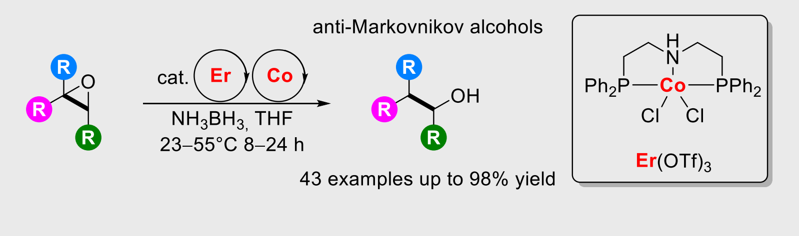
ACS Catalysis

pubs.acs.org/acscatalysis Research Article

Erbium-Catalyzed Regioselective Isomerization−Cobalt-Catalyzed Transfer Hydrogenation Sequence for the Synthesis of Anti-Markovnikov Alcohols from Epoxides under Mild Conditions

Xin Liu, Lars Longwitz, Brian Spiegelberg, Jan Tönjes, Torsten Beweries, and Thomas Werner*

Cite This: *ACS Catal.* 2020, 10, 13659−13667 Read Online



ABSTRACT: Herein, we report an efficient isomerization−transfer hydrogenation reaction sequence based on a cobalt pincer catalyst (1 mol %), which allows the synthesis of a series of anti-Markovnikov alcohols from terminal and internal epoxides under mild reaction conditions (≤55 °C, 8 h) at low catalyst loading. The reaction proceeds by Lewis acid (3 mol % $Er(OTf)_3$)-catalyzed epoxide isomerization and subsequent cobalt-catalyzed transfer hydrogenation using ammonia borane as the hydrogen source. The general applicability of this methodology is highlighted by the synthesis of 43 alcohols from epoxides. A variety of terminal (23 examples) and 1,2-disubstituted internal epoxides (14 examples) bearing different functional groups are converted to the desired anti-Markovnikov alcohols in excellent selectivity and yields of up to 98%. For selected examples, it is shown that the reaction can be performed on a preparative scale up to 50 mmol. Notably, the isomerization step proceeds via the most stable carbocation. Thus, the regiochemistry is controlled by stereoelectronic effects. As a result, in some cases, rearrangement of the carbon framework is observed when tri- and tetra-substituted epoxides (6 examples) are converted. A variety of functional groups are tolerated under the reaction conditions even though aldehydes and ketones are also reduced to the respective alcohols under the reaction conditions. Mechanistic studies and control experiments were used to investigate the role of the Lewis acid in the reaction. Besides acting as the catalyst for the epoxide isomerization, the Lewis acid was found to facilitate the dehydrogenation of the hydrogen donor, which enhances the rate of the transfer hydrogenation step. These experiments additionally indicate the direct transfer of hydrogen from the amine borane in the reduction step.

KEYWORDS: *epoxides, cobalt, transfer hydrogenation, alcohols, anti-Markovnikov*

Alcohols are important building blocks in organic chemistry and have a wide variety of applications as pharmaceuticals, agrochemicals, solvents, or fragrances.[1] The direct synthesis from olefins by formal hydration of the carbon−carbon double bond is a common synthetic pathway both for the production of bulk and specialty chemicals.[2] In accordance with Markovnikov's rule, the hydroxyl group is generated at the most substituted carbon atom in most of these processes. The direct hydration of olefins to anti-Markovnikov alcohols is a long standing challenge in catalysis and only rarely reported.[3−5] The access to alcohols with an anti-Markovnikov selectivity requires different strategies (Scheme 1). In industry, olefins are often converted to anti-Markovnikov alcohols in a homologation reaction by hydroformylation and subsequent reduction (Scheme 1A).[6−10] For lab-scale applications, a hydroboration/oxidation sequence is often used to synthesize anti-Markovnikov alcohols.[11,12] Besides these well-established methods, the reductive opening of epoxides has recently emerged as a powerful alternative strategy (Scheme 1B).[13−15]

The three major challenges in this transformation are the control of the regioselectivity of the epoxide opening, inhibition of the formation of allylic alcohols, and reduction of substituted epoxides.

In previous studies, the reduction of alkyl epoxides using classic heterogeneous reduction catalysts such as Pd/C usually gave the respective alcohols with Markovnikov selectivity.[16−18] The use of homogeneous catalysts for the (transfer) hydro-

Received: July 28, 2020
Revised: September 29, 2020

https://dx.doi.org/10.1021/acscatal.0c03294
ACS Catal. 2020, 10, 13659−13667

Scheme 1. Synthetic Pathways Toward anti-Markovnikov Alcohols and Current Challenges

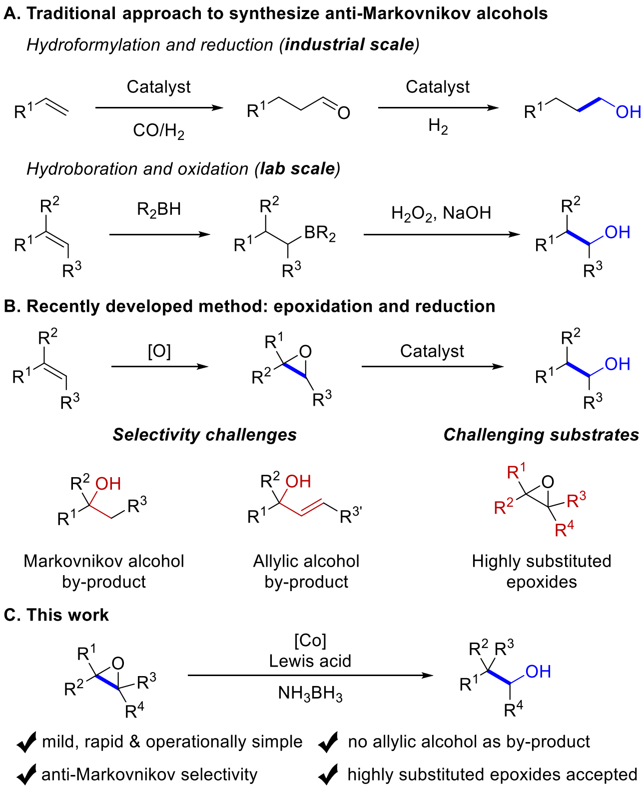
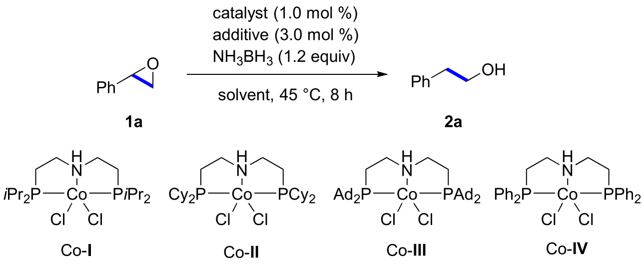


Table 1. Catalyst Screening and Parameter Optimization for the Cobalt-Catalyzed Transfer Hydrogenation of Epoxides[a]



entry	catalyst	additive	solvent	conv./%	**2a**/%
1	Co-I	$AlCl_3$	THF	82	62[c]
2	Co-II	$AlCl_3$	THF	73	51[c]
3	Co-III	$AlCl_3$	THF	66	0[d]
4	Co-IV	$AlCl_3$	THF	85	74[c]
5	Co-IV	LiOTf	THF	49	43
6	Co-IV	$InCl_3$	THF	43	39
7	Co-IV	TfOH	THF	52	47
8	Co-IV	$Zn(OTf)_2$	THF	>99	80[c]
9	Co-IV	$Er(OTf)_3$	THF	>99	95
10	Co-IV	$Er(OTf)_3$	toluene	60	52
11	Co-IV	$Er(OTf)_3$	CH_2Cl_2	36	33
12	Co-IV	$Er(OTf)_3$	*n*-hexane	75	71
13[b]	Co-IV	$Er(OTf)_3$	THF	41	38

