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Regio- and Stereoselective Synthesis of Fluoroalkenes by Directed Au(I) Catalysis

Benjamin C. Gorske, Curren T. Mbofana, and Scott J. Miller*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520

scott.miller@yale.edu

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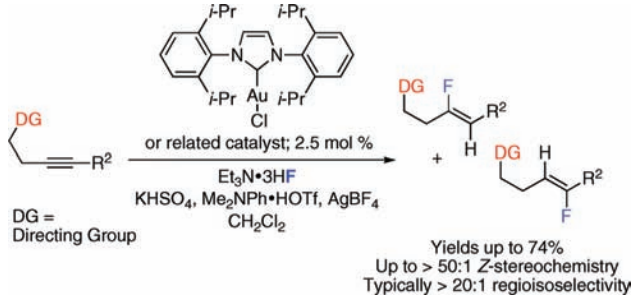
ABSTRACT



Au-catalyzed hydrofluorination reactions of a range of functionalized alkynes are reported. In the presence of an appropriate directing group, localized with particular spacing from the pendant alkyne, regioselective and predictable conversion of the alkyne to the *Z*-vinyl fluoride may be achieved. In selected cases, yields and selectivities are excellent. Additional experiments with two directing groups installed have established some initial principles with respect to a hierarchy of directing groups and their capacity for influencing hydrofluorination regioselectivity.

Fluorine is an element of special interest in organic chemistry. Its electronegativity, highest of all the known elements, contributes to its special properties, which include formation of strong bonds to carbon,[1] low atomic polarizability,[2] and strong inductive characteristics.[3] The field of medicinal chemistry has especially benefited from the development of chemical techniques for incorporating fluorine into organic molecules. Fluorine is now routinely introduced to impart metabolic stability to medicinal compounds.[4] Coupled with its electronegativity, fluorine's small size has made it an attractive choice for isosteric substitutions of hydrogen or other functional groups, especially those containing oxygen. In this regard, fluoroalkene isosteres of peptide amide bonds have become increasingly prevalent as structural and mechanistic probes in both biological[5] and chemical studies.[6]

In light of the importance of fluoroalkenes, many efforts toward efficient regio- and stereoselective syntheses of these moieties have been reported.[7] Of these, we were especially intrigued by a methodology developed by Sadighi and coworkers employing a Au(I) catalyst[8] to add HF across an alkyne.[9] Using $Et_3N{\cdot}3HF$ as a nucleophilic fluorine source, $KHSO_4$ as an additive, and various cocatalysts, *trans*-hydrofluorination was achieved in good yields (Scheme 1).

(1) Cox, J. D.; Gundry, H. A.; Head, A. J. *Trans. Faraday Soc.* **1964**, *60*, 653.
(2) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(3) Banks, H. D. *J. Org. Chem.* **2006**, *71*, 8089.
(4) Böhm, H,-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
(5) (a) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823. (b) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107. (c) Otaka, A.; Mitsuyama, E.; Watanabe, J.; Watanabe, H.; Fujii, N. *Biopolymers* **2004**, *76*, 140. (d) Urban, J. J.; Tillman, B. G.; Cronin, W. A. *J. Phys. Chem. A* **2006**, *110*, 11120.
(6) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707.
(7) (a) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151. (b) Sano, S.; Kuroda, Y.; Saito, K.; Ose, Y.; Nagao, Y. *Tetrahedron* **2006**, *62*, 11881. (c) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332, and references therein.
(8) For recent reviews of Au catalysis in organic chemistry, see (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

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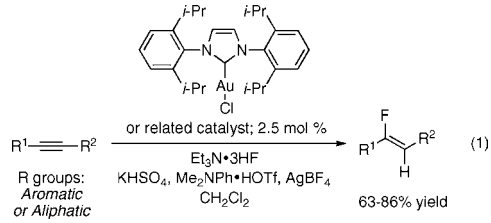
Scheme 1. Au-Catalyzed Hydrofluorination of Alkynes

