Organocatalysis

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# Deconstructing Covalent Organocatalysis

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*Dedicated to Professor François Diederich*

*Modern organocatalysis has rapidly evolved into an essential component of contemporary organic synthesis. One of the most distinctive aspects of organocatalytic processes is the biomimetic nature in which the catalyst engages the substrate, often forming covalently bound intermediates in a manner reminiscent of enzyme catalysis. Indeed, the process of intramolecularization is often accompanied by a conformational change of the catalyst scaffold, further accentuating this analogy with biological systems. The isolation and study of these catalytic intermediates facilitate the rapid generation of conformation and reactivity profiles to assist in organocatalytic reaction development and/or clarify reaction outcomes. Emulating the formative advances that have derived from studying reaction intermediates in mechanistic organometallic and enzymatic catalysis, the deconstruction of covalently bound organocatalysis intermediates is gaining momentum as a design strategy.*

## 1. Introduction

Nature has evolved a vast arsenal of synthetic machinery capable of assembling the array of building blocks that are essential for life to flourish on earth. Perfected over billions of years, these processes are performed recurrently in living organisms with incomparable efficiency and selectivity. Consequently, natural enzymes remain a rich, diverse source of inspiration for the rational design of synthetic small-molecule catalysts. Their ability to orchestrate function through subtle changes in structural flexibility and rigidity ensures unparalleled precision in synthesis, a behavior that synthetic chemists are continually trying to emulate.[1,2] Whereas enzyme-inspired "blueprints" are evident in a plethora of functional small molecules,[3] they are perhaps most obvious in organocatalysts.[4] Often, these catalysts function through analogous substrate activation mechanisms;[5] these range from hydrogen-bonding interactions through to the formation of discrete covalently bound intermediates.[6] Indeed, the structural, conformational, and reactivity similarities that exist between these synthetic small molecules and their natural macromolecular counterparts render the study of biological catalysis of practical value in organocatalytic reaction development.[7] Pertinent examples include the manner in which proline can engage a carbonyl compound to create a reactive enamine,[8] mirroring the behavior of type I aldolases,[9] or the exquisite efficiency by which short peptides can pre-organize reactants in a catalytic transformation.[10] Understanding the decisive interactions that are involved in any catalytic process is an integral part of reaction development[11] and can often facilitate the design of novel processes. Of those actively engaged in contemporary catalysis, practitioners of organocatalysis are particularly fortunate to be able to rely on advances in structural biology[12] and supramolecular chemistry[7,13] to guide research and provide inspiration for novel catalyst architectures.

A feature common to many bio- and organocatalytic reactions is the formation of an initial (covalently bound) intermediary [catalyst–substrate] complex (Figure 1, [S–Cat*]). Aided by advances in spectroscopic and crystallographic techniques, the field of structural biology continues flourishing as a result of the now routine study of such species.[14] Just as biologists utilize these techniques to address the interplay of structure and function in biomacromolecules, so too has the organocatalysis community adopted a comparable synergistic approach to sustain innovation in this exciting field (Figure 1). In this Minireview, the merits of reaction deconstruction are briefly highlighted using selected examples from the recent organocatalysis literature. Dismantling catalytic cycles to identify and study reactive intermedi-

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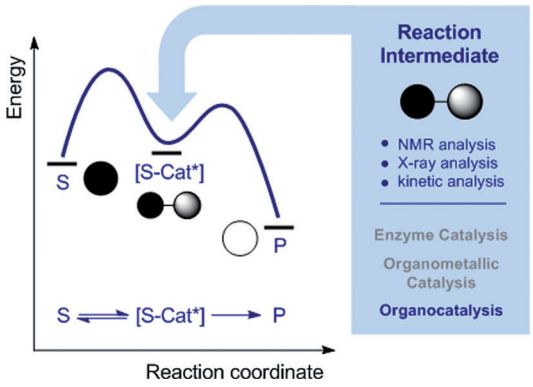


***Figure 1.*** Deconstructing covalent organocatalysis: parallels with enzymes and lessons from structural biology. (The rate-determining step in organocatalytic processes need not be the formation of the substrate–catalyst intermediate.)

ates can confer a range of advantages for reaction design; this strategy has been proven to be highly effective in mechanistic organometallic and biocatalysis. Moreover, the bio-inspired nature of many organocatalytic intermediates renders them excellent platforms from which to study non-covalent interactions.

