EDGE ARTICLE

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A difluorocarbene-triggered annulation/ring expansion cascade *via* sequential single-atom-insertions: direct assembly of 2-fluoroquinazolinones from azo compounds

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An efficient difluorocarbene-mediated tandem strategy for the synthesis of 2-fluoroquinazolin-4(3*H*)-ones *via* a sequential single-atom-insertion process has been developed. The method features a unique cascade starting from readily available azo compounds, which undergo an initial difluorocarbene-triggered annulation to form 3-halobenzopyrazole intermediates. These key intermediates are then converted into the final 2-fluoroquinazolinones through a second difluorocarbene-triggered ring expansion. This metal-free, redox-neutral protocol exhibits broad substrate scope and excellent functional group tolerance. Mechanistic investigations, including intermediate detection experiments, control experiments, isotopic labeling experiments, HRMS analysis, and Hammett studies, support the proposed reaction pathway and identify the formation of the halobenzopyrazole intermediate as a key step. The synthetic utility of the products is further demonstrated through diverse derivatizations and preliminary biological evaluation, revealing promising antitumor activity for certain fluorinated compounds compared to their defluorinated analogues, highlighting the value of the retained fluorine atom.

Introduction

Skeletal editing has emerged as a transformative strategy in modern synthetic chemistry, enabling direct modification of molecular cores without the need for *de novo* synthesis.[1] Among these approaches, single-atom-insertion stands out for its exceptional atom- and step-economy, offering a powerful tool for the rapid diversification of heterocyclic scaffolds.[1f–i,2] Despite its potential, the development of efficient and general methods for single-atom skeletal editing remains a significant challenge, particularly those capable of preserving valuable functional groups such as fluorine.
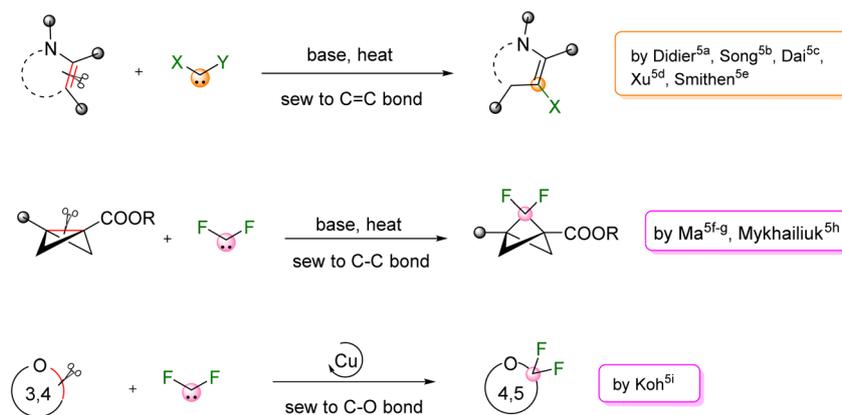
Carbene-mediated single-atom-insertion protocols have gained attention as versatile tools for precise skeletal editing, with recent advances demonstrating remarkable scope in the C=C bond cleavage system.[3–5] Notably, research groups including those of Didier,[5a] Song,[5b] Dai,[5c] Xu,[5d] and Smithen[5e] have successively reported the synthesis of halogenated heterocycles using halocarbene precursors (Fig. 1a). This kind of transformation retains the halogen atom, endowing the product with enhanced potential for further functionalization. However, among carbene insertions, only limited examples

have achieved fluorine retention. This is notably the case for difluorocarbene (:CF₂), which has been employed as a one-carbon unit in ring-expansion reactions.[5a,f–i,6] For instance, the synthesis of difluorinated bicyclo[1.1.1]pentanes from bicyclo[1.1.0]butanes (BCBs) *via* difluorocarbene insertion into a C–C bond has been reported by Ma[5f,g] and Mykhailiuk.[5h] Koh's group also developed a copper-catalyzed approach for skeletal expansion of oxygen-containing heterocycles by incorporation of CF₂ into a C–O bond.[5i] Beyond these limited examples, further studies revealed that fluorine retention during difluorocarbene insertion remains challenging. Specifically, Koh's group[5j] and Song's group[6] independently realized the single-atom-insertion of difluorocarbene into C–N and N–N bonds, both resulting in complete fluorine loss. Nevertheless, in Song's work, although fluorine loss occurred, the transformation provided a new skeletal editing route to quinazolin-4(3*H*)-ones, a privileged class of nitrogen-containing heterocycles with broad pharmaceutical relevance.[7] Given fluorine's crucial role in enhancing drug potency, metabolic stability, and target specificity,[8] the development of strategies to incorporate fluorine into this pharmacophore is highly desirable. Although some methods have striven to introduce fluorinated functional groups into this skeleton,[9] the direct construction of 2-fluoroquinazolin-4(3*H*)-ones remains unexplored. To address this gap, we herein report a novel difluorocarbene-mediated tandem process that enables the

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a) Single-atom-insertion of halocarbenes into C=C, C-C and C-O bonds with halogen retained

