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Simple and Efficient Stereocontrol of Radical Allylations of β-Hydroxy Esters

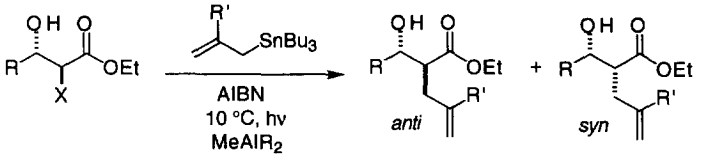
Michèle Gerster, Laurent Audergon, Nadira Moufid and Philippe Renaud*

Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg

Abstract: Highly stereoselective radical allylations of non-protected β-hydroxy esters have been achieved after formation of chelated aluminum alkoxides upon treatment with $MeAlR_2$. This approach combines very high selectivities, excellent reproductibility and simplicity of the manipulations. Interestingly, diethyl malate is allylated after treatment with 1.1 equiv. of MAD to the *threo* (*syn*) isomer with almost complete diastereoselectivity (> 95% ds), this stereochemical outcome is opposite to the one observed in the well-known alkylation of the corresponding enolate.

1,2-Asymmetric induction in free radical reactions is a topic of great interest.[1] Ester substituted radicals possessing a center of chirality in β-position have been intensively investigated.[2] Good stereoselectivities were only observed when the substituents at the stereogenic center are well differentiated in size. A model based mainly on minimization of allylic 1,3-strain is used to rationalize the results.[3] β-Oxy esters are of particular importance since they are readily available in enantiopure form and have been therefore used as starting material for numerous synthesis of natural products and analogues.[4] For these esters, beside the allylic strain based control,[5] a second strategy for efficient stereochemical control with inversion of products stereochemistry was developed: this approach is based on chelation-control by using Lewis acids.[6] However, it gives high selectivities exclusively with a β-methoxy substituent, the benzyloxy group which is easier to deprotect gave unsatisfactory results. Recently, we have reported that in situ generated aluminum alkoxides are particularly powerful for controlling the stereoselectivity of reactions of 2-hydroxy-substituted radicals.[7,8] In this report, we demonstrate that the same approach can be applied to different types of β-hydroxy ester radicals.

The five radical precursors *syn*- and *anti*-**1**, *syn*- and *anti*-**2** and *anti*-**3** have been prepared and submitted to allylation conditions; the results are summarized in the Table. In the absence of additive, the stereoselectivity was low (entries 1, 3, 6, 8 and 10: *anti/syn* 1.6-3.4:1) and the major isomer was always the *anti* one. When the reaction was run after treatment of the free alcohol with 1.1 equiv. of Me_3Al, the *anti* selectivity was increased with the radical precusors **1** and **2** (entries 2, 4, 5, 7 and 9), however the effect was



syn- and *anti*-**1** (R = Me, X = SePh)
syn- and *anti*-**2** (R = 2-furyl, X = SePh)
anti-**3** (R = CO_2Et, X = Br)

4 (R = Me, R' = H)
5 (R = 2-furyl, R' = H)
6 (R = CO_2Et, R' = H)
7 (R = CO_2Et, R' = CO_2Me)

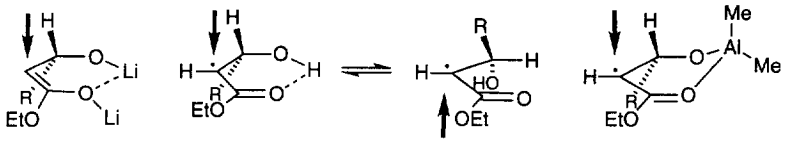
Table. Radical allylation of β-hydroxyesters in the presence of additive of type $MeAlR_2$

