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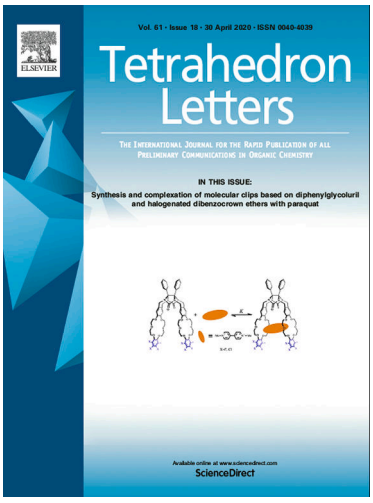

*m*CPBA-mediated Dioxygenation of Unactivated Alkenes for the Synthesis of 5-Imino-2-tetrahydrofuranyl Methanol Derivatives

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ABSTRACT

A *m*CPBA-mediated, metal-free, intramolecular dioxygenation reaction of unactivated alkenes is reported. In the presence of *m*-chlorobenzoic peracid, different unsaturated amide substrates could be cyclized *via* epoxide intermediates, producing the corresponding 5-imino-2-tetrahydrofuranyl methanol products in up to 94% yield at room temperature.

Introduction

The 1,2-diol structures are important skeletons, ubiquitously found in pharmaceuticals and their intermediates, such as the glycoprotein processing inhibitor swainsonine,[1] the anticancer agent anisomycin,[2] the immunomodulator cytoxazone,[3] and other bioactive molecules[4] (Figure. 1). Since the pioneering work reported by Sharpless,[5] a number of useful strategies for alkene dioxygenation have been developed for the preparation of such compounds, the majority of these methods are based on catalysis by transition metals, such as osmium,[6] iron,[7] palladium,[8] rhodium,[9] and others[10] (Scheme 1, a). Despite the synthetic utility, the toxicity and high cost of transition metals limit its application. Therefore, the developing of new processes in metal-free manner for dioxygenation of alkenes has become a hot issue for chemists.

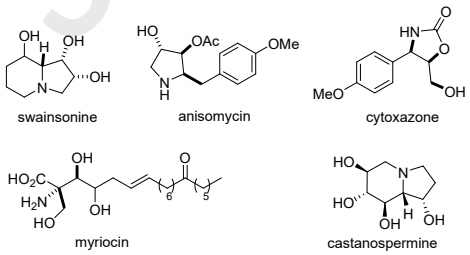
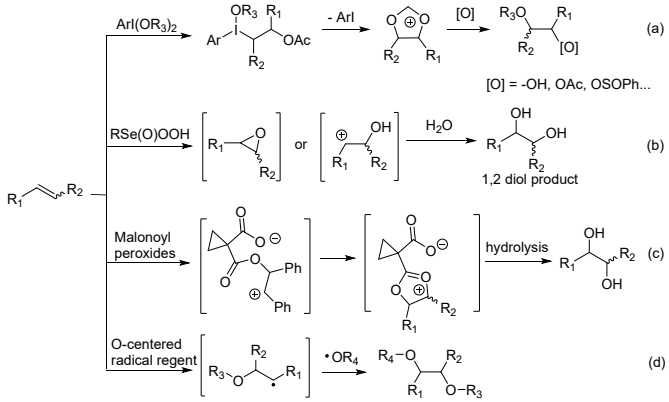


Figure. 1 Biologically active compounds containing 1,2-diols structures.

For example, aryliodine compounds have been shown to catalysis the diacetylation of alkenes,[11] and when an appropriate chiral hypervalent iodine catalyst was used, an asymmetric reaction could also be achieved (Scheme 1, a).[12] In another example, Moriyama[13] has described a catalysis diacetylation by organic selenium compounds, in which *in situ*-generated peroxyseleninic acid oxidized C=C double bonds to epoxides (Scheme 1, b). In addition, Tomkinson has reported that malonoyl peroxides can mediate alkene dihydroxylation via a dioxonium or oxiranium ion intermediate (Scheme 1, c).[14] Finally, in the presence of an *O*-centered radical reagent, alkene dihydroxylation can also proceed in a radical reaction pathway (Scheme 1, d).[15] Among the various metal-free methods for dioxygenation of alkenes mentioned above, substrate adaptability and atomic economy problems are still exists.

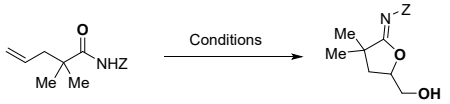


Scheme. 1 Metal-free strategies used for dioxygenation of alkenes.

