On the Constitutional Stability of η^1-Allylmetal Compounds

Reinhard W. Hoffmann* and André Polachowski

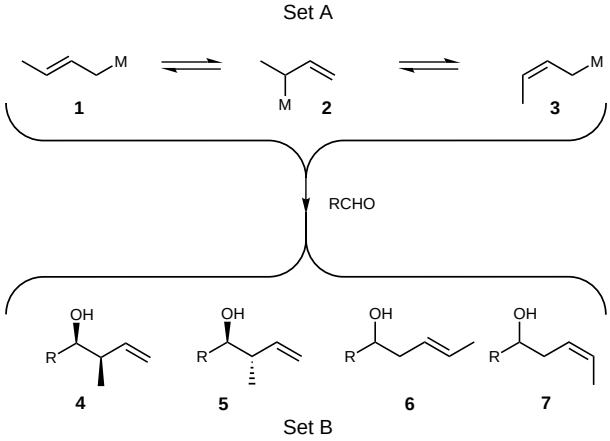
Abstract: Many η^1-allymetal species undergo a rapid haptotropic rearrangement. The stereochemical outcome of reactions of these allylmetal species with aldehydes depends on whether the haptotropic rearrangement is faster or slower than the reaction with the aldehyde. We present here a test system based on kinetic resolution, by which just this information becomes available. Thus, haptotropic rearrangement of cyclohexenyllithium, -magnesium chloride, -titanium triisopropoxide, and -titanium tetraisopropoxide, was found to be faster than addition to the aldehyde **9**. Borotropic rearrangement in cyclohexenyldiethylborane was found to be slower than the addition to the aldehyde **9**.

Keywords: allyl complexes · kinetic resolution · rearrangements

Introduction

Efficient synthesis of polyfunctional open-chain compounds requires reactions in which stereogenic centers are generated simultaneously with the formation of the molecular backbone. It is for this reason that stereocontrolled aldol addition of enolates and stereoselective addition of allyl metal compounds to aldehydes were intensively studied since the 1980s.[1] The addition of η^1-crotylmetallic compounds to aldehydes[2, 3] is in several instances complicated by a concurrent haptotropic rearrangement of the allylmetal compounds comprising the compounds **1**–**3**.[4, 5]

On reaction of any member of the set A of compounds **1** to **3** with an aldehyde, the product may be any member of the set B of compounds **4** to **8** or a mixture thereof (Scheme 1). Unless the C–C-bond formation is reversible,[6] the members of the set B do not interconvert, that is the outcome of the reaction is kinetically controlled. The selectivity attained depends then on distinct low-energy pathways that connect individual members of set A with those of set B. But it also depends on the relative rate of reaction with respect to the haptotropic rearrangement of the allylmetal compounds within the set A. Given the complexity of the system it testifies to the intuition and tenacity of chemists that highly stereoselective carbon–carbon bond-forming reactions have been developed based on such transformations. Representative cases are that for $M = SnR_3$, where both **1** and **3** lead to **4**,[7] for $M = B(OR)_2$ **1** leads specifically to **5,** and **3** specifically



Scheme 1. The possible outcomes from the reaction of η^1-crotyl metallic compounds with aldehydes.

to **4**.[4] For $M = Ti(OR)_3$ it is likely that the lowest energy pathway is the one connecting compound **1** to **5**.[8] For most other cases, including metals such as lithium, magnesium, zinc, chromium, samarium, and indium, only tentative mechanistic discussions are possible at present.[3, 5]

Even if the position of the equilibrium in set A is known,[9, 10] on account of the Curtin Hammett principle this may not be relevant to the stereoselectivity attained on reaction with an aldehyde when the equilibration within set A is more rapid than the addition to the aldehyde. Rate constants for haptotropic rearragentments of allylmetal compounds have been determined in some cases,[10, 11, 12] but in the absence of knowledge about the rate of reaction with an aldehyde these data do not delineate which mechanistic situation[13]—Curtin Hammett (dynamic kinetic resolution) or non-Curtin Hammett (thermodynamic or dynamic thermody-

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namic resolution)—prevails in a given system. To answer these questions, all one needs to know is whether the rate of additon of an allylmetal compound to an aldehyde is faster or slower than the haptotropic rearrangement within the former.

We report here on a study to gain just this information by a test based on kinetic resolution of enantiomeric compounds.[14, 15] We assume that the haptotropic rearrangement proceeds in a suprafacial manner and that the rate of the rearrangement between the members of set A may be represented by the rate of equilibration between **2** and **3**. That is, we assume that the rate of equilibration **1** $\rightleftharpoons$ **2** and **3** $\rightleftharpoons$ **2** are of the same order of magnitude. If this is the case, the system **1**, **2**, **3** may be approximated by a different system **8**, in which the haptotropic shift of the metal constitutes an enantiomerization.

At this point, the problem delineated above is reduced to the problem of defining the configurational stability of a species such as **8** on a time scale defined by the rate of reaction with which this species reacts in a bimolecular reaction, a problem for which we found a solution several years ago.[14, 15] Moreover, due to the geometric restraints present in **8** the products of the reaction with an aldehyde are confined to the structures **4** and **5**.