### *1.1. Historical Overview of Organocatalysis*

Until recently, contemporary enantioselective catalysis was dominated by biological and metal-based processes,[15] but with the rapid emergence and maturation of organocatalysis this duo has evolved into a trio.[16] Within a relatively short time frame, modern organocatalysis has found application in all branches of synthesis ranging from the preparation of biologically important compounds through to materials science. However, examples of what may now be described as organocatalytic transformations are already prevalent in the historic literature. Whilst Wöhler and Liebig's report on the cyanide-catalyzed benzoin condensation arguably is the first report,[17] the definition "*Organische Katalysatoren*" first appeared in the works of Langenbeck.[18] In the ensuing decades, isolated examples of transformations mediated by small organic molecules appeared. Unsurprisingly, cinchona alkaloids feature prominently in the development of the field owing to their availability in optically active form.[19] Pioneering examples include Bredig and Fiske's cinchona alkaloid catalyzed cyanohydrin formation (1912)[20] and Prelog and Wilhelm's mechanistic studies on this transformation.[21] After a 50 year pause in the literature, Pracejus reported the addition of methanol to phenyl methyl ketene mediated by *O*-acetylquinine (1960),[22] and this was followed by Wynberg's first highly enantioselective application of chiral organic bases in the addition of thiophenols to cyclic enones.[23] Amino acids, in particular proline, have an equally prominent lineage in the development of modern organocatalysis. Just as Stork's introduction of enamine chemistry refined classic carbonyl reactivity,[8] so too was the development of a catalytic enantioselective variant a significant landmark; the now celebrated Hajos–Parrish–Eder–Sauer–Wiechert reaction[24] to generate the Wieland–Miescher ketone.[25] Unsurprisingly, this powerful approach to stereoselective C–C bond formation features prominently in a number of landmark natural product synthesis strategies. Pertinent examples include steroid syntheses by Woodward and co-workers[26] and the aldolization route to the dithiadecalin precursor of erythromycin.[27] The use of (*S*)-phenylalanine by Danishefsky and Cain to affect an enantioselective cyclodehydration of a trione in the synthesis of estrone is also masterful.[28] The potential of iminium ion intermediates in enantioselective synthesis is evident from the pioneering studies of Baum and Viehe[29] and Jung and co-workers.[30] Similarly, the α-functionalization of α,β-unsaturated aldehydes using a chiral amine[31] by Yamada et al. may now be considered a forerunner of dienamine activation,[32] and the enamine perfluoroalkylation[33] by Kitazume and Ishikawa appears to be a distant relative of modern photoredox catalysis.[34] A more comprehensive account of the history and genesis of organocatalysis can be found elsewhere.[35] Whilst these early examples provided inspiration for many of the reactivity principles in common usage today, two papers published independently in 2000 recognized the potential of organocatalysis, firmly establishing it as an indispensable branch of contemporary synthetic organic chemistry. Mirroring the enamine reactivity of type I aldolases, List, Barbas, and Lerner reported that direct asymmetric aldol reactions between acetone and simple aldehydes could be catalyzed by L-proline (**1**; Figure 2).[36] The mechanistic intricacies of this and related transformations that proceed via an enamine intermediate remain highly topical and will be addressed in the following section. Simultaneously, Ahrendt, Borths, and MacMillan reported the first highly enantioselective organocatalytic Diels–Alder reaction mediated by an imidazolidi-


