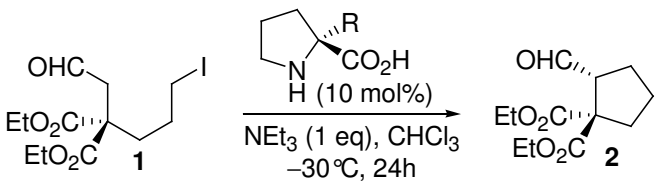
2.2.2 Research Area "Organocatalytic Asymmetric α-Alkylation of Aldehydes" (B. List)

Involved: N. Vignola, A. Majeed Seayad

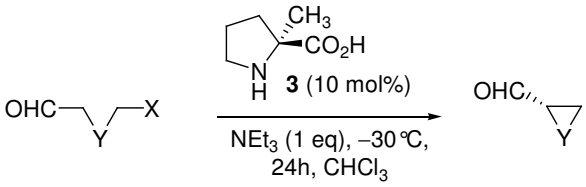
Objective: α-Alkylations of carbonyl compounds are central carbon-carbon-σ-bond forming reactions in organic synthesis. Asymmetric variants generally rely on the use of chiral auxiliaries and a variety of efficient examples have been reported in the last three decades. Despite its potential as a broadly useful synthetic methodology, the development of a general catalytic asymmetric α-alkylation reaction has proven extremely challenging and the only two reported strategies are limited in scope. Although chiral α-branched aldehydes are particularly valuable synthetic intermediates, neither direct nor indirect catalytic asymmetric α-alkylations of aldehydes have previously been described. The aim of this project has been to develop the first, efficient, and highly enantioselective direct aldehyde α-alkylation reactions.

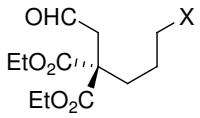
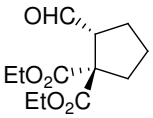
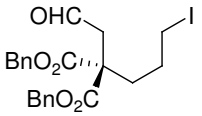
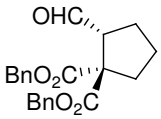
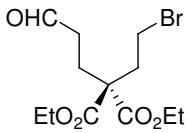
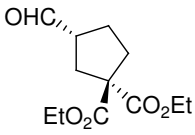
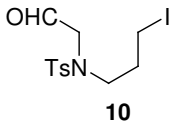
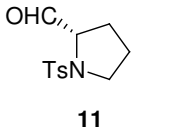
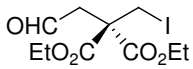
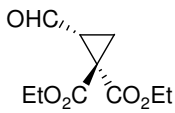
Results: Based on our previous successful use of proline enamine catalysis of a variety of asymmetric reactions, we initially investigated the intermolecular α-alkylation reaction of cyclohexanone and propionaldehyde with benzylbromide catalyzed by proline in the presence of triethylamine. Not surprisingly however, we only identified products of proline benzylation. We then studied intramolecular alkylations of aldehydes and to our excitement found these reactions to work quite well. For example, the proline-catalyzed intramolecular alkylation of aldehyde **1** gave cyclopentane derivative **2** in 80% yield and in promising 68% *ee*. After optimizing the reaction conditions, and screening several proline derivatives and other amines as alternative catalysts, we found that commercially available (S)-α-methyl proline (**3**) significantly improved both rate and enantioselectivity of the reaction. Treating aldehyde **1** with catalyst **3** (10 mol%) in chloroform at –30 °C in the presence of triethyl amine furnished cyclopentane carbaldehyde **2** in excellent yield (92%) and enantioselectivity (95% *ee*).



R = H: 80%, 68% ee
R = Me (**3**): **92%, 95% ee**

We also studied the scope of this novel reaction. Varying the leaving group (I, Br, OTs) furnished product **2** in similar high enantioselectivities although the cyclization of tosylate **5** was particularly slow. Replacing ethyl- with benzyl groups as in ester **6** furnished the corresponding product (**7**) in almost identical enantioselectivity and yield.



