1,3-Stereoinduction in Radical Reactions

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Dedicated to Professor Gerhard Zimmermann on the occasion of his 70th birthday

The possibility of steering the stereoselectivity of the trapping reactions of acyclic radicals possessing a stereogenic center in the 3-position is of great importance, both with respect to the synthesis of natural products bearing stereogenic centers in the 1,3-position and to the free radical polymerization of vinyl monomers. However, most radical polymerizations are more or less unselective,[1a] with the exception of a few sterically highly demanding methacrylates.[2] On the other hand it has been shown during the last few years that acyclic radicals can react with high stereoselectivity;[1, 3] the addition of Lewis acids has proved to be

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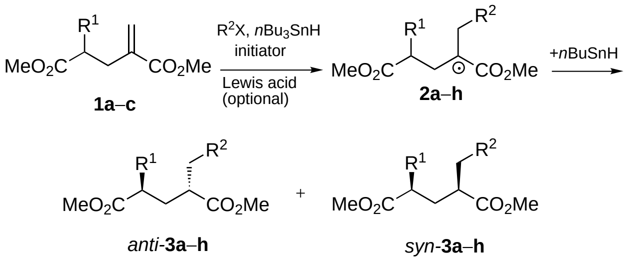
particularly important for controlling the configuration.[4] Until now, attention has focused on stereocontrol by 1,2- or 1,4-induction, while 1,3-stereoinduction has rarely been examined,[5] and when, the examples chosen were less interesting as models for radical polymerization. Porter et al. reported on the allyltributyltin-mediated addition of iodoalkanes to oxazolidinonacrylamides, which afforded 1,3-disubstituted products with good stereoselectivity.[6] Remarkable effects in chelation-controlled reactions of γ-alkoxy-α-ester radicals were observed by Nagano et al.[7] For the first time now, we have examined the chelation-controlled 1,3-stereoinduction of the trapping reaction of γ-alkyl-α-ester radicals **2** (Scheme 1), which are also of interest as models for radical polymerizations of acrylic esters. As trapping reaction we chose hydrogen transfer, and assumed that the stereochemical effects observed in this process should be transferable to the radical addition reaction in the chain propagation step of polymerizations.[1, 8]



1	a	b	c
R^1	Me	*n*Pr	*c*Hex

2, 3	a	b	c	d	e	f	g	h
R^1	Me	*n*Pr	*c*Hex	Me	*n*Pr	*c*Hex	Me	Me
R^2	*t*Bu	*t*Bu	*t*Bu	*c*Hex	*c*Hex	*c*Hex	Et	Me

Scheme 1. Tributyltin hydride mediated additions of haloalkanes R^2X ($X = Br$, I; $R^2 = t$Bu, *c*Hex, Et, Me) to methyl γ-alkyl-α-methyleneglutarates **1** via radicals **2** affording products *anti*-**3** and *syn*-**3**.

Table 1. Results of the reactions of **1a–c** with R^2X: Yields and product ratios [*anti*-**3**]:[*syn*-**3**].

Entry	R^1	R^2	Lewis acid (equiv)	T[b] [°C]	Yield[c] [%]	[*anti*-**3**]:[*syn*-**3**][d]
1	Me	*t*Bu	–	−78	81[e]	52:48
2	Me	*t*Bu	$LiClO_4$ (2)	−78	93	18:82
3	Me	*t*Bu	$Sc(OTf)_3$ (2)	−78	58	1:99
4	Me	*t*Bu	$MgBr_2 \cdot OEt_2$ (2)	−78	83	2:98
5	Me	*t*Bu	$MgBr_2 \cdot OEt_2$ (2)	70	44	39:61
6	*n*Pr	*t*Bu	$MgBr_2 \cdot OEt_2$ (1)	−78	92	2:98
7[f]	*c*Hex	*t*Bu	$MgBr_2 \cdot OEt_2$ (1)	−78	50	3:97
8[f]	Me	*c*Hex	$MgBr_2 \cdot OEt_2$ (1)	−78	64	53:47
9[f]	Me	*c*Hex	$MgBr_2 \cdot OEt_2$ (2)	70	58	65:35
10	*n*Pr	*c*Hex	$MgBr_2 \cdot OEt_2$ (1)	−78	98	53:47
11	*n*Pr	*c*Hex	$MgBr_2 \cdot OEt_2$ (2)	70	95	73:27
12[f]	*c*Hex	*c*Hex	$MgBr_2 \cdot OEt_2$ (1)	−78	62	52:48
13[f]	*c*Hex	*c*Hex	$MgBr_2 \cdot OEt_2$ (2)	70	58	81:19
14	Me	Et	$MgBr_2 \cdot OEt_2$ (2)	−78	100[e]	85:15
15	Me	Et	$MgBr_2 \cdot OEt_2$ (2)	40	53[e]	81:19
16[f]	Me	Me	$MgBr_2 \cdot OEt_2$ (2)	−78	58[e]	85:15
17	Me	Me	$MgBr_2 \cdot OEt_2$ (2)	40	50[e]	85:15