Results and discussion

Inspired by the works aboat *m*CPBA-mediated alkene aminohydroxylation reactions.[16-17] We reasoned that the cyclohydroxylation may be generated through a tandem epoxidation and epoxide ring-opening sequence. Compared with aryliodine or selenium catalyzed methods, the *m*CPBA-mediated process is more simple and effective. In the initial investigation, *N*-phenyl-2,2-dimethyl-4-pentenamide **1a** was chosen as a model substrate. The reaction parameters including the oxidants, additives, and solvents, were examined to determine the optimal reaction conditions, and the results are summarized in **Table 1**. The reaction could be carried out at room temperature in hexafluoroisopropanol (HFIP), and $HNTs_2$ was essential for the transformation, as a low yield was obtained in the absence of $HNTs_2$ (entry 2). Then, several acid additives were tested, which resulted in reduced isolated yields (entries 3-6). The solvent screening determined that hexafluoroisopropanol remarkably promoted the transformation, while the use of DCM, CH_3CN, THF or ^{i}PrOH as the solvent led to a low reactivity or not achieving the conversion (entries 7-10). Increasing the amount of *m*CPBA to 2.0 equivalents further increased the yield of **2a** to 83% (entry 11). Among the different oxidants tested, DDQ, AcOOH, and H_2O_2 were ineffective for the transformation (entries 12–14). These results clearly showed that the *m*CPBA/$HNTs_2$/HFIP system was optimal for **1a** dioxygenation.

Table 1 Optimization of reaction conditions.[a]

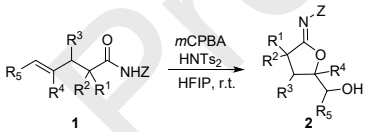


1a **2a**

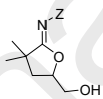
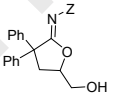
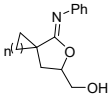
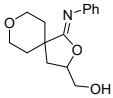
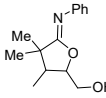
Entry	Solvent	Oxidant (equiv.)	Additive (equiv.)	**2a** Yield%
1	HFIP	*m*CPBA (1.5)	$HNTs_2$ (1.5)	78
2	HFIP	*m*CPBA (1.5)	-	8
3	HFIP	*m*CPBA (1.5)	TFA (1.0)	60
4	HFIP	*m*CPBA (1.5)	TfOH (1.0)	65
5	HFIP	*m*CPBA (1.5)	BF_3OEt_2 (1.0)	60
6	HFIP	*m*CPBA (1.5)	PhCOOH (1.0)	16
7	DCM	*m*CPBA (1.5)	$HNTs_2$ (1.0)	15
8	CH_3CN	*m*CPBA (1.5)	$HNTs_2$ (1.0)	10
9	THF	*m*CPBA (1.5)	$HNTs_2$ (1.0)	-
10	^{i}PrOH	*m*CPBA (1.5)	$HNTs_2$ (1.0)	-
11	HFIP	*m*CPBA (2.0)	$HNTs_2$ (1.0)	83
12	HFIP	DDQ (2.0)	$HNTs_2$ (1.0)	-
13	HFIP	AcOOH (5.0)	$HNTs_2$ (1.0)	-
14	HFIP	H_2O_2 (5.0)	$HNTs_2$ (1.0)	-

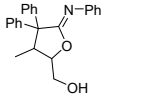
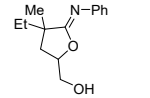
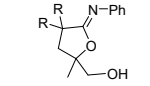
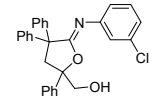
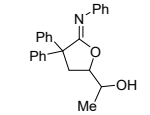
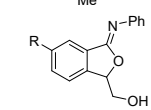
[a]The reactions were conducted on 0.2 mmol **1a** as substrates for 15 h, and isolated yields are given.

