ORGANIC LETTERS

2001
Vol. 3, No. 22
3459−3462

Diastereocontrol by Trialkylaluminums in the Synthesis of Tetrahydrofurans via Radical Cyclization

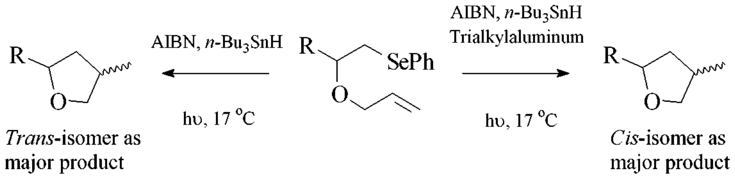
Cecilia Ericsson and Lars Engman*

Department of Organic Chemistry, Institute of Chemistry, Uppsala University,
Box 531, S-751 21, Uppsala, Sweden

lars.engman@kemi.uu.se

Received July 13, 2001

ABSTRACT



The influence of various Lewis acids in the radical cyclization of β-allyloxyalkyl phenyl selenides was investigated. Whereas the unperturbed cyclization afforded *trans*-2,4-disubstituted tetrahydrofurans as the major products (*cis*/*trans* ≈ 1/4.5), cyclization in the presence of trialkylaluminums (3 equiv) afforded predominantly (*cis*/*trans* ≈ 7/1) the corresponding *cis*-isomers.

In addition to metal-mediated synthesis, radical chemistry has emerged during the last 15 years as one of the most interesting methods for carbon−carbon bond formation.[1] Once it was established that radical reactions are often "well-behaved" in the sense that chemo- and regioselectivity can be controlled without much difficulty, the attention was focused (and still is) on the stereoselectivity of radical transformations.[2] Whereas enantioselective reactions of radicals are still rare, diastereoselectivity control in acyclic systems has seen remarkably rapid progress recently.[3] Diastereoselective reactions of cyclic radicals are also not uncommon. The vast majority of stereoselective radical reactions are 5-*exo*-cyclizations of variously substituted (including oxa and aza analogues) 5-hexenyl radicals. Diastereoselectivity in these systems is primarily governed by conformational and steric effects as described by the Beckwith−Houk transition state model.[4] Thus, 1- or 3-substituted 5-hexenyl radicals afford predominantly *cis*-disubstituted products, whereas 2- and 4-substituted derivatives give the corresponding *trans*-isomers in excess. Selectivity rarely exceeds 4/1 in favor of the major diastereomer, though. Significant perturbation of Beckwith−Houk selectivities can be obtained by Lewis acid complexation[5] or by the stereochemical influence of the anomeric effect.[6] By variation of

---

(1) Giese, B. *Radicals in Organic Synthesis: Formation of C−C bonds*; Pergamon Press: Oxford, 1986. Regitz, M., Giese, B., Eds. *Houben-Weyl, Methoden der Organishen Chemie*, Band E19a, C-Radikale, Teil 1+2; Georg Thieme Verlag: Stuttgart, 1989. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 715 and 779. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: Chichester, 1995.

(2) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions − Concepts, Guidelines and Synthetic Applications*; VCH: Weinheim, 1996. See also: Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React*. **1996**, *48*, 301.

(3) For representative examples, see: Easton, C. J.; Merrett, M. C. *Tetrahedron* **1997**, *53*, 1151. Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, É.; Jung, G. *J. Org. Chem*. **1995**, *60*, 288. Morikawa, T.; Washio, Y.; Harada, S.; Hanai, R.; Kayashita, T.; Nemoto, H.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 271. Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J. *J. Org. Chem*. **1994**, *59*, 1166. Porter, N. A.; Carter, R. L.; Mero, C. L.; Roepel, M. G.; Curran, D. P. *Tetrahedron* **1996**, *52*, 4181. Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc*. **1989**, *111*, 8311. Crich, D.; Davies, J. W. *Tetrahedron Lett*. **1987**, *28*, 4205. Sibi, M. P.; Ji, J. *J. Org. Chem*. **1997**, *62*, 3800. Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett*. **1997**, *38*, 5955. Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc*. **1996**, *118*, 9200. Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc*. **1995**, *117*, 11029.

