Stereoselectivity of the Transfer of Hydrogen Atoms to Cyclic Alkyl Radicals

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The addition of cyclohexane to alkylmaleic anhydrides **1a–f** via cyclic radicals **2a–f** gave a mixture of (*Z*)- and (*E*)-2,3-dialkylsuccinic anhydrides **3a–f**. The stereoselectivity of the hydrogen transfer from cyclohexane to radicals **2a–d** was measured in the temperature range of 200–260°C, and the relative activation parameters of the formation of (*Z*)- and (*E*)-**3** were determined. The stereoselectivity of the hydrogen transfer from cyclohexylmercuric hydride at 25°C was measured as well. The results are rationalized assuming steric interactions in the transition state of H donor and β substituent and of α and β substituent, respectively. An X-ray structure analysis of the highly strained addition product (*Z*)-**3d** was performed.

With the increasing use of radical reactions in organic synthesis a more detailed understanding of the reactivities and selectivities is of decisive importance[1]. Especially important is an exact knowledge of the stereoselectivity of hydrogen transfer and the possibility of controlling it, since this reaction is frequently the decisive product-forming step in radical reactions[2].

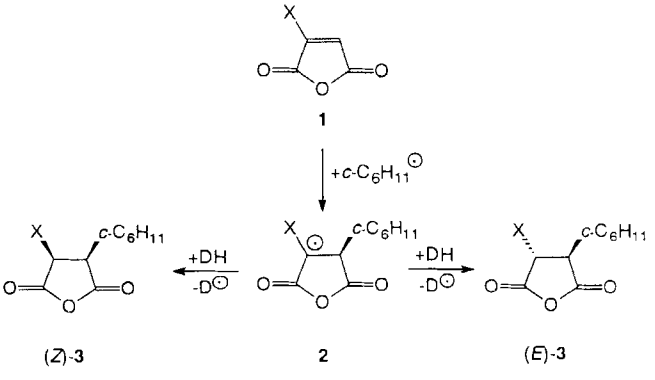
The influence of the β substituent, the hydrogen donor, and the temperature on the stereoselectivity of the hydrogen transfer to 1-alkenyl radicals[3,4] and to cyclic alkyl radicals, for example **2a**[5], was studied. It was shown that the stereoselectivity is determined by the steric interaction between hydrogen donor and β substituent of the respective radicals in the transition state of the hydrogen transfer. Giese and Kretzschmar observed a strong influence of the α substituent of cyclic radicals **2** on the stereoselectivity[6]. However, the reasons for this effect are not known[2].

Alkanes add to alkenes in a thermally initiated free radical chain reaction ("ane reaction")[7]. The radical chain is initiated by a molecule-induced homolysis of alkane and alkene to give two alkyl radicals[8]. We have shown that the ane reaction is suitable to study the stereoselectivity of the addition of cyclohexane to cyclic alkene **1a** via radical **2a** to give the diastereomers (*E*)-**3a** and (*Z*)-**3a** at elevated temperatures between 200 and 400°C. Cyclohexane is the hydrogen donor to radical **2a** in this reaction. The relative activation parameters of selectivity could be measured, and an isoselective relationship was observed comparing the results of the ane reaction and the tributyltin hydride-mediated addition reaction[5]. The occurence of an isoselective relationship points to a common reaction mechanism of the two different free radical chain reactions.

We have now measured the temperature dependence of the diastereoselectivity of hydrogen transfer to cyclic alkyl radicals **2a–d** having α substituents with the same polar, but different steric effects. We thought that the relative activation parameters of selectivity should give a more detailed picture of the effects of the α substituents.

Results

The radicals **2** were obtained by addition of a cyclohexyl radical to substituted maleic anhydrides **1**. Transfer of hydrogen from hydrogen donors DH to the planar π alkyl radical **2** leads to the formation of (*Z*)-**3** and (*E*)-**3** whose ratio was determined by GC analysis. All products **3** were unambiguously identified by comparison with authentic compounds or isolation of the products and characterization by ^{1}H-NMR spectroscopy. A single-crystal X-ray structure analysis of (*Z*)-**3d** was performed (Figure 1).



	a	b	c	d	e	f	g
X	Me	Et	c-C_6H_{11}	t-Bu	CF_3	Ph	F

DH = c-C_6H_{12}, c-$C_6H_{11}HgH$

Two different free radical chain addition methods were used: Firstly, the mercury method[6] with cyclohexylmercuric hydride as hydrogen donor at 25°C and secondly, the

