ASYMMETRIC SYNTHESIS ENABLED BY METAL-FREE CATALYSIS

Aldrichimica ACTA

VOL. 39, NO. 3 • 2006

Enzymes in Organic Synthesis

Modern Strategies in Organic Catalysis

sigma-aldrich.com

ALDRICH®
Advancing Science

Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation

Dr. Gérald Lelais

Professor D. W. C. MacMillan

*Gérald Lelais and David W. C. MacMillan**
Department of Chemistry
California Institute of Technology
1200 E. California Blvd., Mail Code 164-30
Pasadena, CA 91125, USA
Email: dmacmill@caltech.edu

Outline

1. Introduction

Enantioselective organocatalysis has become a field of central importance for the asymmetric synthesis of chiral molecules. In the last ten years alone, this field has grown at an extraordinary pace from a small collection of chemically unique reactions to a thriving area of general concepts, atypical reactivities, and widely applicable reactions.[1–4] Moreover, novel modes of substrate activation have been achieved using organic catalysts that can now deliver unique, orthogonal, or complementary selectivities in comparison to many established metal-catalyzed transformations. The present review will discuss the advent and development of one of the youngest subfields of organocatalysis, namely iminium activation. The first section will introduce the concept of iminium catalysis and the rationale for the development of a broadly general catalyst. The following sections will describe the most significant types of transformations in which the concept of iminium activation has been successfully applied including cycloadditions, conjugate additions, Friedel–Crafts alkylations, Mukaiyama–Michael additions, transfer hydrogenations, and enantioselective organocatalytic cascade reactions.

2. Iminium Activation: Concept Development and Catalyst Design

In 1999, our laboratory introduced a new strategy for asymmetric synthesis based on the capacity of chiral amines to function as enantioselective LUMO-lowering catalysts for a range of transformations that had traditionally employed Lewis acids. This strategy, termed iminium activation, was founded on the mechanistic postulate that (i) the LUMO-lowering activation and (ii) the kinetic lability towards ligand substitution that enable the turnover of Lewis acid catalysts might also be available with a carbogenic system that exists as a rapid equilibrium between an electron-deficient and a relatively electron-rich state (**Scheme 1**).[5] With this in mind, we hypothesized that the reversible formation of iminium ions from α,β-unsaturated aldehydes and amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis, thereby providing a new platform for the design of organocatalytic processes. On this basis, we first proposed (in 2000) the attractive prospect that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.[5]

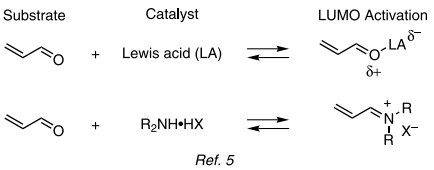
2.1. First-Generation Imidazolidinone Catalyst

Preliminary experimental findings and computational studies demonstrated the importance of four objectives in the design of a broadly useful iminium-activation catalyst: (i) The chiral amine should undergo efficient and reversible iminium ion formation. (ii) High levels of control of the iminium geometry and (iii) of the selective discrimination of the olefin π face should be achieved in order to control the enantioselectivity of

the reaction. (iv) In addition, the ease of catalyst preparation and implementation would be crucial for the widespread adoption of this organocatalytic technology. The first catalyst to fulfill all four criteria was imidazolidinone **1** (**Figure 1, Part A**). As suggested from computational modeling, the catalyst-activated iminium ion, MM3-**2**, was expected to selectively form as the depicted *E* isomer to avoid nonbonding interactions between the substrate olefin and the *gem*-dimethyl substituents on the catalyst framework. In terms of enantiofacial discrimination, the calculated iminium structure MM3-**2** revealed that the benzyl group of the imidazolidinone moiety would effectively shield the *Si* face of the iminium ion, leaving the *Re* face exposed for selective bond formation. The effectiveness of imidazolidinone **1** as an iminium-activation catalyst was confirmed by its use in enantioselective Diels–Alder reactions,[5] nitrone additions,[6] and Friedel–Crafts alkylations employing electron-rich pyrrole systems.[7] However, a diminished reactivity was observed when heteroaromatics such as indoles and furans were used as π nucleophiles in similar Friedel–Crafts conjugate additions. To overcome such limitations, we embarked upon studies to identify a more reactive and versatile amine catalyst. This led ultimately to the discovery of the "second-generation" imidazolidinone catalyst **3** (**Figure 1, Part B**).[8]

2.2. Second-Generation Imidazolidinone Catalysts

Preliminary kinetic studies with the first-generation catalyst **1** indicated that the overall rates of iminium-catalyzed reactions were influenced by the efficiency of both the initial iminium ion and the carbon–carbon bond-forming steps. We hypothesized that imidazolidinone **3** would form the iminium ion **4** more efficiently and, hence, increase the overall reaction rate, since the participating nitrogen lone pair is positioned away from structural



Scheme 1. Iminium Activation through LUMO Lowering.

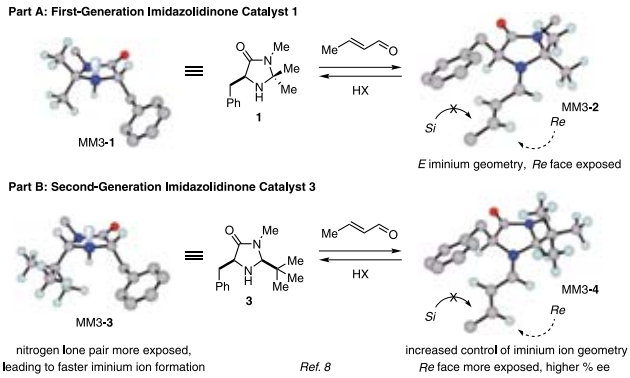


Figure 1. Computational Models of the First- and Second-Generation Imidazolidinone Catalysts (**1** and **3**) and of the Corresponding Iminium Ions.

impediments. This is in contrast to the CH_3–lone pair eclipsing orientation in MM3-**1** and the fact that π nucleophiles that engage the activated iminium ion **2** encounter a retarding interaction with the illustrated methyl substituent. The reactive enantioface of iminium ion **4** is free from such steric obstruction and should exhibit increased reactivity towards the formation of carbon–carbon bonds. In terms of our design criteria for enantiocontrol, the catalyst-activated iminium ion **4** was anticipated to selectively populate the *E* isomer to avoid nonbonding interactions between the carbon–carbon double bond and the *tert*-butyl group. In addition, the benzyl and *tert*-butyl groups on the imidazolidinone framework effectively shield the *Si* face of the activated olefin, leaving the *Re* face exposed to a large range of nucleophiles. Indeed, since their introduction in 2001, imidazolidinone catalysts of type **3** have been successfully applied (≥90% ee's, ≥75% yields) to a broad range of chemical transformations, including cycloadditions,[9,10] conjugate additions,[8,11,12] hydrogenations,[13] epoxidations, and cascade reactions.[14,15]