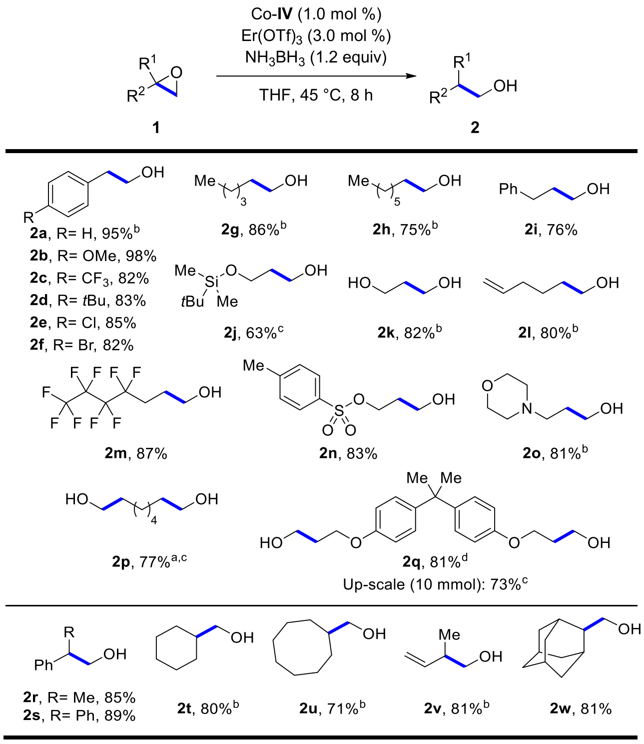
[a] Reaction conditions: **1a** (0.50 mmol, 1.0 equiv), catalyst (1.0 mol %), additive (3.0 mol %), NH_3BH_3 (0.60 mmol, 1.2 equiv), solvent (1.5 mL), 45 °C, 8 h. The yield was determined by GC using mesitylene as the internal standard. [b] T = 23 °C, t = 24 h. [c] The Markovnikov alcohol (1-phenylethanol) was detected as the side product. [d] Acetophenone and 2-phenylacetaldehyde were formed.

genation or hydrosilylation reaction of epoxides has been widely investigated.[13,19−25] However, in these cases, typically catalysts based on precious metals are employed, and often only moderate selectivity toward the anti-Markovnikov products is achieved. Most recently, Beller and co-workers reported the selective hydrogenation of epoxides catalyzed by an iron-triphos and cobalt−tetraphos complex in the presence of Lewis and Brønsted acidic additives.[14,26] However, high catalyst loadings and drastic reactions conditions, e.g., high hydrogen pressures are required. A different approach for epoxide reduction was reported by Gansäuer and Norton.[15] A cooperative catalyst system based on Ti/Cr was used for the radical reduction of epoxides at relatively low hydrogen pressures, although high catalyst loadings and long reaction times had to be employed. Notably, the allylic alcohol was detected as a by-product when internal epoxides were used as substrates. Due to our general interest in the use of catalysts based on non-precious metals,[27,28] we report here an efficient isomerization−transfer hydrogenation reaction sequence based on a cobalt pincer catalyst which allows the synthesis of anti-Markovnikov alcohols from terminal and internal epoxides under mild reaction conditions (Scheme 1C). The use of transfer hydrogenation reagents instead of molecular hydrogen has the advantage that high pressure equipment can be avoided, and often, new and interesting reactivities arise.[29,30] Ammonia borane is an attractive alternative to commonly used hydrogen transfer agents such as alcohols since it is nonvolatile and harmless.[31−35]

We started our study by investigating the catalytic activities of a series of well-known cobalt complexes[36,37] in the transfer hydrogenation of styrene oxide (**1a**) (Table 1, entries 1−4). Notably, Co-I has been reported by the groups of Luo and Liu for the transfer hydrogenation of alkynes using ammonia borane as the hydrogen source.[36] Initially, we performed the conversion of **1a** in the presence of 3.0 mol % of $AlCl_3$ as the Lewis acidic additive and ammonia borane as the hydrogen donor. The cobalt pincer complex Co-**IV** was found to be the most efficient catalyst. At a catalyst loading of only 1.0 mol %, the anti-Markovnikov alcohol **2a** was obtained in 74% yield after 8 h at 45 °C (Table 1, entry 4). We compared the performance of the phenyl-substituted PNP−pincer complex Co-**IV** to other earth abundant metal catalysts under these conditions.[38] Notably, iron or manganese PNP complexes gave only phenylacetaldehyde as the main product. Other hydrogen donors such as alcohols or molecular hydrogen were found to cause side reactions.[38] Beside $AlCl_3$, we also evaluated different Lewis acids (LAs) and a Brønsted acid as additives for the isomerization of **1a** (entries 5−9).[39,40] The use of $InCl_3$, LiOTf or trifluoromethanesulfonic acid (TfOH) led to significantly lower yields of <50% for the desired product **2a** (entries 5−7). An improved yield of 80% was achieved when $Zn(OTf)_2$ was used as an additive (entry 8). However, erbium triflate which has previously been reported as a catalyst for the isomerization of epoxides[39] proved to be the most efficient additive leading to **2a** in an excellent yield of 95% (entry 9). We also considered other solvents which are commonly used in transfer hydrogenation reactions such as toluene, CH_2Cl_2, or *n*-hexane (entries 10−12). However, in these solvents, lower yields of 52, 33, and 71% were obtained, respectively. Remarkably, the reaction could be carried out even at room temperature, and a yield of 38% was obtained after 24 h (entry 13).

With the optimal reaction conditions in hand, we explored the scope of the Co-**IV**-based system on the isomerization−transfer hydrogenation of different terminal epoxides **1** to yield the corresponding anti-Markovnikov alcohols **2** (Table 2). The initial isomerization of the epoxide proceeds via the most stable carbocation followed by a [1,2]-hydride shift to yield the corresponding aldehyde as an intermediate.[39,41] Subsequently, the aldehyde is hydrogenated to the corresponding alcohol. Thus, aryl substituted epoxides **1a**−**f** were regioselectively converted to the desired anti-Markovnikov alcohols **2a**−**f** with yields up to 95%. We turned our attention to alkyl-substituted epoxides **1g** and **1h**. The conversion of these substrates is of particular interest since the reaction of alkyl-substituted epoxides, for example, hexene oxide (**1g**), usually leads to a mixture of regioisomers using classical hydrogenation catalysts.[15−19] However, under our standard reaction conditions, alcohols **2g** and **2h** were successfully obtained with anti-Markovnikov selectivity. Notably, various functional groups are tolerated under the reaction conditions, and epoxides bearing different functionalities such as a siloxane group **1j**, additional hydroxyl **1k**, alkenyl **1l**, perfluoroalkyl **1m**, tosyl **1n**, or a morpholine-substituted epoxide **1o** were converted to the respective alcohols **2j**−**o** in good to excellent yields up to 87%. Also, bisepoxides were successfully converted to the respective diols, and the effectiveness of the methodology was demonstrated at 10 mmol scale in the conversion of bisphenol A diglycidyl ether (**1q**) to diol **2q** which was obtained in 73% yield. Additionally, we could prove that also 1,1-disubstituted epoxides are suitable substrates. A series of these compounds **1r**−**1w** were converted, and the anti-Markovnikov alcohols **2r**−**2w** were obtained in yields up to 89%.

