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Chemoselective Aliphatic C−H Bond Oxidation Enabled by Polarity Reversal

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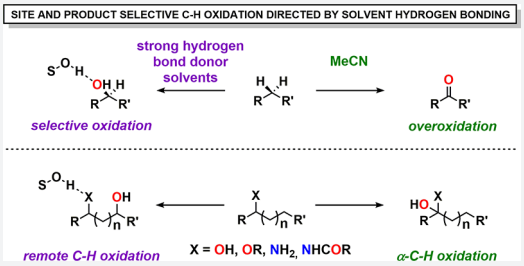
Supporting Information

ABSTRACT: Methods for selective oxidation of aliphatic C−H bonds are called on to revolutionize organic synthesis by providing novel and more efficient paths. Realization of this goal requires the discovery of mechanisms that can alter in a predictable manner the innate reactivity of these bonds. Ideally, these mechanisms need to make oxidation of aliphatic C−H bonds, which are recognized as relatively inert, compatible with the presence of electron rich functional groups that are highly susceptible to oxidation. Furthermore, predictable modification of the relative reactivity of different C−H bonds within a molecule would enable rapid diversification of the resulting oxidation products. Herein we show that by engaging in hydrogen bonding, fluorinated alcohols exert a polarity reversal on electron rich functional groups, directing iron and manganese catalyzed oxidation toward a priori stronger and unactivated C−H bonds. As a result, selective hydroxylation of methylenic sites in hydrocarbons and remote aliphatic C−H oxidation of otherwise sensitive alcohol, ether, amide, and amine substrates is achieved employing aqueous hydrogen peroxide as oxidant. Oxidations occur in a predictable manner, with outstanding levels of product chemoselectivity, preserving the first-formed hydroxylation product, thus representing an extremely valuable tool for synthetic planning and development.



Selective oxidation of unactivated aliphatic C−H bonds constitutes a potentially very useful reaction because it introduces functionality in otherwise inert aliphatic skeletons.[1−4] However, the differentiation among multiple C−H bonds with powerful oxidizing agents and predictability in site selectivity are often unsurmountable problems that prevent the widespread incorporation of these reactions in synthetic planning. Another critical issue is represented by product chemoselectivity because the first formed products are generally more susceptible to oxidation than the starting substrate, and they are thus overoxidized or obtained in relatively low yield, a problem that is commonly encountered in the hydroxylation of methylenic C−H bonds, which in fact constitute the most represented aliphatic unit in organic molecules.[5]

In order to fully develop the power of C−H bond oxidation in organic synthesis, intense research efforts have been devoted to uncover the factors that govern C−H bond reactivity, pointing toward the important role played by bond strengths as well as by steric, electronic, stereoelectronic, and torsional effects in these processes.[2,6,7] On the basis of these elements, C−H bonds are recognized to bear an innate relative reactivity against oxidizing agents,[8] which defines the site selectivity in the oxidation of molecules containing different C−H bonds. However, this is basically unaffected by the nature of the oxidant, a factor that effectively limits the potential of the reaction. Since C−H oxidizing species generally display a strong electrophilic character, C−H bonds in proximity to electron donating groups such as those of amines, amides, ethers, and alcohols are more reactive toward these reagents than those close to electron withdrawing groups, which are instead deactivated.[9] Efforts have also been devoted to modify the innate relative reactivity of C−H bonds by introducing directing groups.[10−15] Alternatively, interaction of Lewis or Brønsted acids with amines builds up positive charge onto these groups and deactivates via polarity reversal the adjacent C−H bonds, directing oxidation to the most remote and less deactivated C−H bonds.[7,16−18]

Recently, kinetic studies on hydrogen atom transfer (HAT) from aliphatic C−H bonds to the cumyloxy radical (CumO$^{\bullet}$) have shown that fluorinated alcohols can strongly influence the HAT reactivity.[7,19] With substrates bearing hydrogen bond acceptor (HBA) functional groups, a decrease in the rate constant for HAT from the aliphatic C−H bonds to CumO$^{\bullet}$ was measured on going from acetonitrile to 2,2,2-trifluoroethanol (TFE), with the observed decrease in rate being dependent on the functional group HBA ability. This behavior was explained in terms of solvent hydrogen bonding to the substrate HBA center that, by increasing the extent of positive charge on the functional group, reverses the polarity of the

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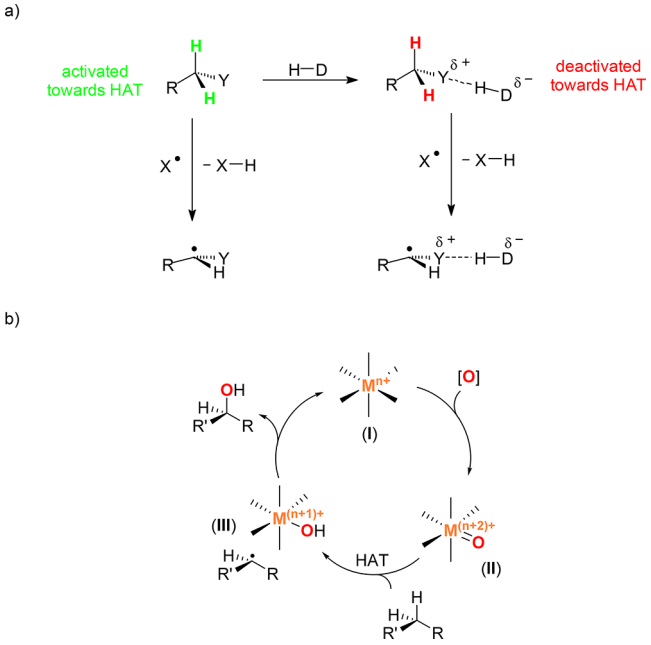
proximal C−H bonds that are thus deactivated toward HAT to the electrophilic CumO• (Scheme 1a, where Y represents an HBA group, H−D an HBD solvent, and X• = CumO•).