Substrate	Product	Yield (%)	ee (%)
			
1 (X = I)	**2**	92	95
4 (X = Br)	**2**	90	94
5 (X = OTs)	**2**	20	91
		94	95
6	**7**		
		92	97
8	**9**		
		52	91
10	**11**		
		70	86
12	**13**		

If structural isomer **8** was treated with catalyst **3**, aldehyde **9** was obtained in 92% yield and 97% *ee*. Much to our delight we found that extending this new reaction to the synthesis of heterocycles worked equally well. Thus subjecting amino aldehyde **10** to the reaction conditions furnished (*S*)-*N*-tosyl prolinal (**11**) in high enantioselectivity. Furthermore, we were able to extend our methodology to alternative cyclization modes such as the 3-exo-tet cyclization of aldehyde **12** to cyclopropane **13** in high yield and enantioselectivity.

Our process represents the first catalytic asymmetric α-alkyation of aldehydes and we are currently expanding the substrate scope of the reaction and develop an intermolecular variant.

Publication resulting from this research area: 430

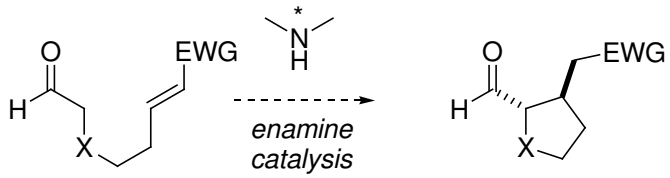
External funding: none

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

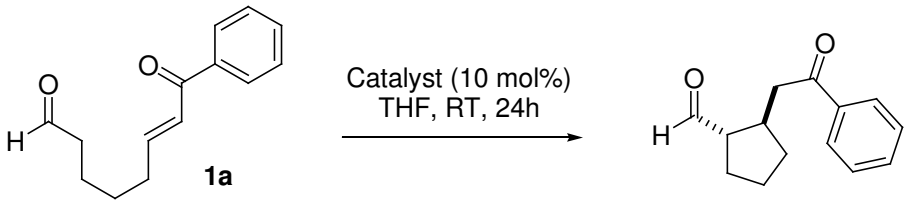
2.2.3 Research Area "Organocatalytic Asymmetric Intramolecular Michael Reaction of Aldehydes" (B. List)

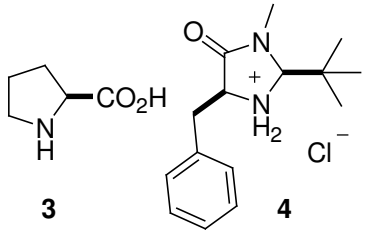
Involved: M. H. Fonseca, D. Monge Fernández, J. Seayad

Objective: We have recently developed novel organocatalytic asymmetric cyclization reactions of aldehydes, including a new enolexo-aldolization and an α-alkylation reaction. In this context we realized that although there are a number of reports on elegant catalytic enantioselective intermolecular Michael reactions, *intramolecular* catalytic asymmetric Michael reactions of aldehydes are unknown. We felt such a process to be of high value, particularly if included in strategic reaction sequences such as the Robinson annulation. The aim of this project was to develop an efficient catalytic enantioselective cyclization of formyl enones in a process that constitutes the first catalytic asymmetric intramolecular Michael reaction of aldehydes.



