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, and study mechanisms of homogenous catalytic reactions (B. List, K.-R. Pörschke, M. Klußmann, N. Maulide).

Since leadership of the department of homogenous catalysis was taken over by Professor Benjamin List in 2005, it has grown significantly from ca. 15 members to currently > 50 members, including the groups of Professor K.-R. Pörschke, who has been a group leader at the institute since two decades now, Dr. M. Klußmann (group leader since 2007), and now also of Dr. N. Maulide, who has joined the department in 2009.

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 mechanism by which organocatalysts activate their substrates.

Furthermore, in 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.

Research in the laboratory of **Professor Pörschke** aims at a deeper mechanistic understanding of transition metal catalyzed reactions. The group conducts fundamental research in the areas of coordination chemistry, organometallic chemistry, homogeneous catalysis, and solid state phase properties. 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).

During the last almost four years, the group of **Dr. Klußmann** has made its name in the "hot area" of oxidative cross-couplings. They investigate reactions that allow the coupling of two C-H-fragments, establishing a C-C-unit and formally two H atoms. The substrates are activated under oxidative conditions, ideally resulting in water as the only byproduct. A breakthrough was achieved last year with the discovery of the completely metal free "Autoxidative Carbon–Carbon Bond Formation from Carbon–Hydrogen Bonds".

The group of **Dr. Maulide** was established in 2009 after its leader has obtained a prestigious and highly competitive Max-Planck Research group leader position, which is fully supported by central MPG funds. The group has diverse activities in the area of organic synthesis and catalysis. Accordingly, within a short period, the Maulide team has already published three papers in Angewandte Chemie on entirely different subjects, including a new variant of the Claisen rearrangement, Pd-catalysis, and a novel ylide transfer reaction. The group has attracted funding from various sources and is currently massively growing.

2.2.1 Research Area "Crystal Structures of Proline Derived Enamines" (B. List)

Involved: D. A. Bock, C. W. Lehmann

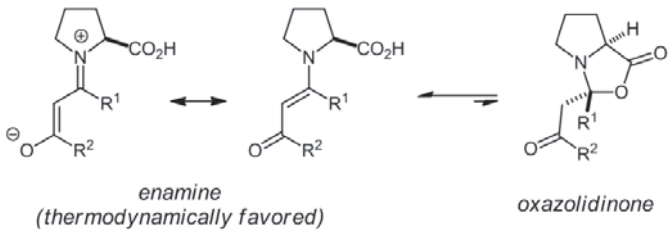
Objective: Within the last ten years, enamine catalysis, the catalytic activation of carbonyl compounds via enamine intermediates and a concept originally devised in our laboratory, has grown into a powerful approach to organic synthesis. Among the many different primary and secondary amine catalysts that have been developed in this field, the amino acid proline remains a privileged motif and there are literally dozens of reaction types that are catalyzed with this wonderful natural product. Proline derived enamines of aldehydes and ketones are key intermediates in the catalytic cycles of these reactions. Surprisingly though, such enamines have remained entirely hypothetical and long resisted attempts at their structural characterization. Such information however, appears to be highly valuable towards understanding the mechanistic details with which proline catalyzes carbonyl transformations. Here we report and discuss crystal structures of a series of stabilized enamines of proline and of some of its analogues.

Results: The main difficulty in previous attempts at characterizing proline enamines has been the tendency of carbonyl compounds to reversibly react with proline giving oxazolidinones instead of the enamines. Rather than the enamine, thermodynamics favor the oxazolidinone constitutional isomer, in which one C—O- and one C—H-σ-bond are gained at the expense of one C—C-π-bond and one O—H-σ-bond:

In view of the catalytic action of proline, oxazolidinone formations with aldehyde or ketone substrates are best described as *parasitic equilibria* since they are presumably not leading to product but inhibit its formation. While aldehyde derived "Seebach-oxazolidinones" have long been known, their ketone analogues have only recently been detected and characterized by us and later isolated also by Seebach and Eschenmoser *et al.* Interestingly, the condensation product of acetone and proline has also been detected by Metzger *et al.* using mass spectrometry. In light of our previous careful NMR-spectroscopic characterization of this adduct as an oxazolidinone, their assignment as an enamine appears to be questionable though. In addition, Seebach and Eschenmoser *et*

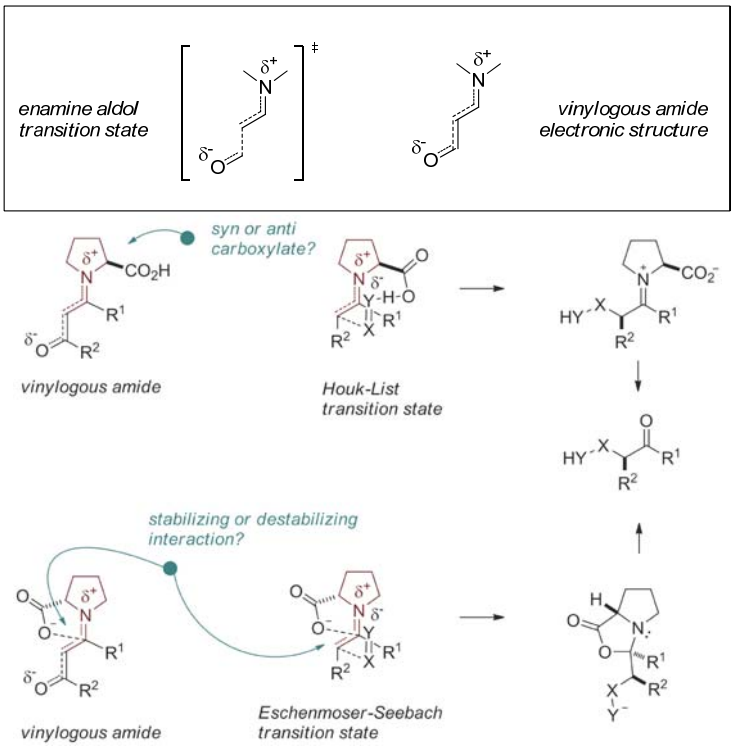
al. have partially characterized an ammonium salt of the prolyl enamine of cyclohexanone. Disappointingly though, crystallographic data on proline enamines are entirely lacking. In fact, to the best of our knowledge and based on a search of the Cambridge Structural Database (CSD, Version 5.31, Nov 2009) crystal structures of any proline derived enamines have not been reported previously.

At the outset of this work several years ago, we wondered whether or not it is possible to crystallize proline enamines that are formally derived of 1,3-dicarbonyl compounds. We hypothesized that, in contrast to the situation of the parent unconjugated system, such structures may in fact be more stable than the corresponding oxazolidinones since cyclization would interrupt conjugation of the vinylogous amide system.

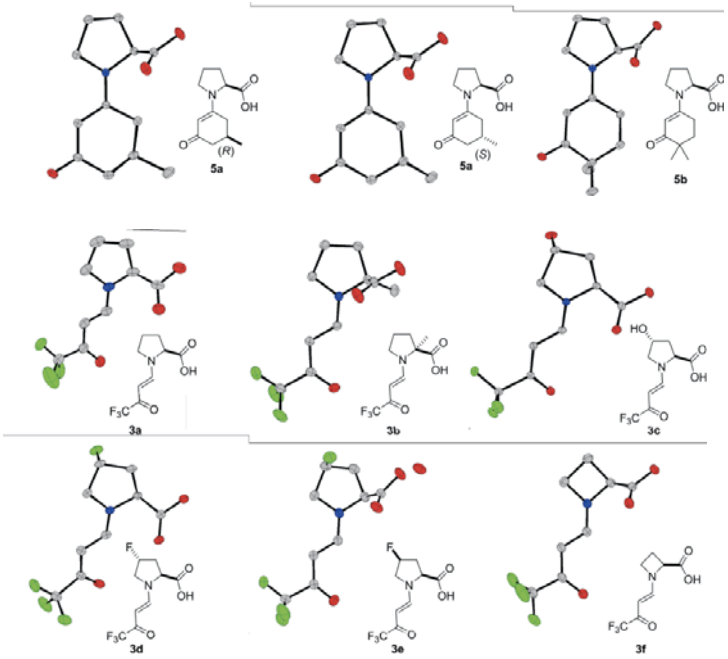


Indeed, proline derived vinylogous amides (or enaminones) have been reported previously and characterized spectroscopically as enamines. More important for the present discussion is that such vinylogous amides may be considered transition state models of a proline enamine engaging in the reaction with an electrophile. In both cases is electron density removed from the electron rich enamine-π-system. This electronic redistribution should impact the enamine geometry. For example, because of the partial iminium ion character of the vinylogous amide (and in fact of the corresponding bond-forming transition state), the sp^3-character and consequently pyramidalization at nitrogen should be reduced. Similarly, the enaminone conjugation will influence the bond-lengths of the system such that the enamine double bond will be *longer* than that expected for the analogous unconjugated proline enamine. The C—N bond of the enamine system in turn, is expected to be *shorter*, reflecting the beginning π-character of this bond. We reasoned that crystal-structural information on such vinylogous amides would provide additional valuable information on stereochemical aspects of such enamines, *i.e.* double bond configuration and *syn*- vs. *anti*-positioning of the carboxylate relative to the enamine double bond, which corresponds to an (*E*)- vs. (*Z*)-configuration at the forming iminium ion.

