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Catalytic Methods for Direct Access to Chiral High-Added-Value Products

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Abstract: This account summarizes the activities of the first three years of our young research group working in the field of homogeneous asymmetric catalysis.

Keywords: Asymmetric catalysis · Building blocks · Dual activation catalysis · Lewis acids · Practicality

1. Introduction

The research focus of our synthetically oriented group is structured around one central theme: the development of practical catalytic asymmetric methodologies for the direct preparation of high-added-value products by C–C or C–X bond formation.

As a former process research chemist at F. Hoffmann-La Roche in Basel, it is the corresponding author's long-term objective to increase the spectrum of catalytic asymmetric procedures with the potential for technical scale applications. Analyzing the current situation of asymmetric catalysis, it becomes evident that applications on a technical scale in pharmaceutical industry are largely limited to asymmetric hydrogenations and various enzyme catalyzed processes.[1] The main issues of the majority of catalytic asymmetric procedures are that the catalysts, the substrates or the reaction conditions in general are either too complex, too expensive, too sensitive or too toxic. Moreover many of the existing methodologies currently representing the state-of-the-art in asymmetric catalysis have a rather limited scope and even small structural deviations are often not tolerated. Many modern catalytic asymmetric procedures lead to complex product mixtures which are difficult to separate. This is especially the case for the bulk of organocatalytic procedures. However, in addition to practicality, the scope and efficiency of a process are of general importance for the application to the preparation of structurally complex functionalized molecules and also to render catalytic asymmetric C–C and C–X bond formations a more useful tool in medicinal chemistry in order to prepare libraries of enantiopure compounds. To assert asymmetric catalysis as a broadly applicable device in pharmaceutical industry, the above-mentioned criteria should be considered for future developments.

In our research program we incorporate two central strategies using mother nature as guide: the development of catalysts which function *via* highly organized transition states leading to elevated levels of stereocontrol and, where possible, to use multiple activation modes allowing for mild reaction conditions and high turnover numbers. This account illustrates the progress of the first three years in our young research group since its start in fall 2004.

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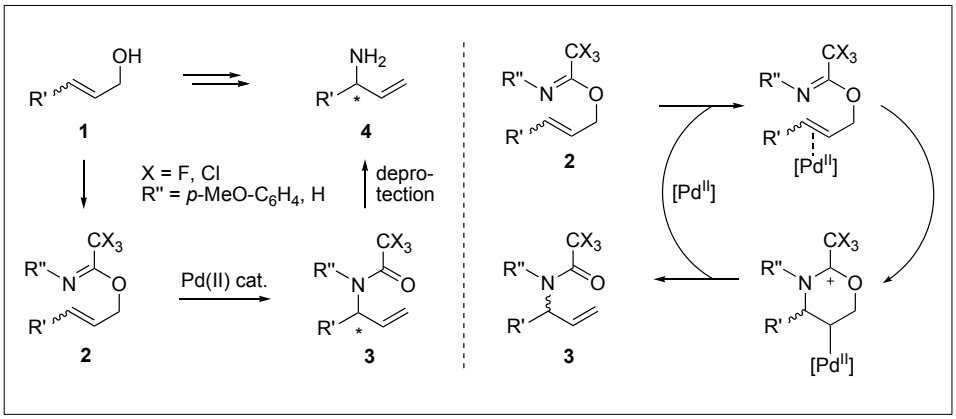
2. The Development of Practical Catalysts for Enantioselective aza-Claisen Rearrangements

In modern synthetic chemistry soft Lewis acids such as Pd(II), Pt(II) or Au(I) have become more and more important, since coordination of these carbophilic cations to olefins or alkynes results in a net transfer of electron density to the metal center thus activating the unsaturated system for the attack of nucleophiles. The soft Lewis acid can thus be regarded as a chemoselective (owing to its low oxophilicity) and possibly chiral proton substitute.[2]

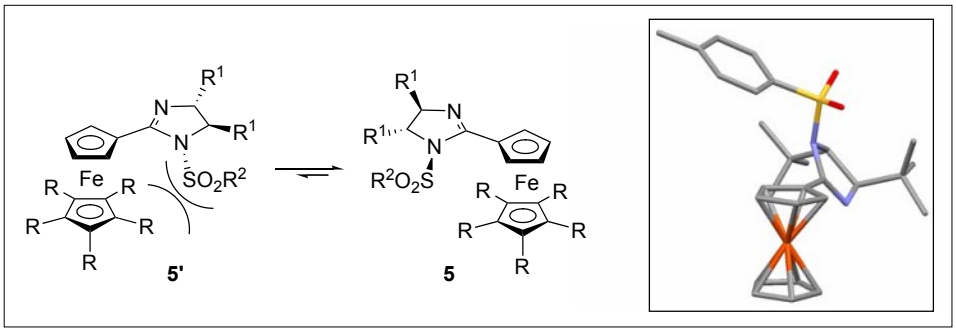
For example, the Pd(II) catalyzed aza-Claisen rearrangement[3] of allylic trichloro-[4] and trifluoroacetimidates[5] enables the transformation of achiral allylic imidates **2**, readily prepared in a single step from allylic alcohols **1**, to chiral enantioenriched allylic amides **3** (Scheme 1).

Since the trihaloacetamide protecting groups can be readily removed, the overall transformation leads to allylic amines **4** as valuable building blocks. There is ample evidence that these reactions proceed *via* a cyclization induced rearrangement mechanism, in which the olefin moiety of **2** coordinates to the Pd(II) complex and is thereby activated for a nucleophilic attack by the imidate N atom (Scheme 1).[6]

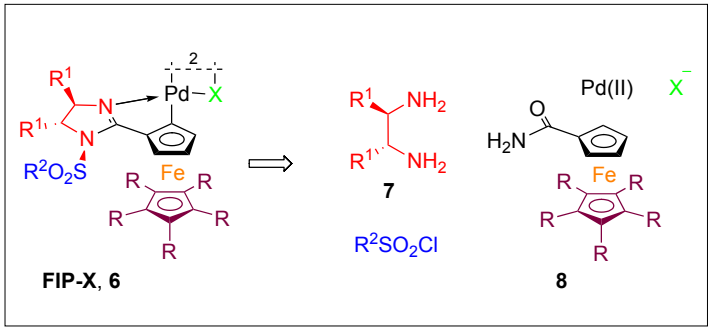
Our group has developed the first *highly active* enantioselective catalysts for the aza-Claisen rearrangement of trifluoroacetimidates:[5e–f] planar chiral ferrocenyl imidazoline palladacycle (FIP) catalyst systems have been created in which a bulky *N*-arylsulfonyl residue is the key structural element to permit a direct diastereoselective cyclopalladation. Steric repulsion between the residue R^1 at the imidazoline-5-position and the sulfonyl group effects



