

VIP Very Important Paper

Remote Fluorination of α,β -Unsaturated Carbonyls via Silyl Dienol EthersDaria V. Galaktionova,^[a] Sara Y. Siddiqui,^[a] and Justin T. Mohr^{*[a]}

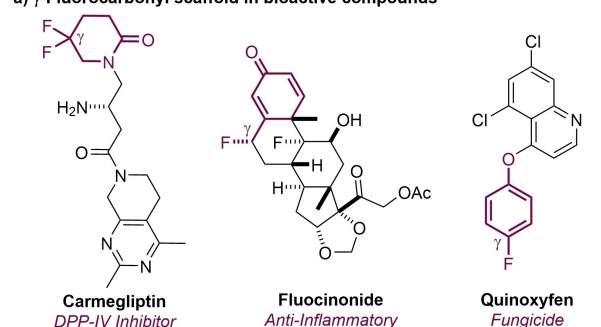
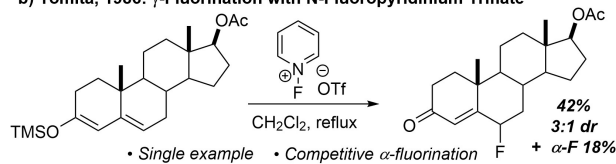
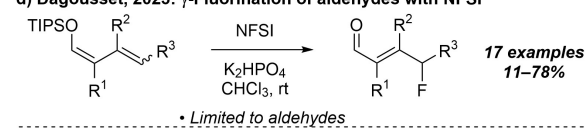
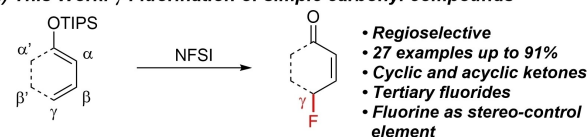
We report a general, regioselective, and metal free γ -fluorination of α,β -unsaturated carbonyls via silyl dienol ethers that are readily prepared from simple ketones and aldehydes. The transformation displays broad scope including 27 cyclic and acyclic siloxydienes providing γ -fluoro compounds in 28–91% yield. Notably, the reported conditions are also suitable for the

synthesis of challenging tertiary fluorides. The regioselectivity of the reaction was studied on a series of acyclic siloxydienes and was observed to be sensitive to the conformational flexibility of the substrate. Diversification of the γ -fluorocarbonyls demonstrates the promise of fluorine as a stereocontrol element.

Introduction

Pharmaceutical, agrochemical, and functional materials industries have been massively impacted by fluorinated organic compounds. Approximately 20% of marketed pharmaceuticals include fluorinated motifs.^[1] The merit of organofluoride compounds is attributed to the unique properties of the fluorine atom, which manifest desirable qualities such as increased metabolic stability, lipophilicity, and bioavailability.^[2] Among fluoroorganic compounds, γ -fluorinated carbonyls are relatively unexplored, given that current carbonyl fluorination technology is dominated by methods forging C–F bonds α or β to a carbonyl. Hence, methods that incorporate fluorine or fluoroalkyl groups at the remote γ -site are of great synthetic value (Scheme 1a).^[3]

Existing strategies granting access to remotely fluorinated carbonyls include visible light photoirradiation of steroids,^[4] 1,5-HAT processes,^[5] and metal-mediated ring-opening of cyclobutanols,^[6] which suffer from substantial substrate limitations. Hydrofluoro-methylation of alkenes has been utilized to access γ -fluoro carbonyls as well,^[7] however, this involves C–C bond formation as opposed to C–F bond formation, leading to limitations from a diversification standpoint. Furthermore, although α -fluoro carbonyl compounds are traditionally accessed through a variety of enolate equivalents, analogous methods utilizing a dienolate or similar synthon for distal γ -fluorination remains largely undeveloped.^[3a,b] To the best of our knowledge, γ -fluorination of carbonyls enabled by

a) γ -Fluorocarbonyl scaffold in bioactive compoundsb) Tomita, 1986: γ -Fluorination with N-Fluoropyridinium Triflatec) Shia and Poss, 1995: γ -Fluorination of steroids with NFSId) Dagousset, 2023: γ -Fluorination of aldehydes with NFSIe) This Work: γ -Fluorination of simple carbonyl compoundsScheme 1. γ -Fluorination of carbonyl compounds.

