2.2 Department of Homogeneous Catalysis

Director:

Benjamin List (born 1968)

Further group leaders:

Martin Klußmann (born 1974)

Bill Morandi (born 1983)

Klaus-Richard Pörschke (born 1949)
until March 2016

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
2012-2014	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
2014	Arthur C. Cope Scholar Award, USA
2014	Thomson Reuters Highly Cited Researcher Prize
2015	Carl Shipp Marvel Lectures in Organic Chemistry of Illinois
2016	Gottfried Wilhelm Leibniz-Prize
1999-2016	ca. 250 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*

2015- Editor in Chief of *Synlett* (Thieme)

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 and new catalytic reactions, expand the substrate scope of other catalytic transformations, 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, B. Morandi).

During the last three years, the department grew again noticeably, mainly due to the formation of the group of Bill Morandi comprising now thirteen co-workers. During the evaluation period between 2014 and 2016, 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 and retired in 2016, by Dr. M. Klußmann, who has been a group leader here since 2007, and of Dr. B. Morandi, who has joined the department in 2014.

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, provided the proof of concept, and then significantly advanced “asymmetric counteranion directed catalysis” (ACDC). Initially merely an idea, this approach has progressed within the department, but now also at many other institutions around the globe, into a truly general strategy for highly enantioselective 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.

Professor Pörschke has a longstanding expertise in the coordination and catalytic chemistry of Ni, Pd, and Pt, which often have been used in combination with main

group metal compounds (Li, Mg, Al, Ge, Sn). During the last decade, additional lines of research came into focus, such as Organometallic Plastic Crystals (OMPCs) of Ni, Co, Rh, and Ir, and bispidine-modified cisplatin-related Pt complexes as potential cytostatic compounds. Most recently, the group has discovered a process (in several variations) which allows cesium and rubidium to be separated quantitatively and with 100% selectivity from about any given source. Publications on this topic are forthcoming.

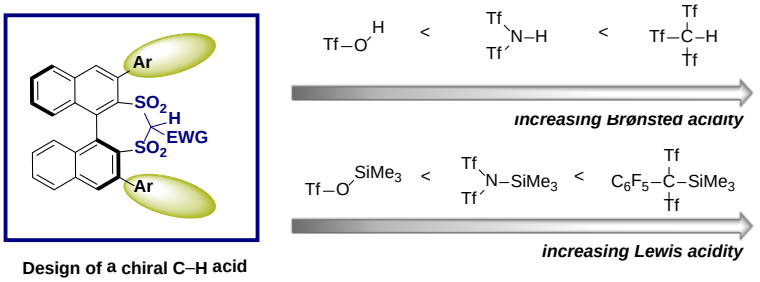
The group of **Dr. Klußmann** is developing novel synthetic methods and investigating reaction mechanisms in homogeneous catalysis, with an emphasis on oxidative methods for the functionalization of C-H bonds. Such reactions hold a great potential for sustainable chemistry, yet their mechanisms are often poorly understood. The mechanistic studies in the group thus aim at uncovering novel reactivities, understanding fundamental principles and providing inspiration for new applications.

The group of **Dr. Morandi** was established in 2014 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 design of novel catalytic reactions for the efficient and sustainable transformation of widely available starting materials. Among other projects, the group has already pioneered three different major areas: (1) the conceptualization of “shuttle catalysis” and its application to HCN-free reversible transfer hydrocyanation; (2) the invention of selective approaches to the defunctionalization of polyols; (3) the development of catalytic amination methods for the direct preparation of unprotected primary amines. As a result, several awards have been given to Bill Morandi.

2.2.1 Research Area "C–H Acids for Organic Synthesis" (B. List)

Involved: T. Gatzenmeier, D. Höfler, M. Leutzsch, M. van Gemmeren, Y. Xie, P. Wedemann

Objective: Despite the recent success in enantioselective catalysis with chiral Brønsted acids and Lewis acids, many unreactive substrate classes, such as unsaturated esters, remained out of reach for reasons of insufficient catalyst activity. Based on the well-established acidity trends for Brønsted and Lewis acids (Scheme 1), we proposed the design and synthesis of novel catalysts, whose enhanced activity would rely on a highly acidified C–H bond. The aim of this project is to establish C–H acids as a novel, highly acidic catalyst class. We introduce tetrasulfonyl propenes as a new motif for organocatalysis.

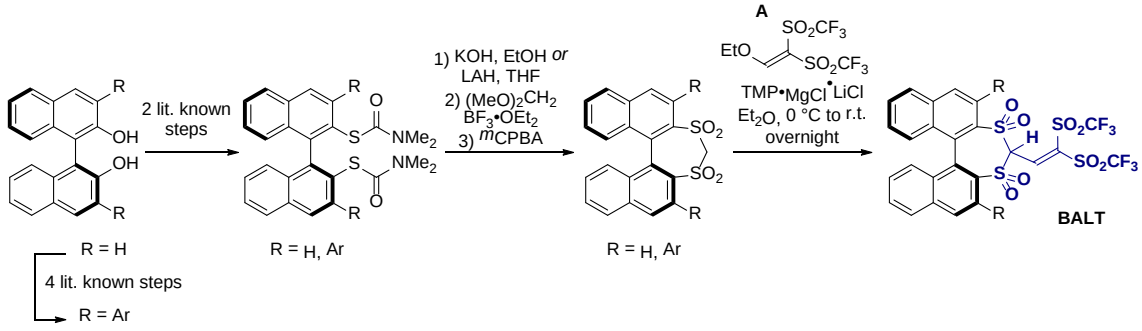


Scheme 1. Design of a chiral C–H acid catalyst (left); trend of Brønsted and Lewis acidities on triflated center-atoms (right).

Results:

A) BINOL-Derived Chiral C–H Acids

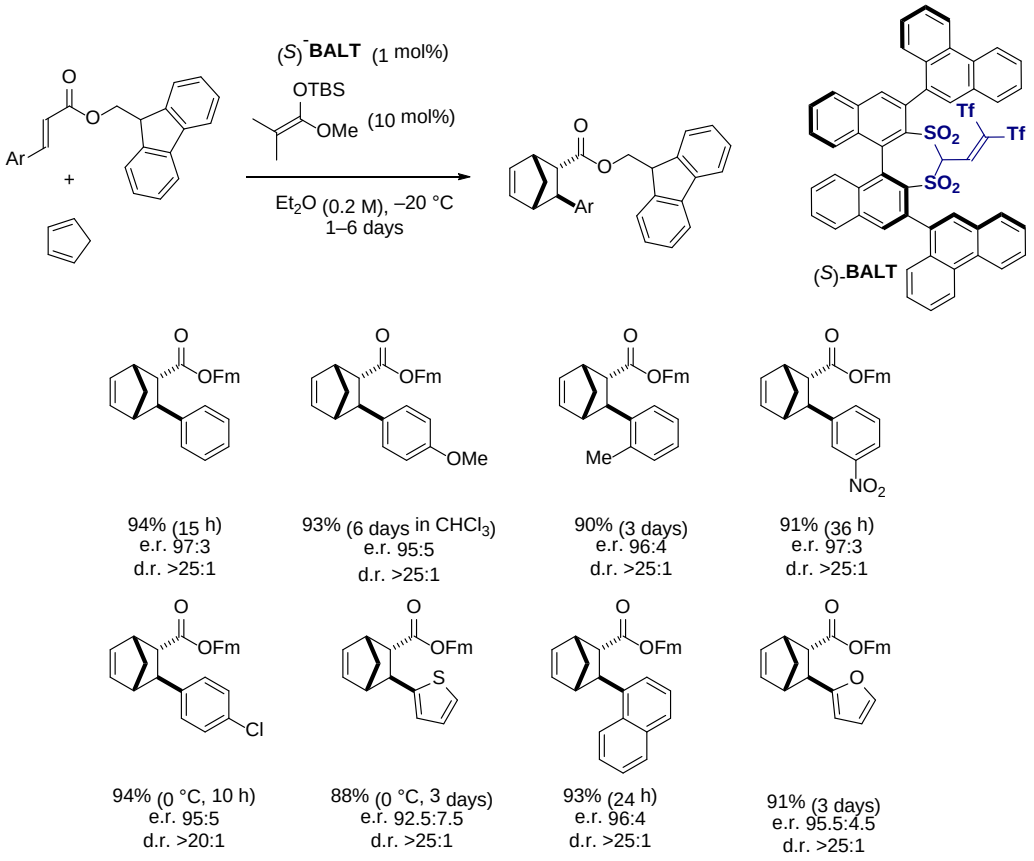
Based on the rationale of acidifying the C–H bond with electron-withdrawing groups, preferentially triflyl groups, a variety of chiral C–H acid catalysts have been designed, synthesized and tested. The first chiral C–H acid catalysts with stronger acidity than disulfonimides were obtained from 3,3'-substituted BINOL-derived disulfones and bistriflyl vinyl enol **A**.



Scheme 2. Synthetic strategy for novel chiral C–H acids.

These binaphthyl-allyl-tetrasulfones (BALTs) show very high activities, both in Brønsted and Lewis acid-catalyzed reactions. Upon silylation the newly developed C–H

acids become extremely active Lewis acid catalysts for highly enantioselective Diels–Alder reactions of cinnamates with cyclopentadiene. The reaction of various 9-fluoroenylmethyl cinnamates and cyclopentadiene gave very high yields and excellent enantioselectivities using only 1 mol% catalyst loading and a catalytic amount of a silyl ketene acetal.



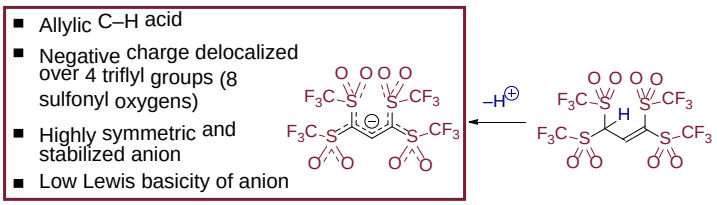
Scheme 3. Asymmetric Diels–Alder reaction of cinnamates and cyclopentadiene (Fm: 9-fluoroenylmethyl).

While many other chiral Lewis acids have previously been developed and applied in enantioselective Diels–Alder reactions, unactivated cinnamates had long remained a very challenging substrate class. Our work is the first example of this transformation and the first asymmetric counteranion-directed catalytic Diels–Alder reaction.

B) 1,1,3,3-Tetratriflylpropene (TTP) in Brønsted and Lewis Acid Catalysis

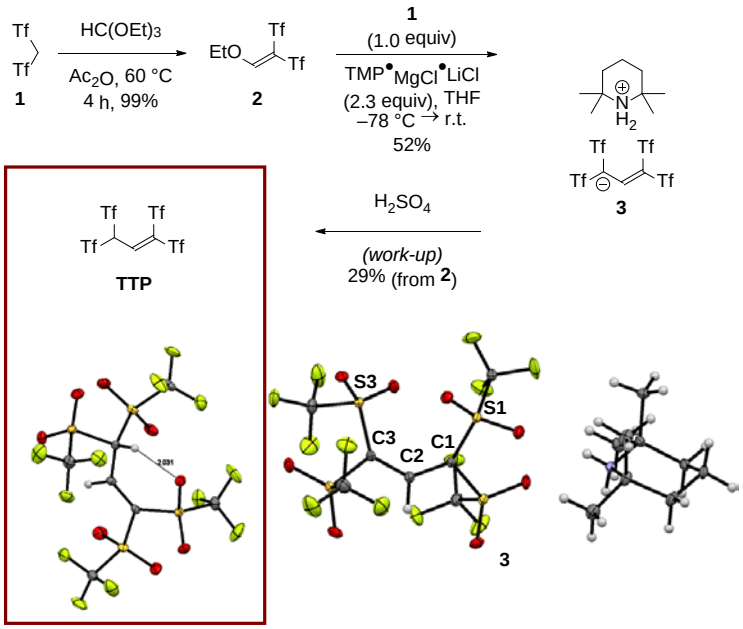
We also focused on the development of achiral, allylic C–H acids with increased acidity. Substituting the rather electron-rich binaphthyl backbone of chiral C–H acids with two triflyl groups was expected to lead to a dramatic increase in acidity as four

equally strong electron-withdrawing groups should provide a highly stabilized, symmetric anion. These considerations led to the design and development of 1,1,3,3-tetratriflylpropene (**TTP**, Scheme 4) whose activity was closely compared to other strong, structurally related organic Brønsted and Lewis acids.



Scheme 4. Design of tetratriflylpropene (**TTP**).

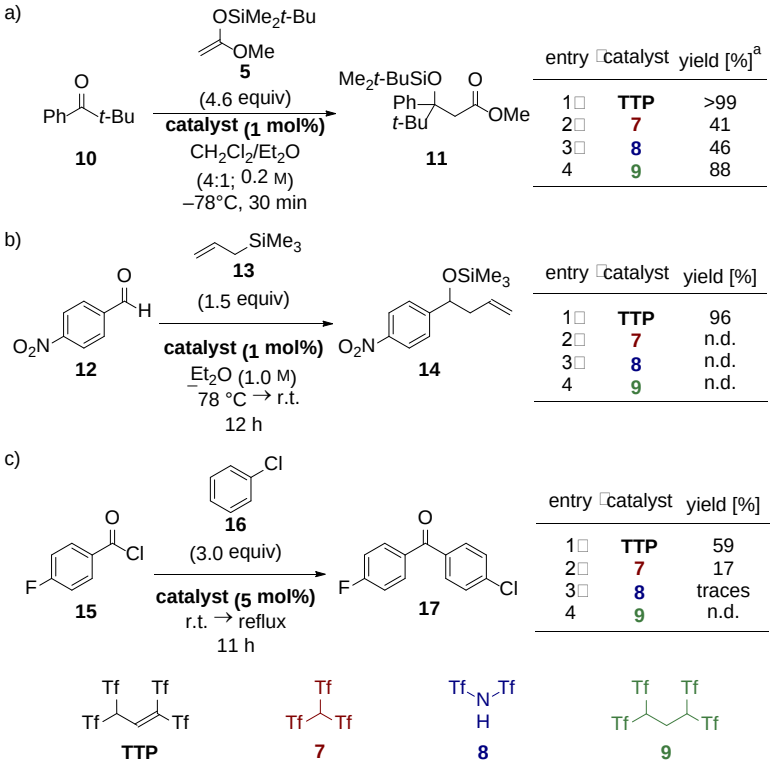
In analogy to our previous synthesis of chiral allyltetrasulfones, the novel, allylic C–H acid **TTP** can readily be obtained via a two-step synthesis (Scheme 5) starting from commercially available bistriflylmethane (**1**). Starting material **1** is first converted almost quantitatively to enol ether **2**, which is then treated with bistriflylmethane (**1**) and TMP base (= 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex solution) to give the TMP•TTP salt (**3**). Ammonium salt **3** can be either isolated or directly converted to **TTP** with an acidic work-up.



Scheme 5. Synthesis of **TTP** and X-ray analysis.

TTP was tested in a variety of synthetically relevant C–C bond forming reactions (Scheme 6) and compared to Tf_3CH (**7**), Tf_2NH (**8**), and diacid **9**. In the Mukaiyama aldol reaction of silyl ketene acetal **5** to the sterically demanding ketone **10**, **TTP** proved to be the most active catalyst, but **9** also showed a very promising activity (Scheme 6a). The Hosomi–Sakurai reaction of electronpoor *p*-nitrobenzaldehyde (**12**) with allylsilane **13** was chosen as another useful synthetic reaction (Scheme 6b). Due to the nitro group in the *para* position of **12** the Lewis basicity of the aldehyde is reduced rendering the commonly accepted activation mode via coordination of a Lewis acid to the oxygen's lone pair electron of **12** less favorable.

Surprisingly, only **TTP** gave the desired homoallylic silyl ether **14** in almost quantitative yields under these reaction conditions. Lastly, a Brønsted acid catalyzed Friedel–Crafts acylation reaction of electronpoor chlorobenzene **16** with benzoylchloride **15** was carried out for each catalyst (Scheme 6c). When **8** and **9** were employed, no desired product could be isolated. Carbon acid **7**, however, was able to give at least 17% of product while **TTP** gave, satisfyingly, 59% yield.



Scheme 6. Application of **TTP** and comparison with other catalysts. ([a]Triphenylmethane was added to reaction a) and the yield was determined by ^{1}H NMR analysis. n.d. = not detected.)

TTP hence looks very promising in Lewis and Brønsted acid catalyzed reactions. In comparison to the prominent, very active organic acids **7**, **8**, and **9**, **TTP** constantly showed the highest activity.