3. Cycloaddition Reactions

3.1. Diels–Alder Reaction

The Diels–Alder reaction is arguably one of the most powerful organic transformations in chemical synthesis. In particular, asymmetric catalytic variants have received unprecedented attention, presumably due to their capacity to rapidly afford complex enantioenriched carbocycles from simple substrates.[16] It is not surprising therefore that the Diels–Alder reaction has become a benchmark transformation by which to evaluate new asymmetric catalysts or catalysis concepts. In keeping with this tradition, our original disclosure of the concept of iminium catalysis was made in the context of enantioselective catalytic Diels–Alder reactions. In these studies, a range of α,β-unsaturated aldehydes were exposed to a variety of dienes in the presence of chiral imidazolidinone **1** to afford [4 + 2] cycloaddition adducts with high levels of enantioselectivity (**Table 1**).[5] Remarkably, the presence of water exhibited beneficial effects on both reaction rates and selectivities, while facilitating the iminium ion hydrolysis step in the catalytic cycle. Computational studies suggest an asynchronous mechanism for the reaction,[17,18] where attack of the diene onto the β-carbon atom of the iminium ion is rate-limiting,[17] and the π–π interaction between the olefinic π system of the iminium ion (dienophile) and the phenyl ring of the benzyl group on the imidazolidinone moiety accounts for the selectivity of the reaction.[5,18]

Since our initial iminium catalysis publication, amine-catalyzed Diels–Alder reactions of α,β-unsaturated aldehydes have been investigated in much detail.[10,19–25] For example, catalyst immobilization (on solid support[19,20] or in ionic liquids[22]) has demonstrated the capacity for imidazolidinone recycling, while maintaining good levels of asymmetric induction.[19b] Moreover, the scope of the reaction was recently extended to include α-substituted acrolein dienophiles as reaction partners.[24]

Another important application of the iminium catalysis concept concerned the development of enantioselective Type I[10,23] and Type II[10] intramolecular Diels–Alder reactions (IMDA). For these transformations, both catalysts **1** and **3** proved to be highly efficient, affording bicyclic aldehyde products in good yields and with excellent enantio- and diastereoselectivities. Importantly, the utility of this organocatalytic approach was demonstrated by both the short and efficient preparation of the marine metabolite solanapyrone D via Type I IMDA and the development of an early example of an enantioselective, catalytic Type II IMDA reaction (**Scheme 2**).[10,26a]

In 2001, a long-standing challenge for the field of asymmetric catalysis remained the use of simple ketone dienophiles in Diels–Alder reactions with high levels of enantioselectivity. The success of chiral Lewis acid mediated Diels–Alder reactions up until that point was founded upon the use of dienophiles such as aldehydes, esters, quinones, and bidentate chelating carbonyls that achieve high levels of lone-pair discrimination in the metal-association step, an organizational event that is essential for enantiocontrol. In contrast, Lewis acid coordination is traditionally a nonselective process with ketone dienophiles, since the participating lone pairs are positioned in similar steric and electronic environments (**Scheme 3, Part A**).[9] Diastereomeric activation pathways in this case often lead to poor levels of enantiocontrol and ultimately have almost completely precluded the use of simple ketone dienophiles in asymmetric catalytic Diels–Alder reactions.[26b] Having demonstrated the utility of iminium activation to provide LUMO-lowering catalysis outside the mechanistic confines of lone-pair coordination,[5–8] we hypothesized that amine catalysts might also enable simple ketone dienophiles to function as useful substrates for enantioselective Diels–Alder reactions. In this case, the capacity to perform substrate activation through specific lone-pair coordination is replaced by the requirement for selective π-bond formation (**Scheme 3, Part B**).[9] With this in mind, our laboratory developed the first general and enantioselective catalytic Diels–Alder reaction using simple α,β-unsaturated ketones as dienophiles (**Table 2**).[9] Importantly, whereas methyl ketones were usually poor substrates, higher-order derivatives (R = Et, Bu, isoamyl) afforded good levels of enantiocontrol and high endo selectivities.

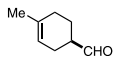
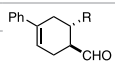
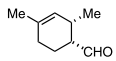
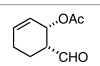
3.2. [3 + 2] Cycloaddition

The 1,3 cycloaddition of nitrones to alkenes is a fast and elegant way to prepare isoxazolidines that are important building blocks for biologically active compounds.[27] In this context, asymmetric Lewis acid catalyzed nitrone cycloadditions have been successfully accomplished with α,β-unsaturated imide substrates.[28] However, only limited examples of monodentate carbonyl substrates as nitrone-cycloaddition partners have been reported with chiral Lewis acids, presumably due to competitive coordination (and deactivation) of the Lewis basic nitrone component by the catalytic Lewis acid.[29–31] As this deactivation issue cannot arise in the realm of iminium activation, we were able to successfully apply our organocatalytic, LUMO-lowering strategy to the [3 + 2] cycloaddition of nitrones to α,β-unsaturated aldehydes (**Table 3**).[6] Recently, a polymer-supported version of catalyst **1** was also used in the nitrone cycloaddition with promising results.[32] Subsequently, Karlsson and Högberg expanded the scope of the reaction to achieve the 1,3-dipolar cycloaddition of nitrones to cyclic α,β-unsaturated aldehydes, allowing for the formation of fused bicyclic isoxazolidines.[33,34]

3.3. [2 + 1] Cycloaddition

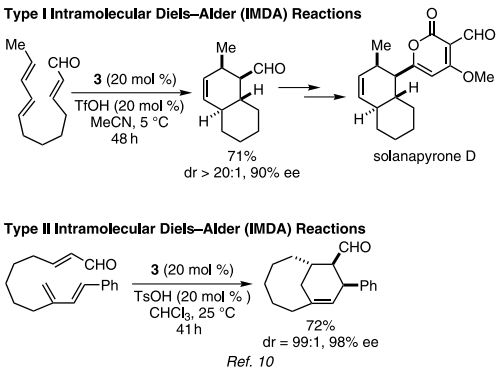
The enantioselective construction of three-membered hetero- or carbocyclic rings remains an important objective in synthetic organic chemistry, and the important advances made in iminium ion activation have enabled the asymmetric construction of α-formyl cyclopropanes and epoxides. For cyclopropane synthesis, our laboratory introduced a new type of amine catalyst, **6**, that is capable of performing the enantioselective stepwise [2 + 1] union of sulfonium ylides and α,β-unsaturated aldehydes (**Table 4**).[35] It should be mentioned that the iminium species derived from amine catalysts **1** or **3** were completely inert to the same sulfonium ylides used. However, proline, a usually

Table 1. Organocatalyzed Diels–Alder Cycloadditions of α,β-Unsaturated Aldehydes[a]