[a] D. V. Galaktionova,⁺ S. Y. Siddiqui,⁺ Prof. Dr. J. T. Mohr
Department of Chemistry
University of Illinois–Chicago
845 West Taylor St, Chicago, IL 60607 (USA)
E-mail: jtmohr@uic.edu

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a dienolate-type intermediate was demonstrated in only three reports at the outset of our studies. In 1986, Tomita and co-workers reported a single example for γ -fluorination of a steroidal system using N-fluoropyridinium triflate as an electrophilic fluorine source, where competitive α -fluorination

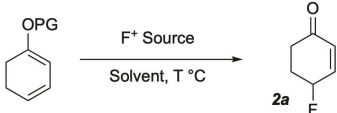
was observed as well (Scheme 1b).^[8] Later, Shia and Poss presented six more examples of γ -fluorination utilizing *N*-fluorobenzenesulfonimide (NFSI) as the fluorine source (Scheme 1c). This approach was limited to octalone- and steroid-derived substrates and required a strong base with a stoichiometric borate, presumed to form a boron dienolate.^[9] While we were preparing this manuscript, Dagousset and co-workers disclosed a fluorination protocol using dienol silyl ether nucleophiles, however the scope was limited to aldehyde-derived systems (Scheme 1d).^[10] Given the small quantity of existing reports, and the scope limitations therein, a generalized method enabling site-selective remote fluorination of simple carbonyl compounds is still in need.

As part of our general interest in distal functionalization of carbonyls, we drew inspiration from previous work in our group that demonstrated direct regioselective γ -halogenation and γ -amination of linearly conjugated lithium dienolates generated in situ.^[11,12] In an initial attempt, we investigated the reaction of the Li dienolate generated from cyclohexenone with NFSI to gain direct access to γ -fluorocyclohexenone **2a**, which proceeded with little success. Although fluoro enone **2a** was obtained as the sole isomer, the reaction was very low yielding. We then chose to investigate the silyl-protected dienol ether congeners as neutral enolate equivalents,^[13] envisioning improved compatibility with common electrophilic sources of F, which proved much more successful. We disclose herein a general protocol that demonstrates a widely applicable approach to remote regiocontrolled C–F bond formation for the facile construction of γ -fluorocarbonyl systems (Scheme 1e).

Results and Discussion

Our investigation commenced with examining the reaction of cyclohexenone-derived *tert*-butyldimethyl silyl (TBS) dienol ether and NFSI in a series of solvents (Table 1, entries 1–6). Significant reactivity was only observed in polar aprotic solvents, with DMF furnishing γ -fluoro enone **2a** in 37% yield (entry 6). Recovery of cyclohexenone was encountered as a side product, presumably through undesired attack upon the silyl ether. We reasoned that hydrolysis could be mitigated with a more robust protecting group; accordingly, different O-protecting groups were explored next (entries 7–10). Bulkier and more robust protecting groups generally improved the yield of fluoro enone **2a** (entries 7–10, cf. entry 6). As such, we chose to replace the TBS group with a triisopropylsilyl (TIPS) group, which delivered the desired fluoro enone in 40% yield with minimal recovery of hydrolyzed cyclohexanone. Notably, a phosphate-protected dienol ether was unreactive under these reaction conditions (entry 7) and the trimethyl silyl (TMS)-protected dienol ether underwent hydrolysis exclusively (entry 8). Implementing Dagousset's conditions in our system led to formation of fluoro enone **2a** in only 7% yield. When NFSI was replaced with the more electrophilic Selectfluor reagent, the reaction was unsuccessful (entry 13). Finally, reaction temperature and reagent order of addition were

Table 1. Optimization of reaction conditions for γ -fluorination.^[a]

