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An Efficient C–H Oxidation Protocol for α-Hydroxylation of Cyclic Steroidal Ethers

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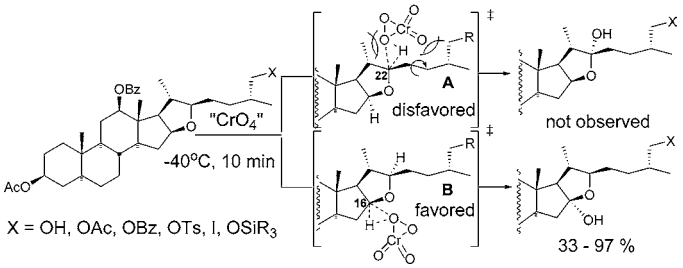
ABSTRACT



Various C-16 hydroxy steroids have been prepared with the aid of CrO_3/Bu_4NIO_4. Out of the two possible reaction courses, transition state B is favored because of less steric interference between substrate and CrO_4. Thus, C–H bonds at C-16 are oxidized selectively.

The availability of efficient synthetic methods for the α-hydroxylation of cyclic ethers has been of considerable interest in organic chemistry. Many oxidations mediated by transition-metal complexes and organic oxidants have been investigated. For example, dioxiranes including DMDO[1] and TFMDO,[2] and transition-metal complexes such as manganese,[3] copper,[4] vanadium,[5] iron,[6] cobalt,[7] and ruthenium,[8] have achieved various levels of success. While chemical and biochemical hydroxylations[9] often proceed with high stereo- and regioselectivity, chemoselective α-hydroxylation of cyclic ethers remains an open question.

In our efforts to synthesize structurally complex and biologically hyperactive cephalostatin 1,[10] we envisioned C−H oxidation α to cyclic ethers as an important value-added operation with regard to improved access to the north unit of cephalostatin 1 (Scheme 1).

Recently, we reported oxidation of both activated and nonactivated C−H bonds under the catalytic influence of Cr^{VI}.[11] Catalytic chromoyl diacetate,[12] together with H_5IO_6,[13] was found to produce a powerful C−H oxidant. Herein, we discuss the subject of regio-, stereo-, and chemoselective α-hydroxylation of steroidal cyclic ethers related to the cephalostatin targets. Our initial survey revealed that some

† Cephalostatin Support Studies. 30. Oxidation 5. For part 29, see: Wei, Li.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 4061.

(1) Dimethyldioxirane: (a) Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511. (b) Bovicelli, P.; Lupattelli, P.; Fracassi, D. *Tetrahedron Lett.* **1994**, *35*, 935. (c) Bovicelli, P.; Lupattelli, P.; Fracassi, D. *Tetrahedron Lett.* **1993**, *34*, 6103. (d) Voigt, B.; Porzel, A.; Adam, W.; Adam, G. *Tetrahedron* **1996**, *52*, 10653.

(2) Methyl(trifluoromethyl)dioxirane: Curci, R.; Accolti, L.; Fiorentino, M.; Fusco, C.; Adam, W. *Tetrahedron Lett.* **1992**, *33*, 4225.

(3) (a) MacDonnell, F. M.; Fackler, N. L. P.; Stern, C.; O'Halloran, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 7431. (b) Miyafuji, A.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10339. (c) Miyafuji, A. *Synlett* **1997**, *7*, 836.

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(5) Kelm, H.; Kruger, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2344.

(6) LeCloux, D.; Barrios, A. M.; Lippard, S. J. *Bioorg. Med. Chem.* **1999**, *7*, 763.

(7) Reetz, M. T.; Toellner, K. *Tetrahedron Lett.* **1995**, *36*, 9461.

(8) (a) Che, C.; Ho, C.; Lau, T. *J. Chem. Soc., Dalton Trans.* **1991**, *5*, 1259. (b) Che, C.; Leung, W. *J. Chem. Soc., Chem. Commun.* **1987**, *18*, 1376.

(9) Pellissier, H.; Santelli, M. *Org. Prep. Proc. Int.* **2001**, *33*, 1−58.