Additionally, following the logic outlined before, the question of how much oxazolidinone character is already developed in the transition state might potentially be answered by such structural investigations. According to a recent proposal by Eschenmoser and Seebach, the reaction of the proline enamine with an electrophile involves an anionic cyclization of the *syn*-configured carboxylate into the enamine α-carbon with concomitant bond formation at its β-carbon in the sense of an electrophile induced lactonization. This mechanism has already been discussed by Hajos before and leads directly to an oxazolidinone. If the postulated bond-formation between the carboxylate-oxygen and the enamine α-carbon in the transition state would indeed contribute to its stabilization, the question must then be asked if such an interaction should not also occur in the corresponding vinylogous amide system. Alternatively, C—O-bond formation may actually *destabilize* both the enaminone and, in fact, the corresponding transition state by interrupting conjugation.



The crystal structures of a series of enamines **3** and **5** could be elucidated successfully and yielded the solid state molecular conformations shown.

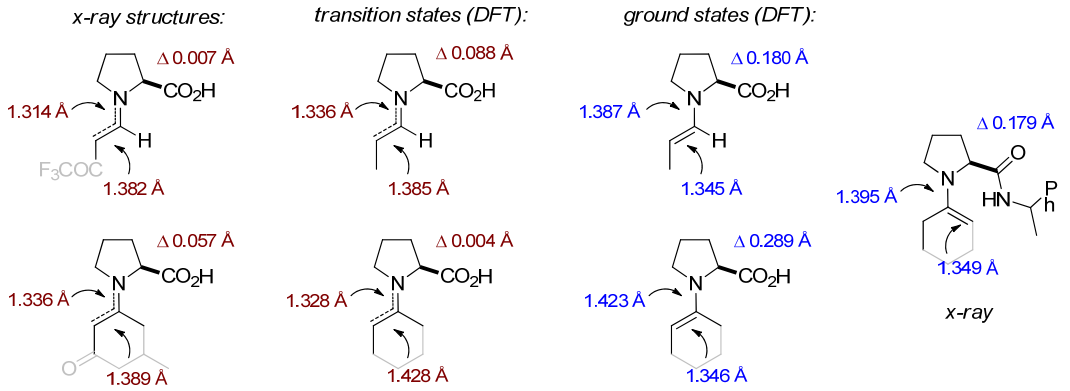


Several observations have been made: (1) Consistent with our hypothesis that resonance interruption should generally favor the enamine constitutional isomer, the corresponding oxazolidinone form is not displayed in any of the ten structures. Also, potential near attack conformations of a carboxylate oxygen engaging in a reaction with the enamine α-carbon are not observed. (2) As expected, the studied enamines exclusively display an (*E*)-geometry. (3) Of the ten structures obtained, nine display an *anti*-arrangement of the carboxylic acid and the enamine double bond. (4) All enamine structures show intermolecular hydrogen bonding interactions between the carboxylic acid and the ketone carbonyl group.

Interpreting these results in line with our original hypothesis that 1,3-dicarbonyl-derived proline enamines, to a some degree, may be viewed as transition states models of the corresponding proline-catalyzed transformations such as the aldol reaction, we notice the following: (1) The *anti*-arrangement of the (*E*)-enamine and the carboxylate, which is also required in the Houk-List transition state but stands in contrast to that suggested by Eschenmoser and Seebach *et al.*, is generally preferred in the crystal structures of the studied enamines. (2) No evidence for a positive interaction of the carboxylate with the enamine α-carbon, as suggested by Seebach and Eschenmoser for the transition state of proline catalyzed reactions has been obtained in the investigated enamine structures. (3) The intermolecular hydrogen-bonding between the carboxylate and keto groups observed in all of our crystal structures chemically resembles the intramolecular hydrogen bond proposed in the Houk-List transition state.

It is instructive to compare the obtained X-ray structures with the calculated ground and transition state structures.

As we had expected, the double bond length (1.382 Å) in the X-ray structure of proline enaminone **3a** is longer than that of the calculated enamine ground state of the proline enamine of propionaldehyde (1.345 Å) but quite similar to that in the corresponding transition state (1.385 Å).



These structural similarities are also observed in the ketone series: The enamine double bond length in compound **5a** (1.389 Å) and in the cyclohexanone Houk-transition state (1.428 Å) are significantly longer than that calculated for the corresponding ground state (1.342 Å) and also that found in an X-ray structure of a proline amide-derived cyclohexanone enamine (1.349 Å) previously obtained by Eschenmoser *et al*. Moreover, the enamine C—N-bond-lengths in the cyclohexanone series are very similar in both the structure of **5a** and the DFT-structure of the corresponding transition state further validating our transition state/enaminone analogy.

We have described the first X-ray structures of both aldehyde and ketone derived proline enaminones and compared their structures with the calculated Houk-List and the postulated Seebach-Eschenmoser transition states. Obviously, one should interpret such structures carefully and drawing conclusions on possible transition states from X-ray structures is challenging in general. Nonetheless, we note that the vast majority of the ten X-ray structures we have been able to obtain, are consistent with our previously proposed transition states of proline catalyzed aldol, Mannich-, α-amination, and-aminoxylation reactions. After the submission of this manuscript, Gschwind *et al*. have for the first time detected aldehyde-derived proline enamines by NMR spectroscopy. Remarkably, only the *anti*-conformer is observed in solution similarly to the results we report within this manuscript.

Publications resulting from this research area: 295

External Funding: Deutsche Forschungsgemeinschaft

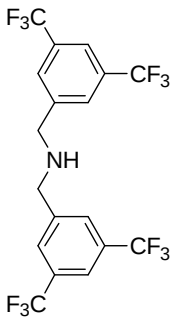
Cooperations: none

2.2.2 Research Area "Catalytic Asymmetric Epoxidation of Electron-Deficient Olefins" (B. List)

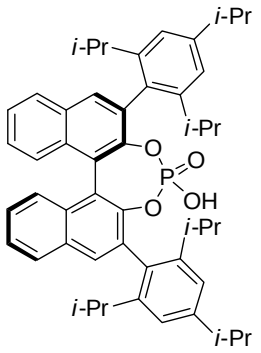
Involved: O. Lifchits, C. M. Reisinger, X. Wang

Objective: As one of the most synthetically useful transformations, the catalytic asymmetric epoxidation of olefins continues to define the state of the art in asymmetric synthesis. Despite recent advances in expanding the scope of epoxidation to challenging substrate classes, the reaction of simple cyclic and linear enones and α-branched enals has been rather limited in efficiency, selectivity, and generality. Our previous work with amine catalysis and asymmetric counteranion-directed catalysis (ACDC) demonstrated the potential of these mild yet powerful activation modes in enantioselective transformations, including the epoxidation of unbranched enals. The aim of this project was to identify catalyst systems based on primary aminocatalysis and ACDC to develop simple, efficient and highly enantioselective methodologies for the epoxidation of enones and α-branched enals.

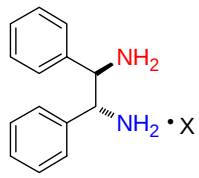
Results: Following our recent discovery that the achiral secondary amine catalyst **1** paired with a chiral phosphoric acid TRIP (**2**) effectively catalyzes the epoxidation of unbranched enals, we wished to explore other challenging substrate classes. Focusing on the epoxidation of cyclic enones **3** with hydrogen peroxide, we found that primary amines were significantly more effective in catalyzing the epoxidation of these more congested substrates. In addition, a second amine site in the catalyst proved to be essential for better enantioselectivity, presumably because it coordinates and directs hydrogen peroxide to one of the enantiofaces of the double bond. Based on these findings, two equally effective catalyst combinations **5** and **6a** were identified for the epoxidation of cyclic enones. Both catalyst salts feature a chiral bifunctional primary amine and an acid co-catalyst. While the chiral amine in the catalyst pair **5** benefits from an additional ACDC effect of the chiral acid, the readily prepared cinchona-based amine in **6a** was found to be effective with achiral co-catalyst trifluoroacetic acid (TFA). Gratifyingly**,** the pseudoenantiomeric cinchona-derived amine in catalyst pair **6b** could deliver the opposite enantiomer of the epoxide product with equal efficiency and selectivity.



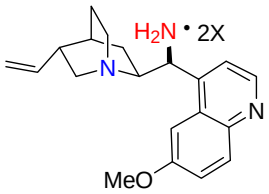
1



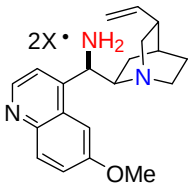
2 ((*R*)-TRIP)



5 (X = (*S*)-TRIP)

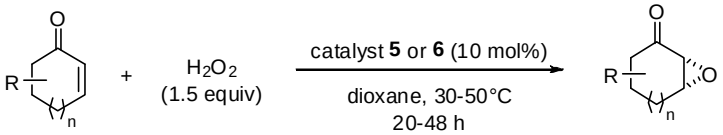


6a (X = TFA)

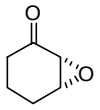


6b (X = TFA)

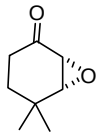
Using the optimal catalyst systems **5** and/or **6a-b** and aqueous hydrogen peroxide, a broad range of cyclic enones were epoxidized with excellent enantioselectivity.



