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Towards an Understanding of Cram/*anti*-Cram Selectivity on Addition of Crotylboronates to α-Methylbutyraldehyde

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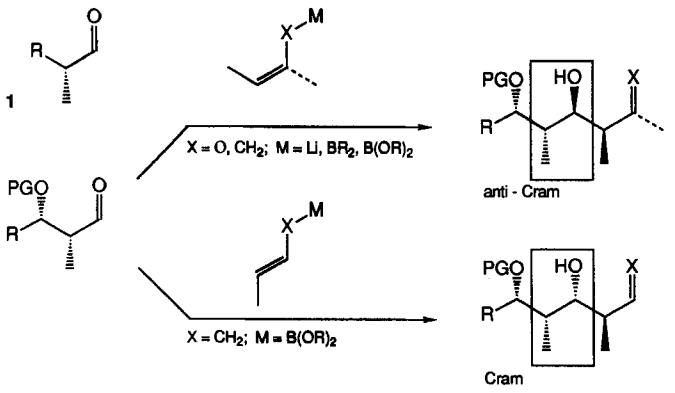
The diastereoselectivity on addition of γ-substituted allylboronates to α-methylbutyraldehyde (**9**) did not depend on the size of the substituent in the reagent, but only on its location in the *Z* or *E* position. This finding required a reinterpretation of the reasons for the attendant reversal in diastereoselectivity. New hypotheses are presented based on force-field calculations on model structures for the transition states.

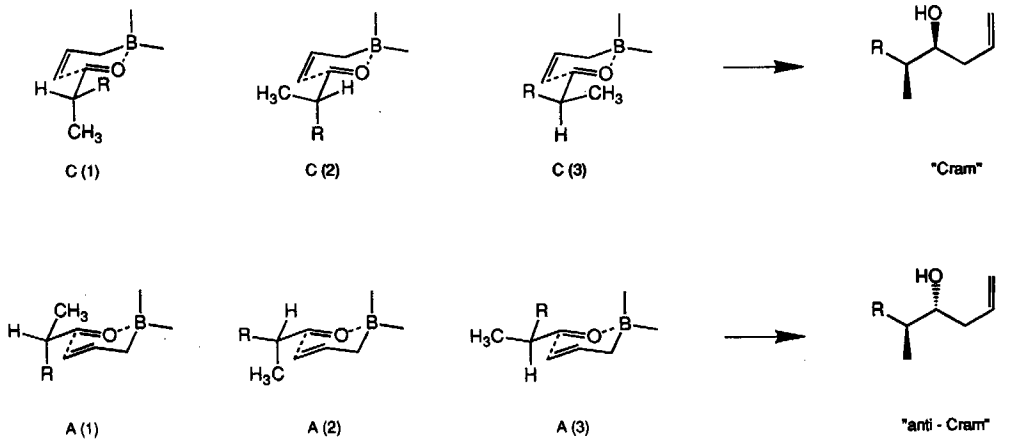
Creation of new stereogenic centers by 1,2-asymmetric induction from an existing stereogenic center constitutes one of the principal transformations in stereoselective synthesis. The nucleophilic addition of an organometallic reagent to aldehydes, having a stereogenic center in the α position would be a typical example. The utility of this transformation derives from the predictability of the sense of asymmetric induction, which is defined either by Cram's rule[2] or the concepts of chelation versus non-chelation control in additions to α- or β-alkoxy aldehydes[3]. The existence of Cram's rule is equivalent to the statement that the stereogenic center of the aldehyde determines the sense of asymmetric induction, whereas the achiral reagent at best influences the extent of asymmetric induction. Given the generality of this notion, exceptions are the more disturbing, as their causes are not fully understood. A peculiar situation is found in the addition of achiral *Z*-crotylboronates[4,5] or of boron and lithium *Z*-enolates[6] to aldehydes of the type **1** which gave preferentially the *anti*-Cram diastereomer.

Moreover, sometimes unusually high levels of asymmetric induction in favour of the Cram isomer have been noted on reaction of the same or similar aldehydes with the corresponding *E*-crotylboronates[4,7]. Being concerned about this aberrant behaviour[4,8], we tried to give an explanation for these findings.

Scheme 1



Scheme 2



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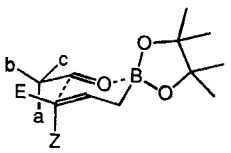
Asymmetric induction in addition reactions to the aldehyde **1** depends on the transition-state conformation around the bonds connecting the inducing stereogenic center and the reacting prochiral group. For the addition of an allylboronate to a chiral aldehyde **1** three transition-state conformations leading to the Cram product [C(1)–C(3)] and three transition states leading to the *anti*-Cram product [A(1)–A(3)] have to be considered. We assumed previously[4,8] that C(1) represents the lowest energy transition state leading to the Cram product and that A(3) is the one which generates the *anti*-Cram product. Accordingly, an *E*-positioned methyl group on the allylboronate would destabilize A(3) and not C(1). Hence, *E*-crotylboronates should give a higher proportion of the Cram product. Correspondingly, a *Z*-positioned methyl group should destabilize C(1) and not A(3). This could lead to a reversal of the sense of asymmetric induction such that the *anti*-Cram product could be formed in preference. These effects are caused by steric interactions across the newly forming C–C bond, e.g. of *E* with b and of *Z* with a in Scheme 3. These effects should become more and more pronounced the shorter the newly forming bond is in the transition state. According to ab initio calculations for the transition states of the addition of boron enolates[9] or of allylboronates[10] to formaldehyde this bond length is about 2.0–2.2 Å. Since the interactions across the newly forming bond are of steric origin – avoidance of 1,3-diaxial-type interactions – these effects, and therefore the level of the diastereoselectivity, should critically depend on the size of the *Z* or *E* substituent on the allylboronate.

