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Asymmetric Organocatalysed Synthesis of (*R*)-Mandelic Acid Esters and α-Alkoxy Derivatives from Commercial Sources

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Optically active mandelic acid esters represent a highly valuable class of building blocks in organic synthesis and recurrent motifs embedded in bioactive compounds and drugs. Herein, we provide an enantioselective one-pot synthesis based on Knoevenagel condensation/asymmetric epoxidation/domino ring-opening hydrolysis (DROH) sequence to the crude mandelic acids, which underwent a final esterification step to (*R*)-methyl mandelates. These products have been obtained in good to high overall yield and enantioselectivity, using commercially and widely available reagents and catalyst including aldehydes, phenylsulfonyl acetonitrile, cumyl hydroperoxide, water and an *epi*-quinine-derived urea as the organocatalyst. Moreover, the versatility of the process has been demonstrated to prepare the corresponding α-alkoxy esters in highly enantioselective manner, when using primary alcohols in a domino ring-opening esterification (DROE) step. This system is a first example of non-enzymatic catalytic one-pot protocol which allows a straightforward asymmetric synthesis of highly valuable mandelic acid derivatives from aldehyde feedstocks.

Introduction

Optically active mandelic acid derivatives are recognized as useful small molecules, often employed as building blocks in asymmetric synthesis, as chiral solvating agents and mostly in the pharmaceutical and chemical industries.[1] Indeed, they are found in the structure of drugs, exemplified by Cefamandole, a second generation cephalosporin antibiotic,[2] or being key-precursor for preparation of well-known antiplatelet drug Clopidogrel,[3] and by Homatropine used as a mydriatic for the pupil dilatation[4] (Figure 1).

In consideration of the importance of mandelic acids and esters, a variety of enantioselective methodologies have been developed over the last decades.[5] Interestingly, the biocatalytic preparation of mandelic acids has been investigated using different classes of enzymes, where the most common are nitrilases,[6] followed by lipases[7] and dehydrogenases[8] (Scheme 1A).

More recently, cascade biocatalytic oxidative processes have been devised to obtain mandelic acids starting from aldehydes[9] or styrene epoxides.[10] Notable features of the biocatalysed processes are i) mild reaction conditions; ii) limited use of organic solvents and iii) high enantioselectivity. However, the main disadvantage is the lack of generality in terms of stereocontrol and conversion attainable, both strongly substrate

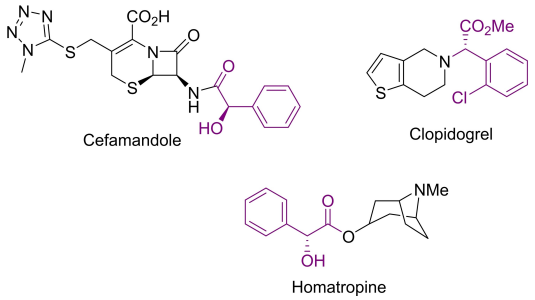
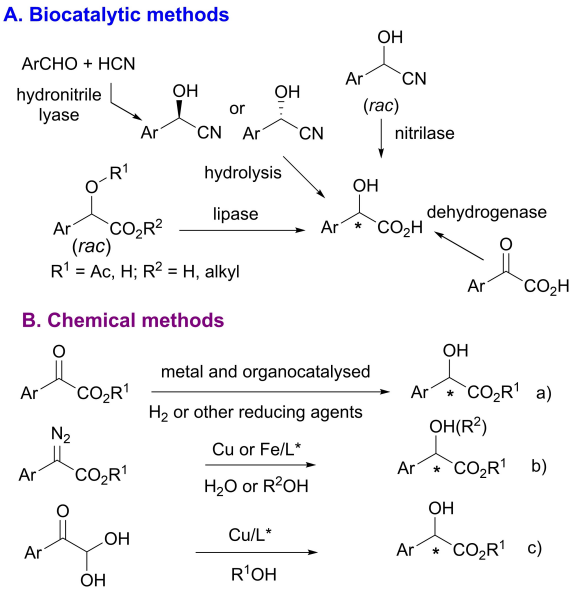


Figure 1. Examples of optically active drugs containing mandelic acid subunits.



