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Base Catalysis Enables Access to α,α -Difluoroalkylthioethers

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Abstract

A nucleophilic addition reaction of aryl thiols to readily available β,β -difluorostyrenes provides α,α -difluoroalkylthioethers. The reaction proceeds through an unstable anionic intermediate, prone to eliminate fluoride and generate α -fluorovinylthioethers. However, the use of base-catalysis overcomes the facile β -fluoride elimination, generating α,α -difluoroalkylthioethers in excellent yields and selectivities.

Graphical Abstract

Functionalization reactions of alkenes are essential transformations for synthetic organic chemistry. Although many of these reactions occur *via* interactions of the alkene HOMO with electrophiles,¹ alkenes also react with nucleophiles through the π^* LUMO. To access the LUMO, alkenes typically require activation by a limited set of π -electron-withdrawing groups (EWG), such as carbonyl, nitrile, or nitro groups.^{1b} Similar to these EWGs, fluorinated substituents also activate alkenes for nucleophilic attack.² Unlike EWGs that activate the π bond through resonance and facilitate attack at the β -carbon,³ fluorination activates the alkene's α -carbon for attack⁴ through σ -withdrawing inductive effects, while also deactivating the β -carbon through resonance effects.⁵ This activation of alkenes by fluorine has been utilized in nucleophilic hydrofluorination reactions to generate trifluoromethanes (Scheme 1a),⁴ and in various acid-promoted intramolecular or base-mediated intermolecular C–F functionalization reactions to deliver monofluorinated

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Author Contributions

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Supporting Information

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Experimental procedures, spectroscopic data for new compounds and mechanistic experiments (PDF)

products.^{2, 6} However, nucleophilic hydrofunctionalization reactions of difluoroalkenes with alternate nucleophiles have not been generally developed.

Inspired by the use of *gem*-difluoroalkenes as mechanism-based inhibitors,⁷ we envisioned that alternate heteroatom-based nucleophiles, such as thiols, might undergo analogous hydrofunctionalization reactions by nucleophilic addition followed by protonation. However, prior attempts to add thiols across *gem*-difluoroalkenes afforded α -fluorovinylthioether products through an addition / elimination process (Scheme 1b).^{2, 6b, 8} To avoid the elimination of F⁻, we present a mild, base-catalyzed reaction to furnish α,α -difluoroalkylthioethers in high yield and selectivity (Scheme 1c), which complements earlier methods to access the α,α -difluoroalkylthioether group, including: 1) nucleophilic substitution reactions of silylated⁹ or halogenated¹⁰ difluoroalkyl intermediates that require multi-step preparations; 2) radical processes with limited functional group compatibility,^{10b, 10c, 11} or 3) oxidative methods that utilize harsh fluorinating reagents.¹² In contrast, the present reaction uses only catalytic quantities of a mild base, enabling access to products bearing many sensitive functional groups. Thus, this reaction should facilitate access to bioactive compounds bearing α,α -difluoroalkylthioethers, including anti-cancer¹³ and anti-inflammatory¹⁴ agents and agrichemicals.¹⁵

After extensive optimization, we identified a general base-catalyzed protocol for adding aryl thiols to β,β -difluorostyrenes. We selected a styrene-based substrate to stabilize the proposed intermediate anion (**A**) through resonance. Initial attempts to functionalize difluorostyrene **1** with thiophenol involved catalytic amounts of inorganic bases, which either generated non-fluorinated disubstituted alkene **3** (likely arising from sequential C–F functionalizations),^{8a, 8b} or which did not react (Figure 1). When higher quantities of inorganic base were employed, large amounts of α -fluorovinylthioethers formed. In contrast, catalytic quantities of organic bases generated the desired α,α -difluoroalkylthioether in modest to excellent yield and selectivity. Of the bases evaluated 1,1,3,3-tetramethylguanidine (TMG) provided the best yield and selectivity for product **2** over product **4** (entries 1–4). Notably, the use of preformed PhSNa as a base only formed small amounts of eliminated product **4** (entry 5), which suggests that ArSH might not serve as the H⁺ donor, but rather TMG–H⁺. Subsequent evaluation of solvents revealed that chlorinated solvents provided the best yield and selectivity, with 1,2-dichloroethane (DCE) proving optimal (entries 1, 5–11).

