Stereodivergent Access to Enantioenriched Epoxy Alcohols with Three Stereogenic Centers via Ruthenium-Catalyzed Transfer **Hydrogenation**

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S Supporting Information

ABSTRACT: The resolution technique of stereodivergent reaction on racemic mixtures (stereodivergent RRM) was employed for the first time in ruthenium complex catalyzed transfer hydrogenation of racemic epoxy ketones, providing a new and very simple method that allows access to enantioenriched epoxy alcohols with three stereogenic centers in a one-step fashion. The protocol features simple reaction conditions, practical operation, ability to scale up, and broad group tolerance.

xploitation of new methods realizing the rapid access to Highly important chiral building blocks is a popular research topic in both academic and industrial domains. Enantioenriched epoxy alcohols (EEA) with three stereogenic centers serve as important building blocks and starting materials in a variety of fields such as organic synthesis, chemical engineering, medicinal industry, and agrochemical production.¹ The state-of-the-art synthesis of such molecules mainly relies on three strategies. As shown in Scheme 1a, epoxidation of stoichiometric chiral allylic alcohols and reduction of chiral epoxy ketones are commonly used methods to produce the target EEAs, but the limited commercial availabilities of these chiral reagents prevent the wide utility of such a strategy, and in some cases, the diastereoselectivities of the reaction are hard to control.² Asymmetric catalytic approaches are more attractive to achieve the synthesis of EEAs with three stereocenters, but it is relatively surprising that to date extremely fewer one-step asymmetric catalytic methods have been developed to achieve this purpose, and in most cases multiple steps are needed, which result in relatively lower atom economy and higher cost.³ A selected fourstep asymmetric catalytic synthesis route is shown in Scheme 1b.3c To date, the most frequently used catalytic strategy allowing access to EEAs is still kinetic resolution of racemic allylic alcohols via asymmetric epoxidation, albeit with 50% theoretical yield.⁴ The representative milestone report was introduced by Sharpless in 1981 (Scheme 1c).^{4b} It can be seen that despite all these achievements, new methods leading to the rapid synthesis of EEAs are still highly needed.







The strategy of divergent reactions on racemic mixtures (divergent RRM), proposed by Kagan in 2001,⁵ has been widely accepted as a powerful technique allowing access to chiral molecules directly using racemic substrates.^{5,6} The strategy is advantageous in assembling structurally diversified molecules and shortening the synthetic routes in complex molecule

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synthesis such as natural products.⁷ However, to the best of our knowledge, this technique has not been used to achieve the onestep synthesis of EEAs using hydrogenation of easily available racemic epoxy ketones. The challenge is that the inherent substrate preference for the product stereoselectivity must be overcome. As illustrated in Scheme 2, a matched case favors both

Scheme 2. Challenge of Overcoming Substrate Preference in Divergent RRM



the substrate preference and the catalyst preference, thus leading to the formation of chiral product 2; however, a mismatched pair produces not only the catalyst-controlled product 3 but also minor product *ent*-2 due to the inherent substrate preference, thereby resulting in the enantioselectivity erosion of product 2. In the worst case, both enantiomers of the substrate would not match the chiral catalyst and provide both products with low ee values.^{6a}

In this context, we envisioned using transfer hydrogenation⁸ of racemic epoxy ketones through the technique of divergent RRM to realize the rapid synthesis of EEAs (Scheme 1d). If successful, this will provide one of the most simple and direct methods to achieve the above purpose. To our pleasure, the protocol could afford two separable diastereoisomers of EEAs in a one-step fashion, and the reaction employs very simple reaction conditions, tolerates various functional groups, and constitutes a complementary method to the classical kinetic resolution approach. Herein we report the results.

As shown in Table 1, we selected easily available racemic trans-1a as the model substrate for the study, and Noyori-type ruthenium complexes $A-C^9$ were surveyed. The first test of catalyst A^{9a} (5 mol %) in DMF led to the formation of both isomers but with 2a as the major one and with lower ee value (Table 1, entry 1), indicating the strong substrate control mentioned in Scheme 2. Changing the solvents to DCE and THF did not give better results (Table 1, entries 2 and 3), and lowering the temperature to 40 °C still could not overcome the substrate preference, leading to the formation of 2a as the major product (Table 1, entries 5-6). The reaction without additional solvent also failed (Table 1, entry 7). Catalyst \mathbf{B}^{9b} showed better ability in suppressing the substrate control, and 2a can be formed with up to 80% ee (Table 1, entries 8-10). Then we found that catalyst C, reported initially by Ikariya,^{9c} showed slightly better results considering the product distribution (Table 1, entries 11 and 12), and the use of PrOH could produce 2a and 3a in comparable yields with good level of enantioselectivity (Table 1, entry 13). Similar results were observed using dioxane as the solvent (Table 1, entry 14), and the reaction in the absence of additional solvent could also perform well (Table 1, entry 15). Then we decreased the catalyst loading to 2 mol %, and different levels of product enantioselectivity were detected with the variation of solvents (Table 1, entries 16–19). To our pleasure, the reaction without additional solvent using 2 mol % of C provided 2a and 3a in 46%





^{*a*}Reaction conditions: racemic **1a** (0.2 mmol), HCO_2H/Et_3N (1:3 v/ v, 1 mL), solvent (1 mL), under argon atmosphere; all yields are isolated yields and were based on **1a**; ee values were determined via HPLC analysis on a chiral stationary phase.

and 45% yields, with 90% and 98% ee, respectively (Table 1, entry 20). We also tested the reaction using mixed solvents, but inferior results were afforded (Table 1, entries 21-23); therefore, the conditions shown in entry 20 were established as the optimal ones.

