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Access to fluorinated dienes through hydrofluorination of 2-En-4-ynoates†

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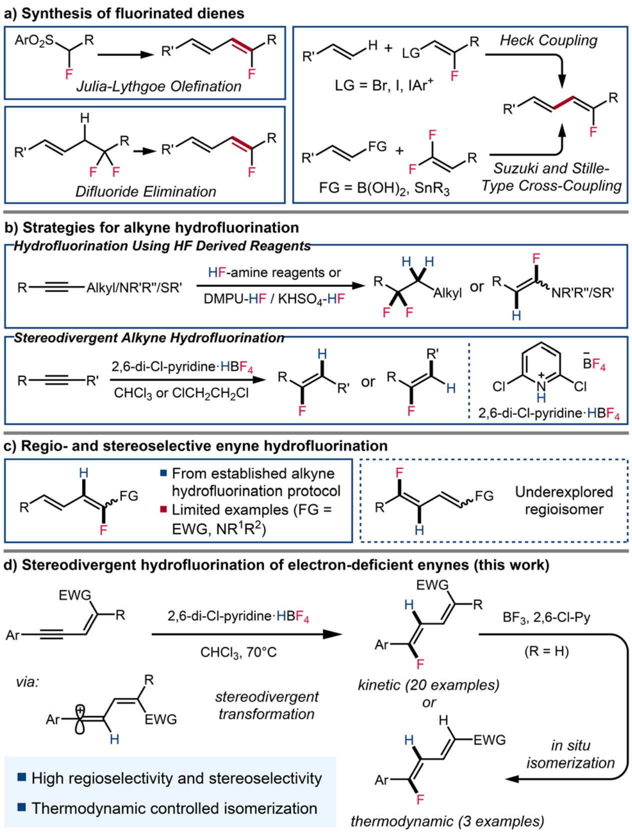
The hydrofluorination of enynoates has been developed for the synthesis of fluorinated dienoates. Using a pyridinium tetrafluoroborate salt that is easily prepared on large scale, this approach enabled the direct conversion of these substrates to fluorinated targets through a vinyl cation mediated process. This approach was applied to a range of aryl-substituted enynoates to deliver the (*Z*)-configured products with high levels of stereo- and regioselectivity. Mechanistic studies were conducted to provide insights into the stereochemical outcome and reaction efficiency under different reaction conditions.

Introduction

Fluorinated molecules have gained particular interest in the fields of medicinal and agricultural chemistry in recent decades.[1] The introduction of a fluorine atom into organic molecules has become an important approach to modulate their physicochemical properties, lipophilicity, and metabolic stability. Fluorinated dienes and polyenes that serve as analogues of bioactive lipids have received particular attention.[2] Among methods for the introduction of fluorine atoms in a selective manner, hydrofluorination of unsaturated bonds is one of the most significant and exploited pathways, but this strategy is rarely applied to the synthesis of fluorinated dienes and polyenes.[3]

Various methods have been developed to synthesize C(sp^2)-fluorinated dienes, allowing for the selective synthesis of products of various substitution patterns and stereochemistry (Scheme 1a). One of the most common ways to synthesize fluorinated dienes is the coupling of pre-functionalized vinyl fluorides with olefins.[4] However, this approach typically requires less accessible starting materials. Geminal difluorides are also common precursors to monofluorodienes. Mono-elimination of fluorine in aliphatic geminal difluorides has led to the synthesis of conjugated vinyl fluorides.[5] *gem*-Difluoroalkenes have also been shown to be good coupling partners, either under Stille conditions or with boronic acids under rhodium catalysis, resulting in the selective formation of the desired monofluorodiene.[6] α-Fluorinated aryl sulfones, reacting with α,β-unsaturated carbonyls *via* Julia olefination, have also been demonstrated to give rise to fluorinated dienes in good yields.[7] However, this method tends to result in modest to moderate stereoselectivity. While most of the existing methods for the synthesis of fluorinated dienes require the



Scheme 1 Enyne hydrofluorination for accessing fluorinated dienes.