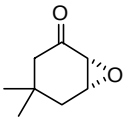
3 **4**



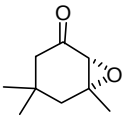
4a
cat **5**: 68%, 96:4 er
cat **6a**: 58%, 3:97 er



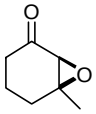
4b
cat **5**: 80%, 97:3 er



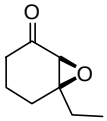
4c
cat **5**: 76%, 98:2 er



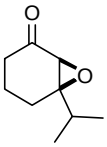
4d
cat **5**: 63%, 96:4 er



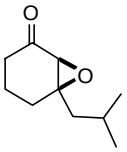
4e
cat **6a**: 70%, 98:2 er



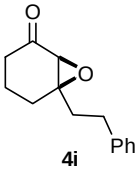
4f
cat **6a**: 73%, 98.5:1.5 er



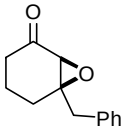
4g
cat **6a**: 79%, 99:1 er



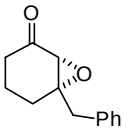
4h
cat **6a**: 73%, 98:2 er



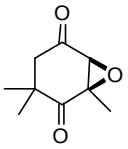
4i
cat **6a**: 84%, 98.5:1.5 er



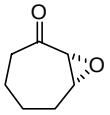
4j
cat **6a**: 78%, 99:1 er



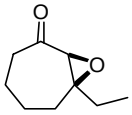
4j
cat **6b**: 77%, 98.5:1.5 er



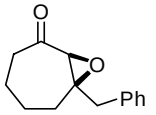
4k
cat **6a**: 49%, 96:4 er



4l
cat **5**: 82%, 99:1 er

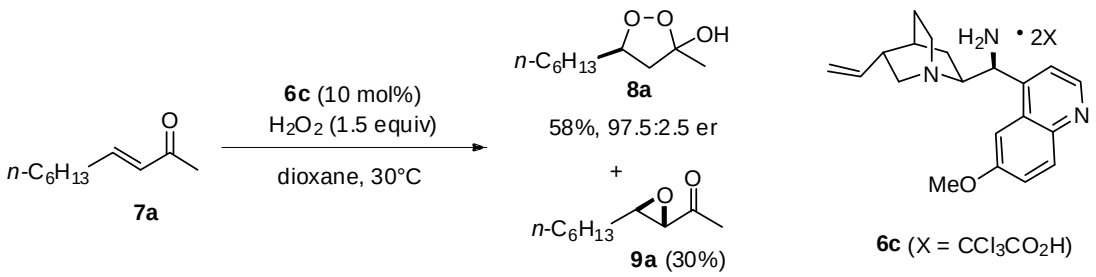


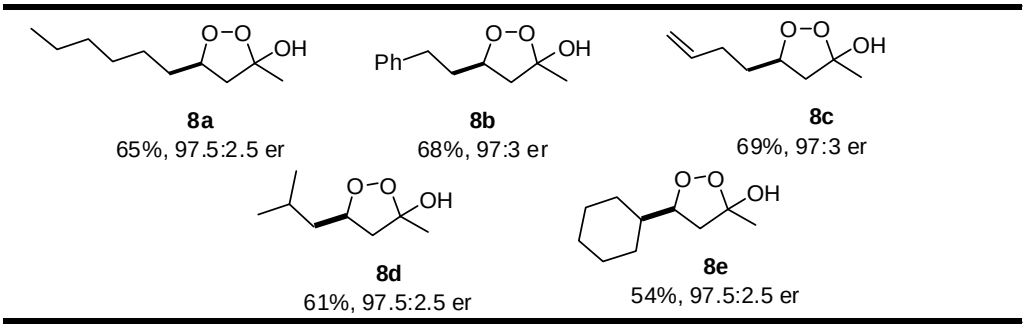
4m
cat **6a**: 85%, >99.5:0.5 er



4n
cat **6a**: 85%, >99.5:0.5 er

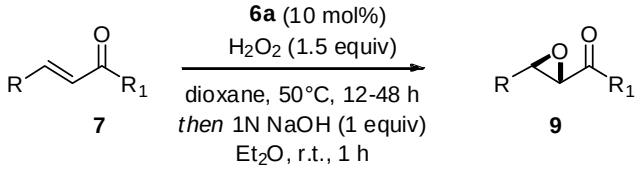
We next turned our attention to linear aliphatic enones, which have presented considerable challenges to previous methods. Remarkably, when 2-decenone **7a** was subjected to aqueous hydrogen peroxide and catalyst **6c**, peroxyhemiketal **8a** was obtained in 58% yield and 97.5:2.5 er along with 30% of the expected epoxide **9a**. Optimization of conditions allowed for the formation of a range of peroxyhemiketal products in useful yields and excellent enantioselectivities.

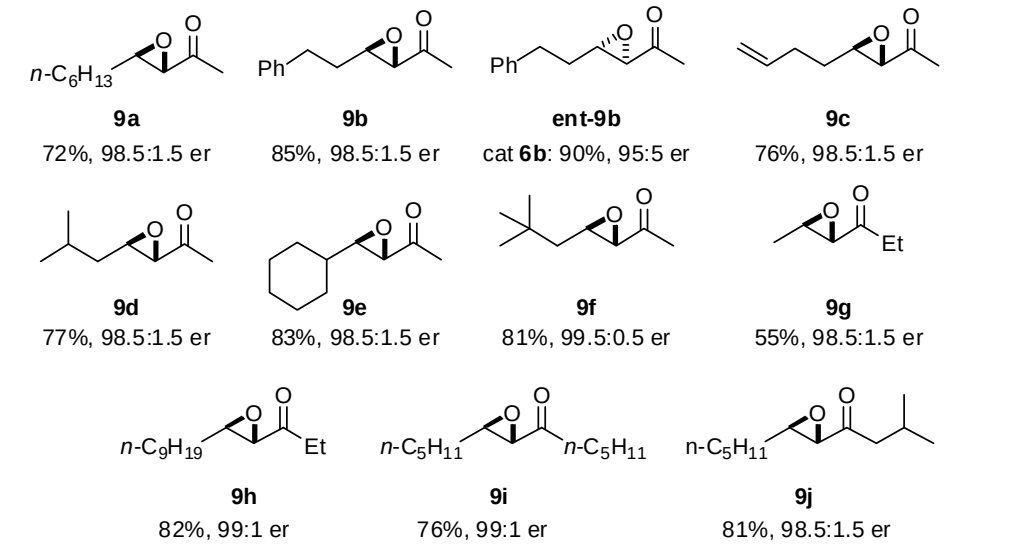




conditions: **6c** (10 mol%), H_2O_2 (3 equiv), dioxane, 32°C, 36-48 h

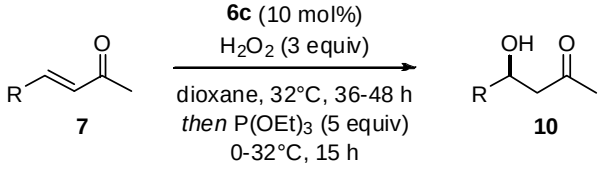
Slightly modified conditions for epoxidation followed by a basic workup provided the epoxides **9** in good yields and very high enantioselectivities.

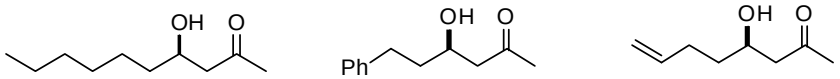




Peroxyhemiketals **8** contain a 1,2-dioxolane subunit which is present in many natural products and bioactive molecules. In addition, as a further illustration of their

usefulness, these compounds could be converted to β-hydroxyketones **10** in a one-pot operation by adding a reducing agent ($P(OEt)_3$) at the end of the reaction. This method to access β-hydroxyketones complements the asymmetric proline-catalyzed aldol reactions, in which α-unsubstituted aldehydes still present a significant challenge.





10a 59%, 97:3 er

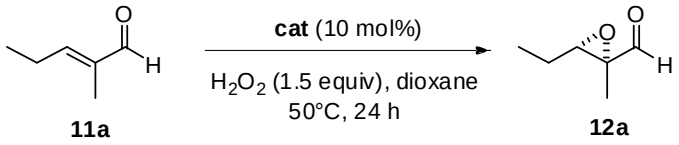
10b 53%, 96.5:3.5 er

10c 55%, 96:4 er

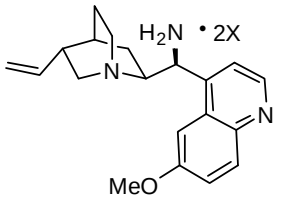
10d 56%, 96.5:3.5 er

10e 46%, 96:4 er

Recognizing the success of cinchona amine-based salts **6** in the epoxidation of sterically demanding substrates, we next examined α-branched enals, for which no direct asymmetric epoxidation methodology existed. Gratifyingly, the epoxidation of (*E*)-methylpent-2-enal **11a** with catalyst salt **6a** delivered the desired product **12a** with an encouraging er of 93:7 and dr of 75:25. Optimization of the catalyst system revealed that the additional and matched ACDC effect of (*R*)-TRIP as the acid co-catalyst dramatically improved the stereoselectivity to 99.5:0.5 er and 96:4 dr.

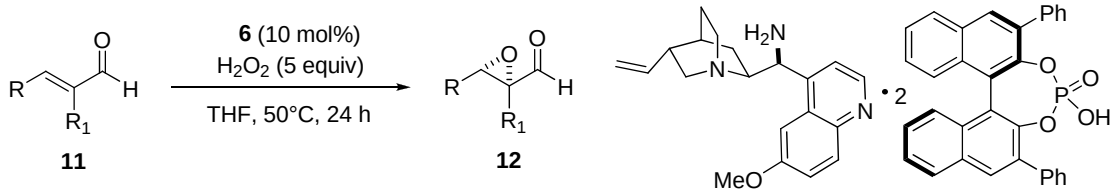


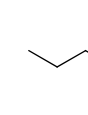
catalyst	conversion, %	er (**12a**)	dr (**12a**)
6a	38	93:7	75:25
6d	84	99.5:0.5	96:4



6a (X = CF_3CO_2H)
6d (X = (*R*)-TRIP)

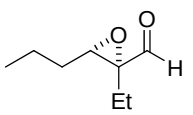
After further optimization to achieve complete conversion, a range of α,β-disubstituted and α-substituted enals were epoxidized with good yields and consistently excellent enantioselectivity.