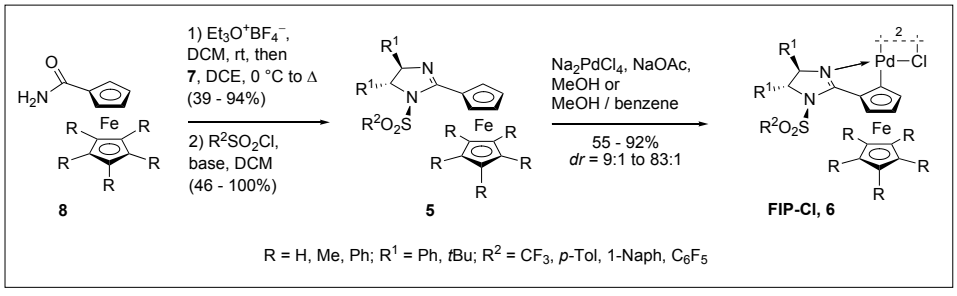
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

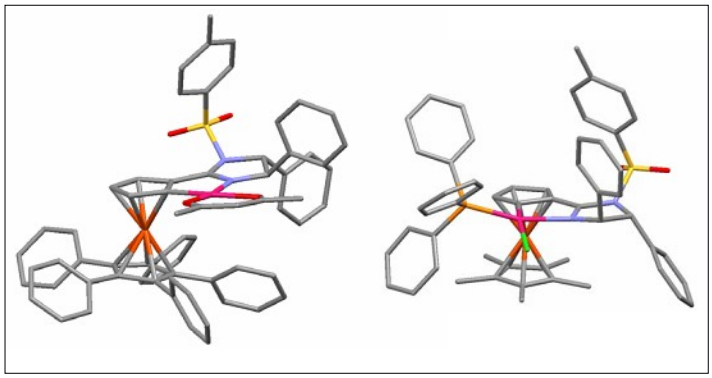


Fig. 1.

a transfer of chirality to the sulfonylated nitrogen atom resulting in a preferred equilibrium conformation in which the sulfonyl group points away from the ferrocenyl floor (Scheme 2) and, as a consequence, allows for a diastereoselective cyclopalladation. The hypothesis of chirality transfer to the *N*-sulfonyl group was confirmed by X-ray crystal structure analysis. The sulfonylated N atom is significantly pyramidalized thus minimizing unfavorable steric interactions with the neighboring substituents.

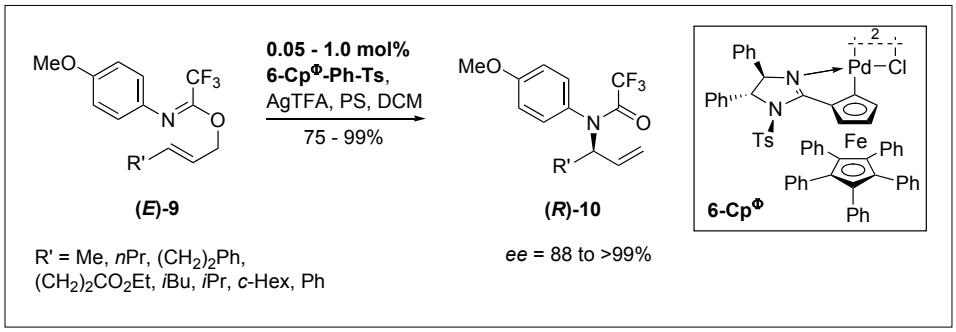
A highly modular concept led to catalysts **6** in which both the steric demand and the electronic properties can be adjusted by five independent modules: a) the cyclopentadienyl spectator ligand C_5R_5, b) the imidazoline part being synthesized from an enantiomerically pure C_2 symmetric diamine **7**, c) the residue on the amino nitrogen, d) the counterion X^- and e) the oxidation state of the Fe ion (Scheme 3).

The air-stable crystalline imidazolines **5** are readily prepared in two steps from amides **8**[5d,7] (Scheme 4).

Cyclopalladation gives the air-stable dimeric complexes FIP-Cl **6** in good yield and with good diastereoselectivity with regard to the planar chirality.[8] The validity of the catalyst design was proven by X-ray crystal structure analysis of monomeric acac and PPh_3 derivatives which show that the substituents at the imidazoline 4-position indeed point away from the Cp spectator ligand (Fig. 1).

Investigation of the catalyst modules revealed that the C_5R_5 ligand and the Fe oxidation state play the most important roles: complex **6-Cp$^\Phi$** possessing the extremely bulky Cp^Φ ligand ($Cp^\Phi = C_5Ph_5$) provided after activation with AgO_2CCF_3 a highly active ferrocenium catalyst thus allowing the use of unprecedented low catalyst amounts whilst still providing useful reaction rates for a broad range of substrates (Scheme 5). With aliphatic α-unbranched substituents R' at the allylic 3-position, (*R*)-**10** is formed in excellent yield with just 0.05 to 0.1 mol% catalyst loading providing the highest enantioselectivities obtained so far for substrates (*E*)-**9** (*ee* = 95 to >99%).[5e] Even for the case of α-branched substituents R', a substitution pattern which could not be realized before, the rearrangement proceeds with acceptable rates using 0.1 to 0.5 mol% catalyst precursor (*ee* = 96–97%). Furthermore, for the first time aromatic substituents are also well tolerated (*ee* = 88% for R' = Ph).

An opposite absolute configuration of the major enantiomers of rearrangement products **10** starting from either (*E*)- or (*Z*)-**9** may be accounted for by the working model depicted in Fig. 2. Assuming that the olefin coordinates to Pd *trans* to the imidazoline N atom due to a *trans* effect,[9] the imidate N atom will attack the olefin *via* a



Scheme 5.

