J|A|C|S
COMMUNICATIONS

Published on Web 06/05/2007

# Reversible C−F Bond Formation and the Au-Catalyzed Hydrofluorination of Alkynes

Jennifer A. Akana, Koyel X. Bhattacharyya, Peter Müller, and Joseph P. Sadighi*

*Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139*

Received April 4, 2007; E-mail: jsadighi@mit.edu

Organofluorine compounds have found widespread and growing use in the pharmaceutical, materials, and other industries.[1] Transition metals offer great potential improvements in the scope, selectivity, and convenience of fluorination chemistry. Their use in C−F bond formation, however, has only begun to be explored.[2] Examples to date include electrophilic fluorinations of arene[2a] and enol[2b,c] C−H bonds, the reductive elimination of aryl[2d] or acyl[2e] C−F bonds, and nucleophilic halide displacement reactions.[2f,g]

Recent years have seen a resurgence in gold catalysis,[3] notably in the formation of C−C,[4] C−N,[5] and C−O[6] bonds from alkynes. We now report the reversible addition of a gold(I) fluoride across an unactivated alkyne. This addition is a likely key step in a new hydrofluorination of alkynes under mild conditions, using gold(I) precatalysts and a relatively benign HF source.

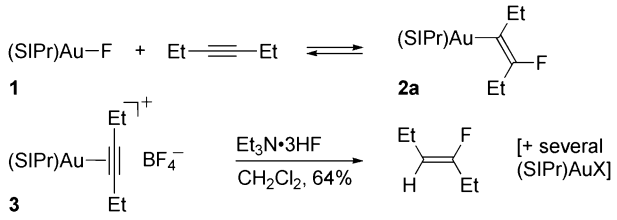
The gold(I) fluoride complex (SIPr)AuF (**1**; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene)[7] reacts with excess 3-hexyne (150 equiv) in $CH_2Cl_2$ solution at 20 °C. After 10 min, the reaction mixture displays a new triplet resonance ($\delta$ −95.5 ppm, $J$ = 21 Hz), representing >95% of the original peak area of **1** (relative to $C_6H_5F$ internal standard), in its $^{19}F$ NMR spectrum. This resonance is assigned to the $\beta$-(fluorovinyl)gold complex **2a**, formed by addition of fluoride and gold(I) across the alkyne (Scheme 1). Removal of solvent and excess alkyne from **2a**, over a period of 30 min, results in quantitative regeneration of **1**. Rapid (≤5 min) concentration affords mixtures of **1** and **2a**, which regain equilibrium within 2 h after redissolution in $CD_2Cl_2$.

Analysis of mixtures formed from different concentrations of **1** and 3-hexyne at 20 °C gives an equilibrium constant of 2.7 ± 0.2 $M^{-1}$ for the addition process, corresponding to $\Delta G°$ = −0.58 ± 0.04 kcal/mol (Table S1, Supporting Information). Certain $[Co^{III}]X$ complexes react with acetylene reversibly, forming *trans*-$\beta$-halovinyl products,[8] but fluoride addition was not observed. The addition of AgF across an alkyne is known but requires a highly electrophilic substrate.[9,10] Reversible metal-mediated C−F bond rupture has been demonstrated intramolecularly in α-fluoride elimination from Ru and Os trifluoromethyl complexes.[11]

Addition product **2b**, formed from **1** and 1-phenyl-1-propyne, proved more amenable than **2a** to isolation and crystallization. Dissolution of **1** in a 1:1 mixture of 1-phenyl-1-propyne and $CH_2Cl_2$, followed by vapor diffusion of *n*-pentane at −40 °C, afforded crystals of **2b** suitable for X-ray diffraction. The resulting structure (Figure 1) displays a 1,1-arrangement of the phenyl group and gold and confirms the *trans*-arrangement of gold and fluorine about the vinylic C=C bond.

