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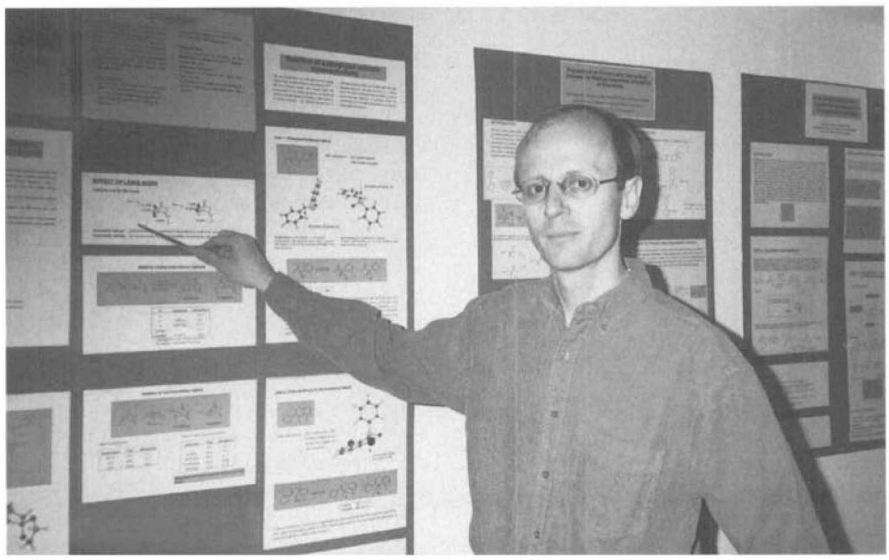
Heteroatom-Substituted Radicals: 1,2-Asymmetric Induction

Philippe Renaud*



Philippe Renaud is born in Neuchâtel in 1959. After his undergraduate studies at the University of Neuchâtel, he continued his education at the ETH-Zürich and received the Ph.D. in 1986 under the supervision of Prof. *D. Seebach*. From October 1986 to December 1987 he was a postdoctoral associate of Prof. *M.A. Fox* at the University of Texas at Austin. In 1988, he started an independent research program at the University of Lausanne. The *Alfred Werner Fellowship*, which he obtained in 1992, allowed him to continue his research work in Lausanne. In October 1993, he moved to the University of Fribourg as an associate professor. His group is active in the field of synthetic organic chemistry based on the use of free radical intermediates with emphasis on stereochemical aspects.

Abstract. Radical reactions became during the last decade a very useful tool in organic synthesis. Spectacular progress has been made in the control of the stereoselectivity of these reactions. This contribution presents our recent results with 1- and 2-heteroatom-substituted radicals in cyclic and acyclic systems. Several examples dealing with the use of *Lewis* acids to achieve high stereochemical control are presented.

1. Introduction

The development of new methods for the formation of C–C bonds has attracted the interest of synthetic chemists for a long time. An impressive number of procedures based on ionic and concerted reactions have been developed. High level of stereochemical control have been obtained and several models allowing to rationalize and predict the stereochemical outcome of these reactions have been elaborated. During the last fifteen years, radical reactions have become a useful tool in organic synthesis thanks to pioneering work of several groups [1]. The control of the stereoselectivity attracted much attention. Rules were developed for cyclization reactions [2] and also for reactions in rigid systems [3]. The stereoselectivity of reactions going through acyclic radicals were long neglected due to the fact that they were considered as essentially non-stereoselective. However, recent developments have denied this belief. Particular attention was devoted to radical possessing and adjacent chiral center ('1,2-asymmetric induction') and several systems were found to be suitable to reach high stereoselectivities [4]. Interestingly, the models which were used to describe the stereoselectivity of ionic reactions were found also suitable for radical reactions. For instance, radicals stabilized by ester groups ('ester enolate radicals') have been investigated in detail and minimization of allylic 1,3-strain ($A^{1,3}$ strain) was found to be determinant for the stereochemical outcome of the reactions [5]. The *Felkin-Anh* model was adapted to the reaction of oxygen-substituted radicals [6]. In this report, we describe our contribution to the comprehension and the control of 1,2-asymmetric induction. Examples of nitrogen-, sulfur-, and oxygen-substituted radicals are presented.

*Correspondence: Prof. P. Renaud
Université de Fribourg
Institut de Chimie Organique
Pérolles
CH–1700 Fribourg

2. 1-Amino-Substituted Radicals

Radical additions onto enamines have been investigated from a stereochemical and from a synthetic viewpoint. A stereoselective method for the reductive alkylation of enamines using Bu_3SnH as reducing agent has been developed (*Scheme 1*) [7–9].