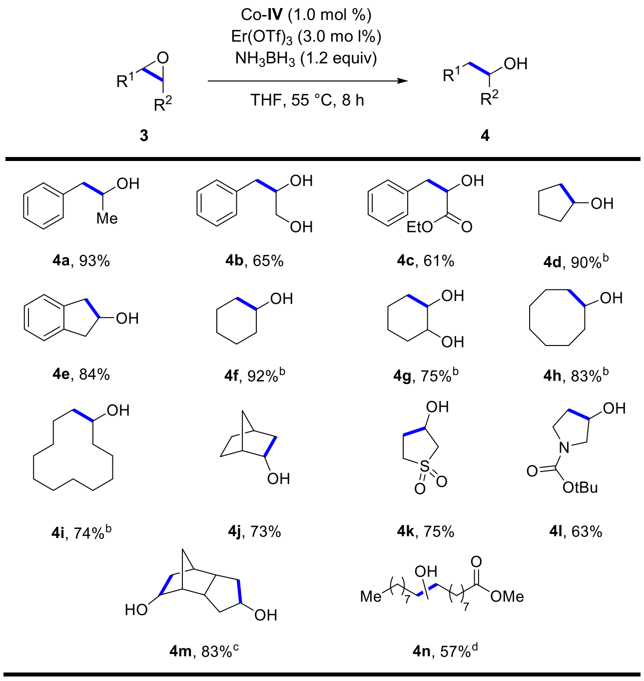
Table 2. Scope for the Synthesis of Anti-Markovnikov Alcohols from Terminal Epoxides[a]



[a]Reaction conditions: **1a**−**w** (0.50 mmol, 1.0 equiv), Co-**IV** (1.0 mol %), Er(OTf)$_3$ (3.0 mol %), NH$_3$BH$_3$ (0.60 mmol, 1.2 equiv), THF (1.5 mL), 45 °C, 8 h. Isolated yields are given. [b]The yield was determined by GC using mesitylene as the internal standard. [c]The yield was determined by ^{1}H NMR using mesitylene as the internal standard. [d]The amount of NH$_3$BH$_3$ was 2.0 equiv, and the reaction time was 16 h.

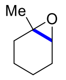
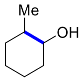
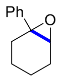
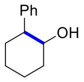
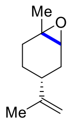
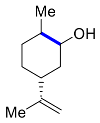
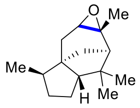
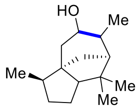
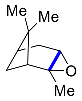
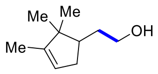
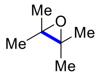
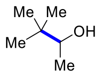
One drawback of the previously reported iron-based catalytic system was the limitation to the conversion of terminal epoxides.[14] The main reason for this is probably that in the case of internal epoxides, the epoxide will isomerize to the respective ketone, which is significantly harder to reduce.[42] This prompted us to study the conversion of 1,2-disubstiuted epoxides **3** (Table 3) and tri- and tetra-substituted epoxides **5** (Table 4). In the case of epoxides **3,** the isomerization occurs via the most stable carbocation again followed by a 1,2-hydride shift to afford the respective ketone which is subsequently reduced to the corresponding alcohol **4**.[39,40] Notably, in the presence of cobalt complex Co-**IV** at slightly elevated temperature of 55 °C, it was possible to convert *β*-methylstyrene oxide (**3a**) into 1-phenylpropan-2-ol (**4a**) in an isolated yield of 93%. Other *β*-substituted styrene oxide derivatives **3b** and **3c** bearing an alcohol or ester moiety were converted to the respective products **4b** and **4c** in yields up to 65%. Cyclic starting materials with different secondary ring sizes **3d**−**j** were accepted as substrates, and the alcohols **4d**−**j** were obtained in yields up to 92%. Also, heterocyclic substrates such as sulfone derivative **3k** and an epoxidized Boc-protected pyrrolidine **3l** were converted leading to the desired alcohols **4k** and **4l** in 75 and 63% yield, respectively. Dicyclopentadiene

Table 3. Scope for the Conversion 1,2-Disubstituted Epoxides in the Isomerization−Cobalt-Catalyzed Transfer Hydrogenation Sequence[a]



[a]Reaction conditions: **3a**−**l** (0.50 mmol, 1.0 equiv), Co-**IV** (1.0 mol %), Er(OTf)$_3$ (3.0 mol %), NH$_3$BH$_3$ (0.60 mmol, 1.2 equiv), THF (1.5 mL), 55 °C, 8 h. Isolated yields are given. [b]The yield was determined by GC using mesitylene as the internal standard. [c]The amount of NH$_3$BH$_3$ was 2.0 equiv, and the reaction time was 16 h. [d]The product was obtained as a mixture of two regioisomers.

Table 4. Scope and Limitation for the Conversion of Tri- and Tetra-substituted Epoxides[a]

substrate		product	yield **6**/ %
	**5a**		**6a**, 89%[b,c]
	**5b**		**6b**, 84%[d]
	**5c**		**6c**, 75%[d]
	**5d**		**6d**, 81%[d]
	**5e**		**6e**, 60%
	**5f**		**6f**, 56%[b]

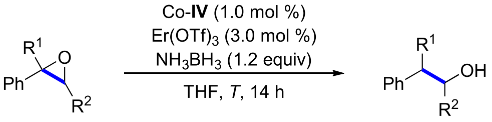
[a]Reaction conditions: **5a**–**f** (0.50 mmol, 1.0 equiv), Co-**IV** (1.0 mol %), Er(OTf)$_3$ (3.0 mol %), NH$_3$BH$_3$ (0.60 mmol, 1.2 equiv), THF (1.5 mL), 55 °C, 8 h. Isolated yields are given. [b]The yield was determined by GC using mesitylene as the internal standard. [c]dr = 4:1. [d]The product was obtained as a mixture of diastereoisomers.[38]

dioxide (**3m**) was converted to the respective diol **4m** in a good yield of 83%. Epoxidized methyl oleate (**3n**) gave the desired alcohol **4n** in 57% yield as a mixture of two possible regioisomers.

Having established the use of the Co-**IV** as an efficient method for the synthesis of anti-Markovnikov alcohols from epoxides, we further studied the scalability of this method (Scheme 2).

Thus, we converted terminal epoxide **1a** and 1,1- and 1,2-disubsituted substrates **1r** and **3a** on a multi gram scale under our standard reaction conditions and obtained the corresponding products yields up to 85%.

Scheme 2. Upscaling Studies[a]



1a, R^1= H, R^2= H, 50 mmol	**2a**, R^1= H, R^2= H, 85% (**5.11 g**)
1r, R^1= Me, R^2= H, 50 mmol	**2r**, R^1= Me, R^2= H, 77% (**5.16 g**)
3a,[b] R^1= H, R^2= Me, 50 mmol	**4a**, R^1= H, R^2= Me, 83% (**5.57 g**)

[a]Reaction conditions: epoxide (50 mmol, 1.0 equiv), Co-**IV** (1.0 mol %), Er(OTf)$_3$ (3.0 mol %), NH$_3$BH$_3$ (1.2 equiv), THF (80 mL), 45 °C. [b] 55 °C, 14 h. Isolated yields are given.

Furthermore, we evaluated the conversion of even more challenging tri- and tetra-substiuted epoxides (Table 4). Tri-substituted substrates **5a**–**c** were converted to the corresponding anti-Markovnikov alcohols **6a**–**c** in yields up to 89%. Cedrene oxide (**5d**) was also successfully converted, and the corresponding alcohol **6d** was isolated in 81% yield. However, the initial stereochemical information is lost at both stereocenters of the epoxides (at the first stereocenter due to the formation of the higher substituted carbocation and at the second stereocenter due to the formation of the ketone intermediate). Notably, when α-pinene oxide (**5e**) was used as the substrate 2,2,3-trimethyl-3-cyclopentene-1-ethanol (**6e**) was obtained as the product. This can be explained by LA-catalyzed rearrangement of **5e** to form campholenic aldehyde as an intermediate which is subsequently reduced to **6e**.[38,43] Also, tetramethylethylene oxide (**5f**) could be converted. In this case, the epoxide opening initiates a Wagner–Meerwein rearrangement which is followed by a 1,2-hydride shift to yield 3,3-dimethyl-2-butanone as an intermediate. The subsequent Co-**IV** catalyzed transfer hydrogenation leads to 3,3-dimethylbutan-2-ol (**6f**) in 56%.

