2.2. Department of Homogeneous Catalysis

Director:

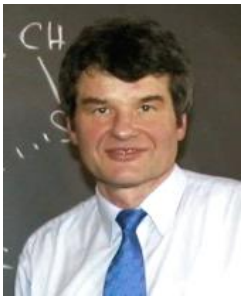
Benjamin List (born 1968)

Further group leaders:

Martin Klußmann (born 1974)

Nuno Maulide (born 1979)
left the Institute in September 2013

Klaus-Richard Pörschke (born 1949)



Curriculum Vitae: Benjamin List

1968	Born in Frankfurt/Main, Germany
1993	Chemistry Diploma, Freie Universität Berlin
1997	Ph.D., Johann Wolfgang Goethe-Universität Frankfurt, with Prof. J. Mulzer
1997-1998	Postdoc, Scripps Research Institute, La Jolla, USA, with Prof. R. Lerner
1999-2003	Assistant Professor (Tenure Track), Scripps Research Institute, La Jolla, USA
2003-2005	Group Leader at the Max-Planck-Institut für Kohlenforschung
2004-	Honorary Professor at the Universität zu Köln
2005-	Director at the Max-Planck-Institut für Kohlenforschung
2012-	Managing Director of the Max-Planck-Institut für Kohlenforschung

Awards and Honors

1997-1998	Feodor-Lynen Fellowship of the Alexander von Humboldt Foundation
1994-1995	NaFoeG-Graduate Fellowship of the Senate of Berlin
2000	Synthesis-Synlett Journal Award
2003	Carl-Duisberg-Memorial Award
2004	Degussa Prize for Chiral Chemistry
2004	Lieseberg Prize
2004	Lecturer Award of the German Chemical Industry Fund
2005	Visiting Professorship, Gakushuin University, Tokyo, Japan
2005	Society of Synthetic Chemistry, Japan: 2005 Lectureship Award
2005	AstraZeneca European Lecturer
2005	Novartis Young Investigator Award
2006	JSPS Fellowship, Japan
2006	100 Masterminds of Tomorrow, Germany
2006	Wiechert Lectureship, FU Berlin, Germany
2007	Fonds der Chemischen Industrie Award, Germany
2007	OBC Lecture Award
2007	AstraZeneca Research Award in Organic Chemistry
2008	Visiting Professorship, Sungkyunkwan University, Korea
2009	Organic Reactions Lectureship, USA
2009	Boehringer-Ingelheim Lectureship, Canada
2009	Thomson Reuters Citation Laureate

2010	High Levels Lectureship for Graduate Students, University of Science and Technology of China, Hefei
2010	New Honors Program Lectureship, National University of Singapore
2011	Boehringer-Ingelheim Lectureship, Harvard University, USA
2011	ERC-Advanced Grant
2012	Novartis Chemistry Lectureship Award 2012-2013
2012	Otto-Bayer-Prize, Germany
2013	Musher Memorial Lecture, Jerusalem, Israel
2013	Novartis Lectureship, UC Berkeley, USA
2013	Horst-Pracejus-Prize, Germany
2013	Mukaiyama Award, Japan
2013	Ruhrpreis, Mülheim, Germany
1999-2013	ca. 180 Plenary and Name Lectureships

Other Activities / Committees

2004	Co-Editor (with C. Bolm), Special Edition: "Organocatalysis", *Advanced Synthesis & Catalysis*
2004	Co-Editor (with K. N. Houk), Special Edition: "Enantioselective Organocatalysis", *Accounts on Chemical Research*
2005-	Co-Editor, *Synfacts* (Thieme)
2005-2011	Coordination of the DFG Priority Program (SPP1179) "Organocatalysis"
2006	Editor "Organocatalysis", *Chemical Reviews*
2006-	Member of the Selection Committee for Max Planck Group leaders
2008-	Editorial Advisory Board, *Beilstein Journal of Organic Chemistry*
2008-2009	Editor "Asymmetric Organocatalysis", *Topics in Current Chemistry*
2009-2010	Co-Editor (with K. Maruoka) "Asymmetric Organocatalysis", *Science of Synthesis Reference Library*
2010-	Editorial advisory panel, *Nature Communications*
2011-	Regional Editor of *Synlett* (Thieme)
2011-	Academic Advisory Board *Advanced Synthesis and Catalysis*
2011	Co-Editor (with K. Maruoka) "Asymmetric Organocatalysis", *Science of Synthesis* (Thieme)
2011	Editor "Asymmetric Organocatalysis", *Beilstein Journal of Organic Chemistry*

Research in the Department of Homogeneous Catalysis

Researchers in our Department continue focusing on the development of new catalysis concepts within the areas of organocatalysis and transition metal catalysis. We explore new catalysts, expand the substrate scope of certain catalytic reactions, apply asymmetric catalysis in natural product and pharmaceutical synthesis, study mechanisms of homogeneous catalytic reactions, and explore catalysis with textile-supported catalysts (B. List, K.-R. Pörschke, M. Klußmann, N. Maulide).

During the last three years, the Department grew again significantly, mainly due to the expansion of the group of Nuno Maulide to about twenty co-workers. During the evaluation period between 2011 and 2013, the Department consisted altogether of four groups, in addition to that of the head of the Department, Professor Benjamin List, those led by Professor K.-R. Pörschke, who has been a group leader at the institute since over twenty years, by Dr. M. Klußmann, who has been a group leader here since 2007, and of Dr. N. Maulide, who has joined the Department in 2009 and left in the fall of 2013 to take a chair at the University of Vienna.

The group of **Professor List** primarily advances enantioselective organocatalysis as a fundamental approach complementing the already more advanced fields of biocatalysis and transition metal catalysis. The List group has a profound interest in developing "new reactions", designs and identifies new principles for the development of organocatalysts, expands the scope of already developed catalysts such as proline, uses organocatalysis in the synthesis of natural products and pharmaceuticals, and also investigates the mechanisms by which organocatalysts activate their substrates.

Since 2005, the group has first conceptualized and then significantly advanced another approach to asymmetric catalysis, asymmetric counteranion directed catalysis (ACDC). Initially, merely an idea, this approach has progressed within the Department but now also at other institutions around the globe, into a truly general strategy for asymmetric synthesis and has found utility in organocatalysis but also in transition metal catalysis and Lewis acid catalysis. This area is now the main research field in the List group. More recently, a new approach to heterogeneous catalysis was developed, in which organic catalysts are immobilized on inexpensive textile materials and used as efficient and recyclable catalysts.

Research in the laboratory of **Professor Pörschke** continues to center on transition metal complexes. The group conducts fundamental research in the areas of coordination chemistry, organometallic chemistry, homogeneous catalysis, and solid state phase properties (organometallic plastic crystals). Transition metals under focus are Ni, Pd, and Pt, which are often used in combination with main group metal compounds (Li, Mg, Al, Ge, Sn). As a new line of research, the group now also investigates cisplatin-related metal complexes as potential cytostatic compounds.

The group of **Dr. Klußmann** has focused on mechanistic and synthetic studies in the area of oxidative cross-coupling catalysis. They investigate reactions that allow the coupling of two C–H-fragments, establishing a C–C-unit. The substrates are activated under oxidative conditions, ideally resulting in water as the only byproduct.

The group of **Dr. Maulide** was established in 2009 after its leader had obtained a prestigious and highly competitive Max-Planck Research Group Leader position, which is fully supported from central MPG funds. The group has diverse activities in the area of organic synthesis and catalysis and published extensively within the last four years. As a result many awards have been secured and calls to different universities were obtained by Nuno Maulide. In the meantime, the group has left to the University of Vienna.

2.2.1 Research Area "Catalysis with Chiral Imidodiphosphates" (B. List)

Involved: J. H. Kim, I. Čorić, S. Liao, S. Vellalath, Q. Wang

Objective: The field of Brønsted acid catalysis has acquired wide popularity and importance in recent years. However, reactions of small aliphatic substrates that do not possess sterically demanding protecting groups, large aromatic or planar surfaces, or bulky substituents are still rare. This might be due to the inability of current synthetic Brønsted acid catalysts to provide a truly compact chiral microenvironment. We therefore propose the development of "confined acid catalysts" (Figure 1). The aim of this project was to design and synthesize novel confined Brønsted acid catalysts based on a C_2-symmetric imidodiphosphoric acid, possessing an extremely sterically demanding chiral microenvironment.

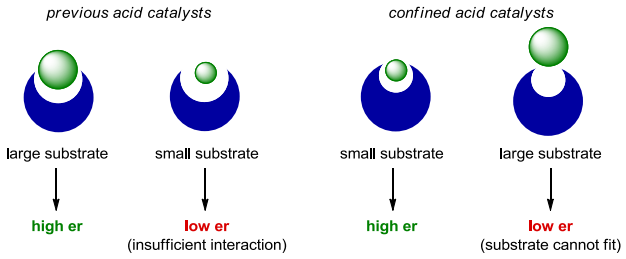
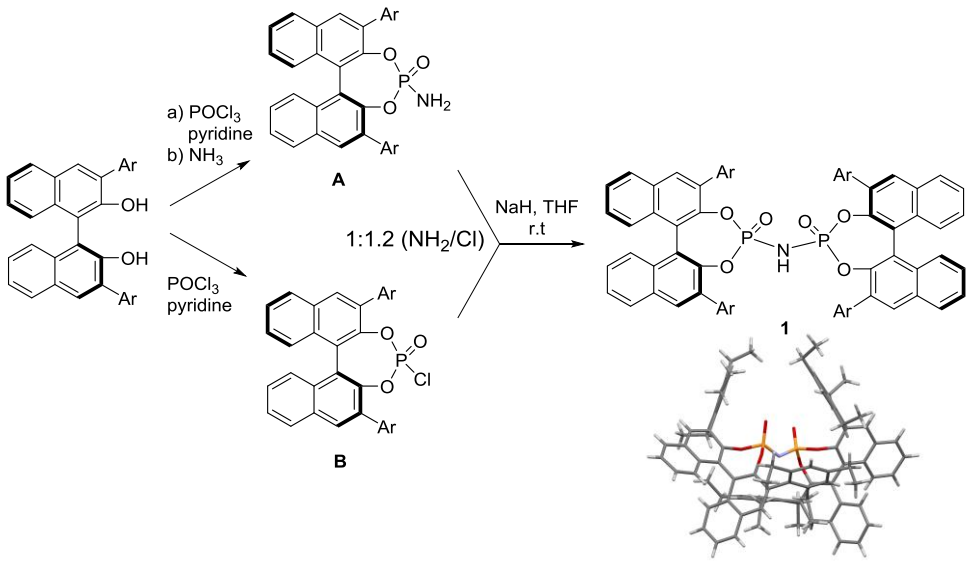


Figure 1. Schematic comparison of the expected performance of chiral confined acids and phosphoric acid type catalysts with large and small substrates.

Results: C_2-Symmetric imidodiphosphoric acids, based on the interlocking of two identical BINOL subunits, were designed and prepared (Scheme 1).



Scheme 1. Synthetic strategy for C_2-symmetric imidodiphosphoric acids.

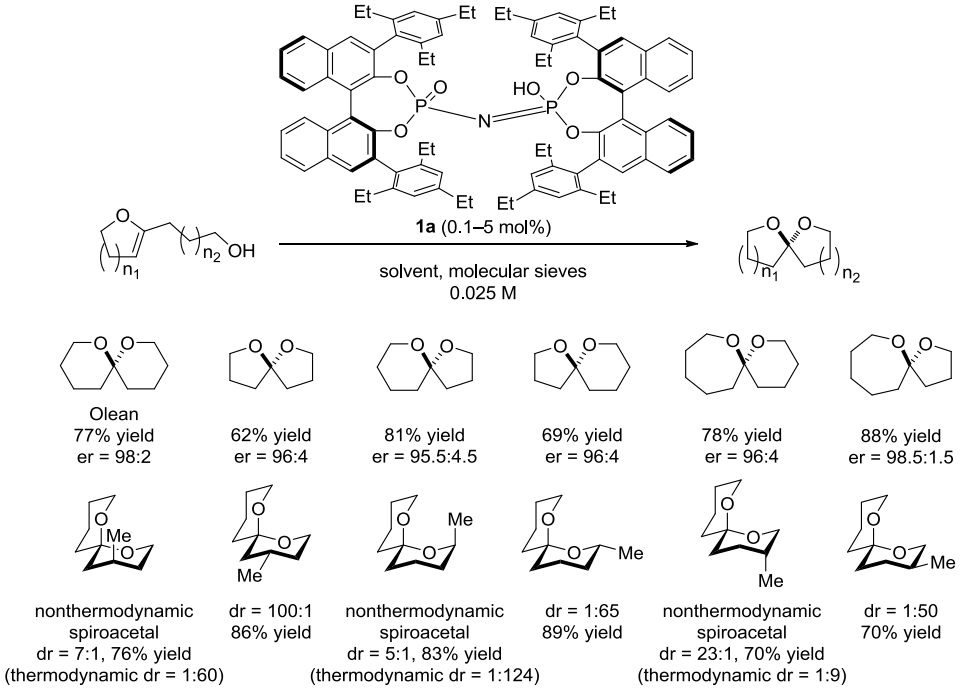
Starting from readily available 3,3'-substituted BINOL-derivatives, synthetic intermediates **A** and **B** are obtained in a single step. Their coupling under basic conditions directly affords the desired C_2-symmetric imidodiphosphoric acid **1**.

A) *O,O*-acetals

As part of our interest in asymmetric acetalization reactions, we have developed direct enantioselective syntheses of spiroacetals and cyclic *O,O*-acetals from aldehydes. Although *O,O*-acetals are among the most common stereocenters in organic molecules, their catalytic asymmetric syntheses have only been achieved recently due to problems associated with asymmetric additions to oxocarbenium ions using chiral Brønsted acid catalysts.

Spiroacetalization

Spiroacetal natural products are widely found in insects, plants, and bacterial and marine sources, and display a diverse set of biological activities. Their spiroacetal subunit is not only essential for the bioactivity but is also a privileged pharmacophore in drug discovery. An extensive screening of a wide range of known chiral Brønsted acids gave only disappointing results in the generation of both the 5,5- and the 6,6-spiroacetal. Extremely sterically demanding Brønsted acid catalyst **1a** efficiently catalyzed the asymmetric conversion of small and further unfunctionalized hydroxy enolether substrates (Scheme 2).



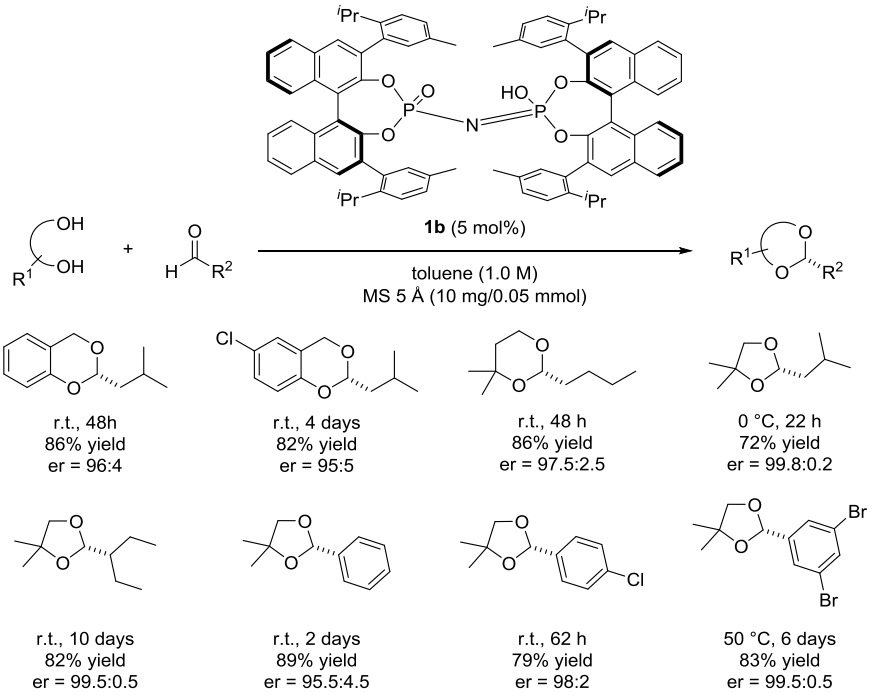
Scheme 2. Catalytic asymmetric spiroacetalization.

Various spiroacetals were obtained with high enantioselectivity by the formation of either 6- or 5-membered rings. Catalyst **1a** also enabled the first catalytic asymmetric

synthesis of the natural product olean. A variety of non-thermodynamic spiroacetals could be formed with diastereomeric ratios ranging from 5:1 to 23:1, against a strong thermodynamic preference of up to 1:124.

Asymmetric acetalization

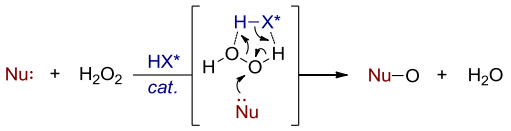
Although our laboratory has pursued the direct asymmetric acetalization of aldehydes with alcohols for many years now, and has investigated numerous chiral Brønsted acid catalysts, unfortunately, very little success towards this goal has been encountered. Here the newly developed class of chiral confined Brønsted acids finally enables this elusive transformation with excellent selectivity and scope. In a condensation reaction of diols and aldehydes imidodiphosphoric acid **1b** delivered chiral *O,O*-acetals in high yield and with high enantioselectivity (Scheme 3).



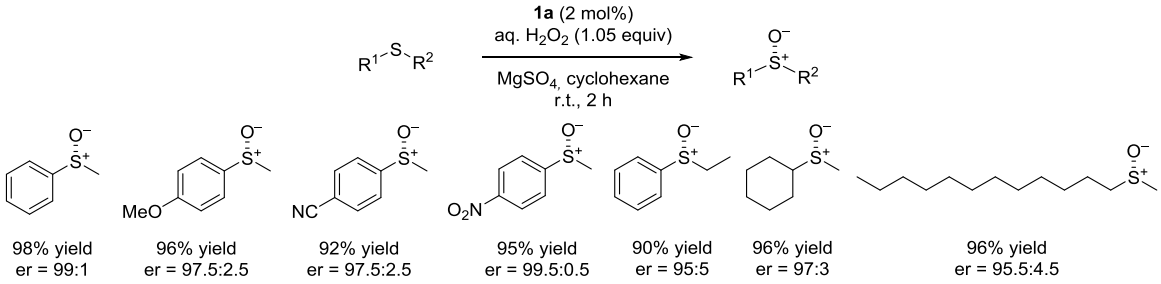
Scheme 3. Catalytic asymmetric acetalization.

B) Sulfoxidation

Despite significant efforts to utilize H_2O_2 in asymmetric oxidation catalysis, only few general systems work well with this abundant, environmentally benign, atom economic, and relatively safe oxidant. In asymmetric organocatalysis, H_2O_2 has been employed in the epoxidation of α,β-unsaturated carbonyl compounds, Baeyer-Villiger reactions, and in oxidations catalyzed by ketones, iminium salts, or carboxylic acids. All of these reactions rely on the nucleophilic properties of H_2O_2, to form covalent adducts with electrophilic substrates or catalysts. We envisioned an alternative scenario, in which H_2O_2 could be electrophilically activated towards nucleophilic substrates with a chiral Brønsted acid catalyst (Scheme 5).



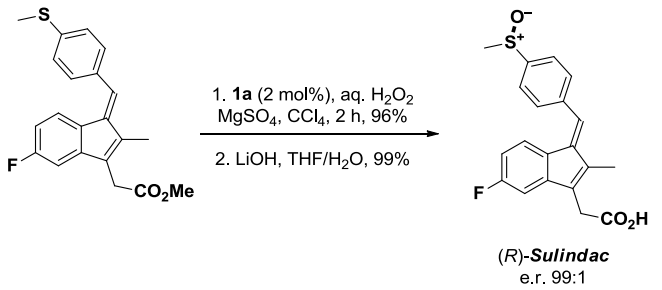
Scheme 5. Activation of H_2O_2 with a chiral Brønsted acid catalyst.



Scheme 6. Catalytic asymmetric sulfoxidation.

Imidodiphosphoric acid catalyst **1a**, which presumably binds hydrogen peroxide inside its chiral cavity, was found to catalyze an efficient sulfoxidation reaction of sulfides (Scheme 6). Other known common Brønsted acids gave much lower enantioselectivity.

The methodology has been applied to the enantioselective synthesis of the non-steroidal anti-inflammatory drug Sulindac, which has recently found additional utility in cancer treatment (Scheme 7).



Scheme 7. Enantioselective synthesis of Sulindac.

In summary, we have developed chiral imidodiphosphates to be of use in tackling current challenges with reactions that include small volume and/or loosely organized transitions states. With our new catalysts, we have developed the first catalytic asymmetric spiroacetalization, direct acetalization of aldehydes with diols, and asymmetric sulfoxidation with hydrogen peroxide.

2.2.2 Research Area "Organotextile Catalysis" (B. List)

Involved: J.-W. Lee, T. James

Objective: Homogeneous catalysis plays a central role in modern chemistry at both research and production scales, facilitating the synthesis of molecules which were once considered an insurmountable challenge. However, in contrast to heterogeneous catalysis, many homogeneous processes require significant effort to recover catalytic components from reaction media. Approaches which utilize the exquisite control of homogeneous catalysts with the practicality and recyclability of heterogeneous systems are highly sought after. To date there is no general approach to provide inexpensive and accessible solid materials on which a desired organic molecule can be mounted. To address this challenge we developed a facile immobilization of various functionalized organocatalysts onto textile material by irradiation with ultra violet light (UV) (Figure 1). This process allows immobilization of a desired molecule on the solid support, by covalent C–C bond formation, to generate organotextile catalysts, which can be used for various transformations with unprecedented numbers of cycles.

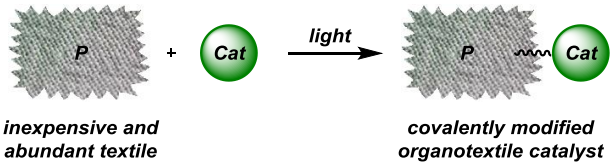


Figure 1. Schematic representation of approach taken towards the functionalization of textile surfaces with organic catalysts.

Results: To show the generality of our methodology, the immobilization of different organocatalysts was investigated; a Lewis base catalyst **1**, a Brønsted acid catalyst **2** and bifunctional chiral catalyst **3** (Figure 2). The immobilization process was conducted by UV irradiation of a solution of an organic catalyst in the presence of a textile material (Nylon 6,6), which facilitated covalent bond formation between the textile surface and unsaturated sites present within the catalyst structure (Scheme 1). The inclusion of a cross-linker (pentaerythritol tetraacrylate, PETA) allowed control of catalyst loading on the solid surface. The variation of the

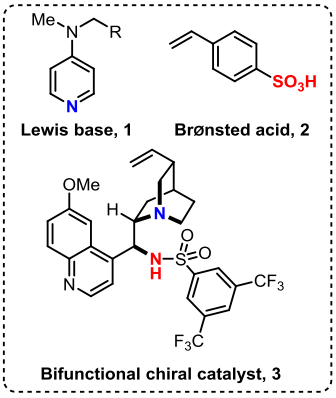
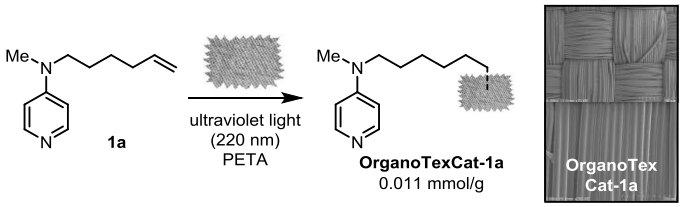


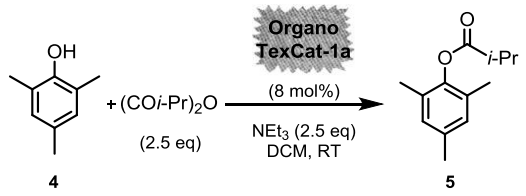
Figure 2. Examples of organocatalysts investigated in these studies.