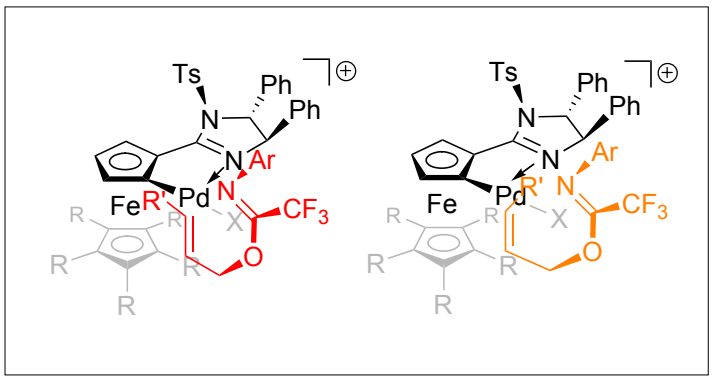
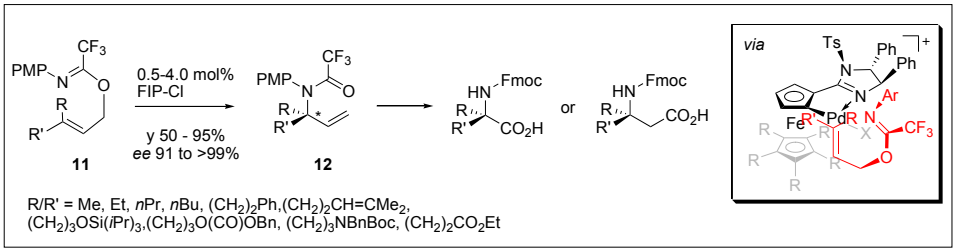
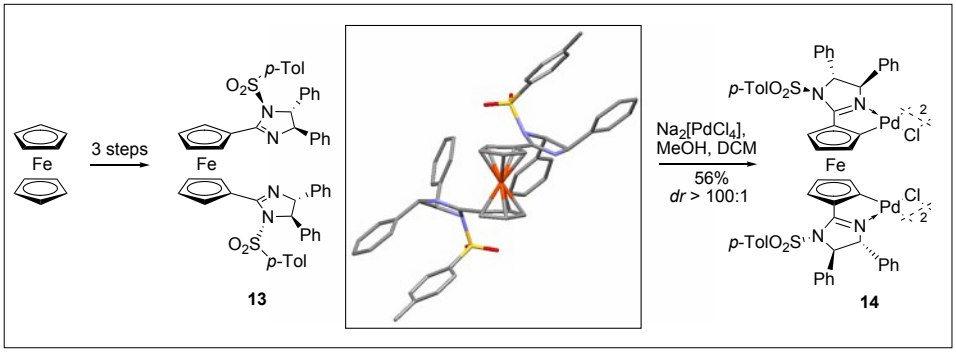


Fig. 2.



Scheme 6.



Scheme 7.

highly organized transition state from the face remote to the Pd atom (outer-sphere attack). Increased steric interactions of the coordinated olefin with a bulky substituted Cp spectator ligand presumably results in a higher face selectivity of the olefin coordination explaining the higher enantioselectivity as compared to the use of catalyst derivatives bearing an unsubstituted Cp. The exceptional activity of the catalyst derived from **6-Cp$^{\Phi}$** may be rationalized by the electron withdrawing nature of the Cp$^{\Phi}$ ligand thus decreasing the electron density of the Pd(II) central metal ion, but also by a high tendency to form the monomeric catalytically active species due to steric overcrowding in a dimer as well as by an accelerated release of the rearrangement product as a result of repulsive steric interactions between product and catalyst.

The high activities further allowed us to develop for the first time an enantioselective catalytic method to form allylic amines with N-substituted quaternary stereocenters by aza-Claisen rearrangement (Scheme 6).[5g] In this context we have shown that the enantioselectivity determining step is most likely the enantioface selective olefin coordination allowing for almost perfect enantiocontrol even for substrates **11**, in which the two substituents at the allylic 3-position have an identical size (*e.g.* R = CH_3/R' = CD_3: *ee* = 96% for **12**). Higher catalyst loadings are necessary (0.5–4 mol%), since the additional substituent R at the allylic 3-positions hampers the nucleophilic attack of the imidate N-atom at the olefin.

The remarkable activity of **6-Cp$^{\Phi}$** is in fact restricted to *E*-configured substrates. Synthetically more attractive is a catalyst which is highly active for *Z*-isomers, since geometrically pure substrates are needed to obtain high enantioselectivities and *Z*-olefins are in general more readily available in isomerically pure form, *e.g.* by semihydrogenation of triple bonds. To achieve this goal the electron density of the second Cp ligand had to be further decreased, yet avoiding a complicated catalyst preparation. Ferrocenyl bisimidazoline bispalladacycles **14** fulfill these requirements. The ligand preparation requires only three steps from ferrocene taking advantage of the C_2 symmetry (Scheme 7). As was shown by X-ray crystal structure analysis the ligands **13** also possess strongly pyramidalized sulfonylated N atoms, resulting again in a preferred conformation in which both sulfonyl residues point away from the ferrocenyl core. This preferred conformation permitted the first diastereoselective direct biscyclopalladation (Scheme 7).

The resulting bispalladacycle complexes **14** are C_2 symmetric dimers as revealed by X-ray analysis (Fig. 3). The high diastereoselectivity of the biscyclopalladation is remarkable, since in principle, seven different diastereomeric dimers could have been formed.

Complex **14** is to date the only *highly active* enantioselective catalyst for the aza-Claisen rearrangement of (*Z*)-configured trifluoroacetimidates **9** (Scheme 8).[5f,h] The rearrangements, which proceed in general under almost solvent-free conditions, were found to be equally effective on mg- and g-scale and tolerant to many important functional groups. The monomeric structure of the active catalyst species (Scheme 8), which is in this case not a ferrocenium species, was determined by NMR.

