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Iron-catalysed regioselective hydrogenation of terminal epoxides to alcohols under mild conditions

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The reduction of epoxides has been recognized as an important method for the synthesis of alcohols using stoichiometric amounts of metal hydride reducing agents. However, homogeneous catalysis-enabled hydrogenation processes with molecular hydrogen remain scarce. Here, we present a general methodology for the synthesis of primary alcohols in high yields, selectively and under mild conditions, from aliphatic and aromatic epoxides. Crucial for the hydrogenation of terminal epoxides is the presence of an $Fe(BF_4)_2{\cdot}6H_2O$/tetraphos catalyst system. Compared to existing methods, which make use of noble metals, the presented protocol shows broad substrate scope and good functional group tolerance. The generality of this is showcased by transformation of various natural products, including steroids, terpenoids, sesquiterpenoids and drug derivatives, which give the desired alcohols in moderate to excellent yields. Mechanistic studies confirm the distinct feature of the catalyst system, which is active for Meinwald rearrangement of epoxides as well as for carbonyl hydrogenations.

Owing to the broad application of primary alcohols in life sciences (pharmaceuticals, agrochemicals, flavouring, fragrances and so on) and the chemical industry (bulk/fine chemicals, specialties)[1], the development of efficient methodologies for their synthesis continues to be scientifically interesting and of practical value. In past decades, numerous examples of the use of olefins as easily available feedstocks have been reported. For example, a stimulating anti-Markovnikov hydration via triple relay catalysis was disclosed in ref. [2] (Fig. 1a). Despite these achievements, hydroformylation/hydrogenation reactions still prevail in the bulk-scale production of primary alcohols (Fig. 1c)[3–7]. On the other hand, the most common synthetic methodology in laboratories starting from olefins makes use of sequential hydroboration/oxidation reactions (Fig. 1b)[8]. Although this two-step process has proved to be very general, it requires stoichiometric amounts of borane reagents and it is challenging to develop scalable production processes. To overcome these problems, we proposed that selective hydrogenation of terminal epoxides in the presence of molecular hydrogen allows for a straightforward approach to such anti-Markovnikov-type alcohols (Fig. 1d). Obviously, epoxides are readily available from alkenes via a one-step oxidation process[9–12], as well as from other methods[9,13].

One of the key challenges in this transformation is the control of regioselectivity given the competition between two different epoxide ring opening possibilities, which leads to primary and/or secondary alcohols (Fig. 2a)[14–16]. Indeed, when using heterogeneous catalysts such as Pd/C, the reactions are limited to aryl epoxides, while secondary alcohols are the major product in the case of alkyl epoxides[17–19]. On the other hand, Raney Ni has been used for producing primary alcohols via the hydrogenation of terminal epoxides, but these reductions require high temperature and high-pressure H_2 (150 °C and 62 bar H_2) and the catalyst is difficult to handle (Fig. 2b)[20].

In contrast, homogeneous catalysis-enabled hydrogenation of terminal epoxides[15,16,21] (rather than hydrosilylation/hydrolysis or hydrogen atom transfer process[22–24]) to form primary or secondary alcohols has barely been investigated. Rare examples include the use of noble metal complexes, based on rhodium[15] and ruthenium[16,21], which exhibited poor selectivity to primary alcohols, along with the generation of oligomers, aldehydes or saturated hydrocarbon by-products (Fig. 2c).

There is currently increasing focus on catalytic hydrogenations utilizing first-row transition metals[25,26] (particularly iron[27–33]) due to their natural abundance, low price and often lower toxicity. Complementary to the recent success of such reactions[34–41], we now report a practical iron-catalysed hydrogenation of terminal epoxides under mild conditions with excellent regioselectivity, thereby paving the way for a general synthesis of primary alcohols from olefins (Fig. 1d).