Scheme 1. (a) Schematic Diagram of the Polarity Reversal Concept and (b) Simplified C−H Hydroxylation Mechanism, Entailing Initial Hydrogen Atom Transfer (HAT) from a Substrate C−H Bond to High Valent Metal−Oxo Species II



Along similar lines, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was shown to promote selective benzylic C−H oxidation of methylarenes to benzaldehydes via HAT to the phthalimide *N*-oxyl radical. In this case, hydrogen bonding to the oxygen atom of the first formed aldehyde product deactivates the formylic C−H toward HAT, preventing overoxidation to the carboxylic acid.[20,21]

We envisioned that these effects could offer a tool to manipulate the relative reactivity of aliphatic C−H bonds in metal catalyzed oxidations, where the reaction is initiated by HAT from the substrate to a high valent metal−oxo species (Scheme 1b).[22,23] With these bonds site-selectivity and product chemoselectivity are far more challenging than in the oxidation of benzylic C−H bonds because more powerful oxidants are typically required. With these concepts in hand, herein we show that fluorinated alcohol solvents strongly deactivate electron rich functional groups by virtue of hydrogen bonding interactions directing iron and manganese catalyzed oxidation toward a priori stronger and unactivated C−H bonds. As a result, selective hydroxylation of methylenic sites in hydrocarbons and remote C−H oxidation of alcohol, ether, amide, and amine substrates can be accomplished. Oxidations occur in a predictable manner, with outstanding levels of product chemoselectivity, preserving the first-formed hydroxylated product, thus representing an extremely valuable tool for synthetic planning.

RESULTS AND DISCUSSION

We initiated our study by analyzing the oxidation of a model alkane substrate (hexane, **1**) with H_2O_2 (0.2 equiv) using 1 mol % of catalyst [Fe(CF_3SO_3)$_2$(pdp)] (**Fe(pdp)**) and [Mn(CF_3SO_3)$_2$(pdp)] (**Mn(pdp)**) (Scheme 2a).[24,25] Reactions were performed in MeCN, TFE, and HFIP as solvents. Results are collected in Scheme 2b. In all cases, mixtures of 2-hexanol (**1a**), 3-hexanol (**1b**), 2-hexanone (**1c**), and 3-hexanone (**1d**) were obtained, but most interestingly, the relative alcohol to ketone ratios are largely dependent on the solvent. In MeCN, the reaction with **Fe(pdp)** (entry 1) provides oxidation products with an overall 54% yield, and the sum of the two alcohols (**1a** and **1b**) represents 46% of the products. Related values were observed with **Mn(pdp)** (entry 4, 52% yield, 38% selectivity toward the alcohols). The product pattern observed under these experimental conditions is in good agreement with literature precedents and can be rationalized considering the easier oxidation of the alcohol as compared to the hydrocarbon substrate.[24,25] When the same reactions were performed in TFE or HFIP (entries 2 and 3 for **Fe(pdp)** and 5 and 6 for **Mn(pdp)**), selectivity patterns changed in a very remarkable manner. In TFE, selectivity toward the alcohol products increases up to 86% and 92% for the iron and manganese catalyst (entries 2 and 5), and to an outstanding 98−99% in HFIP (entries 3 and 6). Remarkably, the use of a typical oxidation catalyst such as the porphyrin-based [Mn(TCPP)Cl] in combination with iodosylbenzene as oxidant, commonly used together with these complexes,[26] exhibits an analogous reactivity pattern. [Mn(TCPP)Cl] afforded the alcohol and ketone products in a 3:2 ratio and an overall 14% yield in MeCN, and only alcohol products (6% yield) in HFIP (see Table S1).

Further optimizations were performed in TFE and involved the screening of different catalysts structurally related to Fe- and Mn-based pdp complexes (see Scheme 2a and Tables S2 and S3).[12] **Fe(mcp)** and **Mn(mcp)** provide slightly reduced yields, while retaining or further improving the high chemoselectivity toward the alcohol products. Iron catalysts bearing electron rich pyridine ligands (**Fe(**^{dMM}**pdp)** and **Fe(**^{dMM}**mcp)**) exhibit improved selectivities toward the alcohol (93 and 91%), while the opposite effect is observed when an electron withdrawing group is installed on the pyridine ligand (80% for **Fe(**^{Cl}**pdp)**). Of notice, selectivities toward the alcohols observed with the manganese catalysts are less sensitive to analogous changes in the electronic properties of the pyridines, and remain high (≥93%) in all cases. Finally, catalysts bearing pyridines with sterically bulky silyl groups were explored.[12,27] Gratifyingly, **Fe(**^{TIPS}**mcp)** and **Mn(**^{TIPS}**mcp)** provided the highest product yields of the series (entries 7 and 8, 63 and 58%, respectively) while retaining very high chemoselectivity toward the alcohols (91 and 96%). With the optimal catalysts in hand, the impact of the solvent was further analyzed (entries 9−14, reactions run at 0 °C), employing lower catalyst loading (0.5 mol % was chosen after optimization) and a larger amount of H_2O_2 (0.5 equiv), which represents a more challenging condition because the larger amount of oxidant should favor overoxidation. For both catalysts, in MeCN, alcohols were obtained as minor products: 16% for **Fe(**^{TIPS}**mcp)** (entry 9) and 19% for **Mn(**^{TIPS}**mcp)** (entry 12). Instead, in TFE (entries 10 and 13), chemoselectivities were high: 86 and 89% for **Fe(**^{TIPS}**mcp)** and **Mn(**^{TIPS}**mcp)**, respectively. Most remarkably, in HFIP (entries 11 and 14) alcohols were obtained with outstanding selectivities (97%). Considering the slightly improved performance of **Mn(**^{TIPS}**mcp)**, this catalyst was chosen for further development of the reaction. Control