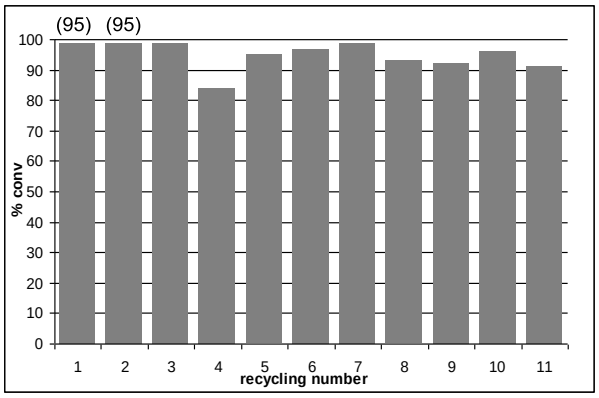
amount of PETA could affect the immobilization pathway by changing the degree of branching points. Further optimization of catalyst loading and catalytic activity was simply conducted by changing UV irradiation time. Lewis basic catalyst **1a**, Brønsted acid catalyst **2** and bifunctional organocatalyst **3a** were equally well tolerated under the photochemical reaction conditions, yielding textile catalysts. DMAP derivative **1a** was successfully immobilized on the textile support to generate catalyst **OrganoTexCat-1a**. The SEM image of the obtained catalyst showed irreversible polymerization of organic substances on the surface, again without significant physical damage to the textile material. Catalyst loading was determined by acid/base titration.



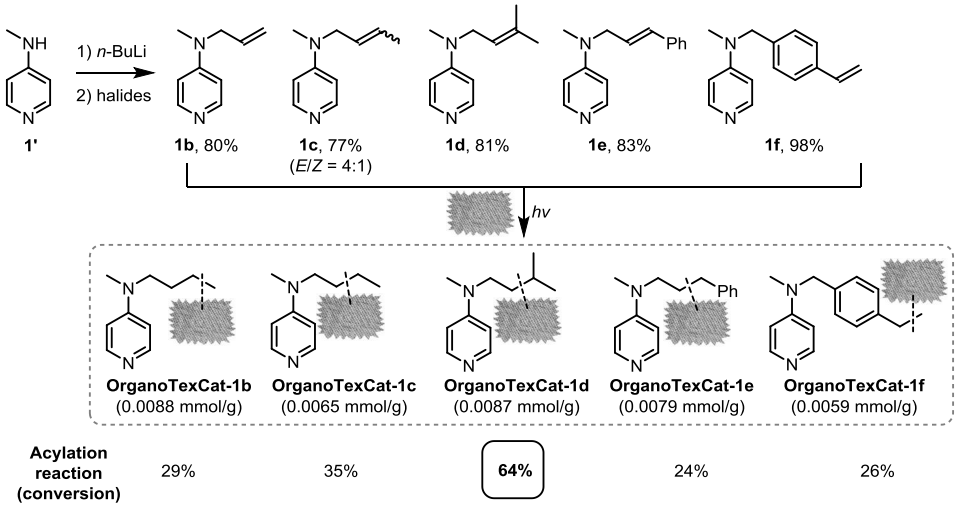
Scheme 1. Immobilization of DMAP derivative **1a** on textile.

The catalytic activity of **OrganoTexCat-1a** was evaluated in the acylation of sterically demanding phenol **4** with anhydride **5** (Scheme 2). In the absence of **OrganoTexCat-1a**, or in the presence of blank polyamide, almost no conversion was observed under otherwise identical reaction conditions. However, the employment of **OrganoTexCat-1a** in this transformation led to the formation of the ester **5** in near quantitative yields. After full conversion of phenol **4**, the catalyst was simply recovered by decanting the liquid phase, washing with dichloromethane and drying. Several recycling experiments showed the robustness of **OrganoTexCat-1a**; for more than 10 cycles no significant erosion of the catalytic activity was observed. It is noteworthy that the catalyst could be deactivated by forming an acid-base complex with the carboxylic acid by-product. However, the catalytic activity could simply be recovered by washing the catalyst with NEt_3 to regenerate it with good activity (recycle 4 to 5).



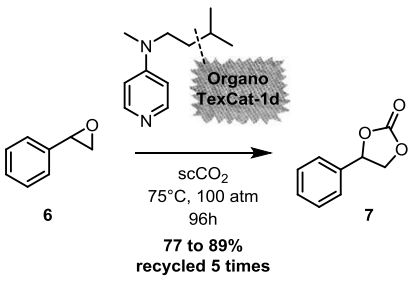


Scheme 2. Acylation of phenol **4** to ester **5** and demonstration of catalyst recycling.



Scheme 3. Evaluation of formation and catalytic ability of various immobilized DMAP derivatives.

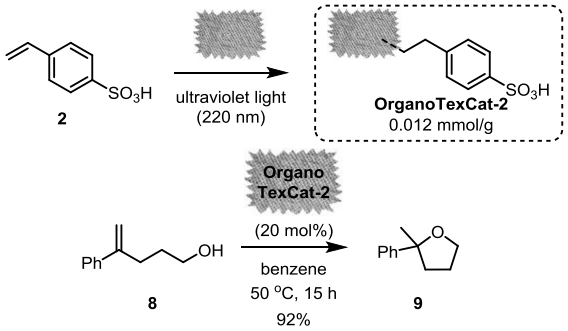
To investigate the effect of the olefin-containing side chain, we screened various DMAP derivatives (**1b**-**1f**) which were immobilized onto the textile material under identical immobilization conditions; a direct comparison of the relative catalyst activity is presented (Scheme 3). A longer side chain and higher substitution on the olefin are beneficial in terms of catalytic activity as observed in the case of **OrganoTexCat-1d**. This effect is quite general in heterogeneous catalysis due to a more efficient mass transfer and higher flexibility of the catalytically active site. Olefins with higher substitution can, in principle, provide a more stable radical intermediate, which facilitates selective immobilization without any side reaction. However, inferior catalytic activity was observed with **OrganoTexCat-1e**, although the catalyst immobilization was efficient.



Scheme 4. Organotextile catalyzed cyclic carbonate formation.

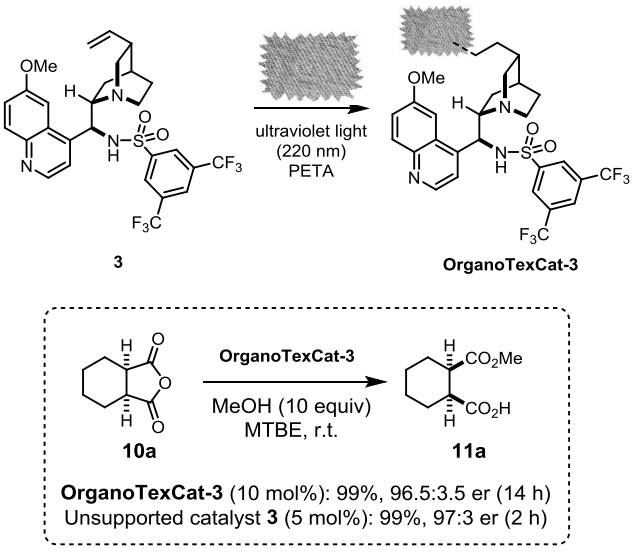
Catalyst **OrganoTexCat-1d** also showed good activity and recyclability in cyclic carbonate formation (Scheme 4). The treatment of styrene oxide **6** with supercritical carbon dioxide in the presence of **OrganoTexCat-1d** led to the formation of carbonate **7** in good yield. This result highlights the high stability of catalyst **OrganoTexCat-1d** under high pressures (100 atm) and temperatures (up to 75 °C).

A facile immobilization of a commercially available Brønsted acid, the sulfonic acid **2**, was achieved giving **OrganoTexCat-2** with good catalyst loadings (Scheme 5). **OrganoTexCat-2** showed good activity in the intramolecular hydroetherification, affording the corresponding tetrahydrofuran **9**, from the alcohol **8**, in excellent yield. No background reaction was observed in the absence of the catalyst under reaction conditions. It is noteworthy that the immobilized catalyst is easy to handle and displays robust stability for the transformation, the primary advantages of solid-supported catalysts.



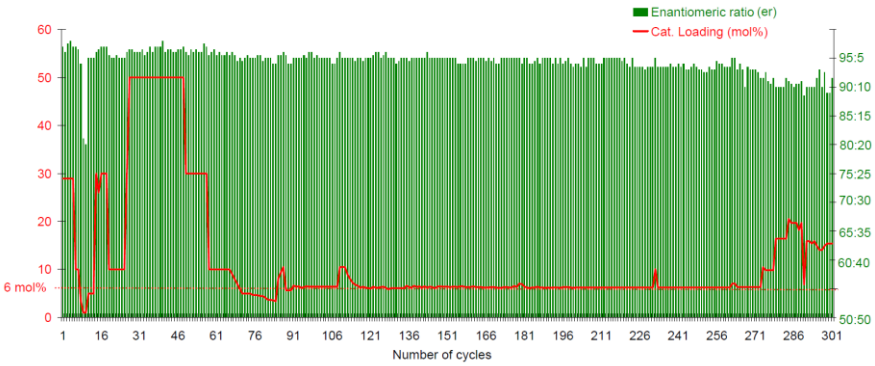
Scheme 5. Intramolecular hydroetherification of alcohol **8** catalyzed by **OrganoTexCat-2**.

Finally, we aimed to develop a textile material furnished with a chiral organocatalyst. Cinchona alkaloids have been widely used in the area of asymmetric organocatalysis and naturally bear an olefin group appended to the molecular scaffold. It was postulated that this alkene could be utilized as a handle to allow immobilization onto the textile support. As shown, the quinine-derived sulfonamide **3** was successfully immobilized under UV irradiation, giving **OrganoTexCat-3** (Scheme 6). The obtained catalyst showed comparable enantioselectivity to the homogeneous unsupported system in the desymmetrization of the anhydride **10a** to the hemiester **11a**, although a longer reaction time was required. The robustness of this approach was investigated by the recycling of **OrganoTexCat-3** through numerous iterative cycles of catalytic desymmetrization of **10a** to **11a** (Scheme 7). The asymmetric methanolysis could be repeated more than 300 times without significant erosion of catalytic activity and enantioselectivity. These recycling experiments



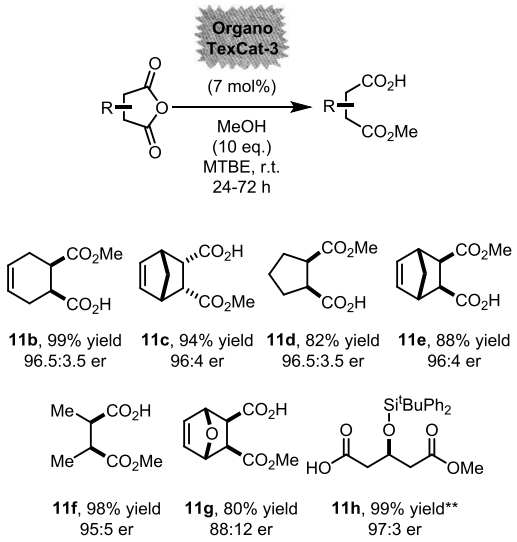
Scheme 6. Immobilization of bifunctional catalyst **3** and demonstration of catalytic ability in the desymmetrization of *meso*-anhydride **10a**.

illustrate the robustness of the textile supported catalyst and clearly demonstrate the power of heterogeneous organocatalysis.



Scheme 7. Recycling of **OrganoTexCat-3** in the desymmetrization of **10a** for over 300 cycles.

Further application of the chiral textile catalyst was conducted by investigating the substrate scope (Scheme 8). Various *meso*-anhydrides were smoothly transformed into enantio-enriched hemiesters with excellent yields (up to 99%) and enantioselectivities (er up to 97:3). Bi- and tri-cyclic compounds could also be used to afford the expected products with high enantioselectivities, showing a comparable selectivity to the homogeneous catalytic systems. Due to the flexibility, compatibility and robustness of textile catalysts, we envisioned a continuous reactor system with our catalyst material. Enantio-enriched product **11h** was obtained in excellent yield (>99%) and enantioselectivity (up to 97:3 er) by using an iterative continuous fixed-batch approach. The textile-filled column was reused for more than 10 cycles, on multiple gram scales, showing identical activity and enantioselectivity.



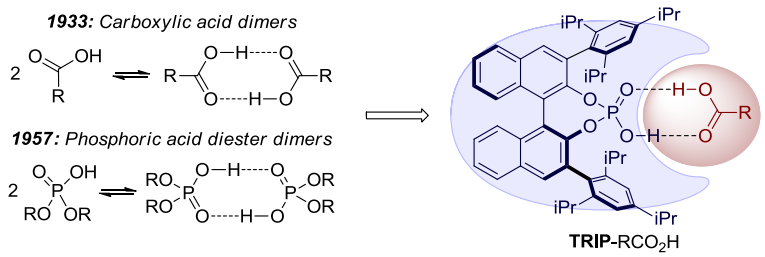
Scheme 8. Scope of desymmetrization of *meso*-anhydrides catalyzed by **OrganoTexCat-3**.

2.2.3 Research Area "Activation of Carboxylic Acids in Organocatalysis" (B. List)

Involved: M. R. Monaco, S. Prévost, B. Poladura, M. Diaz de los Bernardos, M. Leutzsch, R. Goddard

Objective: During the last years, organocatalysis has become a general approach to asymmetric synthesis. Its success is arguably due to the detailed codification of general activation modes for some classes of substrates. Enamine and iminium ion catalysis, hydrogen bonding catalysis and Brønsted acid or base catalysis represent powerful tools for the transformations of certain imine, carbonyl or closely related substrates. Interestingly however, a well-defined and general activation mode for carboxylic acids, a useful and abundant chemical class, has not yet been established. The aim of this project is to identify a novel, simple and efficient system for the enhancement of their reactivity and for the control of their asymmetric reactions.

Results: Carboxylic acids, as well as phosphoric acid diesters, feature both a hydrogen-bond acceptor and a hydrogen-bond donor. Since intramolecular stabilization in apolar media is structurally not possible, they reach mutual stabilization by "self-association" in an apolar environment. This dimerization was first observed at the beginning of the 20th century and is nowadays accepted as a general phenomenon. This self-assembly is presumably sterically hampered for bulky binaphtol derived phosphoric acid diesters, which have recently raised the attention of the scientific community due to their role as privileged organocatalysts in the field of asymmetric Brønsted acid catalysis.



Scheme 1. Heterodimeric self-assembly for the activation of carboxylic acids in organocatalysis.

On this basis, we hypothesized that a small carboxylic acid molecule could enter the catalytic pocket in the absence of repulsive forces and a heterodimeric species may be established. This interaction may additionally influence the electronic structure of carboxylic acids, thus representing a strategy for their activation.

The formation of the heterodimer was investigated by NMR analysis. The ^{1}H NMR spectrum reveals that the addition of carboxylic acid in apolar media reduces the rotational freedom of the 3,3´-substituents of **TRIP** phosphoric acid, suggesting its presence in the catalytic pocket. Diffusion-Ordered Spectroscopy (DOSY) measurements showed the change of the translational diffusion coefficients of both species upon self-assembly, thus confirming the variation of the hydrodynamic volumes.

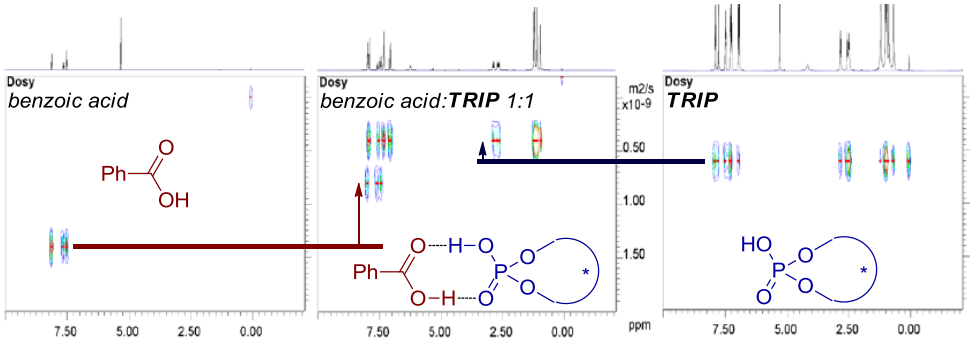


Figure 1. DOSY measurements of benzoic acid and **TRIP** phosphoric acid mixtures.

The strength of the association could be evaluated. As for 1:1 host-guest complexes, the binding isotherms of **TRIP** with benzoic acid and acetic acid were plotted following the shift of the phosphorous signal in the ^{31}P NMR spectrum and the association constants, $K_{a,}$ were determined *via* a non-linear regression approach (**TRIP**·BzOH *Ka* = (3981 ± 98) M^{-1}, **TRIP**·AcOH *Ka* = (1948 ± 26) M^{-1}).

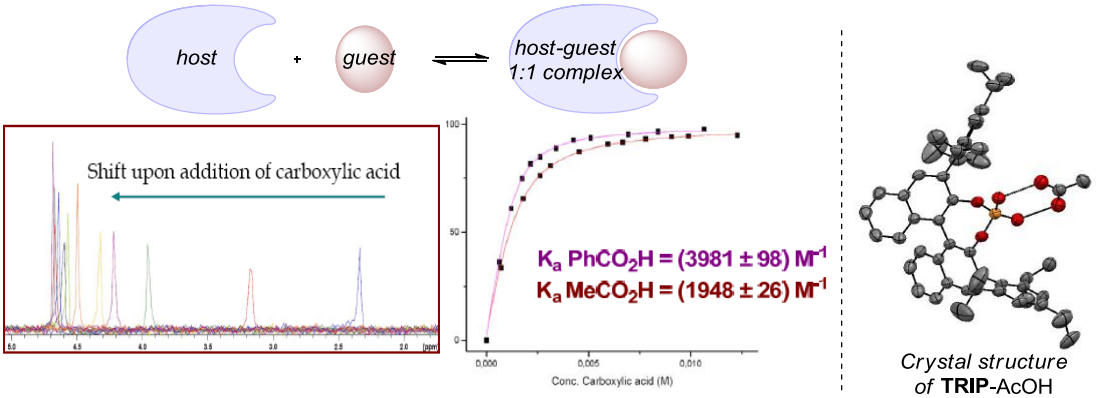
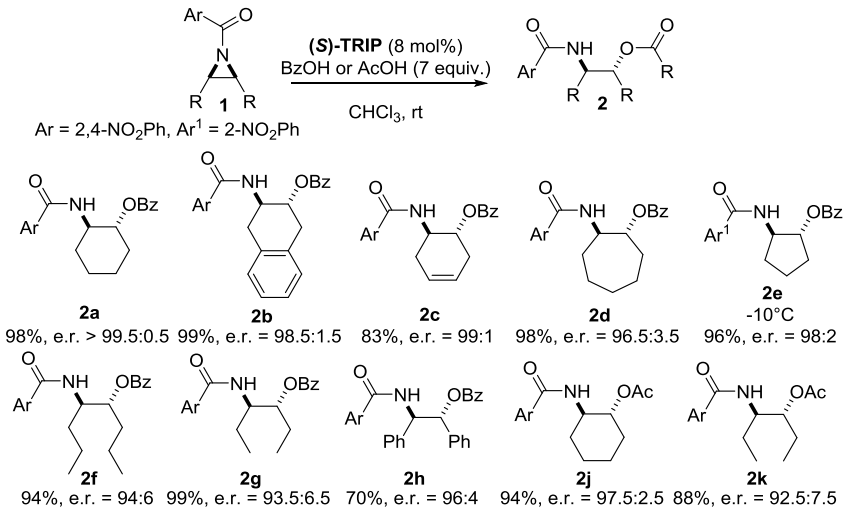


Figure 2. Determination of binding constants *via* ^{31}P NMR titration and crystal structure of **TRIP**-AcOH.

Final confirmation of the heterodimer formation was then obtained by cocrystallizing acetic acid and **TRIP**, which gave a crystal suitable for X-ray analysis.

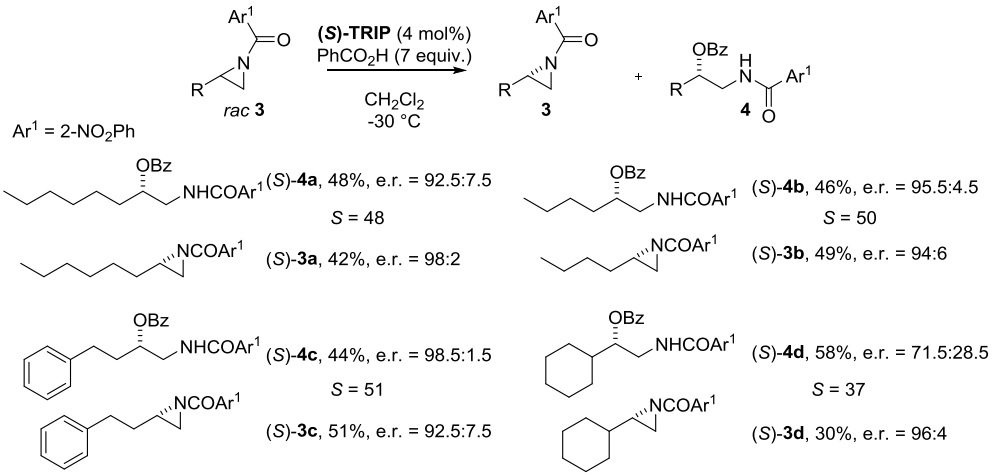
The upfield shift of the proton signals of carboxylic acid in the NMR spectrum fascinatingly suggested that the self-assembly with phosphoric acid raises the energy of its HOMO orbital. This leads to the somewhat counterintuitive possibility that, despite being a stronger acid, the phosphoric acid is formally behaving like a base within the dimer due to the strong effect of the P=O bond. Therefore we started to investigate the role of the heterodimeric system as a source of nucleophilic carboxylic acids. The ring opening of aziridines has been chosen as ideal testing ground for our concept since an asymmetric catalytic conversion leading to amino alcohols has not yet been reported.

The novel system turned out to be effective in the desymmetrization of *meso*-aziridines with benzoic acid. The scope of the reaction confirms generality of the approach. Indeed, several different cyclic and acyclic substrates successfully reacted affording the expected products **2a-k**. The reactions with acetic acid gave comparably high yields and enantioselectivities albeit with the need of longer reaction time and higher nucleophile concentration, which confirms the importance of the affinity between **TRIP** and the carboxylic acid for the reacting system.



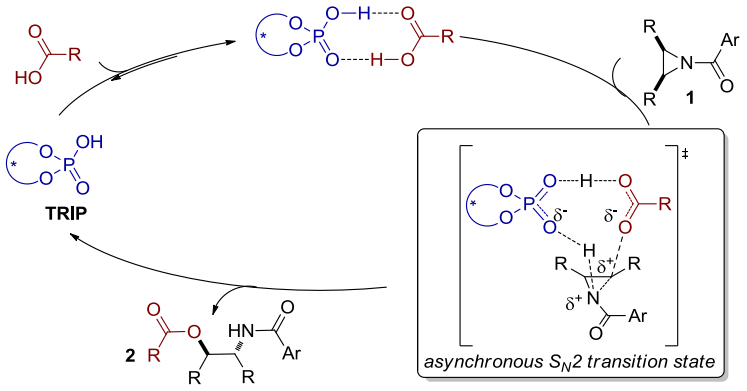
Scheme 2. Scope of the ring opening desymmetrization of *meso*-aziridines with carboxylic acids.

Next we turned our attention to the kinetic resolution of terminal aziridines. Lowering the temperature to -30 °C, high selectivity factors could be reached both for linear substrates as well as for branched ones (*S* from 37 to 51). The high regioselectivity of the reaction is remarkable and probably due to a partial positive charge on the aziridine fragment in the reaction transition state.



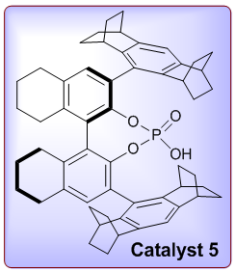
Scheme 3. Scope of the ring opening kinetic resolution of terminal aziridines with carboxylic acids.

A catalytic cycle can be proposed. The chiral nucleophile is first generated by self-assembly and then the aziridine is engaged in the nucleophilic attack, which possibly occurs through a concerted transition state in which the electrophile benefits from an additional Brønsted acid activation. A highly asynchronous S_N2 pathway is suggested by the exclusivity of *trans*-products in the desymmetrization strategy and by the perfect regioselectivity of the kinetic resolution, which reveals a strong localized δ^+ charge at the reacting centre.

