Regiodivergent reductive opening of epoxides by catalytic hydrogenation promoted by a (cyclopentadienone)iron complex

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ABSTRACT: The reductive opening of epoxides represents an attractive method for the synthesis of alcohols, but its potential application is limited by the use of stoichiometric amounts of metal hydride reducing agents (e.g., $LiAlH_4$). For this reason, the corresponding homogeneous catalytic version with H_2 is receiving increasing attention. However, investigation of this alternative has just begun, and several issues are still present, such as use of noble metals/expensive ligands, high catalytic loading and poor regioselectivity. Herein we describe the use of a cheap and easy-to-handle (cyclopentadienone)iron complex (**1a**), previously developed by some of us, as pre-catalyst for the reductive opening of epoxides with H_2. While aryl epoxides smoothly reacted to afford linear alcohols, aliphatic epoxides turned out to be particularly challenging, requiring the presence of a Lewis acid co-catalyst. Remarkably, we found that it is possible to steer the regioselectivity with a careful choice of the Lewis acid. A series of deuterium labeling and computational studies were run to investigate the reaction mechanism, which seems to involve more than a single pathway.

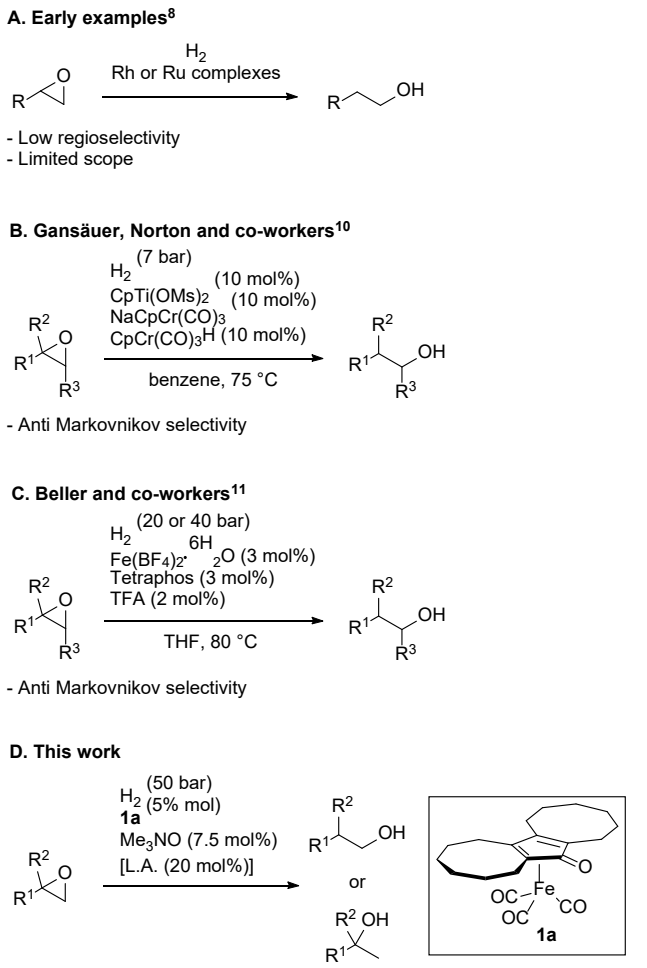
INTRODUCTION

Catalytic methodologies for the preparation of alcohols represent a compelling research topic, given the importance of this class of compounds for both fine chemical and pharmaceutical industry. So far, olefins have represented the main gateway to alcohols through hydration, but the regiocontrol of this reaction still represents an issue: while secondary and tertiary alcohols may be prepared by acid-catalyzed Markovnikov hydration, the selective formation of primary alcohols is more difficult to attain. The hydroboration/oxidation [1] and the hydroformylation/hydrogenation sequence [2] represent the most widely used routes to primary alcohols on laboratory and industrial scale, respectively. Additionally, direct access to primary alcohols from alkenes by triple relay catalysis has been also realized by Grubbs and co-workers. [3] Despite these achievements, the current context of growing concern about sustainability makes the development of atom-economical catalytic routes avoiding the use of precious metals quite urgent. The reductive opening of epoxides (readily prepared by olefin oxidation[4] or other methods[5]) is an alternative route to alcohols traditionally performed using metal hydride reagents such as $LiAlH_4$.[6] The catalytic version of this reaction by hydrogenation is very appealing, because it involves a cheap and clean reductant such as H_2 and produces no stoichiometric waste. Despite its potential, however, the catalytic hydrogenation of epoxides is little precedented: only a few reports, based on heterogeneous [7] or homogeneous transition metal catalysis (Scheme 1 A),[8] have appeared in the literature, most of which suffer from serious limitations (narrow scope, low selectivity, use of precious metals).[9] In 2019, a breakthrough in this area was made simultaneously by two different research groups, who reported the regioselective anti-Markovnikov hydrogenation of epoxides. Gansäuer, Norton and co-workers achieved this goal using a multicatalytic system consisting of $CpTi(OMs)_2$, $NaCpCr(CO)_3$ and $CpCr(CO)_3H$ (Scheme 1 B), [10] whereas Beller and co-workers employed a $Fe(BF_4)_2{\cdot}6H_2O$/tetraphos/TFA catalyst system (Scheme 1 C).[11] More recently, Rueping and co-workers realized a regiodivergent methodology for the reductive opening of epoxides using pinacolborane instead of H_2,[12] in which the regioselectivity can be tuned by changing the magnesium catalyst: Markovnikov with $MgBu_2$, and anti-Markovnikov with $Mg(NTf)_2$.[13] Although these contributions represent a remarkable advancement, they still suffer from one or more drawbacks such as high catalytic loading, use of relatively expensive ligands (e.g., phosphines) and/or need for poorly atom-economic reducing agents.

Herein, we report a new methodology for the catalytic hydrogenation of terminal epoxides relying on the use of the (cyclopentadienone)iron complex (CIC) **1a** (Scheme 1 D), previously developed by some of us.[14] CICs have recently attracted remarkable interest because they are readily available and air-stable pre-catalysts which, upon *in situ* activation, can catalyze

several transformations involving hydrogen transfer (e.g., hydrogenation, transfer hydrogenation, 'hydrogen borrowing' transformations), or other types of mechanism.[15]

Scheme 1. Reported examples of homogeneous catalysis-enabled epoxide opening by catalytic hydrogenation.