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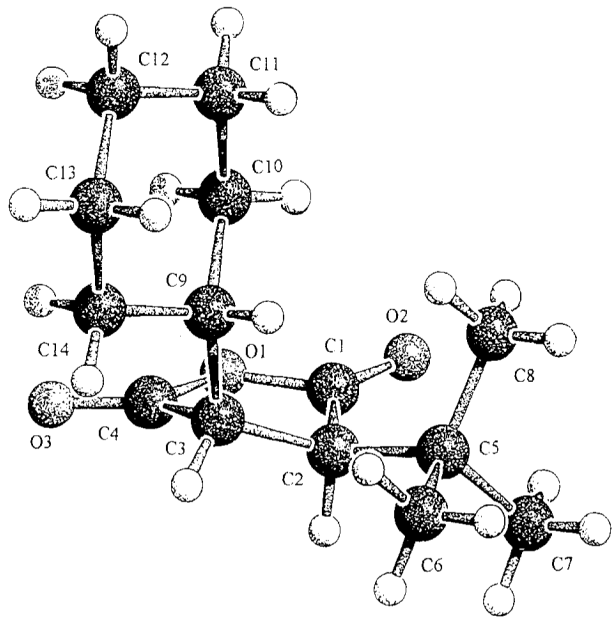


Figure 1. Schakal plot of (*Z*)-**3d**. Selected bond lengths [pm] and interbond angles [°]: C(1)–C(2) 149.6(5), C(2)–C(3) 154.4(5), C(3)–C(4) 150.5(5), C(1)–O(1) 138.7(5), C(4)–O(1) 139.3(6), C(2)–C(5) 154.1(4), C(5)–C(6) 152.3(5), C(5)–C(7) 153.4(5), C(5)–C(8) 152.7(4), C(3)–C(9) 154.8(4), C(11)–C(12) 149.3(6); C(1)–C(2)–C(3) 102.9(3), C(2)–C(3)–C(4) 100.7(3), C(1)–C(2)–C(5) 118.0(3), C(3)–C(2)–C(5) 123.6(2), C(2)–C(3)–C(9) 118.6(2), C(4)–C(3)–C(9) 109.6(3)

ane reaction[7] with cyclohexane as hydrogen donor in the temperature range from 200 to 260°C. No isomerisation of the stereoisomeric addition products **3** could be observed under the conditions of the ane reaction with exception of **3f** (X = Ph). The mercury method gave no addition product applied to **1e** (X = CF_3). Cyclohexylsuccinic anhydride was formed instead. The results are presented in Figure 2 and Table 1. The relative activation parameters of the formation of the stereoisomers derived from the data of Figure 2 are compiled in Table 1. For comparison, the data of Giese and Kretzschmar[6] are also given.

The results using cyclohexane as hydrogen donor are remarkable. The ratio of the addition products [(*Z*)-**3**]:[(*E*)-**3**] decreases with rising temperature. However, the selectivity decreases only in the case of substituent X = Me, whereas the selectivity increases in the case of X = Et, *c*-C_6H_{11}, *t*Bu (Figure 2). The selectivity is correlated with steric substituent constants E_s[9] of the α substituent (Figure 3).

The differences of the activation energies are lowest for radical **2b** and not – as one could expect – for **2a**. However, with the exception of **2a** the differences of activation energies $E_{A,E} - E_{A,Z}$ increase with increasing steric effect of the α substituent from 6.4 (**2b**) through 10.6 (**2c**) to 16.8 kJ · mol^{-1} (**2d**) and accordingly the stereoselectivity increases. Since also the ratios of the *A* factors $lg(A_E:A_Z)$ increase in the same direction from 0.76 (**2b**) through 1.62 (**2c**) to 2.76 (**2d**), the compensation effect leads to an isoselective temperature[10] of 227 K with [(*Z*)-**3**]:[(*E*)-**3**] = 3. The differences of the activation energies are approximately the same for radicals **2a** and **2c**, whereas the ratios of the *A* factors are different, thus giving different selectivities.