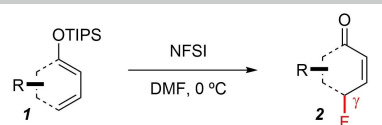
					
Entry	PG	F ⁺ Source	Solvent	Temp (°C)	Yield [%] ^[a]
1	TBS	NFSI	CH ₂ Cl ₂	23	N.D.
2	TBS	NFSI	THF	23	6
3	TBS	NFSI	MeCN	23	5
4	TBS	NFSI	DMSO	23	26
5	TBS	NFSI	DMA	23	36
6	TBS	NFSI	DMF	23	37
7	P(O)(OEt) ₂	NFSI	DMF	23	N.D.
8	TMS	NFSI	DMF	23	N.D.
9	Ph ₃ Si	NFSI	DMF	23	38
10	TIPS	NFSI	DMF	23	40
11 ^[b]	TIPS	NFSI	DMF	23	54
12 ^[c]	TIPS	NFSI	CHCl ₃	23	7
13	TIPS	Selectfluor	DMF	23	N.D.
14 ^[b]	TIPS	NFSI	DMF	0	89

[a] ¹⁹F NMR yield from reaction of dienol ether (0.2 mmol, 1 equiv) added to NFSI (0.2 mmol, 1 equiv) in solvent (1 mL, 0.2 M) for 16 h using trifluorotoluene (C₆H₅CF₃) as an internal standard. [b] NFSI solution was added to dienol ether. [c] Dagousset's conditions were used: NFSI (1.5 equiv), K₂HPO₄ (2 equiv) in CHCl₃ (0.1 M) at r.t. for 20 h. N.D. = Not detected.

found to be important factors for successful fluorination. Addition of a NFSI solution dropwise to a solution of siloxydiene **1a** improved yield to 54% (entry 11). Conducting the addition at 0 °C and holding this temperature for at least 8 h increased yield to 89% (entry 14).^[14] Qualitative observations suggest that NFSI and DMF react over time, therefore using a freshly prepared NFSI solution and reduced temperature may mitigate effects from this decomposition. Lower temperatures were particularly important for volatile product compounds, including model enone **2a**. Metals, bases, and other additives provided no improvement in reactivity or yield. Ultimately, we selected conditions consisting of TIPS-derived siloxydiene, NFSI (1.05 equiv) in DMF at 0 °C to be optimal.

Having established suitable reaction conditions to obtain γ -fluoro enone **2a** in high yield, we sought to study the generality of this methodology with a variety of TIPS siloxydienes. We surveyed several endocyclic cyclohexenone-derived TIPS dienol ethers bearing substitution at the α' -carbon, which provided exclusive γ -selectivity and good yields in several cases (Table 2, entries 1–4). Reduced yields of the γ -fluoro enones were observed with dienol ethers bearing a benzyl group (entry 2) and a *t*-Bu ester moiety (entry 4). The *anti*-configured γ -fluoro enones prevailed in these substrates, although the observed diastereoselectivities were modest. Increasing steric bulk at the α' -position with a *gem*-diphenyl substituent proceeded with excellent yield for fluoro enone **2e** (entry 5). Surveying the effect of β' substitution next, β' -phenyl substituted dienol ether **1f** provided fluoro enone **2f** in modest yield with an apparent preference for the *anti* diastereomer (entry 6). Conversely, β' -methyl substituted dienol ether **1g** underwent fluorination in much higher yield, yet

Table 2. Scope of endocyclic siloxydienes.^[a]

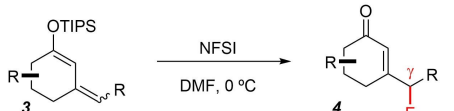
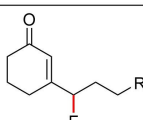
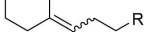
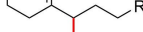
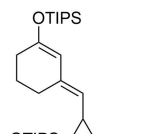
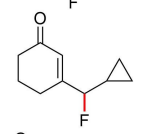
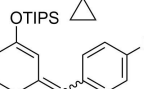
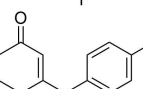
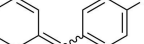
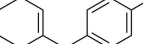
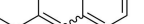
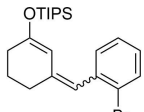
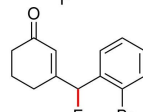
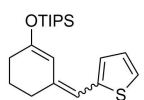
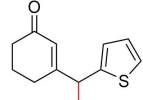
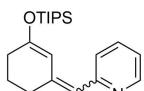
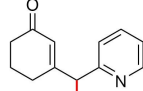
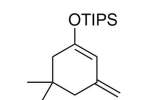
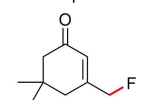
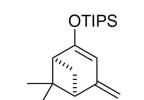
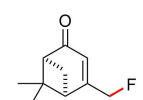
				
