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Doctoral Dissertation

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Department of Chemical Technology
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ABSTRACT OF DOCTORAL DISSERTATION

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Advances in Amine Catalysis: Brønsted Acids in Iminium and Enamine Activation

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Opponent(s) Prof. Albrecht Berkessel
Supervisor Prof. Ari Koskinen
(Instructor) Dr. Petri Pihko

Abstract

Condensation of aldehydes and ketones with primary and secondary amines results in the formation of reactive imines and iminium salts. Additionally, a loss of a proton form an iminium species leads to the formation another active intermediate: enamine. Iminium salts and enamines are more reactive than their parent compounds and thus their formation can be exploited in amine catalysis. In fact, activation of carbonyl compounds by iminium and enamine catalysis has attracted wide attention in the last decade and become a practical tool for the synthetic organic chemists.

In the summary part of this thesis reactions activated via iminium ion or enamine formation are reviewed focusing on the role of the Brønsted acid co-catalyst. The described catalysts consist of a primary or secondary amine iminium or enamine catalyst and an acid co-catalyst and can often be derived from nature's chiral pool. The Brønsted acid co-catalysis plays a central role in the iminium and enamine catalysis. In the iminium catalysis the co-catalyst functions as a general acid catalyst in the iminium formation and as a general base catalyst in the some times required removal of hydrogen from the nucleophile when it has reacted to form the initial iminium intermediate. In enamine catalysis these modes are already combined in the formation of the reactive enamine species. Thereafter the co-catalyst may be used to activate and orient the approaching electrophile.

In this thesis enamine catalysis was utilized in the synthesis of polypropionate building blocks by asymmetric aldol reactions. Also, combined enamine-iminium catalysis was employed in the synthesis of alpha-substituted enals, which in turn were utilized as substrates in iminium catalyzed transformations. For the iminium catalyzed transformation of alpha-substituted enals a novel aniline catalyst was developed.

Keywords amine catalysis, enamine, iminium, organocatalysis, Brønsted acid

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Kehittyvä amiinikatalyysi: Brønsted-hapot iminium- ja enamiiniaktivoinnissa

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Tiivistelmä

Reaktiivisia imiinejä ja iminiumsuoloja syntyy, kun aldehydejä ja ketoneja kondensoidaan primääristen ja sekundaaristen amiinien kanssa. Näistä imiineistä voidaan lisäksi muodostaa enamiineja, kun imiinin alfa-asemasta poistetaan protoni. Sekä iminiumsuolat että enamiinit ovat reaktiivisempia kuin alkuperäiset karbonyyliyhdisteet, mikä mahdollistaa niiden muodostumisen hyödyntämisen amiinien katalysoimissa reaktiossa. Iminium- ja enamiinikatalyysiä tutkitaankin nykyään laajasti sekä hyödynnetään synteettisen orgaanisen kemian tarpeisiin.

Väitöskirjan yhteenveto-osassa on tarkasteltu iminium- ja enamiinikatalysoituja reaktioita. Erityistä huomiota on kiinnitetty Brønsted-happokokatalyytin rooliin. Iminium- ja enamiinikatalyytit koostuvat reaktiivisen funktionaalisuuden muodostavasta primäärisestä tai sekundaarisesta amiinista ja happokokatalyytistä. Iminiumkatalyysissä kokatalyytti toimii yleisenä happokatalyyttinä iminium suolan muodostuksessa. Lisäksi kokatalyytti konjugaattiemäs voi toimia yleisenä emäskatalyyttinä välivaiheiden protonisiirtoreaktioissa. Enamiinin muodostukseen tarvitaan sekä kokatalyyttin yleistä happo- että emäskatalyysiä. Reaktiivisen enamiinin synnyttyä happoa voidaan käyttää aktivoimaan ja ohjaamaan lähestyvää elektrofiiliä.

Väitöskirjaan liittyvässä tutkimuksessa enamiinikatalyysiä hyödynnettiin polypropionaattien rakennusosien synteesiin. Lisäksi kehitettiin uusi synteesimenetelmä alfa-substitoiduille akroleiineille hyödyntämällä sekä enamiini- että iminiumaktivointia reaktion katalysoimisessa. Menetelmällä saatuja tuotteita käytettiin edelleen iminiumkatalysoiduissa epoxidointireaktioissa uudenlaisen aniliinikatalyytin avulla.

Asiasanat amiinikatalyysi, imiini, enamiini, Brønsted-happo, organokatalyysi

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Research work reported in this thesis has been carried out in the Department of Chemical Technology, Helsinki University of Technology, during 2003-2007. Additionally, part of the research was done in the Max-Planck-Institut für Kohlenforschung, in Mülheim an der Ruhr, Germany during October-December 2005, in the research group of Professor Benjamin List. Funding from Academy of Finland, Tekes, Glycoscience Graduate School, TES, and Association of Finnish Chemical Societies is gratefully acknowledged.

I wish to thank my supervisor docent Petri Pihko for welcoming me into his research group and providing me with a challenging and rewarding thesis project. Petri's enthusiasm for chemistry and science has been an inspiring example of what a curious mind can attain. Thanks for sharing it and believing in me! Thanks are also due to Professor Ari Koskinen for excellent tuition and advice throughout my studies. Ben deserves my sincerest gratitude for giving me the opportunity to work under his guidance in MPI. I feel that the short months in Mülheim matured me immensely both as a chemist and as a person.

I would also like to thank the people who have been collaborating on the projects described in this thesis. Sara Källström and Professor Reko Leino from Åbo Akademi University were part of the allylation project and helped in great extent in preparing publication **II**. People in MPI, especially Sonja Mayer, were very helpful in the early stages of the development of iminium promoted transformations of α-substituted acroleins, a scheme which thereafter grew into the primary amine project partly uncovered within publication **IV.**

Dr. Matthew Gaunt and Dr. Mathias Christmann have carefully checked the manuscript and Antti Kataja as well as Dr. Alan Stewart aided in revising the language of this thesis.

My students Inkeri Majander, Päivi Toivonen, Jatta Kaavi, Ellen Hallvar, Tom Blencowe, Linda Norrgard, and Essi Karppanen deserve big thanks for their assistance in the lab. Inkeri and Päivi helped me with extending the scope of In-mediated allylations, Jatta K. prepared some valuable catalysts, and Ellen, Tom, and Linda did fine work screening catalysts for aldol condensations. Additionally, Dr Melanie Clarke and Inkeri were superb team-mates in the primary amine catalysis project.

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Along one's path towards the ultimate goal of finally graduating there are decisive moments that determine how smoothly and quickly that day will be reached. Often there are people that can be directly linked to those moments. Päivi K. deserves thanks for pushing me to the right direction at a critical stage of my undergraduate studies thus showing me the highway to graduate studies. Timo, on the other hand, gave some invaluable advice on career planning and much needed encouragement that led to priceless experiences and an adventure in Germany.

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Santtu, your love and care has urged me to continue when things have seemed too difficult and you have always shared my joy at the times of success. This journey would have had no meaning without you!

I dedicate this thesis to Mama and Papa.

Helsinki, May 2007

Anniina Erkkilä

TABLE OF CONTENTS

LIST OF PUBLICATIONS

This thesis consists of an overview and of following publications which are referred to in the text by their Roman numerals.

I **Consecutive Proline-Catalysed Aldol Reactions and Metal-Mediated Allylations: Rapid Entries to Polypropionates.** Källström, S.*; Erkkilä, A.*; Pihko, P. M.; Sjöholm, R.; Sillanpää, R.; Leino, R. *Synlett*, **2005**, *5*, 751-756.

II **Mild Organocatalytic α-Methylenation of Aldehydes.** Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538-2541.

III **Simple Primary Anilines as Iminium Catalysts for the Epoxidation of α-Substituted Acroleins.** Erkkilä, A.; Pihko, P. M.; Clarke, M.-R. *Adv. Synth. Catal.* **2007**, *349*, 802-806.

IV **Rapid Organocatalytic Aldehyde-Aldehyde Condensation Reactions.** Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205-4216.

V **Iminium catalysis.** Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, in press.

*Equal contribution.

AUTHOR'S CONTRIBUTION

The author has contributed to the publications as stated below.

I The author designed most experiments together with P.M.P. The author and S.K. carried out the experimental and analytical work (except the X-ray crystallographic analyses) equally except for the optimization of the aldol reactions, which were done by the author. The author interpreted the results and wrote the article with the co-authors. The authors have agreed that both A.E. and S.K. may use this publication in their doctoral dissertations.

II The author designed most experiments, carried out the experiments and analyses, and interpreted the results. The article was written together with the co-author.

III The author designed and carried out the epoxidation experiments as well as performed the experimental and analytical work and interpreted the results. The article was written together with the co-authors.

IV The author designed and carried out the experiments and analyses and interpreted the results. The article was written together with the co-author.

V The author planned the outline of the review together with the co-authors and coordinated the project. The author wrote chapters 4–6.1.1 and 7 of the review.

ABBREVIATIONS AND DEFINITIONS

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
Bz	
Cbz	benzyloxycarbonyl
CNA	cyanoacetic acid
CSA	camphorsulfonic acid
d	day(s)
DBA	dibromoacetic acid
DBSA	*para*-dodecylbenzenesulfonic acid
DCA	dichloroacetic acid
DCM	dichloromethane
DFA	difluoroacetic acid
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNBA	2,4-dinitrobenzoic acid
DNSA	2,4-dinitrophenyl sulfonic acid
DPP	diphenyl phosphate
dr	diastereomeric ratio
E	electrophile
EDG	electron donating group
ee	enantiomeric excess
ent	enantiomer of
Et	ethyl
EWG	electron withdrawing group
h	hour(s)
HOMO	highest occupied molecular orbital
HX	any Brønsted acid
IBAL	*iso*-butyraldehyde
IPA	*iso*-propyl alcohol
LUMO	lowest unoccupied molecular orbital
m	*meta*
MBA	(mono)bromoacetic acid
MCA	(mono)chloroacetic acid
Me	methyl
MIA	(mono)iodoacetic acid
MOM	
Ms	methanesulphonyl (mesityl)
MsOH	methanesulphnoic acid ($MeSO_3H$)
MTBE	methyl *tert*-butyl ether
NMO	*N*-methylmorpholine *N*-oxide
Nu	nucleophile
o	*ortho*
ONBA	*ortho*-nitrobenzoic acid
p	*para*
Ph	phenyl
PNBA	*para*-nitrobenzoic acid
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
Pr	propyl
i-Pr	*iso*-propyl
R	arbitrary substituent
rt	room temperature

s	second(s)
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBA	tribromoacetic acid
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TfOH	triflic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TRIP	3,3'-bis(2,4,6-triisopropyl-phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
Ts	*para*-toluenesulfonyl (tosyl)
X	conjugate base of an acid

1 INTRODUCTION

The field of asymmetric catalysis has for long been dominated by metal catalysis. Although pure organic molecules have been used to catalyze organic reactions since the dawn of synthesis, they have regretfully been overlooked as transporters of stereochemical information.

While metal catalysis blossomed throughout the 20th century, culminating to the Nobel Prize award to Knowles, Noyori, and Sharpless in 2001, only scattered examples of attempts to utilize pure organic molecules in asymmetric catalysis were published.[1] During the endeavors to synthesize complex steroid structures in early 1970's Hajos and Parrish in Roche and Eder, Sauer, and Wiechert in Schering reported astonishing stereoselectivities in Robinson annulation reaction.[2] The culprit – or rather the hero – behind the observed stereochemical induction was a small amino acid: proline.

Metal catalysis was only truly rivaled in early 2000's when a number of investigations seeded by the first publications from the groups of List (amine catalysis *via* enamine formation) and MacMillan (amine catalysis *via* iminium formation) appeared. Since then this new area of catalysis, pertinently named organocatalysis, has been under rapid growth. The term organocatalysis, however, was documented for the first time already in 1900.[3]

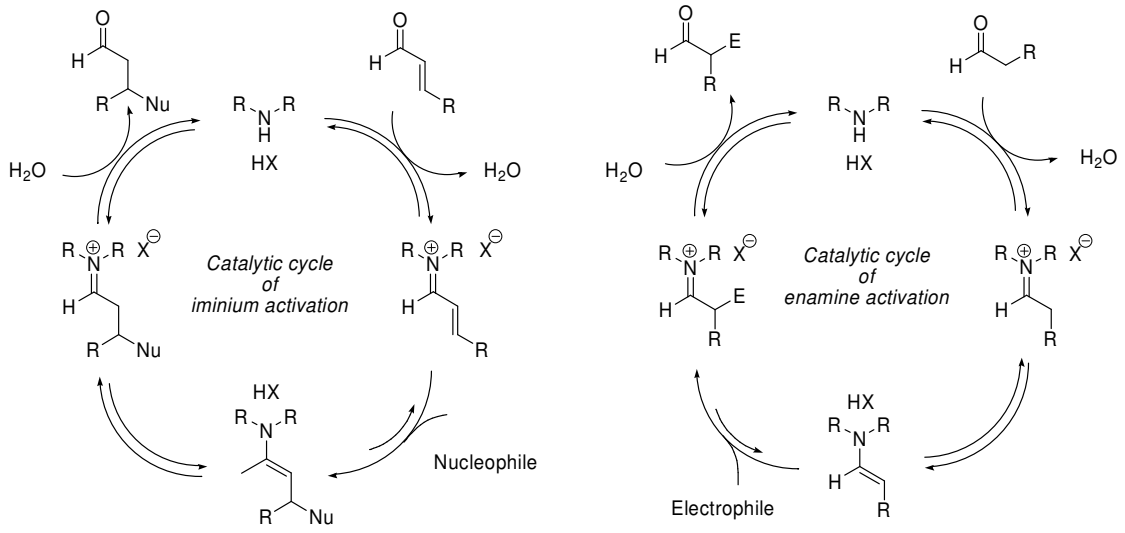
During the research work discussed in this thesis, the focus of our research has evolved from the utilization of the enamine catalyzed aldol reactions in the synthesis of polypropionate building blocks[4,I] to employment of enamine-iminium catalysis in the synthesis of α-substituted enals[II,IV] and to their utilization[III] in iminium catalyzed transformations.[V] During this trajectory, we have become increasingly aware of the role of the acid co-catalyst.

The principal aim of the following chapters is to present a general overview of reactions catalyzed by Brønsted acid salts of primary and secondary amines. The reactions that are included are those involving the formation of either *an iminium ion* or *an enamine* between the catalyst and the substrate within the catalytic course of reaction. Special attention is paid to the role of the Brønsted acid co-catalyst in the catalytic cycle.

