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Sustainable radical reduction through catalyzed hydrogen atom transfer reactions (CHAT-reactions)

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ABSTRACT

A system with coupled catalytic cycles is described that allows radical reduction by catalyzed hydrogen atom transfer (CHAT) from transition metal hydrides. These intermediates are generated through H_2 activation. Radical generation is carried out by titanocene catalyzed electron transfer to epoxides. The reaction provides a novel entry into the atom-economical reduction of radicals that has long been considered as a critical issue for the industrial application of radical chemistry.

1. Introduction

High raw materials' costs and increased sensitivity to environmental concerns render the development of reactions that minimize the generation of waste, the use of energy, and the consumption of expensive and toxic starting materials, a highly appealing goal for chemical research.[1] Atom-economical reactions are especially attractive in this respect because all atoms of the substrates become part of the desired product.[2]

Catalytic hydrogenation reactions are amongst the most powerful atom-economical transformations because not only economical but environmental issues are directly addressed.[3] Moreover, spectacular examples of the control of chemo-, diastereo-, and enantioselectivity have been reported. The award of the Nobel Prize to Knowles[4] and Noyori[5] in 2001 and the many industrial applications of catalytic hydrogenation amply highlight the exceptional importance of this particular field of research.

More recently, the use of hydrogen as reagent in direct catalytic methods for reductive carbon–carbon bond formation has been pioneered by the group of Krische.[6] These catalytic reductive additions that proceed under complete atom-economy promise to take organic chemistry beyond stoichiometric organometallic reagents.[7] The importance of these findings is exceptional as a novel and unique approach to one of the most important areas of organic synthesis has been opened. Moreover, through this work it has become clear that hydrogen can indeed be utilized for other reactions than 'simple' hydrogenation reactions.

Here, we report on our results in the field of sustainable radical reduction by catalytic hydrogen atom transfer (CHAT) reactions.[8]

Owing to their high versatility, selectivity, and compatibility with densely functionalized substrates radical reactions are frequently employed in the synthesis of complex molecules.[9] However, limitations also exist. One of the unresolved problems is constituted by catalytic, environmentally benign, and atom-economical reduction of carbon centered radicals.[10] In the realm of chain reactions, the use of stannanes, silanes, or cyclohexadienes has resulted in many chemically excellent reactions. However, the necessity of employing these reagents in stoichiometric amounts and their high price and/or toxicity often precludes applications on large scale.[11] Recently, it has been established that water and alcohols complexed by boranes can be used efficiently as hydrogen atom donors. However, as chain carrying reagents, the boranes still have to be employed in stoichiometric amounts.[12]

Transition metal hydrides constitute highly attractive hydrogen atom donors for two reasons. First, due to the low strength of their M–H bonds,[13] radical reduction possesses a high thermodynamic driving force and proceeds swiftly. Second, many of these complexes can be generated through the activation of H_2.

In this context, Norton has devised a unique radical chain cyclization of dienes catalyzed by $Cp(CO)_3CrH$ with H_2 as terminal reductant as shown in Figure 1.[14]

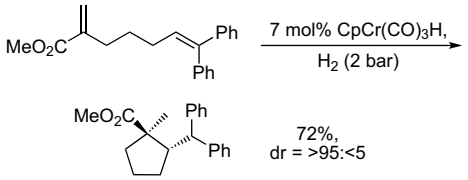

Figure 1. Norton's catalytic cyclizations mediated by H_2.

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However, this very interesting reaction is somewhat restricted in scope because radical generation with $Cp(CO)_3CrH$ is not a general process.[15] Indeed, both the acrylate and the diaryl substituted olefin are essential for the success of the transformation. Other potentially interesting metal hydrides for this reaction, such as $HV(CO)_4(dppb)$, fail to activate H_2 after hydrogen atom transfer and therefore have to be employed in stoichiometric amounts.[16]

In order to overcome this limitation, reactions featuring different sets of reagents for radical generation and reduction are highly attractive. Ideally this can be achieved by coupling independent catalytic cycles. In this manner the extremely powerful arsenal of catalytic hydrogenation methods can be made accessible for radical reduction as shown in Figure 2.

In order to establish the feasibility of this concept, we chose the titanocene catalyzed[17] reductive epoxide opening as a highly chemo- and regioselective method of radical generation. During the last decade, this reaction, that is based on Nugent's and RajanBabu's stoichiometric process,[18] has proven useful in a number of applications.[19] These include the enantioselective generation of radicals,[20] unusual cyclizations,[21] tandem reactions,[22] and epoxypolyene cyclizations.[23] Moreover, a number of unusual hydrogen atom donors have been described for the reduction of the β-titanoxy radicals generated.[24] Most notably, the group of Oltra and Cuerva has introduced the use of water complexed by titanium for radical reduction.[25] The high functional group tolerance displayed in these transformations suggests that other transition metal catalyzed reactions may be unaffected under these conditions.[22d] Therefore, we embarked on the examination of systems for the metal catalyzed activation of H_2 for CHAT-reactions.