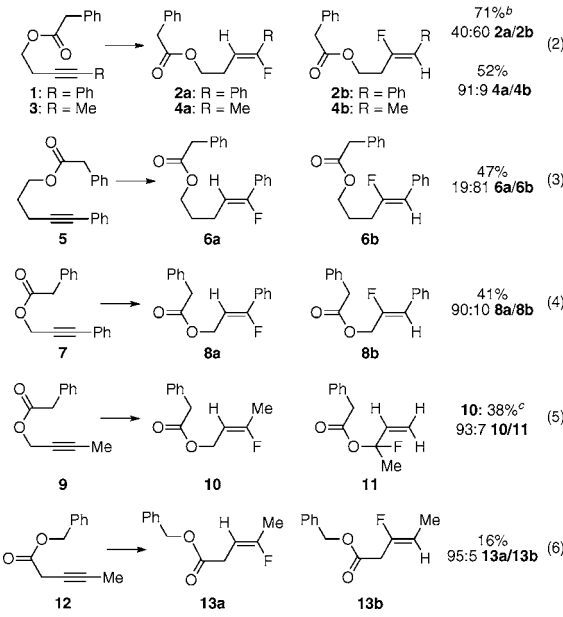


Modest regioselectivity for alkyl/aryl alkyne substrates was improved by adding electron-withdrawing groups to the aromatic ring substituents. Although other alkyne hydrohalogenations using Au catalysis have been reported, these reactions utilize electrophilic halogen sources, for the most part excluding fluorine.[10] Also, the substrate scope of these reactions has been limited to propargyl acetates.

Given our interest in fluoroolefins as mechanistic probes,[6] we sought to expand the methodology for Au-catalyzed nucleophilic fluorination of alkynes by developing new avenues for regiocontrol that would expand both the utility and substrate scope of the reaction. Specifically, we envisioned a classical heteroatom-directed reaction that might confer a high degree of selectivity for a broad range of substrates.[11] Here we report the realization of this design in the carbonyl-directed hydrofluorination of alkynes under Au(I) catalysis. We demonstrate that this concept is broadly applicable and engenders regioselectivities that exceed those originally reported for this reaction system. As such, this methodology could facilitate access to new compounds for fundamental research and the development of pharmaceuticals.

We commenced our investigations by examining ester **1**. We were intrigued to observe that hydrofluorination of this substrate under the conditions in eq 1 (Scheme 1) exclusively yielded *Z*-products as a 40:60 mixture of regioisomers **2a** and **2b** (Scheme 2, eq 2). A significant amount of the minor regioisomer **2a** was obtained, which was fluorinated at the site distal to the ester and opposite that expected for hydrofluorination of simple alkylaryl internal alkynes, suggesting that the ester exhibited a directing effect. This directing effect was significantly more pronounced with dialkyl alkyne substrate **3**, giving 91:9 regioselectivity, again with exclusive *Z*-stereoselectivity (Scheme 2, eq 2). We then examined alkynes **5**, **7**, and **9** to determine how the regioselectivity is affected by the length of the alkyl chain connecting the alkyne and the directing ester (Scheme 2, eqs 3−5). Substrate **5** was found to favor regioisomer **6b** (19:81), approaching the regioselectivity expected for an unfunctionalized alkylarylalkyne (7:93)[9] and suggesting that the directing effect of the ester is attenuated, but not abolished, by the insertion of a single methylene unit in **5**

Scheme 2. Ester-Directed Hydrofluorination of Alkynes[a]



[a] Yields reported as the average combined yield of all isomers for two reactions, unless otherwise noted. Isomeric ratios determined by ^{19}F NMR. [b] Yield determined using an internal ^{19}F NMR standard. [c] Isolated yield of the major product.

vs **1**. Shortening the distance between the carbonyl group and the alkyne by removal of a methylene unit from **1** (as in **7**) largely suppressed the formation of regioisomer **8b** compared to **2b**. Interestingly, although **9** gave similar yields of regioisomer **10**, the minor product in this case was an allylic fluoride **11**. Propargyl acetates are known to undergo a variety of skeletal rearrangements in the presence of cationic Au, including 1,2- and 1,3-acyl shifts to give Au vinyl carbenoids and Au allenes, respectively.[12] The allylic fluoride could be envisioned to arise from nucleophilic attack of F^- on the intermediate formed by such a 1,3-acyl shift. We also examined β,γ-alkynyl ester substrate **12**, but yields were poor, possibly due to facile enolization of this compound.

Since propargyl esters easily rearrange and cannot completely overcome the innate regioisomeric preferences in the hydrofluorination of arylalkylalkynes, we sought to examine other, more robust directing groups that might coordinate more strongly to Au and enhance regioselectivity (Table 1). Among these, carbamate-bearing compounds proved particularly revealing. The 2,2,2-trichloroethoxycarbonyl (Troc) group proved to be a superior directing group, delivering fluoroalkenes exclusively over other rearranged products with excellent regioselectivity for both alkylarylalkynes (entry 1, 92:8; 69% yield) and dialkylalkynes (entry 2, >50:1; 57% yield). Intriguingly, a minor isomer in the latter case proved