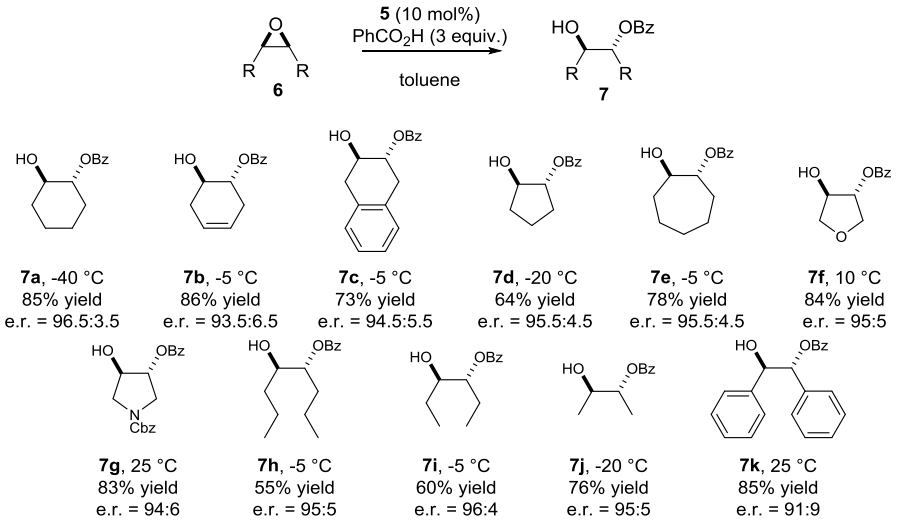


Scheme 4. Proposed mechanism for the activation of carboxylic acids in organocatalysis.

Encouraged by the results achieved in the ring opening of aziridines, we turned our attention to the reaction of carboxylic acids with epoxides. Our system indeed proved to be suitable. However, the enantioselectivity achieved with **TRIP** phosphoric acid was only modest. A novel binaphtol derived phosphoric acid catalyst **5**, in which the 3,3´-substituents are fused polycyclic moieties, gave



significantly improved results, delivering monoprotected glycols **7** from the corresponding *meso*-epoxides **6** in good yields and enantioselectivities.



Scheme 5. Scope of the ring opening desymmetrization of *meso*-epoxides with carboxylic acids.

In summary, the first approach to the activation of carboxylic acids in organocatalysis has been developed. The self-assembly between chiral phosphoric acids and carboxylic acids has been observed by analytical methods and has been applied to interesting methodologies, such as the asymmetric ring opening of aziridines and epoxides. A cooperative mechanism has been suggested: the carboxylic acid prevents the catalyst degradation by limiting the direct interaction with the electrophile, while the phosphoric acid activates and directs the nucleophilic attack of the carboxylic acid partner.

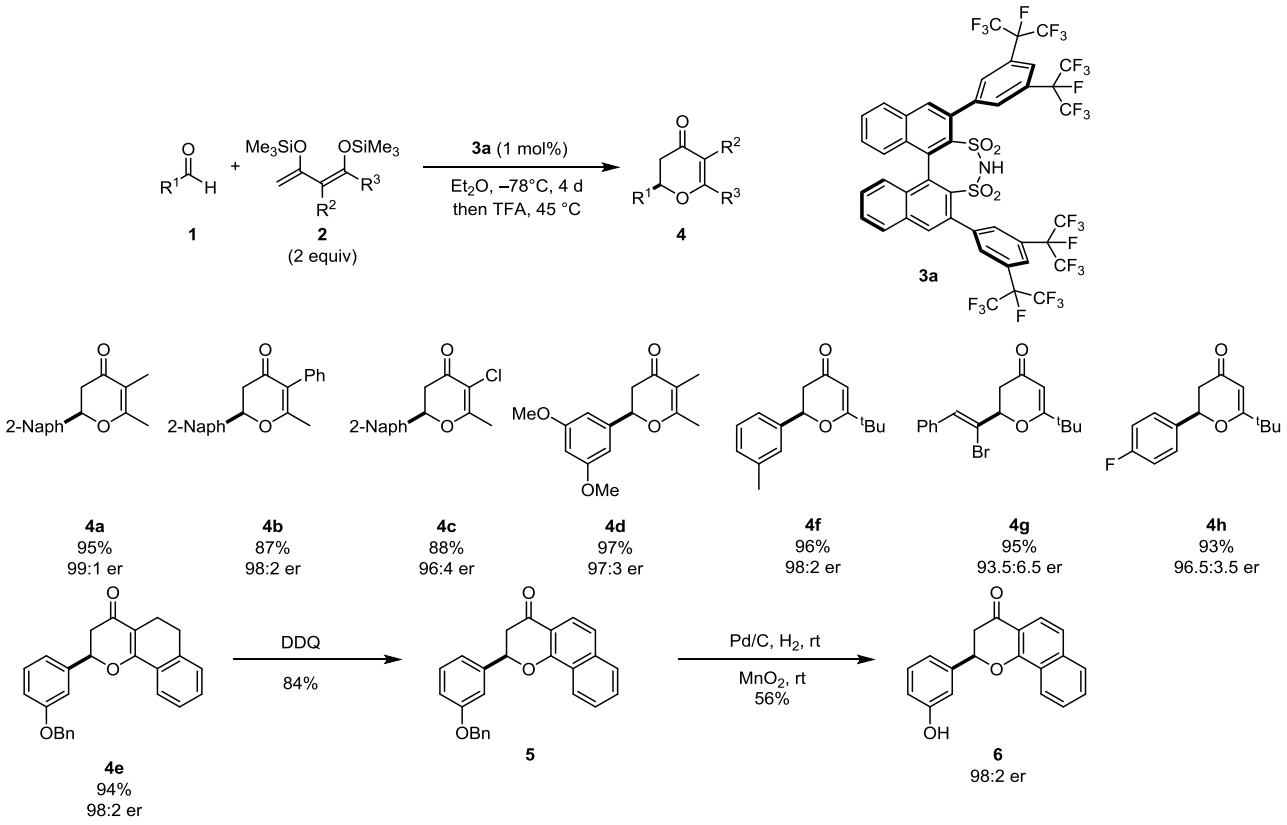
2.2.4 Research Area "Lewis Acid Organocatalysis" (B. List)

Involved: S. Gandhi, P. García-García, J. Guin, M. Leutzsch, C. Rabalakos, M. van Gemmeren (né Mahlau), Q. Wang

Objective: Organocatalysts function by donating or removing electrons or protons, defining four distinct activation modes: Brønsted base catalysis, Brønsted acid catalysis, Lewis base catalysis, and Lewis acid catalysis. While the areas of Lewis base, Brønsted acid and base organocatalysis are relatively well developed, organic Lewis acid catalysis was until recently almost unexplored. Our group has developed chiral analogs of triflimide (Tf_2NH), which is a powerful achiral Mukaiyama aldol pre-catalyst that generates the highly reactive Lewis acid Tf_2NTMS as the actual catalyst. These catalysts exploit the concept of asymmetric counteranion-directed catalysis (*ACDC*) developed by our group, by pairing the catalytically active silylium ion equivalent with a chiral disulfonimide anion, which is responsible for the stereoinduction. Based on these results we were interested in the application of this type of catalysts to further reactions known to be challenging for metal-based Lewis acid catalysts. Additionally, the very low catalyst loadings achieved in our work on the Mukaiyama aldol reaction spurred our interest in developing new, even more active variants of our disulfonimide catalysts, in order to equal the extremely low catalyst loadings sometimes achieved in transition metal or biocatalysis.

Results: In spite of some progress in the development of catalytic systems for hetero-Diels-Alder reactions (HDA) these reactions are still very limited in their scope of dienes, and both substituted and functionalized dienes have proven to be highly challenging substrates. In particular, substituted 1,3-bis(silyloxy)-1,3-dienes **2**, which are readily synthesized in one step from commercially available and inexpensive 1,3-diketones, had not been reported in asymmetric catalysis prior to our studies, conceivably due to a competing achiral silylium catalyzed background reaction. This rendered them ideal model substrates to expand the applicability of our catalytic system. In order to achieve high enantioselection in these reactions, we developed the perfluoroisopropyl version **3a** of the initially introduced disulfonimide. This catalyst promoted the highly enantioselective HDA of aldehydes **1** and dienes **2** to give a variety of products in good to excellent enantioselectivities. The disulfonimide system was found to be suitable for tetrasubstituted diene substrates, thus giving access to 2,5,6-trisubstituted dihydropyridines **4a-e** in high yields and excellent enantioselectivities. On the aldehyde side, electronrich or electronically unbiased aromatic aldehydes, as well as

cinnamaldehyde derivatives were suitable electrophiles, giving for example **4f-h** in excellent yields and enantioselectivities. The utility of our methodology was further demonstrated by the first asymmetric synthesis of a potent aromatase inhibitor, which was achieved by oxidation of **4e** to the aromatic product **5** and subsequent removal of the benzyl group to give the desired pharmacologically active compound **6** without loss of enantiopurity (Scheme 1).

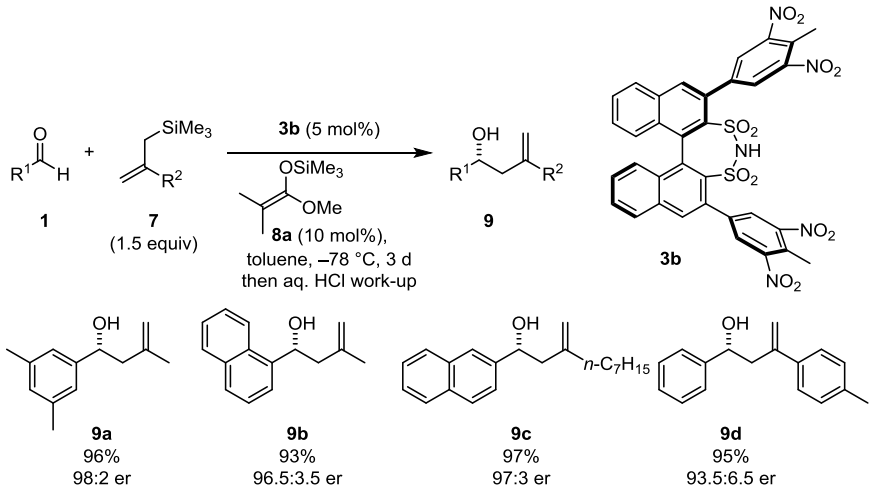


Scheme 1. Disulfonimide catalyzed asymmetric hetero-Diels–Alder reactions.

Another reaction, which has traditionally posed great difficulties to enantioselective Lewis acid catalysis is the Hosomi-Sakurai reaction, which shares a number of mechanistic features with the Mukaiyama-aldol reaction. Thus, prior to our studies, only a limited number of enantioselective methodologies were known for this reaction and we reasoned that our ACDC approach using disulfonimides as catalysts should allow for the enantioselective catalysis of this reaction. Indeed we realized the catalytic asymmetric methallylation of aldehydes utilizing the nitro-substituted catalyst **3b**.

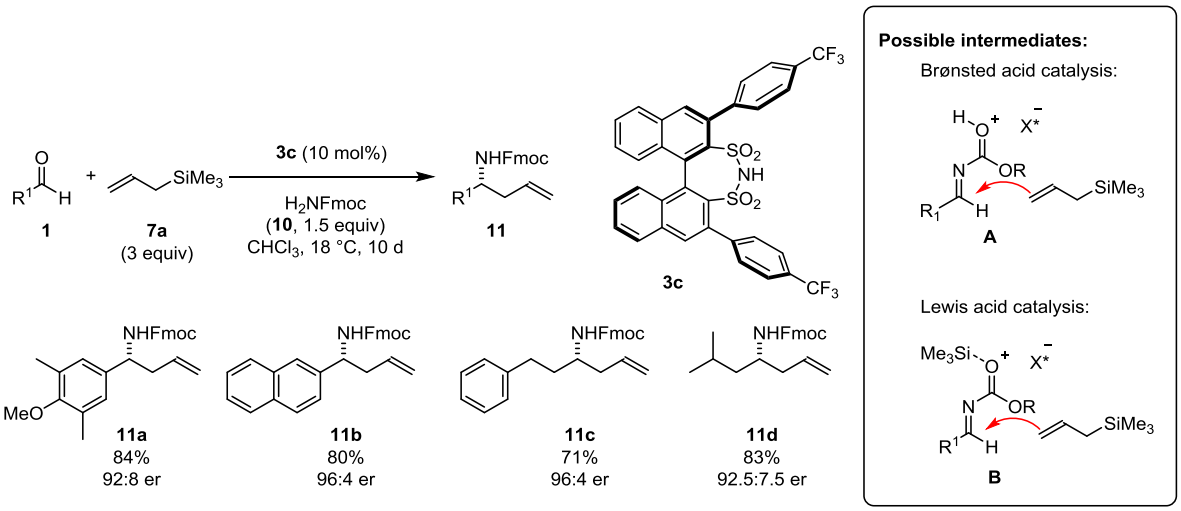
A variety of aldehydes **1** and allylsilane nucleophiles **7**, bearing both aliphatic and aromatic substituents, could be employed and the allylation products **9** were

obtained in high yields and enantioselectivities (Scheme 2). As in many metal-based systems, simple allyltrimethyl silane could not be employed, due to its dramatically lower reactivity. The optimized conditions for this reaction involved the use of silyl ketene acetal **8a** in catalytic amounts, which accelerated the initial silylation of the precatalyst.



Scheme 2. The asymmetric counteranion-directed catalytic Hosomi-Sakurai reaction.

Just as chiral enantiopure homoallylic alcohols, the corresponding homoallylic amines are valuable intermediates in the synthesis of natural products and pharmaceutically active compounds. Despite the elegance of this strategy, direct asymmetric reactions between aldehydes, carbamates or amines and allyltrimethyl silane were unknown prior to our studies. Instead, the corresponding homoallylic amines were accessed by stereoselective allylations of preformed imines or other, indirect methods.



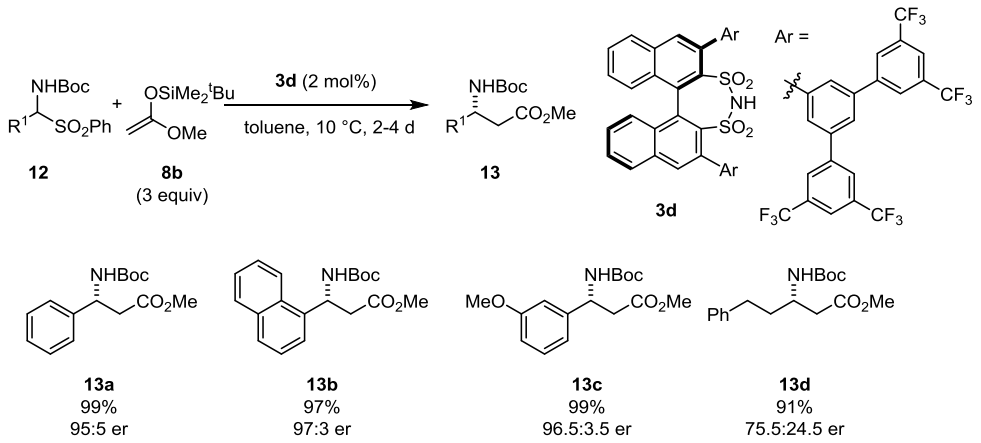
Scheme 3. Disulfonimide catalyzed enantioselective three-component aminoallylations.

The development of *para*-substituted catalyst **3c** and the optimization of nitrogen-source and reaction conditions allowed us to develop a highly enantioselective direct aminoallylation of aldehydes (Scheme 3).

The reaction between aldehydes **1**, allyltrimethyl silane (**7a**) and 9-fluorenylmethyl carbamate (H_2NFmoc, **10**) gave both aromatic (**11a** and **11b**) and aliphatic (**11c** and **11d**) products with high yield and enantioselectivity. As one equivalent of water is released in the catalytic cycle of this three-component reaction, we were interested whether this reaction proceeds through Brønsted acid catalysis (intermediate **A**) or Lewis acid catalysis (intermediate **B**). As silylium ion equivalents are highly water sensitive, the reaction mixture would have to be completely dry, in order for intermediate **B** to be involved. Considering the self-healing capability of our disulfonimide catalysts (using up two equivalents of nucleophile per molecule of water) and the observed necessity for three equivalents of nucleophile in our reaction, we assume that this reaction is in fact Lewis acid catalyzed. This interpretation is further corroborated by the fact that identical enantioselection was obtained, when presilylated catalyst and preformed imine were reacted with trimethylallyl silane **7a**.

Having discovered the ability of the disulfonimide catalysts to activate (*in situ* generated) imines, we became interested in the generation of the β^3-amino ester scaffold, which is present in a large number of synthetically valuable intermediates, and can be generated by the enantioselective Mannich reaction between an ester enolate equivalent and an imine. However, methods known for this transformation often suffer from the instability of the imine substrates. As these imines are in many cases prepared by elimination from amino sulfones, we reasoned that it should be possible to combine the Mannich reaction and the *in situ* generation of the imine using Lewis acid organocatalysis. Indeed, using the sterically demanding catalyst **3d**, the reaction of *N*-Boc-amino sulfones **12** with commercially available silyl ketene acetal **8b** could be catalyzed to give β^3-amino esters **13**.

Aromatic substrates with different substitution patterns were found to give excellent yields and enantioselectivities under the optimized reaction conditions (**13a-c**, Scheme 4). Although currently achieved stereoselections are modest, the methodology was shown to be applicable to aliphatic *N*-Boc-amino sulfones, giving for example **13d**. These products are usually difficult to access, as their imine precursors are even less stable than their aromatic counterparts.



Scheme 4. Enantioselective Mukaiyama-Mannich reactions starting directly from *N*-Boc-amino sulfones.

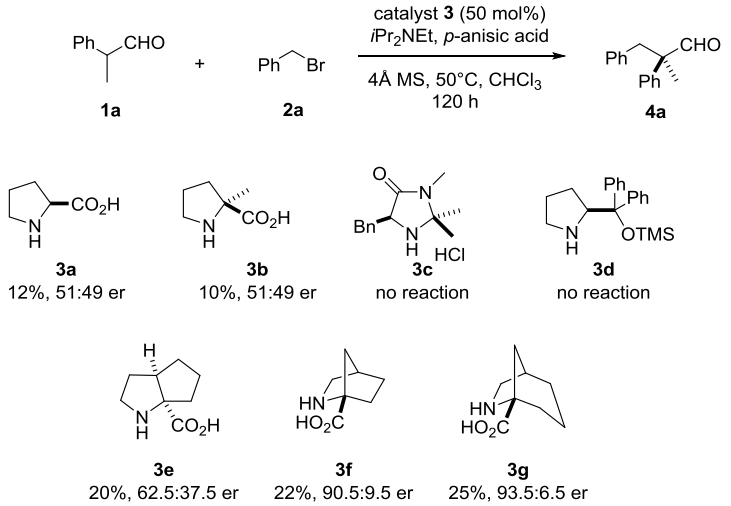
We proceeded to investigate the mechanism of this two-step process and found that the elimination from the *N*-Boc-amino sulfone to give the proposed imine substrate is rate limiting, as the reaction of a preformed imine under identical conditions was significantly faster giving nearly identical selectivity. The rate limiting step was also determined from NMR measurements.

2.2.5 Research Area "Secondary Amine Catalysis" (B. List)

Involved: I. Corić, P. S. J. Kaib, A. Lee, M. Leutzsch, S. C. Pan, M. van Gemmeren (né Mahlau)

Objective: Asymmetric S_N2-α-alkylations of carbonyl compounds with alkyl halides are powerful transformations that commonly involve chiral auxiliaries or phase transfer catalysts. Despite some progress towards organocatalytic variants, such as an intramolecular proline catalyzed reaction of halo-aldehydes developed by our group, and several studies combining enamine catalysis with radical or S_N1-pathways, the intermolecular S_N2-reaction of aldehydes and alkyl halides has remained elusive and has been termed a "holy grail" of organocatalysis. The goal of this research project was to develop a system capable of catalyzing this reaction.

Results: When developing such a catalytic system, the plethora of undesired side reactions has to be considered. Amongst them, avoiding self-aldolization of the substrate, racemization of the product, and catalyst alkylation are considered to be crucial. To achieve this goal we chose to study α-branched aldehydes, thus generating α-quaternary products and avoiding the issue of product racemization. We further designed our catalytic system based on the following considerations: Using a buffer of acid and base additives might be able to retain the potential advantages of adding base, while eliminating some of the undesired side effects. More specifically, this system should accelerate enamine formation and prevent very acidic or basic conditions throughout the course of the reaction, thus reducing catalyst alkylation to a minimum.

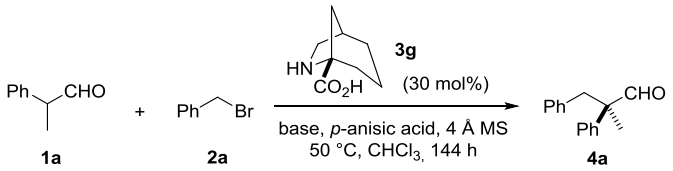


Scheme 1. Catalyst evaluation.

We commenced our study by screening various potential catalysts, including several newly developed, sterically hindered proline analogs (Scheme 1).

A preliminary screening of catalysts revealed these new catalysts to be highly promising and a screening of reaction conditions was undertaken in order to achieve catalyst turnover. As the base additive was considered to be crucial, due to the predicted ion pairing between the protonated base and the carboxylate moiety of the catalyst, we screened various bases and identified tetramethylguanidine as the base of choice, which enabled both catalyst turnover and optimal enantioselectivity (Table 1).

Table 1. Influence of the base[a].



Entry	Base	Yield [%][b]	e.r.[c]
1	DMAP	30	65:35
2	imidazole	33	61:39
3	DBU	20	79:21
4	1,3-diphenylguanidine	60	88:12
5	1,3-di-(*o*-tolyl)-guanidine	63	90:10
6	1,1,3,3-tetramethylguanidine	80	95.5:4.5
7	2',2'-(naphthalene-1,8-diyl)-bis(1,1,3,3-tetramethylguanidine)	80	53:47

[a] Conditions: aldehyde **1a** (0.1 mmol) and benzyl bromide **2a** (0.5 mmol), catalyst **3l** (0.03 mmol), *p*-anisic acid (0.5 mmol), base (0.5 mmol), 4 Å MS (80 mg) in chloroform (0.5 mL) at 50 °C for 144 h. [b] Determined by GC-MS using *n*-dodecane as internal standard. [c] Determined by GC analysis on a chiral stationary phase.

We also studied the reaction stoichiometry with regard to acid, base and alkylating agent and found that molecular sieves have a beneficial effect on the reaction. The reaction is best conducted using five equivalents of buffer and alkylating agent in chloroform at 50 °C in the presence of molecular sieves.

