ORGANIC LETTERS

2002
Vol. 4, No. 24
4257−4260

Stereoselective Intermolecular Carboazidation of Chiral Allylsilanes

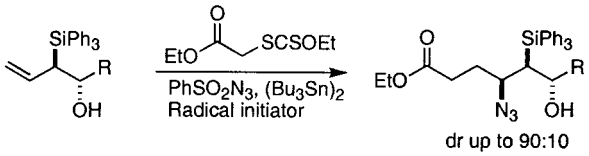
Laurent Chabaud,[†] Yannick Landais,*[,†] and Philippe Renaud*[,‡]

Université de Bordeaux 1, Laboratoire de Chimie Organique et Organométallique, 351, Cours de la Libération, F-33405 Talence Cedex, France, and University of Berne, Department of Chemistry and Biochemistry, Freiestrasse 3, CH-3000 Berne 9, Switzerland

philippe.renaud@ioc.unibe.ch

Received August 30, 2002

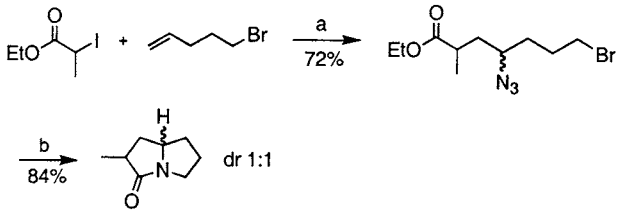
ABSTRACT



Easily available chiral allylsilanes were used as substrate for carboazidation reactions. For the first time, a substantial control of the stereochemistry of the azidation of acyclic nonconjugated radicals was achieved.

The use of free radical reactions in multistep synthesis has steadily increased over the last years, mainly because of their compatibility with a large number of functional groups and their high potential to perform sequential transformations.[1] Recently, we have developed a novel method allowing the efficient formation of carbon−nitrogen bonds by reaction of radicals with sulfonyl azides.[2] This process has been extended successfully to intra- and intermolecular carboazidation reactions.[3,4] This last reaction has led to a very short and efficient two-step procedure for the preparation of the backbone of pyrrolizidine and indolizidine alkaloids (see Scheme 1 for a typical example). However, the control of the stereochemistry of the intermolecular carboazidation of acyclic olefins was not possible in the systems examined so far.

Scheme 1. Two-Step Preparation of 3-Methylpyrrolizidinone by Carboazidation of 5-Bromopent-1-ene[a]



[a] (a) $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), *t*BuON=NO*t*Bu (3 mol %), refluxing benzene. (b) In/NH_4Cl, refluxing EtOH; then Et_3N (5 equiv)/refluxing EtOH.

The control of the stereoselectivity of radical reactions has reached a level that was unexpected a decade ago.[5] However, the stereoselectivity of reactions of acyclic alkyl radicals that are not substituted by strongly stabilizing moieties such as

* Email for additional corresponding author: y.landais@lcoo.u-bordeaux.fr.
[†] University of Bordeaux.
[‡] University of Berne.

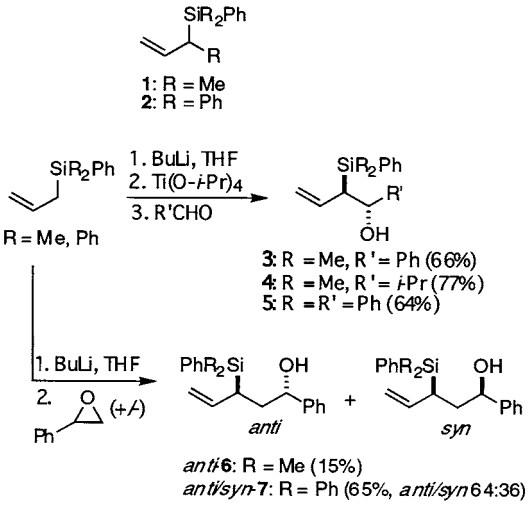
(1) For a general review on radical reactions, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1988. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 4, p 715. 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 Synthesis*; Wiley: Chichester, 1995. Chatgilialoglu, C.; Renaud, P. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; p 501.
(2) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496.
(3) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717.
(4) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460.