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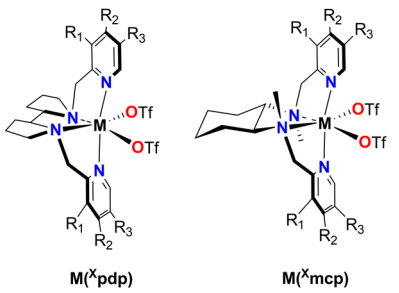
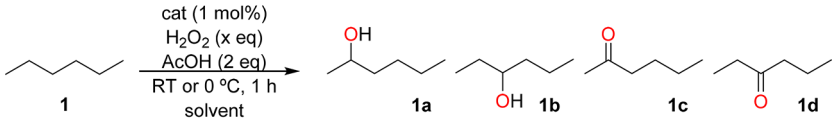
Scheme 2. (a) Catalysts Employed in This Work and (b) Optimization of Reaction Conditions for the Oxidation of Hexane (1)

a)



	R_1	R_2	R_3
Fe(pdp)	H	H	H
Mn(pdp)	H	H	H
Fe(mcp)	H	H	H
Mn(mcp)	H	H	H
Fe(^{dMM}pdp)	Me	MeO	Me
Mn(^{dMM}pdp)	Me	MeO	Me
Fe(^{dMM}mcp)	Me	MeO	Me
Mn(^{dMM}mcp)	Me	MeO	Me
Fe(^{Cl}pdp)	H	Cl	H
Mn(^{Cl}mcp)	H	Cl	H
Fe(^{TIPS}pdp)	H	H	Si(*i*Pr)$_3$
Fe(^{TIPS}mcp)	H	H	Si(*i*Pr)$_3$
Mn(^{TIPS}mcp)	H	H	Si(*i*Pr)$_3$
Mn(^{Me2N}pdp)	H	Me_2N	H

b)



Entry	Catalyst	H_2O_2 (equiv)	Yield (%)[a] (% alcohol)[b]	Solvent
1	**Fe(pdp)**	0.2	54(46)	MeCN
2		0.2	58(86)	TFE
3		0.2	86(98)	HFIP
4	**Mn(pdp)**	0.2	52(38)	MeCN
5		0.2	41(92)	TFE
6		0.2	66(99)	HFIP
7	**Fe(^{TIPS}mcp)**	0.2	63(91)	TFE
8	**Mn(^{TIPS}mcp)**	0.2	58(96)	TFE
9[c]	**Fe(^{TIPS}mcp)**	0.5	59(16)	MeCN
10[c]		0.5	48(86)	TFE
11[c]		0.5	**69(97)**	**HFIP**
12[c]	**Mn(^{TIPS}mcp)**	0.5	56(19)	MeCN
13[c]		0.5	59(89)	TFE
14[c]		0.5	**59(97)**	**HFIP**

[a]With respect to H_2O_2, determined by GC-FID against an internal standard. Yields are calculated considering that 2 equiv of H_2O_2 are necessary for the formation of the ketone products (**1c** and **1d**). [b]100 × ([**1a**] + [**1b**])/([**1a**] + [**1b**] + [**1c**] + [**1d**]). [c]0.5 mol % catalyst was used; oxidations performed at 0 °C. Full details on the product distributions are provided in Table S1.

experiments indicated that no oxidation products were formed in the absence of the catalysts (see Table S4).

The high preference for the alcohol product in the oxidation of hexane in fluorinated alcohols is outstanding and unprecedented. Indeed, the hydroxylation of methylenic sites with high product chemoselectivity is a long-standing goal in C−H oxidations, because the resulting secondary alcohol is usually oxidized to the corresponding ketone under the reaction conditions, a process that can lead to loss of stereochemistry.[5,28,29] TFE and HFIP engage in hydrogen bonding with the first formed alcohol product, thus preventing overoxidation to the ketone via polarity reversal and consequent deactivation of the α-C−H bond (Scheme 1a, Y = OH, H−D = TFE or HFIP, X$^{\bullet}$ = high valent metal−oxo species (**II** in Scheme 1b)). This picture is nicely supported by the stronger HBD ability of HFIP as compared to TFE (quantified on the basis of Abraham's α_2^H parameter: α_2^H = 0.771 and 0.567 for HFIP and TFE, respectively),[30] that accordingly leads in all cases to significantly higher selectivities for the alcohol product in HFIP. Thus, the current reaction provides a unique entry into highly chemoselective hydrocarbon hydroxylation.

