

Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

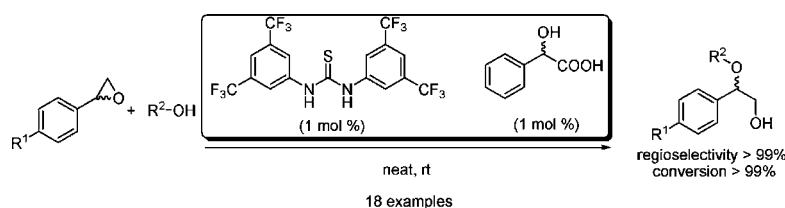
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ABSTRACT



We present a mild and efficient method for the completely regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid-type organocatalytic system comprised of mandelic acid (1 mol %) and *N,N'*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (1 mol %). Various styrene oxides are readily transformed into their corresponding β -alkoxy alcohols in good to excellent yields at full conversion. Simple aliphatic and sterically demanding, as well as unsaturated and acid-sensitive alcohols can be employed.

Catalytic epoxide ring opening reactions with neutral^{1–3} and charged nucleophiles^{1,2,4,5} provide access to a broad spectrum of valuable intermediates; the addition of alcohols leads to the synthetically important class of β -alkoxy alcohols.^{2,4,6,7} Classical Brønsted acid catalysis is the most widely used method for epoxide openings through protonation of the basic

epoxide oxygen that facilitates the ring opening with the nucleophile.⁸ The use of strong mineral acids is naturally limited to acid-stable compounds; Lewis acids have also been widely used as catalysts for epoxide ring openings.^{2,6} Nature, however, uses an entirely different path for epoxide hydrolysis, which is key for removing unsaturated toxic organic compounds (through epoxidation and subsequent hydrolysis).⁹ There are numerous enzymes that catalyze this reaction, and a common motif is the activation of the epoxide through (double) hydrogen bonding to, e.g., tyrosine residues.¹⁰ Such enzymatic ring opening reactions are mild but also often sensitive toward pH and solvent.^{11,12} Recently, we have successfully utilized this motif, inter alia,¹³ for epoxide

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Table 1. Alcoholysis of Styrene Oxides with Mandelic Acid (**5a**)

| no. ^a | R ¹ | 1 | alcohol (R ² -OH) 2 | prod. | <i>t</i> [h] | % ^d |
|------------------|----------------|-----------|---------------------------------------|---------------------|--------------|----------------|
| 1 | H | 1a | | 2a 4a | 18 | 85 |
| 2 | H | 1a | | 2b 4b | 22 | 86 |
| 3 | F | 1b | | 2b 4c | 24 | 57 |
| 4 | <i>t</i> Bu | 1c | | 2b 4d | 15 | 65 |
| 5 | H | 1a | | 2c 4e | 21 | 73 |
| 6 ^b | H | 1a | | 2d 4f | 15 | 74 |
| 7 ^b | F | 1b | | 2d 4g | 18 | 57 |
| 8 ^b | <i>t</i> Bu | 1c | | 2d 4h | 16 | 65 |
| 9 | H | 1a | | 2e 4i | 21 | 94 |
| 10 | H | 1a | | 2f 4j | 20 | 73 |
| 11 | H | 1a | | 2g 4k | 23 | 89 |
| 12 | H | 1a | | 2h 4l | 18 | 80 |
| 13 | H | 1a | | 2i 4m | 23 | 78 |
| 14 ^c | H | 1a | | 2j 4n | 32 | 41 |
| 15 | H | 1a | | 2k 4o | 16 | 65 |
| 16 | F | 1b | | 2k 4p | 17 | 63 |
| 17 | <i>t</i> Bu | 1c | | 2k 4q | 39 | 70 |
| 18 ^b | H | 1a | | 2l 4r | 18 | 58 |

^a Reaction conditions: 1 equiv of **1**, 12 equiv of alcohol, and 1 mol % of **3** and **5a** respectively; rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. No polymers of styrene oxide were detected. All reference experiments showed no conversion at the presented reaction time if not otherwise noted. Reactions were monitored by GC/MS. Regiochemistry was determined by NMR experiments (³J CH-coupling) and fragmentation in MS. ^b At 50 °C. ^c 3 mol % of **5a**; 2 equiv of alcohol; at 50 °C. ^d Yield of isolated product.