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utilization of fluorine containing fragments and/or multiple synthetic steps from non-fluorinated starting materials, direct hydrofluorination of enynes could provide a reliable synthetic pathway and expand the toolbox for the construction of fluorinated dienes.

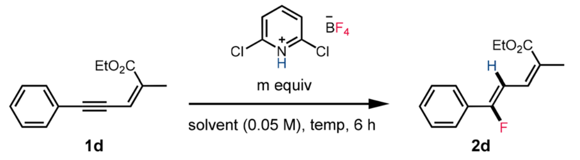
Recent advances have led to hydrofluorination emerging as an efficient and effective pathway for the incorporation of fluorine into unsaturated compounds, including the synthesis of alkenyl fluorides from alkynes.[8] Numerous amine-modulated hydrogen fluoride sources have been investigated to achieve this transformation.[9] However, reports by both Olah and Hammond indicate that generally, even with careful control of the reaction conditions, these HF derived reagents deliver the *gem*-difluoride product without allowing isolation of the presumed alkenyl fluoride intermediate, except in special cases where the alkyne bears a heteroatomic substituent (Scheme 1b, top).[10]

Considering that tetrafluoroborate salts are safe, stable, and affordable fluoride sources,[11] our group has developed a novel pyridinium tetrafluoroborate based reagent for hydrofluorination (Scheme 1b, bottom).[12] This reagent enabled the stereoselective hydrofluorination of alkynes, delivering vinyl fluoride products with good to excellent regio- and stereoselectivity under mild conditions, with the stereochemical outcome dependent on both substrate structure and reaction conditions. We aimed to broaden the application of this novel hydrofluorinating reagent to the synthesis of a wider array of fluorinated compounds, particularly fluorinated dienes through the hydrofluorination of enynes. Although alkyne hydrofluorination has been extensively studied, the synthesis of fluorinated dienes through the formation of C(sp^2)–F bonds remain significantly underreported, with only few isolated examples of enyne hydrofluorination reported as special cases following established protocols for alkyne hydrofluorination.[13] These methodologies have primarily yielded fluorinated dienes with specific regioselectivity, placing fluorine atoms α to an existing functional group. To the best of our knowledge, the construction of other regioisomers through enyne hydrofluorination remains unknown (Scheme 1c). While approaches toward fluorinated dienes *via* the formation of carbon-carbon bonds has enabled access to these regioisomers, the synthesis usually involves multiple steps, and in some cases proceeds through unstable intermediates.[14] Hence, the synthesis of fluorinated dienes bearing alternate selectivity *via* enyne hydrofluorination could present a useful alternative (Scheme 1d).

Results and discussion

We initiated our investigation using **1d** as our standard substrate and 2,6-dichloropyridinium tetrafluoroborate salt as both the hydrogen and fluoride source (Table 1). Upon testing the optimal conditions we applied in our previous alkyne hydrofluorination reaction,[12] we found that product **2d** could be obtained in a moderate yield of 45% with excellent regio- and stereoselectivity. We found that 2.0 equiv. of pyridinium reagent was most efficient for this transformation (50% yield, entry 2), while less or more pyridinium salt led to lower yields. Various weakly coordinating solvents were tested (entries 2, 5–8) and chloroform was found to give the best result (entry 2). Variation of concentration revealed that diluted reaction conditions gave better yields (see ESI†). We also tested various reaction temperatures (entries 9–12) and found that conducting the reaction at 70 °C provided the highest yields. Various additives were also tested, however we found that in this reaction the additives either lowered the yields or otherwise had little impact. Moreover, in some cases, cyclization of the substrate was competitive with hydrofluorination, while prolonged reaction times were also found to cause decomposition of the target product (see the ESI† for discussions of product stability and side product formation). The synthesis of 2,6-dichloropyridinium tetrafluoroborate was reoptimized and reproducibly scaled to 150 mmol (see the ESI†).