2 BRØNSTED ACID SALTS OF PRIMARY AND SECONDARY AMINES AS ORGANOCATALYSTS

The use of amines as catalysts in organic reactions is expanding the area of asymmetric catalysis. Already in the late 19th and early 20th century amine catalysts were reported to promote reactions such as the classical Knoevenagel condensation[5] and the decarboxylation of β-keto acids.[6] Also, it is noteworthy, that the first amine-catalyzed asymmetric reactions were described already in 1912 by Bredig.[1a] Chiral amines have held a key role in metal catalysis where they have been utilized extensively as ligands.[7] Recently, amines have been broadly used as nucleophilic[8] and phase transfer[9] catalysts as well as in non-covalent Brønsted-base activation.[10] Generally only quaternary and tertiary amines such as cinchona alkaloids are suitable for these types of catalysis. However, primary and secondary amines can serve as covalently binding iminium and enamine catalysts giving rise to reactive intermediates.

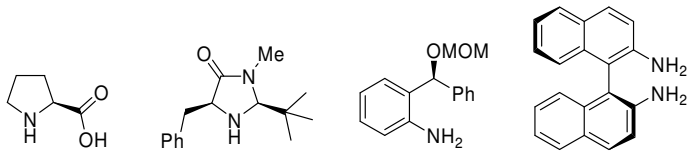
Generation of an iminium ion from an unsaturated carbonyl compound lowers the LUMO energy of the system and is thus beneficial to the reactivity of the compound. The iminium ion is reversibly formed by condensation of amine with an enal or an enone. Similarly, an enamine is furnished from a carbonyl compound by addition of amine and elimination of water. The formation of the enamine proceeds *via* an iminium ion intermediate, which is reversibly deprotonated to yield the reactive enamine (with elevated HOMO energy). In some circumstances, iminium ion intermediates of saturated systems can also be utilized.



Scheme 1. Iminium and enamine catalysis

It is noteworthy, that the formation of both iminium ion and enamine involves major contribution from an acid co-catalyst. The acid co-catalyst aids the formation of the iminium ion, and in the formation of the enamine the counter base of the co-catalyst deprotonates the iminium ion intermediate. However, the role of the co-catalyst may extend beyond the formation of reactive species. For example, in the iminium mechanism the co-catalyst is closely associated with the reacting iminium ion and may thus be involved in the outcome of the reaction. It may even be argued that the reactive species is the iminium salt rather than the (naked) iminium ion.

Along the lines of the above-mentioned co-catalyst incorporation, most but not all amine catalysts used in reactions activated by enamine or iminium ion formation consist of an amine *and* a Brønsted acid co-catalyst and thus exist as their Brønsted acid salts[a]. Much obliged to Nature's subtle efficiency, amino acids form a fascinating class of amine catalysts: they incorporate both the amine and the Brønsted acid functionality within a single unit. Amino acids and other small molecules where both the amine and the acid functionality can be found within single molecular framework can thus be treated (and will be treated within the following discussion) as internal Brønsted acid salts of amines.[b]



1 **2**·HX **3**·HX **4**·2HX

Figure 1. Amine catalysts

In the following discussion reactions activated *via* amine catalysis by the means of iminium or enamine formation are highlighted focusing on recent developments and the role of the Brønsted acid co-catalyst.

2.1 Iminium Catalysis

The ability of carbonyl compounds to form iminium ions with primary and secondary amines leads to high susceptibility to react with nucleophilic species. The high reactivity of the iminium ions of enals and enones can be accounted for by the low LUMO energy of empty π*-orbital of the conjugated double bond. The activated soft electrophilic site at the 4-position is prone to

[a] In practice amine salt catalysts are either prepared prior to use by precipitation of an amine with desired acid or are formed in situ by addition of equivalent amounts of amine and Brønsted acid.

[b] Amino acids exist predominantly as zwitterions in solution at neutral *p*H. As such can they can be considered either intra- or intermolecular salts.

both cyclo- and nucleophilic additions. When a saturated carbonyl species is activated by iminium ion formation the LUMO energy of both the imine π*-orbital and the near-by σ*-orbital are lowered. This facilitates aldol and Knoevenagel-type condensations and cleavage of the C-X σ-bond adjacent to α-carbon, respectively. The modes of iminium activation are presented in Figure 2.

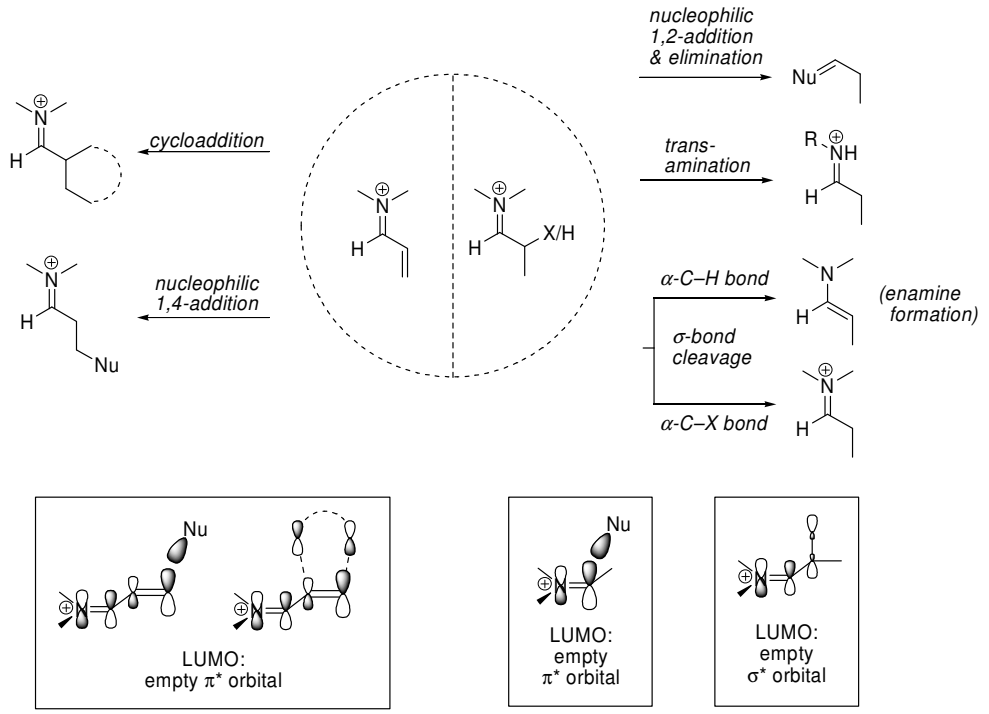


Figure 2. Modes of iminium activation

Reactions relying on iminium catalysis have been extensively reviewed by us[V] and others.[11] A short summary on the recent developments of the iminium catalysis is presented below to give the reader an overview of the area before the multiple functions of the acid co-catalyst are discussed in detail. A full general account on iminium catalysis can be found in our review article.[V]

Additions and Condensations – Reactions Promoted by Iminium Catalysis

Pyrrolidine holds a privileged architecture among secondary amines for iminium catalysis. Its Brønsted acid salts have repeatedly been the first choice of catalysts in the nonasymmetric iminium-catalyzed additions to enals and enones.[12] Moreover, transformations with saturated carbonyl compounds are often catalyzed with pyrrolidine[13,II,IV] although other achiral primary and secondary amines have also been used.[14] Hence catalysts based on pyrrolidine structure have found wide use in iminium catalysis.

MacMillan and co-workers introduced the Brønsted acid salts of imidazolidinones,[15] illustrated in Figure 3, to iminium catalysis around the turn of the millennium. Thereafter this type of catalysts has successfully been applied to cyclo- and conjugate additions of β-substituted enals and enones. The reactions generally proceed in high yields and the products are obtained in respectable enantioselectivities.

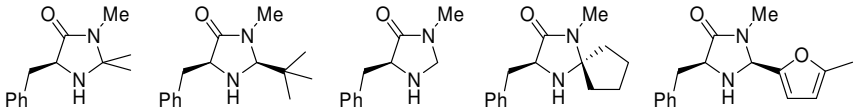
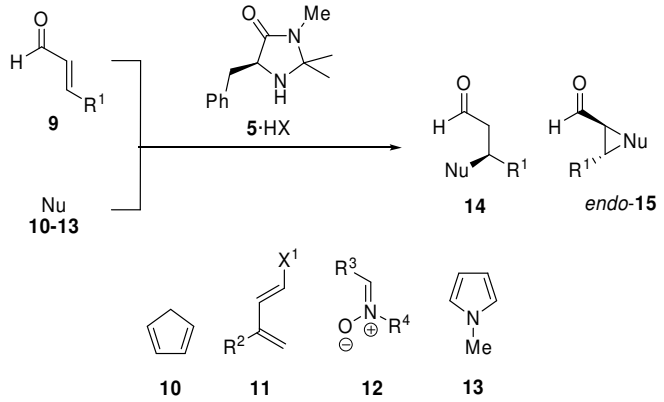


Figure 3. Imidazolidinone catalysts for iminium catalysis

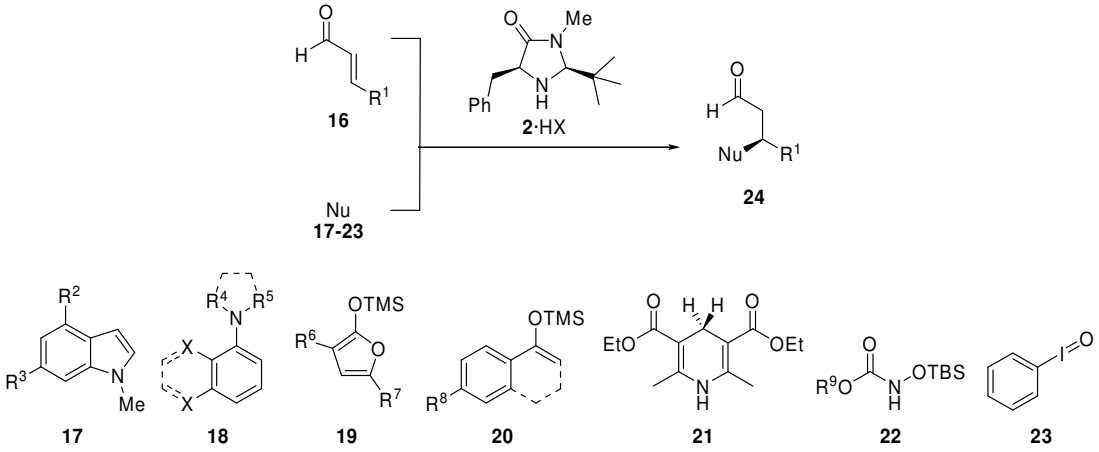
In their seminal publication MacMillan and co-workers employed **5** to the Diels-Alder reactions between cyclopentadiene and β-substituted enals.[16] Subsequently, the iminium catalyzed Diels-Alder reaction gained substantial attention and the reaction has become the proving ground for almost all upcoming ideas and new catalysts. MacMillan's group also utilized the first generation imidazolidinone catalyst **5** in [3+2]-cycloaddition[17] of enals and in Friedel-Crafts alkylation of *N*-methyl pyrrole (Scheme 2).[18] Typically HCl has been used as a strong acid co-catalyst with the first generation imidazolidinone catalyst.



Scheme 2. First generation imidazolidinone catalyst **5** promotes cyclo- and conjugate additions to enones

Demands for higher reaction efficiencies and stereoselectivities soon led to the emergence of other imidazolidinone catalysts (Figure 3). Interchange of the two methyl groups to a larger *tert*-butyl side chain provided one of the most widely used catalyst in iminium catalysis: the second generation catalyst **2**. MacMillan and co-workers employed it first to the Friedel-Crafts alkylation of indoles, where only poor enantioselectivities and reaction rates were obtained with catalyst **5**.[19] Soon several reports ensued as MacMillan and others investigated the utility of the catalyst **2** in intramolecular Diels-Alder reaction,[20] Friedel-Crafts alkylation,[21] Mukaiyama-

Michael reactions,[22] transfer hydrogenation reaction,[23] as well as in several other transformations[24] of β-substituted enals as partly illustrated in Scheme 3.



Scheme 3. Second generation imidazolidinone **2** catalyzes a range of transformations

Other imidazolidinone derivatives (Figure 3) have been investigated as iminium catalysts in the Friedel-Crafts addition of furans to enals[25], the Diels-Alder[26] and transfer reductions reactions[27] of enones and enals and in domino reaction sequences.[28] Modifications of the side chain of first and second generation catalysts (Figure 4) have also allowed additional transformations.[29] **25** was employed in intramolecular aza-Michael reaction[30] and utilization of **23** enabled the addition of nitroalkanes to enals.[29b] Along with the development of the structural features of the amine catalyst, increasingly more attention has been paid to the nature of the co-catalyst. As a result of the often concise optimizations, co-catalysts vary from relatively weak DCA to strong $HClO_4$.