Results

Development of iron/tetraphos-catalysed hydrogenation of terminal epoxides. We initiated our investigations by testing the hydrogenation of styrene oxide (**1a**) as a benchmark reaction with hydrogen gas in the presence of $Fe(BF_4)_2{\cdot}6H_2O$ and different phosphines (80 °C, 20 bar H_2). Although standard ligands such as PPh_3, dppf (1,1′-bis(diphenylphosphino)ferrocene) and triphos (1,1,1-tris(diphenylphosphinomethyl)ethane) remained inactive, the desired primary alcohol 2-phenylethanol (**2a**) was obtained in 68% yield using a specific tetradentate ligand, tris(2-(diphenylphosphanyl)phenyl)phosphane (tetraphos). Surprisingly, applying a derivative of this latter ligand (tris(2-(diphenylphosphanyl)ethyl)phosphane) gave much lower conversion (<5%). Adding base (2.0 mol% KO^{t}Bu) as co-catalyst significantly decreased the yield of **2a**. Inspired by our previous work[35], we found that the activity was improved (to afford the desired product in 94% yield) by adding 2 mol% trifluoroacetic acid (TFA). Additionally, other 3d transition metal salts, such as $Co(BF_4)_2{\cdot}6H_2O$, $Cu(BF_4)_2{\cdot}xH_2O$, $Ni(acac)_2$ could not catalyse the hydrogenation reaction (Supplementary Table 1). Next, the hydrogenation of a less reactive and thus more challenging aliphatic epoxide substrate—1,2-epoxyhexane—was tested under the same conditions. Here, full conversion was achieved, but unfortunately only 17% yield of desired alcohol was obtained. Nevertheless, decreasing the substrate concentration (0.083 M) and using dioxane instead of THF as solvent led to an 84% yield of **2b** with TFA as additive (Supplementary Table 2)[35]. Control experiments indicated

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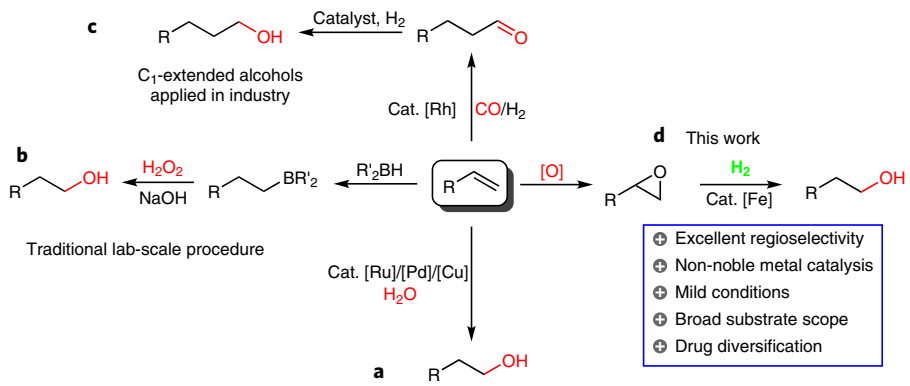

Fig. 1 | Synthesis of primary alcohols from olefins. a, Hydration via triple relay catalysis. **b**, Hydroboration/oxidation process. **c**, Hydroformylation/hydrogenation process. **d**, Homogenous iron catalysis for epoxide hydrogenation.

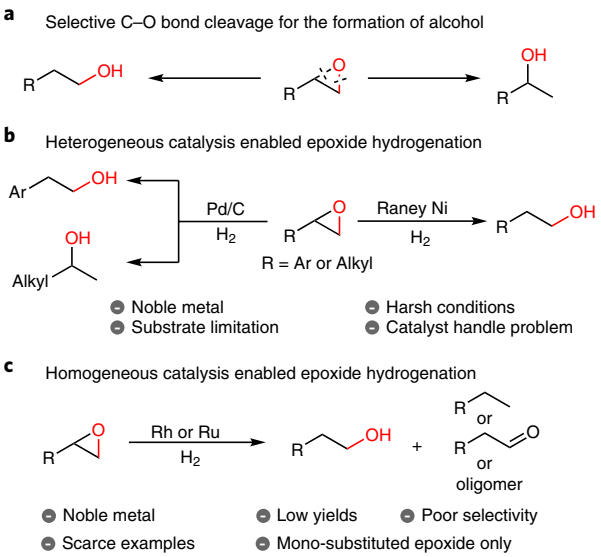

Fig. 2 | Hydrogenation of terminal epoxides to alcohols. a, Selective C–O bond cleavage for the formation of alcohols. **b**, Heterogeneous catalysis enabled epoxide hydrogenation. **c**, Homogeneous catalysis-enabled epoxide hydrogenation.