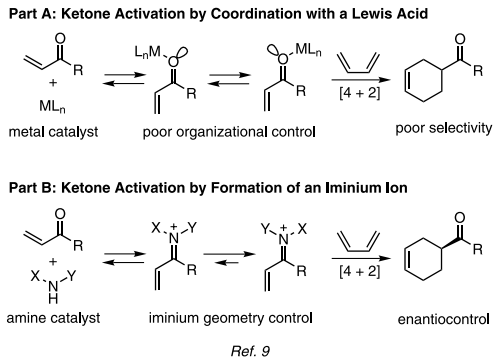
Diene	R in (*E*)-RCH=CHCHO	Product	Yield (%)	Endo:Exo	ee[b] (%)
CpH	Me		75	1:1	90[c]
CpH	Pr		92	1:1	90[c]
CpH	*i*-Pr		81	1:1	93[c]
CpH	Ph		99	1:1.3	93[c]
CpH	furan-2-yl		89	1:1	93[c]
1,3-cyclohexadiene	H		82	14:1	94[c]
$H_2C=C(Me)CH=CH_2$	H		84	—	89
$H_2C=C(Ph)CH=CH_2$	H		90	—	83
$H_2C=C(Ph)CH=CH_2$	Me		75	—	90
(*E*)-$H_2C=C(Me)CH=CHMe$	H		75	5:1	90
(*E*)-$H_2C=CHCH=CHOAc$	H		72	11:1	85

[a] **1**•HCl (20 mol %), MeOH–H_2O, 23 °C, 3–24 h. [b] Of the endo product. [c] Using 5 mol % of catalyst.

Ref. 5

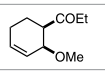
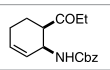
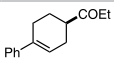
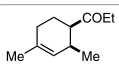
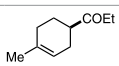


Scheme 2. Type I and II Organocatalytic Intramolecular Diels–Alder (IMDA) Reactions.

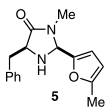


Scheme 3. The Use of Simple Ketones as Dienophiles in the Diels–Alder Reaction.

Table 2. Organocatalyzed Diels–Alder Cycloadditions of α,β-Unsaturated Ketones[a]

Dienophile R	Dienophile R^1	Diene	Product	Endo:Exo	ee[b] (%)
Me	Et	CpH		25:1	90
Me	*n*-Bu	CpH		22:1[c]	92
Me	*i*-Am	CpH		20:1	92
Pr	Et	CpH		15:1	92
i-Pr	Et	CpH		6:1	90
H	Et	H_2C=CHCH=CHOMe		>200:1[d]	96
H	Et	H_2C=CHCH=CHNHCbz		>100:1[d]	98
H	Et	H_2C=C(Ph)CH=CH_2		>200:1[e,f]	90
H	Et	(*E*)-H_2C=C(Me)CH=CHMe		>200:1[d]	90
H	Et	H_2C=C(Me)CH=CH_2		>200:1[c,f,g]	85
2-cycloheptenone		CpH		18:1	90
2-cyclooctenone		CpH		6:1	91
(*E*)-2-cyclopentadecenone		CpH	n=2,3,10	5:1[h]	93

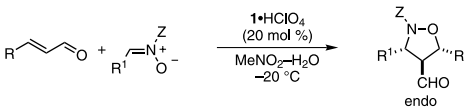
[a] **5**•$HClO_4$ (20 mol %), H_2O, 0 °C; 78–92% yields. [b] Of the endo product. [c] No solvent was used. [d] EtOH, –30 °C. [e] EtOH, –40 °C. [f] Ratio of regioisomers. [g] –20 °C. [h] 1,2-*trans*-tricyclo[15.2.1.0]eicos-18-en-3-one was obtained.



5

Ref. 9

Table 3. Organocatalytic 1,3-Dipolar Cycloaddition[a]



R	R^1	Z	Yield (%)	Endo:Exo	ee[b] (%)
Me	Ph	Bn	98	94:6	94
Me	Ph	allyl	73	93:7	98
Me	Ph	Me	66	95:5	99
Me	4-ClC_6H_4	Bn	78	92:8	95
Me	4-ClC_6H_4	Me	76	93:7	94
Me	4-$MeOC_6H_4$	Bn	93	98:2	91
Me	4-MeC_6H_4	Me	82	93:7	97
Me	2-Naph	Bn	98	95:5	93
Me	Cy	Bn	70	99:1	99
H	Ph	Bn	72	81:19	90
H	Ph	Bn	80	86:14	92[c]
H	4-MeC_6H_4	Bn	80	85:15	90[c]
H	4-ClC_6H_4	Bn	80	80:20	91[c]
H	2-Naph	Bn	82	81:19	90[c]
H	4-$MeOC_6H_4$	Bn	83	91:9	90[c]

[a] 35–160 h. [b] Of the endo product. [c] Using 20 mol % of **1**•TfOH.

Ref. 6

poor catalyst for iminium activation, provided good levels of conversion and moderate enantioselectivities. The zwitterionic iminium ion derived from catalyst **6** and the α,β-unsaturated aldehyde enables both iminium geometry control and directed electrostatic activation of the approaching sulfonium ylides. This combination of geometric and electronic control is believed to be essential for enantio- and diastereocontrol in forming two of the three cyclopropyl bonds.

Recently, Jørgensen and co-workers have demonstrated that the epoxidation of a broad range of substituted α,β-unsaturated aldehydes can be carried out in good yields and with high levels of enantioselectivity in the presence of amine **7** and a stoichiometric amount of an oxidizing agent (**Table 5**).[36] In addition, our group has found that catalyst **3** can perform the same reaction with similar results.[37]

3.4. [4 + 3] Cycloaddition

Several laboratories are currently investigating the potential of iminium catalysis for the asymmetric catalytic construction of other cycloaddition products. For example, an elegant approach for the preparation of enantioenriched seven-membered rings has recently been described by Harmata and co-workers.[38] This study involves the organocatalytic, asymmetric [4 + 3] cycloaddition of dienes with silyloxypentadienals in the presence of amine catalyst **3** (**eq 1**). It is notable that, among all asymmetric [4 + 3] cycloaddition reactions that have been reported to date, this methodology represents the first organocatalytic version.