Entry	Dienol Ether	Product	dr (syn/anti)	Yield [%]
1	1a R = H	2a		89 ^[b]
2	1b R = Bn	2b	1:1.3	58
3	1c R = Allyl	2c	1:3.2	75 ^[b]
4	1d R = CH ₂ CO ₂ t-Bu	2d	1:3.5	52 ^[b]
5	1e	2e		86
6	1f R = Ph	2f	1:4	39
7	1g R = Me	2g	1.2:1	73 ^[b]
8	1h	2h		55 ^[b]
9	1i	2i		73 ^[b,c]

[a] Isolated yield (average of two runs) from reaction of dienol ether (0.3 mmol, 1 equiv), NFSI (0.315 mmol, 1.05 equiv) in 2.5 mL of DMF (0.12 M) at 0 °C. [b] ¹⁹F NMR yield (average of two runs) with trifluorotoluene (C₆H₅CF₃) as internal standard. [c] The α-fluorocycloheptenone was detected in 26% yield by ¹⁹F NMR. See the Supporting Information for details.

poor diastereoselectivity was observed (entry 7). Dienol ether **1h**, bearing a neopentyl γ-carbon, experienced only a slight reduction in yield of the fluorinated enone **2h** (entry 8). γ-Fluorination of the TIPS dienol ether derived from cycloheptenone (**1i**), which exhibits less conformational rigidity than the corresponding cyclohexenone system, proceeded to the γ-fluoro product in very good yield, although the α-fluoro isomer was observed as well in 23% yield (entry 9). Different additives were screened with siloxydiene **1i** in an effort to improve the observed regioselectivity, but to no avail.^[14]

Given the success of endocyclic dienol ether substrates, we next evaluated exocyclic TIPS dienol ethers (Table 3). Gratifyingly, exocyclic dienol ethers bearing γ-alkyl groups underwent fluorination in high yields as well (entries 1–3). We detected no significant difference in reactivity of the two geometric isomers. Notably, in the case of fluoro enone **3c**, no cyclopropyl fragmentation was observed (entry 3). Exocyclic dienol ethers containing aromatic functionalities at the γ-carbon underwent fluorination as well, although in slightly reduced yields (entries 4–9). The presence of either electron-donating (OMe) or withdrawing substituents (NO₂) at the *para*-position was well-tolerated providing the fluorinated products **4e** and **4f** in 53% and 57% yield, respectively (entries 5 and

Table 3. Scope of exocyclic siloxydienes.^[a]

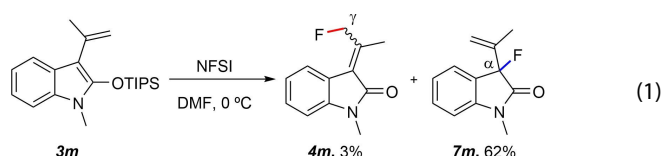
				
Entry	Dienol Ether	Product	Yield [%]	
1	 3a R = H	 4a	75	
2	 3b R = Ph	 4b	88	
3	 3c	 4c	78 ^[b]	
4	 3d R = H	 4d	53	
5	 3e R = OMe	 4e	53	
6	 3f R = NO ₂	 4f	57	
7	 3g	 4g	36	
8	 3h	 4h	60 ^[b,c]	
9	 3i	 4i	36	
10	 3k	 4k	52 ^[b]	
11	 3l	 4l	76 ^[b]	

[a] Isolated yields (average of two runs). See Table 2 for reaction conditions. [b] ¹⁹F NMR yield (average of two runs) with trifluorotoluene (C₆H₅CF₃) as internal standard. [c] ¹⁹F NMR yield after 7 h. Compound **4h** is unstable and decomposes under the reaction conditions at longer times. Isolated fluoro enone **4h** decomposes at room temperature in air and cannot be stored.