A series of cyclic and bicyclic alkane substrates containing methylenic sites were then submitted to the optimized conditions. Results are collected in Table 1 and highlight the generality of the above-described observations. Oxidation of cyclohexane (**2**, entry 1) in MeCN gives preferentially cyclohexanone **2b** over cyclohexanol **2a** (**2a**:**2b** = 0.7) in 67% yield. Instead, in TFE the product chemoselectivity toward the alcohol is dramatically altered (**2a**:**2b** = 23, entry 2), and the effect is further enhanced in HFIP (entry 3), where **2a** accounts for 97% of the oxidation products. Analogous observations are noted in the oxidation of cyclooctane (**3**), where cyclooctanol **3a** is obtained as the major product in MeCN, with a modest selectivity over cyclooctanone **3b** (55%, entry 4), that increases in TFE (77%, entry 5) and HFIP (85%, entry 6). Oxidation of norbornane **4** is particularly interesting. In MeCN (entry 7) oxidation produces the *exo* alcohol **4a**$_{exo}$, with >99% selectivity over the *endo* alcohol **4a**$_{endo}$, along with the corresponding ketone **4b** (**4a**$_{exo}$:**4b** = 1.3). Reactions in TFE and HFIP increase both yield (entries 8 and 9, 82 and 80%, respectively) and chemoselectivity for **4a**$_{exo}$ (**4a**$_{exo}$:**4b** = 14.4 and 18 for TFE and HFIP, respectively), without altering the selectivity over **4a**$_{endo}$. Of notice, the large **4a**$_{exo}$/**4a**$_{endo}$ ratio reflects the hydroxylation stereospecificity, in good agreement with

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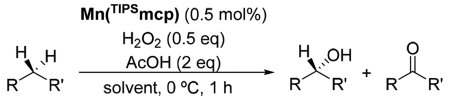
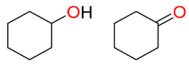
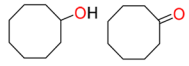
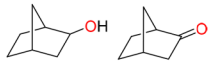
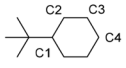
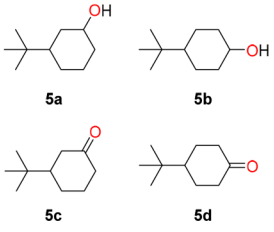
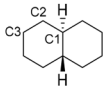
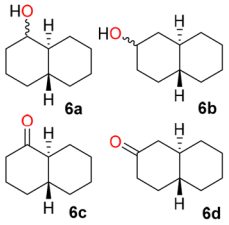
Table 1. Oxidation of Methylenic C−H Bonds of Hydrocarbons in Different Solvents



Entry	Substrate	Products	Solvent	Product yields (%)[a]	Yield (%)[a]	Hydroxylation selectivity (%)
				2a/2b		
1			MeCN	17/50	67	40
2			TFE	68/6	74	96
3	**2**	**2a** **2b**	HFIP	68/4	72	97
				3a/3b[b]		
4			MeCN	24/28	58	55
5			TFE	48/4	64	77
6	**3**	**3a** **3b**	HFIP	47/2	56	85
				4a[c]**/4b**		
7			MeCN	24/36	60	57
8			TFE	72/10	82	94
9	**4**	**4a** **4b**	HFIP	72/8	80	95
				5a[d]**/5b**[e]**/5c/5d**		
10			MeCN	13/5/36/12	66	44
11			TFE	51/18/4/2	75	96
12	**5**	**5a** **5b** **5c** **5d**	HFIP	62/23/2/2	89	98
				6a[f]**/6b**[g]**/6c/6d**		
13			MeCN	8/13/12/26	59	53[c]
14			TFE	23/33/4/2	62	95[c]
15	**6**	**6a** **6b** **6c** **6d**	HFIP	28/36/2/2	68	97[c]

[a]With respect to H_2O_2, determined by GC-FID against an internal standard. Yields are calculated considering that 2 equiv of H_2O_2 are necessary for the formation of the ketone products. [b]6−12% cyclooctene oxide formed. [c]$\mathbf{4a}_{exo}$ is obtained with >99 selectivity over $\mathbf{4a}_{endo}$ in all solvents. [d]**5a** is obtained as a mixture of axial and equatorial alcohol products. $\mathbf{5a}_{ax}$:$\mathbf{5a}_{eq}$ ratios are 1:5, 1:3, and 1:3 for MeCN, TFE, and HFIP, respectively. [e]**5b** is obtained as a mixture of axial and equatorial alcohol products. $\mathbf{5b}_{ax}$:$\mathbf{5b}_{eq}$ ratio is 2:3 in all solvents. [f]**6a** is obtained as a mixture of axial and equatorial alcohol products. $\mathbf{6a}_{ax}$:$\mathbf{6a}_{eq}$ ratios are 1:3, 1:5, and 1:2 for MeCN, TFE, and HFIP, respectively. [g]**6b** is obtained as a mixture of axial and equatorial alcohol products. $\mathbf{6b}_{ax}$:$\mathbf{6b}_{eq}$ ratios are 1:2, 1:2, and 2:5 for MeCN, TFE, and HFIP, respectively.

previous mechanistic studies in MeCN for these types of catalysts.[31,32]

Oxidation of *tert*-butylcyclohexane (**5**) is also very interesting. Products resulting from oxidation at C1, C2, and the *t*Bu moiety are not observed, reflecting a combination of steric, stereoelectronic, torsional, and bond strength contributions. As expected, oxidation concentrates at C3 and C4 and in HFIP provides alcohols **5a** and **5b** over ketones **5c** and **5d** with 98% selectivity (entry 12), in sharp contrast with the results obtained in MeCN (entry 10) and those of previous studies on the oxidation of **5** by HAT reagents where predominant formation of the ketone products was observed.[5,12,33] The ratio for oxidation at C3 (**5a** + **5c**) and C4 (**5b** + **5d**) is ∼3. By taking into account the different number of C−H bonds at C3 and C4, these values denote a slight preference for oxidation at the former site, in line with previous findings.[5,12,33] Equatorial alcohols are formed preferentially over axial ones ($\mathbf{5a}_{eq}$:$\mathbf{5a}_{ax}$ = 3 and $\mathbf{5b}_{eq}$:$\mathbf{5b}_{ax}$ = 1.5 in HFIP), a behavior that reasonably reflects the higher reactivity of equatorial C−H bonds toward HAT reagents.[34,35]

