Emergence of a Novel Catalytic Radical Reaction: Titanocene-Catalyzed Reductive Opening of Epoxides

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Abstract: The preparatively important catalytic opening of epoxides to β-titanoxy radicals via single-electron transfer (SET) is described. These radicals can be reduced to alcohols or participate in C−C bond-forming reactions. A key step in the catalytic cycle is the conceptually novel protonation of titanium−oxygen and −carbon bonds. Our method combines the advantages of radical reactions, e.g., high functional group tolerance and stability of radicals under protic conditions, with the ability of organometallic complexes to determine the course of transformations in reagent-controlled reactions.

Introduction

The development of efficient chain reactions has led to numerous free radical transformations since the beginning of the 1980s.[1] The factors affecting the control of stereo- and chemoselectivity of these transformations are by now well-understood.[2] However, once the free radical is generated, usually from halides or organomercury compouds, subsequent transformations are substrate controlled, and selectivities cannot readily be influenced or overruled by reagents. An interesting alternative access to radicals is the formation of radical anions via single-electron transfer (SET) from low-valent metal complexes.[3] Here, the course of the reaction is determined by the steric and electronic influences of the metal and its ligands. When this influence overrules the selectivity imposed by the substrate, a reagent-controlled reaction is obtained. Although this concept is well established in organometallic reactions, a realization of this concept in radical chemistry has remained elusive. Radical precursors are usually carbonyl compounds such as aldehydes or ketones.[4] The resulting anions can be dimerized (pinacol coupling) or can add inter- or intramolecularly to double bonds. The development of highly active electron donor reagents, e.g., SmI_2, has led to intense activity in this field recently.[5] However, more traditional and cost-effective reagents, e.g., titanium(III) complexes, can often be used with similar efficiency.[6] Attractive substrates for reductive opening via SET are epoxides,[7] which are readily available from suitable precursors such as olefins or carbonyl compounds. The resulting β-alkoxy radicals are interesting synthetic intermediates. However, the β-metaloxy functionality requires that the subsequent radical reaction is faster than trapping with a second equivalent of electron-transfer reagent. The β-metaloxy metal species resulting from this trapping undergoes rapid elimination, resulting in overall deoxygenation of the epoxide. Thus, the sterically undemanding, highly active electron donor SmI_2 is not suitable for this reaction but leads to deoxygenation.[8] Excellent stoichiometric reagents for the reductive opening without deoxygenation in most cases are titanocene(III) reagents accessible from titanocene dichloride by simple in situ reduction with zinc powder.[7] Intra- and intermolecular C−C bond-forming reactions as well as reduction to alcohols with hydrogen atom donors are possible. Although very good results can be obtained in this fashion, a disadvantage of this reaction is the inevitable use of stoichiometric amounts of titanocene dichloride. Clearly, it is more desirable to use only catalytic amounts of the complex, especially when titanocenes are to be used for the improvement of reagent control, that have to be synthesized in a number of steps.[9]

An intriguing recent development in this respect is the emergence of catalytic redox reactions from stoichiometric processes. The general idea is to remove oxygen-containing products of the stoichiometric transformations from active metal species while regenerating a metal chloride by silylation with Me_3SiCl. In situ reduction to the redox-active low-valent metal halide with a suitable, readily available stoichiometric reductant, usually a metal powder, closes the catalytic cycle. The first

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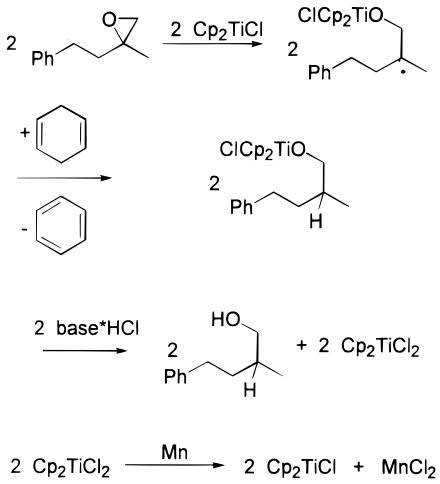

Figure 1. Anticipated mechanism for reductive opening of epoxides.

example of the successful realization of this concept is Fürstner's McMurry coupling, catalytic in titanium.[10] The stoichiometric reagent combination applied was zinc powder and Me_3SiCl. Even more useful is the Nozaki−Hiyama coupling catalytic in chromium developed by the same group.[11] Subsequently, similar processes for catalytic pinacol couplings[12] and various other transformations[13] have been devised by other groups. However, limitations exist. First, groups sensitive to the highly reactive Me_3SiCl, e.g., epoxides, alcohols, and certain aldehydes, are not tolerated. Second, readily reducible groups can be activated by Me_3SiCl toward electron transfer, e.g., aromatic aldehydes and ketones in pinacol couplings.[14] Third, although the high oxophilicity of Me_3SiCl allows efficent trapping of metal oxo species, straightforward conversion of less polar carbon−metal bonds to alkyl silanes and metal chlorides is, for the same reason, precluded. Also, recycling of $(Me_3Si)_2O$, the byproduct of the reaction after hydrolysis, is hard to achieve. Thus, stoichiometric amounts of waste are inevitably produced. This is especially disadvantageous for applications on a large scale.

In this full paper, we wish to disclose our results on the development of a conceptually novel titanocene-catalyzed reductive opening of epoxides,[15] exploiting the fact that radicals are normally stable under protic conditions[1a,2c,16] and avoiding the above-mentioned disadvantages of silylation. The resulting transformation is a rare example of a transition-metal-catalyzed radical reaction with reagent control.[12c,d,15,16]

Results and Discussion

With the above-mentioned points in mind, we decided to investigate protonation of titanium−oxygen and −carbon bonds as a means to achieve catalytic turnover. The anticipated mechanism for the catalytic reaction is depicted in Figure 1.

Several requirements for efficient turnover become apparent. (1) The acid employed must be weak enough not to open the epoxide but must be strong enough to protonate titanium−oxygen bonds. (2) The acid must not oxidize the metal powder or any catalytically active titanium(III) species. (3) The resulting base must not coordinate to and deactivate any titanium species in the catalytic cycle. (4) The metal powder must reduce titanocene dichloride fast and efficiently to the redox-active titanium(III) species. (5) The resulting alcohols should not deactivate any titanium species in the catalytic cycle. (6) The Lewis acid formed during the reduction of titanocene dichloride must not interfere with the catalytic cycle.

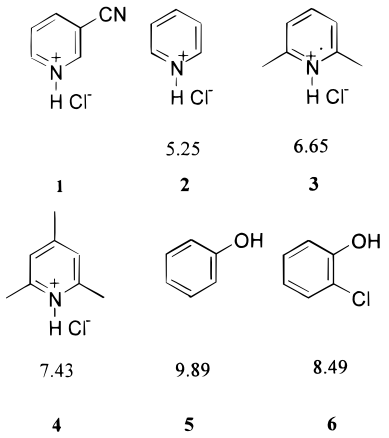

Figure 2. Acids used in this study.

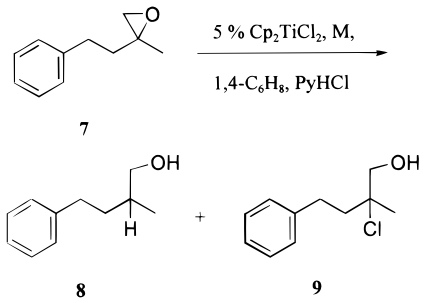

Figure 3. Reductive opening of epoxide **7**.

To achieve protonation of the metal−oxygen bond, the acidity of the proton donor must be higher than that of typical alcohols To ensure complete protonation, the pK_a difference with typical alcohols (MeOH = 15.5)[17] should be at least 3. The acid should not have a pK_a lower than that of pyridine hydrochloride (5.25), which opens epoxides to chlorohydrins as a mild acid in chloroform.[18] A resonable window for the pK_a is thus 5.25−12.5. See Figure 2 for the acids tested in this investigation.

Optimization of the Reaction. We decided to optimize the reductive opening of epoxide **7** in the presence of 1,4-cyclohexadiene as hydrogen atom donor, a stoichiometric reductant, and the indicated acid as outlined in Figure 3. Table 1 summarizes the results of our studies.

Expectedly, the strong acid **1** gave almost exclusively **9** by opening of the epoxide via an S_N1 mechanism. Pyridine hydrochloride **2** and 2,6-lutidine hydrochloride **3** yielded some of the desired product **8** with Zn as reductant. However, chlorohydrin **9** could also be detected in the crude reaction mixture. Thus, the S_N1 pathway was still operating to a significant amount. 2,4,6-Collidine hydrochloride **4** with zinc powder as reductant lead to a distinct improvement. The amount

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Table 1. Optimization of the Reductive Opening of **7**

acid	metal	time/h	**7**:**8**:**9**[a]
1	Zn	16	2:0:98
1	Mn	16	1.5:0.5:98
2	Zn	35	28:32:26
2	Mn	16	50:4:46
3	Zn	36	30:43:22[b]
3	Mn	16	2:92:6[c]
4	Zn	36	15:73:12[d]
4	Mn	16	2:96:2[e]
5	Zn	16	77:13:10
5	Mn	16	82:12:6
6	Zn	16	82:6:12
6	Mn	16	84:6:10

[a] Determined by GC analysis and ^{1}H NMR of the crude mixture. [b] 5% of a product containing an aldehyde group are also formed. [c] 85% isolated yield. [d] 71% isolated yield. [e] 88% isolated yield.

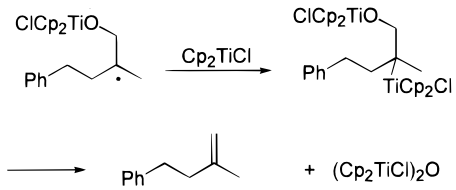

Figure 4. Deoxygenation of epoxides without 1,4-cyclohexadiene.

of chlorohydrin was reduced and conversion significantly improved. With manganese as reductant and **4**, hardly any **9** was formed. **8** could be isolated in 88% yield. The difference between Mn and Zn was even more pronounced in the case of 2,6-lutidine hydrochloride **3**. Only 6% of **9** and 92% of **8** could be detected in the crude mixture. The isolated yield of **8** was 85%. Presumably, $ZnCl_2$, formed during the reduction of Cp_2TiCl_2, complexed and slowly opened the epoxide in addition to protic opening. $MnCl_2$ was not Lewis-acidic enough to initiate this side reaction. Without 1,4-cyclohexadiene as hydrogen atom donor, a complex mixture of products was obtained, consisting mainly of the deoxygenated product and **9**. Deoxygenation occurs via trapping of the radical with titanium(III) and subsequent elimination of titanium-oxo species as shown in Figure 4.