Results

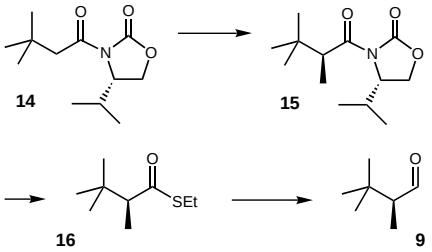
Development of the test reaction

The test is based on the kinetic resolution which may occur on reaction of a chiral substrate with a chiral reagent. Since the present study is devoted to the reaction of allylmetal compounds with aldehydes, we had to choose a chiral aldehyde such as **9** as the reaction partner.

This entails the inconvenience that one has to deal with four products **10**–**13** instead of two on account of the fact that the aldehyde group is prochiral and gives rise to an additional stereogenic center upon reaction with **8** (Scheme 2). Relevant for the test is the ratio between (**10** + **11** = set C) and (**12** + **13** = set D).[13, 16] To determine this ratio structural assignments have to be made to all four products. This among other factors[15, 17] determined the choice of the aldehyde **9**: The aldehyde chosen should a) be available in enantiomerically pure form, b) have a low tendency to racemize, c) react in high yield with the substrates **8**, d) lead to a significant level of kinetic resolution on reaction with the allylmetal compound **8**, and e) also allow for easy quantitation of the ratio of the products **10**–**13**.

In the initial phase of this work we tested a variety of aldehydes (2-benzyloxypropanal, 2-dibenzylamino-3-phenylpropanal, 2-methylpentanal, 2,3-dimethyl-butanal, 2-phenylpropanal) which did not meet all of the requirements. 2,3,3-Trimethylbutanal (**9**) was eventually chosen as the best compromise. The racemic aldehyde **9** was prepared by oxidation of 2,3,3-trimethylbutanol.[18]

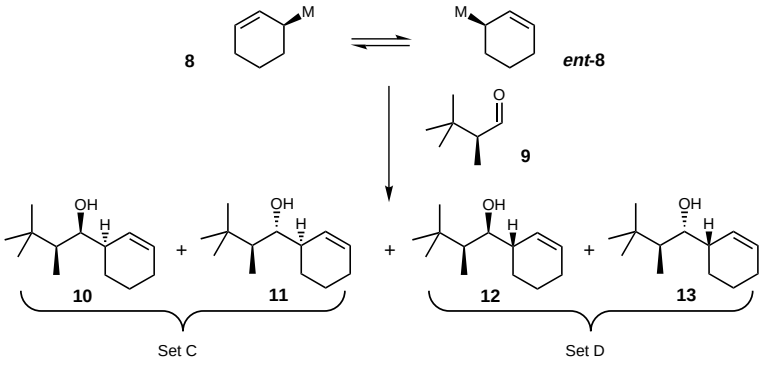
The synthesis of the enantiomerically pure aldehyde **9** started with the alkylation of the Evans[19] acyloxazolidinone **14** with lithium diisopropylamide and methyl iodide to give 90% of diastereomerically pure **15** (Scheme 3). The latter



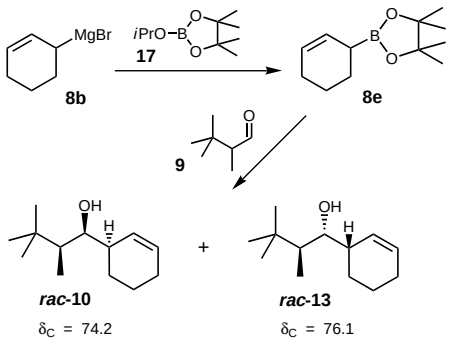
Scheme 3. Synthesis of **9** starting from acyloxazolidinone **14**.

was converted[20] to the thioester **16** in 93% yield. Reduction of **16** following the Fukuyama protocol[21] failed when triethylsilane was used, but could be achieved in 89% yield when the less sterically demanding ethyldimethylsilane was used as the reductant. The enantiomeric purity of greater than 95% of the thioester **16** was ascertained with reference to racemic **16** (prepared in the same manner), by using heptafluorobutyrylcamphoratoeuropium as a chiral NMR shift reagent. Reduction of **16** to the aldehyde **9** is assumed [21] to proceed without loss of enantiomeric purity.

Next, the expected reaction products **10** to **13** had to be prepared and their structures had to be assigned. To this end, the cyclohexenylboronate **8e** was generated according to Scheme 4. It was obtained in 81% yield by reaction of cyclohexenylmagnesium bromide (**8b**) with isopropoxytetramethyldioxaborolane **17**.[22] Reaction of **8e** with the racemic aldehyde **9** furnished two alcohols, to which we assign

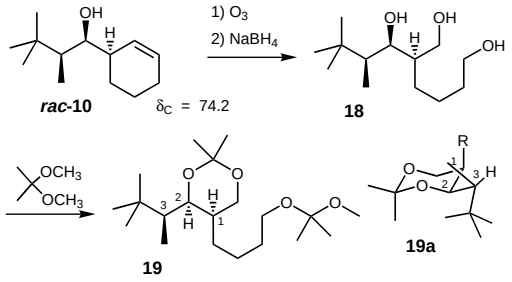


Scheme 2. Reaction of **8** with **9**, leading to four products (**10**–**13**).