Finally, oxidation of *trans*-decalin (**6**) yields a mixture of alcohol (**6a** and **6b**) and ketone (**6c** and **6d**) products from oxidation at C2 and C3 methylenic sites (entries 13−15). In HFIP, **6a** and **6b** account for 97% of the oxidation products, and are obtained in 64% yield. Oxidation at C3 appears to be slightly favored over C2, presumably because the latter is sterically more encumbered. Most interestingly, hydroxylation occurs preferentially at the equatorial over the axial C−H bond ($\mathbf{6a}_{eq}$:$\mathbf{6a}_{ax}$ = 2 and $\mathbf{6b}_{eq}$:$\mathbf{6b}_{ax}$ = 2.5).

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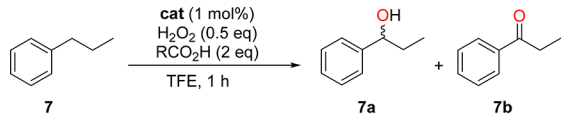
The unique chemoselectivity attained in fluorinated alcohols suggests that enantioselective hydroxylation of methylenic sites may be possible in these solvents without requiring large excess of the substrate due to the chiral nature of the catalysts. Oxidation of propylbenzene (**7**) with 1 mol % catalyst, 0.5 equiv of H_2O_2, and 2 equiv of AcOH in TFE led to the formation of the corresponding benzylic alcohol (**7a**) in 92% selectivity but with a modest 8% ee (Scheme 3). However,

Scheme 3. Oxidation of Propylbenzene (7) in TFE with Different Catalysts[a]



Mn(TIPSmcp) / AcOH / 0 °C	12% (8% ee)	2%
Mn(dMMpdp) / 2-eha / -35 °C	24% (66% ee)	2%
Mn(Me2Npdp) / 2-eha / -35°C	44% (60% ee)	7%

[a]Yields (with respect to H_2O_2) are shown below each of the products (**7a** and **7b**), and the enantiomeric excess of **7a** is written in parentheses.

catalyst screening using different **Mn(**^{X}**mcp)** and **Mn(**^{X}**pdp)** complexes and optimization of both the nature of the carboxylic acid additive and the temperature enabled the ee to be significantly increased while the selectivity for the alcohol product was kept above 90% (see Table S7). The best results were obtained with 2-ethylhexanoic acid in combination with **Mn(**^{dMM}**pdp)** or **Mn(**^{Me2N}**pdp)** at −35 °C, which afforded 1-phenyl-1-propanol with an enantiomeric excess of 66% and 60%, respectively (Scheme 3 and Table S8). Under identical experimental conditions, comparable ee's were also observed in the oxidation of ethylbenzene and *p*-methylethylbenzene (Table S7). For comparison, when the same reaction was performed in MeCN with the **Mn(**^{Me2N}**pdp)** catalyst under analogous reaction conditions, the ketone is the largely dominant product (7% of **7a** (10% ee) and 39% of **7b**).

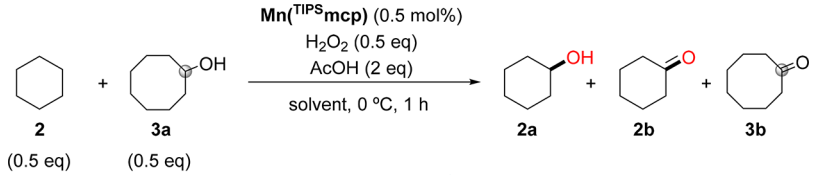
Most importantly, as compared to previous examples of HAT based enantioselective benzylic oxidation,[36] the results obtained in this study clearly indicate that the use of fluorinated alcohols preserves the first formed chiral alcohol from overoxidation, avoiding moreover the use of relatively large substrate/oxidant ratios.

Intermolecular competition experiments were also carried out, in order to evaluate the relative reactivity of the substrate C−H and product HOC−H bonds under the reaction conditions. For this purpose, oxidation of a 1:1 mixture of cyclohexane (**2**) and cyclooctanol (**3a**) was carried out in MeCN, TFE, and HFIP (Scheme 4). In MeCN, the main product (47% yield) corresponded to cyclooctanone (**3b**), derived from oxidation of **3a**, while smaller amounts of cyclohexane oxidation products (**2a** and **2b**) were obtained (8% combined yield). In fluorinated alcohols, the reactivity trend was completely reversed and the hydroxylation of **2** was preferential so that 31% and 34% yield of **2a** was obtained in TFE and HFIP, respectively. Product **3b** was obtained in only 10% and 4% yield, along with trace amounts of cyclooctanediol products **3c** and **3d** (*vide infra*). The complementary experiment using cyclohexanol (**2a**) and cyclooctane (**3**) as substrates (see Scheme S2) led to similar results, confirming that in fluorinated solvents C−H bonds are preferentially oxidized over HOC−H bonds. These results further demonstrate that by deactivating the C−H bond α to the OH group fluorinated alcohols exert a protective role, thus making oxidation of the first formed alcohol product much more difficult than in non-HBD or weaker HBD solvents.