Future directions: We intend to continue with the exploration of new applications for the synthesized chiral and achiral C–H acids, the design of new motifs with confined structures and enhanced acidity, the measurement of pK_a values as well as computational and spectroscopical investigations to evaluate the activation mechanisms for Lewis acid catalysis. Further applications of **TTP** to synthetical useful reactions, which require strong Brønsted or Lewis acid activation, are currently investigated.

Publications resulting from this research area: 28

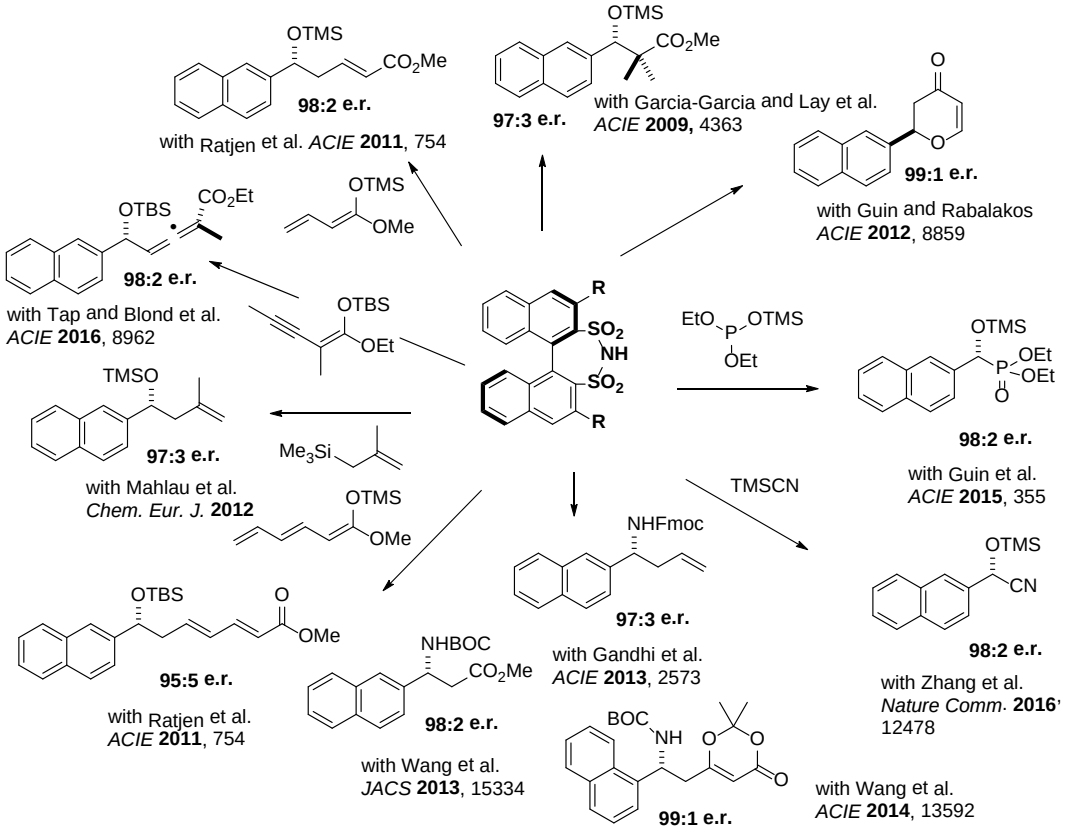
External funding: European Research Council Advanced Grants (HIPOCAT and CHAOS)

Cooperations: J. Lingnau, C. Farès (Mülheim/Ruhr, DE), I. Leito (University of Tartu, EE)

2.2.2 Research Area "Silylium ACDC" (B. List)

Involved: H. Y. Bae, A. Blond, T. Gatzenmeier, J. Guin, D. Höfler, P. S. J. Kaib, S. Lee, M. Leutzsch, R. Properzi, K. Rabalakos, L. Schreyer, A. Tap, M. van Gemmeren, V. Wakchaure, Q. Wang, Y. Xie, Z. Zhang

Objective: The field of Lewis acid organocatalysis has gained momentum in recent years as we expanded our asymmetric counteranion-directed catalysis (ACDC) concept to silylium-based Lewis acid catalysis (Scheme 1). Accordingly, in situ generated silylium ions, paired with an enantiopure counteranion, function as powerful and highly enantioselective Lewis acid catalysts. This strategy has proven to be successful in a variety of Mukaiyama-type Si-transfer reactions and also in non-Si-transfer reactions, such as the Diels–Alder reaction of cinnamates. Attractive features of silylium-based Lewis acid organocatalysis include the in situ regeneration of the catalyst ('self-healing') and relatively low catalyst loadings.

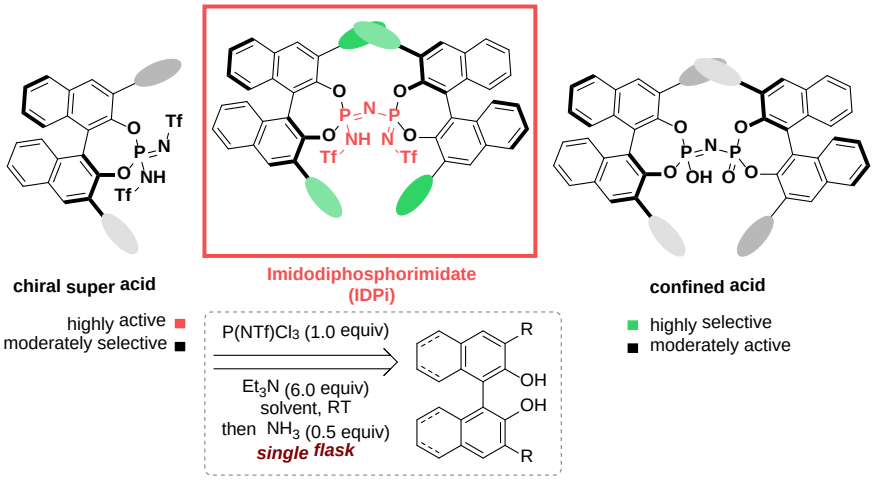


Scheme 1. Silylium-ACDC using chiral disulfonimide catalysts.

However, reactions of small aliphatic substrates that do not possess sterically demanding protecting groups, large aromatic surfaces, or bulky substituents, are still

rare. We therefore proposed the development of highly active “confined acid catalysts”, namely C_2-symmetric imidodiphosphorimidates (IDPi), possessing a sterically extremely demanding chiral microenvironment.

Results: IDPi acids, based on the interlocking of two identical BINOL subunits, were designed and prepared (Scheme 2).



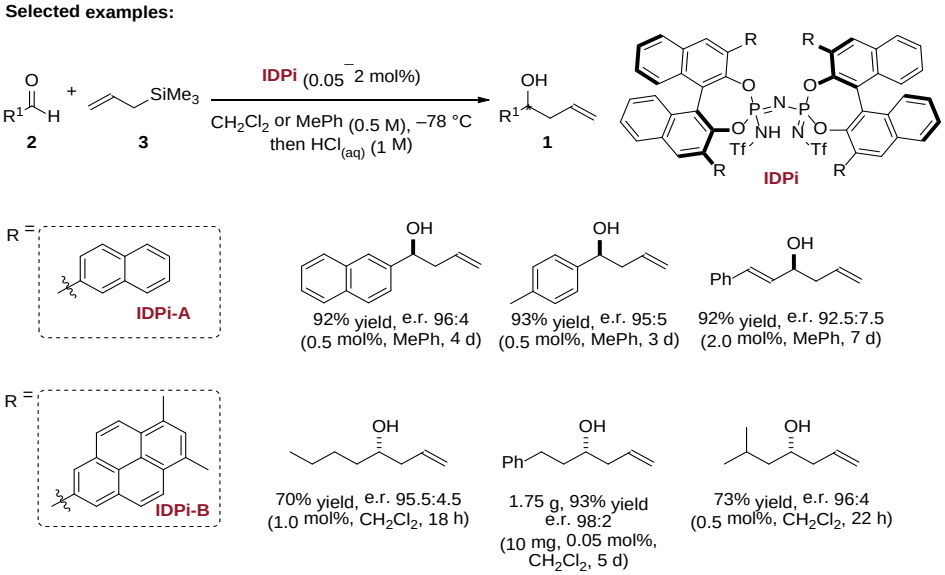
Scheme 2. Design of highly acidic sterically constrained imidodiphosphorimidate (IDPi) Brønsted acids, and its single flask synthetic procedure.

So far, IDPi acids are the most active and enantioselective catalysts ever made in this research group and currently help to solve some very challenging problems in asymmetric catalysis.

A) Hosomi–Sakurai Reaction

The enantioselective allylation of aldehydes to form homoallylic alcohols is one of the most frequently used carbon–carbon-bond forming reactions in chemical synthesis and, for several decades, has been a testing ground for new asymmetric methodology. However, a general and highly enantioselective catalytic addition of the inexpensive, non-toxic, air and moisture stable allyltrimethylsilane to aldehydes, the Hosomi–Sakurai reaction, has remained elusive. Due to the low nucleophilicity of this reagent (Mayr nucleophilicity: N = 1.6), its employment in asymmetric, catalytic addition reactions to aldehydes requires extremely reactive Lewis acids, and previously reported catalysts were found to be insufficiently active in this transformation. Imidodiphosphorimidates (IDPi) enable this allylation, converting various aldehydes with aromatic and aliphatic groups, at catalyst loadings ranging from 0.05 to 2.0 mol% with excellent enantioselectivities (Scheme 3). Our results show that confined

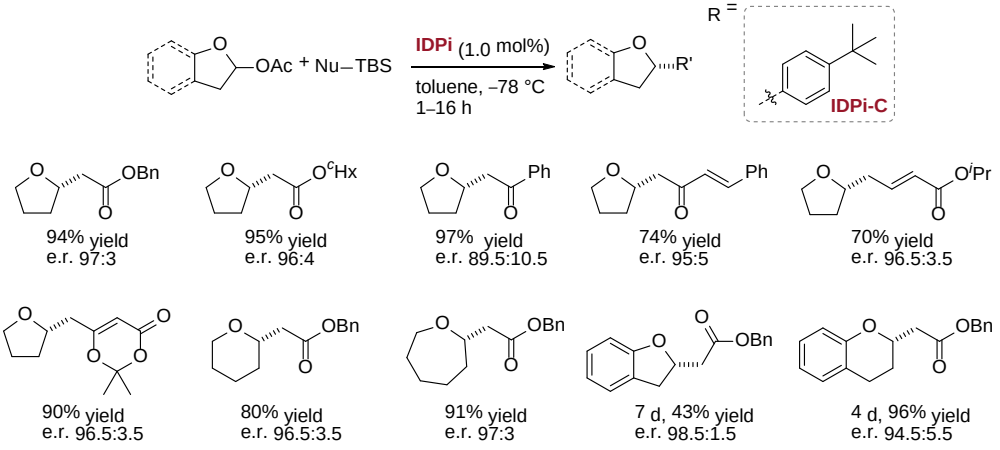
organocatalysts with extreme acidity and steric demand can overcome current synthetic limitations and solve a long standing problem in chemical synthesis.



Scheme 3. Synthetic applications of the Hosomi–Sakurai reaction.

B) Enantioselective Synthesis of *O*-Heterocycles

Oxygen containing heterocycles are essential building blocks for natural products, especially for carbohydrate chemistry. In spite of their frequent appearance, direct general methods to access these chemicals are quite limited. We extended our silylium-ACDC concept further to produce optically enriched heterocycles via unbiased oxocarbenium ion intermediates. The recently developed imidodiphosphorimidate catalyst proved to be an efficient catalytic system due to its high acidity as well as its extremely confined structure. As a result, five-, six-, and seven-membered *O*-heterocycles as well as a chromane and a dihydrobenzofuran were synthesized with moderate to high yields and high enantioselectivities (Scheme 4).



Scheme 4. Enantioselective synthesis of *O*-heterocycles.

Future directions: Our rationally constructed, extremely active IDPi acid catalysts feature a highly tunable and sterically demanding active site and selectively process small and loosely bound substrates, promising high utility in various other challenging chemical reactions.

Publications resulting from this research area: 12, 16, 28, 34, 36, 38

External funding: European Research Council Advanced Grant (HIPOCAT), German Research Foundation: RESOLV Cluster of Excellence (fellowship to H.-Y. Bae)

Cooperations: M. Klußmann (Mülheim/Ruhr, DE)

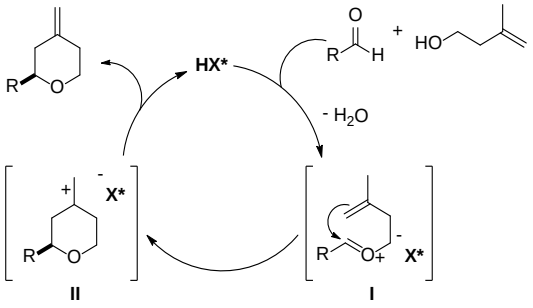
2.2.3 Research Area "Catalytic Asymmetric Reactions of Aldehydes with Olefins" (B. List)

Involved: M. W. Alachraf, N. Dupré, P. S. J. Kaib, M. Leutzsch, L. Liu, S. Prévost, A. Tap, G. C. Tsui, V. Wakchaure, Q. Wang, Y. Xie

Objective: The field of Brønsted acid organocatalysis has acquired wide popularity in recent years. However, typically used substrates such as imines are relatively basic and it is of high priority in our group to expand the scope of useful substrates to less basic but equally interesting substrates such as aldehydes, ketones, and olefins. The aim of this project was to investigate catalytic asymmetric reactions involving carbonyl electrophiles and alkenes as nucleophiles. Highly attractive examples include the Prins-, carbonyl ene-, and Torgov cyclization, and the hetero-Diels–Alder reaction of aldehydes with dienes.

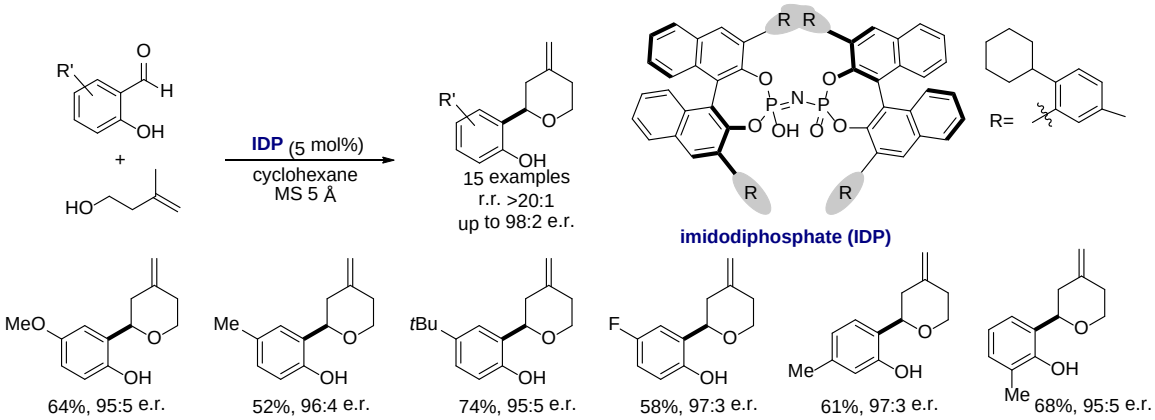
Results:

A) Catalytic Asymmetric Prins Cyclization



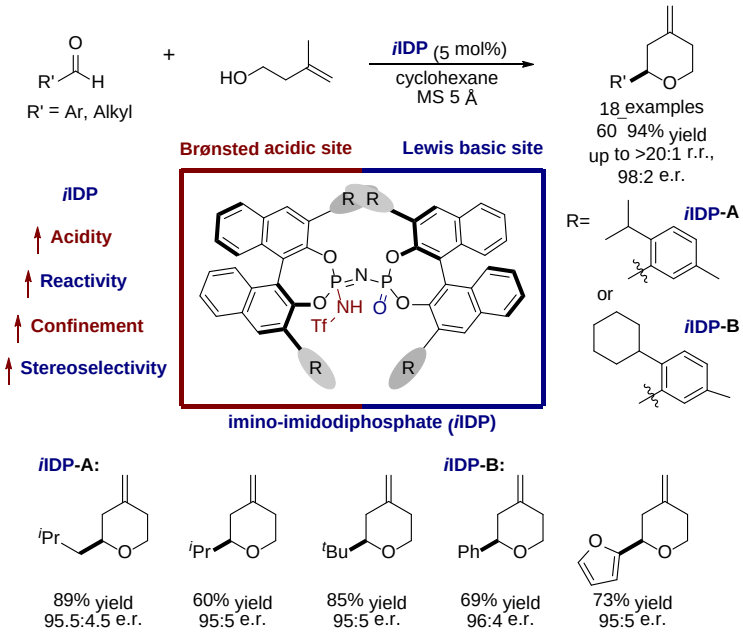
Scheme 1. Mechanistic cycle of the Prins cyclization.

