S.-H. Cai, S. Song, L. Ye, C. Feng and T.-P. Loh, *J. Am. Chem. Soc.*, 2016, **138**, 15869–15872; (*b*) H.-J. Tang, L.-Z. Lin, C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2017, **56**, 9872–9876; (*c*) W.-J. Yoo, J. Kondo, J. A. Rodríguez-Santamaría, T. V. Q. Nguyen and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2019, **58**, 6772–6775; (*d*) X. Yu, A. Maity and A. Studer, *Angew. Chem., Int. Ed.*, 2023, **62**, e202310288.
20 (*a*) K. Sinha, J. Das, P. B. Pal and P. C. Sil, *Arch. Toxicol.*, 2013, **87**, 1157–1180; (*b*) H. Sies and D. P. Jones, *Nat. Rev. Mol. Cell Biol.*, 2020, **21**, 363–383.