[a] The relative configuration of the free acids of *syn*-**3a** and *syn*-**3d** was confirmed by single-crystal X-ray analysis.[13]. The relative configurations of all other products **3** were assigned on the basis of their ^1H NMR, ^{13}C NMR, and GC data. [b] Alkyl iodides were employed at −78 °C or 40 °C, alkyl bromides at 70 °C. [c] Yield of isolated product, unless specified otherwise. [d] Diastereomeric ratio was determined by capillary gas chromatography of crude reaction material. [e] Yield was determined by capillary gas chromatography. [f] Incomplete conversion at time of analysis or workup.

Addition of an alkyl radical R^2 to alkenes **1** generated radicals **2**, which were then trapped by tributyltin hydride to yield a mixture of diastereomeric products *anti*-**3** and *syn*-**3**. Usual processing of the addition reaction of *t*BuI to alkene **1a** at −78 °C afforded product **3a** unselectively (Table 1, entry 1). Addition of chelating Lewis acids such as $LiClO_4$ (Table 1, entry 2), $Sc(OTf)_3$ (Table 1, entry 3, $Tf = F_3CSO_2$), and especially $MgBr_2 \cdot OEt_2$ (Table 1, entry 4) provided product **3a** at −78 °C in good yields and excellent *syn*-selectivities of [*anti*-**3a**]:[*syn*-**3a**] = 2:98. Considering selectivity, conversion, yield, and costs $MgBr_2 \cdot OEt_2$ was chosen as the most suitable additive for further studies. With increasing reaction temperature, the stereoselectivity of the trapping reaction decreases as expected, but even at 70 °C the observed ratio is still [*anti*-**3a**]:[*syn*-**3a**] = 39:61 (Table 1, entry 5). Remarkably, the stereoselectivity is largely independent of the steric effect of the γ-alkyl group R^1. Thus, also for radicals **2b** (Table 1, entry 6) and **2c** (Table 1, entry 7) high *syn*-selectivity is observed at −78 °C. In contrast, alkyl substituent R^2 exerts a remarkable influence on the stereoselectivity. Addition of R^2 = cyclohexyl to alkene **1a** to give radical **2d** and subsequent hydrogen transfer yields products **3d** unselectively at −78 °C (Table 1, entry 8). Contrary to this, at 70 °C *anti*-selectivity [*anti*-**3d**]:[*syn*-**3d**] = 65:35 (Table 1, entry 9) is observed. The same applies to radicals **2e** (Table 1, entries 10, 11) and **2f** (Table 1, entries 12, 13). Overall, in the reaction series at 70 °C the *anti*-selectivity increases slightly with increasing steric demand of substituent $R^1 = Me < n$Pr < *c*Hex (Table 1, entries 9, 11, 13), reaching [*anti*-**3f**]:[*syn*-**3f**] = 81:19 (Table 1, entry 13).

The addition reactions of ethyl and methyl to alkene **1a** show high *anti*-selectivity for the radicals **2g** (Table 1, entry 15) and **2h** (Table 1, entry 17) at 40 °C as well, but remarkably also at −78 °C (Table 1, entries 14, 16).

