Reagent-Controlled Stereoselectivity in Titanocene-Catalyzed Epoxide Openings: Reductions and Intermolecular Additions to α,β-Unsaturated Carbonyl Compounds

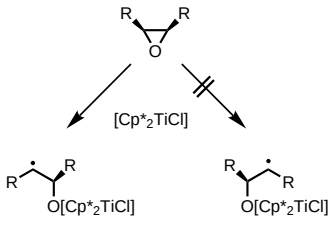
Andreas Gansäuer,* Harald Bluhm, Björn Rinker, Sanjay Narayan, Michael Schick, Thorsten Lauterbach, and Marianna Pierobon[a]

Abstract: The generation and addition reactions of metal bound radicals derived from normal and *meso* epoxides by electron transfer from titanocene(III) reagents is described. The control of enantioselectivity and diastereoselectivity of these transformations is investigated by variation of the ligands of the metal complex. The reaction can lead to unprecedented and highly selective reactions, in which synthetically useful alcohols may be prepared. The synthesis presented also circumvents the use of toxic metals. Another advantage is that there is no loss of two functional groups as usually observed in reductive radical chain reactions.

Keywords: asymmetric catalysis · diastereoselectivity · epoxides · radical reactions · titanium

Introduction

The control of stereoselectivity of radical reactions has lately attracted considerable interest.[1] While diastereoselective substrate controlled reactions have been actively investigated over the last two decades[2] the first examples of highly enantioselective catalytic transformations have been reported only recently.[3] Our conceptually novel approach to enantioselective radical reactions is relying on electron transfer to *meso* epoxides from chiral, enantiomerically pure titanocene catalysts and ensuing enantioselective epoxide opening as shown in Figure 1.[4]



Cp* = Cp with chiral substituent

Figure 1. Enantioselective opening of *meso* epoxides through electron transfer.

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This transformation is based on the achiral stoichiometric titanocene mediated opening of epoxides described by Nugent and RajanBabu[5] that we have developed into a catalytic reaction by protonation of titanium oxygen and titanium carbon bonds.[6]

The use of epoxides as radical precursors has a number of very attractive advantages over traditional substrates. Epoxides can be readily prepared from olefins or carbonyl compounds by a number of well established methods.[7] Highly enantioselective access to epoxides[8] and hence radicals is easily achieved. Our reaction does not require the use of toxic stannanes or silanes that have to be prepared prior to use or tend to be unstable under ambient conditions.[9] Last but not least after epoxide opening the preparatively useful alcohol group is formed. Thus, the typical disadvantage of reductive radical chain reactions, the loss of two functional groups, is avoided.

Because our method does not constitute a radical chain reaction it is complementary to other highly enantioselective catalytic radical reactions, for example Sibi's catalytic complexation of radicals and radical traps in enantioselective additions[10] or Roberts' chiral hydrogen donor reagents in polarity reversed catalysis.[11]

Results and Discussion

Enantioselective reductive opening of *meso* epoxides: We decided to begin our investigation with the opening of epoxide **1** that is readily synthesized from (*Z*)-2-butene-1,4-diol in two steps. After reductive opening alcohol **2** is obtained as shown in Scheme 1.

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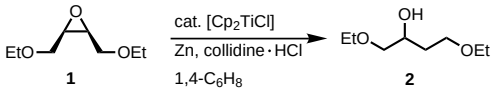
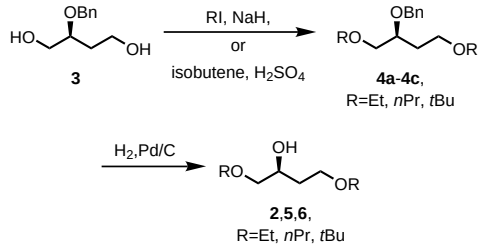


Scheme 1. Test reaction for catalyst evaluation.

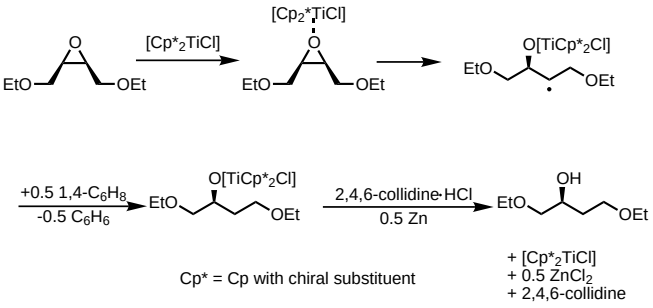
This choice is advantageous because the absolute configuration of **2** obtained in catalytic enantioselective reactions can be determined by comparison with authentic samples from derivatives of (*S*)-malic acid as shown in Scheme 2.



Scheme 2. Synthesis of enantiomerically pure samples for determination of absolute configuration.

Because a hydrogen atom is transferred in the reduction, product analysis is not hampered by the formation of diastereoisomers. This point will be thoroughly treated later in the addition reactions to acrylates.

Varying the ethyl substituents to other alkyl groups allows simple variation of the substrate's steric bulk to probe the size of the catalyst's chiral pocket. The crucial point for enantioselectivity is revealed by inspection of the catalytic conditions as shown in Scheme 3.



Scheme 3. Planned catalytic cycle for enantioselective epoxide opening.

The first intermediate which is crucial to the enantioselective electron transfer should be a titanocene(III)–epoxide complex. To induce selectivity in the reductive opening of this intermediate to the pivotal β-titanoxy radical the substrate's enantiotopic groups R should fit in the chiral pocket of the catalyst to allow steric distinction between the two groups by the ligands of titanium as depicted in Figure 2.

Since these residues R are pointing away from the epoxide's initial binding partner, the titanium atom, a useful catalyst would need a deep and conformationally rigid chiral pocket to mediate a highly selective radical formation. Thus, the reaction described here is conceptually different from the preparatively useful enantioselective openings of *meso* epoxides by S_N2 reactions because in our case the pivotal radical intermediate has to be formed with high selectivity, whereas in S_N2 reactions the path of the incoming nucleophile has to be controlled by the catalyst.[12]

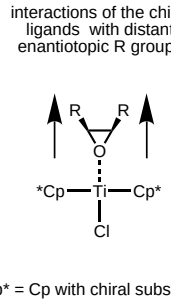


Figure 2. Crucial intermediate for epoxide opening.

Inspection of the extensive literature on chiral enantiomerically pure titanocene and zirconocene complexes[13] suggested complex **7**, which has been described by Vollhardt and Halterman,[14] as especially promising. Our reasoning was based on the well established superiority of phenylmenthol over menthol as chiral auxiliary in asymmetric synthesis. This is usually explained in terms of π-stacking interactions restricting conformational freedom to allow highly ordered transition structures.[15] We hoped that a similar mechanism of conformational locking would be operating in titanocene **7** by interaction of the phenyl ring with the cyclopentadienyl group. To test the validity of this hypothesis the two menthol and *neo*-menthol based catalysts **8** and **9** that were first synthesized by Kagan et al.,[16] were also prepared. Both complexes lack the pivotal phenyl group for conformational locking and additionally allow an evaluation of the merits of equatorial and axial positioning of the cyclopentadienyl group for asymmetric catalysis. Finally, we also decided to investigate Brinzinger's catalyst **10**,[17] possessing a chiral titanium atom that leads to a tight chiral pocket centred around the metal. Complex **10** has recently been used in enantioselective catalysis with great success.[18] All complexes investigated are shown in Figure 3.

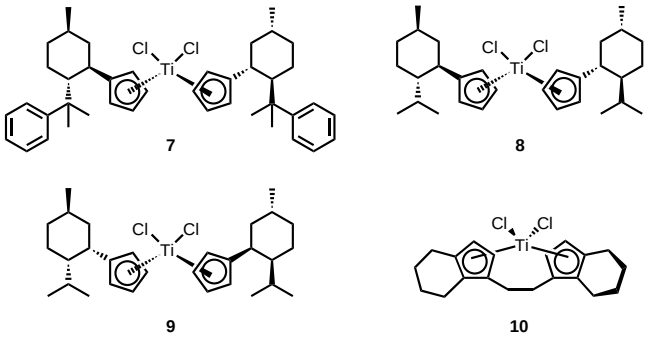


Figure 3. Catalysts investigated in the opening of **1**.

The results of the opening reactions of **1** in the presence of 10 mol% of titanocene complex are summarized in Table 1.

Gratifyingly, alcohol **2** was obtained with catalyst **7** in reasonable yields and with very high enantioselectivity (enantiomeric ratio: *er* 96.5:3.5, (*S*)-**2** formed preferentially, entry 1). Much to our surprise complex **8** reacted with essentially the same enantioselectivity (*er* 97:3, entry 2) and yield indicating that the phenyl group is not necessary for achieving high selectivity. This result is also of substantial practical importance. Catalyst **8** can be readily synthesized from *neo*-menthol, that is available in both enantiomeric

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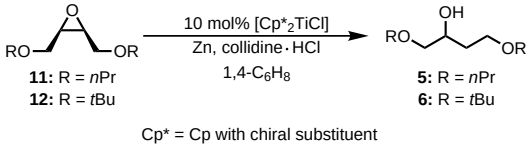
Table 1. Catalytic enantioselective opening of **1** in the presence of 10 mol% catalyst.

Entry	Catalyst	Yield [%]	*ee* [%][a]
1	**7**	71	93[b]
2	**8**	76	94[b]
3	**9**	45–51	20–52[c]
4	**10**	55	56[c]

[a] By GC on an heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV1701 (1/4) column; [b] (*S*) formed preferentially; [c] (*R*) formed preferentially.

forms, in three steps without the need of column chromatography. Complex **7** has to be prepared from (+)-pulegone in six steps involving a tedious separation of diastereoisomers by chromatography.[14] It should also be noted that only (+)-pulegone is commercially available at a reasonable price and therefore only the enantiomer of **7** shown is accessible. Complex **9** with the axially positioned cyclopentadienyl group gave unsatisfactory and varying results (entry 3). The reasons for this behavior are unclear at present, although we noted that reactions with **9** are very sensitive to traces of oxygen and water. Unquestionably, this axial orientation is not well suited for highly selective epoxide openings. Brintzinger's complex **10** also gave unsatisfactory results. Epoxide **1** was opened with low selectivity (*er* 78:22, entry 4) and with low yield (55%). Presumably, the tight chiral pocket centred around titanium does not allow for an efficient chirality transfer to the distant regions of the catalyst and hence substrate binding.

To further evaluate the complexes we also investigated the opening reactions of epoxides **11** and **12** shown in Scheme 4. The results are summarized in Table 2.



11: R = *n*Pr
12: R = *t*Bu

5: R = *n*Pr
6: R = *t*Bu

Cp* = Cp with chiral substituent

Scheme 4. Other substrates investigated in the enantioselective epoxide opening.

Table 2. Catalytic enantioselective opening of **11** and **12** in the presence of 5–10 mol% catalyst.