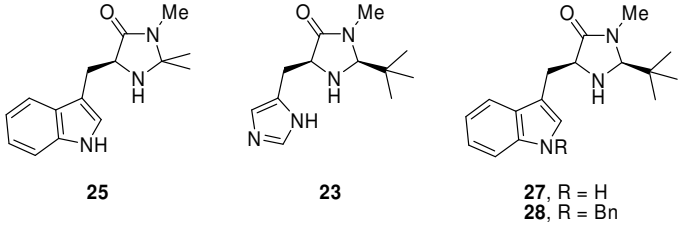


Figure 4. Modified first and second generation imidazolidinone catalysts

The imidazolidinone catalysts are more or less limited to catalyze reactions between carbon nucleophiles and linear (often aromatic) β-substituted enals. One approach to overcome these limitations is the utilization of diaryl prolinol ethers that have successfully been introduced in context of enamine catalysis (Figure 5).[31]

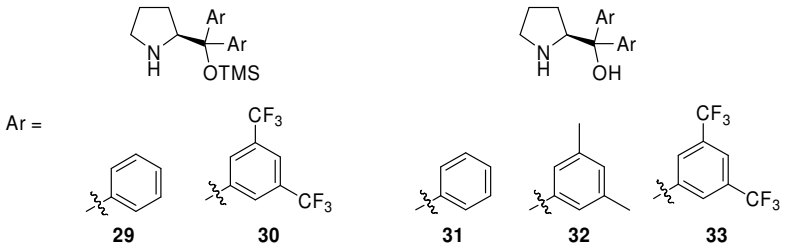
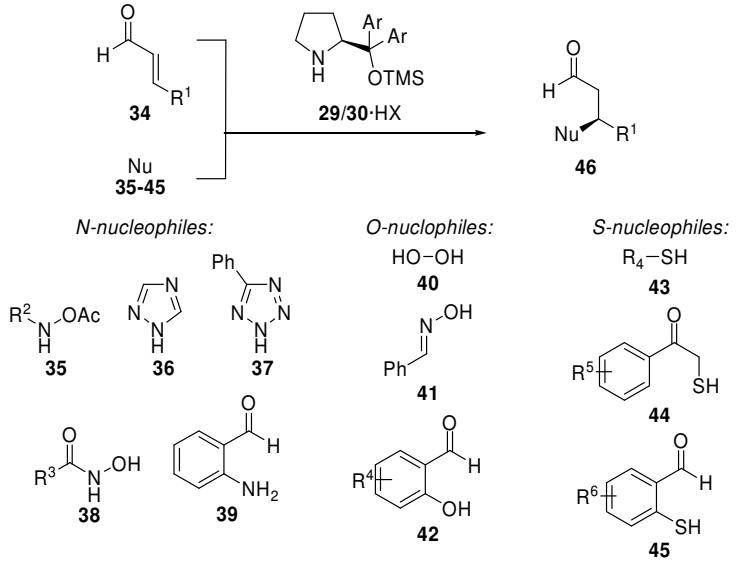


Figure 5. Diaryl prolinols and their esters are efficient iminium catalysts

Although some examples with activated carbon nucleophiles have been published,[32] diaryl prolinol ethers have been particularly successful in additions of heteroatom nucleophiles to enals and enones. Jørgensen and co-workers disclosed that catalyst **30** is efficient in promoting the epoxidation of enals with hydrogen peroxide.[33] Subsequently Cordova and co-workers applied the catalyst to a related aziridination reaction.[34] Several groups have reported asymmetric conjugate additions with *N*-,[35] *O*-,[36] as well as with *S*-nucleophilic species[37] as such and in conjunction with enamine mediated reactions in domino reaction cascades (Scheme 4).[38] An asymmetric hydrophosphination reaction has also been reported.[39] Recently, a [3+2] addition of nitrones to enals and an ene reaction were added to the list of diaryl prolinol ether catalyzed reactions.[40] Interestingly the prolinol catalyst favors the use of rather weak benzoic acid co-catalyst; in certain cases the use of co-catalyst has been omitted.



Scheme 4. Diaryl prolinol ethers catalyze conjugate additions of a wide range of heteroatom nucleophiles

The corresponding unprotected diaryl prolinols have also been investigated as iminium catalysts. Lattanzi and Zhao applied prolinol derivatives such as **32** to asymmetric expoxidation of enones.[41] Interestingly the facial selectivities of these epoxidations were opposite to those achieved with diaryl prolinol ethers. Additionally, Chen and co-workers succeeded in [3+2] cycloaddition between enals and cyclic azomethine imines with the aid of catalyst **33**.[42] Chen

and Deng also published a **31**-promoted vinylogous Michael addition of α,α-dicyanoolefines to enals.[43]

Only few examples of iminium catalysis have been reported with catalysts that incorporate both the co-catalytic acid functionality and the iminium forming amine within single catalyst unit. Although the seminal investigations in the 20th century often employed amino acids as the catalytic species,[44] the approach was quickly abandoned at the dawn of contemporary iminium catalysis.[c]

The groups of Jørgensen and Ley independently investigated this type of catalysts in iminium mediated additions of 1,3-dicarbonyl compounds and nitroalkanes.[45] These reactions are clearly exceptional, as the only other reactions successfully promoted by amine catalysts with internal acid functionality are those involving reactive enamine intermediates at some point of the reaction (namely domino reactions).[46] The design of most of these iminium catalysts is based on or inspired by the imidazolidinone architecture, but also proline derivatives have been used (Figure 6).[d]

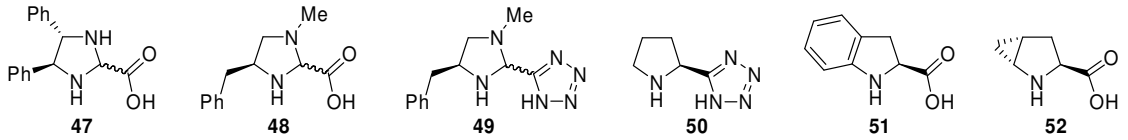


Figure 6. Iminium catalyst containing both the amine and the acid functionality in single unit

With the above described catalysts in hand, the scope of the iminium catalyzed reactions still excludes sterically demanding substrates such as α-substituted enals and most enones, as well as less active nucleophiles and electrophiles. To this end, several catalysts with novel more diverse framework have been presented.

Hydrazide-based catalysts **53** and **54** from the laboratories of Tomkinson[47] and Ogilvie[48] have displayed increased reactivity towards β-substituted enals whereas Brønsted acid salts of primary amines have offered a particularly attractive solution for the efficient imine activation of enones (Figure 7).[49]

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[c] MacMillan reportedly began the development of his seminal Diels-Alder and [3+2] cycloaddition studies by screening some amino acids, but dropped them quickly as they were ineffective. See refs 16b and 17b for further details.

[d] Chin and co-workers have speculated that the active catalytic species form when the catalyst decomposes under the reaction conditions to a diamine and formic acid.[45g]

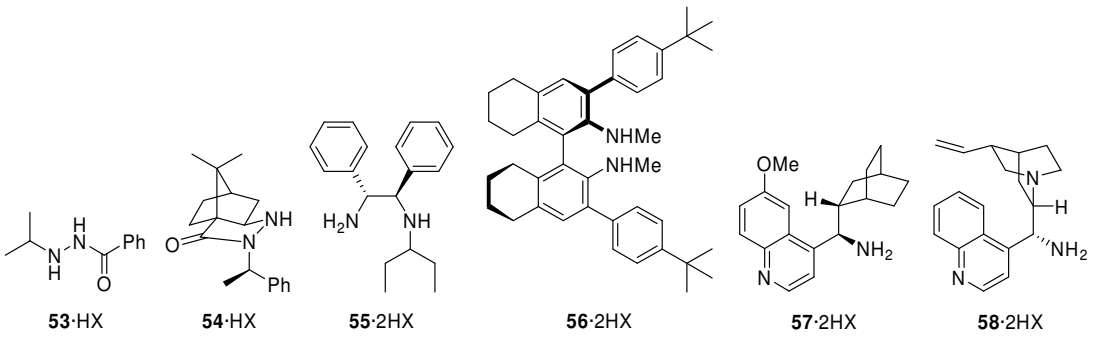


Figure 7. Hydrazine, diamine, and primary amine catalysts for iminium catalysis

Similarly, α-substitution has been addressed with primary amine catalysts (Figure 8). Ishihara and co-workers investigated two distinct diamine catalysts **59** and **4** in the Diels-Alder reaction between α-acyloxyacroleins and dienes with successful results.[50] We, on the other hand, employed TFA-salts of *o*-substituted anilines, such as **60**, to the iminium catalyzed transformations of less reactive α-alkyl substituted acroleins.[III] Also pyrrolidine based diamine catalysts have been successful with simple cyclic α,β-disubstituted enals.[51]

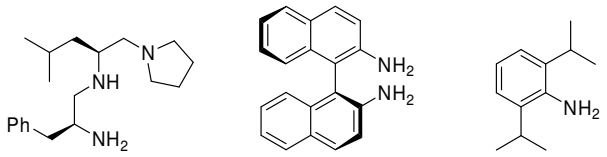


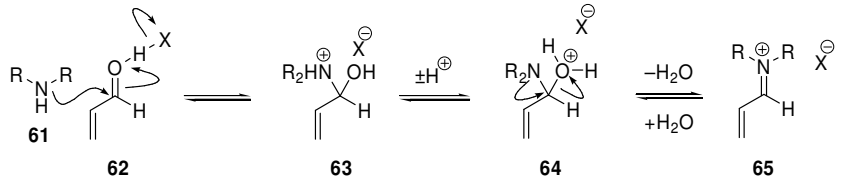
Figure 8. Primary amine catalysts for the iminium promoted transformations of α-substituted acroleins.

The development of contemporary iminium catalysis has evolved from the utilization of Seebach's imidazolidinones to the use of sophisticated primary amine derivatives in a less than a decade. Imidazolidinones have been applied to the widest variety of reactions, but also diaryl prolinol derivatives have found wide use in heteroatom functionalizations. Later, primary amine catalysts have addressed the challenges of enone activation and α-substitution. Along with the diversification of the structure of the amine catalyst consideration of the role of the acid co-catalyst has become more common.

Multiple Roles of Brønsted Acid Co-Catalysis

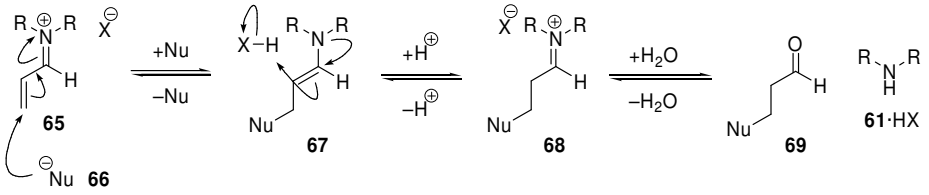
The effect of the acid co-catalyst has been investigated in number of accounts on iminium catalysis. However, in most cases this has only been done briefly and few systematic studies have been reported. In the following discussion an outlook on the role of the co-catalyst is presented based on the accessible information on the co-catalytic effect and its reflection to reaction efficiency.

Scheme 5 shows the formation of iminium species from an unsaturated carbonyl compound. The acid co-catalyst first participates in the iminium formation by activating the enal **62** towards the nucleophilic attack of the amine catalyst **61**. After donating the acidic proton, the counter anion of the co-catalyst stabilizes the positive charge on the proceeding intermediates **63** and **64** until it sits after dehydration on the thus formed iminium ion **65**. The kinetics of iminium ion formation and hydrolysis have been extensively investigated by Jencks.[52] Under alkaline reaction conditions the decreasing solution *p*H speeds up the rate of iminium formation suggesting the existence of general acid co-catalysis. However, when the of the solution turns acidic the rate is rapidly decreased. Hence it can be concluded that a strong acid co-catalyst increases the available concentration of the iminium ion as well as speeds up its formation. The presence of water, on the other hand, aids the hydrolysis of the iminium ion.



Scheme 5. Formation of iminium species is aided by the acid co-catalyst

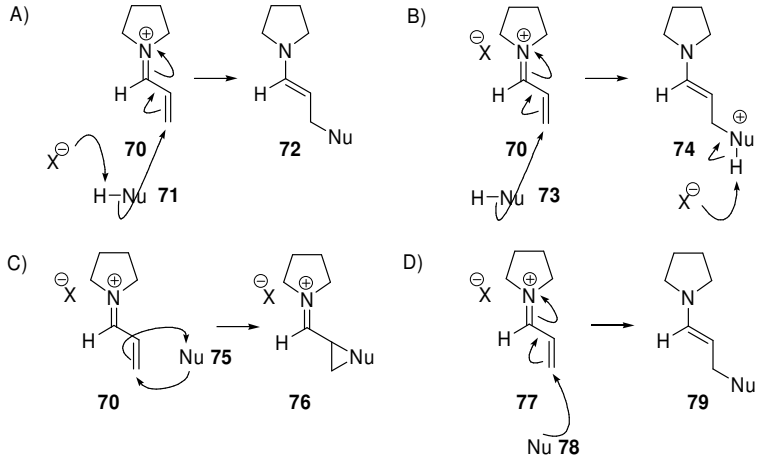
Attack on the *C–C* π-bond of the unsaturated iminium intermediate **65** continues the catalytic cycle (Scheme 6). The rate of the addition step is dependent of the nature of the nucleophilic species. Addition of the nucleophile results in an enamine **67** that may then react further with an electrophile or be protonated to generate iminium complex **68** which is then hydrolyzed to liberate the catalyst **61** and the product **69**. Close inspection of the mechanism of the full catalytic cycle reveals that one equivalent of acid per free amine of the catalyst is required for the catalyst turnover.



Scheme 6. Mechanism of iminium mediated conjugate addition of nucleophilic species

A closer examination of the nucleophilic addition step reveals four alternative addition mechanisms. In the conjugate addition cases the *Nu-H* hydrogen must be removed to unmask the final addition product. The counter ion of the co-catalyst may function at this stage as a general base catalyst and its basicity may affect the reaction efficiency. In cycloadditions to iminium ions there is seldom need for such operations since the final adduct is obtained directly. Alternatively, in conjugated additions the nucleophile may change oxidation state during the

addition step and no removal of hydrogen is required. These addition modes are illustrated in Scheme 7.



Scheme 7. Modes of nucleophile addition to iminium ions a) preceding or concerted removal and b) subsequent removal of hydrogen from the nucleophile, c) cycloaddition, and d) reductive addition

Both primary and secondary amines can form Schiff bases with carbonyl compounds (Figure 9). Schiff bases formed from secondary amines always exist in the charged form i.e. as iminium ions. Primary amines can form deprotonated imines in addition to the charged protonated iminium ions. The reactivity of imines and iminium ions is different. The retinal isomerization has been shown to accelerate substantially when the imine formed form a primary amine is alkylated with Meerwein's reagent to form the charged secondary amine iminium species.[53] We observed similar reactivity transition in the aniline-catalyzed epoxidation of enals where strong Lewis acids showed no co-catalytic activity. Presumably the Lewis acid-imine complexes are less reactive that the corresponding protonated iminium ions, as they are unable to protonate the catalyst-substrate imine complex to form the charged iminium species.[III]

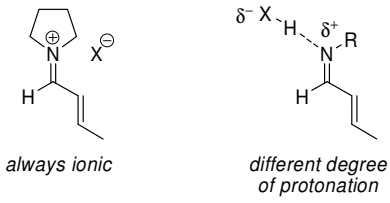
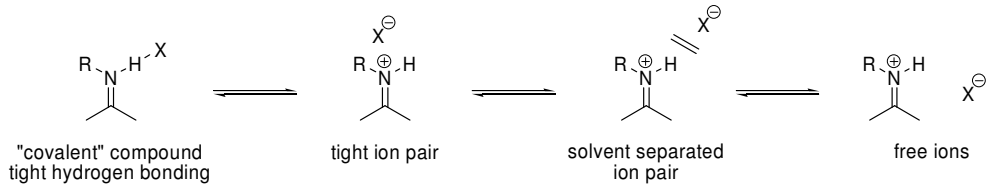


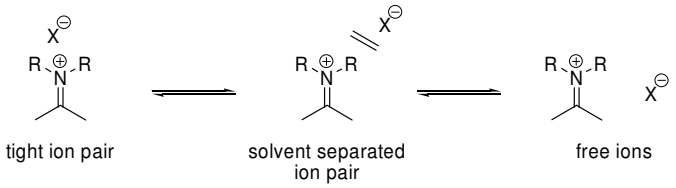
Figure 9. Diverse forms of iminium ions formed form secondary and primary amines

The actual reactive iminium ion may exist in varying forms as illustrated in Schemes 8 and 9. The dissociation scheme proposed by Winstein as a result of his pioneering studies of solvolysis reactions is well applicable to the iminium salts as well.[54] The nature of the ion pairing of the iminium ion and the conjugate base of the co-catalyst likely affects also the reactivity of the system. Mayr and co-workers reported that the halogen iminium salts of aldehydes show specific electrostatic interactions between the aldehyde hydrogen and the halogen anion

resembling hydrogen bonding.[55] Iminium ions formed from secondary amines likely form tight ion pairs with the counter anion. However, the acid can alternatively form a hydrogen bond to the iminium ion formed from primary amine catalyst and carbonyl compound.