Scheme 3

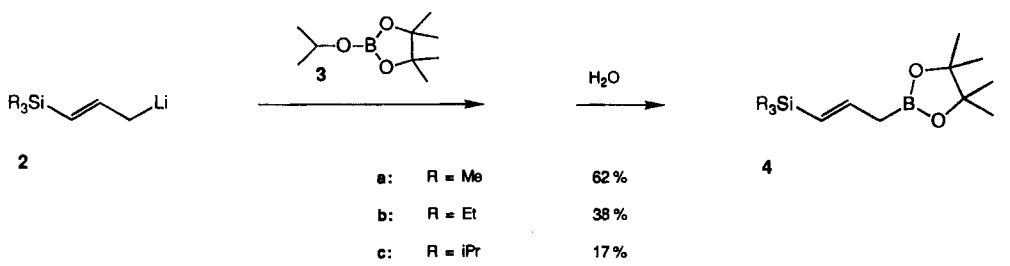


In order to evaluate this prediction, we synthesized a number of *E*- or *Z*-γ-substituted allylboronates and report here on the asymmetric induction incurred on their addition to α-methylbutyraldehyde (**9**).

Synthesis of the γ-Substituted Allylboronates

We wanted to vary the steric demands of the γ substituent in the allylboronate from methyl over trimethylsilyl, triethylsilyl, to triisopropylsilyl. We felt, that the *tert*-butyl derivative **4** should also be included.

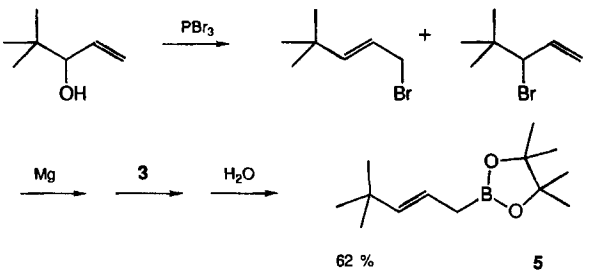
Scheme 4



The *E*-γ-trimethylsilylboronate **4a** had been prepared by Matteson[11] from (trimethylsilylallyl)lithium **2a** and trimethyl borate. Following his procedure we generated the allylboronate **4a** using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[12] (**3**) as the borylating agent.

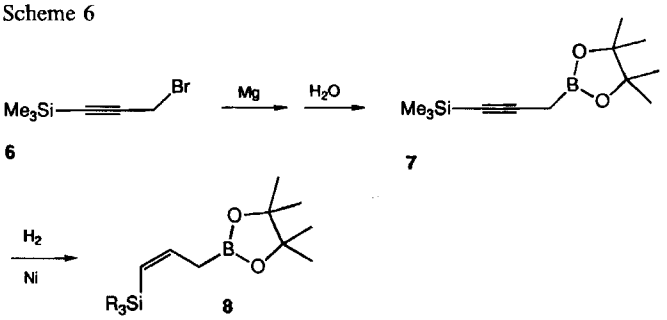
In a similar manner we generated the corresponding triethylsilyl and triisopropylsilyl compounds **4b** and **4c** starting from the appropriate allylsilanes[13,14]. The yields were not optimized. In order to complement the series we prepared the *tert*-butyl-substituted allylboronate **5** by the sequence shown in Scheme 5.

Scheme 5



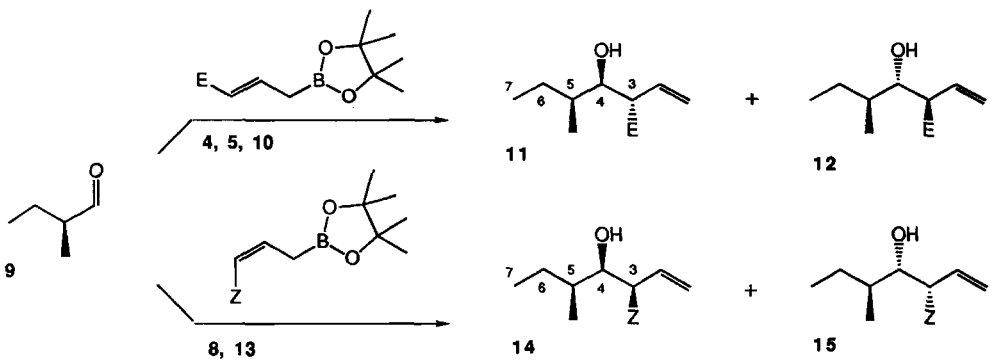
As a further representative of *Z*-γ-substituted allylboronates the (*Z*-trimethylsilylallyl)boronate **8** was prepared starting from the silylated propargyl bromide **6**[15]. The borylation of the derived Grignard reagent had been shown to give mixtures of the propargylic and allenic boronates in which the former predominates[16]. In our hands, borylation with **3** turned out to be fully regioselective, giving the propargylboronate **7** in 62% yield.

Scheme 6



Various attempts to partially hydrogenate the triple bond in **7** remained unsatisfactory. The best we could attain was

Scheme 7



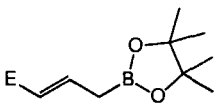
a 9:1 *Z*/*E* mixture on hydrogenation of **7** over Raney nickel in the presence of ethylenediamine.

Addition of the Allylboronates to α-Methylbutyraldehyde (9)

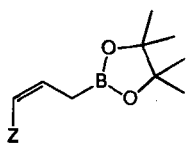
The (γ-trimethylsilyl- and -triethylsilylallyl)boronates **4a** and **4b** were added to α-methylbutyraldehyde (**9**) at room temperature. In order to enforce a reaction of the more hindered (triisopropylsilyl- or *tert*-butylallyl)boronates **4c** and **5** at room temperature, 4 kbar of pressure were applied. The reactions were terminated after 3–4 days, and the diastereomer ratios were determined from the ^{13}C-NMR spectra, cf. Table 1. Finally, in order to facilitate the comparison of the data, the addition of the *Z*-crotylboronate **13** and of the *E*-crotylboronates **10** to the aldehyde **9** was repeated[17] at room temperature.