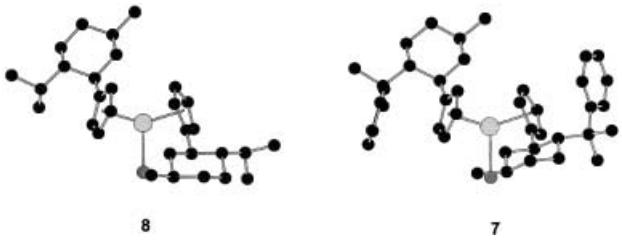
Entry	Catalyst	Substrate	Product	Yield [%]	*ee* [%]
1	**7**	**11**	**5**	60	92[a,b]
2	**7**	**12**	**6**	68	74[b,c]
3	**8**	**11**	**5**	70	91[a,b]
4	**8**	**12**	**6**	66	86[b,c]
5	**10**	**12**	**6**	31	20[a,d]

[a] By GC on an Ivadex 7/OV-1701; G/294 column; [b] (*S*) formed preferentially; [c] by GC on an heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV1701 (1/4) column; [d] (*R*) formed preferentially.

Epoxide **11** containing the *n*-propyl ether reacted with essentially the same selectivity as **1** (*er* 96:4, entry 1 and *er* 95.5:4.5, entry 3) indicating that the *n*-alkyl chain has no significant influence on the fitting of the substrate into the chiral pocket. The yields of **5** were also comparable. This changed dramatically when the *tert*-butyl substituted epoxide **12** was employed. Enantioselectivity dropped substantially with complexes **7** and **8** (*er* 87:13, entry 2 and *er* 93:7, entry 4) and in the case of catalyst **10** almost disappeared (*er* 60:40, entry 15). Additionally the yield of **6** was very low. This indicates that the chiral pockets of all catalysts, especially that of **10**, are not wide enough to accommodate the bulkier substrate **12** for a highly selective reaction. Complex **8** gave the best results in the opening of **1**, **11**, and **12** and thus constitutes the most selective and easiest to prepare catalyst of the titanocenes employed.

Comparison of the catalyst structures: With these results in mind we turned our attention towards an understanding of the characteristic structural features of the complexes **7**, **8**, and **9**. Because of the low selectivity **10** and its structure, that has been studied extensively, will not be discussed here.[17]

We managed to obtain crystals suitable for X-ray crystallography by slow evaporation of concentrated solutions of **7** in $CHCl_3$ and of **8** and **9** in CH_2Cl_2.[19] The striking feature of the structure of **7** and **8** is the relative orientation of the phenyl ring and the cyclopentadienyl group in **7** and the orientation of the 2-propyl group and the cyclopentadienyl group in **8** as shown in Figure 4.



8 **7**

Figure 4. X-ray structures of complexes **7** and **8**.

The phenyl group and the hydrogen of the 2-propyl group occupy similar positions in space resulting in a conformational fixation of the cyclopentadienyl ligand in both cases. Thus, **7** and **8** feature the same conformational locking of the cyclopentadienyl group in the solid state. This results in a rigid chiral pocket that is responsible for efficient catalysis. It seems that a minimization of steric interactions constitutes the underlying principle for this organization and not π-interactions that are absent in **8**. Thus, our original assumption based on π-stacking for choosing **7** as the starting point proved to be wrong. However, the anticipated and successfully realized conformational rigidity of the chiral pockets is guaranteed by the alternative mechanism of minimization of steric interaction.

We have been able to demonstrate that both complexes possess the same conformational preferences in solution by a combination of modern NMR techniques.[19] The structure of **9** is less compact in the solid state and in solution as indicated by a disorder in the structure due to rotation of the 2-propyl group.

Although we have thus far not been able to determine the structure of the redox active titanium(III) complexes, it seems reasonable that the ligand conformation should not be

dramatically altered by the reduction of titanium. Unfortunately, the paramagnetic titanium(III) complexes are not amenable to modern NMR techniques. Computational studies towards the understanding of the catalytically active species are currently being pursued.

Enantioselective opening of *meso* epoxides and C–C bond formation—Control of diastereoselectivity: We then turned to the enantioselective openings of *meso* epoxides with ensuing C–C bond formation. In these cases a second issue of selectivity in addition to the enantioselectivity of epoxide opening is raised. After the radical formation diastereoselectivity of the addition step to a radical trap, for example an acrylate, is also amenable to reagent control by the titanocene complex. To achieve this goal it is mandatory that the catalyst remains bound to the radical as titanocene alkoxide. In the catalytic transformation it is therefore essential that protonation of the titanium oxygen bond is distinctly slower than the desired radical addition reaction. This scenario is depicted in Figure 5. The problem of these two competing rates is easy to address experimentally. If the diastereoselectivity is independent of the titanocene employed protonation must be faster than radical addition.

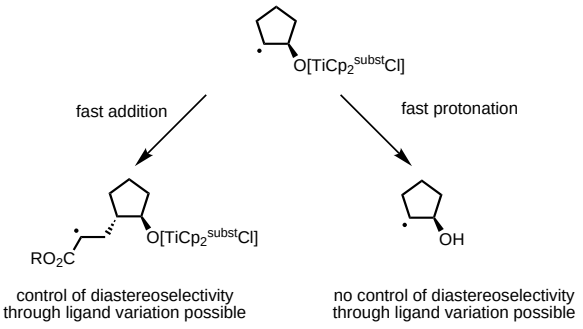
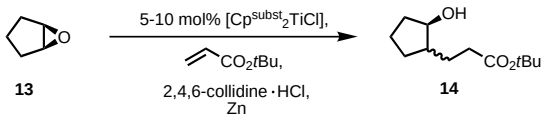


Figure 5. Kinetic prerequisites for controlling the diastereoselectivity of addition reactions to acrylates.

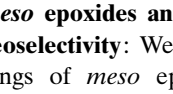
We decided to employ achiral catalysts first to initially separate the different problems of enantioselectivity and diastereoselectivity and render the investigation easier to carry out practically. Our results with cyclopentene oxide **13** as substrate in the reaction yielding hydroxyester **14** as shown in Scheme 5 are summarized in Table 3.



Scheme 5. Test reaction for control of diastereoselectivity of addition reactions.

The selectivity observed in the case of the $[Cp_2TiCl_2]$ (entry 1) was reasonable and increasing the bulkiness of the titanocene by introducing sterically demanding alkyl substituents greatly enhanced the performance of the reaction. Protonation is therefore substantially slower than radical addition and reagent control is straightforward to achieve.

Table 3. Opening of cyclopentene oxide **13** with substituted titanocene complexes.

Entry	Catalyst	Yield [%]	*dr* (*trans*:*cis*)[a]
1	$[Cp_2TiCl_2]$	68[b]	86:14
2	$[(MeCp)_2TiCl_2]$ (**15**)	72	94:6
3	$[(c\text{HexCp})_2TiCl_2]$ (**16**)	75	95:5
4	 (**17**)	61	95:5
5	$[(t\text{BuCp})_2TiCl_2]$ (**18**)	63	>97:<3

[a] Determined by ^{1}H NMR of the crude product; [b] 5 mol% catalyst.

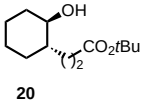
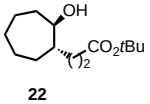
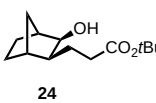
Already the introduction of the small methyl substituent in catalyst **15** resulted in a noticeable improvement of the reaction (*dr* 94:6, entry 2). With bis(*tert*-butylcyclopentadienyl)titanium dichloride (**18**) the control of diastereoselectivity was excellent. The *trans* diastereoisomer was obtained almost exclusively (*dr* >97:3, entry 5). The other complexes gave lower but still very high selectivities. It is interesting to note that complex **16** gave the highest yield (entry 3). Therefore, exceedingly high selectivity is obtained at the cost of a slight reduction in catalytic activity.

Preferential formation of the *trans* product can be readily explained by shielding of the *cis* face of the radical through the cyclopentadienyl group and its bulky alkyl groups. Thus, these examples constitute cases of a matched reagent and substrate control leading to unprecedented high diastereoselectivity in transition metal catalyzed radical chemistry.

Compared to Renaud's otherwise excellent use of stoichiometric amounts of bulky aluminum reagents[20] our method has the distinct advantage of employing the metal complex only in catalytic quantities.

To test the applicability of the ligand induced control of diastereoselectivity we also investigated other *meso* epoxides including a case of mismatched reagent and substrate control. The results are summarized in Table 4.

Table 4. Reagent control in diastereoselective opening reactions of *meso* epoxides.[a]

Entry	Catalyst	Substrate	Product	Yield [%]	*dr*
1	Cp_2TiCl_2	 **19**	 **20**	90	64:36
2	**18**	**19**	**20**	74	73:27
3	Cp_2TiCl_2	 **21**	 **22**	82	77:23
4	**18**	**21**	**22**	90	94:6
5	Cp_2TiCl_2	 **23**	 **24**	71	82:18
6	**18**	**23**	**24**	68	53:47

[a] For details of assignments see Experimental Section.

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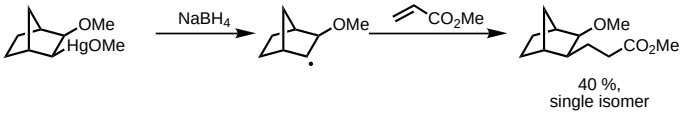
Both cyclohexene and cycloheptene oxide (**19** and **21**) reacted with improved selectivity when catalyst **18** was employed (entries 2 and 4). Hydroxyester **22** was obtained in excellent yield and unprecedented selectivity. Equatorially substituted cyclohexene radicals are known to react with lower selectivity and our examples are in line with this observation.[21] Both cases also represent examples of matched substrate and reagent control.

A more demanding problem is constituted by mismatched reagent and substrate control where a substrate controlled course of the reaction is to be overwhelmed by the influence of a reagent. We have addressed this issue in the reaction of norbornene oxide **23** (entries 5 and 6). Giese's seminal studies revealed that a methoxy substituted norbornyl radical exclusively yielded adducts of *exo* addition as shown in Scheme 6.[22]



Scheme 6. Giese's *exo*-selective addition to a norbornyl radical.

Our results suggest that the titanocene catalysts could indeed compensate the exceptionally high intrinsic selectivity of the norbornyl system. [Cp_2TiCl_2] resulted in the formation of *endo* adduct as minor component (82:18, entry 5) whereas the bulky catalyst **18** yielded in a 53:47 mixture of the isomers (entry 6) and lead to the formation of the *endo* adduct in reasonable amounts for the first time and completely eroded the outstanding substrate control exercised by the bicyclo[2.2.1] system.

With these results at hand we turned our attention to the use of the best chiral enantiomerically pure catalysts **7** and **8** in the opening reaction of cyclopentene oxide **13** and cycloheptene oxide **21** with concomitant C–C bond formation. The results are summarized in Table 5.