Scheme 1. Synthetic tools to prepare optically active mandelic acid derivatives.

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specific, thus limiting the number of mandelic acid derivatives obtainable.

Amongst the chemical methods available, mostly represented by chiral ligand metal-catalysed systems, a significant number of reductive procedures from α-keto esters have been successfully developed (Scheme 1Ba).[11] Copper-[12] or iron-catalysed[13] processes, where water is involved as a highly desirable reagent, have been developed via C–H oxidation of α-diazoesters (Scheme 1Bb). Intramolecular asymmetric Cannizzaro reaction of glyoxal monohydrates, mediated by a chiral Cu-complex, has been disclosed to afford a great variety of sterically encumbered mandelate esters with high enantioselectivity (Scheme 1Bc).[14] Additional metal-catalysed approaches have been used to access this class of compounds.[15]

The development of cascade multienzymatic reactions to enantioenriched mandelic acid derivatives increased significantly over the last years, with additional benefits for the sustainability of the entire process.[16] On the other hand, the chemical methods still required starting reagents to be synthesized, before their use in the key asymmetric reaction, as commonly done in a classical *stop and go* approach.

We recently disclosed a new class of 1-phenylsulfonyl-1-cyano epoxides,[17] which can be one-pot generated and ring-opened by different nucleophiles via domino ring-opening cyclization (DROC) or esterification (DROE) processes to give privileged nitrogen α-substituted carboxylic acid derivatives, including piperazinones,[18] tetrahydro-1,4-benzodiazepin-2-ones[19] and α-amino esters[20] (Scheme 2a).

One-pot Knoevenagel condensation/asymmetric epoxidation/domino ring-opening operations, involving commercially available feedstocks and organocatalyst, enabled to prepare the products in good to high overall yield and enantioselectivity.

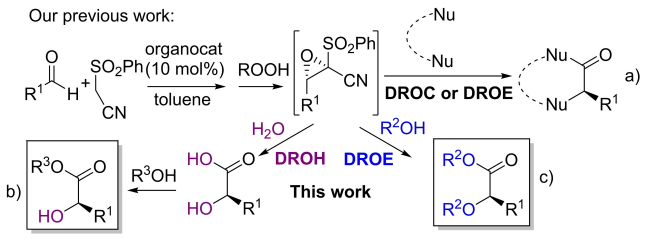
Interestingly, although water represents a poor nucleophile, racemic 1,1-dicyano epoxides have been ring-opened by water under refluxing conditions, to give α-hydroxy carboxylic acids.[21] Hence, we envisioned that our approach might be exploited to set up a one-pot asymmetric synthesis of mandelic acids, using water as a challenging nucleophile in a DROH step of the epoxide intermediate, then followed by esterification (Scheme 2b). Moreover, when using alcohols, the corresponding α-alkoxy esters would have been obtained (Scheme 2c), which are exclusively prepared via enantioselective metal-catalysed OH insertion of hazardous α-aryl-α-diazo esters.[22] Herein, we illustrate an enantioselective new approach, using commercially available reagents and catalyst to mandelic esters and their α-alkoxy derivatives, obtained in good to high yields and enantioselectivity. This work represents a first one-pot asymmetric chemo-synthesis of these valuable compounds and an uncommon example of water and alcohols as pertinent reactants in highly selective epoxide ring-opening reactions.

Results and Discussion

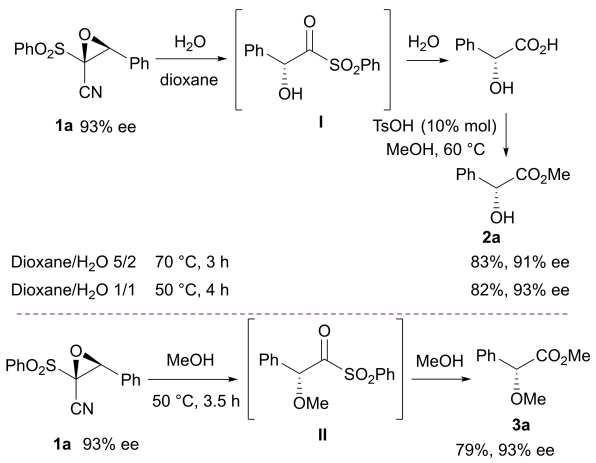
To verify the feasibility of the one-pot sequence illustrated in Scheme 2, a preliminary investigation on enantioenriched model (*S*,*S*)-epoxide **1a** of the DROH and DROE steps, using water and MeOH respectively, has been undertaken (Scheme 3).