openings with strong nucleophiles. We demonstrated that the effects of hydrogen-bonding organocatalysis and water as the solvent are *cooperative* and termed this “hydrophobic amplification”.¹⁴ Apparently, the approximately neutral pH and the presence of water also are key factors in THP-templated epoxide openings in cascade reactions leading to structures akin to Brevetoxin A.¹² As water can effectively compete with weaker nucleophiles, we set out to develop an alternative approach that relies on using *two* cooperative

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hydrogen-bonding catalysts. With regards to the choice of mild acid (**5**) to be used with *N,N*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (**3**),¹⁵ we were helped by the fact that we observed that undistilled styrene oxide (**1a**) readily reacted with various alcohols while freshly distilled **1a** did not. As the oxidation product of **1a** is mandelic acid (**5a**),^{9,16} this acid was our first choice. The initial results were very promising and encouraged us to examine this remarkable reaction further.

While carboxylic acids are known to increase the reaction rates of some nucleophilic organocatalytic reactions¹⁷ this is a rare example of a cooperative Brønsted acid-type organocatalytic system.¹⁸ Optimization of the reaction conditions led to a protocol that utilizes 12 equiv of the alcohol as nucleophile and solvent; this effectively suppresses the formation of byproducts resulting from attack of the product on **1** (see Supporting Information for details).

Styrene oxides can readily be transformed into β -alkoxy alcohols in good to excellent yields; all catalyzed reactions are completely regioselective and show full conversion. Both simple aliphatic and sterically demanding (Table 1, entries 1–10), as well as unsaturated (entries 12, 13) and especially acid-labile alcohols (entries 14–18) can be utilized. In general, the reaction times depend more on the nature of the epoxide substrate (**1**) than on the alcohol (**2**). The more reactive **1c** leads nearly in all cases to faster conversions (Table 1, entries 4 and 8); the sole exception is the reaction of cinnamyl alcohol (**2k**) with **1c**. An electron-deficient styrene oxide (**1b**) leads to longer reaction times and lower yields. The reactions of styrene oxides with *tert*-butanol (**2d**, entries 6–8) were all carried out at 50 °C and afforded yields from 57% to 74% without byproduct formation. All reference experiments for these reactions (entries 6–8) showed no conversion; even after 17 days the reference experiment of entry 8 without **3** showed less than 5% conversion. No decomposition or polymerization reactions could be detected for the acid-labile substrates **2j**, **2k**, and **2l**.

Table 2. Solvent Effect on the Alcoholysis of Styrene Oxide with Ethanol^a

| solvent | time [h] | temp. [°C] | conv. of 1 [%] |
|------------------|----------|------------|-----------------------|
| ethanol | 22 | rt | >99 |
| acetonitrile | 48 | rt | – |
| acetonitrile | 20 | 50 | ~9 |
| THF | 48 | rt | >99 |
| toluene | 20 | rt | – |
| toluene | 16 | 50 | >99 |
| <i>n</i> -hexane | 48 | rt | >99 |

^a Reaction conditions: 1 equiv of **1**, 2 equiv of **2b**, 2 vol equiv of solvent, and 1 mol % of **3** and **5a**, respectively, rt.

We examined various solvents for the conversion of solid alcohols or epoxides (Table 2) with our test reaction and

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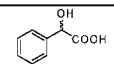
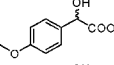
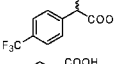
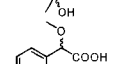
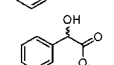
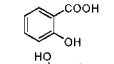
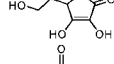
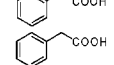
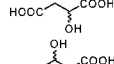
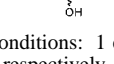
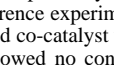
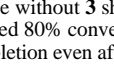
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found a remarkable solvent effect. Reactions in ethanol were more than two times faster than reactions in nonpolar or aprotic solvents.¹⁹ To optimize our cooperative catalyst system, we also varied the ratio between **3** and **5a**²⁰ and utilized various mandelic acid derivatives.²¹