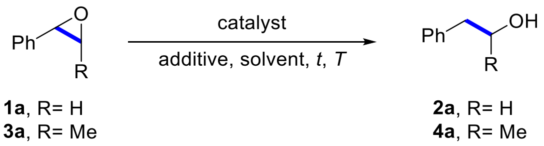
We further evaluated the efficiency of the Co-**IV** system by comparing it to classical hydrogenation catalysts and Beller's reported catalytic systems in the presence of molecular hydrogen for the conversion of the terminal epoxide **1a** (45 °C, 8 h) and the internal epoxide **3a** (55 °C, 8 h). Under our standard reaction conditions, we obtained **2a** and **4a** in 95% and 93% yield, respectively (Table 5, entry 1). In contrast, the use of previously reported Fe-tetraphos catalyst in combination with trifluoroacetic acid (TFA) gave **2a** and **4a** in lower yields of 63% and <5%, respectively (Table 5, entry 2).

The use of recently reported Co-triphos system in combination with Zn(OTf)$_2$ as isomerization catalyst led to slightly increased yields of 78% for **2a** and 62% for **4a** (entry 3). Subsequently, we repeated both reactions using Er(OTf)$_3$ as additive to catalyze the isomerization (entries 4 and 5). Even though this led to a general improvement in the yields for **2a** and **4a,** the Co-**IV** system still gave the best results. This clearly demonstrates not only the superiority of Er(OTf)$_3$ as the isomerization catalyst but also the higher efficiency of catalyst Co-**IV**. The traditional hydrogenation catalysts Pd/C, PtO$_2$ and the Wilkinson catalyst gave **2a** only in low yields of <15% usually as a mixture of the Markovnikov and anti-Markovnikov product (entries 6–8). Notably, the conversion of internal epoxide **3a** to the desired anti-Markovnikov product **4a** was unsuccessful in the presence of these catalysts.

Finally, we performed a detailed mechanistic investigation to get a better insight into the mechanism of this reaction sequence. Therefore, we monitored the conversion of the model substrate **1a** under the standard reaction conditions (Figure 1A).

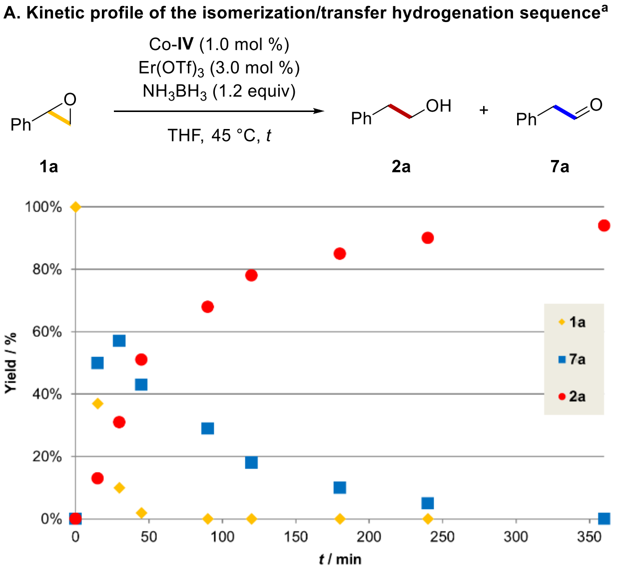
The epoxide **1a** is initially isomerized to the aldehyde **7a** which is subsequently hydrogenated to yield the alcohol **2a**. After 15 min, > 60% of the starting material was already converted to **7a** (50%) and the final product **2a** (13%). Several control experiments were performed (Figure 1B). In the absence of the catalyst Co-**IV** or ammonia borane, the epoxide **1a** was fully converted (entry 2 and 3). Notably, the isomerization product **7a** was the only observed product. This was also the dominant product when molecular hydrogen was used instead of ammonia borane (entry 4). In the absence of Er(OTf)$_3$, no conversion of the starting material **1a** was detected (entry 5). This supports the proposed two-step

Table 5. Hydrogenation of Terminal Epoxide **1a** and Internal Epoxide **3a** with H_2 in the Presence of Known Catalysts under Our Reaction Condition[a]



entry	catalyst (mol %)	additive (mol %)	hydrogen source	solvent	conv.[b] **1a**/%	yield **2a**/%	conv[c] **3a**/%	yield **4a**/%
1	Co-**IV** (1.0)	$Er(OTf)_3$ (3.0)	NH_3BH_3[d]	THF	>99	95	>99	93
2	$Fe(BF_4)\cdot H_2O$ (2.0), tetraphos (2.0)	TFA (2.0)	H_2 (20 bar)	THF	>99	63	6	<5
3	$Co(NTf_2)_2$ (3.0), triphos (6.0)	$Zn(OTf)_2$ (7.0)	H_2 (40 bar)	THF	>99	78	>99	62
4	$Fe(BF_4)\cdot H_2O$ (2.0), tetraphos (2.0)	$Er(OTf)_3$ (3.0)	H_2 (20 bar)	THF	>99	71	>99	36
5	$Co(NTf_2)_2$ (3.0), triphos (6.0)	$Er(OTf)_3$ (3.0)	H_2 (40 bar)	THF	>99	85	>99	67
6	Pd/C (10)		H_2 (20 bar)	toluene	20	8 (6)[e]	15	(5)
7	PtO_2 (10)		H_2 (20 bar)	toluene	15	4 (5)[e]	10	-
8	$Rh(PPh_3)_3Cl$ (10)		H_2 (20 bar)	THF	16	1 (8)[e]	6	-

[a] The yield was determined by GC using mesitylene as the internal standard. [b] T = 45 °C, t = 8 h. [c] T = 55 °C, t = 8 h. [d] NH_3BH_3 (0.6 mmol, 1.2 equiv). [e] The yield of the Markovnikov alcohol product is given in brackets.


A. Kinetic profile of the isomerization/transfer hydrogenation sequence[a]

B. Control experiments

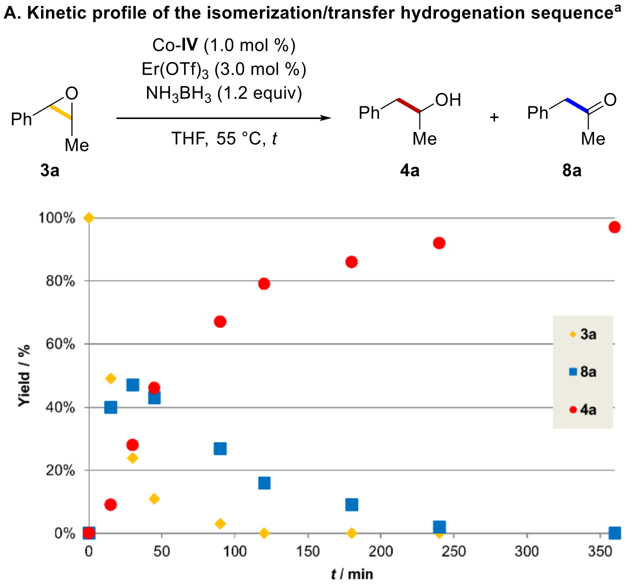
en-try	Co-**IV** (mol %)	$Er(OTf)_3$ (mol %)	NH_3BH_3 (equiv)	conv. **1a** (%)	yield **2a** (%)	Yield **7a** (%)
1	1	3	1.2	>99	95	–
2	–	3	1.2	>99	–	94
3	1	3	–	>99	–	91
4	1	3	–[b]	97	5	79
5	1	–	1.2	0	–	–

Figure 1. Kinetic profile (A) and control experiments (B) for the conversion of styrene oxide (**1a**). [a] Reaction conditions: **1a** (0.5 mmol), Co-**IV** (1 mol %), $Er(OTf)_3$ (3 mol %), NH_3BH_3 (1.2 equiv), THF (1.5 mL), 45 °C, 8 h. The conversion and yields were determined by GC using mesitylene as the internal standard. [b] H_2 (1 bar), NH_3BH_3 (1.0 mol %).

reaction sequence which proceeds via (1) an initial $Er(OTf)_3$-catalyzed isomerization of the starting material **1a** to the aldehyde **7a** followed by (2) the Co-catalyzed transfer hydrogenation of **7a** to the anti-Markovnikov alcohol **2a**.