Recent efforts have focused on the direct generation of secondary allylic amines by aza-Claisen rearrangement of imidates bearing different aliphatic groups on the imidate N. These reactions, which were

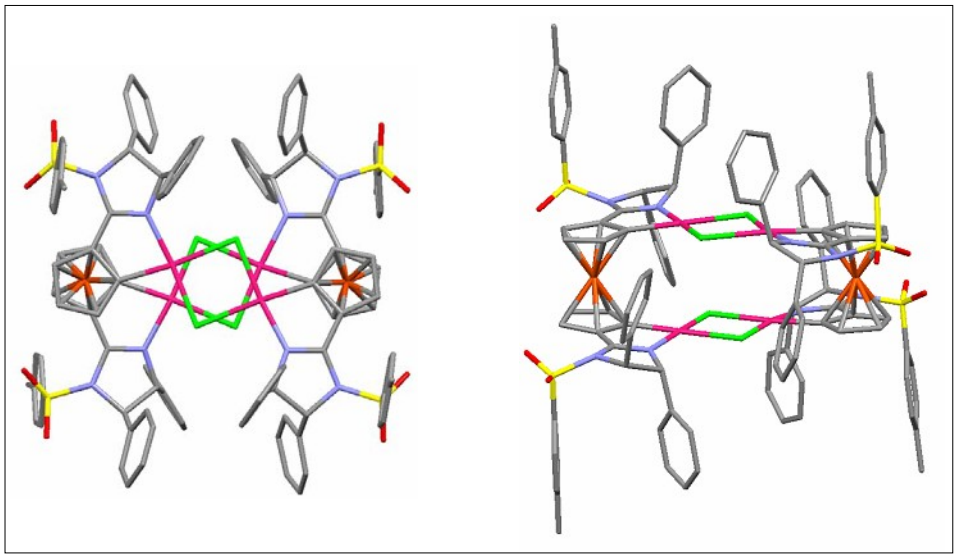
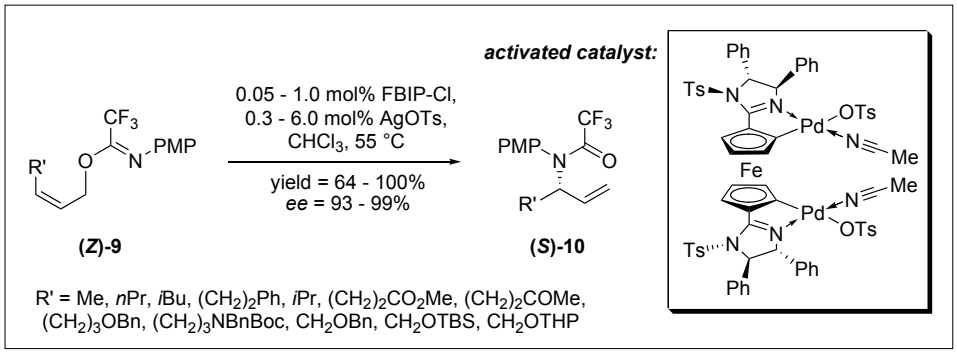
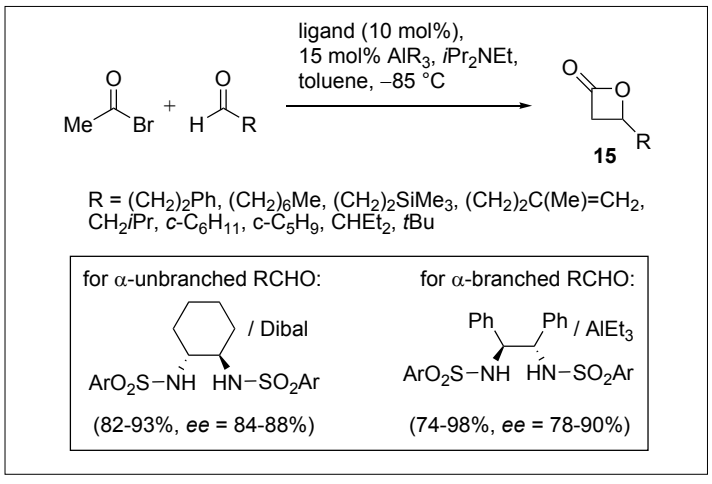


Fig. 3.



Scheme 8.



Scheme 9.

previously unknown even in a non-enantioselective fashion, are also characterized by excellent generality, enantioselectivity and low catalyst loadings.[10]

The described results show that ferrocenyl imidazoline palladacycle catalysts have the capability to differentiate enantiotopic olefin faces. In addition, and in contrast to many other palladacycles or most Pd-phosphine complexes, they are highly robust against thermal and oxidative decomposition and allow for an ample electronic and steric adjustment of the Lewis acid reactivity. The discovery of these readily available catalysts is proposed to pave the way to successfully address various unsolved problems in asymmetric catalysis for reactions which rely on activation of olefins by soft Lewis acids. Studies along these lines will be published in due time.

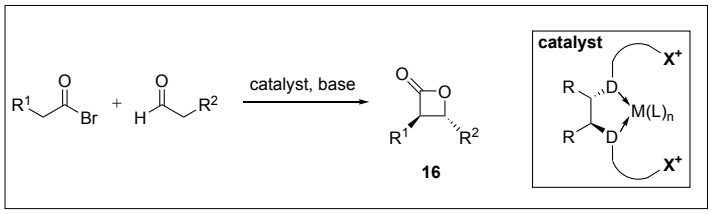
3. The Development of Practical Catalysts for the Enantioselective Preparation of β-Lactones

β-Lactones can be regarded as activated aldol equivalents, since they easily undergo ring opening reactions due to their intrinsic ring strain.[11] Various hard nucleophiles are able to regioselectively cleave the acyl–oxygen bond thus providing the corresponding β-hydroxy carbonyl derivatives. Accordingly, the development of catalytic asymmetric [2+2] cycloadditions of ketenes[12] and aldehydes offers the possibility to replace catalytic asymmetric ester or amide aldol reactions, which in most cases require the preformation, isolation and purification of moisture sensitive silyl ketene acetals. From both a technical and economical point of view, the use of silyl protecting groups is an issue on production scale.

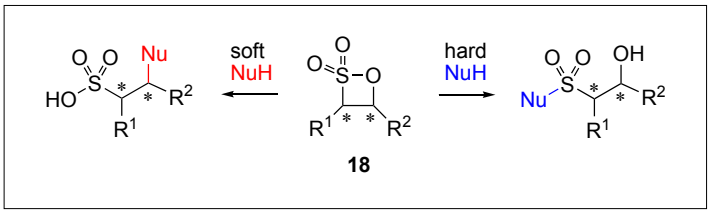
We have described the development of an efficient and practical aluminum-bissulfonamide catalyzed enantioselective formation of β-lactones **15** by [2+2] cycloaddition of unsubstituted ketene (generated *in situ* from acetylbromide by dehydrobromination) with various α-unbranched and -branched aliphatic aldehydes (Scheme 9).[13] Compared to alternative Lewis acid catalyzed methods our system offers the advantage of operational simplicity as the ligand synthesis requires just a single sulfonylation step from commercially available enantiomerically pure diamines. The products are formed in high to excellent yields with *ee* values typically ranging from 78 to 90% using 10 mol% of the bissulfonamide ligand. The key finding of this work is a remarkable rate acceleration by using an Al/ligand ratio of 1.5:1, which might be explained by Lewis acid activation of the Lewis acid catalyst,[14] *e.g.* by coordination of the sulfonyl groups in the active Al-sulfonamide complex to an achiral Al-entity.