Table 1 | Hydrogenation of benchmark epoxides with various catalysts

Catalyst \ Reaction	1a → 2a		1b → 2b	
	With TFA	Without TFA	With TFA	Without TFA
$Fe(BF_4)_2{\cdot}6H_2O$/tetraphos	+	–	+	–
$Ru(acac)_3$/[a] triphos	×	–	×	×
$Rh(PPh_3)_3Cl$	×	×	×	×
(*S*)BINAP/(*S*)diamine-$RuCl_2$[b]	×	×	×	×
PtO_2	–	×	×	×
Pd/C[c]	+	–	×	×

Reaction conditions: from **1a** to **2a**: **1a** (0.5 mmol), catalyst (3.0 mol%), ligand (3.0 mol%), TFA (2.0 mol%), THF (4.0 ml), H_2 (20 bar), 80 °C, 18 h; from **1b** to **2b**: 1,4-dioxane (6.0 ml), H_2 (40 bar), yields were determined by GC using *n*-hexadecane as internal standard. [a]$HNTf_2$ was the additive in cases without TFA. [b]KO^{t}Bu was the additive in cases without the TFA. [c]Hexan-2-ol was formed as major product from **1b**. GC, gas chromatography. Yields: +, >80%; –, 20–80%; ×, <20%.

that the synergistic combination of ligand and iron is crucial for both epoxide hydrogenation processes.

Despite the enormous developments of 3d metal catalysis in recent years, a comparison of these newly developed systems with their noble metal congeners reveals in most cases that the latter complexes are still superior regarding activity and productivity. Remarkably, in our transformation, state-of-the-art molecular-defined noble metal catalysts such as $Ru(acac)_3$/triphos, Wilkinson's catalyst $Rh(PPh_3)_3Cl$ and Noyori's catalyst (*S*)BINAP/(*S*)diamine-$RuCl_2$, either with additive or under additive-free conditions, displayed significantly lower or no activity at all (Table 1 and Supplementary Tables 4 and 5).

Even industrially applied heterogeneous catalysts, for example Adams' catalyst (PtO_2) and Pd/C, performed worse. Notably, when Pd/C was used the primary alcohol was selectively formed in the case of styrene oxide, while the secondary alcohol was obtained as the major product, along with primary alcohol, from 1,2-epoxyhexane[17]. Similarly, PtO_2 showed activity towards aryl epoxide hydrogenation, but did not form the desired product from the alkyl epoxide (Table 1 and Supplementary Tables 4 and 5). These comparison experiments highlight the unique reactivity of the iron/tetraphos system for epoxide hydrogenation.

Substrate scope of terminal epoxides. Having suitable reaction conditions in hand, we explored the reactivity of different epoxides (Fig. 3). In all cases of mono- and di-substituted terminal epoxides, the desired primary alcohols were obtained with good yields and excellent regioselectivities. The hydrogenation process proceeds under comparatively mild conditions and tolerates valuable substituents and functional groups, including fluoro, bromo, chloro, trifluoromethyl and dimethylamino, irrespective of location at the *ortho*, *meta* or *para* position. Notably, ester **2o**, amide **2q**, olefins **2r** and **2v**, even ketone **2s**, which are typically sensitive to reduction, remained stable with this method. However, hydrogenation of alkyne to the corresponding alkene also occurred under such conditions. The substrates containing a nitrile or nitro group failed to give the desired primary alcohols. This is in accordance with the results in Supplementary Table 6, which were obtained using additional equimolar equivalents of substrates containing reducible functional groups (see Supplementary Information). In general, the protocol