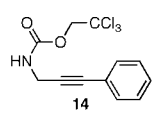
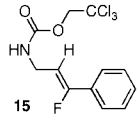
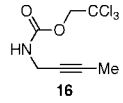
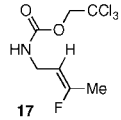
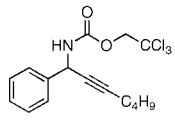
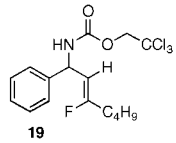
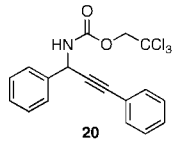
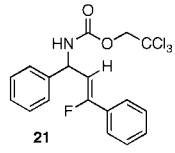
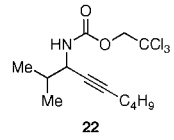
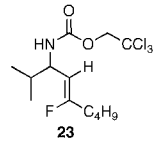
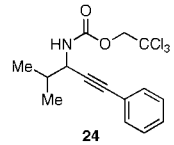
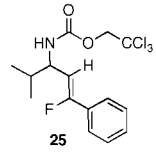
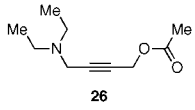
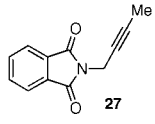
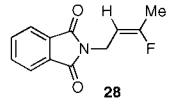
(9) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736.

(10) (a) Yu, M.; Zhang, G.; Zhang, L. *Tetrahedron* **2009**, *65*, 1846. (b) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147.

(11) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(12) (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (b) Mauleón, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513. (c) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647.

Table 1. Nitrogen-Containing Directing Groups for Hydrofluorination of Alkynes

entry	alkyne	major product	yield; regioisomer ratio [a]
1	 **14**	 **15**	69%; 92:8
2	 **16**	 **17**	57% [b]; >50:1; 83:17 *Z*/*E*
3	 **18**	 **19**	68%; >50:1
4	 **20**	 **21**	65%; 98:2
5	 **22**	 **23**	74%; >50:1
6	 **24**	 **25**	65%; 92:8
7	 **26**	N.A.	No reaction
8	 **27**	 **28**	53%; >50:1; 84:14 *Z*/*E*

[a] Reported as the average combined yield of all isomers for two reactions, unless otherwise noted. [b] Yield determined using an internal ^{19}F NMR standard.

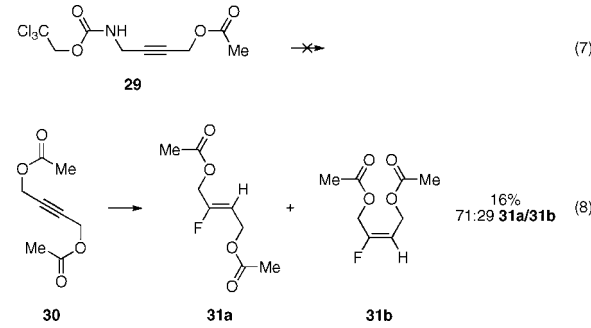
to be the *E*-fluoroalkene. The Boc group was considered as an alternative but was avoided given its potential vulnerability to HF. In addition, intramolecular attack of the Au-activated alkyne by the carbamoyl carbonyl followed by loss of the *tert*-butyl group has been reported to give cyclic urethanes in analogous reactions.[13] Notably, no cyclization/cleavage products of this type were detected with Troc-substituted compounds.

We further examined the scope of this methodology by investigating both dialkyl- and alkylarylsubstrates with sterically demanding substituents at the junction between the directing group and the alkyne (Table 1, entries 3−6). We were pleased to observe that these modifications had little impact on the regioselectivity of the reaction (regioselectivities from 92:8 to >50:1 were observed in this series; yields 65−74%). In fact, regioselectivity improved modestly when a phenyl group was exchanged for an isopropyl group at this position (Table 1, entries 4 and 6**)**, while substrates with a terminal butyl group (entries 3 and 5) reacted with complete regioselectivity. Overall, these results demonstrate that the Troc group is a stable, general, and potent directing group for the regioselective hydrofluorination of alkynes.

Surprisingly, no reaction was observed with tertiary amine-bearing substrate **26**. This observation is interesting since the reaction conditions include 1.5 equiv of triethylamine as a component of the fluorinating reagent. However, phthalimide **27** was found to exhibit excellent regioselectivity (>50:1). In reactions of substrate **27**, the presence of a terminal methyl group once again resulted in formation of small amounts of *E*-fluoroalkene.