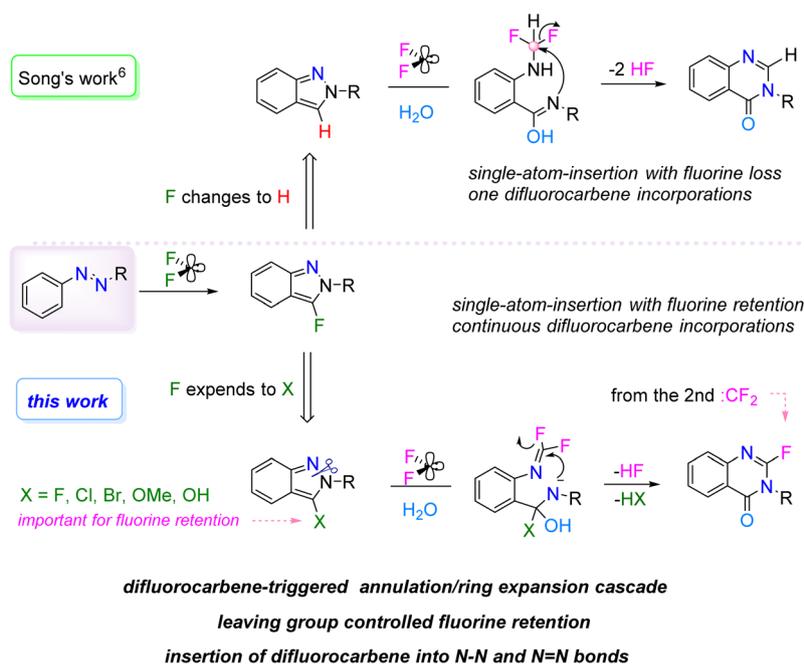**b) Single-atom-insertion of difluorocarbene into N-N bond**

Fig. 1 Carbene-mediated skeletal editing.

direct conversion of azo compounds into 2-fluoroquinazolin-4(3H)-ones (Fig. 1b). The transformation process involves an initial cyclization of azobenzene initiated by difluorocarbene to form a key fluorinated benzopyrazole intermediate, which subsequently undergoes a second difluorocarbene insertion to furnish the final product.[10–12] This strategy not only achieves single-atom-insertion with retention of fluorine but also unveils a previously unrecognized reactivity of difluorocarbene,[13–15] wherein it facilitates both annulation with azo compounds and insertion into the corresponding intermediate in a single operation. To our knowledge, reaction systems that allow continuous difluorocarbene incorporation are still limited.[16]

Results and discussion

Our investigation began with the hypothesis that azo compounds might engage with difluorocarbene in a [2 + 1] cycloaddition pathway. To our surprise, treatment of azobenzene with $BrCF_2CO_2Et$ under basic conditions did not yield the expected diaziridine or rearrangement-annulation products as with dichlorocarbene. Instead, unexpected 2-fluoroquinazolin-4(3H)-one **3a** was isolated in good yield (Table 1, entry 1). Monitoring the reaction by TLC (thin layer chromatography) revealed the rapid formation and subsequent consumption of an intermediate, which was identified as 3-fluoro-1-phenyl-1H-benzo[d]pyrazole after careful isolation and

Table 1 Verification of the optimal conditions[a]
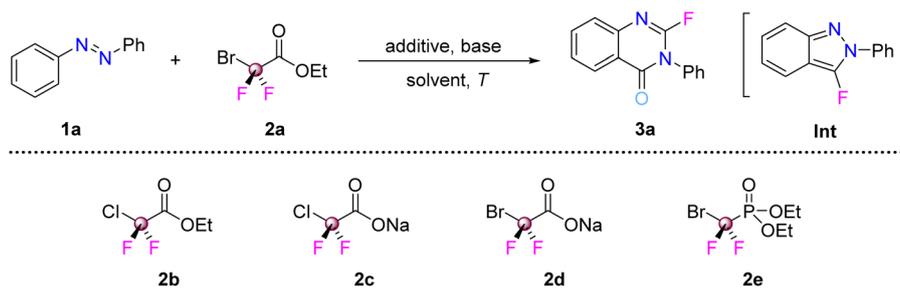
Entry	2	Base	Solvent	T (°C)	Yield (%)
1	2a	Na$_2$CO$_3$	MeCN	120	72 (68)[b]
2	2a	K$_2$CO$_3$	MeCN	120	24
3	2a	Cs$_2$CO$_3$	MeCN	120	n.d.
4	2a	NaHCO$_3$	MeCN	120	24
5	2a	K$_3$PO$_4$	MeCN	120	18
6[c]	2a	Et$_3$N	MeCN	120	63
7	2a	Na$_2$CO$_3$	PhCl	120	n.d.
8	2a	Na$_2$CO$_3$	DCM	120	Trace
9	2a	Na$_2$CO$_3$	1,4-Dioxane	120	n.d.
10	2a	Na$_2$CO$_3$	THF	120	n.d.
11	2a	Na$_2$CO$_3$	MeCN	130	68
12	2a	Na$_2$CO$_3$	MeCN	100	Trace
13	2b	Na$_2$CO$_3$	MeCN	120	10
14	2c	Na$_2$CO$_3$	MeCN	120	n.d.
15	2d	Na$_2$CO$_3$	MeCN	120	n.d.
16	2e	Na$_2$CO$_3$	MeCN	120	n.d.
17[d]	2a	Na$_2$CO$_3$	MeCN	120	64
18	2a	—	MeCN	120	n.d.
19[e]	2a	Na$_2$CO$_3$	MeCN	120	71
20[f]	2a	Na$_2$CO$_3$	MeCN	120	88

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (1 mmol, 5.0 equiv.), base (2.0 equiv.), and NaBr (0.1 mmol, 0.5 equiv.) in MeCN (4.0 mL) at 120 °C under an air atmosphere for 48 h; NMR yields using CH$_2$Br$_2$ as an internal standard; n.d. = not detected. [b] Isolated yield. [c] Et$_3$N (0.1 mmol, 0.5 equiv.). [d] Without NaBr. [e] 1 mmol scale, 72 h. [f] **Int** instead of **1a**.

