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# Synthesis of Benzylic Alcohols by C−H Oxidation

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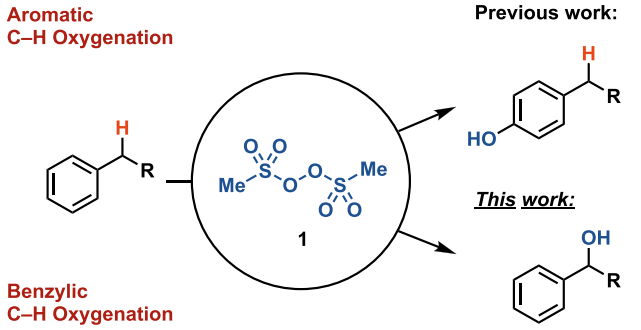
Supporting Information

**ABSTRACT:** Selective methylene C−H oxidation for the synthesis of alcohols with a broad scope and functional group tolerance is challenging due to the high proclivity for further oxidation of alcohols to ketones. Here, we report the selective synthesis of benzylic alcohols employing bis(methanesulfonyl) peroxide as an oxidant. We attempt to provide a rationale for the selectivity for monooxygenation, which is distinct from previous work; a proton-coupled electron transfer mechanism (PCET) may account for the difference in reactivity. We envision that our method will be useful for applications in the discovery of drugs and agrochemicals.

Nature has developed numerous enzymes, which introduce oxygen functionality selectively to substrates without the need for prefunctionalization.[1] Among the most relevant functionalization reactions that enzymes catalyze during phase one metabolism is the oxygenation of aliphatic C−H bonds.[2] Benzylic C−H bonds are often targeted by enzymes due to their relatively low bond dissociation energy (BDE) of around 90 kcal·mol$^{-1}$.[3] For the diversification of small molecule drug candidates and the identification of metabolites, it is therefore desirable to develop efficient methodologies for the selective oxidation of benzylic C−H bonds to alcohols without the need for *de novo* syntheses.[4] Current methods provide direct access to the corresponding phenones.[5] While phenones can often be reduced to alcohols,[6] the conversion of benzylic C−H bonds to benzylic alcohols without the need for a reduction step is currently an unsolved problem and provides a complementary approach to prior art. Herein, we present the selective monooxygenation of primary and secondary benzylic C−H bonds: the problem of chemoselective reduction of phenones to alcohols in the presence of other carbonyl functionality is eliminated, and alkenes as well as alkynes, typically sensitive to oxidative reaction conditions,[5a,7] are tolerated, as are basic amines. The transformation proceeds with bis(methanesulfonyl) peroxide (**1**) as oxidant and provides benzylic mesylates that are converted to benzylic alcohols under mild conditions (Scheme 1). A possible reason for the unusual selectivity for monooxygenation may be a proton coupled electron transfer (PCET) mechanism by mesyloxyl radicals, which differs from the H atom abstraction pathway (HAA) commonly described for reactions of O-centered radicals.[8]

Cytochrome P450 enzymes feature heme active sites, which have been inspiration for the design of catalysts featuring porphyrin derived ligands around iron metal centers.[9] Three decades ago, Groves et al. reported the enantioselective

**Scheme 1. Bis(methanesulfonyl) Peroxide as Reagent for Late-Stage Oxygenation Reaction**




benzylic monooxygenation of simple substrates such as ethylbenzene with chiral iron and manganese porphyrin catalysts and iodosobenzene as the limiting reagent.[7,10] Following that discovery, a variety of nonporphyrin ligands such as salen derivatives and *N*,*N*′-(2-pyridylmethyl)diamine ligands have been developed by Que and co-workers to avoid the problem of ligand oxidation often observed with heme-type catalysts. After further optimization of the nonporphyrin ligands,[11] the White group reported the selective oxidation of tertiary C−H bonds in 2007 using iron(II) complexes featuring an *N*,*N*′-(2-pyridylmethyl)diamine ligand and $H_2O_2$ as oxidant.[12] This catalyst system was optimized throughout the past decade for useful C−H oxidation reactions such as selective methylene oxidation to the corresponding ketones, even in the presence of electron-rich aromatic substituents.[5a,13] The selective formation of alcohols by methylene oxidation is challenging with these types of catalysts because the initially formed alcohols are competent substrates for a fast second oxidation to the ketone.[14] Many methods employing oxidants such as hydroperoxides, hypervalent iodine reagents, and electrochemistry have been reported that provide access to phenones by oxidation of secondary benzylic C−H bonds.[5b,c,15] Benzylic monooxygenation to give benzyloxy phthalimides was achieved by the Chang group, albeit with ten equivalents of substrates to obtain synthetically useful yields.[16] The subsequently developed selective nitrooxylation of benzylic C−H bonds enabled the use of the substrate as limiting reagent.[17] For the phenones, the benzyloxy phthalimides, and nitrooxylated products, a reduction can provide benzylic alcohols, but the reduction reactions are often