(10) Pettit, G. R.; Tan, R.; Xu, J. P.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 953 and references therein.

(11) Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978 and references therein.

(12) (a) Miayura, N.; Kochi, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 2368. (b) Krauss, H. L. *Angew. Chem.* **1958**, *70*, 502. (c) Harris, A. D.; Trebellas, J. C.; Jonassen, H. B. *Inorg. Synth.* **1967**, *9*, 83. (d) Suggs, J. W.; Ytuarte, L. *Tetrahedron Lett.* **1986**, *27*, 437.

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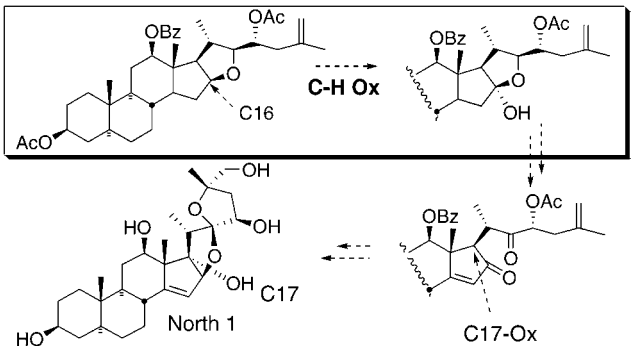
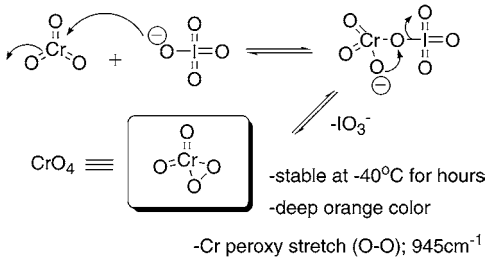
Scheme 1



spiroketal substrates underwent decomposition or isomerization due to the strong acidity of H_5IO_6 required in the catalytic protocol. Therefore, stoichiometric oxidation conditions viz. (CrO_3 (3 equiv), Bu_4NIO_4 (3 equiv), MeCN/CH_2Cl_2 (3:1, 0.1 M), −40 °C, 10 min)[14] were employed in all the C−H oxidations.

We propose that a neutral dioxo, monoperoxo CrO_4 is generated *in situ* by the reaction of CrO_3 with Bu_4NIO_4. This species, which is structurally similar to dioxiranes,[15] presumably serves as the active C−H oxidant (Scheme 2).

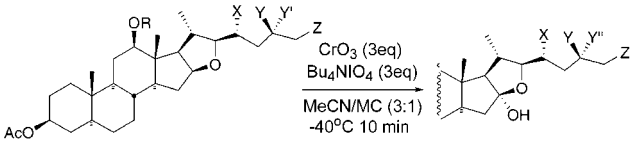
Scheme 2. Proposed Mechanism for Generation of CrO_4



The attack of the periodate on Cr followed by loss of Bu_4NIO_3 produces the dioxoperoxy Cr^{VI} species. The generated oxidant is stable at -40 °C for several hours and has an orange color typical of Cr^{VI}. A Cr peroxy stretch is observed at 945 cm^{-1} in the IR spectrum.

We first assessed the compatibility of the Cr^{VI} oxidant with various functional groups (Table 1). While acetate, benzoate, olefin, iodide, TBDPS, and tosylate functionalities (entries 1, 2, 4, 5, and 7−9) are stable to oxidation conditions, primary alcohol (entry 3) is rapidly converted to carboxylic acid along with formation of the C16−OH. The substrate bearing a TBS protecting group (entry 6) gave a low yield, due to its marginal stability under the acidic reaction conditions (pH 2). The TBDPS protected steroid (entry 7) gave substantially improved yield. Oxidation-susceptible olefin and iodide moieties (entry 1, 2, 8, and 9), which ultimately give epoxides under the influence of DMDO or *m*-CPBA, are inert under this oxidation condition, highlighting the chemoselectivity of the Cr-mediated C−H oxidation.