characterization. This finding indicated that the reaction did not achieve the cyclopropanation product *via* a direct carbene insertion into the N=N bond, but rather underwent a tandem sequence involving the annulation of azobenzene with difluorocarbene to a fluorinated benzopyrazole, followed by a second difluorocarbene-triggered ring expansion. The reaction conditions for the cascade were investigated then. The effects of different bases (K$_2$CO$_3$, Cs$_2$CO$_3$, NaHCO$_3$, K$_3$PO$_4$, and Et$_3$N) on the yield of **3a** were studied. However, it was determined that Na$_2$CO$_3$ was the most promising, affording **3a** in 68% yield out of all six bases tested (Table 1, entries 2–6). Other solvents (PhCl, DCM, 1,4-dioxane, and THF) proved unsuitable for this reaction, leading to either trace amounts or no formation of **3a** (entries 7–10). Elevating the reaction temperature did not improve the product yield, whilst lowering it considerably reduced the reaction efficiency (entries 11 and 12). Next, the impact of difluorocarbene precursors (**2b–2e**) was evaluated, with BrCF$_2$CO$_2$Et emerging as the preferred reagent (entries 13–16). Control experiments (either no additive or no base) were also carried out (entries 17 and 18). When NaBr was omitted from the reaction, the yield of **3a** was reduced slightly from 72%

to 64%. We speculate that the presence of bromide ions may moderate the generation rate of difluorocarbene, avoiding the rapid accumulation of highly reactive :CF$_2$ that tends to undergo side reactions (*e.g.*, dimerization).[17] A slower, more controlled release of difluorocarbene facilitates its sequential reaction with both the azobenzene substrate and the fluoro-benzopyrazole intermediate, thereby improving the reaction yield and reducing byproduct formation. When the base was omitted from the reaction, no product was detected. Scale-up synthesis of product **3a** demonstrated maintained isolated yield at a 1.0 mmol scale (entry 19). The identified intermediate was also tested under the standard conditions, giving the desired product in high yield (entry 20).

Once the optimal conditions were determined, the scope of the azobenzene substrate was investigated (Fig. 2). Various symmetrical aryl azo compounds (**1a–1r**) were reacted with BrCF$_2$CO$_2$Et under the optimized reaction conditions, affording the desired products (**3a–3r**) in 32–90% yields. When the azo substrate contained electron-donating groups, such as alkyl and alkoxy substituents, on the aryl ring, the reaction occurred smoothly, affording the corresponding products **3e–3h** in 62–
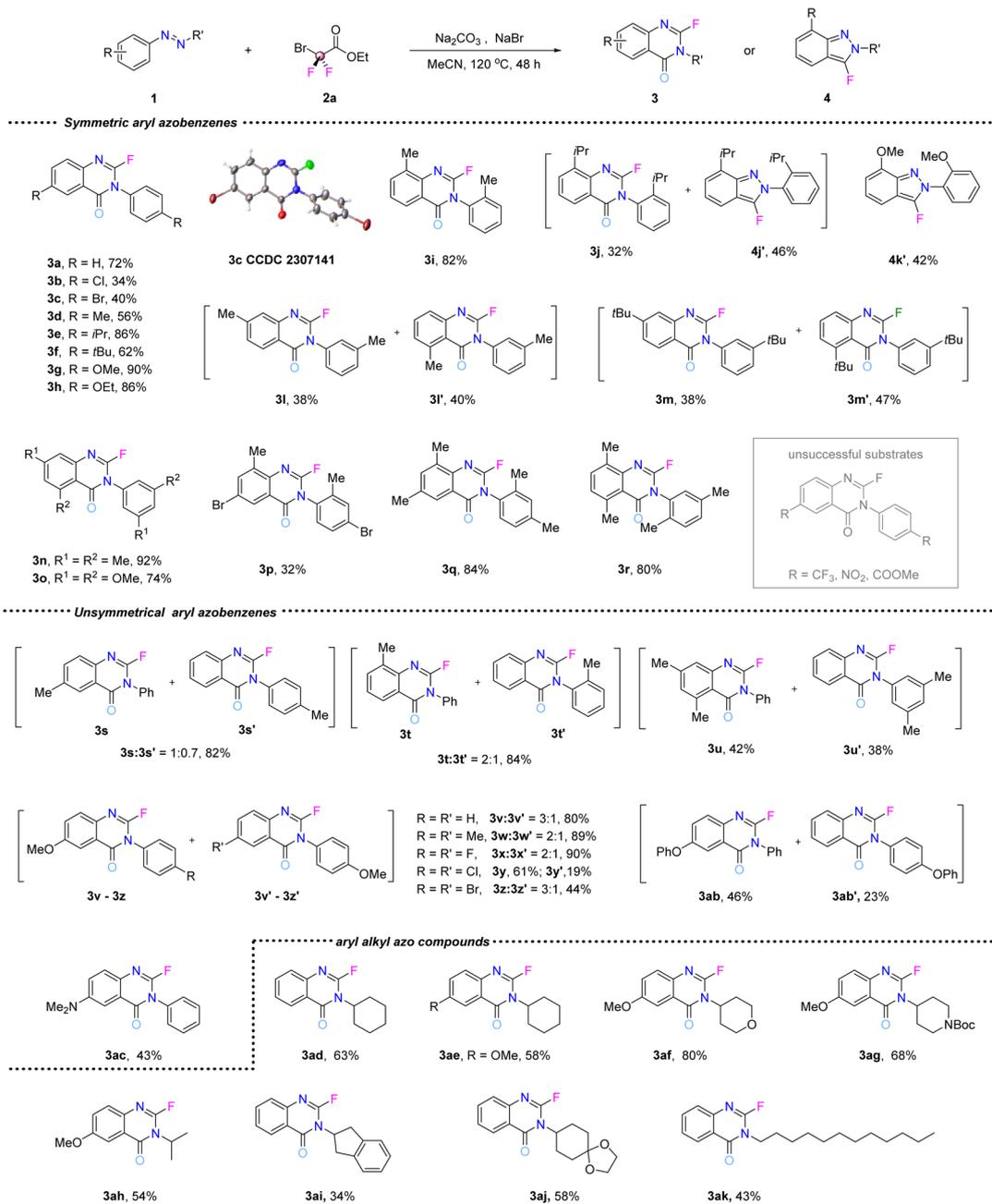
Fig. 2 Substrate scope. All reactions unless otherwise stated were carried out with **1** (0.2 mmol), BrCF$_2$CO$_2$Et (1 mmol), NaBr (0.1 mmol) and Na$_2$CO$_3$ (0.4 mmol) in MeCN (4 mL) heated at 120 °C for 48 h.

