Invited paper

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Organocatalysis emerging as a technology

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Abstract: During the last 20 years, organocatalysis has significantly advanced as a field. Thanks to contributions from hundreds of groups and companies around the world, the area has risen from a few mechanistically ill-defined niche reactions, to one of the most vibrant and innovative fields in chemistry, providing several well-defined generic activation modes for selective catalysis. Organocatalysis is also on the rise in industrial settings, especially for the production of enantiomers, which are of use in fine chemistry, pharma, crop-protection, and fragrance chemistry. Here we will look at some of the specific elements of organocatalysis that we think are particularly attractive and contribute to this successful development.

Keywords: Emerging technologies; new directions in chemistry research.

Introduction

Only two decades ago, selective catalysis was essentially synonymous with transition metal- and enzyme catalysis. A revolution has taken place since and nowadays organocatalytic approaches dominate many areas of asymmetric synthesis. In fact, the majority of publications appearing these days in the entire field of asymmetric synthesis cover organocatalytic transformations. However, this dominance is not yet seen in industrial asymmetric catalysis, where enzymes are on the rise and metal-catalyzed hydrogenations are considered universally applicable, despite specific limitations.

Change is coming along though, as environmentally friendly, green organic molecules, sustainably obtained from renewable sources, catalyze challenging carbon–carbon bond forming transformations with exceptionally high enantioselectivities. Organocatalysts with incredible reactivity are rationally designed and enable unprecedented reactions, rivaling the efficiency of the very best transition metal catalysts and enzymes. Covalently immobilized organic molecules can be recycled hundreds of times. Confined acids are being developed, the reactivity of which can be fine-tuned over more than 10 pKa units, simultaneously displaying enzyme like selectivity, and catalyzing possibly the majority of all catalyzable transformations.

Given this exciting development, it may be only a matter of time until the academic revolution in asymmetric synthesis will repeat itself in industry, establishing organocatalysis as a reliable and broadly general technology. Here we take a look at six aspects of organocatalysis that we believe will aid in this transition.

Sustainability

With nature's surplus of enantiopure molecules at chemists' disposal, a plethora of low-cost and abundant building blocks are readily available for the construction of organocatalysts. Sugars [1–3], the cinchona

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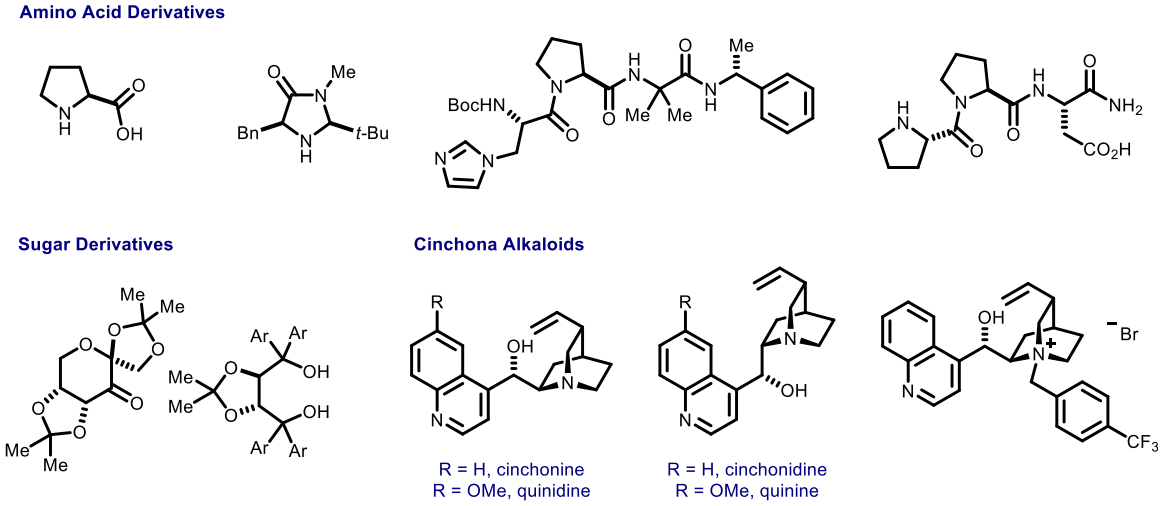


Fig. 1: Representative organocatalysts derived from natural compounds.

alkaloids [4, 5], and amino acids [6–9] are just three classes of chiral compounds that have already found widespread use across academia for catalyst synthesis, as well as their direct use of, for enabling asymmetric transformations, although some of these involve metal salts (Fig. 1).