Scheme 4. Synthesis of *rac*-**10** and *rac*-**13** from **8b**.

structures *rac*-**10** and *rac*-**13**: The alcohols could be separated by chromatography. The alcohol which revealed a ^{13}C NMR signal at $\delta = 74.2$ was then subjected to ozonolysis followed by acetalization to provide the compound **19** (Scheme 5).

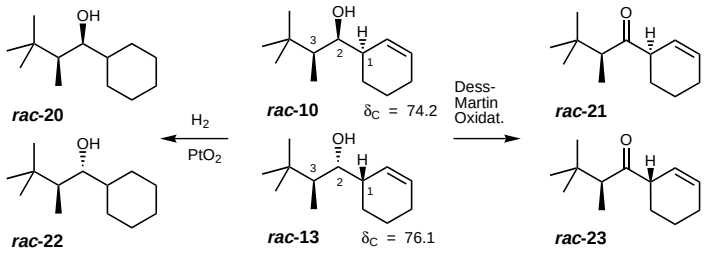


Scheme 5. Conversion of *rac*-**10** into **19a.**

The dioxane ring in **19** is in a chair conformation as seen from the $\delta(^{13}C)$ values ($\delta = 18.8$, 29.7, 99.6) of the acetonide moiety.[23] The branched substituent at C-2 should be equatorial. The H,H coupling constant $J_{1,2} = 2.3$ Hz indicates that the alkyl chain at C-1 is axial. This means that the alcohol associated with the signal at $\delta = 74.2$ should be either **10** or **13**. Regarding the conformation about the C-2/C-3 bond compound **19** would have to relax two *syn*-pentane interactions, which results in a skewed arrangement.[24] The H,H coupling contant $J_{2,3}$ of 2.3 Hz is in line with such an interpretation, see **19a**, whereas the ozonolysis product (not shown) from alcohol **13** would be expected to have a large coupling constant $J_{2,3}$. This establishes structure **10** for the alcohol, which exhibits a ^{13}C NMR signal at $\delta = 74.2$, obtained from the reaction of **8e** with the aldehyde **9**.

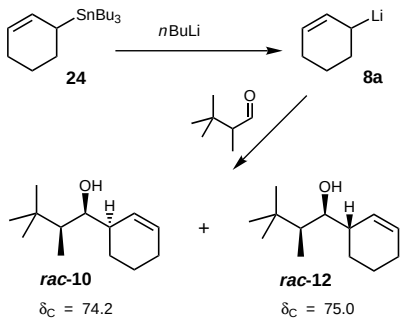
The mixture of alcohols obtained ($\delta = 74.2$ and $\delta = 76.1$) was oxidized with the Dess–Martin reagent to give a mixture of two ketones **21** and **23**. The alcohols therefore have different relative configuration at C1 and C3 (Scheme 6).

Hydrogenation of the mixture of alcohols **10** and **13** gave rise to a mixture of two alcohols **20** and **22**. The alcohols **10** and **13** therefore differ also in the configuration at C-2. This establishes the relative configuration of **13** and **10** as the ones shown in Scheme 6.



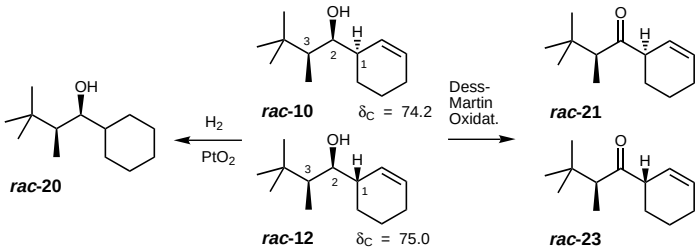
Scheme 6. Establishment of the relative configurations of **13** and **10**.

In a second series of experiments cyclohexenyllithium (**8a**) was generated from cyclohexenyltributyltin (**24**) and added to the aldehyde **9** (Scheme 7). This resulted in two alcohols, one with a ^{13}C NMR signal at $\delta =$ 74.2, identified as **10**, and one



Scheme 7. Reaction of **8a** with **9** to give *rac*-**10** and *rac*-**12**.

with a ^{13}C NMR signal at $\delta = 75.0$. The structure of the latter, **12**, was established by the transformations given in Scheme 8.



Scheme 8. Establishment of the relative configuration of **12.**

Hydrogenation of the mixture obtained led to a single alcohol **20**. This indicated that **10** and **12** have the identical relative configuration at C-2 and C-3. Oxidation of the mixture of **10** and **12** gave a mixture of two ketones **21** and **23**, showing that the two adducts differ in the configuration at C-1. This establishes the structure of **12** as shown in Scheme 8.

Therefore the structure of the alcohols **10**, **12**, and **13** of the four possible reaction products between an allylmetal compound **8** with the aldehyde **9** have been assigned. Any fourth diasteromer to be obtained would by exclusion have the structure **11**.