90% yield. However, electron-deficient substituents, such as trifluoromethyl, nitro, and ester groups, were not successfully transformed into the target products. Azo substrates featuring weakly electron-withdrawing groups, like chloride or bromide substituents, were transformed into their corresponding heterocyclic products in low yields (**3b** and **3c**, 34% and 40%, respectively). An alkyl substituent at the *ortho* position of the phenyl ring led to the isolation of both the final product (**3j**, 32%) and a fluorobenzopyrazole intermediate (**4j′**, 46%). A m-ethoxyl substituent only afforded the fluorobenzopyrazole intermediate (**4k′**, 42%). When **4j′** and **4k′** were subjected to the

reaction under the standard conditions, the corresponding **3j** was isolated in 6% yield, while **3k** was only detected by HRMS. The distinct outcomes of *ortho*-substituted substrates reveal that steric hindrance (for **4j′**) primarily slows the second difluorocarbene-triggered ring expansion, while electronic or coordinative interference (for **4k′**) completely inhibits this step, highlighting the differential sensitivity of the two cascade steps to substituent properties. For the *ortho*-isopropyl substrate (**4j′**), the hindrance is purely steric. This slows but does not completely block the second difluorocarbene insertion, allowing a low-yield conversion to **3j**. In contrast, for the *ortho*-
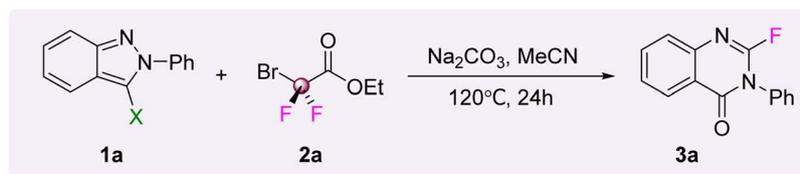
1	4a	4b	4c	4d	4e	4f
X	F	Cl	Br	OMe	OH	H
3a (%)	99	99	88	90	16	-

Fig. 3 Reactions of benzopyrazole derivatives and difluorocarbene.

methoxy substrate (**4k′**), the proximal oxygen atom with lone pairs likely causes electronic or coordinative interference.[5j,18] This deactivates the nitrogen center, inhibiting its nucleophilic attack on the second difluorocarbene and thereby halting the reaction completely. Regio-isomers (**3l** & **3l′** and **3m** & **3m′**, 38–47%) were obtained when substrates with substituents in the *meta*-position on the phenyl ring were reacted. Multiple substituted phenyl azo compounds also delivered the corresponding products (**3n–3r**, 32–92%). Unsymmetric aryl azo compounds produced inseparable isomers in most cases (**3s–3ac, 3s′–3ab′**). For the majority of examples, the difference in electronic effects between the two aromatic rings was too small to achieve good regioselectivity. Nonetheless, this electronic difference did influence the ratio of the two isomers. Azo compounds featuring electron-donating groups were found to be more reactive than those without substituents or with electron-withdrawing substituents. Furthermore, the corresponding product was formed as the predominant product when the phenyl ring featured the electron-donating substituents. In particular, only a single product (**3ac**) was formed in 43% yield when the phenyl ring featured the strongly electron-donating *N,N*-dimethyl group. The results revealed that electron-rich phenyl rings might have contributed to the formation of a necessary transition state during the reaction. Finally, the tolerance of aryl–alkyl azo compounds was investigated (**3ad–3ak**). The desired products were isolated in 34–80% yield when alkyl, cyclohexyl, heterocyclic alkyl groups substituted azo compounds were used, which makes the reaction potentially more attractive in drug molecule synthesis.

As the fluorobenzopyrazole skeleton was confirmed as the intermediate in the reaction cascade, the single-atom insertion step starting from this intermediate was optimized. The modified conditions while removing the NaBr additive and shortening the reaction time enabled efficient conversion to the corresponding product. The ring expansion process leading to a quinazolin-4(3*H*)-one scaffold from the fluorobenzopyrazole appears analogous to the results reported by Song for substrates unsubstituted at the 3-position. The key distinction lies in whether the fluorine atom is retained. This fluorine retention seems to be a specific outcome stemming from the use of a fluoro-substituted benzopyrazole intermediate, rather than representing a fundamentally novel reaction paradigm.