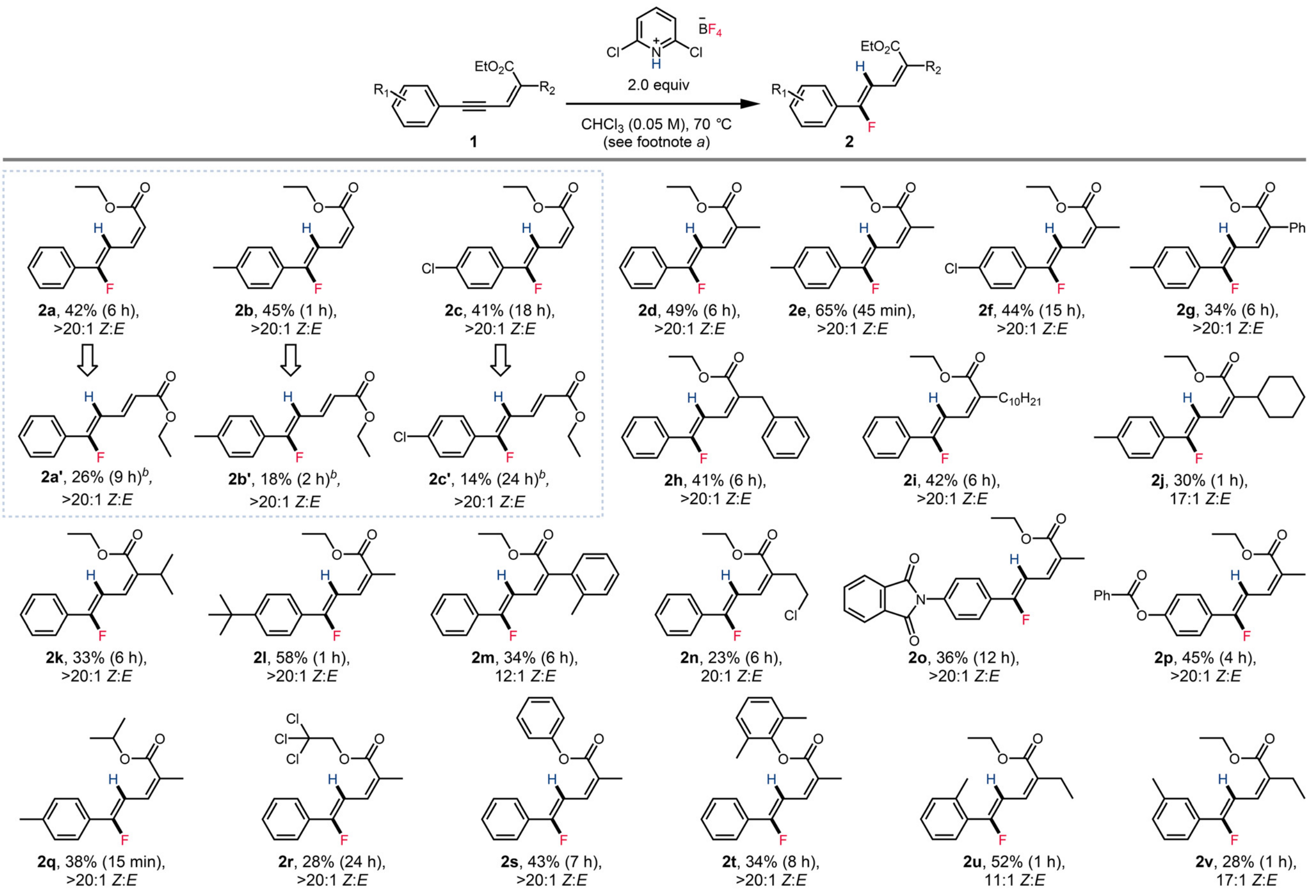
Table 1 Optimization of reaction conditions[a]



