Titanocene-Catalyzed Reductive Epoxide Opening: The Quest for Novel Hydrogen Atom Donors

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Received 5 May 2004; revised 23 June 2004

Abstract: Novel hydrogen atom donors for the reductive titanocene-catalyzed epoxide opening are presented. While the potentially attractive cyclopentadienes gave only moderate yields of the desired alcohols, substituted, nontoxic, and commercially available 1,4-cyclohexadienes, e.g. γ-terpinene, in combination with more elaborate catalysts gave better or similar results than the much more expensive and carcinogenic 1,4-cyclohexadiene. In the practically important reactions of Sharpless epoxides and their derivatives excellent levels of regioselectivity for the epoxide opening could be obtained. The toxic and unpleasant to handle *tert*-butyl thiol could be replaced while increasing the yields of the desired products.

Key words: epoxides, titanium, reductive ring opening, H-atom donors, γ-terpinene

Over the past three decades, radicals have been increasingly utilized as reactive intermediates in organic synthesis.[1] Their ease of generation, high functional group tolerance and predictable behavior in many transformations has led to numerous developments of novel methods for the efficient formation of C–C and C–H bonds. However, limitations also exist. In this context, one of the more demanding problems is constituted by the efficient and environmentally safe reduction of carbon centered radicals through hydrogen atom donors.[2] Although excellent results in radical chain reactions have been achieved by using stannanes or silanes as reductants in chain reactions,[1] the toxicity and/or sensitivity of the reagents combined with their high prices can render large scale applications unattractive. Also, from a fundamental point of view hydrogen atom abstraction ought to be a kinetically favorable process in order to maintain a fast chain propagation.

Especially the last limitation does not necessarily apply to radical chemistry mediated or catalyzed by electron-transfer. Because no chain reaction needs to be maintained relatively slow transformations can be realized if the radicals generated are not reduced by a second equivalent of the reductant too swiftly. In this undesired scenario an organometallic species is generated and the typical radical reactivity cannot be exploited. This is often the case with the most popular electron-transfer reagent samarium diiodide,[3] that has been used with excellent success over the last two decades, because reductive trapping of radicals by samarium diiodide is rather efficient.[4] A practical disadvantage of samarium diiodide is constituted by the high price of the metal (870 € per mol) that renders large scale applications unattractive. This point is of major importance especially when compared to the catalytic conditions described below that use the much cheaper metal powders manganese (ca. 7 € per mol) and zinc (ca. 3 € per mol) as stoichiometric reductants.

A convenient and attractive alternative to samarium diiodide-induced reactions is constituted by opening of readily available epoxides[5] mediated through electron-transfer from titanocene(III) chloride as introduced by Nugent and RajanBabu.[6] The β-titanoxy radicals generated with excellent regioselectivity are usually fairly unreactive towards a reduction by a second equivalent of the titanocene reagent and can thus be utilized in a number of applications unusual for radical chemistry.[7,8] This feature can also be exploited in the hydrogen atom transfer from 1,4-cyclohexadiene that is quite slow[9] for radical reduction to obtain alcohols from epoxides.[6] This limits the usefulness of the reagent. An example can be found in the more difficult but preparatively highly pertinent cases of the reduction of Sharpless epoxides and their derivatives to 1,2- or 1,3-diols, respectively, when more reactive reductants, e.g. *tert*-butyl thiol that is toxic and foul smelling, have to be used.[6c,d]

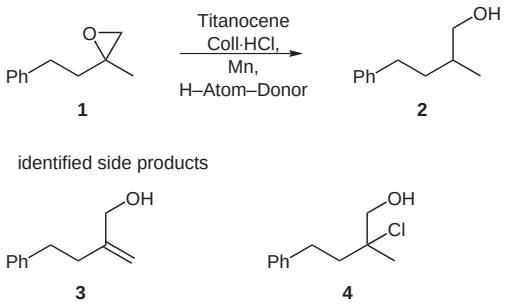
This relative persistence of the radicals is even more pronounced under the catalytic conditions[10] that we have devised to introduce the concept of reagent control to these reactions.[10,11] A number of unusual radical reactions could also be realized in this manner.[12]

To exploit this relative persistence, we decided to investigate substituted 1,4-cyclohexadienes and other reagents hitherto unexplored as hydrogen atom donors for our model substrate **1** as shown in Scheme 1. Our choice of these compounds was based on their low bond dissociation energies. The potential hydrogen atom donors are shown in Figure 1.