2. Results

We started our investigation with the reductive opening of **1** in the presence of H_2 and $Cp(CO)_3CrH$[26] (**2**), $RhCl(PPh_3)_3$ (**3**, Wilkinson's catalyst),[27] and $IrCl(CO)(PPh_3)_3$ (**4**, Vaska's complex).[28] We were especially interested in the use of **2** and **4** because both complexes do not hydrogenate unactivated olefins. This could be critical for the realization of radical cyclizations[29] with H_2 as terminal reductant. However, it is clear that an essential factor for the success of the CHAT-reaction is an efficient H_2 activation. Therefore **3** constitutes an especially appealing catalyst even though it also constitutes an active hydrogenation catalyst. The test reaction and the mechanism of olefin formation leading to **6** are shown in Figure 3. Our initial results with 'Cp_2TiCl' as electron transfer catalyst are summarized in Table 1.

The results obtained with **2** as catalyst for hydrogen atom transfer already reveal important features about the CHAT-reaction. With Zn as the reductant, the use of 10 mol % Cp_2TiCl_2 results in the formation of a 1:1 mixture of **5** and **6** in 50% overall yield. Reducing the loading of Cp_2TiCl_2 to 5 mol % leads to an increase in the overall yield of **5** and **6** to 58%. Gratifyingly, **6** is formed in only 4% yield. Clearly, with 10 mol % Cp_2TiCl_2 the reductive trapping of the β-titanoxy radicals formed after electron transfer by a second equivalent of titanium competes quite efficiently with the hydrogen atom transfer. Presumably, this is due to a relatively sluggish H_2 activation by $Cp(CO)_3Cr$. The use of Mn, a much slower reductant for Cp_2TiCl_2, instead of Zn also results in noticeable improvement of the reaction. In this case, 60% of **5** and only 4% of **6** are formed.

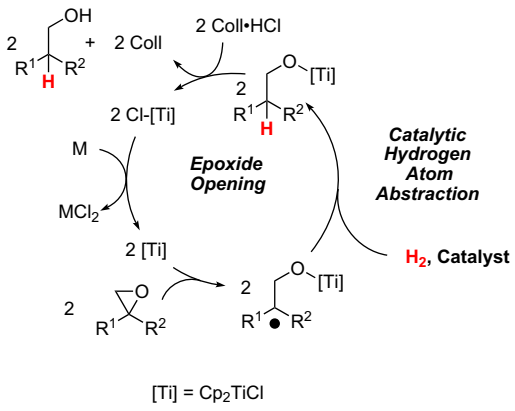


Figure 2. Coupled catalytic cycles for sustainable radical reduction by H_2.

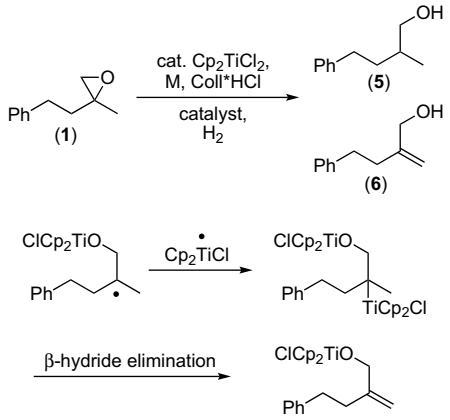


Figure 3. Test reaction for the optimization of the CHAT-reaction and key step in the formation of **6**.

With 10 mol % Cp_2TiCl_2 and 5 mol % **3**, **5** was obtained in 68% yield. With a H_2 pressure of 4 bar an increased yield of 84% was obtained. No formation of **6** was observed. As for the use of **2** it seems that the efficiency of the CHAT is critically dependent on a swift H_2 activation. Gratifyingly, from these findings it is clear that the H_2 activation by **3** is compatible with the catalytic reductive epoxide opening. This is supported by two features of the catalysts involved. First, Wilkinson's catalyst is stable toward strong Lewis acids, such as $BF_3 \cdot Et_2O$,[30] and should therefore tolerate the mildly acidic protic conditions of the titanocene catalyzed oxirane opening. Second, titanocenes are stable under typical hydrogenation conditions and activate H_2 only slowly after reaction with alkyl lithium reagents.[31]

Since H_2 activation seems to be the critical step for the use of **3**, a hydrogen pressure of 4 bar was directly applied for the opening of **1** in the presence of **4**. While the conversion of the substrate (96%) was excellent, **5** was obtained in only 71% yield together with 25% of **6**. This highlights the inferior ability to activate H_2 of Vaska's complex **4** compared to **3**.[27,28] It is clear, however, that **4** is also not interfering with the titanocene catalyzed epoxide opening. This finding renders further investigations into the use of Ir-complexes an attractive target. The heterogeneous catalysts Pd/C and Rh/C were also investigated. However, erratic results were observed. Moreover, **5** was obtained in low yields (not shown).