Scheme 8. Ion pairing of iminium ions formed from primary amines

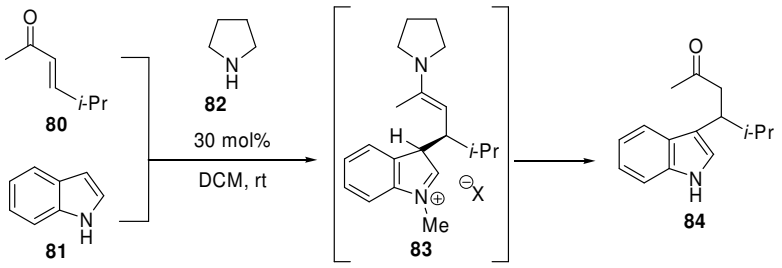


Scheme 9. Ion pairing of iminium ions formed form secondary amines

Several studies on the effect of the acid co-catalyst attest that the presence of a strong acid is beneficial to the reactivity of the system. Xiao and co-workers noticed an apparent trend between the increasing strength of the co-catalysts and the reaction efficiency in the reaction between enone **80** and indole **81** (Table 1).[56] This is consistent with the hypothesis that a stronger acid increases the concentration of the iminium intermediate and therefore accelerates the reaction. Although the indole addition requires involvement of the counterbase in the removal of the proton from the intermediate **83**, this is likely to have little influence on the reaction rate, presumably because the formation of the initial reactive iminium ion from the enone is slow. The reaction rate of the iminium species may be dependent of the concentration of the iminium species or the reactivity of the iminium salt.

Additional reports on the effect of the co-catalyst support the hypothesis that strong acids have a favorable effect on the reaction rate. Also, without reported optimization of the co-catalyst, strong acids have been utilized as co-catalysts in Diels-Alder[16,26,57] and [3+2] cycloadditions[17,58]. The requirement of strong acid co-catalyst in cycloadditions is consistent with the redundancy of base co-catalysis in such reactions.

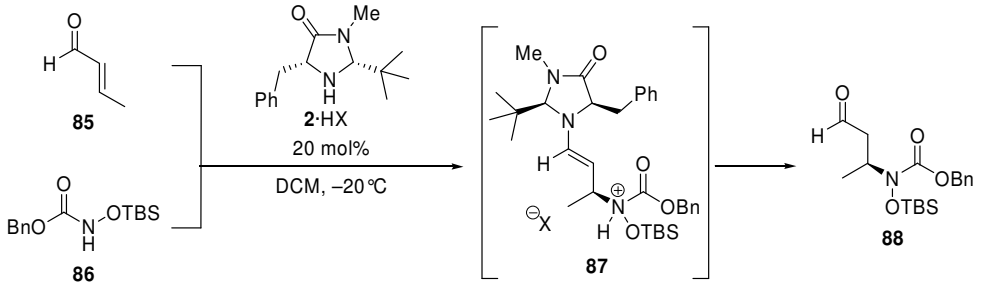
Table 1. Increasing acidity of the co-catalyst reduces the reaction efficiency of Friedel-Crafts alkylation of indole[56]



Entry	HX	pK_a	Time [h]	Yield [%]
1	DCA	1.35	120	33
2	TFA	0.52	120	14
3	HCl	-6.1	96	40
4	PTSA	-6.2	10	90
5	$HClO_4$	-10.00	**6**	**92**

As shown in Table 2, a strong acid co-catalyst was also required in the addition of siloxycarbamate **86** to enals such as crotonaldehyde **85**.[24b] Although the reaction proceeds *via* proton abstraction from the enamine intermediate **87**, the increasing acidity of the co-catalyst enhances the reaction rate. The expendable proton at the intermediate state is rather acidic so even a relatively weak co-catalyst conjugate base is adequate for its removal. However, the existence of the enamine intermediate **87** likely explains the enantioselectivity trend (see discussion on page 27).

Table 2. Increasing acidity of the co-catalyst enhances the reaction efficiency of the *N*-conjugate addition

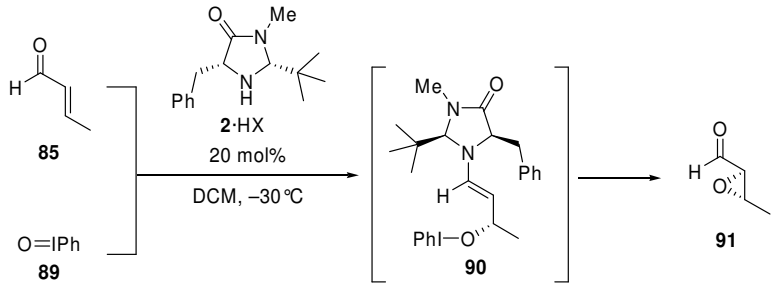


Entry	HX	pK_a	Yield [%]	*ee* [%]
1	TFA	0.52	29	81
2	HCl	-6.1	32	69
3	**PTSA**	**-6.2**	**70**	**87**

Examples of similar positive influence of strong acids on the stereoselectivity of asymmetric conjugate addition reactions have been disclosed repeatedly. MacMillan and co-workers reported that the increasing acidity of the co-catalyst produced appreciable improvement of the

enantioselectivity in the epoxidation of enals with iodosobenzene (Table 3).[24c] As in the cycloadditions, the addition mechanism does no include any proton removal, thus only the rate of iminium ion formation and hydrolysis is controlled by the co-catalyst.

Table 3. Increasing strength of the co-catalyst improves the enantioselectivity of the epoxidation reaction



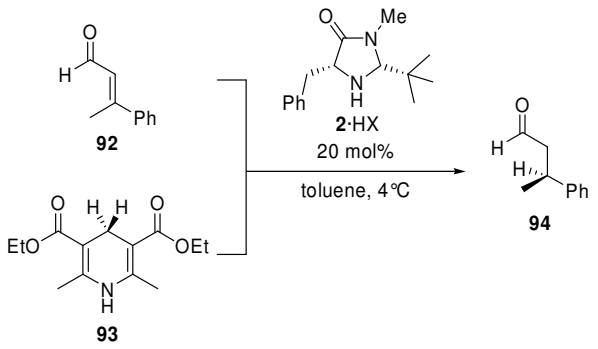
Entry	HX	pK_a	Yield [%]	*ee* [%]
1	CNA	2.47	27	69
2	DCA	1.35	27	72
3	TFA	0.52	42	72
4	PTSA	-6.2	50	76
5	$HClO_4$	-10.00	68	88
6	TfOH	-14	74	87

Also the selectivity and efficiency of the conjugate reduction of enals with catalyst **2** is successfully enhanced by addition of strong acid co-catalyst (Table 4).[59] In this example, the yields are unaffected by the nature of the co-catalyst, but its effect on the enantioselectivity is pronounced.

In light of the above examples, it may be surprising that an opposing co-catalytic trend was observed in the Friedel-Crafts reaction between cinnamaldehyde and *N*-methyl pyrrole.[18] The findings indicate that the reaction rates and selectivities improve when acidity of the co-catalysts decreases (Table 5). In this case, however, a decrease of pK_a over 0.52 led to eroded rates. The authors explained the detected trend by dual role of the catalyst.

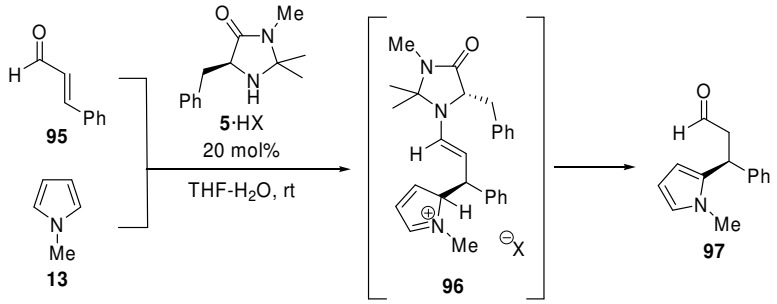
Besides the involvement of the co-catalyst in the formation of the reactive iminium ion, its conjugate base acts as a general base catalyst in the irreversible abstraction of proton from the enamine intermediate **96**. If the latter step is fast, the enantioselectivity of the first step is transmitted intact to the final product. However, if the loss of proton is slow, not only does it slow down the reaction, but it also erodes the enantioselectivity due to the reversibility of the conjugate addition step. A strong base increases the rate of the proton removal. Hence the increasing strength of the conjugate base of a weaker acid co-catalyst is beneficial to both the efficiency and the selectivity of the reaction.

Table 4. Increasing acidity of the co-catalyst enhances the enantioselectivity of the conjugate reduction reaction



Entry	HX	pK_a	Solvent	Yield [%]	*ee* [%]
1	MsOH	-2.60	Et_2O	93	7
2	HNO_3	-1.30	Et_2O	89	62
3	HF	3.7*	Et_2O	98	48
4	HBr	-9.00	Et_2O	**93**	**82**
5	MsOH	-2.60	toluene	93	7
6	HNO_3	-1.30	toluene	89	62
7	HF	3.7*	toluene	98	48
9	HCl	-6.10	toluene	70	81
8	HBr	-9.00	toluene	**93**	**82**

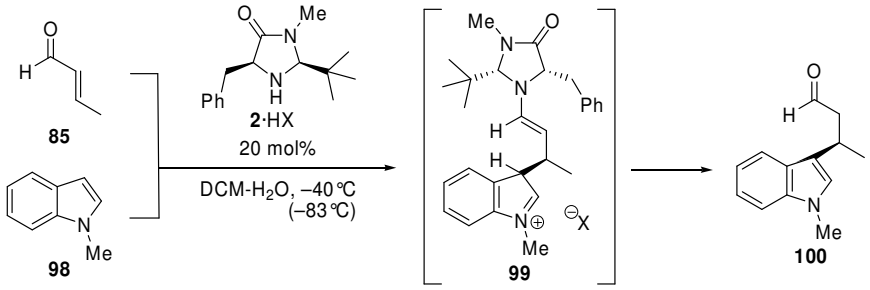
Table 5. Decreasing acidity of the co-catalyst enhances the reaction efficiency and selectivity of the Friedel-Crafts alkylation of *N*-methyl pyrrole



Entry	HX	pK_a	Conversion [%]	*ee* [%]
1	AcOH	4.76	n.r.	
2	CNA	2.47	trace	80
3	ONBA	2.21	n.r.	
4	DCA	1.35	<5	80
5	TFA	0.52	**76**	**81**
6	TCA	0.51	64	81
7	HCl	-6.10	63	77
8	PTSA	-6.2*	41	55
9	TfOH	-14*	44	42

The results gained from the optimization of the acid co-catalyst in the Friedel-Crafts alkylation of indole by Austin and MacMillan[21a] follow the findings made in the pyrrole conjugate addition in respect of pK_a of the acid and the reaction efficiency. The demand for a general base catalyst strongly manifests itself in the reaction rate. The fastest reaction rates, however, were displayed neither by the strongest nor by the weakest of the studied acids but by the one sitting in the middle of the pK_a-range: TFA. Although these results were obtained with only three different acids they nevertheless suggest that the nature of the optimal co-catalyst is dependent of the nature of the nucleophile or the substrate.

Table 6. Addition of *N*-methyl indole to crotonaldehyde requires relatively weak acid co-catalyst

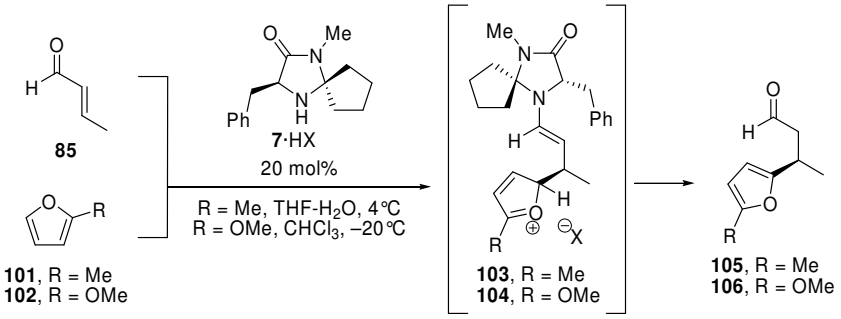


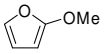
Entry	HX	pK_a	Time [h]	Yield [%]	ee [%]
1	ONBA	2.21	22	88	88
2	TFA	0.52	**1.5 (48)**	**70 (84)**	**85 (92)**
3	PTSA	-6.2	4 (13)	98 (15)	88 (80)

Influence of the nature of the substrate to the choice of the acid co-catalyst may be best illustrated by the reactions between crotonaldehyde and furans **101** and **102** studied by Brown and MacMillan.[25] Interestingly, the results summarized in Table 7 show opposing trends with the two substrates. The methyl substituted furan **101** exhibited highest reaction rates with the most acidic co-catalysts, although the best enantioselectivities were obtained with the weakest acid. In contrast, both the efficiency and the stereoselectivity improved with the decreasing acidity in the case of the methoxy-substituted furan **102**.

As in the case of *N*-methyl pyrrole addition to enals a relatively strong conjugate base is required. This favors the removal of proton from the enamine intermediate to reform furan over retroconjugate addition that could compromise the enantioselectivity. However, the reaction rate may still be determined by the turnover of the catalyst. The catalyst turnover is increasingly enhanced by the increasing acidity of the co-catalyst hence leading to the observed bipolar efficiency-selectivity trend with the 2-methylfuran **102**.