The stereochemical assignment of the diastereomers **11e**, **12e** and **14e**, **15e** can be considered as secured[17,18]. The structures of the other products were tentatively assigned on the basis of the established simple diastereoselectivity of the crotylboronate addition reaction[19] (*Z* → 3,4-*syn*[20]; *E* → 3,4-*anti*) and of characteristic differences in the ^{13}C-NMR-chemical shifts of C-6 and 5-CH_3[21].

Table 1. Cram/*anti*-Cram selectivities in the addition of γ-substituted allylboronates to α-methylbutyraldehyde



		Products		
		Yield	Cram-/anti-Cram	
4a	E = Me_3Si	79%	**11a, 12a**	73:27
4b	= Et_3Si	ca 70%	**11b, 12b**	74:26
4c	= iPr_3Si	50%	**11c, 12c**	72:28
5	= tBu	66%	**11d, 12d**	75:25
10	= Me	46%	**11e, 12e**	77:23



8	Z = Me_3Si	82%	**14a, 15a**	28:72
13	= Me	49%	**14e, 15e**	30:70

The data obtained clearly show that asymmetric induction is not increased by increasing the bulk of the γ substituent on the allylboronate, rather the diastereoselectivity is practically independend of the size of the γ substituent. All that counts is, whether there is a γ substituent and whether it is located in the *Z* or *E* position. These findings are therefore inconsistent with the previous interpretation[4,8] outlined in the introduction. This required a revised or totally different interpretation of the observed reversal of the Cram/*anti*-Cram selectivity in going from the *E*- to the *Z*-crotylboronate reagents.

Force-Field Calculations

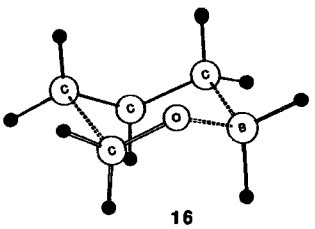
In order to find out what was wrong with our original interpretation, we carried out force-field calculations of the competing transition states for addition to the diastereotopic faces of the aldehyde **9**. This appeared justified, because the non-hydrogen groups at the stereogenic center in α-methylbutyraldehyde **9**, ethyl and methyl, do not differ significantly in their polar properties. It is probably their difference in spatial requirements that counts. Such differences can ordinarily be evaluated by force-field calculations.

We followed a treatment pioneered by Houk[22]. It involves the ab initio calculation of the structure for the transition state of a given reaction, using only a minimum number of atoms and groups, namely those which undergo a bond change. Fortunately, such calculations had already been done by Houk[10] for the addition of allylborane to formaldehyde. This core transition structure **16** was then considered as a rigid description of the transition state. The groups which define the stereogenic center and other relevant groups, e.g. a *Z*- or *E*-positioned methyl group on the allylboronate, were subsequently added, and the steric interactions caused by these changes were evaluated by force-field calculations, relaxing all the bonds except that of the transition state core. This treatment should give good results for the steric effects of substituents. Polar substituent effects, especially those that change the position of the transition

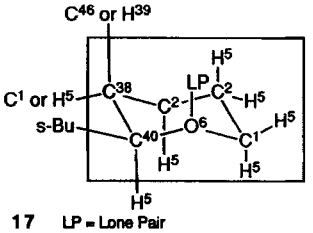
state along the reaction coordinate cannot be properly evaluated by this treatment. However, the addition of allylboronates to aldehydes should resemble more a pericyclic process[8] than an addition of a polar nucleophile to an aldehyde. Therefore, the treatment of the allylboronate addition by a force-field calculation appears not to be contraindicated.

Instead of modeling the transition state with a boron-containing structure, we used the simpler substitute structure **17** containing a carbon atom in place of the boron atom. We also omitted the oxygen substituents at the former boron atom, since they would be remote from those places, where the structural variations occur that we want to investigate.

Scheme 8



16

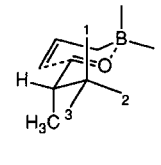


17 LP = Lone Pair

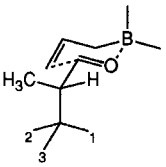
The atom types were chosen to be product-like, i.e. C-2 was chosen as sp^2, C-1, C-38, and C-40 were chosen as sp^3. On the sp^2-type oxygen a lone pair was fixed in the "in-plane" position. Finally, new atom types were defined for C-38, C-40, C-46, and H-39 such, that in structure **17** all the atoms directly connected to the ring took equilibrium values, which corresponded to those of the ab initio calculation of the transition-state structure **16** for the allylborane/formaldehyde reaction.

In the next step, a *Si*- or *Re*-configurated 2-butyl group was added to C-40, and the conformational energy minima for the *sec*-butyl group were searched; the structure of each minimum conformation was fully relaxed except for those atoms in the box of structure **17**. Calculations were carried out using the MM2 force field[23], and the steric energies found for each minimum conformation were determined. This led to the data displayed in Scheme 9 for the reaction of the allylboronate with 2-methylbutyraldehyde.

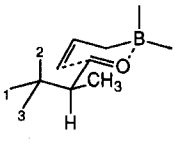
Scheme 9



C (1.1) = 0.00



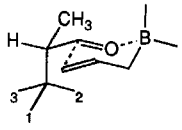
C (2.1) = 2.69



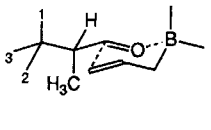
C (3.1) = 1.29

C (1.2) = 0.29 C (2.2) = 3.35 C (3.2) = 0.84

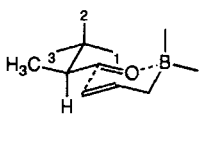
C (1.3) = 0.03 C (2.3) = 1.55 C (3.3) = 0.17



A (1.1) = 0.81



A (2.1) = 1.40



A (3.1) = 0.63

A (1.2) = 1.46 A (2.2) = 4.62 A (3.2) = 0.22

A (1.3) = 0.03 A (2.3) = 1.62 A (3.3) = 0.20

All energies in kcal/mol.

One notes that the C(2)- and A(2)-type transition states have significantly higher strain energy than the other transition-state structures. In the (2)-type transition states the newly forming bond comes in *gauche* to two alkyl groups; in the other transition states there is only one such *gauche* interaction.

