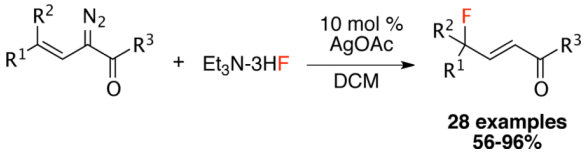
Published in final edited form as:
Org Lett. 2013 December 20; 15(24): . doi:10.1021/ol403017e.

Silver-Catalyzed Vinylogous Fluorination of Vinyldiazoacetates

Changming Qin and **Huw M. L. Davies**
Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322 USA

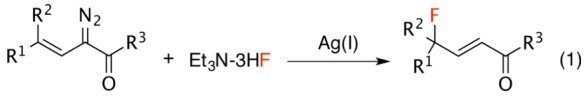
Huw M. L. Davies: hmdavie@emory.edu

Abstract



A silver-catalyzed vinylogous fluorination of vinyldiazoacetates 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-stablized vinylcarbenes derived from vinyldiazoacetates 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 used.[6c,6d,7h] In this communication, we report a silver-catalyzed vinylogous fluorination to generate highly functionalized γ-fluoro-α,β-unsaturated carbonyls (eq. 1).[8]



(1)

(1)

Our fluorination study began with examination of different fluoride sources using the styryldiazoacetate **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

Correspondence to: Huw M. L. Davies, hmdavie@emory.edu.

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.ac.org.

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. 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 di-substituted vinyldiazoacetates **5a–g**. When these vinyldiazoacetates 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 vinyldiazoacetates (Scheme 2). A particularly interesting example is the synthesis of the fluorinated farnesol derivative **6g**.

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 ^{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 vinyldiazoacetate **3c** in 80% isolated yield was achieved in 5 min when 20 mol% of silver triflate was used as catalyst (Scheme 4).

In summary, we have developed a silver catalyzed vinylogous fluorination of vinyldiazoacetates. 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 towards developing an enantioselective version of this fluorination methodology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