Additionally, we performed the reaction monitoring and the control experiments with β-methylstyrene oxide (**3a**) as the model substrate for 1,2-disubstituted epoxides (Figure 2).

Also, in this case, the epoxide **3a** is initially isomerized, and ketone **8a** is obtained which is subsequently hydrogenated to


A. Kinetic profile of the isomerization/transfer hydrogenation sequence[a]

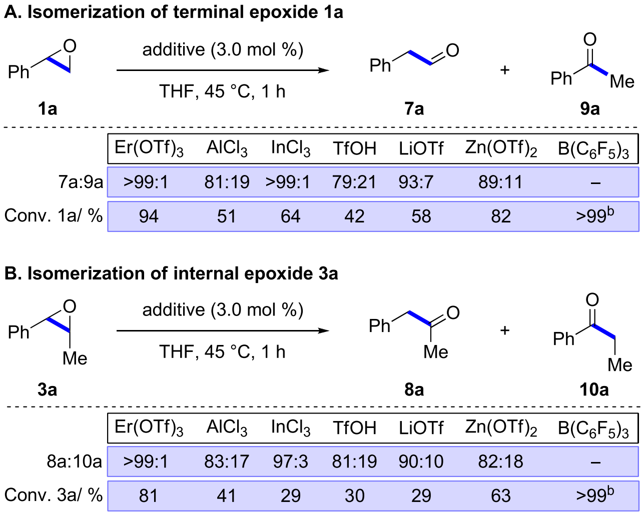
B. Control experiments

en-try	Co-**IV** (mol %)	$Er(OTf)_3$ (mol %)	NH_3BH_3 (equiv)	conv. **3a** (%)	yield **4a** (%)	yield **8a** (%)
1	1	3	1.2	>99	93	–
2	–	3	1.2	>99	–	90
3	1	3	–	>99	–	88
4	1	3	–[b]	96	6	85
5	1	0	1.2	0	–	–

Figure 2. Kinetic profile (A) and control experiments (B) for the conversion of β-methylstyrene oxide (**3a**). [a] Reaction conditions: **3a** (0.5 mmol), Co-**IV** (1.0 mol %), $Er(OTf)_3$ (3.0 mol %), NH_3BH_3 (1.2 equiv), THF (1.5 mL), 55 °C, 8 h. The conversion and yields were determined by GC using mesitylene as the internal standard. [b] H_2 (1 bar), NH_3BH_3 (1.0 mol %).

yield the alcohol **4a** (Figure 2A). After 15 min, 49% of the starting material was converted and 40% of **8a** and 9% of the final product **4a** formed. As mentioned above, the initial epoxide opening and isomerization proceeds via the more stable benzylic carbocation which explains the regiochemistry of the final product **4a**. Similar results were also obtained in the control experiments (Figure 2B). Full conversion of **3a** was achieved in the absence of the catalyst Co-**IV** or ammonia borane, yielding the **8a** as the only product (entry 2 and 3). When molecular hydrogen was used instead of ammonia borane **8a** was also the main product (entry 4). As for the conversion of terminal epoxide **1a**, no reaction of **3a** was observed in the absence of Er(OTf)$_3$ (entry 5). These experiments additionally support the proposed two-step reaction sequence.

These results prompted us to study both the isomerization and the reduction of the intermediate in more detail. Thus, we investigated the impact of selected LAs on the isomerization step of the reaction sequence at 45 °C (Figure 3). In the presence of 3.0 mol % Er(OTf)$_3$, a conversion 94% of **1a** was observed after 1 h (Figure 3A), which is accordance with the monitored conversion of **1a** under the standard reaction conditions (Figure 1A). Notably, the selectivity toward the aldehyde **7a** over ketone **9a** was >99:1. All other tested LAs proved to be less efficient and led to lower selectivities and/or conversions. The isomerization of the internal epoxide **3a** was also investigated (Figure 3B); in the presence of Er(OTf)$_3$, a conversion of 81% for **3a** after 1 h at 45 °C was obtained. In this case, an excellent selectivity of >99:1 toward the ketone **8a** was achieved. All other tested isomerization catalysts which are frequently used led to lower conversions and poor selectivities towards **8a**.



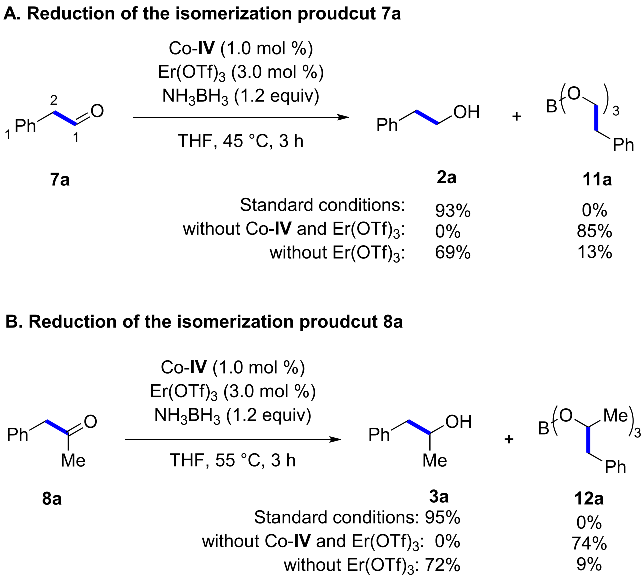
A. Isomerization of terminal epoxide 1a

	Er(OTf)$_3$	AlCl$_3$	InCl$_3$	TfOH	LiOTf	Zn(OTf)$_2$	B(C$_6$F$_5$)$_3$
7a:9a	>99:1	81:19	>99:1	79:21	93:7	89:11	–
Conv. 1a/ %	94	51	64	42	58	82	>99[b]

B. Isomerization of internal epoxide 3a

	Er(OTf)$_3$	AlCl$_3$	InCl$_3$	TfOH	LiOTf	Zn(OTf)$_2$	B(C$_6$F$_5$)$_3$
8a:10a	>99:1	83:17	97:3	81:19	90:10	82:18	–
Conv. 3a/ %	81	41	29	30	29	63	>99[b]

Figure 3. Study on the isomerization of terminal epoxide **1a** (A) and internal epoxide **3a** (B) in the presence of different LAs.[a] [a]Reaction conditions: **1a** (0.5 mmol), additive (3 mol %), THF (1.5 mL), 45 °C 8 h. The reaction temperature was 45 °C for substrate **3a**. [b]Polymerization upon addition of B(C$_6$F$_5$)$_3$.



	2a	11a
Standard conditions:	93%	0%
without Co-**IV** and Er(OTf)$_3$:	0%	85%
without Er(OTf)$_3$:	69%	13%

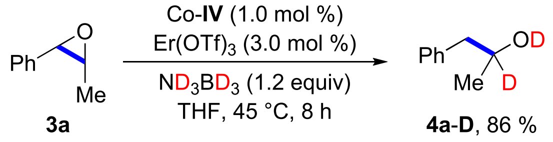
	3a	12a
Standard conditions:	95%	0%
without Co-**IV** and Er(OTf)$_3$:	0%	74%
without Er(OTf)$_3$:	72%	9%

Figure 4. Study on the reduction of the isomerization products **7a** (A) and **8a** (B) under different conditions.