Several experiments support the proposed addition / protonation pathway over a mechanism involving S-based radicals. First, the reaction ran smoothly in the absence of light and O₂, which are known radical initiators. Second, although the reaction utilizes TMG (which can have inorganic impurities that can oxidize a thiolate)¹⁶, other amine bases that lack such impurities (e.g. purified Et₃N) are competent base catalysts (Table 1, entry 2). Third, when running the reaction in CD₂Cl₂ (which can transfer •D)¹⁷ D was not incorporated into the product. Fourth, reactions run in presence of radical traps (e.g. 1,4-dicyanobenzene and BHT) proceed to full conversion and comparable yields. In contrast, reactions run in the presence of TEMPO, both with and without TMG, gave no desired product and generated (PhS)₂, presumably by transfer of H• from PhSH to TEMPO and subsequent homocoupling

of the resulting PhS•. Thus under our conditions, S-based radicals are not likely reactive intermediates.

The optimized reaction conditions enabled coupling between thiophenol and a broad spectrum of functionalized β,β -difluorostyrenes (**5a–n** and **1**), with selectivity generally exceeding 25:1 (Scheme 2). The reaction tolerated many useful functional groups on the β,β -difluorostyrene, such as halides (**6c**, **6i**, **6k**), ethers (**2**, **6a–c**, **6h**), thioethers (**6b**), and nitrogenous functional groups (**6d**, **6e**, **6l–n**). *Ortho*-substituted β,β -difluorostyrenes required higher reaction temperatures (**6c**, **6g**, **6i**). Carbonyl-containing compounds were also tolerated (**6j**, **6l**), and notably a substrate bearing an α,β -unsaturated ester reacted exclusively at the fluorinated position, with no evidence of irreversible Michael addition (**6j**). Electron-rich and -neutral β,β -difluorostyrenes generally provided high yields and selectivities, and required low temperatures and short reaction times (**2**, **6a–e**, **6h**). In contrast, under standard reaction conditions, electron-deficient substrates reacted sluggishly, affording products in modest yields and selectivities. To reach full conversion, these reactions required higher temperatures and longer times (**6k–n**). However, these harsher conditions afforded more α -fluorovinylthioether side product (6.6:1–13:1).

To determine whether the reduced selectivity arose from the instability of the product or of the anionic intermediate **A**, purified products **2**, **6d**, and **6n** were resubjected to the reaction conditions (Scheme 3a). ^{19}F NMR analysis of the reaction mixtures showed no evidence of degradation, suggesting that β -fluoride elimination from **A** occurs more rapidly for electron-deficient species than for electron-rich or -neutral species (Scheme 3b).

Further, under the optimized conditions heteroaromatic *gem*-difluoroalkenes reacted smoothly (Scheme 4). Electron-rich and -deficient N-based heterocycles (indole **8a**, pyridine **8b**, pyrrole **8c**), and S-based heterocycles (benzothiophene **8d**, phenothiazine **8e**, thiazole **8f**) all provided good yield and selectivity, suggesting that the reaction conditions should apply to a broad spectrum of biologically relevant heteroaromatic compounds.

A broad scope of functionalized aryl thiol nucleophiles were also tolerated (Scheme 5). Aryl thiols bearing halides (**10h**, **10e**), ethers (**10a**, **10b**, **10f**), trifluoromethane (**10g**), carbonyl groups (**10b**), and even a secondary amide (**10c**) afforded α,α -difluoroalkylthioether products, confirming that electron-rich, -neutral, and -weakly-deficient aryl thiols generally reacted smoothly. Thiols bearing strong electron-withdrawing groups (e.g. nitrile **10i**) required higher temperatures and extended reaction times. Notably, all reactions demonstrated excellent selectivity (>25:1) regardless of the nature of the nucleophile. Finally, the mild conditions tolerated many useful protecting groups, including a Ts-protected indole (**8a**), an acetal (**8b**), a Boc-protected amine (**8f**), benzyl- and *p*-methoxybenzyl-protected alcohols and amines (**6c**, **6h**, **8e**), and an acetyl-protected amine (**10c**), all potentially useful in multistep synthetic sequences.