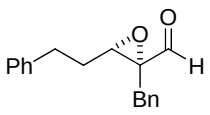
12a

cat **6e**: 43%, 92:8 dr
98.5:1.5 er



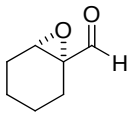
12b

cat **6e**: 64%, 83:17 dr
99:1 er



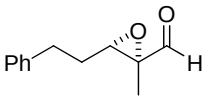
12c

cat **6e**: 77%, 90:10 dr
99:1 er



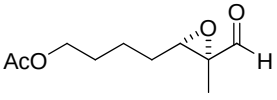
12d

cat **6e**: 70%, 98.5:1.5 er



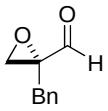
12e

cat **6e**: 75%, 95:5 dr
98.5:1.5 er



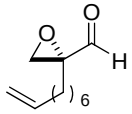
12f

cat **6e**: 66%, 93:7 dr
99:1 er



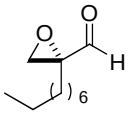
12g

cat **6d**: 78%, 99:1 er



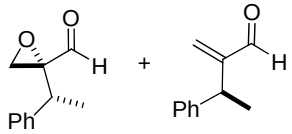
12h

cat **6d**: 74%, 98.5:1.5 er



12i

cat **6d**: 78%, 99:1 er



12j **11j**

kinetic resolution at 53% conversion

cat **6d**: 44%, 96:4 er cat **6d**: 47%, 97:3 er

In summary we developed highly enantioselective, general and operationally simple protocols for the epoxidation of hitherto challenging classes of electron-deficient olefins. Both cyclic and linear enones, as well as α-branched aldehydes could be epoxidized by employing the easily prepared cinchona-derived amine catalyst in combination with either achiral or chiral acid co-catalyst.

Publications resulting from this research area: 95,135, 348

External Funding: Deutsche Forschungsgemeinschaft; Fonds der Chemischen Industrie

Cooperations: none

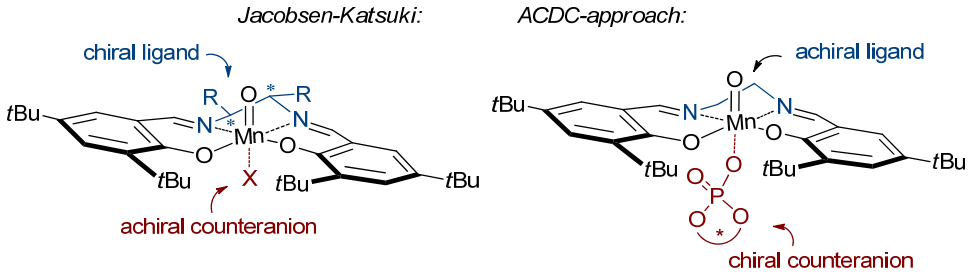
2.2.3 Research Area "Asymmetric Counteranion-Directed Transition Metal Catalysis" (B. List)

Involved: S.-H. Liao, G.-X. Jiang, Y.-W. Fang, R. Halder

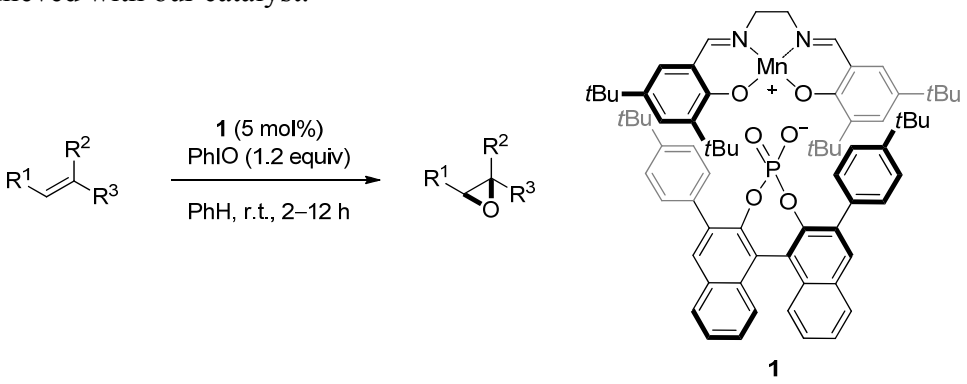
Objective: Inspired by pioneering contributions on chiral Brønsted acid mediated reactions and our own studies in aminocatalysis, a new concept for asymmetric synthesis–asymmetric counteranion-directed catalysis (ACDC) has been developed in our group. According to this concept, catalytic reactions that proceed via cationic intermediates can be performed highly enantioselectively by the incorporation of a chiral counteranion into the catalyst. After our initial proof of this concept with organocatalytic transfer hydrogenations and epoxidations, ACDC has recently been extended to transition-metal catalysis with our palladium-catalyzed Tsuji–Trost-type α-allylation of aldehydes and Toste's gold-catalyzed allene cyclizations. The aim of this project is to further explore the potential of the ACDC concept as a general strategy for asymmetric synthesis, especially in transition-metal catalyzed reactions, such as Mn-catalyzed epoxidation, Pd-catalyzed aza-Claisen rearrangement, Ru-catalyzed hydrovinylation of olefins, and Ru-catalyzed olefin metathesis.

Results:

A) Stimulated by an important contribution from Kochi et al., Jacobsen and Katsuki have significantly advanced the catalytic asymmetric epoxidation of unfunctionalized alkenes by introducing chiral Mn^{III}-salen catalysts. These complexes display a broad substrate scope although certain olefin classes still fail to be converted with high enantioselectivity. Interestingly, cationic Mn-salen complexes are C_2-symmetrical and inherently chiral–even when the salen ligand itself is achiral. In case of the Jacobsen-Kastuki epoxidation, the chiral backbone of the salen ligand fixes the complex in one of the two enantiomorphic confirmations. We hypothesized that a chiral counteranion should also be able to induce a preference for one of the two enantiomorphic conformations. Specifically, chiral binol-derived phosphate anions are ideally suited for our purposes, because in addition to possibly inducing one enantiomorphic conformation of the cationic complex, these ions may also amplify the chiral microenvironment around the metal center with suitable substituents at the 3,3'-positions of the phosphates. Overall, this may lead to a new type of chiral Mn-salen catalyst with unique properties.



For the catalyst elaboration, modification on both achiral salen ligands and chiral phosphate anions was carried out, and complex **1** stood out as the most efficient Mn-salen/phosphate combination. Under optimized conditions (5 mol% catalyst, 1.2 equiv of PhIO as oxidant and benzene as solvent), various alkenes can be epoxidized smoothly at room temperature with high level of enantioselectivity. These observed stereoselectivities closely resemble those obtained with the Jacobsen catalyst, although in the cases of electron-deficient alkenes and styrene, slightly higher enantioselectivities are achieved with our catalyst.



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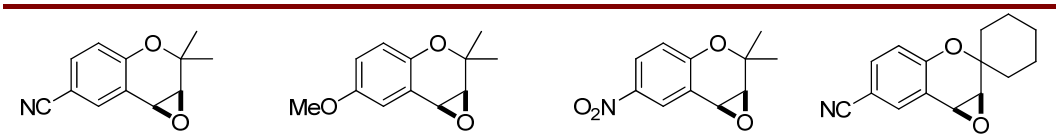
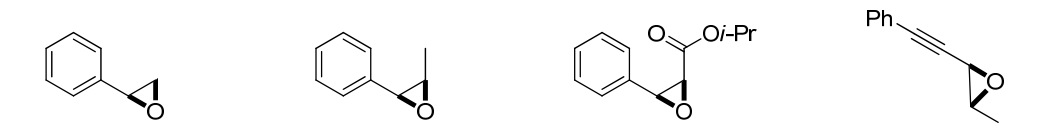
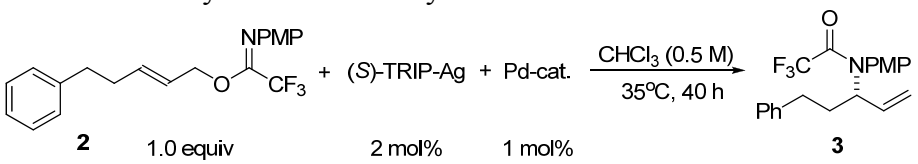




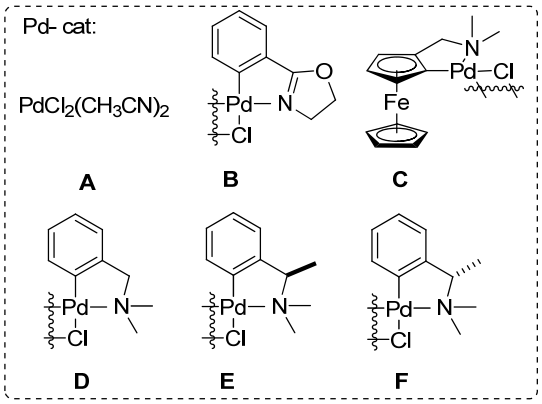
Usually, neutral donor ligands are added to the Jacobsen-Katsuki epoxidation reaction mixture to increase the reactivity and enantioselectivity, but with our catalyst system this is not necessary. The high activity of our ion-pair catalyst may result from the weakened covalent character of the sterically overloaded ("frustrated") manganese-

phophate Lewis pair. Other metal-salen/phosphate ion pair-catalyzed reactions are under investigation.