Table 1
CHAT-reaction of **1** with Cp_2TiCl_2 in THF (0.1 M, red.=reductant) at 25 °C

cat./mol %/red.	Ti/mol %	**5**/%	**6**/%
2/10/Zn	10	26	24
2/10/Zn	5	54	4
2/10/Mn	10	64	4
3/5/Mn	10	68	—
3/5/Mn[a]	10	84	—
4/5/Mn[a]	10	71	25
4/10/Mn[a]	5	63	11

[a] 4 bar H_2.

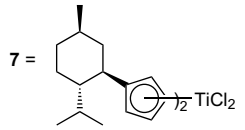


Figure 4. Structure of Kagan's complex **7**.

We have previously demonstrated that substituted titanocenes, such as Kagan' s complex **7**[32] (Fig. 4), can be noticeably superior to Cp_2TiCl_2 in the reductive epoxide opening.[24] Our results with **7** as electron transfer catalyst in the opening of **1** are summarized in Table 2.

With **2**, an improved yield of 71% of **5** could be obtained together with 3% of **6** in the presence of Zn. The use of Mn resulted in a yield of only 55% of **5** and 3% of **6**. This remarkable difference in performance compared to Cp_2TiCl_2 may be surprising at first glance. However, **7** is reduced much more slowly than Cp_2TiCl_2 and hence reductive regeneration of the Ti(III) species seems to be too slow with Mn for an efficient turn-over. With **3** the situation is different. A lower yield of **5** is obtained both at 4 bar and at 1 bar H_2 pressure (76% and 52%, respectively) than with Cp_2TiCl_2. It seems that the high steric demand of both catalysts reduces the overall efficacy of the CHAT. The use **4** and **7** leads to better results than with Cp_2TiCl_2 and **4**. This suggests that the increased steric bulk of **7** retards radical reduction by a second equivalent of the Ti(III)-reagent. However, formation of **6** (15%) is still too significant for the process to be practically useful. As with Cp_2TiCl_2, employing Pd/C and Rh/C is unsatisfactory.

With these results in hands we turned our attention to a closer examination of the effects of concentration, temperature, and catalyst loading on the performance of the CHAT-reaction with Wilkinson's catalyst **3** and Cp_2TiCl_2. These results are summarized in Table 3.

Without $RhCl(PPh_3)_3$ a complex mixture containing **5** and unidentified side products was obtained in less than 20% yield (entry 1). No formation of **5** was observed without Cp_2TiCl_2 (entry 2) and **1** was reisolated in >85% yield. Both findings render alternative pathways, such as epoxide isomerization to an allylic alcohol and hydrogenation or radical reduction by adventitious water unlikely. Zn also constitutes a suitable reductant resulting in an 81% isolated yield of **5** (entry 3). Decreasing the amount of **3** to 2.5 mol% resulted in a slightly reduced yield of **5** (81%, entry 4). A similar trend was observed when lowering the loading of both Cp_2TiCl_2 to 5 mol% and **3** to 2.5 or 1 mol%, respectively (entries 5 and 6). Curiously, an increase in the concentration results in a deterioration of the isolated yield of **6** (entry 7). This is also the case for varying the reaction temperature (entries 8 and 9).

With these results in hands, we turned our attention to the functional group tolerance of the Rh-CHAT-reaction. The titanocene catalyzed epoxide opening[19] as well as the Rh-catalyzed hydrogenation[33] displays excellent compatibility with a wide range of functionality and hence it can be expected that the CHAT exhibits the same features. As summarized in Table 4, this is indeed the case.

Table 2
CHAT-reaction (4 bar H_2) of **1** with Kagan's complex **7** in 0.1 M THF (0.1 M, red.=reductant) at 25 °C

cat./mol%/red.	**7**/mol%	**5**/%	**6**/%
2/10/Zn[a]	10	71	3
2/10/Mn[a]	10	54	4
2/10/Mn[a,b]	10	47	7
3/5/Mn	10	76	—
4/5/Mn	5	71	14
4/10/Mn	5	78	15

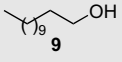
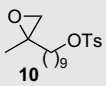
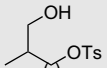
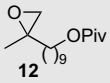
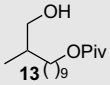
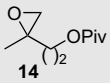
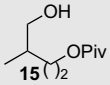
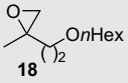
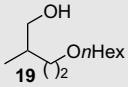
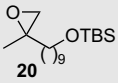
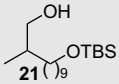
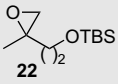
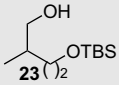
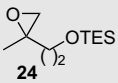
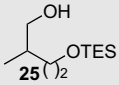
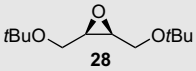
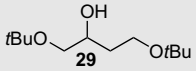
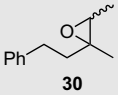
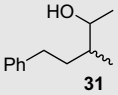
[a] 1 bar H_2.
[b] 0.3 M.