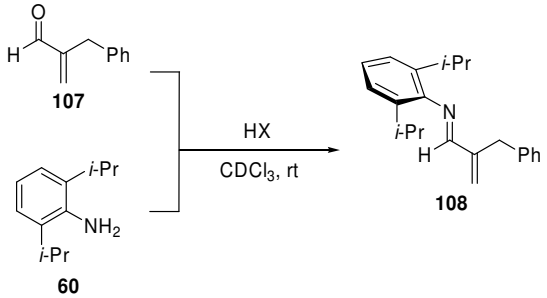
Table 7. Two furans show opposing trends in reaction efficiency relative to the acidity of the co-catalyst



Entry	HX	pK_a	 Conversion [%]	*ee* [%]	 Conversion [%]	*ee* [%]
1	CNA	2.47	34	**71**	**72**	**92**
2	DBA	1.48	n.d.	n.d.	77	91
3	DCA	1.35	51	70	75	90
4	DFA	1.34	50	71	76	93
6	TCA	0.51	72	69	11	76
5	TFA	0.52	83	68	33	81
7	HCl	-6.10	**85**	61	0	n.d.

We studied the influence of the acid co-catalyst in the aniline promoted transformations of α-substituted acroleins. We observed that the decreasing strength of the co-catalyst surprisingly thrusts the acrolein-iminium equilibrium towards the iminium species; the weakest of the studied acids hence allowed the fastest formation and highest concentration of the reactive iminium species (Table 8).[60]

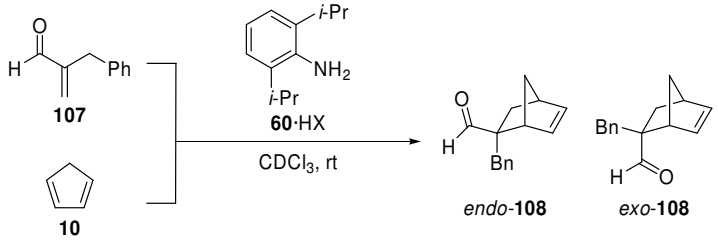
Table 8. Formation of iminium ion from aniline and α-benzyl acrolein is enhanced by the diminishing strength of acid co-catalyst



Entry	HX	pK_a	Time [min]	Conversion [%]
1	TFA	0.52	4	**30**
2	DPP	0.46	4	22
3	PTSA	-6.20	40	4
4	HCl	-6.10	11 h	<1

This feature was also transmitted to the efficiency of the reaction as affirmed by the Diels-Alder reaction between α-benzyl acrolein **107** and cyclopentadiene **10** (Table 9) studied in our group, where there is no requirement for general base catalysis that could otherwise explain the observed trend.[61] Alternatively, the fast rate may be explained by facile hydrolysis of the product iminium ions and thus faster turnover of the catalyst. An iminium ion stabilized by the conjugate anion of a weaker acid is more labile to hydrolysis as the hydrolysis is also catalyzed by the conjugate base.[52]

Table 9. Decreasing acidity of the co-catalyst correlates with increasing reaction efficiency in aniline promoted Diels-Alder reaction

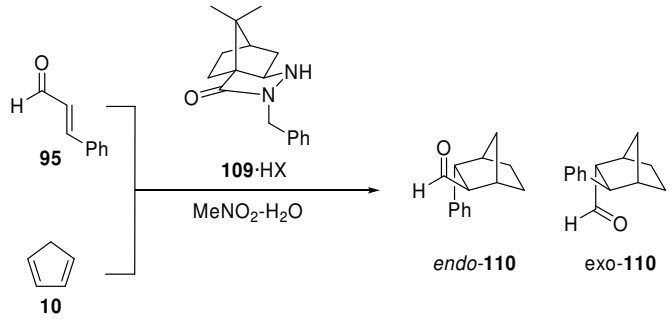


Entry	HX	pK_a	Time [h]	Conversion [%]	*endo*:*exo*
1	TFA	0.52	>3	**100**	**8:1**
2	DPP	0.46	5	50	8.5:1
3	HCl (aq.)	-6.10	5	15	4.9:1
4	MsOH	-6.8*	5	28	4.7:1
5	TfOH (aq.)	-14*	5	23	4:1

In all the aforementioned examples a single choice of co-catalyst has been applicable to the whole substrate scope of the method. However, MacMillan and Jen proposed that it is beneficial to optimize each substrate on individual basis in the intramolecular iminium-activated Diels-Alder reaction.[20d] Besides the use of less acidic co-catalysts (TFA, TCA) with more reactive substrates, they suggested the use of more acidic co-catalysts (such as $HClO_4$) with the less reactive substrates as decreasing basicity of the conjugate base should decrease base catalyzed product epimerization and dimerization of starting material.

Ogilvie and co-workers observed a dependence between the efficiency and type of the co-catalyst in the hydrazide iminium catalyzed Diels-Alder reactions (Table 10).[48b] Initially, it appeared that the strength of the acid and the selectivity and efficiency of the reaction had a strong positive correlation. However, a closer inspection revealed that halogen acids as well as sulfonic acids fall out of the pattern. Whereas halogen acids showed unexpectedly low efficiencies, with sulfonic acids no correlation could be drawn between either the size or the pK_a and the results.

Table 10. Hydrazone catalyzed Diels-Alder reaction

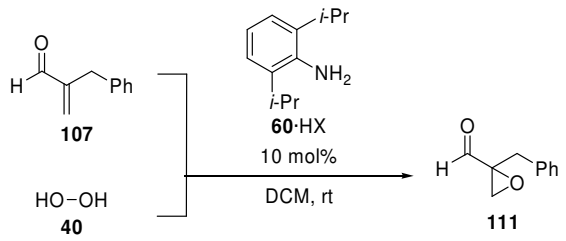


Entry	HX	pK_a	Yield [%]	*exo:endo*	*ee* [%] (*exo*)
1	AcOH	4.76	7	1:1	2
2	TFA	0.52	13	1.7:1	30
3	$HClO_4$	-10.00	82	1.7:1	85
4	$HSbF_6$		59	1.8:1	81
5	HBF_4		98	1.7:1	85
6	HCl	-6.10	11	1.3:1	27
7	HBr	-9.00	40	1.7:1	65
8	HI	-10.00	13	1.2:1	31
9	MsOH	-2.6	8	1.2:1	15
10	PTSA	-6.2	15	1.5:1	41
11	CSA	-3.0	17	1.6:1	57
12	$EtSO_3H$	-6.5	7	1.2:1	24
13	H_2SO_4	-3.00	11	1.1:1	17
14	TfOH	-14	89	1.9:1	88

In my own studies, the choice of the acid co-catalyst influenced the activity of aniline catalyzed epoxidation of α-substituted enals in a significant manner.[III] While very strong acids failed to promote the reaction weaker acids with pK_a between 0.48-1.28 were found to be active. As pK_a increased beyond this point sudden drop of co-catalytic activity was again seen. The narrow pK_a range of efficient co-catalyst is evident from Table 11. It can be questioned whether an acid co-catalyst of this acidity is strong enough to protonate the aniline catalyst (pK_{aH} of an aniline is typically ca. 4.5) and hence function as a general acid co-catalyst. Instead, the acid may serve as a hydrogen bonding catalyst.[e] Similar restricted choice of acid co-catalyst was also observed in the aniline catalyzed transfer hydrogenation of α-substituted acroleins.[62]

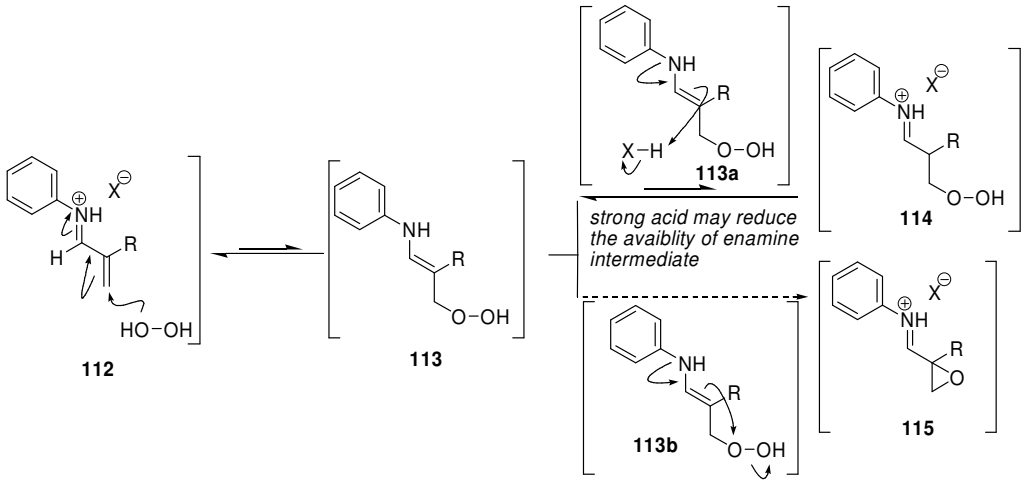
[e] The DPP salt of aniline catalyst **60** lacks conductivity in DCM at rt, which indicates absence of dissociation of the ionic species of the catalysts. The conductivity has not been studied in presence of an enal and thus there is no direct evidence of stabilization of the imine intermediate by hydrogen bonding. *Unpublished results.* Pihko, P. M.; Erkkilä, A.; Murtomäki, L.

Table 11. Epoxidation of α-substituted acrolein proceeds only in narrow co-catalyst pK_a range



Entry	HX	pK_a	Conversion [%]
1	-	-	0
2	AcOH	4.76	0
3	HO_2CCO_2H	4.20	0
4	MCA	2.86	4
5	DCA	1.28	56
6	TCA	0.52	60
7	TFA	**0.51**	**62**
8	DPP	0.48	51
9	MsOH	-0.60*	0
10	PTSA	-6.2*	8
11	Tf_2NH	-13.19*	0

Stronger acids may be inapt for the epoxidation reaction, as they have the power to push the enamine intermediate **109** back to iminium ion **111** before the peroxide has a chance to close the epoxide ring to form **113**. That would lead the reaction path to turn back to the starting material as the equilibrium of the conjugate addition of an *O*-nucleophile generally lies on the side of the starting materials. Another plausible explanation is that the strong acid may protonate the peroxide and thus impairs its nucleophilic character. Alternatively the intermediate **109** is protonated at the *C*-*O* end of the peroxide which favors the equilibrium to shift towards **108**.



Scheme 10. Strong acid co-catalyst may inhibit the enamine mediated closure of the epoxide ring

We conducted an extensive study on the function of the acid co-catalyst in the enamine-imine promoted α-methylenation reaction.[IV] As illustrated in Figure 10, a linear relationship between the acidity of the co-catalyst and the reaction rate was detected with *para*-substituted benzoic acids and phenols. The efficiency of the reaction increased with the decreasing acidity of the benzoic acid co-catalyst and increasing acidity of the much weaker phenols. Maximum efficiency was estimated to be achieved with a co-catalyst with pK_a in the range of 5-6 where the two correlation lines intercept.

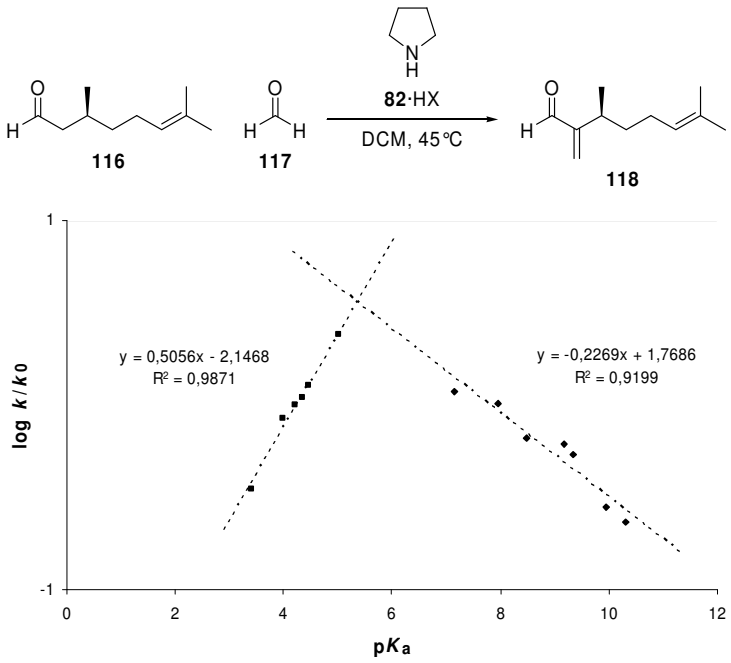
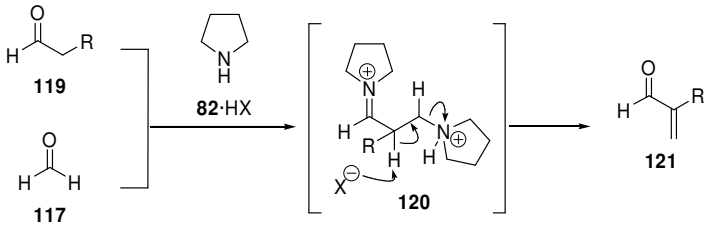


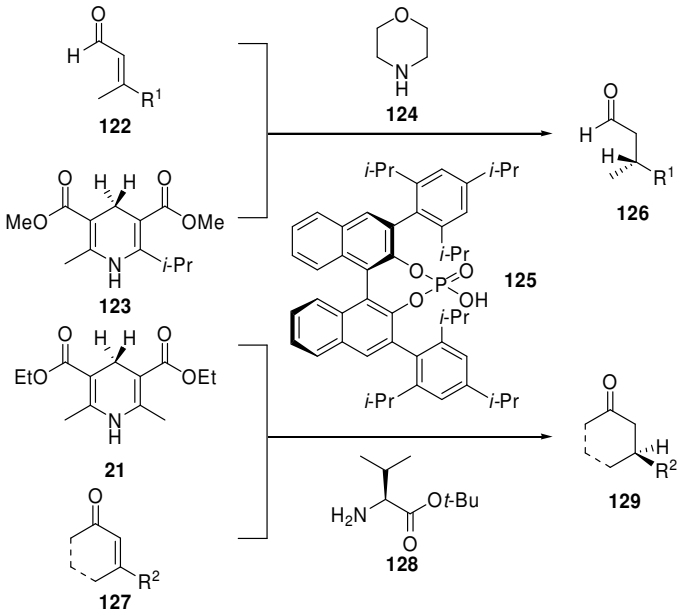
Figure 10. Acidity of phenols (left line) and benzoic acids (right line) correlates with the rate of α-methylenation reaction

Based on kinetic studies we were able to postulate the mechanism of the α-methylenation reaction (Scheme 11). The reaction is of second order with respect to the catalyst salt indicating the presence of two molecules of the catalyst the reaction intermediate **120**. General base catalysis is required for the removal of the proton in the elimination step as well as in the initial enamine formation from aldehyde **119**. This explains the increasing reaction efficiency when the strength of the benzoic acid co-catalyst is decreased. However, when optimal pK_a of the co-catalyst is passed the rate determining step likely shifts to the formation of the iminium ion, hence the decreasing efficiency of the weakening acidity of the phenols.