RESULTS AND DISCUSSION

Pre-catalyst screening. We started our study screening several different CICs in the catalytic hydrogenation of styrene oxide **2a**. Besides pre-catalyst **1a**[14] and Knölker´s complex **1b**,[16] we tested the (tetraphenylcyclopentadienone)iron complex **1c** and CIC **1d**, developed by Renaud and co-workers (Figure 1).[17]

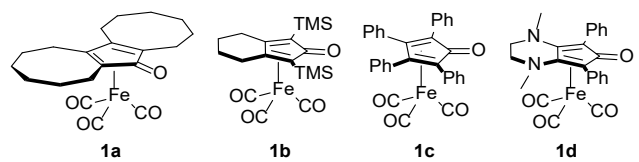
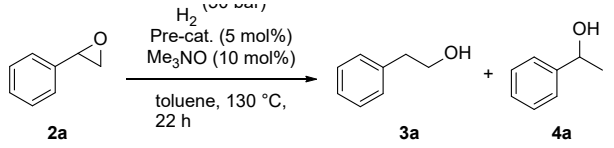


Figure 1. CICs screened in the catalytic hydrogenation of styrene oxide (2a).

The screening (Table 1) was carried out at 130 °C in toluene under 50 bar H_2 with 5 mol% pre-catalyst loading, and the catalytically active species was generated by CO de-coordination in the presence of Me_3NO (10 mol%).[14,18]

Table 1. Screening of CIC pre-catalysts in the hydrogenation of styrene oxide (2a).[a]



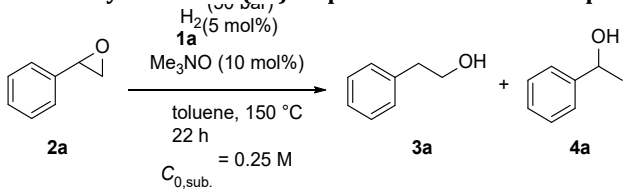
#	Pre-cat.	Conv. (%)[b]	**3a**:**4a** ratio[b]	Yield (%)[b]
1	**1a**	87	91:9	41
2	**1b**	84	91:9	40
3	**1c**	86	88:12	30
4	**1d**	93	88:12	38

[a] Reaction conditions: **2a**/Pre-cat./Me_3NO = 100:5:10; $n_{0,sub.}$ = 0.2 mmol; $C_{0,sub.}$ = 0.5 M in toluene; P_{H2} = 50 bar; T = 130 °C; reaction time: 22 h. [b] Determined by ^1H NMR using benzyl benzoate as internal standard.

Delightfully, product formation was observed with all the CICs tested, along with regioselectivity in favor of the linear alcohol **3a**. As complex **1a** achieved the best balance between conversion and regiocontrol (Table 1, entry 1), we selected it for further studies.

Catalytic hydrogenation of aryl epoxides. We took the hydrogenation of styrene oxide **2a** with pre-catalyst **1a** as model to optimize the reaction conditions. First of all, we found that increasing the temperature from 130 to 150 °C leads to better reproducibility of the results. Thus, all the next studies were conducted at 150 °C. Another important finding was that, despite most previously reported CIC-catalyzed reactions were generally performed with rather high initial substrate concentration ($C_{0,sub.}$ = 0.5-1.5 M),[14,15,17,18] this reaction gives better results at lower $C_{0,sub.}$ values. As can be seen in Table 2, while substrate conversion is always 100%, the yield of products **3a** and **4a** is lower and improves along with decreasing $C_{0,sub.}$ (entry 1, 2, 8, 9). Lowering the concentration also improved the regiocontrol, leading to formation of **3a** as the sole product (Table 2, entries 8, 9). ESI analysis of the crude reaction mixture obtained at $C_{0\ subst.}$ = 0.25 M clearly showed the formation of several oligomers generated by reaction of the alcohol products with substrate **2a** (see the Supporting Information). This finding is in agreement with the observed dependence of the yield of the desired product from $C_{0,sub.}$, as dilution disfavors oligomerization. Variations introduced on type and amount of catalyst activator (Table 2, entries 3-5) showed that anhydrous Me_3NO performs better than the dihydrate form (entry 1 vs. 3) and that 1.5 is the optimal Me_3NO/**1a** ratio (entry 5 vs. 1 and 4). Finally, attempts to decrease the catalyst loading led to decreased yield and selectivity (Table 2, entry 5-6).

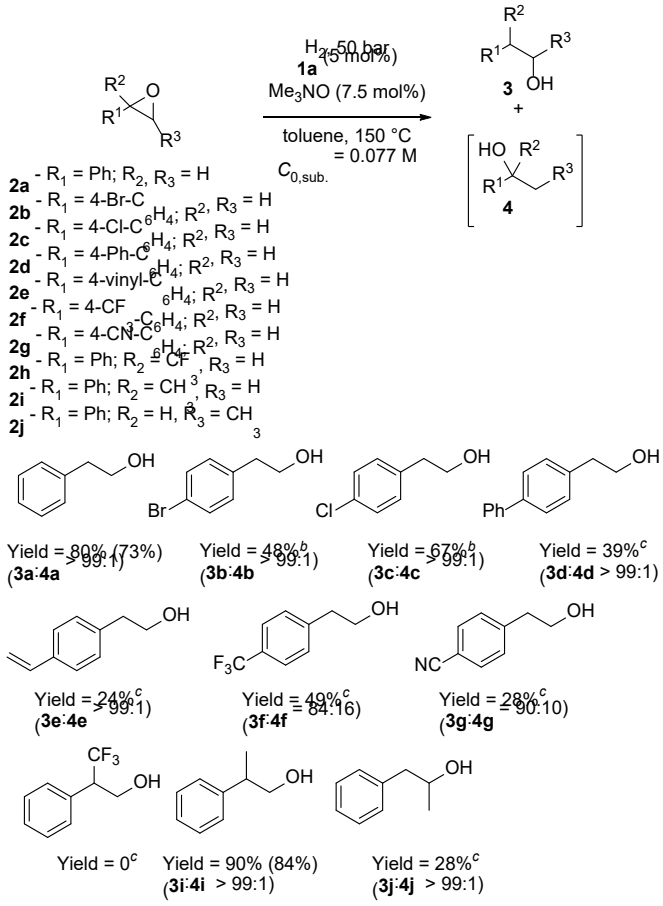
Table 2. CIC-catalyzed hydrogenation of styrene oxide (2a) – Optimization of reaction parameters.[a]



#	Deviations from the conditions above[a]	Conv. (%)[b]	**3a**:**4a** ratio[b]	Yield (%)[b]
1	None	100	94:6	67
2	$C_{0,sub.}$ = 0.5 M	96	93:7	56
3	$Me_3NO{\cdot}2H_2O$ instead of Me_3NO	100	90:10	54
4	**2a**/**1a**/Me_3NO = 100:5:5	100	96:4	65
5	**2a**/**1a**/Me_3NO = 100:5:7.5	100	98:2	74
6	**2a**/**1a**/Me_3NO = 100:3:4.5	100	95:5	63
7	**2a**/**1a**/Me_3NO = 100:1.5:2.3	85	88:12	35
8	**2a**/**1a**/Me_3NO = 100:5:7.5; $C_{0,sub.}$ = 0.125 M	100	> 99:1	78
9	**2a**/**1a**/Me_3NO = 100:5:7.5; $C_{0,sub.}$ = 0.077 M	100	> 99:1	80

[a] Reaction conditions: **2a**/Pre-cat./Me_3NO = 100:5:10; $C_{0,sub.}$ = 0.25 M in toluene; P_{H2} = 50 bar; T = 130 °C; reaction time: 22 h. [b] Determined by ^1H NMR using benzyl benzoate as internal standard.