Enamines derived from cycloalkanones were alkylated with high stereoselectivities with preferential formation of the *cis*-disubstituted cycloalkanes (*Scheme 2, Eqn. 1*). On the other hand, acyclic enamines derived from propiophenone and diethyl ketone (*Scheme 2, Eqn. 2*) gave moderate to high stereoselectivities [10]. A unique model, based principally on minimization of $A^{1,3}$ strain, was deduced from these experimental results and confirmed by semi-empirical calculations [8]. The preferred conformation of the radical intermediates is depicted in *Eqns. 1* and *2* as well as the preferential approach of tin hydride. This methodology was extended to the synthesis of protected primary amines starting from 4-piperidone acetals. The reductive alkylation of enamine **5** produced the tertiary amine **6** which was dealkylated by treatment of the hydrochloride with 2-butylamine *via* a double β-elimination strategy (*Scheme 2, Eqn. 3*) [11].

Interestingly, the diastereoselectivity observed with dialkylamino-substituted radicals is preserved when the N-atom is substituted by electron-withdrawing groups. For instance, reduction with Bu_3SnD of 1-phthalimido-substituted radicals generated from the N,Se-acetal **8**

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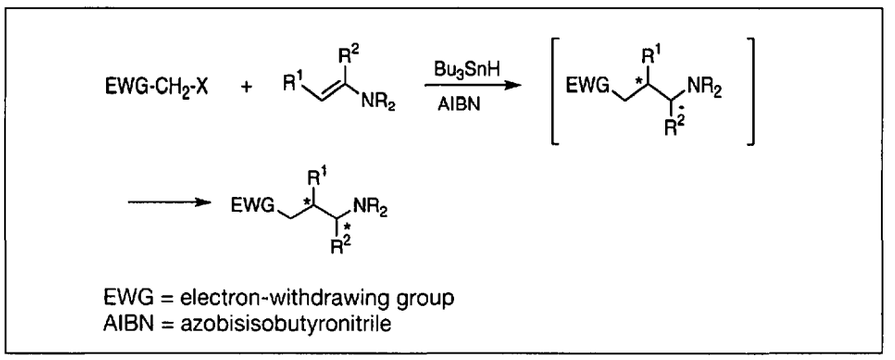
gave the deuterated product **9** (*Scheme 3*, *Eqn. 4*). The same model as before, *i.e.*, minimization of $A^{1,3}$ strain can be used to explain the stereochemistry of this reduction [12].