Further studies investigated the impact of TFE and HFIP on the intramolecular selectivity in the oxidation of alcohol substrates, i.e., in modulating the relative reactivity of unactivated aliphatic C−H bonds versus secondary and primary alcohol functionalities placed on the same molecule (Scheme 5 and Scheme S4). Oxidation of 3-hexanol (**8**) in MeCN forms 3-hexanone (**8a**) in 76% yield as the only detectable product, but oxidation at the most remote methylenic site to form 2,4-hexanediol (**8b**) becomes a competitive path in the fluorinated alcohols, accounting for 20% of the oxidation products in HFIP. Oxidation of alcohols with longer alkyl chains evidence more substantial changes in the reaction selectivity. Thus, 1-hexanol (**9**) is oxidized in MeCN to hexanal (**9a**) and hexanoic acid (**9b**) in 66% combined yield. However, in HFIP, remote methylenic oxidation produces 1,5-hexanediol (**9c**) with 82% selectivity. Oxidations of 2-heptanol (**10**) and 2-octanol (**11**) follow an analogous pattern. Exclusive formation of 2-heptanone (**10a**) and 2-octanone (**11a**) is obtained in MeCN, while 2,6-heptanediol (**10b**) and 2,7-octanediol (**11b**) are the major products (75% and 93% selectivity, respectively) in HFIP. Of notice, in fluorinated alcohols, yields and selectivities for oxidation at the remote methylenic positions increase on going from **8** to **11**. In addition to the above-mentioned α-C−H bond deactivation via solvent hydrogen bonding, this trend also reflects remote C−H deactivation that decreases with increasing distance from the hydroxyl group.

Oxidation of cycloalkanols further illustrates the α-C−H bond deactivation determined by fluorinated alcohols. Oxidation of cyclohexanol (**2a**) in MeCN provides cyclohexanone (**2b**) with excellent chemoselectivity. However, competitive hydroxylation at the most remote C4-methylenic site takes place in HFIP, producing approximately a 1:1 mixture of *cis*- and *trans*-1,4-cyclohexanediols (**2c**), accounting for 45%

Scheme 4. Competitive Oxidation of Cyclohexane (2) and Cyclooctanol (3a) in Different Solvents[a]



MeCN	4%	4%	47%
TFE	31%	6%	10%
HFIP	34%	2%	4%

[a]Yields (with respect to H_2O_2) are shown below each of the products (**2a**, **2b**, and **3b**).

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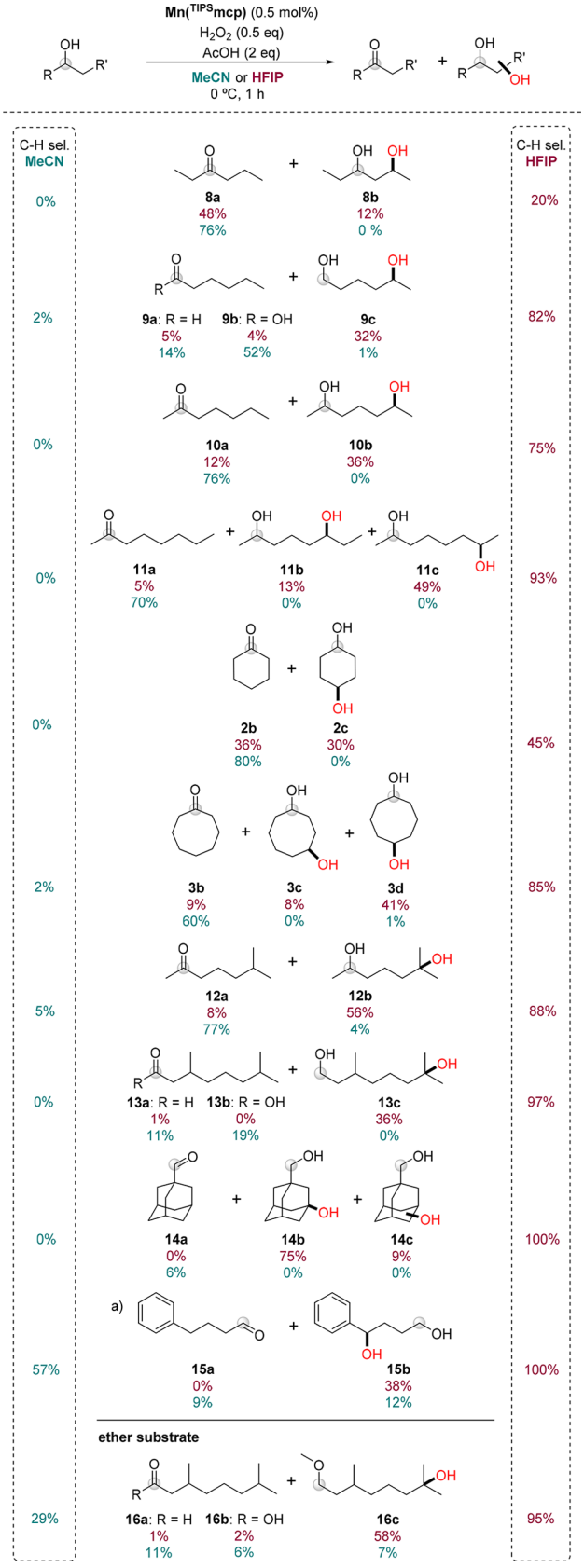
Scheme 5. Impact of the Solvent on the Catalytic Oxidation of Alkanols[a]



[a]Yields (with respect to H_2O_2) are shown below each of the products (purple: yields obtained in HFIP, green: yields obtained in MeCN). [a]**Mn(**^{Me2N}**pdp)** was used as catalyst in this case.

of the oxidation products. As observed with the linear alcohols, deactivation determined by solvent hydrogen bonding decreases with increasing distance from the hydroxyl group and, accordingly, the most remote methylenic sites become the preferred competitive oxidation sites. Thus, oxidation of cyclooctanol (**3a**) changes from nearly exclusive formation of cyclooctanone (**3b**) in MeCN to selective formation of 1,5-cyclooctanediol (**3c**), along with minor amounts of 1,4-cyclooctanediol in HFIP (85% selectivity).