Scheme 2. Catalytic hydrogenation of aryl epoxides: substrate scope.[a]



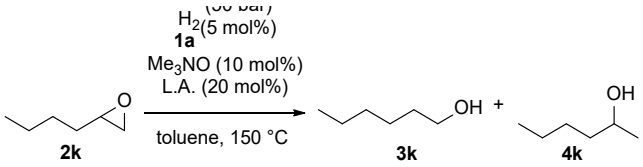
[a] Pre-cat. **1a** (5 mol%); Me_3NO (7.5 mol%); $C_{0,sub.}$ = 0.077 M in toluene; P_{H2} = 50 bar; T = 150 °C; reaction time: 22 h; yields determined by NMR using benzyl benzoate as internal standard; isolated yields in brackets. [b] $C_{0,sub.}$ = 0.083 M; [c] $C_{0,sub.}$ = 0.25 M.

With the optimized reaction parameters in hand, the scope of aromatic epoxides was explored (Scheme 2). *Para*-substituted aromatic epoxides (**2b-g**) gave good conversions to the corresponding linear alcohols, but the yields were lower than the one obtained with the benchmark substrate **2a** (Scheme 2). In the case of 2-[4-(trifluoromethyl)phenyl]oxirane **2f** and 2-[4-(cyanomethyl)phenyl]oxirane **2g**, the presence of an electron-withdrawing group in *para* position led to a lower regioselectivity, seemingly due to the decreased ability to stabilize a positive charge at the benzylic position. A similar effect of the electron-withdrawing substituent is probably responsible for the lack of activity observed with the trisubstituted epoxide **2h**. In sharp contrast, substrate **2i**, featuring a CH_3 instead of a CF_3 benzylic substituent, gave a high yield of linear alcohol (90%). The regioisomeric styrene oxide **2j**, more sterically hindered and less activated at the benzylic carbon, was sluggish to yield the corresponding alcohol **3j**.

Catalytic hydrogenation of alkyl epoxides. Alkyl epoxides are a particularly challenging class of substrates, which defied attempts to perform a regioselective reductive opening until very recently.[11] We tried to apply the **1a**/Me_3NO catalytic system to the hydrogenation of 1,2-exopyhexane **2k**, but very low or no conversion was obtained (see Table S1 in the Supporting Information). With the expectation that an acidic co-catalyst could further activate the epoxide ring to undergo reductive opening, we screened several Lewis acids, obtaining remarkable conversions of 1,2-epoxyhexane (see Table S1 in the Supporting Information). While the linear alcohol was the major

product in most cases, branched alcohols were formed preferentially in the presence of metal isopropoxides. The screening was repeated and GC analysis with an internal standard was performed to evaluate the yields (Table 3).

Table 3. Additive screening in the catalytic hydrogenation of 1,2-epoxyhexane 2k.[a]



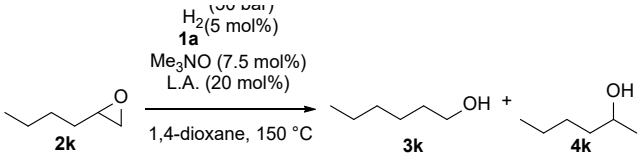
#	L.A.	Conv. (%)[b]	**3k**:**4k** ratio[b]	Yield (%)[b]
1	$Ti(OiPr)_4$	90	9:91	81
2	$Hf(OiPr)_4$	100	5:95	80
3	$Zr(OiPr)_4$	100	3:97	85
4[c]	$Al(OiPr)_3$	100	16:84	54
5	$AlCl_3$	100	62:38	25
6	$Yb(OTf)_3$	100	72:28	33
7	$BF_3{\cdot}OEt_2$	100	> 99:1	17
8	$Al(OTf)_3$	100	> 99:1	19
9[d]	$Al(OTf)_3$	100	> 99:1	29
10[e]	$Al(OTf)_3$	100	> 99:1	37
11[e,f]	$Al(OTf)_3$	100	> 99:1	38
12 [c,e,f,g]	$Al(OTf)_3$	100	84:16	90

[a] Reaction conditions: pre-cat. **1a** (5 mol%); Me_3NO (10 mol%); Lewis acid (20 mol%); $C_{0,sub.}$ = 0.25 M; P_{H2} = 50 bar; T = 150 °C; solvent: toluene; reaction time: 22 h; order of addition: **1a**, Me_3NO, Lewis acid, **2k**, toluene. [b] Determined by GC using *n*-dodecane as internal standard. [c] Reaction performed on 1,2-epoxyoctane; yield determined by ^1H NMR using 1,2,3,4-tetrahydronaphthalene as internal standard. [d] Order of addition: **1a**, Me_3NO, **2k**, solvent, Lewis acid. [e] Order of addition: **1a**, Me_3NO, **2k**, Lewis acid, solvent. [f] Reaction run in 1,4-dioxane. [g] Reaction run with 5 mol% Lewis acid.

Group 4 isopropoxides (i.e. Ti, Hf, Zr) led to preferential formation of the branched alcohol **4k** in good yields (Table 3, entries 1-3). In particular, with $Zr(OiPr)_4$ the secondary alcohol was obtained with high selectivity and good yield (entry 3). $Al(OiPr)_3$ also allowed preferential formation of the branched alcohol, but with lower selectivity and yield (entry 4). In sharp contrast, the other Lewis acids screened led to preferential formation of the linear alcohol **3k** (Table 3, entries 5-10), the best selectivity being obtained with $BF_3{\cdot}OEt_2$ (entry 7) and $Al(OTf)_3$ (entry 8). Unfortunately, although full conversions were observed in all cases, poor yields of product **3k** were obtained. For this reason, the hydrogenation of **2k** in the presence of $Al(OTf)_3$ was investigated more in depth. GC-MS analysis of the reaction crude revealed the presence of by-products deriving from the Friedel-Crafts-type alkylation of toluene with the substrate **2k**. To suppress this undesired reaction, the experimental procedure was changed, postponing the addition of $Al(OTf)_3$ (Table 3, entry 9) and solvent (entry 10) as much as possible: this led to definite but not substantial improvements of the reaction yield. A solvent screening was also performed (Supporting Information, Table S2), on which basis 1,4-dioxane was selected as the best solvent, although it brought only a marginal increase of yield (Table 3, entry 11). Finally, lowering the amount of Lewis acid led to an increase of the yield, but at the expense of the regioselectivity (Table 3, entry 12). Similar to what was observed with aryl epoxides, running the reaction with higher dilution led to a remarkable improvement of the yield (Table 4).

