New silicon-derived environmentally-benign Lewis-acid catalysts for asymmetric synthesis

Small molecule natural products (SMNPs) have played an enormous role in the drug discovery process by providing molecules which itself possess the properties of a useful drug or by serving as lead reagents providing a structural platform from which valuable pharmaceuticals can be elaborated or, perhaps more importantly, by providing insight into types of "privileged structures" which could lead to compounds of therapeutic value. SMNPs analogs often allow for entry into the discovery process at a much more advanced stage that does the screening of standard diversity libraries and the pharmacoviability of SMNPs should be much greater than that of compounds arising from random libraries. However natural products are often of limited access and chemical modifications of natural products are often restricted. Therefore total synthesis is often the only solution but traditional synthetic approaches are often too time-consuming and too expensive for the preparation of multi-gram quantities of these complex molecules derivatives.

A strategy originally proposed by Danishefsky in the US and developed among others by Ghosez in France consists in the development of *short* synthetic sequences to *scaffolds* which retain some essential structural and stereochemical features of the natural product and then create libraries of *natural products analogs* using the techniques of combinatorial chemistry. In this context the group of Ghosez at the European Institute of Chemistry and Biology 3-5 steps sequences of reactions for the synthesis of complex piperidine scaffolds which are ubiquitous in pharmaceuticals and agrochemicals. In the course of these studies, they were faced to limitations resulting from the low reactivity of some of the reactants. Unexpectedly catalysis of these reactions by Lewis acids appear to be unexpectedly difficult in view of the existence of a vast arsenal of organometallic catalysts and more recently of the development of organocatalysis. Most catalysts partially destroyed the reactants leading to complex reaction mixtures. Thus a programme was initiated in Ghosez' group aiming at the design and development of new Lewis acid catalysts complying with the following requirements : (1) highly active (high turn-over), (2) chemoselective (functional tolerance), (3) easily adaptable for asymmetric reactions, (4) non-genotoxic, (5) environmentally friendly. Silicon-derived Lewis acids appeared to be promising candidates to this aim.

The present project was based on the seminal discovery of Ghosez' and Mikami's groups that trialkylsilyltriflimide (Me_3SiNTf_2) acted as extremely powerful Lewis acid catalysts. They exhibit a strong Lewis acidities which could be tuned-up by varying the size of the alkyl groups on silicon and they showed a good tolerance for many acid-sensitive functional groups. An additional advantage of these trialkylsilyl imide catalysts was their easy removal from the reaction mixtures by simple extraction with water. Also these cheap and powerful catalysts were non-genotoxic and environmentally benign.

Our challenge was the design of powerful silicon triflimide catalysts which would allow for enantioselective reactions. An obvious choice was to introduce chiral alkyl substituents on the silicon atom. This was indeed successful with some derivatives of myrtenal. We prepared eight silylated triflimides deived from the terpene myrtenal and tested them but the enantiomeric excesses never exceeded 55%.

J. Leighton at Columbia University and B. List at the Max Planck Institüt, Mülheim respectively studied silicon chloride catalysts derived from chiral aminoalcohols or a trialkylsilyl sulfonimide catalyst derived from a chiral biaryl. They obtained excellent enantioselectivities but only for a limited number of applications since the catalytic activity was too low. Thus it became clear to us that a successful design of the "ideal" silicon-derived catalyst would *first* required the understanding of the structural parameters controlling the catalytic activity. Accordingly we modified our initial plans.

Our new strategy consisted in preparing a wide variety of silicon derivatives carrying (1) a very good leaving group, (2) two ligands (mostly heterosubstituted) susceptible to be made chiral easily (3) an alkyl or aryl group. Eighteen new compounds have been prepared. They were characterised by

^{1}H, ^{29} Si NMR and in some cases ^{19}F NMR . The Lewis acidity of these new compounds was tested by following by ^{1}H NMR their complexation with methyl acrylate or methyl crotonate. Then the catalytic activity of these potential catalysts was tested on some model reactions (Diels-Alder, alkylation, aldol…). As far as we can tell, this represents the first systematic and comprehensive study of a "structure-catalytic activity" relationship of these electrophilic silicon compounds. As expected, the presence of oxygen, nitrogen or carbene substituents on the silicon atom strongly influenced the catalytic activity of the silicon-derived Lewis acid. This study also led to the discovery of two catalytic species. The first species is derived from a tetracoordinated silicon atom and is tetrahedral. The second species is derived from a pentacoordinated silicon atom and is a bipyramid-trigonal molecule. This should offer even more opportunities for the design of efficient asymmetric catalysts.

The preparation and systematic study of these new Lewis acids took most of our time. However in the last few months we were able to prepare the very reactive triflimide analogs of the Leighton catalysts. As expected they were much more active than Leighton's chlorides and could be used in "catalytic" amounts in contrast to the Leighton's chlorides which have to be used in stoechiometric amounts. However enantiomeric excesses on our model reactions were low. Further experimental and computational studies of the parameters controlling the facial selectivity of these reactions are definitely needed.

The fundamental knowledge acquired during these 18 months study should allow us to select and prepare classes of silicon-derrived Lewis acids which should **ensure** a *satisfactory catalytic activity* for a given reaction and the possibility of varying simply and practically the nature of the *chiral information* in the substituents. The availability of "green", efficient and selective catalysts for reactions allowing to build efficiently complex, highly functionalised scaffolds for the development of new bioactive compounds is obviously of great importance. However we believe that the results obtained in this Marie Curie project offer new perspectives for "green" catalysis, a "hot" area of fundamental importance for pharmaceutical, agrochemical and fine chemical industries. For example we found that our new catalysts were able to activate environmentally safe and non-genotoxic starting materials for alkylation reactions. It is very clear that more applications of these new classes of silicon-derived catalysts should be expected in the context of the development of sustainable chemical transformations both at the laboratory and the industrial level. Contacts have already been established with the representatives of chemical industries in Europe to evaluate the potential of these catalytic systems.

We believe that this concern about environmental safety should be shared by all researchers working in chemical synthesis. Working on a project like this was of great benefit for the education of a 21st century chemist. One drawback , however : the practical importance of the results is such that disclosure of the structure of these new catalysts has to wait for the filing of a suitable patent. However we are convinced that the game is really worth the candle.

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