Chiral functionalized tetrahydropyrans (THPs) are widely used as scaffolds in fragrances and pharmaceuticals, and are substructures in many natural products. The Prins cyclization between an aldehyde and a homoallylic alcohol is a particularly efficient approach to furnish THPs in which oxocarbenium ion **I** reacts intramolecularly with an alkene, creating a stereogenic center present in cation **II** (Scheme 1). We found that enantiodiscrimination can indeed be achieved with our confined imidodiphosphate (IDP) catalysts, which have previously demonstrated excellent enantiocontrol in asymmetric acetalization reactions. Nevertheless, activated substrates such as salicylaldehyde were required to afford functionalized 4-methylene tetrahydropyrans in excellent regio- and enantioselectivity (Scheme 2).



Scheme 2. Catalytic asymmetric Prins cyclization of salicylaldehydes.

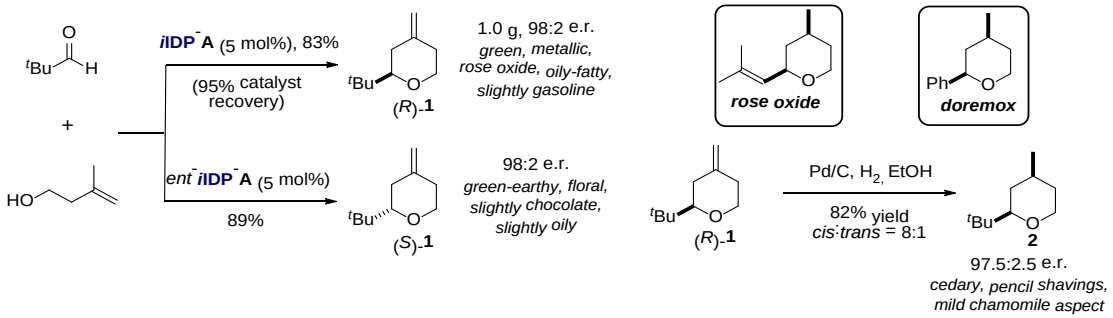
To promote asymmetric Prins cyclizations of unactivated aldehydes, we hypothesized that an approach towards acidifying our IDP catalysts may involve the replacement of an oxo-group with a stronger electron acceptor, such as a NSO_2CF_3 (NTf)-group. We envisioned that a confined imino-imidodi-phosphate (*i*IDP) structure would not only be more acidic than the parent IDP catalyst but also allows for the individual modulation of the acidic and basic component of the inherently bifunctional catalyst. Indeed, various linear, α- and β-branched aliphatic and aromatic aldehydes proved to be suitable substrates for *i*IDP catalysts, yielding excellent enantioselectivities and good yields under our optimized standard reaction conditions (Scheme 3).



Scheme 3. Catalytic asymmetric Prins cyclization using aliphatic and aromatic aldehydes.

Rose oxide and doremox can be obtained via hydrogenation of Prins THP products. (*R*)-**1** could be synthesized on a gram-scale while catalyst ***i*IDP-A** was recovered in 95% yield. For cyclic ether **1**, different scents of the corresponding enantiomers were revealed. (*S*)-**1** can be recognized by its floral and slightly chocolate bouquet.

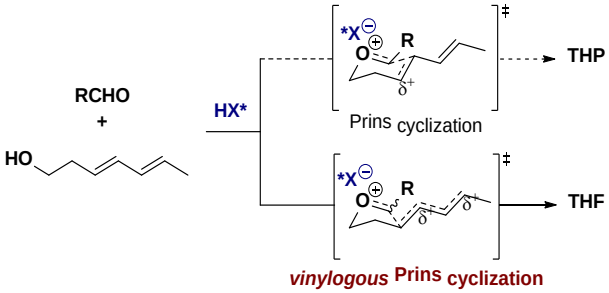
Hydrogenation of product **1** to saturated derivative **2** led to yet another scent, illustrating the fast and straightforward access to diverse scents using our methodology (Scheme 4).



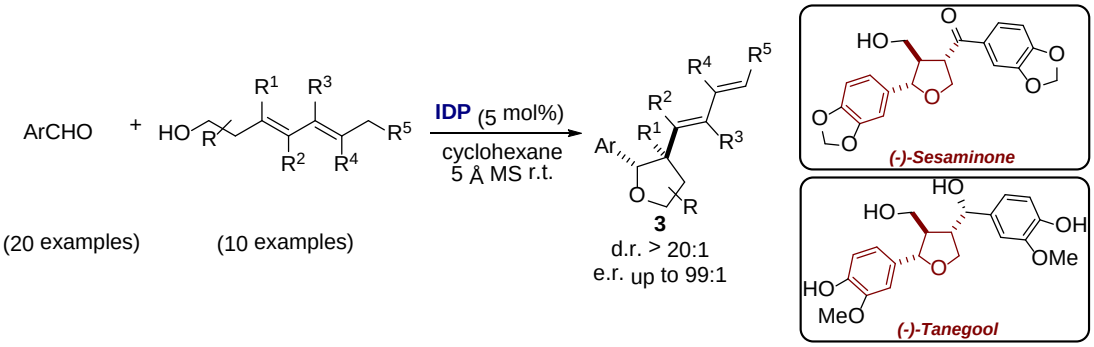
Scheme 4. Hydrogenation of Prins THP products.

B) Catalytic Asymmetric Vinylogous Prins Cyclization

Sporadic reports on the use of Prins cyclizations for the synthesis of tetrahydrofurans (THF) suffer from low diastereoselectivities and a catalytic asymmetric variant has been completely missing. Inspired by our successful previous THP syntheses, we designed a novel Prins cyclization in which a *dienyl* homoallylic alcohol is used instead of a homoallylic alcohol. We expected a vinylogous Prins cyclization to the corresponding THF product via a 5-endo-trig pathway to be preferred, as it would proceed via an allylic cation (Scheme 5).



Scheme 5. Prins cyclization vs. vinylogous Prins cyclization.

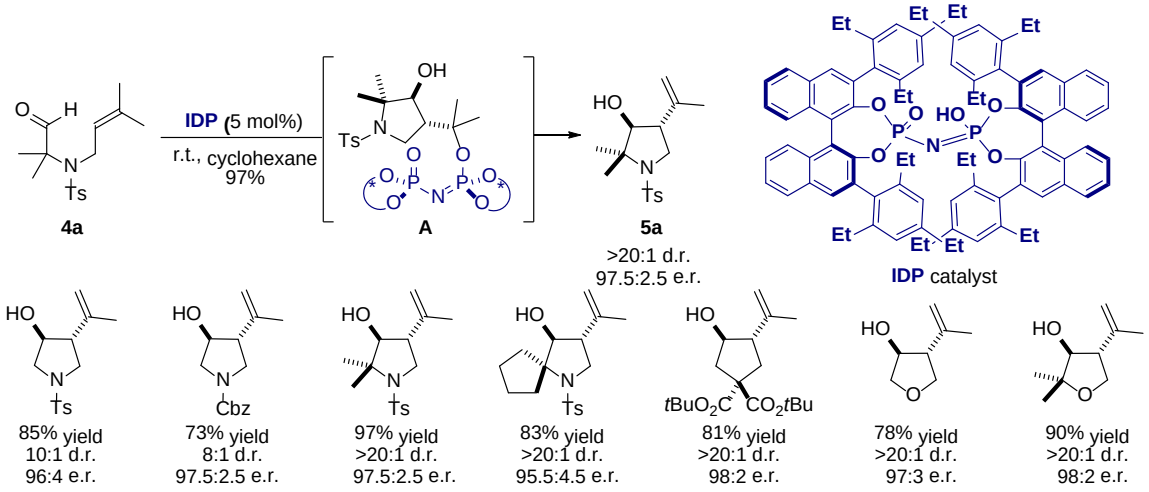


Scheme 6. Vinylogous Prins cyclization using aromatic and heteroaromatic aldehydes.

Under the optimized reaction conditions, various aromatic as well as heteroaromatic and even aliphatic aldehydes were investigated affording the product with good to excellent yield and selectivity. Dienyl alcohols with different substitution patterns were also well tolerated. Highly substituted THFs such as 2,3,4- or 2,3,5-trisubstitued THFs could be accessed by using enantiomerically enriched chiral dienyl alcohols. The stereochemical arrangement of the products matches that of the lignan natural products Sesaminone and Tanegool (Scheme 6).

C) Catalytic Asymmetric Carbonyl-Ene Reaction

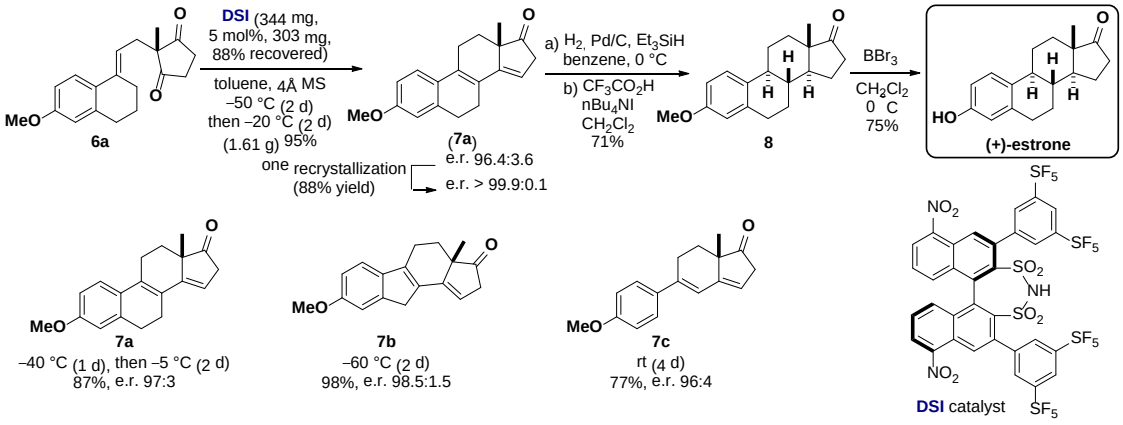
The carbonyl-ene reaction is arguably the most direct and atom economic carbon-carbon bond forming approach to homoallylic alcohols. Intramolecular carbonyl-ene cyclizations are frequently used, also in natural product synthesis and in an industrial route to menthol. Our laboratory has pursued an organocatalytic asymmetric intramolecular carbonyl-ene cyclization for several years. Various reported chiral Brønsted acids such as phosphoric acids, *N*-triflylphosphoramides and disulfonimides were investigated, but unfortunately, all of these acids proved to be active but poorly enantioselective. We now show that a confined imidodiphosphate catalyst (**IDP**), which has previously found utility in asymmetric acetalizations and sulfoxidations, can handle the asymmetric intramolecular carbonyl-ene cyclization. Diverse *trans*-3,4-disubstituted carbocyclic and heterocyclic five-membered rings were obtained in high yields and with good to excellent diastereo- and enantioselectivities (Scheme 7).



Scheme 7. Catalytic asymmetric carbonyl-ene reaction.

D) Catalytic Asymmetric Torgov Cyclization

The Torgov cyclization of **6a** gives diene **7a**, which can be readily transformed to racemic estrone, a female sex hormone. Despite previous efforts towards the development of an asymmetric version of this reaction, high selectivity and turnover numbers had not been achived. To solve this problem, we designed a new chiral disulfonimide (**DSI**) catalyst bearing nitro groups in the 5- and 5'-positions and a pentafluorothio moiety as a sterically bulkier and electronically more withdrawing alternative. With the optimized reaction conditions in hand, we also explored various other diketones. To illustrate the synthetic utility of this method, a gram scale Torgov cyclization and concise synthesis of (+)-estrone were realized. With slightly modified reaction conditions, product **7a** was obtained on gram scale with excellent yield and enantioselectivity. Most of catalyst **DSI** could also be recovered after the reaction. After recrystallization, diene **7a** was submitted to a two-step procedure to yield the fully reduced **8**, which, upon demethylation, gave enantiopure (+)-estrone. This (+)-estrone synthesis via a catalytic asymmetric Torgov reaction is the shortest route reported to date (Scheme 8).



Scheme 8. (+)-Estrone synthesis via catalytic asymmetric Torgov reaction.

Future directions: Further applications of our new Brønsted acid catalysts are currently in progress in our laboratory.

Publications resulting from this research area: 10, 21, 26, 37, 40

External funding: European Research Council Advanced Grant (HIPOCAT), Alexander von Humboldt Foundation (fellowship to Y. Xie and G. C. Tsui)

Cooperations: W. Thiel (Mülheim/Ruhr, DE), Givaudan (Dübendorf, CH)

2.2.4 Research Area "Enol Catalysis" (B. List)

Involved: G. Pupo, R. Properzi, G. A. Shevchenko

Objective: Having recently established a new organocatalytic activation mode for carboxylic acids via supramolecular hetereodimerization, we became interested in the activation of less-acidic ketones. Inspired by enzymatic enolizations, we envisioned that an interaction of the chiral phosphoric acid with the lone pair of the carbonyl and the α-proton would lead to the enolization of the ketone substrate. Furthermore, the resulting "chiral enol-phosphate complex" could possibly interact with an electrophile *via* hydrogen bonding thus resulting in an asymmetric α-functionalization reaction (Figure 1). Reminiscent of enamine catalysis, this design could however overcome some of its limitations. When α-branched ketones are employed as substrates, enamine catalysis, except in rare cases, suffers from the increased steric hindrance of the formed enamine intermediate and therefore, if at all, preferentially reacts via the kinetic enamine, restricting the access to quaternary stereocenters. We envisioned that by shifting to "enol catalysis", we could form the corresponding thermodynamically more stable, higher substituted enol. This design would therefore allow a direct asymmetric access to quaternary and tetrasubstituted chiral centers.

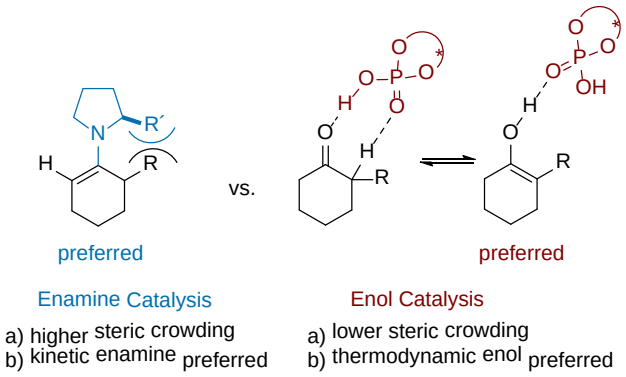
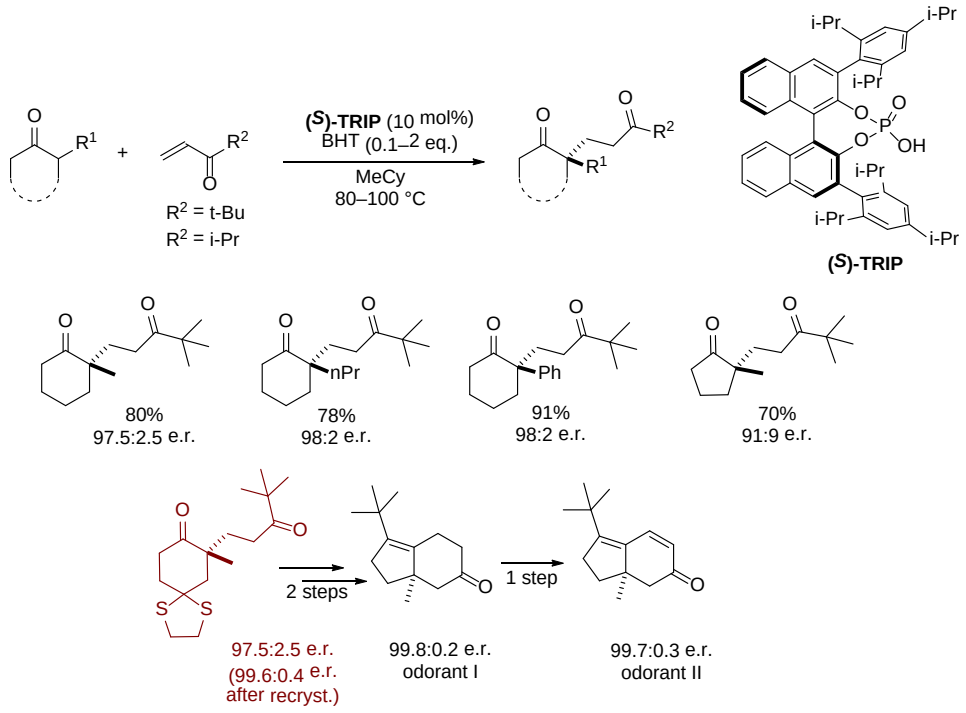


Fig. 1. Enamine vs. enol catalysis.