The results of the studies are summarized in Table 1.

We initially checked the reaction in the absence of any external hydrogen atom donors to exclude any unexpected reaction pathways (entry 1). Even in this case some of the desired product **2** was obtained (<22% in combination with **3** and another unknown impurity) at most under these

SYNTHESIS 2004, No. 15, pp 2567–2573
Advanced online publication: 02.09.2004
DOI: 10.1055/s-2004-831207; Art ID: T05104SS



Scheme 1 Test system for the optimization of epoxide reduction (Coll·HCl = 2,4,6-collidinium hydrochloride).

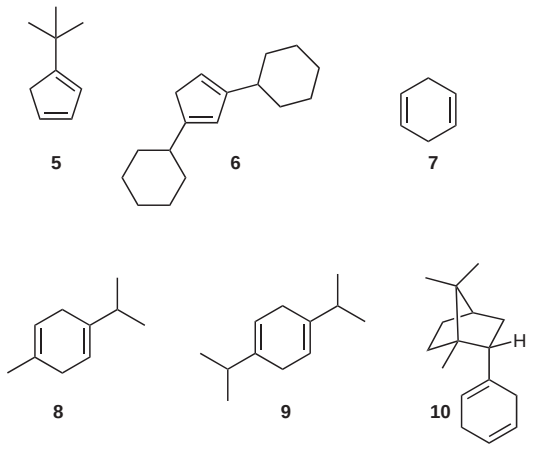


Figure 1 Hydrogen atom donors shown in this study (compounds **5** and **6** as a mixture of isomers).

Table 1 Opening of **1** to Afford **2** in THF in the Presence of 10 mol% Cp_2TiCl_2

Entry	H-Atom Donor	Yield (%)
1	–	<22
2	Ph_3CH	<22
3	**5**	32
4	**6**	30
5	**7**	88[10c]
6	**8**	84
7	**9**	69
8	**10**	66

conditions. It seems, however, that this product results from trapping of the radical by a second equivalent of Cp_2TiCl and concomitant protonation of the Ti–C bond or β-hydride elimination.[13] The presence of **3** renders hydrogen atom transfer from THF unlikely. Some amount of compound **4** was also formed through acid initiated epoxide opening. The finding, that addition of Ph_3CH (entry 2) lead to essentially the same results suggests that this compound did not act as a hydrogen atom donor despite the weak C–H bond (77 kcal/mol). Presumably this is due to a hindered attack for sterical reasons.

Cyclopentadienes were chosen as potential reducing reagents because of the low C–H bond strength (BDE = ca. 80 kcal/mol)[14] and the generation of the stabilized cyclopentadienyl radical after hydrogen atom abstraction. The formation of this intermediate is of potential relevance for the development of hydrogen atom donor catalysts. After reduction of the cyclopentadienyl radical to the anion and protonation in the acidic reaction medium would result in regeneration of the cyclopentadiene as hydrogen atom donor catalyst. Unfortunately, the results summarized in entries 3 and 4 suggest that hydrogen atom transfer is not very efficient (32% of desired product at most) for reasons not fully understood yet.

The 1,4-cyclohexadienes gave satisfying results. Interestingly, the additional steric demand of the two substituents in γ-terpinene (**8**) (entry 6) did not result in any deterioration of the yield of **2** (84%). We were pleasantly surprised by this finding since the titanocene-catalyzed epoxide opening is usually fairly sensitive towards steric crowding. While the overall driving force when using the hexadienes is constituted by the second H-atom transfer, the first transfer is slower and thus rate determining. Consequently the use of overstoichiometric amounts of the reducant is required.

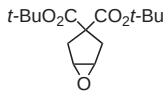
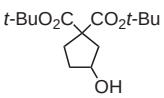
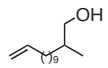
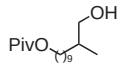
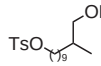
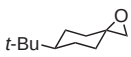
The practical importance of these results is substantial. Since γ-terpinene is less toxic and substantially cheaper (about 25 €/mol) than 1,4-cyclohexadiene (about 220 €/mol), that is a cancer suspect agent, it will certainly replace 1,4-cyclohexadiene in day-to-day use. We have also established that unreacted **8** can be recovered from the reaction mixture in combination with *p*-cymene, the product of hydrogen atom abstraction, quantitatively. If desired this mixture can be transformed into **8** by reduction.