B) The asymmetric Pd^{II}-catalyzed Overman rearrangement of allylic trihaloacetimidates to allylic trihaloacetamides is an efficient approach for the transformation of allylic alcohols to less available chiral allylic amines. Great progress has been achieved with planar chiral oxazoline-based palladacycles COP-X and FOP-X, but the synthesis of these catalysts is not a trivial task. We envisioned that the replacement of the achiral counteranion (i.e. Cl^-) with a chiral phosphate anion in similar though simpler complexes could lead to a new type of catalyst, which may exhibit different activity and selectivity. After an extensive screening of several palladium complexes in combination with chiral binaphthol-derived phosphoric acid silver salt (*S*)-TRIP-Ag, we found that upon treating trifluoroacetimidate **2** with a catalytic amount of Pd complex **F** and (*S*)-TRIP-Ag, the corresponding rearrangement product **3** can be obtained in high yield and enantioselectivity. Further investigation on the substrate scope and synthetic application of the reaction is underway in our laboratory.

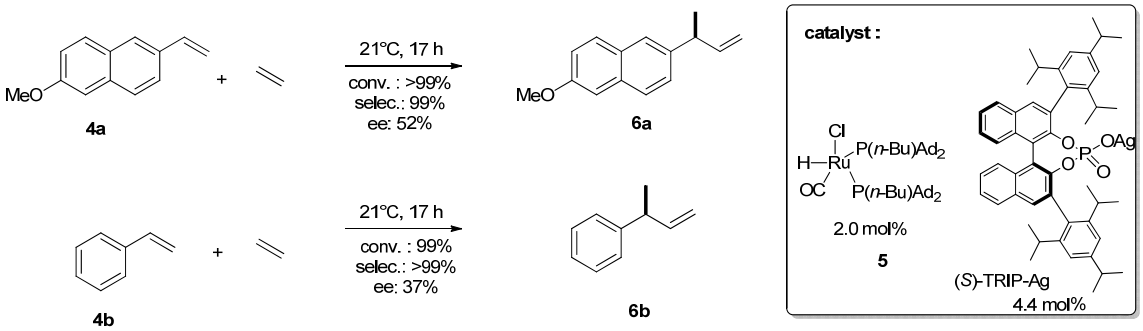


Entry	Pd-cat.	Yield (%)	e.r.
1	A	20	53.1 : 46.9
2	B	94	68.0 : 32.0
3	C	93	92.8 : 7.2
4	D	94	97.3 : 2.7
5	E	96	94.5 : 5.5
6	**F**	**93**	**98.3 : 1.7**
7	F (no Ag salt)	99	50.0 : 50.0
8	(only Ag salt, no Pd)	0	---



C) The asymmetric hydrovinylation of olefins is one of a handful of catalytic asymmetric reactions that uses only feedstock carbon sources for the synthesis of valuable fine chemical intermediates. For the asymmetric hydrovinylation, all successful catalysts are based on Ni complexes incorporating chiral ligands such as azaphospholane, phosphinite, and phosphoramidite. Inspired by the reported results, initially, we extended our ACDC concept to Ni-catalysis but only low enantioselectivity

was achieved. Considering the excellent reactivity and efficiency of Ru-H catalyzed hydrovinylation, we ventured into Ru-ACDC-type catalysis for the development of an asymmetric process. In the presence of a catalytic amount of achiral ruthenium complex **5** and (*S*)-TRIP-Ag, treatment of aromatic olefins **4a, 4b** with ethylene provided the corresponding products **6a** and **6b** in high yields, excellent regioselectivities and promising enantioselectivities. This is the first example of an asymmetric hydrovinylation of olefins using ruthenium catalysis.



Publications resulting from this research area: 347

External Funding: China Scholarship Council Fellowship (S.-H. Liao)

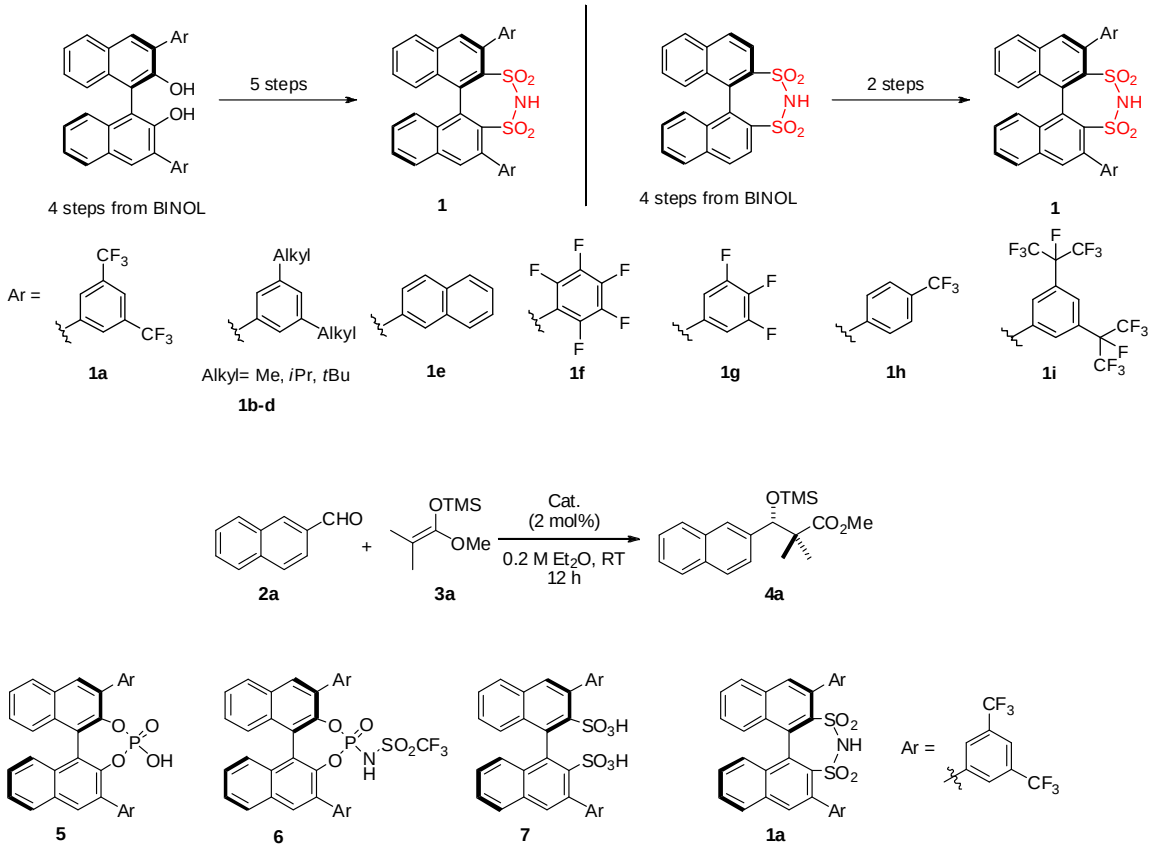
Cooperations: none

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

Involved: F. Lay, Pi. García-García, L. Ratjen, Pa. García-García, K. Rabalakos

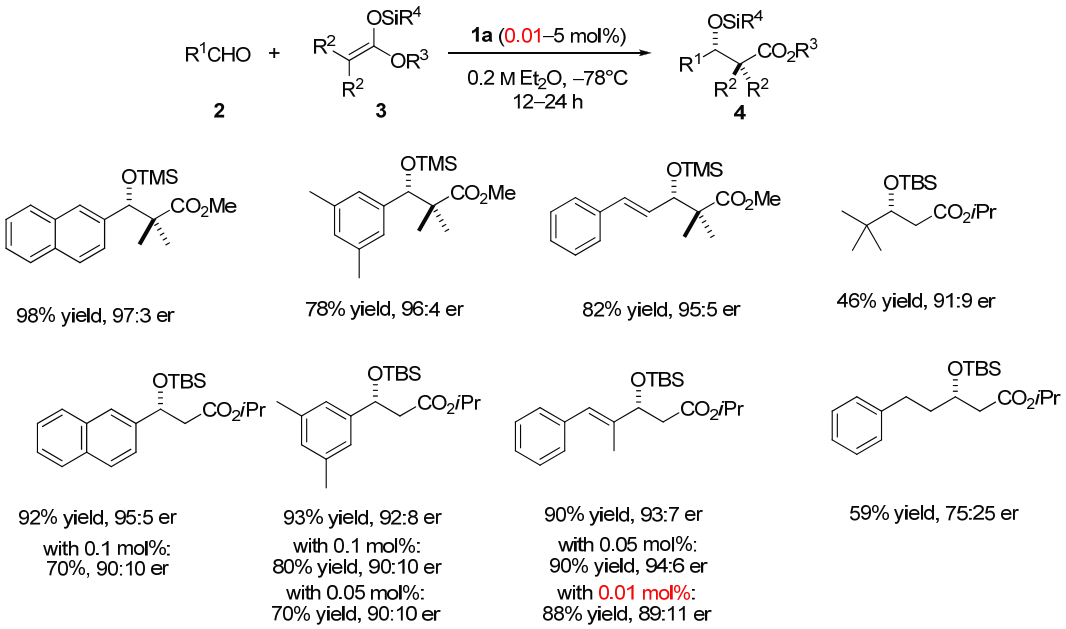
Objective: Organocatalysts function by donating or removing electrons or protons, defining four distinct activation modes: Brønsted base catalysis, Brønsted acid catalysis, Lewis base catalysis, and Lewis acid catalysis. While the vast majority of organocatalysts, including many amines, carbenes, and phosphines, act as Lewis bases, Brønsted acid and base organocatalysis is also growing strongly. Remarkably though, the one area that has been left almost completely unexplored is that of *organic Lewis acid catalysis*. Of particular interest in our laboratory has been the asymmetric *Mukaiyama* aldol reaction, of which most asymmetric variations still require high catalyst loadings of typically 20 mol%. The reason for this high loading is that an achiral yet *catalytically competent* second species is generated during the reaction: a silylium ion equivalent, which can be released if the terminating aldolate silylation step is relatively slow. Inspired by the fact that bistriflimide (Tf_2NH) is a powerful achiral *Mukaiyama* aldol pre-catalyst generating the highly reactive Lewis acid Tf_2NTMS as the actual catalyst, and encouraged by our recently introduced concept of asymmetric counteranion direct catalysis (*ACDC*), the aim of this project has been the development of chiral disulfonimides as chiral Tf_2NH equivalents and their application in enantioselective *Mukaiyama* aldol reactions. Potentially, our approach could offer solutions to the problems encountered in conventional asymmetric Lewis acid catalysis.