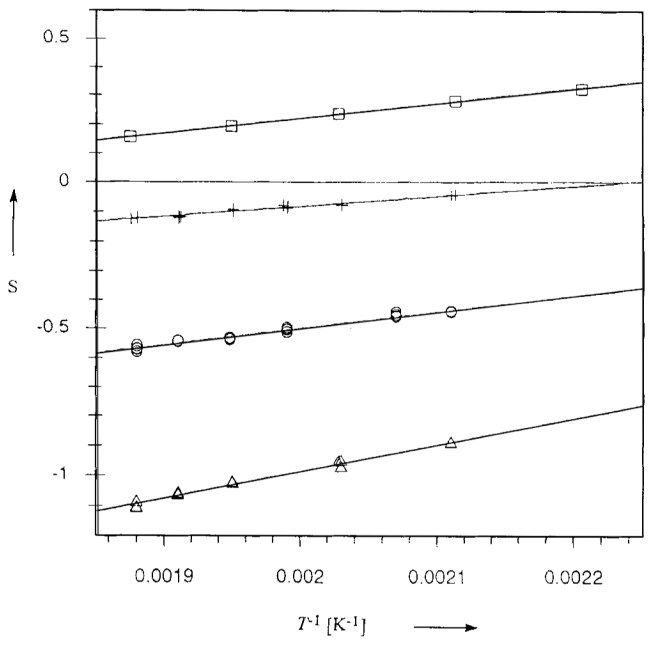


Figure 2. Temperature dependence of the stereoselectivity *S* of the hydrogen transfer from cyclohexane to cyclic radicals **2a–d** (*S* = lg([(*Z*)-**3**]:[(*E*)-**3**]). □ = Me, + = Et, ○ = *c*-C_6H_{11}, △ = *t*Bu

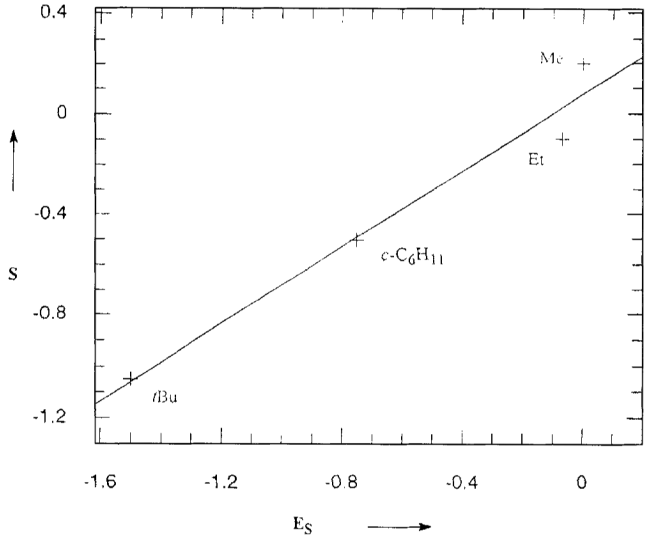


Figure 3. Correlation of the stereoselectivity *S* of the hydrogen transfer from cyclohexane to radicals **2a–d** (200°C) with steric substituent constants E_S of the alkyl substituents (*S* = lg ([(*Z*)-**3**]:[(*E*)-**3**])

Our experiments using the mercury method could reproduce the results of Giese and Kretzschmar[6] (Table 1). Radicals **2a** and **2c** show approximately the same ratio of [(*Z*)-**3**]:[(*E*)-**3**] ≈ 5, whereas a higher selectivity is observed for radical **2d**. In the case of radical **2b** which has not been measured up to now, a low selectivity and a preferred formation of (*E*)-**3b** was observed.

It is most remarkable that at 25°C the ratio [(*Z*)-**3c**]:[(*E*)-**3c**] and [(*Z*)-**3d**]:[(*E*)-**3d**] is 83:17 and 93:7, respectively, with *c*-$C_6H_{11}HgH$ as donor, whereas at 200°C with cyclohexane as H donor the ratio of 27:73 and 11:89, respectively, is reversed.