Increasing the steric demand of the substituents even further in **9** and **10** resulted in only a slight decrease in isolated yields of **2**. In these cases larger amounts of the chlorohydrin **4** (2% with **7** and **8**, 15% with **9**, 7% with **10**), formed through acid initiated epoxide opening through an S_N1 reaction, were produced as a result of the decreased efficiency of the catalytic cycle. Still, this finding is of great potential relevance for the evolution of enantiomerically pure hydrogen atom donors for enantioselective radical reduction. We are currently pursuing this goal.

To establish the scope and limitation of γ-terpinene as hydrogen atom donor a number of epoxides were reduced and the results compared to the reactions using 1,4-cyclohexadiene as shown in Table 2. Gratifyingly, in all cases examined **8** performed similar to or even superior than **7** except for entry 6. It was found, however, that when performing this reaction in the presence of **8** on a 10 mmol scale with a 0.2 M concentration instead of the usual 0.1 M concentration the yield of **20** increased from 69 to 84%.

Another important question in the reductive epoxide opening concerns the use of more complex titanocene cat-

Table 2 Comparison of 1,4-Cyclohexadiene (**7**) and γ-Terpinene (**8**) as Hydrogen Atom Donors

Entry	Substrate	Product	Yield (%) **7**/**8**
1	**1**	**2**	88[10c]/84
2	 **11**	 **12**	72/82
3	 **13**	 **14**	72[10c]/69
4	 **15**	 **16**	69[10c]/78
5	 **17**	 **18**	58[10c]/73
6	 **19**	 **20**	87/69[a]

[a] Ratio of *trans*:*cis* = 82:18; 83:17.

alysts than Cp_2TiCl_2, because the performance of the reaction should also depend on the proper choice of the electron-transfer catalyst. We have recently demonstrated that complexes with an open configuration perform distinctly superior to the ones with a closed configuration in C–C bond forming reactions concerning both yields and diastereoselectivities.[15] As shown in Table 3, the same trend was observed with the complexes depicted in Figure 2 for the reduction of simple epoxides.

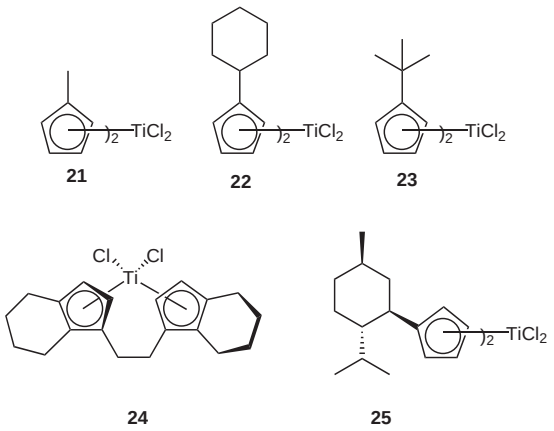
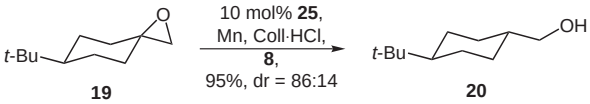


Figure 2 Titanocene complexes used in this study.

In accordance, complex **22**[16] with a closed configuration gave a low 43% yield of **2** (entry 3). The complexes **21**,[17] **23**,[18] **24**,[19] and **25**[20] with open configurations gave better results. The *tert*-butyl substitution seems to result in a ligand too bulky for an efficient reaction (entry 4). It is interesting to note that Kagan's complex **25**[20] performs best, even though its ligands are sterically demanding. A plausible explanation could be that reductive trapping of the β-titanoxy radicals is efficiently suppressed by this bulky arrangement while maintaining a pocket wide enough for substrate binding. Brintzinger's complex **24** performed poorly. It seems that adding three substituents to the cyclopentadienyl ligand shuts down the reactivity almost completely. Curiously, **8** performed better than or similar to **7** in all cases. An even more stunning example for the superiority of **8** is shown in Scheme 2 where an almost quantitative yield of the desired product **20** was obtained. In this case the reagent combination **25**/**8** is even superior to Cp_2TiCl_2/**7**, the sterically least hindered combination (87%, Table 2, entry 6). However, in the cases of the chiral catalysts, **2** was obtained in racemic form. This indicates that a dual approach employing chiral hydrogen atom donors and catalysts is necessary for enantioselective reduction that is currently pursued in our group.