Results: In the initially developed synthesis of chiral binaphthyl-based disulfonimides 3,3'-diaryl substituted (*R*)-BINOL derivatives were used as starting materials. An obvious drawback of this route has been the nine chemical operations required for every 3,3'-diaryl substituted disulfonimide. In the second route, the unsubstituted disulfonimide, readily available on a multigram scale from (*R*)-BINOL, is converted into 3,3'-diaryl substituted disulfonimides via a metalation, halogenation, cross-coupling sequence leading to more than twenty different 3,3'-diaryl substituted disulfonimides.



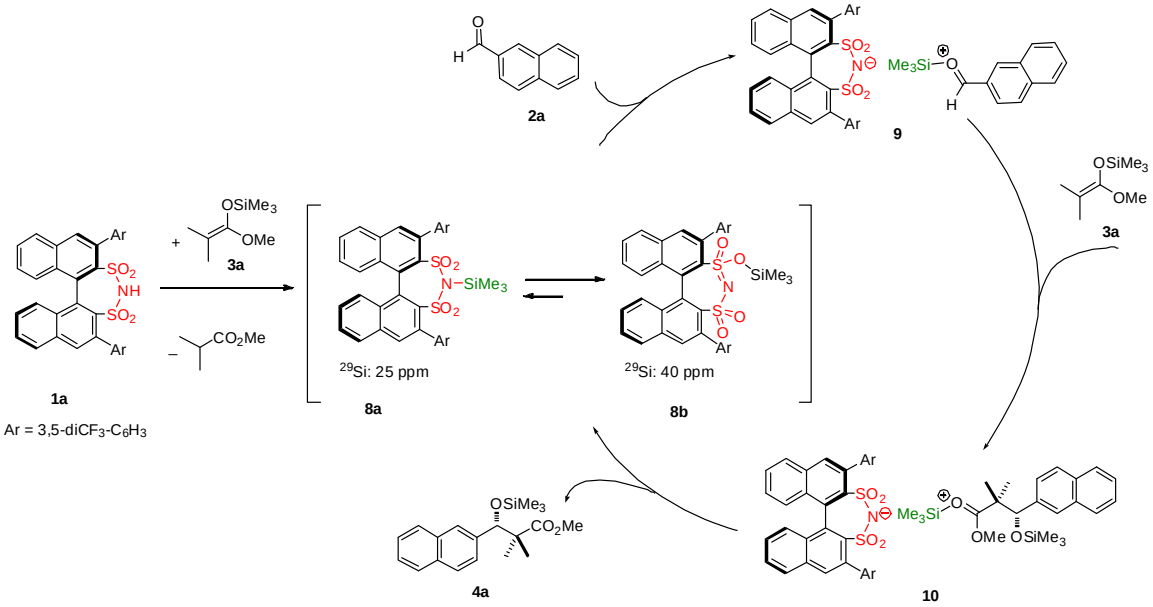
To our delight we found that in contrast to previously developed chiral Brønsted acid catalysts **5**-**7**, chiral binaphthyl-derived disulfonimides showed strong catalytic activity in the *Mukaiyama* aldol reaction. After catalyst screening and optimization of reaction conditions it was found that pre-catalyst **1a** yielded the highest enantioselectivities in Et_2O at −78°C.

Entry	Catalyst	Yield [%]	er
1	**1a**	< 99	90:10
2	**5**	< 2	-
3	**6**	< 2	-
4	**7**	> 2	-



The reaction is well suited for isobutyrate derived ketene acetals, which react with various aromatic aldehydes giving the corresponding aldol products in high yields and enantioselectivities (≥ 95:5 er). An α,β-unsaturated aldehyde could also be employed with the same nucleophile giving the desired product in good yield and with an enantiomeric ratio of 97:3. Even the more challenging acetate derived ketene acetal could be used and upon reaction with different aromatic and α,β-unsaturated aldehydes the corresponding products were obtained in excellent yields and high enantioselectivities (≥ 95:5 er). In the case of 2-naphthaldehyde, 3,5-dimethoxybenzaldehyde, and (*E*)-α-methylcinnamaldehyde, we also investigated the effect of lowering the catalyst loading on the outcome of the reaction. An amount of only 0.1 mol% turned out to be sufficient to give the desired products in good to excellent yields while maintaining high enantioselectivity. Even lower catalyst amounts can be used with good results and the α-methylcinnamaldehyde derived product was obtained in high yield and an enantiomeric ratio of 88:12 with a remarkably low catalyst loading of 0.01 mol%. Finally, aliphatic aldehydes were also tested and provided pivaldehyde and hydrocinnamaldehyde derived products with good yields and reasonable enantioselectivities (≥ 75:25 er).

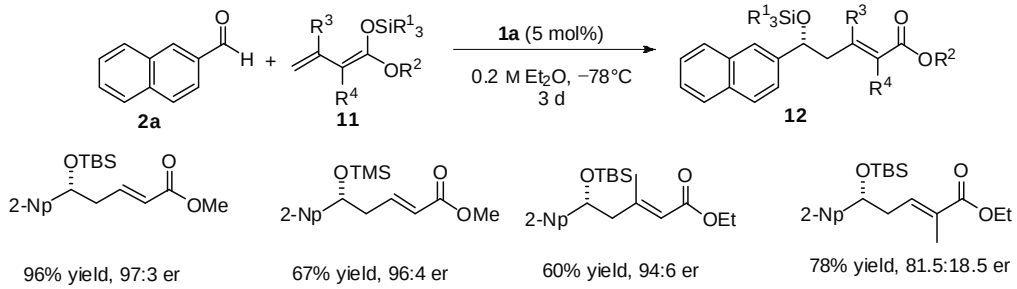
Interestingly, the aldol process is indeed promoted even in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine. This base is known to inhibit any Brønsted acid catalysis and has previously been used to differentiate between Lewis acid- and Brønsted acid-catalyzed pathways. Mechanistically, we propose the reaction to proceed *via* a silylated imide **8**, which is generated upon initial reaction of catalyst **1a** with the ketene acetal. We could demonstrate by ^{1}H-NMR that the ketene acetal **3a** rapidly silylates the catalyst and a more detailed analysis of the *in situ* generated species by NOESY-^{1}H-NMR, ^{29}Si-NMR, and ^{15}N-NMR with ^{15}N enriched **1a**, actually revealed the existence of *N*-*O*-silylotropy. To date it is not clear if *N*-silyl imide **8a,** *O*-silyl imide **8b,** or both are catalytically active species. Aldehyde activation is then realized via silyl transfer from silylated imide **8**, generating an oxonium ion. Asymmetric induction occurs via stereochemical communication within ion pair **9**, consisting of the disulfonimide anion and the *O*-silylated oxonium cation. Its reaction with the ketene acetal then provides the *Mukaiyama* aldol product via ion pair intermediate **10**.



Thus, rather than trying to fight the silylium-catalysis pathway by using a large amount of another competing chiral Lewis acid, as has been tried so hard before, our approach capitalizes on the high inherent silylium-reactivity. Since the chiral disulfonimide counteranion is part of a close contact ion pair, also in the transition state, asymmetric induction is achieved.

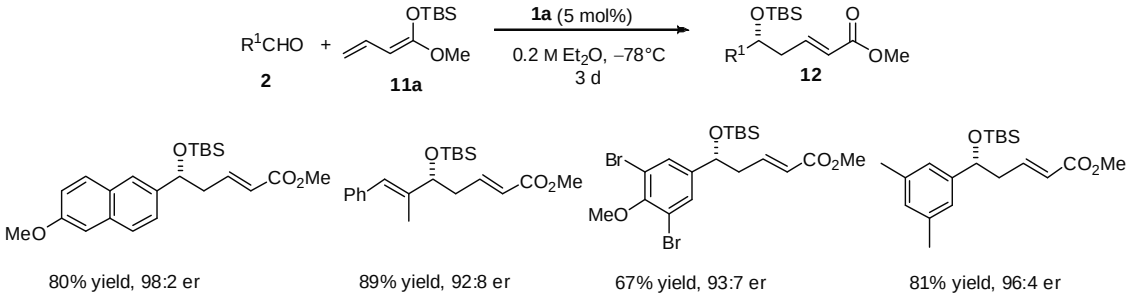
Furthermore, binaphthyl-derived disulfonimide **1a** was also very successfully employed in vinylogous *Mukaiyama* aldol reactions. Studying the influence of the silyl group and the ester substituent in various vinylogous nucleophiles **11** revealed that the silyl group

had only little influence on the reaction outcome, while the ester substituent proved to be important in terms of reactivity. The methyl ester showed high reactivity and delivered products with high isolated yields, while increasing the ester bulkiness