Our current efforts are focused on the development of a *trans*-selective catalytic asymmetric cyclocondensation of acyl halides with aliphatic aldehydes (Scheme 10). This task is attractive since it would provide an alternative platform for the catalytic asymmetric formation of *anti*-aldol products.[15] Moreover, *trans*-configured β-lactones **16** are subunits of a number of bioactive natural and synthetic compounds (*e.g.* the anti-obesity drug Xenical, F. Hoffmann-La Roche).[16]

To achieve this task, we are developing a new concept which might be of general use in asymmetric catalysis and which can be described as contact ion pair directed Lewis acid catalysis.[17] It is assumed that in this case not the corresponding ketene, but an acyl bromide enolate is the reactive species and that the approach of this anionic nucleophile to the aldehyde, which itself is



Scheme 10.



Scheme 11.

activated by a Lewis acid, is directed *via* the formation of a contact ion pair with a positively charged ligand system (*e.g.* a quaternary ammonium moiety, but not a protic system which might deactivate the catalyst after deprotonation). This strategy represents a cooperative combination of the two concepts of phase transfer catalysis and Lewis acid catalysis. In general such an approach has the principal advantage – as compared to a bifunctional Lewis acid/Lewis base systems – that the cationic functionality does not deactivate the Lewis acid by an inter- or intramolecular self-quenching process.

4. Exploring New Synthetically Versatile and Readily Generated Reactive Intermediates for Asymmetric Catalysis

An additional key aspect of our research program concentrates on the application of hitherto unexplored, yet attractive reactive intermediates to asymmetric catalysis to permit rapid access to complex functionalized structures which are usually only available by multistep procedures, if at all.

4.1. *The Application of Sulfenes to Asymmetric Catalysis*

An unsolved problem prior to our studies was the use of sulfenes **17** (Fig. 4) – the sulfonyl analogues of ketenes – in asymmetric catalysis.[18] This may be due to the fact that sulfenes are far less stable than ketenes: they escape isolation due to rapid di- or oligomerization.

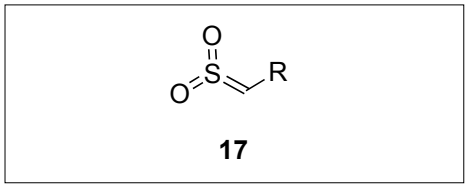
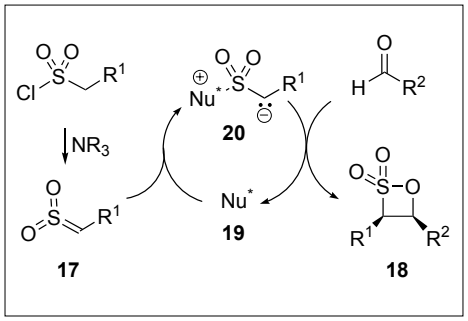


Fig. 4.

By application of sulfenes to asymmetric catalysis it is now possible to prepare a variety of diverse sulfur containing compound classes in highly enantioselective form by economical, sustainable, resource and time saving approaches. Since sulfonyl analogues of carbonyl derivatives are playing an increasingly important role in medicinal chemistry,[19] mainly because they can mimic the structural properties of the transition states leading to tetrahedral intermediates, the development of catalytic asymmetric methods using sulfene substrates is an attractive undertaking.

Particularly interesting targets are β-sultones **18**, highly reactive sulfonyl analogues of β-lactones.[20] In contrast to the latter compounds, β-sultones are a relatively rarely investigated substance class despite their potentially high value as synthetic building blocks (Scheme 11): as a result of their inherent reactivity due to ring strain, β-sultones are prone to regioselective nucleophilic ring opening reactions under mild conditions providing either β-substituted sulfonic acids or β-hydroxy sulfonyl derivatives.[21] These are attractive synthetic targets as they exhibit a variety of biological activity and are currently investigated for the treatment of a number of diseases such as diabetes, peripheral vascular disease, cardiac failure, Alzheimer's disease, atherosclerosis, thrombosis, neurodegenerative disorders or pain relief.

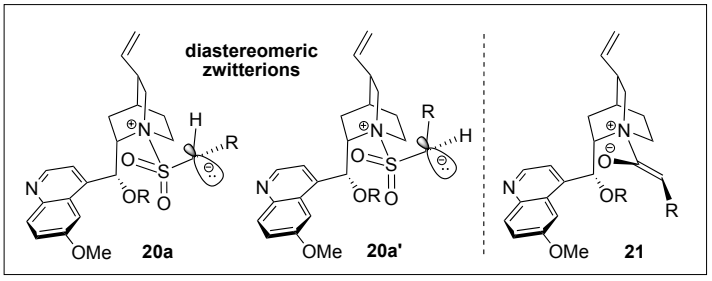
The evolution of this ring-opening strategy was previously limited by the fact that β-sultones had never been prepared in an enantioselective fashion.[22] We assumed that it should be possible to form β-sultones enantioselectively in the presence of catalytic amounts of a chiral nucleophile **19** (Scheme 12). The reactivity of sulfenes **17** normally acting as electrophile would be reverted by formation of an enantiopure nucleophilic zwitterion **20**. The realization of this concept was not trivial not only due to the low stability of sulfene intermediates **17**, but also due to the fact that for non-enantioselective approaches a large excess of a nucleophilic amine was always required to obtain acceptable yields.[22] Moreover this amine had to be sterically undemanding. Bu_3N was for instance found to be too bulky to efficiently promote the cyclocondensation.[22c]