Pleasingly, when working in a 5/2 mixture of dioxane/water at 70 °C,[21] a clean formation of mandelic acid was achieved, which after extraction underwent direct esterification with MeOH to give ester (*R*)-**2a** in 83% overall yield and almost comparable ee value. With a view to increase the conversion and control potential epimerization which can occur either during the capture of the intermediate **I** or during the esterification step, the water content was increased (dioxane/water 1/1) and the reaction performed at 50 °C. Involvement of intermediates of type **I**, has been previously supported by HRMS analysis.[17] These conditions proved to be more effective and product **2a** was recovered in 82% yield and 93% ee. Accordingly, the DROE step was then carried out using MeOH as the nucleophile at 50 °C. We were very pleased to isolate α-alkoxy methyl ester **3a** in 79% yield and 93% ee, after a short reaction time. It has to be noted that the ee value achieved for compounds **2a** and **3a** is identical to the highest ee value achievable in the key asymmetric epoxidation step.[17]

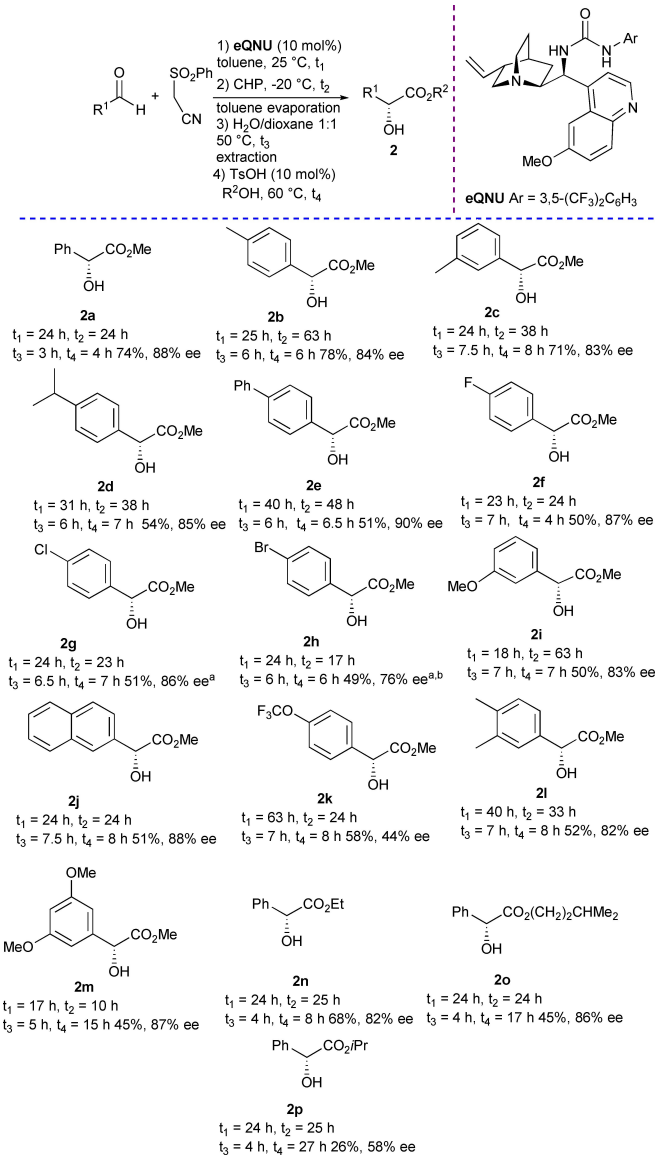
Having established suitable reaction conditions to perform the crucial domino ring-opening sequences, the Knoevenagel condensation/asymmetric epoxidation/DROH sequence followed by esterification to products **2**, was investigated. According to previously optimized conditions,[17] *epi*-quinine derived urea (**eQNU**) was used at 10 mol% to assess the scope and limitation of the process (Scheme 4).



