Stereodivergent alkyne hydrofluorination using a simple and practical reagent

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Abstract: Vinyl fluorides play an important role in drug development as they serve as bioisosteres for peptide bonds and are found in a range of biologically active molecules. The discovery of safe, general and practical procedures to prepare vinyl fluorides remains an important goal and challenge for synthetic chemistry. Here we introduce an inexpensive and easily-handled reagent and report simple, scalable, and metal-free protocols for the regioselective and stereodivergent hydrofluorination of alkynes to access both the *E* and *Z* isomers of vinyl fluorides. These conditions were suitable for a diverse collection of alkynes, including several highly-functionalized pharmaceutical derivatives. Mechanistic and DFT studies support C–F bond formation through a vinyl cation intermediate, with the (*E*)- and (*Z*)-hydrofluorination products forming under kinetic and thermodynamic control, respectively.

The incorporation of fluorine into organic compounds plays a significant role in the pharmaceutical and agrochemical sciences, due to its distinctive capability for modulating the physical and chemical properties of a biologically active scaffold, including solubility, metabolic stability, potency, and bioavailability[1,2]. Among them, vinyl fluorides are privileged structures that notably serve as bioisosteres of peptide bonds, mimicking their charge distribution and dipole moment (Fig. 1A)[3,4].

Established synthetic approaches to vinyl fluorides primarily employ olefination reactions and elimination reactions that require multistep transformations and the preparation of prefunctionalized fluorinated substrates[5-7]. One direct approach for vinyl fluoride synthesis involves the coupling of fluoride ion with vinyl triflates catalyzed by biaryldialkylphosphine complexes of palladium (Fig. 1B, a)[8]. The metal-catalyzed and noncatalytic fluorination of vinyl metal species under oxidative conditions constitutes another approach (Fig. 1B, b)[9-18]. Finally, the dehydrative fluorination of ketones using difluorosulfur(IV) reagents has been reported in the patent literature (Fig. 1B, c)[19]. A more direct method to access vinyl fluorides is the hydrofluorination of alkynes, substrates that are easily accessed from a variety of commercially available starting materials. Several strategies for the hydrofluorination of alkynes have been developed in recent years[20-28]. These include the coinage metal-catalyzed hydrofluorination of alkynes using various Lewis base adducts of hydrogen fluoride (Fig. 1B, d)[20-26]. Although these approaches allow for the preparation of various vinyl fluorides, the corrosivity of HF-based reagents, the inaccessibility or complexity of metal-based catalysts and ligands, and challenges in controlling *E*/*Z*-selectivity and regioselectivity may limit their applicability and scalability. Consequently, the development of operationally simple methods and practical reagents for accessing vinyl fluorides with control of regio- and stereochemistry remains an ongoing challenge.

Considering their low cost, high fluoride content, as well as excellent safety, stability, and handling profiles, tetrafluoroborate (BF_4^-) salts are particularly attractive sources of nucleophilic fluoride[29]. However, aside from the well-developed Balz-Schiemann process, they have seldom been employed in the formation of $C(sp^2)$–F bonds due to the weak nucleophilicity of this anion, and known methods often require the use of exotic functional groups or strongly oxidizing conditions[30]. Given previous reports of alkyne hydrohalogenation that proceed via either the

concerted Ad_E3 mechanism or an Ad_E2 mechanism featuring a vinyl cation intermediate[31], we hypothesized that a partially or wholly protonated alkyne could be sufficiently electrophilic to enable the use of tetrafluoroborate as a nucleophilic fluorinating reagent. Therefore, we posited that an acidic source of tetrafluoroborate could serve as a general and practical hydrofluorinating reagent for alkynes[4]. Indeed, the hydrofluorination of alkynes using a base-modulated acidic source of nucleophilic fluorine was already investigated by Olah and coworkers in the 1970s using the Olah reagent[32], $C_5H_5N{\bullet}9HF$, and this process was recently improved by Hammond, Xu, and coworkers using designer base-complexed sources of hydrogen fluoride[33]. However, both reports reveal that, in general, even under very mild conditions (0 to 50 °C), these reagents deliver the *gem*-difluoride bis(hydrofluorination) product (Fig. 1B, e), without allowing for the isolation of the presumed vinyl fluoride intermediate except in the case of specialized ynamide[34] or alkynyl sulfide substrates[35].