Using the optimal conditions, we investigated the substrate scope and limitations of the protocol. Variation of R^1 unit using chloro- or fluoro-substituted phenyl groups resulted in no obvious influence on the results, delivering the corresponding stereoisomers with excellent enantioselectivities (Scheme 3, 2b/ 3b, and 2c/3c). Naphthyl group-substituted racemic epoxy ketone can also tolerate the reaction conditions, albeit with moderate ee values (Scheme 3, 2d/3d). Then we checked the alteration of R³ moiety using the 4-ClC₆H₄ group, and products 2e and 3e were formed with 83% and 98% ee, respectively (Scheme 3, 2e/3e). Similarly, when R^2 unit was replaced by 3chloro-substituted phenyl ring, the reaction afforded 2f and 3f with good level of enantioselectivities (Scheme 3, 2f/3f). Variation of both R¹ and R² moieties simultaneously proved possible, producing the corresponding products in high level of enantioselectivity (Scheme 3, 2g/3g, 2h/3h, and 2i/3i). Furthermore, changing both R¹ and R³ units was also possible,

Scheme 3. Substrate $Scope^{a,b}$



^{*a*}Racemic 1 (0.2 mmol), C (2.7 mg, 2 mol %), HCO_2H/Et_3N (1:3 v/ v, 1 mL), under argon atmosphere; all isolated yields were based on 1; ee values were determined via HPLC analysis on a chiral stationary phase. ^{*b*}C (1.5 mol %) was used.

producing 2j and 3j with moderate and excellent ee, respectively (Scheme 3, 2j/3j). Moreover, EEAs with two stereocenters could also be formed with good enantioselectivities (Scheme 3, 2k/3k). When R¹ was set as the aliphatic methyl group, the reaction proceeded smoothly, allowing access to 2l and 3l with good ee values (Scheme 3, 2l/3l). Meanwhile, racemic substrates with aliphatic ketone moieties also worked well, and the corresponding products were obtained with moderate to excellent ee (Scheme 3, 2m/3m and 2n/3n). Unfortunately, low

stereoinduction was observed when a substrate with an aliphatic R^2 group was used (Scheme 3, 20/30).

Somewhat to our surprise, the protocol shows higher reactivity toward *trans*-substrates when both *trans*- and *cis*-epoxy ketones are used. As shown in Scheme 4, under the

Scheme 4. Reaction Using a Mixture of trans/cis-1b



standard conditions, only *trans*-1b underwent the reduction, and *cis*-1b displayed almost no reactivity. The possible reason is that the *cis*-aryl group blocks the hydride attack on the carbonyl units.

We were glad to find that the scale-up reaction could work well, and no erosions on the product enantioselectivity were detected (Scheme 5a). Furthermore, the products can be easily

Scheme 5. Scale-up Reaction and Synthetic Applications



transformed to other synthetically useful building blocks. As shown in Scheme 5b, the oxidation of 3c led to epoxy ketone 4a in 90% yield, and the ring opening using NaN₃ resulted in the formation of 4b without erosion of the ee value. Moreover, the protection of the OH group of 3c afforded 4c with excellent enantioselectivity.

On the basis of the above experiments and the literature reports, we proposed the possible reduction modes of the process. As shown in Scheme 6, using racemic **1b** as the model

Scheme 6. Proposed Reaction Modes



substrate, two six-membered transition states between the ketone group and the Ru complex are proposed to explain the formation of the products (Scheme 6, TS-1 and TS-2).¹⁰ In more detail, the (2S,3R)-enantiomer of 1b will afford product 2b under catalyst-controlled selective reduction, and similarly, product 3b will be produced from the (2R,3S)-enantiomer of 1b.

In summary, we have developed a new method allowing access to enantioenriched epoxy alcohols in a one-step fashion. The protocol employs ruthenium-catalyzed direct-transfer hydrogenation on racemic epoxy ketones, and the resolution technique of divergent RRM was found feasible in this process. Different from the conventional classical kinetic resolution of allylic alcohols, this method displays 100% utilization of starting materials and can produce two separable diastereomeric epoxy alcohols, which constitutes one of the most straightforward approaches to make such valuable compounds in a catalytic fashion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01789.

Experimental procedures, spectroscopic data for all new compounds, and crystallographic data for 3j (PDF)

Accession Codes

CCDC 1908563 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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