Further Brønsted acid screening (Table 3) revealed that

Table 3. Brønsted Acid Screening

| no. ^a | acid additive | p <i>K</i> _a | <i>t</i> [h] | conv. [%] ^b | |
|------------------|---|-------------------------|-------------------|------------------------|------|
| 1 |  | 5a | 3.37 | 22 | > 99 |
| 2 |  | 5b | 3.43 ^c | 19 | > 99 |
| 3 ^c |  | 5c | 3.01 ^c | 16 | > 99 |
| 4 |  | 5d | 4.05 ^e | 24 | ~5 |
| 5 |  | 5e | 3.10 ^e | 26 | -- |
| 6 |  | 5f | -- ^f | 26 | -- |
| 7 |  | 5g | 3.00 | 26 | ~12 |
| 8 |  | 5h | 4.10 | 26 | -- |
| 9 ^d |  | 5i | 2.10 ^e | 12 | > 99 |
| 10 |  | 5j | 4.28 | 26 | -- |
| 11 |  | 5k | 3.41 | 26 | -- |
| 12 |  | 5l | 2.93 | 26 | -- |

^a Reaction conditions: 1 equiv of **1**, 12 equiv of ethanol, and 1 mol % of **3** and **5a–l**, respectively, rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. Reference experiments showed no conversion. ^b Reactions were monitored by GC/MS. ^c Reference without **3** showed 12% conversion after 18 h. ^d Reference without **3** showed 80% conversion after 15 h; remarkably, the reaction does not run to completion even after 3 days. ^e Calculated data. ^f No experimental or calculated data available.

only aromatic acids bearing a second coordination center in the α -position (hydroxy or carbonyl) led to appreciable conversions (entries 1–3, 9). The removal or blocking of the α -coordination center (**5j** and **5e**) or removal of the aromatic system dramatically reduces the conversion rates. Aqueous acidity (p*K*_a) appears not to be a good predictor for catalyst activity (entry 12).

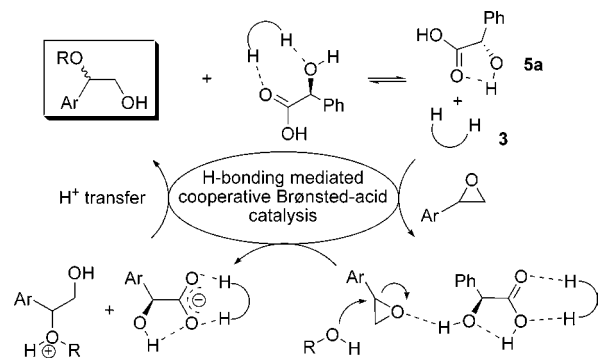
Our experimental findings suggest an H-bonding-mediated cooperative Brønsted-acid catalysis mechanism (Scheme 1).

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(20) Surprisingly, reaction times in all cases are nearly equal, although GC/MS analysis after 15 h showed more than two times faster conversion in case of 7 mol % of **3** than in case of our standard protocol (1 mol % of **3**). The results are available in the Supporting Information.

(21) We observed a nonlinear catalytic effect for the ethanolysis of **1** with a notable rate enhancement in the second half of the reaction period. This is apparently not a case of autocatalysis through product **4b** because addition of 20 mol% of **4b** to our standard test reaction showed no variation relative to our standard protocol. Further mechanistic investigations are currently underway.