The *trans*-addition of fluoride and gold(I) across the triple bond could proceed via displacement of fluoride from **1** by alkyne, followed by nucleophilic addition of fluoride to the resulting cationic gold(I)−alkyne complex. Abstraction of chloride from (SIPr)AuCl by $AgBF_4$ in the presence of 3-hexyne affords an independent route to the cationic complex **3**, $\{(SIPr)Au[\eta^2\text{-}(3\text{-hexyne})]\}^+[BF_4]^-$. This complex decomposes in $CH_2Cl_2$ solution over a period of several days but is stable in the solid state for roughly 2 weeks at ambient temperature.[12]

***Scheme 1***




Treatment of **3** with an organic-soluble fluoride source, $[(Me_2N)_3P]_2N^+F^-$, results in predominant displacement of alkyne by fluoride, re-establishing the equilibrium between **1** and **2a**. In contrast, the reaction of **3** with $Et_3N{\bullet}3HF$ (1 equiv, Scheme 1), a fluoride source that is both nucleophilic and mildly acidic,[13] results in hydrofluorination of the coordinated alkyne to form (*Z*)-3-fluoro-3-hexene[14] (64%, relative to $BF_4^-$, by $^{19}F$ NMR). The same fluoroalkene is observed in >95% yield ($^{19}F$ NMR, relative to internal standard) when **2a** is treated with $CF_3CO_2H$.

This observation of tandem C−F and C−H bond formation led us to seek conditions for a catalytic transformation of alkynes to fluoroalkenes using $Et_3N{\bullet}3HF$. Alkynes react directly with the more harshly acidic reagent pyridine/HF (70% HF), and although fluoroalkenes may be observed as byproducts in some cases, only *gem*-difluoroalkanes are isolated in useful yields.[15] Alkynes activated by highly electron-withdrawing groups undergo *trans*-hydrofluorination on reaction with $[H_2F_3]^-$ salts[16,17] or by heating with CsF in wet DMF.[18] Generally, however, fluoroalkenes are obtained indirectly,[19] and control over the stereochemistry often requires careful strategy.[20] Given the interest in fluoroalkenes for medicinal chemistry,[21] stereoselective addition of HF to alkynes under mild conditions could be important synthetically.

Initial catalytic screening reactions between 3-hexyne and $Et_3N{\bullet}3HF$, using **3** as precatalyst, afforded fluoroalkene in yields up to 53% as judged by $^{19}F$ NMR relative to internal standard. Product yields were not significantly improved by an increase in catalyst loading from 1 to 5 mol %. Reasoning that decreasing acidity, as HF was consumed,[22] caused the reactions to stall before complete conversion was attained, we examined the effects of acidic additives on the reaction efficiencies. The presence of powdered $KHSO_4$, in conjunction with the $CH_2Cl_2$-soluble acid cocatalyst $PhNMe_2{\bullet}HOTf$ (10 mol %), resulted in greatly increased yields of fluoroalkene.

Both SIPr and its imidazolylidene analogue IPr are moderately effective supporting ligands for the catalytic hydrofluorination of 6-dodecyne. Very similar results were obtained using (SIPr)AuO*t*-Bu or (SIPr)AuCl/$AgBF_4$ as precatalysts. The use of less sterically demanding NHCs, or triphenylphosphine, led to poor catalytic conversions (see Table S2, Supporting Information), with rapid precipitation of gold metal. Complete consumption of


10.1021/ja0723784 CCC: $37.00 

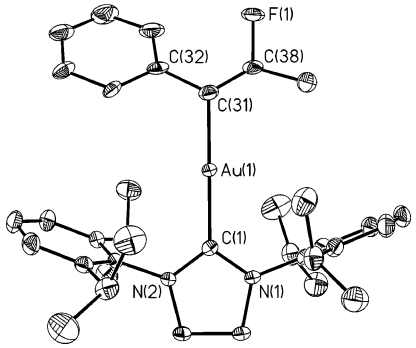
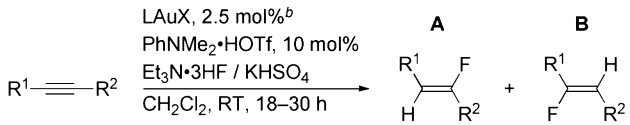
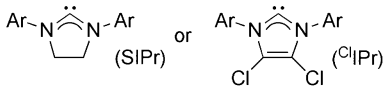