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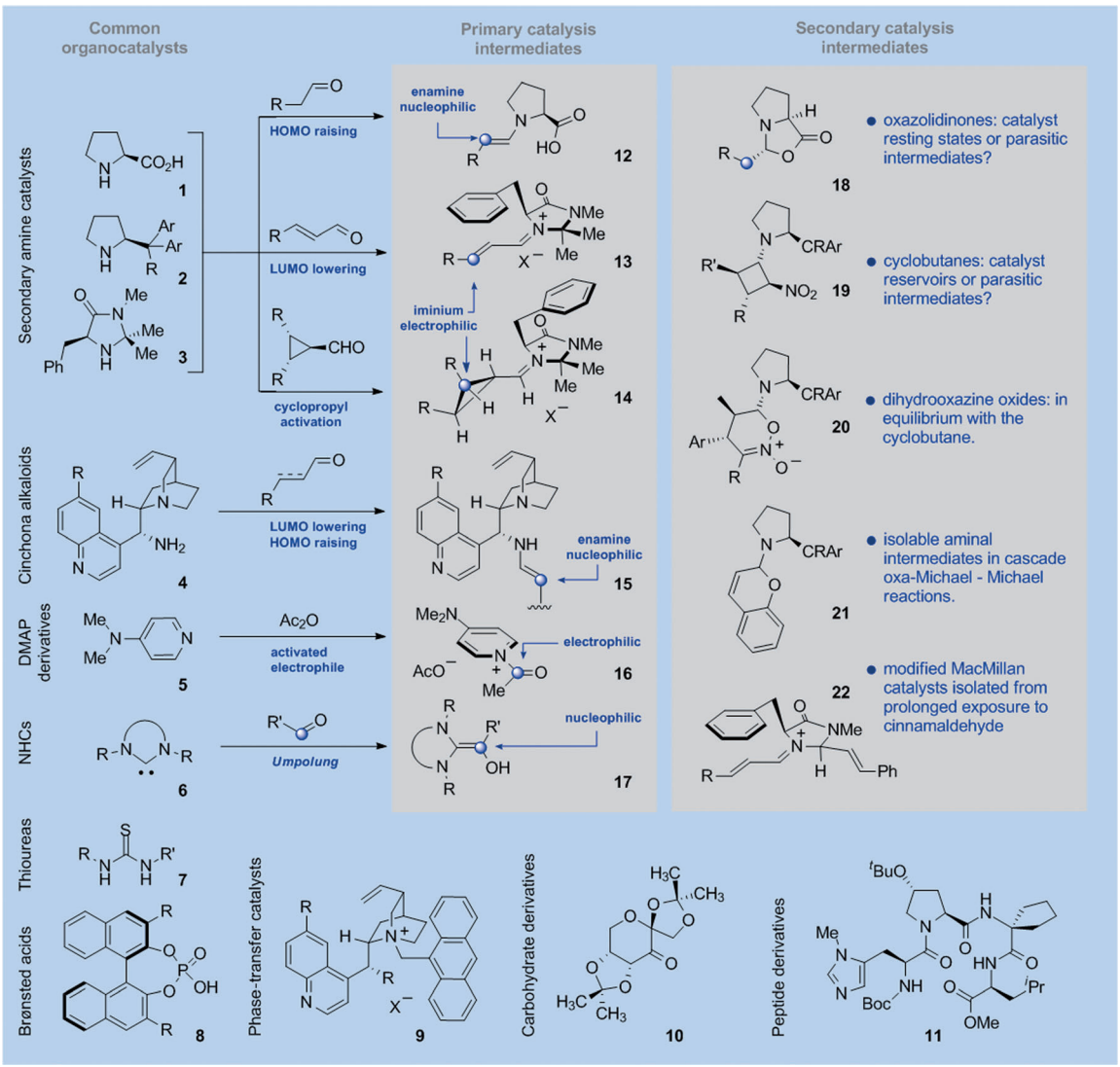


***Figure 2.*** A summary of the major classes of organocatalysts (**1**–**11**), the associated primary (**12**–**17**) and secondary (**18**–**22**) catalytic species, and an overview of activation modes.

none derived from L-phenylalanine, thus introducing the iminium ion activation mode (**3**; Figure 2).[37]

## 2. Studying Primary and Secondary Catalytic Intermediates: Importance, Evidence, and Consequences

Since these pioneering reports, a plethora of highly effective small-molecule organocatalysts have enriched the field of organic synthesis (Figure 2; **1**–**11**). Influential examples include phase-transfer catalysts, such as the quaternary ammonium salts derived from cinchona alkaloids (**9**).[38] Chiral analogues of dimethylaminopyridine (DMAP, **5**),[39] and N-heterocyclic carbenes (**6**)[40] have diversified the landscape of nucleophilic catalysis, whereas the introduction of chiral thioureas (**7**)[41] and Brønsted acids (**8**) provided valuable scaffolds for non-covalent organocatalysis.[42] The versatile epoxidation catalyst developed by Shi and Shu (**10**),[43] which belongs to a structurally diverse class of ketone organocatalysts,[44] exemplifies the importance of carbohydrates in enantioselective catalysis.

In general, organocatalysts are robust materials. This fact not only facilitates the generation of structure–reactivity profiles prior to application in catalysis, but also assists with spectroscopic analyses.[45] Consequently, the physical properties of most common organocatalysts are well documented, ranging from nucleophilicities and basicities[46] to the establishment of acidity scales.[47,48] In more challenging cases, such as carbene catalysis (NHCs), where the active catalyst is usually generated in situ, valuable physical data can be collected from both the pre-catalyst and the active form to help construct guidelines for future applications.[49] In particular, Mayr and co-workers have developed a quantitative approach to organocatalysis based on a series of nucleophilicity and electrophilicity scales.[50,51]

The diversity of activation modes operational in the parent organocatalyst systems is also notable, ranging from the aforementioned generation of discrete covalently bound intermediates (**12**–**17**), some of which include umpolung reactivity profiles (**17**),[52] or the creation of intricate hydrogen-bond networks to facilitate enantioinduction by means of molecular preorganization (**11**).[53] In contrast to organocatalytic transformations based on non-covalent interactions, processes based on covalent interactions benefit from the formation of a discrete, often stable, catalytic intermediate (e.g., enamines,[54] such as **12**) that can be isolated and characterized. This has led to the X-ray crystal structure analysis of numerous primary catalytic species and model systems (e.g., **12**–**17**), including cinchonium salts,[55] acyl pyridinium salts (**16**),[56] and protonated analogues thereof.[57] The given intermediate may be important for effective catalysis, function as a bridge en route to a secondary catalytic species, or simply be a spectator or catalyst reservoir. To delineate its role in catalysis, a synergistic mechanistic approach is essential but this first requires the preparation and isolation of the species of interest. The study of reactive intermediates remains a vibrant yet challenging aspect of physical organic chemistry.[58] Whilst a more detailed survey of this subject is out of the scope of this Minireview, it is important to note that a number of high-profile examples have recently been communicated.[59]

