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Cite this: DOI: 10.1039/c0xx00000x

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Research Article

Vanadium-Catalyzed C(sp³)-H Fluorination Reactions†Ji-Bao Xia,^a Yuyong Ma^a and Chuo Chen^{*a}

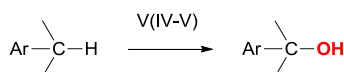
Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

Vanadium(III) oxide catalyzes the direct fluorination of C(sp³)-H groups with Selectfluor. This reaction is operationally simple. The catalyst and the reaction by-product can be removed easily by filtration. Using this method, a fluorine atom can be introduced to the tertiary position of 1,4-cineole and L-menthone selectively.

Nature uses catalytic C-H oxidation reactions extensively to functionalize small molecules. Studying the structures and reactivities of hydroxylases has inspired the development of various iron, manganese, and copper catalysts for C-H oxidation reactions.¹ Their reactivities often complement those of the palladium and rhodium catalysts commonly used for constructing C-C bonds.² Vanadium-complexes are well-known for their ability to transfer an oxygen or a halogen atom to olefins.³ However, vanadium-catalyzed C-H oxidation has not been well-studied.⁴ Recently, we developed an efficient vanadium catalyst for selective benzylic C-H oxygenation with no competing aromatic oxidation.⁵ We report herein a vanadium catalyst system for C(sp³)-H fluorination.

Our previous work



This work

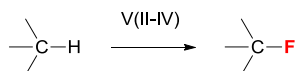


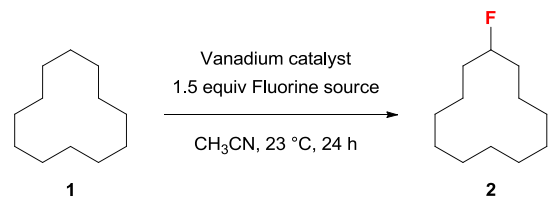
Fig. 1 Development of vanadium-catalyzed oxidative C-H functionalization reactions

Mimoun reported in 1983 that vanadium complexes could catalyze C-H oxygenation through a radical mechanism.⁶ This area of research was later expanded by Shul'pin, Pombeiro, and others.⁷ While several efficient vanadium catalysts have been developed for C-H oxygenation, it has not been shown that vanadium complexes can catalyze C-H halogenation.

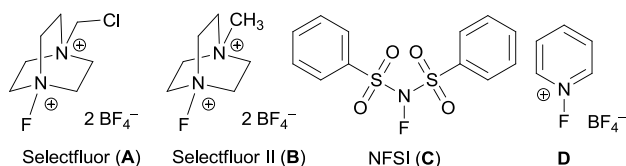
We seek to expand the scope of the vanadium-catalyzed C-H oxidation to C-H fluorination as incorporating fluorine atoms into small-molecules often improves their physical and biological properties.⁸ While there are many efficient methods for introducing fluorine atoms through functional group transformations,⁹ there are only a few studies of catalytic C-H

fluorination reactions. The first example was reported by the Sanford group in 2006.¹⁰ They successfully developed a palladium(II/IV) catalyst system for catalyzing the quinoline/pyridine-directed benzylic C(sp³)-H fluorination and *ortho* C(sp²)-H fluorination. Subsequently, the Yu group developed a versatile palladium catalyst system for directed *ortho* C(sp²)-H fluorination in 2009.¹¹ Methods for catalyzing C(sp³)-H fluorination without using a directing group have also emerged in literatures recently. The Groves group first developed a manganese catalyst system in 2012.¹² The Lectka group then published a copper and an iron catalyst system.¹³ Subsequently, we disclosed a ketone-catalyzed photolytic method¹⁴ and the Inoue group an *N*-oxyl radical-catalyzed method.¹⁵ More recently, the Doyle group developed a palladium-catalyzed allylic C(sp³)-H fluorination reaction¹⁶ and the Hartwig group a silver-promoted oxidative method for C(sp²)-H fluorination of heterocycles.¹⁷ However, there is no report of vanadium-catalyzed C-H fluorination.