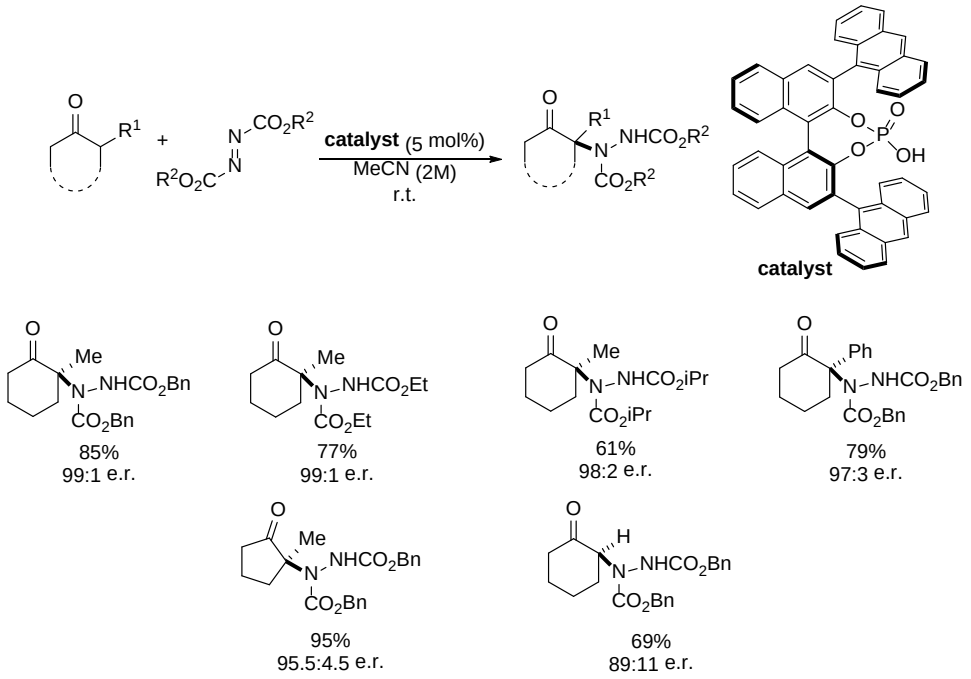
Results: In 2015 we successfully applied this concept to the Brønsted acid-catalyzed Michael addition of α-branched ketones to enones (Scheme 1). α-Alkyl as well as α-aryl substituted ketones were tolerated under the reaction conditions giving the desired products in good yields and excellent enantioselectivities (e.r. up to 98:2) thus underlining the broad applicability of enol catalysis. This novel methodology was then applied as the key step in the total synthesis of novel designer odorants.



Scheme 1. Brønsted acid-catalyzed Michael addition of α-branched ketones to enones.

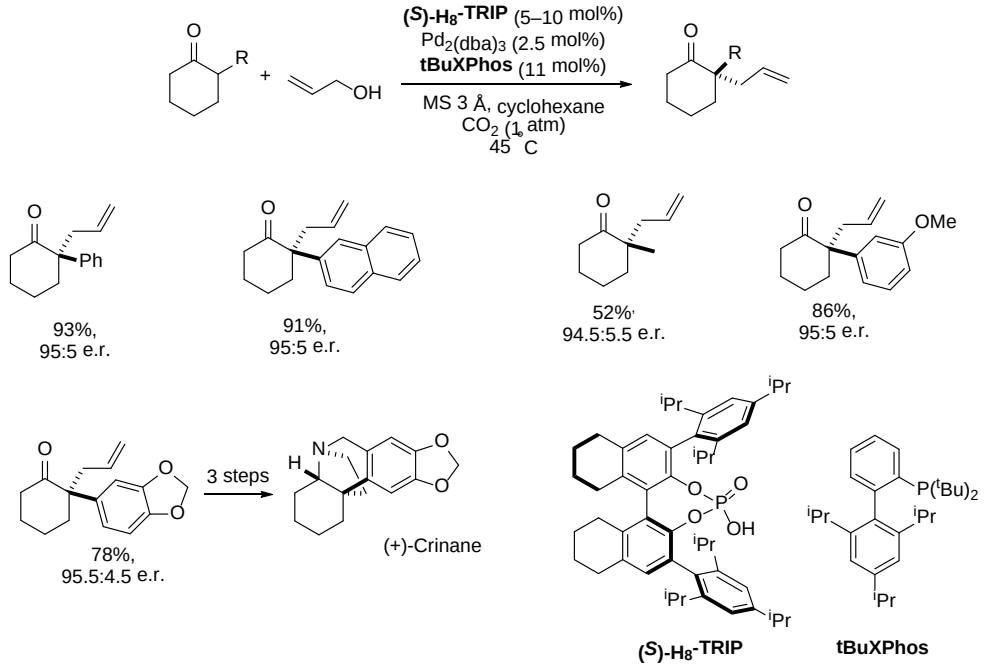
Following the initial results we focused on the exploration of enol catalysis as a generic activation mode. The α-amination of α-branched cyclic ketones (Scheme 2) attracted our attention since this methodology would allow a quick and elegant access to α-amino ketones and 1,2-aminoalcohols, motifs which can be found in numerous natural products and pharmaceuticals.

Gratifyingly, treating ketones with azodicarboxylates in the presence of a chiral phosphoric acid gave the desired products in high yields and excellent enantioselectivities (e.r. up to 99:1). Furthermore, enol catalysis proved to be a valuable tool for the synthesis of tertiary stereocenters as the corresponding product was obtained when cyclohexanone was used as substrate, albeit with slightly diminished enantioselectivity (89:11 e.r.). Interestingly, tetralone and indanone derived substrates resulted in lower yields and enantioselectivities.



Scheme 2. α-Amination of α-branched cyclic ketones.

We then turned our attention towards the direct catalytic asymmetric α-allylation of α-branched ketones (Scheme 3). This fundamental transformation offers an efficient approach towards quaternary all-carbon stereocenters, which are common motifs in natural products and pharmaceuticals. Various indirect methods are known in the literature, but suffer from low atom-economy due to elaborate substrate preparation. We could overcome these drawbacks by using a combination of a Tsuji–Trost type activation of allylic carbonates and enol catalysis using (*S*)-H_8-TRIP as the chiral phosphoric acid. Later we could prove that even allylic alcohol, upon in situ activation by CO_2, was a suitable electrophile giving the desired products in high yields and excellent regio- and enantioselectivities. One of the key features of the protocol is that it only generates water as by-product. This methodology was applied as the asymmetric key step in the so far shortest formal total synthesis of Ameryllidaceae alkaloid (+)-crinane.



Scheme 3. Direct catalytic asymmetric α-allylation of α-branched ketones.

Publications: 17, 20, 32

External funding: Fonds der Chemischen Industrie (fellowship to G. Pupo), "Sustainable Chemical Synthesis" program (fellowship to G. Shevchenko)

Cooperations: Givaudan (Dübendorf, CH)

2.2.5 Research Area "Catalytic Asymmetric Imine Reductions" (B. List)

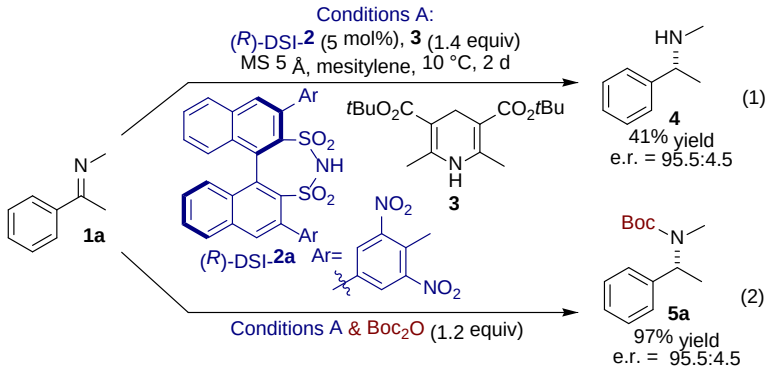
Involved: P. S. J. Kaib, M. Leutzsch, V. N. Wakchaure

Objective: Enantiomerically pure amines, in particular α-chiral amines, represent a privileged pharmacophore that can be found in a vast number of pharmaceutical and agrochemical substances. Catalytic asymmetric imine reductions and reductive aminations of carbonyl compounds are efficient approaches for the construction of optically pure amines. A few years ago, our group developed a Brønsted acid catalyzed asymmetric imine reduction and reductive amination of ketones that make use of Hantzsch esters as hydrogen source. Despite these advances, however, such reductions have been limited to *N*-aryl imines. *N*-Alkyl imines are highly attractive substrates for asymmetric reductions since they would directly furnish the *N*-alkyl amine pharmacophore. Chiral phosphoric acids typically fail in the corresponding Hantzsch ester mediated imine reductions and alternative approaches have only rarely been investigated and remain a major challenge. The aim of this project was to develop a simple, efficient and highly enantioselective methodology for the synthesis of α-chiral *N*-alkyl amines. Furthermore, this methodology should be expanded to an even more challenging reduction of *N*-H imines.

Results:

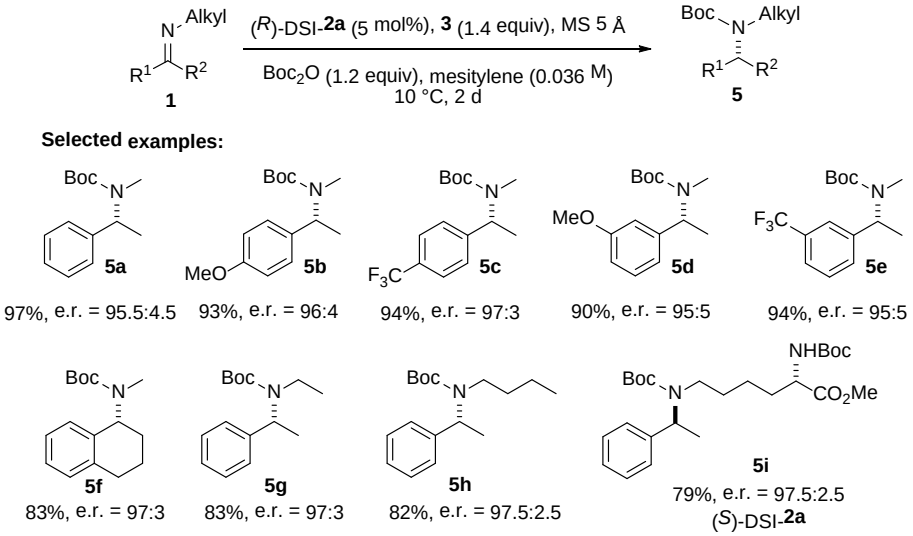
A) Disulfonimide-Catalyzed Asymmetric Reduction of *N*-Alkyl Imines

At the outset of our work, we hypothesized that the high basicity of the desired *N*-alkyl amine products may make the use of stronger Brønsted acid catalysts necessary for the Hantzsch ester mediated reduction of *N*-alkyl imines to achieve high turnover and enantioselectivity. Indeed, our chiral disulfonimide DSI-**2a** catalyzed the transformation more rapidly than the alternative phosphoric acid-based catalysts and also afforded amine **4** with higher enantioselectivity. However, the reaction was still rather sluggish and the product was isolated in only 41% yield (Scheme 1, eq 1). We speculated that the poor isolated yield was still due to catalyst deactivation through salt formation with highly basic amine **4**. It has previously been reported that related product inhibitions can be eliminated by in situ protection. Encouraged by these reports, we investigated the effect of running the reaction in the presence of di-*tert*-butyl dicarbonate (Boc_2O). Remarkably, we found that full conversion to the desired *N*-Boc-protected product **5a** in 97% yield with an identical e.r. of 95.5:4.5 was observed under these conditions (Scheme 1, eq 2).



Scheme 1. Reaction conditions for the disulfonimide-catalyzed asymmetric reduction of *N*-alkyl imines.

With the optimized conditions, a variety of *N*-alkyl imines were efficiently reduced in the presence of (*R*)-DSI-**2a** (5.0 mol%) to afford the corresponding Boc-protected *N*-methyl amines with high yields and enantioselectivity (Scheme 2). Additionally, the method tolerates a large variety of alkyl amines, thus illustrating potential for a general reductive cross-coupling of ketones with diverse amines; it was applied in the synthesis of the pharmaceuticals (*S*)-Rivastigmine, NPS *R*-568 Hydrochloride, and (*R*)-Fendiline.

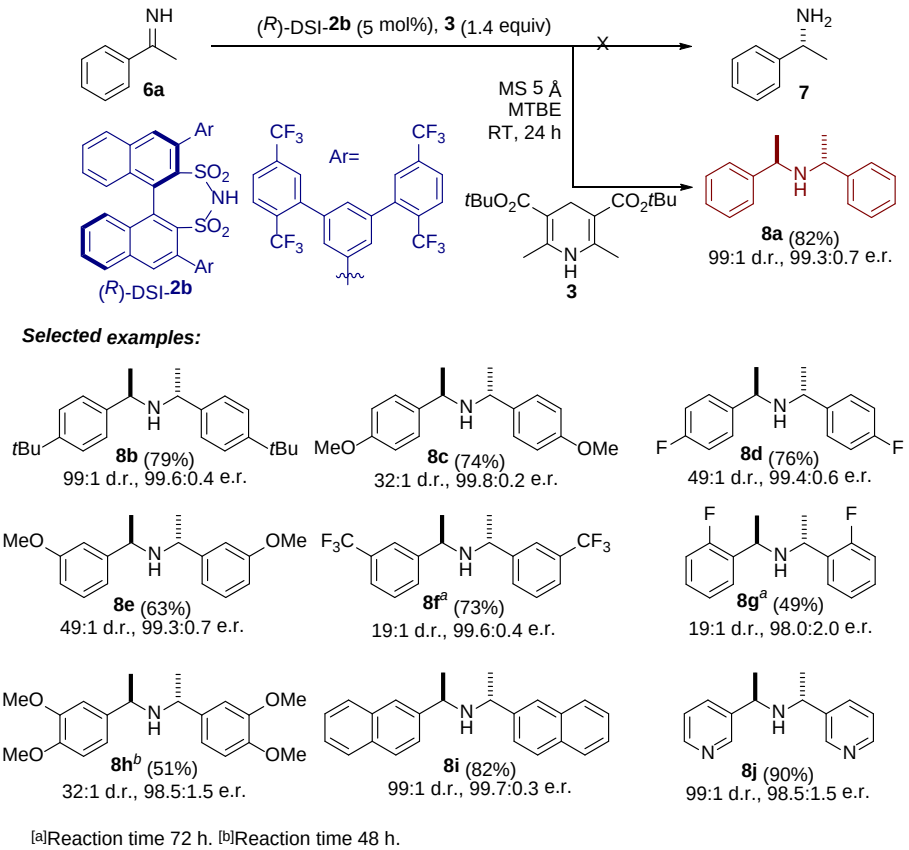


Scheme 2. Scope of the asymmetric reduction of *N*-alkyl imines.