However, under our conditions, the unsubstituted benzopyrazole (**4f**) did not yield any of the desired product, and the starting materials were recovered unchanged (Fig. 3). Besides, some different leaving groups such as Cl, Br, and OMe (**4b–4d**) were tested and all facilitated the formation of the target products, albeit with considerable variation in efficiency (yields ranging from 88% to 99%). The results indicate that the presence of a leaving group at the 3-position of the benzopyrazoles is of paramount importance for the reaction's success, providing a distinctive reaction pathway from the unsubstituted benzopyrazole (**4f**). Free hydroxyl groups only offered the product in a low yield, which may be due to the competition between the hydroxyl and nitrogen atoms when reacting with difluorocarbene (**4e**).

To reduce the limitations of the cascade reaction of azobenzene, the reaction using chlorobenzopyrazoles as the starting substrates was then investigated (Fig. 4). Scale-up synthesis was conducted using the easily accessed **4b**, affording the desired product in 78% yield. Substituents on the *N*-phenyl ring all gave the corresponding products in moderate to excellent yields (**3ba–3bo**, 63–99%). Electron-donating groups such as alkyl groups (**3ba, 3be, 3bl, 3bt**) and methoxyl groups (**3bh, 3bi**) were favorable for the reaction, leading to efficient product synthesis. The introduction of halogens had a relatively small impact on reaction efficiency (**3bb–3bd, 3bm–3bo**). However, when the *ortho*-position was occupied by bulky Br, the yield of the corresponding product was reduced to a moderate level (**3bk**), potentially affected by steric hindrance which was significant in this system. Electron-withdrawing groups (CF_3 and COOEt) were also tolerated by the reaction system but with reduced efficiency (**3bf–3bg, 3bj**). The 3,5-di-CF_3 substituted substrate produced the product only in low yield (**3bu**, 28%). This observation of unfavorable experimental results with electron-withdrawing groups was consistent with findings in the azobenzene reaction system. An *N*-pyridinyl substrate featuring an electron deficient aromatic ring was tested in the reaction, affording the product in 26% yield (**3bv**). However, *N*-alkyl substrates all generated the corresponding product in moderate to good yields (**3bw–3ca**, 42–83%). Among these, phthalimide, cyclohexyl, naphthyl and phenol groups tethered to the chlorobenzopyrazole skeleton *via* an alkyl linker were all tolerated. A saturated heterocyclic ring was also tested to give
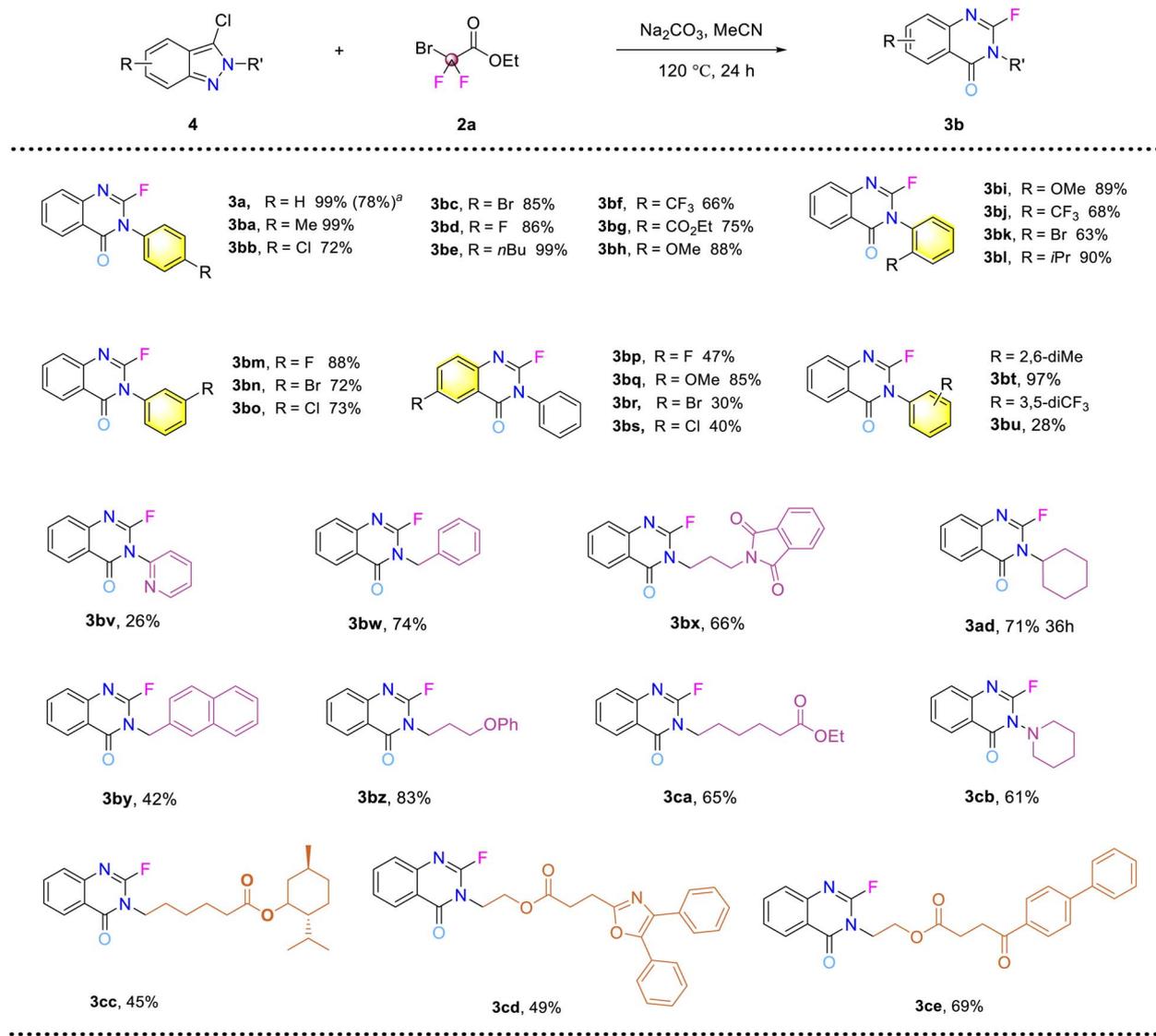
Fig. 4 Substrate scope. All reactions unless otherwise stated were carried out with 4 (0.1 mmol), BrCF$_2$CO$_2$Et (0.3 mmol), and Na$_2$CO$_3$ (0.2 mmol) in MeCN (2 mL) heated at 120 °C for 24 h. [a]1 mmol scale, 48 h.