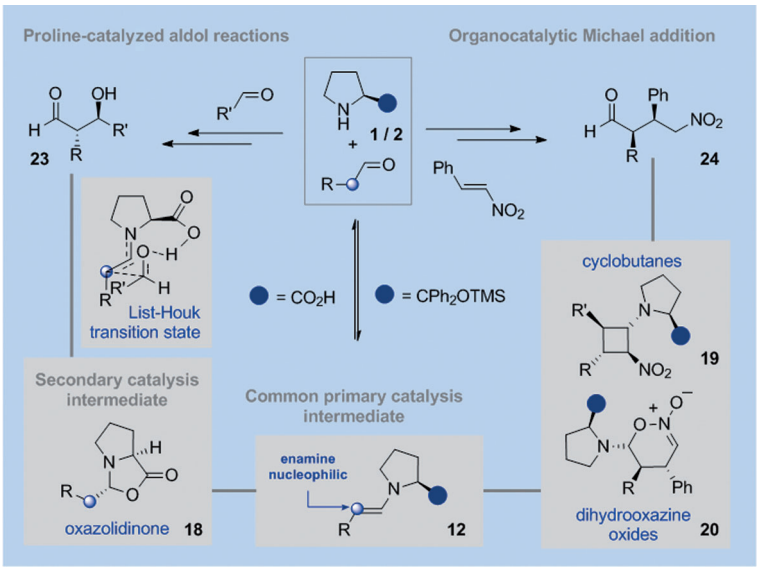


***Figure 3.*** The primary and secondary catalysis intermediates in the proline-catalyzed aldol reaction (left) and the organocatalytic Michael addition of aldehydes to nitroalkenes (right).

In recent years, interest in organocatalytic intermediates has intensified. Through their study, various mechanistic anomalies have been illuminated, new reaction manifolds have been identified, and the intermediates themselves have proven to be valuable platforms for the study of many non-covalent interactions that are more commonly found in complex biomolecules. Motivated by the clear advantages that have derived from studying these species in organometallic and enzymatic catalysis, the notion of "deconstructing covalent organocatalysis intermediates" is presented. To delineate this term further, it is helpful to survey the intermediates that are generated by the union of chiral secondary amines with saturated or α,β-unsaturated aldehydes and ketones.[60] The formation of these primary catalytic species by condensation generates an iminium salt (**13**) and/or an enamine (**12**), with concomitant lowering of the lowest unoccupied molecular orbital (LUMO) or augmentation of the highest occupied molecular orbital (HOMO), respectively (Figure 2, top left). These species can then readily interact with a plethora of nucleophiles and/or electrophiles.

However, it is important to note that these primary catalytic species may also be transformed into secondary intermediates, where their role in catalysis is less obvious. Pertinent examples in the arena of proline catalysis include the so-called parasitic oxazolidinones[61] (**18**) and dihydrooxazine oxides (**20**) in organocatalytic Michael additions of enamines to aldehydes or nitroalkenes, respectively (Figure 3, top right). Clarifying the role of these intermediates in catalysis remains an active field of research and the subject of continued debate.

### *2.1. Case Studies in Proline (Enamine) Catalysis*

Mechanistic studies of the proline-catalyzed aldol reaction, and subsequent induction models to account for the remarkable levels of stereoselectivity, date back several decades.[35] Some of the most compelling insights have come from structural analyses of the primary catalytic enamine. In a seminal publication by Dunitz, Eschenmoser et al. in 1978,[62] the authors discuss the consequences of structurally modifying the amine on the degree of nitrogen pyramidalization (the so-called Dunitz pyramidalization), thus providing valuable stereoelectronic insights into enamine reactivity and illuminating previous stereochemical peculiarities. Similar analyses have been employed to rationalize the preferential reaction of many pyridoxal ansa compounds on their seemingly more hindered face by Breslow[63] and the stereochemical course of nucleophilic additions to α,β-unsaturated iminium ions.[64] Whilst the initial aldol induction models and kinetic analyses[65] relied on the intermediary proline-derived enamine, structural data remained elusive until recently. It was only in 2010 that this primary catalysis intermediate was identified by NMR spectroscopy,[66] revealing that the secondary catalytic species, an oxazolidinone (**18**), functions as a bridge between aldehyde and enamine (**12**) in dipolar aprotic solvents. Concurrently, the X-ray structural analysis of a series of related enaminones was reported by List et al.[67] allowing comparisons to be drawn between the calculated structures and the solid-state data. Throughout, computation has played a crucial role in bridging experimental findings with postulated induction models and in providing rational guidelines for further reaction development.[68]