Scheme 11. Mechanism of the α-methylenation reaction

Inspired by the strong role of the acid co-catalyst in the iminium catalysis, List and Mayer suggested that the role could well be expanded beyond the delivery of protons and stabilization of the iminium transition state. In a recent report,[63] they disclosed that chiral co-catalyst **125** promotes transfer hydrogenation reactions of β-substituted enals in high stereoselectivities, when used in conjunction with an achiral amine, morpholine **124**. List and Martin utilized the same concept in the transfer hydrogenation of enones.[64] This time both the amine **128** and the acid component **125** were chiral.

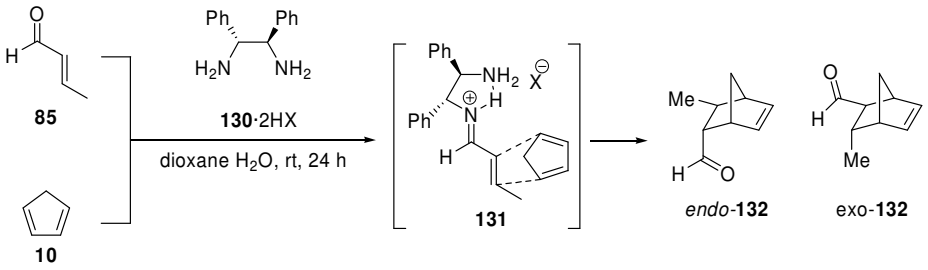


Scheme 12. Chiral co-catalyst transfers stereochemical information in transfer hydrogenation reactions

When a chiral acid co-catalyst is used to transfer stereochemical information it is natural that its structure has a strong influence on the stereoselectivity of the reaction. But what is the effect of the structure of an achiral co-catalyst on the stereoselectivity and does the structure have any influence of the efficiency on the reaction? In hydrogenation reactions co-catalyzed with TRIP **125,** the reaction rate generally decelerates as the size of the co-catalyst is increased. As it can be presumed that the additional substituents on the remote phenyl side chain have only a small influence on the pK_a of the acid it could be proposed that the bulkiness of the acid co-catalyst may hinder its efficiency.

Ha and co-workers proposed that the increasing size of the co-catalyst explains the gradual decrease of stereoselectivity in the bisammonium salt **130** catalyzed Diels-Alder reaction between crotonaldehyde **85** and cyclopentadiene **10** (Table 12).[65] The iminium catalysis likely proceeds *via* a transition state **131** where the second amine is hydrogen bonded to the iminium forming amine to lower its pK_a to facilitate faster formation. A bulky anion could distort the organization of the chiral environment and narrow the energy differences of alternative transition states that lead to unwanted stereoisomers.

Table 12. Increasing size of the acid co-catalyst decreases selectivity in diamine promoted Diels-Alder reaction



Entry	HX	pK_a	Yield [%]	*endo:exo*	*ee* [%] (*endo*)
1	**HCl**	**-6.10**	**96**	**4.8:1**	**79**
2	HBr	-9.00	98	4.3:1	77
3	$HClO_4$	-10.00	96	3.4:1	54
4	DBSA		98	3.3:1	77
5	PTSA	-6.2	61	1.2:1	47

There are few iminium-catalyzed reactions where no acid co-catalyst (external or internal) has been used. As discussed above, the catalytic cycle implies the need of one equivalent of acid per amine catalyst (or at least a proton source). It should be noted, that the proton source should be at least as acidic as the catalyst salt lest the iminium formation become unacceptably slow. How do these reactions with out any co-catalyst work?

It is noteworthy that all reactions proceeding without the aid of co-catalyst are promoted either by diaryl prolinols **31**-**33** or their ethers **29** and **30**. However, the hydroxyl unit of diaryl prolinols is - if not acidic - at least capable of hydrogen bonding. As small amounts of water are present in iminium catalyzed reactions it may well be that water plays the role of a proton transfer catalyst in the diaryl prolinol ester–catalyzed reactions and thus aids the reaction to proceed. Additionally, the reactions discussed above either involve highly active nucleophiles (β-ketoesters or nitroalkanes) or embody a subsequent enamine-catalyzed reaction step. These factors are most likely to contribute to the omission of the acid co-catalyst.

Much of what has been described above regarding the function of the co-catalyst indicates a multiple role of the acid in the catalytic cycle. Since both the catalytic efficiency and the stereoselectivity clearly depend on the nature of the Brønsted acid co-catalyst, it is rather straightforward to draw conclusions that both the proton of the acid as well as its counter ion play pivotal roles in the process. Furthermore, if the acid co-catalyst is bound close enough to the reaction species it is irrelevant which one of the partners of the chiral ion pair brings in the stereochemical information or whether it is the matching combination of both.

Strong acids are beneficial in reactions where the reaction rate is determined only by the rate of the formation of the iminium ions or the turnover of the catalyst from the product to the starting material in the catalytic cycle. On the contrary, reactions where the conjugate base of the co-catalyst is required to shuffle protons during the intermediate states often require use of less acidic co-catalyst. The co-catalyst not only needs to be a good acid; it should be a good base as well. Hence cycloadditions are often performed in the presence of strong acid co-catalyst whereas most conjugate additions require more careful choice of co-catalyst.

In short, it can be concluded that the choice of the acid co-catalyst is crucial to the efficiency and the selectivity of the reaction. This should be taken into account when new iminium catalyzed reactions are developed. The best conditions for an iminium catalyzed reaction can be found close to the pK_a range where the pK_a of the imine forming amine, the nucleophile and the *p*H of the solution are equal.

2.2 Enamine Catalysis

Tautomerization of aldehydes and ketones to corresponding enols allows their use as nucleophilic species. Similarly, deprotonation of an imine or an iminium ion to form enamine species strengthens its nucleophilic character. Elevated HOMO energy makes it more prone to add to electrophiles than the enol form of its parent carbonyl compound. Enamine activation thus enables aldol and Mannich type reactions, Michael additions, and α-heteroatom functionalizations of enolizable aldehydes and ketones as presented in Figure 11.

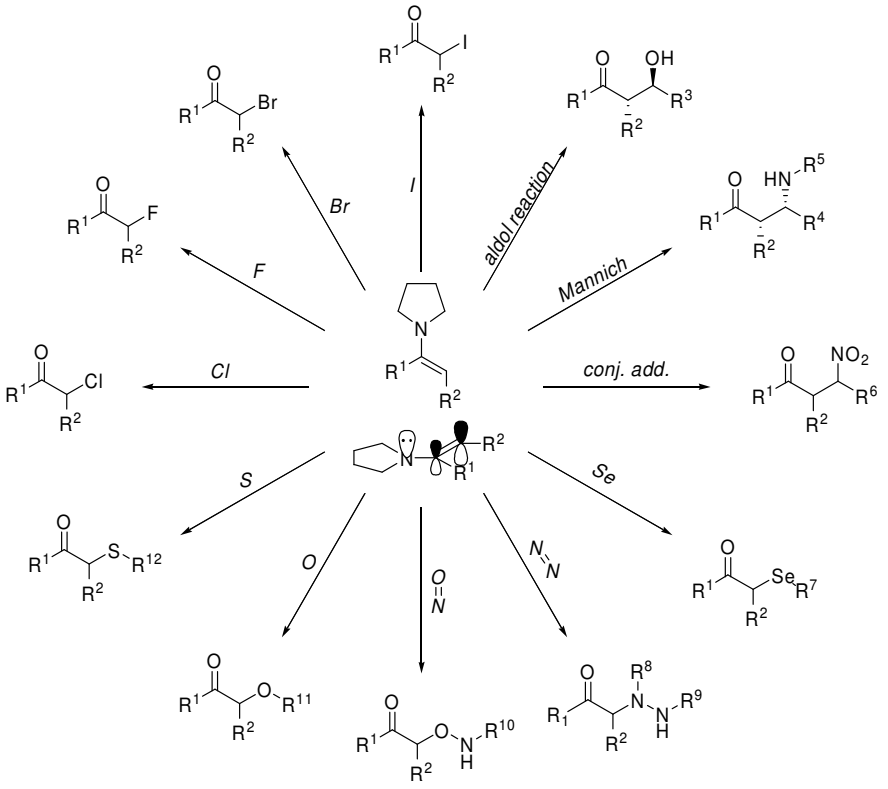
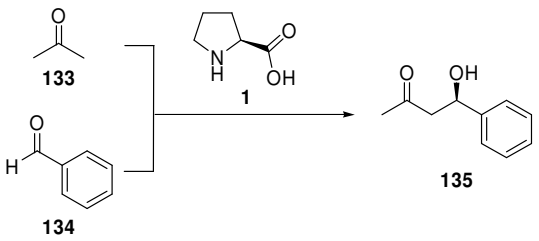


Figure 11. A range of transformations can be promoted by enamine catalysis

The era of preformed enamines[66] precedes the contemporary enamine catalysis and has provided, in addition to enamine biocatalysis, the greatest source of inspiration in the field. Several reviews cover the area of enamine catalysis extensively.[67] In the following, a general overview of the contemporary enamine catalysis is given followed by a discussion on the role of the acid co-catalysis.

From Aldol Reactions to α-Heteroatom Functionalizations

The sole secondary amine amongst the naturally occurring amino acids, proline **1**, has been a focus of a wide range of reports on enamine catalyzed reactions. It was first discovered to catalyze intramolecular aldol reactions by Hajos and Parrish and Eder, Sauer, and Wiechert in 1970's.[2] Almost three decades later List and co-workers reported respective intramolecular *anti*-selective aldol reaction between acetone and aromatic aldehydes (Scheme 13).[68] Various adaptations to specific targets soon followed[69] – cross-aldehyde reaction of aldehydes by Northrup and MacMillan[70] being one of the most engrossing ones as previously this reaction had been only an elusive aspiration. Proline-catalyzed aldol reactions have also been utilized in polyketide[I,71] and natural product synthesis.[4,72]



Scheme 13. Proline catalyzed aldol reaction

In the following years proline was applied to variety of *syn*-selective Mannich reactions of ketones and aldehydes.[73,74] The first conjugate addition of ketones to nitroalkenes was also accomplished by List and co-workers.[75] As reports on α-aminations[76] and α-oxygenations[77] followed proline was rapidly announced to be a privileged catalyst, "the simplest enzyme".[78]

Despite proline's firm grip as the leading catalyst in the realm of enamine catalysis, new catalysts were introduced (Figure 12). At first modifications were mainly focused on varying the size of the amine ring and the type and location of the acid moiety. These variations were primarily reported in attempts to widen the scope or the efficiencies of the already well established aldol and Mannich reactions.[79] However, more profound results were obtained in less explored areas such as in the conjugate additions to nitroalkenes where catalysts such as **139** and **140** were particularly successful.[80] Additionally, relocation of the acid moiety further away from the amine functionality, as in catalyst **141**, allowed efficient access to α-substituted acroleins.[II]

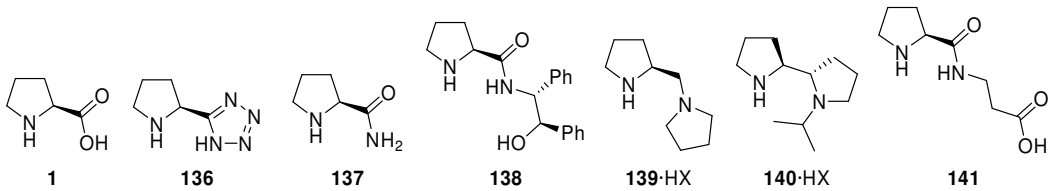


Figure 12. Proline and some of its most successful variants for enamine catalysis

Introduction of additional substituents to the proline core enabled intramolecular α-alkylation of aldehydes[81] as well as improved[I] or even reversed[82] the diasteromeric outcome of aldehyde aldol and Mannich reactions, respectively (Figure 13). Only rare examples of natural or unnatural amino acids other than proline have been reported so far.[83] The most successful of these is the L-threonine *tert*-butyl ether **144** catalyst reported by Barbas and co-workers for *syn*-aldol and *anti*-Mannich reactions.[84] Aldehydes can also be hydroxylated with molecular oxygen in the presence of α-methyl proline **142**.