6). *ortho*-Bromo substitution was also compatible, resulting in 36% yield of the fluorinated product **4g**, with potential for further diversification (entry 7). Heterocyclic moieties at the γ-carbon are also tolerated in the regioselective fluorination: γ-thiophenyl and γ-pyridyl substituted dienol ethers afforded fluorinated products **4h** and **4i** in 60% and 36% yield, respectively (entries 8 and 9). The eminence of fluorinated and heterocyclic motifs in medicinal chemistry makes these results particularly compelling. Fluoro enone **4h** is unstable under the reaction conditions and must be handled with extreme care. Isolated samples of fluoro enone **4h** decomposed when at room temperature over time. Exocyclic dienol ethers derived from isophorone and verbenone furnished the corresponding

fluorinated enones **4k** and **4l** in good yields as well, with no cyclobutane fragmentation observed for the latter case (entries 10 and 11). Although we have demonstrated a wide scope of enone fluorination, isolation of several fluorinated compounds by chromatographic separation was complicated by their volatility, the presence of the corresponding enone, aromatization during column chromatography, and co-elution with silane impurity (TIPSOH).

A change in regioselectivity was observed for oxindole-derived substrate **3m**, which provided tertiary fluoro oxindole **7m** as the major product (Eq 1). This suggested a complex



steric and electronic influence on site selectivity and prompted further investigation. We turned our attention to the fluorination of acyclic silyl dienol ethers where a series of substituted dienol ethers would be accessible (Table 4). In contrast with our cyclic substrates, we observed greater variation in regioselectivity of C–F bond formation. Ketone-derived siloxydienes **5a** led to γ -fluorinated enone **6a** and α -fluorinated enone **7a** in 28% and 26% yield, respectively (entry 1). We suspected the inherent conformational flexibility of acyclic dienol ethers to be responsible for the observed erosion of regioselectivity and reasoned that a rigidly aligned diene may be important to facilitate regiocontrolled fluorination. Ergo, we prepared a series of acyclic siloxydienes bearing methyl substitution at C-2 and/or C-4 (**5b–5e**) to compare regioselectivity. Dienol ether **5b** with a C-4 methyl group underwent preferential γ -fluorination to furnish enone **6b** in a 5:1 ratio to the corresponding α -isomer **7b** (entry 2). Incorporation of a C-2 methyl group in dienol ether **5c** resulted in the γ -fluoro enone **6c** in 53% yield as the major product along with the tertiary α -fluoro isomer **7c** in 38% yield (1.4:1 ratio, entry 3). The trimethyl analogue **5d**, presenting fully substituted carbons at both the α and γ sites, enhanced the yield of γ -fluoro enone **6d** to 66% and reduced the yield of the α -fluoro isomer to 15% (4.4:1 ratio, entry 4). Dienol ether **5e**, lacking the C-2 methyl group, underwent exclusive γ -fluorination to provide tertiary fluoride **6e** in an exceptional 91% yield and no detectable α -fluoro product (entry 5). Taken together, we observed that in the presence of C-2 substitution on the diene, an increased amount of the α -fluoro enone was observed, and dienol ethers with C-4 substitution result in improved γ -fluoro enone yields. This observation is notably distinct from the observations of Fleming and co-workers in alkylation reactions with TMS dienol ethers and thiocarbenium ion electrophiles, where C-2 substitution enhances attack at γ -carbon and C-4 substitution enhances α -attack, suggesting that sterics at the site of bond formation appear most important.^[15] We speculate that in our case the C-2 methyl group may serve as a conformational restraint that can disrupt the coplanarity of the diene, resulting in α -fluorination due to a reduction in

Table 4. Scope of acyclic silyl dienol ethers.^[a]

		γ -fluoro enone 6	α -fluoro enone 7
Entry	Dienol Ether	Products	
1	5a	6a 28%	7a 26%
2	5b	6b 58%	7b 11%
3	5c	6c 53%	7c 38%
4	5d	6d 66%	7d 15%
5	5e	6e 91%	not detected
6	4:1 mixture of 5f and 5g	6f 5% ^[b,c]	6g 32% ^[b]

[a] Isolated yields (average of two runs). See Table 2 for reaction conditions. [b] ^{19}F NMR yield (average of two runs) with trifluorotoluene ($\text{C}_6\text{H}_5\text{CF}_3$) as an internal standard. [c] Compound **6g** proposed based on crude ^{19}F and ^1H NMRs.