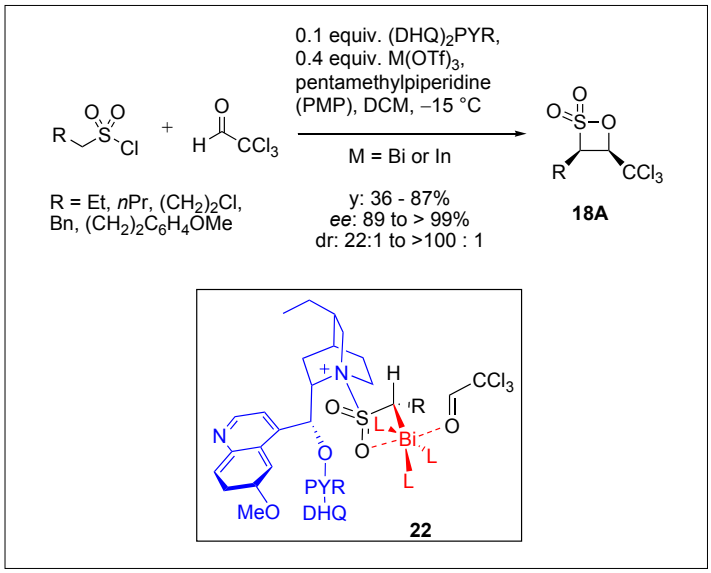
Scheme 12.

Our work was inspired by research initiated by Wynberg *et al.*, who published in 1982 a *cinchona* alkaloid catalyzed [2+2] cycloaddition of ketene and extremely electron poor aldehydes furnishing β-lactones in good yield and with excellent enantioselectivity.[23] However, fundamental structural differences between the anticipated ketene-derived zwitterionic enolate intermediates **21** and reactive sulfene-catalyst adducts like **20a** can be expected (Scheme 13): the S atom and presumably also the α-C atom of **20** (in analogy to the related sulfone carbanions)[24] are pyramidalized. This means that diastereomeric zwitterionic species **20a** and **20a'** might be formed. The absolute configuration of the cycloaddition products **18** thus primarily depends on the reactive configuration of **20a**.

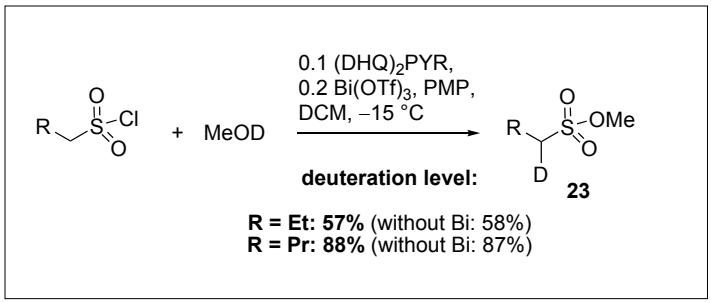
For the asymmetric formation of β-sultones both yield and enantioselectivity are synthetically useful only by employing a Lewis acid co-catalyst in combination with a nucleophilic tertiary amine (Lewis acid – Lewis base catalysis[25]). After a wide screening of metal triflate salts and nucleophilic catalysts, $In(OTf)_3$ and $Bi(OTf)_3$ in



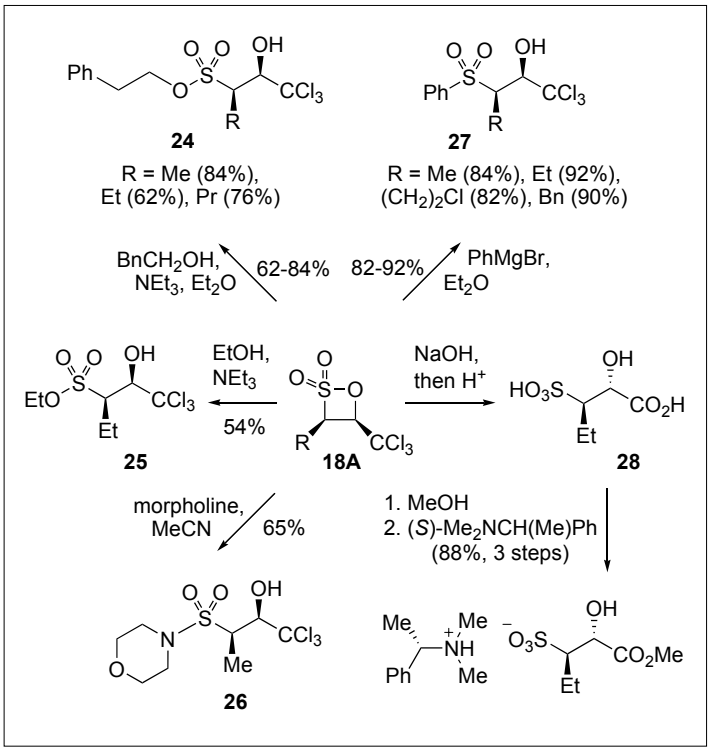
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

combination with $(DHQ)_2PYR$ as nucleophilic catalyst were found to provide the targeted products with excellent stereoselectivity (Scheme 14).[26] The fact that two comparatively soft main group metal salts were identified as the best co-catalysts might indicate that the negatively charged C atom of the generated carbanion directly binds to the metal ion. Since the reaction outcome is poor in the absence of a Lewis acid, it is likely that the aldehyde is further activated by coordination to the metal template within **22**. We assume an open transition state to account for the observed *syn*-selectivity.

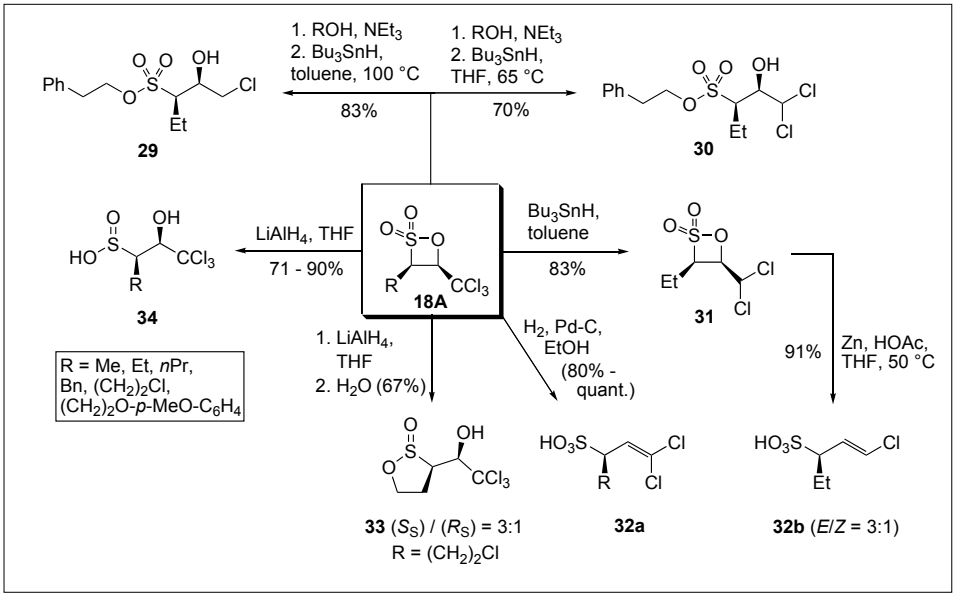
The existence of sulfenes as reactive intermediates could be indirectly proven by deuteration experiments: when sulfonylchlorides were treated with base, catalyst and Lewis acid in the presence of H_3COD, monodeuterated esters **23** were formed (Scheme 15).