Alkanols containing more reactive remote tertiary C−H bonds exhibit even higher hydroxylation selectivities. 6-Methyl-2-heptanol (**12**) afforded 2-methylheptane-2,6-diol (**12b**) as the predominant product in HFIP (88% selectivity), while in MeCN it only represented 5% of oxidized products, which were mainly represented by 6-methyl-2-heptanone (**12a**). The primary alcohol **13**, containing two tertiary C−H bonds, in MeCN gave exclusively the corresponding aldehyde (**13a**) or carboxylic acid (**13b**) products derived from the oxidation of the alcohol functionality. In contrast, oxidation at the tertiary C−H bond located further away from the alcohol was almost exclusively observed in HFIP (97% selectivity). A similar situation was found when 1-adamantanemethanol (**14**) was used as substrate: exclusive formation of the aldehyde product was observed in MeCN whereas only products deriving from hydroxylation of the adamantane C−H bonds were detected in HFIP. In the latter case and as expected, hydroxylation of tertiary C−H bonds (**14b**) was preferred over secondary ones (**14c**) in a combined 84% yield. With 4-phenyl-1-butanol (**15**), reaction in MeCN afforded an almost equimolar mixture of the aldehyde (**15a**) and 4-phenyl-1,4-butanediol (**15b**) products in a 21% combined yield. Benzylic hydroxylation was exclusively observed in HFIP to give diol **15b** in moderate yield (38%). In this case, **Mn(**^{Me2N}**pdp)** was used as catalyst because, as described above for the oxidation of **7**, in benzylic C−H hydroxylations, this complex affords significantly higher yields as compared to **Mn(**^{TIPS}**mcp)**. Finally, oxidation of substrate **16**, containing a methyl ether functionality instead of an alcohol, in MeCN yielded the corresponding aldehyde and carboxylic acid (**16a** and **16b**) as major products, presumably formed via the initial hydroxylation of the activated α-C−H bonds of the methyl ether moiety. Hydrolysis of the resulting α-hydroxy ether will produce the corresponding aldehyde (**16a**), which can be further oxidized to the carboxylic acid (**16b**). The ether functionality was instead preserved in HFIP, and hydroxylation at the remote tertiary C−H bond (**16c**) was accomplished in 58% yield and 95% selectivity.

Finally, we considered the use of fluorinated alcohols as a tool for deactivating C−H bonds that are adjacent to other HBA groups, directing oxidation toward remote C−H bonds (Scheme 6). Interestingly, oxidation of amides also evidences a powerful role of the fluorinated solvents in dictating site selectivity in line with the results obtained previously on the reactions of alkanamides with CumO$^{\bullet}$,[19] where strong deactivation toward HAT of the C−H bonds that are α to the amide nitrogen was observed in TFE. Oxidation of amides was carried out using a large excess of acetic acid (13 equiv), which was necessary to maximize product yields as previously reported by some of us.[12] Oxidation of *N*-pentylacetamide (**17**) in MeCN occurs preferentially at the activated methylenic site α to the amide nitrogen providing hydroxylated product **17a**.[37]

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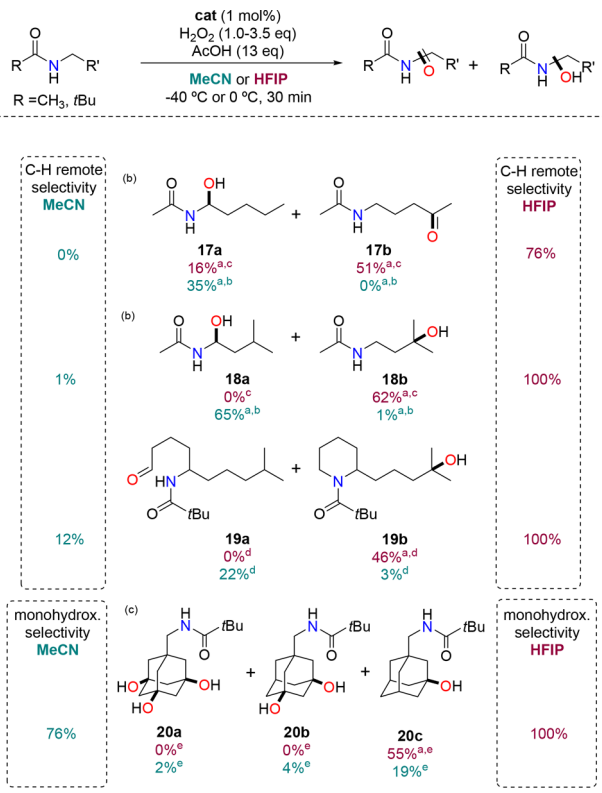
Scheme 6. Impact of the Fluorinated Alcohols on the Catalytic Oxidation of Amides[a]

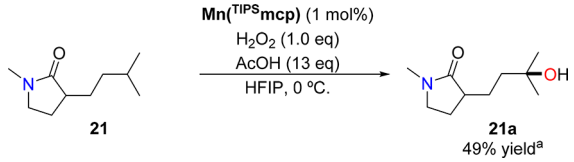


[a]Yields (calculated with respect to the substrate) are shown below each of the products (green: yields obtained in MeCN, purple: yields obtained in HFIP). [a]Isolated yield. Reaction conditions: [b]**Mn(**^{dMM}**pdp)** (1 mol %), H_2O_2 (3.5 eq), AcOH (13 eq), MeCN, −40 °C. [c]**Mn(**^{TIPS}**mcp)** (1 mol %), H_2O_2 (3.5 eq), AcOH (13 eq). HFIP, 0 °C. [d]**Mn(**^{dMM}**pdp)** (1 mol %), H_2O_2 (1.0 eq), AcOH (13 eq), MeCN or HFIP, 0 °C. [e]**Mn(**^{TIPS}**mcp)** (1 mol %), H_2O_2 (1.0 eq), AcOH (13 eq), MeCN or HFIP, 0 °C.