B) Disulfonimide-Catalyzed Asymmetric Reduction of *N*-H Imines: Synthesis of C_2-Symmetric Amines

Subsequently, we became interested in extending our methodology to include the equally attractive and challenging *unsubstituted N*-H imines. We initially hoped that this process could provide direct access to enantioenriched primary amines (Scheme 3). Reductions of this type have rarely been studied and remain a major challenge. Surprisingly, when investigating the reduction of imine **6a** using Hantzsch ester **3** in the

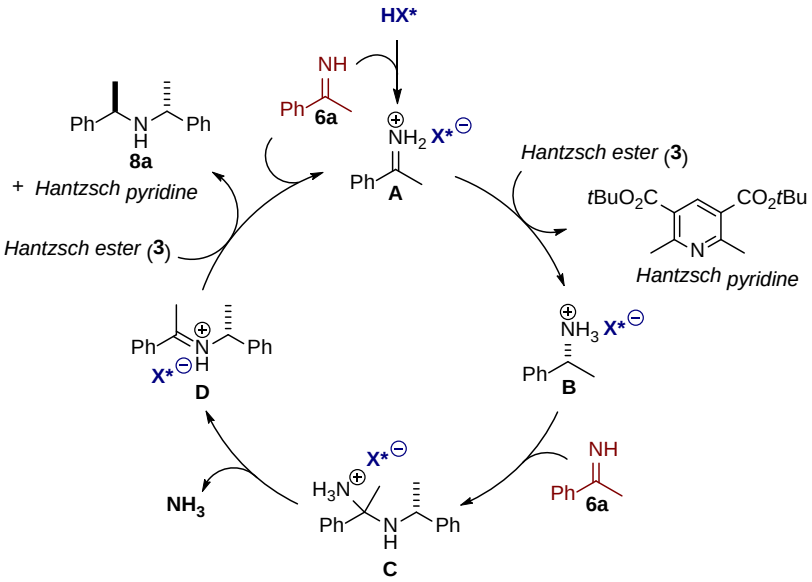
presence of DSI-**2b**, we found that instead of primary amine **7**, the corresponding C_2-symmetric secondary amine **8a** was obtained with outstanding diastereoselectivity and enantioselectivity (Scheme 3). This product has previously been reported as a by-product in a chemoenzymatic dynamic kinetic resolution of racemic primary amine **7**. However, to the best of our knowledge, such an asymmetric reductive condensation of *N*-H imines has previously been unknown. Encouraged by our initial observation and in consideration of the various applications of C_2-symmetric secondary amines, we have developed an asymmetric Brønsted acid catalyzed reductive condensation of *N*-H imines. A variety of *N*-H imines efficiently underwent the reductive condensation in the presence of disulfonimide **2b** (5.0 mol%) to afford the corresponding C_2-symmetric secondary amines in good yields and with outstanding diastereoselectivity and enantioselectivity (Scheme 3).



Scheme 3. Scope of the asymmetric reductive condensation of *N*-H imines.

We currently envision a catalytic cycle that is initiated by protonation of imine **6a** from chiral DSI-**2b** (Scheme 4). The resulting iminium ion pair **A** undergoes reaction with Hantzsch dihydropyridine **3** to give enantiomerically enriched primary amine salt **B** and the corresponding Hantzsch pyridine. Subsequently, amine **B** undergoes a

transimination with substrate **1a**, first to produce aminal **C**, which then liberates ammonia to form secondary iminium ion pair **D**. Finally, a second reduction of intermediate **D** provides diastereo- and enantioenriched secondary amine product **8a**. It is noteworthy that we observed a slight kinetic resolution in the reduction of iminium ion pair **D**, further enhancing the enantiomeric ratio of our C_2-symmetric secondary amine products. Perhaps this explains the superb enantioselectivities observed.



Scheme 4. Catalytic cycle.

Future directions: The focus in the future will be directed towards the development of stronger Brønsted acid catalysts to broaden the substrate scope.

Publications resulting from this research area: 25, 39

External funding: European Research Council Advanced Grant (HIPOCAT)

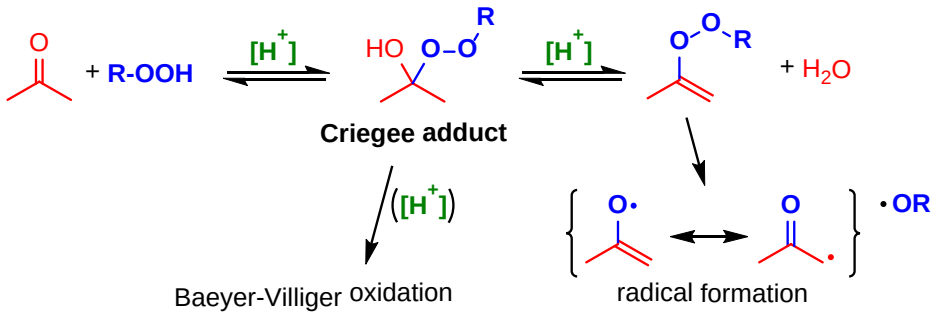
Cooperations: none

2.2.6 Research Area "Alkenyl Peroxide Chemistry" (M. Klußmann)

Involved: E. Böß, A.-E. Bosnidou, J. Demaerel, H. Engler, M. Hasenbeck, S. Karanestora, B. Schweitzer-Chaput, R. Verschueren

Objective: In previous mechanistic studies, we had discovered that the combination of ketones, hydroperoxides or hydrogen peroxide and acid generates radicals. Further studies led us to postulate the formation of highly reactive alkenyl peroxides as intermediates, which rapidly decay by homolytic O–O bond cleavage. We sought to investigate the underlying mechanisms, their importance for peroxide chemistry, as well as potential applications in synthesis.

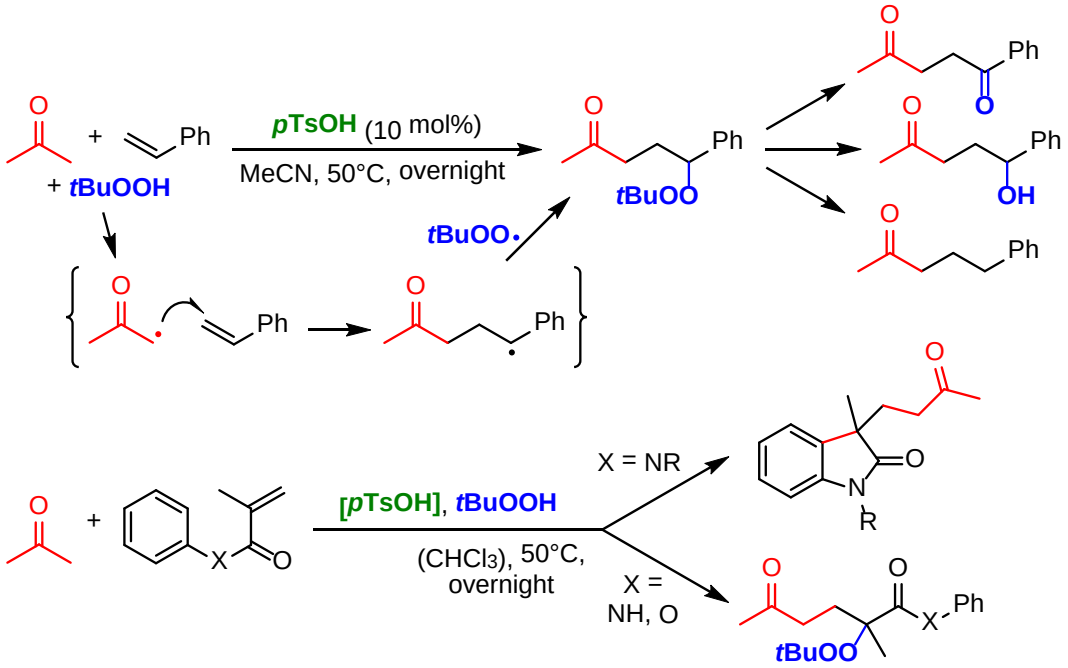
Results: Alkenyl peroxides are a special class of peroxides that are characterized by a significantly weaker O–O bond dissociation energy compared to other peroxides, resulting in homolytic decay at probably ambient temperature or below for most structures. An oxyl and a resonance-stabilized β-oxo-alkyl (or oxyallyl) radical are formed. Reports on this substance class were nearly exclusively limited to theoretical studies of atmospheric chemistry. Our studies revealed that alkenyl peroxides can be easily formed in solution by an acid-catalyzed condensation reaction between ketones and hydroperoxides or hydrogen peroxide. In a very small number of previous publications, this phenomenon was indicated, but our group was the first to rationalize the mechanism.



The mechanistic proposal shown above for the generation of alkenyl peroxides in solution has also implications for the Baeyer–Villiger oxidation of ketones, which shares a common intermediate, the so-called Criegee adduct. Our studies pointed out that the problems associated with the use of hydrogen peroxide as oxidant in Baeyer–Villiger oxidations is due to a competitive formation of alkenyl peroxides, which

generate undesired byproducts. Alkyl hydroperoxides favour alkenyl peroxide formation, while peracids favour rearrangement of the Baeyer–Villiger oxidation.

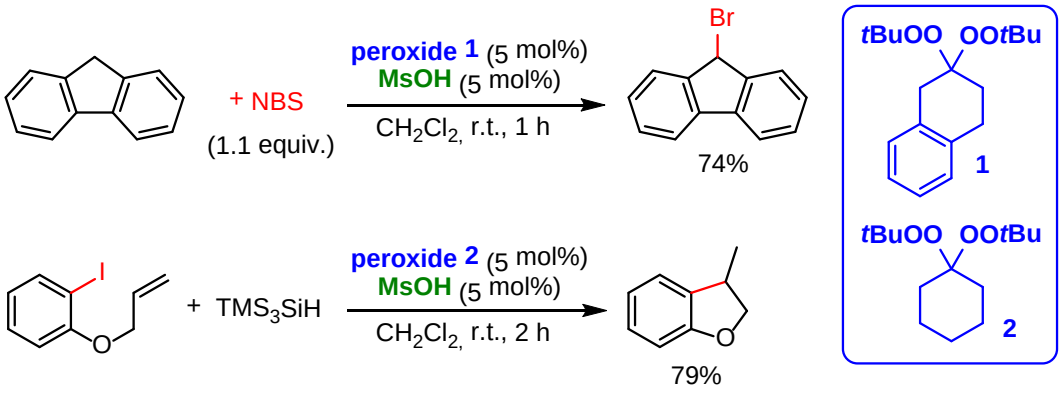
For organic synthesis, alkenyl peroxides offer a simple means to generate radicals from ketones, which is otherwise often limited to more activated 1,3-dicarbonyl compounds. We could form a number of radical addition products of various ketones to styrene derivatives, isolating γ-peroxyketones. These compounds can be easily transformed into synthetically interesting building blocks like 1,4-diketones or homo-aldol products. Addition reactions to *N*-aryl-*N*-alkyl methacrylamides led to radical cascade reactions generating ketone-functionalized oxindoles.



If a large excess of olefins is used, polymerization reactions can be conducted. In collaboration with the group of Prof. Junkers in Belgium, our method was applied to room-temperature radical RAFT polymerizations.

In addition, we found that alkenyl peroxides can be formed somewhat faster by treatment of geminal bisperoxides with acid, compared with the method described above. The radicals so generated can be used to initiate a variety of radical cascade reactions, so that the combination of geminal bisperoxides and acid is effectively a way of generating radical initiators *in situ* at temperatures as low as −20 °C. Given that the initiation rate can be fine-tuned by the peroxide structure and the amount and nature of

the acid, and that geminal bisperoxides are relatively stable, cheap and commercially available compounds, this method might be useful for a wide range of applications.



Future directions: develop new synthetic applications of alkenyl peroxides as precursors of ketone-radicals, develop novel ways of alkenyl peroxide generation, increase the rate of radical generation for low-temperature initiation of chain reactions.

Publications resulting from this research area: 43, 46, 48, 49, 51, 53

External funding: Deutsche Forschungsgemeinschaft (Heisenberg Scholarship to M. Klußmann)

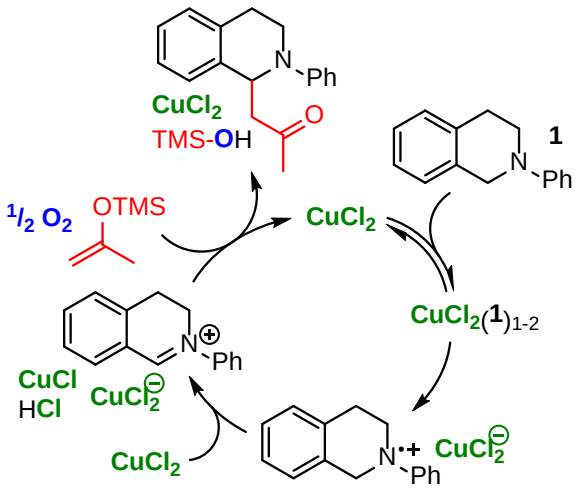
Cooperations: T. Kurtén (Helsinki, FI); T. Junkers (Hasselt, BE)

2.2.7 Research Area "Catalytic Oxidative Reactions and Mechanistic Studies" (M. Klußmann)

Involved: E. Böß, N. Gulzar, K. Jones, M. Scott, A. Sud, H.-L. Yue

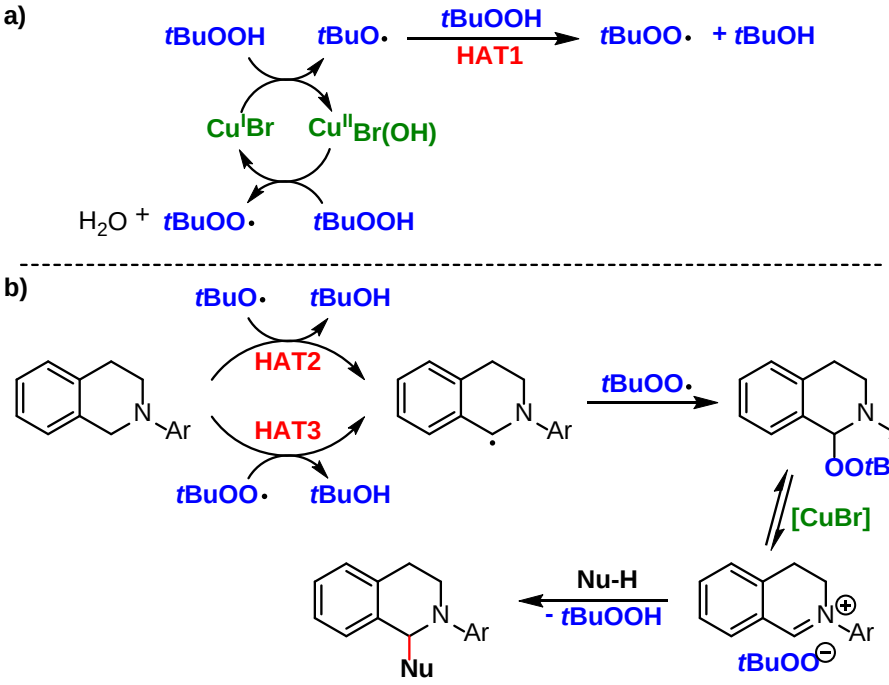
Objective: Our group has a strong interest in detailed mechanistic studies, as these provide inspirations for the development of new synthetic methodology, improve the general understanding of chemical reactivities, and thus also have a direct impact on teaching. Kinetics play a central role in our investigations of reaction mechanisms and we often collaborate with other research groups to tackle a complex mechanistic problem. The findings from recent studies involving peroxide-mediated C–H functionalization reactions go hand in hand with applications in synthesis.

Results: Our group had previously developed oxidative coupling reactions for the formation of C–C bonds from C–H bonds, in particular methods for the functionalization of *N*-aryl tetrahydroisoquinolines. Such reactions gained a lot of attention after the group of C.-J. Li had reported Cu-catalyzed functionalization reactions using *tert*-butyl hydroperoxide (*t*BuOOH) as oxidant. We had reported a related method with a very broad substrate scope using elemental oxygen as the oxidant and we were the first to provide detailed mechanistic studies for this type of reaction. We have studied the kinetics of our oxygen-mediated reaction in detail, which helped to clarify differences in the substrate scope between this and the *t*BuOOH-mediated reaction by Li.