Ring-opening reactions with alcohol, amine or Grignard reagents gave regioselective access to almost enantiopure β-hydroxysulfonates **24** and **25**, sulfonamides such as **26** and sulfones **27** (Scheme 16). No epimerization or racemization was detected during these transformations.

Although β-sultones can also be formed highly enantioselectively from other electron poor aldehydes than chloral, the trichloromethyl group in the cycloaddition products **18A** is synthetically especially useful. It is *e.g.* readily hydrolyzed by aqueous NaOH to furnish α-hydroxy acid **28** (Scheme 16). Moreover, the trichloromethyl group can be partially dechlorinated by Bu_3SnH prior or after the ring-opening step (Scheme 17).

Depending upon the reaction conditions, either the di- or the monochloro derivatives **29**–**31** are selectively obtained. Employing hydrogenation conditions (H_2, cat. Pd/C), dichloroallylsulfonic acids **32** are chemoselectively generated without racemization of the remaining stereocenter, while the corresponding almost enantiopure monochloroolefin **32b** was available by reduction of **31** with Zn/HOAc. Using $LiAlH_4$, it is possible to form β-hydroxysulfinic acids or γ-sultines such as **34** and **33** in good yield and without epimerization.[27]

A similar cycloaddition approach can be used for the catalytic asymmetric formation



Scheme 17.

of β-sultams **35** (Fig. 5).[28] Since β-sultams are at least two orders of magnitude more reactive than β-lactams towards nucleophilic ring opening reactions,[29] they have the potential to act as versatile synthetic building blocks.[30]

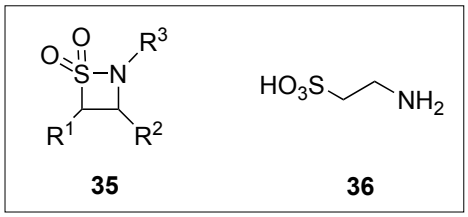


Fig. 5.

β-Sultams can act as irreversible active site directed inhibitors of serine proteases such as elastases as a result of the formation of stable 1:1 enzyme inhibitor complexes, since the active site serine OH is sulfonylated *via* an S–N bond fission taking advantage of the high ring strain.[31] Moreover, β-sultams can serve as DD-peptidase[32] and β-lactamase inhibitors[33] and are *e.g.* interesting for the development of new antibiotics. Moreover, they can be regarded as cyclic sulfonamide derivatives of the ubiquitous β-amino sulfonic acid taurine (**36**), which plays numerous essential physiological roles in the tissues of mammals.[34] Enantiomerically pure taurine derivatives are valuable synthetic targets, since they have *e.g.* been identified as highly potent MMP-13 inhibitors for the treatment of rheumatoid arthritis,[35a] or MMP-2 and -9 inhibitors for cancer treatment (metastasis formation).[35b]

The [2+2] cycloaddition products from sulfonylchlorides and non-nucleophilic imines **37** can either be isolated or directly trapped by nucleophiles such as primary or secondary amines furnishing β-aminosulfonamides **38** with two vicinal stereocenters in synthetically useful yields and good stereoselectivity by a one-pot procedure (Scheme 18).

The described asymmetric methodologies thus permit rapid access to a wide variety of functionalized almost enantiopure sulfur-containing building blocks in very few steps; compounds difficult to access by other means.

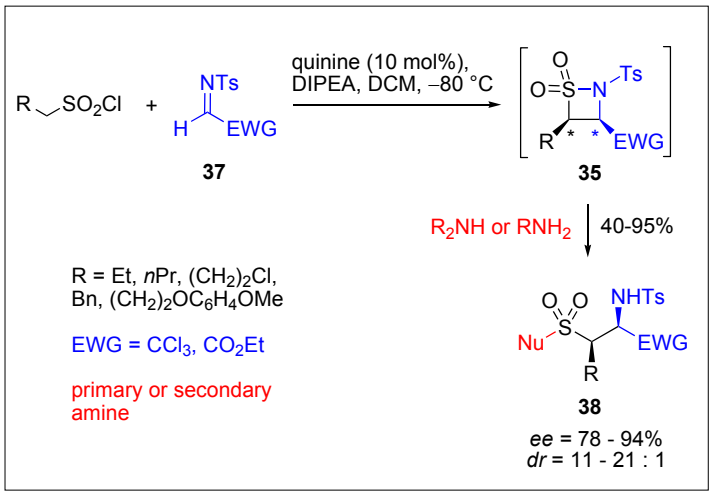
4.2. *The Application of Vinyl Ketenes to Asymmetric Catalysis*

δ-Lactones are subunits of an exceptional number of natural and unnatural products which display a wide range of biological activity. For example, the majority of statin drugs such as Lipitor and Zocor, the world's highest selling drugs in the last years, contain a β-hydroxy-δ-lactone moiety or the corresponding open chain carboxylate.[36] The most direct access to α,β-unsaturated δ-lactones[37] is based on hetero-Diels-Alder (HDA) reactions.[38] In order to generate directly the desired oxidation state, a vinylketene equivalent such as a vinylketene acetal is required as the diene component. So far, only three highly enantioselective catalytic HDA-based methodologies using a vinylketene acetal have been reported,[39–41] all of which are restricted to the use of Brassard type dienes (Brassard's diene: 1,3-dimethoxy-1-(trimethylsiloxy)butadiene) and aromatic aldehydes and require extended reaction times of 2–3 days to provide useful yields.