Next, we investigated the reduction of intermediate **7a** and **8a** under different conditions (Figure 4). Under the standard reaction conditions, the conversion of **7a** led to the desired alcohol **2a** in 93% yield (Figure 4A). Berke and co-workers reported the metal-free reduction of ketones and aldehydes with ammonia borane.[44] Notably, if THF was used as the solvent, the corresponding hydroboration products were obtained as the main products. Thus, as expected, in the absence of both Co-**IV** and Er(OTf)$_3$, the hydroboration product **11a** was obtained in 85% after 3 h at 45 °C. Interestingly, if only Er(OTf)$_3$ is omitted, **2a** is obtained as the major product in 69%, while the boronic acid ester **11a** is formed as a side product in 13% yield. In the absence of Co-**IV**, only the hydroboration product **11a** was obtained in 31% yield. We performed the same set of experiments for the reduction of ketone **8a** (Figure 4B). Also in this case, the hydroboration product **12a** was obtained in 74% yield in the absence of Co-**IV** and Er(OTf)$_3$. In the presence of Co-**IV** alcohol, **3a** was obtained as the major product in 72%, while the yield for **12a** dropped to 9%. Under the respective standard reaction conditions used before for terminal and internal epoxides **1** and **3**, no conversion was observed when boronic acid esters **11a** and **12a** were employed as substrates. This clearly indicates that the reaction of epoxides does not proceed via the respective boronic acid esters as intermediates under our standard conditions.

Obviously, the erbium salt is not only necessary for the isomerization of the epoxide to the corresponding aldehyde or ketone but also for the suppression of the formation of side products and enhancement of the reaction rate of the reduction step. LAs are known to facilitate hydrogenation and dehydrogenation reactions using pincer catalysts.[45−47] They have also been studied as catalysts for the dehydrogenation of ammonia borane.[48] Moreover, cobalt and other non-noble metal pincer systems were reported to catalyze the dehydrocoupling of amine boranes.[49,50] The latter has been used as hydrogen source in transfer hydrogenation reaction before.[36,51] The herein-used Co catalysts were found to readily dehydropolymerize methylamine borane under LA free conditions.[52] Thus, the influence of Er(OTf)$_3$ on the reduction step was further investigated. As mentioned above, the conversion of **1a** gave the desired product **2a** in 95% yield under our standard reaction conditions and in 38% after 24 h at 23 °C, respectively (Table 1, entries 9 and 13). However, at 23 and 45 °C, the Co-**IV** catalyzed dehydrogenation of ammonia borane seemed to be neglectable.[38] Notably, in the presence of Er(OTf)$_3$, only a small amount of molecular hydrogen (approx. 0.1 equiv in regard to the amount of employed ammonia borane) was observed.[38] The products of ammonia borane dehydrogenation were analyzed by ^{11}B NMR spectroscopy, and typical cyclic oligomers were formed. Furthermore, cross experiments to reduce **1a** using molecular hydrogen instead of ammonia borane gave only low conversions and **2a** in yields <10% (e.g. Figure 1B, entry 4).[38] As the direct reduction of the aldehyde intermediate **7a** by ammonia borane and the hydrogenation by molecular hydrogen can be ruled out (Figures 1B and 2B), we conclude that the reduction of **7a** proceeds via a stepwise hydrogen transfer process from the ammonia borane to the carbonyl group. In agreement with these assumptions, **4a-D** was obtained as the final product when **3a** was converted in the presence of ND_3BD_3 in a deuterium-labeling experiment (Scheme 3).

Scheme 3. Deuterium-Labeling Experiments

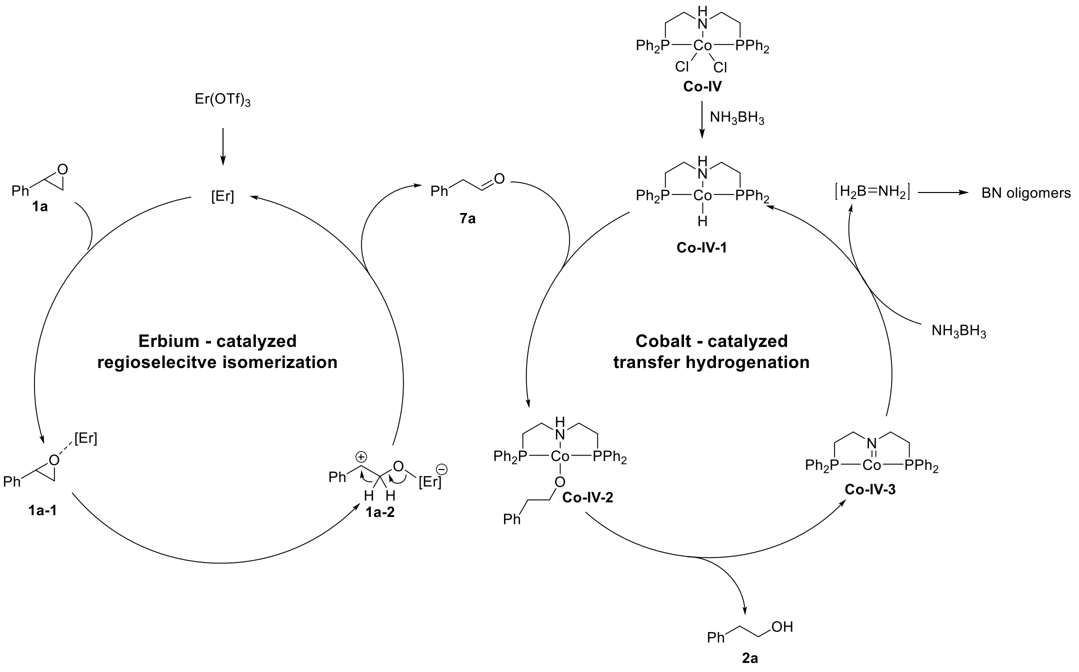


Furthermore, a mercury test was performed, and a similar yield of the alcohol was obtained, indicating that the active species is a homogenous cobalt complex.[38] For the hydrogenation step at the Co complex, we suggest the initial formation of a Co hydride species which has been proposed by Luo and Liu for catalyst Co-**I** in the transfer hydrogenation of alkynes.[36] Indeed, Chirik and co-workers previously reported the formation of a [(PNP)CoH] complex by treating $(PNP)CoCl_2$ with a hydride source ($NaHBEt_3$).[53] The formation of the metal hydride species is likely followed by the coordination of the ketone and subsequent reduction leading to the formation of a Co alkoxide. This is in accordance with the reduction of carbonyl compounds with other metal PNP catalysts.[54] Subsequent protonation of the alkoxide with ammonia borane and hydride transfer to the cobalt would lead to the formation of the corresponding alcohol, regenerate the Co hydride species, and form transient aminoborane $H_2B{=}NH_2$, which further couples to yield spectroscopically observed oligomeric B−N products.

Based on these findings, we propose the mechanism depicted in Scheme 4. In the first catalytic cycle, the epoxide, for example, styrene oxide (**1a**), is regioselectively isomerized to intermediate **7a**. This isomerization occurs via the activation of the epoxide **1a** by the erbium-salt, followed by the formation of **1a−2**. A subsequent [1,2]-hydride shift leads to intermediate **7a**. The aldeyhyde **7a** enters the second catalytic cycle in which **7a** is reduced by **Co-IV-1** to the anti-Markovnikov alcohol **2a** and **Co-IV-3**. The latter is reduced by ammonia borane to form BN oligomers as the side product regenerating **Co-IV-1**.

In summary, we report a catalytic system based on Er(OTf)$_3$ as a highly efficient isomerization catalyst in combination with a cobalt PNP complex that enables the transfer hydrogenation of the carbonyl intermediate. This system allows the conversion of numerous epoxides to anti-Markovnikov alcohols at low reaction temperatures (≤55 °C) and short reaction times (8 h). Notably, comparably low loadings for the transfer hydrogenation (1.0 mol %) and isomerization catalyst (3.0 mol %) were required. Ammonia borane was used as a bench-stable and practical hydrogen source avoiding the use of molecular hydrogen at high pressures. It was shown that this catalytic system is more efficient compared to other known protocols. Moreover, it is broadly applicable and allows the conversion of a variety of terminal (23 examples) and 1,2-disubstituted internal epoxides (14 examples) into the desired anti-Markovnikov alcohols in excellent selectivity and yields of

Scheme 4. Mechanistic Proposal for the Erbium-Catalyzed Regioselective Isomerization−Cobalt-Catayzed Transfer Hydrogenation Sequence of the Model Substrate Styrene Oxide (1a)



up to 98%. It was shown that the reaction can even be performed on larger scale (50 mmol). Notably, the regiochemistry of the reaction is controlled by electronic effects, namely, the formation of the most stable carbocation in the rearrangement step. Thus, the conversion of tri- and tetra-substituted epoxides was also possible but was in some cases accompanied by a rearrangement of the carbon framework. Detailed mechanistic investigations support the proposed two-step reaction sequence which proceeds via an initial isomerization catalyzed by the LA followed by a transfer hydrogenation catalyzed by the Co−PNP complex. It was also revealed that a stepwise transfer of hydrogen from the ammonia borane to the substrate takes place rather than dehydrogenation of ammonia borane and subsequent hydrogenation. Moreover, a significant influence of the LA on the transfer hydrogenation step was observed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03294.