It turned out that both catalysts reacted to give the desired products **14** (entries 1 and 2) and **22** (entries 3 and 5) in reasonable yields with high enantioselectivity and with high diastereoselectivity. For **22** the *ee* value refers to the *ee* of the major isomer. The value for the minor isomer could not be obtained. In the case of purification of **22** higher yields could be obtained by careful chromatography (low polarity of eluents, larger column size) than by microdistillation and chromatographic filtration. Cyclohexene oxide **21** was opened with similar enantioselectivity (*ee* $\approx$80–82%). However, in the case of **8** the product **22** obtained was contaminated with small amounts of polymeric material that could not be removed by chromatography or microdistillation.

Table 5. Enantioselective opening of cyclopentene and cycloheptene oxide **13** and **21**.

Entry	Catalyst	Substrate	Product	Yield [%]	*ee*[a] [%]	*dr*
1	**7**[b]	**13**	**14**	69	73	>97:3
2	**8**[c]	**13**	**14**	72	81[d]	>97:3
3	**7**[a]	**21**	**22**	61	82	87:13
4	**8**[b]	**21**	**22**	78[e]	80	87:13

[a] For details of determination see Experimental Section. [b] 5 mol% catalyst; [c] 10 mol% catalyst; [d] 83% by ^{19}F NMR of the Mosher esters; [e] by column chromatography, 54% by distillation and chromatography.

Thus, our chiral catalysts **7** and **8** control both enantioselectivity of epoxide opening and diastereoselectivity of the ensuing addition reaction to an acrylate with high efficiency. The examples of Table 2 and 5 constitute the first examples of catalytic enantioselective radical generation and should therefore be of general interest to the fields of both catalysis and radical chemistry.

Control of diastereoselectivity in addition reactions to 2,2-disubstituted epoxides: An interesting point to investigate the influence of the titanocene catalyst is constituted by the opening of 2,2-disubstituted epoxides containing chiral centers. During the addition of the radical to the acrylate, the radical becomes pyramidalized and the bulky titanocene moiety will be able to interact with both the incoming radical acceptor and the groups of the radical responsible for controlling the stereochemical course of the reaction in the two transition structures. A unique feature of our reaction is constituted by the possibility to influence the course of the reaction through reagent control by the action of the catalyst. A dependence of the diastereoselectivity of the overall reaction on the titanocene and its substituents can therefore be expected. This notion is shown in Figure 6 for the camphor derived radical **A**.

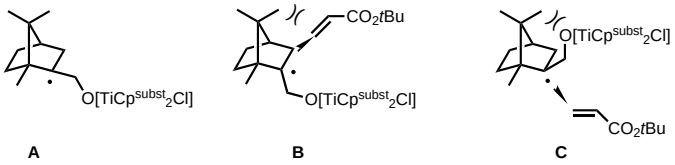


Figure 6. Plausible transition structures for addition reactions to radical **A**.

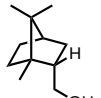
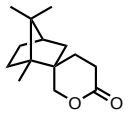
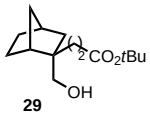
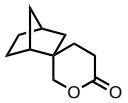
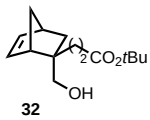
The selectivity of the addition reaction of radical **A** will depend on the relative magnitude of interactions of the bulky titanocene moiety with the bulky bridging dimethyl group and of the radical trap with the dimethyl group in transition structures **B** and **C**. This effect should clearly depend on the ligands of the titanocene. From a mechanistic point of view it is also interesting to probe the catalysts binding pocket size to gain information about the generality of our reactions.

Useful models for the description of diastereoselectivity in the reactions of cyclic radicals with exocyclic substituents involving A-strain have been developed by Giese and Metzger.[23] For reasonable to high selectivities very bulky groups, for example *tert*-butyl are necessary.

It is of general interest to find out if this analogy can be transferred to our metal bound radicals that do not involve A-strain effects[24] in order to gain a complete understanding of the factors affecting selectivity in radical reactions. Our results of the camphor derived and other systems are summarized in Table 6.

Already, with [Cp_2TiCl_2] approach of both radical traps, acrylonitrile and 1,4-cyclohexadiene, (entries 1 and 3) occurred predominantly from the favorable *exo* side. This trend was

Table 6. Reagent control in the opening of epoxides containing bicyclo[2.2.1] systems.[a]

Entry	Catalyst	Substrate	Product	Yield [%]	*dr*
1	$[Cp_2TiCl_2]$	 **25**	 **26**	54	57:43
2	**18**	**25**	**26**	36	79:21
3	$[Cp_2TiCl_2]$	**25**	 **27**	56	67:33
4	**18**	**25**	**27**	39	77:23
5	$[Cp_2TiCl_2]$	 **28**	 **29**	77	> 97: < 3
6	**18**	**28**	**29**	51	> 97: < 3
7	$[Cp_2TiCl_2]$	**28**	 **30**	89	> 97: < 3
8	$[Cp_2TiCl_2]$	 **31**	 **32**	69	> 97: < 3

[a] For details of assignments see Experimental Section.

increased with the bulkier $[(t\mathrm{BuCp})_2TiCl_2]$ in both cases (entries 2 and 4). Thus, interaction of $CH_2O[TiCp^{subst}{}_2Cl]$ with the bridging geminal dimethyl group is more important than the interactions of the latter group with the approaching radical trap as shown in Figure 7.

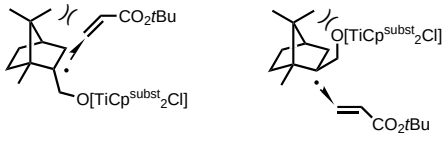


Figure 7. Qualitative analysis of steric factors controlling the reactivity of radical **A**.

The very high intrinsic selectivity of the camphor system is therefore for the first time in radical chemistry overwhelmed by the action of a catalyst.

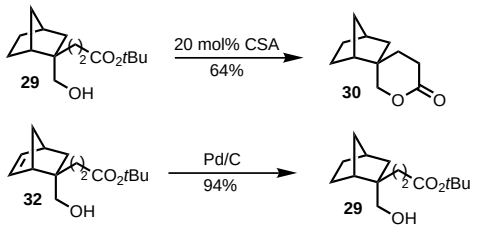
This situation, although at first glance reminiscent of Giese's and Metzger's system, has the added advantage of reagent control by ligand variation over the above-mentioned substrate controlled reactions.

In the case of the norbornyl **28** and norbornenyl **31** epoxides investigated (entries 5–8) the observed selectivity was excellent. Obviously, replacing the geminal dimethyl group with a methylene group resulted in the loss of unfavorable interactions with the radical trap while maintaining a more favorable positioning of $CH_2O[TiCp^{subst}{}_2Cl]$ in a staggered transition structure compared with an eclipsed transition structure.

The cooperative nature of these effects leads to outstanding diastereoselectivity. The observation that use of the bulky catalyst **18** does not affect the stereochemical outcome of the reaction is in line with this argument.

Thus, the most important factor governing selectivity in these reactions is the positioning of the bulky $CH_2O[TiCp^{subst}{}_2Cl]$ in the sterically most favorable position and not the unhindered approach of the radical trap. Selectivity can be increased by variation of the catalyst's ligand size. To the best of our knowledge this reagent controlled approach to controlling diastereoselectivity is novel in catalyzed radical reactions.

The assignment of the structures was made on the basis of NOE studies for **30** and by transformation of **29** to **30** and **32** to **29** as shown in Scheme 7.

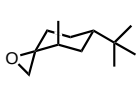
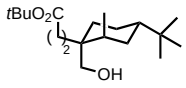
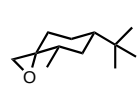
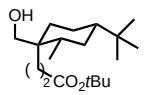


Scheme 7. Chemical correlations for the structural determination of **29** and **32** (CSA = camphorsulfonic acid).

The last examples shown in Table 7 have been investigated to probe the effect of the bulky titanocene catalyst in sterically less demanding situations.

With epoxide **33** (entry 1) containing the axially positioned methyl group the product **34** was obtained as a single isomer. The use of **18** as catalyst did not result in any changes in selectivity. The relative configuration was assigned as *trans* according to estimations of the ^{13}C NMR shifts of both diastereoisomers of **34**. Due to the γ-effect[25] the *trans* diastereoisomer (CH_3 vs. CH_2OH) has a substantially lower shift of the CH_2OH group (68.3 ppm) than the *cis* isomer (CH_3

Table 7. Reagent control in the opening of axially and equatorially substituted cyclohexane derived epoxides **33** and **35**.

Entry	Catalyst	Substrate	Product	Yield [%]	*dr*
1	Cp_2TiCl_2	 **33**	 **34**	73	> 95: < 5
2	Cp_2TiCl_2	 **35**	 **36**	77	56:44
3	**16**	**35**	**36**	45	48:52

0947-6539/03/0902-0536 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 2

vs. CH_2OH) (71.3 ppm). The observed value of 67.4 ppm therefore suggests the structure of **34** shown in Table 7. This assignment was also confirmed by the transformation of **34** to the corresponding lactone **37** and estimation of the corresponding ^{13}C NMR shifts. In the case of epoxide **35** (entries 2 and 3) hydroxyester **36** is obtained as 55:45 mixture of isomers (assignment as shown due to the ^{13}C NMR shifts of the CH_2OH groups considering the γ-effect) with $[Cp_2TiCl_2]$ as catalyst and 48:52 mixture of isomers with **18** as catalyst.

Transition structures similar to Giese's and Metzger's analysis[23] shown in Figure 8 readily explain the observed selectivities.

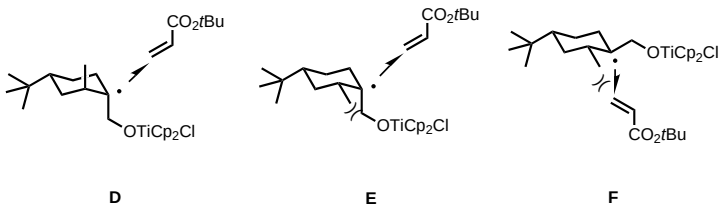


Figure 8. Plausible transition structures **D**–**F** for the reactions of epoxides **33** and **35**.

In the case of epoxide **33** the repulsion between the bulky $CH_2O[TiCp_2Cl]$ group and the axial methyl group results in blocking of the bottom face in structure **D** and therefore leads to the observed diaxial arrangement of the methyl and hydroxymethylene group in the product through equatorial attack of the radical trap.

Interestingly Renaud observed the opposite axial attack of Bu_3SnH in reactions of nitrogen substituted cyclohexyl radicals with axially positioned substituents.[26a] However, a conceptually similar exception to Giese's *anti* rule[2a] has been reported by Renaud for the case of 2-oxacycloalkyl radicals in which approach of the radical *cis* to a large tert butyl substituent has been observed.[26b] Our method achieves the same goal by the use of a catalyst and therefore complements traditional free radical reactions and should be of general interest in the synthesis of axially disubstituted cyclohexane derivatives, for example in modified steroids.

The situation is less clear cut in the case of epoxide **35** containing the equatorial methyl group. It seems that due to the competing unfavorable interactions both transition structures **E** and **F** shown in Figure 8 are accessible that result in the mixture of products obtained.