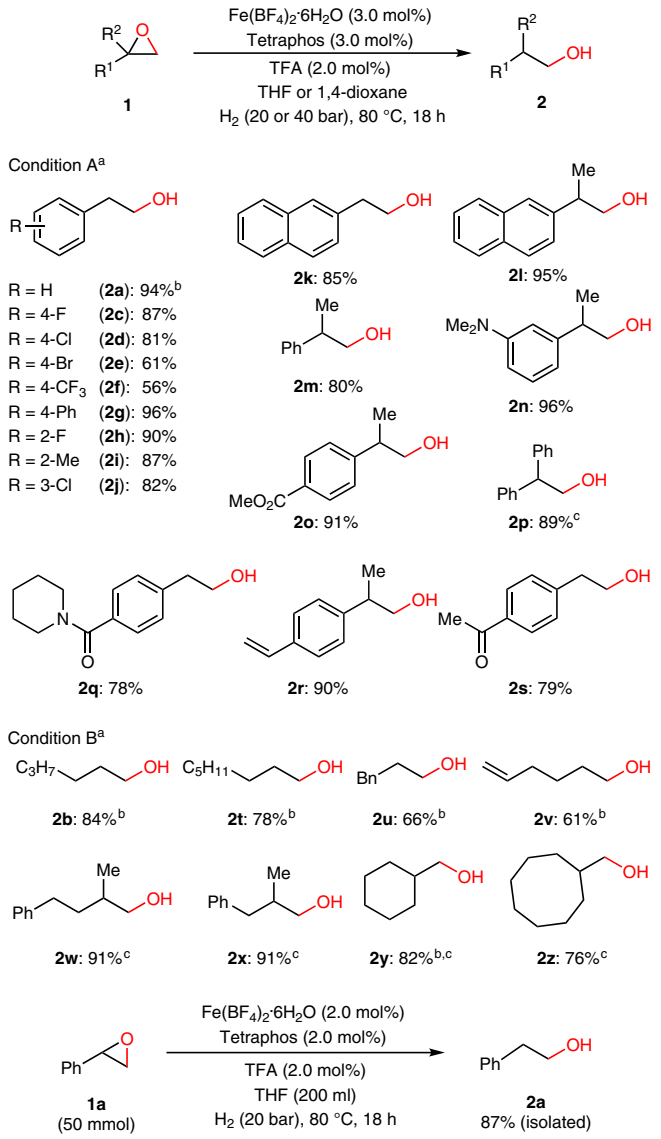

Fig. 3 | Iron-catalysed hydrogenation of terminal epoxides. [a]**1** (0.5 mmol), $Fe(BF_4)_2{\cdot}6H_2O$ (3.0 mol%), tetraphos (3.0 mol%), TFA (2.0 mol%), 80 °C, 18 h, isolated yields. Condition for A: THF (4.0 ml), H_2 (20 bar). Conditions for B: 1,4-dioxane (6.0 ml), H_2 (40 bar). [b]Yields were determined by GC using *n*-hexadecane as internal standard. [c]120 °C.