Table 1. Activation parameters for the stereoselectivity of the transfer of hydrogen from cyclohexane to the alkyl radicals **2** and ratio of the products [(*Z*)-**3**]:[(*E*)-**3**] using the hydrogen donor cyclohexane and cyclohexylmercuric hydride

Radical **2**	ΔE_A[a] [kJ · mol^{-1}]	$\Delta \lg A$[a]	T [°C]	[(*Z*-**3**]:[(*E*)-**3**] C_6H_{12} (200°C)	$C_6H_{11}HgH$ (25°C)
a	9.7 ± 0.3	0.79 ± 0.03	180–260	66:34	(84:16[2])
b	6.4 ± 0.1	0.76 ± 0.01	200–260	48:52	45:55
c	10.6 ± 0.1	1.62 ± 0.01	200–260	27:73	83:17 (80:20[c])
d	16.8 ± 0.2	2.76 ± 0.01	200–260	11:89	93:7 (95:5[c])
e	–	–	200–260	–[b]	–
f	–	–	200–260	84:16–77:23	74:26 (73:27[c])
g	–	–	–	–	(70:30[c])

[a] In each case the value for (*E*)-**3** − the value for (*Z*)-**3**. − [b] The main addition product (*E*)-**3e** could be identified unambiguously by ^{1}H-NMR spectroscopy. It could be shown by GC-MS that a minor addition product (<3%) was formed, possibly (*Z*)-**3e**. − [c] Data from ref.[6]; T = 0–5°C.

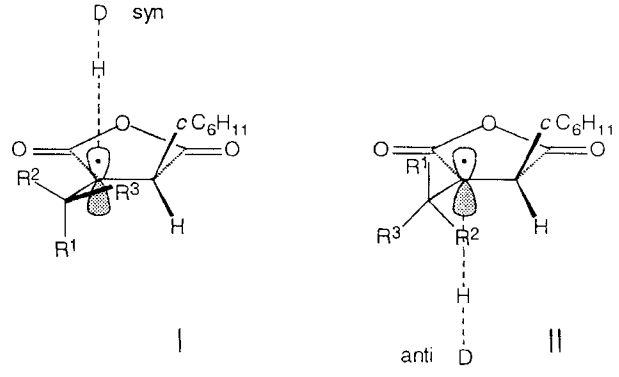
The structure of the products (*E*)-**3a–d** and (*Z*)-**3a–d** could be calculated satisfactorily with the MM2 method[11] as could be shown by comparison with the X-ray structure of (*Z*)-**3d**. Figure 1 shows a significant deformation of (*Z*)-**3d**. The strain of the products (*Z*)-**3** compared to the respective products (*E*)-**3** increases from **3a** through **3b** and **3c** to **3d**.

Discussion

Since the approach of the hydrogen donor DH upon radical **2** from the *anti* side with respect to the β substituent *c*-C_6H_{11} is less hindered than from the *syn* side (Scheme 1), the activation energy for the formation of (*Z*)-**3** is expected to be lower than for the formation of (*E*)-**3**[5]. That is observed in all cases using cyclohexane as hydrogen donor. However, it is obvious that the differences of the activation energies are influenced by the α substituent X. Likewise, a preferred *anti* selectivity and formation of (*Z*)-**3** is observed using cyclohexylmercuric hydride as hydrogen donor in most cases. However, the *syn* selectivity in the case of radical **2b** (X = Et) is surprising (Table 1). Giese observed a strong *syn* selectivity in hydrogen transfer reactions to comparable cyclic alkyl radicals **4** using tributyltin hydride as hydrogen donor[12]. In analogy to ionic alkylation reactions of enolates **5**[13], this stereoselectivity was explained by a preferred conformation of radical **4** in which substituent R = C_8H_{17}, *c*-C_6H_{11}, *t*Bu is turned away from the β substituent methyl at the cyclic radical. In this conformation, one face of the radical is shielded by R, and the attack occurs from the opposite side. However, this model considering ground state conformations of radicals **4** and enolates **5** ignores the Curtin-Hammett principle[14] and is not suited to explain the measured relative activation parameters and the *syn* selectivities observed in the case of radicals **2b–d** using cyclohexane as hydrogen donor. Inspection of the possible transition states gives a straightforward rationalisation of the observed selectivities.