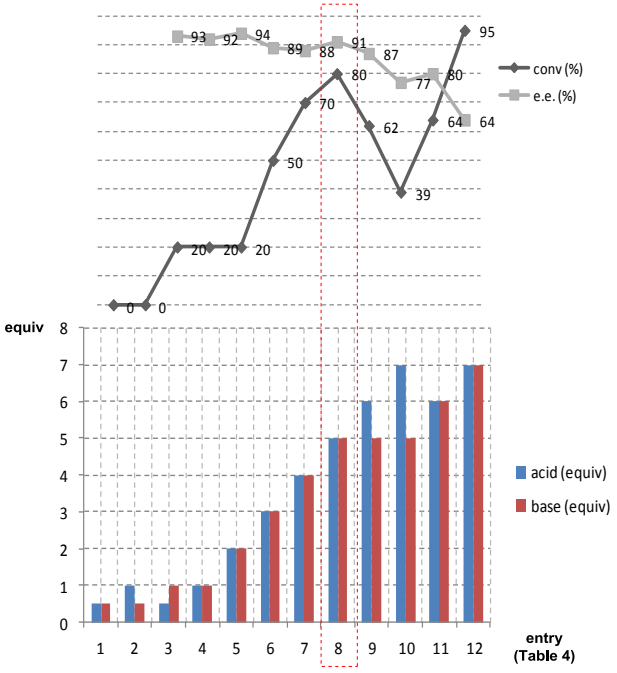
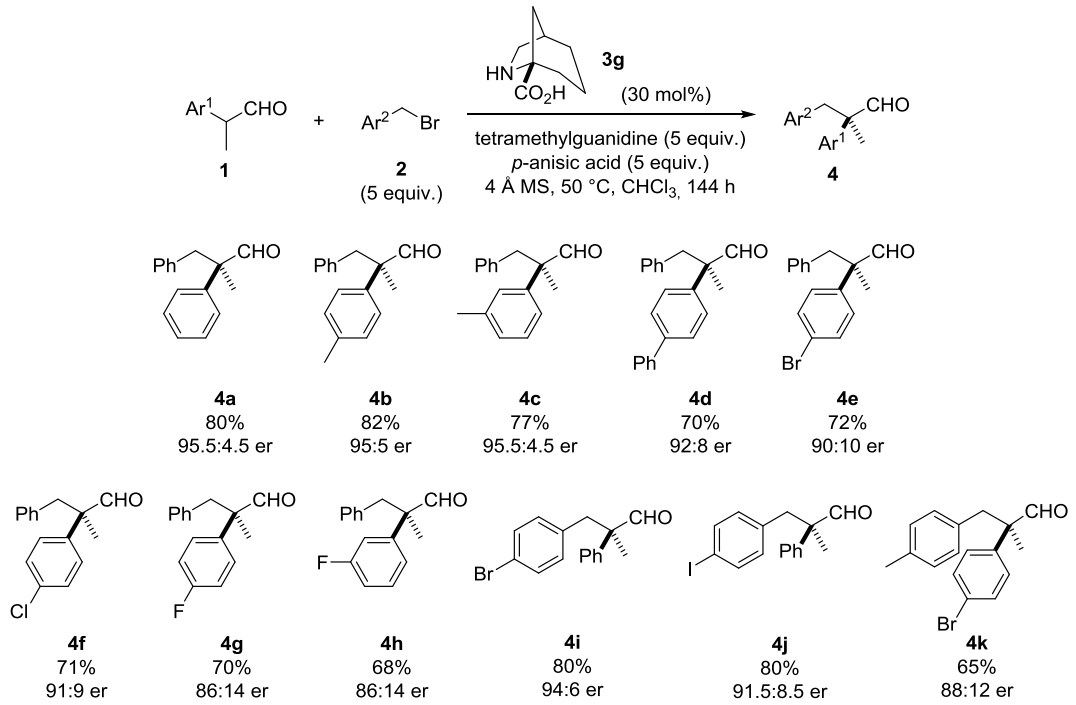


Figure 1. Evaluation of the amount of acid and base.

Using our optimized reaction conditions we explored the scope of our newly developed S_N2-α-alkylation of α-branched aldehydes and found that a number of substrates reacted smoothly giving moderate to good yields and

enantioselectivities (Scheme 2). The use of substituted benzyl bromide derivatives was also confirmed to be possible. As expected, α-unbranched aldehydes turned out to be unsuitable as substrates, giving predominantly double alkylated products and self-aldolization products.



Scheme 2. Substrate scope.

The absolute configuration of our model product **4a** was determined to be (*R*) and we could rationalize this by analogy to our previous intramolecular reaction, for which transition state **B** was computationally determined. Thus we suggested a transition state **A** for our current catalytic system (Figure 2).

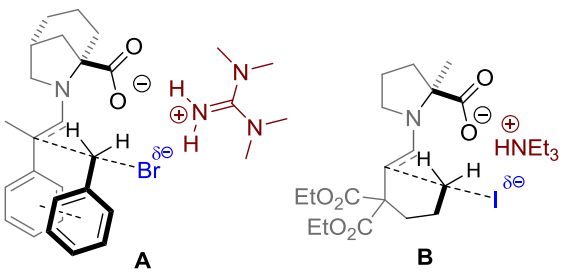
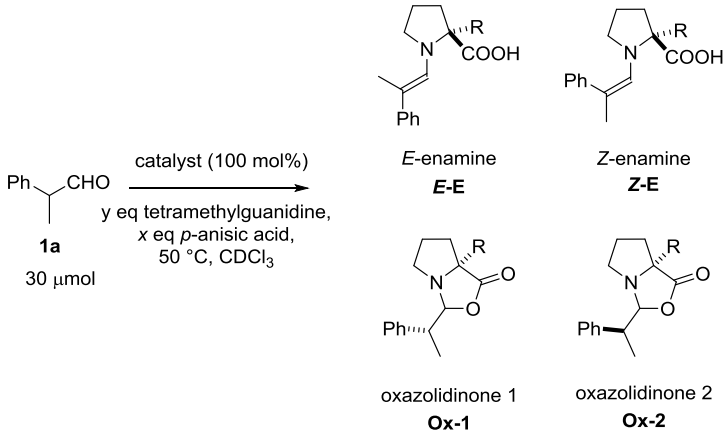


Figure 2. Proposed transition state of the intermolecular α-alkylation (**A**). Calculated transition state of the intramolecular α-alkylation (**B**).

In order to confirm the suggested roles of acid and base in the reaction, we conducted NMR experiments using different ratios of acid and base with proline (**4a**) and our optimal catalyst **3g**. These experiments confirmed that the reaction between catalyst and substrate is greatly enhanced by the addition of acid and/or base and that the base additionally shifts the equilibrium between enamine and oxazolidinone towards the enamine intermediate.

Thus, we concluded that the buffer utilized in this reaction works in the following way: The role of the base is to solubilize the catalyst and to increase the ratio, in which the enamine intermediate is formed.

Table 2. Equilibrium between catalysts and aldehyde in $CDCl_3$ with various equivalents of additives.



Entry	x	y	Catalyst	Ratio aldehyde : intermediates	Ratio Intermediates *E*-E : *Z*-E : Ox-1 : Ox-2
1	0	0	**3a**	> 99 : 1	-
2	0	1	**3a**	74 : 26	46 : 5 : 0 : 0
3	1	0	**3a**	71 : 29	0 : 0 : 5 : 4
4	1	1	**3a**	87 : 13	4 : 1 : 4 : 4
5	2	2	**3a**	89 : 11	5 : 1 : 6 : 5
6	5	5	**3a**	84 : 16	9 : 2 : 2 : 2
7	0	0	**3g**	98 : 2	0 : 0 : 1 : 2
8	1	0	**3g**	96 : 4	0 : 0 : 1 : 1
9	0	1	**3g**	84 : 16	19 : 6 : 21 : 28
10	1	1	**3g**	93 : 7	0 : 0 : 3 : 4
11	2	2	**3g**	89 : 11	3 : 1 : 7 : 8
12	5	5	**3g**	88 : 12	12 : 1 : 14.5 : 17

The role of the acid is to prevent undesired side effects of the base. As tetramethyl guanidine is a strong base and stabilizes the more nucleophilic anionic form of the catalyst, alkylation could potentially deactivate the catalyst. The alkylated catalyst was in fact observed by GC-MS even under optimal conditions. The alkylation could be prevented by the acid, which can reduce the catalyst's nucleophilicity. Additionally, strong bases such as guanidines are known to promote enolate alkylations. Thus the acid may also act by preventing a competing non-enantioselective reaction.

In summary, we developed the first catalytic asymmetric α-alkylation of α-branched aldehydes utilizing a buffer system and a bulky proline analog as catalyst. Although this

catalytic system is rather complicated and not applicable to linear aldehydes at the current state, we believe that our discovery represents progress towards the development of universally applicable S_N2-α-alkylations of carbonyl compounds with alkyl halides.

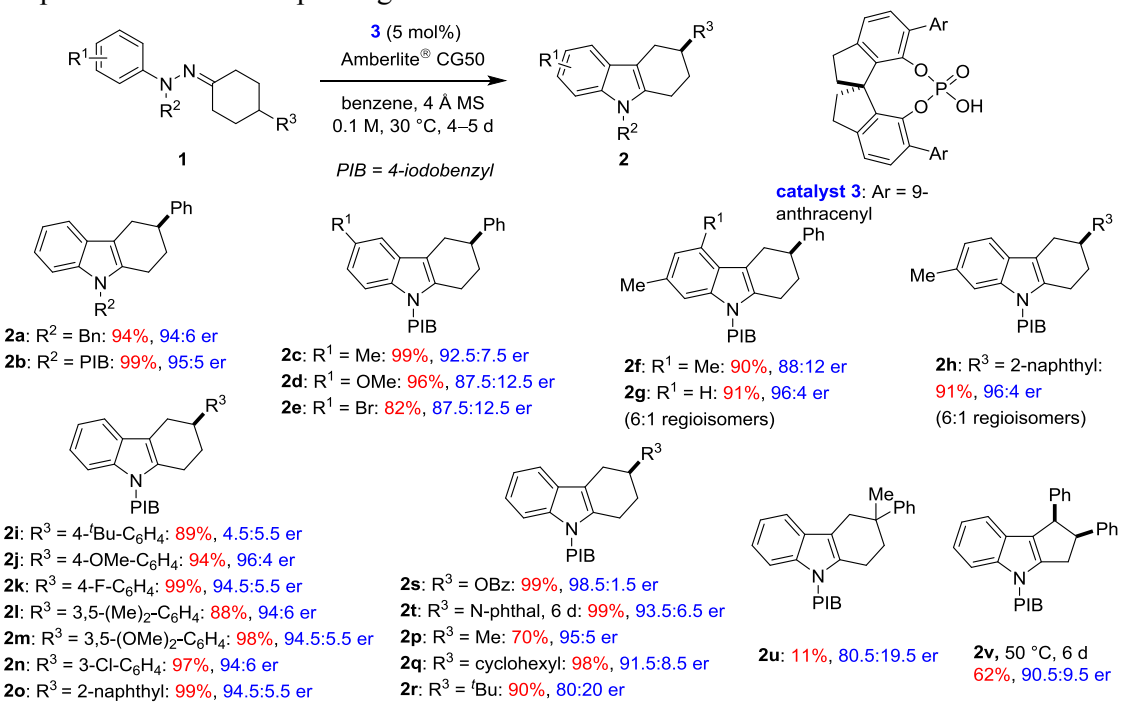
2.2.6 Research Area "The [3,3]-Diaza Cope Rearrangement in Asymmetric Catalysis" (B. List)

Involved: S. Müller, M. J. Webber, A. Martínez, L. Kötzner, F. Pesciaioli, C. K. De

Objective: The [3,3]-sigmatropic rearrangement is a well-established versatile pericyclic reaction, which has been successfully utilized in organic synthesis. Interestingly, the utility of the [3,3]-diaza Cope rearrangement remained limited. This rearrangement is a powerful synthetic principle utilized to generate a C–C bond at the expense of an N–N bond. It forms the basis of important and fundamental acid-catalyzed transformations such as the Fischer indolization, its associated reactions and the benzidine rearrangement, of which asymmetric versions despite their synthetic and scientific relevance have remained elusive to date. Chiral Brønsted acids, which have been established as a powerful tool in organocatalysis, may be capable of catalyzing these [3,3]-diaza Cope rearrangements leading to enantio-enriched indole derivatives and aromatic diamines.

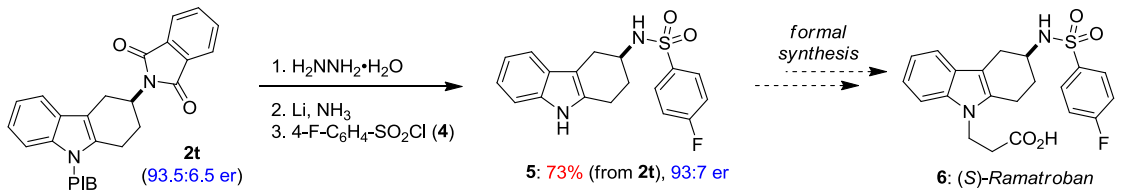
Results: Although numerous methods are known for the construction of indoles, one of the most abundant heterocyclic compounds in nature, the acid-mediated Fischer indolization remains one of the most widely used procedures. Nevertheless, catalytic asymmetric Fischer indolizations have remained difficult to implement so far. Our strategy relies on the indolization of 4-substituted cyclohexanone-derived phenylhydrazones to give chiral tetrahydrocarbazoles *via* a [3,3]-diaza Cope rearrangement. However, to enable the use of a chiral Brønsted acid at substoichiometric loadings catalyst poisoning due to ammonia formation during the course of the reaction had to be addressed. As expected, the use of *N*-benzyl-protected hydrazone **1a** with a catalytic amount (5 mol%) of phosphoric acid led to a dramatic decrease in the reaction rate. Unfortunately, reaction condition screenings did not give any improvement. When testing different additives, the addition of Amberlite® CG50, a weakly acidic cation exchange resin, was found to have a beneficial effect on the catalyst reactivity and increased the yield. We thus investigated the scope of our reaction under the optimized conditions. The *N*-benzyl-protected hydrazone **1a** and the iodinated analogue **1b** both gave the corresponding products in 94% and 99% yield and enantiomeric ratios of 94:6 and 95:5, respectively. Despite the different electronic properties of their protecting group, both hydrazones gave 6-substituted tetrahydrocarbazoles in good yields and high enantioselectivities (**2c**–**2e**). Phenylhydrazones with substituents at different ring positions were also found to be suitable substrates (**2f**–**2h**). Hydrazones in which R^3 consists of a substituted aromatic ring (**2i**–**2o**) or an aliphatic group (**2p**–**2r**) gave the desired products in typically good yields and with high levels of enantioselectivity. Heteroatom-substituted

substrates were also well suited and gave the desired products in 99% yields (**2s**–**2t**) and with high levels of enantioselectivity. Tetrahydrocarbazole **2u** bearing a quaternary stereogenic center proved to be a challenging substrate. Interestingly, the hydrazone derived from cyclopentanone gave the desired product **2v** in 62% yield and 90.5:9.5 er at elevated temperatures and after a prolonged reaction time.



Scheme 1. Catalytic asymmetric Fischer indolization.

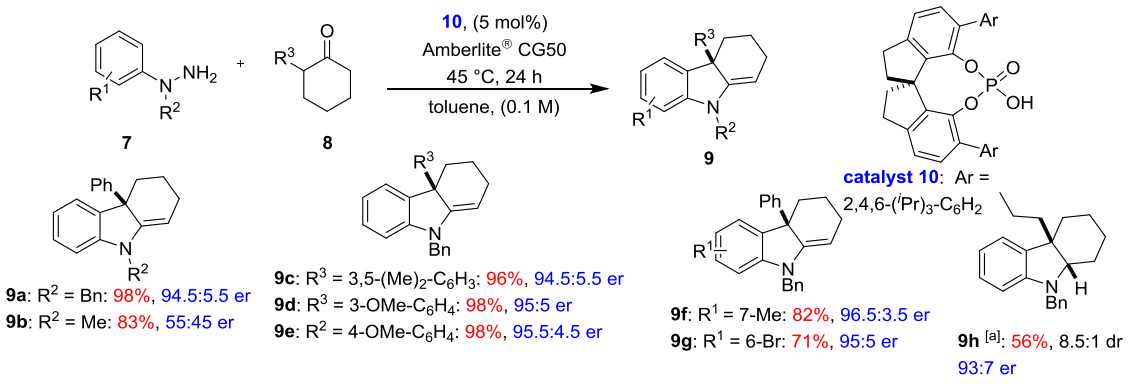
As application of the developed method, a formal synthesis of the thromboxane receptor antagonist Ramatroban (**6**) was targeted. Indolization of hydrazone **1t** on a 2.0 mmol scale proceeded without compromising the yield or enantioselectivity. In this process 55% of catalyst **3** were recovered. Starting from tetrahydrocarbazole **2t**, a three-step sequence of deprotection of the phthalimide, debenzylation under Birch conditions and subsequent sulfonylation gave the literature-known intermediate **7** in good overall yield without diminishing the initial optical purity.



Scheme 2. Application of the catalytic asymmetric Fischer indolization.

3,3-Disubstituted fused indolines are privileged substructures of diverse natural products and biologically active molecules for which the [3,3]-diaza Cope rearrangement could be a complementary synthesis strategy based on the Fischer indolization. Starting from *N*-

benzyl-*N*-phenylhydrazine (**7a**) and 2-phenylcyclohexanone (**8b**) in the presence of a variety of chiral phosphoric acids and the weakly acidic Amberlite® CG50 as additive, indoline-enamine **9a** was obtained in promising yields and enantioselectivities. Further tuning of the reaction conditions revealed that the hindered SPINOL phosphoric acid STRIP (**10**) is the best catalyst for this transformation. The scope of the reaction was evaluated under the optimized conditions. Indolines **9** could be obtained typically in quantitative yields and with high levels of enantioselectivity irrespective of the aryl substituent at R^3 (**9a**, **9c**–**9e**).



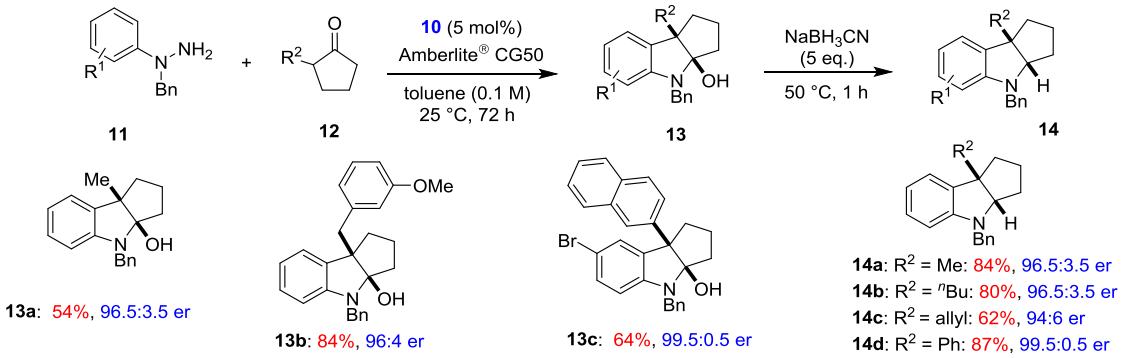
[a] After in situ reduction of the unstable enamine with $NaBH_3CN$.

Scheme 3a. Interrupted asymmetric Fischer indolization with α-substituted cyclohexanone.

Remarkably lower er was obtained when the protecting group on the hydrazine was modified from Bn to Me (**9b**). Irrespective of the electronic and steric nature of the substituents R^1 the desired products **9f**–**9g** could be isolated in good yields and with high level of enantioselectivity. 2-Alkylcyclohexanones were found to be less reactive, thus the reaction was performed at elevated temperature, and product **9h** was obtained after *in situ* reduction of the corresponding unstable enamine with $NaBH_3CN$ in moderate yield and good enantioselectivity and diastereoselectivity (8.5:1 dr). The major diastereoisomer was found to be the *cis*-fused system with an er of 93:7.

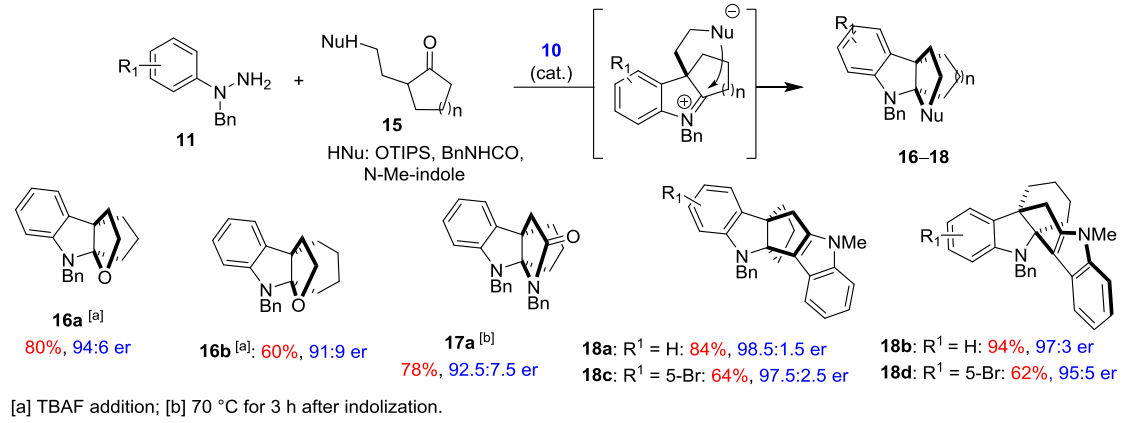
Inspired by these findings, a similar transformation with 2-substituted cyclopentanones was pursued which were beforehand found to be challenging for the Fischer indolization. Interestingly, the reaction yielded 2-hydroxyindolines **13**, rather than the corresponding indoline-enamines. Both alkyl and benzyl substituents were well-tolerated (**13a**–**13c**). By incorporating a reductive step we could achieve a more stable product and increase the yield. Once the indolization was judged to be completed, addition of $NaBH_3CN$ gave an improved yield of the reduced indoline **14a**. Following

this reaction sequence, reduced indoline products (**14b**–**14d**) were obtained in good yields and high enantioselectivities.



Scheme 3b. Interrupted asymmetric Fischer indolization with α-substituted cyclopentanone.

Encouraged by these results, this method was applied for the synthesis of more complex molecules using a suitable design of the starting ketone with an appropriate tethered nucleophile or pro-nucleophile. The Fischer indolization pathway could be interrupted by the attack of a nucleophile on the iminium functionality, which is formed upon loss of NH_3.



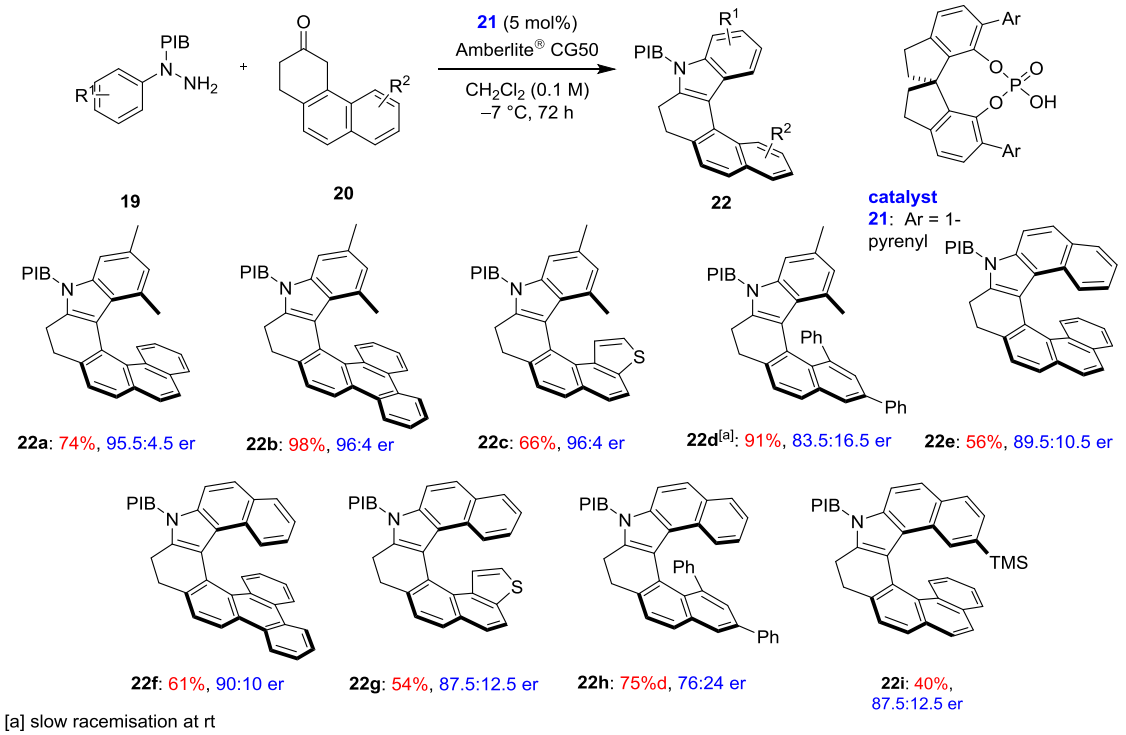
[a] TBAF addition; [b] 70 °C for 3 h after indolization.

Scheme 3c. Synthesis of the polycyclic indolines *via* interrupted asymmetric Fischer indolization.

Ketones containing a γ-silyl ether on the side chain were reacted with hydrazine **11a** and, after *in situ* treatment with TBAF, led to the corresponding [3.3.3]- and [3.3.4]-oxapropellane furoindolines **16a** and **16b** in good yields and enantioselectivities. For amide-containing ketones, an elevated reaction temperature was required upon completion of the indolization to accelerate the ring closure by nucleophilic attack of the amide N-atom. Following this reaction sequence indoline **17a** was obtained in moderate yield and with good enantioselectivity. Finally, incorporation of an electronrich *N*-methylindole moiety into the side chain gave the polycyclic indolines (**18a**–**18d**) bearing two vicinal quaternary

stereocenters in good yields and enantioselectivities. To the best of our knowledge, interrupted Fischer indolization featuring a carbon-based nucleophile was unprecedented.

