Regiodivergent Hydroborative Ring Opening of Epoxides via Selective C−O Bond Activation

Marc Magre, Eva Paffenholz, Bholanath Maity, Luigi Cavallò,* and Magnus Rueping*

ABSTRACT: A magnesium-catalyzed regiodivergent C−O bond cleavage protocol is presented. Readily available magnesium catalysts achieve the selective hydroboration of a wide range of epoxides and oxetanes yielding secondary and tertiary alcohols in excellent yields and regioselectivities. Experimental mechanistic investigations and DFT calculations provide insight into the unexpected regiodivergence and explain the different mechanisms of the C−O bond activation and product formation.

INTRODUCTION

The broad presence of hydroxyl moieties in pharmaceuticals, agrochemicals, and fragrance chemistry have led to the development of efficient protocols for their synthesis.1 In this regard, epoxides can be easily converted to alcohols via a ring-opening reaction. It is well-known that nonsymmetrical epoxides afford mixtures of regioisomers, where ratios between linear and branched alcohols are strongly dependent on the reducing agent employed.2 In past decades, great efforts have been made to overcome regioselectivity problems of the ring-opening reaction of epoxides.2 The catalytic C−O bond cleavage is limited because of the high stability of the corresponding metal-alkoxide products, which impedes the regeneration of the metal hydride intermediate.3 One of the most employed catalytic methods for the ring-opening of epoxides is transition-metal-catalyzed hydrogenation, either by using heterogeneous or homogeneous catalysts.4 In all cases, high temperatures and H2 pressures are required, leading to poor selectivity along with the generation of oligomers or saturated hydrocarbons as byproducts (Scheme 1a).5

Alkaline-earth metals are among the most abundant metals in the crust of the earth. Despite their abundance and low toxicity, their application has been mainly focused on the hydrofunctionalization of polarized unsaturated bonds.6,7 Since the first structurally characterized magnesium−hydride complex by Jones and Stasch and co-workers,8 great efforts have been carried out to understand the Mg−H reactivity and its application as a valuable alternative to transition-metal hydride species.6 As a result, magnesium complexes, mostly containing anionic β-diketiminate ligands,9 have been successfully applied to the hydroboration of polarized and unpolarized unsaturated

Scheme 1. Catalytic Methods for the Regioselective Ring Opening of Epoxides

a) Catalytic hydrogenation and hydroboration of epoxides

b) This work: Ligand-controlled regiodivergent hydroboration

Amide ligand, via (TF2N)2Mg−Bpin

Alkyl ligand, via BuMg−H

species.

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bonds. In certain cases, even low-cost and readily available dialkylmagnesium could be applied as a catalyst. Given the current limitations in the catalytic regiodivergent ring opening of epoxides, we decided to explore whether simple magnesium catalysts would allow for the selective C–O bond activation, leading to either branched or linear alcohols in good yields and with broad functional group tolerance (Scheme 1b). We here report the development of such a regiodivergent reaction and explain the mechanism supported by experiment and computation.

We began our investigations with the magnesium-catalyzed hydroboration of styrene oxide 1a by evaluating the activity and selectivity of readily available MgBu₂ (Table 1). When the catalyst loading was decreased, the activity was maintained (Table 1 entry 1 vs 2). Whereas all catalytic methods for the hydroboration of epoxides provided the linear regioisomer, the magnesium catalyst provided the branched product. The regioselectivity could be improved by decreasing the reaction temperature (Table 1, entry 2 vs entry 3). Testing different solvents led to a small increase in regioselectivity when THF was used (Table 1, entry 4). Finally, by decreasing the reaction concentration (Table 1, entry 5), we reached better results. It should be pointed out that performing the catalytic reaction in neat conditions (Table 1, entry 6) resulted in a lower regioselectivity.

Following this optimization, we explored the scope and limitations of the MgBu₂-catalyzed regioselective hydroboration of epoxides (Scheme 2) starting with monosubstituted terminal epoxides, which lead to secondary alcohols, important synthesis building blocks also found in several natural products, were studied (1t–1v), the corresponding alcohols 2t–2v could be isolated in good yields, although higher temperatures were required.

