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Enantioselective One-Pot Synthesis of α,β-Epoxy Ketones via Aerobic Oxidation of Cyclopropanols

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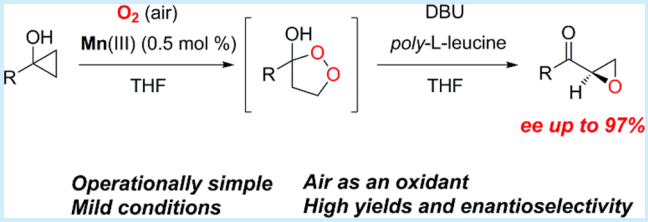
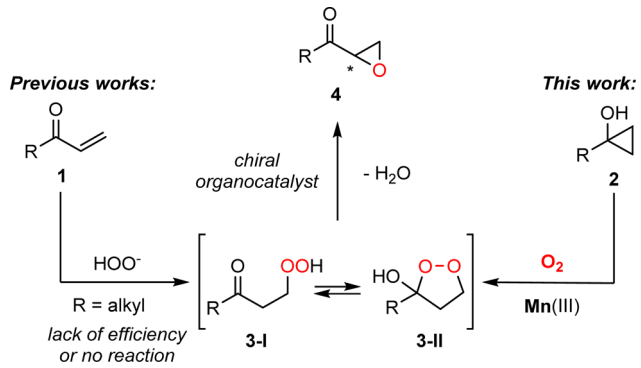
Supporting Information

ABSTRACT: An efficient, mild, and environmentally benign method was developed for the asymmetric synthesis of 2-oxyranyl ketones from easily available tertiary cyclopropanols. The one-pot protocol includes the aerobic oxidation of cyclopropanol derivatives catalyzed by Mn(III) complexes followed by the poly-L-leucine-assisted stereoselective elimination of water from the intermediate peroxides with DBU to afford the corresponding epoxy ketones in high yields and good-to-excellent enantioselectivities (up to 97%).



Enantiomerically enriched α,β-epoxy ketones are highly valuable starting materials for the production of numerous chiral compounds (e.g., pharmaceuticals, agrochemicals, fragrances, etc.).[1] Moreover, the epoxy ketone structural motif is responsible for the high bioactivity of several natural products.[2] Since the initial report by Wynberg in 1976,[3] the majority of methods to obtain enantiomerically enriched epoxy ketones are based on the epoxidation of α,β-unsaturated ketones by using the Weitz−Scheffer reaction and its modifications.[4] Despite extensive studies in this field, the developed methods are mostly limited to the reactive aromatic chalcone-type ketones, while the epoxidation of other enone substrates remained an arduous task due to long reaction times, low conversions, and poor enantioselectivities.[5] These shortcomings arise from the insufficient reactivity of the enone double bond toward the addition of hydroperoxide anion. For this reason, alkyl vinyl ketones **1** continue to be a challenging family of substrates for this type of epoxidation (Scheme 1).[5a,c]

Scheme 1. Alternative Methodology for the Preparation of Chiral 2-Oxyranyl Ketones 4 from Tertiary Cyclopropanols 2 via β-Peroxyketone Intermediates 3



Due to growing interest to the cyclopropanol chemistry,[6,7] we envisioned filling the existing gap by using easily available cyclopropanols **2** as starting compounds[8] for the synthesis of chiral epoxy ketones **4**. Tertiary cyclopropanols **2** are readily oxidized under the aerobic conditions by using transition-metal catalysts[9] to afford β-peroxyketones **3-I**, which are in equilibrium with 1,2-dioxolane form **3-II**. We assumed that the peroxides **3** can be further stereoselectively transformed into chiral 2-oxyranyl ketones **4** by means of asymmetric organocatalytic methods. Here, we report a general approach for the synthesis of chiral 2-oxyranyl ketones **4** by using the aerobic oxidation of tertiary cyclopropanols **2** to peroxyketone intermediates **3** followed by stereoselective elimination of water.

To achieve this goal, the following major steps must be implemented: (1) development of the effective aerobic oxidation protocol yielding β-peroxyketones **3**; (2) finding the conditions and organocatalyst suitable for the enantioselective conversion of **3** into **4**; and (3) combination of these two processes into the one-pot procedure. The first oxidation step was studied on a model compound 1-(2-phenylethyl)-cyclopropanol (**2a**) (Scheme 2). Among different transition-metal complexes used to catalyze the aerobic oxidation of cyclopropanols,[9] manganese salts were found to be the most effective, affording high yields of β-peroxyketones.[9d,e,g] Shortcomings of the previously used procedure[9d] were the use of benzene as a solvent and molecular oxygen as an oxidant. We found that the aerobic oxidation of cyclopropanol **2a** can be easily achieved in less toxic solvents by simple stirring of a solution of **2a** and a manganese catalyst under air in open flask, affording peroxide **3a** in high yield (up to 95% according to NMR analysis). The best results were achieved in environmentally benign dimethyl carbonate (DMC),[10] THF, and 2-