With both $Al(OTf)_3$ and $BF_3{\cdot}OEt_2$, decreasing $C_{0,sub.}$ to 0.125 M led to a substantial improvement of the yield (Table 4, entry 2 vs. 1; entry 5 vs. 4). However, a further reduction of $C_{0,sub.}$ resulted in a decrease of the yield (Table 4, entry 3 vs. 2; entry 6 vs. 5). Based on this results, 0.125 M was selected as optimal value of $C_{0,sub.}$ for the branched-selective hydrogenation of alkyl epoxides.

Table 4. Effect of $C_{0,sub.}$. on the yield of the catalytic hydrogenation of 1,2-epoxyhexane (2i) to yield the linear alcohol 3k.[a]



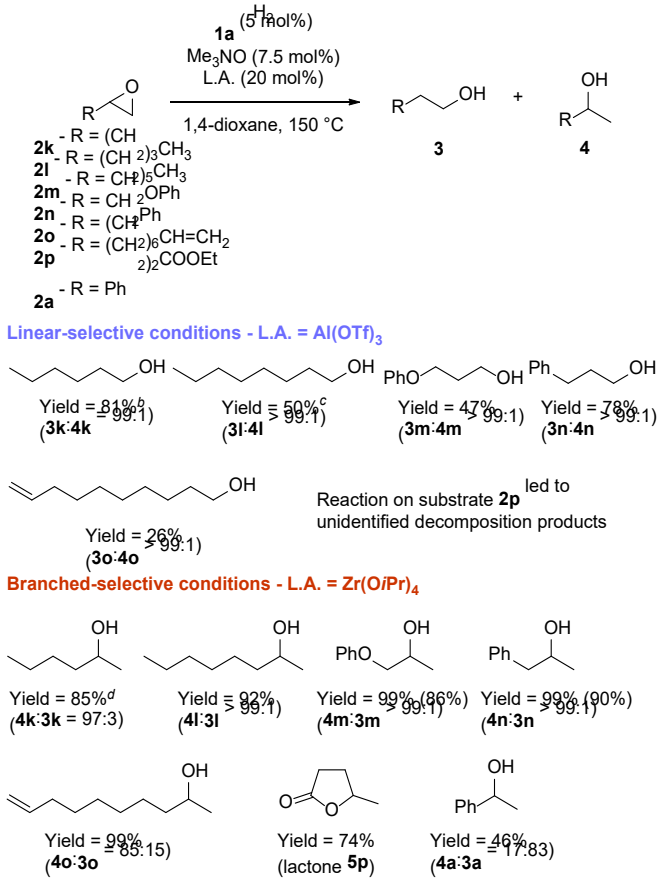
#	L.A.	$C_{0,sub.}$ (M)	Conv. (%)[b]	**3k**:**4k** ratio[b]	Yield (%)[b]
1	$Al(OTf)_3$	0.250	100	> 99:1	38
2	"	0.125	100	93:7	63
3	"	0.063	100	99:1	23
4[c]	$BF_3{\cdot}OEt_2$	0.250	100	> 99:1	17
5	"	0.125	100	91:1	81
6	"	0.063	100	> 99:1	64

[a] Reaction conditions: pre-cat. **1a** (5 mol%); Me_3NO (7.5 mol%); Lewis acid (20 mol%); solvent: 1,4-dioxane; P_{H2} = 50 bar; T = 150 °C; reaction time: 22 h; order of addition: **1a**, Me_3NO, **2k**, Lewis acid, solvent. [b] Determined by GC using *n*-dodecane as internal standard. [c] Carried out in toluene.

Regiodivergent catalytic hydrogenation of epoxides. Overall, the above-described experiments allowed us to develop a regiodivergent methodology for epoxide reductive opening by hydrogenation based on the iron pre-catalyst **1a**: a simple switch of Lewis acid co-catalyst allows to steer the regiocontrol towards either the linear (with $Zr(OTf)_4$) or the branched alcohol (with $Al(OTf)_3$ and $BF_3{\cdot}OEt_2$). We applied these two sets of conditions to the catalytic hydrogenation of several alkyl epoxides, obtaining the results shown in Scheme 3. To our delight, under the two sets of optimized conditions the linear alcohols (**3i-l**) and their branched isomers (**4k-n**) could be synthesized

in good yields and with good to excellent selectivity, thus confirming the validity of the iron-catalytic regiodivergent methodology. It should be noted that in the hydrogenation of substrate **2k** the best yield of linear alcohol **3k** was obtained using $BF_3{\cdot}OEt_2$ instead of $Al(OTf)_3$. Remarkably, the alkene functionality of substrate **2o** was unaffected by the reaction conditions, unlike the ester group of **2p**: under the linear-selective conditions, the hydrogenation of **2p** led to extensive decomposition of the substrate with no desired product. Instead, under the branched selective conditions, γ-valerolactone (**5p**) was obtained in good yield, without a trace of the γ-hydroxyester product. The branched-selective conditions were also tested with an aryl epoxide (styrene oxide **2a**), but in this case it was not possible to overcome the intrinsic regiochemical preference of the substrate: 2-phenylethanol **3a** remained the main product, although with decreased selectivity (83:17 **3a**:**4a** vs. > 99:1 in the absence of Lewis acid).