Table 2 Substrate scope.[a,]



1 **2**

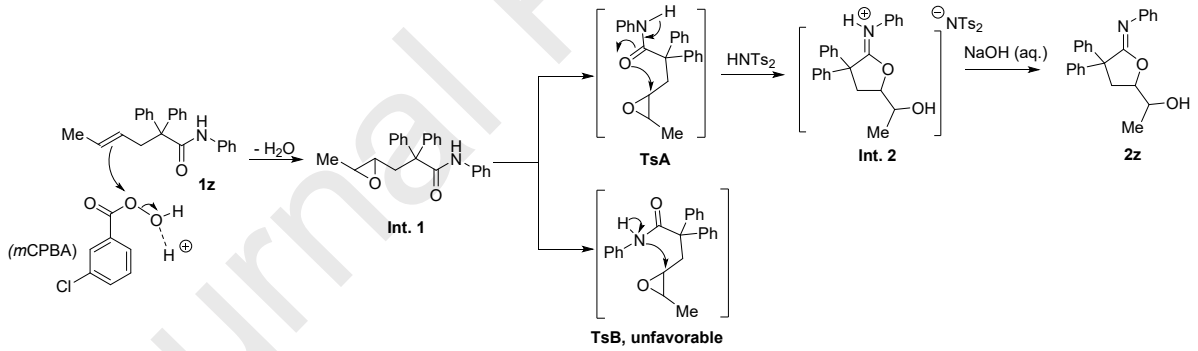
Entry	Substrate	Product	Yield[b]
1	Z = Ph, **1a**		**2a**, 83%
2	Z = *p*-$CH_3C_6H_4$, **1b**		**2b**, 84%
3	Z = *o*-ClC_6H_4, **1c**		**2c**, 72%[b]
4	Z = *m*-ClC_6H_4, **1d**		**2d**, 65% [b]
5	Z = *p*-ClC_6H_4, **1e**		**2e**, 76%[b]
6	Z = *p*-$NO_2C_6H_4$, **1f**		**2f**, 73%[b]
7	Z = *p*-$CF_3C_6H_4$, **1g**		**2g**, 80%
8	Z = *p*-MeC_6H_4, **1h**		**2h**, 76%
9	Z = *p*-FC_6H_4, **1i**		**2i**, 77%
10	Z = *o*-ClC_6H_4, **1j**		**2j**, 54%[b]
11	Z = *m*-ClC_6H_4, **1k**		**2k**, 51%[b]
12	Z = *p*-ClC_6H_4, **1l**		**2l**, 60%[b]
13	Z = *p*-BrC_6H_4, **1m**		**2m**, 64%[b]
14	Z = OMe, **1n**		**2n**, 57% [b]
15	Z = Bn, **1o**		**2o**, 75% [b]
16	n = 1, **1p**		**2p**, 84%
17	n = 3, **1q**		**2q**, 81%
18	n = 4, **1r**		**2r**, 64%
19	**1s**		**2s**, 73%
20	**1t**		**2t**, 83 %, d,r.= 1:1.4[c]

Entry	Substrate	product	Yield[b]
21	**1u**		**2u**, 88%, d.r.= 1:1.2[c]
22	**1v**		**2v**, 85%, d,r.= 1:1.2[d]
23	R= Ph, **1w**		**2w**, 87%
24	R= Et, **1x**		**2x**, 83%
25	**1y**		**2y**, 85% (1.7 g in 76%)
26	**1z**		**2z**, 94% yield,d.r.= 5:1[d]
27	R=H, **1aa**		**2aa**, 85% (2.0 g in 83%)
28	R=Cl, **1ab**		**2ab**, 89%
29	R=CH_3, **1ac**		**2ac**, 78%

[a]The reactions were conducted on 0.2 mmol **1** as substrate with $HNTs_2$ (1.0 equiv.) and *m*CPBA (2.0 equiv.) at room temperature for 15 h, isolated yield. [b]Reaction time extended to 24 h. [c]d.r. = diastereoselectivity, as determined by isolated yield. [d]As determined by ^{1}H NMR spectrum.