  

Pertinent to this particular discussion is the recent computational analysis of the proline-catalyzed propanal self-aldol reaction by Sharma and Sunoj.[69] In reconciling the differences between the Houk–List and Seebach–Eschenmoser models to rationalize stereoselectivity, the authors demonstrate that convergence of both the enamine and oxazolidinone pathways (Figure 3) is likely under the reaction conditions, underscoring the value of synergy between experiment and theory. In a recent analysis of the List–Houk model, Armstrong, Rzepa et al. note that ten years after the initial report, seemingly small systems such as this one continue to be challenging, especially in understanding the role of dispersion interactions in rationalizing selectivity.[70]

The conceptually related organocatalytic addition of linear aldehydes to nitroolefins has become an excellent platform for evaluating new catalyst architectures for enamine activation. This is largely on account of Seebach's seminal reports detailing the addition of pre-formed enamines to nitroalkenes and the formulation of the general "topological rule".[71] The first highly stereoselective catalytic variant of this transformation was reported in 2005 by Hayashi and co-workers,[72] utilizing the well known Jørgensen–Hayashi diarylprolinol derivative **2** (Figure 3, right).[73] Reminiscent of proline-catalyzed aldol reactions, this transformation has also been the subject of intense mechanistic efforts to elucidate the role of the primary and secondary catalytic species.[74] The linear enamines derived from the Jørgensen–Hayashi catalyst **12** were isolated and extensively studied by crystallography and spectroscopy, which provided valuable information for rationalizing the outcome of these transformations.[75] However, a recent series of studies by Seebach, Hayashi and co-workers[76] and Blackmond[77] et al. have concentrated largely on a secondary catalytic cyclobutane species. Whereas Blackmond and co-workers reported on the beneficial role of cyclobutane **19** in furnishing high stereoselectivities, Seebach argued that its stability results in catalyst sequestration.[78] In a combined experimental and computational analysis of this transformation, Pihko and co-workers concluded that dihydrooxazine oxides **20** are the important on-cycle participants in catalysis, and that the cyclobutanes may be considered as catalyst resting states or reservoirs (Figure 3).[79]

Similar aminal intermediates (**21**) were identified by Wang and co-workers in the development of an enantioselective organocatalytic oxa-Michael–Michael cascade process to access chromans,[80] and prolonged exposure of certain MacMillan imidazolidinones to aldehydes has been reported to cause catalyst modification (Figure 2, right; **22**),[81] demonstrating that more than one catalytically competent species can potentially be generated in situ.

### 2.2. Iminium Ion Activation: Opportunities and Insights

These examples provide compelling evidence that a more careful analysis of organocatalysis intermediates may prove to be judicious in reaction development; additional evidence can be found in the realm of iminium ion activation. One of the most prominent transformations of recent years is the Jørgensen epoxidation of α,β-unsaturated aldehydes by hydrogen peroxide catalyzed by diarylprolinol derivative **2** (Figure 4, left).[82] The apparent simplicity of this catalytic cycle is deceiving, as has recently been reported by Jørgensen and co-workers.[83] Whilst the reaction proceeds via the expected iminium/enamine manifold, the secondary intermediate peroxyhydrate **30** has been implicated in accelerating the reaction by functioning as a phase-transfer catalyst. In a structural study of the iminium salt, Seebach et al. concluded that the silyl group is likely to be responsible for discriminating the two planar faces of the electrophile, leading to the exquisite levels of enantioselectivity observed in this reaction.[45,64,73] Motivated by these studies, and the apparent lability of the silyl group,[45] we developed a small-molecule organocatalyst (Figure 4, right; **31**) bearing a robust fluorine substituent in benzylic position.[84]

It was envisaged that upon union of the catalyst and an α,β-unsaturated aldehyde, a transient β-fluoroiminium salt (**32**) would be generated, which benefits from stabilizing