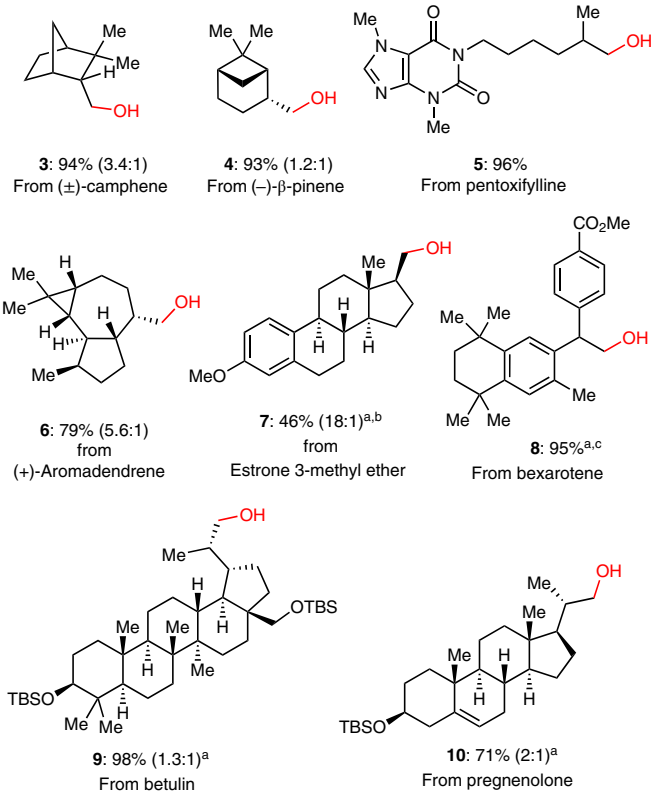

Fig. 4 | Iron-catalysed hydrogenation of epoxides derived from natural products and drug derivatives. Reaction conditions: epoxide (0.5 mmol), $Fe(BF_4)_2{\cdot}6H_2O$ (3.0 mol%), tetraphos (3.0 mol%), TFA (2.0 mol%), 1,4-dioxane (6.0 ml), H_2 (40 bar), 120 °C, 18 h, isolated yields. The major isomers obtained after conversion are displayed. [a]0.3 mmol scale. [b]$Fe(BF_4)_2{\cdot}6H_2O$ (5.0 mol%), tetraphos (5.0 mol%). [c]H_2 (20 bar), THF as solvent.

is easily scalable, as reflected by the reaction of **1a** performed on a 50 mmol scale, which furnished a comparably high yield even at lower catalyst loading (2 mol%).

We were particularly delighted to find that this iron-catalysed hydrogenation also occurs with epoxides derived from several classes of natural products, including steroids, terpenoids, sesquiterpenoids and drug derivatives, which demonstrate the wider applicability of our system (Fig. 4).

More specifically, the constituent of essential oil terpenes such as (±)-camphene (**3**), (−)-β-pinene (**4**) and (+)-aromadendrene (**6**) gave the primary alcohols in high yield and selectivity. Furthermore, bio-active betulin (**9**), a triterpene that is naturally abundant in the bark of birch trees and is active against a variety of tumours, as well as pentoxifylline (**5**) and bexarotene (**8**), which are drugs to treat muscle pain in people with peripheral artery disease and cutaneous T cell lymphoma (CTCL) furnished the corresponding products, all in >90% yield. As examples for important steroids, estrone 3-methyl ether (**7**) and pregnenolone (**10**) afforded the desired alcohols, too. As expected from our selectivity studies, the inherent amide, silyloxy, alkene and ester substituents were well tolerated (Fig. 4).

Mechanistic investigations. Considering the unique ability of the iron/tetraphos complex for regioselective hydrogenation of terminal epoxides to primary alcohols, we were attracted to the mechanism of this transformation. To support the homogeneous nature of this catalytic process, we conducted poisoning experiments using three different epoxides in the presence of an excess of mercury, which furnished comparable product yields (Fig. 5a). Notably, the hydrogenation of epoxides (**1a** and **1b**) to primary alcohols has been tested with several in situ generated iron catalysts. However, only in the presence of the tetraphos ligand did the desired reaction take place. Furthermore, this transformation was also realized in the presence of the well-defined Fe(tetraphos)FBF_4 complex in 92% and 81% yields, respectively. We believe these results clearly exclude iron nanoparticles as the active catalyst species and support the homogeneous nature of the active catalyst. Performing kinetic studies with styrene oxide (**1a**) and 1,2-epoxyhexane (**1b**), 2-phenylacetaldehyde (**2a′**) and *n*-hexanal (**2b′**) were detected as major intermediates during the reactions, respectively. More specifically, **1a** was quickly isomerized to **2a′**, followed by rate-determining hydrogenation to afford the corresponding alcohol **2a** (Fig. 5b). However, the rate of Meinwald rearrangement[42–45] from 1,2-epoxyhexane (**1b**) to *n*-hexanal (**2b′**) was much slower than styrene