Second, if the ethyl group is turned such that it sticks "out of the way", the related transition states leading to the Cram or the *anti*-Cram product have essentially the same steric energy, c.f. C(1.3)/A(1.3), C(3.3)/A(3.3), and C(2.3)/A(2.3). This is equivalent to saying that if the *sec*-butyl group behaves like an isopropyl group, there is no asymmetric induction. The asymmetric induction is therefore determined by the energy and number of the other low-energy transition-state conformations which are available to the ethyl group. For the Cram product these are by and large the four transition states C(1.1), C(1.2), C(1.3), and C(3.3). For the formation of the *anti*-Cram product there are only three transition states with steric energies lower than 0.6 kcal: A(1.3), A(3.3), and A(3.2). This accounts qualitatively for the preferential formation of the Cram product.

In a more quantitative treatment one can evaluate the Boltzmann distribution for passage across the individual transition states: We considered only transition-state conformations which constitute energy minima and only those which are less than 2.5 kcal/mol in steric energy above the best transition state. By this treatment the Cram/*anti*-Cram selectivity may be approximated. This treatment neglects any differences in the slope of the rotational potentials separating the individual conformers.

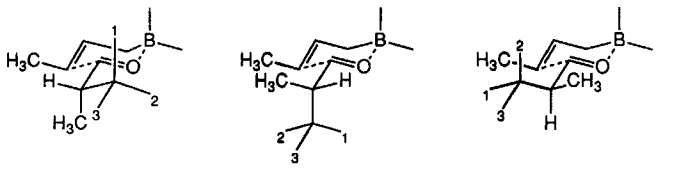
$$\frac{[\text{Cram}]}{[\textit{anti}\text{-Cram}]} = \frac{\sum e^{-SE_C/RT}}{\sum e^{-SE_{AC}/RT}} \qquad (1)$$

SE_C = steric-strain energy of a transition state leading to the Cram diastereomer

By using equation (1) the Cram/*anti* Cram selectivity was calculated to 54:46, the experimental value for the addition of the allylboronate **10** (E = H) to the aldehyde **9** was 60:40[4]. This agreement may well be fortuitous.

Nevertheless, similar calculations were performed for the reactions of the *E*- and *Z*-crotylboronates. Now, the additional methyl group interferes with the ethyl side chain of the aldehyde **9** such that the number of low-energy conformations for the ethyl group is altered. This leads to distinct changes in the calculated diastereoselectivities which reproduce the experimentally observed trends.

Scheme 10

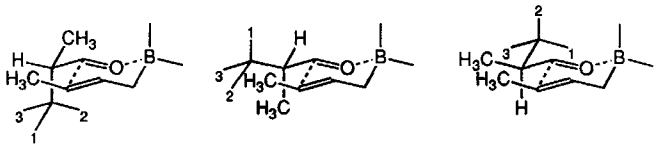


C (1.1) = 0.00 C (2.1) = 2.98 C (3.1) = *

C (1.2) = 0.51 C (2.2) = 6.44 C (3.2) = 1.90

C (1.3) = 0.20 C (2.3) = 3.08 C (3.3) = 1.36

*: This conformation gave no local minimum



A (1.1) = 1.03 A (2.1) = 3.16 A (3.1) = 1.98

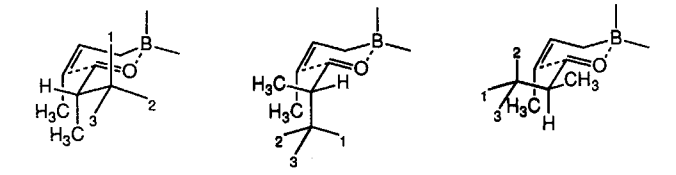
A (1.2) = 1.48 A (2.2) = 6.51 A (3.2) = 1.70

A (1.3) = 0.19 A (2.3) = 3.05 A (3.3) = 1.49

All energies in kcal/mol.

Comparing the data for the *E*-crotyl series with those for the allyl series we see that the presence of the *E*-methyl group now destabilizes all of the A(3)-type transition states, as postulated before[4,8], but only one of the previously favored C-type transition states, mainly C(3.3). This leads to an increase of the Cram selectivity, calculated to 65:35, compared to the experimental value of 77:23.

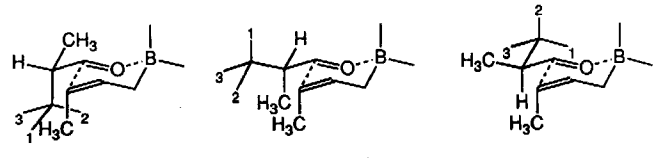
Scheme 11



C (1.1) = 1.40 C (2.1) = 4.35 C (3.1) = 1.77

C (1.2) = 1.55 C (2.2) = 7.60 C (3.2) = 0.52

C (1.3) = 1.38 C (2.3) = 3.45 C (3.3) = 0.04



A (1.1) = 2.49 A (2.1) = 3.24 A (3.1) = 0.17

A (1.2) = 2.35 A (2.2) = 7.33 A (3.2) = 0.13

A (1.3) = 1.27 A (2.3) = 3.40 A (3.3) = 0.00

All energies in kcal/mol.

Vice versa a *Z*-positioned methyl group now destabilizes all three of the formerly favored C(1)-type transition states, whereas only one of the formerly favored transition states leading to the *anti*-Cram product is destabilized, namely A(1.3). The balance thus swings in favor of the formation of the *anti*-Cram product: The calculated Cram/*anti*-Cram selectivity is 38:62 compared to the experimental value of 30:70.

The calculated selectivities were always smaller than the experimental ones. This may have to do with the fact, that we used as the core transition state that of the addition of allyl*boranes*, and not that of allyl*boronic* acid to formaldehyde. The latter should be a better model for the reaction of the allylboronates, but the data were not available to us at the time these calculations were begun. In the allyl*borane* transition state the forming C–C bond is longer than in the allyl*boronic* acid transition states. Therefore, the calculated sensitivities to steric effects across the forming carbon–carbon bond are too low for the allylboronate addition.