While aryl thiol nucleophiles reacted efficiently, alkyl thiols reacted poorly, giving mainly addition / elimination products, presumably due to a mismatched thiol-base pair. To assess whether a dual nucleophile system could avoid this undesired reactivity of alkyl thiols, an aryl thiol was reacted with **1** in the presence of an alkyl thiol under the harshest conditions

explored (Figure 2). Under these conditions, the aryl thiol selectively coupled to form aryl thioether **2** with <1% formation of alkyl thioether **11**, likely because the increased acidity of the aryl thiol allows preferential deprotonation, and the resulting thiolate is more nucleophilic than the neutral thiol. Further, attempts to use the present conditions for reactions of alcohol and N-heterocycle nucleophiles proved ineffective. To address this limitation, we are currently optimizing alternate conditions for these nucleophiles.

In summary, we developed a new base-catalyzed strategy to generate α,α -difluoroalkylthioethers by directly adding aryl thiol nucleophiles to β,β -difluorostyrenes. This reaction proceeds *via* an unstable anionic intermediate that is prone to eliminate F^- ; however, the mild conditions avoid this undesired unimolecular elimination. The catalytic reaction enables access to a variety of functionalized α,α -difluoroalkylthioethers in high yield and selectivity versus the α -fluorovinylthioether. Combined with direct preparations of β,β -difluorostyrenes² by olefination¹⁸ and cross coupling¹⁹ chemistry, the present reaction should facilitate access to this underutilized functional group in medicinal and agrichemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Undesired Reactivity with Inorganic Bases.

Figure 2.
Coupling of Aryl Thiol over Alkyl Thiol.

a) Previous Nucleophilic Addition Reactions of *gem*-Difluoroalkenes^[4]

b) Nucleophiles Typically React via Addition/Elimination^[2, 6]

c) Proposed Base-catalyzed Strategy

Scheme 1.

Base Catalyst Enables Nucleophilic Addition to *gem*-Difluoroalkenes.

Scheme 2. Scope of Distinct β,β -Difluorostyrenes^[a]

[a] Standard conditions: **5a–n** (1.0 equiv), PhSH (2.0 equiv), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ^{19}F NMR analysis of the reaction mixture, unless otherwise indicated. Yields represent an average of two runs. [b] PhSH (3.0 equiv). [c] Selectivity = 13:1. [d] Selectivity = 6.6:1. [e] Selectivity = 8:1. PMB = 4-methoxybenzyl, Tf = trifluoromethylsulfonate.

b) For EWG, α -Fluorovinylthioether Arises from Decomposition of A

Scheme 3.

Decomposition of Anionic Intermediate A Reduces the Selectivity for e^- -Deficient Substrates.

Scheme 4. Scope of Heteroaromatic β,β -Difluorostyrenes.^[a]

[a] Standard conditions: **7a–n** (1.0 equiv), PhSH (2.0 equiv), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ^{19}F NMR analysis of the reaction mixture. Yields represent an average of two runs. [b] PhSH (3.0 equiv). Ts = 4-toluenesulfonyl.

Scheme 5. Scope of Distinct Aryl Thiols.^[a]

[a] Standard conditions: **1** (1.0 equiv), ArSH **9a-j** (2.0 equiv), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ¹⁹F NMR analysis of the reaction mixtures. Yields represent an average of two runs. [b] ArSH (3.0 equiv).

Table 1Optimization of the Reaction Conditions.^[a]

<p>Ar = 3,4,5-(OMe)₃-C₆H₂</p> <p>(Desired) (Undesired)</p>				
entry	base	solvent	conv/yield [%] ^[b]	2:4 ^[b]
1	TMG	DCE	>99/96	>25:1
2	Et ₃ N	DCE	>99/82	>25:1
3	DMAP	DCE	>99/67	>25:1 ^[e]
4	TBD	DCE	>99/77	>25:1
5 ^[c]	PhSNa	DCE	15/<1	N/A
6	TMG	PhNO ₂	94/60	4:1
7	TMG	DMF	>99/36	1:1.2
8	TMG	PhMe	56/8	>25:1
9	TMG	MeCN	83/15	1:3.5
10 ^[d]	TMG	DCM	>99/88	>25:1
11 ^[c]	TMG	DCE	>99/91	>25:1

^[a] Standard conditions: **1** (1.0 equiv), PhSH (2.0 equiv), solvent (0.50 M), base (25 mol %), 80 °C, 4 h.^[b] Determined by ¹⁹F NMR standardized with PhCF₃ (1.0 equiv).^[c] Solvent (0.25 M), base (5.0 mol %), 70 °C, 0.5 h.^[d] 40 °C.^[e] Reaction generated a sulfoxide side product. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.