Tertiary alcohols are present in several natural products or drug derivatives. Thus, the synthesis of enantiomerically pure tertiary alcohols is of great interest. In regard to a few catalytic asymmetric reactions are known, with the catalytic asymmetric addition of carbon-nucleophiles to ketones as the most synthetically used approach. Motivated by the above results, we decided to test the MgBu₂-catalyzed hydroboration protocol for both (R)- and (S)-enantiomers of 2,2-disubstituted epoxides 1m–1n and 1q. Importantly, no loss of enantioselective excess was observed and the tertiary alcohols were obtained in excellent yields. This good performance was also extended when chiral epoxides derived from natural products or drug derivatives were tested under the same reaction conditions. When L-camphor (1w), α-thujone (1x), and l-menthone (1y)-derived epoxides were studied, good yields and excellent regio- and diastereoselectivities were obtained. We were also pleased to see that sterol-derived epoxides 1z and 1aa also underwent hydroboration effectively with excellent yields and regio- and diastereoselectivities.

The findings make us wonder whether less reactive oxacyclic rings, such as oxetanes and oxolanes, could also be applied in the Mg-catalyzed ring opening. To the best of our knowledge, there is no catalytic method reported for the hydroboration reaction involving these unreactive compounds. To our delight, the hydroboration could also be applied and monosubstituted oxetanes containing aryl substituents (1ab–1af) underwent ring opening to give the corresponding branched alcohols 2ab–2af in good yields and excellent regioselectivities. This good performance was also maintained when alkyl substituents are present at the 2-position (1ag–1ah), although lower conversions were observed. When symmetrical oxetanes 1ai–1aj were tested, the corresponding alcohols 2ai–2aj were also isolated in moderate to good yields. Encouraged by these results, we decided to study the MgBu₂-catalyzed hydroboration of 2-phenyloxolane. Unfortunately, even under harsher reaction conditions, no conversion was observed for these less reactive oxacycles. Thus, we wondered if the replacement of the ligand (i.e., butyl) would have an effect on the catalytic activity. Inspired by our recent findings in which (i) Mg(OR)₂ (where (OR)₂ = BINOL) was shown to activate HBpin toward ketone reduction via a cooperative magnesium-ligand activation, and (ii) Mg(NTf₂)₂ acting as an efficient Lewis acid toward allyne activation, we decided to replace MgBu₂ by Mg(NTf₂)₂ and to evaluate the influence on both the activity and the selectivity. To our surprise, the application of Mg(NTf₂)₂ in the hydroboration of 2,2-disubstituted epoxide 1i resulted in the linear alcohol product 4a (2ai) (Scheme 3).
Scheme 2. Scope of the MgBu₂-Catalyzed Hydroboration of Epoxides and Oxetanes

\[ \text{Monosubstituted epoxides} \]

| R₁ | R₂ | R₃ | Product | Yield | Enantiomeric Excess |
|-----|-----|-----|---------|-------|---------------------|
| 2a  | 95% | 69:19 b/l | 94:6 b/l |
| 2b  | 94% | 90:10 b/l | 90:10 b/l |
| 2c  | 92% | 99:1 b/l | 99:1 b/l |
| 2d  | 93% | 99:1 b/l | 99:1 b/l |
| 2e  | 90% | 99:1 b/l | 99:1 b/l |
| 2f  | 91% | 99:1 b/l | 99:1 b/l |
| 2g  | 94% | 99:1 b/l | 99:1 b/l |
| 2h  | 97% | 99:1 b/l | 99:1 b/l |

\[ \text{2,2-Disubstituted epoxides} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| 2i  | 98% | 94:6 b/l | 94:6 b/l |
| 2j  | 95% | 99:1 b/l | 99:1 b/l |
| 2k  | 93% | 99:1 b/l | 99:1 b/l |
| 2l  | 79% | 95:5 b/l | 95:5 b/l |
| 2m  | 90% | 99:1 b/l | 99:1 b/l |
| 2n  | 93% | 99:1 b/l | 99:1 b/l |
| 2o  | 95% | 99:1 b/l | 99:1 b/l |