Kinetic resolution on reaction of allylmetal compounds 8 with the aldehyde 9

A given enantiomer of the aldehyde **9** may react with a different rate with each enantiomer of the allylmetal compound **8** (kinetic resolution). The test to be carried out depends on the magnitude of this kinetic resolution. The kinetic resolution is numerically equivalent to the ratio of the amounts of product alcohols **10** + **11** = set C formed to that of the alcohols **12** + **13** = set D when carrying out the reaction of the *racemic* organometallic compounds with the *racemic* aldehyde **9**. In the case that the haptotropic rearrangement of the allylmetal compound **8** is faster than the addition to the aldehyde **9**, the set C/set D product ratio should be the same when using either *enantiomerically pure* or *racemic* aldehyde **9**. However, for the case that the haptotropic rearrangement of **8** is slower than the additon to the aldehyde **9**, reaction with the *enantiomerically pure* aldehyde should give a set C/set D product ratio approaching the value of 1:1 on high conversion,

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whereas on reaction with the *racemic* aldehyde **9** the set C/set D product ratio should still reflect the kinetic resolution. A meaningful test system then requires that the ratio of products of set C to the one of set D should be different from 1:1 in an analytically significant manner on reaction of the allylmetal compound **8** (racemate) with the *racemic* aldehyde. This means that the ratio should be greater than 1.2.[17] The product ratio of the alcohols **10**–**13** obtained can be readily determined from the ^{1}H and ^{13}C NMR spectra of the crude alcohol mixtures.

At this point a series of allylmetal compounds **8** were screened to evaluate which compounds show a sufficient kinetic resolution in the reaction with the aldehyde **9**. The results are summarized in Table 1.

Table 1. Product ratios on reaction of cyclohexenyl metal compounds **8** with the racemic aldehyde **9.**

		Relative amounts [%]				Total yield [%]	Set C/ Set D
8[a]	M	**10**	**11**	**12**	**13**	**10–13**	ratio
a	Li	57	0	43	0	83	57:43
b	MgCl	55	0	44	0	81	55:45
c	BaCl	62	0	38	0	62	62:38
d	$CeCl_3$	52	0	32	16	55	52:48
e	$B(OR)_2$	29	0	0	71	84	29:71
f	BEt_2	31	0	0	69	86	31:69
g	$Ti(OiPr)_3$	77	0	23	0	70	77:23
h	$Ti(OiPr)_4^-$	63	0	26	11	75	63:37
i	$SnCl_3$	90	0	10	0	41	90:10

[a] Reaction conditions: **a**: THF, −78 °C, 30 min; **b**: THF, 0 °C, 30 min; **c**: 3-chlorocyclohexene, **9**, Ba, THF, −78 °C, 40 min; **d**: cyclohexenyllithium, $CeCl_3$, THF, −78 °C, 3 h; **e**: petroleum ether, 0 °C, 36 h; **f**: diethyl ether, 20 °C, 3 h; **g**: cyclohexenyllithium, $Ti(OiPr)_3Cl$, THF, −78 °C,15 h to 20 °C; **h**: cyclohexenyllithium, $Ti(OiPr)_4$, THF, −78 °C, 3.5 h, then 20 °C, 30 min; **i**: 3-bromocyclohexene, $SnCl_2$, NaI, THF, 20 °C, 24 h.

The product ratios obtained are a consequence of the interplay of several preferences inherent in the reaction partners: That is the ratio between supra- and antrafacial reaction at the allylic system, the level and direction of simple diastereoselection on the formation of the new carbon–carbon bond, and the level of 1,2-induction (Cram versus anti-Cram selectivity) of the aldehyde **9**. The absence of the product **11** can be attributed to a high asymmetric induction from the aldehyde **9**. A detailed discussion of the product ratios obtained is beyond the scope of the present paper. The only data relevant for the application of the kinetic resolution test are the set C/set D product ratio and the total yield of products. Of the reactions reported in Table 1, the kinetic resolution (the set C/set D product ratio) was too low for the reaction of the cyclohexenyl cerium system (**8d**) and the yields were too low[15] for the barium (**8c**) and the tin trihalide (**8i**) systems in conjunction with the level of kinetic resolution to render the kinetic resolution test meaningful. Likewise the cyclohexenyl chromium, zinc, and samarium reagents **8**—data not given in the table—resulted in unacceptable low yields. Thus we found ourselves limited with the present reagent system to the lithium, magnesium, boron, and titanium cases.

Relative rates of haptotropic rearrangement of 8 and its addition to the aldehyde 9

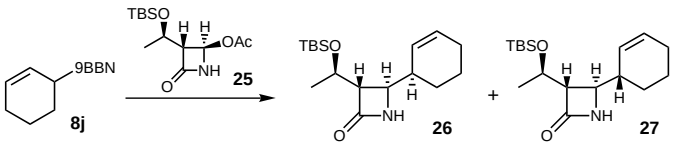
At this point, at last, the test reaction to determine the relative rate of the haptotropic rearrangement of cyclohexenyl metal compounds **8** with respect to the rate of their addition to the aldehyde **9** could be run. The test is based on a comparison of the set C/set D product ratios on reaction with *racemic* aldehyde **9** versus those obtained by using *enantiomerically pure* **9** (Table 2).

Table 2. Set C/set D product ratios on reaction of cyclohexenyl metal compounds **8** with racemic and enantiomerically pure aldehyde **9**.