Molecules exhibiting helical chirality have recently attracted enormous attention, in fields as diverse as catalysis, materials science, molecular self-assembly and biology. Our interest in the field was stimulated by our recent progress in the above-mentioned development of a catalytic asymmetric variant of the Fischer indole synthesis. We hoped that in accordance with the established mechanism of the Fischer indolization, a chiral Brønsted acid might promote an enantioselective [3,3]-sigmatropic rearrangement upon condensation of a phenyl hydrazine **19** with an appropriate polyaromatic ketone **20** and furnish enantio-enriched azahelicenes of type **22**.

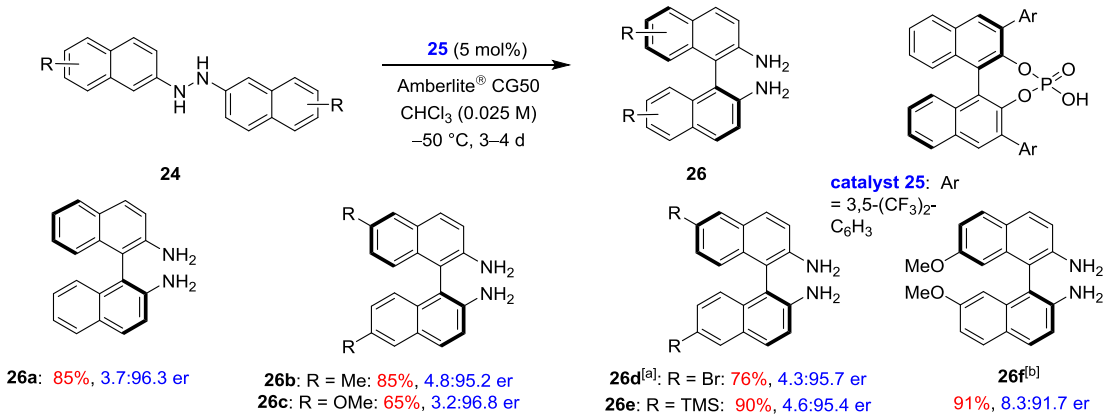


Scheme 4. Synthesis of enantio-enriched azahelicenes *via* asymmetric Fischer indolization.

By evaluating various chiral phosphoric acids as catalysts, it was found that the increase of the π-surface of the 3,3'-substituents led to higher enantioselectivity. Optimizing the reaction conditions, it was found that catalyst **21** in CH_2Cl_2 at –7 °C gave the highest enantioselectivity in our reaction. We started to study the substrate scope under the optimized conditions, combining different hydrazines and ketones. Hydrazine **19a** reacted smoothly with different polycyclic ketones, giving the corresponding [6]-azahelicenes **22a–c** in good yields and enantioselectivities. When hydrazine **19b** was reacted with the same ketones lower enantioselectivities were obtained for compounds **22e–h**. Most synthesized compounds were sensitive to oxidation after prolonged storage under

air. Since fully oxidized helicenes show interesting properties, compound **22a** was oxidized to the corresponding azahelicene **23a**. After some reaction screening we could get helicene **23a** in the presence of tetrachlorobenzoquinone (chloranil) and diphenylphosphate (DPP) in $CHCl_3$ at 50 °C in good yields.

In light of the mechanistic similarities between Fischer indole synthesis and benzidine rearrangement, we envisioned that a catalytic enantioselective benzidine rearrangement of N,N'-dinaphthylhydrazines could potentially be a powerful and general approach towards BINAM derivatives catalyzed by a chiral phosphoric acid *via* [3,3]-diaza Cope rearrangement. We started our studies by reacting hydrazine **24a** with different chiral Brønsted acid catalysts. Spirocyclic phosphoric acid catalysts, which provided excellent results in all three previous projects, gave inferior results in terms of both yield and er. Evaluation of binaphthyl-based phosphoric acids gave only moderate results except for catalyst **25**, which gave product **26a** in promising yield and enantioselectivity. Screening of standard reaction parameters showed that product **26a** could be obtained in good yield and with high level of enantioselectivity at 0.025 M and –50 °C.



[a] Reaction was run at –30 °C with 10 mol% catalyst loading. [b] Reaction was run at –45 °C with 10 mol% catalyst loading.

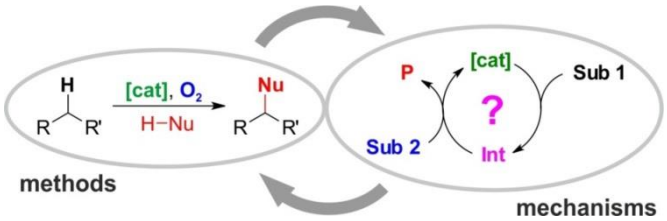
Scheme 5. Catalytic asymmetric benzidine rearrangement.

The scope of the reaction was explored under the optimized conditions. The reaction showed good generality towards different hydrazines allowing the synthesis of various BINAM derivatives with electronically diverse substituents at different ring positions. Hydrazines with substituents at the 6- or 7-position gave the corresponding BINAM derivatives (**26a**–**26f**) irrespective of their electronic nature with good yields and with high level of enantioselectivity.

2.2.7 Research Area "Oxidative Coupling Reactions – Methods and Mechanisms" (M. Klußmann)

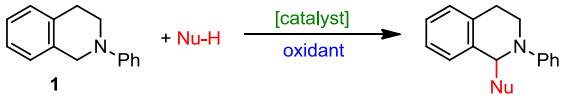
Involved: E. Böß, P. Karier, K. M. Jones, T. Hillringhaus, C. Schmitz, J. Demaerel, B. Schweitzer-Chaput, N. Gulzar, N. Uemiya

Objective: The transformation of two C–H bonds into a new C–C bond can be achieved by oxidative coupling, e.g. by using a catalyst together with a terminal oxidant.[38] We aim to develop sustainable oxidative coupling reactions, using simple and cheap catalysts and low molecular weight oxidants. Additionally, we investigate the mechanisms of these reactions to gain inspirations for the development of new and improved methods:



Scheme 1. Research interests of the Klußmann group.

Results: One area which has enjoyed rapid growth is the coupling α to nitrogen in tertiary amines, the most successful and widely studied being *N*-aryl tetrahydroisoquinolines (THIQ) **1**.[42] The mechanism of these reactions including the nature of intermediates and the role of catalyst and oxygen, however, remained essentially unknown.

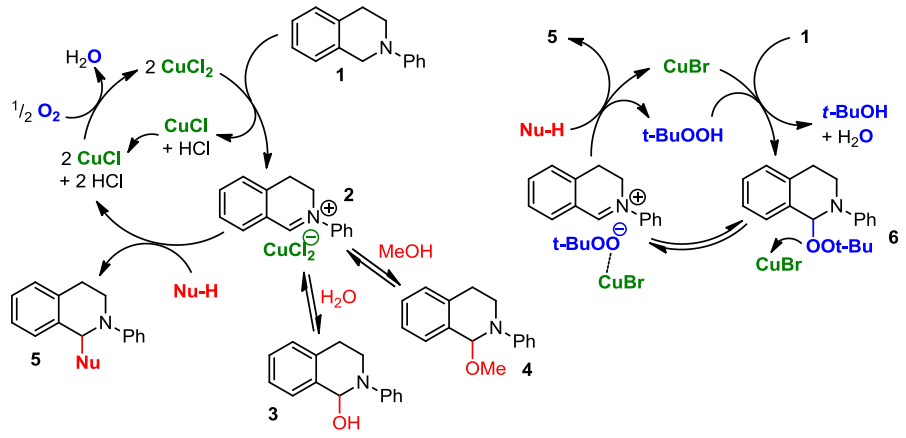


Scheme 2. Oxidative coupling reactions with *N*-phenyltetrahydroisoquinoline.

We have provided the first dedicated mechanistic studies in this field for two copper-catalyzed methods.[40,45] The first, using $CuCl_2$*$2H_2O$ as catalyst and oxygen as oxidant, was developed in our own group and still represents one of the simplest and most sustainable methods for this type of reaction which additionally has the broadest reported nucleophile scope. We could observe an iminium cuprate salt **2** as key intermediate, which is formed by oxidation of **1** with Cu(II).[40] In the presence of water

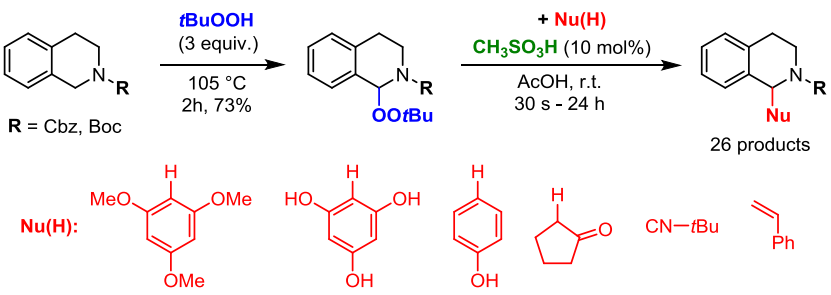
or methanol (a preferred solvent), this species is in equilibrium with a hemiaminal **3** or a hemiaminal ether **4** which provide a reservoir for the reactive iminium ion **2**. Addition of nucleophiles to the iminium provides the desired, thermodynamically preferred, coupling products **5**. Reoxidation of Cu(I) to Cu(II) by oxygen regenerates the catalyst.

The second method, using CuBr as catalyst and *tert*-butylhydroperoxide as oxidant, was reported by the group of C.-J. Li and has been most influential by inspiring many other research groups worldwide. We could establish a mechanism based on our studies which clarified the role of catalyst, oxidant and key intermediate **6**, a peroxide formed through a radical pathway initiated by CuBr and *tert*-butylhydroperoxide.[45]



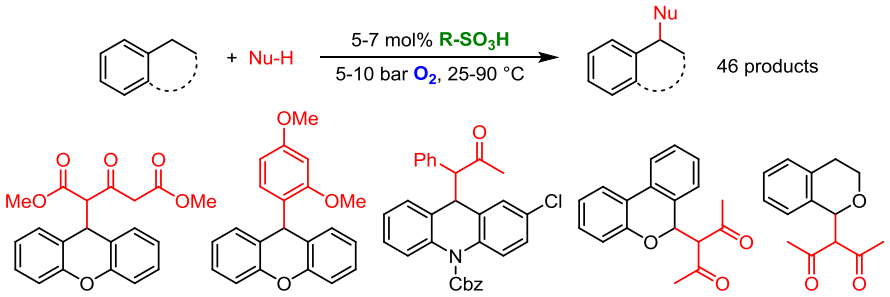
Scheme 3. Proposed reaction mechanisms of Cu-catalyzed oxidative coupling reactions with *N*-phenyltetrahydroisoquinolines.

The discovery that peroxide **6** converts to the reactive iminium ion intermediate by Lewis acid catalysis inspired us to develop an oxidative coupling of *N*-carbamate-protected THIQ's by Brønsted acid catalysis.[46] These compounds can be conveniently deprotected in contrast to *N*-aryl-THIQ's.



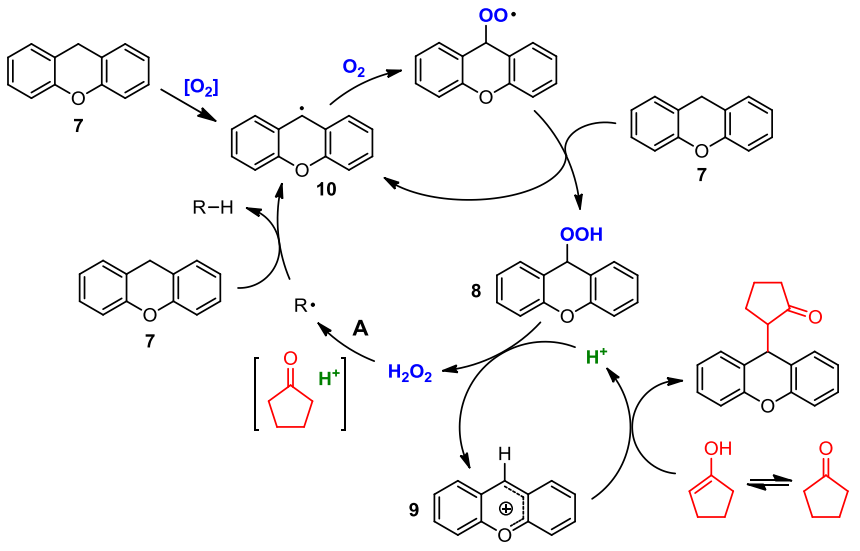
Scheme 4. Oxidative coupling with *N*-carbamoyltetrahydroisoquinolines *via* intermediate peroxides.

Recently, we had discovered a surprising oxidative coupling that proceeds without any redox-active catalyst. For example, xanthene is coupled with ketones by simply stirring the substrates under oxygen at ambient temperature and pressure in the presence of catalytic amounts of a strong Brønsted acid like methanesulfonic acid. The reaction is mostly limited to xanthene and ketones, but at high partial pressure of oxygen, the scope can be extended.[44]



Scheme 5. Autoxidative coupling at elevated partial pressure of oxygen.

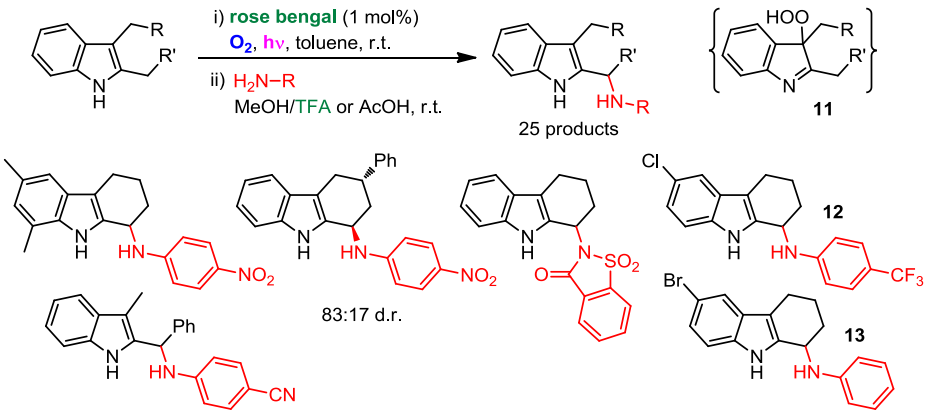
A mechanistic study of this reaction, with the coupling of xanthene **7** with cyclopentanone as model reaction, revealed the autoxidation of xanthene to hydroperoxide **8** as the key step.[49] In the presence of a strong Brønsted acid, the hydroperoxide group is substituted by the ketone nucleophile, probably *via* xanthylium ion **9**. Interestingly, the reaction proceeds faster than the rate limiting autoxidation. The waste product hydrogen peroxide accelerates the reaction by a synergistic action of Brønsted acid and ketones that generates radicals (path **A**, mechanism not yet fully understood).



Scheme 6. Proposed mechanism of the autoxidative coupling of xanthene with cyclopentanone.

We assume that under these conditions, perketals or related structures are formed that decompose into radicals, which in turn abstract a hydrogen atom from xanthene. The resulting xanthenyl radicals **10** are quickly trapped by oxygen, thereby accelerating the autoxidation to form more of the key intermediate **8**.

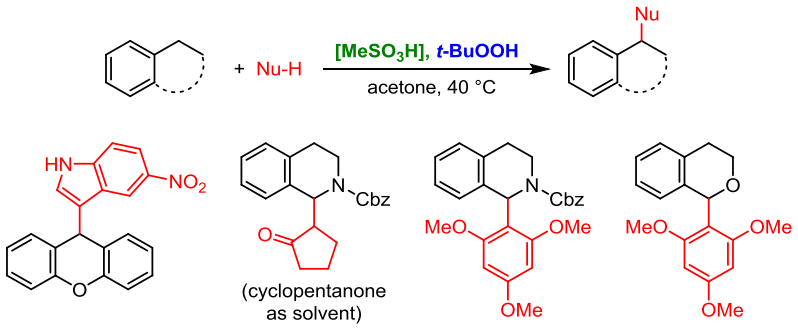
This discovery has inspired several still ongoing research projects. For example, we have developed a programme of C–H functionalization *via* Intermediate PeroxideS, termed CHIPS, which will provide means to derive valuable products from C–H bonds in a sustainable manner, only requiring catalysis and oxygen as the only stoichiometric reagent. As a proof-of-principle, we have developed a photochemical and Brønsted acid catalyzed two-step method to functionalize tetrahydrocarbazole derivatives *via* hydroperoxides **11**, which enables the synthesis of potent antiviral compounds like **12**- and **13**.[48]



Scheme 7. C–H amination of indole-derivatives *via* intermediate hydroperoxides.

In a related project, we have used hydroperoxides derived from the reaction of phenols with singlet oxygen to synthesize spirolactones.[47] And by applying the discovery of the synergistic effect of hydro(gen)-peroxide, ketones and Brønsted acid catalysis, we have developed novel ways of performing oxidative coupling reactions without involvement of redox-active catalysts.[49]

These studies are expected to have broader implications for the understanding of radical and autoxidation chemistry.



Scheme 8. Oxidative coupling reactions by the synergistic action of a Brønsted acid catalyst, hydroperoxide and ketone solvents.

Future directions

Our group will continue with a combination of mechanistic studies and method development, with the goal of developing novel sustainable methods for the C–H functionalization of various organic compounds and gaining an improved understanding of the underlying reaction mechanisms. In particular, we will focus on the principle of CHIPS (C–H functionalization *via* Intermediate PeroxideS) and on the newly gained mechanistic insight into the synergistic action of acid, hydroperoxide and ketone solvents.

Using the principle of CHIPS, we want to develop one-pot methods to functionalize C–H bonds by visible light and simple acid catalysts, for C–H bonds in allylic or heterocyclic compounds (along the lines of Scheme 7).

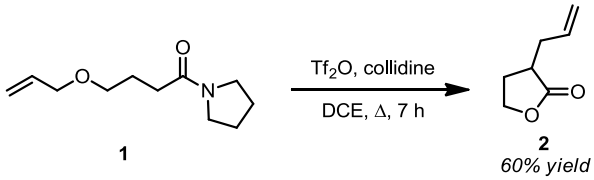
The mechanistic insight from the autoxidative coupling reaction (Scheme 6) has already allowed us to develop oxidative coupling reactions without the use of redox-active catalysts (Scheme 8). We have found indications that the intermediate radicals ("R·" in Scheme 6) are ketone-derived, this knowledge will be used to develop novel radical reactions to functionalize ketones. We have already achieved a hydrofunctionalization and a 1,2-difunctionalization of olefins with ketones, depending on reaction conditions. The reactions are reminiscent of the so-called SOMO-catalysis. Further studies towards the extension of these methods as well as an elucidation of their mechanisms are expected to be a major focus of our group's future research activities.

2.2.8 Research Area "Electrophilic Domino Rearrangements of Keteniminium Derivatives" (N. Maulide)

Involved: L. Carvalho, I. Jurberg, C. Madelaine, D. O'Donovan, B. Peng, D. Petkova, V. Valerio, M. Winzen

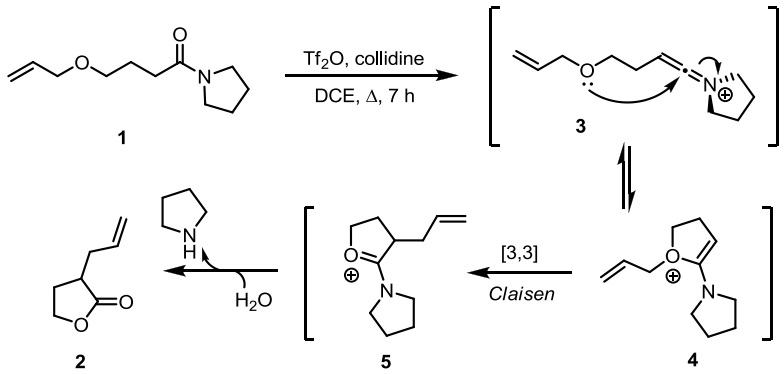
Objective: The selective activation of amides with suitable electrophilic reagents allows access to novel reactivity manifolds and opens up intriguing perspectives in synthesis. We have previously reported on the discovery of new pericyclic domino transformations of keteniminium salts generated *via* electrophilic activation of amides. Herein we report progress made since the original observations of 2009 and 2010.

Results: This area of research is predicated on our original observation that electrophilic activation of the γ-alkoxyamide **1** under the typical conditions for generation of an intermediate keteniminium salt (triflic anhydride and a base) did not lead to the anticipated [2+2] cycloadduct. Instead, we were surprised to observe the *exclusive* formation of α-allyl butyrolactone **2** (Scheme 1).



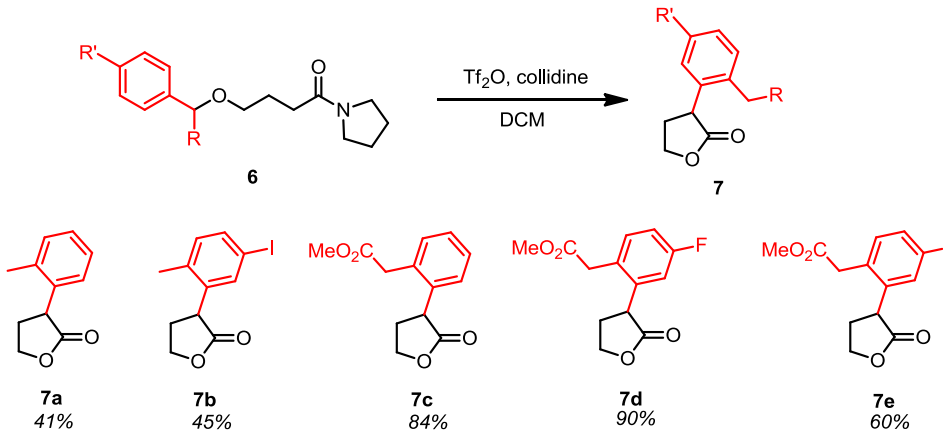
Scheme 1

Mechanistically (Scheme 2), we believe that after initial activation of the amide carbonyl by the electrophilic reagent, elimination to form keteniminium **3** probably takes place. The enhanced electrophilicity of this intermediate then triggers an unusual nucleophilic addition step. This generates a vinyl-allyl-oxonium **4** poised to undergo a [3,3]-sigmatropic rearrangement. Such a reorganization should lead to the stabilized carbenium ion **5**, hydrolysis of which then accounts for the formation of lactone **2**.



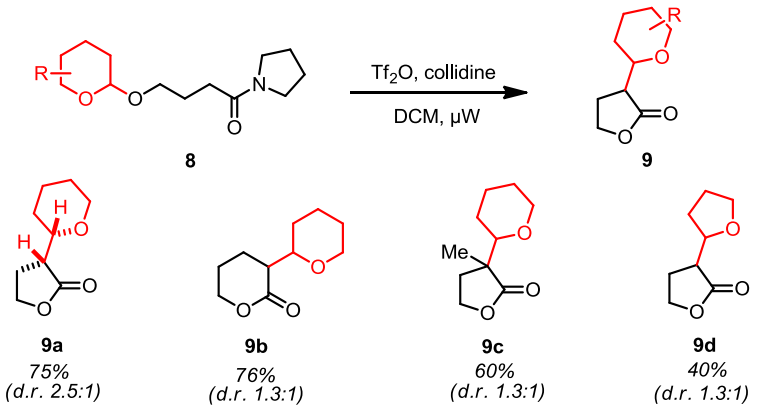
Scheme 2

In this reporting period, a "benzyl Claisen" rearrangement – a transformation that has been scarcely investigated prior to our work – was developed starting from readily available benzyl ether starting materials **6**. As depicted, ω-benzyloxyamides smoothly rearranged to α-arylated lactone products **7** in moderate to excellent yields (Scheme 3). Particularly interesting was the beneficial effect of an ester appendage at the benzylic position, leading to much improved yields of the products **7c-e**. This "metal-free" arylation process would later inspire us to explore related sulphur-based rearrangement sequences (cf. Section 2.2.10 – Sulfur area).

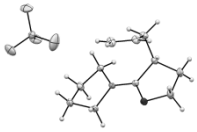


Scheme 3

In addition, we were also able to study an intriguing THF- and THP-migration from simple protected alcohols **8** into complex lactone products **9**. In this reaction (Scheme 4), an otherwise innocuous and benign protecting group actually functions as a reactive handle for a pivotal C–C bond forming transformation.