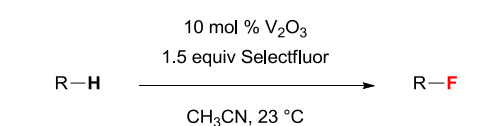
Because vanadium complexes are known to catalyze C-H oxygenation and olefin halogenation, we believe that they can also promote C-H fluorination. To search for an effective vanadium catalyst for C-H fluorination, we examined the reactivities of a series of vanadium complexes using cyclododecane (**1**) as the substrate and Selectfluor as the standard fluorinating reagent (Table 1). Unlike our previous benzylic C-H oxygenation reactions,⁵ vanadium(V) complexes did not catalyze the fluorination of **1** (entries 1-4), and vanadium(IV) complexes gave only a trace amount of fluorocyclodecane (**2**) (entries 5-7). In contrast, vanadium(III) and vanadium(II) complexes were more reactive (entries 8-12). For example, fluorination of **1** in the presence of 20 mol % V(acac)₃ and 20 mol % Cp₂V led to the formation of **2** in 21% and 13% yields, respectively (entries 10 and 12). Among all the vanadium complexes examined, vanadium(III) oxide (V₂O₃) was the most effective catalyst, giving **2** in 65% isolated yield at 10 mol % loading (20 mol % by vanadium) (entry 11). Although **2** could be further fluorinated under the reaction conditions, there were only ~5% of the difluorination products based on ¹⁹F NMR analyses (>10: 1 monofluorination vs. difluorination). In terms of the fluorinating reagent, Selectfluor (F-TEDA, **A**) was the only effective fluorine atom donor. There was no reaction when using Selectfluor II (**B**), NFSI (**C**), or N-fluoropyridinium salts (**D**) as the source of fluorine (entries 13-15). We have also confirmed that a vanadium catalyst is required for this reaction (entry 16),¹⁸ and acetonitrile is the only suitable solvent.

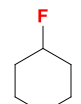
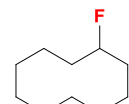
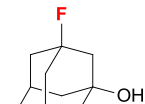
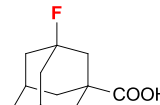
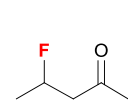
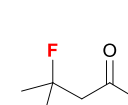
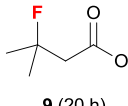
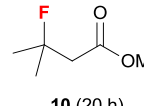
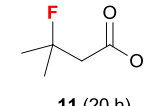
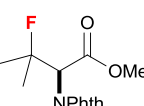

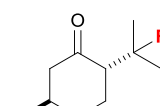
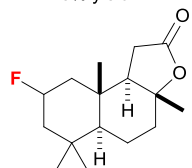
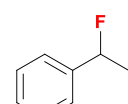
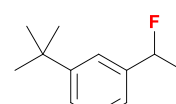
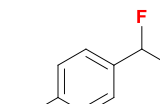
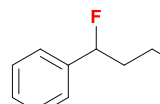
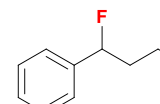
Table 1 Development of the vanadium-catalyzed C–H fluorination reaction^a


Entry	Catalyst loading	Catalyst	Fluorine source	Yield ^b
1	10 mol %	V ₂ O ₅	A	0%
2	20 mol %	VO(O ⁱ Pr) ₃	A	0%
3	20 mol %	VO(OSiPh ₃) ₃	A	0%
4	20 mol %	VOF ₃	A	0%
5	20 mol %	V(O)SO ₄	A	0%
6	20 mol %	VO ₂	A	<5%
7	20 mol %	Cp ₂ VCl ₂	A	<5%
8	20 mol %	VF ₃	A	<5%
9	20 mol %	VBr ₃	A	<5%
10	20 mol %	V(acac) ₃	A	21%
11	10 mol %	V ₂ O ₅	A	73% (65%) ^c
12	20 mol %	Cp ₂ V	A	13%
13	10 mol %	V ₂ O ₅	B	0%
14	10 mol %	V ₂ O ₅	C	0%
15	10 mol %	V ₂ O ₅	D	0%
16	10 mol %	–	A	0%



^aConditions: **1** (0.2 mmol), catalyst (0.04 mmol, or 0.02 mmol for V₂O₅ and V₂O₃), Selectfluor (0.3 mmol), CH₃CN (2 mL), 23 °C. ^bBased on crude ¹⁹F NMR spectra using C₆H₅F as the external standard. ^cIsolated yield in parenthesis.