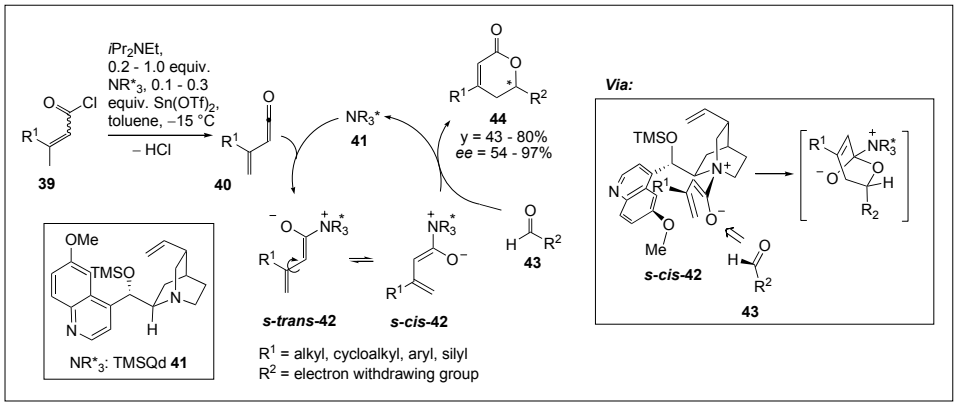
We have reported an alternative concept to circumvent the preformation of moisture- and acid-sensitive vinylketene acetals.[42] Substituted vinylketenes **40** are formed *in situ* by HCl-elimination from α,β-unsaturated acid chlorides **39**.[43] Vinylketenes were previously not useful as substrates for catalytic asymmetric Diels-Alder reactions as a result of their tendency to preferentially undergo [2+2] cycloaddition reactions and due to their inherent instability (dimer- and polymerization).[12a] However, we demonstrated that these species can be trapped and at the same time activated as diene component by an enantiopure nucleophilic tertiary amine, *e.g.* the cinchona alkaloid derivative TMS-Qd **41**, thus forming an enantiomerically pure zwitterionic dienolate **42** which is reactive enough to undergo an enantioselective HDA reaction with highly activated aldehydes such as chloral ($R^2 = CCl_3$, Scheme 19).

To obtain acceptable yields a Lewis acid co-catalyst such as $Sn(OTf)_2$ was required. This co-catalyst is not directly involved in the cycloaddition step itself, but simply facilitates the deprotonation of the activated methyl group of **39**. The catalyst system of the first generation thus proved the reaction principle, but is limited by the fact that the reaction outcome is highly dependent upon the steric bulk of the substituent R^1 in 3-position of the diene system: only sterically demanding substituents allow for high enantioselectivities as a consequence of the remote stereocontrol yet hamper the deprotonation of the reactive methyl group. Moreover, high enantioselectivities were limited to the use of choral. Non-activated aldehydes, *e.g.* benzaldehyde or even *p*-nitrobenzaldehyde, gave no target product.

To overcome these limitations, it was envisaged that the Lewis acid should function as a directing template in the [4+2]-cycloaddition step to activate the



Scheme 18.



Scheme 19.

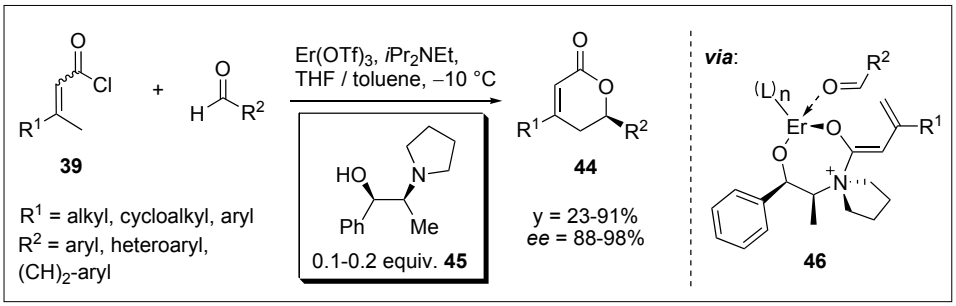
aldehyde dienophile and to take benefit from a highly organized transition state in a bifunctional catalyst system. The studies were based upon the hypothesis that a Lewis acid such as a lanthanide salt offering an exceptionally high number of coordination sites would be required to bind both aldehyde and dienolate, plus additional ligands to control reactivity and stereoselectivity.

The combination of $Er(OTf)_3$ and a catalytic amount of the commercially available norephedrine derivative **45** (Scheme 20) can promote an unprecedented [4+2]-cycloaddition of α,β-unsaturated acid chlorides and a broad range of aromatic and heteroaromatic aldehydes by a cooperative Lewis acid/Lewis base mode of action providing valuable δ-lactone building blocks with excellent enantioselectivity.[44]

Our mechanistic studies have shown that the amino alcohol acts as a ligand which activates the diene substrate by formation of a nucleophilic dienolate, which then adds *via* a vinylogous aldol addition to the aldehyde to form the stereocenter. The aldehyde is assumed to be activated by the same Er(III)-center in **46** since large coordination numbers of 7–10 are typical for Er(III). Turnover is achieved by subsequent lactonization. A key characteristic of the catalyst system is its simplicity, since the commercially available nucleophilic amino alcohol ligand can be prepared from inexpensive norephedrine in a single step by bisalkylation. Moreover $Er(OTf)_3$ is comparatively inexpensive (*ca.* seven times less expensive than $Sc(OTf)_3$). This and related catalysts should be attractive for alternative reactions which rely on a cooperative catalysis mechanism. Studies along these lines are underway.

5. Conclusions

Despite all progress made in the area of homogeneous asymmetric catalysis it is still a very long journey ahead for the development of technical catalytic asymmetric procedures with the ultimate goal to efficiently prepare chiral high-added-value products on production scale *via* C–C and C–X bond formation. Nevertheless, several of the described projects should already have the potential to serve as useful tools for applications *e.g.* in medicinal chemistry in order to rapidly prepare new libraries of functionalized chiral building blocks owing to operational simplicity, broad applicability and in general excellent stereoselectivity. The strategy to design readily accessible catalysts operating by defined simultaneous activation modes allowing for highly organized transition states is an evolutionary process which should finally result in the progress required to yield large crop from the key technology asymmetric catalysis.



Scheme 20.

Acknowledgments

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