J|A|C|S
ARTICLES

Published on Web 07/02/2010

Ruthenium-Catalyzed Hydroxylation of Unactivated Tertiary C−H Bonds

Eric McNeill and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received May 30, 2010; E-mail: jdubois@stanford.edu

Abstract: The combination of catalytic $RuCl_3$ and pyridine with $KBrO_3$ as the stoichiometric oxidant is shown to efficiently promote the hydroxylation of unactivated tertiary C−H bonds. Substrates possessing different polar functional groups — ester, epoxide, sulfone, oxazolidinone, carbamate, and sulfamate — are found to engage in this reaction to give alcohol products in yields generally exceeding 50%. As judged based on efficiency, ease of operation, substrate scope, and selectivity toward tertiary C−H centers, the method appears competitive with other C−H hydroxylation processes.

Methods for catalytic C−H bond functionalization have appeared as transformative tools for fine chemicals synthesis.[1] Reactions that enable the selective hydroxylation of sp^3 C−H centers are of particular interest, given the myriad natural products and designed molecules that possess alcohol or alcohol-derived groups.[2−4] The effectiveness of most processes that rely on transition metal complexes to mediate C−H oxidation, however, is often limited by unwanted pathways such as oxidative ligand degradation and/or catalyst multimerization. Ruthenium tetraoxide, RuO_4, is an intriguing species in this regard — a potent oxidant that can be generated under catalytic conditions and that does not require support of an ancillary ligand set. As a stoichiometric oxidant, RuO_4 is generally regarded as indiscriminate, reacting with π-systems, saturated C−H bonds, aromatic rings, etc.[5] We have devised, however, a protocol for selective tertiary (3°) C−H hydroxylation using conditions in which RuO_4 is generated catalytically (Figure 1). The operational simplicity of this method and its compatibility with a range of substituted materials hallmark this process.

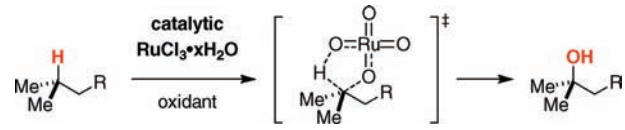


Figure 1. Ruthenium-catalyzed hydroxylation of 3° C−H bonds.

First described by Djerassi, RuO_4 can be obtained as a solution in CCl_4 but is more typically generated in catalytic quantities from a lower-valent ruthenium precursor and a stoichiometric oxidant.[6,7] Seminal investigations by Bakke and Waegell have shown that the combination of $RuCl_3$ (2−4 mol %) and $NaIO_4$ in a ternary solvent mixture (CCl_4/MeCN/H_2O) is capable of hydroxylating 3° C−H bonds in the natural product cedrane and a small number of related compounds.[8,9] Detailed kinetic and computational studies give weight to a mechanism involving concerted asynchronous [3 + 2] cycloaddition between RuO_4 and the substrate C−H bond.[10,11] Accordingly, such a process makes possible the stereospecific hydroxylation of optically active 3° C−H centers, a particularly desirable feature of this hydroxylation method. Questions surrounding the reaction scope, however, are a primary concern given the perception of RuO_4 as a powerful, nonselective oxidant.

(1) For recent reviews, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, *34*, 5061. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (e) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (f) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(2) For representative examples of metal-catalyzed C−H oxygenation, see: (a) Kim, C.; Chen, K.; Kim, J.; Que, L., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 5964. (b) Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978. (c) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (d) Lee, S.; Fuchs, P. L. *Org. Lett.* **2004**, *6*, 1437. (e) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (f) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (g) Company, A.; Gómez, L.; Fontrodona, X.; Ribas, X.; Costas, M. *Chem.—Eur. J.* **2008**, *14*, 5727. (h) Vermeulen, N. A.; Chen, M. S.; White, M. C. *Tetrahedron* **2009**, *65*, 3078. (i) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (j) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654.

(3) For examples of catalytic, nonmetal mediated C−H hydroxylation, see: (a) Brodsky, B. H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391. (b) Litvinas, N. D.; Brodsky, B. H.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4513.

(4) For examples of selective C−H oxidation with stoichiometric oxidants, see: (a) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1, and references therein. (b) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247. (c) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

(5) Martín, V. S.; Palazón, J. M.; Rodríguez, C. M.; Nevill, C. R., Jr. Ruthenium(VIII) Oxide. In *e-EROS: Encyclopedia of Reagents for Organic Synthesis*; New York: John Wiley and Sons, 2006.