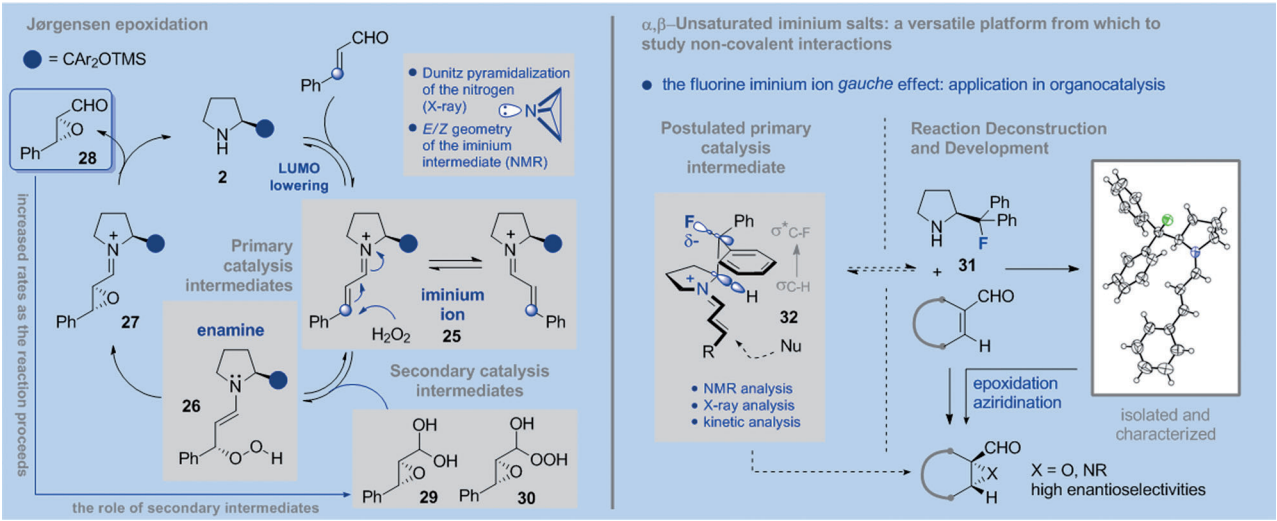


***Figure 4.*** The Jørgensen epoxidation of α,β-unsaturated aldehydes: mechanistic insights (left) and application of the fluorine-iminium ion *gauche* effect for molecular preorganization (right).

hyperconjugative ($\sigma_{C-H} \rightarrow \sigma_{C-F}^*$) and electrostatic interactions ($N^+ \cdots F^{\delta-}$), ultimately favoring the synclinal *endo* arrangement.[85]

The consequence of the fluorine-iminium ion *gauche* effect is to position one of the shielding phenyl groups of the fluorine-bearing carbon atom over the pendant iminium chain, thus controlling molecular preorganization prior to addition of an external nucleophile (e.g., $H_2O_2$). Isolation and crystallographic and spectroscopic analyses of numerous primary catalysis intermediates[86] validated this hypothesis leading to the development of a novel small-molecule catalyst for enantioselective epoxidation and aziridination.[87] This example underscores the value of iminium platforms in studying non-covalent interactions: These phenomena may ultimately be incorporated in reaction design. A logical extension of this preliminary study was to utilize the fluorine-iminium ion *gauche* effect to probe the influence of the phenyl shielding group in orchestrating enantioinduction in iminium ion intermediates derived from the MacMillan oxazolidinone (Figure 5, top).[88] The strategic incorporation of configurationally defined benzylic fluorine substituents allowed for the generation of two diastereoisomers, which subsequently function as "conformer equivalents" of the primary catalysis intermediate[89] in the Friedel–Crafts alkylation of *N*-methyl pyrrole.[90,93] Recently, we also reported the conformational analysis, reactivity, and catalysis performance of a range of electronically modulated analogues of the MacMillan first-generation catalyst.[91] Remarkably, a clear correlation between the electronic nature of the aryl shielding groups, as a function of the component of the traceless quadrupole moment tensor orthogonal to the plane ($Q_{zz}$), and the enantioselectivity of this reaction was observed. Structural data could be collected on all three staggered conformers with the aryl shielding group partitioned by 60°, and reconciled with differences in reactivity. Through a process of reaction deconstruction and molecular editing of the primary catalytic intermediate, it was possible to glean valuable insights, complement existing theoretical studies,[92] and formulate guidelines for future catalyst design.[93] We also successfully applied the process of reaction deconstruction to the development of the first catalytic enantioselective dichlorination of *meso*-cyclopropane carbaldehydes (**38** and **39**; Figure 6).[94] Central to the working hypothesis was the notion that a putative cyclopropyl iminium ion intermediate (**34**, **35**) would display characteristics reminiscent of the cyclopropyl carbinyl cation (**33**), such as the bisected geometry of the cyclopropane and iminium moieties. Ultimately, this would lead to a formal umpolung of the γ-position of conventional dienamines ($d^4 \rightarrow a^4$; **36**→**37**) and bypass the current reliance on linear carbonyl substrates with various degrees of unsaturation. Consequently, the iminium salt was isolated, allowing for structural analysis and the investigation of exploratory (stoichiometric) addition reactions. This approach to reaction design facilitated the preliminary validation of the underlying physical organic principles of cyclopropyliminium activation and accelerated the development of new catalytic transformations.