Table 3 Comparison of Different Catalysts in the Opening of **1** to Give **2**

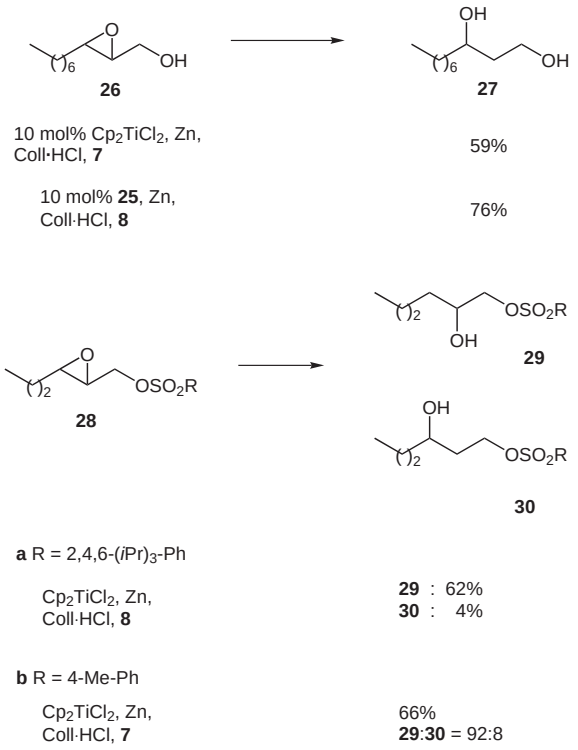
Entry	Catalyst	H-Atom Donor	Yield (%)
1	**21**	**7**	72
2	**21**	**8**	72
3	**22**	**8**	43
4	**23**	**7**	55
5	**24**	**7**	21
6	**24**	**8**	24
7	**25**	**7**	83
8	**25**	**8**	85



Scheme 2 Opening of **19** in the presence of 10 mol% **25** and **8**.

Amongst the preparatively most useful epoxides are Sharpless epoxides[21] and their derivatives. This is mainly due to the ease of their preparation in high enantiomeric purity. Methods for their regioselective opening by hydride reagents (DIBALH and RedAl®) have been established.[22] However, the functional group tolerance in these transformations is not high and milder methods are still desirable. We have therefore applied our method to the opening of Sharpless epoxides and their derivatives to investigate the regioselectivity of epoxide opening under catalytic conditions. The results are summarized in Scheme 3.

Gratifyingly, the opening of the unprotected 2,3-epoxy alcohol **26** proceeded to give the 1,3-diol **27** with essentially complete regioselectivity (>97:<3 by ^{1}H NMR) with both catalysts investigated. In line with the previous results, Kagan' s complex **25** and **8** performed distinctly superior



Scheme 3 Reductive opening of Sharpless epoxides and their sulfonate esters.

than Cp_2TiCl_2 and **7**, giving the 1,3-diol in a yield of 76%. In a similar system Nugent and RajanBabu's stoichiometric reaction employing *tert*-butyl thiol, gave a regioselectivity of 95:5 in favor of the 1,3-diol, which was obtained in 69% yield. Through the use of γ-terpinene as hydrogen atom donor the utilization of the unpleasantly smelling *tert*-butyl thiol in the stoichiometric reaction could be avoided without problems. Our method therefore seems clearly superior for practical use.

Regioselectivity of epoxide opening could be almost completely reversed by employing the epoxides' sulfonate esters as starting materials. It turned out that a small but noticeable dependence of regioselectivity in favor of the 1,2-diol derivatives **29** was observed when the steric bulk of the sulfonate was changed. Employing the bulky 2,4,6-trisisopropylbenzenesulfonate **29a** a higher and preparatively useful selectivity of 94:6 was observed compared to the tosylate **29b** (91:9). Curiously, electronic effects turned out to be less important. The brosylate resulted in a slightly decreased regioselectivity of 89:11.

In the stoichiometric reaction the use of silylated Sharpless epoxides has been reported to yield the 1,2-derivatives with a selectivity (91:9)[6d] similar to the one observed in our system.

In summary, we have devised a simple economically and ecologically benign system for the highly regioselective epoxide opening that employs the cheap and nontoxic γ-terpinene as hydrogen atom donor. Because substituted cyclohexadienes and titanocenes can also be used with good success our method offers potential for enantioselective catalysis. Moreover, the method is also applicable to the highly selective opening of Sharpless epoxides to 1,3-diols and their sulfonate esters to derivatized 1,2-diols in good yields.