Conclusion

The opening of *meso* epoxides through electron transfer from titanocene(III) catalysts occurs with high enantioselectivity and represents the first example of a catalytic enantioselective radical generating reaction. Furthermore, the diastereoselectivity of the ensuing addition reaction to acrylates is also controlled by the ligands of titanium. Diastereoselectivity of the addition reactions of radicals derived from 2,2-disubstituted epoxides also proceeds under reagent control and is governed by the sterically most favorable positioning of the bulky titanocene moiety. In accord with this hypothesis, introduction of bulkier ligands can result in higher selectivities.

Experimental Section

General procedures: All reactions were performed in oven-dried (100 °C) glassware under N_2 or Ar. 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. The products were purified by flash chromatography[27] on Macherey-Nagel silica gel 60 and Merck silica gel 50 (eluents given in brackets, CH refers to cyclohexane, EE to ethyl acetate, Et_2O to diethyl ether, MTBE to *tert*-butyl methyl ether, and PE to petrol ether, b.p. 30–60 °C). Yields refer to analytically pure samples. Isomer ratios were determined from suitable ^1H NMR integrals of cleanly separated signals or by GC-analysis. NMR: Bruker AMX 300, AM 400, DRX 500, Varian XR 200, and MERCURY 300 HFCP; ^1H NMR: tetramethylsilane (0.00 ppm) in the indicated solvent, $[D_5]$benzene (7.16 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 C_6D_6 (128.06 ppm) as internal standards in the same solvent; integrals in accord with assignments, coupling constants are measured in Hz and always constitute J(H,H) coupling constants. An asterisk (*) indicates the signals of the minor diastereoisomer. Combustion analyses: Mr. Hambloch, Institut für Organische Chemie, Universität Göttingen; Mrs. Bähr, Institut für Organische Chemie und Biochemie, Universität Freiburg, and 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.

Collidine hydrochloride was dried prior to use by gentle heating under vacuum. The following compounds were purchased, prepared according to literature procedures, or have already been described in the literature: **1**,[28] **2**,[28] **3**,[29] **7**,[14] **8**,[16] **9**,[16] **10**,[17] **13**, **15**,[30] **16**,[31] **18**,[32] **19**, **21**, **23**, **25**,[33] **26**,[34] **28**,[35] **31**,[35] **33**,[36] **36**.[36]

General procedure 1 (GP 1)

Reductive epoxide opening: The epoxide (1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.80 mmol), Cp_2TiCl_2 (12.4 mg, 0.5 mmol) and zinc dust (98.1 mg, 1.5 mmol) were added to a suspension of dried 2,4,6-collidine hydrochloride (236 mg, 1.5 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for the indicated time. Unreacted Zn was decanted off and the reaction flask was rinsed with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with 2 N HCl (30 mL) and H_2O (30 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the crude product purified by flash chromatography.

General procedure 2 (GP 2)

Epoxide opening and ensuing addition to α,β-unsaturated carbonyl compounds: The epoxide (1.0 mmol), *tert* butyl acrylate (389 mg, 3.0 mmol), Cp_2TiCl_2 (12.4 mg, 0.5 mmol) and zinc dust (131 mg, 2.0 mmol) were added to a suspension of dried 2,4,6-collidine hydrochloride (394 mg, 2.5 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for the indicated time. Unreacted Zn was decanted off and the reaction flask was rinsed with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with 2 N HCl (30 mL) and H_2O (30 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the crude product purified by flash chromatography, microdistillation or both.

Preparation of epoxides 11 and 12

(*Z*)-1,4-Dipropoxy-but-2-ene oxide (11): A mixture of (*Z*)-1,4-dipropoxy-but-2-ene[37] (12.7 g, 80 mmol), methyltrioxorhenium (100 mg, 0.4 mmol),[38] 3-cyano pyridine (833 mg, 8.0 mmol), hydrogen peroxide (16.2 mL of a 30% solution in H_2O, 160 mmol), and CH_2Cl_2 (48 mL) was stirred for 65 h. Ice (9.5 g) and MnO_2 (12 mg) were added and after 1 h the

mixture was extracted with CH_2Cl_2 (2×50 mL). After drying ($MgSO_4$) the solvent was evaporated, petrol ether (100 mL) added, filtered, and the solvent evaporated again. The resulting crude product was distilled to give **11** (11.3 g, 75%). ^{1}H NMR (400 MHz, C_6D_6): δ = AB-signal ($\delta_{A1} = 3.31$, $\delta_{B1} = 3.42$, $J_{AB} = 11.3$ Hz, additionally split by $^3J = 6.4$, 3.9 Hz, 2H), AB-signal ($\delta_{A2} = 3.18$, $\delta_{B2} = 3.27$, $J_{AB} = 9.1$ Hz, additionally split by $^3J = 6.6$, 6.6 Hz, 2H), 3.01 (m, 2H), 1.50 (qt, $^3J = 7.4$, 6.6 Hz, 4H), 0.91 (t, $^3J = 7.3$ Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 73.0$, 68.2, 54.4, 23.4, 10.8; IR (neat): $\tilde{\nu} = 2965$, 2875, 1690, 1465, 1385, 1355, 1325, 1255, 1110, 1050, 955, 910, 845, 780, 760 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{20}O_3$ (188.3): C 63.80, H 10.71; found: C 63.67, H 10.86.

(*Z*)-1,4-Di-*tert*-butoxy-but-2-ene oxide (12): *m*CPBA (9.12 g (70%), 37 mmol) was added to a solution of (*Z*)-1,4-di-*tert*-butoxy-but-2-ene[39] (5.0 g, 25 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred for 8 h. After filtration, the organic layer was extracted with 1M NaOH (2×40 mL) and dried ($MgSO_4$). After evaporation of the solvent the crude product was distilled to yield **12** (3.62 g, 67%). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 3.51 - 3.43$ (m, 4H), 3.15 (dt, $^3J = 7.8$, 3.9 Hz, 2H), 1.07 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 72.9$, 60.8, 55.6, 27.5; IR (neat): $\tilde{\nu} = 2975$, 1470, 1390, 1365, 1235, 1195, 1080, 1025, 890, 840 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{24}O_3$ (216.3): C 66.63, H 11.17; found: C 66.38, H 11.18.

Synthesis of authentic samples of (*S*)-2, -5, and -6 from (*S*)-3

Synthesis of (*S*)-2: Compound **(*S*)-3**[29] (981 mg, 5.0 mmol) was added in portions at $-15\,^\circ$C to a suspension of NaH (95%, 264 mg, 10.5 mmol) in dry DMF (6 mL). After 10 min EtBr (1.19 g, 11.0 mmol) was added in DMF (6 mL) and the mixture was allowed to react for 14 h at room temperature. After dilution with DMF (10 mL). H_2O (20 mL) was added and the mixture was extracted with EE (3×30 mL). The combined organic layers were washed with H_2O (20 mL), dried ($MgSO_4$) and the solvent evaporated. After silica gel filtration (EE:CH 15:85 $\rightarrow$ 50:50) the crude product was purified by Kugelrohr distillation to give **(*S*)-4a** (969 mg, 77%). $[\alpha]_D^{27} = -14.1$ ($c = 1$ in CH_2Cl_2); R_f (EE:CH 15:85) = 0.47; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39 - 7.22$ (m, 5H), AB-signal ($\delta_{A1} = 4.57$, $\delta_{B1} = 4.71$, $J_{AB} = 11.7$ Hz, 2H), 3.74 (dtd, $^3J = 7.3$, 5.0, 5.0 Hz, 1H), 3.57 – 3.46 (m, 3H), AB-signal ($\delta_{A2} \approx 3.40$, $\delta_{B2} = 3.45$, $J_{AB} \approx 7.1$ Hz, additionally split by $^3J \approx 7.0$, 2.3, 7.0, 2.3 Hz, 2H), 1.90 – 1.70 (m_{AB}, 2H), 1.21 (t, $^3J = 7.0$ Hz, 3H), 1.17 (t, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 139.1$, 128.4, 128.0, 127.6, 75.5, 73.5, 72.3, 67.0, 66.9, 66.3, 32.5, 15.4; IR (neat): $\tilde{\nu} = 3480$, 3030, 2975, 2870, 2805, 1725, 1705, 1605, 1495, 1455, 1355, 1310, 1275, 1210, 1115, 1065, 1030, 900, 820, 735, 700 cm^{-1}; HRMS (EI/70 eV): *m*/*z*: calcd for $C_{15}H_{25}O_3^+$: 253.1804; found: 253.1813 [M^++H].

The triether **(*S*)-4a** (252 mg, 1.0 mmol) was dissolved in Et_2O (10 mL) under a hydrogen atmosphere and Pd/C (10%, 106 mg, 0.1 mmol) was added. After stirring for 2 h at room temperature the catalyst was filtered off and the solvent evaporated to yield pure **(*S*)-2** in quantitative yield. $[\alpha]_D^{29} = +1.3^\circ$ ($c = 1$ in CH_2Cl_2); for spectral details see below.

Synthesis of (*S*)-5: According to the preparation of **(*S*)-4a** compound **(*S*)-4b** (590 mg, 42%) was obtained by reaction with *n*PrBr (1.35 g, 11.0 mmol). $[\alpha]_D^{27} = -31.0$ ($c = 1$ in CH_2Cl_2); R_f (EE/CH 15:85) = 0.61; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39 - 7.23$ (m, 5H), AB-signal ($\delta_{A1} = 4.57$, $\delta_{B1} = 4.72$, $J_{AB} = 11.7$ Hz, 1H), 3.74 (dtd, $^3J = 7.7$, 5.0, 5.0 Hz, 1H), 3.57 – 3.46 (m, 4H), AB-signal ($\delta_{A2} \approx 3.40$, $\delta_{B2} = 3.42$, $J_{AB} \approx 6.6$ Hz, additionally split by $^3J \approx 6.6$, 6.6 Hz, 2H), AB-signal ($\delta_{A3} \approx 3.30$, $\delta_{B3} = 3.35$, $J_{AB} \approx 9.3$ Hz, additionally split by $^3J \approx 6.8$, 6.8 Hz, 2H), 1.70 – 1.90 (m_{AB}, 2H), 1.60 (qt, $^3J = 7.1$, 6.9 Hz, 2H), 1.56 (qt, $^3J = 7.1$, 7.1 Hz, 2H), 0.93 (t, $^3J = 7.1$ Hz, 3H), 0.90 (t, $^3J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 139.1$, 128.4, 128.0, 127.6, 75.5, 73.9, 73.3, 72.7, 72.4, 67.2, 32.5, 23.1, 23.1, 10.8; IR (film): $\tilde{\nu} = 3470$, 3030, 2960, 2935, 2865, 2800, 1725, 1605, 1495, 1455, 1380, 1310, 1250, 1210, 1115, 1065, 1030, 995, 955, 915, 735, 700 cm^{-1}; HRMS (EI/70 eV): calcd for $C_{17}H_{28}O_3^+$: 280.2036; found: 280.2038 [M^+].