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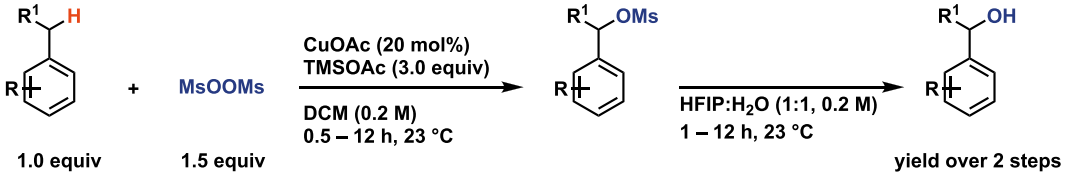
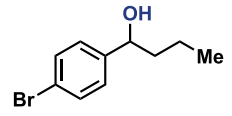
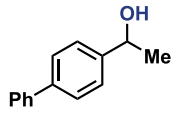
**Table 1. Substrate Scope of Benzylic C−H Oxygenation**

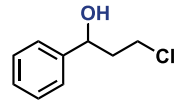



2,[a,b] 78%




3,[c] 79%

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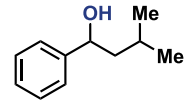
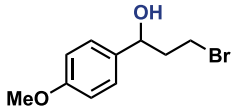
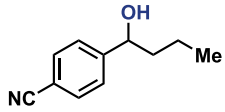


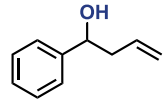

5,[a] 58%



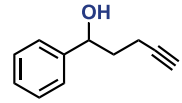

6,[c,d] 84%



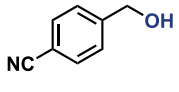

7, 72%



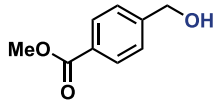

8, 61%



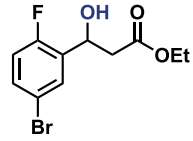

9,[e] 58%



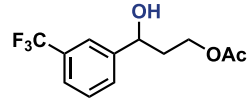

10,[f] 67%



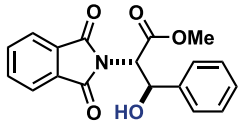

11,[g] 66%



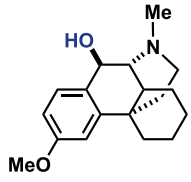

12, 30%



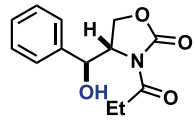

13, 75%



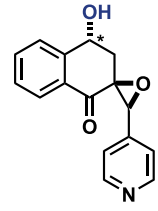

14, 82%




15,[c,h] 53%

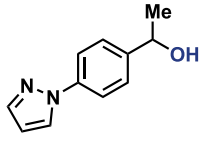



16, 57%

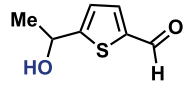



*d.r. = 2:1

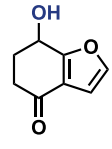
17,[g,h] 65%



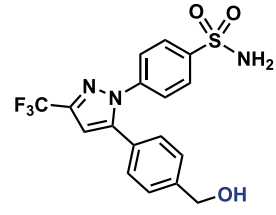

18,[c] 72%




19,[c] 67%




20,[c] 60%




21, 61%

[a]No CuOAc added. [b]2,6-Di-*tert*-butylpyridine (1.5 equiv) was used instead of TMSOAc. [c]5% NaOMe in MeOH (0.2 M) was used instead of HFIP:$H_2O$. [d]Reaction performed at −20 to 0 °C. [e]Aqueous LiOH (0.2 M) in THF was used instead of HFIP:$H_2O$. [f]$Cs_2CO_3$ (3.0 equiv) in DMF:$H_2O$ (0.2 M) was used instead of HFIP:$H_2O$. [g]TFA (2.0 equiv) in THF:$H_2O$ (0.2 M) was used instead of HFIP:$H_2O$. [h]TFA (1.1 equiv) was added.

not compatible with other carbonyl functionalities within the molecule.