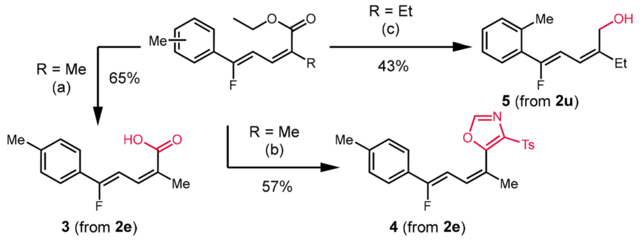
Entry	*m*	Solvent	Temp (°C)	Yield[b] (%)
1	1.0	$CHCl_3$	70	45
2	**2.0**	**$CHCl_3$**	**70**	**50 (43[c])**
3	3.0	$CHCl_3$	70	41
4	4.0	$CHCl_3$	70	39
5	2.0	PhMe	70	21
6	2.0	PhCl	70	34
7	2.0	$PhCF_3$	70	25
8	2.0	1,2-DCE	70	0
9	2.0	$CHCl_3$	20	Trace
10	2.0	$CHCl_3$	40	16
11	2.0	$CHCl_3$	60	39
12	2.0	$CHCl_3$	80	45

[a] Reaction conditions: **1d** (0.1 mmol) and 2,6-dichloropyridinium tetrafluoroborate was added solvent (2.0 mL), stirred at indicated temperature for 6 h. [b] NMR yields, determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [c] Isolated yield. 1,2-DCE = 1,2-dichloroethane.

With the optimized conditions established, we set out to explore the scope of this transformation (Scheme 2). Aryl enynoates bearing mildly electron donating substituents (**2e**, **2l**) and mildly electron withdrawing substituents (**2f**) were tolerated. Enynoates with heteroatomic substituents including phthalimide (**2o**) and benzoyl (**2p**) could also be tolerated. 2,5-Diaryl enynoates (**2g**) were also reactive. Reaction conditions also tolerate various aliphatic and aromatic substitutes, such as benzyl (**2h**), decyl (**2i**), cyclohexyl (**2j**), isopropyl (**2l**), *o*-methylphenyl (**2m**) and 2-chloroethyl (**2n**). Various esters (**2q**–**2t**) could also be applied in this transformation. Substitution at the *ortho* (**2u**) and *meta* (**2v**) positions of the aryl group were also tolerated. Unfortunately, when the aryl



Scheme 2 Substrate scope for the formation of fluorinated dienoates **2**. [a] Reaction conditions: **1** (0.25 mmol), 2,6-dichloropyridinium tetrafluoroborate (0.50 mmol), chloroform (5.0 mL), stirred at 70 °C for indicated duration. [b] 1,2-DCE (0.05 M) was used as solvent.



Scheme 3 Divergent transformations of products. (a) LiOH (4.0 equiv.), THF (0.5 M), 50 °C, 24 h. (b) TosMIC (1.0 equiv.), *n*BuLi (2.0 equiv.), THF (0.5 M), 0 °C, 4 h. (c) DIBAL-H (3.0 equiv.), THF (0.5 M), 0 °C, 2 h.

group of the substrate was replaced by an alkyl group, the hydrofluorination protocol was unsuccessful, and no fluorinated products were observed by ^{19}F NMR (see the ESI† for examples attempted). While the yields obtained were generally found to be modest (*vide infra*), the products were readily purified by column chromatography. In addition, we note that in all cases, the product dienoates were obtained in high regio- and stereoselectivity.

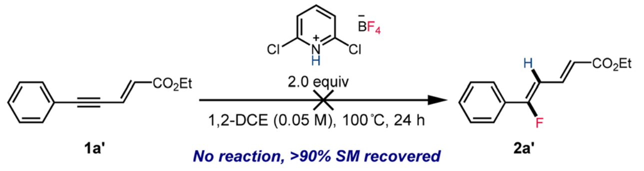
Interestingly, we found that when the enynoate C2 position was unsubstituted, isomerization of the product dienoate was observed when the more polar solvent 1,2-dichloroethane was applied (Scheme 2, boxed examples). Enynoates **1a–1c** could form both stereoisomers under distinct reaction conditions. However, the (*E*)-configured products were obtained in considerably lower yields than the (*Z*) isomer. C2-substituted enynoates were also subjected to similar conditions, but only led to full decomposition of the starting enynoate and dienoate products without the formation of other isomers.

