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# Site-selective and product chemoselective aliphatic C-H bond hydroxylation of polyhydroxylated substrates

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# Site-selective and product chemoselective aliphatic C-H bond hydroxylation of polyhydroxylated substrates

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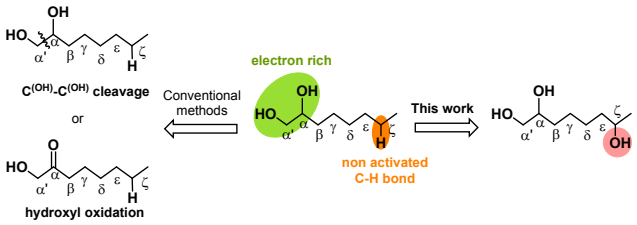
Supporting Information Placeholder

**ABSTRACT:** Site-selective and product chemoselective aliphatic C-H bond oxidation of 1,2-diols and of polyhydroxylated substrates using iron and manganese catalysts and hydrogen peroxide as terminal oxidant is described. The reaction capitalizes on the use of fluorinated alcohol solvents such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which exert a strong polarity reversal in the hydroxyl moieties of 1,2-diols via hydrogen bonding, in turn translating into a strong deactivation of proximal C-H bonds against a HAT initiated oxidation by the putative high-valent and electrophilic metal-oxo species. As a result, site-selective and product chemoselective oxidation of complex polyfunctional molecules such as steroids, sugars and pharmaceuticals is described, where exclusive or predominant C-H bond hydroxylation at a remote and non-activated site takes place. The current report discloses HAT initiated hydroxylations in fluorinated alcohol solvents as methods displaying orthogonal chemoselectivity to contemporary alcohol oxidations providing a useful tool for synthetic planning in densely functionalized molecules.

**KEYWORDS:** Aliphatic hydroxylation, polarity reversal, fluorinated alcohol solvents, hydrogen atom transfer, polyols, manganese, hydrogen peroxide.

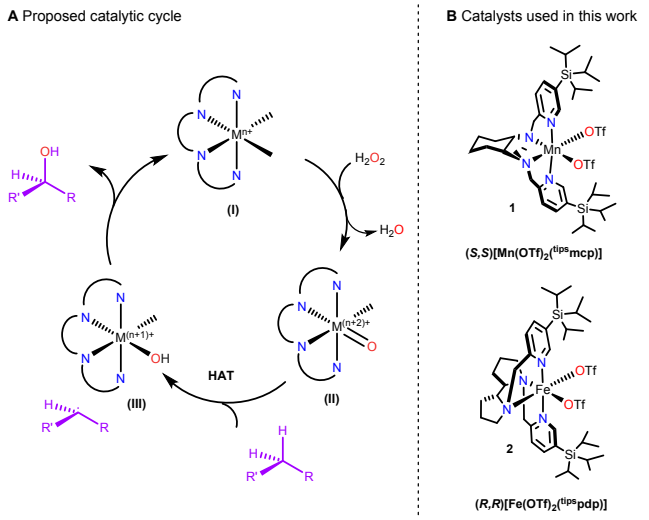
A large number of molecules of biological relevance, including natural products, feature polyhydroxylated moieties, that represent a versatile structural motif amenable to a number of important synthetic transformations. The selective oxidation of these compounds at sites that are remote from the polyhydroxylated moiety represents a synthetically important yet challenging transformation.[1] Chemoselective hydroxylation of unactivated aliphatic C-H bonds is traditionally regarded as incompatible with the presence in the substrate of C-H bonds that are activated by adjacent electron rich groups such as hydroxyl, which typically undergo preferential oxidation.[1a-e, 2] Furthermore, 1,2-diols easily undergo oxidative C-C cleavage reactions, and these transformations find wide utility both in fine chemistry and in the bulk manipulation of olefin derived substrates.[3] It is therefore not surprising that selective oxidation at unactivated C-H bonds in polyhydroxylated substrates without the assistance of protecting groups constitutes a yet unmet challenging target of relevance in organic synthesis (Scheme 1).