Table 2 Scope of the vanadium-catalyzed C–H fluorination^a


		
3 (20 h) ^b 70% NMR yield	4 (20 h) ^b 61% yield	5 (20 h) 74% yield
		
6 (20 h) 70% yield	7 (20 h) 47% NMR yield	8 (20 h) 78% NMR yield
		
9 (20 h) 63% yield	10 (20 h) 85% NMR yield	11 (20 h) 12% NMR yield
		
12 (18 h) 46% yield	13 (24 h) 53% yield	14 (30 h) 75% yield
		
15 (48 h) 61% yield ($\alpha:\beta = 9:1$)	16 (24 h) 67% NMR yield	17 (48 h) 47% yield
		
18 (24 h) 24% yield	19 (24 h) 35% yield	20 (6 h) 43% yield

^aConditions: substrate (0.2 mmol), catalyst (0.02 mmol), Selectfluor (0.3 mmol), CH₃CN (2 mL), 23 °C; NMR yield was based on crude ¹⁹F NMR spectra using C₆H₅F as external standard. ^bSubstrate (1.0 mmol), catalyst (0.02 mmol), Selectfluor (0.2 mmol).

The utility of this reaction was further demonstrated by the selective fluorination of monoterpenes 1,4-cineole and L-menthone. The C–H fluorination preferentially occurred at the tertiary positions to give **13** and **14** in 53% and 75% isolated yields, respectively. Vanadium(III) oxide also catalyzed the fluorination of sesquiterpenoid sclareolide with improved

efficiency and selectivity compared to the manganese-porphyrin catalyst system.^{12a} The C-2 fluoride **15** ($\alpha:\beta = 9:1$) was obtained in 61% yield along with the C-3 α -fluoride in 15% yield (C-2:C-3 = 4:1) as an inseparable mixture of isomers.

Selective benzylic fluorination could also be achieved. Although vanadium(III) bromide and vanadium(III) acetoacetate were effective catalysts for benzylic fluorination at 5 mol % loading, bromine atom-transfer occurred with vanadium(III) bromide, and the yields obtained with vanadium(III) acetoacetate were irreproducible due to facile ligand fluorination. In contrast, vanadium(III) oxide provided reliable results despite higher catalyst loading. Under the standard reaction conditions (10 mol % V_2O_5), benzylic fluorides **16** and **17** could be obtained in 67% NMR yield and 47% isolated yield, respectively. However, the fluorine atom of benzylic fluorides could eliminate under the reaction conditions via a S_N1 -type mechanism, leading to low yields of benzylic fluorides for the more electron-rich substrates. In contrast, the electron-deficient 4-ethylbenzotrile was rather unreactive, giving **18** in only 24% isolated yield. Finally, fluorination of propylbenzene with a chlorine or protected nitrogen atom at the terminal position of the side-chain gave **19** and **20** in 35% and 43% isolated yields, respectively.