Discussion

This interpretation of the Cram/*anti*-Cram selectivity based on the force-field calculations of the transition state made it obvious, why the diastereoselectivities are independent of the steric bulk of the γ substituent on the allylboronate: The interaction of the ethyl side chain with an *E*- or *Z*-positioned methyl group on the allylboronate is already sufficient to destabilize certain transition-state conformations to the point that these do no longer contribute significantly to the overall diastereoselectivity. Obviously, any group larger than a methyl group on the allylboronate would not cause a further increase in diastereoselectivity.

But why did we not reach this conclusion with our former interpretation[4,8]? We had surmised that we could neglect from the six transition states depicted in Scheme 2 all but C(1) leading to the Cram product and A(3) leading to the *anti*-Cram product. The calculations presented here show that this was oversimplified. It is only the C(2)- and A(2)-type transition states that can be neglected in qualitative considerations. The present calculations suggest that the Cram product is formed by the C(1) *and* C(3) transition states, and that the *anti*-Cram product is formed by A(1)- *and* A(3)-type transition states.

In this situation the asymmetric induction depends on the number of low-energy transition-state conformations which are available for the ethyl side chain of the aldehyde en route to either the Cram or the *anti*-Cram products. E.g. for the addition of the *Z*-crotylboronate **13** this would correspond to a statistical contribution to $\Delta S_{anti\text{-}Cram} - \Delta S_{Cram}$ of ca. 2 cal/mol · K. Moreover, since according to these calculations the steric-strain energies of the low-energy transition states differ only marginally, the enthalpic contribution to the asymmetric induction could be smaller than the entropic one. This would imply, that the asymmetric induction in the addition of crotylboronates to α-methylbutyraldehyde and the puzzling reversal of the sense of asymmetric induction in going from the *E*- to the *Z*-crotylboronates could be a consequence of entropy control. Moreover, while we are not aware that entropy control of asymmetric induction has been discussed before, entropy control of selectivity has been

seen in other selective transformations[24,25]. In such a situation, the second term in equation (2) describing diastereoselection, could be larger than the first one. If the first term becomes zero, the temperature dependence of the diastereoselectivity should vanish[24,26].

$$\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger} \quad (2)$$

In order to learn, whether these hypotheses correspond to experimental observations, we tested the temperature dependence of the diastereoselectivity for the addition of the *Z*-crotylboronate **13** to the aldehyde **9**. The diastereomer ratios **15e:14e** are recorded in Table 2.

Table 2. Temperature dependence of the diastereoselectivity on addition of the *Z*-crotylboronate **13** to the α-methylbutyraldehyde **9**

Temp. [°C]	**15e:14e**
25.0	71.8:28.2 ± 0.4
42.0	70.5:29.5 ± 0.2
61.0	68.6:31.4 ± 0.4
81.0	67.8:32.2 ± 0.2

Contrary to the above speculations, the diastereoselectivity shows a noticeable temperature dependence. This corresponded to a $\Delta H^{\ddagger}_{anti\text{-Cram}} - \Delta H^{\ddagger}_{Cram}$ of −0.76 kcal/mol and a $\Delta S^{\ddagger}_{anti\text{-Cram}} - \Delta S^{\ddagger}_{Cram}$ of −0.7 cal/mol · K; i.e. for the temperature range investigated[27] the enthalpic contribution to the diastereoselectivity is about three times larger than the entropic one. Moreover, the entropic term is not dominated by the statistical contribution as assumed above. In retrospect, this means that although the force-field calculations reproduced the diastereoselectivities remarkably well, this could be so, because other important effects besides steric ones were fortuitously balanced by this treatment. This underscores the notion that modelling of diastereoselectivity by present-day force-field calculations on transition-state models is as yet not a reliable procedure.

We acknowledge the skillful help of Dr. *K. Steinbach* in optimizing the analytical GC parameters. We would like to thank the *Deutsche Forschungsgemeinschaft* (SFB 260) and the *Fonds der Chemischen Industrie* for support of this study. We are grateful to the *BASF Aktiengesellschaft* for supply of chemicals.

Experimental

All temperatures quoted are not corrected. – ^{1}H NMR, ^{13}C NMR: Bruker WH-400, AC-300, WH-90, Varian CFT-20, XL-100. – Flash chromatography: silica gel 60 (0.040–0.063 mm, Merck). – Column chromatography: silica gel 60 (0.063–0.200 mm) (Merck). – Analytical gas chromatography: Varian 1700, glass capillary column 30 m × 0.3 mm with 5% SE 52, 120°C. – Preparative gas chromatography: Wilkens Aerograph A-90-P3, 1.5 m × 0.63 cm column with 5% apiezon on chromosorb G, AW-DMCS 60–80 mesh.

1) *4,4,5,5-Tetramethyl-2-[(2E)-3-(trimethylsilyl)-2-propenyl]-1,3,2-dioxaborolane* (**4a**): To a solution of 7.5 ml (50 mmol) of tetramethylethylenediamine in 30 ml of THF was added at −70°C 43 ml (50 mmol) of a 1.16 N solution of *sec*-butyllithium in cyclohexane. Subsequently, 7.9 ml (50 mmol) of allyltrimethylsilane was added dropwise. The solution was stirred for 30 min at −30°C[28] and recooled to −70°C. This solution was added to a precooled solution of 9.30 g (50 mmol) of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[12] (**3**) in 15 ml of THF. The mixture was allowed to reach room temperature over ca. 12 h. 100 ml of dichloromethane, 50 ml of saturated aqueous NH_4Cl solution, and 50 ml of 1 N hydrochloric acid were added sequentially. The organic phase was separated and extracted three times with 50 ml each of water. After drying with $MgSO_4$ and concentration i.vac., the residue was chromatographed on 250 g of silica gel with ether/petroleum ether (b.p. 40–60°C) (4:100) to give 7.48 g (62%) of **4a** as a colorless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 9H), 1.23 (s, 12H), 1.79 (d, *J* = 7.0 Hz, 2H), 5.61 (dt, *J* = 18.4 and 1.5 Hz, 1H), 6.06 (dt, *J* = 18.4 and 7.1 Hz, 1H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = −1.1, 24.7, 83.1, 130.6, 142.0.