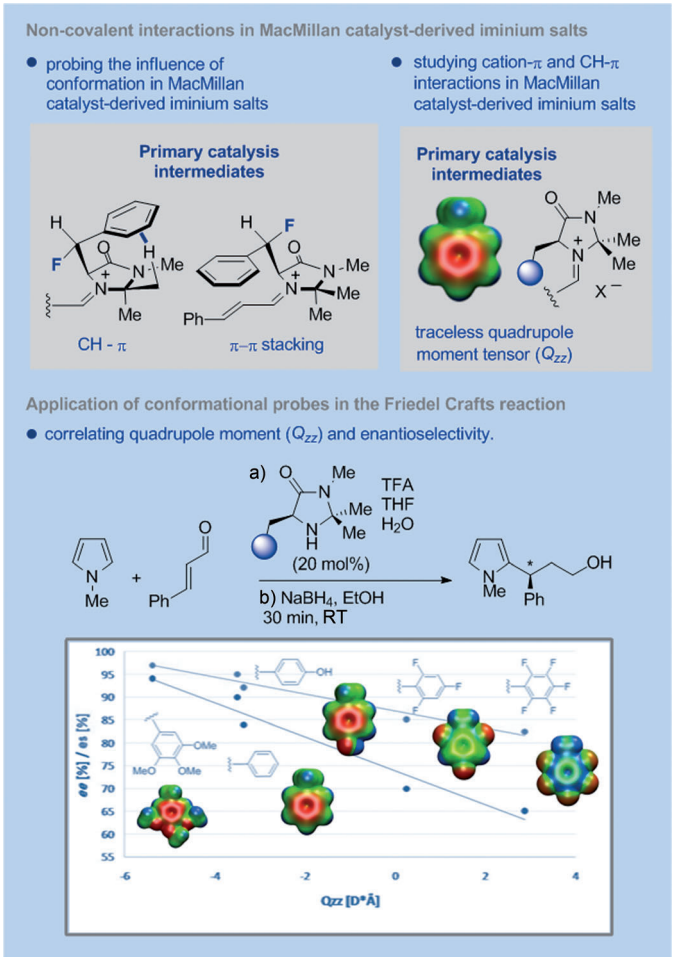


***Figure 5.*** Non-covalent interactions in iminium salts derived from the MacMillan catalyst. Top left: Controlling topology by means of the fluorine *gauche* effect and CH–π/π–π stacking interactions. Top right and bottom: The effect of electronic modulations of the aryl ring on catalyst structure and performance. Bottom: Correlating the quadrupole moment ($Q_{zz}$) and enantioselectivity.

### 2.3. NHC Catalysis and the Breslow Intermediate

N-Heterocyclic carbenes (NHCs, **6**) bring an additional level of diversity to nucleophilic organocatalysis on account of their structural resemblance and reactivity similarities to the coenzyme thiamine (vitamin $B_1$; **40** and **41**). Reactions mediated by NHCs are characterized by the intermediary acyl anion equivalent, more commonly known as the Breslow intermediate (Figure 7, top).[95]

Although these and related intermediates can be generated in situ for mechanistic work,[49,96] their isolation remains highly challenging.[97] Recently, Berkessel, Teles, and coworkers initially succeeded in characterizing the keto form of this important primary catalysis intermediate by NMR spectroscopy and subsequently analyzed related 2,2-diamino enols (**47**).[98] A salient feature of this study aimed at isolating the elusive Breslow intermediate was the identification of an unprecedented spirocyclic orthoamide as the catalytic resting state in the benzoin condensation of aliphatic aldehydes.

In 2013, the same laboratory disclosed an elegant comprehensive account of the solution- and solid-phase

  