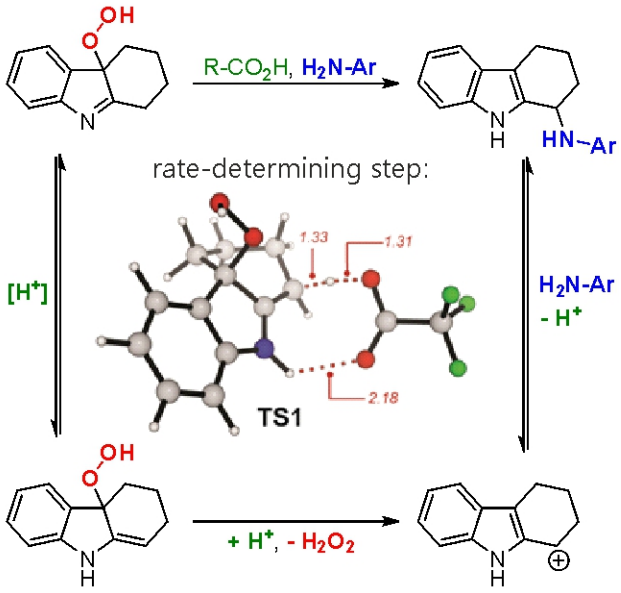


Our mechanistic proposal for the latter method by the group of C.-J. Li was recently challenged by a study from the group of Michael P. Doyle. We had suggested hydrogen atom transfer (HAT) from the amine to intermediate oxyl and peroxyl radicals (formed by Cu-catalysis from *t*BuOOH) as key step, which was dismissed by Doyle's report suggesting electron transfer. In a collaborative effort utilizing different kinetic and computational investigations, we could find strong support for a mechanism via HAT

and also uncovered a competitive system of three different HAT reactions that leads to significant differences in kinetic isotope effects, depending on reaction conditions.



The formation of peroxides as reactive intermediates in C–H functionalization reactions, as in the mechanism shown above, has inspired us to develop this as a general strategy. Especially if the C–H functionalization via Intermediate PeroxideS (CHIPS) could be mediated by the use of elemental oxygen, such reactions could be conducted in a rather sustainable manner. We had thus developed an aerobic method for the functionalization of tetrahydrocarbazol derivatives using visible light, a sensitizer and a Brønsted acid catalyst, which could be used for the synthesis of antiviral compounds. The reaction involved an interesting shift during the substitution of the hydroperoxide group. The mechanism of this reaction was



investigated using kinetic and computational methods, and an acid-catalyzed imine-enamine tautomerization was revealed as the rate controlling step.

An extension of this strategy to other substrate classes is ongoing. In addition, we have developed an oxygenative thiol-ene reaction using *t*BuOOH as oxidant which was inspired by our recent investigations of Brønsted acid catalysis and radical reactions. Finally, we have investigated kinetic aspects of an asymmetric Brønsted acid catalyzed reaction in a collaborative effort together with the group of Prof. Benjamin List.

Future directions: Investigate other amines and amides in oxidative coupling reactions of increased synthetic interest, extend the concept of CHIPS to other substrate classes.

Publications resulting from this research area: 36, 42, 44, 45, 47, 50, 52

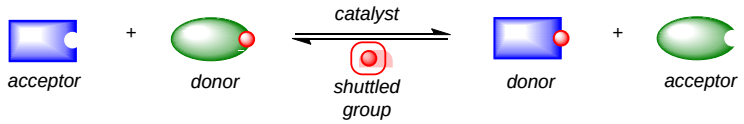
External funding: Deutsche Forschungsgemeinschaft (Heisenberg Scholarship to M. Klußmann); Alexander von Humboldt-Stiftung (stipend to K. Jones); Chinese Scholarship Council (stipend to H.-L. Yue)

Cooperations: M. Bietti (Rome, IT); M. Breugst (Köln, DE); B. List, W. Thiel (Mülheim/Ruhr, DE)

2.2.8 Research Area "Shuttle Catalysis" (B. Morandi)

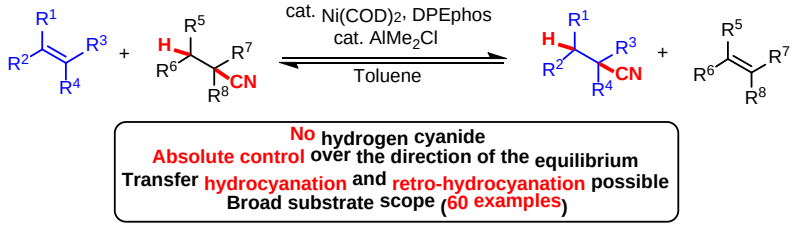
Involved: X. Fang, P. Yu, Y. Lee, B. Cacherat, Z. Lian, G. Prina Cerai, B. N. Bhawal, E. Wöstefeld

Objective: Catalytic reversible reactions, such as alkene metathesis and transfer hydrogenation, have had an auspicious impact on the molecular sciences. We are currently developing "shuttle catalysis" reactions that parallel the mechanism of transfer hydrogenation through the reversible transfer of chemical moieties beyond H_2 (Scheme 1), to address synthetically relevant challenges in catalysis and provide new disconnections for synthetic chemists.



Scheme 1. Schematic representation of the shuttle catalysis concept.

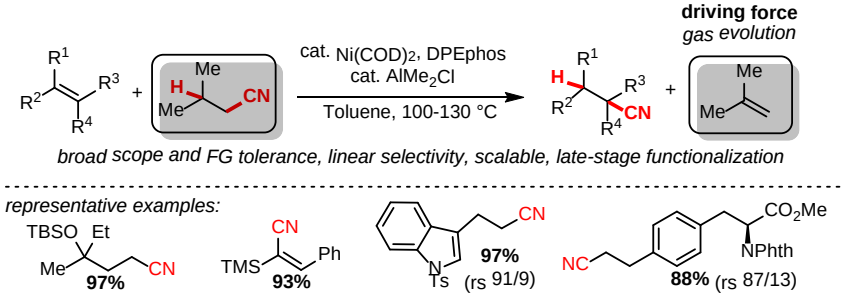
Results: At the outset of our investigations, we targeted the development of a catalytic reversible hydrofunctionalization reaction of alkenes. We selected the hydrocyanation reaction because alkenes and nitriles are very useful synthetic intermediates with complementary reactivity profiles. Furthermore, the hydrocyanation of alkenes has been underexploited in routine laboratory-scale synthesis because traditional approaches rely on the use of volatile and highly toxic hydrogen cyanide (HCN). Additionally, the reverse retro-hydrocyanation is thermodynamically disfavored and has not been realized experimentally. To address these challenges, we have reported a Ni-catalyzed transfer hydrocyanation reaction that efficiently interconverts alkenes and nitriles (Scheme 2).



Scheme 2. Our recently developed transfer hydrocyanation.

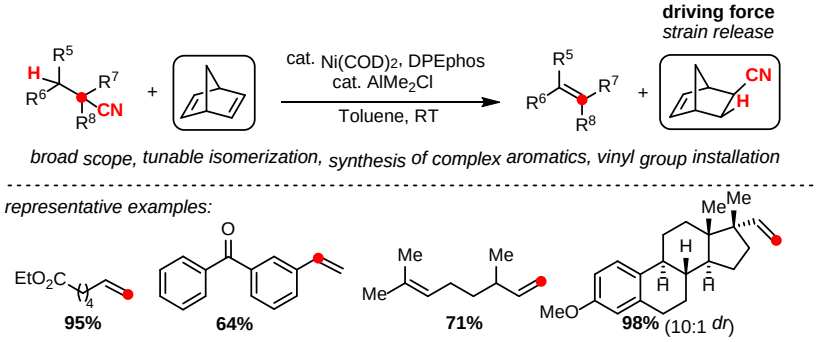
This strategy circumvents the need to employ the highly toxic and volatile reagent hydrogen cyanide, and thus provides a safer approach to hydrocyanation reactions when

compared to traditional approaches. This reaction is also a rare example of transfer functionalization wherein the direction of the equilibrium can be fully controlled using simple driving forces, such as strain release or gas extrusion, to undergo either the forward or reverse reaction with a broad set of structurally different substrates. The forward functionalization reaction can be favored using a sacrificial donor molecule, isovaleronitrile, which is transformed into isobutene, a volatile compound that can escape the reaction mixture thus driving the reaction process to completion (Scheme 3). The method tolerates a broad scope of functional groups, as demonstrated in the late-stage transfer hydrocyanation of bioactive starting materials.



Scheme 3. Forward transfer hydrocyanation of alkenes.

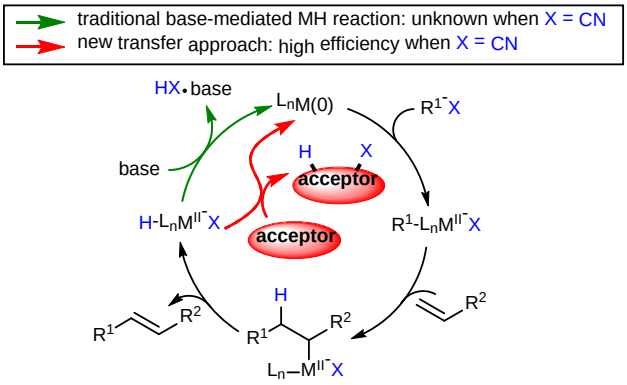
The reverse process, retro-hydrocyanation, can be performed when sacrificial norbornadiene is used to drive the reaction to completion through ring strain release (Scheme 4). Retro-hydrocyanation enables the use of the nitrile group as a removable activating group for the construction of C–C bonds, and this strategy was used both in the synthesis of complex aromatic products and the stereoselective installation of a quaternary vinyl group.



Scheme 4. Retro-hydrocyanation of nitriles.

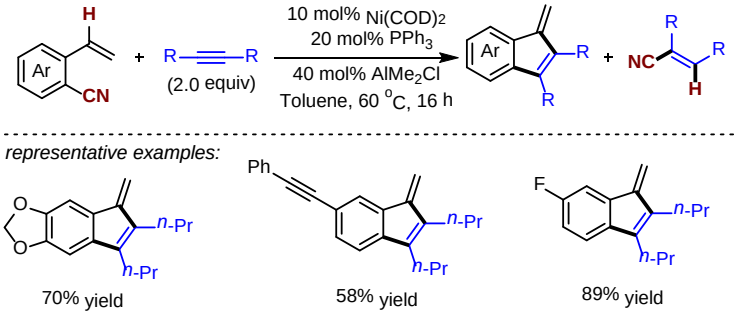
In more recent results, we demonstrated that the transfer hydrocyanation can also be used as a turnover-enabling step in unprecedented cross-coupling reactions (Scheme 5). Using this strategy, we could unlock the Mizoroki–Heck (MH) reaction of aryl cyanide

electrophiles, a process that is difficult to perform under the traditional, basic conditions. Our approach makes use of a key transfer hydrocyanation step instead of a base to regenerate the active Ni(0) species under base-free conditions. This was critical for the success of this reaction because the activation of the C–CN bond usually requires a Lewis-acid that is poorly compatible with the use of base.



Scheme 5. Comparison of classical MH mechanism with the new approach involving transfer hydrocyanation as a turnover-enabling step.

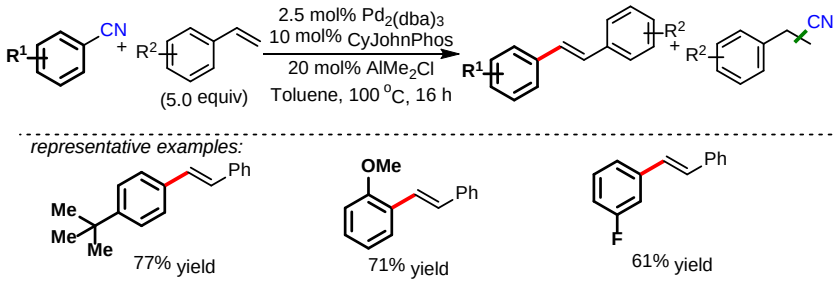
Using this strategy, we could develop two novel Mizoroki–Heck-type reactions of aryl cyanides. Initially, a cascade carbonickelation/MH reaction of 2-cyanostyrenes was achieved using a key alkyne transfer hydrocyanation step (Scheme 6). This reaction led to the facile preparation of benzofulvenes that are useful molecules for synthesis. Labelling studies confirmed that a transfer hydrocyanation of the alkyne took place.



Scheme 6. Cascade carbonickelation of alkynes/MH reaction of 2-cyanostyrenes.

In further work, we targeted the intermolecular MH reaction of arylcyanides and styrenes, a reaction not previously reported in literature (Scheme 7). Following the same concept, the use of an excess of styrene as both cross-coupling partner and HCN acceptor led to the isolation of the MH product in good yields. Overall, this unusual application of the transfer hydrofunctionalization concept is a useful complement to the

use of classical aryl halide electrophiles and demonstrates the potential of reversible transfer reactions to unlock unprecedented reactivity beyond alkene functionalization.



Scheme 7. MH reaction of aryl cyanides.

Finally, in a recently invited perspective article, we have coined the term shuttle catalysis to describe isodesmic reactions, such as our transfer hydrocyanation protocol, which enable the reversible transfer of a reactive intermediate or small molecule between two substrates. In this article we used the "shuttle catalysis" umbrella to link previously isolated examples of transfer reactions from the literature, with the hope of stimulating further research in this exciting area.

Future directions: We are currently exploring the possibility to discover several new transformations following the shuttle catalysis principle, most notably alkene functionalization and carbonylation reactions, as well as novel metathesis reactions.

Publications resulting from this research area: 59, 63-65

External funding: LG Chemicals (stipend to Y. Lee); China Scholarship Council (stipend to P. Yu); Carlsberg Foundation (postdoc fellowship to Z. Lian); The Leverhulme Trust (postdoc fellowship to B. N. Bhawal)

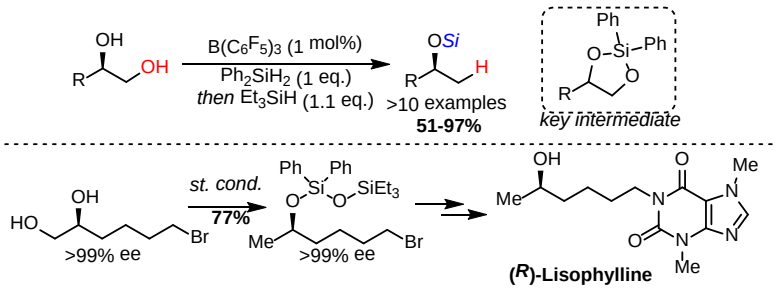
Cooperations: none

2.2.9 Research Area "C–O Bond Activation" (B. Morandi)

Involved: N. Drosos, R. Ramírez-Contreras, G. Prina Cerai, E. Özkal, B. Cacherat, S. Willems, B. N. Bhawal, S. Spandick

Objectives: The alcohol group is one of the most widespread functional groups in organic synthesis. Additionnally, alcohols are ubiquitous in renewable feedstocks, such as carbohydrate derivatives. Therefore, methods for the transformation and functionalization of alcohols are in high demand in synthesis. The research area "C–O bond activation" targets the development of novel transformations employing alcohol derivatives as starting materials, with a particular emphasis on the selective functionalization of polyol derivatives.

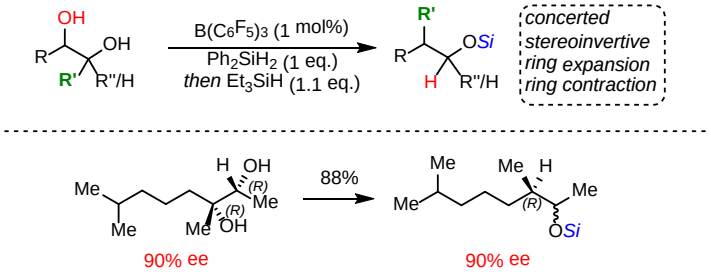
Results: A challenge in polyol chemistry is the selective deoxygenation of a specific hydroxyl group. In this context, we became interested in developing a regioselective deoxygenation of terminal diols because this motif is commonly encountered in renewable feedstocks and synthetic intermediates. We developed a selective deoxygenation of 1,2-terminal diols at the primary position using a simple, commercially available boron catalyst and silane reagents (Scheme 1). A key feature of the reaction is the formation of a cyclic intermediate that enhances the rate of the first deoxygenation step and prevents overreduction. Using this strategy, we could deoxygenate a wide range of substrates and even access a highly enantioenriched 2-alkanol product that was subsequently used in the enantioselective synthesis of an anti-inflammatory drug.



Scheme 1. Selective deoxygenation of diols at the primary position.

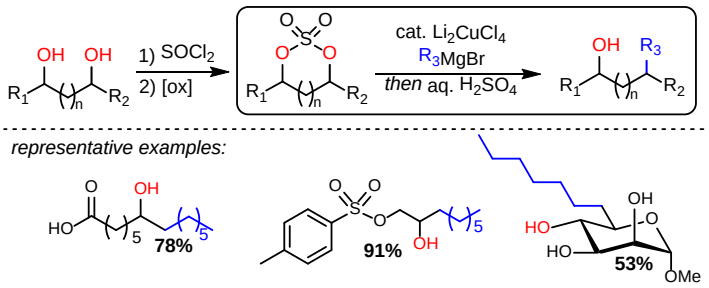
In more recent, unpublished work, we have been able to develop the first example of a reductive pinacol-type rearrangement that can efficiently transform unactivated internal diols (Scheme 2). The reaction is stereospecific and provides novel retrosynthetic

disconnections for the construction of α-substituted alcohols. We are currently exploring the scope of this transformation.