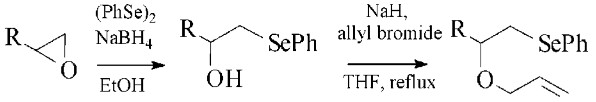
(4) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun*. **1980**, 482. Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun*. **1980**, 484. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem*. **1987**, *52*, 959.

10.1021/ol016429s CCC: $20.00

the steric bulk of the N-substituent, we recently were able to control diastereoselectivity in the preparation of 2,4-disubstituted pyrrolidines via radical cyclization.[7]

In the present paper we report attempts to control diastereoselectivity in the synthesis of tetrahydrofurans via radical cyclization. The preparation of radical cyclization precursors involved regioselective ring-opening of epoxides with benzeneselenolate, followed by O-allylation (Scheme 1).[8]

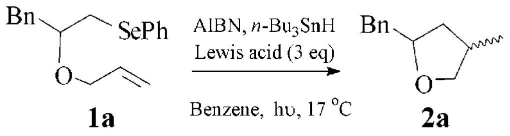
Scheme 1. Synthesis of Radical Precursors



With the perspective to perturb Beckwith−Houk diastereoselectivity by O-complexation, the photoinduced radical cyclization of compound **1a** (Table 1) in the presence of AIBN[9] and n-Bu$_3$SnH was then studied in the presence of 3 equiv of various Lewis acids.[10] In the absence of an additive, this reaction is moderately *trans*-selective (*cis*/*trans* = 1/4.5).

To our disappointment, certain Lewis acids prevented initiation of the radical reaction (Ni(acac)$_2$, (C$_6$F$_5$)$_3$B) or made the reaction proceed with very low conversion (BF$_3$·OEt$_3$, Ti(O-i-Pr)$_4$). Lewis acids containing a nucleophilic group (TiCl$_4$, MeAlCl$_2$, Et$_2$AlCl, GaCl$_3$) converted the starting material either into the corresponding β-chloroselenide (TiCl$_4$) or into allylbenzene (GaCl$_3$, Et$_2$AlCl, and MeAlCl$_2$). Other Lewis acids did not seem to affect the diastereoselectivity at all (Zn(OTf)$_2$, Me$_2$AlOPh).

Table 1. Radical Cyclization in the Presence of Various Lewis Acids



Lewis acid (3 equiv)	yield[a] (%)	*cis*/*trans*-ratio
–	77	1/4.5
Ni(acac)$_2$	0[b]	
(C$_6$F$_5$)$_3$B	0[b]	
BF$_3$·OEt$_2$	34 (56[c])	1/3.5
Ti(O-i-Pr)$_4$	25 (69[c])	1/4
TiCl$_4$	0[d]	
GaCl$_3$	0[e]	
MeAlCl$_2$	0[e]	
Et$_2$AlCl	26[e]	4.5/1
Zn(OTf)$_2$[f]	75	1/4
Me$_2$AlOPh[g]	64	1/4.1
Me$_3$Al	74	5.8/1
Et$_3$Al	79	5.1/1
i-Bu$_3$Al	69	6.8/1

[a] Isolated yield. [b] Only starting material was recovered. [c] On the basis of consumed starting material. [d] 2-Chloro-3-phenylpropyl phenyl selenide was formed. [e] Allylbenzene was formed. [f] Only partly dissolved. [g] The reaction was performed in toluene. One equivalent of phenol was added to Me$_3$Al at −78 °C before selenide, AIBN, and n-Bu$_3$SnH were added.

The best results were obtained with trialkylaluminums. In the presence of 3 equiv of i-Bu$_3$Al, 2-benzyl-4-methyltetrahydrofuran (**2a**) was isolated in 69% yield as a 6.8/1-mixture of *cis*- and *trans*-isomers. To examine the effects of increasing amounts of Lewis acid on diastereoselectivity, radical cyclization of compound **1a** was performed in the presence of 1.5, 3, 6, and 12 equiv of Me$_3$Al, Et$_3$Al, or i-Bu$_3$Al (Table 2). As shown, the *cis*/*trans*-ratio was approximately 4/1 using 1.5 equiv of the trialkylaluminum. The ratio then increased slowly by further addition of Lewis acid. Contrary to our expectations, the sterically most demanding i-Bu$_3$Al did not increase diastereoselectivity beyond those values recorded for Me$_3$Al and Et$_3$Al.