Thus, the combination of **4**, manganese dust, and 1,4-cyclohexadiene constitutes an ideal combination for the titanocene-catalyzed reductive opening of epoxides. Although **3** also constitutes an excellent acid, **4** was preferred since it is a distinctly less hygroscopic compound and is thus more convenient to handle.

Phenols **5** and **6** did not lead to conversions greater than 20% after 16 h. It seems that the formed titanocene(IV) phenoxides cannot be efficiently reduced to redox-active titanocene(III) derivates. Similar observations have been made in studies concerning the reduction of titanocene(IV) derivatives and stoichiometric titanocene induced pinacol couplings with triflate counterions.[6d,19] An economically attractive feature of our conditions was that both collidine and lutidine could be easily recovered after the reaction by simple acid−base extraction.

Although the reaction takes about 16 h to go to completion with **4**, the initial rate of formation of **8** is high. Conversion of **7** to **8** is 65%, 72%, 80%, and 85% after 0.5, 1, 2, and 3 h, respectively. This decrease in reaction rate seems to be due to the lowering of the concentration of **7**. Addition of a second equivalent of **4**, **7**, and Mn results in a catalytic system with activity similar to that observed at the beginning of the reaction.

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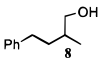
Table 2. Influence of Substitution on Regioselectivity of Epoxide Opening

Compound	t/h	product	yield/ %
 **10**	16	 **11**	81
 **7**	16	 **8**	88
 **12** *a*	30	 **13**	83
 **14**	18	 **15**	47[b]
 **14**	18	 **15**	56[c]

[a] Substrate was a mixture of cis and trans isomers. [b] Formed as 94:6 mixture of 1- and 2-dodecanol. [c] Two equivalents of collidine added to the mixture.

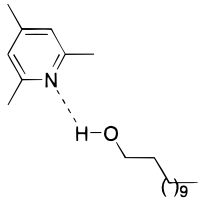


Figure 5. Catalyst acitivation by binding of 1-dodecanol.

Scope and Limitation of the Reductive Opening. With this efficient system in hand, we turned our attention to the scope of substrates. Various differently substituted epoxides containing a number of functional groups were tested as substrates.

As in the stoichiometric transformation,[7] 1,1-disubstituted epoxides, e.g., **7**, are opened to give the less substituted alcohols via formation of the higher substituted radical (Table 2). The same holds true for trisubstituted epoxide **10**. 1,2-Disubstited epoxides, e.g., the cis and trans mixture of cyclododecane oxide **12**, yield the corresponding alcohols cleanly. A more difficult example is the reaction of 1-dodecene oxide **14**. Under the standard conditions, conversion to 1- and 2-dodecanol of about only 50% could be achieved, even after prolonged reaction times. Also, 22% of deoxygenation was observed. It seems that the sterically relatively unhindered radical can be intercepted by a second equivalent of titanium(III) reagent, resulting in reductive elimination of a titanium-oxo species. This was, however, the only case where deoxygenation was observed. We found that addition of 2 equiv of collidine to the mixture significantly accelerated the reaction and led to quantitative conversion to products after 19 h. The reason for acceleration of the reaction in the presence of excess collidine could be removal of 1- or 2-dodecanol or water by means of hydrogen bonding from some titanium species in the catalytic cycle. Thus, the active form of the catalyst can be regenerated by binding of dodecanol, as shown in Figure 5, and the reaction is allowed to proceed to completion smoothly.

Dodecanol was isolated in 55% yield as a 94:6 mixture of 1- and 2-dodecanol. This ratio is somewhat higher than the 88:12 ratio obtained in the stoichiometric system.[7] Two different

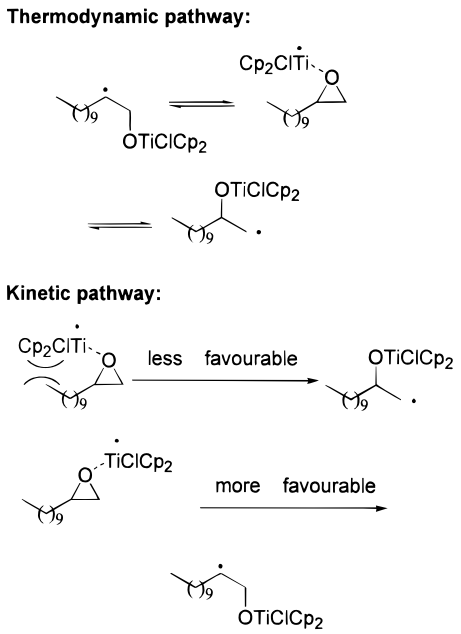


Figure 6. Possible pathways leading to the formation of 2-dodecanol.

mechanisms for the formation of 2-dodecanol are shown in Figure 6.

The thermodynamic path seems to be less likely since formation of the less substituted radical was not observed in any other example. This should have been the case, especially for the trisubstituted epoxide **10**. Also, the ratio of products should depend on the radical trap used if the radicals were equilibrating. This was not observed in addition reactions to acrylates, as will be discussed later. The same 94:6 ratio of products was obtained. Therefore, it seems that, after complexation of the epoxide and electron transfer, the steric interaction of the titanocene and the substituent of the epoxide is responsible for the regioselectivity of the opening. This results in the kinetic pathway described in Figure 6. 1- and 2-dodecanol formed during the course of the reaction seem to complex the catalyst. Therefore, its steric demand increases, and the selctivity of the reaction is improved.

From a synthetic point of view, our method offers a simple and convenient way of catalytically opening epoxides in a manner opposite to that of S_N2 reactions.[20]

Chemoselectivity of the Catalytic Opening. Since the stoichiometric parent system is highly tolerant to sensitive functionality,[7] achieving the same kind of tolerance in catalytic reactions requires an exceptionally mild and selective stoichiometric reductive system with respect to chemoselectivity in electron transfer. Table 3 summarizes the results of our investigations regarding this important aspect of the reaction. Esters **24** and **27**, ketones, and even aromatic ketones (note entries 8 and 9 for two competition experiments) did not interfere.[14] Tosylates **18** and **19** and chlorides **26** and **27**, which are reduced using samarium diiodide,[8a,21] remained intact without any sign of decomposition. It seems that manganese selectively reduces titanocene dichloride[19c] to the catalytically active electron-transfer reagent.

Collidine formed during the course of the reaction by protonation of the titanium oxygen bond neither interfered with the catalytic cycle by complexation of titanium species nor decomposed base sensitive substrates or products of the reaction. Tosylates **18** and **19** did not yield any products of elimination. Also, protecting groups that are prone to migration under basic conditions such as pivalate or silyl ethers did not migrate at all, even when kinetically favorable. Remote unactived double bonds as in **16** or **17**, being in principle susceptibe to attack by radicals, were not affected under the reaction conditions. It seems that hydrogen atom abstraction from 1,4 cyclohexadiene was faster than addition to the double bond. The simple access of epoxides via sulfur ylide chemistry[22] of suitable unsaturated ketones or metal catalyzed epoxidations[23] allows free choice of the positioning of the alcohol after reductive opening. Hydroboration allows formation of the alcohol only at the less substituted, sterically less demanding double bond.[25] Thus, 2-methyl-1,11-dodecadiene would yield predominatly the alcohol resulting from attack at the monosubstituted double bond and not alcohol **17** obtained by our method. A number of functional groups not compatible with boranes, e.g., alcohols, double bonds, and ketones, are readily tolerated.[25]

Table 3. Functional Groups Tolerated under the Optimized Conditions

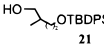
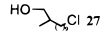
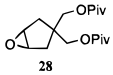
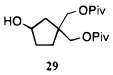
entry	substrate	time h	product	yield %
1	 **16**	16	 **17**	72
2	 **18**	18	 **19**	58
3	 **20**	18	 **21**	86
4	 **22**	12	 **23**	67
5	 **24**	18	 **25**	69
6	 **26**	18	 **27**	74
7	 **28**	16	 **29**	67
8	**7**	60	**8**	75
				95
9	**7**	48	**8**	82
	PhCOMe		PhCOMe	93

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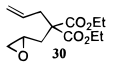
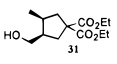
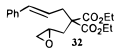
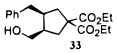
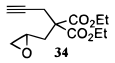
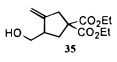
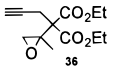
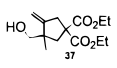
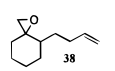
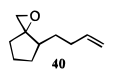
Table 4. Cyclization Studies under Optimized Conditions

entry	substrate	t/h	product	yield %
1	 **30**	30	 **31**	78[a]
2	 **32**	30	 **33**	55[b]
3	 **34**	24	 **35**	73[c]
4	 **36**	48	 **37**	70
5	 **38**	61	 **39**	77[d]
6	 **40**	61	 **41**	66[e]

[a] cis:trans 88:12. [b] cis:trans 86:14. [c] As 91:9 mixture of 5-exo and 6-exo products. [d] As 52:48 mixture of epimers. [e] As 98:2 mixture of epimers.

Cyclization Reactions with Protonation of Titanium Carbon Bonds. Radical cyclizations are among the most powerful and versatile methods for the construction of mono- and polycyclic systems. A fruitful interplay between synthetic and physical organic chemistry has allowed a deep understanding of this transformation. An especially important type of reaction is the formation of five-membered rings via 5-exo cyclization. The application of this methodology has culminated in the elegant total synthesis of a number of natural products.[26] Suitably unsaturated epoxides constitute interesting substrates for this important reaction.

In the cases investigated here, the radical formed after cyclization is trapped with the redox-active titanocene(III) derivative to give an alkyl or vinyl titanocene(IV) chloride, as depicted in Figure 7.

Both titanium−oxygen and −carbon bonds are protonated by collidine hydrochloride to regenerate titanocene dichloride and liberate the cyclization products. Thus, no hydrogen atom donor, i.e., 1,4-cyclohexadiene, is necessary in these reactions, and both additional protons present in the product of the reaction originate from HCl. This efficient way of conducting the reaction becomes possible because the intermediate radicals formed by reductive opening of the epoxide are stable toward protic conditions. The final anionic products after reductive trapping with titanocene(III) chloride are acid sensitive.