Entry	R	R'	Precursor[a]	Additive (equiv.)	Product	Yield (%)	*anti/syn*
1	Me	H	*syn*-**1**[b]	-	**4**	86	1.6:1
2	Me	H	*syn*-**1**[b]	Me_3Al (1.1)	**4**	80	5.8:1
3	Me	H	*anti*-**1**[b]	-	**4**	98	1.7:1
4	Me	H	*anti*-**1**[b]	Me_3Al (1.1)	**4**	97	**20:1**
5	Me	H	*anti*-**1**[b]	Me_3Al (3.0)	**4**	>70	**32:1**
6	2-furyl	H	*syn*-**2**[c]	-	**5**	94	3.4:1
7	2-furyl	H	*syn*-**2**[c]	Me_3Al (1.3)	**5**	62[d]	8.1:1
8	2-furyl	H	*anti*-**2**[c]	-	**5**	90	3.3:1
9	2-furyl	H	*anti*-**2**[c]	Me_3Al (1.3)	**5**	66[d]	12:1
10	CO_2Et	H	*anti*-**3**	-	**6**	91	1.8:1
11	CO_2Et	H	*anti*-**3**	Me_3Al (1.3)	**6**	44	1:1.4
12	CO_2Et	CO_2Me	*anti*-**3**	MAD (1.1)	**7**	40	**1:>25**

a) Precursors **1** and **2** were used in racemic form, *anti*-**3** was obtained in enantiopure form from (2*R*,3*R*)-diethyl tartrate.[9]
b) The relative configuration was assigned from the ^{1}H-NMR coupling constants (HC(2)-HC(3)): *syn*-**1**: J = 5 Hz; *anti*-**1**: J = 8 Hz
c) The relative configuration of **2** were deduced by comparison of the ^{1}H-NMR (HC(2)-HC(3)) coupling constants and the R_f values with those of *syn*- and *anti*-**1**.
d) Unreacted starting material (8-9%) was recovered

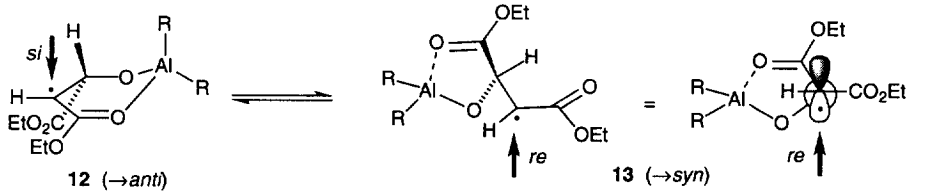
much more pronounced with the *anti* configurated radical precusors (entries 4, 5, 9: 12-32:1) than with the *syn* precursors (entries 2, 6: 5.8-8.1:1). A similar effect was already reported by Guindon.[6a] The highest selectivity was observed with 3 equiv. of Me_3Al (entry 5: *anti/syn* 32:1). Under these conditions, the radical precursor is quantitatively converted to an aluminum alcoholate, the lower selectivity observed with 1.1 equiv. of Me_3Al is presumably due to partial hydrolysis of Me_3Al by traces of moisture. Interestingly, with compound *anti*-**3** the sense of the stereoselectivity was inverted when the reaction was run in the presence of Me_3Al and the *syn* (*threo*) isomer was isolated as major product with a low selectivity (*anti/syn* 1:2.5, entry 11). However, a highly stereoselective reaction (*anti/syn* 1:>25) was observed when the reaction was run after treatment of *anti*-**3** with 1.1 equiv. of MAD (methylaluminum bis[2,6-di(*tert*-butyl)-4-methylphenoxide]). This result compares favorably with the one of Nagano who obtained a *anti/syn* ratio of 1:1.7 with the same substrate in the presence of $Eu(fod)_3$ as Lewis acid.[6c]

The stereochemical outcome of the reactions starting from **1** and **2** are best explained by cyclic models which are very similar to the one proposed for the alkylation of β-hydroxy ester enolate[10] (**8**). The cyclic system is maintained by either hydrogen bonding (**9**) or aluminum complexation (**11**). When the free alcohol was used, the minor isomer can be formed via the acyclic transition state **10** which minimizes $A^{1,3}$ strain. Preliminary ^{13}C-NMR experiments with Me_3Al have shown that the alcoholate derived from *anti*-**1** is completely chelated although the one derived from *syn*-**1** is only partially chelated.[11] This difference in chelation is presumably the cause of the lower stereoselectivities observed with the *syn* isomer since it is expected that radical reactions are faster or at least competitive with the intramolecular complexation processes.