4. 1,4-Addition Reactions

4.1. Friedel–Crafts Alkylations and Mukaiyama–Michael Reactions

The metal-catalyzed addition of aromatic substrates to electron-deficient σ and π systems, commonly known as Friedel–Crafts alkylation, has long been established as a powerful strategy for C–C-bond formation.[39–41] Surprisingly, however, relatively few enantioselective catalytic approaches have been reported that exploit this reaction manifold, despite the widespread availability of electron-rich aromatics and the chemical utility of the resulting products. To further demonstrate the value of iminium catalysis, we also undertook the development of asymmetric Friedel–Crafts alkylations that had been previously unavailable using acid or metal catalysis. Indeed, it has been documented that α,β-unsaturated aldehydes are poor electrophiles for pyrrole, indole, or aryl conjugate additions due to the capacity of electron-rich aromatics to undergo acid-catalyzed 1,2-carbonyl attack instead of 1,4 addition.[42,43] In contrast, we have recently demonstrated that a broad range of π nucleophiles such as pyrroles,[7] indoles,[8] anilines,[11] and silyloxyfuran derivatives[12] can be successfully utilized in 1,4-addition reactions with various α,β-unsaturated aldehydes in the presence of catalytic amounts of chiral amines **1** or **3** (**Scheme 4**). The corresponding conjugate addition adducts were obtained in high yields and excellent enantioselectivities. It is important to note that only 1,4-addition products were formed in all cases, thereby demonstrating the possibility of accessing complementary chemoselectivities when using organic catalysis. The effectiveness of this methodology was further demonstrated by the short and straightforward preparation of a number of enantioenriched natural products and bioactive compounds (**Figure 2**).[8,12,44–46]

4.2. Michael Reactions of α,β-Unsaturated Ketones

Given the inherent problems of forming tetrasubstituted iminium ions from ketones, along with the accordant issues associated with

controlling the iminium ion geometry, it is noteworthy that significant progress has been achieved in the development of iminium catalysts for enone substrates over the past five years. The asymmetric Michael addition of carbanionic reagents to α,β-unsaturated carbonyl compounds was first catalyzed by metalloprolinates in the 1990s.[47–50] Several years later, Kawara and Taguchi reported the first organocatalyzed variant, in which a proline-derived catalyst mediated the addition of malonates to cyclic and acyclic enones with moderate enantioselectivities (56–71% ee's).[51] Further improvements were reached by Hanessian and co-workers, who demonstrated that a combination of L-proline (**8**) and *trans*-2,5-dimethylpiperazine could be used to facilitate the enantioselective addition of nitroalkanes to cyclic enones (**Scheme 5**).[52] Recently, Jørgensen and others reported important expansions of iminium catalysis to the enantioselective conjugate addition of carbogenic nucleophiles such as nitroalkanes,[53] malonates,[54,55] 1,3-dicarbonyl compounds,[56–59] and β-keto sulfones[58] to a number of acyclic α,β-unsaturated ketones (Scheme 5). The utility of this catalytic iminium approach was further corroborated by the one-step preparation of enantiopure biologically active compounds, such as wafarin.[56]

5. Transfer Hydrogenation

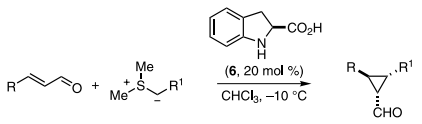
The hydrogen atom is the most common discrete substituent attached to stereogenic centers. Not surprisingly, therefore, the field of asymmetric catalysis has focused great attention on the invention of hydrogenation methods over the past 50 years.[60] While these powerful transformations rely mainly on the use of organometallic catalysts and hydrogen gas, it is important to consider that the large majority of hydrogen-containing stereocenters are created in biological cascade sequences involving enzymes and organic cofactors such as nicotinamide adenine dinucleotide (NADH) or the corresponding flavin derivative ($FADH_2$).[61] On this basis, we hypothesized that the use of small organocatalysts in combination with dihydropyridine analogues to perform metal-free hydrogenations would provide a unique opportunity to further challenge our LUMO-lowering iminium activation concept. Indeed, via this biomimetic strategy, we recently accomplished the selective reduction of β,β-disubstituted-α,β-unsaturated aldehydes in good yields and with excellent enantioselectivities using Hantzsch ester hydride donors and imidazolidinone catalysts (**Table 6**).[13] A notable feature of this transformation is that the sense of induction is not related to the olefin geometry of the starting aldehydes (**eq 2**).[13] As a consequence, mixtures of *E* and *Z* olefins were employed to provide enantiomerically pure hydrogenation adducts, a desirable, yet rare, feature in catalytic hydrogenations. List and co-workers published a variant of this tranformation using our imidazolidinone catalyst **3**.[62,63] It has been our experience that catalyst **3** is inferior to catalyst **11** in terms of rates and selectivities in these types of transfer hydrogenation.

6. Organocatalytic Cascade Reactions

6.1. Cascade Addition–Cyclization Reactions

Given the importance of cascade reactions in modern chemical synthesis,[64–67] we recently expanded the realm of iminium catalysis to include the activation of tandem bond-forming processes, with a view towards the rapid construction of natural products. In this context, the addition–cyclization cascade of tryptamines with α,β-unsaturated aldehydes in the presence of imidazolidinone catalysts **3** and **12** has been accomplished to provide pyrroloindoline adducts in high yields and with excellent levels of enantioselectivity (**Table 7**).[14] Moreover, this amine-catalyzed transformation has been extended to the

Table 4. Organocatalytic Ylide Cyclopropanation[a]

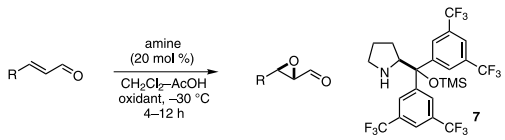


R	R^1	Yield (%)	dr	ee[b] (%)
Pr	PhCO	85	30:1	95
allylOCH$_2$	PhCO	77	21:1	91
Me	PhCO	67	>19:1	90[c]
5-hexen-1-yl	PhCO	74	24:1	96
Ph	PhCO	73	33:1	89
i-Bu	PhCO	63	43:1	96
Pr	4-BrC_6H_4CO	67	72:1	92
Pr	4-MeOC_6H_4CO	64	>11:1	93
Pr	*t*-BuCO	82	6:1	95

[a] 24–48 h. [b] Of the major diastereomer. [c] Carried out at 0 °C.

Ref. 35

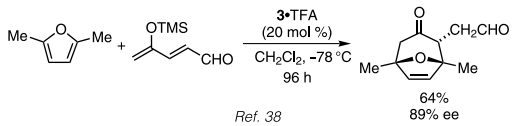
Table 5. Organocatalytic Asymmetric Epoxidation of α,β-Unsaturated Aldehydes