Scheme 2. One-pot organocatalytic synthesis of enantioenriched mandelic acid and α-alkoxy derivatives from aldehydes.



Scheme 3. Preliminary study of the DROH and DROE steps on enantioenriched epoxide **1a**.



Scheme 4. Reaction conditions: 1) Knoevenagel step: (phenylsulfonyl)acetonitrile (0.1 mmol), aldehyde (0.11 mmol), **eQNU** (0.01 mmol) in anhydrous toluene (C = 0.3 M). 2) Epoxidation step: dilution of the reaction with toluene (C = 0.02 M) at −20 °C, then addition of CHP (0.11 mmol). At the end of the reaction, toluene was evaporated. 3) Dioxane (0.5 mL) and water (0.5 mL) were added in the reaction vessel and the reaction mixture stirred at 50 °C. After extraction, the crude mandelic acid was dissolved in alcohol (5 mL), *p*-toluenesulfonic acid (10 mol %) added and stirring maintained at 60 °C.
[a]The DROH step was carried out at 30 °C. [b]In the DROH step a saturated solution of $NaHCO_3$ was used. Yields refer to isolated products; ee were determined by HPLC on a chiral stationary phase.

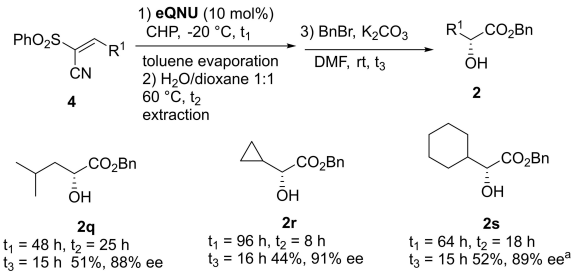
When starting from benzaldehyde as the reagent, the corresponding (*R*)-methyl mandelate **2a** was obtained in 74% overall yield and 88% ee. With a view to explore the feasibility to conduct the DROH step in a greener solvent, acetone/water 1/1 mixture was used. The disappearance of the epoxide proceeded more slowly (8.5 h) and after the esterification step product **2a** was obtained in 48% yield and 88% ee. Although this result is less satisfactory as the one observed when using dioxane, the process can be performed under more sustainable conditions, using acetone as co-solvent in the DROH step.

Electron-donating and phenyl groups in the aromatic ring are well tolerated and the corresponding methyl mandelates **2b-e** have been recovered in high overall yield and fairly good ee values, whereas halogen- and methoxy-substituted mandelate esters **2f-i** were obtained with slightly inferior yield and ee values.

2-Naphthyl methyl mandelate **2j** was recovered in 51% yield and 88% ee. Unfortunately, significant epimerization was observed for mandelate **2k**, bearing the electron-withdrawing CF_3O group at the *para* position of the phenyl ring, which showed 44% ee. *ortho*-Substituted aldehydes were not investigated in the process, being the corresponding epoxides obtainable with significant lower ee values in the epoxidation step.[17]

Doubly substituted onto the aromatic ring mandelates **2l** and **2m**, were also successfully isolated with good yield and up to 87% ee. Next, other mandelate esters were synthesized using different alcohols in the esterification step, starting with benzaldehyde as the reagent. When using primary alcohols of increasing bulkiness, such as ethanol and isoamyl alcohol, esters **2n** and **2o** were isolated with decreased yield, but good ee values, respectively. Unsurprisingly, esterification with sterically demanding isopropanol required longer reaction time, with product **2p** obtained in moderate 26% yield and 58% ee. Overall, these data clearly suggest that a significant degree of epimerization for model substrate (R^1 = Ph) occurs during the esterification step of mandelic acid, according to the nature of the alcohol used and when prolonged reaction time is required. However, partial epimerization of α-ketosulfonyl intermediate **I** during the DROH step of the epoxide by water could occur, affecting the ee value of the product.