10.1021/ol026824y CCC: $22.00
Published on Web 10/30/2002

esters, alkoxy, amino, and aryl groups is usually not controlled.[6] Recently, Porter has observed a very interesting E/Z stereocontrol in Lewis acid promoted radical addition to branched allylsilanes.[7] This result was interpreted as a consequence of a diastereoselective radical bromine atom transfer. We anticipated that such stereocontrol should also be operating with other electrophilic radical traps such as sulfonyl azides.[8] We report here our first attempt to control the stereochemistry of the azidation step by using chiral allylsilanes as substrates for the carboazidation process.[9]

Chiral substituted allylsilanes are easily available by well-established protocols (Scheme 2). For instance, **1** and **2** were

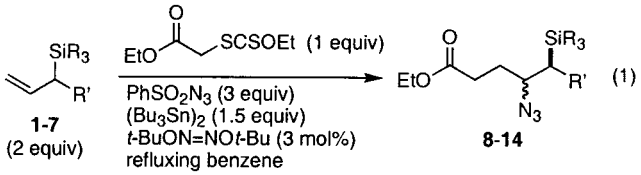
Scheme 2. Chiral Allylsilanes and Their Preparation



prepared in 70% yield through silyl-cupration of the corresponding allylic chlorides.[10] β-Hydroxysilanes **3**−**5** were obtained in diastereomerically pure form (*anti*, >98%) from the corresponding allylsilanes following Yamamoto−Reetz one-pot protocol involving deprotonation of the allylsilane and then transmetalation with Ti(O*i*-Pr)$_4$ followed by coupling with suitable aldehydes.[11] Finally, γ-hydroxysilanes *anti*-**6** and *anti*/*syn*-**7** were prepared by metalation of the allyl(dimethyl)phenylsilane and allyltriphenylsilane followed by reaction with styrene oxide.[12] With allyl(dimethyl)-phenylsilane, a low yield of *anti*-**6** was obtained along with a large amount of the γ-alkylation product (not shown). With allyltriphenylsilane, the coupling occurred mainly at the α-position and provides *anti*- and *syn*-**7** in good yield. The diastereomers were easily separated by chromatography.[13]

Allylsilanes **1**−**7** were then submitted to carboazidation conditions (eq 1). A mixture of allylsilane (2 equiv) and ethyl[(ethoxycarbonothioyl)thio]acetate (1 equiv) was heated under reflux in benzene in the presence of $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), and a substoichiometric amount of di-*tert*-butylhyponitrite (1,2-di-*tert*-butoxydiazene) as initiator. The results are presented in Table 1. β-Azidosilanes

Table 1. Carboazidation of Chiral Allylsilanes **1**−**7** According to Eq 1[14]



entry	silane	product	*syn*/*anti*[a,b]	yield (%)
1	**1**	**8**	73:27	64
2	**2**	**9**	80:20	55
3	**3**	**10**	63:37	71
4	**4**	**11**	>90:10	47
5	**5**	**12**	90:10	29[c]
6	**6**	**13**	80:20	70
7	*anti*-**7**	**14**	≥80:20[d]	30[c]

[a] See below for the attribution of the relative stereochemistry. [b] Ratio estimated from ^{1}H NMR of the crude reaction mixture. [c] Yield of isolated major diastereomer after several purifications by flash chromatography. [d] Not determined with precision because of purification problems.

8−**14** were obtained in moderate to good yields and diastereoselectivities. The preliminary investigations carried out on simple allylsilanes **1** and **2** led to reasonable levels of diastereocontrol. The *syn* β-azidosilanes are formed as the major isomer (vide infra). Diastereomeric ratios were easily estimated using ^{1}H NMR, and the major isomers were isolated by chromatography. However, we were unable to isolate the minor isomer in diastereomerically pure form. The best levels of diastereocontrol were obtained with allylsilanes **4** and **5** having a β-hydroxyl group. Moving the hydroxy group one carbon away, as in γ-hydroxysilane **6**, had no deleterious effect on the diastereocontrol since β-azidosilane **13** was obtained as a 80:20 *syn*/*anti* mixture of diastereomer in 70% yield (entry 6). In the last case (entry 7), it was not possible to determine precisely the diastereoselectivity from ^{1}H NMR of the crude product but flash chromatography afforded only one diastereoisomer of **14** in 30% yield.

The relative configuration of our products was determined through a chemoselective β-elimination of β-silyl azides (Scheme 3).[15] Treatment of major azide **10** with a 1 M

(5) For a general review, see: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

(6) For a review on acyclic radical, see: Giese, B. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 1, p 381.