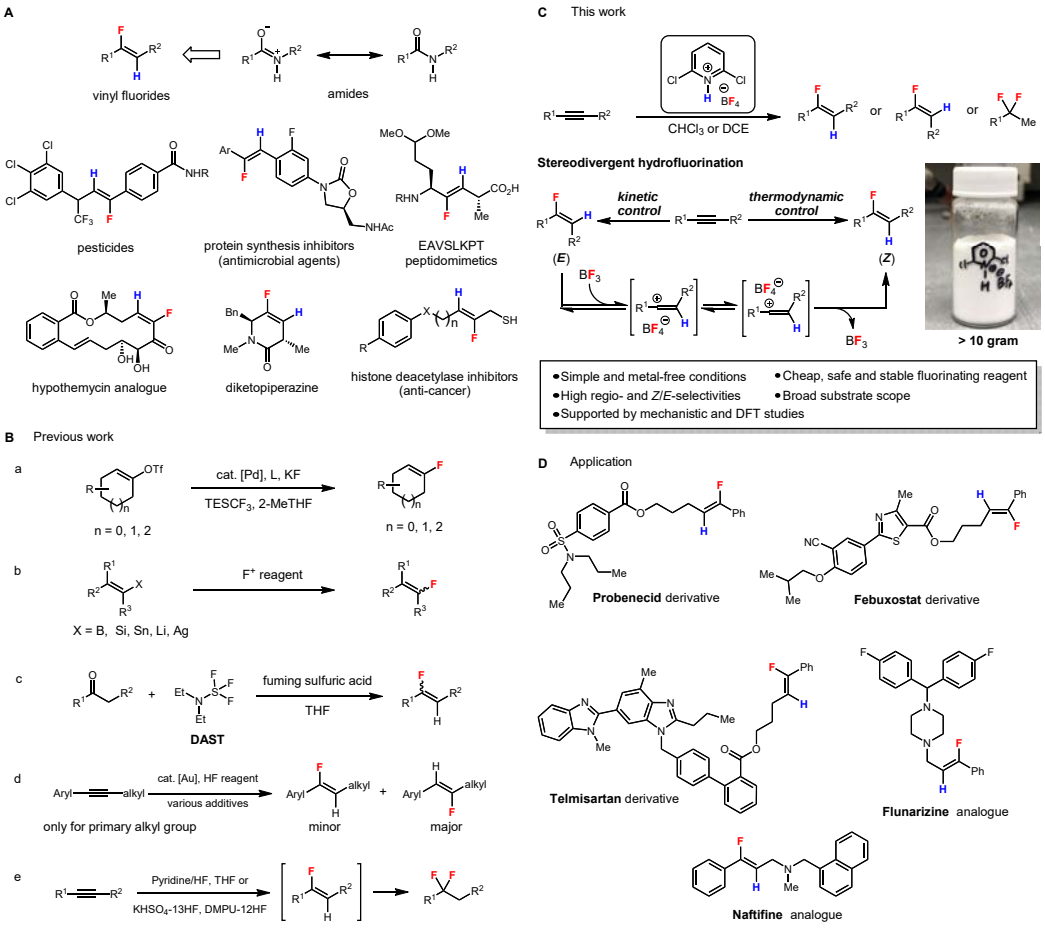


Fig. 1. Strategies for the synthesis of vinyl fluorides. A, Representative bioactive organic molecules demonstrating the ubiquitous nature of vinyl fluorides. **B**, Previous synthetic approaches to vinyl fluorides through the formation of C−F bond. **C**, This work: stereodivergent alkyne hydrofluorination and Mechanistic studies. **D**, Applications in the late-stage functionalization of drug derivatives.

An acidic reagent based on the tetrafluoroborate ion, formally equivalent to HBF_4 (nonexistent as a pure substance), could serve as a controlled source of nucleophilic fluorine. Moreover, we expect the acidity, and thus, the reactivity of such a reagent to be tunable through the variation of the protonated weak base. From the point of view of cost and availability, such a reagent would be nearly ideal for the hydrofluorination of alkynes, provided that the hydrofluorination reactions would proceed with functional group tolerance and control over the regiochemical and stereochemical outcomes. Here, we report the discovery and development of a simple and practical reagent for the stereodivergent hydrofluorination of alkynes which, in most cases,

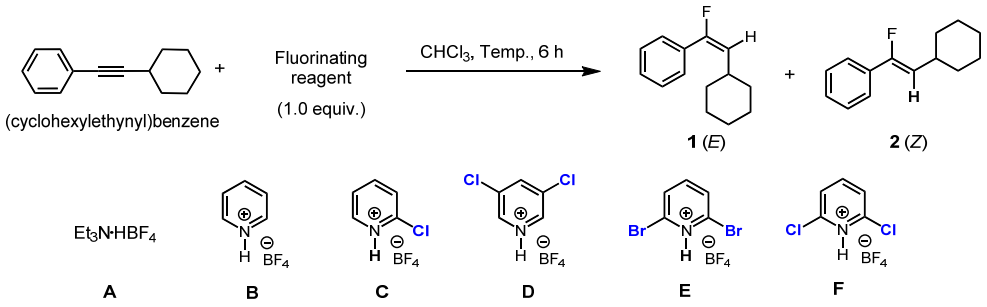
delivers products with excellent control of the regio- and stereoselectivity (Fig. 1C). For certain substitution patterns, we report complementary conditions for the synthesis of either the *E* or *Z* isomer of the hydrofluorination product with good to excellent *E*/*Z* ratios. The conditions reported here are tolerant of a variety of functional groups, and we applied them to the late-stage functionalization of drug derivatives and synthesis of fluorinated drug analogues (Fig. 1D). A mechanistic study of the process was performed through kinetics experiments and density functional theory (DFT) calculations. These studies support the intermediacy of vinyl cations in the hydrofluorination. They also provide insight into the excellent stereochemical control and accounts for the ability to selectively obtain the *E* or *Z* isomer through the variation of reagent and reaction conditions. Previously, vinyl cations have been generated through several approaches[36], including metal catalysis[37,38], photochemical processes[39], ionization of vinyl iodonium[40] and diazonium species[41], (pseudo)halide abstraction with Lewis acids[42,43], as well as protonation of alkynes with strong Brønsted acid[44,45]. In spite of the challenging and specialized conditions that are often required for their generation, the versatility of this intermediate has led to a recent renaissance in their synthetic applications[46]. In this context, the hydrofluorination conditions reported here represent an unprecedentedly mild, stereocontrolled, and functional group compatible approach for utilizing these intermediates.