Scheme 4

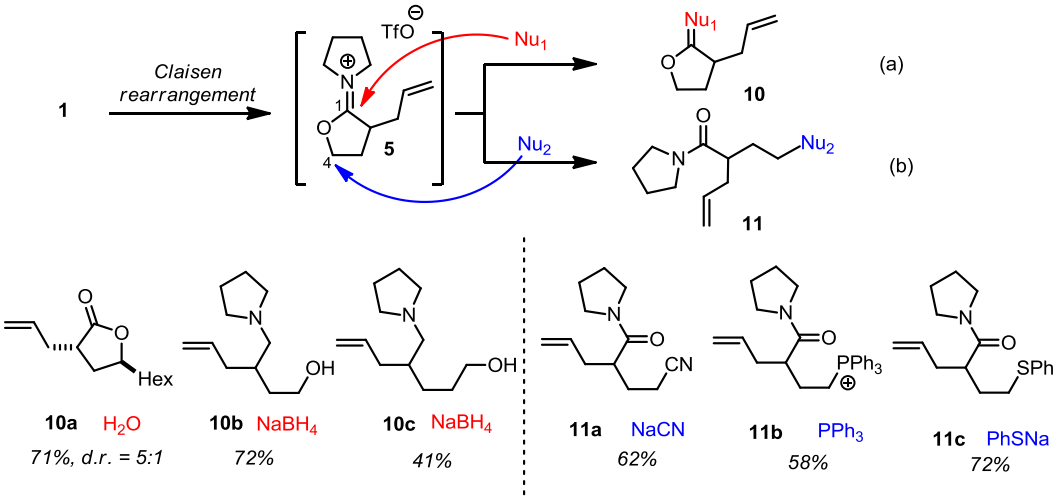


5.BF$_4$

Scheme 5

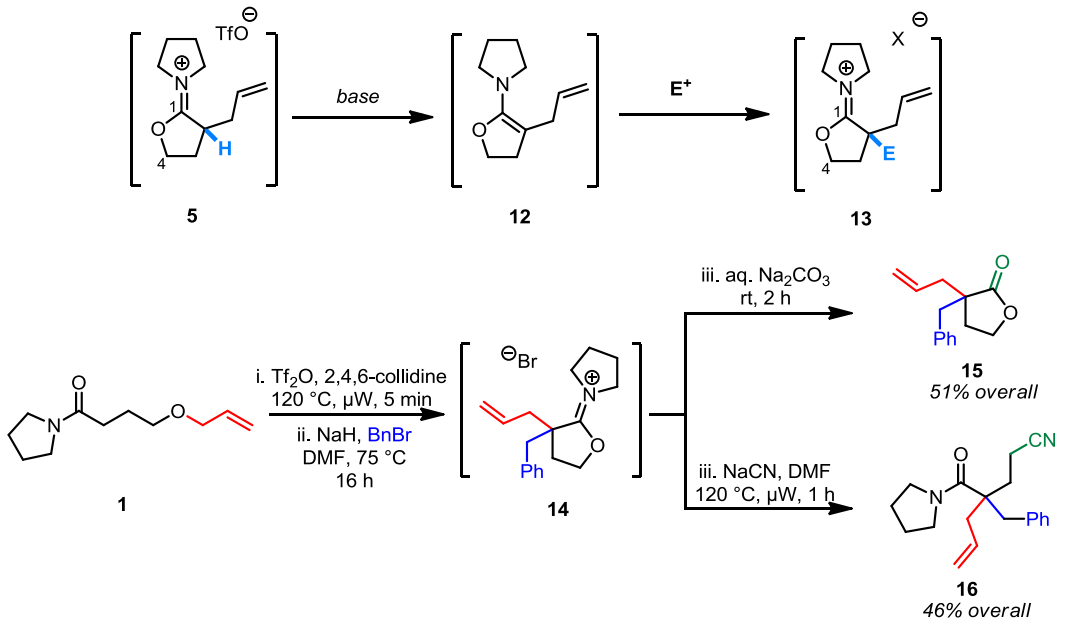
Further investigations on the original transformation revealed that, if the hydrolysis step is avoided, isolation of iminium ether **5** (as the BF_4 salt) is possible and its structure was unambiguously elucidated by single-crystal X-ray analysis (Scheme 5). This suggested opportunities for further functionalization.

We were guided by the recognition of **5**'s *a priori* ambident electrophilicity at either C_1 or C_4, the former being what had been realized through hydrolysis (formal addition of water at C_1, path a, Scheme 6). The range of products **10**/**11** available by realization of this concept has significantly expanded the utility of the original reaction.



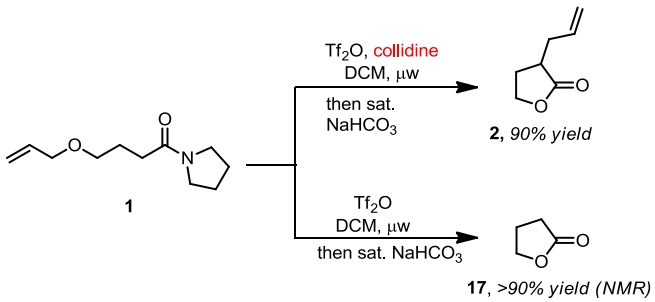
Scheme 6

We also acknowledged the intrinsic C–H acidity of intermediate **5** and speculated that it might lend itself to deprotonation and electrophilic capture (Scheme 7). The product of such a reaction would be the new iminium ether **13**, allowing us to achieve consecutive electrophilic/nucleophilic tandem functionalization sequences. The final products thus obtained are highly decorated derivatives showcasing the ability to achieve multiple (up to three), different C–C bond forming events in a one-pot manner through this process.



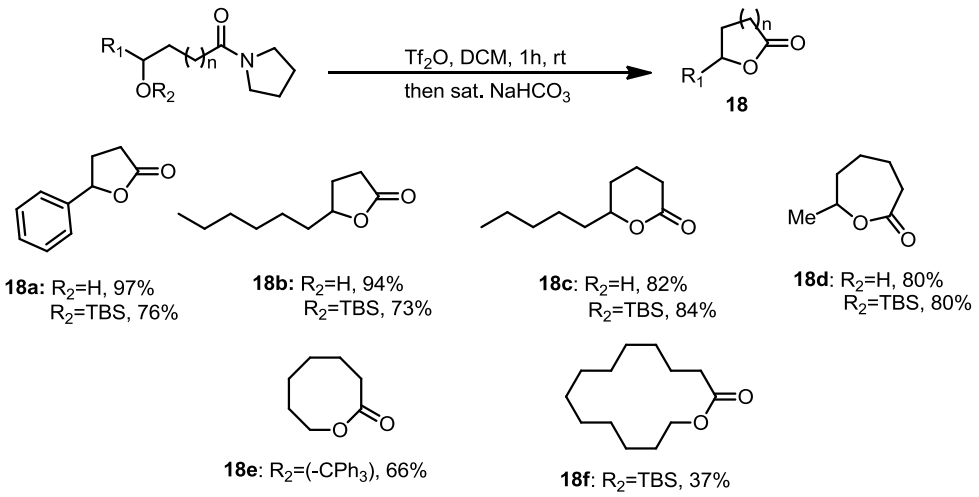
Scheme 7

Finally, we recently developed a novel methodology for direct lactonization of ethers and alcohols onto amides, hinging on our realization that the activation of amide **1** in the absence of a base smoothly led to unsubstituted lactone **17** as the single reaction product after hydrolysis (Scheme 8).



Scheme 8

Through this procedure, within 1 hour at room temperature rings as large as 14 members can be smoothly formed. Mechanistic studies support a pathway consisting of amide activation and intramolecular nucleophilic attack in the case of ether substrates. This direct lactonization allows the synthesis of lactones **18** from fully protected precursors without the need for individual deprotection steps, an advantage that could prove useful in the context of multistep target-oriented synthesis (Scheme 9).



Scheme 9

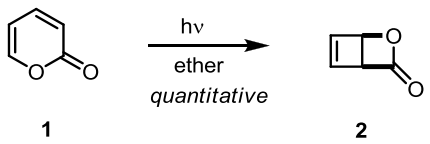
Continuously guided by intuition and serendipitous discovery, the developments described herein form a coherent approach to the synthesis of lactones in general. Future work will focus on broadening the scope of these methodologies and installing asymmetric variants that enable the preparation of optically enriched products in a traceless manner.[64]

2.2.9 Research Area "Catalytic Stereoselective Synthesis and Chemistry of Cyclobutenes" (N. Maulide)

Involved: L. G. Alves, D. Audisio, H. Faustino, F. Frébault, M. Luparia, A. Misale, S. Niyomchon, M. T. Oliveira, M. Padmanaban, C. Souris, E. Wöstefeld, L. Xie

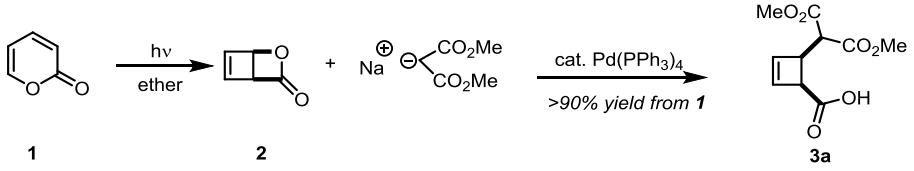
Objective: The preparation of small rings has been a pervasive topic in organic synthesis ever since chemists realized the potentialities and fascinating properties associated with their inherent ring strain. Nevertheless, there is a serious lack of general methodologies for the preparation of optically active functionalized cyclobutane and cyclobutene derivatives. This project aims at the development of a catalytic asymmetric synthesis of cyclobutene building blocks starting from 2-pyrone and the study of their chemistry.

Results: 2-Pyrone **1** is known to undergo photomediated isomerization to the unstable oxabicyclo[2.2.0]hexane **2** (Scheme 1). Historically, this reaction has been the subject of considerable scrutiny, since to date it still constitutes the surest path to the synthesis of the elusive anti-aromatic compound cyclobutadiene (*via* decarboxylation of **2**).



Scheme 1

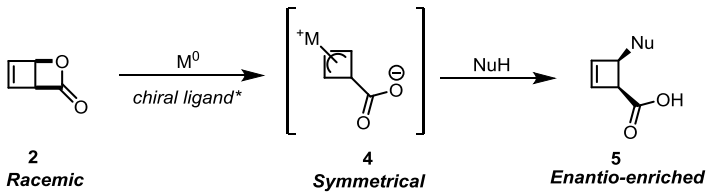
This project has its origins on our realization that compound **2** is, structurally, an allylic ester susceptible of ionization by a suitable zero-valent, electron-rich transition metal. We have previously achieved catalytic stereoselective transformations of **2** employing several nucleophiles, enabling a synthesis of functionalized cyclobutenes in only two operations from 2-pyrone (Scheme 2).



Scheme 2

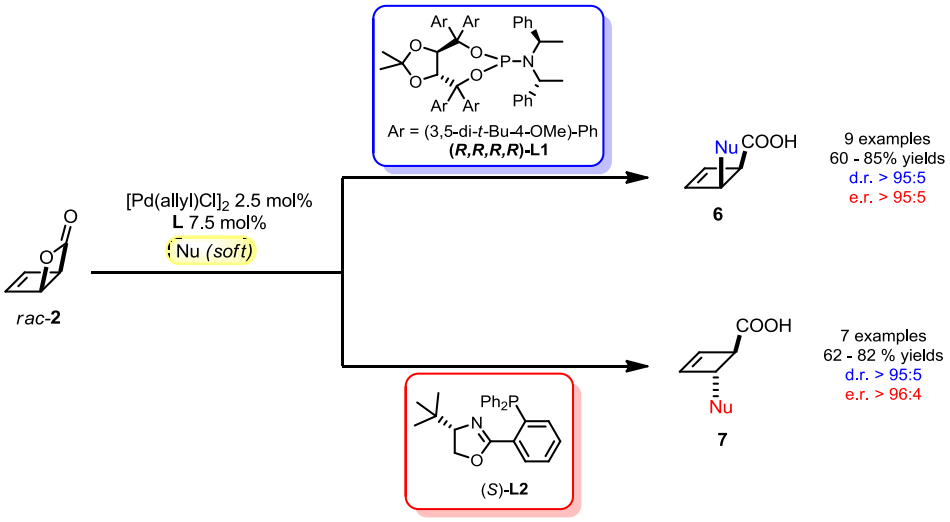
The translation of this chemistry to a catalytic asymmetric version offered opportunities to establish a deracemization process. Indeed, the putative allyl-metal complex **4** formed on interaction of lactone **2** with the palladium catalyst has a plane of symmetry that

effectively erases the stereochemical information contained in the (chiral) racemic starting material. By employing optically pure ligands, one could then envisage the re-inscription of chiral information upon nucleophilic attack and, thus, the obtention of >50% yields of optically enriched cyclobutene products **5** (Scheme 3).



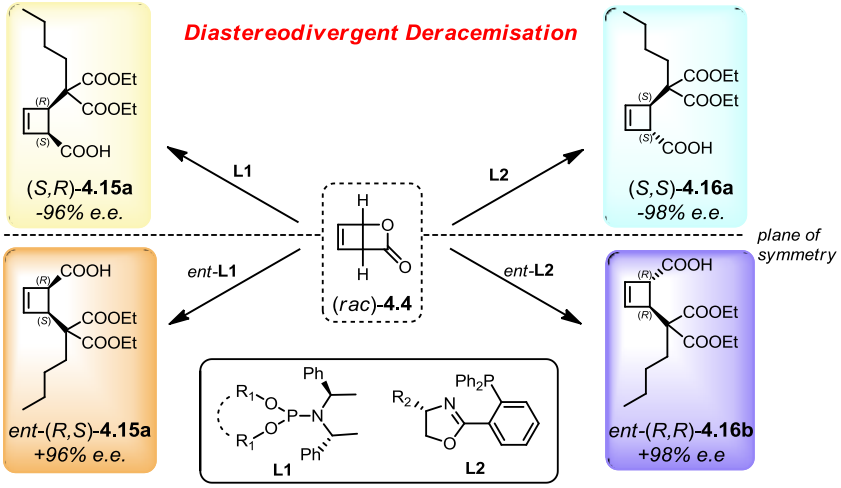
Scheme 3

The reduction of this plan to practice involved the comprehensive screening of a large library of chiral ligands and led to the serendipitous discovery of an unusual ligand-dependent stereochemical outcome. As shown in Scheme 4, phosphoramidites **L1** were highly effective in converting racemic lactone **2** into the *cis*-configured cyclobutene products **6**. The attainment of yields consistently above 50% with very high enantioselectivities confirmed the operation of a dynamic deracemization.



Scheme 4

To our surprise (Scheme 4), the ligand family typified by ligand **L2** proved to be selective for the opposite diastereoisomer, and produced the *trans*-disubstituted cyclobutenes in equally high yields and exquisite selectivities.

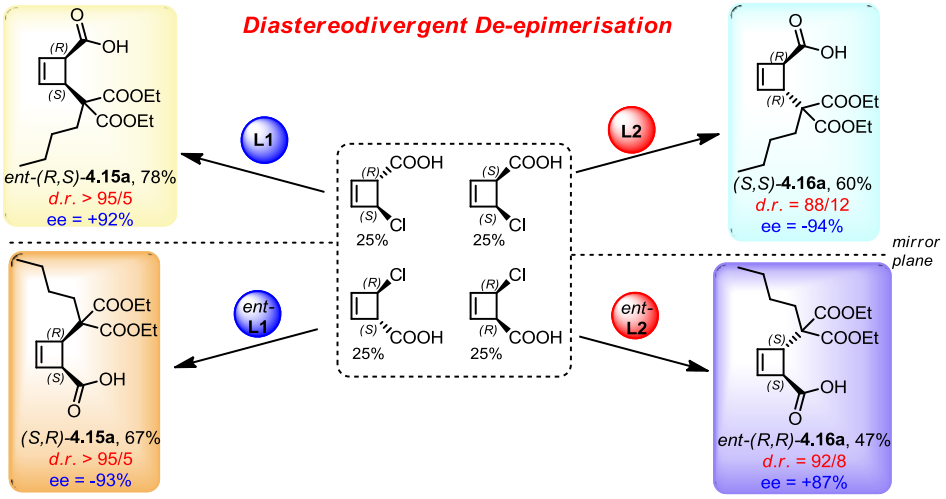


This novel phenomenon was termed "*Diastereodivergent Deracemization*".

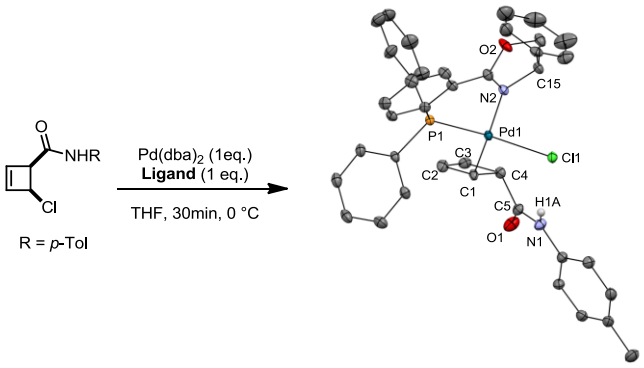
Scheme 5

Through this process, we have been able to convert a racemic substance bearing a number n ($n \geq 2$) of stereogenic centers into each and every one out of the 2^n stereoisomers of the product, at will and by simple modification of the chiral ligand employed, an unprecedented observation in allylic alkylation chemistry (Scheme 5).

Subsequently, we have extended this concept to the Deracemization of epimers, or De-epimerization. The "*Diastereodivergent De-epimerization*" portrayed in Scheme 6 is a novel type of transformation allowing the synthesis of diverse stereoisomers of the product regardless of the stereochemical information contained in the starting materials – a rare metal-catalysed asymmetric transformation that permits the use of diastereomeric mixtures of racemic compounds as substrates.



Scheme 6

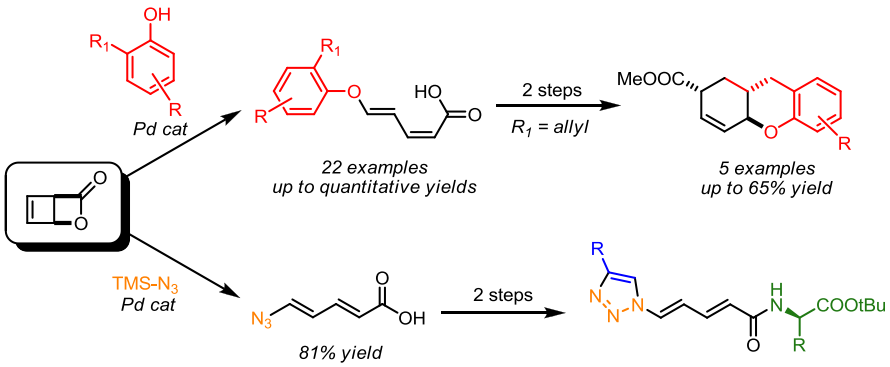


Scheme 7

More recently, we have uncovered several interesting structural features of this system. In this context, rare examples of cyclic σ-allyl palladium complexes were encountered and the first structural (X-ray) and reactivity studies of such species were reported (Scheme 7).

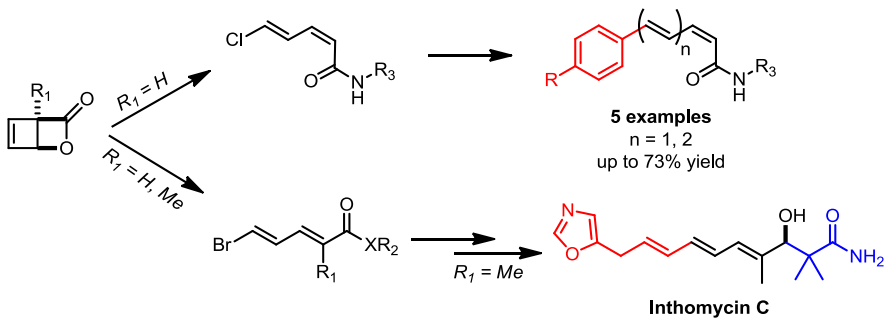
Asymmetric allylations of these and other cyclobutene electrophiles have also been realized.

In addition, we have exploited the potential of stereochemically defined cyclobutenes as starting materials for the synthesis of geometrically pure diene subunits. This has enabled us to prepare aryloxy- and azido-substituted dienes, interesting building blocks for synthetic and biological applications (Scheme 8).



Scheme 8

The use of halogenated cyclobutenes as starting materials enables the synthesis of versatile scaffolds for cross-coupling chemistry. This leads to applications in total synthesis of polyenic natural products, as exemplified with Inthomycin C (Scheme 9).



Scheme 9

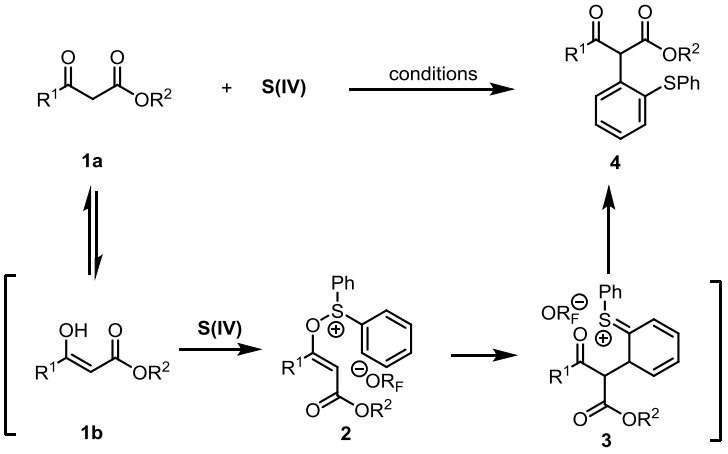
In summary, we have developed a novel catalytic asymmetric synthesis of cyclobutenes, leading to serendipitous discoveries of relevance to the field of asymmetric catalysis. We have thus developed a rare *Diastereodivergent Deracemization* and the first example of a *Diastereodivergent De-epimerization*. Mechanistic studies have revealed unprecedented structural features and additional research in this direction is in progress. Furthermore, the potential of cyclobutenes as starting materials for the preparation of dienes has just barely been tapped as we are currently pursuing further modular and concise applications in total synthesis.

2.2.10 Research Area "New Perspectives in Sulfur(IV) Chemistry" (N. Maulide)

Involved: L. Gomes, X. Huang, S. Klimczyk, F. Kulewei, M. Luparia, B. Peng, J. Sabbatani

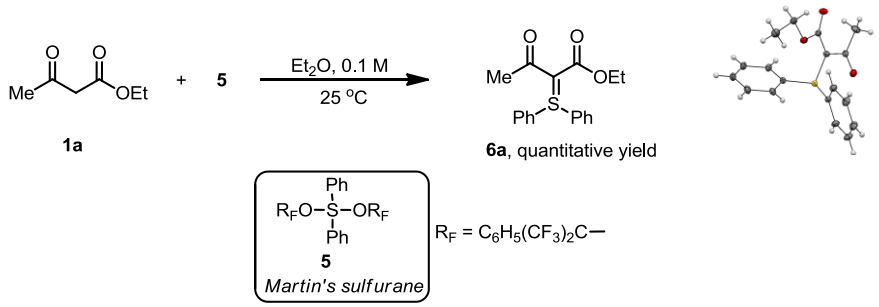
Objective: The aim of this project is the development of novel C–C bond forming transformations exploiting the unique properties of sulfur(IV) intermediates.

Results: Inspired by the Benzyl-Claisen transform developed in the Electrophilic Amide Activation project, we speculated that a carbonyl compound with a favorable enol content (such as β-ketoester **1a**) might be amenable to form a sulfonium-substituted intermediate **2** upon interaction with a suitable sulphur(IV) electrophile (depicted as **S(IV)** in Scheme 1). The vinylallyl ether moiety of **2** should then eventually rearrange into the α-arylated product **4** *via* the dearomatized intermediate **3**.



Scheme 1

This simple yet conceptually appealing hypothesis led us to select Martin's sulfurane **5** as a commercially available, suitable diphenylated sulphur(IV) electrophile and to perform the reaction depicted below. As shown in Scheme 2, admixing the β-ketoester **1a** with Martin's sulfurane **5** led to a single product in essentially quantitative yield – the sulfur ylide **6a**.