***Figure 1.*** X-ray crystal structure of addition product **2b**, shown as 50% ellipsoids. Hydrogens and solvent $CH_2Cl_2$ are omitted for clarity. Selected bond lengths (Å) and angles (deg): Au(1)−C(1) = 2.014(3), Au(1)−C(31) = 2.043(3), C(31)−C(38) = 1.329(9), C(38)−F(1) = 1.400(10), C(1)−Au(1)−C(31) = 176.36(10), C(38)−C(31)−Au(1) = 119.2(8), C(32)−C(31)−Au(1) = 117.7(6), C(32)−C(31)−C(38) = 123.1(10).

***Table 1.*** Substrate Scope[a]




| Entry | $R^1$ = | $R^2$ = | % yield | **A** : **B** |
|---|---|---|---|---|
| **1** | $C_6H_5$ | $C_6H_5$ | 86% | --- |
| **2** | *n*-$C_5H_{11}$ | *n*-$C_5H_{11}$ | 81% | --- |
| **3** | 4-$MeOC_6H_5$ | *n*-$C_6H_{13}$ | 63%[c] | 5 : 1 |
| **4** | $C_6H_5$ | *n*-$C_6H_{13}$ | 78%[c] | 13 : 1 |
| **5** | 4-$MeC(O)C_6H_5$ | *n*-$C_6H_{13}$ | 82% | A only |
| **6** |  | *n*-$C_6H_{13}$ | 74% | A only |

L =  (SIPr) or (ClIPr); Ar = 2,6-(*i*-Pr)$_2C_6H_3$

[a] Conditions: Reactions were performed using 1.5 equiv of $Et_3N$•3HF and 1.0 equiv of $KHSO_4$, at alkyne concentrations of 1.8 M. [b] Entries 1 and 2 are catalyzed by ($^{Cl}$IPr)AuCl/$AgBF_4$. Entries 3−6 are catalyzed by (SIPr)AuO*t*-Bu. [c] Isolated as a mixture of **A** + **B**; composition determined by $^1$H NMR.

6-dodecyne was achieved using a less electron-rich analogue of IPr, 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene ($^{Cl}$IPr).

The substrate scope of this method includes dialkyl-, diaryl-, and aryl/alkyl- or thienyl/alkyl-substituted alkynes (Table 1). For substrates bearing both a phenyl and an alkyl substituent, the predominance of $\beta$-fluorostyrene products is consistent with the preferential formation of α-phenylvinyl complex **2b** by addition of fluoride and gold(I) across 1-phenyl-1-propyne. Catalytic regioselectivities are higher for an electron-poor aryl substituent than for an electron-rich one; however, the electron-rich thienyl substituent (entry 6) also gave exclusive $\beta$-fluorination. No *gem*-difluoroalkanes are detected, and *trans*-hydrofluorination is observed in all cases.

In conclusion, the reaction of an alkyne with an (NHC)gold(I) fluoride results in reversible carbon−fluorine bond formation. Electrophilic (NHC)gold(I) complexes catalyze the *trans*-hydrofluorination of internal alkynes at room temperature, using a mild HF source. This catalysis represents a new, selective, and potentially versatile method for the synthesis of fluoroalkenes.

**Acknowledgment.** We thank the NSF (Grant No. CHE-0349204), Corning, Inc., and the MIT Department of Chemistry for their generous support; MIT NMR facilities are supported in part by NSF Awards CHE-9808061 and DBI-9729592.