**Scheme 1.** Possible oxidation paths for polyhydroxylated molecules, exemplified in 1,2-diols.




Herein we address this problem by describing site-selective and product chemoselective oxidation of unactivated aliphatic C-H bonds in 1,2-diols and in polyhydroxylated molecules using iron and manganese catalysts (Scheme 2B) and hydrogen peroxide as terminal oxidant. C-H hydroxylation with these catalysts entails initial Hydrogen Atom Transfer (HAT) from a substrate C-H bond to a high valent metal-oxo species.[4] (Scheme 2A) We show that these reactions, when conducted in fluorinated alcohol solvents, display orthogonal chemoselectivity to contemporary alcohol oxidation methods.[5]

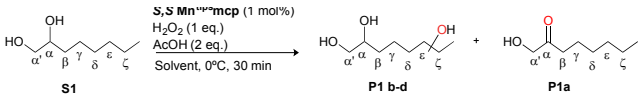
**Scheme 2. A) Proposed mechanistic cycle. B) Structure of the catalysts used in this work.**




We and others have previously described that by engaging in hydrogen bonding, hydrogen bond donor (HBD) solvents such as fluorinated alcohols can strongly deactivate the electron rich C-H bonds that are α- to hydroxyl groups of simple primary and secondary aliphatic alcohols toward electrophilic HAT reagents, preventing their overoxidation to form aldehydes and ketones.[6] Based on this precedent, we considered the oxidation of 1,2-diols and unprotected polyhydroxylated molecules, which represent more challenging targets because their metal chelating ability adds to the well-established oxidation sensitivity of the C–H bonds that are α- to hydroxyl groups.[7] Furthermore, polyhydroxylated carbon skeletons are common in organic molecules of biological interest, being glycosides a paradigmatic example. Bearing these considerations in mind, catalytic oxidation of model substrate 1,2-octanediol (**S1**) was first performed using MeCN, TFE, and HFIP as solvents. In a typical reaction, 1 equiv. of $H_2O_2$ (diluted from an aqueous solution in the solvent of choice), was added via syringe pump during 30 minutes at 0 ºC to a solution of the substrate (1.5 mmols, 1 equiv.) and catalyst ((*S,S*)-**Mn$^{tips}$mcp**, 1 mol%, Table 1).[8]

When the reaction was performed in MeCN, modest substrate conversion was observed (28%), leading to formation of 1-hydroxy-2-octanone **P1a** in 21% yield, as the only oxidation product detected. Instead, when the same reaction was performed in TFE and HFIP, significantly higher substrate conversions were observed, with the reaction chemoselectivity that drastically changed. 1,2,7-Octanetriol **P1b**, resulting from oxidation at the most remote methylenic site, now represents the largely dominant product, accompanied by smaller amounts of isomeric triols **P1c** and **P1d**, whereas hydroxyketone **P1a** is formed in only trace amounts. Remarkably, as compared to TFE, in HFIP yield and selectivity towards **P1b** increase. Use of larger amounts of peroxide (3-5 equiv.) resulted in a mixture of carbonyl containing overoxidized products and a loss of mass balance in the reaction. Delivering the peroxide during 15 or 60 minutes does not change significantly product yields and selectivities, but an improvement in yields was observed when urea-hydrogen peroxide was employed as oxidant.[9] On the other hand, a 1:1 combination of HFIP with other solvents (AcOEt, $CH_3CN$ and $CH_2Cl_2$) resulted in lower product yields and erosion of the chemoselectivity (see Table S3 in the SI for details). The higher conversions observed in the fluorinated alcohol solvents when compared to acetonitrile can be explained in terms of the strong HBD ability of the former solvents that hampers the metal binding ability of the 1,2-diol moiety, preventing catalyst deactivation. In addition, the stronger HBD ability of HFIP as compared to TFE[10] accounts for the higher selectivity towards hydroxylation at the most remote methylenic site. In addition, it is also possible that HFIP helps in activating the $H_2O_2$,[11] and that its strong hydrogen donor ability enhances the electrophilicity of the putative high valent manganese-oxo responsible for the initial HAT.[12]

**Table 1. Catalytic oxidation of 1,2-octanediol (S1) in different solvents.**




| Solvent[a] | Conversion (%) | **P1b-d** Yield (%) (δ:ε:ζ ratio) | **P1a** Yield (%) |
|---|---|---|---|
| $CH_3CN$ | 28 | 0 | 21 |
| TFE | 52 | 22 (6:25:69) | 5 |
| HFIP | 77 | 62 (5:16:79) | 1 |
| HFIP[b] | 79 | 72 (4:18:78) | 1 |

[a] Conversion and yields determined by GC. [b] Urea-hydrogen peroxide was used as oxidant.