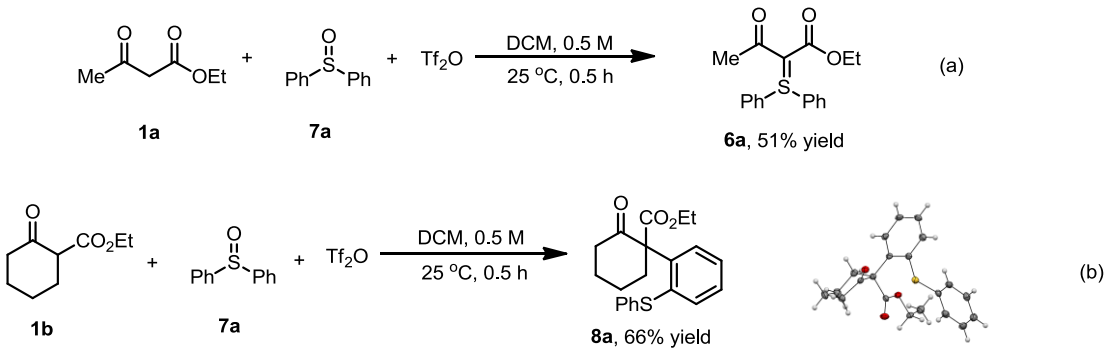


Scheme 2

This fortuitous observation paved the way for the development of a process we termed "ylide transfer", as already communicated in the previous progress report.

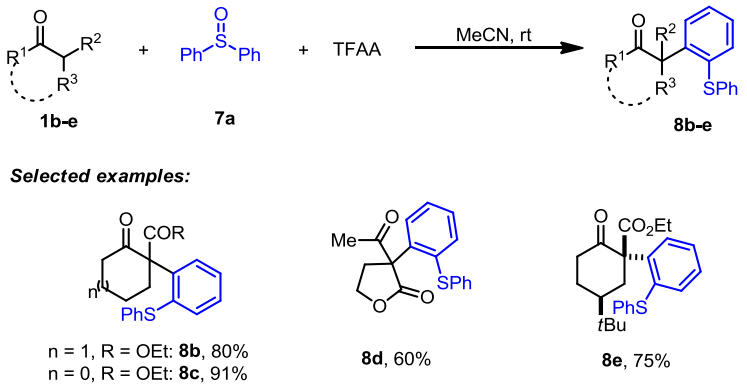
Several lateral observations made during this study prompted us to explore the ylide transfer reaction further. For one, the use of a substituted (cyclic) ketoester under various conditions resulted in the formation of multiple products with rapid consumption of sulfurane **5**. In addition, the relatively high cost of this sulfurane stimulated a search for surrogates.

Treatment of a mixture of ethyl acetoacetate **1a** and diphenyl sulfoxide **7a** with 2.0 equivalents of triflic anhydride led to the corresponding sulfonium ylide **6a** in moderate 51% isolated yield along with several additional, highly polar compounds (Scheme 3a). However, and to our surprise, when ethyl 2-oxocyclohexanecarboxylate **1b** was exposed to similar conditions, the α-arylated ketoester **8a** was isolated in 66% yield, and its structure was unambiguously confirmed by single-crystal X-ray analysis (Scheme 3b).



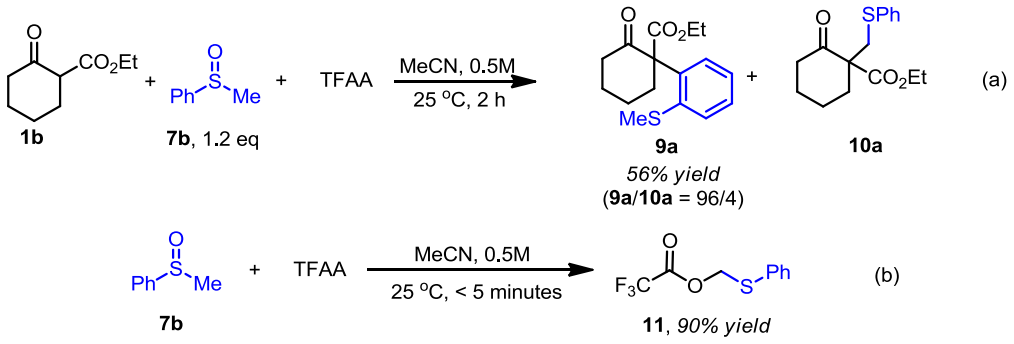
Scheme 3

In addition to six-membered cyclic β-ketoesters, various other active methylene compounds can be employed in this highly regio- and diastereoselective transformation (Scheme 4).



Scheme 4

Aryl alkylsulfoxides could also be employed as donors. The use of phenyl methyl sulfoxide **7b** led to arylated product **9a** as the major adduct of the reaction, together with traces of the "normal" Pummerer product **10a** detected in the reaction mixture (Scheme 5a).

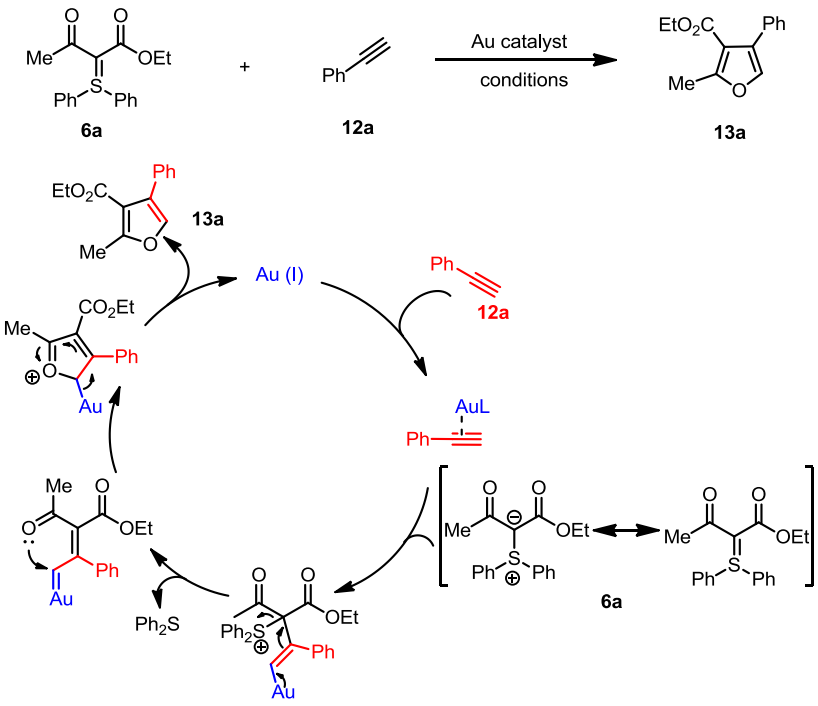


Scheme 5

This result is all the more noteworthy taking into account that exposure of sulfoxide **7b** to the action of TFAA *in the absence of nucleophile* almost instantaneously generates the trifluoroacetate **11** in very high yield (Scheme 5a). Clearly, the mechanism of these arylations is fundamentally different from the classical Pummerer reaction.

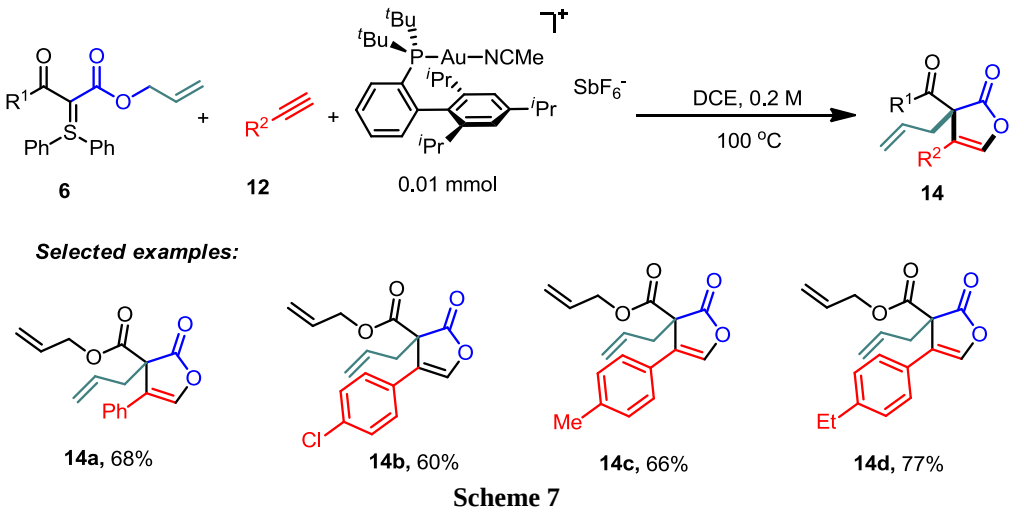
We recently discovered that the stable, easily handled ylide products prepared by our ylide transfer methodology can be activated in the presence of gold catalysts (Scheme

6). In particular, it is possible to perform a formal [3+2] cycloaddition of an ylide **6a** with alkynes such as phenylacetylene **12a**, leading to a trisubstituted furan **13a**.



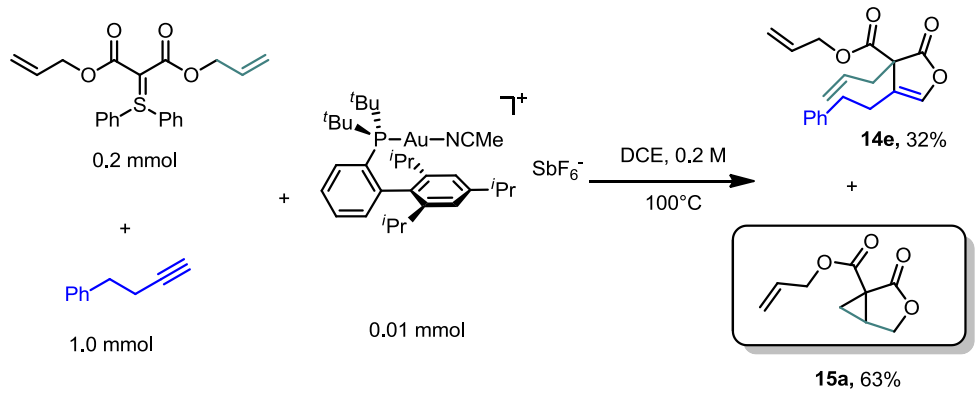
Scheme 6

We further realized that changing the ester moiety of the ylide partner to an allyloxycarbonyl group (as in **6**) induced a subsequent, consecutive rearrangement of the allyl residue, generating a furanone **14** bearing a quaternary center (Scheme 7). As shown, this reaction leads to 3 distinct bond-forming events (highlighted in bold typeset) and holds promise as a general method for preparation of such scaffolds.



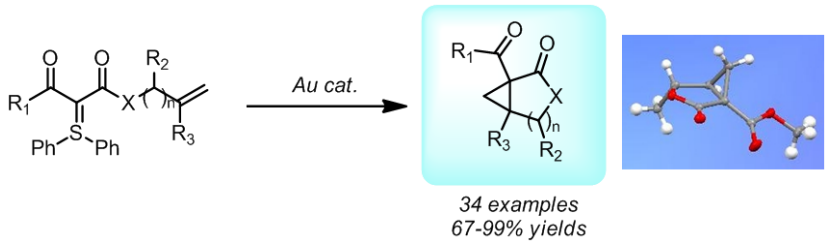
Scheme 7

During these studies, we made another serendipitous observation. As portrayed in Scheme 8, the use of less reactive aliphatic alkynes in the abovementioned furanone synthesis leads to a low yield of the product **14e** as well as an unforeseen by-product: the cyclopropane **15a**!



Scheme 8

Omitting the alkyne from the equation above led exclusively to cyclopropane **15a** in quantitative yield. This laid the ground for the development of an unusual gold-catalysed intramolecular cyclopropanation of sulfonium ylides (Scheme 9).



Scheme 9

Mechanistic studies revealed that this reaction is highly stereoselective and proceeds by an unconventional mechanism implying olefin activation rather than ylide decomposition to a metal carbene.

In summary, we have developed an ensemble of sulfur(IV)-mediated transformations that yield very diverse products (as are sulfonium ylides and α-arylated carbonyl derivatives), yet proceed by interconnected pathways. Subsequently, the unique structural features of the ylide products obtained were exploited in the context of gold-

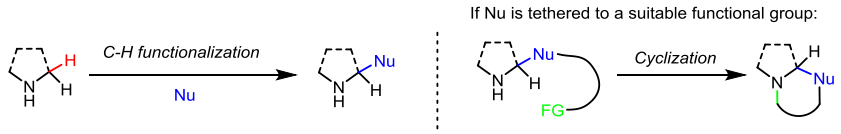
catalysed transformations. The transformations reported herein should find growing synthetic utility among the community.

2.2.11 Research Area "Redox-Neutral C–C bond forming reactions" (N. Maulide)

Involved: I. D. Jurberg, B. Peng, S. Shaaban, M. Wasserloos, E. Wöstefeld

Objective: The emergence of so-called "redox-neutral" transformations proceeding by intramolecular hydride shift processes has led to several intriguing developments. In this project, we aim to exploit the potential of hydride-shift C–H activation processes to achieve simultaneous, *intermolecular* bond formation en route to streamlined total syntheses of bioactive natural products.

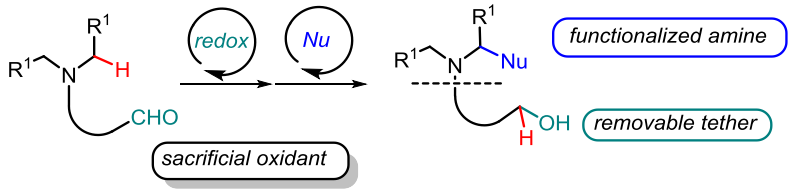
Results: C–H functionalization is an attractive strategy for the efficient and environmentally friendly preparation of organic compounds. We were particularly intrigued by the possibilities afforded through nucleophilic C–H functionalization α- to nitrogen (Scheme 1).



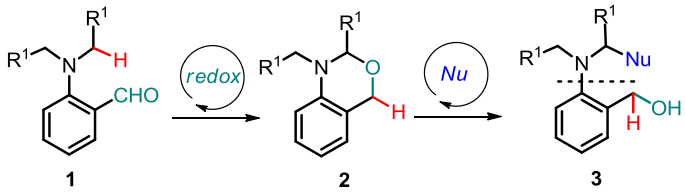
Scheme 1

As shown, judicious functionalization of nitrogen-containing heterocycles should allow the rapid assembly of bicyclic structures found in a plethora of naturally occurring alkaloids.

With this aim in mind, we designed a redox-neutral triggered C–C bond forming strategy. This concept would entail a two-stage sequence comprising redox isomerization and nucleophilic α-functionalization.



Scheme 2

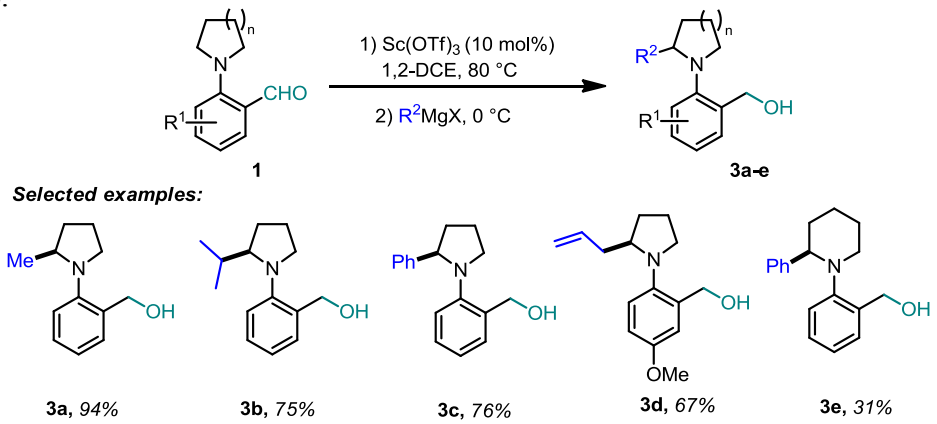


Scheme 3

The proof-of-principle validation of this concept was then designed on aryl-tethered aminoaldehydes such as **1** (Scheme 3).

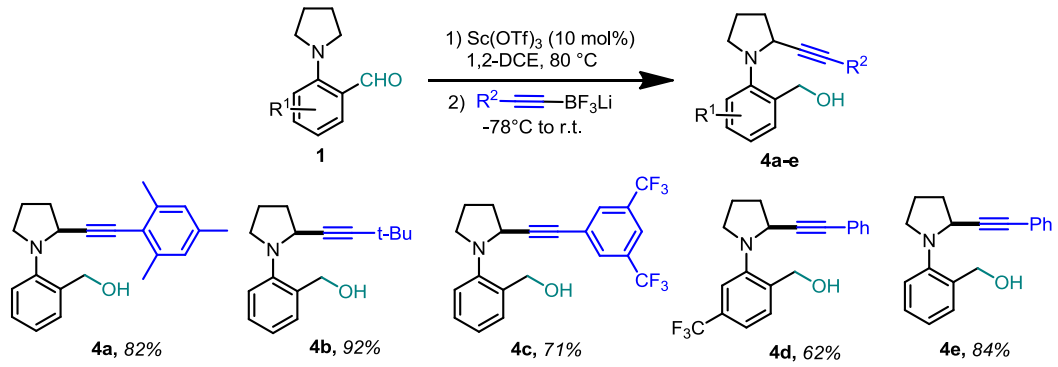
We realized that the intermediacy of benxozazine **2** would, in principle, enable the formation of α-functionalized products **3** through *in situ* nucleophilic addition.

After optimization, we established that the redox-neutral isomerization could be brought about by the action of a mild Lewis Acid, such as scandium(III) triflate. Direct addition of a Grignard reagent led to the functionalized products in moderate to excellent yield (Scheme 4).



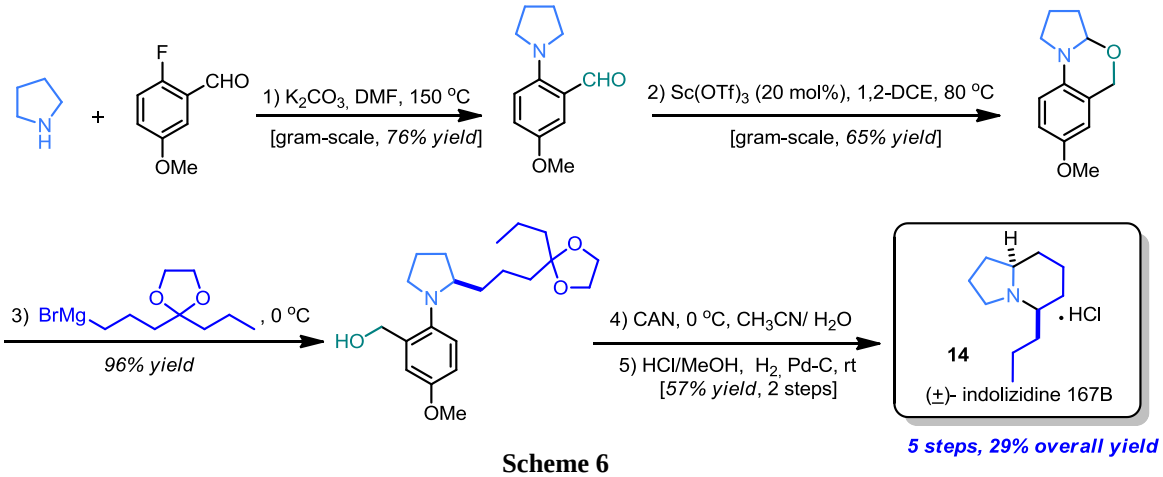
Scheme 4

Alternatively, the construction of sp–sp^3 bonds was also possible by addition of lithium alkynyltrifluoroborates as nucleophiles. The corresponding alkynylated products **4** were formed in a smooth and efficient manner (Scheme 5).



Scheme 5

This strategy was exploited in a short total synthesis of indolizidine 167B (Scheme 6). As depicted, the use of a dioxolanyl-functionalized nucleophile sets the stage for clean deprotection of the *p*-methoxy-substituted aromatic tether under oxidative conditions.



Scheme 6

Simple reductive amination under aqueous acidic conditions directly furnishes the natural product in only 5 steps from pyrrolidine (Scheme 6).

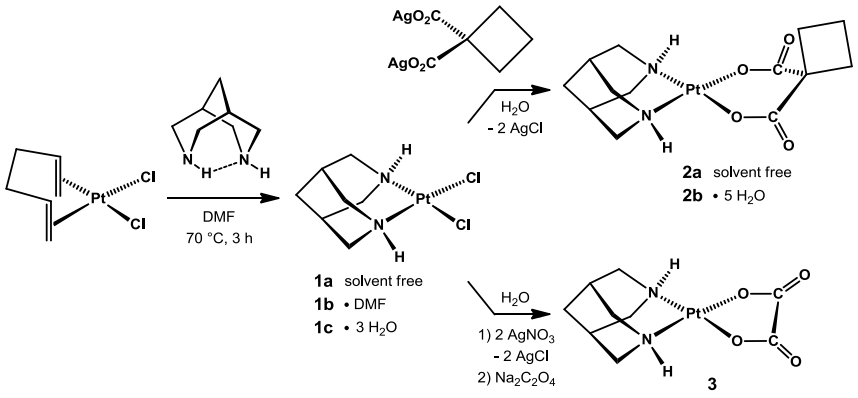
In summary, we have developed a novel approach to C–H functionalization relying on a Lewis-Acid catalysed redox-neutral isomerization. This method opens up interesting perspectives for the direct synthesis of naturally occurring alkaloids. Further steps towards advancing this strategy to asymmetric variants and exploring other redox-neutral transformations are currently underway.

2.2.12 Research area "Bispidine Analogs of Cisplatin, Carboplatin, and Oxaliplatin" (K.-R. Pörschke)

Involved: H. Cui, W. Gamrad, R. Goddard

Objective: Cisplatin is the leading antitumor drug. There are, however, substantial side-effects associated with its administration. Additional major problems are an inherent platinum resistance (esp., toward colon cancer) and the development of an acquired platinum resistance of refractory tumors. Related developments are carboplatin and oxaliplatin. Present research on platinum-based drugs is directed at the reduction of side-effects and the enlargement of the spectrum of activity. Since the parent bispidine (3,7-diazabicyclo[3.3.1]nonane) has become available to us from previous work, we have used it as a possible "carrier ligand" and synthesized the corresponding analogs of cisplatin, carboplatin, and oxaliplatin.

Results: Reaction of (1,5-hexadiene)$PtCl_2$ with bispidine ($C_7H_{14}N_2$) in DMF afforded large pale yellow crystals of the DMF adduct ($C_7H_{14}N_2$)$PtCl_2$·DMF (**1b**) in 87% yield. Recrystallization from the less basic *N*-methyl formamide gave solvent free ($C_7H_{14}N_2$)$PtCl_2$ (**1a**) and from water the trishydrate ($C_7H_{14}N_2$)$PtCl_2$·$3H_2O$ (**1c**) was obtained. Similarly, the Pt–bispidine analogs of carboplatin, both solvent-free ($C_7H_{14}N_2$)$Pt\{(O_2C)_2C_4H_6\}$ (**2a**) and the pentahydrate ($C_7H_{14}N_2$)$Pt\{(O_2C)_2C_4H_6\}$·$5H_2O$ (**2b**), and the analog of oxaliplatin, solvent-free ($C_7H_{14}N_2$)$Pt(C_2O_4)$ (**3**), were prepared.



Of particular interest are the structures of the hydrates **1c** and **2b**. In the solid chloride **1c** the complex molecules are linked by parallel N–H···Cl hydrogen bonds to give infinite bands, which are accompanied on both sides by zigzag-shaped strings of water molecules (Figure 1). In contrast, in crystals of the 1,1′-cyclobutanedicarboxylate **2b** the

complex molecules are monomeric and completely surrounded by a shell of water molecules, easily explaining the enhanced water solubility of this complex (Figure 2).