Table 1. Regio-, Stereo-, and Chemoselective C−H Oxidation of Steroid Substrates



entry	OR	X	Y'	Y	Y"	Z	product	yield (%)
1	OAc	OAc	=CH_2		=CH_2	H	**1**	84
2	OBz	OBz	=CH_2		=CH_2	OBz	**2**	75
3	OBz	H	CH_2OH	H	CO_2H	H	**3**	78
4	OBz	H	CH_2OAc	H	CH_2OAc	H	**4**	97
5	OAc	OAc	CH_2OTs	H	CH_2OTs	H	**5**	88
6	OBz	H	CH_2OTBS	H	CH_2OTBS	H	**6**	33
7	OBz	H	$CH_2OTBDPS$	H	$CH_2OTBDPS$	H	**7**	86
8	OBz	H	CH_2I	H	CH_2I	H	**8**	72
9	OAc	OAc	CH_2I	H	CH_2I	H	**9**	73

The value of this oxidation is its extremely mild conditions combined with exquisite selectivity. The observed retention of configuration strongly suggests that the C−H oxidation proceeds through a concerted "three center two electron" oxenoid insertion into C−H bonds rather than through radical intermediates.[16]

It has been suggested that C−H bonds aligned with oxygen atoms bearing relatively small dihedral angles (H−C−O-nonbonding electron pairs) enjoy pronounced stereoelectronic activation resulting in higher rates of hydrogen atom abstraction than other sites (Scheme 3).[17]

(13) (a) Fatiadi, A. J. *Synthesis* **1974**, 229. (b) Chaudhuri, B. K.; Mukherjee, H. G. *Indian Chem. Soc.* **1979**, *56*, 1098. (c) Rodriguez, C. M.; Ode, J. M.; Martin, V. S. *Tetrahedron* **1992**, *48*, 3571. (d) Xu, L.; Cheng, J.; Trudell, M. K. *J. Org. Chem.* **2003**, *68*, 5388. (e) Vondervoort, L. S.; Bouttemy, S.; Padron, J. M.; Muzart, J.; Alsters, P. L. *Synlett* **2002**, 243. (f) Kim, S. S.; Nehru, K. *Synlett* **2002**, 616. (g) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.

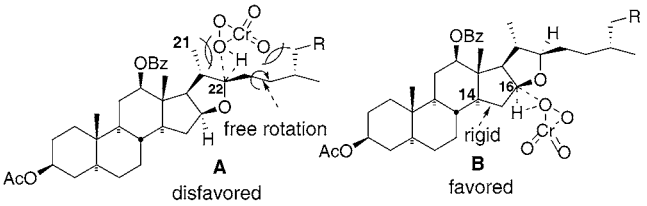
(14) **General Procedure.** Anhydrous chromium trioxide (300 mg, 3 mmol) was finely ground in CH_3CN (5.0 mL) under a positive pressure of argon or nitrogen at ambient temperature. The chromium trioxide suspension was then cooled to −40 °C, and a CH_2Cl_2 (2.5 mL) solution of a substrate (1 mmol) was added in one portion, followed by dropwise addition of a CH_3CN (2.5 mL) solution of Bu_4NIO_4 (1.30 g, 3 mmol) for 10 min. The dark orange reaction mixture was quenched by addition of saturated aqueous Na_2SO_3, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography to give a hemiacetal.

(15) (a) Frohn, M.; Wang, Z.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. (b) Zhang, L.; Lay, P. A. *Inorg. Chem.* **1998**, *37*, 1729. (c) Firouzabadi, H.; Iranpoor, N.; Kiaeezadeh, F.; Toofan, J. *Tetrahedron* **1986**, *42*, 719. (d) Bakac, A.; Wang, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 10325. (e) Valentin, C. D. Gisdakis, P.; Yudanov, I. V.; Rosch, N. *J. Org. Chem.* **2000**, *65*, 2996. (f) Shilov, A. E.; Shul'pin G. B. *Chem. Rev.* **1997**, *97*, 2879.

(16) (a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (b) Adam, W.; Asensio, G.; Curci, R. *J. Org. Chem.* **1992**, *57*, 953.

(17) (a) Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455. (b) Malatesta, V.; Ingold, K. U. *J. Am Chem. Soc.* **1981**, *103*, 609. (c) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463. (d) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122.