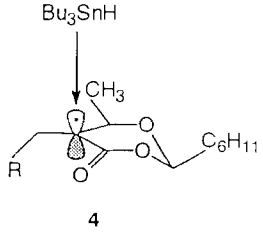
With respect to the α substituent, radicals **2** are acyclic radicals with different conformations of *syn* and *anti* transition states of the hydrogen transfer (Scheme 1). Considering that in the most favorable transition state the attack of the hydrogen donor must occur approximately antiperiplanar[15–19] to the largest ligand R^1 of the α substituent X it can easily be seen (Scheme 1) that in the case of radical **2b** the 1,3-steric interaction of R^1 = Me and β substituent *c*-C_6H_{11} disfavors the *anti* transition state **II** of the hydrogen transfer to radical **2b**. On the other side, the steric interaction of hydrogen donor and β substituent disfavors the *syn* transition state. Using hydrogen donor DH = $C_6H_{11}HgH$ with a reactant-like transition state, the 1,3-steric strain obviously exceeds the interaction of hydrogen donor and β substituent *c*-C_6H_{11}. More product (*E*)-**3b** than (*Z*)-**3b** is observed. In the case of the bulkier hydrogen donor DH = *c*-C_6H_{12} with a more product-like transition state, the steric interaction of cyclohexane and β substituent *c*-C_6H_{11} in the *syn* transition state **I** is 6.4 kJ/mol higher than the 1,3-steric interaction of R^1 = Me and of the β substituent *c*-C_6H_{11} in the *anti* transition state (Table 1). Thus, it can be seen that the differences of the activation energies in the case of radical **2b** must be lower than in the case of radical **2a**.

Scheme 1



2a : $R^1 = R^2 = R^3 = H$ **2c** : $R^1 = R^2 = (CH_2)_5$, $R^3 = H$

2b : R^1 = Me, $R^2 = R^3 = H$ **2d** : $R^1 = R^2 = R^3$ = Me



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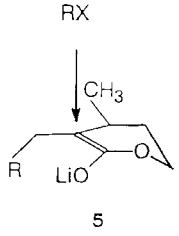

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In the case of radical **2c** the α substituent *c*-C_6H_{11} is oriented approximately orthogonal to the plane of the cyclic radical to give the observed similar selectivity (DH = *c*-$C_6H_{11}HgH$) and similar differences of the activation enthalpies (DH = *c*-C_6H_{12}) as observed for radical **2a**. In the case of radical **2d** *syn* transition state **I** is highly disfavored

because of *syn* interaction between hydrogen donor and β substituent *c*-C_6H_{11} and in addition the steric 1,3-strain of R^3 = Me and of the β substituent. The result is the formation of (*Z*)-**3d** with high selectivity with DH = *c*-$C_6H_{11}HgH$ and the difference of the activation energies E_A [(*E*)-**3d**] − E_A [(*Z*)-**3d**] = 16.8 kJ/mol with DH = *c*-C_6H_{12}. However, (*E*)-**3d** is formed with high selectivity in the latter case because of entropy reasons. In addition, these results give evidence that the steric interaction of ligand R^3 = Me with the β substituent *c*-C_6H_{11} ["1,3-(+)-synperiplanar"] in the *syn* transition state exceeds that of ligand R^1 = Me with the same β substituent ["1,3-(−)-synperiplanar"] in the *anti* transition state (Scheme 1).

The observed selectivities in the case of radicals **2e–g** (X = CF_3, Ph, F) (Table 1) can be rationalized analogously. Radical **2e** is comparable to radical **2d** (E_S [CF_3] = −1.16; E_S [*t*Bu] = −1.54)[9]. Radicals **2f** and **2g** are different compared to the other investigated radicals **2** in as much as α substituent X is symmetrical with respect to the plane of the cyclic radical **2**. Therefore, we expect very similar selectivities of both radicals which are observed. This result gives evidence that the stereoselectivity of hydrogen transfer seems not to be influenced very much by polar effects. Furthermore, we expect and observe a minor selectivity than in the case of radical **2a**. In that case the *syn* transition state **I** is disfavored − in addition to the steric interaction between hydrogen donor and β substituent − by the 1,3-steric strain between β substituent *c*-C_6H_{11} and R^3 = H of α substituent X = Me.

Thus, the stereoselectivity of the hydrogen transfer is controlled by the balance of the 1,3-steric strain of the β substituent and the ligands of the α substituent and the steric interaction of the hydrogen donor and β substituent, respectively, in the transition state.

Conclusion

We have shown that the influence of α substituents at the radical center of cyclic alkyl radicals on the stereoselectivity of hydrogen transfer can be rationalized assuming a transition state with an attack of the hydrogen donor antiperiplanar to the largest ligand of the α substituent X minimizing 1,3-steric strain between β substituent and the ligands of the α substituent. In summa, the stereoselectivity of hydrogen transfer to cyclic alkyl radicals is determined by the balance of the steric interaction between hydrogen donor and β substituent and the 1,3-steric strain of the β substituent and the ligands of the α substituent in the transition state, respectively. Stereoselectivity seems not to be influenced very much by polar effects of the α substituent. The results show that the stereoselectivity can be controlled by the hydrogen donor, the α and β substituent, and the temperature. These results are important for the planning of syntheses where a hydrogen atom is transmitted to a prochiral center.