Some methods for the generation of benzyl cations by UV light irradiation or visible light photoredox catalysis have enabled selective monooxygenation.[18] These methods are limited to electron-rich substrates and are not compatible with olefins and alkynes. Recently, the Stahl and Yoon groups reported selective benzylic alkoxylation reactions using various alcohols.[19] The use of water as a nucleophile leads to the formation of the corresponding phenone products.[19b] Herein, we report a new methodology for C−H oxidation for the synthesis of benzylic alcohols with large electronic scope and



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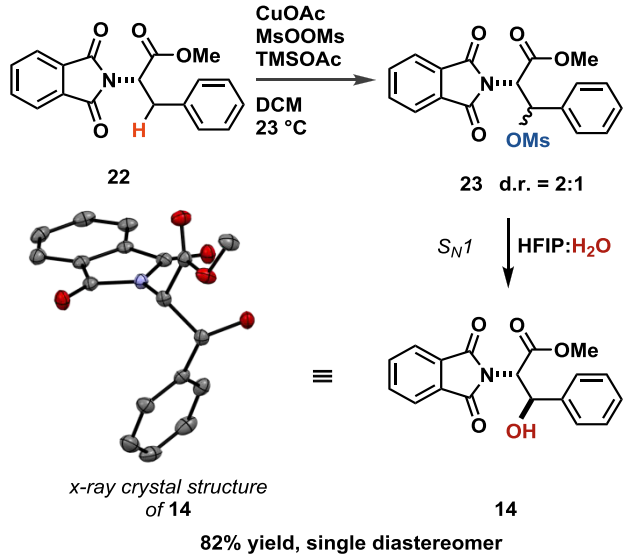
broad functional group tolerance employing bis-(methanesulfonyl) peroxide (**1**), a shelf-stable peroxide that has been sparsely used in synthesis before. In 2018, our group reported late-stage aromatic C−H oxygenation with peroxide **1**, which shows distinct reactivity from other peroxides.[20]

In our reaction setup, we employ copper(I) acetate, peroxide **1**, and TMSOAc in dichloromethane to obtain benzylic mesylates that can be converted to the corresponding alcohols with a mixture of hexafluoroisopropanol (HFIP) and $H_2O$ (Table 1). The scope spans from benzylic positions substituted with 4-methoxy phenylene (**6**) to 4-cyanophenylene (**7**) substituents, a broader electronic scope than reported previously.[18b,19a] The reaction shows compatibility with olefins (**8**) and alkynes (**9**), which are typically sensitive to oxidative conditions and not tolerated in other aliphatic C−H oxidations.[5a] If tertiary, allylic, and propargylic C−H bonds are present (**5**, **8**, and **9**), exclusive functionalization of the benzylic position is observed. Moreover, primary benzylic positions were monooxidized and converted to the benzylic alcohols (**10**, **11**, and **21**), which has not been achieved previously with the substrate as limiting reagent. In general, for substrates that are not oxygenated in high yields, the mass balance of the reaction consists of unreacted starting material. For example, compounds **11** and **17** were formed in yields around 65%, and in both cases, 30% starting material remained. An exceptional case is the $\beta$-hydroxy ester **12**, which was isolated in 30% yield, despite facile elimination of methanesulfonic acid due to the carbonyl group. The respective styrene product was only isolated in 7% yield alongside 10% of unreacted starting material. The instability of the styrene product under the reaction conditions may lead to further decomposition to unidentified side products that could not be isolated. Furthermore, basic amines such as the tertiary amine in the complex small molecule dextromethorphan (**15**) or the pyridine moiety in **17** are tolerated when one equivalent of trifluoroacetic acid (TFA) is added. Carbamates (**16**), esters (**12**, **13**, and **14**), imides (**14**), and epoxides (**17**) are tolerated showing the applicability of the method to complex small molecules. Limitations of the methods are substrates featuring electron-rich primary benzylic positions, which undergo overoxidation to the corresponding aldehydes. For electron-rich substrates with secondary benzylic positions, small amounts of overoxidation can be observed. For example, for compound **15** the corresponding phenone was isolated in 10% yield (see SI).