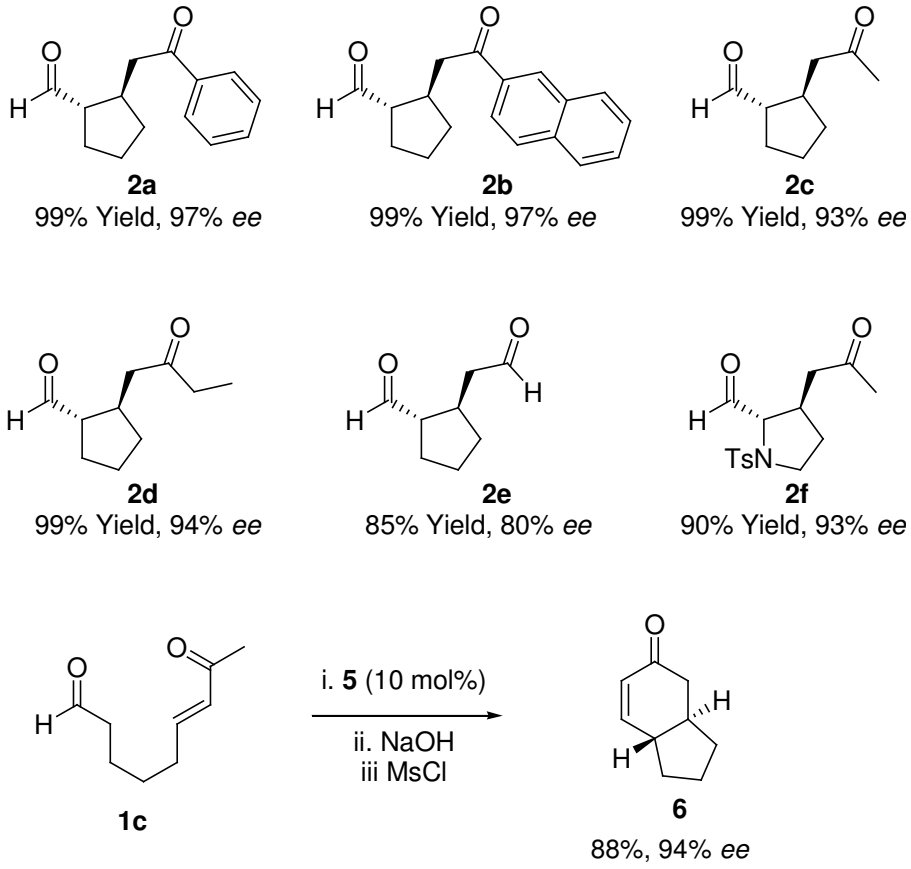
Results: As a model reaction we studied the amine-catalyzed Michael cyclization of formyl enone **1a** to give keto aldehyde **2a**. This reaction was catalyzed by (*S*)-proline (**3**, 10 mol%, RT, DMF, 3d) but as expected, both diastereoselectivity and enantioselectivity were low. Next, we studied MacMillan's commercial imidazolidinone catalysts **4** and **5**. Although they have not previously been used in enamine catalysis**,** we found them to effectively catalyze the cyclization reaction. Interestingly, while the more reactive catalyst **4** provided the product in very high yield (99%) and only 39% *ee*, catalyst **5** gave the product with the same yield and *in excellent 97% ee*.





Cat	Yield	*dr* (*anti*:*syn*)	*ee* (*anti*)
3	85%	2:1	15%
4	99%	19:1	39%
5	99%	24:1	97%

We have extended this reaction to a variety of different substrates that all furnished the desired products in high yields and diastereo- and enantioselectivities. In addition, the reaction could be used in tandem with an intramolecular aldolization to give enone **6**. We are currently using enones such as **6** in a novel approach toward artificial steroids.



Publication resulting from this research area: 361

External funding: none

Cooperation: W. Schrader (Mülheim/Ruhr, DE)