Our approach reduces the amount of titanium complex needed by a factor of 40. Effectively, titanocene dichloride is replaced by collidine hydrochloride, except for the amount needed for catalysis. Compared to cyclization reactions conducted in the presence of stannanes, no toxic and sensitive reagents are needed, and no toxic side-products are generated. Additionally,

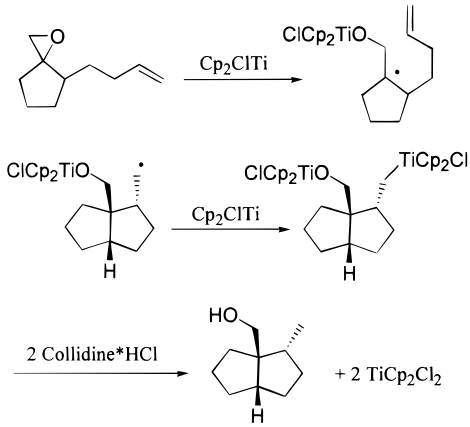


Figure 7. Mechanism of cyclization reactions.

the synthetically valuable alcohol function is obtained in the product. Table 4 summarizes the results of our investigations

Diastereoselectivities for the formation of five-membered rings are in the usual range for radical cyclizations.[27] In accordance with the Beckwith-Houck model,[28] the cis-disubstituted products are formed preferentially. In the case of substrate **34**, the 5-exo and 6-exo products were formed as a 91:9 mixture, reflecting the regioselectivity of epoxide opening. **36** yields **37** as the sole product. The allyl alcohol moiety in **35** and **36** allows further synthetic elaboration of the products.

In the cyclization reaction yielding the bicyclic product **39**, stereoselectivitiy is in the same range as in the stoichiometric reaction.[7] However, in the case of **41**, diastereoselectivity is significantly higher and almost complete (98:2) under our conditions. A 90:10 ratio is obtained with the parent system.[7] It seems that binding of some alcohol present in the reaction mixture by titanium(III) increases the steric demand of the catalyst enough to allow better control of selectivity. The five-membered rings in **39** and **41** are exclusively cis-fused.[7] Thus, the diastereomeric mixtures are epimers at the methyl group bearing carbon atoms, and so only two of four possible diastereoisomers are formed. Our cyclization conditions are being tested in the synthesis of natural products containing five-membered rings in our laboratories.

Intermolecular Addition Reactions to α,*β*-Unsaturated Carbonyl Compounds. An important reaction in radical chemistry is the intermolecular addition to electron-deficient activated olefins. Our method offers a convenient catalytic access to *δ*-hydroxyesters, *δ*-lactones, and *δ*-hydroxynitriles. *δ*-Lactones are ubiquitous in nature. Hydroxyesters and nitriles are crucial intermediates in the synthesis of important classes of compounds, e.g., amino alcohols. See Figure 8 for details.

The mechanism of the catalytic reaction is depicted in Figure 9. After addition of the *β*-titanoxy radical to the double bond, an enol radical is formed that is trapped by titanium(III) to yield an enolate. Both titanium−oxygen bonds are protonated to liberate the product.

With Mn as reductant, yields were low, even after prolonged reaction times. We reasoned that this was due to complexation of titanium by the product, as indicated in Figure 10.

There are two ways of avoiding this problem by binding of the substrate. A stronger Lewis acid, e.g., $ZnCl_2$, could replace

(26) (a) Giese, B.; Kopping, B.; Göbel, T.; Thoma G.; Dickhaut, J.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, p 301. (b) Bazukis, P.; Campos, O. O. S.; Bazukis, M. L. F. *J. Org. Chem*. **1976**, *41*, 3261. (c) Büchi, G.; Wüest, H. *J. Org. Chem*. **1979**, *44*, 546. (d) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (e) Curran, D. P.; Chen. M.-H. *Tetrahedron Lett*. **1985**, *26*, 4991.

(27) (a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem*. **1983**, *36*, 545. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. (c) A. L. J. Beckwith, A. L. H.; Schiesser, C. H. *Tetrahedron Lett*. **1985**, *26*, 373, (d) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem*. **1987**, *52*, 959. (e) RajanBabu, T. V. *Acc. Chem. Res*. **1991**, *24*, 139.

(28) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.

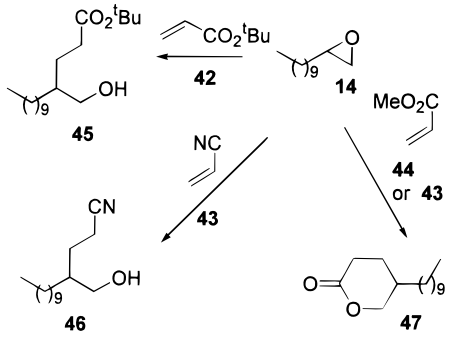


Figure 8. Addition reactions to α,β-unsaturated carbonyl compounds.

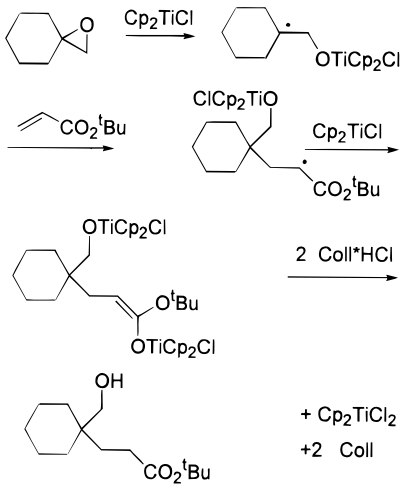


Figure 9. Mechanism of addition reactions to α,β-unsaturated carbonyl compounds.

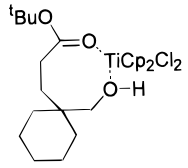


Figure 10. Catalyst deactivation by product inhibition.

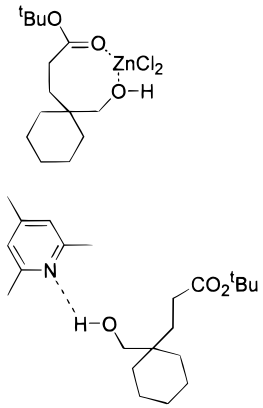


Figure 11. Restoring catalyst activity by binding of the products.

titanium to liberate the active precatalyst. A suitable hydrogen bond acceptor should bind the alcohol to reactivate the catalyst acting as a supramolecular cofactor.[28] See Figure 11 for an illustration of this concept.

Table 5 summarizes the results of our investigations of addition reactions with **14** in the presence of Lewis acids.

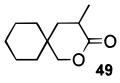
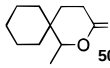
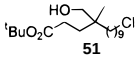
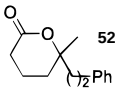
With $ZnCl_2$ as additive, catalyst activity increased dramatically. Although less pronounced, the same effect was observed

Table 5. Optimization of Addition Reactions to α,β-unsaturated Carbonyl Compounds

entry	acceptor	time/h	product	yield/%
1	**42**[a]	66	**45**	68
2	**42**[b]	16	**45**	81
3	**42**[c]	44	**45**	73
4	**43**	16	**47**	83
5	**43**[c]	43	**47**	73
6	**43**[b]	12	**47**	88
7	**43**[a,b]	14	**46**	80
8	**44**[a]	65	**47**	21
9	**44**[b]	16	**47**	72

[a] Mn as reductant. [b] One equivalent of $ZnCl_2$. [c] One mole % catalyst.

Table 6. Addition Reactions under Optimized Conditions

substrate	t/h	product	yield/%
 **48**	24	 **49**	86
10	16	 **50**	78
26	12	 **51**	91
7[a,b]	10	 **52**	65

[a] No $ZnCl_2$ added. [b] **43** as acceptor, 12 h of reflux to complete reaction.

with Zn as reductant. Here, $ZnCl_2$ was formed during reduction of Cp_2TiCl_2. With acrylonitrile as radical acceptor, lactone **47** was obtained as the sole product of the reaction after aqueous workup. Hydroxynitrile was formed in 85% yield after 3 h. $ZnCl_2$-induced cyclization then resulted in formation of **47** in 80% yield after 16 h. Activation of the catalyst by $ZnCl_2$ enabled the use of 1 mol % of catalyst without significant reduction in isolated yields. Compared to the stoichiometric system,[7] the amount of titanium is reduced by a factor of 200!

Interestingly, with Mn and $ZnCl_2$, only hydroxynitrile **46** was formed after 8 h in high yield. $MnCl_2$ formed during reduction of Cp_2TiCl_2 seemed to complex and protect the nitrile group from nucleophilic attack. $ZnCl_2$ should be binding the hydroxy group.

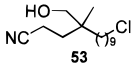
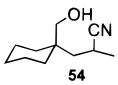
Table 6 summarizes the results of some reactions performed under the optimized conditions.

As expected, a number of functional groups is tolerated, and higher substituted epoxides react without problems to give the desired products in good yields. To achieve sterically more demanding additions to the nitrile group, the reaction mixture had to be refluxed.

Binding the reaction products by a carefully chosen Lewis acid thus allows a highly efficient entry to δ-lactones, δ-hydroxyester, and δ-hydroxynitriles via radicals. These transformations amply demonstrate the usefulness of our concept to combine the advantages of organometallic and radical chemistry.

Hydrogen bonding also constituted a convenient means to achieve catalyst activation. However, if the hydrogen bond acceptor was a powerful ligand, e.g., DMPU, deactivation was observed. 2,4,6-Collidine proved to be a suitable base. Obvi-

Table 7. Collidine as Supramolecular Cofactor in Addition Reactions

substrate	t/h	product	yield/ %
14	16	**46**	81
26	16	 **53**	88
 **46**	30	 **54**	83

ously, complexation of a titanium species in the catalytic cycle was not occurring.

Table 7 summarizes the results of the reactions run under buffered protic conditions. Addition to acrylic acid methyl ester proceeds smoothly to give **47** in good yield. Thus, collidine acts as a supramolecular cofactor to restore catalyst activity via hydrogen bonding. To the best of our knowledge, the concept of restoring catalyst activity via hydrogen bonding is without precedent in the literature.

In summary, we have demonstrated that 2,4,6-collidine or 2,6-lutidine hydrochloride and manganese constitute an exceptionally mild stoichiometric system for titanocene-catalyzed highly regioselective reductive opening reactions of epoxides. Our catalytic conditions feature excellent chemoselectivity, should allow for applications of this chemistry on a large scale, and broaden the usefullness of epoxides as valuable intermediates in synthesis even further. Cyclization reactions can proceed with exceptional diastereoselectivity and allow simple access to structures important for natural product synthesis. Intermolecular additions to α,β-unsaturated carbonyl compounds yield the desired products in high yields, even with 1 mol % of catalyst.