Results and discussion

Reaction development. We commenced the exploration of our hydrofluorination strategy using (cyclohexylethynyl)benzene as a starting material, inspired by the lack of literature precedent employing secondary alkyl-substituted phenylacetylenes as substrates for hydrofluorination (Table 1). We anticipated that the corresponding amine salts of HBF_4 could adjust the acidity and result in more controlled reactivity. A diverse range of amine salts of HBF_4 was evaluated. While it was found that

reagents based on triethylamine (**A**), pyridine (**B**), and 2-chloropyridine (**C**) were unreactive in $CHCl_3$ at room temperature or 70 °C (entries 1-3), we found that the more electron-poor 3,5-dichloropyridinium salt provided a trace of the desired product (entry 4). Continuing with more electron-deficient pyridinium salts, we found that the 2,6-dihalopyridinium salts (**E** and **F**) were more efficient reagents, with the more electron-deficient chlorinated reagent providing the desired product with good yield and excellent stereoselectivity (*Z*/*E* > 50:1, entry 6). We did not detect any *gem*-difluoride product from continued hydrofluorination of the monofluoroalkene, a process that could not be avoided under previous conditions using pyridine/HF or DMPU/HF[32,33]. We further found that yields could be enhanced by using $LiBF_4$ (25 mol %) as an inexpensive additive (entry 7 vs. entry 8). Among a collection of pyridinium salts examined, 2,6-dichloropyridinium tetrafluoroborate (**F**), prepared on large scale (50 mmol) by protonation of 2,6-dichloropyridine with commercially available HBF_4•Et_2O, possessed the best reactivity and handling properties, including excellent crystallinity and low hygroscopicity. In particular, **F** could be stored as a colorless solid in the desiccator for at least a week or in the glovebox indefinitely (> 3 months) without noticeable deterioration or loss of activity. Lastly, we examined HBF_4•Et_2O as another potential reagent. Surprisingly, we found that treatment of the model substrate with HBF_4•Et_2O (1.0 equiv) at room temperature for 6 hours resulted in the formation of desired hydrofluorination product **1** in moderate yield (42% yield) and good selectivity for the *opposite* stereoisomer (*E*/*Z* = 11:1).