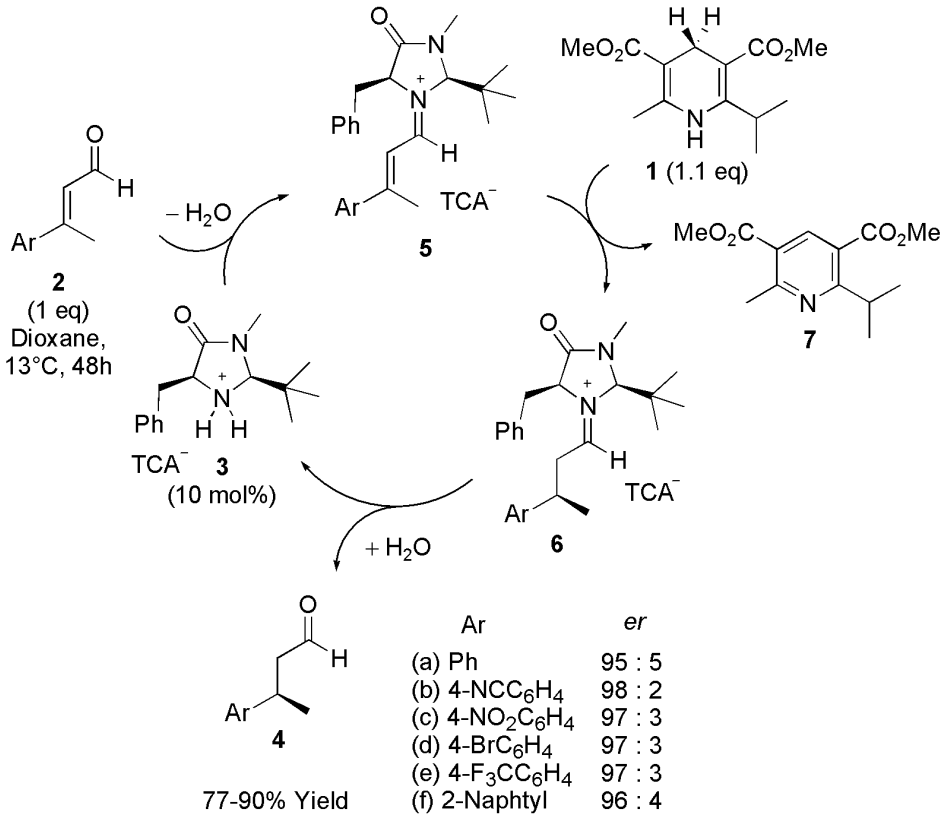
2.2.4 Research Area "Metal-Free Catalytic Hydrogenation" (B. List)

Involved: J. W. Yang, M. H. Fonseca, N. Vignola

Objective: Hydrogenation is arguably the single most important catalytic reaction for the synthesis of enantiomerically pure compounds and is crucial for all living organisms. Previous chemical and biological catalytic asymmetric hydrogenations require metals. However, the removal of metal-impurities from the reaction product can be difficult but is required in the production of pharmaceuticals because of toxicity concerns. The aim of this project has been the development of methodology for the catalytic asymmetric and non-asymmetric transfer hydrogenation of α,β–unsaturated aldehydes via iminium catalysis.

Results: Recently catalysis with small organic molecules has become a rapidly growing area of research and one of its advantages is the general lack of metals. While hydrogenations or transfer hydrogenations have not been catalyzed previously with organic compounds only, we reasoned that a completely metal-free hydrogenation may be realized if organocatalysis would be used in combination with a suitable purely organic hydrogen donor. Specifically, we hoped that asymmetric catalysis of the conjugate reduction of α,β-unsaturated carbonyl compounds may be realized via catalysis with secondary ammonium salts via iminium ion intermediates. Iminium catalysis has recently been introduced as a powerful organocatalytic method for carbonyl transformations such as conjugate- and cycloadditions. As potential hydrogen donor we identified Hantzsch dihydropyridines. Dihydropyridines have been used in hydrid- or hydrogen transfer reactions as synthetic NADH models for the reduction of carbonyl compounds, olefins, and imines. However, while chiral Hantzsch esters have been employed stoichiometrically, the potential of their simple achiral derivatives as cofactors in catalytic asymmetric reductions has never been explored.