All reactions were performed in oven-dried (100 °C) glassware under argon. THF was freshly distilled from $LiAlH_4$ or K. Et_2O was freshly distilled from Na/K. CH_2Cl_2 was freshly distilled from CaH_2. Products were purified by flash chromatography[23] on Macherey-Nagel silica gel 60 and Merck silica gel 50 (eluents given in brackets; MTBE refers to *tert*-butyl methyl ether, CH to cyclohexane and PE to petrol ether, 30–60 °C fractions). Yields refer to analytically pure samples. Isomer ratios were determined from suitable ^{1}H NMR integrals of cleanly separated signals.

NMR: Bruker AMX 300, AM 400, DRX 500, Varian XR 200, and MERCURY 300 HFCP; ^{1}H NMR: tetramethylsilane (0.00 ppm) in the indicated solvent, benzene-d_6 (7.15 ppm) and $CHCl_3$ (7.26 ppm) as internal standard in the same solvent; ^{13}C NMR: tetramethylsilane (0.00 ppm) in the indicated solvent or $CDCl_3$ (77.16 ppm) and benzene-d_6 (128.06 ppm) as internal standards in the same solvent; integrals in accord with assignments, coupling constants are measured in Hz. An asterisk (*) indicates the signals of the minor diastereomer. The word 'both' indicates overlapping signals for two diastereoisomers. Combustion analyses: Mrs. Martens, Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn. IR spectra: Perkin Elmer 1600 series FT-IR, PARAGON 1000, and 1620 as KBr pellets or as neat films on NaCl and KBr plates.

The following compounds were prepared according to published procedures or have already been described in the literature: **1**,[24] **5**,[25] **6**,[26] **9**,[27] **13**,[10c] **15**,[10c] **17**,[10c] **19**,[28] **26**,[29] **28a**.[30] Compound **10** was obtained from 2-*endo*-phenylbornane[31] by modified Birch reduction.[32] Besides **10** the product contained 50% of the starting material. Collidine hydrochloride was dried prior to use by gentle heating under vacuum.

2-Methyl-4-phenylbutan-1-ol (2)[33] (Table 1, entry 6)

A mixture of Cp_2TiCl_2 (25 mg, 0.1 mmol), Mn (82 mg, 1.5 mmol), collidine hydrochloride (236 mg, 1.5 mmol), **8** (0.69 mL, 4.3 mmol) and **1** (171 mg, 1.056 mmol) in THF (10 mL) was stirred for 24 h at r.t. The reaction mixture was treated with MTBE (50 mL) and filtered. The filtrate was washed with H_2O (30 mL), 1 N HCl (30 mL), H_2O (30 mL), aq sat. Na_2CO_3 (30 mL), H_2O (30 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Purification by SiO_2 flash chromatography (7% EtOAc, 93% CH) afforded **2** as a colorless oil (145 mg, 84%).

Table 1, entry 3: Compound **2** (52 mg, 32%) was obtained via the same procedure starting from **1** (162 mg, 1 mmol) and **5** (610 mg, 5 mmol).

Table 1, entry 4: Compound **2** (51 mg, 30%) was obtained via the same procedure starting from **1** (170 mg, 1.049 mmol) and **6** (1155 mg, 5 mmol).

Table 1, entry 7: Compound **2** (116 mg, 69%) was obtained via the same procedure starting from **1** (166 mg, 1.025 mmol) and **9** (787 mg, 4.8 mmol).

Table 1, entry 8: Compound **2** (115 mg, 66%) was obtained via the same procedure starting from **1** (172 mg, 1.062 mmol) and **10** (1.036 mg, 4.8 mmol).

3,4-Epoxycyclopentane-1,1-dicarboxylic Acid Di-*tert*-butyl Ester (11)

Cyclopent-3-ene-1,1-dicarboxylic acid di-*tert*-butyl ester[34] (1.34 g, 5 mmol) was reacted with *m*-chloroperbenzoic acid (1.86 g, 70% solid mixture, 7.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After stirring for 4 h, the white mixture was poured into MTBE (50 mL) and the

MTBE layer was washed with 2 N NaOH (2 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Purification by SiO_2 flash chromatography (8% EtOAc, 92% CH) afforded the desired product as a colorless oil (1.184 g, 84%); mp 66–67 °C; R_f 0.1.

IR (KBr): 2980, 1725, 1460, 1370, 1272, 1153, 1091, 967, 847, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.45 (s, 2 H), 2.88 (d, *J* = 14.5 Hz, 2 H), 2.09 (d, *J* = 14.5 Hz, 2 H), 1.44 (s, 9 H), 1.40 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.9, 81.9, 80.9, 57.5, 55.7, 35.7, 27.9, 27.8.