3. 1-Arylsulfinyl-Substituted Radicals

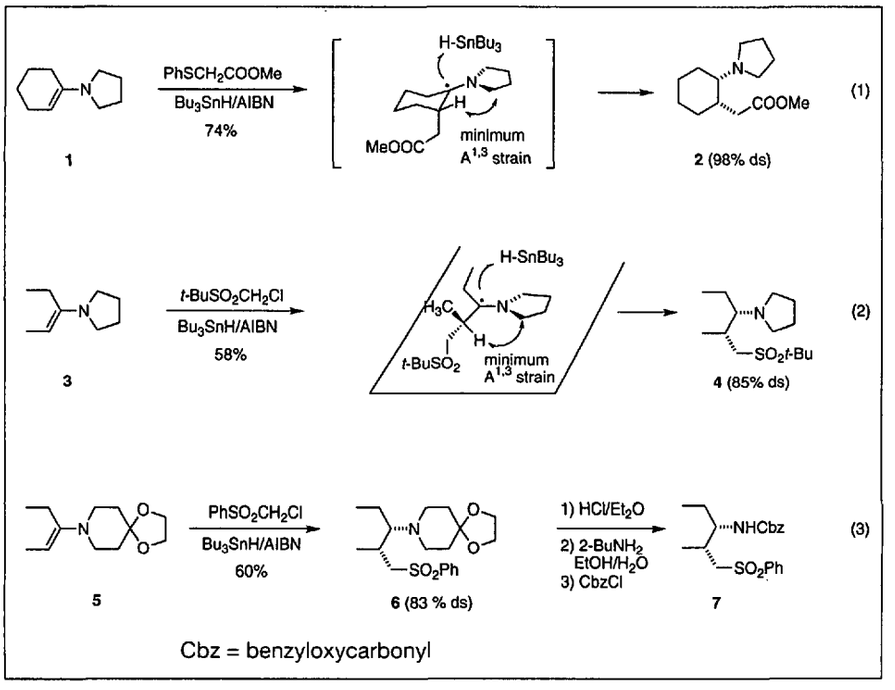
Sulfoxides have been widely used for the synthesis of enantiomerically pure compounds (EPC synthesis). Several strategies based mainly on nucleophilic entities (α-deprotonated sulfoxides) [13], electrophilic entities [14] (alkenyl sulfoxides), [2,3]-sigmatropic rearrangement [15], and *Pummerer* reaction [16] have been reported. Therefore, it was of interest to test the ability of sulfoxides to induce stereoselectivity in radical reactions. Good levels of stereoselectivity were expected since the stereogenic center can be directly attached to the radical center (1,2-asymmetric induction). Since no reports of such reactions was found in the literature at the time we started this project [17], we decided to make a systematic investigation starting with rigid cyclic systems. Six-membered cyclic radicals derived from 4-(*tert*-butyl)-2-(phenylselanyl)thiane 1-oxide **10** and **13** were first investigated (*Scheme 4*) [18]. The stereoselectivity in six-membered ring systems is usually governed by three factors: torsional, steric, and stereoelectronic effects. The torsional effects, which have been introduced by analogy with the case of cyclohexanone reduction, are not dominant. Steric effects are of two types: 1,2-interactions favoring the *anti* mode of approach and 1,3-diaxial interactions disfavoring the axial attack at the radical center. The reactions starting from the axial sulfoxide **10** were first investigated (*Eqn. 5*). The allylation and deuteration reactions gave preferentially the equatorial substituted compounds **11-eq** and **12-eq**. This indicates that steric 1,3-diaxial interactions are the governing factor. The higher selectivity observed in the allylation reaction is attributed to the larger size of the allylstannane relative to the tin deuteride. In the second case, *i.e.*, the allylation and deuteration of **13** (*Eqn. 6*), both the 1,2- and 1,3-interactions should favor the introduction of substituents in equatorial position. However, the percentage of equatorial allylation diminished (**14-eq** (60%) relatively to **11-eq** (70%)) and for the deuteration reaction the selectivity was reversed and **15-ax** was the major isomer (87% ds). Steric effects do not properly account for these results. Only a stereoelectronic effect orienting the attack at the radical center *anti* to the lone pair of electrons of the S-atom which permit a good overlap between this lone pair and the bond being formed may explain these results.

Since the selectivities obtained in the six-membered ring systems were moderate, we decided to investigate the effect of external factors such as the solvent and *Lewis*-acidic additives to enhance it. A study of the tetrahydrothiophen-2-yl 1-oxide radical (*Scheme 5*) gave us important informations [19][20]. The role of the solvent was first investigated for the radical allylation of **16**. Benzene and THF, which can coordinate sulfoxides at sulfur *anti* to the S–O bond, gave the lowest selectivities (70% and 69% ds). This effect was explained by complexation of the radical as depicted in **17a** and **17b**. In a non-coordinating solvent such as CH_2Cl_2, a diastereoselectivity of 82% was obtained. Protic solvents gave slightly higher selectivities (EtOH: 83% ds and 2,2,2-trifluoro-