Table 1. Optimization of reaction conditions for hydrofluorination

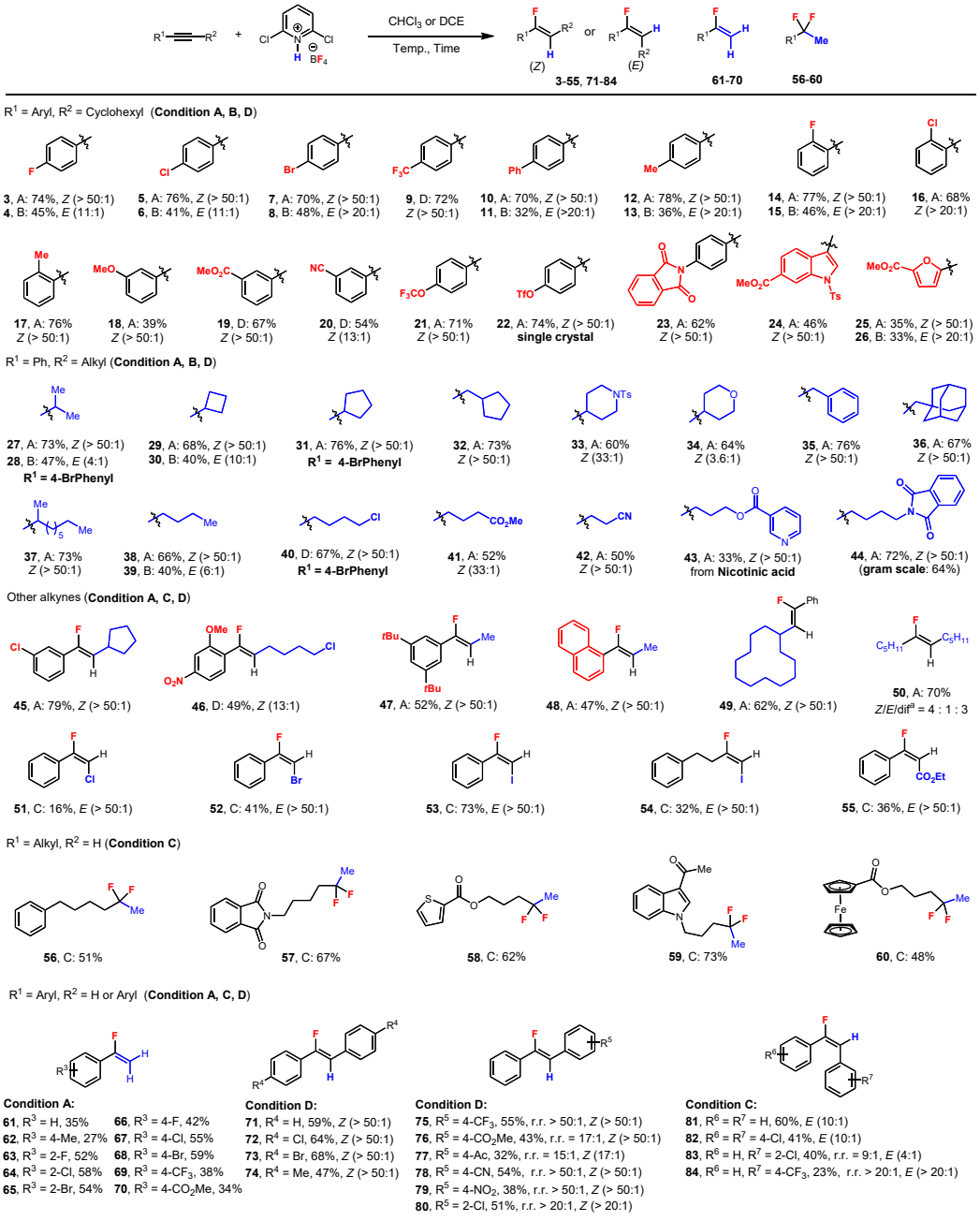


Entry	Fluorinating reagent	Temp./°C	Yield/%	*Z*/*E*
1	**A**	70	0	—
2	**B**	70	0	—
3	**C**	70	0	—
4	**D**	70	< 5	1 : 5
5	**E**	70	45	> 50 : 1
6	**F**	70	74	> 50 : 1
7	**F**	70	82[a](76)[b]	> 50 : 1
8	HBF_4•Et_2O	r.t.	42	1 : 11

[a]$LiBF_4$ (25 mol %) was added as an additive. [b]Isolated yield.

Substrate scope. Under these optimized conditions, we set out to investigate the scope of this hydrofluorination reaction (Table 2). Using reagent **F** for hydrofluorination, aryl alkyl acetylenes bearing electron-withdrawing (e.g., products **9**, **19**, **20**, **22**) to electron-donating (e.g., products **23**, **24**, **25**) aryl substituents reacted effectively to afford the (*Z*)-configured fluoroalkene products in moderate to good yields and excellent regio- and stereoselectivities. Moreover, several common functional groups on the aryl ring including a methyl ester (**19**), a cyano group (**20**), a trifluoromethanesulfonyl ester (**22**), and a phthalimide (**23**) were tolerated. Heteroaryl alkyl acetylenes, including an indole and a furan likewise delivered the desired product (**24**, **25**). We determined the structure of the product **22** by X-ray single-crystal diffraction structure analysis for confirmation of the alkene stereochemistry.

Table 2. Substrate scope of alkynes



Condition A: fluorinating reagent **F** (1.0 equiv), $LiBF_4$ (25 mol%), $CHCl_3$ (0.2 M), 70 to 90 °C. Condition B: $HBF_4{\cdot}Et_2O$ (1.0 equiv), $CHCl_3$ (0.2 M), r.t., 6 h. Condition C: fluorinating reagent **F** (3.0 equiv), $CHCl_3$, 80 to 100 °C, 12 h. Condition D: fluorinating reagent **F** (2.0 equiv), DCE, 70 to 100 °C, 12 h. [a]*gem*-difluoroalkane. See supporting information for detailed conditions.