Anal. Calcd for $C_{15}H_{24}O_5$ (284.35): C, 63.36; H, 8.51. Found: C, 63.34; H, 8.43.

3-Hydroxycyclopentane-1,1-dicarboxylic Acid Di-*tert*-butyl Ester (12) (Table 2, entry 2)

A: Following the procedure for the preparation of **2**, compound **11** (284 mg, 1 mmol) was reacted with **7** (0.410 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (8% EtOAc, 92% CH) afforded the desired product as a colorless oil (205 mg, 72%).

B. Following the procedure for the preparation of **2**, compound **11** (284 mg, 1 mmol) was reacted with **8** (0.69 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (8% EtOAc, 92% CH) afforded the desired product as a colorless oil (234 mg, 82%); mp 52–53 °C; R_f 0.1.

IR (KBr): 3290, 2977, 1718, 1368, 1283, 1170, 1140, 1080, 1030, 964, 854, 739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.31 (br s, 1 H), 2.29–2.14 (m, 5 H), 1.88 (dddd, ^2J = 13.5 Hz, ^3J = 8.5 Hz, ^3J = 8.5 Hz, ^3J = 5.1 Hz, 1 H), 1.74–1.67 (m, 1 H), 1.44 (s, 9 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 171.3, 81.7, 81.2, 73.4, 60.7, 43.2, 35.3, 31.8, 27.9, 27.8.

Anal. Calcd for $C_{15}H_{26}O_5$ (286.36): C, 62.91; H, 9.15. Found: C, 63.05; H, 9.09.

2-Methyldodec-11-en-1-ol (14)[10c] (Table 2, entry 3)

Following the procedure for the preparation of **2**, compound **13** (196 mg, 1 mmol) was reacted with **8** (0.69 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (2% EtOAc, 98% CH) afforded the desired product as a colorless oil [148 mg, 69% of **14,** the remaining 3% (by NMR) was 2-chloro-2-methyldodec-11-en-1-ol].

2,2-Dimethylpropionic Acid (11-Hydroxy-10-methylundecyl) Ester (16)[10c] (Table 2, entry 4)

Following the procedure for the preparation of **2**, compound **15** (284 mg, 1 mmol) was reacted with **8** (0.69 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (5% EtOAc, 95% CH) afforded the desired product as a colorless oil (223 mg, 78%).

Toluene-4-sulfonic Acid (11-Hydroxy-10-methylundecyl) Ester (18)[10c] (Table 2, entry 5)

Following the procedure for the preparation of **2**, compound **17** (354 mg, 1 mmol) was reacted with **8** (0.69 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (6% EtOAc, 94% CH) afforded the desired product as a colorless oil [271 mg, 73% of **18**, the remaining 3% (by NMR) was toluene-4-sulfonic acid (10-chloro-11-hydroxy-10-methylundecyl) ester].

***cis*- and *trans*-(4-*tert*-Butylcyclohexyl)methanol (20) (Table 2, entry 6)**

A. Following the procedure for the preparation of **2**, compound **18** (168 mg, 1 mmol) was reacted with **7** (0.410 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (6% EtOAc, 94% CH) afforded the desired product as a colorless oil (148 mg, 87%, *trans*:*cis* = 82:18).

B. Following the procedure for the preparation of **2**, compound **18** (168 mg, 1 mmol) was reacted with **8** (0.690 mL, 4.3 mmol). Purification by SiO_2 flash chromatography (6% EtOAc, 94% CH) afforded the desired product as a colorless oil (117 mg, 69%, *trans*:*cis* = 83:17).

C. Reaction on 10 mmol scale at 0.2 M concentration in THF. Compound **18** (1.680 g, 10 mmol), Cp_2TiCl_2 (250 mg, 1.0 mmol), Mn (820 mg, 15 mmol), Coll·HCl (2.360 g, 15 mmol), and **8** (6.9 mL, 43 mmol) were reacted in THF (50 mL). Purification by SiO_2 flash chromatography (6% EtOAc, 94% CH) afforded the desired product as a colorless oil (1.432 g, 84%, *trans*:*cis* = 82:18).