		***rac*-9**		**(S)-9**	
8	M	Set C/Set D	Yield	Set C/Set D	Yield
a	Li	57:43	83	56:44	85
b	MgCl	55:45	81	54:46	76
e	$B(OR)_2$	29:71	84	47:53	79
f	BEt_2	31:69	86	50:50	83
g	$Ti(OiPr)_3$	77:23	70	75:25	73
h	$Ti(OiPr)_4^-$	63:37	75	76:39	69

In the case of the lithium compound **8a**, the set C/set D product ratio is the same when using either racemic or enantiomerically pure aldehyde **9**. This indicates that the haptotropic rearrangement within **8a** is faster than addition to the aldehyde **9**. The same result would be obtained if cyclohexenyllithium were symmetrical, that is if the lithium cation is bound in a trihapto manner.[25] Allylic Grignard reagents are monohapto bound.[26] Therefore the absence of a significant difference in the set C/set D product ratios on reaction with either racemic or enantiomerically pure aldehyde **9** again signals that racemization of **8b** is faster than its addition to **9**.

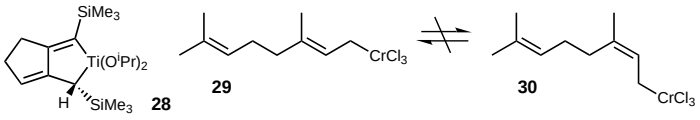
Allylboronates such as **8e** are known to be constitutionally stable.[27] Haptotropic rearrangement in the absence of Lewis acids[28] is slow on a macroscopic time scale. Therefore on reaction of **8e** with either racemic or enantiomerically pure **9** different product ratios must result. This indeed is found. In contrast to allylboronates, allylboranes undergo a rapid allylic rearrangement,[12] even at low temperatures. The results in Table 2 show that addition of **8f** to aldehyde **9** proceeds faster than the allylic rearrangement within **8f**. The haptotropic rearrangement in cyclohexenyl-9-BBN (**8j**) is likely slower[11] than that of **8f**. This would be in line with the finding of Rossi et al.[29] that a 1:1 mixture of diastereomeric products **26** and **27** resulted from the reaction of racemic **8j** with the enantiomerically pure β-lactam **25** (Scheme 9).



Scheme 9. Reaction of **8j** with **25**.

Allyltitanium reagents have been assumed to undergo a rapid haptotropic rearrangement. The results obtained here show that for both **8g** and **8h** this rearrangement is faster than

the addition to the aldehyde **9**. On the other hand, an allyltitanium species **28** has been reported recently[30] that is configurationally stable on a macroscopic time scale.



Finally, some related observations should be mentioned regarding other allylmetal species, for which the present test system was not applicable. Knochel et al.[31] reported that geranyl and neryl-chromium species **29** and **30** do not interconvert more rapidly than they add to benzaldehyde.[32]

Conclusion

The two mechanistic scenarios on addition of allylmetal compounds to an electrophile (aldehyde)—haptotropic rearrangement faster or slower than reaction—may be differentiated by a test based on kinetic resolution. With the test system comprising cyclohexenyl metal systems **8** and the aldehyde **9** we were able to show for the lithium (**8a**), magnesium (**8b**), and titanium compounds (**8g, h**) that reaction with **9** is slower than the haptotropic rearrangement. The opposite was found for the cyclohexenyldiethylborane **8f**.

Experimental Section

All temperatures quoted are not corrected: ^{1}H NMR, ^{13}C NMR: Bruker AC-300, AMX-500; boiling range of petroleum ether: 40–60 °C; flash chromatography: silica gel Si60, E. Merck AG, Darmstadt, 40–63 μm.

***rac*-2,3,3-Trimethylbutanal** (**9**): Dimethylsulfoxide (0.71 mL, 0.78 g, 10 mmol) was added dropwise to a solution of oxalyl chloride (0.77 g, 6.0 mmol) in dichloromethane (20 mL) at −78 °C. After stirring for 15 min a solution of *rac*-2,3,3-trimethylbutanol[18] (0.58 g, 5.0 mmol) in dichloromethane (10 mL) was added dropwise. Stirring was continued for 15 min at −50 °C. Finally, triethylamine (2.8 mL, 20 mmol) was added and the mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl solution (20 mL) was added, the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and concentrated. Distillation of the residue furnished **9** (422 mg, 74 %) as a colorless oil of b.p.$_{68}$ = 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 9H), 0.88 (d, J = 6.9 Hz, 3H), 2.01 (dq, J = 6.9 and 3.2 Hz, 1H), 9.63 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.9, 27.5, 32.6, 55.4, 205.6; elemental analysis calculated for $C_7H_{14}O$: C 73.63, H 12.36, found: C 73.52, H 12.41.