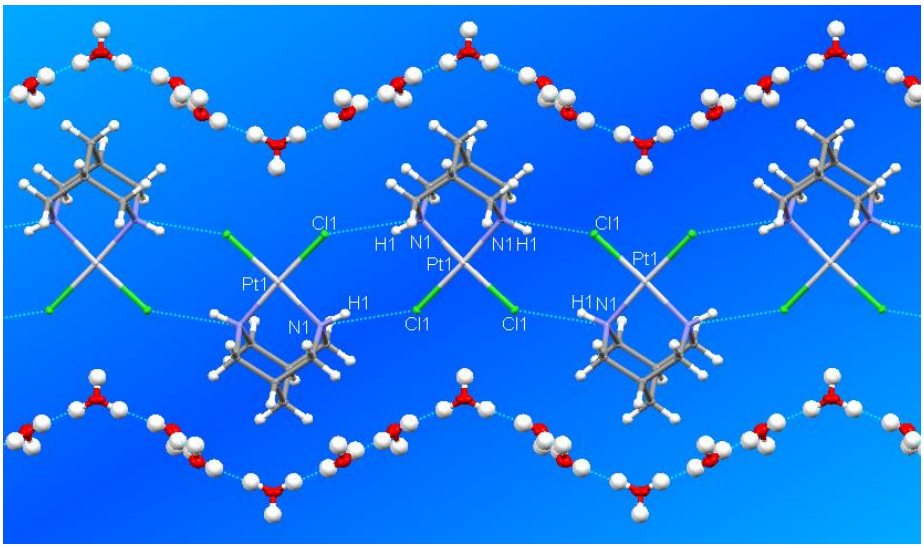


Figure 1. Crystal structure of $(C_7H_{14}N_2)PtCl_2 \cdot 3H_2O$ (**1c**).

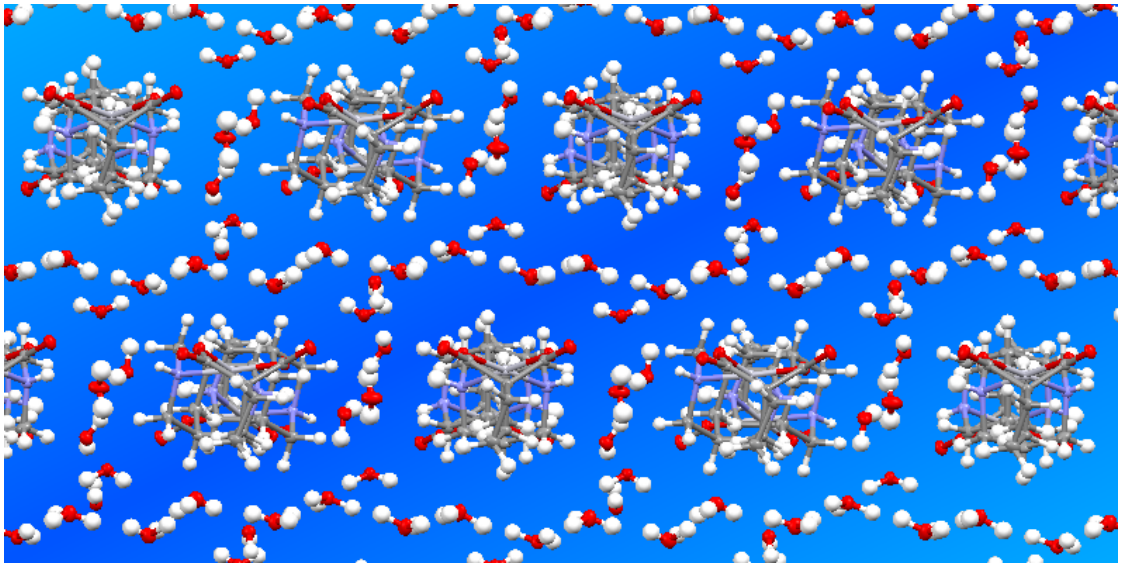
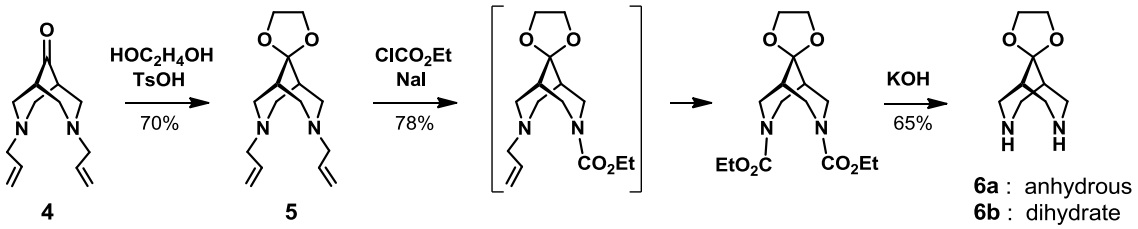


Figure 2. Crystal structure of $(C_7H_{14}N_2)Pt\{(O_2C)_2C_4H_6\} \cdot 5H_2O$ (**2b**).

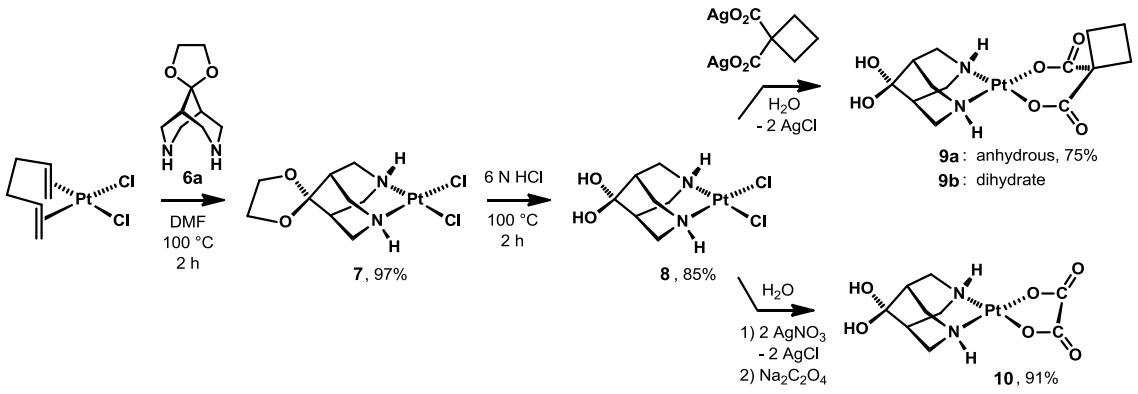
Cytotoxicity of **1**, **2**, and **3** was tested against human cancer cell lines K562 (chronic myeloid leukemia), A2780 (ovarian cancer), and its cisplatin-resistant subline A2780 CisR. All bispidine–Pt complexes showed significant cytotoxic activity in the μM range. While the cytotoxic potency compared to their parent analogs was somewhat reduced, except for **1** toward A2780 CisR, the resistance factor of **1** for A2780 and its subline

A2780 CisR was significantly smaller (more favorable) than for cisplatin. This appears relevant to the problem of platinum resistance and encourages further studies.

Subsequently, two hydroxy groups were introduced as substituents in 9-position of the bispidine to improve solubility. This was achieved by converting the bispidin-9-one **4** with glycol into spiro[3,7-diallylbispidin-9,2′-[1,3]dioxolane] (**5**) and cleavage of the substituents at N to give crystalline spiro[bispidin-9,2′-[1,3]dioxolane] dihydrate (**6b**), which was dehydrated to anhydrous crystalline **6a**.



The ketal **6a** was reacted with (1,5-hexadiene)$PtCl_2$ to form water-insoluble **7**, which excludes its application as a possible antitumor drug. Hydrolytic cleavage of the glycolic protecting group in **7** gave yellow needles of anhydrous (bispidin-9,9-diol)-platinum(II)dichloride (**8**) which dissolves moderately in water. From **8** the carboplatin derivative **9a**, forming dihydrate **9b**, and the oxaliplatin derivative **10** are accessible.



In the crystal, the molecules of **8** are pairwise associated by twofold OH···O* hydrogen bonds between the geminal diol groups (Figure 3). These dimeric entities are further associated by hydrogen bonds to form infinite strands. A similar association is found in crystals of the dihydrate **9b**, whose water molecules are clustered in pockets (Figure 4).

While **10** is virtually insoluble in water, precluding biological studies, the possible anticancer potency of **8** and **9b** is presently under investigation.

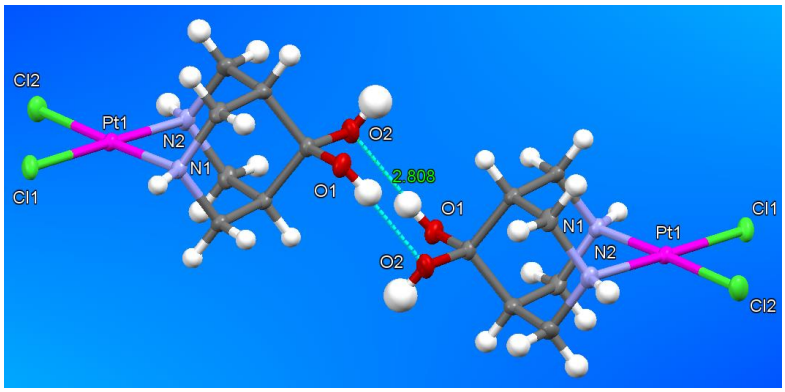


Figure 3. Crystal structure of $\{(HO)_2C_7H_{10}(NH)_2\}PtCl_2$ (**8**)
(shown is the dimerization *via* twofold OH···O* hydrogen bonds).

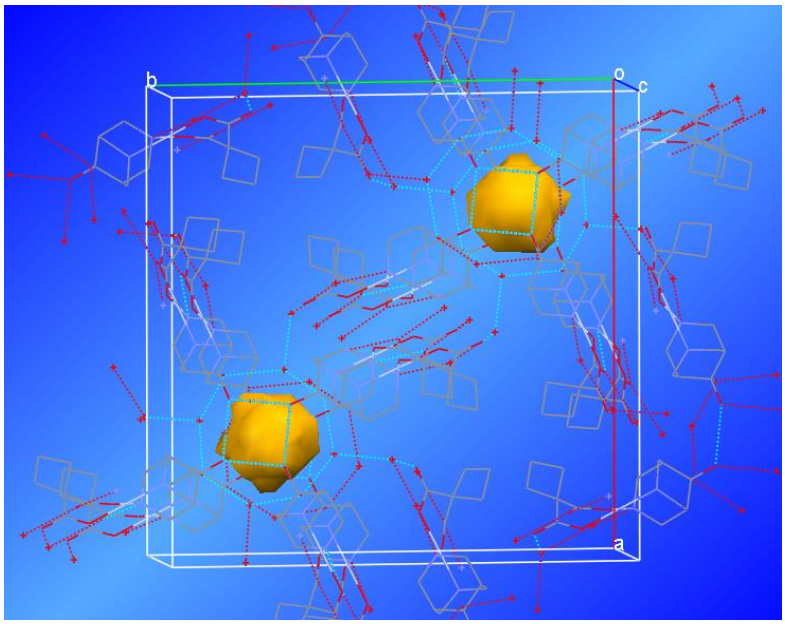


Figure 4. Crystal structure of $\{(HO)_2C_7H_{10}(NH)_2\}Pt\{(O_2C)_2C_4H_6\}\cdot 2H_2O$ (**9b**)
(shown is the association of complex molecules around the water pockets).

2.2.13 Research area "Structure and Solubility of 4-Oxopiperidinium Salts" (K.-R. Pörschke)

Involved: A. Dreier, W. Gamrad, R. Goddard

Objective: 9-Bispidinone, which contains two fused 4-piperidone rings, easily undergoes hydration to form 9,9-bispidindiol. In order to better understand this ketone hydration, we turned our attention to "4-piperidinone hydrate hydrochloride", which is a chemical feedstock in the pharmaceutical industry. We anticipated that this compound is actually 4,4-dihydroxypiperidinium chloride and became interested in the factors which render this quite simple geminal diol stable.

Results: Commercial "4-piperidinone hydrate hydrochloride" (**A**) is extremely soluble in water, but insoluble in all organic solvents. From DMF/water or acetone/water mixtures single-crystals of **A** have been obtained. X-ray structure analysis proved **A** to be 4,4-dihydroxypiperidinium chloride in which the cations are fourfold NH···Cl and OH···Cl hydrogen bonded to chloride anions in a 3D network (Figure 1). Dehydration with $SOCl_2$ afforded the ketone 4-oxopiperidinium chloride (**B**), which gave single-crystals from anhydrous DMF. Crystalline **B** forms infinite double-strands of molecules which are associated *via* NH···Cl···HN bridges, whereas the keto functions are not involved (Figure 2). Solid **B** is strongly hygroscopic and the hydration reaction **B**→**A** of the single-crystals can be followed under a microscope in a short time. Intriguingly, in a solution of either **A** or **B** in pure water (where chloride becomes hydrated) the ketone is only partially hydrated to give an about 9:1 geminal-diol/ketone mixture. This indicates that it is essentially the OH···Cl hydrogen bonds which stabilize crystalline **A**.

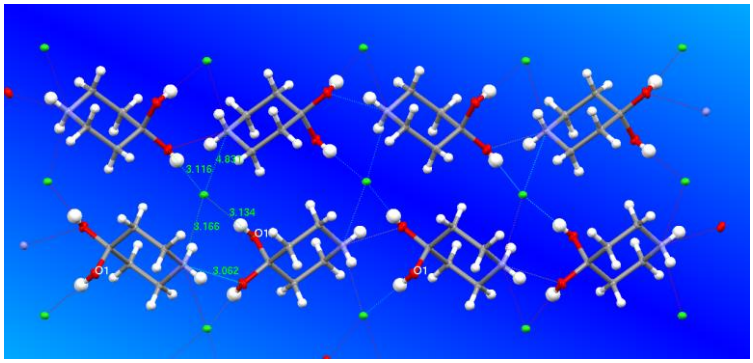


Figure 1. 3D-Structure of the diol **A**.

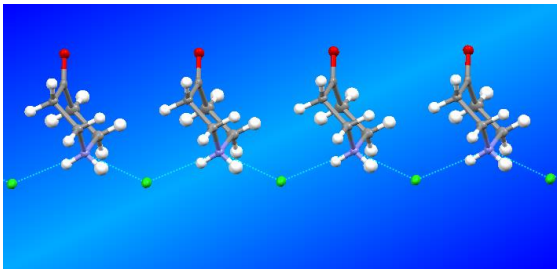


Figure 2. Linear association of the ketone **B**.

By anion exchange the 4-oxopiperidinium salts $[(O=)C_5H_8NH_2]X$ with weakly coordinating anions X = BF_4, ClO_4, OTf, and NTf_2 have been prepared. These solids are non-hygroscopic and their properties in aqueous solution are the same as for **A** and **B**. For $[(O=)C_5H_8NH_2]$OTf (**C**) and $[(O=)C_5H_8NH_2]NTf_2$ (**D**) chain structures similar to that of **B** have been determined. Thus, in these compounds the anions X bridge the ammonium groups by acting as "hydrogen bond acceptors" toward the ammonium protons (NH···X hydrogen bonds). The anions are apparently not basic enough to stabilize also the corresponding geminal diols by OH···X hydrogen bonds, which therefore are not formed.

The anion X = $Al\{OC(CF_3)_3\}_4$ is even less basic. When the anion exchange is carried out in either diethyl ether or CH_2Cl_2 as a solvent, the solute complexes $[(O=)C_5H_8NH_2(OEt_2)_2][Al\{OC(CF_3)_3\}_4]$ (**E**) and $[(O=)C_5H_8NH_2(CH_2Cl_2)]$-$[Al\{OC(CF_3)_3\}_4]$ (**F**) can be crystallized. The cocrystals of **E** consists of separate cations and aluminate anions, and two ether molecules are bound to the ammonium group *via* NH···O(ether) hydrogen bonds. Interestingly, pairs of piperidinium cations appear to be stabilized by N–CH···O(ketone) hydrogen bonds (Figure 3).

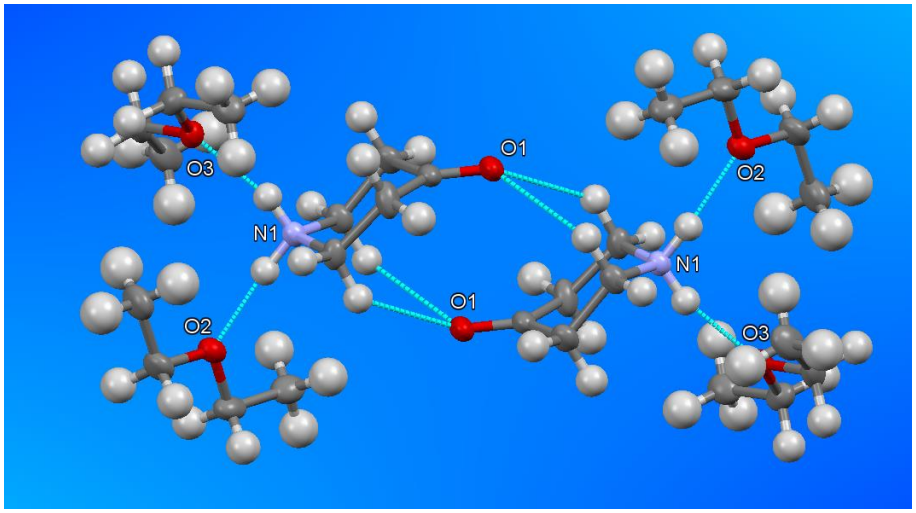


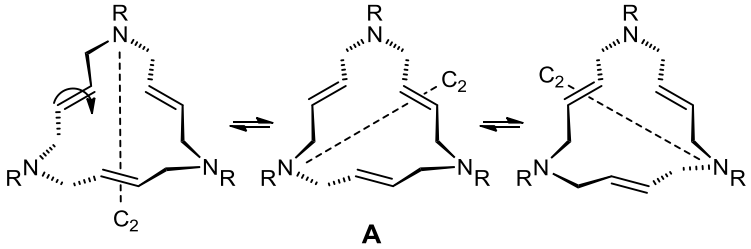
Figure 3. Structure of the piperidinium bis(etherate) **E** (shown are two cations).

2.2.14 Research area "Ni(0) Complexes of Polyunsaturated Aza Ligands" (K.-R. Pörschke)

Involved: W. Gamrad, R. Goddard

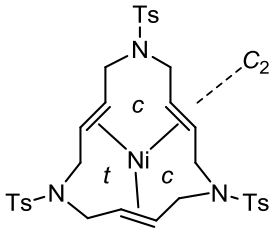
Objective: There is an enduring interest in zero-valent Ni(0), Pd(0), and Pt(0) complexes, since these are active precursor complexes for catalytic reactions. While typical ligands (e.g. COD) have ene functions in 1,5-sequence, we have studied cyclic and acyclic polyunsaturated aza molecules having two ene and one yne function in 1,6,11-sequences and used them as ligands for nickel(0). Mixing alkene and alkyne functions will introduce different carbon hybridization states into the ligands and should induce different conformations of the chain, together with associated variable donor–acceptor properties. A detailed conformational analysis was performed on the resulting product complexes.

Results: In the first part of the project (*E*,*E*,*E*)-1,6,11-tris(4-tosyl)-1,6,11-triazacyclopentadeca-3,8,13-triene (**A**) was coordinated to Ni(0), supplementing previous studies for Pd(0) and Pt(0) by A. Roglans. The structure of the uncoordinated macrocycle **A** can be thought of as (idealized) C_2-symmetrical, with the C_2-axis passing through the center of one C=C bond and the opposite N-atom. The NMR spectra indicate rotations of the C=C moieties about their vinylic C–C bonds, resulting in 60° jumps of the C_2-axis.



A

When **A** is coordinated to a metal center such as Ni(0), rotations about the vinylic C–C bonds are no longer possible. The triazacyclotriene ligand in **B** forms three formal azanickelacyclohexanic rings with the metal in a chair–chair–twist (c,c,t) conformational combination, resulting in an overall rigid C_2 symmetrical structure and the presence of a pair of enantiomers.



B

Reacting (*E,E*)-1,6,11-tris(4-tosyl)-1,6,11-triazacyclopentadeca-3,8-diene-13-yne (**C**) with Ni(0) affords mononuclear **D**, which can accept a further Ni(0) to give the dinuclear **E**. The structure of **D** is C_S-symmetrical and resembles a chair, with the 15-membered ring providing the seat, the two tosyl groups at $NCH_2C{\equiv}CCH_2N$ representing the front legs, and the other tosyl group forming the back rest (Figure 1).

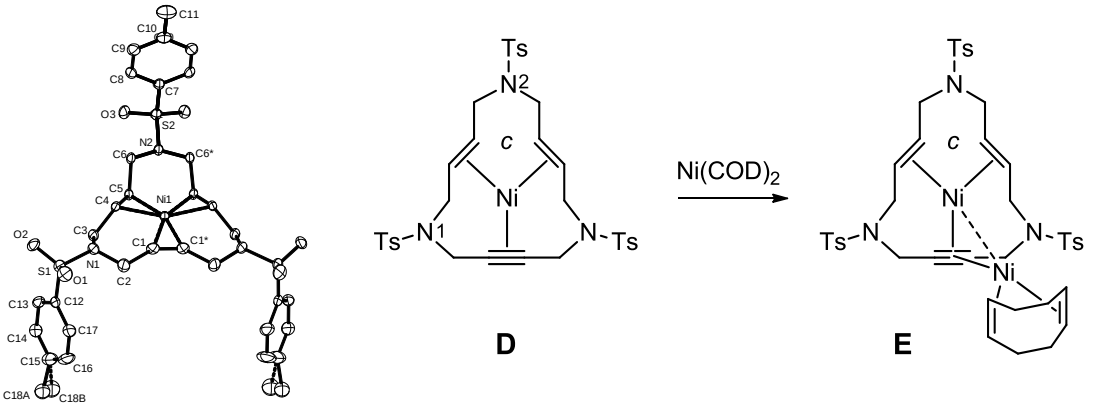
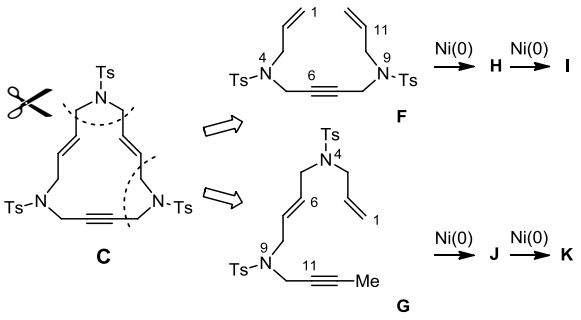


Figure 1. Structure of **D**.

Isolation of **D** and **E** raised the question as to how the structure and properties of these complexes are affected by replacing the cyclic ligand by *acyclic* analogs. Formal excision of a $CH_2N(TS)CH_2$ entity can occur at two sites to give ligands **F** and **G**, for which complexes **H–K** have been synthesized.



Complex **H** shows a C_2-symmetrical structure and packs in parallel columns, made up of identical C_2 symmetrical molecules having the same chirality and orientation (Figure 2). These are stacked such that the phenyl groups of adjacent molecules lie almost parallel to one another. The dinuclear **K** (Figure 3) crystallizes in well-formed spherulites (Figure 4).

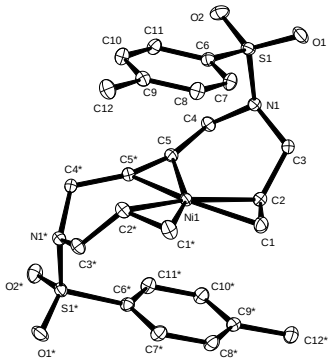


Figure 2. Structure of **H**.

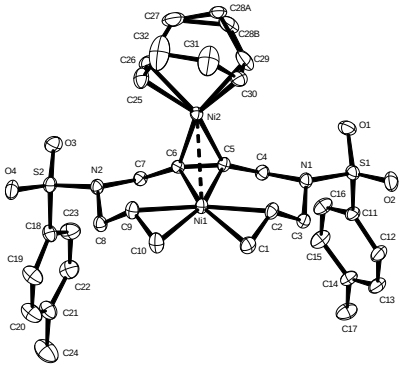


Figure 3. Structure of **K**.

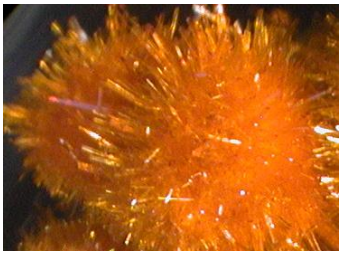


Figure 4. Spherulites of **K**.

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