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Silver-Catalyzed Vinylogous Fluorination of Vinyl Diazoacetates

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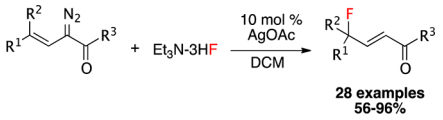
ABSTRACT



A silver-catalyzed vinylogous fluorination of vinyl diazoacetates to generate γ-fluoro-α,β-unsaturated carbonyls is presented. Application of this method to the fluorination of farnesol and steroid derivatives was achieved.

The development of new methods for achieving selective fluorination is a current research area of intense interest.[1] Organofluorine compounds display broad utility as valuable pharmaceuticals, agrochemicals, materials and tracers for positron emission tomography.[2] γ-Fluoro-α,β-unsaturated carbonyls represent a versatile class of intermediates in organic synthesis and are prevalent motifs in biologically relevant compounds such as steroids, amino acids and metalloprotease inhibitors.[3] Traditional approaches for the synthesis of γ-fluoro-α,β-unsaturated carbonyls mainly rely on electrophilic fluorination of conjugated enol ethers[4] and Wittig-type reaction of α-fluoro aldehydes or ketones.[5] Recently, we[6] and others[7] have described that metal-stabilized vinylcarbenes derived from vinyl diazoacetates can selectively display electrophilic reactivity at the vinylogous position instead of the carbene site. This type of behavior is especially favorable when silver catalysts are

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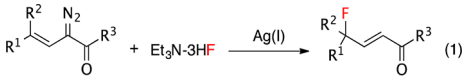
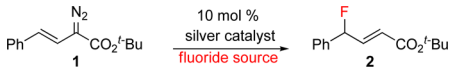
used.[6c,d,7h] In this paper, we report a silver-catalyzed vinylogous fluorination to generate highly functionalized γ-fluoro-α,β-unsaturated carbonyls (eq 1).[8]



Our fluorination study began with examination of different fluoride sources using the styryl diazoacetate **1** as the model substrate. Among fluoride sources examined, many of the standard nucleophilic sources of fluoride failed to give any fluorinated products (Table 1, entries 1–6), but Deoxo-Fluor and DAST[9] can provide the desired product **2** in 44% and 55% yield, respectively (Table 1, entries 7 and 8). The use of triethylamine trihydrogen fluoride[10] dramatically improved the yield to 90% (Table 1, entry 9). After determining the effect of different silver salts (Table 1, entries 9–11), we chose silver acetate and triethylamine trihydrogen fluoride in dichloromethane as our standard fluorination conditions. In all of these reactions, the ratio of vinylogous versus carbenoid fluorination is $>20/1$.

Having developed the optimized conditions, the scope of the vinylogous fluorination was examined with a variety of vinyldiazo derivatives. The reaction was found to be quite general as illustrated in Scheme 1. The size of ester group (*tert*-butyl to methyl) did not affect the efficiency of this reaction, affording the desired products **4a**–**c** in high yields (92–94%). A particularly interesting example is the substrate **3d** with a substituted allyl ester. The desired product **4d** was isolated in 85% yield and no intramolecular cyclopropanation was observed. Moreover, when an amide was used as the acceptor group, the reaction can still afford the desired product **4e** in 60% isolated yield.

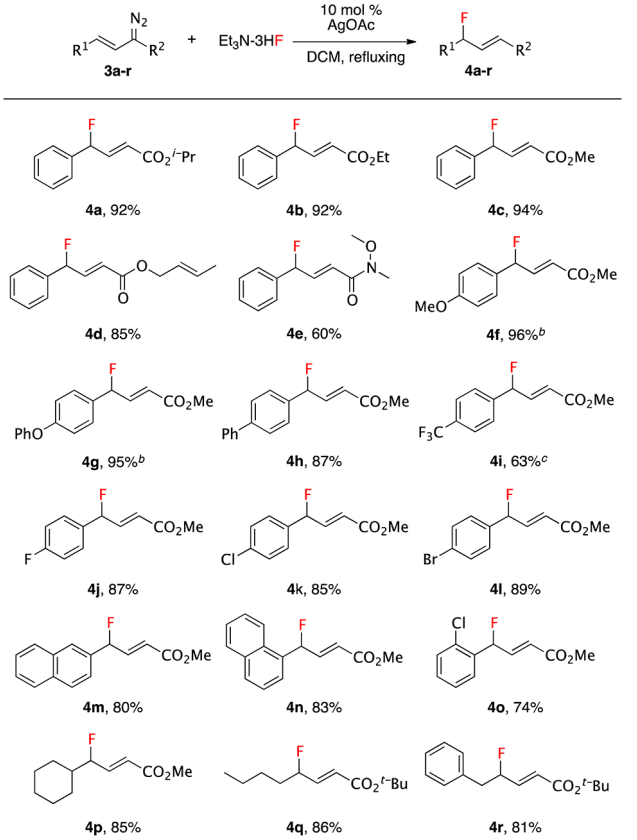
Table 1. Vinylogous Fluorination Optimization[a]



entry	catalyst	fluoride	yield[b] (%)
1	AgOAc	TMAF	<5
2	AgOAc	TBAF[c]	<5
3	AgOAc	TBABF	<5
4	AgOAc	KHF_2[d]	<5
5	AgOAc	Fluolead	<5
6	AgOAc	TASF	<5
7	AgOAc	deoxo-Fluor	44
8	AgOAc	DAST	55
9	AgOAc	Et_3N–3HF	90
10	$AgSbF_6$	Et_3N–3HF	88
11	AgOTf	Et_3N–3HF	90

[a] Vinyl diazoacetate (0.4 mmol, 1.0 equiv), silver catalyst (10 mol %), and fluoride source (2.0 mmol, 5.0 equiv) under reflux in dichloromethane. [b] Isolated yield; < 5 refers to no observation of product **2** from ^{1}H NMR analysis prior to chromatography. [c] 1.0 M in THF. [d] Dry DMF as solvent at 90 °C.