\[ \text{Symmetrical disubstituted epoxides} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| 2p  | 93% | 95:5 b/l | 95:5 b/l |
| 2q  | 92% | 99:1 b/l | 99:1 b/l |
| 2r  | 92% | 95:5 b/l | 95:5 b/l |
| 2s  | 95% | 98:2 b/l | 98:2 b/l |
| 2t  | 58% b | | |
| 2u  | 85% b | | |
| 2v  | 69% b | | |

\[ \text{Enantiopure 2,2-disubstituted epoxides} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| (+)-2m | 92% | 98% ee | |
| (-)-2m | 95% | 98% ee | |
| (+)-2n | 90% | 96% ee | |
| (-)-2n | 92% | 99% ee | |
| (+)-2q | 88% | 98% ee | |
| (-)-2q | 89% | 98% ee | |

\[ \text{Enantiopure epoxides derived from natural products or drug derivatives} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| 2w  | 61% | 95:5 b/l | 95:5 b/l |
| 2x  | 59% | 99:1 b/l | 99:1 b/l |
| 2y  | 63% | 99:1 b/l | 99:1 b/l |
| 2z  | 90% | 99:1 b/l | 99:1 b/l |
| 2aa | 92% | 99:1 b/l | 99:1 b/l |

\[ \text{Monosubstituted oxetanes} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| 2ab | 95% | 99:1 b/l | |
| 2ac | 90% | 99:1 b/l | |
| 2ad | 92% | 99:1 b/l | |
| 2ae | 89% | 99:1 b/l | |
| 2af | 92% | 99:1 b/l | |
| 2ag | 50% | 99:1 b/l | |
| 2ah | 55% | 99:1 b/l | |

\[ \text{Symmetrical oxetanes} \]

| R₁ | R₂ | Product | Yield | Enantiomeric Excess |
|-----|-----|---------|-------|---------------------|
| 2ai | 50% | 99:1 b/l | |
| 2aj | 70% | 99:1 b/l | |

*1a−1aj (1 mmol), HBpin (1.5 equiv), MgBu₂ (5 mol %, 0.5 M in heptane), THF [0.5 M], 40 °C for 24 h. Isolated yields. *2Toluene [1 M], 10 mol % MgBu₂, 90 °C. *3Enantioselectivities were determined by HPLC. Diastereoselectivities were determined by ¹H NMR. (R)- and (S)-1m, (S)-1n, and (R)- and (S)-1o epoxides were used in 99% ee purity. (R)-1n epoxide was used in 97% ee purity (all isolated from preparative HPLC; for more information, see Supporting Information). Epoxides 1w, 1x, 1y, 1z, and 1aa were diastereomerically pure. *4MgBu₂ (5 mol %, 0.5 M in heptane), toluene [1 M], 75 °C for 24 h.
This complete regioselectivity switch is very interesting and points to a different HBpin activation and ring-opening mechanism. Several 2,2-disubstituted terminal epoxides with sterically hindered or polyaromatic ring substitutions (4b and 4c) as well as linear and cyclic alkyl substituents (4d−4l) were then applied (Scheme 4). The scope could also be extended diaryl-substituted substrate and 2,2-diphenylethan-1-ol 4m was obtained quantitatively. Overall, the Mg(NTf2)2-catalyzed hydroboration results in good yields and complete selectivity toward linear alcohols.

Thus, we successfully developed a regiodivergent ring opening of epoxides by applying two readily available and low-cost magnesium catalysts. On one hand, our MgBu2−HBpin catalytic system can be applied to a broad range of substrates providing branched alcohols with excellent chemoselectivity and regioselectivities without the loss of enantioselectivity. On the other hand, the use of Mg(NTf2)2 as catalyst provides the complementary ring-opening reaction leading to the linear alcohols. Considering the unexpected regiodivergence observed by using either MgBu2, or Mg(NTf2)2, we decided to conduct several experiments to gain insight into the different reaction mechanisms (Scheme 5).