Dichloromethane is the reaction solvent of choice. The use of more polar solvents such as HFIP causes the peroxide to react with the aryl substituent (see SI).[20] Copper(I) acetate serves as a radical initiator,[21] and is crucial for electron-rich and electron-poor arenes but is not necessary for electron-neutral arenes: electron-rich arenes undergo deleterious side reactions without copper(I) present and electron-poor arenes are unreactive. TMSOAc serves as a base to deprotonate the methanesulfonic acid byproduct to give TMSOMs and acetic acid. Secondary benzylic mesylates in the presence of methanesulfonic acid undergo facile elimination to the corresponding styrene, which reacts with **1** to give the dimesyloxylated addition product (see SI). Furthermore, in the case of electron-rich substrates, the benzylic cation is stabilized and the benzylic mesylate can ionize. In such cases, the mesylate group is substituted by acetate *in situ* to yield stable benzylic acetates. For electron-neutral and electron-poor arenes, this substitution reaction is slow but can lead to a mixture of the acetate and mesylate products. In these cases 2,6-di-*tert*-butylpyridine can be used to selectively obtain the benzylic mesylate products, if desired. The conditions for the formation of the benzylic alcohols depend on whether the mesylate or the acetate product is obtained in the oxidation reaction (Table 1).

Another feature of the reaction is the potential of achieving high diastereoselectivity for the transformation if appropriate functional groups are present: the (*S*)-phenyl alanine derivative **22** is converted to a single diastereomer of the alcohol **14** (Scheme 2). Although the benzylic oxidation reaction yields a

**Scheme 2. Diastereoselective Oxygenation of Phenylalanine Derivative 22**




mixture of diastereomers of the benzylic mesylates **23** in a ratio of 2:1, substitution of the mesylate group with formally hydroxide in the HFIP:$H_2O$ mixture leads to the formation of a single diastereomer **14** in 82% yield. This result supports the hypothesis that the substitution reaction follows an $S_N1$ pathway with anchimeric assistance from lone-pairs on neighboring oxygen atoms.

The high selectivity for monooxidation in our reaction may be due to a distinct reaction mechanism compared to other methodologies.[13d,19] The mesyloxyl radicals formed after initiation may generate a benzylic radical by either HAA or PCET, for which the electron and the proton originate from different sites of the substrate.[22] To provide a rationale as to why our reaction differs from previous reactions, we conducted a Hammett analysis and performed an intermolecular kinetic isotope effect (KIE) experiment (Scheme 3). The Hammett-slope ($\rho = -2$) substantiates positive charge built up in the selectivity-determining transition state of the reaction and is more negative than typically observed for the generation of benzylic radicals via HAA, which generally gives $\rho$-values around −1.[23] The intermolecular KIE of 1.8 is lower than typical KIE values found for HAA by oxygen centered radicals ($k_H/k_D \geq 5$).[5c,8b] The positive charge built up in combination with the observed KIE value are consistent with a concerted transition state in which the electron is transferred from the $\pi$-system of the aryl substituent, and the proton originates from the benzylic position (Scheme 4). A stepwise process is improbable because the individual electron and proton transfer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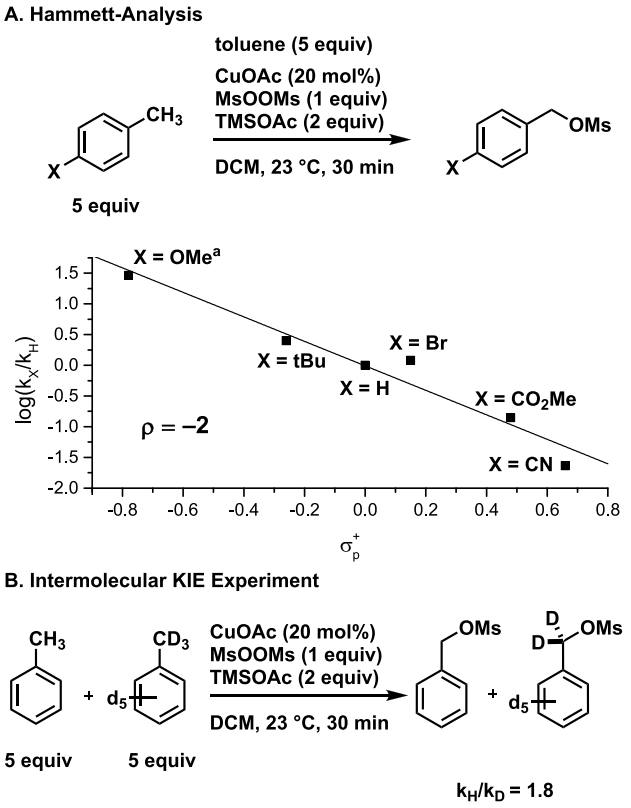
**Scheme 3. Hammett–Plot (A) and KIE Experiment (B)**