We next explored the scope of alkyl substituents on the substrate. A range of primary, secondary, cyclic or acyclic alkyl-substituted alkynes could be employed in

the hydrofluorination to furnish respective products again with moderate to good yields and excellent regio- and stereoselectivities (**27**-**39**). Remarkably, substrates with potentially sensitive functional groups including a primary chloro, a carboxymethyl, a cyano, a pyridyl, and a phthalimido group also delivered the monofluoroalkene products, highlighting the mildness and good functional group tolerance of this protocol (**40**-**46**). This scalability of the procedure was demonstrated by the gram-scale preparation of **44**, which proceeded with unchanged regio- and stereoselectivities and only a slightly reduced yield (1.65 g, 64%). The protocol was insensitive to steric effects on the alkyl substituent, with a methyl group (**47**, **48**) and a cyclododecyl (**49**) group giving similar yields, with no loss in regio- and stereoselectivities. It is noteworthy that in all reactions employing aryl-substituted alkynes, the monofluoroalkene products were delivered with exclusive regioselectivity, with C–F bond formation occurring adjacent to the aryl group. These results were complementary to the gold-catalyzed hydrofluorination which delivers the fluorine to the carbon adjacent to the alkyl group[20-25]. However, a reduction in selectivity was observed for a dialkylacetylene substrate, which gave the *gem*-difluoroalkane in addition to the monofluorinated product (**50**). A variety of 1-haloalkynes (I > Br > Cl in reactivity) and ethyl phenylpropiolate were also suitable substrates for this reaction, in which a single regio- and stereoisomer was produced in each case (**51**-**55**). During the course of optimization, we found that tetrafluoroboric acid in diethyl ether (HBF_4•Et_2O) could also deliver hydrofluorination product. However, the predominant stereoisomer formed under these conditions was the *E* isomer. With commercially available reagent, we briefly explored the substrate scope of these conditions (condition B). Substrates bearing mildly electron-withdrawing or electron-donating substituents could afford the monofluoroalkene products with moderate to good *E*-selectivity (*E*/*Z* ratio from 4:1 to > 20:1).

The hydrofluorination reaction could also be applied to terminal alkynes and diarylacetylenes. When using terminal alkyl-substituted alkynes as substrate *gem*-difluorides were obtained as the primary product with exclusive internal regioselectivity. A variety of functional groups such as an amide, an ester, an indole, as well as a ferrocene derivative were well tolerated (**56**-**60**). On the other hand, terminal aryl-substituted alkynes could be employed in this hydrofluorination to give the corresponding monofluoroalkene as the major product with moderate yields (**61**-**70**). With 1,2-dichloroethane as the solvent, diarylacetylenes could give corresponding monofluoroalkene products in modest to good yields and excellent *Z*-selectivities (**71**-**74**). For unsymmetrical substrates, when one of the benzene rings was substituted by an electron-withdrawing group (e.g., 4-CO_2Me, 2-Cl), the hydrofluorination product proceeded with excellent *Z*-selectivities and regioselectivity for fluorination nearer to the more electron-rich aryl group (**75**-**80**). Finally, it was found that by switching to chloroform as the solvent, the monofluoroalkene product could be formed with *E*-selectivity (**81**-**84**).

Synthetic applications. To demonstrate the potential applicability of this new hydrofluorination method to the late-stage modification of structurally complex substrates, including biologically active molecules and natural products, we explored several readily available alkynes derived from *exo*-norborneol (**85**) and ferrocene (**86**), natural products (1*S*)-(+)-10-camphorsulfonic acid (**87**) and estrone (**88**, **89**), as well as drug molecules probenecid (**90**), febuxostat (**92**) and telmisartan (**94**) to afford monofluoroalkene products with moderate to good yields and high regio- and stereoselectivities (Fig. 2a). In addition, terminal alkyl-substituted alkynes derived from drug molecules probenecid and febuxostat could also be employed in the dihydrofluorination to form *gem*-difluorides with moderate yields and exclusive regioselectivity (**91**, **93**). These examples demonstrated that our hydrofluorination and difluorination protocols were suitable for the late-stage, protecting-group-free

modification of biologically active molecules and could tolerate a range of functional groups and heterocycles including ketones (**87**-**89**), esters (**90**-**94**), a ferrocene (**86**), a sulfonate (**87**), a sulfonamide (**90**, **91**), a nitrile (**92**, **93**), a thiazole (**92**, **93**), and benzimidazoles (**94**).