Experimental Section:

General Procedures. All reactions were performed in oven-dried (100 °C) glassware under N_2. THF was freshly distilled from $LiAlH_4$. CH_2Cl_2 was freshly distilled from CaH_2. Products were purified by flash chromatography[29] on Merck silica gel 50 (eluents given in brackets, MTBE refers to *tert*-butyl methyl ether 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 or by GC analysis: ^{1}H, tetramethylsilane (0.00 ppm) in the indicated solvent, benzene-d_5 (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 $CDCl_3$ (77.00 ppm) and benzene-d_6 (128.00 ppm) as internal standards in the same solvent; Bruker AMX 300 and Varian XR 200; integrals in accord with assignments, coupling constants are measured in hertz. Combustion analyses were done by F. Hambloch, Institute of Organic Chemistry, University of Göttingen. IR spectra were obtained using a Perkin-Elmer 1600 series FTIR as KBr pellets or as neat films on NaCl plates.

2-Chloro-2-methyl-4-phenylbutan-2-ol 9. To a suspension of **1** (843 mg, 6.0 mmol) and zinc chloride (307 mg, 2.3 mmol) in THF (15 mL) was added **7** (243 mg, 1.5 mmol). The resulting mixture was stirred for 12 h at room temperature. After addition of MTBE (50 mL), the mixture was extracted with 2 N HCl (2 × 10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). After drying ($MgSO_4$) and evaporation of the solvents, the crude material was purified by silica gel chromatography (10% MTBE, 90% PE) to give 238 mg of **9** as an 84:16 mixture of 2-chloro-2-methyl-4-phenylbutan-2-ol **9a** and 1-chloro-2-methyl-4-phenylbutan-1-ol **9b** (80%).

R_f (10% MTBE, 90% PE): 0.15. ^{1}H NMR (300 MHz, $CDCl_3$): **9a** δ = 7.32−7.20 (m, CH_{Ar}, 5H), AB-system (δ_A = 3.69, δ_B = 3.63, J_{AB} = 11.8 Hz, additionally split by ^3J = 6.8 Hz, CH_2OH), AB-system (δ_A = 2.85, δ_B = 2.77, J_{AB} = 13.6 Hz, additionally split by ^3J_A, ^3J_A = 5.9 Hz, ^3J_B, ^3J_B = 5.6 Hz, CH_2Ar), 2.21−2.01 (m, CHCH_2CH_2Ar), 1.97 (t, ^3J = 6.9 Hz, ^3J = 6.9 Hz, OH), 1.61 (s, CH_3); **9a** (only clearly separated signals) δ = AB-system (δ_A = 3.57, δ_B = 3.55, J_{AB} = 9.8 Hz, CH_2Cl), 2.74 (m, CH_2Ar), 1.35 (s, CH_3). ^{13}C NMR (50 MHz,-$CDCl_3$): **9a** δ = 141.35, 128.44, 128.31, 126.00, 75.21, 71.05, 42.33, 30.82, 26.14; **9b** δ = 141.88, 128.24, 125.92, 71.94, 54.20, 41.14, 30.13, 24.40. IR (film): 3405, 3035, 2935, 2925, 2865, 1600, 1495, 1455, 1380, 1170, 1060 cm^{-1}. Anal. Calcd for $C_{11}H_{15}ClO$ (198.7): C, 66.50; H, 7.61. Found: C, 66.22; H, 7.76.

2-Methyl-4-phenylbutan-1-ol 8[30] **(Table 1, Entry 6).** To a suspension of **3** (215 mg, 1.5 mmol) in THF (10 mL) was added epoxide **7**[31] (0.165 mL, 1.0 mmol), 1,4-cyclohexadiene (0.41 mL, 4.3 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), and manganese (82 mg, 1.5 mmol). After the mixture was stirred for 16 h, excess manganese was decanted off and MTBE (50 mL) was added. The organic layer was washed with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL) and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (25% MTBE, 75% PE) to give 140 mg of **7** (85%).

General Procedure 1. Reductive opening of epoxides in the presence of **4**.

2-Methyl-4-phenylbutan-1-ol 8 (Table 1, Entry 8). To a suspension of **4** (236 mg, 1.50 mmol) in THF (10 mL) was added epoxide **7** (165 μL, 1.00 mmol), 1,4-cyclohexadiene (0.410 mL, 4.3 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), and manganese (82 mg, 1.50 mmol). After the mixture was stirred for 16 h, excess manganese was decanted off, and MTBE (50 mL) was added. The organic layer was washed with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL) and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (25% MTBE, 75% PE) to give 144 mg of **8** (88%).

1-Cyclohexylethanol 11.[7] According to general procedure 1, **4** (472 mg, 3.0 mmol), **10**[32] (0.280 mL, 2.0 mmol), 1,4-cyclohexadiene (0.85 mL, 8.50 mmol), titanocene dichloride (25.0 mg, 0.10 mmol), and manganese (164 mg, 3.0 mmol) were reacted for 16 h. After silica gel chromatography (25% MTBE, 75% PE), 208 mg of **11** was obtained (81%).

Cyclododecanol 13. According to general procedure 1, **4** (236 mg, 1.5 mmol), **12** (182 mg, 1.0 mmol), 1,4-cyclohexadiene (0.41 mL, 4.3 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), and manganese (60 mg, 1.1 mmol) were reacted for 30 h. After silica gel chromatography (25% MTBE, 75% PE), 153 mg of **13** was obtained (83%).

1-Dodecanol 15 (Table 2, Entry 4). According to general procedure 1, **4** (236 mg, 1.5 mmol), **14** (0.220 mL, 1.0 mmol), 1,4-cyclohexadiene (0.41 mL, 4.3 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), and manganese (60 mg, 1.1 mmol) were reacted for 30 h. After silica gel chromatography (25% MTBE, 75% PE), 86 mg of **13** was obtained (47%) as a 94:6 mixture of 1- and 2-dodecanol.

1-Dodecanol 15, (Table 2, Entry 5). According to general procedure 1, **4** (236 mg, 1.5 mmol), **14** (0.220 mL, 1.0 mmol), 1,4-cyclohexadiene (0.41 mL, 4.3 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), 2,4,6-collidine (0.265 mL, 2.0 mmol), and manganese (60 mg, 1.1 mmol) were reacted for 30 h. After silica gel chromatography (25% MTBE, 75% PE), 104 mg of **13** was obtained (55%) as a 94:6 mixture of 1- and 2-dodecanol.

General Procedure 2. Addition of trimethylsulfoxonium ylide to ketones.

1,2-Epoxy-2-methyldodec-11-ene 16. To a suspension of trimethylsulfoxonium iodide (1.54 g, 7.0 mmol) in THF (50 mL) was added sodium hydride (144 mg, 6.0 mmol), and the mixture was stirred for

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(30) Namy, J. L.; Boireau, G.; Abenhaim, D. *Bull. Soc. Chim. Fr.* **1971**, 3191.

(31) Charlton, J. J.; Williams, G. J.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 1271.

(32) Mousseron, M.; Jacquier, R.; Mousseron-Canet, M.; Zagdoun, R. *Bull. Soc. Chim. Fr.* **1952**, 1042.

30 min at room temperature. After addition of dodec-11-en-2-one[33] (910 mg, 5.0 mmol), stirring was continued for 16 h. The mixture was poured into MTBE (50 mL), washed with H_2O (2 × 50 mL), and dried ($MgSO_4$). After evaporation of the volatiles, the crude product was purified by chromatography on silica gel (5% MTBE, 95% PE) to give 522 mg of **16** (53%).

R_f (5% MTBE, 95% PE): 0.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (ddt, ^3J = 17.0 Hz, ^3J = 10.2 Hz, ^3J = 6.8 Hz, CH_2CHCH_2), 4.99 (ddt, ^3J = 17.0 Hz, $^2J \approx {}^3J \approx$ 1.5 Hz, $CHCH^ZH^E$), 4.93 (dm, ^3J = 10.2 Hz, $CHCH^EH^Z$), AB-system (δ_A = 2.57, δ_B = 2.60, J_{AB} = 4.9 Hz, $COCH_2$), 2.04 (td, ^3J = 7.2 Hz, ^3J = 6.8 Hz, $CH_2CH_2CH_2$, 2H), 1.30−1.63 (m, 14H), 1.28 (s, $-CH_3$). ^{13}C NMR (50 MHz, benzene-d_6): δ = 139.18, 114.50, 56.13, 53.10, 37.02, 34.19, 30.03, 29.91, 29.79, 29.48, 29.30, 25.52, 21.03. IR (film): 3075, 3030, 2975, 2925, 2855, 2985, 1820, 1730, 1640, 1485, 1465, 1455, 1415, 1390, 1370, 1270, 1145, 1110, 1060, 995, 905, 800, 725, 705, 630 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O$ (196.3): C, 79.53; H, 12.32. Found: C, 79.28; H, 12.02.

Toluene-4-sulfonic Acid (10,11-Epoxy-10-methylundecyl) Ester 18. According to general procedure 2, toluenesulfonic acid (10-oxoundecenyl) ester[34] (1.80 g, 5.3 mmol), trimethylsulfoxonium iodide (1.54 g, 7.0 mmol), and sodium hydride (144 mg, 6.0 mmol) were reacted for 16 h. After silica gel chromatography (40% MTBE, 60% PE), 656 mg of **18** was obtained (34%).

R_f (40% MTBE, 60% PE): 0.37. ^{1}H NMR (300 MHz, $CDCl_3$): δ = AA′XX′-signal centered at δ = 7.34 and 7.78, 4.01 (t, $^3J \approx$ 6.6 Hz, 11′−H_2), AB-signal (δ_A = 2.57, δ_B = 2.60, $J_{AB} \approx$ 5.1 Hz, $COCH_2$), 2.45 (s, Ar-CH_3), 1.47−1.65 (m, 4H), 1.23−1.42 (m, 12H), 1.30 (s, CH_3). ^{13}C NMR (50 MHz, C_6D_6): δ = 144.1, 134.58, 129.78, 128.13, 70.32, 56.17, 53.14, 36.97, 29.94, 29.72, 29.59, 29.17, 29.09, 25.57, 25.45, 21.12, 21.05. IR (film): 3035, 2930, 2855, 1715, 1600, 1495, 1465, 1390, 1360, 1305, 1290, 1190, 1175, 1100, 955, 815, 665 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_4S$ (354.4): C, 64.37; H, 8.53. Found: C, 64.51; H, 8.80.

2,2-Dimethylpropionic Acid (10,11-Epoxy-10-methylundecyl) Ester 24. According to general procedure 2, 2,2-dimethyl-propionic acid (10-oxoundecenyl) ester (1.35 g, 5 mmol), trimethylsulfoxonium iodide (1.54 g, 7.0 mmol), and sodium hydride (144 mg, 6.0 mmol) were reacted for 13 h. After silica gel chromatography (20% MTBE, 80% PE), 840 mg of **24** was obtained (59%).