We subsequently wished to expand the scope of our study to include doubly functionalized alkynes **29** and **30** (Scheme 3). In so doing, we aspired to determine the relative directing

Scheme 3. Hydrofluorination of Dicarbonyl Substrates[a]



[a] Yield determined using an internal ^{19}F NMR standard and reported as the average combined yield of all isomers for two reactions.

abilities of various types of carbonyl groups in the context of a direct competition experiment. Unfortunately, attempts to hydrofluorinate **29** were unsuccessful, yielding primarily unreacted substrate. Likewise, hydrofluorination of **30** also did not proceed appreciably but did deliver comparably small quantities of *E*- and *Z*-fluoroalkene. These findings, together with the lack of reactivity observed for substrate **26**, suggest that bis-functionalized alkynes can interrupt the catalytic cycle. To gain insight as to the cause of this interruption, we attempted to ascertain the nature of the initial Au−substrate complex. ^{1}H NMR indicated that the chemical shifts of the complexed substrate, including those of the acetyl group and urethane proton, were significantly altered. This data raises the possibility that the presence of two directing groups either (a) inhibits the rate of nucleophilic attack of the Au-activated alkyne by fluoride, possibly in a competitive mode (**32**), or (b) compromises the activation of the alkyne by the Au catalyst, perhaps via an inductive effect. A further possibility invokes the bidentate nature of the bis-functionalized alkynes as a potential cause for sequestration of the metal such that

productive complexation to the alkyne cannot occur (Figure 1, **33** and **34**), an attractive hypothesis considering the

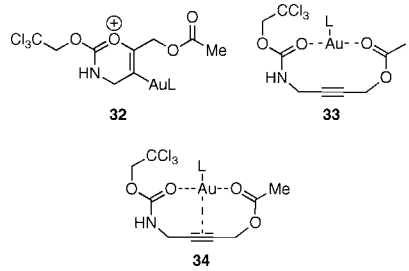


Figure 1. Possible intermediates representing interruptions of the catalytic cycle for the hydrofluorination of **29**.

perturbation of both the acetyl and urethane signals in the ^{1}H NMR spectrum.[14] These ideas remain speculative at this time and await further experimental examination before a definitive explanation may be advanced.

In light of what is known about the mechanism of this reaction,[9] we have considered the mechanistic hypothesis shown in Figure 2 as a possible basis for the successful cases of regioselectivity we have observed. Following counterion exchange with silver tetrafluoroborate, the Au catalyst could complex to both the carbonyl oxygen and the alkyne of the substrate (**35**). Nucleophilic attack of the activated alkyne by fluoride could then occur such that the more energetically favored ring is preferentially formed in intermediate **36**. Protonation of the Au and reductive protodeauration of **37** would extrude the product **38** and regenerate the active catalytic species. Given the trend observed in Scheme 2, it appears that $n = 1$ (Figure 2) is optimal for regioselectivity within this substrate class. These mechanistic proposals are hypothetical and preliminary and await further experimental work for possible validation.

(13) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763.

(14) Au(I)−alkene complexes containing an N-heterocyclic carbene ligand have also been reported; see: Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350, and references therein.

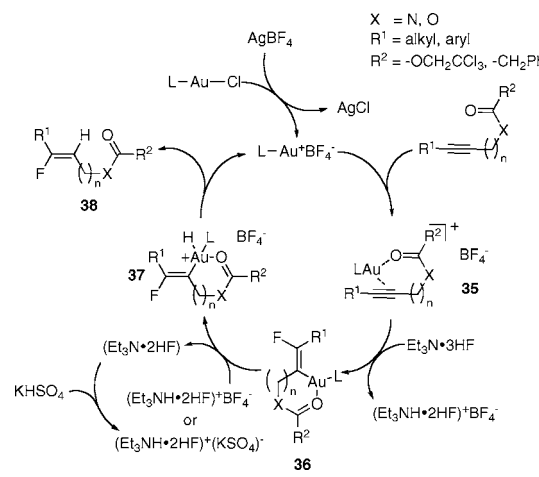


Figure 2. A mechanistic hypothesis for the directed hydrofluorination of alkynes.

In summary, we have achieved the regio- and stereoselective synthesis of fluoroalkenes by using carbonyl groups to direct the Au(I)-catalyzed hydrofluorination of alkynes. Troc-carbamates were found to be the best directing group, both in terms of regioselectivity and stability to the reaction conditions, delivering the desired fluoroalkenes with significant regioselectivity in all cases examined. Such reactions may be useful for the synthesis of fluoroolefins of interest in medicinal and physical organic chemistry. Future work will entail generalization of these reactions further, potentially in a ligand-dependent way through studies of catalyst modification.

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

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