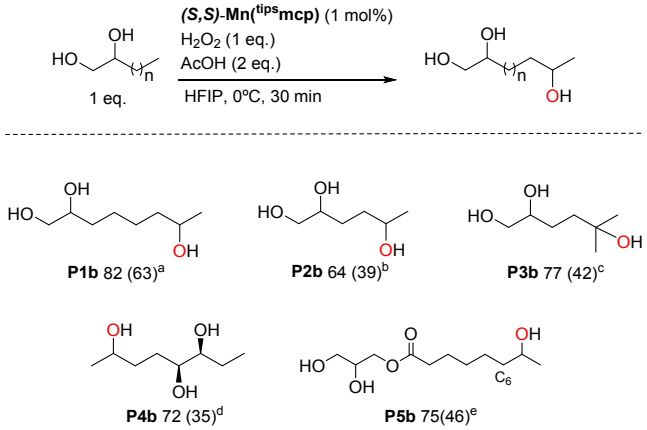
It is interesting to notice that the trends in chemoselectivity and product yields observed in the oxidation of diol **S1** are basically reproduced when 2-octanol (**S0**) was used as substrate, although the formation of significant amounts of 2-octanone (5%) and 2,5-octanediol (10%) suggests an enhanced deactivation in the case of the diol (see Table S6 in the SI for details).

The oxidation of **S1** in HFIP was further explored with a series of related iron and manganese catalysts (see Table S1 in the SI).[13] Related iron catalysts have been pioneered by White in late stage aliphatic C-H oxidation reactions.[14] While all the catalysts exhibited the same product profile, manganese catalysts systematically delivered higher product yields than the iron counterparts in the oxidation of this substrate. (*S,S*)-**Mn$^{tips}$mcp**[8] was chosen for further exploration of the reaction.

A series of 1,2-diol substrates containing alkyl chains and a glycerol monoester were then subjected to oxidation under the optimized conditions on a 1.5 mmol scale (Scheme 3) in order to allow isolation of products. Oxidation of 1,2-hexanediol (**S2**) gives preferentially 1,2,5-hexanetriol (**P2b**, 39% yield) resulting from hydroxylation at the most remote methylenic site, over 1-hydroxy-2-hexanone (**P2a**, 11% yield) formed by HAT initiated α-C-H bond hydroxylation. Analogously, with 5-methyl-1,2-hexanediol (**S3**), hydroxylation occurs preferentially at the remote tertiary C-H bond to give triol **P3b** in 42% yield (55% GC yield) over 1-hydroxy-5-methyl-2-hexanone **P3a** (5% GC yield).[15] With 3,4-octanediol (**S4**), oxidation occurs preferentially at the most remote δ-methylene site, delivering 3,4,7-octanetriol (**P4b**) in 35% yield, along with the two hydroxyketone products (**P4a** and **P4a'**) in a combined 13% yield. Partial oxidation of the diol moiety, while retaining intact the ethyl group, indicates that secondary aliphatic C-H bond oxidation starts to be competitive with diol oxidation only when this site is spaced by at least two methylene groups from the closest OH group. More proximal C-H bonds are deactivated toward HAT to the high valent metal-oxo species by the electron-withdrawing character of the hydrogen bonded diol moiety. Interestingly, as the length of the alkyl chain is increased, both product yield and chemoselectivity for the remote C-H hydroxylation product are improved. For example, oxidation of 1,2-octanediol (**S1**) gives 1,2,7-octanetriol (**P1b**) in 63% yield

along with 1,2,6-octanetriol (**P1c**) in 14% yield, while **P1a** is formed in <1%. Analogous observations derive from the oxidation of the glycerol monoester drug monoctanoin (**S5**). Oxidation occurs selectively at the most remote methylenic position delivering the hydroxylation product at C-7 (**P5b**) in 46% yield, along with the isomeric products hydroxylated at C-6 and C-5 in 10% and 4% yield (**P5c** and **P5d**). In line with previous observations, no products deriving from oxidation of the glycerol moiety are observed. These observations can be explained on the basis of the progressive decrease of the deactivating effect exerted by the hydrogen bonded 1,2-diol moiety on the C-H bonds of the alkyl chain as these bonds are further spaced from this strong electron withdrawing moiety.