Table 2. Radical Cyclization of Compound **1a** in the Presence of Various Trialkylaluminums

Lewis acid	equiv	yield[a] of **2a** (%)	*cis*/*trans*-ratio
Me$_3$Al	1.5	84	2.1/1
Me$_3$Al	3	74	5.8/1
Me$_3$Al	6	60	7.6/1
Me$_3$Al	12	55 (85[b])	7.8/1
Et$_3$Al	1.5	87	4.7/1
Et$_3$Al	6	81	6.3/1
Et$_3$Al	12	80	7.1/1
i-Bu$_3$Al	1.5	71	3.5/1
i-Bu$_3$Al	3	69	6.8/1
i-Bu$_3$Al	6	45	6.9/1
i-Bu$_3$Al	12	55	6.9/1

[a] Isolated yield. [b] Reaction time = 30 h (instead of 15 h); a second portion of AIBN and Bu$_3$SnH was added after 15 h.

The poor conversion of starting material was a drawback with Me$_3$Al and i-Bu$_3$Al. When 12 equiv of Me$_3$Al was used, the yield dropped to 55%. However, if the reaction time was extended to 30 h and a second portion of AIBN and n-Bu$_3$-

---

(5) Renaud, P.; Andrau, L.; Schenk, K. *Synlett* **1999**, 1462. Delouvrié, B.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11395. Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265. Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. Feldman, K. S.; Romanelli, A. L.; Ruckle, Jr, R. E.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100. For a general review on the use of Lewis acids in free radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(6) Villar, F.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 8655. Beckwith, A. L. J.; Page, D. M. *J. Org. Chem.* **1998**, *63*, 5144.

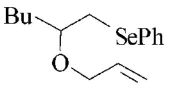
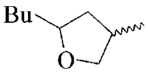
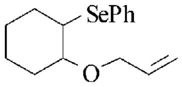
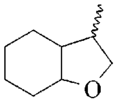
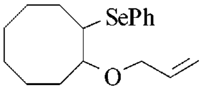
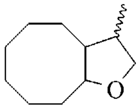
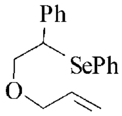
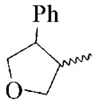
(7) Besev, M.; Engman, L. *Org. Lett.* **2000**, *2*, 1589.

(8) Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157.

(9) Low-temperature initiation using Et$_3$Al and a small amount of O$_2$ was also tried. Although the diastereoselectivities were further improved (*cis*/*trans* = 15/1 for compound **2a** at −78 °C in toluene with 3 equiv of Et$_3$Al), the reactions never did proceed to full conversion.

(10) Maruoka and co-workers have reported a remarkable template effect of ATPH [aluminum tris(2,6-diphenylphenoxide)] in the preparation of 2-methyl-3-butyltetrahydrofuran by radical cyclization. In the absence of the Lewis acid, the trans isomer was formed with high selectivity (*cis*/*trans* = 3/97) whereas in the presence of ATPH the *cis* isomer predominated (*cis*/*trans* = 92/8). Ooi, T.; Hokke, Y.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1181.

Table 3. Radical Cyclization in the Absence/Presence of 3 equiv of Et_3Al

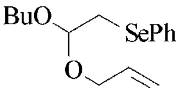
Entry	Starting material	Product	Without Lewis acid		3 equiv. of Et_3Al	
			Yield[a] (%)	*Cis*/*trans*-ratio	Yield[a] (%)	*Cis*/*trans*-ratio
1	 **1b**	 **2b**	60 (97[b])	1 / 4.5	72 (92[b])	7.4 / 1
2	 **1c**	 **2c**	66 (80[b])	1 / 3.2[c]	76 (87[b])	11.4 / 1[c]
3	 **1d**	 **2d**	61[d]	1 / 7.6[c]	71[e]	6.8 / 1[c]
4	 **3**	 **4**	72	1 / 3.8	77	1 / 1.7

[a] Isolated yield. [b] NMR yield (volatile products). [c] *endo*/*exo*-Ratio of *cis*-fused products. [d] In additon, 21% of *trans*-fused products was also obtained. [e] In addition, 12% of *trans*-fused products was also obtained.