$C_{12}H_{25}BO_2Si$ (240.2) Calcd. C 60.00 H 10.49
Found C 59.90 H 10.67

2) *4,4,5,5-Tetramethyl-2-[(2E)-3-(triethylsilyl)-2-propenyl]-1,3,2-dioxaborolane* (**4b**): 1.65 ml (11 mmol) of tetramethylethylenediamine, 10 ml (11 mmol) of a 1.1 N solution of *sec*-butyllithium, 1.72 g (11 mmol) of allyltriethylsilane[13], and 2.05 g (11 mmol) of **3** were allowed to react as described under 1). The crude product was chromatographed on 75 g of silica gel with dichloromethane to give 1.39 g (45%) of a colorless oil. The ^{1}H NMR spectrum showed the presence of ca. 25% of unreacted allyltriethylsilane. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52 (q, *J* = 7.9 Hz, 6H), 0.91 (t, *J* = 7.9 Hz, 9H), 1.23 (s, 12H), 1.82 (d, *J* = 7.1 Hz, 2H), 5.52 (dt, *J* = 18.5 and 1.4 Hz, 1H), 6.08 (dt, *J* = 18.5 and 7.2 Hz, 1H). – The material gave a deviant combustion analysis.

3) *4,4,5,5-Tetramethyl-2-[(2E)-3-(triisopropylsilyl)-2-propenyl]-1,3,2-dioxaborolane* (**4c**): 0.61 ml (4.1 mmol) of tetramethylethylenediamine, 2.5 ml (3.8 mmol) of a 1.53 N solution of *n*-butyllithium in hexane, 0.73 g (3.7 mmol) of allyltriisopropylsilane[14], and 0.68 g (3.7 mmol) of **3** were allowed to react as described under 1). The crude product was purified by flash chromatography (15 cm column) with petroleum ether (b.p. 40–60°C)/ether (100:2) to give 0.20 g (17%) of **4c** as a colorless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.07 (m, 21H), 1.23 (s, 12H), 1.84 (d, *J* = 7.1 Hz, 2H), 5.48 (dt, *J* = 18.8 and 1.4 Hz, 1H), 6.11 (dt, *J* = 18.8 and 7.3 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = 11.0, 18.6, 24.8, 83.2, 123.9, 144.3.

$C_{18}H_{37}BO_2Si$ (324.4) Calcd. C 66.65 H 11.50
Found C 66.01 H 11.45

4) *(2E)-1-Bromo-4,4-dimethyl-2-pentene:* To a solution of 14.03 g (123 mmol) of 3-hydroxy-4,4-dimethyl-1-pentene[29] in 30 ml of ether was added at −30°C over 10 min a solution of 4.21 ml (45 mmol) of PBr_3 in 8 ml of ether. After reaching room temperature over ca. 12 h, 30 ml of ether and 30 ml of saturated aqueous NaCl solution were added. The phases were separated, and the aqueous phase was extracted twice with 5 ml each of ether. The combined organic extracts were washed with 10 ml of saturated aqueous $NaHCO_3$ solution, twice with 5 ml each of brine, and once with 5 ml of water. After drying with $MgSO_4$, the solution was concentrated and the residue distilled to give 13.81 g (63%) of the bromo compound as a colorless liquid with b.p. 75–77°C/40 Torr, cf. ref.[30]. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9H), 3.96 (d, *J* = 7.4 Hz, 2H), 5.59 (dt, *J* = 15.2 and 7.6 Hz, 1H), 5.77 (d, *J* = 15.4 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2, 33.0, 34.0, 121.5, 147.0. – The product contained ca. 5% of 3-bromo-4,4-dimethyl-1-pentene and was used as obtained.

5) *2-[(2E)-4,4-Dimethyl-2-pentenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* (**5**): 9.72 g (0.4 mol) of magnesium turnings in 30 ml of ether was activated with iodine. Now, few drops of a solution of 7.10 g (40 mmol) of (2*E*)-1-bromo-4,4-dimethyl-2-pentene in 13 ml of ether were added. As soon as the reaction started the mixture was cooled to −5°C[30], and the residual solution was added dropwise over 2 h. The mixture was stirred for 1 h at room temperature, cooled to −60°C, and added by canula at −75°C to a solution of 7.10 g (38 mmol) of **3** in 20 ml of ether. After reaching room temperature over ca. 12 h, 40 ml of saturated aqueous NH_4Cl solution and 40 ml of 1 N hydrochloric acid were added. The organic phase was separated, and the aqueous phase was extracted three times with 10 ml each of ether. The combined organic phases were washed with 5 ml each of brine and water and dried with $MgSO_4$. Concentration i.vac. led to 6 g of a residue which was bulb-to-bulb-distilled from a bath of 50−100°C/10^{-2} Torr to give 5.30 g (62%) of **5** as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9H), 1.24 (s, 12H), 1.61 (d, *J* = 6.3 Hz, 2H), 5.36 (dt, *J* = 15.5 and 6.5 Hz, 1H), 5.45 (d, *J* = 15.6 Hz, 1H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 29.9, 32.9, 83.1, 119.3, 142.1. − For analysis a sample was purified by flash chromatography with petroleum ether (b.p. 40−60°C)/ether (100:4).