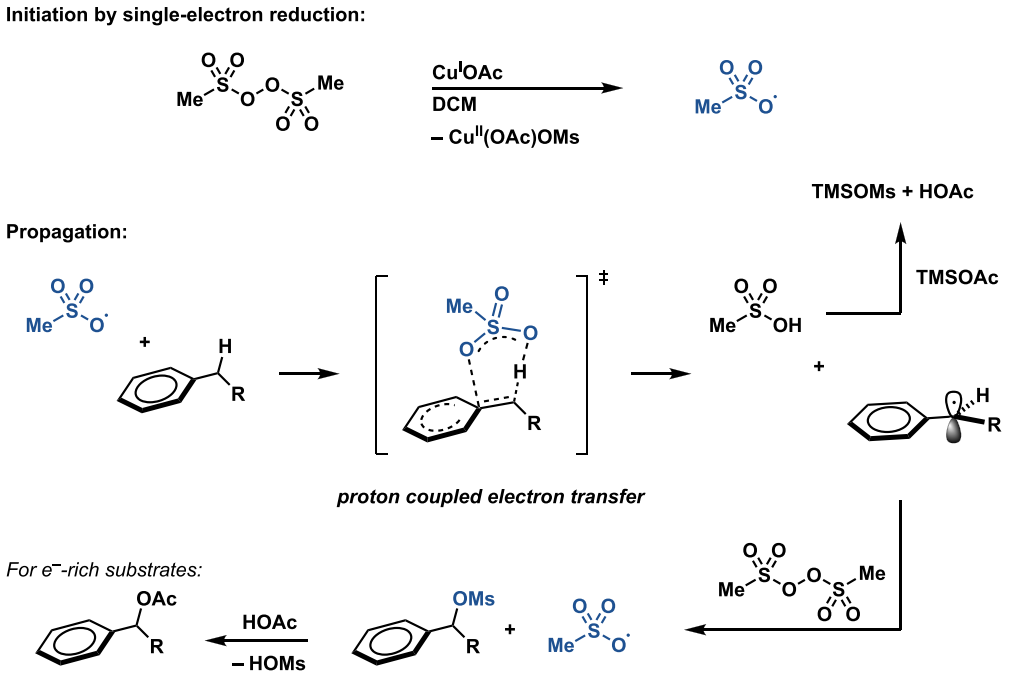



[a]In the case of X = OMe, the benzylic acetate was obtained instead of the benzylic mesylate.

steps would involve high energy intermediates: an arene radical cation or a benzylic anion as intermediates would be inconsistent with the broad scope of substrates.[24] Previously identified CT interactions of the mesyloxyl radical with the arene $\pi$-system could be a possible explanation for the unique reactivity of mesyloxyl radicals.[20] Density functional theory (DFT) at the B3LYP-D3BJ/def2-TZVPP level is in agreement with the proposed PCET pathway: a CT interaction between the mesyloxyl radical and the arene precedes a PCET transition state with a low barrier of 1.2 kcal·mol$^{-1}$. The positive natural charge of 0.4 on the benzylic hydrogen that is transferred to the mesyloxy unit is more reminiscent of a proton transfer rather than the transfer of a hydrogen atom. However, based on a low degree of natural spin density of approximately 0.2 on both the carbon and oxygen atoms on the hydrogen transfer trajectory, a partial HAA character cannot be ruled out.[25] The computational method was selected based on its agreement with the experimentally determined KIE value of 1.8 (see SI). Our proposed mechanism may also justify the observed selectivity for monooxidation: a second PCET is slowed down by the electron-withdrawing effect on the aromatic ring by the $\alpha$-oxygen substituent ($\Delta\sigma_p^+ \approx 0.3$) for electron-neutral and -poor arenes.[26] For electron-rich substrates, this effect is less strong, and overoxidation can be observed (see SI). In contrast, HAA would be expected to be less sensitive to electron density on the arene as charge built-up in the transition state is expected to be smaller in comparison to PCET.[27] The generated benzylic radical may react further with another equivalent of peroxide to give the desired benzylic mesylate and another mesyloxyl radical. Further oxidation of the benzylic radical intermediate to a benzylic cation followed by nucleophilic attack of mesylate can be excluded as addition of ethanesulfonic acid, which reacts instantaneously with TMSOAc, does not lead to the formation of benzylic ethanesulfonates (see SI).

In conclusion, we have presented a method for the synthesis of benzylic alcohols via selective monooxidation of alkylated benzenes to the benzylic mesylates. The broad substrate scope and functional group tolerance stand out compared to previous

**Scheme 4. Plausible Mechanism for Benzylic Oxidation**



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methodologies. We anticipate that this method will be useful for a variety of applications for the development of drugs and agrochemicals.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b09496.

Crystallographic data of **14** (CIF) and **16A** (CIF)
Experimental procedures and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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