Table 3
Investigation of the CHAT-reaction (4 bar H_2) of **3** with Cp_2TiCl_2 in THF (red.=reductant)

Entry	**3**, red./mol%	Ti/mol%	*c*/M, *T*/°C	**5**/%
1	—, Mn	10	0.2, 25	<20[a]
2	5, —	—	0.2, 25	0
3	5, Zn	10	0.2, 25	81
4	2.5, Mn	10	0.2, 25	81
5	2.5, Mn	5	0.2, 25	72
6	1, Mn	5	0.2, 25	73
7	1, Mn	5	0.4, 25	55
8	1, Mn	5	0.2, 50	46
9	1, Mn	5	0.2, 0	34

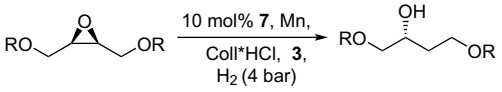
[a] Together with two unknown compounds.

Table 4
Influence of substitution pattern and investigation of functional group tolerance of the Rh-CHAT-reaction (4 bar H_2) with Cp_2TiCl_2 (10 mol%) and **3** (5 mol%) in THF at 25 °C

Entry	Substrate	Product	Yield/%[a]
1	 **8**	 **9**	41
2	**1**/PhCOMe	**5**/PhCOMe	81/87
3	 **10**	 **11**	82
4	 **12**	 **13**	71
5	 **14**	 **15**	68, 66:34
6	 **16**	 **17**	67
7	 **18**	 **19**	69
8	 **20**	 **21**	79
9	 **22**	 **23**	76
10	 **24**	 **25**	63
11	 **26**	 **27**	66
12	 **28**	 **29**	57
13	 **30**	 **31**	71[a,b]

[a] dr (**30**)=50:50.
[b] dr (**31**)=52:48.

Table 5
Investigation of the CHAT-reaction (4 bar H_2) in the enantioselective opening of *meso*-epoxides in THF (red.=reductant) at 25 °C



R = *n*Pr: **32**
R = Et : **34**

R = *n*Pr: **33**
R = Et : **35**

Entry	Sub.	**3**/mol %	Product	Yield	*R*/*S*
1	**28**	10	**29**	60	93:7
2	**32**	5	**33**	64	97:3
3	**34**	5	**35**	75	96:4

With 1-dodecene oxide **8** a low yield of 41% of 1- and 2-dodecanol (88:12) was obtained. However, the yield obtained in the presence of γ-terpinene (52%) is low, too.[24] In general, the reaction conditions tolerate sensitive functionality. Acetophenone can be reisolated in 87% yield, when added to the reduction of **1**, while the yield of **5** remains essentially unchanged (81%, entry 2). Tosylates (entry 3), chlorides (entry 6), and *n*-alkyl ethers (entry 7) remain unaffected. The pivalates **12** and **14** behave differently (entries 4 and 5). While **12** gives the desired product in good yield, with **14**, the expected product **15** was obtained in 45% yield together with 23% of the product of pivalate migration. Silyl groups can also be subjected to our conditions (entries 8–10). As expected, the TBS group is more robust than the TES group.[34] The reaction of **26** is especially noteworthy (entry 11). In titanocene based methodology the reduction of benzylic radicals is notoriously difficult and requires thiols or selenols.[18] Bulky ethers in the close vicinity of a secondary radical center are tolerated (entry 12). Finally, for trisubstituted epoxides (entry 13) a reduced loading (5 mol %) of Cp_2TiCl_2 is mandatory for avoiding the formation of the undesired allylic alcohol by-products and for obtaining the desired product in good yield. Alcohol **31** was obtained in 71% yield as a 52:48 mixture of diastereoisomers. This particular CHAT is hence not stereoselective.

To probe the sensitivity of our reaction toward the substitution pattern of the titanocene catalyst and substrate structure further,[35] we investigated the enantioselective opening of three *meso*-epoxides by **7** (Table 5).