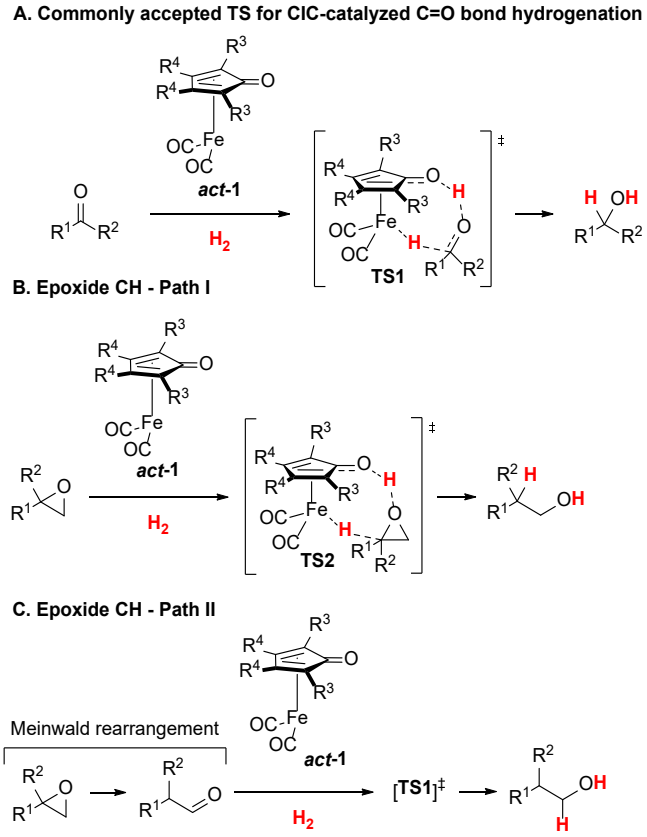
Scheme 3. Regiodivergent catalytic hydrogenation of alkyl epoxides.[a]



[a] Reaction conditions: pre-cat. **1a** (5 mol%); Me_3NO (7.5 mol%); L.A. (20 mol%) = $Al(OTf)_3$ for obtaining primary alcohols / $Zr(OiPr)_4$ for obtaining secondary alcohols; $C_{0,sub.}$ = 0.125 M; P_{H2} = 50 bar; T = 150 °C; solvent: 1,4-dioxane; reaction time: 22 h; yields determined by ^1H NMR using 1,2,3,4-tetrahydronaphthalene as internal standard; isolated yields in brackets. [b] L.A. = $BF_3{\cdot}OEt_2$; yield determined by GC using *n*-dodecane as internal standard. [c] Yield determined by ^1H NMR using benzyl benzoate as internal standard. [d] $C_{0,sub.}$ = 0.25 M; toluene; yield determined by GC using *n*-dodecane as internal standard.

Mechanistic investigation. The mechanistic view commonly accepted for C=O bond reductions promoted by CICs involves an outer-sphere mechanism with a pericyclic TS (**TS1** in Scheme 4 A) in which a hydride and a proton are simultaneously transferred, respectively, to the carbonyl carbon and oxygen.[17,18b,19] Since ring strain enhances the reactivity of the C–O single bond of epoxides, we conceived that the **1a**-catalyzed reductive opening could occur directly through an analogous outer-sphere mechanism (Path I in Scheme 4 B, **TS2**). An alternative pathway, similar to the one proposed by Beller and coworkers for their $Fe(BF_4)_2{\cdot}6H_2O$/tetraphos/TFA methodology,[11] would be the

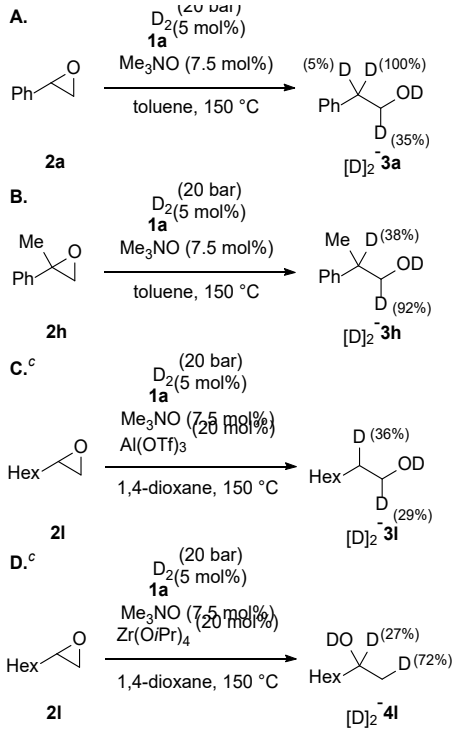
Scheme 4. Mechanistic pathways for CIC-catalyzed hydrogenation.



Meinwald rearrangement of the epoxide to form the corresponding aldehyde, which then would be reduced through the classical **TS1** (Path II in Scheme 4 C). To investigate which of these two pathways are operative, we carried out several control experiments using D_2 (Scheme 5). In the reductive deuteration of styrene oxide **2a** (Scheme 5 A) we observed a larger extent of deuterium incorporation at the C-2 of the alcohol. And indeed, the DFT calculations discussed below (see Scheme 8) show that the TS for the direct reduction at the benzylic position (**TS2-*n***) is 9.6 kcal/mol lower in energy than the direct reduction at the less hindered terminal position (**TS2-*iso***). The 35% incorporation at the 1-position could be explained by Path II (Scheme 4 C). This is again corroborated by the DFT calculations, that show that the transition state for the Meinwald rearrangement catalyzed by **1a** lies 1.1 kcal/mol below the one for the direct reduction at the benzylic position. The overall level of deuteration is too high with 135%. There are two

possible explanations for this: the aldehyde formed in the Meinwald rearrangement can undergo H/D exchange in the benzylic position via enolization or tautomerization. Alternatively, the calculations have shown that, at these high temperatures, dehydrogenation becomes a possible reaction and thus the C-1 could have been enriched in deuterium by a dehydrogenation/deuteration pathway (*vide infra*). The reductive deuteration of 2-methyl-2-phenyloxirane (**2h**, Scheme 5 B) clearly follows mostly the Meinwald rearrangement pathway which is preferred in view of the better stabilization of the carbocation intermediate. Here also is a surplus of deuterium, which should be due mostly to the H/D exchange reaction. At this stage we cannot exclude that some direct reduction at the benzylic position also takes place although this would seem less likely in view of the steric hindrance. The reductive deuteration

Scheme 5. Deuteration experiments.[a,b]

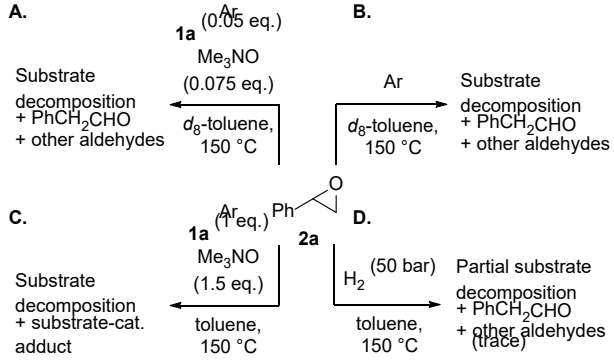


[a] Reaction conditions: Pre-cat. **1a** (5 mol%); Me_3NO (7.5 mol%); $C_{0,sub.}$ = 0.083 M; P_{D2} = 20 bar; T = 150 °C; solvent: toluene; 5 h. [b] Percentages of deuteration (in round brackets) measured by ^1H NMR analysis of the products purified by flash chromatography; [c] $C_{0,sub.}$ = 0.125 M; L.A. (either $Al(OTf)_3$ or $Zr(OiPr)_4$, 20 mol%); solvent: 1,4-dioxane.