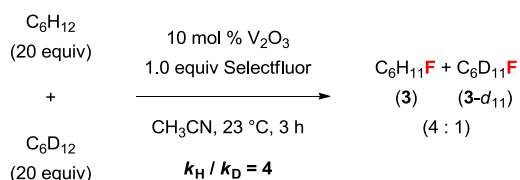


Fig. 2 KIE study of the vanadium-catalyzed C–H fluorination

We have also conducted some preliminary mechanistic studies. A competition experiment using a 1:1 ratio of cyclohexane and cyclohexane- d_{12} gave a 4:1 mixture of **3** and **3- d_{11}** (Figure 2). The primary kinetic isotope effect (KIE) ($k_H / k_D = 4$) indicates that C–H abstraction is the rate-limiting step. This fluorination reaction is highly oxygen-sensitive, suggesting that it may proceed through a radical mechanism. While the nature of the active catalyst is not clear, we believe that a vanadium(II/III) or (III/IV) cycle rather than a vanadium(III/V) cycle is involved because vanadium(V) complexes could not promote this reaction. It is also likely that vanadium(III) oxide was first oxidized to a vanadium(IV) species, which served as the active catalyst. The fluorination reaction proceeded equally well in wet acetonitrile. Since we did not observe any Ritter reaction products or ketones, we believed that the alkyl radical initially generated was not oxidized to a carbocation before being trapped by a fluoride. However, there was no reaction when using water as a cosolvent. It is likely that the addition of a large excess amount of water deactivated the catalyst by altering its structure.

In summary, we have found that commercially available vanadium(III) oxide can catalyze the direct conversion of a C–H group to C–F. This heterogeneous catalyst can be easily removed by filtration along with the Selectfluor by-product H-TEDA. This operationally simple method provides improved efficiency for C–H fluorination at non-benzylic positions compared to existing methods. We are now exploring further utilities of vanadium complexes in catalytic oxidation reactions.

Experimental Section

General procedure for the vanadium(III) oxide-catalyzed C(sp³)-H fluorination reaction. To a 4 mL clear vial charged with vanadium(III) oxide (V_2O_5 , 3.0 mg, 0.02 mmol, 10 mol%) and Selectfluor (106.3 mg, 0.3 mmol, 1.5 equiv) was added anhydrous acetonitrile (2.0 mL), and the reaction substrate (0.2 mmol, 1.0 equiv). The reaction mixture was then degassed three times by freeze-pump-thaw cycles and stirred at room temperature for 6–48 h. Upon completion, the reaction mixture was poured into diethyl ether (20 mL), filtered, concentrated and purified by silica gel flash column chromatography using diethyl ether/pentane as the eluent.

Acknowledgements

Financial support was provided by NIH/NIGMS (R01-GM079554) and the Welch Foundation (I-1596).