Alcohols **29**, **33**, and **35** were isolated with enantioselectivities identical to those of the reactions performed with 5 equiv of 1,4-cyclohexadiene as radical reductant.[20,24] For *tert*-butyl ether **28**, 10 mol % of **3** was required to obtain a 60% yield of **29**. With 5 mol %, only 44% of **29** was obtained. This suggests that with a sterically demanding titanocene and a substrate containing bulky groups, the hydrogen atom transfer from the rhodium hydride species can become rather slow. It is clear, however, that in general radical reduction by rhodium hydrides is fully compatible with the enantioselective titanocene catalyzed radical generation and hence with the use of sterically demanding titanocenes.[35]

3. Conclusion

In summary, we have developed a system of combined catalytic cycles for a sustainable reduction of radicals via catalyzed hydrogen atom transfer reactions (CHAT-reactions). Our approach unites titanocene catalyzed reductive epoxide opening with the rhodium, iridium, and chromium catalyzed H_2 activation. Because of their different affinities toward the substrates and ligands, the early and late transition metal catalysts are mutually compatible. Our process tolerates a wide range of functional groups incompatible with nucleophilic ring opening by hydride reagents. Opening of *meso*-epoxides occurs with high enantioselectivity. The regioselectivity of ring opening is complementary to S_N2 reactions.

4. Experimental section

4.1. General

All reactions were performed in oven-dried (100 °C) glassware under Ar. THF was freshly distilled from K. CH_2Cl_2 was freshly distilled from CaH_2. The products were purified by flash chromatography on Merck silica gel 50 (eluents given in brackets, EE refers to ethyl acetate, CH to cyclohexane) according to the procedure of Still.[36] Yields refer to analytically pure samples. Isomer ratios were determined by suitable ^1H NMR integrals of cleanly separated signals. NMR: Bruker DRX 300, AMX 300, AM 400; DRX500 ^1H NMR, $CHCl_3$ (7.26 ppm) or C_6D_5H (7.16 ppm) in the indicated solvent as internal standard in the same solvent; ^{13}C NMR, $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm) as internal standard in the same solvent; integrals in accordance with assignments, coupling constants are measured in hertz and always constitutes *J*(H,H) coupling constants. IR spectra: Perkin–Elmer 1600 series FT-IR and Thermo Nicolet 380 as neat films on KBr plates or via ATR measurements. Mass Spectrometry: EI Thermoquest Finningan MAT 95 XL, calibration against PFK; ESI Bruker Daltonics microTOF-Q, calibration against HCO_2Na. Combustion analytics was performed on a vario micro-cube from Elementar, Hanau.

Epoxides **1**,[37] **10**,[17b] **12**,[17b] **16**,[17b] **19**,[35] **20**,[17b] **22**,[43] **28**,[20a] **30**,[42] **32**,[20a] and **34**[20a] were prepared according to literature procedures. Compounds **8** and **9** are commercially available. 3-Methylbutenyl-pivalate,[38] 1-(3-methylbut-enyloxy)hexane,[39] and 1-triethyl-(3-methylbut-3-enyloxy)silane[40] were prepared according to literature procedures. Throughout the Experimental section collidine refers to 2,4,6-collidine, PE to petrol ether (30–40°), MTBE to methyl *tert*-butyl ether, and *m*-CPBA to *meta*-chloro perbenzoic acid.

4.2. General procedures for the radical generation and reduction by hydrogen atom transfer

GP: a mixture of titanocene catalyst, dry collidine hydrochloride (394 mg, 2.50 mmol), hydrogenation catalyst, and metal dust was placed under an atmosphere of hydrogen gas. Then, a solution of epoxide (1.00 mmol) in dry THF was added. The mixture was stirred under a hydrogen atmosphere (1 or 4 bar) at 25 °C unless otherwise noted for the indicated time, diluted with CH_2Cl_2 (20 mL), and washed with phosphate buffer (10 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The volatiles were removed under reduced pressure and the crude product was purified by SiO_2 chromatography.

4.2.1. Table 1

*4.2.1.1. Entry 1: synthesis of 2-methyl-4-phenylbutan-1-ol (**5**)*[24]. According to GP, **1**[37] (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Zn dust (197 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (42 mg, 26%) and **6** (39 mg, 24%).

4.2.1.2. Entry 2. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Zn dust (197 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (89 mg, 54%) and **6** (6 mg, 4%).

4.2.1.3. Entry 3. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (105 mg, 64%) and **6** (6 mg, 4%).

4.2.1.4. Entry 4. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (111 mg, 68%).

4.2.1.5. Entry 5. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (138 mg, 84%).

4.2.1.6. Entry 6. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **4** (39 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 9:1) yielded **5** (117 mg, 71%) and **6** (41 mg, 25%).

4.2.1.7. Entry 7. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **4** (78 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 9:1) yielded **5** (103 mg, 63%) and **6** (18 mg, 11%).

4.2.2. Table 2

4.2.2.1. Entry 1. According to GP, **1** (162 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Zn dust (197 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (117 mg, 71%) and **6** (5 mg, 3%).