The triether **(*S*)-4b** (280 mg, 1.0 mmol) was dissolved in Et_2O (10 mL) under a hydrogen atmosphere and Pd/C (106 mg, 10%, 0.1 mmol) was added. After stirring for 2 h at room temperature the catalyst was filtered off and the solvent evaporated to yield pure **(*S*)-5** in quantitative yield. $[\alpha]_D^{28} = +1.2^\circ$ ($c = 1$ in CH_2Cl_2); for spectral details see below.

Synthesis of (*S*)-6: In a pressure bottle isobutene (ca. 40 mL, 24 g, 430 mmol) was condensed into a solution of **3**[29] (981 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) at $-45\,^\circ$C. After the addition of H_2SO_4 (0.53 mL, 10.0 mmol) the closed bottle was allowed to warm to room temperature and stirring was continued for 18 h. After addition of H_2O (20 mL) at $0\,^\circ$C isobutene was allowed to evaporate and after washing and drying ($MgSO_4$) the solvent was evaporated. The crude product was purified by silica gel chromatography (EE:CH 5:95) to yield **4c** that was contaminated with side products due to alkylation of the aromatic ring (621 mg).

The contaminated **4c** (308 mg) was dissolved in Et_2O (10 mL) under a hydrogen atmosphere and Pd/C (106 mg, 10%, 0.1 mmol) was added. After stirring for 2 h at room temperature the catalyst was filtered off and the solvent evaporated to yield pure **(*S*)-6** in quantitative yield. $[\alpha]_D^{26} = -0.1^\circ$ ($c = 1$ in CH_2Cl_2); for spectral details see below.

1,4-Diethoxybutan-2-ol and (*S*)-1,4-diethoxybutan-2-ol (2):

Table 1, entry 1: Racemic **2**: According to GP 1 **1** (160 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), [Cp_2TiCl_2] (12.5 mg, 0.5 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 12:88) gave **2**[28] (84 mg, 52%). GC conditions for racemic **14**: Heptakis-(2,6-di-*O*-methyl-1,3-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4), column 70 °C, 70 kbar H_2; (*R*) = 26.0 min, (*S*) = 27.4 min.

Use of catalyst 7: According to GP 1 **1** (160 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **7** (68 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 20 h. Silica gel chromatography (Et_2O:PE 12:88) gave **2**[28] (115 mg, 71%). Major enantiomer: (*S*) (93% *ee*).

Table 1, entry 2: According to GP 1 **1** (160 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **8** (53 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 12:88) gave **2**[28] (123 mg, 76%). Major enantiomer: (*S*) (94% *ee*). $[\alpha]_D^{26} = +1.2^\circ$ ($c = 1$ in CH_2Cl_2).

Table 1, entry 3: According to GP 1 **1** (160 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **9** (53 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 12:88) gave **2**[28] (73 mg, 45%). Major enantiomer: (*R*) (20% *ee*).

Table 1, entry 4: According to GP 1 **1** (160 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **10** (53 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 12:88) gave **2**[28] (90 mg, 55%). Major enantiomer: (*R*) (56% *ee*).

1,4-Dipropoxybutan-2-ol and (*S*)-1,4-dipropoxy-butan-2-ol (5):

Table 2, entry 1: Racemic **5**: According to GP 1 **11** (188 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), Cp_2TiCl_2 (12.5 mg, 0.5 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (CH:EE 8:1) gave **5** (89 mg, 47%). R_f (Et_2O:PE 15:85) = 0.11; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.02 - 3.90$ (m, 1H), AB-signal ($\delta_{A1} = 3.59$, $\delta_{B1} = 3.64$, $J_{AB} = 9.4$ Hz, additionally split by $^3J = 6.3$, 5.9 Hz, 2H), 3.43 (t, $^3J = 7.0$ Hz, 2H), 3.39 (t, $^3J = 7.0$ Hz, 2H), AB-signal ($\delta_{A2} = 3.37$, $\delta_{B2} = 3.43$, $J_{AB} = 9.4$ Hz, additionally split by $^3J = 7.0$ Hz, 2H), 3.03 (d, $^3J \approx 2.8$ Hz, 1H), 1.74 (ddd, $^3J = 6.3$, 5.9, 5.9 Hz, 2H), 1.60 (qt, $^3J = 7.3$, 7.0 Hz, 2H), 1.59 (qt, $^3J = 7.3$, 7.0 Hz, 2H), 0.91 (t, $^3J = 7.0$ Hz, 6H); ^{13}C NMR (APT-spectrum at 75 MHz, $CDCl_3$): δ = "–" 74.9, "–" 73.2, "–" 73.0, "+" 69.50, "–" 68.7, "–" 33.3, "–" 23.0, "–" 22.9, "+" 10.7, "+" 10.6; IR (film): $\tilde{\nu} = 3455$, 2975, 2930, 2870, 1490, 1445, 1380, 1355, 1300, 1210, 1115, 915, 795 cm^{-1}; HRMS (EI/70 eV): *m*/*z*: calcd for $C_{10}H_{23}O_3$: 191.1647; found: 191.1647 [M^++H]. GC conditions for racemic **5**: 25 m Ivadex 7/OV-1701;G/294, 0.8 bar H_2, (*S*) = 32.93 min, (*R*) = 33.32 min.

Use of catalyst 7: According to GP 1 **11** (188 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **7** (34 mg, 0.05 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (CH:EE 8:1) gave **5** (115 mg, 60%) major enantiomer: (*S*) (92% *ee*).

1,4-*tert*-Butoxy-butan-2-ol and (*S*)- 1,4-*tert*-butoxy-butan-2-ol (6):

Table 2, entry 2: Racemic **6**: According to GP 1 **12** (216 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), [Cp_2TiCl_2] (12.5 mg, 0.05 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 15:85) gave **6** (139 mg, 64%). R_f (Et_2O:PE 15:85) = 0.14; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.91 - 3.79$ (m, 1H), AB-signal ($\delta_{A1} = 3.54$, $\delta_{B1} = 3.60$, $J_{AB} = 8.7$ Hz, additionally split by $^3J = 7.3$, 5.2, 5.6, 5.2 Hz, 2H), AB-signal ($\delta_{A2} = 3.29$, $\delta_{B2} = 3.32$, $J_{AB} = 8.7$ Hz, additionally split by $^3J = 6.6$, 5.2 Hz, 2H), 3.31 (d, ^3J

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≈2.8 Hz, 1H), AB-signal ($\delta_{A3}=1.69$, $\delta_{B3}=1.75$, $J_{AB}=8.7$ Hz, additionally split by $^3J=7.3, 5.2, 5.6, 5.2, 3.5$ Hz, 2H), 1.21 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (APT-Spectrum at 75 MHz, $CDCl_3$): δ = "−" 73.2, "−" 73.0, "+" 70.4, "−" 66.0, "−" 59.9, "−" 33.8, "+" 27.6, "+" 27.6; IR (neat): $\tilde{\nu}=3480, 2975, 2935, 2870, 1475, 1390, 1365, 1255, 1235, 1195, 1085, 1020, 955, 915, 885, 850, 805, 740$ cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{26}O_3$ (218.3): C 66.01, H 12.00; found: C 65.81, H 11.73; GC conditions for racemic **6**: Heptakis-(2,6-di-*O*-methyl-1,3-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4), column 95 °C, 70 kbar H_2; (*S*) = 21.9 min, (*R*) = 23.3 min.

Use of catalyst 7: According to GP 1 **12** (216 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **7** (68 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 15:85) gave **6** (150 mg, 68%). Major enantiomer: (*S*) (74% *ee*).

Table 2, entry 3: According to GP 1 **11** (188 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **8** (53 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (Et_2O:PE 1:9) gave **5** (135 mg, 71%) major enantiomer: (*S*) (91% *ee*), $[\alpha]_D^{28}=+1.2°$.

Table 2, entry 4: According to GP 1 **12** (216 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), **8** (52.5 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (236 mg, 1.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (Et_2O:PE 15:85) gave **6** (145 mg, 67%) major enantiomer: (*S*) (86% *ee*).

Table 2, entry 5: According to GP 1 **12** (162 mg, 0.75 mmol), 1,4-cyclohexadiene (290 mg, 3.6 mmol), **10** (29 mg, 0.75 mmol), zinc dust (98 mg, 1.5 mmol) and hydrochloride (177 mg, 1.1 mmol) in THF (10 mL) for 16 h. Silica gel chromatography (Et_2O:PE 15:85) gave **6** (49 mg, 30%) major enantiomer: (*R*) (20% *ee*).

Preparation of bis[η^5(1-methylcyclohexyl)-cyclopentadienyl]titanium dichloride (17): A solution of cyclopenta-2,4-dienylidene-cyclohexane[40] (5.8 g, 40 mmol) in dry Et_2O (40 mL) was cooled to 0 °C under inert atmosphere. Methyl lithium (25 mL of a 1.5 M solution in Et_2O, 38 mmol) was added over a period of 30 min, and the resulting yellow suspension of (1-methyl-cyclohexyl)-cyclopentadienyl lithium stirred for 2 h at 0 °C. Dry Et_2O (40 mL) was cooled to 0 °C under inert atmosphere and $TiCl_4$ (1.86 mL, 17 mmol) was added dropwise. Then the suspension of (1-methyl-cyclohexyl)-cyclopentadienyl lithium was added and stirring was continued for 2 h at 0 °C. The reaction mixture was allowed to reach room temperature overnight. After cooling again to 0 °C the reaction was quenched by addition of a solution of NaCl (4 g, 68 mmol) in 1N HCl (40 mL). The resulting mixture was filtrated and the residue washed with MTBE. After dissolving the crude product in CH_2Cl_2 red crystals of **17** (5.3 g, 63%) were obtained by slow evaporation of the solvent. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.57$ (t, $^3J=2.7$ Hz, 4H), 6.45 (t, $^3J=2.7$ Hz, 4H), 1.76–1.65 (m, 4H), 1.63–1.48 (m, 16H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=150.5, 120.2, 117.2, 38.7, 37.6, 26.1, 23.8, 22.3$; IR (KBr): $\tilde{\nu}=3130, 3100, 3085, 2990, 2925, 2855, 1480, 1450, 1390, 1375, 1265, 1160, 1110, 1050, 965, 940, 910, 845, 830, 670, 645$ cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{34}TiCl_2$ (441.31): C 65.32, H 7.77; found: C 65.06, H 7.66; X-ray structure available upon request.