a good result (3cb, 61%). Meanwhile, in order to demonstrate the potential of this reaction for modifying drug molecules, substrates from a natural fragment (menthol) and two drug molecule fragments (oxaprazine and fenbufen) were studied, yielding the corresponding products in moderate yields (3cc–3ce, 45–69%).

In order to show the potential impact of fluorine atom retention on the biological activity of the products, some fluorine-containing and non-fluorinated compounds (3bw, 3by, 3cc–3ce vs. 3bw′, 3by′, 3cc′–3ce′) were synthesized and their inhibitory effects on tumor cell proliferation were preliminarily evaluated. Notably, two fluorinated compounds displayed promising activity against SW480 cells, with IC$_{50}$ values of 28.67 ± 2.48 μM for 3by and 14.88 ± 0.91 μM for 3cc. In contrast, none of the non-fluorinated counterparts showed detectable inhibition at 25 μM (Fig. 5, left, see the SI for details). These preliminary biological results are consistent with the well-recognized role of fluorine in enhancing drug potency and target specificity, confirming that the retained fluorine atom in our products is crucial for their antiproliferative activity, which highlights the practical value of our fluorine-retaining synthetic strategy. To further demonstrate the utility of this protocol, synthetic derivatizations were performed (Fig. 5, right). We demonstrated that product 3a could be subjected to a wide range of chemical modifications to synthesize compounds with biological and pharmacological relevance. Defluorination reduction of 3a using NaBH$_4$ delivered the dihydroquinazolinone derivative 5 in 54% yield (reaction a). Nucleophilic substitution with TMSCN yielded cyanide product 6 in moderate yield (reaction b). Hydrolysis under alkaline conditions gave quinazoline-dione skeleton 7 in 85% yield (reaction c). Nucleophilic substitution reaction also proceeded smoothly with phenols and amines, affording the corresponding products in moderate to high yields (reactions d–h, 8–12, 60–86%). Notably, product 3a was
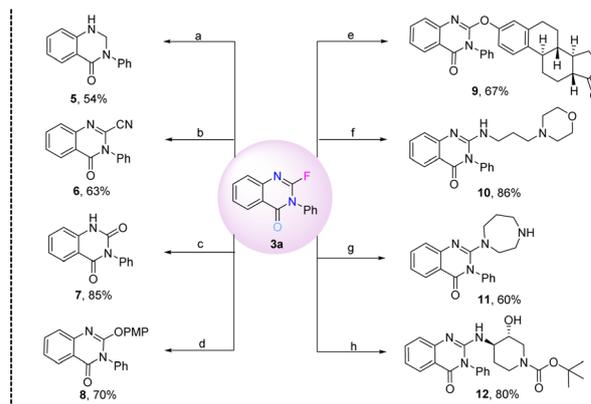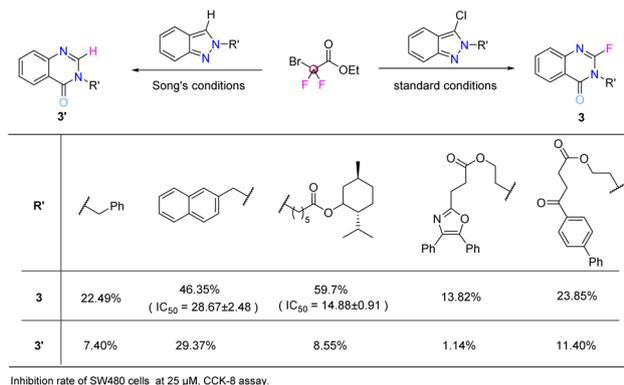
Fig. 5 Synthetic applications. (a) NaBH$_4$, THF, reflux, 2 h. (b) KF, TMSCN, 18-crown-6, dry CHCl$_3$, 55 °C, 10 h. (c) KOH, H$_2$O, 80 °C, 12 h. (d) 4-Methoxyphenol, K$_2$CO$_3$, MeCN, 90 °C, 16 h. (e) Estrone, K$_2$CO$_3$, MeCN, 90 °C, 16 h. (f) Morpholine, Et$_3$N, EtOH, reflux, 2 h. (g) Homopiperazine, EtOH, N$_2$, reflux, 6 h. (h) *tert*-Butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate, EtOH, 120 °C, 24 h.

successfully tethered to estrone, generating **9** in 67% yield under mild conditions. Three different pharmacologically relevant amine moieties delivered the amination products with good reaction efficiency (reactions f–h).