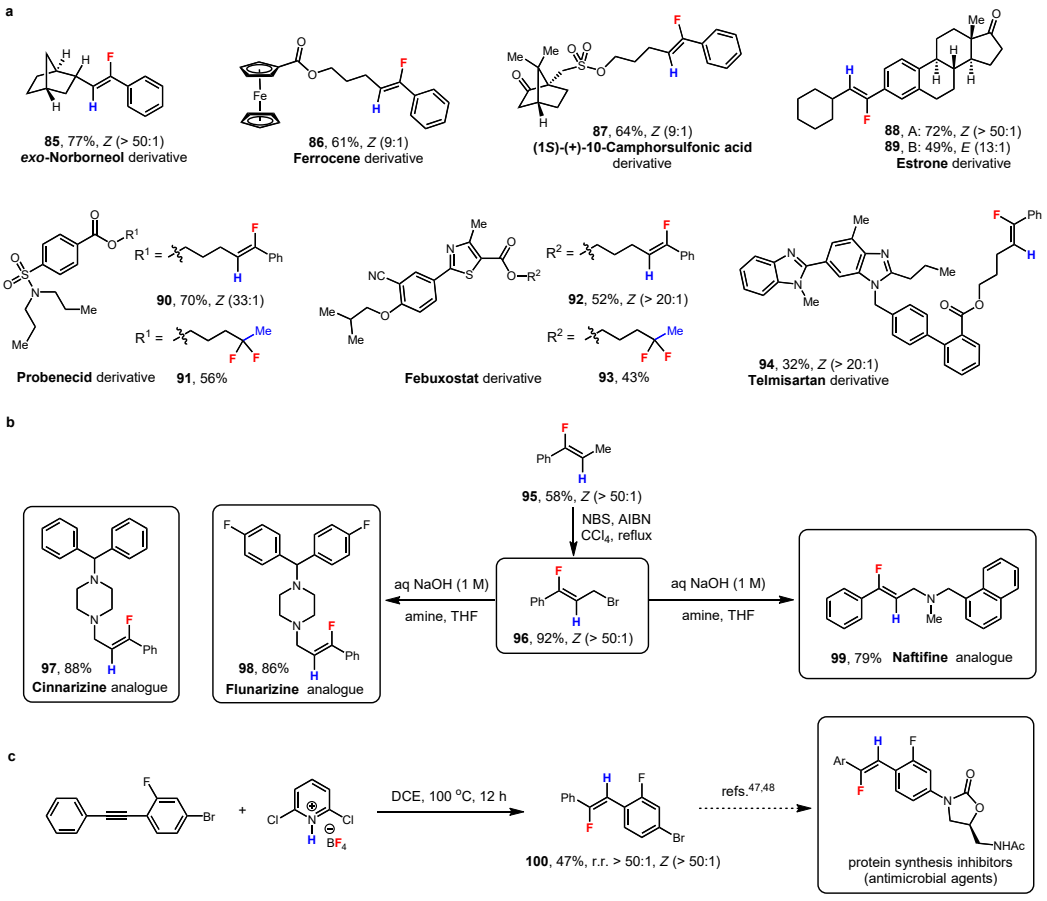


Fig. 2. Synthetic applications of stereodivergent alkyne hydrofluorination. a, The late-stage modification of biologically active molecules or complex natural products. **b**, The synthesis of different fluorinated analog of drug molecules. **c**, The preparation of key intermediate for the synthesis of antimicrobial agents with high regio- and *Z*/*E*-selectivities. See supporting information for detailed conditions.

To explore other applications of this chemistry, we prepared **95** on 5-mmol scale to access fluorinated analogues of antihistamines cinnarizine (**97**), flunarizine (**98**) and antifungal drug naftifine (**99**) (Fig. 2b). Via allylic bromination of **95**, we prepared a common brominated intermediate **96**, which could be applied to the synthesis of all

three analogues. Moreover, we also prepared vinyl fluoride **100**, a known precursor for the synthesis of antimicrobial agents (protein synthesis inhibitors) through the coupling with 2-oxazolidone (Fig. 2c)[47,48]. These transformations illustrated in above study demonstrates the excellent potential of this method for future applications in a drug discovery setting.

Mechanistic discussion. The experimental results have demonstrated that 2,6-dichloropyridinium tetrafluoroborate is an effective fluorinating reagent for stereodivergent alkyne hydrofluorination. As shown in Table 2, high levels of *Z*-selectivity are obtained in a polar solvent (*i.e.* DCE, condition D), while reactions in a less polar solvent (*i.e.* chloroform, condition C) or under lower temperatures (see SI) completely switch the stereoselectivity to favor *E*-products. Mechanistic studies were then performed to investigate whether the hydrofluorination occurs through a concerted or stepwise mechanism and the origin of the divergent stereoselectivity. DFT calculations[49] of the hydrofluorination of 1,2-diphenylacetylene **101** indicated a stepwise Ad_E2-type protonation-fluorination mechanism with a BF_4^-/vinyl cation ion-pair intermediate (Fig. 3a). Prior to the alkyne protonation, the H···F hydrogen bond in the fluorinating reagent **F** dissociates to release a free pyridinium cation as the proton source. Two protonation transition states were located (**TS-1** and **TS-1a**), in which the tetrafluoroborate anion is *syn* and *anti* to the pyridinium, respectively. Bonding interactions between BF_4^- and the alkyne were not observed in either protonation transition state, which is likely due to the weak nucleophilicity of BF_4^-. The stepwise hydrofluorination mechanism is confirmed by the intrinsic reaction coordinate (IRC) calculations, which indicated that **TS-1** and **TS-1a** lead to BF_4^-/vinyl cation ion pairs **102** and **102a**, respectively, rather than the hydrofluorination products. Fluorination of the highly electrophilic vinyl cation with BF_4^- (via **TS-2** and **TS-2a**) is very facile, which makes protonation (**TS-1**) the rate-determining step. This mechanistic picture is consistent with experimental Hammett analysis and kinetics studies, which indicated a ρ value of –3.43 consistent