(6) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838.

(7) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(8) Bakke, J. M.; Lundquist, M. *Acta Chem. Scand.* **1986**, *B40*, 430.

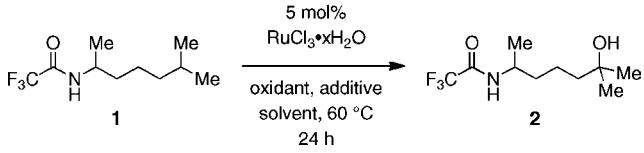
(9) (a) Tenaglia, A.; Terranova, E.; Waegell, B. *Tetrahedron Lett.* **1989**, *30*, 5271. (b) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1344. (c) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Org. Chem.* **1992**, *57*, 5523.

(10) (a) Bakke, J. M.; Brænden, J. E. *Acta Chem. Scand.* **1991**, *45*, 418. (b) Bakke, J. M.; Bethell, D. *Acta Chem. Scand.* **1992**, *46*, 644. (c) Bakke, J. M.; Frøhaug, A. E. *Acta Chem. Scand.* **1994**, *48*, 160. (d) Bakke, J. M.; Frøhaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 310. (e) Bakke, J. M.; Frøhaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 507.

(11) Drees, M.; Strassner, T. *J. Org. Chem.* **2006**, *71*, 1755.

10.1021/ja1046999

Table 1. Evaluation of Reaction Conditions for C−H Hydroxylation[a]



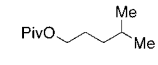
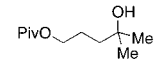
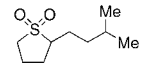
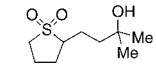
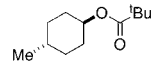
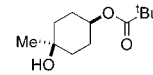
Entry	Oxidant	Solvent	Additive	Conv[b]
1	$NaIO_4$	CCl_4/MeCN/H_2O	none	25
2	$NaIO_4$	EtOAc/MeCN/aq. $H_2PO_4^-$	none	35
3	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	none	15
4	$NaIO_4$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	50
5	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	70(62)
6	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	quinuclidine	<5
7	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	imidazole	20
8	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridazine	25
9	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyrazine	<5
10	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	2,2-bpy	0
11	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyr N-oxide	30
12	Oxone	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	<5
13	NaOCl	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	15
14	$KBrO_3$	CCl_4/MeCN/H_2O	pyridine	35
15	$KBrO_3$	EtOAc/MeCN/H_2O	pyridine	75(67)
16	$KBrO_3$	MeOAc/MeCN/H_2O	pyridine	80(73)
17	**$KBrO_3$**	**MeCN/H_2O**	**pyridine**	**75(74)**

[a] Reactions were conducted on a 0.25 mmol scale. Conditions: 5 mol % $RuCl_3 \cdot xH_2O$, 3 equiv of oxidant, 10 mol % additive, 0.06 M, 60 °C, 24 h. [b] Yields determined by ^1H NMR integration of unpurified reaction mixtures relative to an internal standard; see Supporting Information for details. Values in parentheses refer to isolated yields of pure product.

To examine the capacity of RuO_4 to selectively oxidize starting materials having some degree of polar group substitution, trifluoroacetamide **1** was chosen as an initial test substrate. Reaction of **1** with 5 mol % $RuCl_3 \cdot xH_2O$ and 3 equiv of $NaIO_4$ for 24 h at 60 °C in a mixture of CCl_4, MeCN, and H_2O, conditions employed for cedrane oxidation, afforded low conversion (25%) to the desired alcohol **2** (Table 1, entry 1).[8,9] On a positive note, more than 90% of the mass balance could be accounted for as unreacted starting material and product. Wanting to avoid the use of CCl_4, a protocol described by Fuchs for oxidation of steroidal ethers was also tried (entry 2).[12] Neither the solvent change nor a switch to $KBrO_3$ as the terminal oxidant (entry 3) greatly affected the reaction outcome.