When the same reaction is performed in HFIP, ketoamide **17b** resulting from oxidation of the most remote methylenic site is also formed as the major product in 51% yield. In this case, formation of the δ-C═O in **17b** instead of the hydroxyl group is not understood and, indeed, lowering the amount of oxidant to prevent overoxidation did not change the outcome of the reaction. Oxidation of amide **18** features competition between the α-C−H bond and a remote tertiary γ-C−H bond. In MeCN, oxidation occurs almost exclusively at the most activated α-C−H bond to form product **18a** in 65% yield.[37] A complete reversal in site selectivity is observed in HFIP, where **18b** is exclusively formed in 62% yield. Similary, in MeCN, amide **19**, bearing a remote tertiary C−H bond in the ε position with respect to the amide group,[16] almost exclusively afforded formyl amide **19a** following ring opening of the first formed product deriving from hydroxylation of the secondary α-C−H bond. In HFIP, exclusive formation of product **19b** deriving from hydroxylation of the remote tertiary C−H bond was instead observed. Furthermore, the oxidation of *N*-1-adamantylmethyl pivalamide **20** in MeCN results in a mixture of products deriving from hydroxylation of two (**20b**) and three (**20c**) tertiary C−H bonds of the adamantane core. Instead, when the reaction is performed in HFIP, exclusive formation of monohydroxylated product **20a** is observed in 55% yield. This result evidences a synergistic deactivating role of the amide and hydroxyl groups upon hydrogen bonding to the fluorinated alcohol.

Selective hydroxylation of lactam **21** at the remote tertiary C−H bond, which has been recently accomplished through oxygen methylation,[38] was successfully achieved in HFIP to form **21a** in 49% yield, without the need of covalent modification of the substrate (Scheme 7).

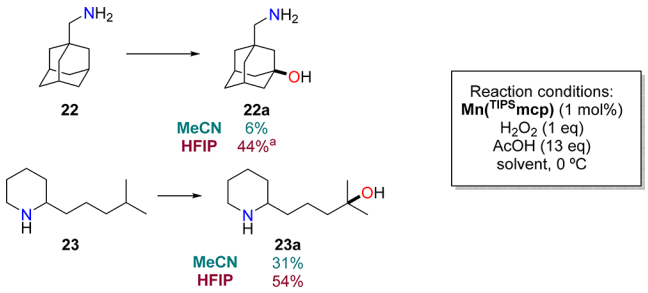
Scheme 7. Oxidation of Lactam 21 in HFIP, without Covalent Modification



[a]Isolated yield.

Primary and secondary amines could also be successfully hydroxylated in fluorinated solvents (Scheme 8). Most

Scheme 8. Impact of Fluorinated Solvents on the Catalytic Oxidation of Amines[a]



[a]Yields (calculated with respect to the substrate) are shown below each of the products (green, MeCN; purple, HFIP). [a]Isolated yield

remarkably, in HFIP, 1-admantylmethylamine (**22**) and 2-(4-methylpentyl)piperidine (**23**) were hydroxylated at the tertiary adamantane C−H bonds and most remote tertiary C−H bond, respectively, to furnish the corresponding aminoalcohols (**22a** and **23a**) in 44% and 54% yield, respectively, again without the need to deactivate the amine functionality via a covalent modification.

CONCLUSIONS

The origin of the effect of fluorinated alcohols in modulating the relative reactivity of aliphatic C−H bonds deserves some final discussion. These alcohols are strong HBD solvents and display a non-nucleophilic character, which endows them with the ability to stabilize charged intermediates. These solvents have been recently shown to strongly impact on a number of aliphatic C−H functionalizations.[28,39−45] However, as pointed out in two recent reviews,[46,47] the accurate role of HFIP and TFE in these processes has not been fully elucidated and tentative explanations associated with their strong HBD ability have been generally proposed. The current work provides, on the other hand, solid evidence that fluorinated alcohols induce a polarity reversal to HBA groups, strongly deactivating proximal C−H bonds toward oxidation by high valent metal oxo species, which proceeds via an initial HAT. By virtue of this effect, alcohols, ethers, amines, and amides, commonly understood as

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critical functional groups in C−H oxidations, and able moreover to strongly activate adjacent C−H bonds toward electrophilic HAT reagents, become oxidatively robust functionalities that can be used to direct C−H oxidation toward remote positions in a predictable manner. A synthetically relevant consequence of this effect is that efficient hydroxylation of methylenic sites can be accomplished with outstanding product chemoselectivity. Therefore, the current reactions open novel paths for C−H bond oxidation with orthogonal chemoselectivity to that occurring in conventional solvents. Finally, the current work focuses on metal catalyzed oxidations, but it is envisioned that the effects described herein, being substrate based, will have general applicability in HAT promoted functionalization reactions, and therefore will have a very important and rapidly implemented impact in synthetically useful C−H functionalization procedures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.7b00532.

Synthesis of complexes and substrates, experimental details, product characterization, results of screening, oxidation of alcohols in TFE, and control experiments (PDF)

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Notes

The authors declare no competing financial interest.

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