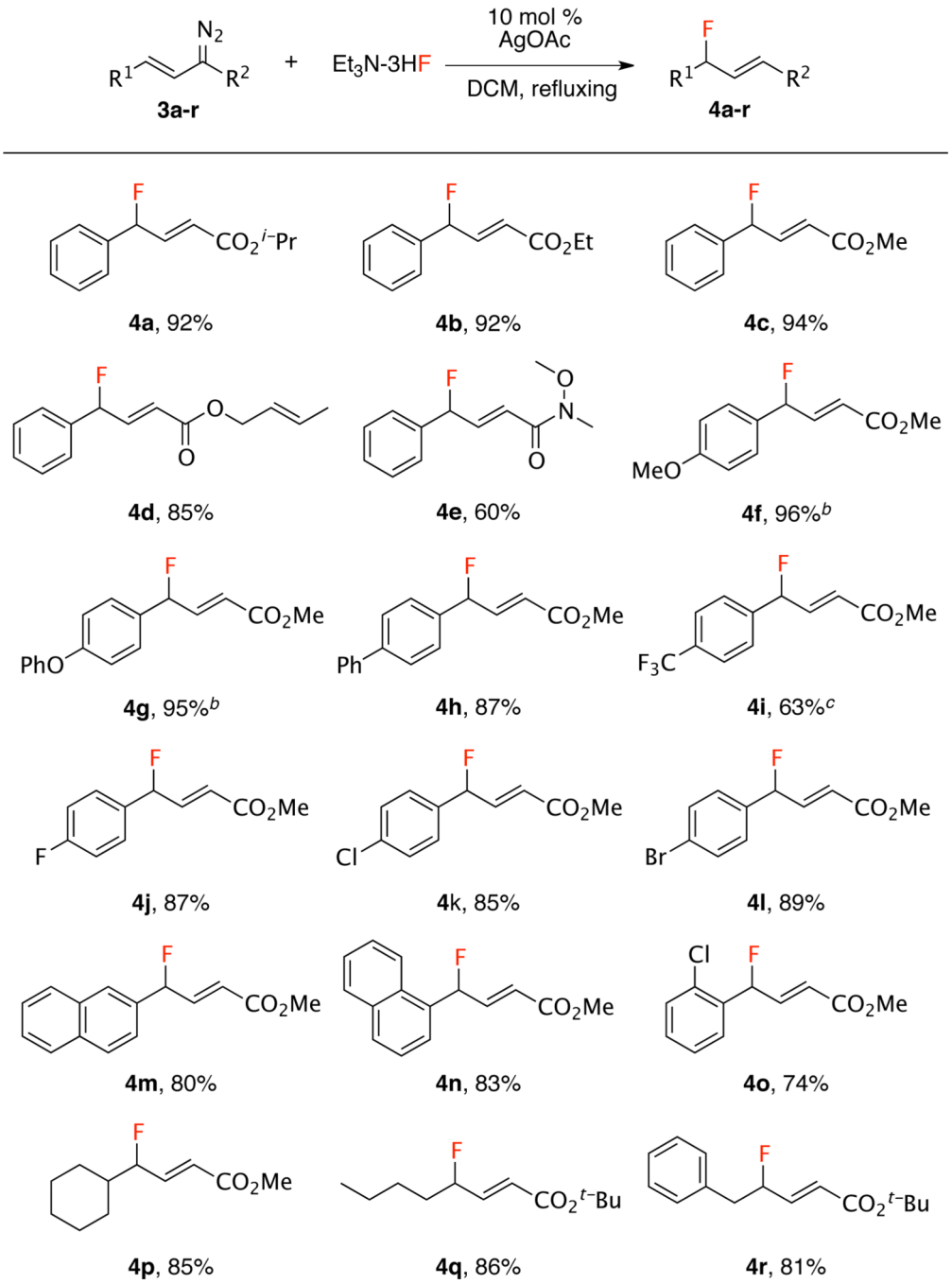
Acknowledgments

This work was supported by the National Institutes of Health (GM099142).