(7) Porter, N. A.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773.

(8) The silyl group is expected to stabilize polarized transition states bearing a partially positive charge in β-position. Therefore, transition state conformations allowing such a stabilization should be favored. See refs 20 and 21.

(9) Diasteroselective azidation of β-silyl Barton ester are reported by Masterson and Porter in the preceding paper: Porter, N. A.; Masterson, D. S. *Org. Lett.* **2002**, *4*, 4253−4256.

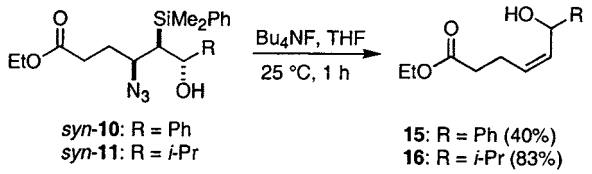
(10) Laycock, B.; Kitching, W.; Wickman, G. *Tetrahedron Lett.* **1983**, *24*, 5785.

(11) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. Ikeda, Y.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1986**, 59, 657.

(12) Schaumann, E.; Kirschning, A. *Tetrahedron Lett.* **1988**, *29*, 4281.

(13) The relative stereochemistry of **6** and **7** was assigned by analogy to the reaction with propylene oxide where product stereochemistry was proven by X-ray crystallography (results to be published).

Scheme 3. Determination of Relative Configuration of 2-Azidosilanes[a]



syn-**10**: R = Ph
syn-**11**: R = *i*-Pr

15: R = Ph (40%)
16: R = *i*-Pr (83%)

[a] *syn* and *anti* refer to the relative configuration at the two adjacent centers bearing the silyl and the azido groups.

solution of TBAF at room temperature led stereospecifically to the corresponding (*Z*)-allylic alcohol **15** in 40% yield.[16] Interestingly, under these reaction conditions, the azido group fragments faster than the hydroxy group. Similarly, the azide **11** afforded the (*Z*)-allylic alcohol **16** in 83% yield. Assuming the *anti*-stereospecificity for this fluoride-mediated Peterson-like elimination, it is possible to correlate the (*Z*)-configured allylic alcohols **15** and **16** with *syn*-**10** and *syn*-**11** (Scheme 3).[17]

With the relative configuration of our β-azidosilanes in hand, we then attempted to rationalize the stereochemistry of the process. Since the intermediate radicals are nonconjugated, none of the classical model to rationalize the stereochemistry of radical reactions can be applied.[18] However, Curran and Giese have reported one example of high 1,2-asymmetric induction in nonconjugated acyclic radicals.[19] The model they propose to rationalize the stereochemical outcome is not applicable to our system because it requires a bulky substituent at the radical center to achieve a high stereocontrol. However, their model is based on the need to pyramidalize the transition state into roughly staggered conformation to avoid gauche interactions between large groups. The same principle should apply to our system together with the well-established behavior of silanes that should favor an approach of electrophilic reagents *anti* to silyl groups.[20] Indeed, it was anticipated that, as bonding between the radical center and the sulfonyl azide develops, a partial positive charge would appear at the carbon atom as a result of the high electrophilicity of the radical trap (see Figure 1), and this partial positive charge is best stabilized

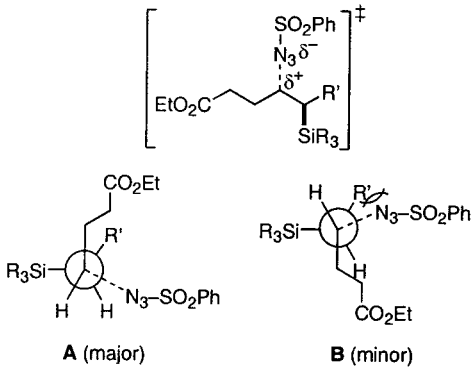


Figure 1. Rationalization of the 1,2-asymmetric induction observed during the carboazidation of chiral allylsilanes.

by a coplanar electron-rich C−Si bond (silicon β-effect).[21] On the basis of these two assumptions (pyramidalized staggered transition state and silicon β-effect) we propose the models **A** and **B** depicted in Figure 1 to explain the stereochemical outcome of the carboazidation of chiral allylsilanes. These two models are characterized by (1) a quasi staggered transition state; (2) the orthogonal relationship between the bulky silyl group and the $CH_2CH_2CO_2Et$ substituent at the radical center; and (3) the formation of a C−N bond nearly *anti* to the silyl group. Model **A**, leading to the major *syn* product, is favored relative to model **B** by the absence of steric interactions between the incoming sulfonyl azide and the $CH_2CH_2CO_2Et$ substituent.[22] This model fits well with the experimental results: increasing the size of the silyl group (entries 3/5, Table 1) and the size of the R′ group (entries 3/4, Table 1) are both leading to an enhancement of the diastereoselectivity.