Scheme 1. Proposed Catalytic Cycle for Epoxide Alcoholysis through H-Bonding-Mediated Cooperative Catalysis



It is likely that co-catalyst **3** coordinates to the acid **5a** through double H-bonding, stabilizes **5a** in the chelate-like

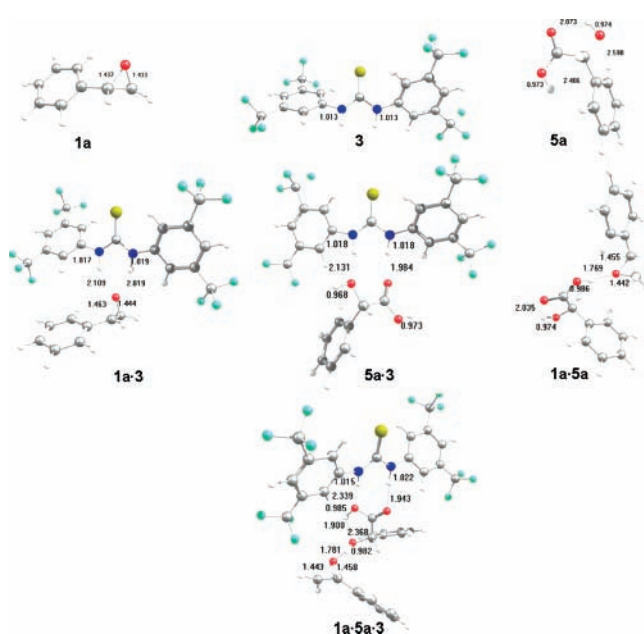


Figure 1. Minimum-energy structures of monomers **1a**, **3**, and **5a**, binary (**1a·3**, **5a·3**, and **1a·5a**) and ternary complexes (**1a·5a·3**) optimized at B3LYP/6-31+G(d,p).

cis-hydroxy conformation, and acidifies the α -OH proton via an additional intramolecular H-bond. The epoxide then is activated by a single-point hydrogen bond that facilitates regioselective nucleophilic attack of the alcohol at the benzylic position. Such monodentate binding was recently suggested for diol catalysts.²² The incipient oxonium ion reprotonates the mandelate and affords the β -alkoxy alcohol product.

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Table 4. Stabilization Energies, H-Bond Distances and Bond Lengths at B3LYP/6-31+G(d,p)

| complex | ΔH_0 [kcal/mol] | HB distance [Å] | bond length [Å] |
|----------------|-------------------------|---|-------------------------|
| 1a•3 | -9.2 | NH \cdots O 2.109 | N-H 1.017 |
| | | NH \cdots O 2.019 | N-H 1.019 |
| | | | C ¹ -O 1.463 |
| | | | C ² -O 1.444 |
| 5a•3 | -11.9 | NH ¹ \cdots O ¹ 2.131 | N-H ¹ 1.018 |
| | | NH ² \cdots O ² 1.984 | N-H ² 1.018 |
| | | | O-H 0.973 |
| | | | O-H (α) 0.968 |
| 1a•5a | -5.7 | OH \cdots O 1.769 | O-H 0.986 |
| | | | O-H (α) 0.974 |
| | | | C ¹ -O 1.455 |
| | | | C ² -O 1.442 |
| | | NH ² \cdots O ² 1.943 | N-H ² 1.022 |
| | | OH (α) \cdots O 1.781 | O-H 0.985 |
| | | | O-H (α) 0.982 |
| 1a•5a•3 | -20.0 | NH ¹ \cdots O ¹ 2.339 | C ¹ -O 1.458 |
| | | | C ² -O 1.443 |
| | | | N-H ¹ 1.015 |
| | | | |

DFT computations lend credibility to the suggested mechanism. At the B3LYP/6-31+G(d,p) level^{23,24} a binary complex between **3** and **5a** is thermochemically favored by 2.7 and 6.2 kcal/mol as compared to complexes **1a•3** and **1a•5a**

(Figure 1, Table 4). The rather strong complexation of epoxides with thiourea derivatives was recently found by us¹⁴ and Connon et al.²⁵ The ternary complex has an overall binding energy relative to its components of remarkable 20.0 kcal/mol, and this explains the concept of cooperativity of the two catalysts. This prompted us to use an NMR titration to determine the **5a•3** complexation energy but found, even upon inclusion of elaborate DOSY experiments, that the binding is too strong to be measured with conventional means. Further experimental and computational studies are underway.

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Supporting Information Available: Experimental and computational details as well as characterization of all new compounds. This material is free of charge via the Internet at <http://pubs.acs.org>.

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