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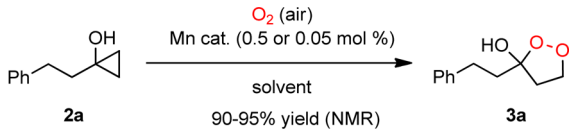
Scheme 2. Aerobic Oxidation of Cyclopropanol 2a[a]



solvents: dimethyl carbonate (DMC), THF, MeTHF
Mn catalysts: $Mn(OAc)_2$, $Mn(acac)_3$, MnCl(OEP)[b]

[a]Reaction conditions: **2a** (0.5 mmol) and Mn catalyst were dissolved in 0.5 mL of a solvent and stirred under air (open vial) until full conversion of starting material (TLC monitoring). [b]OEP = 2,3,7,8,12,13,17,18-octaethylporphyrin.

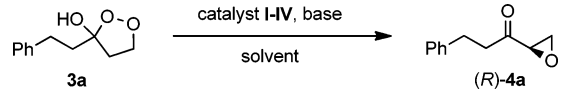
methyltetrahydrofuran (MeTHF) with 0.5 mol % of manganese acetate and acetylacetonate catalysts (see Table S1, entries 2, 3, and 6–8). The latter was especially effective, allowing the rate of aerobic oxidation to increase and affording the full conversion of starting material within 3 h even at 0.05 mol % loading. The formation of minor amounts of identified byproducts can be further suppressed by performing the oxidation at 0 °C (see Table S1, entry 11).

It has been demonstrated that metalloporphyrins that are easily soluble in many organic solvents may also be effectively used as oxidation catalysts.[11] In our hands, 0.5 mol % of MnCl(OEP) catalyst (OEP = 2,3,7,8,12,13,17,18-octaethylporphyrin) afforded peroxide **3a** in nearly quantitative yield in dimethyl carbonate as a solvent (see Table S1, entry 12). However, oxidation proceeded considerably slower compared with the other manganese salts, presumably as a result of additional steric hindrance caused by the porphyrin ligand. Other potential oxygen carriers like iron and cobalt porphyrin complexes were inefficient in catalyzing the aerobic oxidation of **2a**.

The main task of the current study was to perform the enantioselective transformation of peroxide **3a** into epoxy ketone **4a**. To find the suitable conditions, several well-known organocatalysts were first tested. Our initial attempts with cinchona-alkaloid-derived primary amine **I** (as TFA salt),[5a,12] thiourea **II**, and squaramide **III** failed to afford the desired epoxy ketone **4a** (Table 1, entry 1). However, commercially available poly-L-leucine (PLL on silica gel, catalyst **IV**)[13] in the presence of 1 equiv of DBU as a base resulted in the fast and quantitative conversion of peroxide **3a** into epoxy ketone **4a** with 86% ee (Table 1, entry 2). Although application of PLL for the asymmetric epoxidation of chalcones was commenced by Juliá and Colonna in the early 1980s[14] and the initial protocol was improved in the following intensive studies,[5c,15] we report here for the first time the enantioselective transformation of prochiral aliphatic peroxyketones using PLL catalyst. The composition of PLL used in our experiments was analyzed by MALDI MS.[16] Both catalysts (commercially purchased and prepared in our laboratory by polymerization of L-leucine *N*-carboxyanhydride with 1,3-diaminopropane initiator)[17] had a number-average degree of polymerization (DP_n) of about 17–18 and average molecular weight close to 2000–2100 (see the Supporting Information). These catalysts were used in the following screening of suitable reaction condition to transform peroxide **3a** into epoxy ketone **4a** (Table 1).

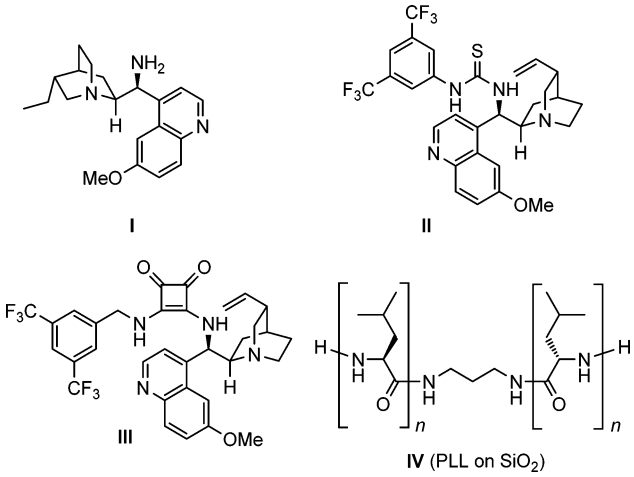
Starting from **3a**, in the presence of 7.5 mol % of PLL the reaction was completed within 1 h and 2-oxyranyl ketone **4a** was obtained in 86% ee at 20 °C (Table 1, entry 2). Lowering