R	Amine	Oxidant	Yield (%)	dr[a]	ee (%)
Me	**3**•HClO$_4$	PhINNs	88	7:1	93
Pr	**3**•HClO$_4$	PhINNs	72	—	88
Cy	**3**•HClO$_4$	PhINNs	77	—	92
4-penten-1-yl	**3**•HClO$_4$	PhINNs	95	—	92[b]
BzOCH$_2$	**3**•HClO$_4$	PhIO	89	—	85
MeO$_2$C(CH$_2$)$_2$	**3**•HClO$_4$	PhINNs	86	—	90
Ph	**3**•HClO$_4$	PhINNs	92	—	92[b]
4-NO$_2$C$_6$H$_4$	**3**•HClO$_4$	PhINNs	89	—	97[b]
4-BrC$_6$H$_4$	**3**•HClO$_4$	PhINNs	93	—	93[b]
Ph	**7**	H_2O_2	80	>13:1	96[c,d]
2-NO$_2$C$_6$H$_4$	**7**	H_2O_2	90	>10:1	97[c,d]
2-MeC$_6$H$_4$	**7**	H_2O_2	65	9:1	96[c,d]
4-ClC$_6$H$_4$	**7**	H_2O_2	63	19:1	98[c,d]
Et	**7**	H_2O_2	>90	>32:1	96[c,d,e]
i-Pr	**7**	H_2O_2	75	49:1	96[c,d]
BnOCH$_2$	**7**	H_2O_2	84	24:1	94[c,d]
EtO$_2$C	**7**	H_2O_2	60	9:1	96[c,d]

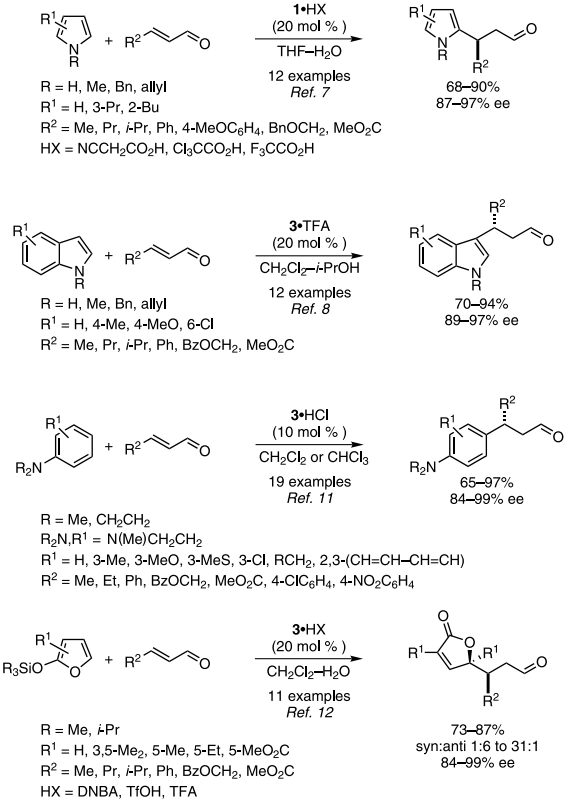
[a] Isolated as single diastereomers unless noted otherwise. [b] Reaction conducted in $CHCl_3$–AcOH at –40 °C. [c] Reaction conducted in CH_2Cl_2 at rt with 10 mol % catalyst. [d] The enantiomeric epoxide was obtained. [e] More than 90% conversion was observed; however, due to the volatility of the product, the α,β-epoxy aldehyde was transformed into the corresponding alcohol, which was isolated in 43% yield (not optimized).

Ref. 36,37



Ref. 38

eq 1



Scheme 4. Organocatalytic 1,4-Addition Reactions of Electron-Rich Aromatics to α,β-Unsaturated Aldehydes.

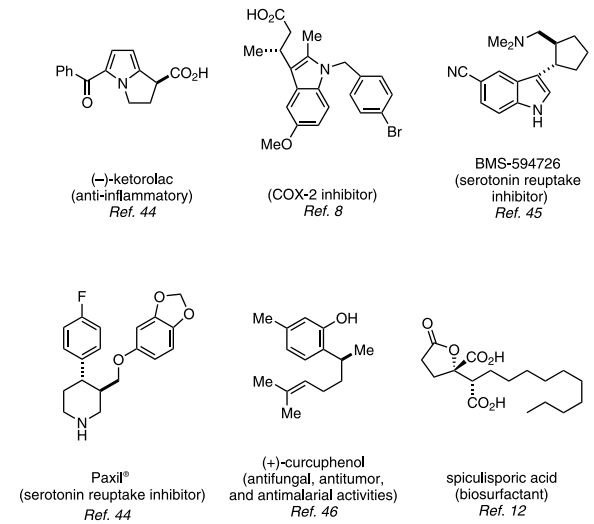
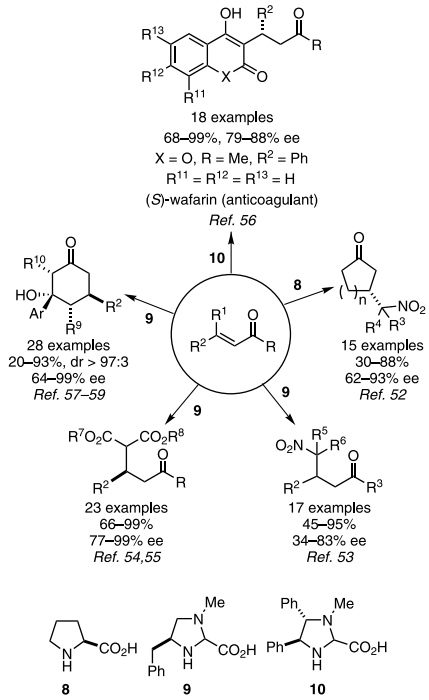
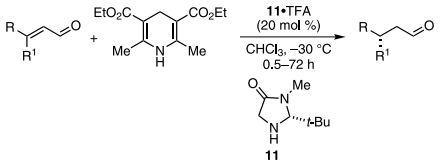


Figure 2. Examples of Natural Products and Bioactive Compounds Prepared by the Organocatalytic 1,4 Addition of Aromatics to α,β-Unsaturated Aldehydes.



Scheme 5. Organocatalytic 1,4 Addition to α,β-Unsaturated Ketones. One-Step Preparation of Pharmaceutically Relevant Adducts such as Wafarin.

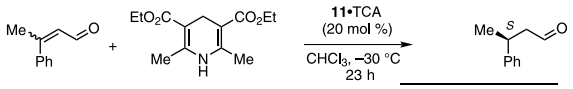
Table 6. Organocatalytic and Enantioselective Transfer Hydrogenation



R	R¹	*E*/*Z*[a]	Yield (%)	ee (%)
Ph	Me	>20:1	91	93[b]
Ph	Et	>20:1	74	94
3,4-$Cl_2C_6H_3$	Me	>20:1	92	97
Cy	Me	5:1	91	96[b]
Cy	Et	3:1	95	91[c]
MeO_2C	Me	>20:1	83[d]	91[e]
$TIPSOCH_2$	Me	>20:1	74	90
t-Bu	Me	>20:1	95[d]	97[f]

[a] *E*/*Z* ratio of the starting aldehydes. [b] At –45 °C. [c] Using 10 mol % catalyst. [d] Yield determined by NMR. [e] At –50 °C. [f] Using 5 mol % catalyst at 23 °C.