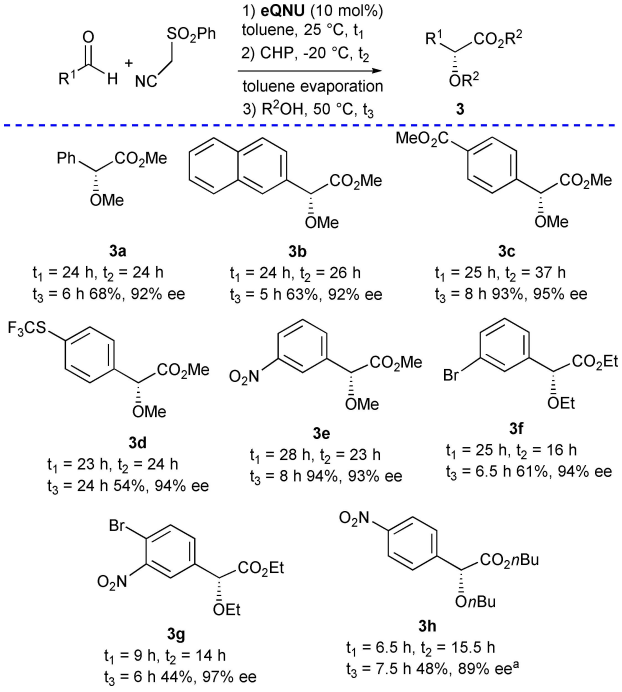
Next, the one-pot sequence has been studied starting from β-aliphatic alkenes **4**, with a view to further assess the scope (Scheme 5). In this case, the crude α-hydroxy acid underwent esterification under basic conditions with benzyl bromide. Interestingly, the methodology appears not to be restricted to aromatic α-hydroxy acid derivatives, being the (*R*)-configured acyclic and cyclic α-hydroxy benzyl esters **2q-s** obtained in good overall yield and high ee values (88–91% ee).



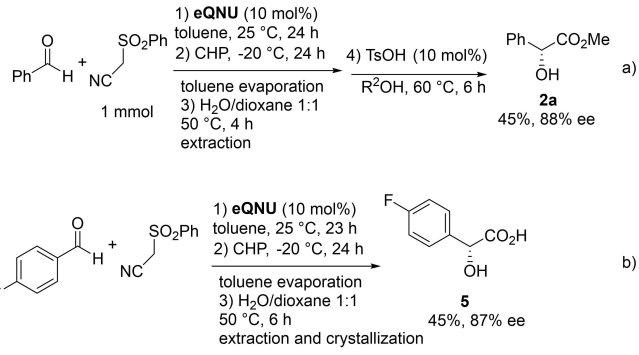
Scheme 5. Reaction conditions as reported in Scheme 4 starting from 0.1 mmol of the alkene **4**. After extraction, the crude mandelic acid was dissolved in 200 μL of DMF, K_2CO_3 (0.06 mmol) and benzyl bromide (0.1 mmol).
[a]The DROH step was carried out at 80 °C. Yields refer to isolated products; ee were determined by HPLC on a chiral stationary phase.

Moreover, a one-pot approach to the α-alkoxy esters **3** has been investigated, using primary alcohols as the nucleophiles (Scheme 6).

Delightfully, when using methanol, compounds **3a** and **3b** were obtained in fairly good yield and high ee values. Interestingly, when using aldehydes bearing different EWG as the reagent, the corresponding α-methoxy methyl esters **3c-e** were recovered in high yield and enantioselectivity, in contrast to what observed in Scheme 4. Ethanol and butanol proved to be also effective in the DROE step, yielding products **3f-h** with high enantioselectivity. It is worth mentioning the excellent 97% ee, achieved in the case of product **3g**, bearing nitro and bromine groups in the phenyl ring. Notably, in the one-pot sequence reported in Scheme 6, epimerization is essentially a negligible event, when using primary alcohols and sensitive compounds.[23]



Scheme 6. Reaction conditions as reported in Scheme 4 up to the epoxidation step. At the end of the reaction, toluene was evaporated. 3) R^2OH (1 mL) was added in the reaction vessel and the reaction mixture stirred at 50 °C. Yields refer to isolated products; ee were determined by HPLC on a chiral stationary phase.
[a]The DROE step was carried out at 60 °C.



Scheme 7. Scale up of model reaction from benzaldehyde to mandelate methyl ester **2a** and application of the one-pot methodolgy for the synthesis of building block **5**.