nucleophilicity at the γ -site when deconjugated. Consistent with this finding, Fleming and co-workers found a similar change in site selectivity in a single example of sulfonylation of a 2-methyl siloxy ketene acetal, which indicates a remarkable dependence on the nature of the *electrophile* in regiocontrol.^[16] This deconjugation hypothesis is also in accord with the diminished regioselectivity in fluorination of cycloheptenone-derived dienol ether (**1i**, Table 2, entry 9), which exhibits greater conformational flexibility compared to locked coplanar dienes in cyclohexenone systems. Further investigations are currently ongoing to further elucidate regiocontrol effects. Despite variable site selectivity in our acyclic substrates, the ability of sterically congested dienol silanes to provide challenging tertiary fluorocarbonyl scaffolds is a promising entry into these exciting structures. Finally, a 4:1 mixture of siloxydienes **5f** and **5g** derived from citral proceeded with complete γ -selectivity to form fluoro enone **6g** in 32% yield with a small amount of the isomeric primary fluoride **6f** in 5% yield and hydrolyzed citral as the primary side product (entry 6).

Enones are highly functionalized synthetic intermediates and, given a few literature reports of F influencing stereocontrol,^[17] we sought to examine potential stereoselective transformations in our systems. We began with epoxidation of γ -fluoro enone **3b** with H_2O_2 and NaOH ^[18] at room temperature or at 0°C in MeOH and at 50°C in 1,4-dioxane.^[19] However, we observed a mixture of non-fluorinated products in the presence of strong base. Switching to 1 M K_2CO_3 in THF led to the desired epoxide **8** (1.4:1 dr) in good yield (Scheme 2a).^[20] Similar dr was observed for the 1,4-cyanation of γ -fluoro enone **3b**, which proceeded in excellent yield to form a quaternary center adjacent to the fluoride (Scheme 2b). Hydrogenation of fluoro enone **3b** with H_2 (1 atm) in EtOAc ^[21] at room temperature furnished the saturated fluoro ketone **10** and the corresponding defluorinated ketone in 75% and 14% yield, respectively.^[14] The *p*-fluorophenol **11** can be accessed in high yield via metal-mediated oxidative aromatization of fluoro enone **2b**.^[22] Next, we looked for analogous fluorine-mediated stereocontrol in our rigid endocyclic γ -fluoro enones. A promising result was obtained with thio-conjugate addition on fluoro enone **2a**, delivering substituted ketone **12** in 49% yield (over two steps from dienol ether **1a**) with a 9:1 *anti*/*syn* ratio as determined by crude ^{19}F and ^1H NMR. The ratio was reduced to 2:1, however, following flash column chromatography on SiO_2 . When the crude 9:1 mixture was treated with *p*-TsOH $\cdot$ H_2O (1 equiv) in CH_2Cl_2 at room temperature for 16 h, a 1.8:1 dr was observed. An isolated sample of