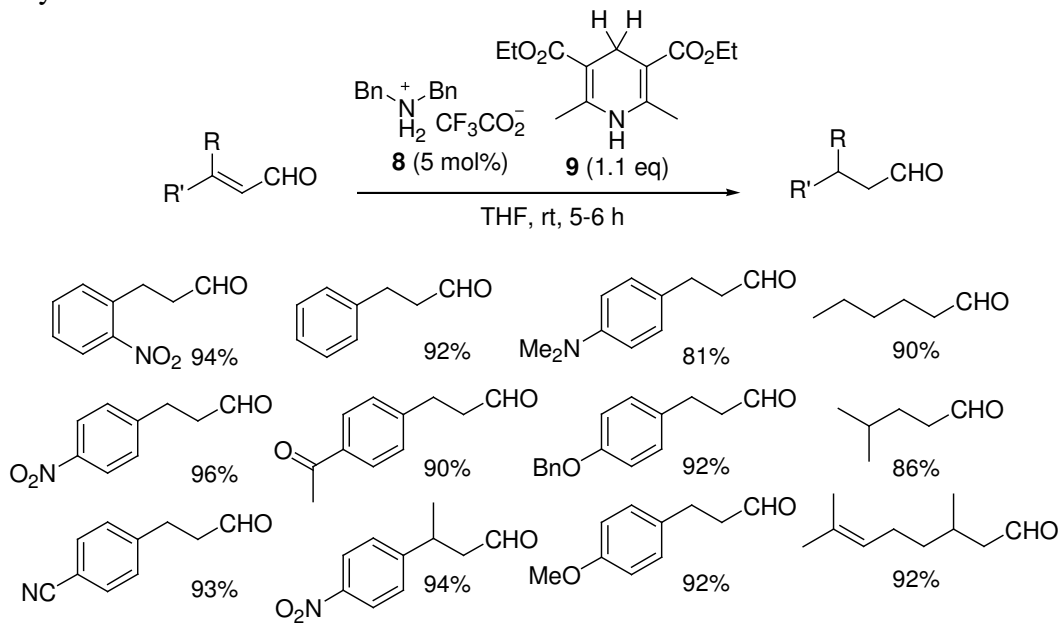
After an extensive screening of several synthetic Hantzsch dihydropyridines and chiral ammonium salt catalysts, we found that upon treating aromatic, trisubstituted α,β-unsaturated aldehydes **2** with a slight excess of dihydropyridine **1** and a catalytic amount of imidazolidinone salt **3** at 13 °C in dioxane, the corresponding saturated aldehydes **4** were obtained in high yields and enantioselectivities.



The reactions are generally clean and highly chemoselective and carbonyl reduction products have not been detected. We also investigated the influence of the olefin geometry. Remarkably, when we subjected both the isolated pure (*E*)- or (*Z*)-isomers of 4-nitro-substituted derivative **2c** to our reaction conditions, the same (*R*)-enantiomer of product **4c** was obtained and with the same enantioselectivity of 97:3 *er*. Similarly, (*E*)/(*Z*)-mixtures always gave the same result and, independent of their exact ratio, all furnished (*R*)-**4c** in 97:3 *er*. Thus, our process is *enantioconvergent*, a highly desirable yet rare feature of a catalytic asymmetric reaction, where a mixture of stereoisomers furnishes only one product enantiomer. Mechanistically, we assume the reaction to proceed via the formation of iminium ion **5**, which accepts a hydride and a proton from dihydropyridine **1** to give iminium ion **6** and pyridine **7**, and upon hydrolysis saturated aldehyde **4**. The enantioconvergence is explained with a fast (*E*)/(*Z*)-isomerization at the stage of the iminium ion, presumably via the formation of a dienamine intermediate.

In summary we have described the first completely metal-free catalytic asymmetric hydrogenation. In our iminium catalytic reaction α,β-unsaturated aldehydes are highly efficiently reduced via transfer hydrogenation from a dihydropyridine. Attractive features of the process are (a) its high yields, chemo-, and enantioselectivities, (b) its enantioconvergence, and (c) its simplicity and practicality. Applications in the synthesis of chiral pharmaceuticals may be envisioned.

In addition to this asymmetric variant we have previously established a non-asymmetric, though highly efficient and chemoselective version, in which we use dibenzyl ammonium salt **8** as the catalyst and commercially available Hantzsch ester **9** as hydride donor.



Publication resulting from this research area: 434

External funding: none

Cooperations: none