$C_{13}H_{25}BO_2$ (224.2) Calcd. C 69.66 H 11.24
Found C 69.80 H 11.30

6) *4,4,5,5-Tetramethyl-2-[3-(trimethylsilyl)-2-propinyl]-1,3,2-dioxaborolane* (**7**): A Grignard reagent was prepared from 21.90 g (0.9 mol) of magnesium turnings in 65 ml of ether and 16.75 g (88 mmol) of 3-bromo-1-(trimethylsilyl)-1-propyne[15] as described under 5), the bromo compound being added over 6.5 h. The cold (−40°C) Grignard solution was added by canula to a solution of 13.68 g (74 mmol) of **3** in 20 ml of ether at −65°C. After reaching room temperature over ca. 12 h, the mixture was recooled to −60°C, whereupon 33.7 ml (88 mmol) of a 2.6 N ethereal solution of HCl was added. After reaching room temperature, the mixture was filtered, and the solution was washed twice with 15 ml each of water. After drying with $MgSO_4$, the solution was concentrated i.vac. The residual brown oil (13.1 g) was bulb-to-bulb-distilled at 80°C/0.1 Torr to give 10.9 g (62%) of **7** as a slightly yellow oil. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 9H), 1.26 (s, 12H), 1.85 (s, 2H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.01, 24.4, 82.8, 83.7, 103.0. − The material was used as obtained for the next step.

7) *4,4,5,5-Tetramethyl-2-[(2Z)-3-(trimethylsilyl)-2-propenyl]-1,3,2-dioxaborolane* (**8**): To a solution of 2.40 g (10 mmol) of the compound 7 obtained under 6) in 20 ml of ethanol were added 0.25 ml (3 mmol) of ethylenediamine and ca. 4 g of Raney nickel (commercial product which had been washed three times with ethanol). The vessel was evacuated and filled with hydrogen three times. Hydrogenation was initiated by vigorous stirring at room temperature. When the rate of hydrogen uptake slowed down (51 min; ca. 230 ml of H_2) the vessel was evacuated and filled with nitrogen. The mixture was filtered and washed three times each with 5 ml of ethanol. The combined filtrates were concentrated, and the oily residue was taken up in 30 ml of ether. After washing three times with 5 ml each of water, the organic phase was dried with $MgSO_4$ and concentrated to give 1.04 g (43%) of **8** as a colorless oil. Analytical GC showed the presence of a 91:9 mixture of **8** and its *E* isomer. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 9H), 1.23 (s, 12H), 1.82 (d, *J* = 8.2 Hz, 2H), 5.46 (d, *J* = 13.9 Hz, 1H), 6.42 (dt, *J* = 13.9 and 8.2 Hz, 1H). − A small sample was purified by flash chromatography with petroleum ether (b.p. 40−60°C)/ether (100:2).

$C_{12}H_{25}BO_2Si$ (240.2) Calcd. C 60.00 H 10.49
Found C 59.79 H 10.65

8) *(3R*,4S*,5R*)- and (3R*,4S*,5S*)-5-Methyl-3-(trimethylsilyl)-1-hepten-4-ol* (**11a** and **12a**): 7.45 g (31 mmol) of **4a** and 2.67 g (31 mmol) of 2-methylbutanal (**9**) were combined and stirred for 4 d at room temperature. A solution of 4.63 g (31 mmol) of triethanolamine in 20 ml of petroleum ether (b.p. 40−60°C) and 15 ml of dichloromethane was added. After stirring for 1 d, the mixture was filtered through 80 g of silica gel with dichloromethane. The filtrate was concentrated i.vac., and the residue was bulb-to-bulb-distilled at 60−80°C/0.1 Torr. Flash chromatography (16 cm column) with petroleum ether (b.p. 40−60°C)/ether (100:4) gave 4.88 g (79%) of **11a**/**12a** as a colorless liquid.

11a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 1.16 (dqd, *J* = 14.8, 7.4, and 1.9 Hz, 1H), 1.41−1.51 (m, 2H), 1.46 (d, *J* = 4.5 Hz, 1H), 1.87 (dd, *J* = 10.6 and 5.9 Hz, 1H), 3.59 (dd, *J* = 10.4 and 5.6 Hz, 1H), 4.92 (ddd, *J* = 17.1, 2.1 and 0.8 Hz, 1H), 5.02 (dd, *J* = 10.2 and 2.2 Hz, 1H), 5.79 (dt, *J* = 17.1 and 10.5 Hz, 1H). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = −2.1, 11.3, 13.9, 26.1, 39.2, 40.3, 74.4, 114.5, 136.3.

12a: ^{13}C NMR (25 MHz, $CDCl_3$): δ = −2.3, 11.0, 15.0, 24.5, 39.5, 39.7, 75.7, 114.1, 135.4.

The diastereomer ratio was determined by analytical GC to be 73:27.

$C_{11}H_{24}OSi$ (200.3) Calcd. C 65.93 H 12.07
Found C 65.78 H 11.95

9) *(3R*,4R*,5R*)- and (3R*,4R*,5S*)-5-Methyl-3-(trimethylsilyl)-1-hepten-4-ol* (**15a** and **14a**): 0.34 g (1.4 mmol) of **8** (containing 10% of **4a**), 0.12 g (1.4 mmol) of **9**, and 0.21 g (1.4 mmol) of triethanolamine were allowed to react as described under 8) to give 0.23 g (82%) of **14a**/**15a**.

15a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 1H), 1.21−1.40 (m, 1H), 1.46−1.58 (m, 2H), 1.93 (t, *J* = 10.0 Hz, 1H), 3.67 (ddd, *J* = 9.3, 6.1, and 3.0 Hz, 1H), 4.81 (br. d, *J* = 17.1 Hz, 1H), 4.88 (dd, *J* = 10.3 and 2.0 Hz, 1H), 5.57 (dt, *J* = 17.0 and 10.3 Hz, 1H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.4, 11.9, 16.5, 21.5, 38.8, 40.9, 77.8, 113.0, 137.6.

14a: ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.5, 10.9, 11.9, 27.3, 38.2, 41.0, 75.2, 113.1, 137.3.

The diastereomer ratio was determined by analytical GC to be 28:72.

$C_{11}H_{24}OSi$ (200.4) Calcd. C 65.93 H 12.07
Found C 65.43 H 12.09

10) *(3R*,4S*,5R*)- and (3R*,4S*,5S*)-5-Methyl-3-(triethylsilyl)-1-hepten-4-ol* (**11b** and **12b**): 1.37 g (ca. 4 mmol) of the crude allylboronate **4b**, 0.34 g (4 mmol) of **9**, and 0.67 g (4.5 mmol) of triethanolamine were allowed to react as described under 8) to give 0.92 g (ca. 70%) of **11b**, **12b**.