Mechanistic insights into the reaction were gained through several experiments. When 2-methylbenzimidazole was present, the carbene-capture byproduct (**13**) was formed as the dominant product instead of compound **3a** (Fig. 6a). Furthermore, the reaction proceeded smoothly in the presence of radical scavengers such as BHT or 1,1-diphenylethylene, affording the desired product **3a** in good yield, indicating that radical species were not involved (Fig. 6b). Isotopic labelling experiments were

subsequently performed to determine the origin of the oxygen atom in the target product. Using three equivalents of H$_2$^{18}O, **3a** was isolated as a 55 : 100 (HRMS ratio) mixture of ^{18}O-**3a** and ^{16}O-**3a** (Fig. 6c), suggesting that carbonyl oxygen likely originated from trace water in the solvent. In order to further identify some potential intermediates in the reaction process, high-resolution mass spectrometry (HRMS) analysis was performed during the early stages of the reaction (Fig. 6d). As noted, intermediate **Int** (**4a**) was detected and successfully isolated, while other possible intermediates (**4e**, **B**, **D**) were detected only by HRMS. Notably, intermediate **4e**, presumably formed *via* hydrolysis of **4a**, was identified as a side intermediate rather
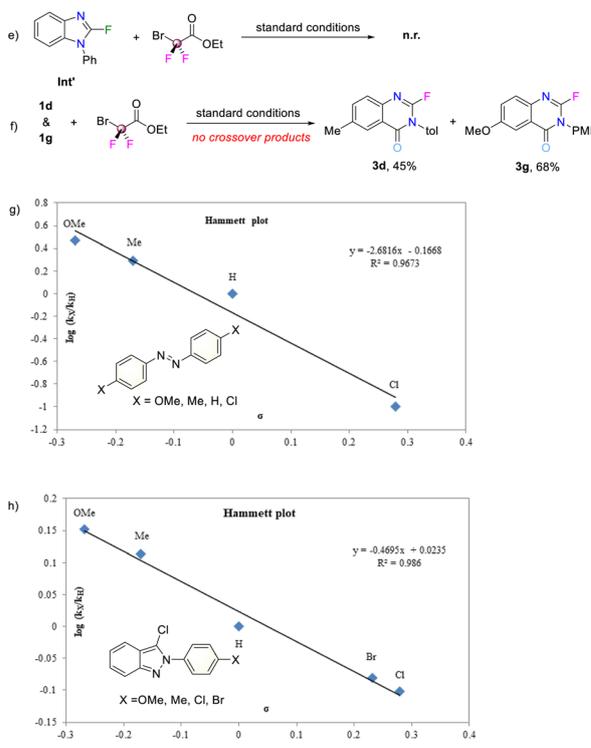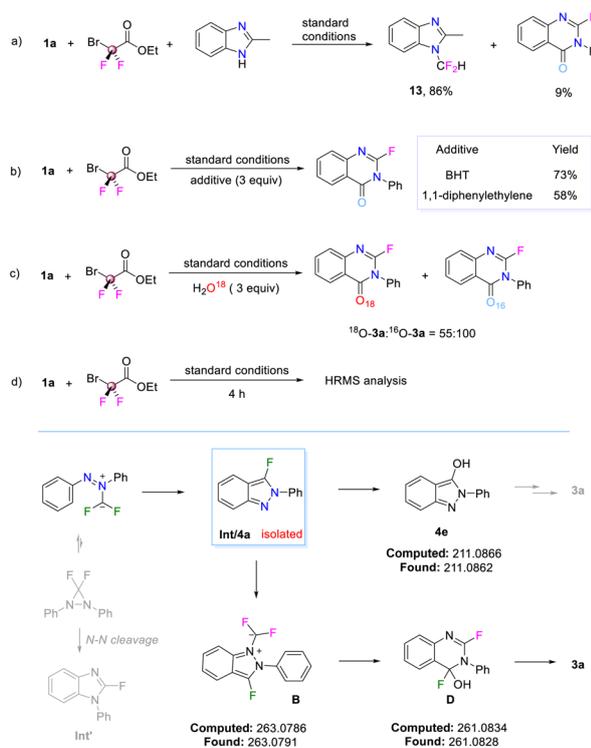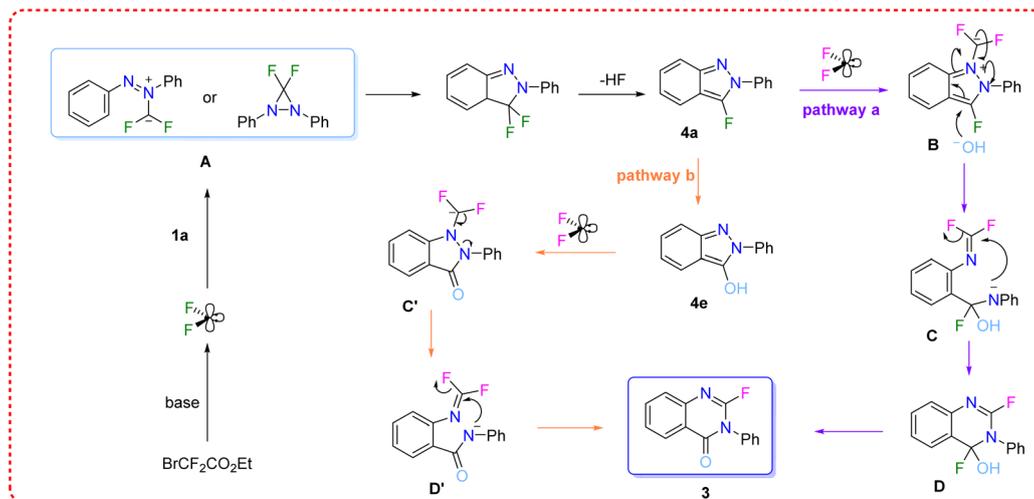

Fig. 6 Mechanistic studies.