References

1. For recent leading reviews see: Liang T, Neumann C, Ritter T. Angew. Chem., Int. Ed. 2013; 52:8214. Liu G. Org. Biomol. Chem. 2012; 10:6243. [PubMed: 22733139] Hollingworth C, Gouverneur V. Chem. Commun. 2012; 48:2929. Furuya T, Kamlet AS, Ritter T. Nature. 2011; 473:470. [PubMed: 21614074] Grushin VV. Acc. Chem. Res. 2010; 43:160. [PubMed: 19788304] Furuya T, Klein JEMN, Ritter T. Synthesis. 2010; 11:1804. [PubMed: 20953341] For recent examples of fluorination, see: Mazzotti AR, Campbell MG, Tang P, Murphy JM, Ritter T. J. Am. Chem. Soc. 2013; 135:14012. [PubMed: 24040932] Sladojevich F, Arlow SI, Tang P, Ritter T. J. Am. Chem. Soc. 2013; 135:2470. [PubMed: 23397884] Braun MG, Doyle AG. J. Am. Chem. Soc. 2013; 135:12990. [PubMed: 23947740] Braun MG, Katcher MH, Doyle AG. Chem. Sci. 2013; 4:1216. Shunatona HP, Fruh N, Wang Y, Rauniyar V, Toste FD. Angew. Chem., Int. Ed. 2013; 52:1. Li Z, Song L, Li C. J. Am. Chem. Soc. 2013; 135:4640. [PubMed: 23506151] Truong T, Kilmovica k, Daugulis O. J. Am. Chem. Soc. 2013; 135:9342. [PubMed: 23758609] Zhang Z, Wang F, Mu X, Chen P, Liu G. Angew. Chem., Int. Ed. 2013; 52:7549. Liu W, Groves JT. Angew. Chem., Int. Ed. 2013; 52:6024. Fier PS, Luo J, Hartwig JF. J. Am. Chem. Soc. 2013; 135:2552. [PubMed: 23384209] Ye Y, Sanford MS. J. Am. Chem. Soc. 2013; 135:4648. [PubMed: 23485148] Xue C, Jiang X, Fu C, Ma S. Chem. Commun. 2013; 49:5651. Liu W, Huang X, Cheng M, Nielsen RJ, Goddard WA III, Groves JT. Science. 2012; 337:1322. [PubMed: 22984066] Barker TJ, Boger DL. J. Am. Chem. Soc. 2012; 134:13588. [PubMed: 22860624] Topczewski JJ, Tewson TJ, Nguyen HM. J. Am. Chem. Soc. 2011; 133:19318. [PubMed: 22059470] Katcher MH, Sha A, Doyle AG. J. Am. Chem. Soc. 2011; 133:15902. [PubMed: 21894884] Lee E, Kamlet AS, Powers DC, Neumann CN, Boursalian GB, Furuya T, Choi DC, Hooker JM, Ritter T. Science. 2011; 334:639. [PubMed: 22053044] Katcher MH, Doyle AG. J. Am. Chem. Soc. 2010; 132:17402. [PubMed: 21087003] Tang P, Furuya T, Ritter T. J. Am. Chem. Soc. 2010; 132:12150. [PubMed: 20695434] Watson DA, Su MJ, Teverovskiy G, Zhang Y, Garcia-Fortanet J, Kinzel T, Buchwald SL. Science. 2009; 325:1661. [PubMed: 19679769]