Table 1. Asymmetric Transformation of Peroxide 3a into 2-Oxyranyl Ketone 4a[a]



entry	cat. (mol %)	solvent	base	temp (°C)	time (h)	ee[b] (%)
1	I–III (20%)	DMC		20	50	*c*
2	IV (7.5%)[d]	THF	DBU	20	1	86
3	IV (2.5%)	THF	DBU	20	1	34
4	IV (7.5%)	MeTHF	DBU	20	1	88
5	IV (7.5%)	toluene	DBU	20	1	74
6	IV (7.5%)	DME	DBU	20	1	68
7	IV (7.5%)	MTBE	DBU	20	1	64
8	IV (7.5%)	CH_2Cl_2	DBU	20	1	58
9	IV (7.5%)	DMC	DBU	20	1	48
10	IV (7.5%)	dioxane	DBU	20	1	32
11	IV (7.5%)	CH_3CN	DBU	20	1	16
12	IV (7.5%)	THF	DIPEA	20	12	70
13	IV (7.5%)	THF	TMP[e]	20	12	78
14	IV (7.5%)	THF	DBU	40	1	66
15	**IV (7.5%)**	**THF**	**DBU**	**−25**	**24**[f]	**94**

[a]Yield of 2-oxyranyl ketone **4a** for all reactions was considered as quantitative according to NMR. [b]Enantiomeric excess was determined by HPLC analysis using an AD-H column. [c]No epoxide **4a** formed. [d]Calculated according to average molecular weight of PLL polymer. [e]TMP = 2,2,6,6-tetramethylpiperidine. [f]The reaction mixture was stirred in a freezer at −25 °C for 24 h.



the amount of catalyst inevitably leads to a drastic decrease of the enantioselectivity (Table 1, entry 3). In addition, the used solvent strongly affects the enantiomeric purity of the product (Table 1, entries 4–11) with the highest ee values achieved in THF and MeTHF (86% and 88% ee, respectively).[18] Weaker bases than DBU also reduced the reaction rate and enantioselectivity of the product (Table 1, entries 12 and 13). Temperature is another important factor in the stereoselective epoxide formation: the ee of product **4a** dropped from 86% to 66% when the temperature was raised from 20 to 40 °C (Table 1, entry 2 vs 14). Lowering the temperature to −25 °C led to a noticeable improvement of the selectivity: **4a** was obtained with high 94% ee (Table 1, entry 15).

On the basis of the results of optimization studies, an operationally simple one-pot protocol for the conversion of cyclopropanols **2** into enantiomerically enriched 2-oxyranyl ketones **4** was attained under the following conditions: aerobic

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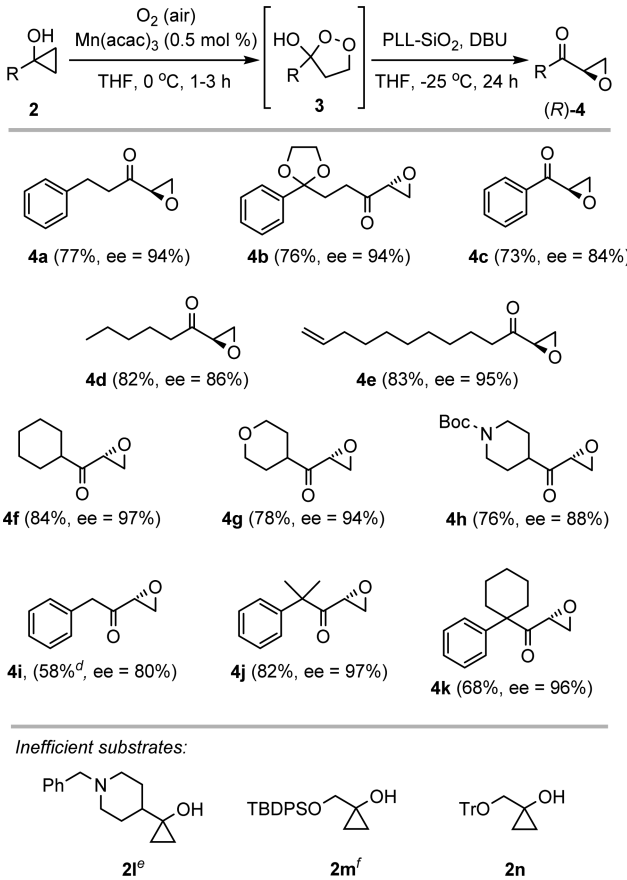
oxidation at 0 °C; THF as a solvent; 0.5 mol % of $Mn(acac)_3$ as an oxidation catalyst. The subsequent epoxide formation by using silica gel supported PLL and DBU at −25 °C. The products, epoxy ketones **4**, are isolated after filtration of the catalyst and evaporation of the solvent followed by purification with flash silica gel chromatography. Using these conditions at a 1.5 mmol scale, the isolated yield of epoxy ketone **4a** from cyclopropanol **2a** was 77% and the ee was 94% (Scheme 3).