Ref. 13



Starting Aldehyde	Yield (%)	*ee* (%)
E	91	93
Z	90	87
E:*Z*, 1:1	88	90

Ref. 13

eq 2

enantioselective construction of furanoindoline frameworks (**eq 3**), a widely represented substructure among natural isolates of biological relevance.[14] Interestingly, a large variation in enantioinduction was observed upon modification of the reaction solvent; high-dielectric-constant media afforded one enantiomer, while low-dielectric-constant solvents provided its mirror image. Application of the pyrroloindoline-forming protocol to natural product synthesis has been accomplished in the first enantioselective total synthesis of (–)-flustramine B (78% yield and 90% ee), a biologically active marine alkaloid.[14]

6.2. Cascade Catalysis: Merging Iminium and Enamine Activations

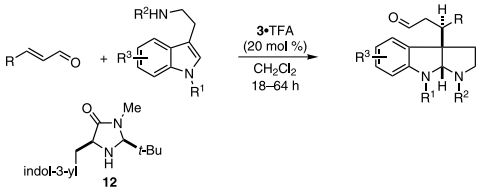
The preparation of natural products with complex molecular structures has traditionally focused on a "stop-and-go" sequence of individual reactions. However, in biological systems, molecular complexity is formed in a continuous process, where enzymatic transformations are combined in highly regulated catalytic cascades.[68] With this in mind, and given the discovery in our laboratory that imidazolidinones can enforce orthogonal modes of substrate activation in the forms of iminium (LUMO-lowering)[5–14] and enamine (HOMO-raising)[69–71] catalyses (**Scheme 6**),[15] we recently questioned whether the conceptual blueprints of biosynthesis might be translated into a laboratory "cascade catalysis" sequence. Specifically, we proposed to combine imidazolidinone-based iminium and enamine transformations to enable rapid access to structural complexity from simple starting materials and catalysts, while achieving exquisite levels of enantiocontrol. As proof of concept, imidazolidinone **13** catalyzed the conjugate addition–chlorination cascade sequence of a diverse range of nucleophiles and α,β-unsaturated aldehydes to give the corresponding products with high levels of diastereo- and enantioselectivities (**Table 8**).[15]

Further expansion of this new cascade approach allowed the invention of other enantioselective transformations, such as the formal asymmetric addition of HCl and HF across trisubstituted olefin systems, which, to our knowledge, has no precedent in asymmetric synthesis.[72] Perhaps most important was the discovery that two discrete amine catalysts can be employed to enforce cycle-specific selectivities (**Scheme 7**).[15] Conceptually, this result demonstrates that these cascade-catalysis pathways can be readily modulated to provide a required diastereo- and enantioselective outcome via the judicious selection of simple amine catalysts.

7. Conclusions

Over the past six years, the field of asymmetric catalysis has bloomed extensively (and perhaps unexpectedly) with the introduction of a variety of metal-free-catalysis concepts that have collectively become known as organocatalysis. Moreover, the field of organocatalysis has quickly grown to become a fundamental branch of catalysis, which can be utilized for the construction of enantiopure organic structures, thus providing a valuable complement to organometallic and enzymatic activations. While substrate scope remains an important issue for many organocatalytic reactions, an increasingly large number of transformations are now meeting the requisite high standards of "useful" enantioselective processes. Most notably, the concept of iminium catalysis has grown almost hand in hand with the general field of organocatalysis. The set of amine catalysts covered in this review is shown in **Figure 3**. Since the introduction of the first highly enantioselective organocatalytic Diels–Alder reaction in 2000, there has been a

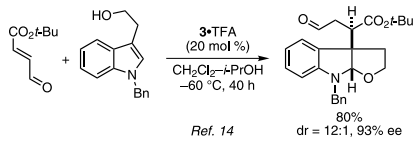
Table 7. Organocatalytic Pyrroloindoline Construction.



R	R^1	R^2	R^3	Yield (%)	dr	ee (%)
Bz	allyl	Boc	H	92	13:1	94
$BzOCH_2$	allyl	Boc	H	66	22:1	91
MeO_2C	allyl	Boc	H	93	44:1	91
MeO_2C	allyl	Boc	5-Me	94	50:1	92
MeO_2C	allyl	Boc	5-MeO	99	10:1	90
MeO_2C	allyl	Boc	6-Br	86	31:1	97
MeO_2C	allyl	Boc	7-Me	97	17:1	99
H	allyl	Boc	H	85	—	89[a]
H	allyl	EtO_2C	H	89	—	89[a]
H	prenyl	EtO_2C	H	89	—	89[a]
H	Bn	$allylO_2C$	H	83	—	89[a]
H	Bn	Boc	H	82	—	90[a]

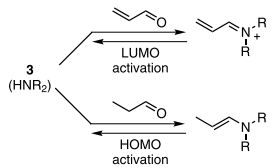
[a] Reaction performed at –85 °C in CH_2Cl_2–H_2O (85:15) with catalyst **12**•TFA.

Ref. 14



Ref. 14

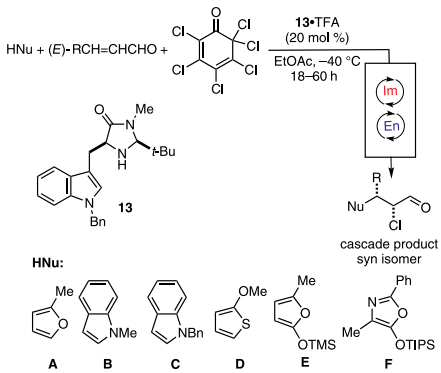
eq 3



Ref. 15

Scheme 6. Imidazolidinones: Organocatalysts for LUMO or HOMO Activation.

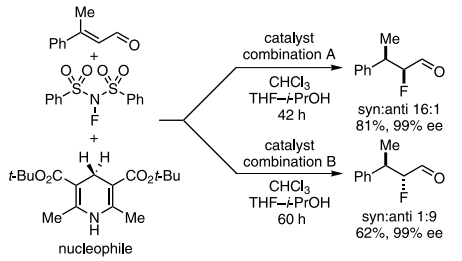
Table 8. Cascade Organocatalysis: Addition–Chlorination Sequence



HNu	R	Yield (%)	dr	ee (%)
A	Me	86	14:1	99[a]
A	Pr	74	13:1	99[a]
A	EtO_2C	80	22:1	99[b]
A	$AcOCH_2$	82	11:1	>99
B	Ph	83	9:1	99
B	*i*-Pr	67	12:1	>99
C	Me	75[c]	12:1	>99[b]
D	Me	77[c]	11:1	99[a]
E	Me	71[c]	>25:1	>99[d]
F	Me	97[c]	9:1	>99

[a] At –50 °C. [b] At –60 °C. [c] Using 10 mol % catalyst. [d] At –55 °C.