2. (a) Ametamey SM, Honer M, Schubiger PA. Chem. Rev. 2008; 108:1501. [PubMed: 18426240] (b) Hagmann WK. J. Med. Chem. 2008; 51:4359. [PubMed: 18570365] (c) Müller K, Faeh C, Diederich F. Science. 2007; 317:1881. [PubMed: 17901324] (d) Jeschke P. ChemBioChem. 2004; 5:570.(e) Phelps ME. Proc. Natl. Acad. Sci. 2000; 97:9226. [PubMed: 10922074] (f) Hougham, GG.; Cassidy, PE.; Johns, K.; Davidson, T. Fluoropolymers: Synthesis and Properties. Kluwer Academic; 1999. (g) Banks, RE.; Smart, BE.; Tatlow, JC., editors. Organofluorine Chemistry: Principles and Commerical Applications. Plenum Press; New York: 1994.
3. (a) Chen J, Zheng F, Huang Y, Qing F. J. Org. Chem. 2011; 76:6525. [PubMed: 21739972] (b) Fan S, He C, Zhang X. Tetrahedron. 2010; 66:5218.(c) Orvieto F, Koch U, Matassa VG, Muraglia E. Bioorg. Med. Chem. Lett. 2003; 13:2745. [PubMed: 12873506] (d) Yoder NC, Kumar K. Chem. Soc. Rev. 2002; 31:335. [PubMed: 12491748] (e) Takeuchi Y, Shiragami T, Kimura K, Suzuki E, Shibata N. Org. Lett. 1999; 1:1571.(f) Poulter CD, Dolence JM. Tetrahedron. 1996; 52:119.(g) Pikul, S.; Mieling, GE.; Mieling, KK.; Solinsky, KM.; De, B.; Almstead, NG.; Natchus, MG. U. S. Patent. 6,852,751B2. 2005 Feb..
4. (a) Poss AJ, Shia GA. Tetrahedron Lett. 1995; 36:4721.(b) Purrington ST, Woodard DL, Cale NC. J. Fluorine Chem. 1990; 48:345.(c) Fleming L, Goldhill J, Paterson L. Tetrahedron Lett. 1979; 20:3205.
5. (a) Jiang H, Falcicchio A, Jensen KL, Paixão MW, Bertelsen S, Jørgensen KA. J. Am. Chem. Soc. 2009; 131:7153. [PubMed: 19419172] (b) Oldendorf J, Haufe G. J. Prakt. Chem. 2000; 342:52.(c) Davis FA, Kasu PVN, Sundarababu G, Qi H. J. Org. Chem. 1997; 62:7546.
6. (a) Davies HML, Saikali E, Clark TJ, Chee EH. Tetrahedron. Lett. 1990; 31:6299.(b) Davies HML, Hu B, Saikaki E, Bruzinski PR. J. Org. Chem. 1994; 59:4535.(c) Sevryugina Y, Weaver B, Hansen J, Thompson J, Davies HML, Petrukina MA. Organometallics. 2008; 27:1750.(d) Hansen J, Davies HML. Chem. Sci. 2011; 2:457.(e) Morton D, Dick AR, Ghosh D, Davies HML. Chem. Comm. 2012; 48:5838. [PubMed: 22572866] (f) Valette D, Lian Y, Haydek JP, Hardcastle KI, Davies HML. Angew. Chem., Int. Ed. 2012; 51:8636.(g) Smith AG, Davies HML. J. Am. Chem. Soc. 2012; 134:18241. [PubMed: 23098215] (h) Qin C, Davies HML. J. Am. Chem. Soc. 2013; 135:14516. [PubMed: 24025195]