of the aliphatic epoxide **2l** (Scheme 5 C) does not take place without Lewis acid and, indeed, the TSs for the reduction of 1,2-epoxybutane lie very high (Scheme 9). Here, we assume that the reaction takes place entirely via the Meinwald rearrangement and thus the deuterium incorporation at the C2 position probably stems from H/D exchange, although we cannot rule out the possibility of a direct reduction of the L.A.-activated epoxide in the position of the incipient carbocation. In this case we note that the level of deuteration is well below 100%. This could be caused by the presence of water in the solvent dioxane which could lead to D/H exchange at the catalyst. Alternatively, we note that dioxane is a known hydrogen donor in transfer hydrogenation reactions and the hydrogen could also stem from this source.[20] To probe this latter possibility we carried out the **1a**/$Zr(OiPr)_4$-catalyzed hydrogenation of **2l** with H_2 using d_8-dioxane as solvent. We did not observe any incorporation of D in the reduction product and thus this theory can be dismissed (see the Supporting Information). The reductive deuteration of **2l** in the presence of $Zr(OiPr)_4$ as L.A. (Scheme 5 D) leads to selective formation of the secondary alcohol. This clearly shows that no Meinwald rearrangement takes place. Yet the L.A. does play a role in the activation of the epoxide without actually creating a carbocation. For this reason, the attack of the deuteride now goes to the least hindered position. The deuteration at C-2 could be caused by dehydrogenation/deuteration of the alcohol. The incomplete deuteration could be due to D/H exchange from H_2O or dioxane. In this respect it is important to mention that the reduction probably takes a short time (about 1 h) to reach completion, as shown by a kinetic experiment (see the Supporting Information), while our deuteration experiments were run overnight.

Control experiments (Scheme 6) were carried out to ascertain if the Meinwald rearrangement takes place with styrene oxide under the reaction conditions (see the Supporting Information for details). Styrene oxide (**2a**) was heated at 150 °C in d_8-toluene either in the presence and in the absence of **1a** (5 mol%)/Me_3NO (7.5 mol%), and the reaction was monitored by ^1H NMR using benzyl benzoate as internal standard (Scheme S1-2 and Table S3-4 in the Supporting Information). In the presence of the catalyst (Scheme 6 A), **2a** underwent gradual decomposition and, simultaneously, the NMR signals of phenylacetaldehyde became visible. However, after reaching a maximum (13.5% conversion at t = 2.5 h), at long reaction times the $PhCH_2CHO$ signal intensity decreased, seemingly due to decomposition, and other aldehyde products were also detected (8.5% conversion at t = 22 h). Interestingly, formation of phenylacetaldehyde and other aldehyde byproducts took place also in the absence of catalyst, yet at slightly lower rate (Scheme 6 B). Substrate **2a** was then reacted under Ar with a stoichiometric amount of activated catalyst at 150 °C in toluene (Scheme 6 C). Flash chromatography of the reaction crude allowed to isolate a substrate-catalyst adduct whose structure could not be unambiguously assigned. In a last experiment (Scheme 6 D), styrene oxide **2a** was reacted with H_2 (50 bar) at 150 °C in toluene without catalyst. The crude reaction mixture was concentrated and analyzed by ^1H NMR. Partial substrate decomposition was observed (less than in the reaction run under Ar), together with formation of some phenylacetaldehyde.

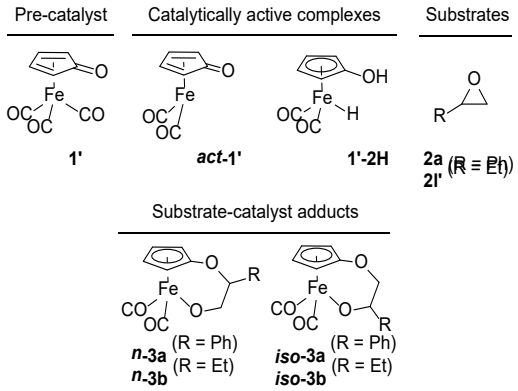
Scheme 6. Control experiments.



Overall, from these mechanistic investigations it can be concluded that, in the **2a**-catalyzed epoxide hydrogenation, at least two different mechanistic manifolds coexist (Path I and Path II in Scheme 4), the main one depending on type of substrate and reaction conditions. The viability of Path II is demonstrated by detection, in the control experiments, of the aldehyde deriving from the Meinwald rearrangement.

Computational studies. We carried out density functional theory computations to explore the reaction mechanisms and to rationalize the experimental observations. Our computations were carried out at the M06L level under the consideration of solvation effect (SCRF = SMD) of 1,4-dioxane as solvent. All computational details are given in the Supporting Information. In our computation we used the parent model pre-catalyst **1'** without ring substituents at the cyclopentadienone ring, which mimics real pre-catalyst **1a**, as well as styrene oxide (**2a**) as aromatic substrate and 1,2-epoxybutane (**2l'**, 2-ethyloxirane) as aliphatic substrate for **2l** (Figure 2). We used the computed Gibbs free energies in our discussion.

Figure 2. Computed complexes, substrates and adducts.



Before studying the epoxide hydrogenation itself, we focused our attention on the following, related aspects:

- *Activation of pre-catalyst **1'** to form the catalyst **act-1'*** (Figure 2),[21] which was found exergonic in the presence of Me_3NO as reported in the literature (see Scheme S8 in the Supporting Information).[17,18b]

- *Formation of complex **1'-2H** (Figure 2) by reaction of **act-1'** with H_2* (see Scheme S9 A in the Supporting Information).[22] In agreement with the literature,[17,18b] both coordination of H_2 to ***act*-1'** and formation of complex **1'-2H** were found exergonic, with a kinetic barrier of 17.3 kcal/mol corresponding to a concerted transition state. For comparison, the coordination and activation of D_2 were also computed, and similar results were found. From the $\Delta G^{\ddagger}$ corresponding to the TSs leading to complex **1'-H₂** and **1'-D₂**, a kinetic isotope effect (KIE) of 4.57 was calculated.

