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Fourier-Transform Mass Spectrometry (FTMS)

Some MALDI ion formation processes take place after desorption, by gas-phase protonation (cationization) reactions in the MALDI plume. If this is the dominant process, fragmentation will be controlled by relative proton (cation) affinities of matrix and analyte. Very limited proton affinity (PA) data on nonvolatile MALDI matrices is available. We are measuring them by bracketing reactions in the FTMS instrument using gaseous reference bases of known PA. We have determined the proton affinity values of the MALDI matrices 2,5-DHB, 4-HCCA, and sinapic acid [15]. The PA values of some common matrix fragments were also measured and found to differ siginificantly from that of the parent molecule. In some cases, this difference amounts to 60 kJ/mol (15 kcal/mol). Furthermore, no correlation between fragmentation of analytes and the PA of the matrices were found.

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Stereoselectivity Control of Free-Radical Reactions Using *Lewis* Acids

Philippe Renaud*

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 stereocontrolled procedures based on ionic and concerted reactions have been developed. During the last 15 years, radical reactions became a useful tool in organic synthesis. For a long period of time, they were considered as essentially non-stereoselective. However, recent developments have completely altered this belief, and subsequently rules were developed to rationalize and predict the stereochemical outcome of cyclization reactions, reactions in rigid systems, and even reactions in acyclic systems [1]. A few years ago, strongly encouraged by the attribution of the *Alfred Werner* Fellowship, we decided to investigate the use of *Lewis* acids in order to control the stereoselectivity of radical reactions. Some of our recent results are depicted below.

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Philippe Renaud was born in Neuchâtel in 1959. After undergraduate study at the University of Neuchâtel, he continued his education at the ETH-Zürich through 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. He starts in 1988 an independent research program at the University of Lausanne. In 1992, he obtained the *Alfred Werner Fellowship* which allows 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.

Michèle Gerster (left) *and* Anna-Reine Fhal (right) *are two graduate students strongly involved in the use of* Lewis *acids in radical reactions*

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interfacing of liquid chromatography with MALDI-MS. We have shown that a new matrix consisting of a graphite/glycerol or silicon/glycerol slurry can be used very generally for sensitive MALDI-MS on peptides, proteins, oligosaccharides (*Fig.*), polar and apolar polymers up to molecular weights of 15 kDa [13][14].

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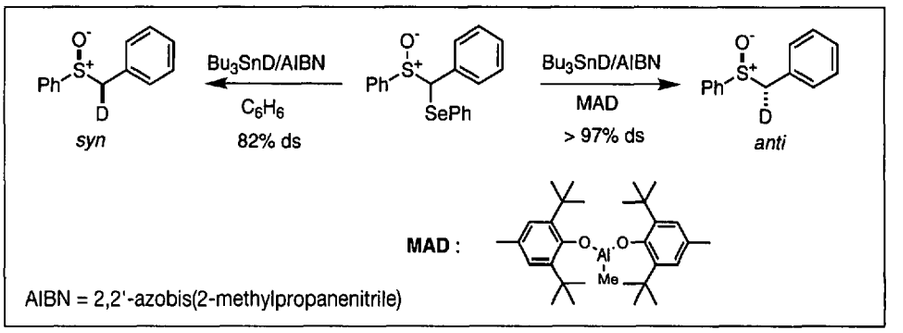
Michèle Gerster (left) *and* Anna-Reine Fhal (right) *are two graduate students strongly involved in the use of* Lewis *acids in radical reactions*

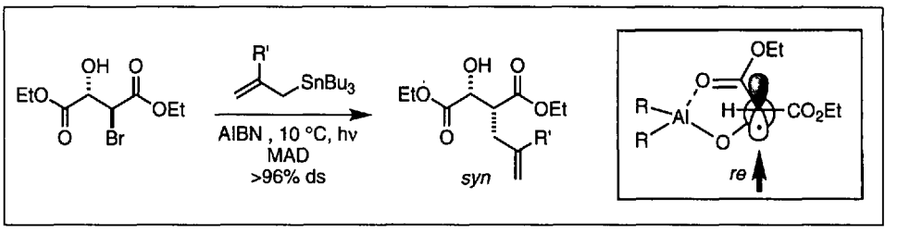
Diastereoselectivity Control Using Monocomplexation

During our study of the allylation reactions of cyclic sulfoxides, we discovered that protic solvents which form hydrogen bonds with the O-atom of the S–O bond enhanced the stereoselectivity. Use of oxophylic *Lewis* acids gives even better results, exceptionally high levels of stereocontrol are reached with bulky aluminum derivatives. For instance, the allylation of the tetrahydrothiophen-2-yl radical gives a modest 70:30 *trans*/*cis*-mixture of isomers in benzene, however, the presence of methylaluminum di[(4-bromo-2,6-di(*tert*-butyl)phenoxide] (MABR) allows us to enhance the diastereoselectivity to a *cis*/*trans*-ratio of 98.7:1.3 [2]. The same approach was successfully applied to acyclic sulfinylated radicals. In this case, the sense of the diastereoselectivity can be fully reversed by using bulky *Lewis* acids (*Scheme 1*) [3]. This strategy is not limited to sulfoxides, similar results were obtained with cyclic and acyclic 2-hydroxy- and 2-alkoxyalkyl radicals [4].