4.2.2.2. Entry 2. According to GP, **1** (162 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (105 mg, 54%) and **6** (6 mg, 4%).

4.2.2.3. Entry 3. According to GP, **1** (162 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **2** (20 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (1.7 mL) for 20 h under H_2 (1 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (76 mg, 47%) and **6** (11 mg, 7%).

4.2.2.4. Entry 4. According to GP, **1** (162 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (205 mg, 1.30 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 8 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (125 mg, 76%).

4.2.2.5. Entry 5. According to GP, **1** (162 mg, 1.00 mmol), **7** (26.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **4** (39 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 9:1) yielded **5** (116 mg, 70%) and **6** (23 mg, 14%).

4.2.2.6. Entry 6. According to GP, **1** (162 mg, 1.00 mmol), **7** (26.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **4** (78 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 9:1) yielded **5** (126 mg, 78%) and **6** (24 mg, 15%).

4.2.3. Table 3

4.2.3.1. Entry 1. According to the GP, **8** (162 mg, 1.00 mmol), dry collidine hydrochloride (205 mg, 1.30 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 12 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **8** (160 mg, 99%).

4.2.3.2. Entry 2. According to the GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (205 mg, 1.30 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h. SiO_2 chromatography (PE/Et_2O 85:15) yielded 34 mg of a mixture of compounds consisting of about 90% of **5** (yield <20%).

4.2.3.3. Entry 3. According to the GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (205 mg, 1.30 mmol), **3** (46 mg, 0.05 mmol), and Zn dust (197 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (133 mg, 81%).

4.2.3.4. Entry 4. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (23 mg, 0.025 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (133 mg, 81%).

4.2.3.5. Entry 5. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (23 mg, 0.025 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (119 mg, 72%).

4.2.3.6. Entry 6. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (9.3 mg, 0.01 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 8 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (120 mg, 73%).

4.2.3.7. Entry 7. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (9.3 mg, 0.01 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (2.55 mL) for 8 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (90 mg, 55%).

4.2.3.8. Entry 8. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (9.3 mg, 0.01 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 8 h at 50 °C under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (76 mg, 46%).

4.2.3.9. Entry 9. According to GP, **1** (162 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (9.3 mg, 0.01 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h at 0 °C under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (56 mg, 34%).

4.2.4. Table 4

*4.2.4.1. Entry 1: synthesis of dodecan-1-ol and docean-2-ol (**9**).* According to GP, **8** (184 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF

(4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 9:1) yielded **9** (74 mg, 41%) as 88:12 mixture of 1- and 2-dodecanol.

4.2.4.2. Entry 2. According to GP, **1** (162 mg, 1.00 mmol), acetophenone (120 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **5** (133 mg, 81 %) and acetophenone (105 mg, 87 %).

*4.2.4.3. Entry 3: synthesis of 11-hydroxy-10-methyl-undecyl-4-tosylate (**11**)*[17b]. According to GP, **10**[17b] (355 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/Et_2O 85:15) yielded **11** (294 mg, 82%).

*4.2.4.4. Entry 4: synthesis of 11-hydroxy-10-methyl-undecyl-pivalate (**13**)*[17b]. According to GP, **12**[17b] (286 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/MTBE 4:1) yielded **13** (202 mg, 71%).

*4.2.4.5. Entry 5: synthesis of 2-(2-methyloxiran-2-yl)ethyl-pivalate (**14**).* A mixture of 3-methylbut-enyl-pivalate[38] (5.25 g, 31.0 mmol), *m*-CPBA (11.7 g, 45.0 mmol), and CH_2Cl_2 (250 mL) was stirred for 5 h. The mixture was washed with K_2CO_3 solution (2×50 mL) and was extracted with CH_2Cl_2 (3×50 mL) and dried ($MgSO_4$). The volatiles were removed under reduced pressure and the crude product was purified by SiO_2 chromatography (CH/EE/NEt_3=90:10:1) yielded **14** (3.02 g, 52%). ^1H NMR (400 MHz, C_6D_6, rt) δ=4.19–4.03 (m, 2H), 2.36 (d, *J*=5.1 Hz, 1H), 2.27 (d, *J*=4.7 Hz, 1H), 1.77–1.58 (m, 2H), 1.23 (s, 9H, H-1), 1.14 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6, rt) δ=177.5, 61.0, 54.3, 53.0, 38.7, 36.0, 27.3, 21.1. IR (film) ν 2970, 1725, 1480, 1460, 1395, 1365, 1285, 1150, 1035, 905, 880, 795, 770, 535. ESIHRMS calcd for $C_{10}H_{18}O_3Na$ 209.1154, found 209.1148.