Ref. 15



Catalyst combination A: (2*R*)-**11** (7.5 mol %) and (5*S*)-**1** (30 mol %).
Catalyst combination B: (2*R*)-**11** (7.5 mol %) and (5*R*)-**1** (30 mol %).
In both reactions, the enamine catalyst, **1**, and elecrophile, $(PhSO_2)_2NF$, were added after consumption of the nucleophile.
Ref. 15

Scheme 7. Organocatalytic Cascade Reactions Employing Two Discrete Catalysts.

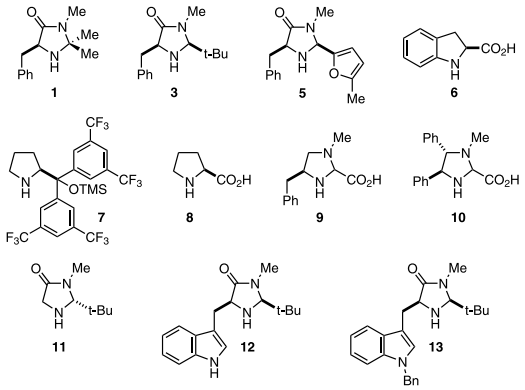


Figure 3. Amine Catalysts Covered in This Review.

large expansion in the field of iminium catalysis and the area of organocatalysis as a whole. Indeed, at the time of writing of this review, there exist currently over 40 discrete transformations that can be performed with useful levels of enantiocontrol (≥90% ee). As such, the future for iminium catalysis and the field of organocatalysis appears to be a bright one, with perhaps application to industrial processes being the next major stage of development. One thing is certain, there are many new powerful enantioselective transformations waiting to be discovered using these novel modes of activation.

8. Acknowledgments

The authors would like to acknowledge the tremendous efforts of the MacMillan group past and present (1998–2006), without whom the concept of iminium catalysis would only be that, a concept. Financial support was provided by the NIH National Institute of General Medical Sciences (R01 GM66142-01) and kind gifts from Amgen, Merck Research Laboratories, Eli Lilly, Bristol-Myers Squibb, Johnson and Johnson, Pfizer, GlaxoSmithKline, AstraZeneca, and the Astellas Foundation. D. W. C. M. is grateful for the support from the Sloan Foundation and the Research Corporation. G. L. is grateful to the Swiss National Science Foundation (Stefano Franscini Fond), the Roche Foundation, and the Novartis Foundation for postdoctoral fellowship support.

9. References and Notes

(1) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
(2) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(3) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
(4) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
(5) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(6) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
(7) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
(8) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
(9) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.
(10) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.
(11) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.
(12) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
(13) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.
(14) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.
(15) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.
(16) For recent reviews of enantioselective Diels–Alder reactions, see: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, Chapter 4.1. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (c) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (d) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, Chapter 33.1. (e) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
(17) Zora, M. *J. Mol. Struct. (Theochem)* **2002**, *619*, 121.
(18) Kozlowski, M. C.; Panda, M. *J. Org. Chem.* **2003**, *68*, 2061.
(19) (a) Benaglia, M.; Celentano, G.; Cinquini, M.; Puglisi, A.; Cozzi, F. *Adv. Synth. Catal.* **2002**, *344*, 149. (b) For a recent review on polymer-supported organic catalysts, see Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.
(20) Selkälä, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv. Synth. Catal.* **2002**, *344*, 941.
(21) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120.
(22) Park, J. K.; Sreekanth, P.; Kim, B. M. *Adv. Synth. Catal.* **2004**, *346*, 49.
(23) Selkälä, S. A.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2005**, 1620.
(24) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504.
(25) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141.
(26) (a) For an example of asymmetric Lewis acid catalyzed Type II IMDA, see Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 3678. For recent examples of asymmetric Lewis acid catalyzed Diels–Alder reactions of ketone dienophiles, see: (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) Hawkins, J. M.; Nambu, M.; Loren, S. *Org. Lett.* **2003**, *5*, 4293. (e) Singh, R. S.; Harada, T. *Eur. J. Org. Chem. 2005*, 3433.
(27) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
(28) For recent reviews on catalytic asymmetric 1,3-dipolar cycloadditions, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (b) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 6. (c) Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507.

(29) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968.
(30) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 7.
(31) Kezuka, S.; Ohtsuki, N.; Mita, T.; Kogami, Y.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197.
(32) Puglisi, A.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Eur. J. Org. Chem.* **2004**, 567.
(33) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923.
(34) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782.
(35) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.
(36) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.
(37) Lee, S.; MacMillan, D. W. C. California Institute of Technology, Pasadena, CA. Unpublished results, 2005.
(38) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.
(39) *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1963–1965; Vol. 1–4.
(40) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, 1973.
(41) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*; Dekker: New York, 1984.
(42) Strell, M.; Kalojanoff, A. *Chem. Ber.* **1954**, *87*, 1025.
(43) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer: Heidelberg, 1999; Vol. 2.
(44) This methodology was further employed for the preparation of the medicinal agent (–)-ketorolac, making use of our second-generation catalyst **3**: Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728.
(45) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437.
(46) Kim, S.-G.; Kim, J.; Jung, H. *Tetrahedron Lett.* **2005**, *46*, 2437.
(47) Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.
(48) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.
(49) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.
(50) (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223.
(51) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805.
(52) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.
(53) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.
(54) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661.
(55) Ramachary, D. B.; Barbas, C. F., III *Chem. Eur. J.* **2004**, *10*, 5323.
(56) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955.
(57) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272.
(58) Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077.
(59) Gryko, D. *Tetrahedron: Asymmetry* **2005**, *16*, 1377.
(60) (a) Akabori, S.; Sakurai, S.; Izumi, Y.; Fujii, Y. *Nature* **1956**, *178*, 323. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 1. (c) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.
(61) Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. *Molecular Biology of the Cell*, 4th ed.; Garland Science: New York, 2002.
(62) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660.
(63) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108.
(64) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
(65) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.
(66) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.
(67) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
(68) For selected reviews on this topic, see: (a) Katz, L. *Chem. Rev.* **1997**, *97*, 2557. (b) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577. (c) Khosla, C.; Gokhale, R. S.; Jacobsen, J. R.; Cane, D. E. *Annu. Rev. Biochem.* **1999**, *68*, 219. (d) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.
(69) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
(70) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722.
(71) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
(72) For other recent examples of organocatalytic cascade reactions, see: (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (b) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710.

Paxil is a registered trademark of SmithKline Beecham Corporation.

About the Authors

Gérald Lelais was born in 1976 in Sorengo (TI), Switzerland. He studied chemistry at the Swiss Federal Institute of Technology Zürich (ETH-Zürich), Switzerland, where he obtained his B.S. degree in 2000 and his Ph.D. degree in 2004, working under the guidance of Professor Dieter Seebach. His research focused on the multistep synthesis of β-amino acids and their incorporation into β peptides for structural investigations. In May 2004, he joined the group of Professor David W. C. MacMillan at the California Institute of Technology in Pasadena, California, as a postdoctoral fellow of the Swiss National Science Foundation (Stefano Franscini Fond), the Roche Foundation, and the Novartis Foundation. His current research interests include the development of new organocatalytic reactions and their application in the total synthesis of natural products.