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Experimental

^1H NMR: Bruker AM 300, solvent $CDCl_3$, internal standard tetramethylsilane (TMS). − MS: Finnigan MAT 212 (for GC/MS coupled with a Varian 3700). − Analytical GC: Carlo Erba HRGC with FID detector and fused silica capillary column DB1 27 m. − Autoclave: high-grade steel tube with 140 ml volume. − Solvents were purified and dried in the usual way.

Starting Materials **1**: Methylmaleic anhydride (**1a**) was commercially available. **1b–f** were synthesized by literature procedures[6,20].

Addition Products **3**: Compounds **3** are described[6] with the exception of **3e**. They were independently synthesized using the mercury method[6].

Addition Products **3b, c, d, f**: 10 mmol of maleic anhydride **2b, c, d, f** and 2.8 g (10 mmol) of cyclohexylmercuric chloride were dissolved in 20 ml of dichloromethane. Then a solution of 3.0 g (80 mmol) of $NaBH_4$ in 4 ml of water was added. After 20 min the solution was dried with $MgSO_4$, and the filtrate was subjected to bulb-to-bulb distillation.

*(E)-2-Cyclohexyl-3-(trifluoromethyl)succinic Anhydride [(E)-***3e**]: A mixture of 80 ml of cyclohexane and 50 mg (0.3 mmol) of (trifluoromethyl)maleic anhydride was heated for 8 h in an autoclave at 240°C under N_2. Cyclohexane was removed, and the residue was subjected to column chromatography yielding 13 mg (25%) of (*E*)-**3e**. − ^1H NMR ($CDCl_3$): δ = 1.0–1.9 (m, 11 H, *c*-C_6H_{11}), 3.19 (dd, 1 H, 2-H), 3.62 (m, 1 H, 3-H); $J_{2,1'}$ = 4.7, $J_{2,3}$ = 4.7, $J_{3,F}$ = 13.4 Hz. − MS (EI, 70 eV), *m/z* (%): 232 (4), 148 (19), 109 (33), 82 (91), 67 (100), 55 (56). − MS (CI, isobutane), *m/z* (%): 251 (100) [MH^+].

X-Ray Structure Analysis of (Z)-2-tert-Butyl-3-cyclohexylsuccinic Anhydride (**3d**): Suitable crystals for the X-ray analysis were obtained by slow evaporation of the solvent (hexane) at 3°C. Data collection was carried out on a Siemens AED 2 diffractometer using ω/2Θ scan mode at room temperature. The structure was solved by direct-method technique using the program SHELLXTL PLUS (VMS). No correction for absorption was applied. Anisotropic full-matrix least-square refinements were carried out for all non-H atoms. H Atoms were calculated with a C–H distance of 1.08 Å and refined isotropically using fixed thermal *U* values of 0.08. Crystal data: Formular $C_{14}H_{22}O_3$, crystal system and space group: monoclinic $P2_1/c$, unit cell dimensions (Å): *a* = 11.650(2), *b* = 6.568(1), *c* = 18.626(4), β = 105.42(3)°, Volume 1373.9(4) $Å^3$, *Z* = 4, final *R* value (observed data) *R* = 0.049. Final parameters, and a list of bond lengths and angles are deposited at Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW England.

Competitive Kinetic Measurements: The reactions of alkenes **1a–f** (10 mmol) with cyclohexane (10 ml) were carried out in Duran glas ampoules sealed in vacuo (outer diameter 7 mm, inner diameter 4 mm, length 170 mm, filled with 0.3 ml of reaction mixture). The solutions were deoxygenated by 3–4 freeze-thaw cycles. For each measurement three ampoules were used to carry out the reaction. The reaction temperature was controlled by a thermostat. The solution was analyzed by GC. Products were identified by comparison of the retention times of independently synthesized reference compounds and GC-MS analysis. For quantitative measurements naphthalene was used as internal standard. No isomerisation of the addition products **3** could be observed under reaction conditions with the exception of **3f**.

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