### MECHANISTIC STUDY

**Control Experiments.** We assumed that the regiodivergency is caused by the nature of the different magnesium catalysts. However, given that BH3 is capable of catalyzing the hydroboration of olefins,16 and due to examples in the literature that describe the decomposition of HBpin to BH3 by alkali salts,17 we decided to investigate if BH3 could catalyze the hydroboration of epoxides to either a linear or branched alcohol. Therefore, BH3·THF and BH3·SMe2 were tested in the reaction. However, both did not efficiently catalyze the hydroboration (Scheme 5a), providing low conversions and a mixture of branched and isomerization byproduct (for more detail, see the Supporting Information). Subsequently, we investigated the deuterium incorporation by using DBpin (Scheme 5b).

When the MgBu2-catalytic system was tested, the secondary alcohol 2d-d1 was isolated with full D-incorporation at the β-methyl moiety. This result suggested that the BuMg-D species in situ formed would attack the least substituted carbon of the epoxide ring (Scheme 5b1). Moreover, no isomerization was observed. We also carried out the same D-incorporation experiments by using Mg(NTf2)2. In this case, quantitative D-incorporation was observed at the least substituted carbon (Scheme 5b2). This result, together with the complete regiodivergence observed, suggests that the latter mechanism operates via a 1,2-H shift,18a producing an aldehyde intermediate, which finally undergoes reduction via a D-addition. This epoxide isomerization is in agreement with the work reported by Weinwald18a and Mazet using Pd or Ir catalysts.18b,c Consequently, we carried out an isomerization experiment (Scheme 5c). When epoxide 1i was mixed with catalytic amounts of Mg(NTf2)2 complex, we observed the formation of aldehyde 5. This result supports the notion that Lewis acidic Mg(NTf2)2 is an efficient catalyst for the Meinwald rearrangement (1,2-H shift)18a of terminal disubstituted epoxides to the corresponding aldehyde, which is in agreement with the control experiments (Scheme 5b). Finally, we conducted a racemization experiment (Scheme 5d). As shown, MgBu2 catalyzes the ring opening of an enantiopure epoxide without loss of enantioselectivity (Scheme 2, compounds 2m, 2n, and 2q). When enantiopure epoxide 1m was tested in the presence of Mg(NTf2)2 catalyst,
...which two THF molecules are coordinated to Mg, and we considered it as the starting state in the catalytic cycle. The overall pathway is divided into two sections: ring opening of the epoxide (Figure 1) and metathesis of the Mg–O and H–B bonds (Figure 2).