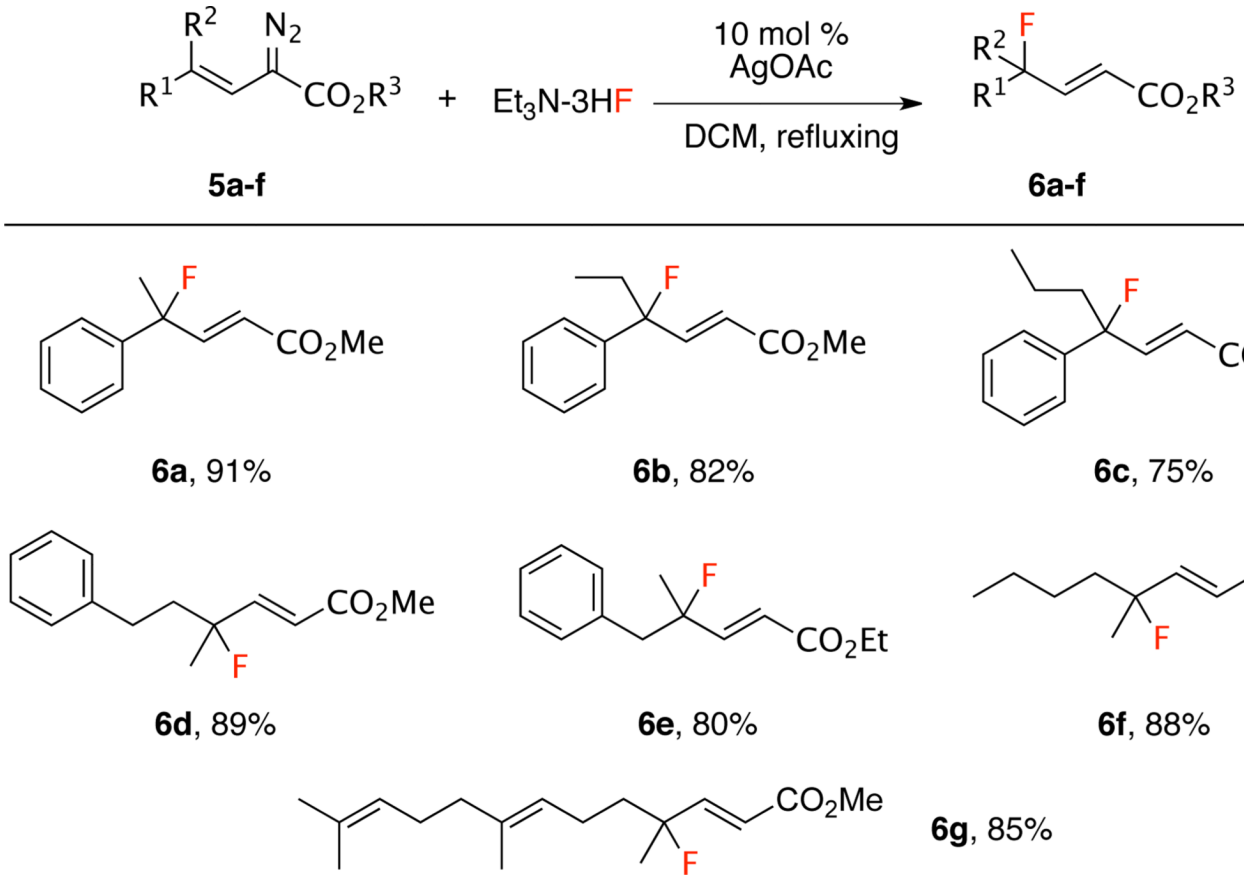
7. (a) Wang X, Xu X, Zavalji PY, Doyle MP. J. Am. Chem. Soc. 2011; 133:16402. [PubMed: 21932856] (b) Xu X, Zavalij PY, Hu W, Doyle MP. J. Org. Chem. 2013; 78:1583. [PubMed: 23301562] (c) Qian Y, Zavalij PJ, Hu W, Doyle MP. Org. Lett. 2013; 15:1564. [PubMed: 23477672] (d) Wang X, Abrahams QM, Zavalij PY, Doyle MP. Angew. Chem. Int. Ed. 2012; 51:5907.(e) Qian Y, Xu X, Wang X, Zavalij PJ, Hu W, Doyle MP. Angew. Chem., Int. Ed. 2012; 51:5900.(f) Barluenga J, Lonzi G, Riesgo L, Lopez LA, Tomas M. J. Am. Chem. Soc. 2010; 132:13200. [PubMed: 20825189] (g) Pagar VV, Jadhav AM, Liu RS. J. Am. Chem. Soc. 2011; 133:20728. [PubMed: 22128862] (h) Yue Y, Wang Y, Hu W. Tetrahedron Lett. 2007; 48:3975.
8. Previous transformations on carbenoid fluorination of diazo compounds have been achieved under acidic conditions: Olah GA, Welch JT. Synthesis. 1974:896. Setti EL, Mascaretti OA. J. Chem. Soc. Perkin Trans I. 1988:2059. Pasceri R, Bartrum HE, Hayes CJ, Moody CJ. Chem. Commun. 2012; 48:12077.
9. (a) Singh RP, Shreeve JM. Synthesis. 2002; 17:2561.(b) Middleton WJ. J. Org. Chem. 1975; 40:574.(c) Lal GS, Pez GP, Pesaresi RJ, Prozonic FM. Chem. Commun. 1999:215.(d) Lal GS, Pez GP, Pesaresi RJ, Prozonic FM, Cheng H. J. Org. Chem. 1999; 64:7048.
10. (a) Haufe G. J. Prakt. Chem. 1996; 338:99.(b) Nelson TD, Crouch RD. Synthesis. 1996:1031.
11. (a) Begue JP, Bonnet-Delpon D. J. Fluorine Chem. 2006; 127:992.(b) Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr. Science. 1995; 270:283. [PubMed: 7569975]
12. (a) Lee E, Hooker JM, Ritter T. J. Am. Chem. Soc. 2012; 134:17456. [PubMed: 23061667] (b) Pimlott SL, Sutherland A. Chem. Soc. Rev. 2011; 40:149. [PubMed: 20818455] (c) Ametamey SM, Honer M, Schubiger PA. Chem. Rev. 2008; 108:1501. [PubMed: 18426240] (d) Adam MJ, Wilbur DS. Chem. Soc. Rev. 2005; 34:153. [PubMed: 15672179]
13. Pelphrey P, Hansen J, Davies HML. Chem. Sci. 2010; 1:254.