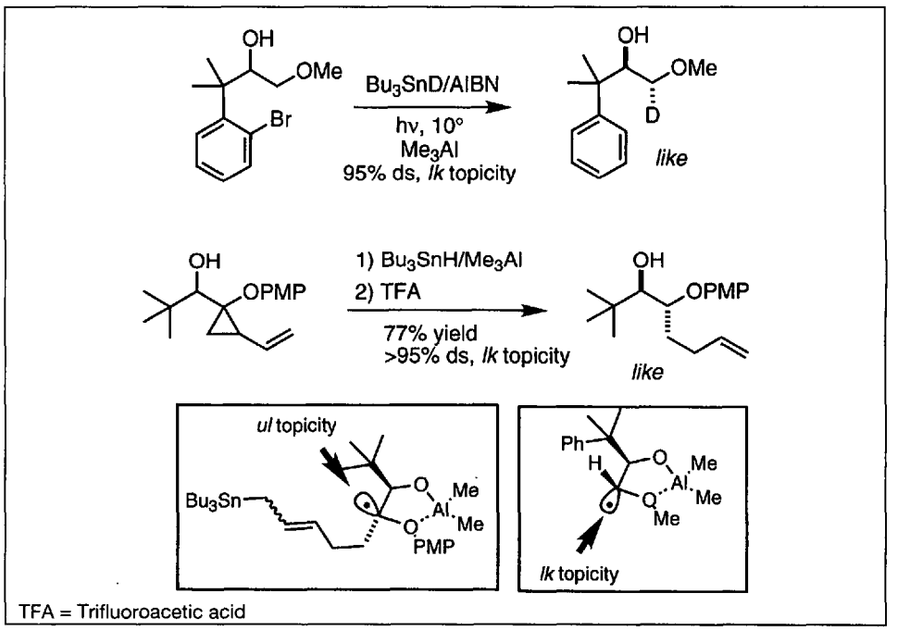
Scheme 1



Scheme 2



Scheme 3



Diastereoselectivity Control Using Chelation

Our approach in this field is based on practical considerations. We were looking for efficient and simple ways to control the stereoselectivity of 2-hydroxyalkyl radicals. The reported strategies employed in such systems used protected hydroxy groups. We have developed a method directly based on the free alcohol *via* formation of aluminum-alkoxide derivative upon treatment with methylaluminum derivatives. This method is particularly efficient for β-hydroxy esters such as ethyl 3-hydroxybutyrate and diethyl malate (*Scheme 2*) [5]. In the last case, the allylation in the presence of MAD furnishes the *threo*(*syn*)-product. This stereochemical outcome is complementary to the well-known alkylation of the corresponding enolate.

Our approach can also be used with 1,2-dioxy-substituted radicals. With secondary radicals, the stereochemistry is explained by a model related to the *Cram* chelation model (*Scheme 3*, above) demonstrating again the similarity between the models used for ionic and radical reactions [6]. Interestingly, tertiary radicals behave differently, and attack of the radical chelate occurs *syn* to the bulky neighboring group (anti-*Cram* chelation model). One example of this type is depicted in *Scheme 3*, below [7]. This peculiar behavior is best explained by pyramidalization of the radical and by reaction of the most stable conformer with small radical traps such as tin hydride *syn* to the bulky neighboring substituent.

Enantioselectivity Control

Chiral *Lewis* acids are very promising for the development of catalytic enantioselective radical reactions. In our first approach, we have performed enantioselective radical C,C bond formation directed by chiral *Lewis* acids [8]. *N*-(2-Iodopropionyl)oxazolidinones are allylated with allylstannane in the presence of chiral aluminum-based *Lewis* acids prepared from Me_3Al and chiral diols/diamides ligands (*Scheme 4*). The observed enantioselectivities using stoichiometric amounts of chiral additive are still modest (≤ 34% ee). By analogy to cycloaddition reactions, a model is proposed to rationalize the sense of the enantioselectivity.