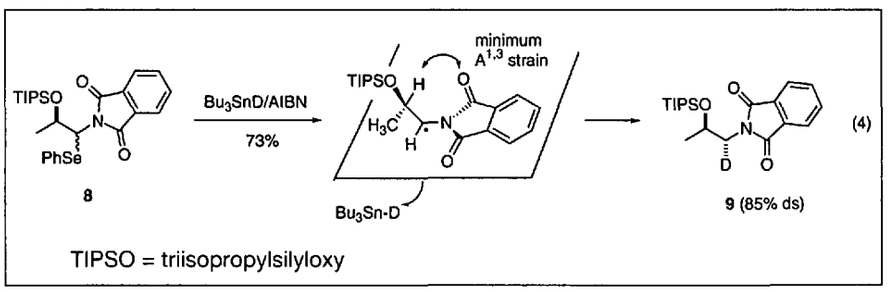
Scheme 1



Scheme 2



Scheme 3



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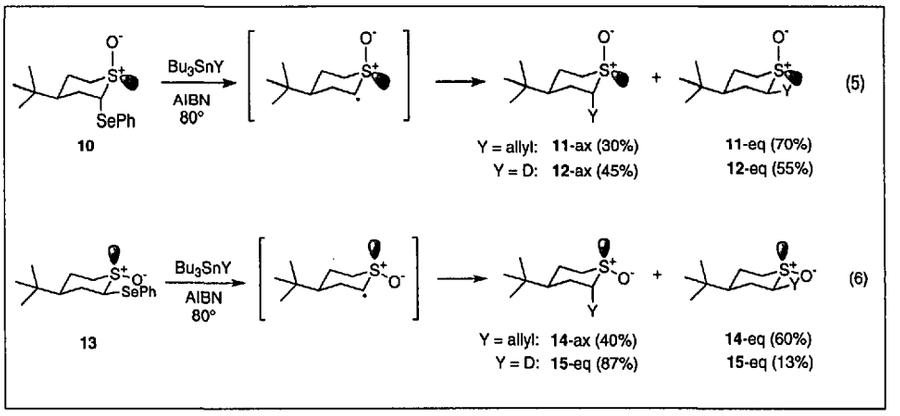
ethanol (TFE): 89% ds). This result was attributed to hydrogen bonding with the O-atom of the sulfoxide as depicted in **17c**. Different *Lewis* acids have been tested to enhance the stereoselectivity of the reaction. Traditional *Lewis* acids gave moderate enhancement. For instance, a diastereoselectivity of 90% ds was obtained with the very mild lithium perchlorate in propionitrile. Exceptionally high stereoselectivities (> 98% ds) were obtained by the use of bulky aluminum-based *Lewis* acids such as methylaluminum di(2,6-di(*tert*-butyl)-4-methylphenoxide) (MAD) and methylaluminum di(4-bromo-2,6-di(*tert*-butyl)phenoxide) (MABR). In the latter case, the use of only 10% of additive allowed to get an enhancement similar to the one obtained with the best traditional *Lewis* acids used stoichiometrically (90% ds).

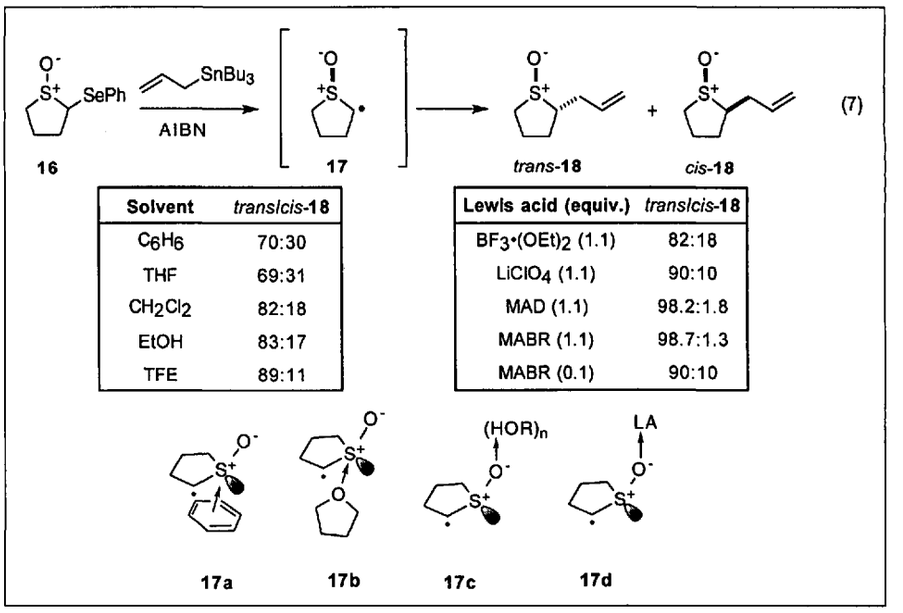
The results obtained in cyclic systems have been transposed to acyclic ones. A good control of the stereoselectivity has been achieved with sulfinylated benzyl radicals (*Scheme 6*) [21]. In the absence of *Lewis* acid, the deuteration of **19** gave preferentially *syn*-**22** (82% ds). The stereochemical outcome can be explained by a transition-state model which minimize the $A^{1,3}$ strain as depicted in **20**, preferential attack occurred *anti* to the Ph group. In the presence of bulky *Lewis* acids such as MAD, the diastereoselectivity is opposite and *anti*-**22** is preferentially formed (> 97% ds). Transition-state model **21** based on minimization of allylic 1,3-strain allows to rationalize this result. Attack is occurring *anti* to the complexed O-atom.