(4*S*)-3-(3′3′-Dimethylbutanoyl)-4-isopropyl-oxazolidine-2-one (**14**): A solution of *n*-butyllithium in hexane (20.7 mL, 31.5 mmol) was added dropwise at −78 °C to a solution of (4*S*)-4-isopropyl-oxazolidin-2-one (3.88 g, 30.0 mmol) in THF (150 mL). After 30 min 3,3-dimethylbutanoyl chloride (4.44 g, 33.0 mmol) was added and the mixture was stirred for 1 h at −78 °C. The mixture was poured into saturated aqueous $NaHCO_3$ solution (300 mL), the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Flash chromatorgaphy of the residue with petroleum ether/diethyl ether (3:1) gave **14** (6.14 g, 90 %) as an almost colorless oil. $[\alpha]_D^{20}$ = +72.6 (c = 1.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 1.01 (s, 9H), 2.30 (m, 1H), 2.69 (d, J = 14.7 Hz, 1H), 3.00 (d, J = 14.7 Hz, 1H), 4.11–4.21 (m, 2H), 4.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 17.9, 28.5, 29.5, 31.3, 45.9, 58.4, 62.9, 154.0, 171.8; elemental analysis calculated for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16; found: C 63.53; H 9.35; N 6.23.

(2′*S*,4*S*)-3-(2′,3′,3′-Trimethylbutanoyl)-4-isopropyl-oxazolidine-2-one (**15**): A solution of *n*-butyllithium in hexane (17.7 mL, 26.8 mmol) was added dropwise at 0 °C to a solution of diisopropylamine (4.12 mL, 29.3 mmol) in THF (70 mL). After stirring for 20 min the mixture was cooled to −78 °C and a solution of **14** (5.55 g, 24.4 mmol) in THF (15 mL) was added. After the mixture had been stirred for 1 h at −78 °C, methyl iodide (7.63 mL, 122 mmol) was added. After stirring for a further 8 h at −78 °C the mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl solution (60 mL) was added, the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated to leave a slightly yellowish solid product. This was recrystallized twice from petroleum ether/diethyl ether (5:1) to furnish diastereomerically pure **15** (5.30 g, 90 %) of m.p. 100 °C. $[\alpha]_D^{20}$ = +115 (c = 1.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.97 (s, 9H), 1.14 (d, J = 7.0 Hz, 3H), 2.33 (m, 1H), 3.86 (q, J = 7.0 Hz, 1H), 4.12–4.22 (m, 2H), 4.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 14.6, 17.9, 27.3, 28.4, 33.3, 44.5, 58.5, 62.9, 153.9, 176.6; elemental analysis calculated for $C_{13}H_{23}NO_3$: C 64.70, H 9.61, N 5.80; found: C 64.73, H 9.47, N 5.78.

Ethyl (2*S*)-2,3,3-trimethylbutanoylthioate (**16**): A solution of *n*-butyllithium in hexane (54 mL, 100 mmol) was added at −78 °C dropwise to a solution of ethane thiol (8.6 g, 0.14 mol) in THF (300 mL). After stirring for 30 min the mixture was allowed to warm to 0 °C, which resulted in a white suspension. A solution of **15** (9.82 g, 40.7 mmol) in THF (300 mL) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature, and aqueous sodium hydroxide solution (250 mL, 0.5 M) was added. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 75 mL), the combined extracts were dried with $MgSO_4$ and concentrated. The residue was filtered with petroleum ether/diethyl ether (3:1) over a short column of silica gel in order to remove the oxazolidinone. The filtrates containing **16** were concentrated and distilled to give **16** as a colorless oil (6.57 g, 93 %) of b.p. $_{20}$ 78 °C; $[\alpha]_D^{20}$ = +114.5 (c = 1.03, $CHCl_3$, $[\alpha]_D^{20}$ = +122 (c = 1.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 9H), 1.08 (d, J = 7.0 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H), 2.41 q, J = 7.0 Hz, 1H), 2.79 (dq, J = 14.8 and 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.7, 23.2, 27.7, 33.3, 58.1, 202.8; elemental analysis calculated for $C_9H_{18}OS$: C 62.02, H 10.41; found: C 61.83, H 10.45.

(*S*)-2,3,3-Trimethylbutanal (**9**): Palladium on carbon (10 %, 0.79 g) was added to a solution of **16** (5.19 g, 29.8 mmol) in dichloromethane (30 mL) followed by addition of dimethylethylsilane[33] (3.94 g, 44.7 mmol). After 1 h the mixture was filtered over Kieselgur, the filtrate was concentrated, and the residue was distilled to give **9** (3.03 g, 89 %) as a colorless oil of b.p.$_{68}$ = 54 °C; $[\alpha]_D^{20}$ = +18.1 (c = 2.01, ethanol) cf. ref. [34]: $[\alpha]_D^{20}$ = +17.82 (c = 2, ethanol), *ee* = 94 %.

2-(2-Cyclohexenyl)-tetramethyl-1,3,2-dioxaborolane (**8e**): To a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**17**)[22] (3.93 g, 21.1 mmol) in THF (25 mL) was added at −78 °C a solution of cyclohexenyl magnesium bromide (28 mL, 21.1 mmol) in THF. After the mixture had been allowed to warm to room temperature overnight it was poured into diethyl ether (72 mL), 1N aqueous hydrochloric acid (21 mL), and saturated aqueous NH_4Cl solution (21 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with brine (30 mL), dried with Na_2SO_4, and concentrated. Distillation of the residue furnished **8e** (3.56 g, 81 %) of b.p.$_{-8}$ = 93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 12H), 1.40–1.82 (m, 4H), 1.96 (m, 2H), 5.61–5.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 24.1, 24.7, 24.8, 25.0, 83.1, 126.0, 127.6.