Table 3, entry 1: **3-(*trans*-2-Hydroxy-cyclopent-(*R*)-1-yl)-propionic acid-*tert*-butylester (*trans*-14) and 3-(*cis*-2-hydroxy-cyclopent-(*R*)-1-yl)-propionic acid-*tert*-butylester (*cis*-14)**:

Table 3, entry 1: According to GP 2 **13** (420 mg, 5.0 mmol), acrylic acid *tert*-butylester (962 mg, 7.5 mmol), Cp_2TiCl_2 (62 mg, 0.25 mmol), zinc dust (654 mg, 10 mmol) and collidine hydrochloride (1.97 g, 12.5 mmol) in THF (50 mL) for 15 h. Silica gel chromatography (MTBE:PE 30:70) gave ***trans*-14** (620 mg, 58%) and ***cis*-14** (102 mg, 10%). ***trans*-14**: R_f (MTBE:PE 30:70) = 0.21; ^{1}H NMR (300 MHz, C_6D_6): $\delta=3.51$ (dd, $^3J\approx11.9, 5.7$ Hz, 1H), 2.23–2.18 (m, 2H), 1.77–1.27 (m, 4H), 1.39 (s, 9H), 1.20 (br s, 1H), 0.91 (dd, $^3J\approx11.9, 8.0$ Hz, 1H); ^{13}C NMR (50 MHz, C_6D_6): $\delta=173.2, 79.7, 78.7, 47.8, 34.9, 34.5, 30.1, 29.4, 28.1, 22.1$; IR (neat): $\tilde{\nu}=3430, 2955, 2870, 1730, 1455, 1420, 1390, 1365, 1320, 1255, 1155, 1095, 1065, 970, 850, 755$ cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{22}O_3$ (214.3): C 67.26, H 10.35; found: C 67.21, H 10.50.

***cis*-14**: R_f (MTBE:PE 30:70) = 0.28; ^{1}H NMR (300 MHz, C_6D_6): $\delta=3.66$ (br s, 1H), AB-signal ($\delta_A=2.16$, $\delta_B=2.19$, $J_{AB}=16.2$ Hz, additionally split by $^3J=6.8, 7.0$ Hz, 2H), 1.95–1.33 (m, 8H), 1.36 (s, 9H), 0.86–1.00 (m, 2H); ^{13}C NMR (APT-Spectrum at 50 MHz, C_6D_6): δ = "−" 173.76, "−" 79.87, "+" 73.32, "+" 46.7, "−" 34.99, "−" 34.81, "−" 29.38, "+" 28.08, "−" 24.22, "−" 22.06; IR (neat): $\tilde{\nu}=3440, 2955, 2925, 2870, 1730, 1455, 1420, 1390, 1365, 1255, 1155, 1020, 995, 965, 915, 845, 755$ cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{22}O_3$ (214.3): C 67.26, H 10.35; found: C 67.38, H 10.21.

Table 3, entry 2: According to GP 2 **13** (168 mg, 2.0 mmol), acrylic acid *tert*-butylester (769 mg, 6.0 mmol), **15** (55 mg, 0.2 mol), zinc dust (262 mg, 4.0 mmol), and collidine hydrochloride (790 mg, 5.0 mmol) in THF (20 mL) for 19 h. Silica gel chromatography (MTBE:PE 3:7) gave ***trans*-14** (290 mg, 1.4 mmol, 68%) and ***cis*-14** (18 mg, 0.1 mmol, 4%).

Table 3, entry 3: According to GP 2 **13** (168 mg, 2.0 mmol), acrylic acid *tert*-butylester (769 mg, 6.0 mmol), **16** (82 mg, 0.2 mmol), zinc dust (262 mg, 4.0 mmol), and collidine hydrochloride (790 mg, 5.0 mmol) in THF (20 mL) for 19 h. Silica gel chromatography (MTBE:PE 3:7) gave ***trans*-14** (308 mg, 1.4 mmol, 71%) and ***cis*-14** (15 mg, 0.1 mmol, 3%).

Table 3, entry 4: According to GP 2 **13** (168 mg, 2.0 mmol), acrylic acid *tert*-butylester (769 mg, 6.0 mmol), **17** (88 mg, 0.2 mmol), zinc dust (262 mg, 4.0 mmol) and collidine hydrochloride (790 mg, 5.0 mmol) in THF (20 mL) for 19 h. Silica gel chromatography (MTBE:PE 3:7) gave ***trans*-14** (250 mg, 1.2 mmol, 58%) and ***cis*-14** (14 mg, 0.1 mmol, 3%).

Table 3, entry 5: According to GP 2 **13** (168 mg, 2.0 mmol), acrylic acid *tert*-butylester (769 mg, 6.0 mmol), **20** (72 mg, 0.2 mmol), zinc dust (262 mg, 4.0 mmol), and collidine hydrochloride (790 mg, 5.0 mmol) in THF (20 mL) for 19 h. Silica gel chromatography (MTBE:PE 3:7) gave ***trans*-14** (271 mg, 1.3 mmol, 63%).

3-(*trans*-2-Hydroxy-cyclohex-(*R*)-1-yl)-propionic acid-*tert*-butylester (*trans*-20) and 3-(*cis*-2-hydroxy-cyclohex-(*R*)-1-yl)-propionic acid-*tert*-butylester (*cis*-20):

Table 4, entry 1: According to GP 2 **19** (98 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 2.0 mmol), Cp_2TiCl_2 (12.4 mg, 0.5 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 g, 2.5 mmol) in THF (10 mL) for 17 h. Silica gel chromatography (EE:CH 1:9) gave ***cis*-20** (74 mg, 32%) and ***trans*-20** (133 mg, 58%). ***trans*-20**: R_f (CH:EE 89:11) = 0.18 ; ^{1}H NMR (400 MHz, C_6D_6): $\delta=3.02$ (ddd, $^3J\approx13.2, 9.8, 4.5$ Hz, 1H), 2.30 (ddd, $^3J=15.6, 8.5, 6.7$ Hz, 1H), 2.20 (ddd, $^2J=15.6$, $^3J=8.4, 7.0$ Hz, 1H), 2.18–2.06 (m, 1H), 1.84 (ddd, $^2J=12.3$, $^3J=8.4, 7.0$ Hz, 1H), 1.60–1.31 (m, 4H), 1.38 (s, 9H), 1.24–0.89 (m, 4H), 0.71 (dd, $^3J\approx13.2, 3.0$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=173.7, 79.7, 74.1, 45.0, 36.1, 33.0, 31.3, 30.5, 28.1, 25.9, 25.2$; IR (neat): $\tilde{\nu}=3425, 3930, 2855, 1730, 1450, 1365, 1255, 1155, 1045, 845$ cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{24}O_3$ (228.3): C 68.38, H 10.59; found: C 68.15, H 10.40.

***cis*-20**: R_f (CH:EE 89:11) = 0.23; ^{1}H NMR (400 MHz, C_6D_6): $\delta=3.68$ (s, 1H), 2.16 (dd, $J=7.1, 5.4$ Hz, 1H), 2.15 (dd, $J=7.3, 5.5$ Hz, 1H), 1.80 (dt, $J=14.6, 7.2$ Hz, 1H), 1.75–1.40 (m, 6H), 1.39 (s, 9H), 1.35–1.05 (m, 4H), 1.03 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=173.7, 79.8, 67.7, 44.8, 33.5, 33.4, 28.1, 27.4, 27.2, 25.9, 20.7$; IR (neat): $\tilde{\nu}=3455, 2930, 1730, 1450, 1365, 1255, 1155, 975, 945, 855$ cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{24}O_3$ (228.3): C 68.38, H 10.59; found: C 68.48, H 10.71.

Table 4, entry 2: According to GP 2 **19** (196 mg, 2.0 mmol), acrylic acid *tert*-butylester (768 mg, 6.0 mmol), **18** (72 mg, 0.2 mmol), zinc dust (262 mg, 4.0 mmol) and hydrochloride (788 mg, 5.0 mmol) in THF (15 mL) for 19 h. Silica gel chromatography (EE:CH 11:89) gave ***cis*-20** (87 mg, 19%) and ***trans*-20** (250 mg, 55%).

3-(*trans*-2-Hydroxy-cyclohept-(*R*)-1-yl)-propionic acid-*tert*-butylester (*trans*-22) and 3-(*cis*-2-hydroxy-cyclohept-(*R*)-1-yl)-propionic acid-*tert*-butylester (*cis*-22):

Table 4, entry 3: According to GP 2 **21** (112 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 2.0 mmol), [Cp_2TiCl_2] (12.4 mg, 0.5 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 g, 2.5 mmol) in THF (10 mL) for 17 h. Silica gel chromatography (EE:CH 1:9) gave **22** (199 mg, 82%) as 77:23 mixture of the *trans* and *cis* isomers.

Table 4, entry 4: According to GP 2 **21** (229 mg, 2.0 mmol), acrylic acid *tert*-butylester (768 mg, 6.0 mmol), **18** (72 mg, 0.2 mmol), zinc dust (262 mg, 4.0 mmol) and hydrochloride (788 mg, 5.0 mmol) in THF (15 mL) for 19 h. Silica gel chromatography (EE:CH 1:9) gave ***trans*-22** (301 mg, 62%), a 95:5 mixture of ***trans*-22** and ***cis*-22** (115 mg, 24%) and ***cis*-22** (20 mg, 4%). ***cis*-22**: R_f (CH:EE 75:25) = 0.50; ^{1}H NMR (400 MHz, C_6D_6): $\delta=3.68$ (ddd, $^3J=8.2, 5.1, 3.1$ Hz, 1H), 2.23 (dt, $^2J=15.5$, $^3J=7.8$ Hz, 1H), 2.18 (dt, $^2J=15.5$, $^3J=7.7$ Hz, 1H), 1.88 (ddt, $^2J=14.3$, $^3J=8.2, 7.2$ Hz, 1H), 1.72–1.36 (m,

11H), 1.39 (s, 9H), 1.36–1.15 (m, 1H), 1.04 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 173.5, 79.7, 71.6, 44.7, 35.8, 34.1, 28.7, 28.5, 28.1, 27.7, 27.0, 22.0; IR (neat): $\tilde{\nu}$ = 3445, 2925, 1730, 1455, 1390, 1365, 1255, 1150, 1035, 960, 850 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_3$ (242.4): C 69.38, H 10.81; found: C 69.28, H 10.90.

***trans*-22**: ^{1}H NMR (400 MHz, C_6D_6): δ = 3.25 (dd, $^3J \approx$ 13.5, 5.1 Hz, 1H), 2.27 (ddd, ^2J = 15.8, ^3J = 8.2, 6.2 Hz, 1H), 2.19 (dt, ^2J = 15.8, ^3J = 8.2 Hz, 1H), 2.01–1.89 (m, 1H), 1.71–1.39 (m, 7H), 1.39 (s, 9H), 1.38–1.19 (m, 4H), 1.07 (s, 1H), 1.00 (dt, $^3J \approx$ 13.5, 9.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 173.4, 79.7, 76.2, 47.0, 36.80, 33.4, 30.2, 29.3, 28.2, 27.1, 22.6; IR (neat): $\tilde{\nu}$ = 3435, 2980, 1730, 1455, 1390, 1360, 1255, 1155, 1025, 850, 755 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_3$ (242.4): C 69.38, H 10.81; found: C 69.22, H 10.76.