The control of the stereoselectivity of reactions going *via* sulfinylated alkyl radicals was our next challenge. Preliminary experiments showed clearly that the problem would not be easy to solve. Indeed, the cyclization reaction starting from 1-chloroalkyl sulfoxide **23** (*Scheme 7*, *Eqn. 9*) was nonselective relative to the sulfur center and the *trans*-disubstituted cyclopentane derivatives **24a** and **24b** were formed in a 1:1 ratio. However, based on calculations and examination of X-ray crystal structure of methyl aryl sulfoxides, we decided to examine *o*-chlorophenyl sulfoxides [22]. Good levels of stereoselectivities were obtained with this particular chiral template. For instance, the radical allylation depicted in *Eqn. 10* gave a low stereoselectivity (66% ds) with the phenyl sulfoxide **25**. Using the *o*-chlorophenyl sulfoxide **26**, a diastereoselectivity of 90% was obtained under the same reaction conditions. The radical intermediate **27** exists in two different conformations: *s-cis* and *s-trans* (in both conformations, the singly occupied orbital is perpendicular to the the S–O bond for optimal overlap) [23]. When X is an H-atom, these two conformations are of similar energies and reactions are non-stereoselective. When a Cl-atom is introduced, the *s-cis*-conformation is more stable due to strong destabilizing steric interactions between the Me group and the Cl-atom and preferential attack occurs *anti* to the aryl moiety.

Scheme 4



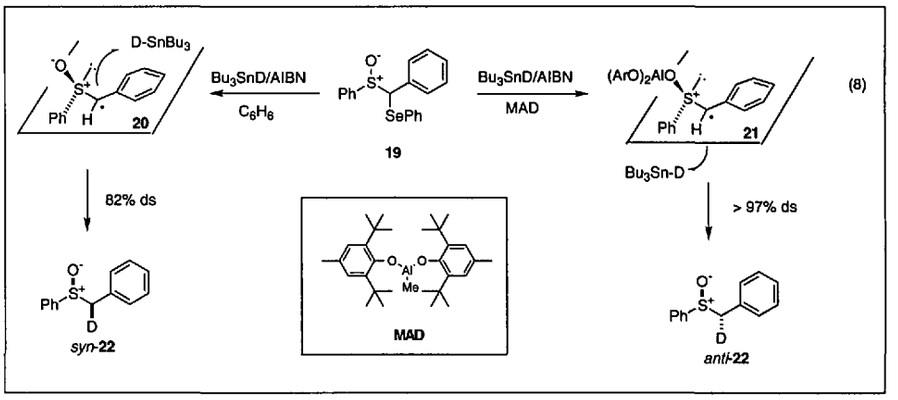
Scheme 5



Solvent	trans/cis-18
C_6H_6	70:30
THF	69:31
CH_2Cl_2	82:18
EtOH	83:17
TFE	89:11

Lewis acid (equiv.)	trans/cis-18
$BF_3{\cdot}(OEt)_2$ (1.1)	82:18
$LiClO_4$ (1.1)	90:10
MAD (1.1)	98.2:1.8
MABR (1.1)	98.7:1.3
MABR (0.1)	90:10

Scheme 6



4. 2-Oxy-Substituted Radicals

2-Oxy-substituted radicals are highly interesting intermediates for EPC synthesis since they can potentially be generated