1-(Cyclohex-2-enyl)-2,3,3-trimethylbutanol (**10** and **13**): Molecular sieves (A3, 0.5 g) were added into a solution of 2,3,3-trimethylbutanal (**9**) (0.343 g, 3.00 mmol) in petroleum ether (3 mL) at 0 °C. A solution of **8e** (0.312 g, 1.5 mmol) in petroleum ether (2 mL) was subsequently added. After 36 h the mixture was filtered and saturated aqueous NH_4Cl solution (10 mL) was added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 15 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/ diethyl ether (10:1) furnished the alcohols **10** and **13** (total yield 247 mg, 84 %). The diastereomer ratio was determined from the ^{1}H NMR spectra of the crude product.

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10: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 5.2$ Hz, 3H), 0.91 (s, 9H), 1.44–1.55 (m, 4H), 1.74–1.81 (m, 2H), 1.97 (m, 2H), 2.11 (m, 1H), 3.65 (dd, $J = 8.5$ and 1.1 Hz, 1H), 5.50–5.56 (m, 1H), 5.73–5.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.8$, 20.8, 25.0, 25.4, 28.1, 33.2, 40.6, 43.5, 74.2, 128.1, 129.4.

13: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $J = 7.0$ Hz, 3H), 0.97 (s, 9H), 1.35–1.79 (m, 6H), 1.97 (m, 2H), 2.41 (m, 1H), 3.51 (d, $J = 8.1$ Hz, 1H), 5.42–5.48 (m, 1H), 5.91–5.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 12.6, 20.8, 21.9, 25.1, 29.0, 33.3, 39.5, 44.2, 76.1, 130.4, 131.7.

A solution of *n*-butyllithium in hexane (1.58 mL, 3.00 mmol) was added in the top compartment of a two-compartment reaction vessel[35] to a solution of tributyl-2-cyclohexenyltin (**24**) (1.11 g, 3.00 mmol) in THF (10 mL) at $-100\,^\circ$C. After this mixture was allowed to warm to $-78\,^\circ$C over 3 h it was added to a solution of **9** (0.514 g, 4.50 mmol) in THF (5 mL) precooled in the lower compartment of the reaction vessel. After the mixture had been stirred for 30 min, saturated aqueous NH_4Cl solution (10 mL) was added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2×10 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/diethyl ether (10:1) furnished **10** and **12** (total 0.49 g, 83%). The diastereomer ratio was determined in the crude product by NMR spectroscopy.

12: ^{1}H NMR (300 MHz, $CDCl_3$, selected data): $\delta = 0.84$ (d, $J = 5.0$ Hz, 3H), 3.57 (dd, $J = 8.8$ and 1.2 Hz, 1H), 5.81–5.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.6$, 21.4, 25.2, 26.2, 28.2, 33.0, 40.3, 43.6, 75.0, 128.6, 128.7.

Reaction with cyclohexenylmagnesium chloride and the aldehyde **9** was carried out in a similar manner in the two-compartment reaction vessel at $0\,^\circ$C.

Reaction with cyclohexenyltitanium triisopropoxide was carried out in the two-compartment reaction vessel as follows: Cyclohexenyllithium was generated from cyclohexenyltributyltin (**24**, 1.5 mmol) as described above. This solution was transferred by cannula to chlorotitanium triisopropoxide (0.430 g, 1.65 mmol) in THF (5 mL) at $-78\,^\circ$C. After stirring for 1 h, reaction with **9** was effected at this temperature.

Reaction with cyclohexenyltitanium tetraisopropoxide was carried out in a similar manner at $-78\,^\circ$C by using 1.1 equivalents of titanium tetraisopropoxide.

Cyclohexenyldiethylborane was generated in the following manner: Cyclohexenyltributyltin (**24**) (23.7 g, 63.8 mmol) was added dropwise under argon to a solution of bromodiethylborane (8.48 g, 57.0 mmol) in anhydrous dichloromethane (40 mL) at $-50\,^\circ$C. After stirring for 15 h at room temperature, distillation furnished the cyclohexenylborane **8f** (6.44 g, 75%) as a colorless pyrophoric liquid, b.p.$_{0.13} = 38\,^\circ$C. The physical properties corresponded to those in ref. [36]. Reaction with **9** was carried out as described for **8e** above.