We have demonstrated that the carboazidation of chiral allylsilanes enables the stereoselective construction of polyfunctional β-silyl azides having up to three contiguous stereogenic centers. Further elaboration of these substrates is at hand. For instance, oxidation with retention of configuration of the C−Si bond should allow for the introduction of an additional hydroxy group.[23] Moreover, the results presented here extend considerably the scope of the carboazidation process for the asymmetric synthesis of alkaloids such as pyrrolizidinones and indolizidinones. Finally, this work demonstrates further the unique role of silyl group in the control of the stereochemistry of nonconjugated acyclic radicals. Further applications of this concept in radical-mediated asymmetric synthesis are anticipated.

(14) **Experimental Procedure.** *Caution*: as sulfonyl azides are capable of exploding, it is strongly recommended to apply standard safety rules and to use a safety shield. A solution of ethyl [(ethoxycarbonothioyl)thio]-acetate (0.05 mL, 0.39 mmol), allylsilane (0.39 mmol), benzenesulfonyl azide (192 mg, 1.05 mmol), $(Bu_3Sn)_2$ (0.27 mL, 0.52 mmol), and di-*tert*-butylhyponitrite (2.5 mg, 0.015 mmol) in benzene (1.5 mL) was heated under reflux. The reaction was monitored by TLC and further portions of di-*tert*-butylhyponitrite (2.5 mg, 0.015 mmol) were added every 1.5 h. Upon completion, the solvent was removed under reduced pressure, the crude product was filtered through silica gel (hexane, then hexane/EtOAc 9:1), and the combined fractions were concentrated in vacuo. The residue was purified by chromatography (hexane/EtOAc).

(15) Arimoto, M.; Yamaguchi, H.; Fujita, E.; Nagao, Y.; Ochiai, M. *Chem. Pharm. Bull.* **1989**, *37*, 12, 3221. Bernhard, W.; Fleming, I. *J. Organomet. Chem.* **1984**, *271*, 281.

(16) The coupling constant $J = 9$ Hz between the two vicinal olefinic protons and NOESY experiments allowed us to assign unambiguously the (*Z*)-stereochemistry for the double bond of **15** and **16**.

(17) A detailed study of the stereospecificity of this elimination is currently underway in Bordeaux. Chabaud, L.; Landais, Y. Unpublished results.

(18) The stereochemical outcome of radical addition to branched allylsilane was rationalized by a Felkin−Anh transition state (ref 7).

(19) Thoma, G.; Curran, D. P.; Geib, S.; Giese, B.; Damm, W.; Wetterich, F. *J. Am. Chem. Soc.* **1993**, *115*, 8585.

(20) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(21) A radical β to a SiR_3 group is known to be stabilized by ~3 kcal/mol: Auner, N.; Walsh, R.; Westrup, J. *J. Chem. Soc., Chem. Commun.* **1986**, 207.

(22) For a related example, see: Angelaud, R.; Landais, Y. *Tetrahedron Lett.* **1997**, *38*, 233.

(23) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1. Landais, Y.; Jones, G. *Tetrahedron* **1996**, *52*, 7599. Tamao, K. In *Advances in Silicon Chemistry*; Jai Press Inc.: Greenwich, CT 1996; Vol. 3, p 1.

Acknowledgment. This work was supported in France by CNRS and the Région Aquitaine and in Switzerland by the National Science Foundation and the Federal Office for Science and Education (OFES/BBW). We are very grateful to Professor Ned A. Porter for helpful discussions. as well as for informing us about his results prior to publication.

Supporting Information Available: Representative experimental procedures including preparation and characterization of allylsilanes **1**−**7**, their carboazidation, and the *anti* elimination of **10** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026824Y