R_f (20% MTBE, 80% PE): 0.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (t, $^3J \approx$ 6.6 Hz, CH_2OPiv), AB-signal (δ_A = 2.57, δ_B = 2.60, $J_{AB} \approx$ 5.1 Hz, $COCH_2$), 1.47−1.63 (m, 4H), 1.28−1.40 (m, 12 H), 1.30 (s, CH_3), 1.19 s, $-C(CH_3)_3$. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.61 ($-C(O)OR$), 64.43, 57.03, 53.92, 38.74 ($-C(CH_3)_3$), 36.76, 29.65, 29.49, 29.42, 29.30, 29.21, 27.24 ($-C(CH_3)_3$), 25.92, 25.25, 20.93 (CH_3). IR (film): 3030, 2930, 2855, 1730, 1540, 1480, 1460, 1395, 1365, 1285, 1155, 1035, 940, 900, 800, 770 cm^{-1}. Anal. Calcd for $C_{17}H_{32}O_3$ (284.4): C, 71.79; H, 11.34. Found: C, 72.03; H, 11.33.

2-(9-Chlorononyl)-2-methyloxirane 26. According to general procedure 2, 11-chloro-2-undecanone (1.02 g, 5.0 mmol), trimethylsulfoxonium iodide (1.54 g, 7.0 mmol), and sodium hydride (144 mg, 6.0 mmol) were reacted for 13 h. After silica gel chromatography (8% MTBE, 92% PE), 853 mg of **26** was obtained (78%).

R_f (8% MTBE, 92% PE): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (t, $^3J \approx$ 6.8 Hz, CH_2Cl), AB-signal (δ_A = 2.60, δ_B = 2.56, $J_{AB} \approx$ 4.9 Hz, $COCH_2$), 1.76 (tt, $^3J \approx$ 7.2 Hz, 2H), 1.60−1.29 (m, 14 H), 1.30 (s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.17, 53.14, 37.02, 32.87, 30.00, 29.82, 29.42, 29.72, 29.15, 27.10, 25.52, 21.07 (CH_3). IR (film): 2930, 2855, 1465, 1390, 1310, 900, 800 cm^{-1}. Anal. Calcd for $C_{12}H_{23}ClO$ (218.8): C, 65.88; H, 10.60. Found: C, 66.09; H, 10.34.

2,2-Dimethylpropionic Acid 3-(2,2-Dimethylpropionyloxymethyl)-6-oxabicyclo[3.1.0]hex-3-yl Methyl Ester 28. To an ice-cooled solution of 2,2-dimethylpropionic acid 1-(2,2-dimethylpropionyloxymethyl)-cyclopent-3-enyl methyl ester (2.964 g, 10 mmol) in CH_2Cl_2 (50 mL) was added mCPBA (70%) (3.700 g, 15 mmol), and the mixture was stirred for 12 h. After washing with 2 N NaOH (20 mL), drying ($MgSO_4$), and evaporation of the solvent, the crude product is purified by silica gel chromatography (12% MTBE, 88% PE) to give 2.75 g of **28** as a colorless solid.

Mp: 39 °C. R_f (12% MTBE, 88% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.31 (s, CH_2OPiv, 2H), 3.80 (s, CH_2OPiv, 2H), 2.98 (s, $CHOCH$, 2H), 1.70 (d, $^2J \approx$ 14.7 Hz, 2H), 1.18 (d, $^2J \approx$ 14.7 Hz, 2H), 1.13 (s, $C(CH_3)_3$), 1.12 (s, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.31, 177.08, 68.14, 67.23, 57.52, 44.49, 38.88, 38.86, 33.93, 27.23. IR (KBr): 2975, 1730, 1480, 1395, 1365, 1285, 1165, 990 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_5$ (312.4): C, 65.36; H, 9.03. Found: C, 65.66; H, 9.13.

2-Methyldodec-11-en-1-ol 17. According to general procedure 1, **16** (182 mg, 0.93 mmol), **4** (219 mg, 1.40 mmol), titanocene dichloride (11.0 mg, 0.05 mmol), manganese (76.0 mg, 1.40 mmol), and 1,4-cyclohexadiene (0.420 mL, 4.3 mmol) were reacted for 16 h. After silica gel chromatography (30% MTBE, 70% PE), 132 mg of **17** was obtained (72%).

R_f (20% MTBE, 80% PE): 0.26. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (ddt, ^3J = 17.0 Hz, ^3J = 10.2 Hz, ^3J = 6.8 Hz, CH_2CHCH_2), 4.99 (ddt, ^3J = 17.0 Hz, $^2J \approx$ 2.1 Hz, ^4J = 1.5 Hz, $CHCH^ZH^E$), 4.93 (ddt, ^3J = 10.2 Hz, $^2J \approx$ 2.1 Hz, $^4J \approx$ 1.1 Hz, $CHCH^EH^Z$), AB-signal (δ_A = 3.42, δ_B = 3.51, $J_{AB} \approx$ 10.6 Hz, additionally split by ^3J = 5.7 Hz, ^3J = 6.8 Hz, $CHCH_2OH$), 2.04 (td, ^3J = 7.2 Hz, ^3J = 6.8 Hz, CH_2CHCH_2), 1.53−1.66 (m_c, $CHCH_2OH$), 1.49 (s,1-OH), 1.05−1.44 (m, 14H), 0.91 (d, ^3J = 6.4 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.19 (CH), 114.06 ($CHCH_2$), 68.35 (CH_2OH), 35.74, 33.81, 33.14, 29.92, 29.58, 29.49, 29.14, 29.03, 28.93, 26.96, 16.59 (CH_3). IR (film): 3335, 2925, 2860, 1640, 1465, 1035, 990, 910 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O$ (198.3): C, 78.72; H, 13.21. Found: C, 78.44; H, 13.47.

Toluene-4-sulfonic Acid (11-Hydroxy-10-methylundecyl) Ester 19. According to general procedure 1, **18** (300 mg, 0.85 mmol), **4** (189 mg, 1.20 mmol), titanocene dichloride (10.0 mg, 0.04 mmol), manganese (66.0 mg, 1.20 mmol), and 1,4-cyclohexadiene (0.360 mL, 4.25 mmol) were reacted for 16 h. After silica gel chromatography (60% MTBE, 40% PE), 176 mg of **19** was obtained (58%).

R_f (60% MTBE, 40% PE): 0.48. ^{1}H NMR (300 MHz, $CDCl_3$): δ = AA′XX′-signal centered at δ = 7.34 and 7.79, 4.01 (t, $^3J \approx$ 6.6 Hz, 11′-H_2), AB-signal (δ_A = 3.42, δ_B = 3.50, J_{AB} = 10.4 Hz, additionally split by $^3J \approx$ 5.9 Hz, $^3J \approx$ 6.6 Hz, CH_2OH), 2.45 (s, 4-CH_3), 1.57−1.67 (m_c, $CHCH_2OH$), 1.42 (s,OH), 1.06−1.41 (m, 14H), 0.91 (d, ^3J = 6.8 Hz, 2′-CH_3). ^{13}C NMR (APT-spectrum, 50 MHz, $CDCl_3$): δ = "−" 144.59, "−" 133.13, "+" 129.76, "+" 127.83, "−" 70.71, "−" 68.34, "+" 35.73, "−" 33.11, "−" 29.83, "−" 29.42, "−" 29.34, "−" 28.89, "−" 28.79, "−" 26.92, "−" 25.57, "−" 25.30, "+" 21.63 (Ar-CH_3), "+" 16.59 ($-CH_3$). IR (film): 3555, 3385, 2925, 2855, 1600, 1495, 1465, 1360, 1305, 1290, 1210, 1190, 1175, 1095, 1040, 945, 815, 770, 725, 665, 575, 555 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_4S$ (356.5): C, 64.01; H, 9.05. Found: C, 64.19; H, 9.18.

4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutan-1-ol 21. According to general procedure 1, **20**[35] (340 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.5. mg, 0.05 mmol), manganese (82 mg, 1.50 mmol), and 1,4-cyclohexadiene (0.425 mL, 4.3 mmol) were reacted for 16 h. After silica gel chromatography (25% MTBE, 75% PE), 294 mg of **21** was obtained (86%).

R_f (25% MTBE, 80% PE): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69−7.88 (m, CH_{Ar}, 4H), 7.44−7.36 (m, CH_{Ar}, 6H), 3.80−3.66 (m, CH_2OSi, 2H), AB-signal (δ_A = 3.53, δ_B = 3.47, $J_{AB} \approx$ 10.9 Hz, additionally split by ^3J = 5.3 Hz, ^3J = 6.4 Hz, $CHCH_2OH$), 1.86 (ddddq, ^3J = 6.4 Hz, $CHCH_2OH$), 1.69−1.44 (m, $SiOCH_2CH_2$, 2H), 1.05 (s, 9H), 0.90 (d, ^3J = 6.8 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.52, 133.37, 129.67, 127.67, 68.24, 62.48, 36.75, 33.88, 26.79, 19.11. IR (film): 3360, 3070, 2930, 2860, 1590, 1470, 1430, 1390, 1110, 1000 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_2Si$ (342.2): C, 73.63; H, 8.82. Found: C, 73.62; H, 9.09.

4-Benzyloxy-2-methylbutan-1-ol 23.[36] According to general procedure 1, **22**[37] (192 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.5. mg, 0.05 mmol), manganese (82 mg, 1.50 mmol),

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and 1,4-cyclohexadiene (0.425 mL, 4.3 mmol) were reacted for 16 h. After silica gel chromatography (30% MTBE, 70% PE), 130 mg of **23** was obtained (67%).

2,2-Dimethylpropinoic Acid (11-Hydroxy-10-methylundecyl) Ester 25. According to general procedure 1, **24** (279 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.0 mg, 0.05 mmol), manganese (82.0 mg, 1.50 mmol), and 1,4-cyclohexadiene (0.450 mL, 4.80 mmol) were reacted for 16 h. After silica gel chromatography (20% MTBE, 80% PE), 212 mg of **25** was obtained (69%).