5[(1-Methoxy-1-methyl-ethoxy)-butyl]-2,2-dimethyl-4-(1,2,2-trimethyl-propyl)-1,3-dioxane (**19**): A stream of ozone in oxygen was introduced at $-78\,^\circ$C into a solution of **10** (316 mg, 1.61 mmol) in methanol (15 mL) and dichloromethane (15 mL) until the blue color of the solution persisted. Excess ozone was purged from the mixture with nitrogen. $NaBH_4$ (363 mg, 9.6 mmol) was added at $-78\,^\circ$C in small portions, and the mixture was allowed to warm to room temperature. Aqueous NaOH (1M, 30 mL) was added, the phases were separated, and the aqueous phase was saturated with NaCl and extracted with ethyl acetate (5×15 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. Flash chromatography with ethyl acetate furnished the triol **18** (295 mg, 79%) as colorless crystals of m.p. 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 0.90 (broad d, 3H), 1.33–1.44 (m, 4H), 1.47–1.62 (m, 4H), 3.61–3.70 (m, 4H), 3.93 (d, $J = 5.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.1$, 23.5, 25.7, 27.8, 32.8, 33.4, 44.3, 46.2, 62.4, 63.6, 73.0. To a solution of **18** (150 mg, 0.64 mmol) in 2,2-dimethoxypropane (4.29 g, 41.2 mmol) was added at room temperature pyridinium *p*-toluene sulfonate (83 mg, 0.33 mmol). After the mixture had been stirred for 10 h at 39 °C, water (25 mL) was added. The phases were separated and the aqueous phase was saturated with NaCl. The aqueous phase was extracted with *tert*-butyl methyl ether (4×15 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/diethyl ether (10:1) furnished **19** (184 mg, 83%) as a colorless oil. The signal assignments in the ^{1}H and ^{13}C NMR spectra mentioned are based on 500 MHz H,H- and H,C-correlation spectra and NOESY experiments. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (s, 9H), 0.83 (d, $J = 7.1$ Hz, 3H), 1.03–1.08 (m, 1H), 1.15–1.20 (m, 1H), 1.26 (qd, $J = 7.1$ and 2.3 Hz, 1H), 1.31 (s, 6H), 1.31 (s, 3H), 1.41 (s, 4H), 1.49–1.61 (m, 3H), 1.73–1.87 (m, 1H), 3.17 (s, 3H), 3.37 (m, 2H), 3.75 (dd, $J = 12.0$ and 1.5 Hz, 1H), 3.96 (dd, $J = 12.0$ and 1.8 Hz, 1H), 4.03 (dd, $J = 2.3$ and 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 10.0$, 18.8, 23.6, 24.4, 24.5, 27.4, 29.7, 30.3, 33.7, 40.5, 45.3, 48.3, 60.5, 63.2, 70.2, 98.3, 99.6; elemental analysis calculated for $C_{20}H_{40}O_4$: C 69.72, H 11.70; found: C 69.53, H 11.64.

1-(2-Cyclohexenyl)-2,3,3-trimethyl-1-butanone (**21** and **23**): Dess–Martin reagent (0.89 g, 2.09 mmol) was added to a solution of **10** and **13** (4:1, 298 mg, 1.52 mmol) in dichloromethane (10 mL) and pyridine (1.22 mL). After stirring for 2 h at room temperature, the mixture was partitioned between *tert*-butyl methyl ether (30 mL) and semisaturated aqueous $NaHCO_3$ solution (30 mL). Sodium thiosulfate (0.60 g, 2.4 mmol) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (2×30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/diethyl ether (7:1) furnished the diastereomeric ketones **21** and **23** in a 4:1 ratio (0.28 g, 95%).

21: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (s, 9H), 0.97 (d, $J = 7.0$ Hz, 3H), 1.49–1.93 (m, 4H), 1.97 (m, 2H), 2.61 (q, $J = 7.0$ Hz, 1H), 3.20 (m, 1H), 5.61–5.66 (m, 1H), 5.79–5.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.1, 20.9, 24.7, 25.1, 27.6, 33.6, 50.6, 52.6, 124.2, 129.6, 216.2.

23: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 0.96 (d, $J = 7.2$ Hz, 3H), 1.47–1.85 (m, 4H), 1.94 (m, 2H), 2.60 (q, $J = 7.1$ Hz, 1H), 3.14 (m, 1H), 5.64–5.69 (m, 1H), 5.76–5.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.1, 20.4, 23.7, 24.7, 27.6, 33.4, 50.6, 52.8, 123.6, 130.1, 215.4.

1-Hydroxy-2,3,3-trimethylbutylcyclohexane (**20** and **22**): Platinum dioxide (ca. 10 mg) was added to a solution of the alcohols **10** and **13** (3:7, 114 mg, 0.58 mmol) in ethanol (1.5 mL). The solution was stirred for 15 h under an atmosphere of hydrogen. The mixture was filtered over a small pad of Kieselgur, which was washed with *tert*-butyl methyl ether (30 mL). The combined filtrates were concentrated, and the residue was purified by flash chromatography with petroleum ether/diethyl ether (5:1) to give a 3:7 mixture of the alcohols **20** and **22** (106 mg, 93%).

20: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (d, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 1.08–1.26 (m, 7H), 1.40 (q, $J = 7.1$ Hz, 1H), 1.63–1.77 (m, 4H), 1.95–1.99 (m, 1H), 3.48 (dd, $J = 6.1$ and 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 7.8, 26.1, 26.2, 26.5, 28.2, 29.6, 29.8, 33.0, 42.6, 43.2, 75.7; elemental analysis calculated for $C_{13}H_{26}O$: C 78.72, H 13.21; found: C 78.64, H 13.51.

22: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $J = 7.1$ Hz, 3H), 0.94 (s, 9H), 1.12–1.47 (m, 6H), 1.64 (m, 4H), 1.75 (m, 3H), 3.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.8$, 25.0, 26.3, 26.7, 26.9, 29.0, 31.5, 33.4, 41.1, 45.7, 77.9.

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