We performed three further derivatizations to demonstrate the synthetic utility of the fluorinated dienoate products (Scheme 3). The saponification of **2e** afforded the α,γ-unsaturated carboxylic acid **3** in 65% yield. Cyclization with *p*-toluenesulfonylmethyl isocyanide (TosMIC) afforded oxazole **4** in 57% yield.[15] Reduction of the ester moiety with DIBAL-H afforded the alcohol **5** in 43% yield. We also performed two reactions on mmol scale to demonstrate the scalability of this protocol. Substrate **1u** was subjected to conditions at 1.25 mmol scale to successfully synthesize **2u** in 49% yield. Similarly, **1t** was reacted at 2.5 mmol scale to provide **2t** in 35% yield.

The observation that reactions of substrates **1a, 1b**, and **1c** in the less polar solvent chloroform (ε = 4.81) or under lower temperatures (see the ESI†) favored the formation of stereo-retention products while reactions conducted in the more polar solvent 1,2-dichloroethane (ε = 10.36) provided the dienoate product with reversed stereochemistry prompted us to investigate the sequence of events in this isomerization and the origin of the divergent stereoselectivity. Two potential pathways for the formation of 2-*trans* isomers were proposed, which primarily concerned whether the olefin isomerization occurs before or after the enynatee hydrofluorination. To validate the potential reaction pathway, **1a′** was synthesized and subjected to the reaction conditions (Scheme 4). However, even at elevated temperatures, **1a′** remained unreactive, and all material was recovered after 24 h. Additionally, no **1a′** was observed during the hydrofluorination of **1a**, instead we observe near quantitative starting material recovery, which strongly suggested that the olefin isomerization occurred following the fluorinated dienoate formation.

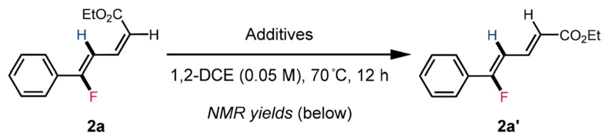
The mechanism of diene isomerization was investigated (Table 2). Upon heating **2a** under reaction temperature, no isomerization was observed. However, as $Et_2O{\cdot}BF_3$ was added, a 12% isomerization product was observed, suggesting that the isomerization is a Lewis acid-promoted process. The addition of 2,6-dichloropyridine further enhanced conversion, indicating the possibility of an addition-elimination type mechanism for *E*/*Z* isomerization (Scheme 5).

The increasing proportion of **2a′** over 12 hours is consistent with gradual equilibration that favors the thermodynamically preferred stereoisomer over prolonged reaction times (Scheme 6, top). The increase in reaction temperature was also found to favor the formation of **2a′** (Scheme 6, bottom).



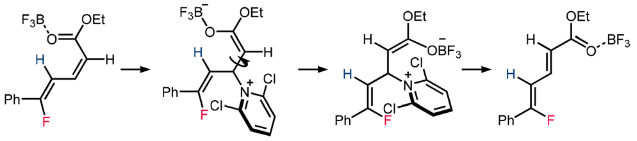
Scheme 4 Attempted hydrofluorination of **1a′**.