Conclusions

In a few years, great progress has been accomplished in *Lewis*-acid-controlled radical reactions. Our contribution to this field has allowed to define suitable metals,

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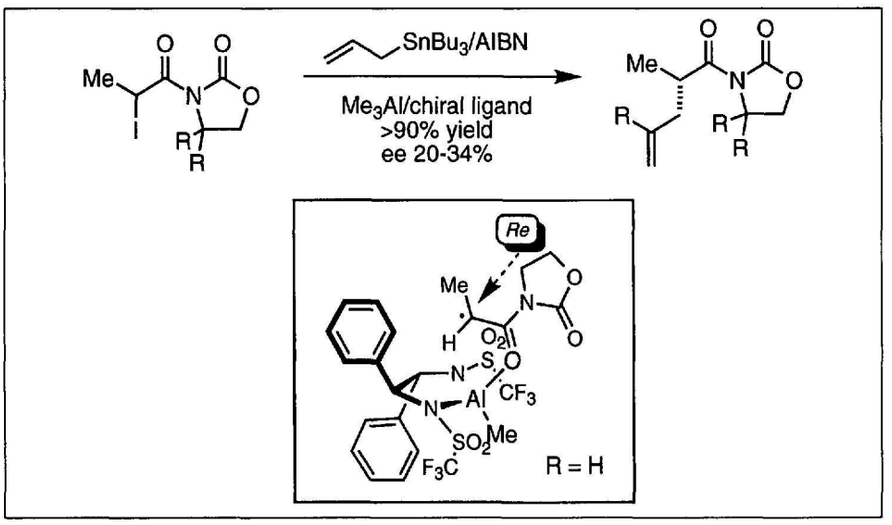
Scheme 4



in particular aluminum, for these reactions. We have also developed several different strategies for the control of the stereochemistry. Further investigation of the broad and hot topic of catalytic enantioselective radical reactions should enhance the range of possible applications of free-radical reactions.

This work would never have been possible without the enthusiastic assistance of young and talented coworkers. I particularly thank *A.-R. Fhal*, *M. Gerster*, and *N. Moufid* for their contributions. This work was financially supported by the *Fonds National Suisse de la Recherche Scientifique* and by the *Stiftung für Stipendien auf dem Gebiete der Chemie* through the *Alfred Werner Fellowship* program.

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Electronic Asymmetry: Theoretical Background, Ligand Design, and Applications

Thomas R. Ward*

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1. Relatives of the d^0 Bent $[Cp_2ML_3]$ Family. An Extended *Hückel* Molecular Orbital (eHMO) and Structure-Correlation Study of the Edge-Bridged Tetrahedron (EBT-5)

When one thinks of five coordination, the trigonal bipyramid (TB-5) and the square pyramid (SPY-5) immediately come to mind. Their interconversion, *via* the *Berry* mechanism, has been thoroughly studied [5]. In the field of d^0 organometallic chemistry, the bent metallocene Cp_2M fragment (Cp = cyclopentadienyl) occupies a central position. Considering cyclopentadienyls as six-electron donors occupying a single coordination site, $[Cp_2ML_3]$ com-

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I was born in Fribourg on January 8th 1964 as the last of six children of *John E. Ward* and *Ada Lovinger Ward*. As an American citizen, I obtained Swiss nationality in 1976. I am married to *Anouck Visinand* and father of two sons, *Benjamin Roald* and *Samuel*.
After obtaining my *baccalauréat* from Collège St.-Michel in June 1983, I entered the University of Fribourg the same year as a chemistry student. I graduated in 1987 with organic chemistry as major and inorganic chemistry as minor subjects.
My interests being mostly synthetic but with a pronounced taste for group theory, I opted for a Ph.D. in organometallic chemistry at the ETH-Zürich in the group of Prof. *L.M. Venanzi*. The project I studied dealt with the synthesis and coordination properties of C_3-symmetric phosphine ligands and their use as acetalization catalysts [1][2]. This work, which was awarded the ETH Silbermedaille, benefited from a fruitful collaboration of Prof. *D. Seebach* as well as of *Ciba-Geigy* which patented our systems. I then moved to Cornell University to work under Prof. *R. Hoffmann*. This theoretical excursion led me into the fascinating field of heterogeneous catalysis: Why is rhodium so efficient at removing NO from car exhaust [3]? On returning to Switzerland, I joined the group of Prof. *C. Floriani* for a second postdoc. My main focus was the synthesis of transition-metal carbides [4]. Soon thereafter, I was awarded the *Alfred Werner* Fellowship and moved to Bern to undertake my independent career in Fall 1993.
I consider myself as a ligand designer fascinated by chirality. My research can be divided into three stages. After having identified a relevant problem from the current literature, I run a series of qualitative molecular orbital calculations which help me rationalize the published observations. Coincidentally, these form the basis for a synthetic project. Thus, I will describe three distinct projects at different stages of achievement: *i*) outlining a problem with the help of molecular orbital theory, *ii*) designing a ligand system, and *iii*) applications.