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

- (a) L. Que, Jr. and W. B. Tolman *Angew. Chem. Int. Ed.*, 2002, **41**, 1114–1137; (b) L. Que, Jr. and W. B. Tolman *Nature*, 2008, **455**, 333–340; (c) C.-L. Sun, B.-J. Li and Z.-J. Shi *Chem. Rev.*, 2011, **111**, 1293–1314; (d) M. Bordeaux, A. Galarneau and J. Drone *Angew. Chem. Int. Ed.*, 2012, **51**, 10712–10723; (e) J. Eames and M. Watkinson *Angew. Chem. Int. Ed.*, 2001, **40**, 3567–3571; (f) T. Punniyamurthy and L. Rout *Coord. Chem. Rev.*, 2008, **252**, 134–154; (g) A. E. Wendlandt, A. M. Suess and S. S. Stahl *Angew. Chem. Int. Ed.*, 2011, **50**, 11062–11087; see also: (h) Y. Ishihara and P. S. Baran *Synlett*, 2010, 1733–1745.; (i) T. Newhouse and P. S. Baran *Angew. Chem. Int. Ed.*, 2011, **50**, 3362–3374.
- (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu *Acc. Chem. Res.*, 2012, **45**, 788–802; (b) S. R. Neufeldt and M. S. Sanford *Acc. Chem. Res.*, 2011, **45**, 936–946; (c) L. Boisvert and K. I. Goldberg *Acc. Chem. Res.*, 2011, **45**, 899–910; (d) B. G. Hashiguchi, S. M. Bischof, M. M. Konnick and R. A. Periana *Acc. Chem. Res.*, 2011, **45**, 885–898; (e) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman *Acc. Chem. Res.*, 2012, **45**, 814–825; (f) J. L. Roizen, M. E. Harvey and J. Du Bois *Acc. Chem. Res.*, 2011, **45**, 911–922; (g) J. F. Hartwig *Acc. Chem. Res.*, 2011, **45**, 864–873; (h) M. Zhou and R. H. Crabtree *Chem. Soc. Rev.*, 2011, **40**, 1875–1884; (i) M. C. Haibach, S. Kundu, M. Brookhart and A. S. Goldman *Acc. Chem. Res.*, 2011, **45**, 947–958.
- (a) K. B. Sharpless and T. R. Verhoeven *Aldrichimica Acta*, 1979, **12**, 63–74; (b) C. S. Neumann, D. G. Fujimori and C. T. Walsh *Chem. Biol.*, 2008, **15**, 99–109; (c) F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova and C. T. Walsh *Chem. Rev.*, 2006, **106**, 3364–3378; (d) A. Butler, M. J. Clague and G. E. Meister *Chem. Rev.*, 1994, **94**, 625–638; (e) A. Butler and J. V. Walker *Chem. Rev.*, 1993, **93**, 1937–1944.
- (a) T. Hirao *Chem. Rev.*, 1997, **97**, 2707–2724; (b) V. Conte, F. Di Furia and G. Licini *Appl. Catal.*, A, 1997, **157**, 335–361; (c) A. G. J. Ligtenberg, R. Hage and B. L. Feringa *Coord. Chem. Rev.*, 2003, **237**, 89–101; (d) J. A. L. da Silva, J. J. R. F. da Silva and A. J. L. Pombeiro *Coord. Chem. Rev.*, 2011, **255**, 2232–2248.
- J.-B. Xia, K. W. Cormier and C. Chen *Chem. Sci.*, 2012, **3**, 2240–2245.
- (a) H. Mimoun, P. Chaumette, M. Mignard and L. Saussine *New J. Chem.*, 1983, **7**, 467–475; (b) H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer and R. Weiss *J. Am. Chem. Soc.*, 1983, **105**, 3101–