Additional experimental results, synthetic procedures, and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Thomas Werner − *Leibniz Institute for Catalysis, Rostock D-18059, Germany;* orcid.org/0000-0001-9025-3244; Email: Thomas.Werner@catalysis.de

Authors

Xin Liu − *Leibniz Institute for Catalysis, Rostock D-18059, Germany*
Lars Longwitz − *Leibniz Institute for Catalysis, Rostock D-18059, Germany*
Brian Spiegelberg − *Leibniz Institute for Catalysis, Rostock D-18059, Germany*
Jan Tönjes − *Leibniz Institute for Catalysis, Rostock D-18059, Germany*
Torsten Beweries − *Leibniz Institute for Catalysis, Rostock D-18059, Germany;* orcid.org/0000-0002-2416-8874

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c03294

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

Chinese Scholarship Council (CSC) to X.L.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to Paul Kamer, a great scientist and inspiring person. X.L. is grateful for the financial support of the Chinese Scholarship Council (CSC). This work was conducted in the scope of the Leibniz Science Campus Phosphorus Research. The support of Prof. J. G. de Vries is very much appreciated. The authors thank Patrick Hasche and Dr. Felix Anke for their experimental support and helpful suggestions.

■ ABBREVIATIONS

NMR, nuclear magnetic resonance; GC, gas chromatography; LA, Lewis acid; Tf, triflate; THF, tetrahydrofuran

■ REFERENCES

(1) Weissermel, K.; Arpe, H.-J.; Lindley, C. R.; Hawkins, S. *Industrial Organic Chemistry*; John Wiley & Sons, 2008; Vol. *2*.

(2) Kresge, A. J.; Chiang, Y.; Fitzgerald, P. H.; McDonald, R. S.; Schmid, G. H. General acid catalysis in the hydration of simple olefins. Mechanism of olefin hydration. *J. Am. Chem. Soc.* **1971**, *93*, 4907−4908.

(3) Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. Primary alcohols from terminal olefins: formal anti-Markovnikov hydration via triple relay catalysis. *Science* **2011**, *333*, 1609−1612.

(4) Hu, X.; Zhang, G.; Bu, F.; Lei, A. Visible-Light-Mediated Anti-Markovnikov Hydration of Olefins. *ACS Catal.* **2017**, *7*, 1432−1437.

(5) Haggin, J. Chemists Seek Greater Recognition for Catalysis. *Chem. Eng. News* **1993**, *71*, 23−27.

(6) Diab, L.; Šmejkal, T.; Geier, J.; Breit, B. Supramolecular Catalyst for Aldehyde Hydrogenation and Tandem Hydroformylation-Hydrogenation. *Angew. Chem., Int. Ed.* **2009**, *48*, 8022−8026.

(7) Takahashi, K.; Yamashita, M.; Ichihara, T.; Nakano, K.; Nozaki, K. High-Yielding Tandem Hydroformylation/Hydrogenation of a Terminal Olefin to Produce a Linear Alcohol Using a Rh/Ru Dual Catalyst System. *Angew. Chem., Int. Ed.* **2010**, *49*, 4488−4490.

(8) Fuchs, D.; Rousseau, G.; Diab, L.; Gellrich, U.; Breit, B. Tandem Rhodium-Catalyzed Hydroformylation-Hydrogenation of Alkenes by Employing a Cooperative Ligand System. *Angew. Chem., Int. Ed.* **2012**, *51*, 2178−2182.

(9) Fleischer, I.; Dyballa, K. M.; Jennerjahn, R.; Jackstell, R.; Franke, R.; Spannenberg, A.; Beller, M. From Olefins to Alcohols: Efficient and Regioselective Ruthenium-Catalyzed Domino Hydroformylation/Reduction Sequence. *Angew. Chem., Int. Ed.* **2013**, *52*, 2949−2953.

(10) Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. Tandem Isomerization/Hydroformylation/Hydrogenation of Internal Alkenes to n-Alcohols Using Rh/Ru Dual- or Ternary-Catalyst Systems. *J. Am. Chem. Soc.* **2013**, *135*, 17393−17400.

(11) Brown, H. C.; Zweifel, G. A stereospecific cis hydration of the double bond in cyclic derivatives. *J. Am. Chem. Soc.* **1959**, *81*, 247.

(12) Brown, H. C. Hydroboration-a powerful synthetic tool. *Tetrahedron* **1961**, *12*, 117−138.

(13) Gansäuer, A.; Klatte, M.; Brändle, G. M.; Friedrich, J. Catalytic Hydrogen Atom Transfer (HAT) for Sustainable and Diastereoselective Radical Reduction. *Angew. Chem., Int. Ed.* **2012**, *51*, 8891−8894.

(14) Liu, W.; Li, W.; Spannenberg, A.; Junge, K.; Beller, M. Iron-catalysed regioselective hydrogenation of terminal epoxides to alcohols under mild conditions. *Nat. Catal.* **2019**, *2*, 523−528.

(15) Yao, C.; Dahmen, T.; Gansäuer, A.; Norton, J. Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis. *Science* **2019**, *364*, 764.

(16) Sajiki, H.; Hattori, K.; Hirota, K. Pd/C(en)-catalyzed regioselective hydrogenolysis of terminal epoxides to secondary alcohols. *Chem. Commun.* **1999**, 1041−1042.

(17) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. Recyclable polyurea-microencapsulated Pd (0) nanoparticles: An efficient catalyst for hydrogenolysis of epoxides. *Org. Lett.* **2003**, *5*, 4665−4668.

(18) Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. Magnetically separable Pd catalyst for highly selective epoxide hydrogenolysis under mild conditions. *Org. Lett.* **2007**, *9*, 3417−3419.

(19) Fujitsu, H.; Shirahama, S.; Matsumura, E.; Takeshita, K.; Mochida, I. Catalytic hydrogenation of styrene oxide with cationic rhodium complexes. *J. Org. Chem.* **1981**, *46*, 2287−2290.

(20) Murru, S.; Nicholas, K. M.; Srivastava, R. S. Ruthenium (II) sulfoxides-catalyzed hydrogenolysis of glycols and epoxides. *J. Mol. Catal. A: Chem.* **2012**, *363−364*, 460−464.

(21) Wylie, W.; Lough, A. J.; Morris, R. H. The hydrogenation of molecules with polar bonds catalyzed by a ruthenium (II) complex bearing a chelating N-heterocyclic carbene with a primary amine donor. *Chem. Commun.* **2010**, *46*, 8240−8242.

(22) Gansäuer, A.; Fan, C.-A.; Piestert, F. Sustainable radical reduction through catalytic hydrogen atom transfer. *J. Am. Chem. Soc.* **2008**, *130*, 6916−6917.

(23) Wenz, J.; Wadepohl, H.; Gade, L. H. Regioselective hydrosilylation of epoxides catalysed by nickel(ii) hydrido complexes. *Chem. Commun.* **2017**, *53*, 4308−4311.