with previously reported vinyl cation-mediated reactions[36] and first-order kinetics in alkyne and H^+ and zero-order kinetics in excess BF_4^- (Fig. 3d, see SI for details). The *E*-selective pathway (shown in black in Fig. 3a) is kinetically favored in both protonation and fluorination steps. The *syn*-protonation transition state **TS-1** is more stable than the *anti*-TS (**TS-1a**) due to more favorable electrostatic interactions between BF_4^- and the pyridinium cation. The *E*-selective fluorination transition state **TS-2** is 0.9 kcal/mol more stable than the *Z*-selective fluorination (**TS-2a**) because of steric repulsions between BF_4^- and the β-phenyl group in **TS-2a**[50]. Therefore, regardless of whether ion pairs **102** and **102a** have sufficient lifetime to interconvert prior to the fluorination, kinetic *E*-selectivity is expected. The relatively low barrier for the reverse reaction of ***E*-81** (via **TS-2**, $\Delta G^{\ddagger}$ = 23.6 kcal/mol) to generate the vinyl cation indicates the *E*-to-*Z* vinyl fluoride isomerization may occur at elevated temperatures through BF_3-mediated fluoride anion elimination followed by fluorination of the vinyl cation via **TS-2a**. A polar solvent would also promote such isomerization by stabilizing ion-pair intermediates **102** and **102a** (see Fig. S15 in SI for computational results with DCE). Because the *Z*-stereoisomer ***Z*-71** is 2.3 kcal/mol more stable than ***E*-71**, high *Z*-selectivity is expected under these thermodynamically controlled conditions.

The BF_3-mediated *E*/*Z*-vinyl fluoride isomerization is verified experimentally under conditions with either 2,6-dichloropyridinium tetrafluoroborate or $Et_2O{\bullet}BF_3$ (Fig. 3b). The addition of 2,6-di-*tert*-butylpyridine did not shut down the $Et_2O{\bullet}BF_3$-mediated isomerization, which excludes the possibility of Brønsted acid-promoted pathway. In addition, the increase of the *Z*-product ratio over a reaction time of 12 h at 70 °C further confirmed the isomerization of the kinetic *E*-isomer to *Z*-vinyl fluoride in the hydrofluorination of di-*p*-tolylacetylene (Fig. 3c). In certain cases, we also observed that better *Z*-selectivity could be obtained by addition of exogenous $Et_2O{\bullet}BF_3$ to promote *E*-to-*Z*-isomerization (*e.g.*, product **86** and **87** in Fig. 2, *Z*/*E* ratio from 3:1 to 9:1).