D. Following the procedure for the preparation of **2**, compound **18** (168 mg, 1 mmol) was reacted with **8** (0.690 mL, 4.3 mmol) and **25** (52.6 mg, 0.1 mmol). Purification by SiO_2 flash chromatography (6% EtOAc, 94% CH) afforded the desired product as a colorless oil (166 mg, 95%, *trans*:*cis* = 86:14); R_f 0.1.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.64 (d, *J* = 7.6 Hz, 2 H)*, 3.44 (d, *J* = 6.3 Hz, 2 H), 1.81–1.68 (m, 4 H) both, 1.52–1.25 (m, 4 H) both, 1.02–0.80 (m, 6 H) both, 0.85 (s, 9 H), 0.83 (s, 9 H)*.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.9, 63.9*, 48.4 both, 40.8, 35.5*, 32.6 both, 30.1 both, 27.2, 27.6*, 26.9, 22.2*.

HRMS: *m*/*z* calcd for $C_{11}H_{22}O$: 170.1671; found: 170.1676.

Table 3, entry 1: Compound **2** (116 mg, 72%) was obtained via the same procedure starting from **1** (159 mg, 0.981 mmol), **21** (26.3 mg, 0.1 mmol) and **7** (0.410 mL, 4.3 mmol).

Table 3, entry 2: Compound **2** (122 mg, 72%) was obtained via the same procedure starting from **1** (167 mg, 1.031 mmol), **21** (26.3 mg, 0.1 mmol) and **8** (0.690 mL, 4.3 mmol).

Table 3, entry 3: Compound **2** (77 mg, 43%) was obtained via the same procedure starting from **1** (156 mg, 0.963 mmol), **22** (41.3 mg, 0.1 mmol) and **8** (0.690 mL, 4.3 mmol).

Table 3, entry 4: Compound **2** (90 mg, 55%) was obtained via the same procedure starting from **1** (162 mg, 1.000 mmol), **23** (30.5 mg, 0.1 mmol) and **7** (0.410 mL, 4.3 mmol).

Table 3, entry 5: Compound **2** (35 mg, 21%) was obtained via the same procedure starting from **1** (167 mg, 1.031 mmol), **24** (38.3 mg, 0.1 mmol) and **7** (0.410 mL, 4.3 mmol).

Table 3, entry 6: Compound **2** (40 mg, 24%) was obtained via the same procedure starting from **1** (165 mg, 1.019 mmol), **24** (38.3 mg, 0.1 mmol) and **8** (0.690 mL, 4.3 mmol).

Table 3, entry 7: Compound **2** (138 mg, 83%) was obtained via the same procedure starting from **1** (165 mg, 1.019 mmol), **25** (52.6 mg, 0.1 mmol) and **7** (0.410 mL, 4.3 mmol).

Table 3, entry 8: Compound **2** (137 mg, 85%) was obtained via the same procedure starting from **1** (160 mg, 0.988 mmol), **25** (52.6 mg, 0.1 mmol) and **8** (0.690 mL, 4.3 mmol).

1,3-Decanediol (27)[35]

A. Adapting the same procedure, starting with Cp_2TiCl_2 (25 mg, 0.1 mol), Zn (98 mg, 1.5 mmol), coll·HCl (236 mg, 1.5 mmol), **26** (172 mg, 1.0 mmol) and **7** (0.48 mL, 4.8 mmol), compound **27**[35] (103 mg, 59%) was obtained after SiO_2 flash chromatography (32% EtOAc, 68% CH).

B. Adapting the same procedure, starting with **25** (27 mg, 0.05 mol), Zn (49 mg, 0.75 mmol), coll·HCl (118 mg, 0.75 mmol) and **8** (0.35 mL, 2.2 mmol), compound **27** (62 mg, 76%) was obtained after SiO_2 flash chromatography (32% EtOAc, 68% CH).

2,4,6-Triisopropylbenzenesulfonic Acid 3-Propyloxiranylmethyl Ester (28a)

To a solution of 3-propyloxiranylmethanol[36] (1.16g, 10 mmol) in CH_2Cl_2 (50 mL) was added pyridine (1.61 mL, 20 mmol) and 2,4,6-triisopropylsulfonyl chloride (3.83 g, 15 mmol) at 0 °C. After stirring for 18 h at r.t., H_2O (50 mL) was added and the mixture was poured onto Et_2O (50 mL). The organic phase was washed with aq HCl (2 N, 2 × 30 mL) and brine (30 mL). After removing the volatiles in vacuum, the crude was purified by SiO_2 flash chromatography (5% EtOAc, 95% CH) to yield **28a** (0.89 g, 23%) as a colorless solid; mp 38–41 °C; R_f 0.4 (CH–EtOAc, 90:10).