As the addition of a nitrogen base can often benefit oxidation reactions with OsO_4, we chose to explore the influence of such a reagent on the hydroxylation event.[13,14] Rather strikingly, the inclusion of 10 mol % pyridine to a reaction containing $NaIO_4$ and **1** resulted in 50% conversion to product (entry 4, Table 1). Further improvement in performance was noted with the use of $KBrO_3$ (entry 5). In both cases, analysis of the unpurified ^1H NMR shows alcohol **2** and recovered starting material **1**, with only trace amounts (<5%) of products ascribed to 2° methylene oxidation. What is most intriguing about this result is that other common nitrogen heterocycles are substantially inferior to pyridine, and in fact some arrest catalysis altogether (entries 6−10). Moreover, despite the oxidizing power of RuO_4, the pyridine ligand does not appear to be converted rapidly to the N-oxide (entry 11). The combination of $KBrO_3$ and pyridine is indeed differential, as other oxidants including Oxone and NaOCl give substantially reduced product conversions (entries 12, 13). Lastly, a re-examination of the influence of solvent revealed a 1:1 mixture of H_2O/MeCN to be optimal (entries 14−17), affording **2** in 74% isolated yield.[15]

Table 2. Comparison of Reaction Conditions for Selected Substrates[a]

Entry	Substrate	Product	Yield(%)[b] A[c]	B[d]	C[e]
1			**52**	**40**	**12**
2			**63**	**48**	**22**
3			**54**	**29**	**20**

[a] Reactions were performed on a 0.25 mmol scale at 60 °C with 5 mol % $RuCl_3 \cdot xH_2O$ and 3 equiv of oxidant. [b] Isolated yield of chromatographed product. [c] MeCN/H_2O 1:1, $KBrO_3$, 10 mol % pyridine. [d] MeCN/H_2O 1:1, $KBrO_3$, no pyridine. [e] MeCN/H_2O/CCl_4 1:2:1, $NaIO_4$, no pyridine.

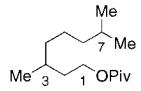
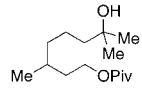
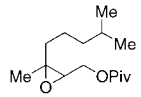
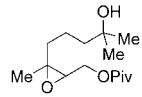
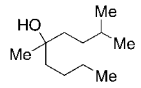
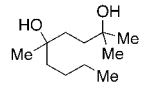
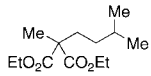
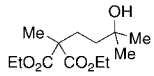
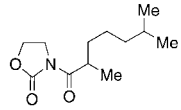
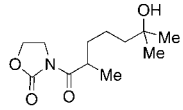
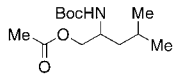
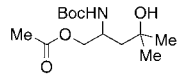
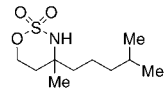
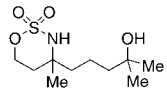
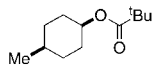
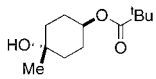
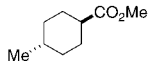
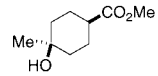
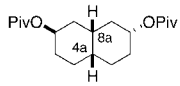
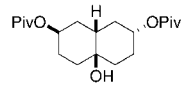
To verify that the results in Table 1 were not specific to **1**, we chose to compare our protocol, pyridine-free conditions, and those previously reported by Bakke and Waegell against a few additional substrates (Table 2). From these collective data, it is evident that the combination of $RuCl_3$, $KBrO_3$, and pyridine (conditions **A**) offers a substantive improvement over the Bakke/Waegell procedure (conditions **C**). Although the influence of pyridine on reaction performance varies to some extent depending on substrate type, in all cases product yields exceeded the pyridine-free control (conditions **B**).

The scope of the Ru-catalyzed hydroxylation process has been examined with substrates of varying complexity (Table 3). Reactions are easily performed with all components being added in a single bolus. Acylated primary (1°) and secondary (2°) alcohols, unprotected 3° alcohols, epoxides, sulfones, acyloxazolidinones, electron-deficient amides, sulfamates, and carbamates are all compatible with the reaction conditions. Due to the highly oxidizing nature of RuO_4, easily oxidized moieties such as alkenes, alkynes, ethers, sulfides, aldehydes, and electron-neutral or -rich aromatic rings should be avoided. As with other C−H oxidation reactions, product yields are influenced by the proximity of electron-withdrawing groups to the site of the C−H bond undergoing modification.[2b−d,3,4] These inductive effects can be exploited for the purpose of influencing positional selectivity, as noted by the formation of one major product with substrates possessing multiple 3° sites (entries 1, 5, 9, 10). The ratios of alcohol isomers in these cases vary from 2.5:1 at the low end (entries 1 and 10) to >20:1 when one of the two 3° C−H centers is more proximal to an electron-withdrawing group(s) (entries 5 and 9). Despite the number of potentially reactive methylene centers in all of the substrates shown in Tables 2 and 3, the mass balance for these reactions is generally >90% substrate and product.