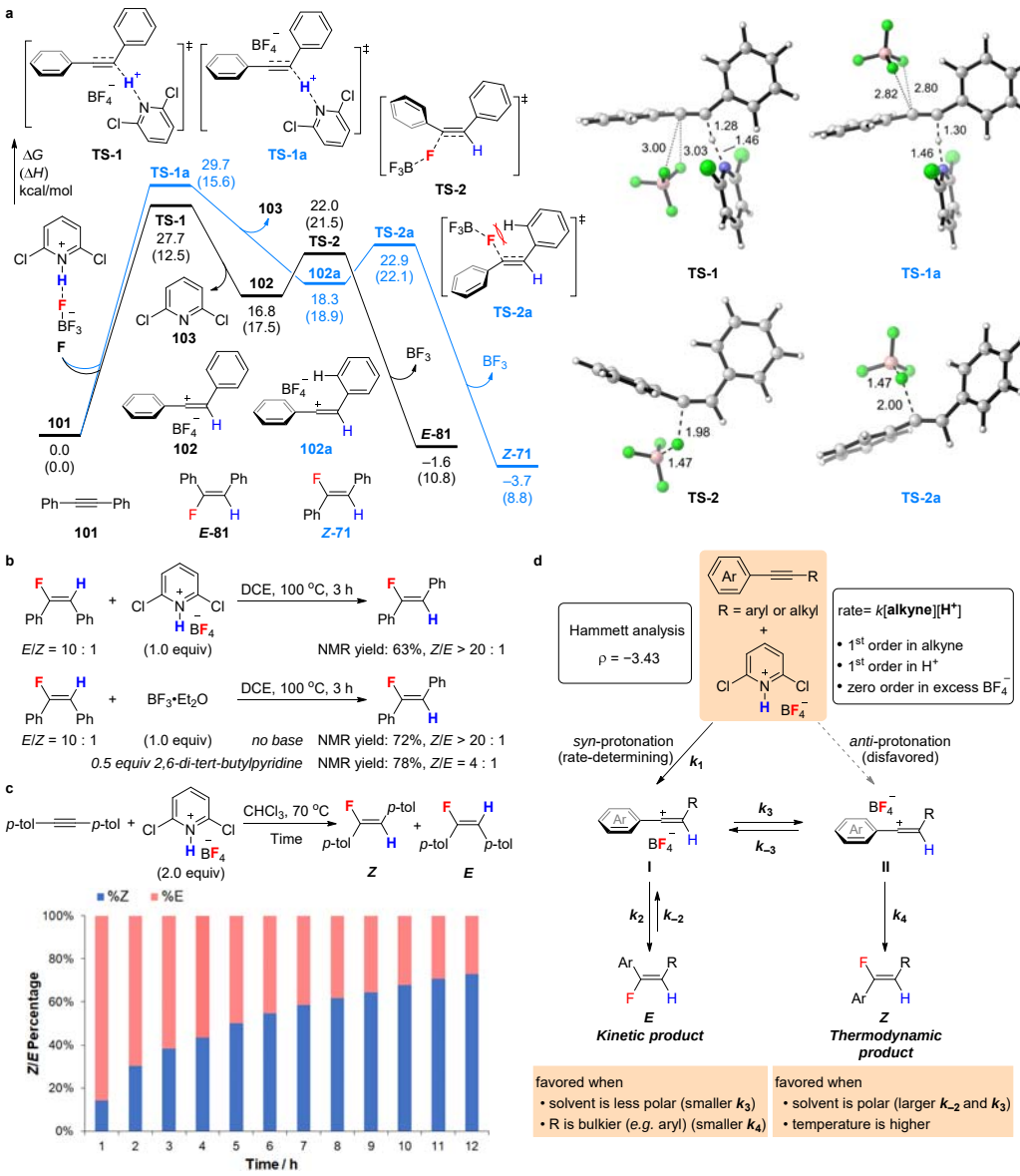


Fig. 3. Mechanistic studies. a. Reaction energy profiles of the hydrofluorination of 1,2-diphenylacetylene **101** with 2,6-dichloropyridinium tetrafluoroborate. All energies were calculated at the M06-2X/6-311+G(d,p)/SMD(chloroform)//M06-2X/6-31+G(d)/SMD(chloroform) level of theory. See Fig. S10 and S11 in SI for the computational results with the cyclohexyl and methyl-substituted alkynes. **b**. *E*/*Z*-isomerization of vinyl fluoride with fluorinating reagent **F** and $Et_2O•BF_3$. **c**. Change of the *Z*/*E*-ratio of the hydrofluorination product over the course of reaction. **d**. Proposed mechanism for the stereodivergent hydrofluorination of alkyne.

Based on these mechanistic studies, a general mechanism is proposed to elucidate the stereoselectivity control in the alkyne hydrofluorination (Fig. 3d). The

rate-determining *syn*-protonation of alkyne (k_1) leads to an ion pair intermediate (**I**), which then undergoes fluorination (k_2) to afford the kinetically favored *E*-vinyl fluoride. The thermodynamically more stable *Z*-product is formed from the isomerization of the *E*-vinyl fluoride, which takes place via BF_3-mediated fluoride dissociation (k_{-2}) and isomerization of the ion pair intermediate (k_3) followed by *Z*-selective fluorination with BF_4^- (k_4). Higher temperatures and polar solvents (*e.g.* DCE) promote such *E*-to-*Z* isomerization, and thus enhance the Z-selectivity. Experimentally, excess BF_4^- (condition A) was also found to favor formation of the Z-isomer (see SI), an effect which may be ascribed to increased availability of BF_4^- for *anti*-attack (k_4) or a change in the solvent polarity due to higher ionic content. On the other hand, lower temperatures, polar solvent, and bulkier alkyne substituents (*e.g.* aryl) that suppress ion pair isomerization (k_3) and the *Z*-selective fluorination (k_4) would lead to higher *E*-selectivity under kinetic control.

Conclusion

We have developed a simple, practical, and metal-free strategy for the regio- and stereoselective controlled mono- and dihydrofluorination of alkynes by employing 2,6-dichloropyridinium tetrafluoroborate as a new, safe, and stable fluorinating reagent. Mechanistic and DFT studies reveal that the stereoselectivity of hydrofluorination results from either kinetic or thermodynamic control in a stepwise protonation-fluorination pathway. We anticipate that this hydrofluorination protocol will find wide applications in drug discovery and related fields by facilitating the preparation of fluorinated molecules of biological interest. Studies further exploiting the synthetic applications of vinyl cation intermediates generated under similar mild conditions are ongoing.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. The x-ray crystallographic coordinates for the structure of **22** are available free of charge from the Cambridge Crystallographic Data Centre under deposition number CCDC 1988001.

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Additional information

Supplementary information is available in the online version of the paper.

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