The effects, surprising at first glance, can be rationalized as follows: The steric 1,3-interaction in the transition state is negligible in the case of the nonchelated radical **2a** due to the conformational flexibility of the alkyl chain, resulting in a practically unselective reaction.[1a, 7] By complexation of the two 1,3-carboxy functionalities of radicals **2** with the Lewis acid, an eight-membered ring system is formed, thus inhibiting the conformational flexibility (Figure 1). Semiempirical calculations[9] with $[Li(OH_2)_2]^+$ as Lewis acid reveal that the eight-membered ring system depicted in Figure 1 is the most stable conformation, irrespective of R^1, although it is not the only one. The ring shows a concave and a convex side (upper side and bottom side in Figure 1, respectively).

The ground states of radicals **2a**, **2d**, **2g**, and **2h**, chelated by $[Li(OH_2)_2]^+$ as Lewis acid were calculated by using the semiempirical PM3 method.[9] The resulting energy differences of conformations A–D are compiled in Table 2.

Bu_3SnH as radical scavenger can transfer hydrogen via transition states $A^{\neq}$ and $D^{\neq}$ leading to *syn*-**3** or via $B^{\neq}$ and $C^{\neq}$ resulting in *anti*-**3** (Figure 2). Radicals **2a–c** (Table 1, en-

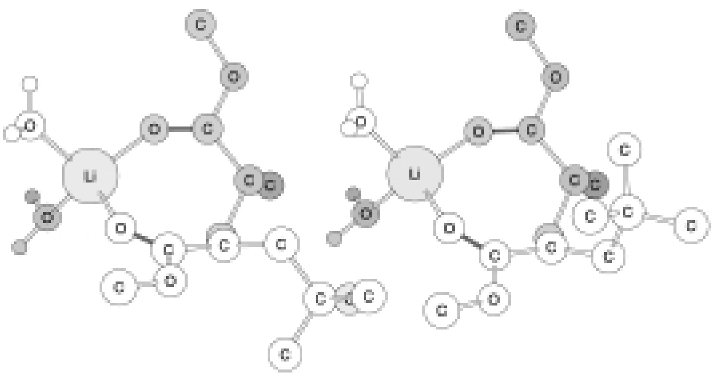


Figure 1. PM3-calculated minimum conformations A (left) and B (right) of radical **2a** (for details see text).

Table 2. Results of PM3 calculations of radicals **2a** ($R^2 = t$Bu), **2d** ($R^2 = c$Hex), **2g** ($R^2 =$ Et), and **2h** ($R^2 =$ Me). Relative energies [kJ mol^{-1}] of conformers A–D.[a]

R^2	A	B[b]	C	D
*t*Bu (**2a**)	0	9.2 (38)	9.6	22.6
*c*Hex (**2d**)	0	3.8 (17)	10.5	17.2
Et (**2g**)	0	–0.5 (11)	8.0	11.0
Me (**2h**)	0	0.3 (11)	11.0	11.6

[a] For conformers A and B, see Figure 1, C and D can be derived analogously from C‡ and D‡ (Figure 2). [b] The rotational barrier for R^2 [kJ mol^{-1}] is given in parentheses.

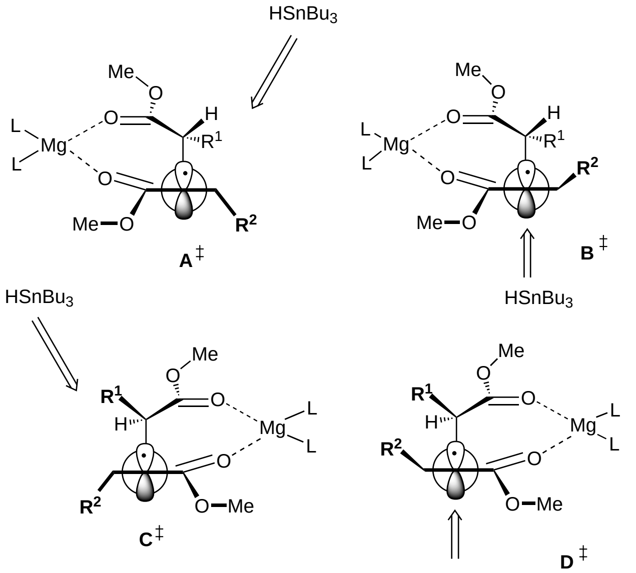


Figure 2. Possible transition states of the hydrogen transfer from Bu_3SnH to radicals **2**. Transition states A‡ and D‡ lead to *syn*-**3**, B‡ and C‡ to *anti*-**3**.