Scheme 1.

Synthesis of Secondary Allylic Fluoridesa

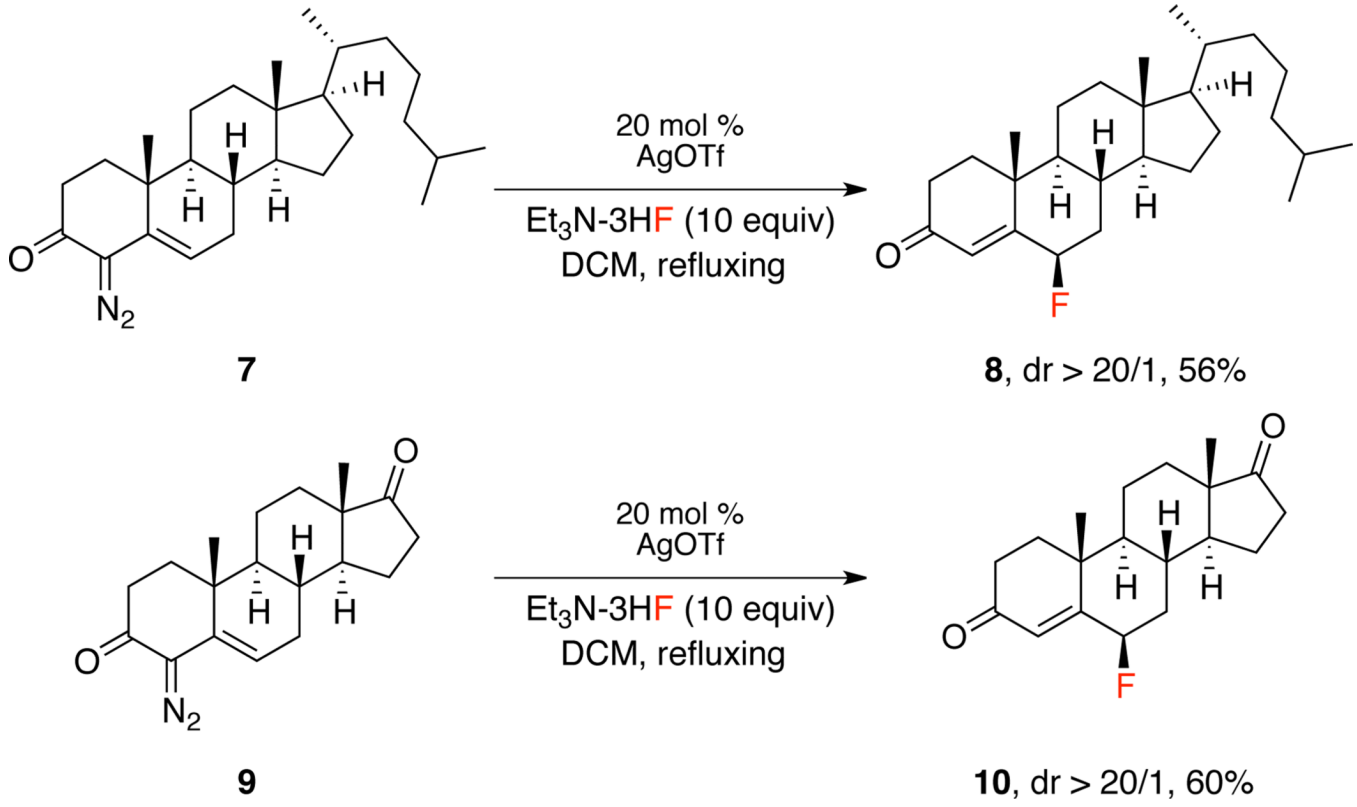
[a]Vinyldiazoacetate (0.4 mmol, 1.0 equiv), silver catalyst (10 mol %), triethylamine trihydrogen fluoride (322 mg, 5.0 equiv), under refluxing in dichloromethane. [b]NMR yield using dibromomethane as internal standard due to product decomposition upon silica gel chromatography. [c]20 mol% AgOTf and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



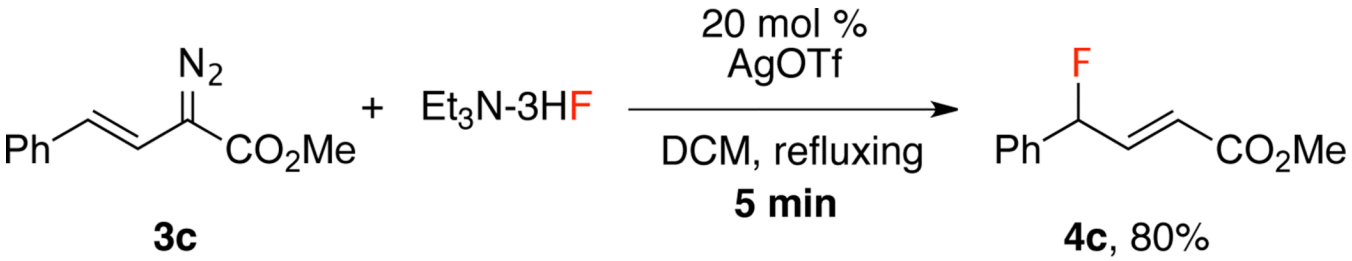
Scheme 2.

Synthesis of Tertiary Allylic Fluoridesa

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



Scheme 3.
Late-Stage Fluorination of Steroids

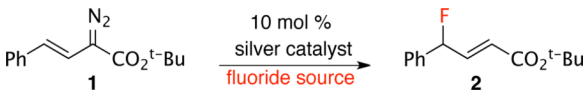


3c **4c**, 80%

Scheme 4.
Rapid Fluorination Conditions

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] Vinyldiazoacetate (0.4 mmol, 1.0 equiv), silver catalyst (10 mol %), fluoride source (2.0 mmol, 5.0 equiv), under refluxing in dichloromethane.

[b] Isolated yield, <5 refers to no observation of product **2** from ^1H NMR analysis prior to chromatography.

[c] 1.0 M in THF.

[d] Dry DMF as solvent at 90 °C.