Scheme 2. Catalytic reductive pinacol-type rearrangement of unactivated diols.

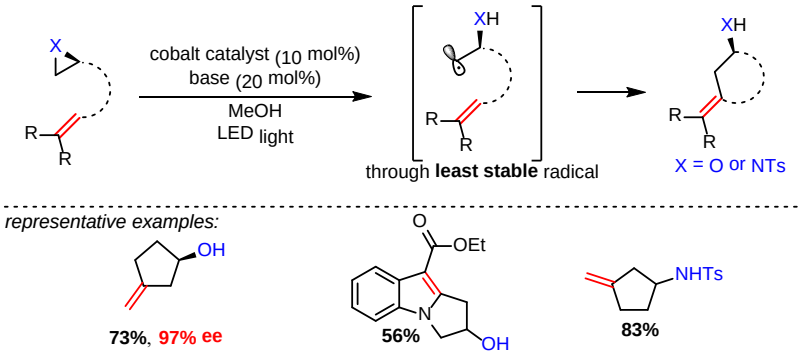
Inspired by the enhanced reactivity of cyclic intermediates in C–O bond reduction, we reasoned that this effect could be harnessed in mechanistically distinct C–O bond cleavage reactions. We thus explored the possibility of using cyclic sulfates, an easily accessible class of electrophiles derived from simple diols, in carbon–carbon bond forming reactions. We have developed a Cu-catalyzed Kumada-type coupling of cyclic sulfates that enables the synthesis of a wide range of functionalized alcohol products in high regio- and chemoselectivity (Scheme 3). The activating effect of the cyclic intermediate is demonstrated by the chemoselective coupling of the cyclic sulfate in the presence of a chemically related tosylate group. Beyond providing a powerful new tool for the construction of functionalized alcohols, this work might encourage the design of new catalytic methods that employ diol-derived cyclic sulfates as electrophiles.



Scheme 3. Copper-catalyzed Kumada-type coupling of cyclic sulfates.

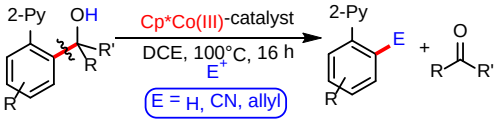
Combining our interest in alkene and C–O bond functionalization, we have developed a Co-catalyzed cross-coupling reaction between epoxides/aziridines and alkenes (Scheme 4). Key to the development of this reaction was the observation that the alkoxide base, generated through S_N2-type epoxide opening by a Co(I)-species, is sufficiently basic to turnover the Co(III)–H species formed at the end of the catalytic cycle. This led to the

development of a fully atom-economical MH-type reaction of epoxides and aziridines, providing a straightforward access to homoallylic alcohols and amines.



Scheme 4. Cobalt-catalyzed cross-coupling between epoxides/aziridines and unsaturated bonds.

Finally, we have also pursued a complementary approach to the functionalization of alcohols that proceeds through the β-alkyl cleavage of C–C bonds. This type of carbon–carbon bond activation usually relies on the use of expensive noble metals such as Pd and Rh. We recently reported the first example of a catalytic C–C bond activation reaction under cobalt catalysis (Scheme 5). A cationic Cp*Co(III) complex could efficiently cleave an arylmethanol starting material using a pyridyl directing group with subsequent trapping of the Co-alkyl intermediate by a suitable electrophile. This new reactivity of cobalt complexes bodes well for the development of sustainable Co-catalyzed C–C bond activation reactions.



Scheme 5. Cobalt-catalyzed functionalized of unactivated C–C bonds.

Future directions: We are currently exploring the application of our boron-catalyzed reaction to the deoxygenation of sugar derivatives. We are also trying to expand the cross-coupling chemistry of cycling sulfates and related alcohol-derived electrophiles to the use of milder coupling partners under Pd and Ni-catalysis, with the goal of developing selective approaches to the functionalization of aliphatic alcohol derivatives.

Publications resulting from this research area: 56, 57, 60-62

External funding: The Leverhulme Trust (postdoc fellowship to B. N. Bhawal)

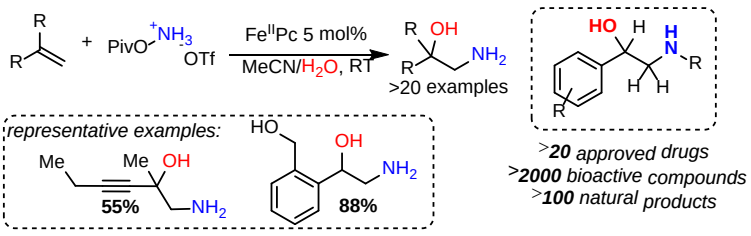
Cooperations: W. Thiel (Mülheim/Ruhr, DE)

2.2.10 Research Area "Direct Catalytic Synthesis of Unprotected Amines" (B. Morandi)

Involved: L. Legnani, G. Prina Cerai

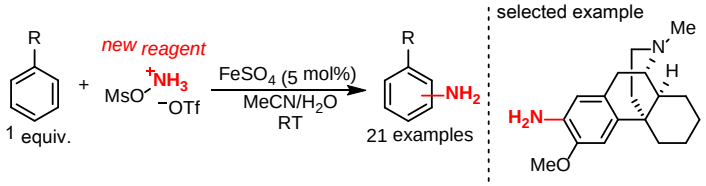
Objectives: The formation of C–N bonds is one of the major challenges in the preparation of bioactive molecules. The direct catalytic amination of hydrocarbons is an attractive approach to address this challenge and has been the subject of intense research efforts. However, most of the methods developed thus far lead to the installation of a protected form of the versatile primary amine group, requiring additional and often challenging protecting group manipulations. In contrast, the research program "Direct Catalytic Synthesis of Unprotected Amines" circumvents the protecting group limitation by enabling a direct access to the desired primary amine. Besides its synthetic potential, this project also addresses a fundamental challenge in catalysis, namely the synthesis of unprotected functionalized molecules that are prone to deactivating coordination of metal catalysts.

Results: Amino alcohols are among the most common bioactive compounds and their synthesis has attracted significant attention. The aminohydroxylation of alkenes is a powerful reaction for the direct preparation of these nitrogen-containing products. However, the conventional methods are limited by the necessity to introduce a protected version of the amino and/or hydroxyl group for efficient reactivity. Since these protecting groups (such as Ts for the amino group) usually need to be cleaved prior to subsequent synthetic steps, we reasoned that a method providing direct access to the free NH_2-group would streamline the preparation of medicinally relevant nitrogen compounds. We have thus developed a Fe-catalyzed preparation of unprotected amino alcohols from alkenes that relies on the use of an easily accessible hydroxylamine-derived reagent (Scheme 1).



Scheme 1. Iron-catalyzed aminohydroxylation of alkenes.

The transformation is particularly effective for the preparation of 2-amino-1-phenylethanols, a structural motif present in over 2000 bioactive compounds and 20 approved drugs, and the utility of the method was demonstrated in the preparation of bioactive compounds. Recently, we could extend the use of a closely related catalytic system and reagent to the direct, innate amination of aromatic substrates (Scheme 2). This novel transformation is operationally simple and can facilitate the amination of a wide range of substrates, including complex bioactive compounds. More importantly, this work is a very rare example of a direct C–H amination reaction leading to the formation of the versatile primary aniline.



Scheme 2. Iron-catalyzed direct C–H amination for the synthesis of primary anilines.

Future directions: We are actively exploring the development of other aminofunctionalization reactions of olefins using the reagents developed in our laboratory. Due to the versatility of nitrogen-centered radicals in hydrogen-atom transfer reactions, we are also planning to explore the use of our catalytic system in aliphatic C–H bond activation. Finally, we are planning to do mechanistic studies to unravel the nature of the aminating species (whether free radical or iron mediated) to provide a foundation for the development of more active systems.

Publications resulting from this research area: 58, 66

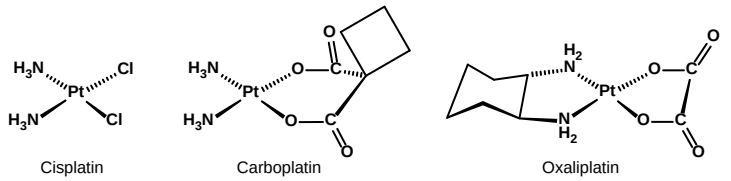
External funding: Fonds der chemischen Industrie (Sachkostenzuschuss)

Cooperations: W. Thiel (Mülheim/Ruhr, DE), J. Bode (Zürich, CH)

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

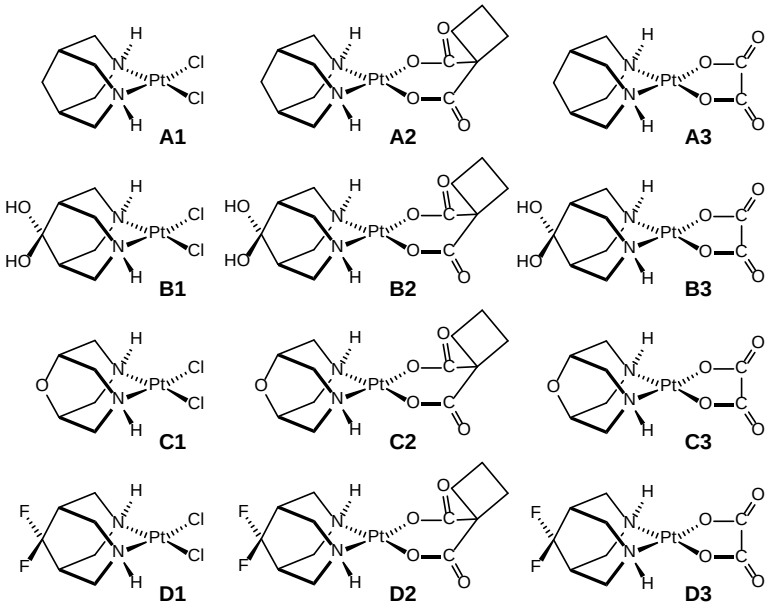
Involved: D. Pollak, R. Mitra, R. Goddard

Objective: Cisplatin, carboplatin, and oxaliplatin represent worldwide clinically administered anticancer drugs. However, there are many problems associated with the



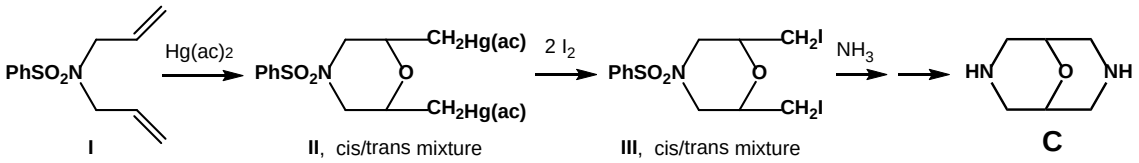
therapy, in particular inherent and acquired platinum resistance, which calls for continued research efforts in this area. Bispidine (3,7-diazabicyclo[3.3.1]nonane) and its congeners represent a limiting case of SAR (structure activity relationships).

In previous work we have synthesized and characterized two series of complexes **A1–A3** and **B1–B3**, in which **A** represents parent bispidine, $C_7H_{12}(NH)_2$, and **B** bispidin-9,9-diol, $(HO)_2C_7H_{10}(NH)_2$. For systematics, we have retained the anions chloride (**1**), 1,1-cyclobutanedicarboxylate (cbdca) (**2**), and oxalate (**3**) in all studies. Compounds **A1–A3** and **B1–B3** displayed cytotoxic potency toward the ovarian cancer cell line A2780 and its Pt resistant subline A2780 CisR similar to that of the standard drugs.

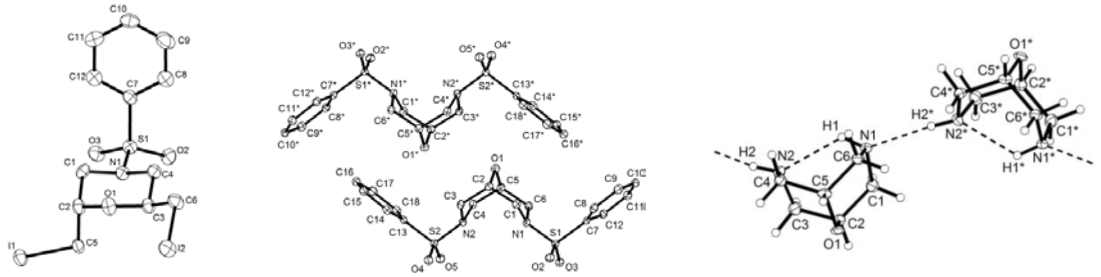


We have now studied complexes **C1–C3** and **D1–D3** in which **C** represents 9-oxa-bispidine, $OC_6H_{10}(NH)_2$, and **D** represents 9,9-difluorobispidine, $F_2C_7H_{10}(NH)_2$.

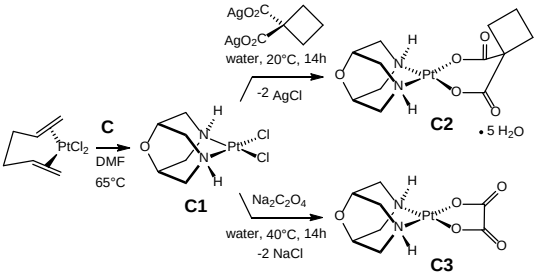
Results: Revisiting the literature synthesis of 9-oxabispidine (**C**), we encountered a series of unexpected problems. These were solved by analyzing **cis/trans-III**, replacing pyridine with THF as a solvent to avoid an unrecognized solute **V·½py**, and altering the work-up.

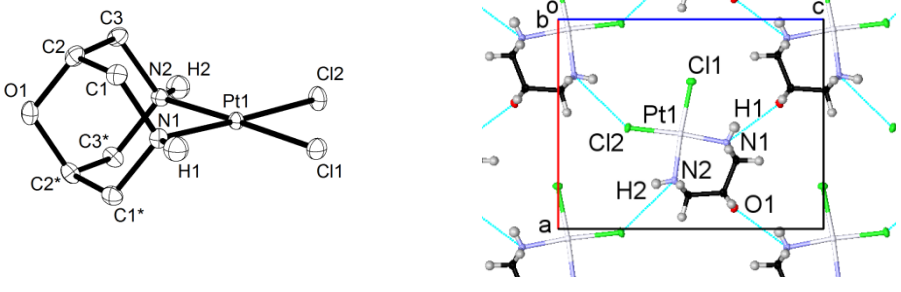


We have characterized two key species (**trans-III** and **V·½py**) and also the highly hygroscopic bispidine **C** by X-ray structure analysis.



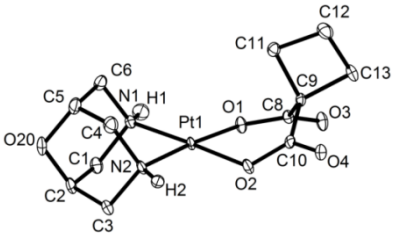
Synthesis of **C1–C3** proceeded on routes we had established before. The dichloride **C1** (crystals were from DMF) is virtually insoluble in most solvents including water. In the crystal, the molecules form a planar 2D network of hydrogen bonds which are strong enough to resist cleavage by water.

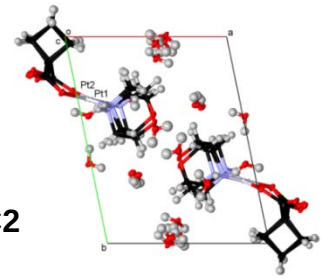




C1

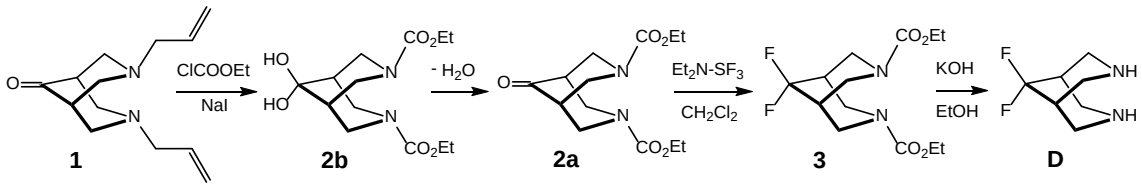
In contrast, the Pt–cbdca complex **C2** forms a pentahydrate, and all individual complex molecules are fully encapsulated by water.