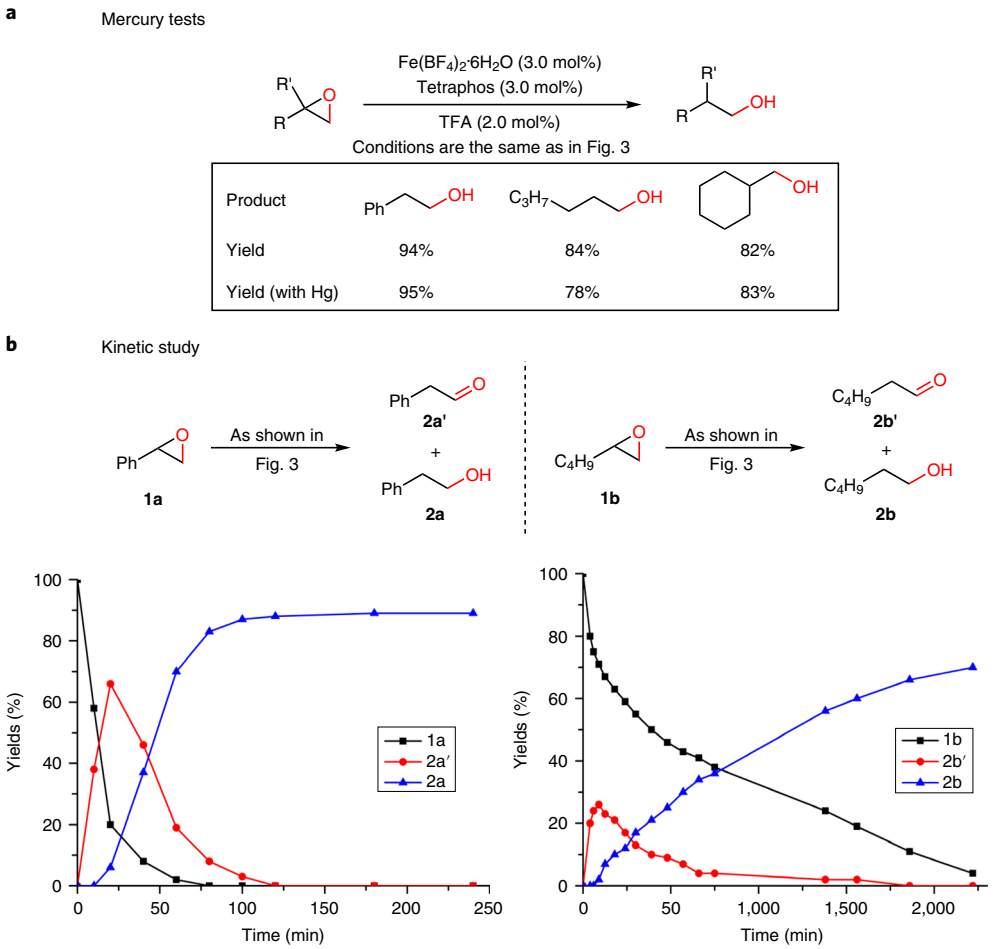

Fig. 5 | Mechanistic findings. a, Mercury tests. **b**, Kinetic studies using **1a** and **1b** as substrates.