Scheme 3. Possible Transition States of C−H Oxidation

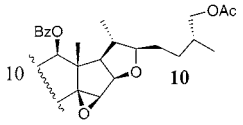
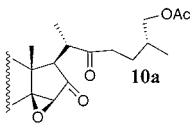
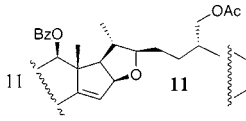
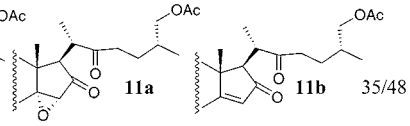
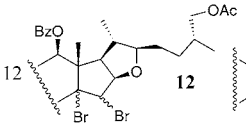
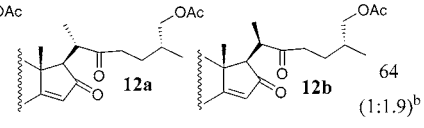
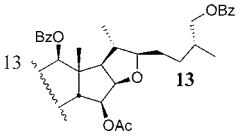
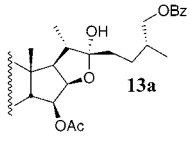


Thus, positions at C16 and C22 are both considered preferred oxidation sites. Transition state **A** is disfavored due to the presence of severe steric interaction between the approaching CrO_4 and the α-C21 methyl and free rotating C23−27 alkyl side chain. Transition state **B** offers a more accessible approach vector, so that the oxidation preferentially generates the C16 lactol.

The unusual chemoselectivity for C−H oxidation over epoxidation is in keeping with a theoretical study that Cr^{VI} peroxo species have higher calculated activation barriers for oxygen transfer to ethylene; they are less prone to epoxidation than similar Mo^{VI} and W^{VI} species.[18]

We next examined the effect of proximal C-14,15 substitution on the C16 oxidation (Table 2). Unlike the substrates

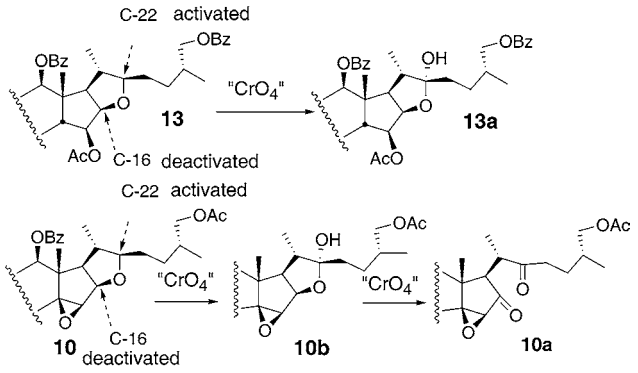
Table 2. C14,15 Substitution Effect on the C−H Oxidation

entry	substrate	product(s)	yield (%)[a]
10			79
11			35/48
12			64 (1:1.9)[b]
13			69

[a] Isolated yield. [b] Ratio determined by ^{1}H NMR integration.

which possess dihydro C-14,15 (Table 1), the presence of oxirane, olefin, and dibromides (entries 10−12) leads to E-ring opened products. The formation of **11a** can be viewed as sequential allylic oxidation, hydroxyl group directed α face epoxidation, and E-ring opening. *Substitution at C-15 with an electron-withdrawing acetate group (entry 13) dramatically changed the site of C−H oxidation.* With C-16 deactivated by the adjacent acetate group, C−H oxidation occurs at C-22 to provide hemiacetal **13a**. This result illustrates an important electronic effect on the regioselectivity of C−H oxidation. It is therefore likely that deactivation of C16 by the oxirane or dibromide moieties enables oxidations of **10** and **12** (Scheme 4) to initially take place at