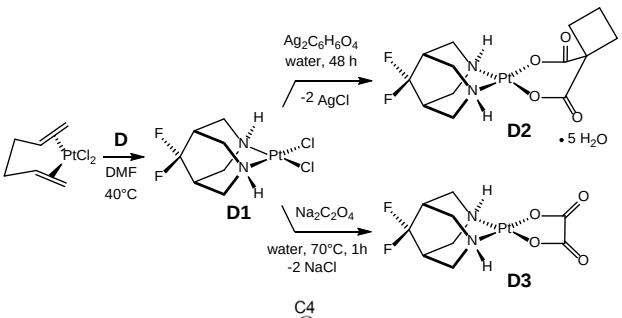


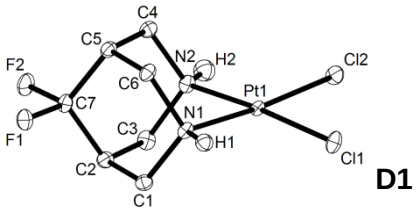
C2

Synthesis of the new 9,9-difluorbispidine (**D**) started from **1** (below) which represents an isolable intermediate of the synthesis of parent **A**. We found that protection of the amino functions as carbamates allowed for a clean reaction, but the ketone had intermediately been converted into the 9,9-diol **2b**. After dehydration of **2b**, ketone **2a** was successfully 9,9-difluorinated by standard techniques to afford **3** which, after deprotection, gave **D**.



The melting points of **A** (198 °C) and **D** (227 °C) are high, in agreement with the presence of a plastically crystalline phase. All isolated bispidines (**A**, **C**, **D**) sublime. Reaction of **D** with (1,5-hexadiene)-$PtCl_2$ affords **D1**, from which **D2** and **D3** are accessible. **D1** crystallizes from water without hydrate formation (in contrast to parent **A1**) and forms a dimer (in contrast to the 2D polymer **C1**). The Pt–cbdca derivative **D2** forms a pentahydrate from water and the structure is isomorphous to those of **A2** and **C2**; thus, 9,9-difluorination does not repel the water surroundings.





D1

Although the complexes of parent **A** show anticancer potency on the µM concentration range, potency of the **B–D** complexes is lower. This is explained by an increased bond polarization of the bispidine skeletons due to the strongly electronegative O or F atoms.

It remains to be determined how lipophilic, but less electronegative substituents such as C or Si at 9-position will alter the anticancer properties of the compounds.

Future directions: No further studies are scheduled due to termination of the group.

Publications resulting from this research area: 68, 71, 73

External funding: none

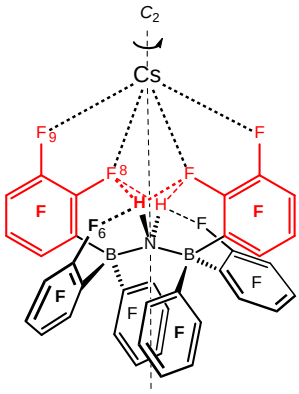
Cooperation: M. Kassack, A. Hamacher (Düsseldorf, DE)

2.2.12 Research Area "FAB Processes for Cesium and Rubidium Exploitation and Radiocesium Separation and Decontamination" (K.-R. Pörschke)

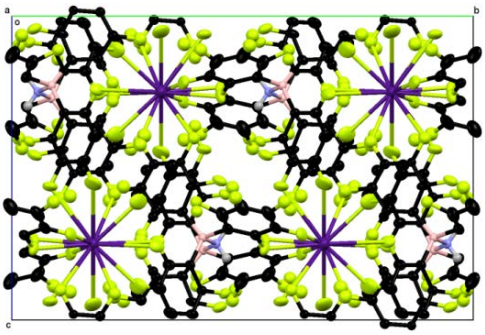
Involved: D. Pollak, R. Goddard

Objective: By serendipity we have discovered a process which might revolutionize the current exploitation of cesium and rubidium, as well as separation of radiocesium for various purposes and radiocesium decontamination.

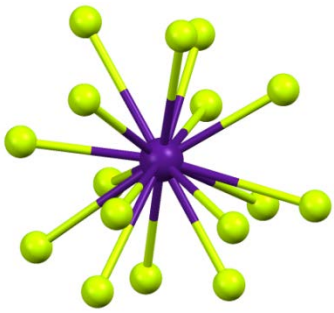
Results: Our interest in weakly coordinating anions (WCAs) has led us to synthesize the new cesium salt, $Cs[H_2NB_2(C_6F_5)_6]$ (**1**). We noticed that **1** is insoluble in water and that it is instantaneously formed by mixing any aqueous solution containing Cs^+ with virtually any source of the $[H_2NB_2(C_6F_5)_6]^-$ anion. The reaction is 100% specific for Cs^+, since only in this case $[H_2NB_2(C_6F_5)_6]^-$ changes its usual asymmetric conformation to an "inverse C_2 symmetric" conformation to form a specific 3D lattice. The X-ray structure of **1** reveals that in the crystal 16 F atoms of five $[H_2NB_2(C_6F_5)_6]^-$ anions surround the Cs^+ cation, which corresponds to a record-setting Werner coordination number of CN = 16 for any ligand element, including hydrogen.



Conformation of **1**



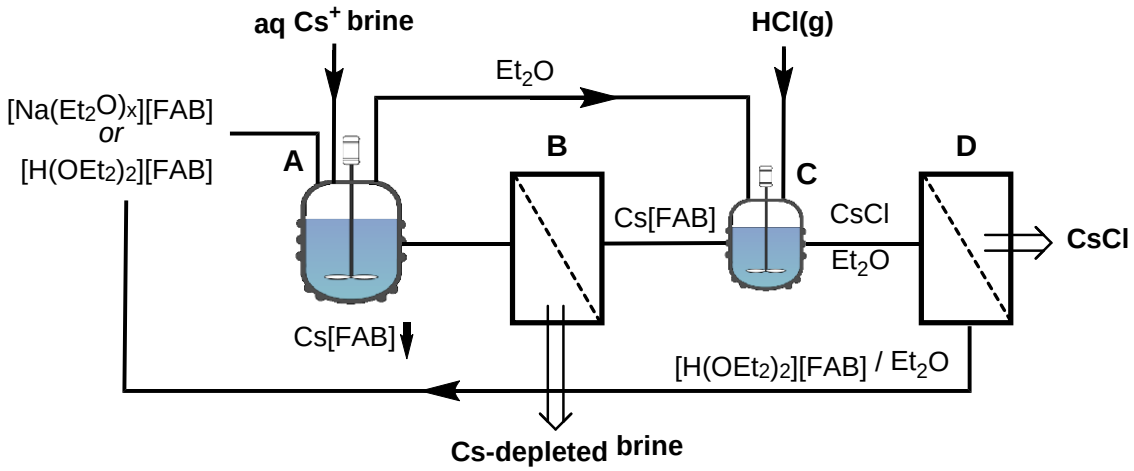
Unit cell of **1**



CsF_{16} coordination in **1**

In the CsF_{16} structure of **1** the largest and least electrophilic monoatomic cation is combined with a (per**f**luoro**a**ryl)**b**orate (FAB) WCA of extremely low basicity, paired with high hydrophobicity. The low electrophilicity entails a low solvation enthalpy of Cs^+, and so the perfectly fitting WCA can compete with the water at Cs^+ on electrostatic grounds. Because of the weak and long $Cs^+\cdots F$ coordination bonds the coordination sphere is large; thus, many F atoms can interact with Cs^+. The high number of cation–anion interactions stabilizes the given 3D network.

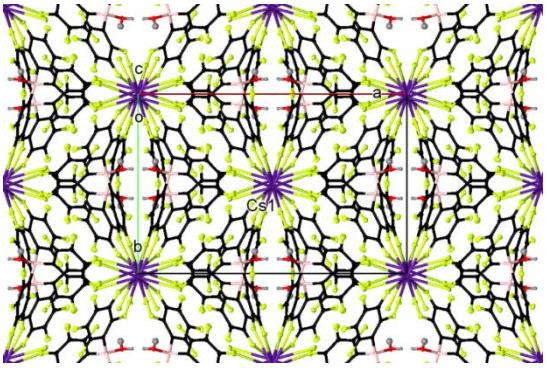
The polymeric **1** precipitates or can be extracted quantitatively from water or acidic solutions containing Cs^+ in concentrations as low as a few ppm. Remarkably, once **1** is isolated from water, it can be cleaved, e.g., by HCl gas in diethyl ether to quantitatively precipitate pure CsCl, with recovery of the FAB WCA in the form of $[H(OEt_2)_2]^+[H_2NB_2(C_6F_5)_6]^-$ (**2**). Feeding **2** back to an aqueous Cs^+ brine and evaporating the organic solvent allows for a cyclic process in which Cs^+ is 100% selectively and quantitatively extracted from any aqueous or acidic Cs^+ solution and "catalytically" converted into, e.g., pure CsCl without formation of byproducts. The following scheme gives a flowchart for the process.



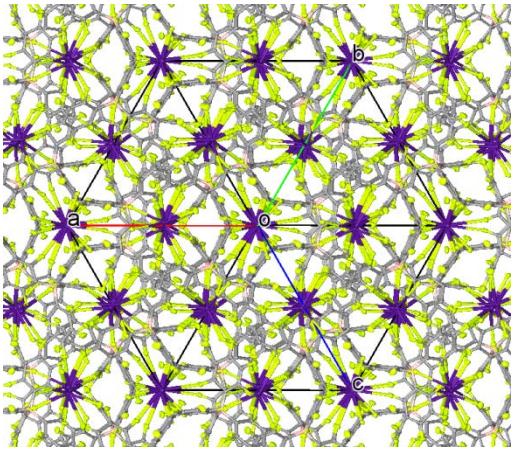
"FAB process" for the exploitation of cesium-containing mineral brines (FAB = **f**luoro**a**ryl**b**orate anion)

In mixer **A** the aqueous or acidic Cs^+ brine is treated with starting Na[FAB] dissolved in some ether (Et_2O or MTBE); the ethereal solvent is distilled off and Cs[FAB] precipitates quantitatively. In separator **B** the precipitated Cs[FAB] is isolated (by filtration or centrifuge) and dried (airstream); the Cs^+-depleted brine is discharged for other uses. In the small mixer **C** the isolated Cs[FAB] is redissolved in the ether distilled from **A**, and the concentrated solution is treated with HCl gas to precipitate CsCl. The product slurry is transferred to separator **D** for isolation of pure CsCl; the ether filtrate containing pure $[H(OEt_2)_2][FAB]$ (or MTBE solvate) is fed back to mixer **A**. Thus, besides the recycled stocks of Na[FAB] reagent and ether solvent, the only reagents which are consumed are the extracted Cs^+ and the equimolar amount of HCl gas. In addition to gaseous HCl, the process is expected to work equally well with other non-aqueous acids such as HBr, H_2SO_4, RCOOH etc. to afford the corresponding Cs salts.

In a similar process, extraction of Cs^+ might occur with $B(C_6F_5)_3$ in aqueous or acidic solutions. $B(C_6F_5)_3$ forms adducts with water such as $(C_6F_5)_3B(OH_2)_x$ (**3**) which in the presence of Cs^+ dimerize to give likewise insoluble $Cs[H(HO)_2B_2(C_6F_5)_6]$ (**4**). The lattice of **4** consists of 2D layers with Cs^+ being only 12-coordinate. For the binding in both 1 and 4 it is decisive that a dinuclear anion of type $[(C6F5)3B(\mu\text{-}X)B(C_6F_5)_3]^-$ is given, featuring a pair of coplanar C_6F_5 groups, one from each $B(C_6F_5)_3$ group. Primary coordination of Cs^+ occurs by two sets of vicinal F atoms of the coplanar C_6F_5 groups, giving rise to a tetradentate chelation by the anion (see drawing of **1**, above).



A quite different situation is given for the anion $[B(C_6F_5)_4]^-$. While the parent $[B(C_6H_5)_4]^-$ forms solvent-free and isomorphous complexes $M[B(C_6H_5)_4]$ with all alkali metals by coordination via the phenyl 6e-donors, this is impossible for the $[B(C_6F_5)_4]^-$ anion. Here, only $Rb[B(C_6F_5)_4]$ and $Cs[B(C_6F_5)_4]$ (and also $Tl[B(C_6F_5)_4]$) form isomorphous 3D networks, giving rise to water-insoluble solids, whereas the lighter alkali metals are increasingly well solvated by water and hence more soluble. Thus, only $Rb[B(C_6F_5)_4]$ and $Cs[B(C_6F_5)_4]$ precipitate from an aqueous solution containing all alkali metals. Worthy of note, these complexes represent the first examples of CN = 15 for any donor atom other than H.



For selective separation of rubidium, a tandem process can be envisaged, in which in the first step Cs^+ is separated by the $[H_2NB_2(C_6F_5)_6]^-$ or $[H(HO)_2B_2(C_6F_5)_6]^-$ anions. In the second step, the solution is treated with $Li[B(C_6F_5)_4]$ to selectively and nearly quantitatively precipitate $Rb[B(C_6F_5)_4]$. Reaction of the latter with an anhydrous acid in ethereal solution affords precipitation of, e.g., pure RbCl together with the recycled anion. By a tandem set-up of two cycles of the given flowchart, the first cycle with $[H_2NB_2(C_6F_5)_6]^-$ or $[H(HO)_2B_2(C_6F_5)_6]^-$ as an extracting anion for Cs^+ and the second with $[B(C_6F_5)_4]^-$ for extracting Rb^+, any brine containing, inter alia, Cs^+ and Rb^+ (but free from Tl^+) may be exploited for these elements in a cyclic process, allowing

selective and quantitative isolation of pure salts CsX and RbX. We suggest the term "FAB process" for referring to the Cs^+ and Rb^+ extraction by fluoroarylborate anions.

There are numerous applications conceivable for the FAB process, notably for Cs:

(a) Exploitation of Cs and Rb minerals. The FAB process avoids the otherwise numerous recrystallizations, handlings of large volumes, and environmental problems associated with current industrial processing of Cs and (less important) Rb.

(b) Environmental issues. Viewing current cesium production, full removal of Cs^+ is a pressing problem because of environmental reasons. Using FAB reagents as an additive to a final settling basin for the brine will allow quantitative sedimentation of Cs[FAB] and Rb[FAB] and full exploitation of the contained Cs and Rb.

(c) $^{135/137}$Cs Fission Product Extraction (FPEX). Nuclear fuel reprocessing occurs by the PUREX and UREX processes. In the joined FPEX process, $^{135/137}Cs^+$ is currently extracted by **c**hlorinated **c**obalt bis(**d**icarbollide), $[CCD]^-$. Cs[FAB] extraction appears superior to current Cs[CCD] extraction, since the FAB reagents are more readily available, more selective, and only a single separation step is necessary, which simplifies the process, reduces costs and waste, and allows for saver execution.

(d) ^{137}Cs technical and radiopharmaceutical applications. The FAB process should allow ready preparation of pure ^{137}Cs[FAB] and other ^{137}CsX radioisotope compounds by the modified FPEX process (see c) and easier handling of the compounds. Typical commercial applications for ^{137}CsX compounds are, inter alia, sewage sludge sterilization, furnace lining controlling, and cancer afterloading therapy.

(e) ^{131}Cs radiopharmaceuticals. ^{131}Cs (t½ = 9.7 d) is used for cancer seed implantation (brachytherapy). For this purpose, ^{131}Cs is prepared by treating an aqueous $^{130}Ba^{2+}$ solution with neutrons to afford ^{131}Ba, which transforms into ^{131}Cs. The (slowly formed) ^{131}Cs must be continuously removed to avoid further neutron capture to give ^{132}Cs. Precipitating $^{131}Cs^+$ with [FAB]– in aqueous solution is expected to allow for fast, quantitative, and continuous separation of pure ^{131}Cs[FAB] from $^{130/131}Ba^{2+}$.

(f) $^{135/137}$Cs decontamination. Waste waters from nuclear plants or discharges form nuclear plant accidents containing $^{135/137}$Cs loadings can be reprocessed, with Cs[FAB]

separation being effective down to the ppm level. $^{135/137}$Cs decontamination of humans or mammals is also conceivable, challenging the current Prussian blue therapy.

Future directions: No further studies are projected due to termination of the group.

Publications resulting from this research area: 72, two patent applications

External funding: none

Cooperations: none

2.2.13 Publications 2014-2016 from the Department of Homogeneous Catalysis

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