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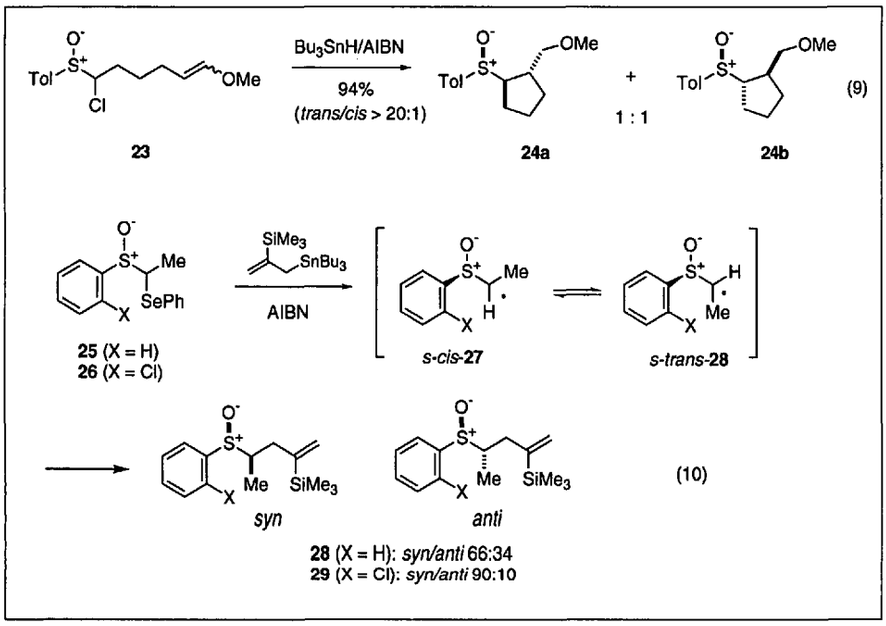
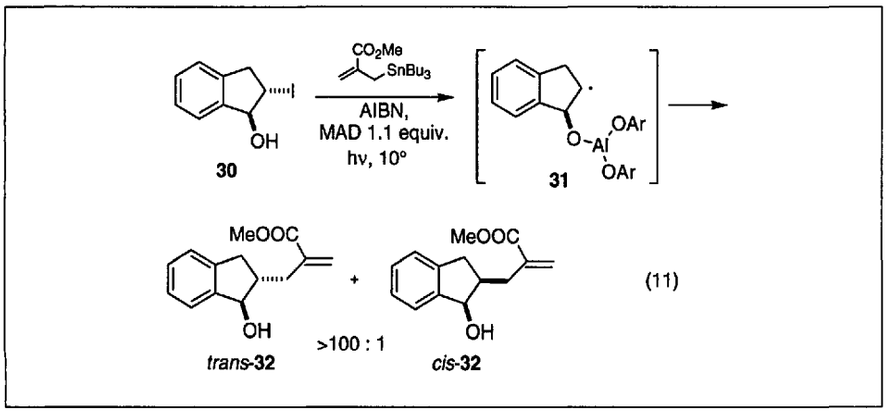
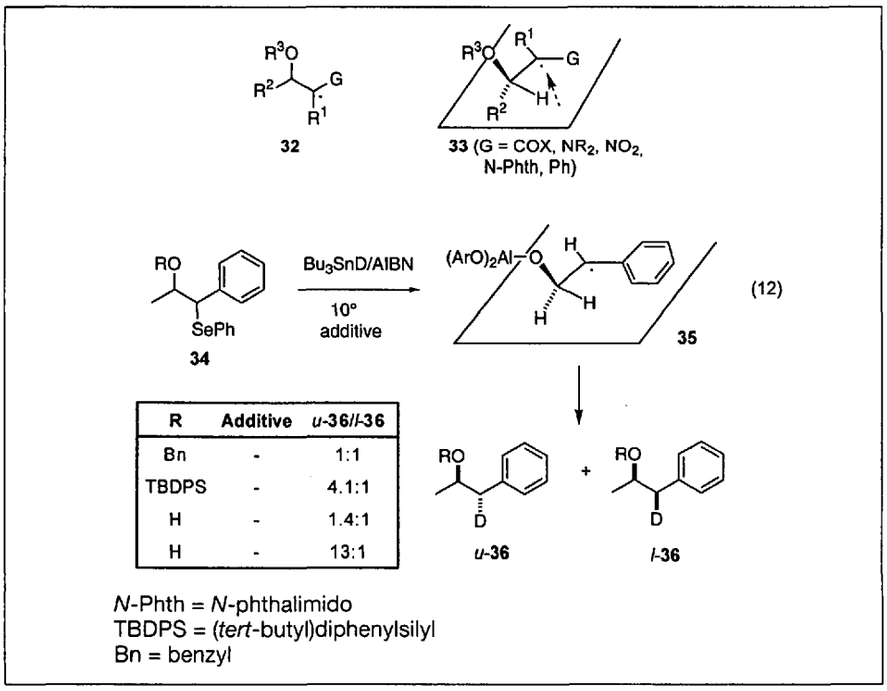
Scheme 7



Scheme 8



Scheme 9



from a wide range of enantiomerically pure compounds. We have investigated radical reactions using the cyclic iodohydrin **30** (*Scheme 8*). The low level of stereoselectivity inherent to this type of system (*Eqn. 11*, *trans*-**32**/*cis*-**32** 1.2:1) cannot be solved by using large protective groups at the O-atom. However, we have demonstrated that very high selectivities can be obtained for this reaction (*trans*-**32**/*cis*-**32** > 100:1) by preforming an aluminum-alkoxide derivative upon treatment of the free alcohol **30** with MAD. Despite the high steric demand of these compounds, the reaction gave satisfactory yields for the formation of C–C bonds.