Finally, to have an idea of the process scalability, compound **2a** was prepared using 1 mmol scale of (phenylsulfonyl)acetonitrile under usual conditions (Scheme 7a).

The corresponding methyl mandelate **2a** has been obtained with somewhat lower yield, but the enantioselectivity was maintained.

(*R*)-4-fluoromandelic acid **5** has been used by AstraZeneca as building block for the synthesis of a key intermediate of the thrombin inhibitor AZD8165.[24] They used classical large scale resolution of racemic 4-fluoromandelic acid, via salt crystallization, using enantiopure (*R*)-1-phenylethylamine. After a first crystallization, the acid was obtained with 95% ee, then a second crystallization with the amine provided compound (*R*)-**5** with 26% yield and >99% ee. In this protocol, the synthesis of racemic 4-fluoromandelic acid was not mentioned, which precluded calculation of compound (*R*)-**5** overall yield from commercial reagents. Our one-pot approach from commercial reagents and catalyst, although performed at a small scale (0.4 mmol), afforded acid (*R*)-**5** in 45% overall yield and 87% ee (Scheme 7b).

Conclusions

We developed a first non-enzymatic catalytic one-pot asymmetric synthesis of high added value (*R*)-mandelic acid derivatives from commercially and widely available reagents, including aldehydes and the organocatalyst. An uncommon domino ring-opening hydrolysis of the in situ generated 1-phenylsulfonyl-1-cyano epoxides has been devised as a new strategy to obtain mandelic acids and their esters. Notably, the scope of the asymmetric process can be extended to access aliphatic α-hydroxy esters with comparable efficiency, starting from the alkenes. When an alcohol is used in the ring-opening process, the α-alkoxy esters have been isolated. The sequences easily provided the products in generally good to high overall yield and enantioselectivity. These five- or four-step single-pot methodologies compete well with other *stop and go* chemosyntheses of mandelic acid derivatives, conveniently reducing the purification procedures to one or two operations.

The work adds to the list of one-pot asymmetric and catalytic protocols enabled by 1-phenylsulfonyl-1-cyano epoxides, serving as a highly versatile example of a formal α-halo acyl halide synthon.[25]

Experimental Section

General Procedure for the Catalytic Asymmetric Synthesis of Compounds 2

To a solution of (phenylsulfonyl)acetonitrile (18.5 mg, 0.1 mmol) and the catalyst **eQNU** (5.8 mg, 0.01 mmol) in anhydrous toluene (350 μL), the proper aromatic aldehyde (0.11 mmol) was added. The reaction was stirred at 30 °C for 15–35 hours (monitored by TLC *n*-

hexane/ethyl acetate 7/3, UV light and potassium permanganate solution). After completion, the mixture was diluted with anhydrous toluene (4.7 mL) and cumene hydroperoxide (tech. 80%, 20 μL, 0.11 mmol) was added at −20 °C. The reaction was stirred at −20 °C for 14–38 hours (monitored by TLC *n*-hexane/ethyl acetate 8/2, UV light, phosphomolybdic acid solution). When the formation of the epoxide was complete, toluene was evaporated under vacuum, the crude was dissolved in 1,4-dioxane (0.5 mL) and water (0.5 mL, 0.5 mmol) was added. The reaction mixture was stirred at 30–50 °C for 3–25 hours until consumption of the epoxide (monitored by TLC, *n*-hexane/ethyl acetate 8/2). After completion, the mixture was basified by adding a saturated solution of Na_2CO_3 (20 mL). The aqueous phase was washed with chloroform (2×30 mL), then acidified with 12 N HCl and extracted with Et_2O (2×40 mL). The combined ethereal layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude α-hydroxy acid was directly dissolved in 5 mL of methanol, ethanol or isoamyl alcohol and *p*-toluenesulfonic acid was added (2 mg, 10% mol). The reaction mixture was stirred at 60 °C for 4–17 hours. After completion, the mixture was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$ (1×30 mL) and with water (1×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the final products without any other purification for **2a**, **2b**, **2c**, **2g**, **2i**, for the other compounds a purification with flash chromatography (*n*-hexane/ethyl acetate 100/0 to 80/20) was necessary.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric catalysis · Organocatalysis · One-pot reaction · Epoxides · Mandelic acids

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