Fig. 7 Proposed mechanism.

than a productive species, as evidenced by its low reactivity when directly used as the substrate (Fig. 3), which implies it does not participate in the main reaction pathway. In a productive pathway, **4a** can further react with difluorocarbene to form the $N=CF_2$ ylide intermediate **B,** which is then converted to intermediate **D** *via* nucleophilic addition by –OH, followed by a ring-opening/ring-closing sequence. In contrast, another possible skeleton (**Int′**), which could be generated by defluorination-rearrangement from a [2 + 1] cycloaddition intermediate, was synthesized and found to be unreactive (Fig. 6e). A competition experiment was carried out to determine whether the reaction was intermolecular or not. A one-pot reaction of substrates **1d** and **1g** with BrCF₂CO₂Et produced only products **3d** and **3g**, with no crossover products detected (Fig. 6f). To assess the influence of electronic effects on the reaction efficiency, Hammett studies were performed using *para*-substituted azobenzenes and *para*-substituted phenyl chlorobenzopyrazoles (Fig. 6g and h). Good linearity was observed plotting the relative rates ($\lg(k_X/k_H)$) against the substitution constant (σ). Negative ρ values (-2.68 for azobenzenes and -0.47 for chlorobenzopyrazoles) indicate positive charge accumulation in the transition states of both the difluorocarbene-triggered annulation and the difluorocarbene-triggered ring expansion steps, respectively. The substantially larger $|\rho|$ value for the azobenzene system suggests that the initial annulation is rate-determining, whereas the smaller $|\rho|$ value for the chlorobenzopyrazole system implies that, although a positively charged transition state is involved, the ring-expansion step is not rate-limiting. Therefore, it can be considered that the generation of intermediate **4a** is the rate determining step of the reaction, and is strongly influenced by the electronic nature of the substituents, consistent with our experimental observations in the azobenzene system.

Based on the experimental results and literature precedent, Fig. 7 illustrates a proposed reaction mechanism for the reaction. Initially, BrCF₂CO₂Et undergoes base-mediated dehalogenation and decarboxylation to generate difluorocarbene. This species reacts with azobenzene to form either an ylide or a 3,3-difluoro-diaziridine intermediate, which rearranges with HF elimination to afford key intermediate **4a**. Intermediate **4a** then proceeds *via* two potential pathways to afford the final product. In pathway a, **4a** reacts with another difluorocarbene to create ylide intermediate **B**. This undergoes ring-opening followed by recyclization with fluoride elimination, yielding the six-membered ring intermediate **D**. Subsequent HF elimination under alkaline conditions affords the final product. An alternative pathway is showcased as pathway b. In this scenario, **4a** undergoes nucleophilic substitution firstly to generate intermediate **4e** which can similarly yield the product through a ring-opening/recyclization cascade facilitated by another difluorocarbene (:CF₂). However, given the low efficiency observed when **4e** was tested experimentally, this pathway is likely less favourable.

Conclusions

In conclusion, this work presents a novel difluorocarbene-mediated tandem process that enables the direct conversion of readily available azo compounds into valuable 2-fluoro-quinazolin-4(3*H*)-ones. The reaction firstly proceeds *via* a difluorocarbene triggered annulation of the azo substrate to form a key fluorinated 3-halobenzopyrazole intermediate, which subsequently undergoes a second difluorocarbene-induced ring expansion *via* single-atom insertion, ultimately delivering the fluorinated quinazolinone product with retention of fluorine atom. The pivotal 3-halobenzopyrazole species, which serves as the mechanistic linchpin connecting the two distinct reactivity modes of difluorocarbene in a single operation, is identified and expanded as a type of complementary substrate. The reaction has broad substrate scope (tolerating various azo compounds and pre-formed benzopyrazoles), and good functional group compatibility under metal-free and redox-neutral conditions. Comprehensive mechanistic investigations, including isotopic labeling, intermediate isolation, HRMS

analyses, and Hammett analyses, provide strong support for the proposed tandem pathway and reveal that the initial annulation step is rate-determining and sensitive to electronic effects. Preliminary biological evaluation demonstrated that certain fluorinated products exhibit promising antiproliferative activity against cancer cell lines, while their defluorinated analogues are inactive, underscoring the critical role of fluorine in modulating bioactivity. Furthermore, the synthetic versatility of the 2-fluoroquinazolin-4(3H)-one scaffold was showcased through diverse derivatization reactions, including linkage with pharmacologically relevant fragments.

Author contributions

B. L. conceptualized the project. Y. T. performed the experiments and analyzed the results. Y. X. and J. W. assisted in performing the experiments. G. Z. performed the experiments on anticancer activity. J. C. and B. L. supervised and directed the project. B. L. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: further details of the experimental procedures, ^{1}H, ^{13}C and ^{19}F NMR, HRMS data, X-ray crystallographic data for **3c**. See DOI: https://doi.org/10.1039/d6sc00897f.

CCDC 2307141 contains the supplementary crystallographic data for this paper.[19]

Acknowledgements

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