Calculations indicate that a bimolecular ring-opening mechanism is operative; see Figure 1. The reaction pathway starts with the transfer of a hydride from A0 to an epoxide molecule coordinated to the Mg of another A0 molecule, via the transition state of TS1. This bimolecular epoxide ring-opening step is required to overcome a free energy span of 24.0 kcal/mol from the reference state corresponding to two A0 molecules. The resulting ionic intermediates A0 and A0 are 27.5 kcal/mol lower in energy than the starting two A0 molecules. The next two steps, from A0 + A0 to A10 + A11, correspond to substantially thermoneutral dissociation of a THF molecule from A0 yielding A10, and to substitution of a THF molecule of A0 by an epoxide molecule, yielding A11. The reaction proceeds by another epoxide opening by hydride transfer from A10 to A11 via another bimetallic transition state, TS2. This ring opening is clearly more facile (ΔG° = 9.0 kcal/mol) than that via TS1 (ΔG° = 24.0 kcal/mol). The reason for this observation is the attractive electrostatic interaction between the two oppositely charged A10 and A11. The resulting two molecules of A12 are highly stable, laying at −108.3 kcal/mol with respect to starting A0. Intermediate A12, having two THF molecules coordinated to the Mg, is the most stable over other possibilities (see Figure S3 in the Supporting Information). The next step, metathesis of the Mg–O and B–H bonds, starts with the replacement of one THF of intermediate A12 by HBpin to generate A13, a step endergonic by 3.4 kcal/mol (Figure 2). Then the alkoxide group migrates to the boron atom via transition state TS3 and a total energy barrier of 5.6 kcal/mol from A12. The resulting zwitterionic intermediate A13 is highly stable and is the lowest point in the potential energy surface. The reaction is completed by hydride transfer from the electron-rich HBpin moiety to the electron-deficient Mg center of A13, via transition state TS4 and an energy barrier of 19.9 kcal/mol. Liberation of product P4 from the formed intermediate A14 regenerates A0 for further catalysis. The overall reaction profile (Figures 1 and 2) reveals that bimetallic hydride transfer via TS1 is the rate-controlling step. Regarding the regioselectivity, we checked the two epoxide opening transition states TS1 and TS2. We thus investigated the hydride transfer step via TS1-R and via TS2-R, where hydride transfer occurs to the substituted C atom of the epoxide (red lines in Figure 1). Consistent with the experimental regioselectivity, transition states TS1 and TS2 are favored by 5.2 and 3.8 kcal/mol as compared to transition states TS1-R and TS2-R (details in Figure S4 in the Supporting Information). The high regioselectivity toward H transfer to the unsubstituted C atom of the epoxide can be easily rationalized in terms of steric effects. In fact, the steric map of the epoxide coordinated intermediate A0, (Figure 3) shows that, as expected, the western quadrants, hosting the unsubstituted C atom of the epoxide, are less hindered than the eastern ones, hosting the substituted C atom.

The catalytic pathway examined by the DFT calculations reveals an explicit role for the THF solvent molecules coordinated to Mg. Therefore, we investigated the feasibility of this mechanism with a noncoordinating solvent, for example, toluene. In this case the starting Mg–H complex is A0, in which two molecules of HBpin are bound to the Mg (Figure S5 in the Supporting Information). The resulting...
activation energy barrier for the hydride transfer step via TS1, 22.5 kcal/mol, is similar to that reported in Figure 1. Furthermore, hydride transfer to the substituted C atom of the epoxide, via transition state TS1-R, is unfavored by 2.3 kcal/mol relative to TS1. Thus, the proposed mechanism can be considered operative both in coordinating and non-coordinating solvents.

**Mg(NTf2)2-Catalyzed Mechanism.** Also in this case we started by analyzing the most stable form of the Mg(NTf2)2 catalyst in the presence of substrate 1i and HBpin (for details, refer to Figure S6 in the Supporting Information). The complex B1, having two THF molecules coordinated to the Mg atom, is found to be the most stable form and it is considered as the starting point of the reaction pathway. Different from the MgBu2-catalyzed mechanism, the formation of the Mg−H complex is unfeasible because of the very high endergonicity associated with the transfer of a hydride from HBpin to Mg (ΔG⧧ = 37.8 kcal/mol, Scheme S1 in the Supporting Information). Thus, for Mg(NTf2)2-catalyzed hydroboration we had to locate an alternative mechanism, devoid of a Mg−H intermediate. The overall reaction pathway is composed of two steps: isomerization of epoxide to aldehyde, followed by hydroboration of the aldehyde (Figure 4).

The reaction starts with the replacement of a THF in B1 by the epoxide molecule 1i generating B1h, a step endergonic by 5.5 kcal/mol. The next step is ring opening of the epoxide by nucleophilic attack via the Sn2-type transition state TS5 (Figure 4). This step requires the overcoming of a free energy barrier of 29.2 kcal/mol from B1 and leads to the formation of the intermediate B2, a charge-separated species. The high-energy intermediate B2 transforms rapidly to the aldehyde-
coordinated species $B_3$ via the 1,2-H transfer transition state $TS_6$, with a negligible activation barrier ($\Delta G^\ddagger = 2.2$ kcal/mol). Coordination of a THF molecule to $B_3$ liberates the aldehyde $S$ and regenerates $B_1$.