Scheme 1. Synthesis of Secondary Allylic Fluorides[a]



[a] Vinyl diazoacetate (0.4 mmol, 1.0 equiv), silver catalyst (10 mol %), triethylamine trihydrogen fluoride (322 mg, 5.0 equiv) under reflux in dichloromethane. [b] NMR yield using dibromomethane as internal standard due to product decomposition upon silica gel chromatography. [c] AgOTf (20 mol %) and 10 equiv of Et_3N–3HF.

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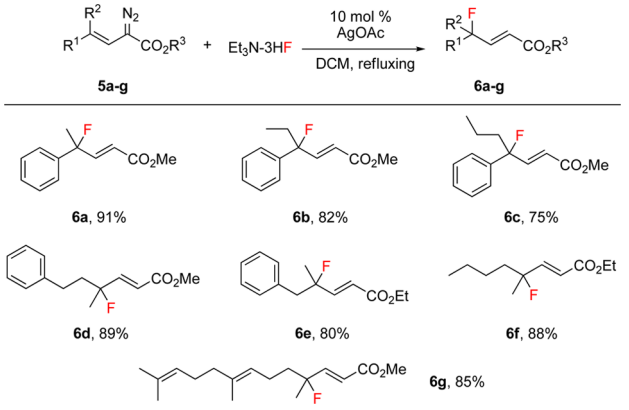
The reaction can tolerate a variety of functionality on the aryl group as illustrated by **4f**–**o** (63–96%). Furthermore, the reaction can also be expanded to alkyl-substituted vinyldiazoacetates as seen from **4p**–**r** (81–86%).

To further evaluate the fluorination method, we designed and synthesized disubstituted vinyl diazoacetates **5a**–**g**. When these vinyl diazoacetates were subjected to the standard conditions, the fluorinated products **6a**–**g** containing quaternary carbon centers were readily formed in good to excellent yields (75–91%) with a variety of aryl- and alkyl-substituted vinyl diazoacetates (Scheme 2). A particularly interesting example is the synthesis of the fluorinated farnesol derivative **6g**.

Scheme 2. Synthesis of Tertiary Allylic Fluorides[a]



[a] Vinyl diazoacetate (0.4 mmol, 1.0 equiv), silver catalyst (10 mol %), triethylamine trihydrogen fluoride (322 mg, 5.0 equiv) under reflux in dichloromethane.

Fluorinated steroids constitute an important class of molecules with significant biological activity.[11] Therefore, we sought to apply this method to late-stage fluorination of steroids (Scheme 3). The steroidal diazo derivatives **7** and **9** were readily formed by a diazo transfer reaction on the corresponding steroids. Under slightly modified reaction conditions using silver triflate, diazo **7** and **9** can be converted to the desired fluorinated steroids **8** and **10** in 56% and 60% yield, respectively. An intriguing feature of this fluorination process is the selective formation of the 6-β-fluoro isomer. A similar selectivity has been seen in vinylogous hydroxylation of steroidal diazo via silver catalysis and has been rationalized to be due to stereoelectronic effects from the conformation of the steroid used.[6e]

Considerable interest has been shown in developing fast fluorination methods because they may be useful in developing positron emission tomography (PET tracers with

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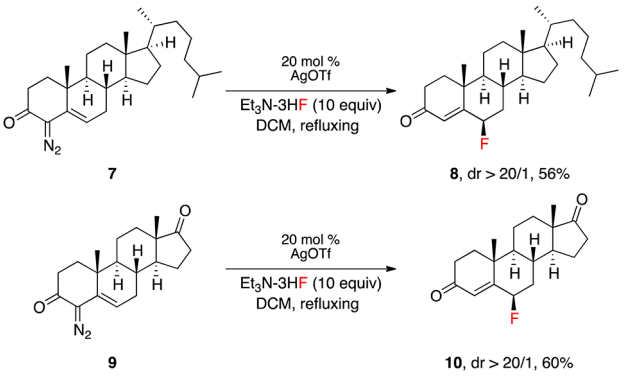
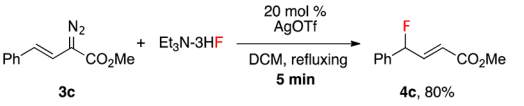
Scheme 3. Late-Stage Fluorination of Steroids



^{18}F labeling, ^{18}F half-life: 110 min).[12] Metal-catalyzed reactions of diazo compounds can be extremely fast[13] and accordingly we explored the possibility of achieving fast fluorination. Indeed, fluorination of vinyl diazoacetate **3c** in 80% isolated yield was achieved in 5 min when 20 mol % of silver triflate was used as catalyst (Scheme 4).

Scheme 4. Rapid Fluorination Conditions



In summary, we have developed a silver-catalyzed vinylogous fluorination of vinyl diazoacetates. This novel methodology is operationally simple and provides a diverse range of γ-fluoro-α,β-unsaturated carbonyl building blocks. The method offers a strategy for rapid late-stage generation of fluorinated compounds that may be used in the synthesis PET radioligands. Future work will be directed toward developing an enantioselective version of this fluorination methodology.

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Supporting Information Available. Experimental procedures and characterization and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.