8 (→*anti*) **9** (→*anti*) **10** (→*syn*) **11** (→*anti*)

The result of the radical allylation of the diethyl malate is particularly striking and interesting. Indeed, in the presence of 1.1 equiv. of MAD or Me_3Al, the stereochemical outcome is opposite to the corresponding enolate alkylation. This rules out the possibility of a reaction involving a six-membered ring transition state (**12**). NMR study of the aluminum alcoholate formed with Me_3Al and *anti*-**3** shows clearly that two species co-exist in solution, both of them have one ester group complexing the aluminum atom, the other ester group is free. This observation let us propose the coexistence of 6- and 5-membered chelates **12** and **13** respectively. Reaction of **12** from the *si* face is possible only if R = Me and leads to the minor isomer, with a very large R group (R = 2,6-di-*t*-butyl-4-methylphenyl), the *si* attack is not possible due to steric hindrance and the reaction proceeds exclusively via chelate **13** (Curtin-Hammett principle). The 5-membered chelate **13** exists preferentially in the depicted conformation in order to minimize $A^{1,3}$ train. This conformer is preferentially attacked from the less hindered *re* face to give the major product *syn*-**7**.[12]



12 (→*anti*) **13** (→*syn*)

In conclusion, we have demonstrated that radicals derived from β-hydroxy esters can be alkylated in highly stereoselecive manner under chelation control by converting the free hydroxy groups to aluminum alcoholates. The direct use of the unprotected alcohol represents an important advantage from a preparative point of view. Further study of the chelation by NMR techniques is actually underway in our laboratory as well as applications of this approach for the control of cyclization reactions.

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References and notes.

(1) Curran, D. P.; Porter, N. A. and Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

(2) a) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412-414. b) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457-4470. c) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett* **1991**, 425-427. d) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* **1992**, *33*, 1863-1866. e) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885-5888.

(3) For a review on allylic strain in radical reactions, see: Giese, B.; Damm, W.; Batra, R. *Chemtracts-Organic Chemistry*, **1994**, 335-370.

(4) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; R. Scheffold, Ed.; Salle & Sauerlander: Frankfurt, **1980**.

(5) See ref. 2e and: a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845-2848. b) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B.; *Tetrahedron Lett.* **1991**, *32*, 27-30. c) Durkin, F.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912-4914. d) Curran, D. P.; Abraham, A. C. *Tetrahedron* **1993**, *49*, 4821-4840. e) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841-4858.

(6) a) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701-9702. b) Guindon, Y.; Guérin, B.; Chabot, C.; Mackintosh, M.; Ogilvie, W. W. *Synlett* **1995**, 449-451. c) Nagano, H.; Kuno, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 987-988.

(7) a) Moufid, N.; Renaud, P. *Helv. Chim. Acta* **1995**, *78*, 1001-1005. b) Moufid, N.; Renaud, P.; Hassler, C.; Giese, B. *Helv. Chim. Acta* **1995**, *78*, 1006-1012. c) Renaud, P.; Gerster, M. *J. Am. Chem. Soc.* **1995**, 6607-6608.

(8) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576-3577.

(9) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214.

(10) a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825-2828. b) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197-200.

(11) This can be attributed to the fact that chelation of the *anti* isomer generates in the most favorable conformation only one gauche interaction, the *syn* isomer generates two gauche interactions, see also ref. 6a.

(12) Tetrahydrofuran-2-yl substituted ester radicals behave similarly, see ref. 6b.

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