*4.2.4.6. Synthesis of 4-hydroxy-3-methylbutyl-pivalate (**15**).* According to GP, **14** (184 mg, 0.99 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **15** (85 mg, 45%) and 4-hydroxy-2-methylbutyl-pivalate (43.0 mg, 23%). ^1H NMR (300 MHz, $CDCl_3$, rt) δ=4.17–4.05 (m, 2H), 3.55–3.46 (m, 2H), 1.83–1.73 (m, 1H), 1.50–1.43 (m, 2H), 1.20 (s, 9H), 0.96 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, rt) δ=178.8, 67.9, 62.8, 38.8, 33.1, 32.1, 27.3, 16.1. IR (film) ν 3350, 2960, 2935, 2875, 1725, 1710, 1480, 1460, 1400, 1365, 1285, 1155, 1035, 975, 940, 895, 770, 475. ESIHRMS calcd for $C_{10}H_{20}O_3Na$ 211.1310, found 211.1305.

*4.2.4.7. Entry 6: synthesis of 11-chloro-2-methylundecan-1-ol (**17**)*[17b]. According to GP, **16**[17b] (219 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/MTBE 4:1) yielded **17** (147 mg, 67%).

*4.2.4.8. Entry 7: synthesis of 2-(2-(hexyloxy)ethyl)-2-methyloxiran (**18**).* A mixture of 1-(3-methylbut-enyloxy)hexane[39] (5.04 g, 29.0 mmol), *m*-CPBA (10.7 g, 44.0 mmol), and CH_2Cl_2 (200 mL) was stirred for 5 h. The mixture was washed with K_2CO_3 solution (2×50 mL) and was extracted with CH_2Cl_2 (3×50 mL) and dried ($MgSO_4$). The volatiles were removed under reduced pressure and the crude product was purified by SiO_2 chromatography (CH/EE=90:10) yielded **18** (2.52 g, 47%).

*4.2.4.9. Synthesis of 4-(n-hexyloxy)-2-methyl-butan-1-ol (**19**).* According to GP, **18** (186 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 95:5) yielded **19** (130 mg, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ=3.51–3.30 (m, 6H), 3.27 (t, *J*=5.7 Hz, 1H), 1.78–1.63 (m, 1H), 1.60–1.44 (m, 4H), 1.32–1.80 (m, 6H), 0.87 (d, *J*=7.2 Hz, 3H), 0.83 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=71.3, 69.3, 68.0, 34.4, 34.4, 31.7, 29.6, 25.9, 22.6, 17.4, 14.1. IR (film) ν 3375, 2955, 2925, 2855, 1460, 1375, 1100, 1040, 930, 725, 575, 490, 410. ESIHRMS calcd for $C_{11}H_{24}O_2Na$ 211.1647, found 211.1669.

*4.2.4.10. Entry 8: synthesis of 11-(tert-butyldimethylsilyloxy)-2-methylundecan-1-ol (**21**)*[17b]. According to GP, **20**[17b] (315 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE:MTBE 85:15) yielded **21** (250 mg, 79%).

*4.2.4.11. Entry 9: synthesis of 4-(tert-butyldimethylsilyloxy)-2-methyl-butan-1-ol (**23**).* According to GP, **22**[43] (220 mg, 1.02 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol) and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH:EE 95:5) yielded **23** (171 mg, 76 %). ^1H NMR (400 MHz, $CDCl_3$, RT) δ=3.69 (ddd, *J*=10.3 Hz, *J*=5.2 Hz, *J*=5.1 Hz, 1H), 3.59 (ddd, *J*=10.6 Hz, *J*=6.2 Hz, *J*=6.1 Hz, 1H), 3.46 (ddd, *J*=11.0 Hz, *J*=7.3 Hz, *J*=4.8 Hz, 1H), 3.33 (ddd, *J*=11.0 Hz, *J*=6.9 Hz, *J*=5.2 Hz, 1H), 2.85 (dd, *J*=7.3 Hz, *J*=5.3 Hz, 1H), 1.83–1.77 (m, 1H), 0.92 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, RT) δ=67.3, 60.9, 36.6, 36.1, 33.6, 17.4, 16.5, -6.3. IR (film) ν 2955, 2930, 2855, 1470, 1460, 1390, 1250, 1090, 1040, 1005, 890, 830, 810, 775, 730, 660. ESIHRMS calcd for $C_{11}H_{26}O_2NaSi$ 241.1600, found 241.1594.