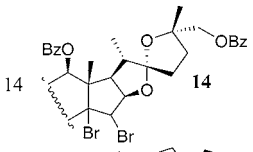
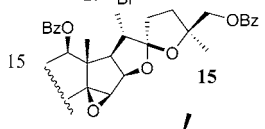
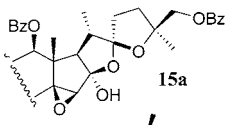
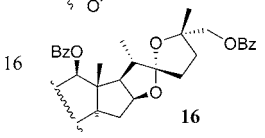
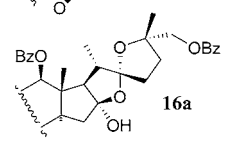
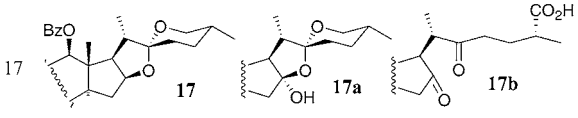
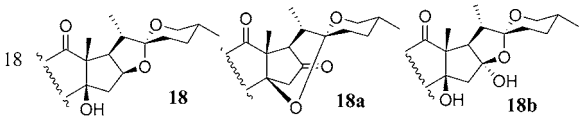
Scheme 4. Electronic Effect on the C−H Oxidation



C22. Sequential oxidation of the ω-hydroxyketone will then afford the E-ring-opened products **10a** and **12a**, respectively.

C−H oxidation of other sized spiroketals (Table 3) was also studied. In the case of dibromide **14**, no reaction

Table 3. C−H Oxidation of Steroid Spiroketals

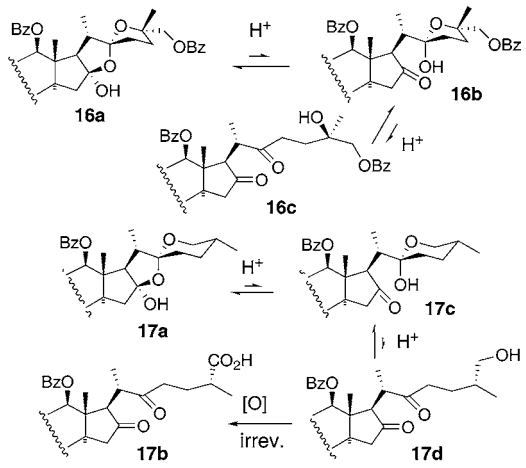
entry	substrate	product	yield (%)
14			NR[a]
15			92[b]
16			91
17			43/45
18			46/41

[a] Reaction conditions: −40 to +25 °C, 2 h. [b] −10 °C, 1 h.

(18) (a) Di Valentin, C.; Gisdakis, P.; Yudanov, I. V.; Rösch, N. *J. Org. Chem.* **2000**, *65*, 2996. (b) Dickmann, M. H.; Pope, M. T. *Chem. Rev.* **1994**, *94*, 569. (c) Amato, G.; Arcoria, A.; Ballistreri, F. P.; Tomaselli, G. A.; Bortolini, O.; Conte, V.; Di Furia, F.; Modena, G.; Valle, G. *J. Mol. Catal.* **1986**, *37*, 165. (d) Mimoun, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 734. (e) Paquette, L. A.; Kobayashi, T. *Tetrahedron Lett.* **1987**, *28*, 3531. (f) Jorgensen, K. A. *Chem. Rev.* **1989**, *89*, 431. (g) Romao, C. C.; Kuhn, F. E. Herrmann, W. A. *Chem. Rev.* **1997**, *97*, 3197.

occurred, presumably because of the combined steric and electronic effect of bromine at C-15. Stoichiometric oxidation of saturated spiroketals **15** and **16** afforded the tertiary alcohols **15a** and **16a**, respectively. It is worth noting that the oxidation of **15** which posseses an oxirane moiety, requires higher reaction temperatures and a prolonged reaction time (−10 °C, 1 h). Unlike the 5/5 spiroketals, oxidation of 5/6 spiroketal **17** results in the formation of the E-ring opened product **17b** together with the hemiacetal **17a**. The formation of **17b** is attributed to the presence of an irreversible alcohol oxidation step (**17d** to **17b** in Scheme 5) which serves to the opening of the 5-ring hemiacetal.