R_f (20% MTBE, 80% PE): 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (t, J = 6.8 Hz, CH_2O), AB-signal (δ_A = 3.42, δ_B = 3.51, J_{AB} ≈ 10.6 Hz, additionally split by ^3J = 5.7 Hz, ^3J = 6.8 Hz, CHCH_2-OH), 1.61 (tt, ^3J = 6.8 Hz, ^3J = 6.8 Hz, CH_2CH$_2$OPiv), 1.51 (br s, 1.42 (s, OH), 1.28−1.36 (m, 14 H), 1.19 s, −C(CH_3)$_3$, 0.91 (d, ^3J = 6.8 Hz, 2′-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.64 −(C(O)-OR), 68.34, 64.45, 38.71 (−C(CH$_3$)$_3$), 35.74, 33.12, 29.88, 29.47, 29.19, 28.57, 27.19 (−C(*C*H$_3$)$_3$), 26.95, 26.90, 25.88, 16.59 (2′-CH$_3$). IR (film): 3395, 2960, 2930, 2855, 1730, 1540, 1480, 1460, 1400, 1365, 1285, 1155, 1035 cm^{-1}. Anal. Calcd for $C_{17}H_{34}O_3$ (286.5): C, 71.28; H, 11.96. Found: C, 71.02; H, 12.16.

11-Chloro-2-methylundecan-1-ol 27. According to general procedure 1, **26** (219 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.0 mg, 0.05 mmol), manganese (82.0 mg, 1.50 mmol), and 1,4-cyclohexadiene (0.450 mL, 4.80 mmol) were reacted for 16 h. After silica gel chromatography (20% MTBE, 80% PE), 163 mg of **27** was obtained (74%).

R_f (20% MTBE, 80% PE): 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (t, ^3J = 6.8 Hz, CH_2Cl), AB-signal (δ_A = 3.42, δ_B = 3.51, J_{AB} ≈ 10.4 Hz, additionally split by ^3J = 5.7 Hz, ^3J = 6.8 Hz, CH_2OH), 1.77 (tt, ^3J = 7.4 Hz, ^3J = 6.8 Hz, CH_2CH$_2$Cl), 1.61 (qddm, ^3J = 6.8 Hz, ^3J = 6.4 Hz, ^3J = 5.7 Hz, CHCH$_2$OH), 1.48 (br s, OH), 1.05−1.44 (m, 14H), 0.91 (d, ^3J = 6.8 Hz, CH_3). ^{13}C NMR (APT spectrum, 50 MHz, benzene-d_6): δ = "−" 68.1, "−" 44.99, "+" 36.14, "−" 33.61, "−" 32.89, "−" 30.37, "−" 29.96, "−" 29.85, "−" 29.22, "−" 27.46, "−" 27.14, "+" 16.90 (*C*H$_3$). IR (film): 3340, 2925, 2855, 1465, 1375, 1310, 1035, 905, 725, 650 cm^{-1}. Anal. Calcd for $C_{12}H_{25}ClO$ (220.8): C, 65.28; H, 11.41. Found: C, 65.07; H, 11.37.

2,2-Dimethylpropionic Acid 1-(2,2-Dimethylpropionyloxymethyl)-3-hydroxycyclopentyl Methyl Ester 29. According to general procedure 1, **28** (313 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.5. mg, 0.05 mmol), manganese (82 mg, 1.50 mmol), and 1,4-cyclohexadiene (0.450 mL, 4.80 mmol) were reacted for 16 h. After silica gel chromatography (30% MTBE, 70% PE), 212 mg of **29** was obtained (67%).

R_f (30% MTBE, 70% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39−4.38 (br m, CHOH), 4.07 (s, CH_2OPiv, 2H), 3.91 (s, CH_2-OPiv, 2H), 1.91−1.70 (m, 4H), 1.58−1.54 (m, 3H), 1.20 (s, C(CH_3)$_3$, 9H), 1.19 (s, C(CH_3)$_3$, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.42, 178.38, 73.31, 68.11, 67.35, 44.97, 41.32, 38.89, 34.55, 29.71, 27.16. IR (film): 3505, 2965, 2875, 1465, 1730, 1475, 1285, 1160, 1035 cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_5$ (314.4): C, 64.94; H, 9.62. Found: C, 64.66; H, 9.42.

2-Methyl-4-phenylbutan-1-ol 8 and 4-Phenyl-2-butanone (Table 3, Entry 8). According to general procedure 1, **7** (313 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.5. mg, 0.05 mmol), manganese (82 mg, 1.50 mmol), 4-phenyl-2-butanol (148 mg, 1.0 mmol), and 1,4-cyclohexadiene (0.450 mL, 4.80 mmol) were reacted for 48 h. After silica gel chromatography (20% MTBE, 80% PE), 124 mg of **8** (75%) and 140 mg of 4-phenyl-2-butanone (95%) were obtained.

2-Methyl-4-phenylbutan-1-ol 8 and Acetophenone (Table 3, Entry 9). According to general procedure 1, **7** (313 mg, 1.0 mmol), **4** (236 mg, 1.50 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), manganese (82 mg, 1.50 mmol), acetophenone (0.120 mL, 1.0 mmol), and 1,4-cyclohexadiene (0.450 mL, 4.80 mmol) were reacted for 48 h. After silica gel chromatography (20% MTBE, 80% PE), 136 mg of **8** (82%) and 114 mg of acetophenone (93%) were obtained.

3-(2,3-Epoxy-prop-1-yl)-3-(3-phenylprop-2-en-1-yl)malonic Acid Diethyl Ester 32. To a solution of 2-(2,3-epoxy-prop-1-yl) diethyl malonate[38] (1.08 g, 5.0 mmol) and cinnamyl bromide (1.48 g, 7.5 mmol) in THF (30 mL) was added sodium hydride (132 mg, 5.5 mmol) at 0 °C. After being stirred for 70 h at room temperature, the mixture was poured on MTBE (50 mL), washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). Silica gel chromatography (25% MTBE, 75% PE) gives 1.59 g of a pale yellow oil. After Kugelrohr distillation, 1.49 g of **32** was obtained as a clear oil (89%).

R_f (20% MTBE, 80% PE): 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19−7.33 (m$_c$, Ph), 6.47 (d, ^3J = 15.4 Hz, PhCH), 6.06 (dt, $^3J_{trans}$ = 15.4 Hz, ^3J = 7.6 Hz, PhCHCH), 4.23 (q, $^3J_{3'}$ = 7.2 Hz, OCH_2), 4.22 (q, ^3J = 7.2 Hz, OCH_2), 2.99−3.05 (m$_c$, CHOCH$_2$), 2.97 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, CH_2CHCHPh), 2.76 (dd, ^2J ≈ 5.1, $^3J_{anti}$ = 4.1 Hz, CHOCH^{syn}H^{anti}), 2.46 (dd, ^2J ≈ 5.1, $^3J_{syn}$ = 2.6 Hz, CHOCH^{anti}H^{syn}), AB-signal (δ_A = 2.04, δ_B = 2.23, J_{AB} = 14.7 Hz, additionally split by ^3J = 7.2 Hz, ^3J = 4.9 Hz, 3-CH_2CHOCH$_2$), 1.27 (t, ^3J = 7.2 Hz, CH_3), 1.26 (t, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (APT-spectrum, 50 MHz, $CDCl_3$): δ = "−" 170.77, "−" 170.70, "−" 137.00, "+" 134.35, "+" 128.53, "+" 127.49, "+" 126.24, "+" 123.73 (C-7), "−" 61.62, "−" 61.52, "−" 56.80, "+" 48.54, "−" 46.83, "−" 37.29, "−" 36.36, "+" 14.11 (*C*H$_3$). IR (film): 3025, 2980, 2935, 1730, 1600, 1575, 1495, 1465, 1445, 1390, 1365, 1320, 1290, 1245, 1210, 1155, 1095, 1030, 970, 860, 745, 695 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_5$ (332.4): C, 68.66; H, 7.28. Found: C, 68.41; H, 7.49.

3-(2,3-Epoxyprop-1-yl)-2-prop-2-ynylmalonic Acid Diethyl Ester 34. According to the procedure described for **32**, (2.169 g, 8.5 mmol) **34** was obtained from 3-(2,3-epoxypropyl)malonic acid diethyl ester (2.162 g, 10 mmol) and propargyl bromide (80% solution in toluene, 14 mmol) after silica gel chromatography (15% MTBE, 85% PE) in 85% yield.

R_f (15% MTBE, 85% PE): 0.30. ^{1}H NMR (300 MHz, benzene-d_6): δ = 4.02−3.93 (m, CH_2OCO, 4H), 2.87 (m$_c$, CHOCH$_2$), AB-signal (δ_A = 3.16, δ_B = 3.08, J_{AB} ≈ 17.0 Hz, additionally split by ^4J = 2.6 Hz, ^4J = 2.6 Hz, CH_2CCH), AB-signal (δ_A = 2.62, δ_B = 2.21, J_{AB} ≈ 14.7 Hz, additionally split by ^3J = 4.2 Hz, ^3J = 4.1 Hz, CH_2CHO), 2.40 (t, ^2J = 3.7 Hz, ^3J = 3.7 Hz, CHOCH^{trans}CH^{cis}), 2.07 (dd, ^2J = 3.7 Hz, ^3J = 5.7 Hz, CHOCH^{trans}CH^{cis}), 1.68 (t, ^4J = 2.6 Hz, CCH), 0.91 (t, ^3J = 6.7 Hz, CH_3), 0.91 (t, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (APT-spectrum, 50 MHz, benzene-d_6): δ = "−" 169.65, "−" 79.16, "+" 72.15, "−" 65.86, "−" 61.73, "−" 56.09, "+" 48.09, "−" 46.16, "−" 36.36, "−" 24.04, "+" 13.91 (*C*H$_3$). IR (film): 3280, 2985, 2935, 1735, 1440, 1290, 1200, 1095, 860 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_5$ (254.3): C, 61.41; H, 7.14. Found: C, 61.44; H, 7.07.

3-(2,3-Epoxyprop-1-yl)-2-prop-2-ynylmalonic Acid Diethyl Ester 36. According to the procedure described for **32**, (1.140 g, 4.3 mmol) **36** was obtained from 3-(2,3-epoxypropyl)-3-methylmalonic acid diethyl ester (1.151 g, 5 mmol) and propargyl bromide (80% solution in toluene, 14 mmol) after silica gel chromatography (15% MTBE, 85% PE) in 85% yield.

R_f (15% MTBE, 85% PE): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27−4.16 (m$_c$, CH_2OCO, 4H), AB-signal (δ_A = 3.03, δ_B = 2.89, J_{AB} ≈ 17.0 Hz, additionally split by ^4J = 2.6 Hz, ^4J = 2.6 Hz, CH_2-CCH), AB-signal (δ_A = 2.72, δ_B = 2.54, J_{AB} ≈ 4.5 Hz, CCH_2O), AB-signal (δ_A = 2.53, δ_B = 2.31, J_{AB} ≈ 16.5 Hz, CH_2CH$_2$O), 2.04 (t, ^4J = 2.7 Hz, CCH), 2.07 (dd, ^2J = 3.7 Hz, ^3J = 5.7 Hz, CHOCH^{trans}-CH^{cis}), 1.29 (s, CH_3), 1.27 (t, ^3J = 7.1, CH$_2$CH_3), 1.26 (t, ^3J = 7.1 Hz, CH$_2$CH_3), 0.91 (t, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (APT-spectrum, 50 MHz, benzene-d_6): δ = "−" 169.82, "−" 169.62, "−" 79.52, "+" 72.34, "−" 61.67, "−" 56.13, "−" 54.13, "−" 53.86, "−" 38.63, "−" 22.27, "+" 13.88, "+" 13.88 (*C*H$_3$). IR (film): 3280, 2980, 2940, 1730, 1440, 1290 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_5$ (254.3): C, 62.67; H, 7.51. Found: C, 62.39; H, 7.57.