**Scheme 3. Catalytic oxidation of 1,2-diol substrates**

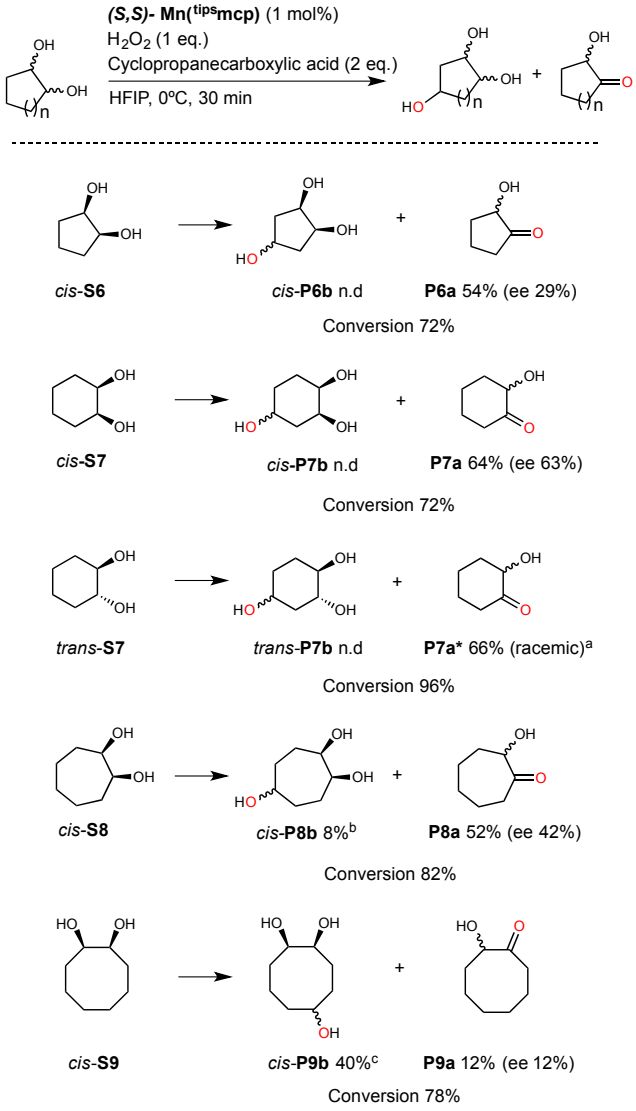



Unless indicated, isolated yields are reported. Conversion (isolated yield %). [a] Isolated with 14% ε–hydroxylated **P1c**. [b] 11% of 1-hydroxy-2-hexanone (**P2a**). [c] 55% GC yield of **P3b** and 5% GC yield of 1-hydroxy-5-methyl-2-hexanone **P3a,** also in this oxidation, two hydroxyketones are identified by GC-MS analysis (~13% combined yield). [d] 7% and 6% of isomeric hydroxyketones (**P4a** and **P4a'**). [e] Isolated with C-6 (**P5c**, 10%) and C-5 (**P5d**, 4%) hydroxylated products.

The reaction was then explored in the oxidation of a series of cyclic 1,2-diol substrates (Scheme 4). Cyclopropanecarboxylic acid was used instead of acetic acid in order to promote enantioselectivity in the reactions.[22] Oxidation of *cis*-1,2-cyclopentanediol (*cis*-**S6**) and *cis*-1,2-cyclohexanediol (*cis*-**S7**) occurs exclusively at the diol moiety producing the corresponding hydroxyketones (**P6a** and **P7a**) in 54% and 64% yield. Oxidation of these compounds proceeds with modest to good levels of enantioselectivity, (29% and 63% ee for **P6a** and **P7a**, respectively).[16] Instead, oxidation of a racemic mixture of *trans*-1,2-cyclohexanol (*trans*-**S7**) produces racemic hydroxyketone **P7a** in 66% yield.