Some important features relative to the stereoselectivity of reactions based on acyclic 2-oxy radicals of type **32** (*Scheme 9*) have been summarized recently by *Giese* [4d]. For instance, it was found that a high stereoselectivity can only be obtained when the group G is a planar and nonlinear radical stabilizing group (ketone, ester, amide, aryl, *N*-phthalimido, and nitro). In those cases, the stereoselectivity results from the allylic strain model (see **33**). As a consequence, radicals of type **33** can only lead to good selectivities when the two groups R^2 and OR^3 at the stereogenic center possess very different steric bulks. For instance, we observed in benzylic radicals that when R^2 is a Me group and R^1 an H-atom, it was impossible to achieve high stereoselections even when a large protective groups R^3 was introduced at the oxygen substituent. The system depicted in *Eqn. 12* was investigated. With a benzyl oxygen protective group, the reaction was not diastereoselective. Introduction of a large (*tert*-butyl)diphenylsilyl protective group enhanced only slightly the selectivity (*u*-**36**/*l*-**36** 4.1:1). However, starting from the non-protected alcohol **34** (R = H), a high ratio of diastereomers (*u*-**36**/*l*-**36** 13:1) was obtained when the radical precursor was treated with 1.1 equiv. of MAD. The model **35**, which is based on minimization of $A^{1,3}$ strain rationalized this result.

We also studied systems where the use of external factors such as complexating agent may allow to modify the ground-state conformation of the radicals in order to control the diastereoselectivity. For instance, we investigated 1,2-dioxy-substituted radicals (*Scheme 10*), as expected from *Giese*'s work, the deuteration reaction depicted in *Eqn. 13* gave preferentially the *unlike*-compounds *u*-**40**. This results can be rationalized by a *Felkin-Anh* electronic transition-state model (**39a**). However, in the presence of magnesium iodide, the stereochemical outcome can be

reversed due to chelation of the transient radicals **39b**. This represents the first example of chelation control for 1-alkoxy-substituted radicals [24].

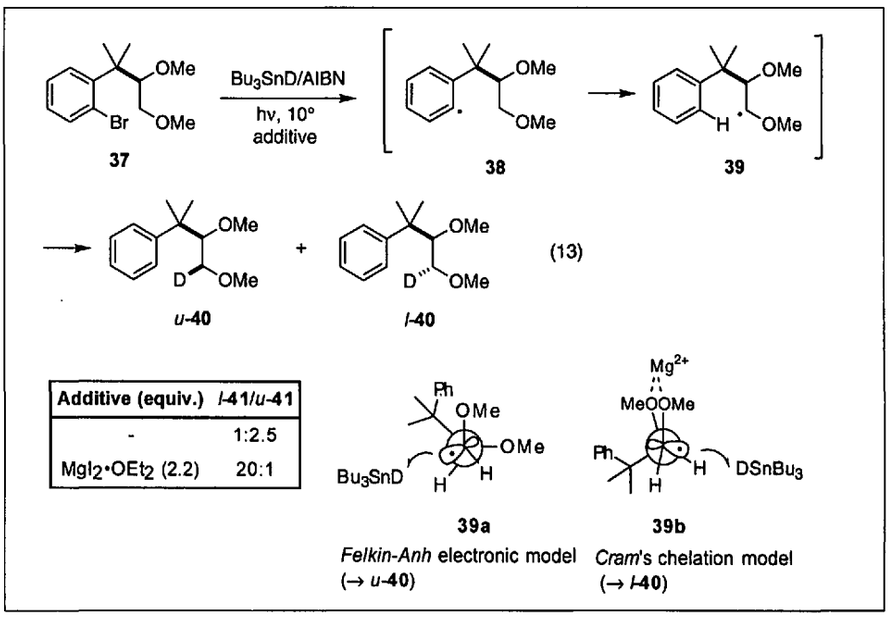
Finally, we have examined β-hydroxy-ester radicals (*Scheme 11*). This system has been examined extensively by *Hart* and others [5]. *Guindon* has discovered for instance that the sense of the stereoselectivity for β-methoxy-ester radicals can be nicely controlled by chelation effects in the presence of magnesium iodide [25]. We have found that a similar degree of stereocontrol was obtained starting directly from β-hydroxy esters [26]. In the absence of additive, the *unlike*-isomer *u*-**43** is preferentially formed (*Eqn. 14*, 77% ds). However, by simple addition of 1.1 equiv. of $AlMe_3$ before running the radical reaction, the sense of stereoselectivity can be change and the *like*-diastereoisomer *l*-**43** is formed preferentially (> 95% ds) presumably *via* the chelated radical **42**. This reaction is very promising from a synthetic point of view. Indeed the reaction is highly stereoselective in the presence of $AlMe_3$, the yields are excellent and the reactions can be run within a few hours on large scale.