3-(3-*exo*-Hydroxy-bicyclo[2.2.1]hept-2-*exo*-yl)-propionic acid-*tert*-butylester (*exo*-24) and 3-(3-*exo*-hydroxy-bicyclo-[2.2.1]hept-2*endo*-yl)-propionic acid-*tert*-butylester (*endo*-24):

Table 4, entry 5: According to GP 2 **23** (110 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), Cp_2TiCl_2 (12 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 64 h. Silica gel chromatography (MTBE:PE 2:3) gave ***exo*-24** (140 mg, 58%) and ***endo*-24** (31 mg, 13%). ***exo*-24**: R_f (MTBE:PE 40:60) = 0.46; ^{1}H NMR (300 MHz, C_6D_6): δ = 3.44 (d, ^3J = 6.4, 1H), 2.40–2.17 (m, 2H), 1.93 (dt, $^2J \approx$ 14.0, ^3J = 7.5 Hz, 1H), 1.84 (d, ^3J = 3.1 Hz, 1H), 1.74 (brs, 1H), 1.63 (dm, $^2J \approx$ 8.0 Hz, 1H), 1.44–1.57 (m, 2H), 1.39 (s, 9H), 1.36–1.17 and 1.07–0.78 (m, 6H), 0.98 (brs, 1H); ^{13}C NMR (APT-spectrum at 50 MHz, C_6D_6): δ = "–" 173.3, "–" 79.5, "+" 76.1, "+" 48.9, "+" 45.3, "+" 41.5, "–" 35.8, "–" 32.7, "–" 29.9, "+" 28.2, "–" 24.5, "–" 24.4; IR (neat): $\tilde{\nu}$ = 3420, 2955, 2875, 1730, 1455, 1420, 1390, 1365, 1290, 1255, 1150, 1090, 1075, 1015, 955, 920, 885, 850, 805, 755 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_3$ (240.3): C 69.96, H 10.06; found: C 70.10, H 10.15.

***endo*-24**: R_f (MTBE:PE 40:60) = 0.31; m.p. 50–52 °C; ^{1}H NMR (300 MHz, C_6D_6): δ = 2.92 (brs, 1H), 2.20 (t, $^3J \approx$ 7.4 Hz, 2H), 1.94 (brs, 1H)*, 1.89 (d, ^3J = 4.9 Hz, 1H), 1.69 (dm, $^2J \approx$ 9.5 Hz, 1H), 1.46–1.66 and 1.01–1.37 (m, 7H), 1.39 (s, 9H), 0.69–0.78 (m, 1H), 0.50 (brs, 1H); ^{13}C NMR (APT-spectrum at 50 MHz, C_6D_6): δ = "–" 172.9, "+" 80.9, "–" 79.7, "+" 52.2, "+" 45.4, "+" 39.5, "–" 36.4, "–" 35.0, "+" 28.1, "–" 26.4, "–" 25.4, "–" 21.7; IR (neat): $\tilde{\nu}$ = 3445, 2950, 2870, 1730, 1455, 1420, 1390, 1365, 1330, 1255, 1220, 1155, 1100, 1060, 1040, 1020, 955, 920, 885, 850, 755 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{26}O_3$ (240.3): C 69.96, H 10.06; found: C 70.03, H 10.08.

Table 4, entry 6: According to GP 2 **23** (110 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), **18** (54 mg, 0.15 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (MTBE/pentane 1:3) gave ***exo*-24** (77 mg, 32%) and ***endo*-24** (87 mg, 36%).

(1*S*,2*R*)-3-(2-Hydroxy-cyclopent-1-yl)-propionic acid-*tert*-butylester (*trans*-14)

Table 5, entry 1: According to GP 2 **13** (84 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 3.0 mmol), **7** (34 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 60 h. Microdistillation and Silica gel chromatography (MTBE/pentane 3:7) gave **14** (147 mg, 69%). GC data of racemic **14**: heptakis(2,6-di-*O*-methyl-*O*-pentyl-β-cyclodextrin/OV 1701 (1/4) column 95 °C, 70 kbar H_2 119.4 min; 122.7 min; GC-data of chiral compound: heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column 95 °C, 70 kbar H_2, major enantiomer 119.4 min; ratio of 87:13 (*ee* 74%).

Table 5, entry 2: According to GP 2 **13** (84 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 2.0 mmol), **8** (53 mg, 0.1 mmol), 1,4-cyclohexadiene (80 mg, 1.0 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 22 h. Silica gel chromatography (EE:CH 10:90) gave **14** (154 mg, 72%). $[\alpha]_D^{23}$ (c = 1 in CH_2Cl_2) = –19.6°; GC-data of chiral compound: heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column 95 °C, 70 kbar H_2 major enantiomer 119.4 min; minor enantiomer 122.7 min in a ratio of 90.5:9.5 (*ee* 81%); After esterification with (*R*)-MTPA-Cl[41] of racemic **16** two signals in the ^{19}F NMR of equal intensity at –71.62 and –71.68 ppm were observed. With the chiral compound the ratio of the two signals was 91.5:8.5 (*ee* 83%).

(1*S*,2*R*)-3-(2-Hydroxy-cyclohept-1-yl)-propionic acid-*tert*-butylester (*trans*-22):

Table 5, entry 3: According to GP 2 **21** (112 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 2.0 mmol), **7** (34 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol) and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 36 h. Microdistillation and Silica gel chromatography (MTBE:PE 1:3) gave **22** (146 mg, 61%) in a *trans*:*cis* ratio of 87:13. GC data of racemic (*trans*)-**22**: 25 m IVADEX7/G286, 230/60–180/1/Min/300, 0.6 bar H_2, 79.0 min; 80.2 min. The minor *cis* diastereoisomers could not be separated and are observed as a broad signal at 79.4 min; GC data of chiral compound: major isomer 79.0 min; ratio of 91:9 (*ee* 82%).

Table 5, entry 4: According to GP 2 **21** (112 mg, 1.0 mmol), acrylic acid *tert*-butylester (256 mg, 2.0 mmol), **8** (53 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 17 h. Silica gel chromatography (EE:CH 8:92) gave **22** (189 mg, 78%). The experiment was repeated under identical conditions and the product was purified by microdistillation and Silica gel chromatography (EE:CH 10:90) to give **22** (130 mg, 54%). In both cases the *trans* to *cis* ratio was 87:13. $[\alpha]_D^{23}$ (c = 1 in CH_2Cl_2) = –13.7°; The mixture was converted to the trifluoro acetate and analyzed by GC. GC data of racemic trifluoroacetate of (*trans*)-**22**: heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column 120 °C, 70 kbar H_2 75.5 min; 76.9 min. The minor *cis* diastereoisomers could not be separated and are observed as a broad signal at 65.8 min. GC data of chiral compound: heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column 95 °C, 70 kbar H_2, major enantiomer 75.5 min; minor enantiomer 76.9 min in a ratio of 90:10 (*ee* 80%).

(1,7,7-Trimethyl-bicyclo[2.2.1]hept-2-yl)-methanol (26): **Table 6, entry 1**: According to GP 1 **25** (166 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), [Cp_2TiCl_2] (25 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and collidine hydrochloride (237 mg, 1.5 mmol) in THF (10 mL) for 19 h. Silica gel chromatography (CH:EE 8:1) gave **26** (91 mg, 55%) as 57:43 mixture of diastereoisomers. The major isomer was assigned as *exo* by comparison of the spectra with those reported in the literature.[34]

Table 6, entry 2: According to GP 1 **25** (166 mg, 1.0 mmol), 1,4-cyclohexadiene (385 mg, 4.8 mmol), [Cp_2TiCl_2] (25 mg, 0.1 mmol), zinc dust (98 mg, 1.5 mmol) and collidine hydrochloride (237 mg, 1.5 mmol) in THF (10 mL) for 19 h. Silica gel chromatography (CH:EE 8:1) gave **26** (60 mg, 36%) as 79:21 mixture of *exo* and *endo* diastereoisomers.

6-(1,7,7-Trimethyl-bicyclo[2.2.1]heptane)-pyran-2-on (27): **Table 6, entry 3**: According to GP 2 **25** (166 mg, 1.0 mmol), acrylonitrile (80 mg, 1.5 mmol), [Cp_2TiCl_2] (25 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 48 h and 5 h of reflux. Silica gel chromatography (CH:EE 8:1) gave **27** (130 mg, 56%) as 67:33 mixture of diastereoisomers. The major isomer was assigned as *exo* due to the similarities in the relevant ^{1}H and ^{13}C NMR signals of **26** and **27**. Compound **27**: m.p. 55 °C; ^{1}H NMR (300 MHz, C_6D_6): δ = 3.84 (d, ^2J = 11.9, 1H), 3.59 (m, 2-H)*, 3.51 (d, ^2J = 11.9 Hz, 1H), 2.09 (m, 2H), 2.01 (m, 2H)*, 1.45 (m, 2H), 1.40 (m, 1H), 1.23 (m, 2H), 1.10 (m, 2H), 1.06 (m, 2H), 1.01 (m, 1-H), 0.80 (m, 1H), 0.74 (m, 1H), 0.68 (s, 1H), 0.66 (s, 3H), 0.62 (s, 3H), 0.61 (s, 3H)*, 0.60 (s, 3H)*, 0.57 (s, 1-H), 0.56 (s, 3H), 0.55 (s, CH_3, 3H), 0.54 (s, CH_3, 3H)*; ^{13}C NMR (75 MHz, C_6D_6): δ = 172.1, 171.6*, 76.4*, 75.6, 51.1, 50.8*, 50.5*, 50.3, 46.2*, 45.9, 44.4, 43.0*, 42.8, 41.7*, 32.9*, 32.2, 31.6, 31.4*, 29.1, 28.9*, 27.6*, 27.4, 22.1, 22.0*, 21.7, 21.0*, 12.6*, 11.6; IR (KBr): $\tilde{\nu}$ = 2935, 1735, 1455, 1385, 1345, 1220, 1150, 1115, 1090, 1060, 1030, 830, 735 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{22}O_2$ (222.3): C 75.63, H 9.97; found: C 75.36, H 10.22.

Table 6, entry 4: According to GP 2 **25** (166 mg, 1.0 mmol), acrylonitrile (80 mg, 1.5 mmol), **18** (36 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 48 and 5 h of reflux. Silica gel chromatography (PE:MTBE 4:1) gave **27** (86 mg, 39%) as 77:23 mixture of isomers.

3-(2-*endo*-Hydroxymethyl-bicyclo[2.2.1]hept-2-*exo*-yl)-propionic acid-*tert*-butyl-ester (29):

Table 6, entry 5: According to GP 2 **28** (124 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), Cp_2TiCl_2 (12.0 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 19 h. Silica gel chromatography (PE:MTBE 4:1) gave **29** (195 mg, 77%). M.p. 48–49 °C; R_f (MTBE:PE 4:1) = 0.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ = AB-signal, δ_A = 3.37, δ_B = 3.35, $J_{AB} \approx$ 13.4 Hz, 2H),

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2.28 (br s, 1H), 2.24–2.17 (m, 2H), 2.20 (dd, ^3J = 7.2, 7.2 Hz, 1H), 2.01 (dm, J = 3.0 Hz, 1H), 1.86 (dd, ^2J = 14.5, ^3J = 7.3 Hz, 1H), 1.67–1.47 (m, 5H), 1.41 (s, 9H), 1.35 (dd, ^2J = 12.3, ^3J = 5.8 Hz, 1H), 1.24 (d, ^2J = 10.3 Hz, 1H), 1.18 (dd, ^2J = 9.0, ^3J = 6.3 Hz, 1H), 1.12–0.98 (m, 1H), 0.70 (dd, ^2J = 12.3, ^3J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 80.7, 65.0, 45.5, 43.5, 40.4, 37.7, 37.2, 30.2, 30.2, 28.5, 28.1, 24.7; IR (KBr): $\tilde{\nu}$ = 3310, 2950, 1730, 1455, 1415, 1365, 1315, 1255, 1155, 1035, 945, 880, 850, 805, 765 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{26}O_3$ (254.4): C 70.83, H 10.30; found: C 70.85, H 10.32.