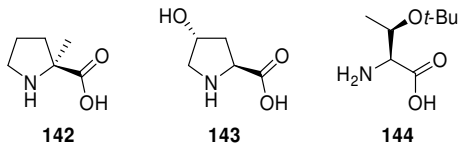
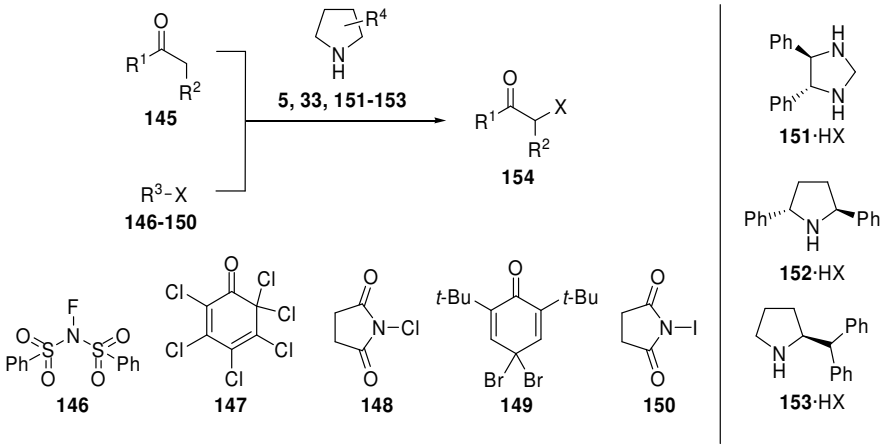


Figure 13. Some amino acid catalysts for enamine catalysis

Scheme 14 illustrates cases where the enamine catalysis concept has been extended to α-halogen functionalizations. Marigo and Jørgensen recently published a comprehensive review of these types of reactions.[85] It is noteworthy, that a pyrrolidine derivate with an external acid source is required to promote these reactions. The groups of Jørgensen and MacMillan fruitfully studied the use of Brønsted acid salts of **151** and **5** in α-chlorination of ketones[86] and aldehydes,[87] respectively. Subsequently, MacMillan and Barbas with their respective co-workers utilized catalyst **5** in the α-fluorination of aldehydes.[88] Furthermore, Jørgensen and co-workers investigated simpler pyrrolidine derivates **151** and **153** in α-bromination,[89] α-iodination,[90] and α-chlorination reactions[91] with flourishing results. Additionally, in their hands diaryl prolinol ether **33** delivered equally good results in the α-fluorination of aldehydes.[92]

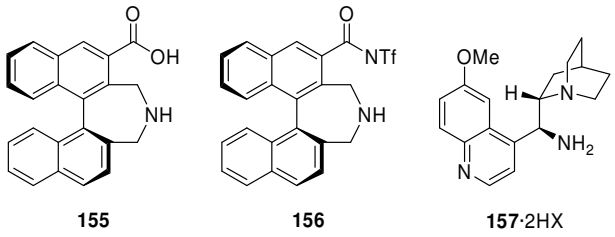


Scheme 14. Pyrrolidiene derivatives promote α-halogenations of aldehydes and ketones

In addition to α-halogenations, imidazolidinones and diaryl prolinols have found use in other transformations activated *via* enamine formation. Jorgensen applied diaryl prolinol ether **33** to the α-sulfenylation of aldehydes. Also γ-amination reaction and aminomethylations have been disclosed.[93] Besides that, MacMillan and co-workers investigated imidazolidinone **2** in the crossed-aldol reaction of aldehydes.[94]

More complex enamine catalysts presented in Figure 14 have been described by the groups of Maruoka and Connon. Maruoka introduced catalyst **155** in the context of aldol reactions between acetone and aromatic aldehydes and later presented the *syn*-selective aldol catalyst

156.[95] Connon, on the other hand, utilized cinchona alkaloid derivates that incorporate primary amine functionality such as **157** in conjugate addition nitroalkanes to aldehydes and ketones.[96]



155 **156** **157**·2HX

Figure 14. More complex enamine catalysts for *syn*-aldol and Michael reactions

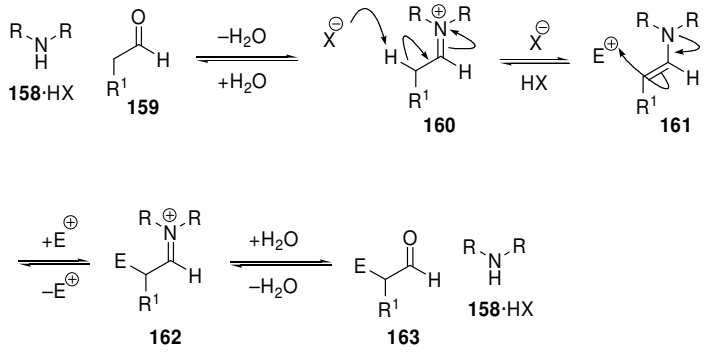
Overall enamine catalysis is dominated by catalysts where both the amine and the acid functionality are within single unit. As such simple amino acid proline holds a special role.

Dominance of Internal Brønsted Acid Co-Catalysis

The emphasis on the development of the new catalysts for enamine catalyzed reactions has been in altering structural features of the catalyst while the roles of the pK_a of the amine and acid functionalities have been mostly disregarded or omitted. Also, in clear contrast to iminium catalysis, the preponderance of reactions activated by enamine formation are catalyzed by amino acids.

Only few systematic studies on the effect of the co-catalytic acid component in enamine mediated reactions are available. In fact, even rudimentary optimizations of the acid co-catalyst are scarce. This may be partly due to the fact that it is difficult to alter an intramolecular acid functionality. Additionally, change of the internal acid also directly influences the pK_{aH} of the amine as well as the whole structure of the catalysts. The role of the acid co-catalyst in enamine catalysis is outlined below based on available literature.

As illustrated in Scheme 15, an enamine-catalyzed reaction proceeds *via* initial formation of iminium species **160** between an amine **158** and a carbonyl compound **159**. It is then transformed to the enamine **161** through elimination of an α-proton by a conjugate base. The thus created enamine may then react with any present electrophile to regenerate an iminium intermediate **162**. Only then does the hydrolysis of the imine unmask the product **163** and the catalytic cycle is complete.



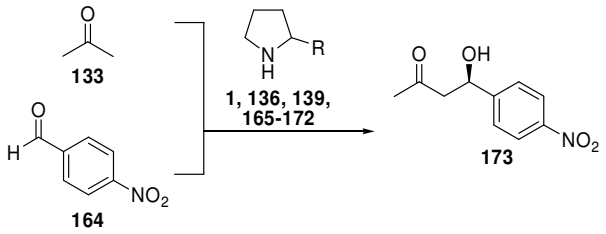
Scheme 15. Mechanism of a reaction promoted by enamine formation

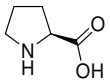
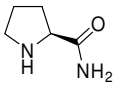
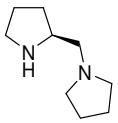
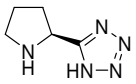
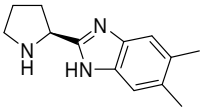
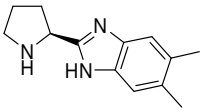
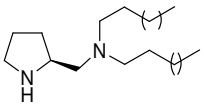
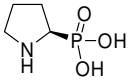
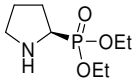
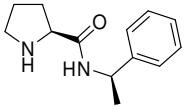
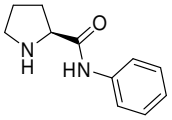
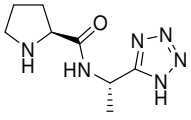
The iminium catalyzed enamine formation has been extensively studied by several groups.[97] As stated above, formation of the reactive enamine species requires abstraction of an α-proton from the initially formed iminium ion. Whereas a strong acid co-catalyst can push the carbonyl-iminium equilibrium towards the iminium species, the basicity of its counter anion determines the rate of enamine formation. The conjugate base of a strong acid has a strong stabilizing effect on the iminium ion but only a weak ability to remove a proton from the α-position. On the other hand, a weak acid decreases the rate of the iminium ion formation but the relatively stronger conjugate base strongly favors the formation of the enamine. Hence both general acid and general base catalysis is required even to form the enamine. As these tendencies are opposing, how should the pK_a of the nucleophilic amine and the acid (or rather its counter base) be matched to achieve maximum catalytic effectiveness?

In addition to iminium-enamine forming steps the acid co-catalyst can be utilized in the activation of the electrophile as it is free of any other occupation after the reactive enamine intermediate has been formed. Organized localization of the acid moiety near the enamine forming amine allows it to direct the approaching electrophile *via* hydrogen bonding or electrostatic interaction. As a consequence, most of the disclosed enamine catalysts incorporate both the amine and the acid functionality within a single catalyst unit.

The extensive number of reports on organocatalytic aldol reactions allows insight to the co-catalytic effect by comparison of the available proline derivatives where the acid functionality has been altered. Table 13 displays the resulting effects of these modifications in the aldol reaction between acetone **133** and *para*-nitrobenzaldehyde **134**. A change of the proline carboxylate moiety to its tetrazole bioisostere changes its solubility while similar acidity is retained. This slightly improves the efficiency of the aldol reaction without a change of stereoselectivity.

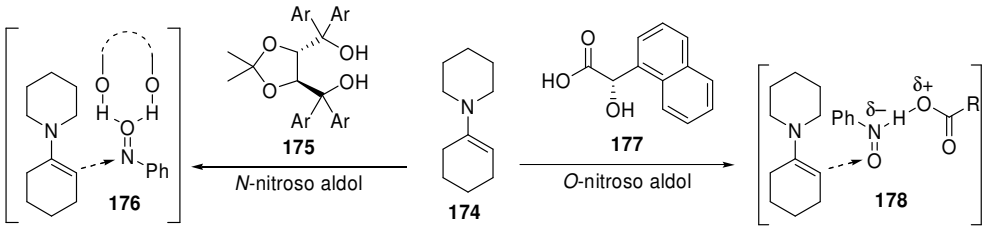
Table 13. Exploration of various proline derivatives as catalyst in the aldol reaction



Entry	Catalyst		Time [h]	Yield [%]	*ee* [%]	Ref
1		**1**	4	75	73?	68
2		**165**	4	<10	n.d.	79h
3		**139**·CSA	4	41	81	79h
4		**136**	4	93	76	79g
5		**166**	8	40	44	79b
6		**167**·AcOH	1	65	49	79b
7		**167**·TFA	72	82	55	79c
8		**168**	43	63	82	79d
9		**169**	24	69	82	79d
10		**170**	8	83	46	79e
11		**171**	36	87	15	79e
12		**172**	24	68	96	79f

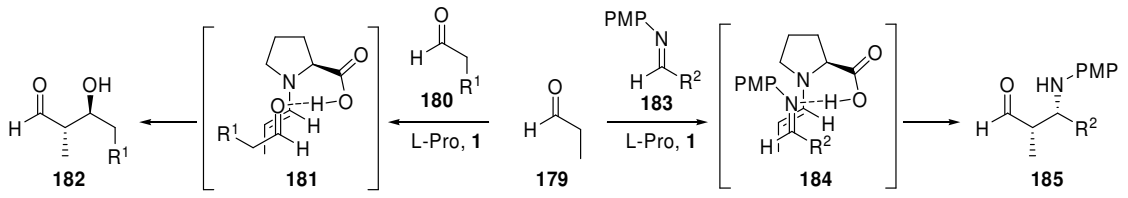
A more pronounced change in stereoselectivity can be seen with the amide analogues of proline (Table 13, entries 2 and 10-12). Both the size and the pK_a of the acid functionality change in these cases leading to longer reaction times and poorer selectivities. Although this kind of comparison gives some indication of the role of the co-catalyst, it is difficult to distinguish between the effect of the catalyst structure and the nature of the co-catalyst.

The effect of an acid co-catalyst may be best illustrated by Brønsted acid catalyzed reactions of preformed enamines. As an example, the first enantioselective acid catalyzed *O*- and *N*-nitroso aldol reactions were recently reported by Momiyama and Yamamoto.[98] Depending on the nature of the acid catalyst they were able to direct the regioselectivity of approaching enamine nucleophile. A carboxylic acid **177** promoted the *O*-nitroso aldol reaction whereas the hydrogen bonding catalyst **176** catalyzed the formation of the *N*-adduct, both in high enantioselectivities. This can be explained by the different coordination of the catalyst, illustrated in Scheme 16. The stronger Brønsted acid catalyst **177** interacts with the nitrogen atom of the *N*=*O* bond allowing attack at the oxygen, whereas **176** activates the oxygen end of the bond resulting in an attack at the nitrogen.



Scheme 16. Different acid catalysts lead to opposite regioselectivity in nitroso aldol reactions of preformed enamines

Similarly the intramolecular acid moiety has been utilized to orient the approaching electrophile. Already in the first contemporary proline-catalyzed reaction the feature was exploited to create the *anti*-aldol[68,69] and *syn*-Mannich[74,73] selectivity (Scheme 17). It is noteworthy that the aldol reaction catalyzed by an enamine catalyst with an external acid co-catalyst provides inferior diastereoselectivities compared to the proline catalyst.[94]

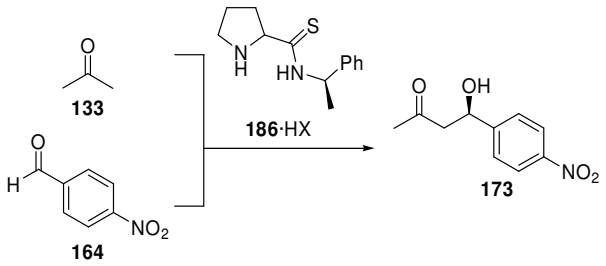


Scheme 17. Intramolecular acid functionality allows steering of the approaching nucleophile *via* hydrogen bonding leading to *anti*-aldol and *syn*-Mannich selectivity

A particularly interesting study on the alteration of the acid functionality in the aldol reaction has been reported by Yamamoto and co-workers.[99] They studied proline diamine derivatives such as **139** in the enamine catalyzed aldol reactions. External acid co-catalyst was used to transform the non-enamine forming amine moiety to its counter acid. As a consequence it could be used both to control the geometry of the enamine formation and to orient the approaching electrophile.

Gryko and co-workers studied the influence of acid additive in the aldol reaction catalyzed by proline derivative equipped with an existing hydrogen bonding functionality (thioamide).[100] They observed that the addition of one equivalent of acid per catalyst molecule enhanced the reaction rates significantly. A closer inspection revealed that the nature of the acid additive has strong influence on the reaction efficiency. A strong dependence was detected between the increasing strength of acetic acid derivatives and both the reaction rate and enantioselectivity (Table 14). The catalyst salts of stronger inorganic acid as well as sulfonic acids failed to promote the reaction.

Table 14. Acid additive has strong influence on the efficiency and selectivity of L-prolinethioamide **186** catalyzed aldol reaction



Entry	HX	p*K*a	Yield [%]	*ee* [%]
1	AcOH	4.76	20	86
2	HCO2H	3.75	24	89
	MIA	3.12	32	91
	MBA	2.86	28	94
3	MCA	2.85	60	93
4	DCA	1.29	**99**	**93**
5	DFA	1.24	**95**	**92**
6	TFA	0.26	81	94

By NMR-studies the authors observed that a formation of iminium species between the catalyst salt and acetone correlated to high reaction efficiency. The iminium ion likely equilibrates with the reactive enamine and thus enhances the reaction rate. Additionally, the acid co-catalyst may stabilize the iminium ion of the formed product and push it toward hydrolysis instead of retroaldolization which may compromise the selectivity of the reaction. Other groups have

reported that the addition of TFA co-catalyst to aldol reactions catalyzed by alternative proline derivatives affords similar results.[101]

The effect of basic additive as well as water in proline catalyzed aldol reaction has been studied extensively.[102] Furthermore, Zhou and Shan disclosed that hydrogen bonding additives namely weak Brønsted acids successfully enhance both the efficiency and the enantioselectivity of the reaction.[103] The authors utilized chiral (*S*)-BINOL which they proposed to enhance the catalytic ability of proline through additional hydrogen-bonding interactions between the catalyst, additive, and approaching substrate.

Only few reactions with a purely external acid source have been published, and very few screening studies of the co-catalyst have been reported. Barbas and co-workers studied the effect of Lewis and Brønsted acids in the pyrrolidine-catalyzed aldol reaction.[104] They observed that acetic acid provided over 2-fold greater initial reaction rates compared to the same reaction without acid. Interestingly, stronger acids such as TfOH, PTSA and CSA gave slower rates. Subsequently, Peng and co-workers disclosed the beneficial effect of substituted phenols in the same reaction. Decreasing acidity of the co-catalyst increased the reaction rates. These observations are consistent with the requirement of general acid catalysis for the iminium formation and the general base catalysis for the subsequent enamine formation. When the enamine formation is rate determining the increasing strength of the co-catalyst conjugate base is beneficial for the reaction.