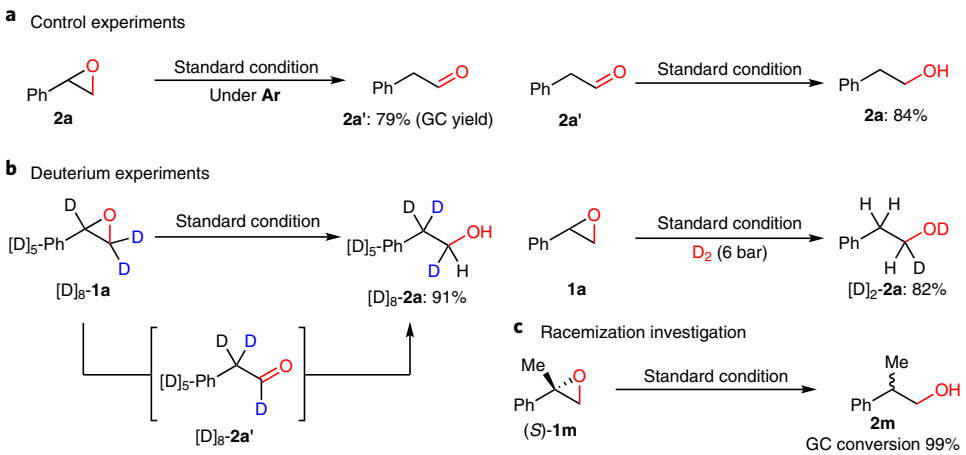

Fig. 6 | Mechanistic studies. a, Control reactions. **b**, Deuterium experiments. **c**, Racemization investigation.

oxide (**1a**), and hydrogenation of *n*-hexanal (**2b′**) should not be the rate-determining step (Fig. 5b).

To further confirm the importance of aldehydes as the intermediates, control reactions with **1a** and **2a′** were executed (Fig. 6a). Using the standard experimental set-up under an argon atmosphere instead of hydrogen, 79% yield of 2-phenylacetaldehyde (**2a′**) was obtained. When employing **2a′** as the substrate, it gave a comparable yield of desired product **2a**. It is worth noting that the aldehyde was formed in the presence of $Fe(BF_4)_2{\cdot}6H_2O$ even without TFA, but the isomerization process does not occur with TFA (2 mol% or 10 mol%) only (Supplementary Table 3). Deuterium experiments employing either $[D]_8$-**1a** or in the presence of D_2 gas confirmed these observations and fully agreed with aldehydes as central intermediates. More specifically, 1,2-deuterium shift of

$[D]_8$-**1a** resulted in the formation of $[D]_8$-**2a′** followed by hydrogenation to give the corresponding product (Fig. 6b). Furthermore, *rac*-**2m** was furnished when applying (*S*)-**1m** as substrate under standard conditions, which indicated that the carbocation is generated in the rearrangement step rather than insertion of Fe–H species into the C–O bond (Fig. 6c). Moreover, several chiral phosphoric acids were tested as the additive using **1m** as the starting materials; unfortunately, no e.e. value was observed in the corresponding products (see Supplementary Information). Overall, the distinctive feature of the $Fe(BF_4)_2{\cdot}6H_2O$/tetraphos system stems from the fact that it is both an active catalyst for the Meinwald rearrangement as well as for hydrogenations.

Conclusion

A general catalytic hydrogenation of aliphatic and aromatic epoxides to primary alcohols with H_2 is described. Key for its success is the use of a molecularly defined iron/tetraphos complex, which shows broad substrate scope and functional group tolerance. The presented methodology works with epoxides derived from several classes of natural products, including steroids, terpenoids, sesquiterpenoids and drug derivatives, which illustrates the wide applicability of this system. Mechanistic studies reveal that this specific catalyst enables both Meinwald rearrangement and hydrogenation under mild conditions. In general, this transformation provides an alternative approach to primary alcohols compared to traditional hydroboration/oxidation of olefins.

Data availability

CCDC 1895726 (S7), 1895727 (S9), 1895728 (S10), 1895729 (9a) and 1895730 (10′) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Further data that support the plots within this paper and other findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

M.B. and W. Liu. conceived and designed the experiments. W. Liu and W. Li performed the experiments and analysed the data. A.S. performed X-ray crystal structure analyses. K.J. participated in the discussions and supported the project. M.B. and W. Liu co-wrote the paper.

Competing interests

The authors declare no competing interests.

Additional information

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