Table 2 Isomerization of fluorinated dienoate

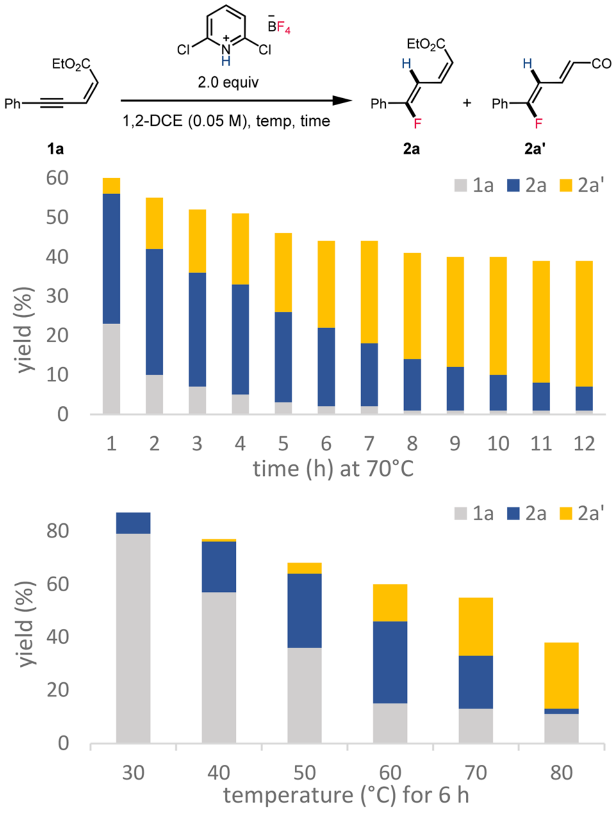


Additives	SM residue (%)	Yield[a] (%)
None	74	0
BF_3OEt_2 (1.0 equiv.)	53	12
BF_3OEt_2 (1.0 equiv.) & 2,6-dichloropyridine (1.0 equiv.)	47	32

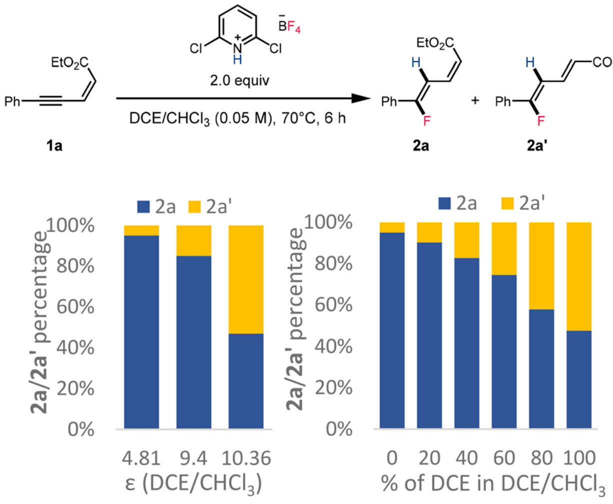
[a] NMR yields, determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.



Scheme 5 Proposed mechanism for isomerization of dienoate **2a**.



Scheme 6 Formation of fluorinated dienoates **2a** and **2a′** over time and at various reaction temperatures.



Scheme 7 Isomerization of fluorinated dienoate **2a** in various solvents.

Further experimental study of the dielectric constant of the solvent suggested that more **2a**′ could be obtained when increasing the dielectric constant of the solvent or increasing the high dielectric component in the solvent mixture (Scheme 7). These observations further supported the hypothesis that formation of both fluorinated dienoate isomers was under thermodynamic control *via* polar intermediates.

Conclusions

In conclusion, we have developed straightforward conditions for the hydrofluorination of enynoates using 2,6-dichloropyridinium tetrafluoroborate as fluorinating reagent. This protocol could be applied in the hydrofluorination of a range of enynoates, and stereodivergent protocols were developed for C2-unsubstituted substrates. Mechanistic studies suggested a pathway for the *E*/*Z* isomerization of C2-unsubstituted fluorinated dienoates that occurs after initial hydrofluorination of the *Z*-configured enynoate, allowing for the rationalization of the observed stereodivergence.

Data availability

All data supporting the findings of this study, including experimental details and spectroscopic characterization data for all compounds, are available within the article and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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