11b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (q, *J* = 7.9 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 1.04−1.21 (m, 1H), 1.25−1.53 (m, 3H), 2.03 (dd, *J* = 10.8 and 5.5 Hz, 1H), 3.57 (dd, *J* = 10.3 and 5.3 Hz, 1H), 4.92 (ddd, *J* = 17.1, 2.1, and 0.7 Hz, 1H), 4.99 (dd, *J* = 10.2 and 2.0 Hz, 1H), 5.84 (dt, *J* = 17.1 and 10.5 Hz, 1H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.0, 7.5, 11.2, 14.1, 26.2, 37.5, 39.4, 74.8, 114.4, 136.5.

12b: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.9, 7.5, 10.9, 15.1, 24.8, 36.8, 39.6, 75.6, 114.0, 135.8.

$C_{14}H_{30}OSi$ (242.5) Calcd. C 69.35 H 12.47
Found C 69.44 H 12.68

11) *(3R*,4S*,5R*)- and (3R*,4S*,5S*)-5-Methyl-3-(triisopropylsily)-1-hepten-4-ol* (**11c** and **12c**): 163 mg (0.5 mmol) of **4c** and 42 mg (0.49 mmol) of **9** were dissolved in ca. 4 ml of pentane and kept for 3 d under 4 kbar pressure. The mixture was treated for 1 d with 75 mg (0.5 mmol) of triethanolamine and filtered through

13 g of silica gel with trichloromethane to give 70 mg (50%) of **11c**, **12c** as a colorless oil.

11c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.02–1.26 (m, 4H), 1.11 (d, *J* = 5.8 Hz, 18H), 1.41 (d, *J* = 5.6 Hz, 1H), 1.43–1.58 (m, 2H), 2.31 (dd, *J* = 11.2 and 2.8 Hz, 1H), 3.57 (m, 1H), 4.95 (dd, *J* = 18.0 and 2.1 Hz, 1H), 4.99 (dd, *J* = 10.6 and 2.3 Hz, 1H), 5.99 (dt, *J* = 17.5 and 10.4 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 11.7, 14.6, 19.1, 19.2, 26.0, 36.2, 39.9, 74.8, 114.8, 136.7.

12c: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 11.6, 15.2, 18.6, 25.1, 35.7, 39.5, 75.1, 114.7, 136.3.

A sample was purified by gas chromatography at 180°C.

$C_{17}H_{36}OSi$ (284.6) Calcd. C 71.75 H 12.75
Found C 71.53 H 12.87

12) *(3R*,4R*,5S*)- and (3R*,4R*,5R*)-3-tert-Butyl-5-methyl-1-hepten-4-ol* (**11d** and **12d**): 220 mg (0.98 mmol) of **5** and 78 mg (0.9 mmol) of **9** in 4 ml of $CDCl_3$ were kept for 4 d under 4 kbar pressure. Workup as under 8) gave 110 mg (66%) of **11d**/**12d** as a colorless oil.

11d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.98–1.18 (m, 2H), 1.32–1.45 (m, 2H), 1.92 (dd, *J* = 10.1 and 1.7 Hz, 1H), 3.51–3.63 (m, 1H), 5.01 (dd, *J* = 17.3 and 2.5 Hz, 1H), 5.20 (dd, *J* = 10.3 and 2.4 Hz, 1H), 5.86 (dt, *J* = 17.2 and 10.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 14.5, 25.9, 28.5, 32.8, 39.9, 56.4, 74.2, 118.5, 135.9.

12d: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9, 15.4, 24.8, 28.6, 32.7, 39.3, 55.8, 74.9, 118.4, 135.6.

A small sample was purified by gas chromatography at 120°C.

$C_{12}H_{24}O$ (184.3) Calcd. C 78.20 H 13.12
Found C 78.01 H 13.12

13) *Temperature Dependence of the Diastereoselectivity on Addition of 2-[(2Z)-2-Butenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* (**13**) *to 2-Methylbutanal* (**9**): 0.5 ml of a 2.0 M solution of **13** in toluene was introduced into a small ampoule. The ampoule was sealed and placed into a flask containing 20 ml of a 0.15 M solution of 2-methylbutanal (**9**) in toluene. The flask was immersed in a heating bath. After the temperature had been equilibrated, the ampoule was crashed with a glass rod. The reaction was allowed to proceed for 18–72 h. Then 2 ml of a 2 M solution of $NaBH_4$ in methanol was added. After stirring for 20 min, the mixture was acidified by addition of 1 N aqueous hydrochloric acid. The phases were separated, and the aqueous phase was extracted three times with 10 ml each of ether. The combined organic phases were dried with $MgSO_4$ and concentrated. The diastereomer ratio of **15e**, **14e** was determined by gas chromatography.

CAS-Registry-Nummern

3: 61676-62-8 / **4a**: 79309-68-5 / **4b**: 129217-77-2 / **4c**: 129217-78-3 / **5**: 129217-79-4 / **6**: 38002-45-8 / **7**: 129217-85-2 / **8**: 129217-80-7 / **9**: 96-17-3 / **10**: 69611-02-5 / **11a**: 129217-81-8 / **11b**: 129217-82-9 / **11c**: 129217-83-0 / **11d**: 129217-81-1 / **11e**: 72985-59-2 / **12a**: 129263-25-8 / **12b**: 129263-26-9 / **12c**: 129263-27-0 / **12d**: 129363-28-1 / **12e**: 73037-25-9 / **13**: 69611-01-4 / **14a**: 129263-29-2 / **14e**: 73037-28-2 / **15a**: 129263-30-5 / **15e**: 73037-29-3 / allyltrimethylsilane: 762-72-1 / allyltriethylsilane: 17898-21-4 / allyltriisopropylsilane: 24400-84-8 / 3-hydroxy-4,4-dimethyl-1-pentene: 24580-44-7 / (2*E*)-1-bromo-4,4-dimethyl-2-pentene: 122152-40-3

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