Scheme 5



A 5/6 spiroketal **18** with a C-14 OH group is oxidized to give the corresponding hemiacetal **18b** along with 6/6 spiroketal **18a**. The structure of **18a** has been unambiguously determined by X-ray crystallography. Oxidation of **18b**, followed by acid-catalyzed transketalization, seems to be a reasonable rationale for the formation **18a**.

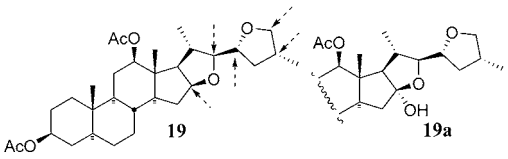
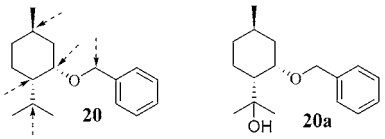
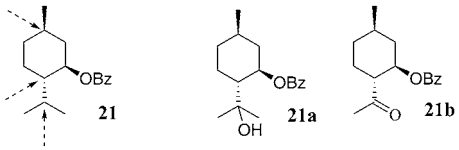
Unusual regioselectivities are observed in the case of bis-tetrahydrofuran **19** and menthol derivative **20** and **21** (Table 4). Out of many products possible (arrows shown for potential oxidation sites in Table 4), C16 hemiacetal **19a** and tertiary alcohol **20a** and **21a** are obtained as the major products. The sterically less hindered tertiary C−H bond of **20** has been oxidized preferentially over *secondary* benzylic position also adjacent to oxygen, the tertiary α position of the acyclic ether, and sterically more hindered tertiary C−H bonds. Formation of ketone **21b** presumably results from hydroxyl directed production of a 1,2-diol from **21a**, followed by oxidative cleavage.

Lastly, we compared our protocol with the highly regarded ruthenium^{VIII}-catalyzed[20] tetrahydrofuran C−H oxidation (Table 5). A hemiacetal **22a** was formed in the presence of

(19) X-ray data for compound **18a** are available from the Cambridge Crystallographic Database.

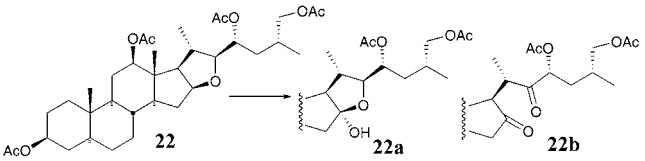
(20) (a) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Org. Chem.* **1992**, *57*, 5523. (b) Carlsen, P.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (c) Scarborough, R. M.; Smith, A. B. *J. Am. Chem. Soc.* **1980**, *102*, 3904.

Table 4. Regioselective C−H Oxidation

entry	substrate	product	yield (%)
19		**19** **19a**	62
20		**20** **20a**	76
21		**21** **21a** **21b**	66/15

RuO_2 and H_5IO_6 in 74% yield after 2 h, while prolonged reaction afforded 17% of C16, 22-diketone **22b**, probably resulting from oxidation of the ω-hydroxyketones in equilibrium with the initially produced hemiacetals. In the case of Cr^{VI}-mediated oxidation, hemiacetal **22a** or diketone **22b** was selectively produced under milder reaction conditions.

Table 5. Cr^{VI}- vs Ru^{VIII}-Mediated C−H Oxidation



entry	conditions	**22a** (%)/**22b** (%)
22	CrO_3/Bu_4NIO_4 (3 equiv), MeCN/MC, −40 °C, 10 min	92/0
23	CrO_3/Bu_4NIO_4 (3 equiv), MeCN/MC, −40 to −20 °C, 2 h	28/62
24	CrO_3/Bu_4NIO_4 (5 equiv), MeCN/MC, −40 to −20 °C, 2 h	0/84
25	RuO_2 (5 mol %), H_5IO_6 (5 equiv), CCl_4/MeCN/H_2O, 25 °C, 2 h	74/0
26	RuO_2 (5 mol %), H_5IO_6 (5 equiv), CCl_4/MeCN/H_2O, 25 °C, 24 h	55/17

In summary, the Cr^{VI} C−H oxidant offers strong inducement to further understand the scope and limitations of this powerful and selective reagent.

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Supporting Information Available: General experimental procedure and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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