General Procedure 3. Cyclization reactions in the presence of **4**.

3-Hydroxymethyl-4-methylcyclopentane-1,1-dicarboxylic Acid Diethyl Ester 31.[7] To a mixture of **4** (394 mg, 2.50 mmol), **30** (256 mg 1.0 mmol), and manganese (82 mg, 1.50 mmol) in THF (10 mL) was added titanocene dichloride (12.5 mg, 0.05 mmol), and the resulting mixture was stirred for 30 h. After addition of MTBE (50 mL), the mixture was washed with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30

(38) Temnikowa, T. I.; Semenowna, S. N. *J. Org. Chem. USSR (Engl. Transl.)* **1966**, *2*, 1171.

mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL) and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (25% MTBE, 75% PE → 50% MTBE, 50% PE) to give 202 mg of **31** as an 88:12 mixture of cis and trans isomers (78%).

3-Benzyl-4-hydroxymethylcyclopentane-1,1-dicarboxylic Acid Diethyl Ester 33. According to general procedure 3, **32** (332 mg, 1.0 mmol), **4** (394 mg, 2.5 mmol), manganese (82.0 mg, 1.5 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 39 h. After silica gel chromatography, 185 mg of **33** was obtained (55%) as an 86:14 mixture of cis and trans isomers.

R_f (40% MTBE, 60% PE): 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.1−7.30 (m_c, 5H), 4.19 (q, $^3J \approx$ 7.2 Hz, CH_2OH), 4.16 (qd, ^3J = 7.2 Hz, ^3J = 0.8 Hz, CH_2O), 3.56−3.81 (m_c, CH_2OH), 3.44−3.64 (m_c, CH_2OH), AB-signal (δ_A = 2.78, δ_B = 2.83, J_{AB} = 10.7 Hz, CH_2Ph), 2.11−2.61 (m, 4H), 2.00 (dd, ^3J = 13.6 Hz, J = 8.7 Hz, CHCH$_2$OH), 1.67 (t, $^3J \approx$ 5.8 Hz, OH), 1.24 (t, ^3J = 7.2 Hz, 3CH_3), 1.21 (t, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (APT-spectrum, 50 MHz, $CDCl_3$): δ = "−" 173.58, "−" 172.86, "−" 141.08, "+" 129.21, "+" 128.9, "+" 128.84, "+" 128.54, "+" 126.20 "+" 126.09, "−" 64.66, "−" 62.52, "−" 61.71, "−" 61.64, "−" 61.54, "−" 58.75, "+" 46.9, "+" 43.9, "+" 43.07, "+" 42.55, "−" 40.63, "−" 40.30, "−" 39.04, "−" 37.19, "−" 36.51,"−" 35.53, "+" 14.05. IR (film): 3445, 3085, 3025, 2980, 2935, 1730, 1600, 1495, 1455, 1390, 1365, 1255, 1180, 1160, 1115, 1095, 1070, 1030, 860, 740, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_5$ (334.4): C, 68.24; H, 7.84. Found: C, 68.13; H, 7.92.

3-Hydroxymethyl-4-methylenecyclopentane-1,1-dicarboxylic Acid Diethyl Ester 35. According to general procedure 3, **34** (254 mg, 1.0 mmol), **4** (465 mg, 3.0 mmol), manganese (170 mg, 3.0 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 24 h. After silica gel chromatography, 187 mg of **35** was obtained (73%) as a 91:9 mixture of 5-exo and 6-exo products.

R_f (40% MTBE, 60% PE): 0.20; ^{1}H NMR (300 MHz, benzene-d_6): δ = 4.90 (q, ^4J = 1.9 Hz, CCH_2, 1H), 4.79 (q, ^4J = 1.9 Hz, CCH_2, 1H), 3.97 (m, CH_2OCO, 4H), AB-signal (δ_A = 3.40, δ_B = 3.34, J_{AB} = 10.7 Hz, additionally split by ^3J = 4.9 Hz, ^3J = 5.7 Hz, CH_2OH), 3.11 (m, CHCH$_2$OH), AB-signal (δ_A = 2.77, δ_B = 2.71, J_{AB} = 8.3 Hz), AB-signal (δ_A = 2.50, δ_B = 2.19, J_{AB} = 11.7 Hz), 0.88 (t, ^3J = 7.2 Hz, CH_3, 6H). ^{13}C NMR (APT-spectrum, 50 MHz, benzene-d_6): δ = "−" 171.63, "−" 171.59, "−" 149.73, "−" 107.61, "−" 64.92, "−" 61.54, "−" 61.38, "−" 59.18, "+" 45.42, "−" 41.84, "−" 37.37, "+" 13.97; 6-exo product, "−" 171. 30, "−" 170.42, "−" 141.73, "−" 112.86, "+" 67.54, "−" 61.55, "−" 61.24, "−" 56.12, "−" 39.49, "−" 39.46, "+" 13.97. IR (film): 3445, 2980, 2935, 1730, 1655, 1450, 1370, 1255, 1190, 1070 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_5$ (256.3): C, 60.92; H, 7.86. Found: C, 61.13; H, 7.73.

3-Hydroxymethyl-3-methyl-4-methylenecyclopentane-1,1-dicarboxylic Acid Diethyl Ester 37. According to general procedure 3, **36** (272 mg, 1.0 mmol), **4** (465 mg, 3.0 mmol), manganese (170 mg, 3.0 mmol), and titanocene dichloride (12.0 mg, 50 μmol) were reacted for 40 h. After silica gel chromatography, 188 mg of **37** was obtained (70%).

R_f (40% MTBE, 60% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (t, ^3J = 1.8 Hz, CCH_2, 1H), 4.82 (t, ^4J = 1.7 Hz, CCH_2, 1H), 4.18 (q, ^3J = 6.8 Hz, CH_2OCO, 2H), 4.17 (q, ^3J = 6.9 Hz, CH_2OCO, 2H), AB-signal (δ_A = 3.39, δ_B = 3.30, J_{AB} = 10.9 Hz, additionally split by ^3J = 3.4 Hz, CH_2OH), AB-signal (δ_A = 3.10, δ_B = 3.02, J_{AB} = 10.9 Hz, additionally split by ^3J = 1.5 Hz CH_2C), 2.50 (d, ^3J = 13.9 Hz), 2.20 (d, ^3J = 13.9 Hz), 1.81 (br t, ^3J = 3.5 Hz, CH$_2$OH), 1.22 (t, ^3J = 7.2 Hz, CH_3, 6H), 1.11 (s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.26, 171.92, 154.13, 106.92, 69.57, 61.72, 61.63, 57.69, 47.43, 43.08, 41.47, 24.20, 14.00. IR (film): 3445, 2980, 2935, 1730, 1660, 1470, 1255, 1190, 1185 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_5$ (270.3): C, 62.20; H, 8.20. Found: C, 61.99; H, 8.35.

(3-Methyloctahydroinden-3a-yl)methanol 39.[7] According to general procedure 3, **38**[7] (166 mg, 1.0 mmol), **4** (394 mg, 2.5 mmol), zinc (131 mg, 2.0 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 61 h. After silica gel chromatography, 130 mg of **39** was obtained (77%) as a 52:48 mixture of diastereomisomers.

(3-Methylhexahydopentalen-3a-yl)methanol 41.[7] According to general procedure 3, **40**[7] (152 mg, 1.0 mmol), **4** (394 mg, 2.5 mmol), zinc (131 mg, 2.0 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 61 h. After silica gel chromatography, 102 mg of **41** was obtained (66%) as a 98:2 mixture of diastereoisomers.

General Procedure 4. Intermolecular additions to α,β-unsaturated carbonyl compounds in the presence of **4**.

4-Hydroxymethyltetradecanoic Acid *tert*-Butyl Ester 45 (Table 5, Entry 2). To a mixture of **4** (940 mg, 6 mmol), **14** (440 μL, 2.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and *tert*-butylacrylate (0.880 mL, 6.0 mmol) in THF (20 mL) was added titanocene dichloride (25.0 mg, 0.10 mmol), and the resulting mixture was stirred for 16 h. After addition of MTBE (50 mL), the mixture was washed with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL) and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (20% MTBE, 80% PE) to give 509 mg of **45** as a 94:6 mixture of regioisomers (81%).

R_f (20% MTBE, 80% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58−3.43 (m, CH_2OH), AB-signal (δ_A = 2.47, δ_B = 2. 25, J_{AB} = 7.6 Hz, additionally split by ^3J = 4.2, 3.4 Hz), 1.77 (t, ^3J = 4.2, CH$_2$OH), 1.67−1.57 (m, 2H), 1.44 (s, C(CH_3)$_3$), 1.26 (m, 14H), 0.88 (t, ^3J = 7.0 Hz, CH_3, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ =173.68, 80.29, 64.95, 40.32, 32.95, 31.93, 31.00, 30.01, 29.67, 29.63, 29.34, 28.14, 27.02, 25.96, 22.68, 14.08. IR (film): 3410, 2920, 2860, 1730, 1655, 1460, 1360 cm^{-1}. Anal. Calcd for $C_{19}H_{38}O_3$ (314.5): C, 72.56; H, 12.18. Found: C, 72.89; H, 12.13.

4-Hydroxymethyltetradecanoic Acid *tert*-Butyl Ester 45 (Table 5, Entry 3). According to general procedure 4, **14** (7.00 mL, 32 mmol), **4** (12.60 g, 80 mmol), *tert*-butylacrylate (7.0 mL, 48 mmol), Zn (3.14 g, 48 mmol), and titanocene dichloride (80.0 mg, 0.32 mmol) were reacted for 44 h. After silica gel chromatography, 7.36 g of **45** was obtained (73%) as a colorless oil.

5-Decyltetrahydropyran-2-one 47 (Table 5, Entry 4). According to general procedure 4, **14** (3.30 mL, 15 mmol), **4** (6.30 g, 40 mmol), acrylonitrile (2.0 mL, 30 mmol), Zn (1.5 g, 23 mmol), and titanocene dichloride (190.0 mg, 0.75 mmol) were reacted for 16 h. After silica gel chromatography, 2.95 g of **47** was obtained as a 94:6 mixture of regioisomers (82%).