(24) Zhang, Y.-Q.; Jakoby, V.; Stainer, K.; Schmer, A.; Klare, S.; Bauer, M.; Grimme, S.; Cuerva, J. M.; Gansäuer, A. Amide-Substituted Titanocenes in Hydrogen-Atom Transfer Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 1523−1526.

(25) Henriques, D. S. G.; Zimmer, K.; Klare, S.; Meyer, A.; Rojo-Wiechel, E.; Bauer, M.; Sure, R.; Grimme, S.; Schiemann, O.; Flowers, R. A., II; Gansäuer, A. Highly Active Titanocene Catalysts for Epoxide Hydrosilylation: Synthesis, Theory, Kinetics, EPR Spectroscopy. *Angew. Chem., Int. Ed.* **2016**, *55*, 7671−7675.

(26) Liu, W.; Leischner, T.; Li, W.; Junge, K.; Beller, M. A General Regioselective Synthesis of Alcohols by Cobalt-Catalyzed Hydrogenation of Epoxides. *Angew. Chem., Int. Ed.* **2020**, *59*, 11321−11324.

(27) Longwitz, L.; Steinbauer, J.; Spannenberg, A.; Werner, T. Calcium-Based Catalytic System for the Synthesis of Bio-Derived Cyclic Carbonates under Mild Conditions. *ACS Catal.* **2018**, *8*, 665−672.

(28) Liu, X.; de Vries, J. G.; Werner, T. Transfer hydrogenation of cyclic carbonates and polycarbonate to methanol and diols by iron pincer catalysts. *Green Chem.* **2019**, *21*, 5248−5255.

(29) Brieger, G.; Nestrick, T. J. Catalytic transfer hydrogenation. *Chem. Rev.* **1974**, *74*, 567−580.

(30) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Commun.* **2015**, *115*, 6621−6686.

(31) Stephens, F. H.; Pons, V.; Tom Baker, R. Ammonia-borane: the hydrogen source par excellence? *Daltron Trans.* **2007**, 2613−2626.

(32) Boom, D. H. A.; Jupp, A. R.; Slootweg, J. C. Dehydrogenation of Amine-Boranes Using p-Block Compounds. *Chem.—Eur. J.* **2019**, *25*, 9133−9152.

(33) Korytiaková, E.; Thiel, N. O.; Pape, F.; Teichert, J. F. Copper(I)-catalysed transfer hydrogenations with ammonia borane. *Chem. Commun.* **2017**, *53*, 732−735.

(34) Wang, F.; Planas, O.; Cornella, J. Bi(I)-Catalyzed Transfer-Hydrogenation with Ammonia-Borane. *J. Am. Chem. Soc.* **2019**, *141*, 4235−4240.

(35) Yang, X.; Xie, Z.; He, J.; Yu, L. Research Progress on Ammonia-Borane Based Direct Transfer Hydrogenation Reactions. *Chin. J. Org. Chem.* **2015**, *35*, 603−609.

(36) Fu, S.; Chen, N.-Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. Ligand-Controlled Cobalt-Catalyzed Transfer Hydrogenation of Alkynes: Stereodivergent Synthesis of Z- and E-Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 8588−8594.

(37) Spiegelberg, B.; Dell'Acqua, A.; Xia, T.; Spannenberg, A.; Tin, S.; Hinze, S.; de Vries, J. G. Additive-Free Isomerization of Allylic Alcohols to Ketones with a Cobalt PNP Pincer Catalyst. *Chem.—Eur. J.* **2019**, *25*, 7820−7825.

(38) For additional information see Supporting Information.

(39) Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Sindona, G.; Tagarelli, A. Erbium(III) Triflate: A Valuable Catalyst for the Rearrangement of Epoxides to Aldehydes and Ketones. *Synlett* **2004**, 2633−2635.

(40) Ranu, B. C.; Jana, U. Indium(III) Chloride-Promoted Rearrangement of Epoxides: A Selective Synthesis of Substituted Benzylic Aldehydes and Ketones. *J. Org. Chem.* **1998**, *63*, 8212−8216.

(41) Nardi, M.; Dalpozzo, R.; Oliverio, M.; Paonessa, R.; Procopio, A. Erbium(III) Triflate is a Highly Efficient Catalyst for the Synthesis of β-Alkoxy Alcohols, 1,2-Diols and β-Hydroxy Sulfides by Ring Opening of Epoxides. *Synthesis* **2009**, 3433−3438.

(42) Brown, H. C.; Wheeler, O. H.; Ichikawa, K. Chemical effects of steric strains—XIII: Kinetics of the reaction of sodium borohydride with carbonyl groups—a convenient tool for investigating the reactivities of aldehydes and ketones. *Tetrahedron* **1957**, *1*, 214−220.

(43) Lewis, J. B.; Hedrick, G. W. Reaction of α-Pinene Oxide with Zinc Bromide and Rearrangement of 2,2,3-Trimethyl-3-cyclopentene Products Derived Therefrom. *J. Org. Chem.* **1965**, *30*, 4271−4275.

(44) Yang, X.; Fox, T.; Berke, H. Ammonia borane as a metal free reductant for ketones and aldehydes: a mechanistic study. *Tetrahedron* **2011**, *67*, 7121−7127.

(45) Bielinski, E. A.; Lagaditis, P. O.; Zhang, Y.; Mercado, B. Q.; Würtele, C.; Bernskoetter, W. H.; Hazari, N.; Schneider, S. Lewis acid-assisted formic acid dehydrogenation using a pincer-supported iron catalyst. *J. Am. Chem. Soc.* **2014**, *136*, 10234−10237.

(46) Spentzos, A. Z.; Barnes, C. L.; Bernskoetter, W. H. Effective pincer cobalt precatalysts for Lewis acid assisted CO_2 hydrogenation. *Inorg. Chem.* **2016**, *55*, 8225−8233.

(47) Tokmic, K.; Jackson, B. J.; Salazar, A.; Woods, T. J.; Fout, A. R. Cobalt-catalyzed and Lewis acid-assisted nitrile hydrogenation to primary amines: a combined effort. *J. Am. Chem. Soc.* **2017**, *139*, 13554−13561.

(48) Stephens, F. H.; Baker, R. T.; Matus, M. H.; Grant, D. J.; Dixon, D. A. Acid Initiation of Ammonia-Borane Dehydrogenation for Hydrogen Storage. *Angew. Chem., Int. Ed.* **2007**, *46*, 746−749.

(49) Glüer, A.; Förster, M.; Celinski, V. R.; Schmedt auf der Günne, J.; Holthausen, M. C.; Schneider, S. Highly Active Iron Catalyst for Ammonia Borane Dehydrocoupling at Room Temperature. *ACS Catal.* **2015**, *5*, 7214−7217.

(50) Han, D.; Anke, F.; Trose, M.; Beweries, T. Recent advances in transition metal catalysed dehydropolymerisation of amine boranes and phosphine boranes. *Coord. Chem. Rev.* **2019**, *380*, 260−286.

(51) Shao, Z.; Fu, S.; Wei, M.; Zhou, S.; Liu, Q. Mild and Selective Cobalt-Catalyzed Chemodivergent Transfer Hydrogenation of Nitriles. *Angew. Chem., Int. Ed.* **2016**, *55*, 14653−14657.

(52) Boyd, T. M.; Andrea, K. A.; Baston, K.; Johnson, A.; Ryan, D. E.; Weller, A. S. A simple cobalt-based catalyst system for the controlled dehydropolymerisation of $H_3B{\cdot}NMeH_2$ on the gram-scale. *Chem. Commun.* **2020**, *56*, 482−485.

(53) Semproni, S. P.; Milsmann, C.; Chirik, P. J. Four-Coordinate Cobalt Pincer Complexes: Electronic Structure Studies and Ligand Modification by Homolytic and Heterolytic Pathways. *J. Am. Chem. Soc.* **2014**, *136*, 9211−9224.

(54) Wei, Z.; Jiao, H. In *Advances in Inorganic Chemistry*; van Eldik, R., Puchta, R., Eds.; Academic Press, 2019; Vol. 73, pp 323−384.