Hydromboration of the aldehyde starts with HBpin insertion into one of the Mg--N(NTf$_2$) bonds of $B_1$, via $TS_7$ and a free energy barrier of 16.4 kcal/mol, to form intermediate $B_4$. One THF molecule of $B_4$ is replaced by $S$ to generate $B_6$, which is less stable than $B_1$ by 4.3 kcal/mol. Hydride transfer from the electron rich HBpin in $B_3$ to the coordinated C=O of $S$, occurs via transition state $TS_8$ and leads to intermediate $B_6$. This step requires the overcoming of an overall free energy span of 25.0 kcal/mol from the reference structures $B_1+5$. The next step is a barrier less and highly exergonic ($\Delta G = -35.0$ kcal/mol) rearrangement of $B_6$ to $B_7$, corresponding to nucleophilic transfer of the alkoxide group from magnesium to boron. The reaction is completed by release of product $PB$, promoted by coordination of a THF molecule to Mg, via transition state $TS_9$ and an energy barrier of 8.5 kcal/mol, regenerating the active catalyst $B_1$.

To rationalize the experimentally observed loss of enantioselectivity in the product, when the reaction is catalyzed by Mg, the reaction starts with the Mg-coordinated alkoxide $B_2$, which is predicted to be the structure from which racemization starts. In $B_2$, the THF is coordinated to the cationic carbon, which is a chiral center. This THF can be replaced with another THF via SN$_2$-type transition state. Therefore, an inversion of configuration is observed at the chiral center in the resulting intermediate, emerging a pathway toward the formation of enantiomer of $PB$.

### CONCLUSIONS

In summary, a new magnesium-catalyzed protocol has been successfully applied to a wide range of terminal and internal epoxides. Depending on the nature of the Mg catalyst, a regiodivergent ring opening is observed. Whereas MgBu$_2$ provides the corresponding branched alcohol, Mg(NTf$_2$)$_2$ allows the formation of the linear regioisomer. To date, all transition-metal-catalyzed hydroborations of epoxides protocols provide the linear alcohol. In contrast, the use of readily available MgBu$_2$ catalyzes the hydroboration of terminal and internal epoxides in excellent regioselectivities toward the branched isomer. Moreover, enantiopure alcohols can also be obtained as a result of the enantiospecific ring opening of optically pure epoxides. Besides, good efficiency is also observed when less reactive oxetanes are applied, which again result in the branched alcohols in good yields and with excellent regioselectivities. To the best of our knowledge, this is the first selective hydroboration of these unreactive compounds. Also, the use of readily available Mg(NTf$_2$)$_2$, containing trifluoromethanesulfonylimide ligands, provides the linear isomer when 2,2-disubstituted terminal epoxides were tested.

By means of control experiments and DFT calculations, we demonstrate that the different activation modes of HBpin are crucial for the regiodivergency observed. Mechanistically, for the MgBu$_2$-catalyzed procedure a bimolecular ring-opening mechanism is proposed in which the epoxide activation and the hydride addition to the least substituted carbon occur simultaneously, providing the corresponding branched alcohols. Also, the Lewis acid Mg(NTf$_2$)$_2$ facilitates the ring opening of epoxides via an isomerization pathway to give the corresponding aldehyde, which subsequently undergoes hydroboration through a dual magnesium-ligand cooperative HBpin activation. Because of the mild reaction conditions, the use of readily available and nontoxic catalysts, the good chemo-, regio-, and stereoselectivities obtained for a wide range of
epoxides, the catalytic system presented can be considered a green alternative to the existing ring-opening protocols and may be further applied to late-stage functionalizations.

### ASSOCIATED CONTENT

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The Supporting Information is available free of charge at https://pubs.acs.org/10.1021/jacs.0c05917. Experimental procedures and analytical data for all compounds, detailed control experiments and DFT calculations, and NMR spectra (PDF)

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