R_f (40% MTBE, 60% PE): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.33 (ddd, ^2J = 11.3, ^3J = 4.6, ^4J = 1.9, CH_2O), 3.94 (dd, ^2J = 11.0, ^3J = 9.8, CH_2O), 2.62 (ddd, ^2J = 17.7, ^3J = 7.1, ^3J = 4.5, CH_2-CO), 2.48 (ddd, ^2J = 17.7, ^3J = 8.6, ^3J = 7.2, CH_2CO), 2.05−1.83 (m, 2H), 1.58−1.44 (m, 1H), 1.29−1.25 (m, 18H), 0.83 (t, ^3J = 7.0 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.45, 73.59, 32.72, 31.80, 31.46, 29.54, 29.49, 29.38, 29.22, 28.99, 26.70, 25.42, 22.59, 14.03. IR (film): 2925, 2855, 1740, 1460, 1245, 1180, 1055 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_2$ (240.4): C, 74.95; H, 11.74. Found: C, 74.73; H, 11.51.

5-Decyltetrahydropyran-2-one 47 (Table 5, Entry 5). According to general procedure 4, **14** (440 μL, 2.0 mmol), **4** (940 mg, 6.0 mmol), acrylonitrile 270 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), and titanocene dichloride (2.5 mg, 0.02 mmol) were reacted for 43 h. After silica gel chromatography, 349 mg of **47** was obtained (73%).

5-Decyltetrahydropyran-2-one 47 (Table 5, Entry 6). According to general procedure 4, **14** (440 μL, 2.0 mmol), **4** (940 mg, 6.0 mmol), acrylonitrile 270 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 12 h. After silica gel chromatography, 423 mg of **47** was obtained (88%).

4-Hydroxymethyltetradecane Nitrile 46 (Table 5, Entry 7). According to general procedure 4, **14** (440 μL, 2.0 mmol), **4** (940 mg, 6.0 mmol), acrylonitrile 270 μL, 4.0 mmol), Mn (220 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (12.0 mg, 0.05 mmol) were reacted for 14 h. After silica gel chromatography, 382 mg of **46** was obtained as a 93:7 mixture of regioisomers (80%).

R_f (20% MTBE, 80% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (dt, ^2J = 9.0, ^3J = 2.5, CH_2OH), 3.54 (dt, ^2J = 9.0, ^3J = 2.5, CH_2OH), 2.43 (t, ^3J = 7.9, CH_2CN), 1.85−1.58 (m, 3H), 1.30−1.26 (m, 16H), 0.88 (t, ^3J = 7.0 Hz, CH_3, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 120.08, 64.66, 39.43, 31.90, 30.57, 29.89, 29.62, 29.58, 29.34, 27.29, 26.83, 22.70, 15.10, 14.13. IR (film): 3430, 2925, 2860,

2250, 1465, 1045 cm^{-1}. Anal. Calcd for $C_{15}H_{29}NO$ (239.4): C, 75.25; H, 12.21; N, 5.85. Found: C, 75.47; H, 12.41; N, 5.70.

5-Decyltetrahydropyran-2-one 47 (Table 5, Entry 9). According to general procedure 4, **14** (440 μL, 2.0 mmol), **4** (940 mg, 6.0 mmol), methylacrylate (360 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 16 h. After silica gel chromatography, 340 mg of **47** was obtained (72%).

4-Methyl-2-oxaspiro[5.5]undecan-3-one 49 (Table 6, Entry 1).[7] According to general procedure 4, **48** (240 μL, 2.0 mmol), **4** (950 mg, 6.0 mmol), methylmethacrylate (580 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 24 h. After silica gel chromatography, 314 mg of **49** was obtained (86%).

1-Methyl-2-oxaspiro[5.5]undecan-3-one 50 (Table 6, Entry 2). According to general procedure 4, **10** (260 μL, 2.0 mmol), **4** (950 mg, 6.0 mmol), methylacrylate (360 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 16 h. After silica gel chromatography, 264 mg of **50** was obtained (78%).

R_f (15% MTBE, 85% PE): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (q, ^3J = 6.8, C*H*O), 2.61−2.42 (m, CH_2CO), 1.94 (dt, ^2J = 14.1, ^3J = 7.6, CH_2CH$_2$CO, 1H), 1.67−1.32 (m, 11H), 1.29 (d, ^3J = 6.8, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ =172.05, 83.74, 34.76, 33.29, 29.03, 26.72, 26.43, 26.04, 21.23, 20.93, 15.47. IR (film): 2930, 2860, 1730, 1450, 1210, 1060 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$ (182.3): C, 72.49; H, 9.95. Found: C, 72.42; H, 9.97.

13-Chloro-4-hydroxymethyl-4-methyltridecanoic Acid *tert*-Butyl Ester 51 (Table 6, Entry 3). According to general procedure 4, **26** (437 mg, 2.0 mmol), **4** (950 mg, 6.0 mmol), *tert*-butylacrylate (600 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), $ZnCl_2$ (273 mg, 2.0 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 12 h. After silica gel chromatography, 571 mg of **51** was obtained (91%).

R_f (25% MTBE, 75% PE): 0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (t, ^3J = 6.8, CH_2Cl), AB-signal (δ_A = 3.27, δ_B = 3.24, J_{AB} = 12.8 Hz, additionally split by ^3J = 6.4 Hz), 2.20 (t, ^3J = 7.5, CH_2CO), 2.02 (t, ^3J = 6.4, CH$_2$O*H*), 1.76 (quin, ^3J = 6.8, 1H), 1.55 (t, ^3J = 7.5, CH_2CH$_2$CO), 1.44 (s, C(CH_3)$_3$), 1.28−1.18 (m, 10H), 0.82 (s, CH_3, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.34, 80.47, 68.81, 45.18, 37.26, 36.61, 32.64, 30.53, 29.99, 29.53, 29.46, 28.89, 28.06, 26.88, 23.31, 21.55. IR (film): 3430, 2930, 2855, 1730, 1710, 1650, 1155, 1040 cm^{-1}. Anal. Calcd for $C_{19}H_{37}ClO_3$ (314.5): C, 65.40; H, 10.69. Found: C, 65.50; H, 10.80.

6-Methyl-6-phenethyltetrahydropyran-2-one 52 (Table 6, Entry 4). According to general procedure 4, **7** (330 μL, 2.0 mmol), **4** (950 mg, 6.0 mmol), acrylonitrile (270 μL, 4.0 mmol), Zn (260 mg, 4.0 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 10 h at room temperature and 12 h at reflux. After silica gel chromatography, 285 mg of **52** was obtained (65%).

R_f (30% MTBE, 70% PE): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.16 (m, CH_{ar}, 5H), 4.09 (dd, ^2J = 11.3, ^4J = 0.8, CH_2O), 4.00 (dd, ^2J = 11.3, ^4J = 1.1, CH_2O), 2.65−2.55 (m, 4H), 1.82 (dt, ^2J = 14.7, ^3J = 6.2, 1H), 1.73 (dd, ^2J = 14.7, ^3J = 6.2, 1H), 1.69−1.64 (m, 2H), 1.11 (s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.59, 141.66, 128.50, 126.04, 128.17, 77.27, 39.83, 32.32, 31.16, 29.98, 27.12, 22.05. IR (film): 3025, 2935, 1735, 1600, 1455, 1190, 1055 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2$ (218.3): C, 77.03; H, 8.31. Found: C, 76.88; H, 8.39.

4-Hydroxymethyltetradecane Nitrile 46 (Table 7, Entry 1). According to general procedure 4, **14** (440 μL, 2.0 mmol), **4** (950 mg, 6.0 mmol), acrylonitrile (270 μL, 4.0 mmol), Mn (220 mg, 4.0 mmol), collidine (1.320 mL, 10 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 37 h. After silica gel chromatography, 365 mg of **46** was obtained (75%) as a 93:7 mixture of regioisomers.

13-Chloro-4-hydroxymethyl-4-methyltridecanenitrile 53 (Table 7, Entry 2). According to general procedure 4, **26** (437 mg, 2.0 mmol), **4** (950 mg, 6.0 mmol), acrylonitrile (270 μL, 4.0 mmol), Mn (220 mg, 4.0 mmol), collidine (1.320 mL, 10 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 36 h. After silica gel chromatography, 397 mg of **53** was obtained (73%).

R_f (40% MTBE, 60% PE): 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (t, ^3J = 6.8, CH_2Cl), br AB-signal (δ_A = 3.38, δ_B = 3.36, J_{AB} = 10.9 Hz, CH_2OH), 2.36−2.31 (m, 2H, CH_2CO), 1.81−1.67 (m, 4H), 1.44−1.22 (m, 15H), 0.86 (s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 120.66, 68.77, 45.19, 37.23, 36.24, 32.62, 32.52, 30.37, 29.46, 29.42, 28.84, 26.84, 23.27, 21.24, 12.20. IR (film): 3455, 2930, 2850, 2250, 1470, 1310, 1045 cm^{-1}. Anal. Calcd for $C_{15}H_{28}ClNO$ (273.9): C, 65.79; H, 10.31; N, 5.12. Found: C, 65.64; H, 10.11; N, 4.94.

3-(1-Hydroxymethylcyclohexyl)-2-methylpropionitrile 54 (Table 7, Entry 3). According to general procedure 4, **48** (370 μL, 2.0 mmol), **4** (945 mg, 6.0 mmol), Mn (260 mg, 4.0 mmol), methacrylonitrile (340 μL, 4.0 mmol), collidine (1.320 mL, 10 mmol), and titanocene dichloride (25.0 mg, 0.10 mmol) were reacted for 36 h. After silica gel chromatography, 263 mg of **54** was obtained (73%).

R_f (50% MTBE, 50% PE): 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ = br AB-signal (δ_A = 3.61, δ_B = 3.53, J_{AB} = 11.0 Hz, CH_2OH), 2.73 (dqd, ^3J = 10.6, 7.2, 3.1, C*H*CN), 1.89 (dd, ^2J = 14.3, ^3J = 10.6, CH_2CHCN, 1H), 1.49−1.43 (m, 10H), 1.35 (d, ^3J = 7.1, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.56, 67.32, 40.37, 37.35, 32.98, 32.47, 26.16, 21.45, 21.34, 20.56, 19.97. IR (film): 3450, 2930, 2855, 2240, 1455, 1050 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$ (181.3): C, 72.88; H, 10.56; N, 7.37. Found: C, 72.68; H, 10.52; N, 7.37.

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