As ring size is increased, the reaction chemoselectivity is systematically changed in favor of triol products deriving from remote C-H hydroxylation. Oxidation of *cis*-1,2-cycloheptanediol (*cis*-**S8**) yields the corresponding hydroxyketone (**P8a**) in 52% yield (42% ee), along with 1,2,5-cycloheptanetriol *cis*-**P8b** (8%, 1:1 d.r.). Instead, oxidation of *cis*-1,2-cyclooctanediol (*cis*-**S9**) provides preferentially 1,2,5-cyclooctanetriol (*cis*-**P9b**, 40%, 1:1 dr), along with 17% of 1,2,4-cyclooctanetriol (*cis*-**P9c**), while the hydroxyketone product (**P9a**) is only obtained as a minor product (12% yield, 12% ee). Taken together, the data collected in Scheme 4 further indicate that C-H bond deactivation exerted by the hydrogen bonded 1,2-diol moiety extends effectively up to position γ, leading to chemoselective oxidation of the diol. δ-C-H bonds experience instead a weaker deactivation and undergo preferential oxidation over the diol moiety.

**Scheme 4. Catalytic oxidation of 1,2-cycloalkanediols**



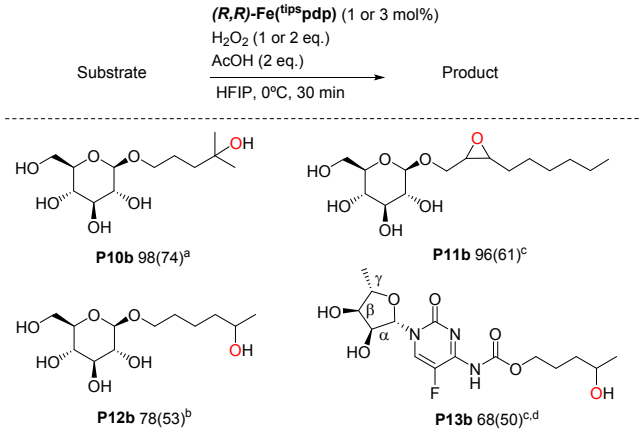

Unless indicated, isolated yields are reported (ee %). [a] Yield determined by GC. [b] 1:1 d.r. isolated with traces of cycloheptane-1,2,4-triol. [c] 1:1 d.r., isolated with 17% of 1,2,4-cyclooctanetriol triol *cis*-**P9c** (total yield 69%). n.d stands for not detected.

The chemoselectivity observed in the remote oxidation of relatively simple 1,2-diol substrates led us to consider the application of the reaction to carbohydrates (Scheme 5). Their selective oxidation in unprotected form is a challenging issue in carbohydrate manipulation.[17] A short optimization protocol identified (*R,R*)-**Fe$^{tips}$pdp**[13d] as the optimum catalyst (see Table S1 in the SI). Effectively, (4-methyl)-1-pentyl β-D-glucopyranoside **S10** and 1-hexyl β-D-glucopyranoside **S12** undergo selective C-H hydroxylation at the exocyclic alkyl chain, without affecting the densely oxygenated glucose moiety, characterized in both cases by 9 C-H bonds that are α- to oxygen atoms. Oxidation of **S10** leads to the exclusive formation of **P10b** deriving from hydroxylation at the remote tertiary C-H bond in 74% yield. Oxidation of **S12** leads instead to the formation of product **P12b**, deriving from

hydroxylation at the most remote methylene site (53%), accompanied by 12% of the corresponding product (**P12c**) deriving from hydroxylation at the next methylene site. The reaction is thus orthogonal to previously described glycoside oxidation methods, that operate on 1,2-diol moieties.[17] Furthermore, **S10** and **S12** are interesting targets for late stage C-H hydroxylation because they can be viewed as models for lipopolysaccharides, endotoxins of gram-negative bacteria.[18] On the other hand, epoxidation of the C=C bond in alkenyl β-D-glucopyranoside **S11** delivers the corresponding epoxide (**P11b**) in 61% yield, again retaining the sugar moiety.

Anticancer drug Capecitabine **S13** exhibits several features which are recognized as recurrent standing problems in the metal catalyzed chemical manipulation of small molecule pharmaceuticals.[19] Capecitabine contains a highly polar, functional group rich core, composed by an *a priori* oxidation sensitive five membered cyclic ether bearing a tertiary C-H bond at $C_\gamma$ , and a 1,2-*syn*-diol moiety at $C_\beta$ and $C_\alpha$. This ether is connected to a fluorinated N-heterocycle, in turn ligated to an alkyl carbamate moiety. Several 4, 5 and 6 membered metal chelating units can be identified, potentially capable of deactivating metal catalysts. Most remarkably, when **S13** was subjected to the standard conditions, oxidation at the remote methylenic site of the alkyl chain proceeds smoothly (68% conversion), leaving the densely functionalized core intact, yielding hydroxylation product **P13b** in 50%–yield, along with 12% of the corresponding carbonyl derivative.