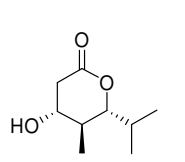
To conclude, in the enamine catalysis the role of the acid co-catalyst may seem less striking than in iminium catalysis. However, its benefits are indisputable. The enamine formation requires both the acid and the base functions of the co-catalyst and its intramolecular placement strongly contributes to the diasteromeric selectivity of the reactions.

3 UTILIZATION OF AMINE CATALYSIS IN SYNTHETIC ENDEAVORS

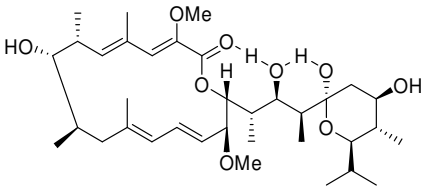
One of the most exceptional features of iminium and enamine catalyzed reactions is the tolerance to the presence of a variety of functional groups within substrate substructure. This phenomenon leads to redundancy of protecting group interchanges and therefore amine catalysis is a very appealing tool for the synthesis of natural and pharmaceutical products. In the following discussion, my research work on amine catalyzed reactions included in this dissertation is highlighted.

3.1 Polypropionate Segments

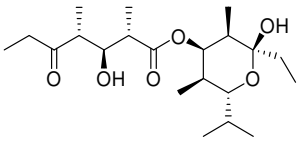
Polypropionates form a subclass of polyketides, a family of natural products representing a wide array of structurally complex compounds. The name polypropionate refers to its common biosynthesis from propionate units. Polypropionate segments are present in many complex natural and pharmaceutical products (Figure 15). Approaches to the synthesis of polypropionate stereotetrads have recently been reviewed in our laboratory.[105] With traditional methods the synthesis of such structures requires several steps per stereocenter and thus the development of new strategies is desirable. For example, the synthesis of Prelactone B **187** utilizing the Evans auxiliary strategy requires eight steps to the natural product,[106] whereas our proline-catalyzed synthesis takes only four steps.[4]



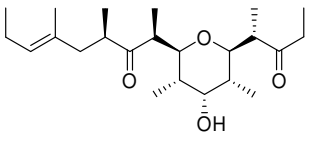
187: Prelactone B



188: Bafilomycin A



189: Dolabriferol

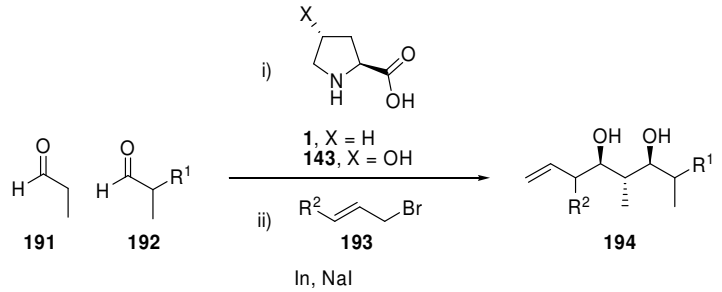


190: Denticulatin B

Figure 15. Polypropionate natural products

To allow fast access to polypropionate segments, we developed a reaction cascade which combines an enamine activated aldol reaction and a metal-mediated allylation in a one pot operation.[I] With this method several (up to four) adjacent stereocenters could be set up in a

single operation (Scheme 18). All chiral information in the final product was derived from the aldol catalyst **1** or **143**. The enantioselectivities obtained in the aldol step were excellent while best diastereoselectivities in the allylation step were obtained in the prenylation reactions.

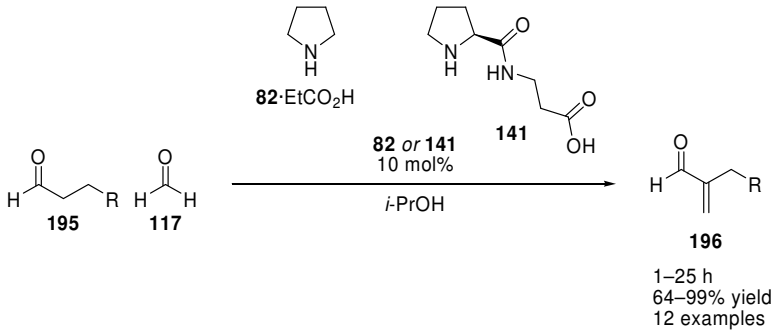


Scheme 18. Synthesis of polypropionate segments *via* an enamine catalyzed aldol reaction and an In-mediated allylation

3.2 α-Substituted Enals

α,β-Unsaturated aldehydes provide a range of possibilities for further synthetic transformations such as carbonyl addition, Diels-Alder reactions and other organocatalytic reactions. Therefore they are versatile synthetic building blocks in the total synthesis of natural products such as polypropionates. Additionally, the structural motif of α-substituted acroleins is present in many natural products as such.

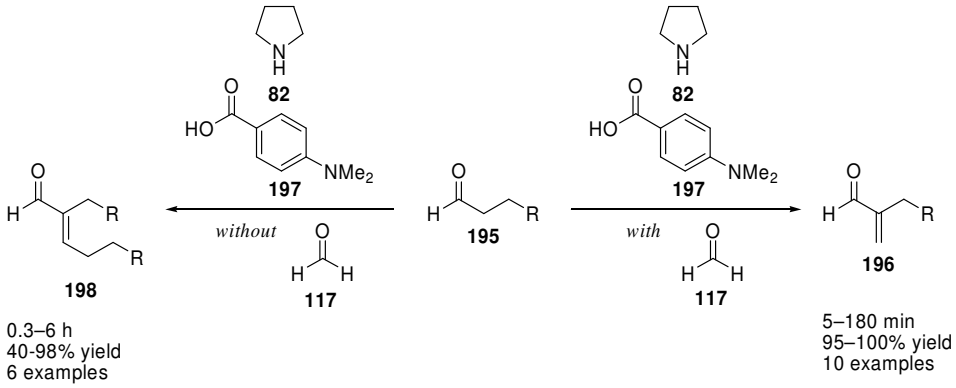
For our first generation α-methylenation method[II] a variety of secondary amine – carboxylic acids combinations as well as number of amino acids and proline-derived dipeptides were screened as catalysts. We identified pyrrolidine propionate **82**·$EtCO_2H$ and simple dipeptide L-proline-β-alanine **141** as the best catalysts for the reaction (Scheme 19). Under the optimized reaction conditions a range of products could be synthesized and even capricious substrates could be subjected to the mild reaction conditions.



Scheme 19. Synthesis of α-substituted acroleins

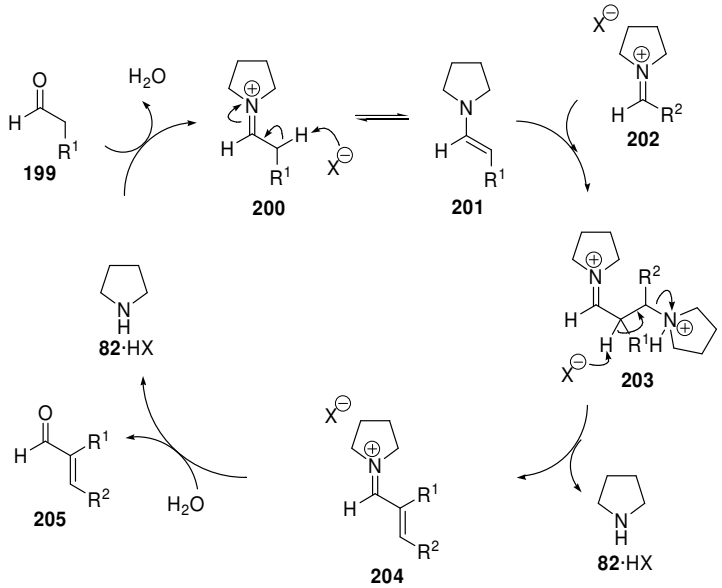
Subsequently, after an exhaustive optimization of the α-methylenation protocol we identified a combination of pyrrolidine **82** and a weak acid co-catalyst **197** in dichloromethane that

outperformed the first generation method and allowed access to α-substituted acroleins and α,β-disubstituted enals in very short reaction times (Scheme 20).[IV] The choice of the acid co-catalyst had a pronounced impact on the reaction rate. The reaction scope was explored both in the synthesis of α-substituted acroleins with the α-methylenation method and in the self-condensation of aldehydes to produce α,β-disubstituted enals.



Scheme 20. Synthesis of α-substituted acroleins and α,β-disubstituted enals

Based on kinetic studies we were able to postulate that the reaction proceeds *via* a Knoevenagel-Mannich-type mechanism that involves both iminium and enamine activation (Scheme 21).



Scheme 21. Mechanism of the α-methylenation reaction

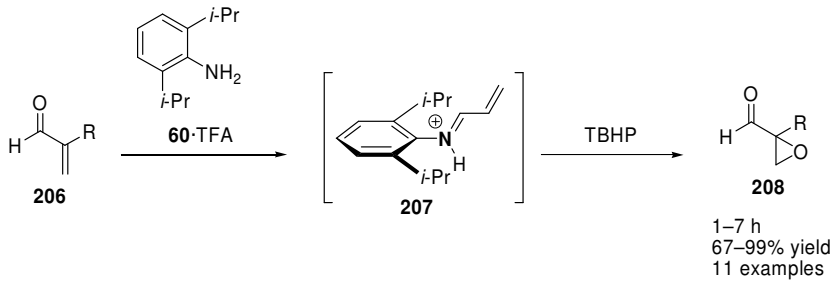
3.3 Functionalized Aldehydes

Organocatalytic epoxidation of enals opens a convenient access to highly functionalized small molecules. Recently, efficient iminium catalyzed reaction protocols for the epoxidation of β-substituted enals were disclosed. However, the organocatalytic epoxidation has been limited

by the substrate scope as only β-substituted enals could have been utilized – a common limitation in iminium catalysis.

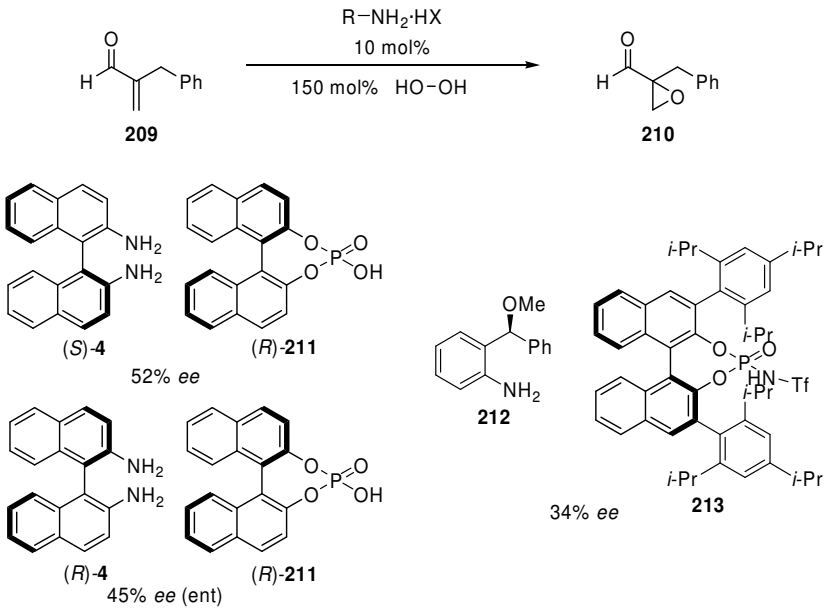
Lately, discoveries by Ishihara and Maruoka have addressed the substrate problem in the limited case of reactive α-oxygenated acroleins using complex primary amine catalysts in the context of Diels-Alder reactions. We, on the other hand, reasoned that appropriately substituted primary amines should be suitable catalysts for the epoxidation of α-substituted enals. Indeed, after intensive screening we were able to identify 2,6-diisopropyl aniline **60** as a powerful catalyst.[III]

We believe that the correlation between the increasing reactivity and the increasing steric hindrance of the aniline *o*- and *m*-substitution can be explained by deconjugation of the iminium ion. This destabilizes the iminium ion, allowing hydrolysis and turnover of the catalyst. Also the choice of the acid co-catalyst influenced the activity of the catalytic system significantly. Very strong acids failed to promote the reaction, but somewhat weaker acids DPP and TFA were found to be highly beneficial. The optimized reaction conditions were applied to a selection of α-substituted enals to provide the corresponding epoxides in high yields (Scheme 22).



Scheme 22. Aniline catalyzed epoxidation of α-substituted enals

Additionally, in preliminary experiments chiral amine catalysts have afforded the epoxidation products in promising although relatively modest enantioselectivities (Scheme 23). The aniline catalyst system has also been studied in the Diels-Alder[61] and transfer hydrogenation reactions[62] of α-substituted acroleins.



Scheme 23. Preliminary results with chiral amine catalysts

4 CONCLUSIONS

Reactions activated *via* iminium ion or enamine formation have been reviewed focusing on the role of the Brønsted acid co-catalyst. Functionalized chiral products can be engendered from saturated aldehydes and ketones as well as from enals and enones in mild and catalytic conditions exploiting small organic molecules as catalysts. The described catalysts consist of a primary or secondary amine and an acid co-catalyst and can often be derived from nature's chiral pool.

The Brønsted acid co-catalysts were shown to play a central role in the iminium and enamine catalysis. In the iminium catalysis the co-catalyst functions as a general acid catalyst in the iminium formation and as a general base catalyst in the sometimes required removal of hydrogen from the nucleophile when it has reacted to form the initial iminium intermediate. In enamine catalysis these modes are already combined in the formation of the reactive enamine species. Thereafter the co-catalyst may be used to activate and orient the approaching electrophile.

Despite the large number of contributions and results obtained in a relatively short period, many challenges remain in terms of reaction efficiency and substrate scope. Deeper understanding of the role of the co-catalyst may open new avenues into unraveling the possibilities of amine catalysis.

The strategic use of amine catalyzed reactions was highlighted by synthesis of polypropionate segments, α-substituted enals, and functionalized aldehydes. Careful choice of the acid co-catalyst was shown to be crucial for the reaction efficiency in the iminium catalyzed reactions. Additionally, a novel catalyst family based on aniline structure was developed for the iminium catalyzed transformations of α-substituted enals.

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