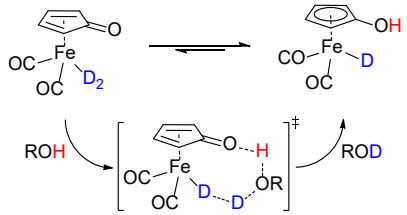
- *Coordination of epoxides **2a** and **2l'** to **act-1'***, which was found of approximately the same strength as for H_2 (Scheme S9 B in the Supporting Information). Interestingly, we found that, after coordination, the epoxides further evolve into the adducts ***n*-3a,b** and ***iso*-3a,b** (Figure 2) with activation energies similar or even lower than in the formation of **1'-2H**. Given the similar energy profiles, coordination/activation of H_2 and coordination/cycloaddition of epoxides are probably competitive processes, which might explain the high H_2 pressure (50 bar), and low concentration of epoxides needed to achieve good yields (see Scheme 2-3).

- *Thermodynamics of epoxide rearrangement to the corresponding aldehyde or ketone, followed by carbonyl hydrogenation* (see Scheme S10 in the Supporting Information). It was found that aldehyde and ketone are much more stable than the corresponding epoxide, their formation being irreversible, and the ketone is more stable than the corresponding aldehyde.

- *Energy profile of the reaction of **1'-2H** with aldehydes and ketones* (Scheme S12 in the Supporting Information) following the commonly accepted outer-sphere mechanism which involves a pericyclic TS.[19] The reaction yielding alcohol + ***act*-1'** has a moderate barrier and is endergonic, indicating that the reverse step is kinetically and thermodynamically more favored. However, the alcohol product forms a stable complex with ***act*-1'**,[23] and the coordination is exergonic. Importantly, starting from ***act*-1'**, the generation of **1'-2H** has a higher barrier than the hydrogenation of aldehydes and ketones (see Scheme S9 A and S12 in the Supporting Information), and thus the former step is rate-determining.[24]

Overall, the computed C=O hydrogenation thermodynamics and kinetics are in agreement with the literature, as it has been experimentally observed that the (hydroxycyclopentadienyl)iron complex **1b-2H** is able to reduce aldehydes at very low temperature (−60 °C), and the reaction becomes reversible above 10 °C.[19a] Moreover, besides the direct H_2 (D_2) activation, the alcohol-assisted H_2 (D_2) activation takes place with a lower barrier (by about 16 kcal/mol)[19b] and accelerates the hydrogenation and dehydrogenation process (Scheme 7). This scenario is compatible with a dehydrogenation/deuteration pathway taking place at the high temperature of the deuteration experiments (150 °C), as in such conditions the H/D exchange is expected to take place easily.

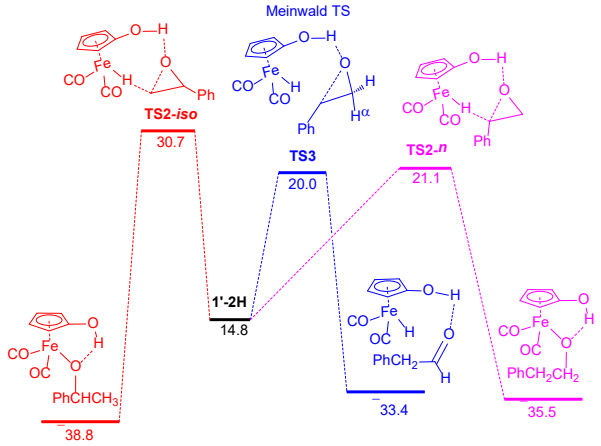
Scheme 7. Alcohol assisted H/D exchange.



Next, we computed the hydrogenation of epoxides to the corresponding alcohols on the basis of the bifunctional outer-sphere mechanism shown in Scheme 4 B (Path I), where the selective nucleophile attack of the Fe-H species should determine the regioselectivity for primary vs. secondary alcohol. Since the secondary alcohol is more stable than the primary one (Scheme S10 in the Supporting Information), the regioselective reaction leading to primary alcohol must be kinetically controlled. The same should be also true for the Meinwald rearrangement-hydrogenation pathway (Path II in Scheme 4 C), as the ketone is more stable than the aldehyde. Scheme 8 shows the simplified Gibbs free energy profiles for the hydrogenation of aromatic epoxide **2a**. For Path I (Scheme 4 B) we found both transition states for the ring opening: **TS2-*n*** for forming the primary alcohol and **TS2-*iso*** for the secondary one. It should be noted that this route follows two steps: i) ring opening; ii) proton transfer to form the coordinated alcohol. The first step has a higher barrier than the second step. As the ring opening leading to the primary alcohol has a much lower barrier compared to

the one forming the secondary alcohol (21.1 vs. 30.7 kcal/mol), the formation of primary alcohol is kinetically favored. In addition, we also located the transition state (**TS3**) of Path II, involving the Meinwald rearrangement of the epoxide to the aldehyde (Scheme 4 C), whereas attempts to find the corresponding TS for ketone formation failed. In **TS3**, the H_α atom is shifted to the next carbon atom during the hydrogen bonding-mediated opening of the epoxide ring: the C-H bond is slightly elongated (1.129 Å) and the HCC angle is 102.8°. Remarkably, the barrier of the Meinwald transition state (**TS3**) is close in energy to the classic ring opening transition state (**TS2-*n***). Thus, this reaction can involve two competitive transition states leading to the formation of primary alcohol, as shown also by the deuteration experiments (see Scheme 5). Since aldehyde hydrogenation has a much lower barrier (Scheme S12 in the Supporting Information) than ring opening, it will not affect the reaction kinetics. The exclusive formation of the primary alcohol ($PhCH_2CH_2OH$), which is kinetically favored, agrees with the experimental observation (see Scheme 1-2).

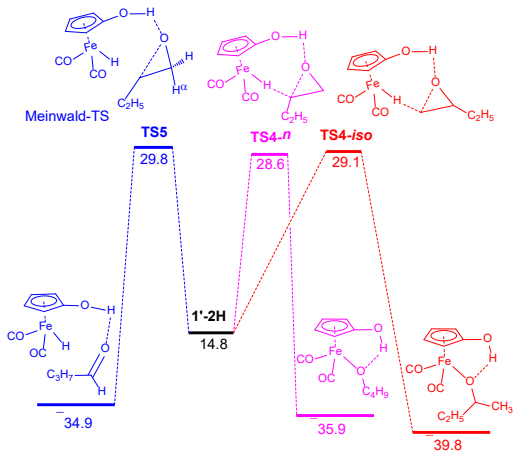
Scheme 8. Gibbs free energy profiles of the hydrogenation of the aryl epoxide 2a promoted by a CIC.[a]



[a] **1'-2H** + aryl epoxide (**2a**), kcal/mol.

In a similar way, we computed the hydrogenation of the aliphatic epoxide **2l'** (Scheme 9).