David W. C. MacMillan was born in 1968 in Bellshill, Scotland. He received his B.S. degree in chemistry in 1990 from the University of Glasgow, Scotland, and his Ph.D. degree in 1996 from the University of California, Irvine, where he worked under the direction of Professor Larry E. Overman. David then moved to Harvard University to undertake postdoctoral studies (with Professor David A. Evans), which he completed in 1998. In that year, he joined the faculty at the University of California, Berkeley. In 2000, MacMillan moved to the California Institute of Technology, where he was promoted to the rank of associate professor and, in 2003, to the rank of full professor. In 2004, MacMillan became the Earle C. Anthony Chair in Organic Chemistry at the California Institute of Technology. MacMillan's research program is centered on chemical synthesis with specific interests in new reaction development, enantioselective organocatalysis, and the rapid construction of molecular complexity.

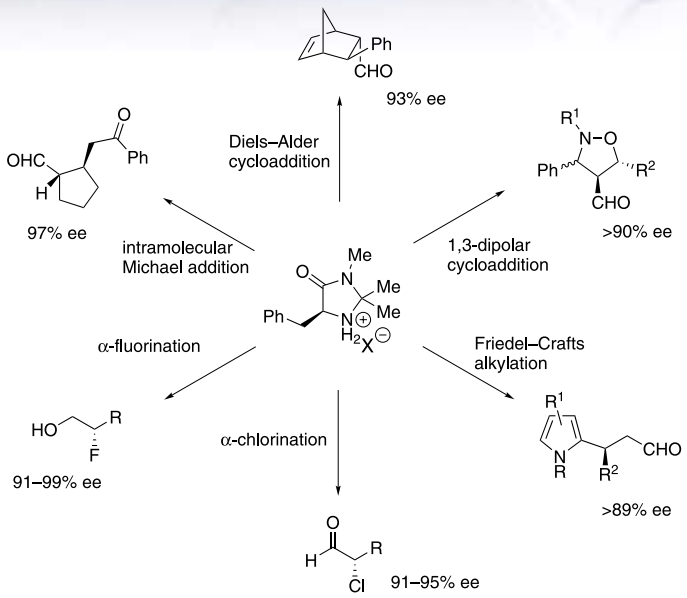
MacMillan Imidazolidinone OrganoCatalysts™

Metal-Free Asymmetric Catalysis

Product Highlights

- Superior enantiocontrol in numerous transformations
- High activities at low catalyst loadings
- Extraordinary functional group tolerance

MacMillan and co-workers have created chiral imidazolidinone organocatalysts that function as the linchpin in a variety of directed enantioselective organic reactions including Diels–Alder and 1,3-dipolar cycloadditions, conjugate additions such as α-fluorinations, α-chlorinations and Friedel-Crafts alkylations, epoxidations, transfer hydrogenations, and organo-cascade reactions. Sigma-Aldrich, in collaboration with Materia, Inc., is pleased to offer ten imidazolidinone organocatalysts that mediate rapid and enantiocontrolled C–C and C–X (X = H, O, halogen) bond formation.

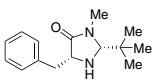


References

(1) For a review on organocatalysis, see Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (2) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (3) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (4) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (5) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(2*R*,5*R*)-(+)-2-*tert*-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

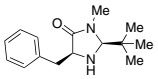
[*390766-89-9*]
$C_{15}H_{22}N_2O$
FW: 246.35



663093-500MG	500 mg	$60.00
663093-1G	1 g	95.00

(2*S*,5*S*)-(–)-2-*tert*-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

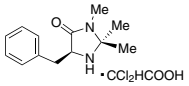
[*346440-54-8*]
$C_{15}H_{22}N_2O$
FW: 246.35



663107-500MG	500 mg	$60.00
663107-1G	1 g	95.00

(5*S*)-(–)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid, 97% NEW

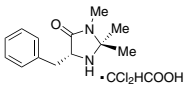
$C_{15}H_{20}Cl_2N_2O_3$
FW: 347.24



663085-500MG	500 mg	$55.00
663085-2G	2 g	150.00

(5*R*)-(+)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid, 97% NEW

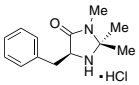
$C_{15}H_{20}Cl_2N_2O_3$
FW: 347.24



663077-500MG	500 mg	$55.00
663077-2G	2 g	150.00

(5*S*)-2,2,3-Trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

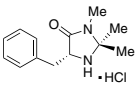
[*278173-23-2*]
$C_{13}H_{18}N_2O{\cdot}HCl$
FW: 254.76



569763-500MG	500 mg	$30.00
569763-2G	2 g	80.60

(5*R*)-(+)-2,2,3-Trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

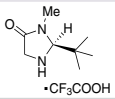
[*323196-43-6*]
$C_{13}H_{18}N_2O{\cdot}HCl$
FW: 254.76



663069-500MG	500 mg	$30.00
663069-2G	2 g	80.00

(*S*)-2-(*tert*-Butyl)-3-methyl-4-oxoimidazolidinium trifluoroacetate NEW

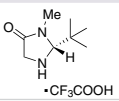
$C_{10}H_{17}F_3N_2O_3$
FW: 270.25



661902-500MG	500 mg	$50.00
661902-2G	2 g	165.00

(*R*)-2-(*tert*-Butyl)-3-methyl-4-oxoimidazolidinium trifluoroacetate NEW

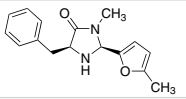
$C_{10}H_{17}F_3N_2O_3$
FW: 270.25



661910-500MG	500 mg	$50.00
661910-2G	2 g	165.00

(2*S*,5*S*)-5-Benzyl-3-methyl-2-(5-methyl-2-furyl)-4-imidazolidinone NEW

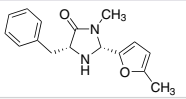
[*415678-40-9*]
$C_{16}H_{18}N_2O_2$
FW: 270.33



668540-250MG	250 mg	$79.50
668540-1g	1 g	215.00

(2*R*,5*R*)-5-Benzyl-3-methyl-2-(5-methyl-2-furyl)-4-imidazolidinone NEW

$C_{16}H_{18}N_2O_2$
FW: 270.33



668842-250MG	250 mg	$79.50
668842-1g	1 g	215.00

MacMillan Organocatalyst Kit I NEW

Kit contains: 569763-500mg, 661902-500mg, 663085-500mg, 663107-500mg, 668540-250mg

674575-1KT	1 KT	$247.00

For more information, please visit us at sigma-aldrich.com/catalysis.

OrganoCatalysts is a trademark of Materia, Inc.