*4.2.4.12. Entry 10: synthesis of triethyl-[2-(2-methyloxiran-2-yl)-ethoxy]silane (**24**).* A mixture of 1-triethyl-(3-methylbut-3-enyloxy)silane[40] (6.00 g, 30.0 mmol), *m*-CPBA (11.7 g, 45.0 mmol), and CH_2Cl_2 (200 mL) was stirred for 5 h. The mixture was washed with K_2CO_3 solution (2×50 mL) and was extracted with CH_2Cl_2 (3×50 mL) and dried ($MgSO_4$). The volatiles were removed under reduced pressure and the crude product was purified by SiO_2 chromatography (CH/EE=95:5) yielded **18** (4.12 g, 63 %). ^1H NMR (400 MHz, C_6D_6, rt) δ=3.58 (dt, *J*=6.5, 1.9 Hz, 2H), 2.45 (d, *J*=5.3 Hz, 1H), 2.27 (d, *J*=5.2 Hz, 1H), 1.75–1.59 (m, 2H), 1.16 (s, 3H), 0.95 (t, *J*=7.9 Hz, 9H), 0.53 (q, *J*=8.0 Hz, 6H). ^{13}C NMR (100 MHz, C_6D_6, rt) δ=59.7, 54.9, 53.5, 40.1, 21.8, 7.0, 4.8. IR (film) ν 2955, 2910, 2875, 1460, 1415, 1240, 1090, 1005, 975, 900, 795, 725, 525. ESIHRMS calcd for $C_{11}H_{24}O_2NaSi$ 239.1443, found 239.1438.

*4.2.4.13. Synthesis of 2-methyl-4-(triethylsilyloxy)butan-1-ol (**25**).* According to GP, **24** (217 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH:EE 9:1) yielded **25** (137 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$, rt) δ=3.74 (dt, *J*=10.3, 5.3 Hz, 1H), 3.63 (dt, *J*=10.3, 5.3 Hz, 1H), 3.52–3.48 (m, 1H), 3.46–3.38 (m, 1H), 3.18 (m, 1H), 1.81–1.72 (m, 1H), 1.57–1.52 (m, 2H), 0.95 (t, *J*=8.1 Hz, 9H), 0.90 (d, *J*=6.8 Hz, 3H), 0.60 (q, *J*=8.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, rt) δ=68.3, 61.4, 37.7, 34.6, 17.5, 6.8, 4.4. IR (film) ν 3350, 2955, 2910, 2875, 1460, 1415, 1385, 1285, 1090, 1040, 1005, 885, 725, 670. ESIHRMS calcd for $C_{11}H_{26}O_2NaSi$ 241.1600, found 241.1594.

*4.2.4.14. Entry 11: synthesis of 2-phenyl-propan-1-ol (**27**).* According to GP, **26** (134 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 4:1) yielded **27** (90 mg, 66 %).

*4.2.4.15. Entry 12: synthesis of 1,4-di-tert-butoxybutan-2-ol (**29**).* According to GP, **28** (216 mg, 1.00 mmol), Cp_2TiCl_2 (24.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/Et_2O 85:15) yielded **29** (124 mg, 57%).

*4.2.4.16. Entry 13: synthesis of 3-methyl-5-phenylpentan-2-ol (**31**)*[41]. According to GP, **30**[42] (176 mg, 1.00 mmol), Cp_2TiCl_2 (12.3 mg, 0.05 mmol), dry collidine hydrochloride (236 mg, 1.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (4.5 mL) for 20 h under H_2 (4 bar). SiO_2 chromatography (CH/EE 95:5) yielded **31** (128 mg, 71%).

*4.2.5. Table 4: synthesis of (R)-1,4-di-tert-butoxybutan-2-ol (**29**)*[20a]

4.2.5.1. Entry 1. According to GP, **28** (216 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride, (394 mg, 2.50 mmol), **3** (92 mg, 0.10 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/Et_2O 85:15) yielded **29** (132 mg, 60%, er 93:7). The enantiomeric ratio was determined by GC on a heptakis(2,6-di-*O*-methyl-O-pentyl)-β-cyclodextrin/OV1701 (1/4) column according to Refs. 20a–c.

*4.2.5.2. Entry 2: synthesis of (R)-1,4-di-n-propoxybutan-2-ol (**33**)*[20a]. According to GP, **32** (188 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/Et_2O 85:15) yielded **33** (122 mg, 64%, er 97:3). The enantiomeric ratio was determined by GC on an Ivadex 7/OV-1701;G/294 column according to Refs. 20a–c.

*4.2.5.3. Entry 3: synthesis of 1,4-diethoxybutan-2-ol (**35**)*[20a]. According to GP, **34** (160 mg, 1.00 mmol), **7** (52.5 mg, 0.10 mmol), dry collidine hydrochloride (394 mg, 2.50 mmol), **3** (46 mg, 0.05 mmol), and Mn dust (165 mg, 3.00 mmol) in dry THF (5 mL) for 16 h under H_2 (4 bar). SiO_2 chromatography (PE/Et_2O 85:15) yielded **33** (122 mg, 75%, er 96:4). The enantiomeric ratio was determined by GC on an Ivadex 7/OV-1701;G/294 column according to Refs. 20a–c.

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