tries 2–7) are trapped *syn*-selectively. Evidently, this takes place via transition state A‡, because in this case steric interactions of the hydrogen donor with the concave side of the chelate-ring system are weaker than those in C‡, taking into account the additional effect of R^1, and also weaker than those of the *t*Bu group with the chelate-ring system in transition state B‡ and even more so in D‡. This interpretation also explains the low influence of R^1 on the stereoselectivity and is supported—in compliance with the Curtin–Hammett principle—by the results of the calculations of radical **2a**, which reveal A as the most stable conformer (Table 2). Furthermore, Table 2 shows that in radicals **2** the energy differences both between conformations A and B and between C and D become smaller with decreasing steric effect of $R^2 = t$Bu > *c*Hex > Et > Me, which should also apply to the corresponding transition states. Accordingly, radicals **2g** and **2h** bearing less sterically demanding R^2 groups are trapped with negligible (**2g**, Table 1, entries 14, 15) or without temperature dependence (**2h**, Table 1, entries 16, 17), but with remarkable *anti*-selectivity. These results support entropic reasons for the observed *anti*-selectivity. The most favorable transition state with the highest activation entropy should be B‡ on account of the attack of the hydrogen donor from the free convex side of **2**—compared to A‡ and C‡—and because of the unhindered rotation of R^2—compared to D‡. Radicals **2d–f** with $R^2 = c$Hex, a medium steric impact substituent, represent the transition from **2a–c** with *syn*-selectivity to **2g** and **2h** with *anti*-selectivity. While these radicals are trapped nearly unselectively at –78 °C (Table 1, entries 8, 10, 12), at +70 °C, the reactions take place with remarkable *anti*-selectivity (Table 1, entries 9, 11, 13). Thus, the activation enthalpy of the reaction providing the *anti* product must be higher than that of the one leading to the *syn* product. The same evidently applies to the activation entropies. At –78 °C the compensation of activation enthalpies and entropies leads to an unselective reaction.[10] Contrary to this, by increasing the temperature *anti*-**3d–f** are formed with considerable preference due to the dominating entropic effect, evidently—as for **3g** and **3f**—via transition state B‡. The increasing *anti*-selectivity with increasing steric demand of R^1 (Table 1, entries 9, 11, 13) indicates that transition state D‡ contributes decreasingly with increasing steric impact of R^1 to the generation of the *syn* product.

We have shown that γ-alkyl-α-ester radicals **2d–h** can be trapped with remarkable *anti*-selectivity at relatively high temperatures of 40 and 70 °C. In contrast to this, high *syn*-selectivity is observed at –78 °C with radicals **2a–c** bearing the sterically demanding neopentyl moiety at the radical center. These results imply that related radicals with 1,3-substituents such as acyloxy, alkoxy, or cyano possibly can also be trapped in a highly selective manner in the presence of Lewis acids, which should be of great interest for the polymerization of, for example, vinyl acetate, vinyl ethers, and acrylonitrile.

Experimental Section

The experiments at –78 °C and 40 °C were performed in dichloromethane, at 70 °C benzene was employed as solvent. In the case of additional $MgBr_2 \cdot OEt_2$, diethyl ether (1/3 of solvent volume) was added. In a typical run, the Lewis acid (see Table 1) was initially stirred with the alkene (0.5 M) for at least 45 min at ambient temperature in the respective mixture of solvents, then the reaction temperature was adjusted to the desired level. At conditions of –78 °C and 40 °C, alkyl iodide (3 equiv) and tributyltin hydride (3 equiv) were added and finally triethylborane (1 M solution in hexane, 1 equiv with respect to alkene) and O_2[11] were injected over a period of 2–4 h. When the reaction was run at 70 °C, the alkyl bromide (3 equiv) was added, followed by a dropwise addition of a solution of tributyltin hydride (3 equiv) and 2,2′-azobisisobutyronitrile (AIBN;

20 mol%, with respect to alkene) in benzene over 3 h. Workup was performed according to usual methods.[12]

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[13] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137280 (*syn*-**3a**) and CCDC 137281 (*syn*-**3d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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