- 3110; (c) M. Bonchio, V. Conte, F. Di Furia, G. Modena and S. Moro *J. Org. Chem.*, 1994, **59**, 6262–6267; (d) E. P. Talsi and K. V. Shalyaev *J. Mol. Catal.*, 1994, **92**, 245–255.
- 7 (a) I. I. Moiseev, A. E. Gekhman and D. I. Shishkin *New J. Chem.*, 1989, **13**, 683–690; (b) G. B. Shul'pin and G. Süß-Fink *J. Chem. Soc. Perkin Trans. 2*, 1995, 1459–1463; (c) T. F. S. Silva, K. V. L. M. V. Kirillova, M. F. G. da Silva, L. M. D. R. S. Martins and A. J. L. Pombeiro *Adv. Synth. Catal.*, 2010, **352**, 171–187; (d) K. Kamata, K. Yonehara, Y. Nakagawa, K. Uehara and N. Mizuno *Nat. Chem.*, 2010, **2**, 478–483.
- 8 (a) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl *ChemBioChem*, 2004, **5**, 637–643; (b) K. Müller, C. Faeh and F. Diederich *Science*, 2007, **317**, 1881–1886; (c) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur *Chem. Soc. Rev.*, 2008, **37**, 320–330; (d) W. K. Hagmann *J. Med. Chem.*, 2008, **51**, 4359–4369.
- 9 (a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel and S. L. Buchwald *Science*, 2009, **325**, 1661–1664; (b) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter *Science*, 2011, **334**, 639–642; (c) V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste *Science*, 2011, **334**, 1681–1684; (d) J. J. Topczewski, T. J. Tewson and H. M. Nguyen *J. Am. Chem. Soc.*, 2011, **133**, 19318–19321; (e) M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin and G. M. Sammis *J. Am. Chem. Soc.*, 2012, **134**, 4026–4029; (f) F. Yin, Z. Wang, Z. Li and C. Li *J. Am. Chem. Soc.*, 2012, **134**, 10401–10404; (g) Z. Li, L. Song and C. Li *J. Am. Chem. Soc.*, 2013, **135**, 4640–4643; (h) C. Zhang, Z. Li, L. Zhu, L. Yu, Z. Wang and C. Li *J. Am. Chem. Soc.*, 2013, **135**, 14082–14085; (i) Z. Li, C. Zhang, L. Zhu, C. Liu and C. Li *Org. Chem. Front.*, 2014, **1**, 100–104; (j) T. J. Barker and D. L. Boger *J. Am. Chem. Soc.*, 2012, **134**, 13588–13591; (k) S. Suzuki, Y. Kitamura, S. Lectard, Y. Hamashima and M. Sodeoka *Angew. Chem. Int. Ed.*, 2012, **51**, 4581–4585; (l) W. Kong, P. Feige, T. d. Haro and C. Nevado *Angew. Chem. Int. Ed.*, 2013, **52**, 2469–2473; (m) J. R. Wolstenhulme, J. Rosenqvist, O. Lozano, J. Ilupeju, N. Wurz, K. M. Engle, G. W. Pidgeon, P. R. Moore, G. Sandford and V. Gouverneur *Angew. Chem. Int. Ed.*, 2013, **52**, 9796–9800; (n) N. A. Cochrane, H. Nguyen and M. R. Gagne *J. Am. Chem. Soc.*, 2013, **135**, 628–631; (o) X. Mu, H. Zhang, P. Chen and G. Liu *Chem. Sci.*, 2014, **5**, 275–280.
- 10 (a) K. L. Hull, W. Q. Anani and M. S. Sanford *J. Am. Chem. Soc.*, 2006, **128**, 7134–7135; (b) K. B. McMurtrey, J. M. Racowski and M. S. Sanford *Org. Lett.*, 2012, **14**, 4094–4097; (c) J. M. Racowski, J. B. Gary and M. S. Sanford *Angew. Chem. Int. Ed.*, 2012, **51**, 3414–3417.
- 11 (a) X. Wang, T.-S. Mei and J.-Q. Yu *J. Am. Chem. Soc.*, 2009, **131**, 7520–7521; (b) K. S. L. Chan, M. Wasa, X. Wang and J.-Q. Yu *Angew. Chem. Int. Ed.*, 2011, **50**, 9081–9084.
- 12 (a) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III and J. T. Groves *Science*, 2012, **337**, 1322–1325; (b) W. Liu and J. T. Groves *Angew. Chem. Int. Ed.*, 2013, **52**, 6024–6027.
- 13 (a) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim and T. Lectka *Angew. Chem. Int. Ed.*, 2012, **51**, 10580–10583; (b) S. Bloom, C. R. Pitts, R. Woltormist, A. Griswold, M. G. Holl and T. Lectka *Org. Lett.*, 2013, **15**, 1722–1724; (c) S. Bloom, J. L. Knippel and T. Lectka *Chem. Sci.*, 2014, **5**, 1175–1178.
- 14 J.-B. Xia, C. Zhu and C. Chen *J. Am. Chem. Soc.*, 2013, **135**, 17494–17500.
- 15 Y. Amaoka, M. Nagatomo and M. Inoue *Org. Lett.*, 2013, **15**, 2160–2163.
- 16 M.-G. Braun and A. G. Doyle *J. Am. Chem. Soc.*, 2013, **135**, 12990–12993.
- 17 P. S. Fier and J. F. Hartwig *Science*, 2013, **342**, 956–960.
- 18 (a) R. D. Chambers, M. Parsons, G. Sandford and R. Bowden *Chem. Commun.*, 2000, 959–960; (b) R. D. Chambers, A. M. Kenwright, M. Parsons, G. Sandford and J. S. Moilliet *J. Chem. Soc. Perkin Trans. 1*, 2002, 2190–2197.