**Supporting Information Available:** Experimental details and characterization data for new compounds; comparison of different precatalysts. Crystallographic data for **2b** are provided as a CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483−4503. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231.
(2) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134−7135. (b) Prakash, G. K. S.; Beier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172−2174 and references cited therein. (c) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362. (d) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342−1358. (e) Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769−4770. (f) Barthazy, P.; Togni, A.; Mezzetti, A. *Organometallics* **2001**, *20*, 3472−3477. (g) Grushin, V. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 994−996.
(3) For reviews, see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346.
(4) Selected references: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160−4161. (b) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062−12063. (c) Marion, N.; Díez-González, S.; de Frémont, P.; Nobel, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647−3650. (d) Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, 4340−4342. (e) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155−3164.
(5) See for example: (a) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627−630. (b) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661−662. (c) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905−4909. (d) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537−3540. (e) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555−4563 and references therein. See also ref 4a.
(6) Selected references: (a) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907−4910. (b) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489−4492. (c) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363−2370. (d) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925−11935. (e) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563−4565. (f) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415−1418. See also refs 4a, 4b.
(7) Laitar, D. S.; Müller, P.; Gray, T. G.; Sadighi, J. P. *Organometallics* **2005**, *24*, 4503−4505.
(8) Fritsch, J. M.; Retka, N. D.; McNeill, K. *Inorg. Chem.* **2006**, *45*, 2288−2295.
(9) Reaction of AgF with perfluoro-2-butyne gives *trans*-addition: (a) Jeffries, P. M.; Wilson, S. R.; Girolami, G. S. *J. Organomet. Chem.* **1993**, *449*, 203−209. (b) Miller, W. T.; Snider, R. H.; Hummel, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 6532−6534.
(10) Alkyne extrusion from ($\beta$-fluorovinyl) complexes: (a) Runge, A.; Sander, W. W. *Tetrahedron Lett.* **1990**, *31*, 5453−5456. (b) Martin, S.; Sauvêtre, R.; Normant, J.-F. *Tetrahedron Lett.* **1982**, *23*, 4329−4332.
(11) Huang, D.; Koren, P. R.; Folting, K.; Davidson, E. R.; Caulton, K. G. *J. Am. Chem. Soc.* **2000**, *122*, 8916−8931.
(12) For another isolable $[(NHC)Au(L)]^+$ complex, see: de Frémont, P; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045−2047.
(13) Alvernhe, G; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562−564.
(14) Boche, G.; Fährmann, U. *Chem. Ber.* **1981**, *114*, 4005−4009.
(15) (a) Olah, G. A.; Li, X.-Y.; Wang, Q.; Prakash, G. K. S. *Synthesis* **1993**, 693−699. (b) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872−3881.
(16) Albert, P.; Cousseau, J. *J. Chem. Soc., Chem. Commun.* **1985**, 961−962.
(17) *trans*-Hydrofluorination of alkynyliodonium salts by $Et_3N$•3HF: Yoshida, M.; Komata, A.; Hara, S. *Tetrahedron* **2006**, *62*, 8636−8645.
(18) Gorgues, A.; Stéphan, D.; Cousseau, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1493−1494.
(19) (a) Hara, S. Stereoselective Synthesis of Monofluoroalkenes Using Cross Coupling Reactions. In *Fluorine Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005; pp 120−139. (b) From fluorinated ylides: Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641−1675.
(20) Selected references: (a) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720−4722. (b) Xu, J.; Burton, D. J. *J. Fluorine Chem.* **2007**, *128*, 71−77. (c) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405−408. (d) Nakamura, Y.; Okada, M.; Koura, M.; Tojo, M.; Saito, A.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2006**, *127*, 627−636. (e) Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445−2447.
(21) (a) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107−3111. (b) Urban, J. J.; Tillman, B. G.; Cronin, W. A. *J. Phys. Chem. A* **2006**, *110*, 11120−11129 and references therein.
(22) Comparison of $Et_3N$•2HF with $Et_3N$•3HF: Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527−6530.

JA0723784