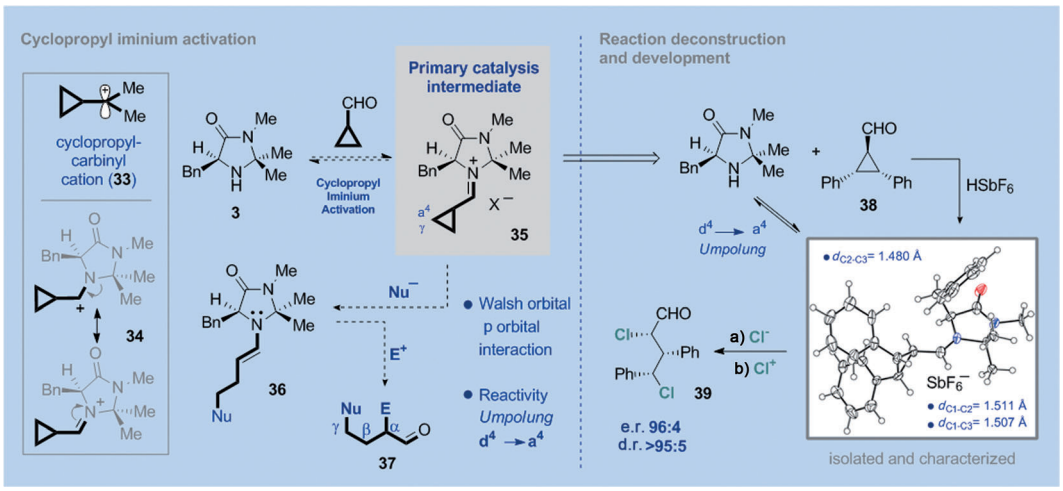


***Figure 6.*** Reactivity umpolung in cyclopropyliminium activation: exploiting the similarities between the cyclopropyl carbinyl cation and the postulated primary catalysis intermediate. Bn = benzyl, Nu = nucleophile.

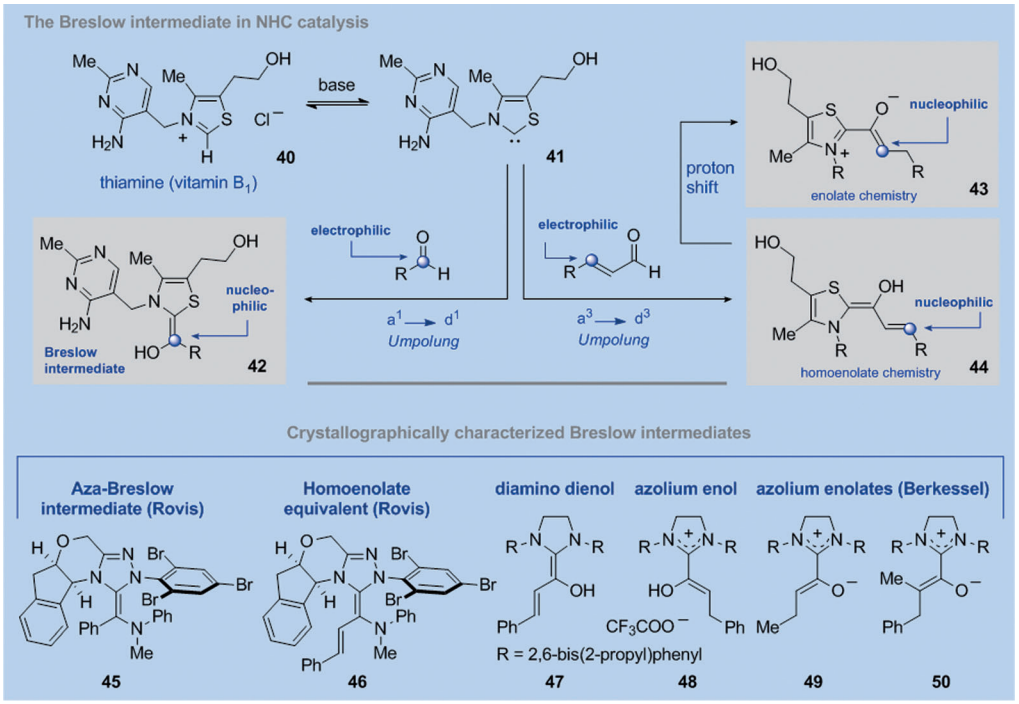


***Figure 7.*** Intermediates generated during NHC-catalyzed processes (top) and isolated analogues reported by the groups of Berkessel and Rovis (**45**–**50**).

structures of these important species, including diamino enols, homoenolates, and azolium enolates (Figure 7, bottom; **47**–**50**).[99] Simultaneously and independently, Rovis and co-workers reported dynamic NMR and X-ray analyses of isolable analogues of the Breslow intermediate derived from triazolylidene carbenes (**45** and **46**). These stable analogues of the Breslow intermediate not only serve as valuable model systems for acyl anion reactivity studies, but also allow for the compilation of valuable physical data, including oxidation potentials, which will facilitate the design of novel oxidative NHC-catalyzed transformations.[100]

## 3. Conclusions

Whilst this review is far from comprehensive, these selected examples are a compelling endorsement for a more rigorous study of organocatalysis intermediates, both in the context of reaction design and in the wider field of physical organic chemistry. The focused study of reactive intermediates by reaction deconstruction is an intuitive step towards reconciling mechanistic discrepancies, clarifying anomalous outcomes, and identifying novel reactivity modes. Moreover, many of these covalently bound intermediates are ideal platforms from which to study non-covalent interactions,

rendering them important for fundamental research in a broader sense.

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