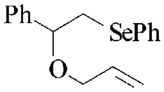
SnH was added after 15 h, 85% of the desired product was isolated. Conversion was not a problem with Et_3Al. Therefore, radical cyclization of a few other substrates was studied in the absence or presence of 3 equiv of Et_3Al (Table 3).

Replacing the benzyl group in the radical precursor for a butyl gave a slightly better *cis*-selectivity (Table 3, entry 1). Compound **1c** (derived from a 1,2-disubstituted epoxide) upon cyclization afforded the 2,3,4-trisubstituted tetrahydrofuran **2c** as a mixture of *exo*- and *endo*-isomers. In the presence of triethylaluminum, formation of the *endo*-isomer was highly favored (*endo*/*exo* = 11.4/1) as compared with the unperturbed reaction (*endo*/*exo* = 1/3.2). A similar dramatic reversion of diastereoselectivity was observed in the cyclization of the cyclooctene oxide derived radical precursor **1d** (Table 3, entry 3). The influence of triethylaluminum on diastereoselectivity in the synthesis of 3,4-disubstituted tetrahydrofurans was also investigated (Table 3, entry 4). As expected, diastereoselectivity was much less changed in favor of the *cis*-isomer in the presence of the Lewis acid.

Scheme 2



5

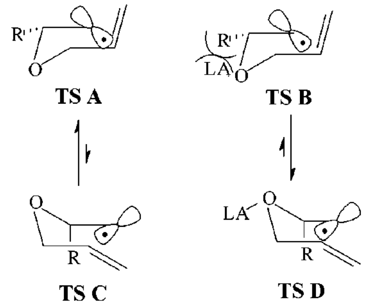


6

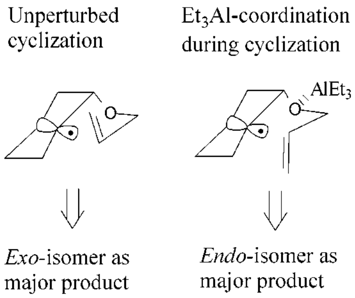
Since compounds **5** and **6** are Lewis acid sensitive, they underwent hydrolysis during reaction/workup and none of the desired products of radical cyclization was isolated (Scheme 2).

Our results with 2,4-disubstituted tetrahydrofurans may be rationalized using the Beckwith–Houk transition state model. In the absence of trialkylaluminum, transition state A (TS A), where the R-group is equatorial, is favored over TS C (Scheme 3). If the Lewis acid is complexed to oxygen, the R-group is forced to adopt an axial position (TS D favored over TS B), resulting in formation of the *cis*-isomer. In support of this hypothesis, compound **1a** when submitted to radical cyclization in THF containing 3 equiv of Et_3Al

Scheme 3. Transition States Considered in the Synthesis of Tetrahydrofurans via Radical Cyclization



Scheme 4. Transition States Considered in the Formation of Compound **2c**



afforded the *trans*-isomer (*cis*/*trans* = 1/5.1) as the major product in 85% yield. Since THF competes with the substrate for Et$_3$Al, no Lewis acid effect is observed.

The preferential formation of the *exo*-isomer of compound **2c** in the unperturbed cyclization reaction may be explained by assuming a *cis*-decalin-like transition state (Scheme 4, left). Complexation by triethylaluminum from above either directs cyclization to occur via a boat conformer (Scheme 4, right) or via the other chair to give *endo*-**2c**.

In conclusion, it was possible to substantially perturb Beckwith−Houk diastereoselectivity in the radical cyclization synthesis of tetrahydrofurans by addition of trialkylaluminums.

Acknowledgment. Financial support by the Swedish Natural Science Research Council is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016429S