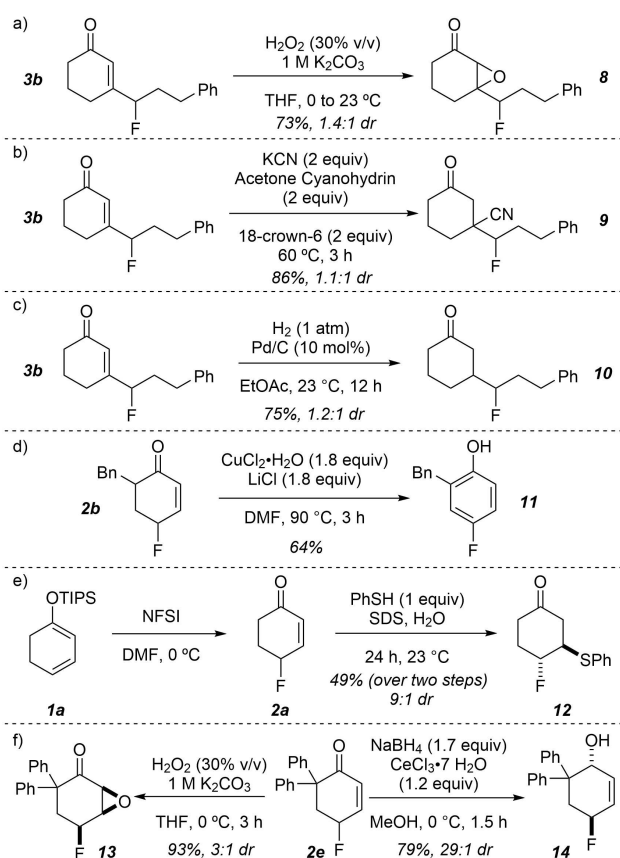
the minor *syn* diastereomer was exposed to similar conditions, resulting in no change in configuration; isomerization was only observed upon heating the reaction mixture to 40°C for 24 h, leading to a 1:1.7 dr. Clearly the high selectivity for the *anti* configuration reflects kinetic control and suggests a key role of the F in the C–S bond forming step. Due to high volatility of fluoro enone **2a**, we turned our attention to solid fluoro enone **2e**. Epoxidation of enone **2e** was achieved in exceptional yield, albeit with only modest diastereoselectivity, favoring the *syn*-epoxide **13** (Scheme 2f). Finally, we were pleased to find that reduction of the carbonyl under Luche conditions^[23] afforded alcohol **14** in high yield and an exceptional diastereoselectivity (Scheme 2f). When the reaction was conducted at room temperature alcohol **14** was isolated in 25% yield and 21:1 dr. Lowering the temperature to 0°C resulted in a dramatically improved yield and diastereoselectivity, favoring the *anti*-alcohol **14** in 79% yield and 29:1 dr. The preference for the *anti*-alcohol is consistent with prior experimental and theoretical studies for diastereoselective 1,2-additions in cyclohexanone systems,^[24] and may suggest that the F atom substantially rigidifies the enone conformation. The ability for γ -fluorine to induce stereoselectivity at the distant carbonyl is particularly fascinating and demonstrates the potential for other assorted diastereoselective transformations. Further investigations highlighting the ability of fluorine to impart stereoinduction are ongoing in our lab to better understand these effects. All the diastereomers were assigned based on coupling constants, HMQC, and NOESY NMR analyses.

Conclusions

In summary, we have developed an effective, general, and regioselective protocol aimed at synthesizing γ -fluorocarbonyl compounds using commercially available NFSI and siloxy-dienes, which are readily prepared derivatives of simple enones. Our method utilizes mild reaction conditions and presents a significant improvement in scope of γ -fluorination, which for the first time encompasses a wide variety of endocyclic, exocyclic, and acyclic dienol ethers. In addition, we have demonstrated the potential of fluorine to serve as a stereocontrol element in subsequent diversification and functionalization reactions utilizing these newly accessible γ -fluoro enones.

Experimental Procedure

Neat dienol silyl ether (0.3 mmol, 1 equiv) was added to an oven-dried 4 mL vial equipped with a magnetic stir bar. The vial was sealed with a rubber septum and then evacuated and backfilled with dry nitrogen (three cycles). After the addition of DMF (1.5 mL) at room temperature ($\sim 23^\circ\text{C}$) to the reaction vial, it was cooled to 0°C . A solution of NFSI (0.32 mmol, 1.05 equiv) in DMF (1 mL) was added dropwise at 0°C . The mixture was stirred at 0°C for 6–8 h and left to warm up



Scheme 2. Synthetic applications of γ -fluoroketones (Isolated yields).

overnight until the reaction was complete (as judged by TLC, additional 6–12 h). Upon completion, the reaction was diluted with Et₂O (12 mL, or EtOAc for nonvolatile compounds **2e**, **2f**, **4b**, **4d–4i**, **4m** and **7m**) and washed with brine (2×4 mL). The combined aqueous phases were back extracted with Et₂O (2×4 mL) (or EtOAc). The combined organic phases were washed with brine (2×4 mL), dried over anhydrous Na₂SO₄, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, basic Al₂O₃ layered over silica gel, or neutral Al₂O₃ layered over silica gel to afford the desired γ -fluorinated enones.

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [25–43]).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: γ -fluorination • siloxydienes • regioselectivity • diastereoselectivity • NFSI

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