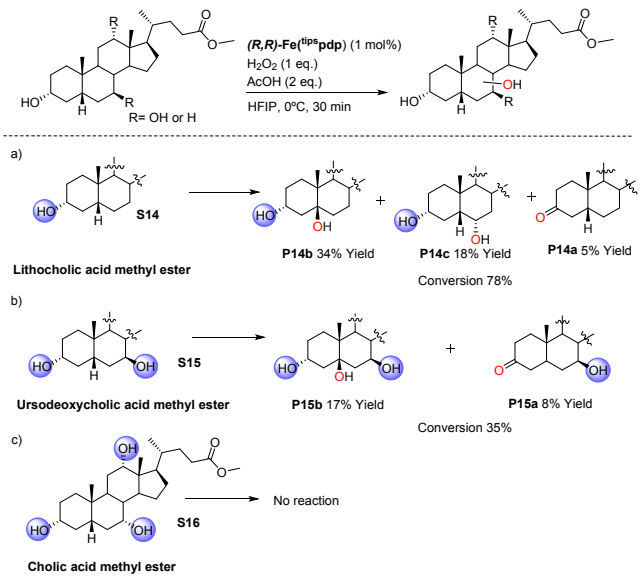
**Scheme 5. Oxidation of glycosides and related polyfunctional molecules.**




Conversion (isolated yield%). [a] 2 x (3 mol% catalyst/1 equiv. $H_2O_2$). [b] 3 mol% catalyst/1 equiv. $H_2O_2$. Isolated with δ-hydroxylated product **P12c** (12% yield, total yield 65%). [c] 1 mol% catalyst/1 equiv. $H_2O_2$. [d] Along with 12% of the corresponding carbonyl derivative (total yield 62%).

The reaction was finally tested in the oxidation of steroidal substrates containing hydroxyl groups (Scheme 6).[13d, 20] Oxidation of unprotected lithocholic acid methyl ester **S14** in HFIP yields two major diol products in a combined 52% yield where the hydroxyl group of the parent substrate is left intact: diol **P14b** (34%), resulting from hydroxylation at the bridgehead C-5 methine and hyodeoxycholic acid methyl ester **P14c** (18%), where stereoselective hydroxylation has taken place at the equatorial C-H bond at the C-6 methylene. Ketone **P14a**, deriving from oxidation of the hydroxyl group at C-3 is detected in only minor amounts (5%). In contrast, **P14a** is the single product (37% yield) in acetonitrile. Hydroxylation of ursodeoxycholic acid methyl ester **S15**, a substrate bearing two hydroxyl groups at C-3 and C-7, also proceeds preferentially at the C-5 methine C-H, albeit with modest substrate conversion (35%) and product yields (17% isolated yield of **P15b** and 8% of **P15a**), a behavior that reasonably reflects the combined deactivation effect of the two hydrogen bonded hydroxyl groups. Along the same path, no reaction takes place when cholic acid methyl ester **S16**, a substrate bearing three hydroxyl groups at C-3, C-7 and C-12, is employed as substrate, in line with the operation of a stronger deactivation of all the steroidal skeletal C-H bonds determined by the three hydrogen bonded hydroxyl groups.

**Scheme 6. Oxidation of hydroxylated steroidal substrates**




Summarizing, the current work describes site-selective and product chemoselective C-H bond oxidation of di- and polyhydroxylated substrates with hydrogen peroxide catalyzed by iron and manganese complexes in fluorinated alcohol solvents. The reaction can be applied to sugars, steroids and other densely functionalized substrates, without the need to protect the hydroxyl functionalities, which become deactivating groups by solvent hydrogen bonding, and play a directing role toward oxidation at remote and unactivated aliphatic C-H bonds. Overall, the reaction opens a new entry for the straightforward construction of functionality at unactivated sites in complex organic molecules via late stage hydroxylation of aliphatic moieties, providing a new and powerful tool to be rapidly implemented in synthetic planning.

## ASSOCIATED CONTENT

Experimental details on the reaction procedures and reaction optimization, product characterization data, GC spectra for determining ratios of regioisomers and X-ray determined structure of **P14b** are included as Supporting Information.

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**Notes**

The authors declare no competing financial interest.

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SYNOPSIS TOC

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