(12) Lee, J. S.; Cao, H.; Fuchs, P. L. *J. Org. Chem.* **2007**, *72*, 5820.
(13) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483, and references therein.
(14) For an example of OsO_4-catalyzed C−H hydroxylation, see: Bales, B. C.; Brown, P.; Dehestani, A.; Mayer, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 2832. For an example of pyridine-assisted OsO_4 hydroxylation of silanes, see: Valliant-Saunders, K.; Gunn, E.; Shelton, G. R.; Hrovat, D. A.; Borden, W. T.; Mayer, J. M. *Inorg. Chem.* **2007**, *46*, 5212.

(15) Analysis of the unpurified reaction mixture by ^1H NMR showed ~15% unreacted starting material and trace products attributed to methylene oxidation.

Table 3. Ruthenium-Catalyzed 3° C−H Hydroxylation[a]

Entry	Substrate	Product	Yield[b]
1			44[c]
2			53
3			51
4			70
5			73[d]
6			26
7			42
8			50
9			57[d]
10			41[e]

[a] Reactions were performed on a 0.25 mmol scale at 60 °C with 5 mol % $RuCl_3 \cdot xH_2O$, 10 mol % pyridine, and 3 equiv of $KBrO_3$. [b] Isolated yields of chromatographed product. [c] 16% of the C3 3° alcohol was also isolated. [d] No other 3° alcohol products were obtained. [e] 17% of the C8a 3° alcohol was also isolated.

Operating on the assumption that RuO_4 is the active oxidant in this catalytic process, we wondered if performing the reaction with $H_2{}^{18}O$ could provide access to ^{18}O-labeled compounds. In the event, use of $H_2{}^{18}O$ as a cosolvent results in the nearly quantitative incorporation of ^{18}O into the product alcohol.[16] As demonstrated with the adamantyl glycine ester shown in Figure 2, 3° C−H oxidation is efficient and, in this example, leads to a single hydroxylated compound. The product alcohol serves as an intermediate en route to Onglyza (saxagliptin), a novel Type II diabetes therapeutic.[17] We envision opportunities to employ this chemistry for the facile, single-step synthesis of ^{18}O-labeled drugs or drug metabolites.

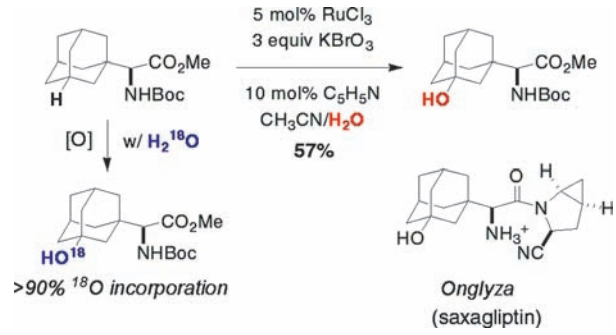


Figure 2. A convenient method for ^{18}O-atom incorporation.

A reaction protocol is described for the selective hydroxylation of 3° C−H bonds that uses catalytic amounts of $RuCl_3$, an inexpensive terminal oxidant, $KBrO_3$, and pyridine as an essential additive. While the specific role(s) of pyridine in this process is undetermined, its influence on reaction performance is pronounced. As judged based on efficiency, ease of operation, substrate scope, and selectivity toward 3° C−H centers, the method appears competitive with other C−H hydroxylation processes.

Acknowledgment. We thank Drs. Jeffrey Robl and Gregory Vite (Bristol-Myers Squibb) for a generous supply of adamantylglycine. E.M. is the recipient of a Stanford Graduate Fellowship. We are grateful to Pfizer for support of this work.

Supporting Information Available: Experimental procedures and analytical data for hydroxylation substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA1046999

(16) For $H_2{}^{18}O$ exchange with Ru-oxo species, see: Wang, C.; Shalyaev, K. V.; Bonchio, M.; Carofiglio, T.; Groves, J. T. *Inorg. Chem.* **2006**, *45*, 4769.

(17) Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.-P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2005**, *48*, 5025.