With the optimized conditions in hand, various substituted pentenamides were examined. The effects of substituents on the *N*-phenyl group of 2,2-dimethylpentenamide were initially tested. The results showed that both electron-rich and electron-deficient substrates were suitable for the transiformation, affording the desired five-membered ring dioxygenation products (**2a-g**) in good yields (65%–84%). Interestingly, compared with the 2,2-dimethyl substituted pentenamides, the more highly sterically hindered 2,2-diphenyl substrates, giving the corresponding tetrahydrofuranyl methanamine derivatives **2h-m** in slightly lower yields (51%–77%). These results indicated that the Thorpe-Ingold effect had less impact on this transformation, even though the Thorpe-Ingold effect has been observed in a number of catalytic difunctionalizations of alkenes.[18] The 2,2-diphenylpentenamides with *N*-methoxyl and *N*-benzyl protecting groups were found to function as suitable substrates for the reaction, giving **2n** and **2o** in 57% and 75% yields, respectively. Furthermore, substrates with different alkyl ring sizes could also be applied to the reaction under the standard conditions, giving the corresponding spiro-tetrahydrofuranyl methanamine products (**2p–r**) in 64%–84% yields. It is noteworthy that a substrate bearing a heterocycle was also suitable, affording the corresponding oxybicyclo **2s** in good yield. To further investigate the substrate scope, various unsaturated amides with more complex substitutions were examined. In these trials, the 2,2,3-trimethyl pentenamide **1t** and 2,2-diphenyl-3-methyl pentenamides **1u** were also tolerated, giving **2t** and **2u** in good yields with moderate diastereoselectivity. Furthermore, a substrate bearing a quaternary carbon center also worked well under the standard conditions, giving the dioxygenation product **2v** in 85% yield with 1:1.2 diastereoselectivity. Moreover, *N*-phenyl-2,2-disubstituted-4-methyl pentenamides **1w** and **1x** were also compatible with the reaction, generating the corresponding tetrahydrofuranyl methanol products **2w** and **2x** with quaternary carbon centers in 87% and 83% yields, respectively. Furthermore, the 2,2,4-triphenyl pentenamide was also applicable to this transiformation, giving **2y** in 85% yield, and gram-level reaction got a slightly lower yield. Notably, the internal olefin substrate of 2,2-diphenyl-5-methylpentenamide **1z** exhibited better reactivity than the other substrates, giving **2z** in up to 94% yield with 5:1 diastereoselectivity. This result further indicated that the substituent on the double bond promoted the reaction. This promotion is possibly because the methyl substituent stabilized the ethylene oxide intermediate. In addition, the substituted vinylbenzamide substrates were also suitable for the dioxygenation (**1aa–1ac**), and the gram-level reaction for the synthesis of **2aa** was tested, giving **2aa** in 85% yield. The electron-withdrawing effect of a chlorine atom substituent was beneficial to obtain a higher yield (**2ab**, 89%), while the methyl-substituted product gave a slightly lower yield (**2ac**, 78%). This result was possible because the strong electron-withdrawing chlorine atom substitution on the benzene ring increased the nucleophilicity of the carbonyl oxygen.

On the basis of these data, a possible reaction mechanism was developed (**Scheme 2**). This transformation proceeds via oxidation of the unsatured amide, which transform into an *in situ*-generated epoxide intermediate (**Int. 1**). Then, the epoxide intermediate subsequently attacked by the oxygen through **TsA**, while the **TsB** transition state involving an attack by a nitrogen is unfavorable, because the nitrogen atom in an amide moiety is usually less nucleophilic than a carbonyl oxygen atom.[19] In the presence of an excess of $HNTs_2$, the cyclization product remains protonated. Finally, a proton can be abstracted from **Int. 2** by treatment with NaOH to give the neutral product **2z**.



Scheme 2 Plausible reaction mechanism.

In conclusion, we have demonstrated a simple and effective *m*CPBA-mediated dioxygenation of unactivated alkenes to afford various 5-imino-2-tetrahydrofuranyl methanol derivatives, which are important motifs in compounds for drug development and biological studies. Notably, the present reaction was conducted at room temperature with inexpensive materials, and was tolerated by a broad range of substrates with good regioselectivity.

Acknowledgments

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Supplementary Material

Supplementary data associated this article provided as a separate electronic file.

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Declaration of Interest Statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Highlights

1. *m*CPBA-mediated Dioxygenation of unactivated alkenes
2. High selectivity for 5-imino-2-tetrahydrofuranyl methanol skeletons
3. Mild reaction conditions and broad substrate scope

Graphical Abstract

_m_CPBA-mediated dioxygenation of Unactivated Alkenes for the Synthesis of 5-Imino-2-tetrahydrofuranyl Methanol Derivatives

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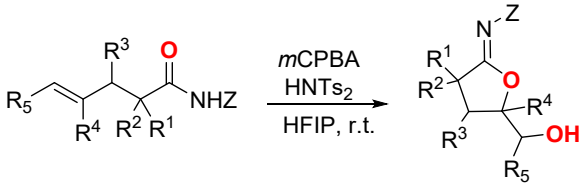

- Alkene dioxygenation with mild conditions
- High selectivity for tetrahydrofuranyl methanol
- 29 examples, up to 94% yield