5. Conclusions

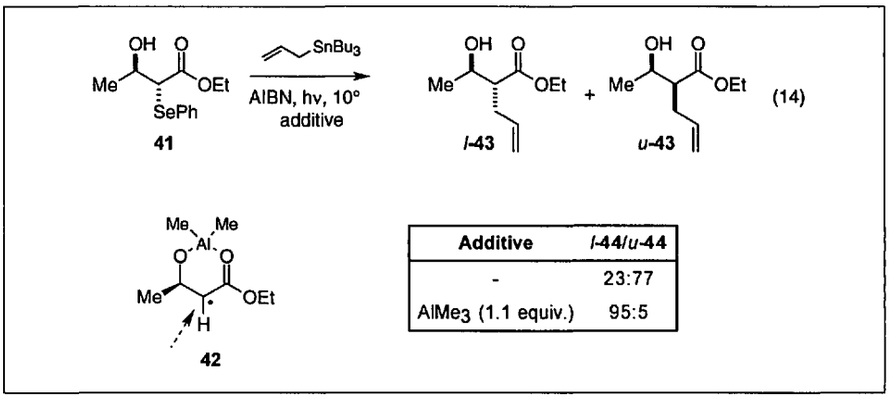
Remarkable progress has been achieved for the comprehension of the stereoselectivity of radical reactions. We have demonstrated on 1-amino- and 1-sulfinyl-, and on some 2-oxy-substituted radicals that the conformation of the radicals dictates the stereochemical outcome of the reactions. Steric effects are of major importance and use of *Lewis* acids has been applied with success to induce large steric differences between the substituents at a stereogenic center. We have also demonstrated that complexating agents can be used to control the conformation of the transient radicals by chelation effects. These observations open new opportunities to develop highly stereoselective radical reactions.

This work would never has been possible without the enthusiastic assistance of several young and talented coworkers. I especially thank *T. Bourquard*, *M. Gerster*, *N. Moufid*, and *A. Stojanovic* for their contribution. This work was financially supported by the *Fonds National Suisse de la Recherche Scientifique*, l'*Office pour l'Education et la Science* (*Progam COST-D2*) and by the *Stiftung für Stipendien auf dem Gebiete der Chemie* through the *Alfred Werner* Fellowship program.

Scheme 10



Scheme 11



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What Can Chips Technology Offer for Next Century's Chemistry and Life Sciences?

Andreas Manz*

Abstract. Microfabrication gives access to surfaces of a few micron square, and the volumes of picoliter and femtoliter size. Integration of combinatorial synthesis, analysis speed, and small-volume handling are the main advantages. Examples of experimental results in drug discovery, analytical chemistry, and microbiology exhibit the potential of the chip-microstructure approach.

Andreas Manz graduated from ETH-Zürich and obtained his Ph.D. in 1986 with a thesis on microelectrodes for use as detectors in open-tubular liquid chromatography. He was with *Hitachi Ltd.* in Japan for a postdoc year and then joined *Ciba-Geigy Ltd.* in Basel for analytical research. Since a few months he has taken the *SmithKline Beecham* Chair of Analytical Chemistry at the Imperial College in London.

'The Incredible Shrinking Laboratory' was a recent headline in *Science* [1], when they were referring to some preliminary results of approaches to miniaturized chemical and biochemical analyzers. This overwhelming interpretation of what is happening in some of todays research labs might be a good reason to have a serious look on what has been experimentally proven and what is pure speculation.

Microfabrication techniques have been widely used in the microelectronics industry for integrated circuits, and there is a small number of physical sensors and actuators on the market, like acceleration sensors controlling airbags of automobiles and ink-jet printer heads. However, chemistry and life sciences seem to have remained nearly untouched. Is that really true? What are the future prospects?

*Correspondence: Prof. Dr. A. Manz
Imperial College of Science, Technology and Medicine
Zeneca/SmithKline Beecham Centre for Analytical Sciences
London SW7 2AY, United Kingdom

The Technology

Based on the experiences made in electronic chip manufacturing, photolithography is now used for the generation of micron-sized mechanical structures on flat silicon wafers. A photo negative, a so-called mask, is used to expose a photosensitive film to light which transfers the two-dimensional pattern of the mask to the photoresist. Parts of the film can be removed to give access to the substrate. The wafer is now further processed, *e.g.*, etched in solution to obtain micron-deep patterns in the silicon substrate. Other types of processes include film deposition and bonding techniques.

As a result, devices with a basically flat surface can contain cavities, channels, electrodes, windows, bridges, and many more. These features are typically 2 μm to several mm in length and width, and 100 nm to