Conversion of 29 to 30: Hydroxyester **29** (50 mg, 0.2 mmol) and 10-camphorsulfonic acid (9.3 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (10 mL). After 19 h of stirring at room temperature and washing with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL) the solvent was evaporated to give pure **30** (23 mg, 64%). For spectral details see: Table 6, entry 7.

Table 6, entry 6: According to GP 2 **28** (124 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), **18** (18 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol) and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (PE:MTBE 4:1) gave **29** (130 mg, 51%).

5-Bicyclo[2.2.1]hepta-2-yliden-tetrahydropyran-2-on (30): **Table 6, entry 7**: According to GP 2 **28** (124 mg, 1.0 mmol) acrylonitrile (161 mg, 3.0 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 19 and 5 h of reflux. Aqueous layer re-extracted with EE (3 × 20 mL). Silica gel chromatography (CH/EE 2:1) gave **30** (161 mg, 89%). M.p. 39–41 °C; R_f (CH/EE 2:1) = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ = AB-signal (δ_{A1} = 4.11, δ_{B1} = 4.06, J_{AB} = 11.2 Hz, 2H), 2.55 (t, ^3J = 7.1 Hz, 2H), 2.26 (dd, ^3J = 3.5, 3.9 Hz, 1H), 2.04 (dm, ^3J = 3.2 Hz, 1H), 1.84–1.62 (m, 2H), AB-signal (δ_{A2} = 1.80, δ_{B2} = 1.66, $J_{AB} \approx$ 14.0 Hz, additionally split by ^3J = 7.0, 7.0 Hz, 2H), 1.59 (dd, J = 12.3, ^3J = 3.5 Hz, 1H), 1.53 (ddd, ^2J = 8.2, ^3J = 2.0, 2.0 Hz, 1H), 1.49 (dd, $^2J \approx$ 10.5, ^3J = 3.0 Hz, 1H), 1.42 (ddd, $^2J \approx$ 10.5, ^3J = 5.5, 4.2 Hz, 1H), 1.35 (ddd, ^2J = 12.6, ^3J = 4.0, 3.0 Hz, 1H), 1.25 (br d, $^2J \approx$ 9.0 Hz, 1H), 1.10 (ddd, ^2J = 12.0, ^3J = 6.0, 2.7 Hz, 1H), 1.09 (dd, ^2J = 12.3, ^3J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 75.7, 43.1, 41.9, 39.5, 37.5, 37.0, 33.0, 28.1, 27.4, 24.0; IR (KBr): $\tilde{\nu}$ = 2945, 1730, 1465, 1390, 1350, 1295, 1240, 1205, 1180, 1065, 1035 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{16}O_2$ (180.2): C 73.30, H 8.95; found: C 73.06, H 8.72.

3-(2-*endo*-Hydroxymethyl-bicyclo[2.2.1]hept-5-ene-2*exo*-yl)-propionic acid-*tert*-butylester (32):

Table 6, entry 8: According to GP 2 **31** (122 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), Cp_2TiCl_2 (13 mg, 0.05 mmol), zinc dust (131 mg, 2.0 mmol) and collidine hydrochloride (394 mg, 5.0 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (CH:EE 5:1) gave **32** (173 mg, 69%). M.p. 44–45 °C; R_f (80% CH, 20% EE) = 0.24; ^{1}H NMR (400 MHz, C_6D_6): δ = 6.11 (d, ^3J = 3.0 Hz, 1H), 5.93 (dd, ^3J = 4.6, 3.3 Hz, 1H), 3.15 (br s, 1H), 2.59 (br s, 1H), 2.53 (br s, 1H), 2.32 (dd, $^2J \approx$ 15.0, ^3J = 7.8 Hz, 1H), 2.26 (dd, ^2J = 13.8, ^3J = 6.2 Hz, 1H), 2.19 (t, ^3J = 7.5 Hz, 1H), 2.17 (dd, ^2J = 13.8, ^3J = 7.4 Hz, 1H), 2.14 (t, ^3J = 7.5 Hz, 1H), 1.76 (dd, ^2J = 14.1, ^3J = 7.3 Hz, 1H), 1.10 (dd, ^2J = 11.7, ^3J = 3.7 Hz, 1H), 0.92 (t, ^3J = 7.1 Hz, 1H), 0.50 (d, ^2J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 136.4, 136.0, 80.1, 66.3, 49.1, 47.7, 42.9, 35.0, 31.9, 31.4, 28.1; IR (KBr): $\tilde{\nu}$ = 3295, 2970, 1725, 1445, 1365, 1310, 1160, 1025, 945, 850, 770, 720 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{24}O_3$ (252.4): C 71.39, H 9.59; found: C 71.38, H 9.56.

Conversion of 32 to 29: A mixture of **32** (90 mg, 0.36 mmol) and Pd/C (10%, 30 mg) in methanol was stirred under a hydrogen atmosphere for 5 h at room temperature. The solvent was removed under reduced pressure and the crude product filtered through silica gel with pentane to yield **29** (85 mg, 94%).

(1*S,2*S**,4*R**)-3-(1-Hydroxymethyl-4-*tert*-butyl-2-methy-cyclohexyl)-propionic acid *tert*-butyl ester (34)**:

Table 7, entry 1: According to GP 2 **33** (182 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), Cp_2TiCl_2 (25 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (PE:MTBE 4:1) gave **34** (227 mg, 73%). ^{1}H NMR (300 MHz, C_6D_6); δ = 3.24 (dd, ^2J = 11.3, ^3J = 5.0 Hz, 1H), 3.11 (dd, ^2J = 11.3, ^3J = 3.9 Hz, 1H), 2.30 (br m, 1H), 2.20 (t, ^3J = 7.6 Hz, 2H), 1.93 (t, ^3J = 7.7 Hz, 2H), 1.80 (br m, 1H), 1.45 (dd, ^2J = 12.8, ^3J = 4.3 Hz, 1H), 1.40 (m, 1H), 1.36 (s, 9H), 1.25 (m, 1H), 0.95 (d, ^3J = 7.2, 1H), 0.78 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ = 175.0, 80.5, 67.4, 42.2, 39.4, 33.6, 32.8, 30.7, 30.5, 28.7, 28.1, 27.6, 27.5, 22.8, 16.1; IR (KBr): $\tilde{\nu}$ = 3490, 2960, 1735, 1465, 1365, 1255, 1165, 1150, 1105, 1045, 920, 845, 760 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{36}O_3$ (312.3): C 73.03, H 11.61; found: C 72.63, H 11.28.

(1*S,2*R**,4*R**)- and (1*R**,2*S**,4*R**)-3-(1-Hydroxymethyl-4-isopropyl-2-methyl-cyclohexyl)-propionic acid *tert*-butyl ester (36)**:

Table 7, entry 2: According to GP 2 **35** (182 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), Cp_2TiCl_2 (25 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol), and collidine hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (CH:EE 5:1) gave **36** (240 mg, 77%) as 56:44 mixture of isomers. M.p. 80 °C; ^{1}H NMR (300 MHz, C_6D_6): δ = 3.42 (d, ^2J = 10.6 Hz, 1H), 3.33 (d, ^2J = 10.6 Hz, 1H), 3.24 (s, 1H)*, 2.20 (m, 4H), 2.19 (m, 2H), 1.72 (m, 3H), 1.57 (m, 3H), 1.40 (s, 9H)*, 1.38 (m, 2H), 1.37 (s, 9H), 1.22 (m, 2H), 0.98 (m, 8H), 0.86 (d, ^3J = 7.0 Hz, 3H), 0.82 (s, 9H), 0.82 (s, 9H)*, 0.78 (d, ^3J = 7.0 Hz, 3H)*; ^{13}C NMR (75 MHz, C_6D_6): δ = 174.6, 174.5*, 80.4*, 80.2, 70.6*, 64.3, 49.1, 49.0*, 39.8, 39.6*, 39.1, 38.5*, 33.4, 33.0, 33.0*, 32.5, 32.1*, 31.0*, 30.8, 28.8* 28.7, 23.6*, 23.1, 23.0*, 17.1*, 17.1; IR (KBr): $\tilde{\nu}$ = 3505, 2960, 2870, 1720, 1470, 1365, 1320, 1215, 1150, 1050, 980, 850, 760 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{36}O_3$ (312.3): C 73.03, H 11.61; found: C 72.92, H 11.62.

Table 7, entry 3: According to GP 2 **35** (182 mg, 1.0 mmol), acrylic acid *tert*-butylester (389 mg, 3.0 mmol), **18** (36 mg, 0.1 mmol), zinc dust (131 mg, 2.0 mmol) and hydrochloride (394 mg, 2.5 mmol) in THF (10 mL) for 15 h. Silica gel chromatography (PE:MTBE 4:1) gave **36** (140 mg, 45%) as 48:52 mixture of diastereoisomers.

9-*tert*-Butyl-7-methyl-2-oxa-spiro[5.5]undecan-3-one (37): Compound **36** (80 mg, 0.26 mmol) was added to a solution of camphorsulfonic acid (51 mg, 0.22 mmol) and the mixture was stirred for 19 h at room temperature. After washing with sat. aq. $NaHCO_3$ (10 mL) and H_2O(10 mL) the organic phase was dried ($MgSO_4$) and the solvent evaporated to yield **37** (50 mg, 82%). M.p. 59 °C; ^{1}H NMR (300 MHz, C_6D_6): δ = 4.06 (d, ^2J = 11.3, ^3J = 5.0 Hz, 1H), 3.88 (d, ^2J = 11.3 Hz, 1H), 2.51 (t, ^3J = 7.5 Hz, 2H), 1.82 (m, 2H), 1.76 (m, 1H), 1.61 (m, 1H), 1.43 (br m, 2H), 1.40 (t, ^3J = 4.0 Hz, 2H), 1.21 (m, 1H), 1.08 (td, ^2J = 12.2, ^3J = 5.2 Hz, 1H), 0.97 (d, ^3J = 7.0 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ = 173.0, 41.2, 34.7, 33.8, 32.4, 29.9, 29.2, 29.0, 27.7, 27.4, 22.3, 11.1; IR (KBr): $\tilde{\nu}$ = 2960, 2865, 1740, 1465, 1375, 1365, 1290, 1240, 1190, 1170, 1125, 1095, 1050, 1040, 1015, 990, 920, 880, 840, 735 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{26}O_2$ (238.2): C 75.58, H 10.99; found: C 75.30, H 11.06.

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