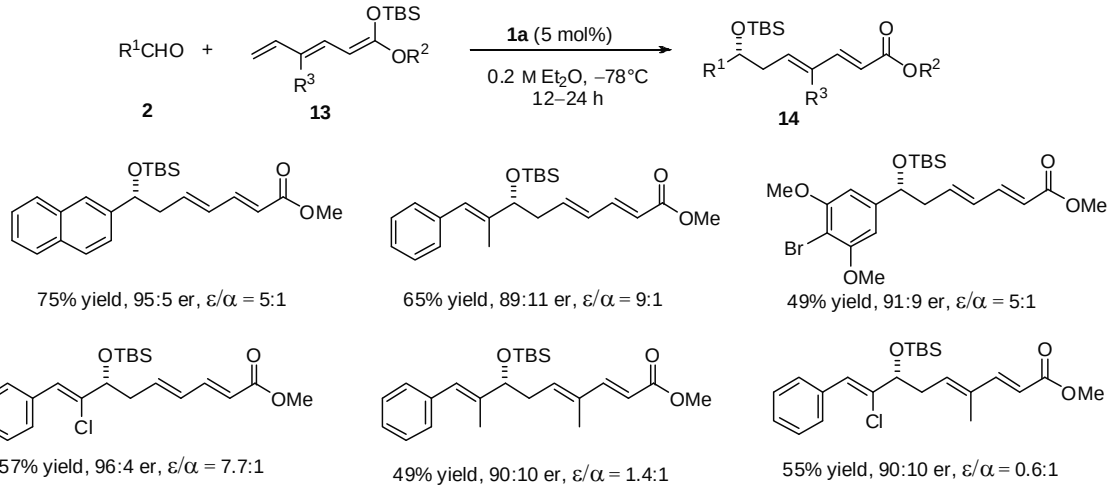
towards a *tert*-butyl group significantly reduced the yields. Introduction of substituents in nucleophiles **11** revealed, that a substituent in β-position is well tolerated, whereas substitution in the α-position furnished the product **12** in somewhat decreased enantioselectivity. All reactions had γ/α-ratios higher than 50:1.

A preliminary evaluation of the aldehyde **2** scope revealed that electron-rich or neutral aromatic aldehydes clearly provide superior results, but electron-poor substrates still enable the reaction to occur, furnishing good enantioselectivities and γ/α-ratios higher than 40:1.



Moreover, our catalytic system could be employed in the previously unexplored bisvinylogous version of the *Mukaiyama* aldol reaction furnishing α,β,γ,δ-unsaturated esters **14** in a single step. The system is particularly suited for aromatic and cinnamaldehyde derivatives, furnishing the desired products **14** in high enantioselectivities and good yields. The introduction of a methyl group (**13**, R^3 = Me), gave products in good enantioselectivities but somewhat lower yields. As predicted by DFT-calculations, the terminal ε-selectivity (up to 9:1) proved to be less distinct compared to the γ-selectivity in the vinylogous systems.

In summary, a highly efficient and enantioselective *Mukaiyama* aldol reaction has been developed with turnover numbers of up to 8,800. Moreover, we have developed



efficient and easily applicable, disulfonimide-catalyzed vinylogous and bisvinylogous *Mukaiyama* aldol reactions. These extended aldolizations display good to excellent enantioselectivities and have a remarkably broad ketene acetal scope. Highly enantioselective catalytic asymmetric bisvinylogous aldol reactions of any type have previously been unknown. The proposed mechanism suggests a general solution to problems of asymmetric Lewis acid catalysis, associated with non-enantioselective "background" reactions promoted by the achiral R_3Si-cation.

Publications resulting from this research area: 364, 382, 424

External Funding: Sanofi-Aventis (L. Ratjen); Deutsche Forschungsgemeinschaft (SPP 1179, Organocatalysis); Alexander von Humboldt Foundation (Stipend to K. Rabalakos); Spanish Ministerio de Educación y Ciencia (Fellowship to Pi. García-García and Pa. García-García)

Cooperations: E. Y.-X. Chen (Fort Collins, USA); V. Dalla (Le Havre, FR); D. Trauner (Munich, DE); A. Fürstner (Mülheim/Ruhr, DE)

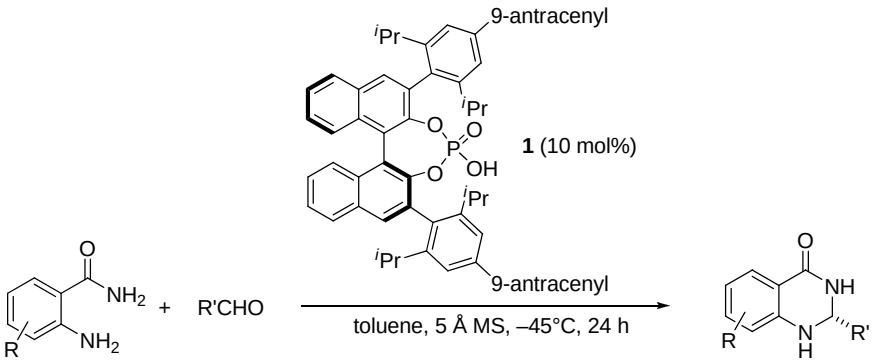
2.2.5 Research Area "Catalytic Asymmetric Acetalizations" (B. List)

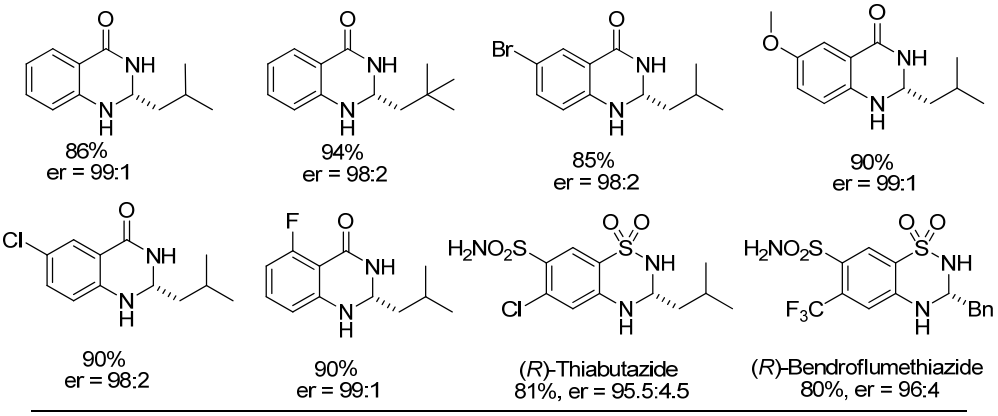
Involved: X. Cheng, S. Vellalath, I. Čorić, S. Müller

Objective: Stereogenic acetals are ubiquitous in natural products, ranging from simple carbohydrates to complex spiroketal polyketides. Controlling their relative and absolute configuration can be extremely important. For example, starch and cellulose only vary in the configuration at their anomeric acetal stereocenter. The importance of chiral acetals is further illustrated by their occurrence in a variety of chiral pharmaceuticals and their potential as diastereocontrolling elements in organic synthesis. Nevertheless, methods for the enantioselective synthesis of stereogenic acetals are very limited and usually based on chiral starting materials or reagents.

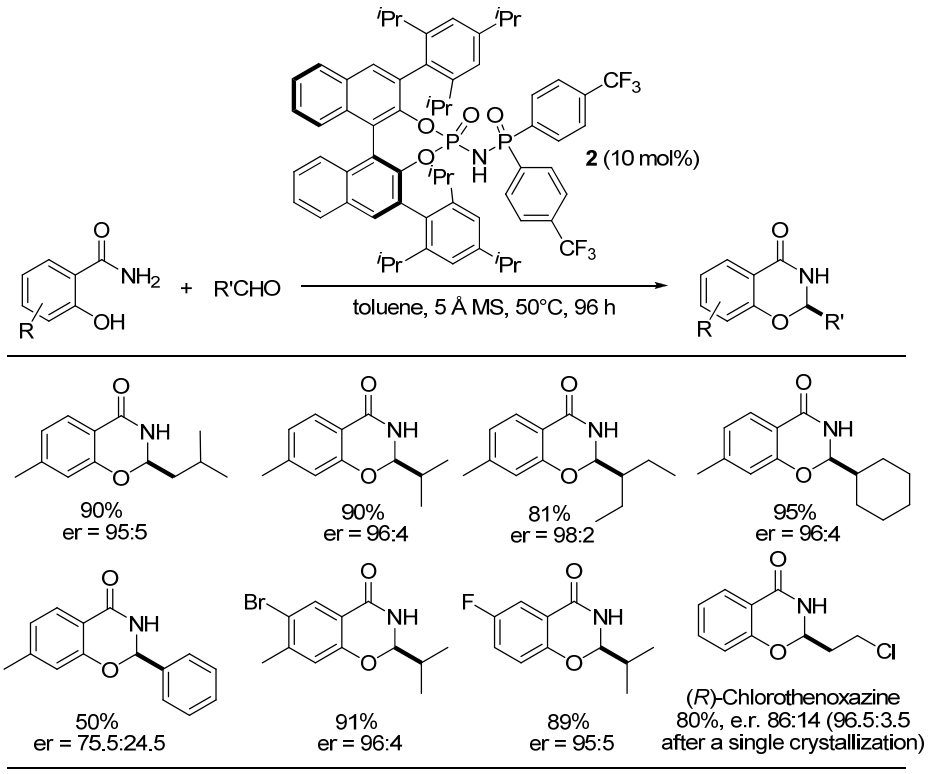
The aim of this project is the development of catalytic and highly enantioselective acetalization reactions resulting in formation of *N*, *N*-, *N*,*O*-, and *O*,*O*-acetals.

Results: As part of our interest in asymmetric acetalization reactions, we have developed direct enantioselective syntheses of cyclic *N*,*N*- and *N*,*O*-acetals from aldehydes. In a condensation reaction of *o*-aminobenzamides and aliphatic aldehydes phosphoric acid catalyst **1**, which we have previously developed in our group, delivered chiral *N*,*N*-acetals in high yield and with high enantioselectivity. The methodology has been applied to the first asymmetric synthesis of several antihypertensive aminal drugs including (*R*)-Thiabutazide.