^{1}H NMR (300 MHz, C_6D_6): δ = 7.20 (s, 2 H), 4.57 (tt, *J* = 6.7 Hz, 2 H), 4.19 (A part of an AB system, dd, $J_{A,B}$ = 11.1 Hz, *J* = 4.3 Hz, 1 H), 3.96 (B part of an AB system, dd, $J_{A,B}$ = 11.1 Hz, *J* = 6.8 Hz, 1 H), 2.90 (ddd, *J* = *J* = 6.8 Hz, *J* = 4.3 Hz, 1 H), 2.61 (tt, *J* = 6.9 Hz, 1 H), 2.47 (ddd, *J* = *J* = *J* = 4.3 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.07 (d, *J* = 7.0 Hz, 6 H), 1.43–0.80 (m, 4 H), 0.67 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 153.9, 151.5, 130.9, 124.1, 67.7, 56.0, 53.1, 34.5, 30.1, 29.9, 24.9, 23.6, 20.1, 13.8.

HRMS: *m*/*z* calcd for $C_{21}H_{34}O_4S$: 382.2178; found: 382.2176.

2,4,6-Triisopropylbenzenesulfonic Acid (2-Hydroxyhexyl) Ester (29a) and 2,4,6-Triisopropylbenzenesulfonic Acid (3-Hydroxyhexyl) Ester (30a)

Adapting the same procedure, starting with Cp_2TiCl_2 (13 mg, 0.05 mmol), Zn (49 mg, 0.75 mmol), coll·HCl (118 mg, 0.75 mmol), **8** (0.35 mL, 2.2 mmol), and **28a** (191 mg, 0.5 mmol), compounds **29a** (119 mg, 62%) and **30a** (8 mg, 4%) were obtained after SiO_2 flash chromatography (3% EtOAc, 97% CH) as colorless solids.

29a

Mp 44–45 °C; R_f 0.2 (CH–EtOAc, 90:10).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.09 (s, 2 H), 4.04 (tt, *J* = 6.8 Hz, 2 H), 3.98 (A part of an AB system, dd, $J_{A,B}$ = 9.8 Hz, *J* = 2.8 Hz, 1 H), 3.84 (B part of an AB system, dd, $J_{A,B}$ = 9.8 Hz, *J* = 7.0 Hz, 1 H), 2.81 (tt, *J* = 6.9 Hz, 1 H), 1.97 (br s, 1 H), 1.26–1.07 (m, 24 H), 0.79 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 154.1, 151.0, 129.4, 124.0, 73.2, 69.9, 34.4, 32.7, 29.8, 27.6, 24.9, 23.7, 22.7, 14.0.

Anal. Calcd for $C_{21}H_{36}O_4S$ (384.57): C, 65.59; H, 9.44. Found: C, 65.53; H, 9.27.

30a

R_f 0.1 (CH–EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 2 H), 4.19 (ddd, *J* = 9.9, 8.8, 5.4 Hz, 1 H), 4.11–3.98 (m, 3 H), 3.68 (m_c, 1 H), 2.81 (tt, *J* = 6.9 Hz, 1 H), 1.80 (dddd, *J* = 14.6, 8.8, 5.9, 3.0 Hz, 1 H), 1.59 (ddt, *J* = 14.3, 9.6, 4.9 Hz, 1 H), 1.65–1.05 (m, 22 H), 0.82 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 150.9, 129.6, 123.9, 67.9, 67.0, 39.9, 36.7, 34.4, 24.9, 23.7, 18.9, 14.1.

HRMS: *m*/*z* calcd for $C_{21}H_{36}O_4S$: 384.2334; found: 384.2336.

Toluene-4-sulfonic Acid (2-Hydroxyhexyl) Ester (29b)[37]

Adapting the same procedure, starting with Cp_2TiCl_2 (25 mg, 0.10 mmol), Zn (98 mg, 1.50 mmol), coll·HCl (236 mg, 1.50 mmol) and **7** (0.45 mL, 4.8 mmol), and **28b**[30] (270 mg, 1.0 mmol), a mixture of **29b** and **30b** (169 mg, 66%, 92:8 mixture of the regioisomers) was obtained after SiO_2 flash chromatography (14% EtOAc, 86% CH).

Acknowledgment

We thank the *Deutsche Forschungsgemeinschaft* (Ga 619/2-1, Gerhard Hess-Programm) and the *Fonds der Chemischen Industrie* (*Dozentenstipendium* to A. G. and *Sachbeihilfen*) for continued financial support of our work.

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