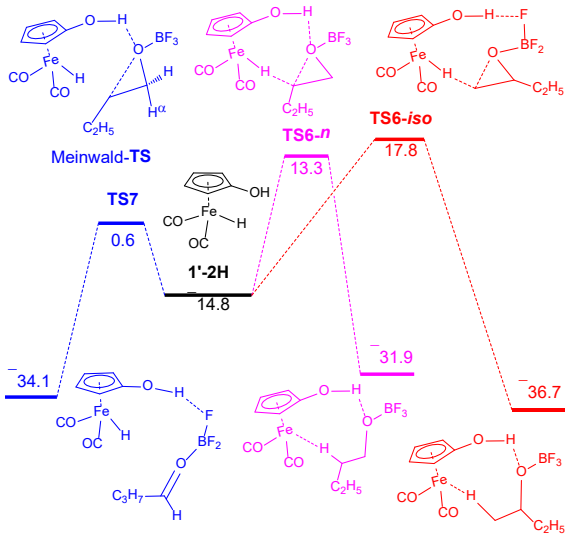
Scheme 9. Gibbs free energy profiles of the hydrogenation of the alkyl epoxide 2l' promoted by CIC 1'.[a]



[a] **1'-2H** + aliphatic epoxide, kcal/mol.

The Gibbs free energy profiles differ quantitatively from those of the hydrogenation of aromatic epoxide **2a** (Scheme 8). For Path I (Scheme 4 B), we found the transition states **TS4-*n*** and **TS4-*iso*** leading, respectively, to primary and secondary alcohol. The two TSs are close in energy (28.6 vs. 29.1 kcal/mol), consistent with the observed possibility to steer the regioselectivity toward either product using suitable experimental conditions (Scheme 3). In addition, we also located the corresponding Meinwald transition state (**TS5**) for the isomerization to aldehyde, whereas the one for the formation of ketone could not be found. Importantly, **TS5** (29.8 kcal/mol) is only slightly higher in energy than **TS4-*n*** and **TS4-*iso***, indicating that all three transition states are competitive and contribute to the formation of primary (**TS4-*n*** and **TS5**) and secondary (**TS4-*iso***) alcohol. Comparing Scheme 8 and 9 it can be seen that the hydrogenation of the aromatic epoxide has much lower barriers than that of the aliphatic one (by approximately 9 kcal/mol). Such large difference is in keeping with the observed reactivity trend, with the aromatic epoxides reacting smoothly (Scheme 2) and the aliphatic ones requiring a Lewis acid co-catalyst to give reasonable conversions (see Table S1 in the Supporting Information and Scheme 3).[25] To investigate the role of the Lewis acids, we computed the BF_3-co-catalyzed ring opening of aliphatic epoxide **2l'** (Scheme 10). It was found that BF_3-mediated reactions have a lower barrier than those without BF_3 (Scheme 9) by 15.3 and 11.3 kcal/mol for the formation of primary and secondary alcohol, respectively. The formation of primary alcohol has a lower barrier than that of the formation of the secondary alcohol (13.3 vs. 17.8 kcal/mol), and this

Scheme 10. Gibbs free energy profiles of the hydrogenation of the alkyl epoxide 2l' promoted by CIC 1' and BF_3.[a]



[a] **1'** + H_2 + aliphatic epoxide (**2l'**)/BF_3, kcal/mol.

energy difference of 4.5 kcal/mol accounts for the preferential formation of primary alcohol that was experimentally observed. It should be noted that **TS6-*n*** has an OH···O hydrogen bond, while **TS6-*iso*** has an OH···F hydrogen bond. Notably, in the former case the computation converged to the OH···O bond even when a structure with OH···F bond was taken as starting point. Likewise, in the case of **TS6-*iso***, optimization of a structure with an OH···O hydrogen bond gave a structure with an

OH···F bond. We also located a TS for the BF_3-mediated Meinwald rearrangement (**TS7**) leading to the formation of aldehyde (which is then reduced to primary alcohol), having much lower barrier (0.6 kcal/mol) than the TSs of direct ring opening (**TS6-*n*** and **TS6-*iso***).

The results of the above-discussed computational studies are in substantial agreement with the experimental data, accounting for the activity and regioselectivity trends. Unfortunately, computation of the $Zr(OiPr)_4$-catalyzed reaction was much more problematic. $Zr(OiPr)_4$ is oligomeric in solution and thus the real structure of the catalyst is not known. Although we were able to show that the barrier for the Meinwald rearrangement catalyzed by this Lewis acid is too high, in conformity with what was found experimentally, we were not able to locate a transition state for the L.A.-assisted reduction of the epoxide.

CONCLUSIONS

An effective protocol for the reductive opening of epoxides with H_2 promoted by the readily available CIC **1a** (activated with Me_3NO) has been developed. While the reaction of aromatic epoxides occurs without need of co-catalysts and yields the linear alcohol product selectively, with aliphatic epoxides a Lewis acid co-catalyst is necessary. Remarkably, a careful choice of the Lewis acid allows to steer the selectivity of aliphatic epoxide opening to either primary or secondary alcohols. Thus, this versatile and regiodivergent methodology provides a convenient catalytic access route to alcohols and represents an improvement compared to the state of the art. Deuterium labeling and computational studies revealed a rather complex scenario, which probably involves more than a single mechanistic pathway.

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ABBREVIATIONS

CIC, (cyclopentadienone)iron complex; TS, transition state.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://

General procedures, experimental details, characterization data of all new compounds as well as NMR spectra (PDF).

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(21) It has been recently suggested that, in the active catalytic complex generated by reaction with Me_3NO, one CO is replaced by Me_3N (a labile ligand which readily dissociates under the reaction conditions), rather than leaving a free coordination site. See: Yagoub, I.; Clémancey, M.; Bayle, P.-A.; Quintard, A.; Delattre, G.; Blondin, G.; Kochem, A. Mössbauer Spectroscopic and Computational Investigation of An Iron Cyclopentadienone Complex. Inorg. Chem. 2021, 60, 11192-11199.

(22) Although this process may also occur through an alcohol-assisted pathway (see Ref. 19a,b), we only studied the direct heterolytic H_2 activation via a frustrated Lewis pair (FLP) transition state (See Ref. 19c) because our reactions are run in aprotic solvent (toluene or 1,4-dioxane).

(23) Such stable alcohol complexes – in which the oxygen atom is coordinated to the iron center and the O-H proton is hydrogen bonded to the carbonyl group of the cyclopentadienone ring – have been experimentally observed (see Ref. 19a).

(24) For comparison, we computed the deuteration of aldehydes and ketones, and we found that it has slightly higher barriers than hydrogenation. Nevertheless, deuterated alcohols have the same coordination energy as the normal alcohols (see Scheme S12 in the Supporting Information).

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