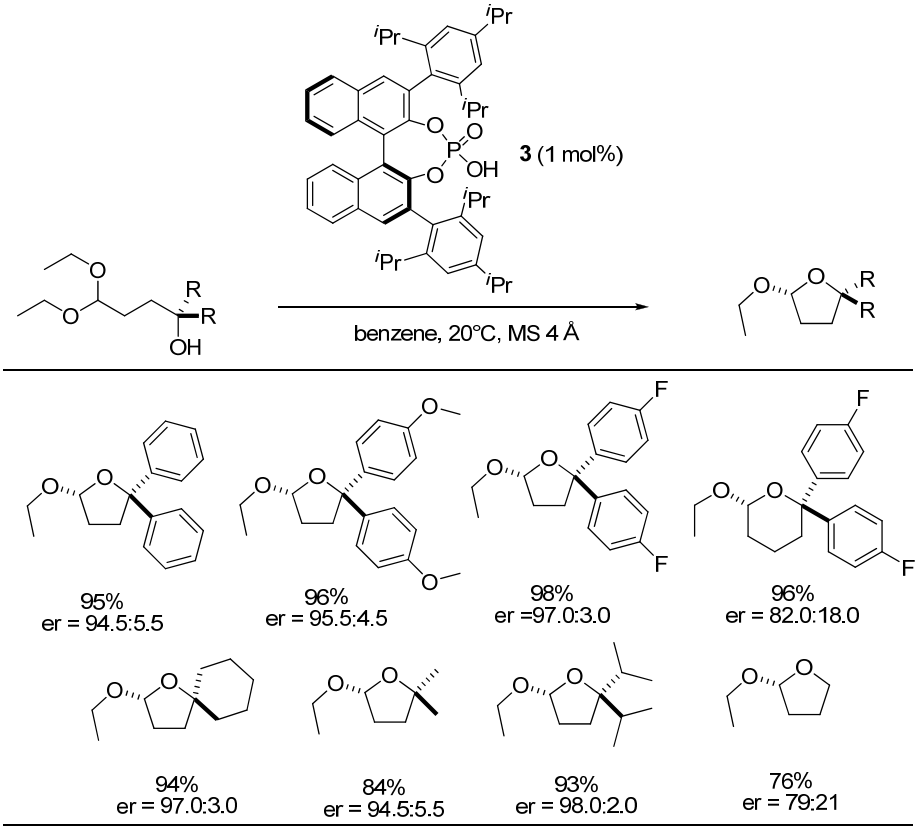




A structurally related condensation reaction of *o*-hydroxybenzamides and aliphatic aldehydes to benzoxazinones proved to be very challenging when we investigated a variety of established chiral catalysts. Therefore we embarked on the development of a new chiral Brønsted acid catalyst for the direct asymmetric synthesis of *N*,*O*-acetals from aldehydes. An *N*-phosphinyl phosphoramide has been designed as a new motif for asymmetric Brønsted acid catalysis. Readily accessible catalyst **2** proved to be highly efficient and enantioselective in catalyzing the first direct asymmetric *N*,*O*-acetalization of aldehydes. The synthetic utility of this methodology was demonstrated with the first catalytic asymmetric synthesis of the analgesic pharmaceutical (*R*)-chlorothenoxazine.

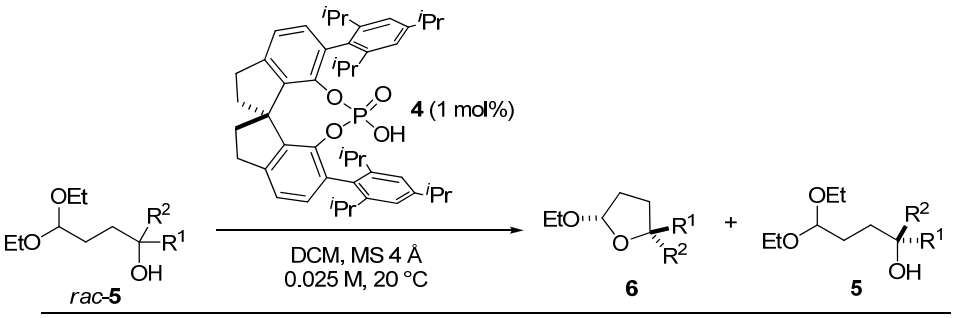


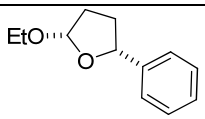
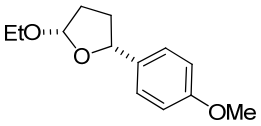
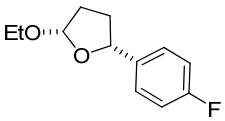
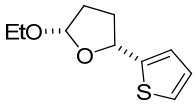
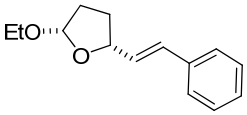
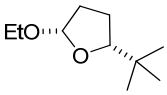
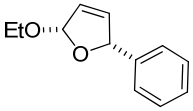
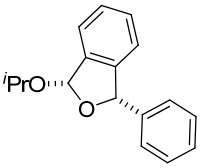
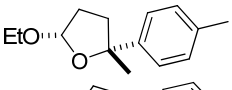
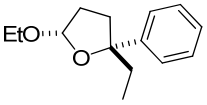
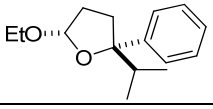
O,*O*-Acetals presented an additional challenge as enantioselective additions to oxocarbenium ion intermediates that could potentially lead to chiral *O*,*O*-acetals, are much less explored compared to additions of nucleophiles to imines. We envisioned a catalytic enantioselective synthesis of this fundamental functional group in organic chemistry via a transacetalization reaction. The chiral phosphoric acid TRIP (**3**) was found to be an efficient and highly enantioselective catalyst for intramolecular transacetalization reaction of hydroxyacetals enabling the asymmetric synthesis of acetals with the acetal carbon as the only stereogenic center. In addition, to the best of our knowledge, this reaction represents the first example of phosphoric acid catalyzed enantioselective addition of nucleophiles to simple *O*,*O*-acetals.

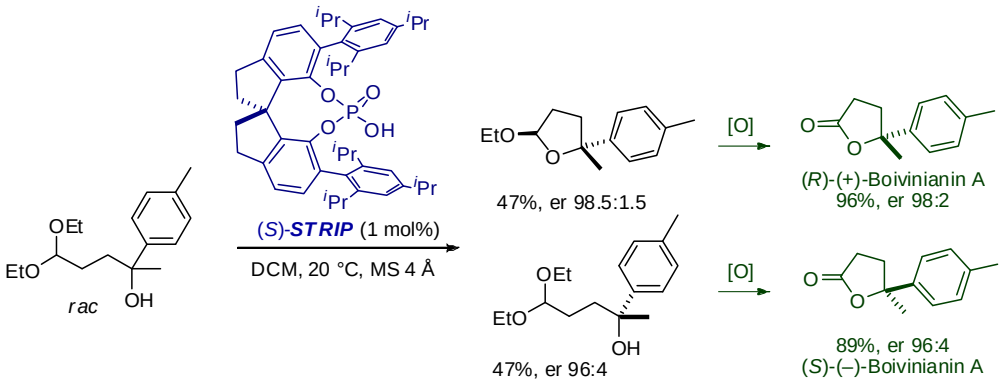


Further expanding on the asymmetric transacetalization reaction we have recently developed a superbly enantioselective kinetic resolution of homoaldol acetals **5** that is catalyzed by *STRIP* (**4**) representing a new class of phosphoric acid catalyst. Our kinetic resolution is a very atom economic method that, unlike common alternative resolution methods, does not require any stoichiometric reagents, and forms ethanol as the only byproduct. The acetal group in cyclic acetals **6** can be easily modified, e.g. oxidized, reduced or substituted giving access to enantioenriched tetrahydrofuranes and γ-

butyrolactones. The current method is applicable to the resolution of a wide range of secondary and tertiary homoaldols.



entry	conv. (time)	**6**	er **6**	dr **6**	er **5**
1	55% (18 h)		97:3	13:1	98.5:1.5
2	55% (16 h)		97:3	12:1	98:2
3	54% (14 h)		96.5:3.5	13:1	97.5:2.5
6	53% (14 h)		97.5:2.5	19:1	98.5:1.5
7	56% (14 h)		98:2	8:1	98:2
8	55% (4 h)		93.5:6.5	19:1	98:2
10	54% (1 h)		89:11	> 50:1	95:5
11	55% (12 h)		89.5:10.5	44:1	96.5:3.5
13	55% (10 h)		98.5:1.5	9:1	96:4
14	55% (12 h)		98.5:1.5	9:1	98.5:1.5
15	55% (28 h)		97.5:2.5	7:1	92:8



This approach could be utilized in a short synthesis of both enantiomers of boivinianin A, illustrating the power of our methodology to access and utilize both homoaldol kinetic resolution products.

In summary, we have developed efficient organocatalytic asymmetric direct *N*,*N*- and *N*,*O*-acetalizations of aldehydes. For *N*,*O*-acetalization a chiral *N*-phosphinyl phosphoramide was developed as a novel powerful Brønsted acid motif. The synthesis of *O*,*O*-acetals was accomplished via a catalytic asymmetric transacetalization reaction, which represents the first example of phosphoric acid catalyzed enantioselective addition of nucleophiles to simple *O*,*O*-acetals. The asymmetric transacetalization was subsequently applied to the highly enantioselective resolution of acetal protected aldehyde homoaldols catalyzed by a newly designed spirocyclic phosphoric acid STRIP.

Publications resulting from this research area: 18, 300, 301, 412

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