Scheme 3. Asymmetric Synthesis of (*R*)-2-Oxyranyl Ketones 4 by Aerobic Oxidation of Tertiary Cyclopropanols 2[a,b]



[a]Typical reaction conditions: cyclopropanol **2** (1.5 mmol), THF (1.5 mL), $Mn(acac)_3$ (0.5 mol %); then PLL (240 mg) on SiO_2, DBU (1.5 mmol). [b]Isolated yields; enantiomeric excess was determined by HPLC analysis using an AD-H column. [c]Using 2 mol % of $Mn(acac)_3$. [d]Yield after quenching of the reaction mixture with 1 M AcOH. [e]No reaction. [f]TBDMS = *tert*-butyldimethylsilyl.

The following examples of oxidation of different functionalized tertiary cyclopropanols **2** to epoxy ketone **4** demonstrate a wide scope of this method (Scheme 3). The reaction proceeds smoothly and affords the corresponding epoxy ketones **4** in good isolated yields (68−84%) and in high enantioselectivities (84−97% ee), giving primary and secondary alkyl- (**4d**, **4f**), phenyl- (**4c**), and alkenyl-substituted (**4e**) epoxy ketones. Even the functionalized compounds bearing 1,3-dioxolane **4b**, tetrahydropyranyl **4g**, and Boc-protected piperidine **4h** moieties were obtained flawlessly.

To test some mechanistic aspects of the aerobic oxidation, a piperidine derivative **2l** was also tested in this reaction. As expected, the reaction did not occur due to the inactivation of manganese catalyst with the amino function of substrate. We also observed the inhibition of aerobic oxidation of **2a** by MnCl(OEP) catalyst in the presence of pyridine and *N*-methylimidazole. A commonly accepted mechanism of the aerobic oxidation of cyclopropanols implies the single-electron transfer (SET) from a cyclopropanol substrate yielding the oxoalkyl radical, which is rapidly intercepted by molecular oxygen.[9] Strong coordination of amino ligands to the manganese catalytic center prevents a weaker binder, such as cyclopropanol, to interact with the metal ion, hence making the SET process less probable.

A one-pot protocol for cyclopropanols **2n** and **2m** failed: the first aerobic oxidation step proceeded smoothly (within 3 h), but the subsequent epoxide forming step was very slow and resulted in the tar formation for compound **2m**. The preparation of benzyl-substituted epoxy ketone **4i** under standard conditions was problematic because of decomposition caused by enolization in the presence of DBU. This process was suppressed by addition of acetic acid at −25 °C after the completion of epoxidation, giving 58% isolated yield of **4i**. The nonenolizable benzyl ketones **4j** and **4k** were obtained in good yields and excellent enantioselectivities (96−97% ee).

To define the stereochemistry of products **4**, the value of optical rotation of **4c** and **4i** (see the Supporting Information) was compared with the literature data for the corresponding *R*-[19] and *S*-isomers,[20] thus confirming the *R*-configuration of compounds obtained. The same stereoconfiguration is expected from the model of Kelly and Roberts.[15a−c,21] The α-helical structure of PLL catalyst and *N*-terminal amino groups are essential for the supramolecular binding of prochiral substrate **3** to provide an oxy-anion hole for the hydrogen bonding of peroxyenolate intermediates, thus favoring a *re* transition state leading to the *R*-enantiomer.

In conclusion, we have developed a practical and efficient one-pot approach for the synthesis of enantiomerically enriched 2-oxyranyl ketones **4** by aerobic oxidation of easily available cyclopropanols **2** via intermediate formation of peroxyketone intermediates **3**, followed by enantioselective epoxide formation in the presence of poly-L-leucine catalyst and DBU. The experimental protocol is operationally simple, utilizing atmospheric oxygen as an eco-friendly reactant and poly-L-leucine as a "green" catalyst. The method affords high yields and good-to-excellent enantiomeric purity of the epoxy ketone products. This strategy can be effectively applied as a straightforward approach to chiral 2-oxyranyl ketones **4**, which are highly demanded synthetic intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01519.

Experimental details and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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