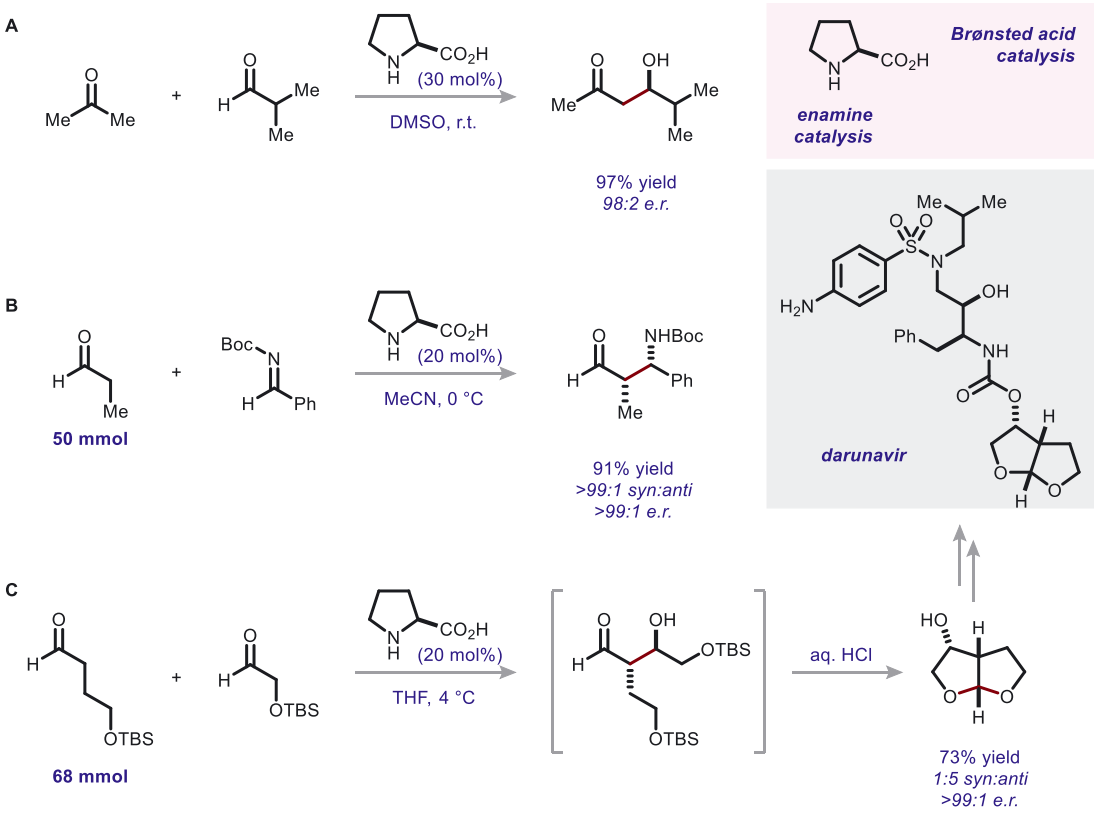
Having been synthesized in the biosphere, these molecules are stable to both air and moisture, in addition to their renewable and sustainable production. In comparison, transition metals such as palladium, platinum, and rhodium, which are widely used in industry and technology, continue to rise in price as finite stocks diminish and typically require complexing with a ligand under inert conditions to become catalytically active.

Arguably the quintessential sustainable organocatalyst, proline demonstrated how a small molecule could impart high levels of enantioselectivity in a given process through the formation of an enamine from the corresponding carbonyl nucleophile, coupled with the acidic chelation of the electrophile, sparking the development of asymmetric enamine catalysis and Brønsted acid catalysis as generic activation modes used in the emerging field of organocatalysis.

Our initial report showed how proline is even capable of catalyzing the aldol reaction of acetone with simple aldehydes, such as isobutyraldehyde, with excellent enantiocontrol [10]. The scalability of proline catalysis was made evident when we reported the highly selective Mannich reaction of aldehydes with *N*-Boc imines on 50 mmol scale [11, 12]. The proline-catalyzed aldol reaction as has since been utilized in a number of large-scale syntheses, such as the key bis-THF fragment of the antiretroviral medication, darunavir, which is on the World Health Organization's List of Essential Medicines (Scheme 1) [13–15].

Accessibility & designability

It remains mysterious why organic chemists, for so long, have failed to identify their own science as a promising platform for catalyst development, when building catalysts from readily accessible organic molecules should have been the most logical and straightforward approach for them. Fortunately, the situation today could not be more different, and as the field of organocatalysis has grown, certain structures have become particularly prominent as the basis for catalyst design. Taking hydrogen-bonding catalysis as an exemplary case, thioureas and squaramides are now typical core units, which were originally thought to activate basic substrates through lowest unoccupied molecular orbital (LUMO) lowering. Substituents are easily attached to each nitrogen atom and can then be modified accordingly to provide the chiral environment and add additional stabilization. For example, when developing a catalytic system for asymmetric Strecker reactions, Jacobsen's group incorporated readily accessible amino acids and salicylaldehydes, which gave



Scheme 1: Initial development and application of proline-catalyzed aldol and Mannich reactions.

access to a large library of catalysts to optimize the process (Scheme 2A) [16, 17]. They subsequently improved the method for large-scale applications by simplifying the catalyst structure and lowering the catalyst loading, utilizing a cheap HCN source, and operating the reaction at non-cryogenic temperatures (Scheme 2B) [18].

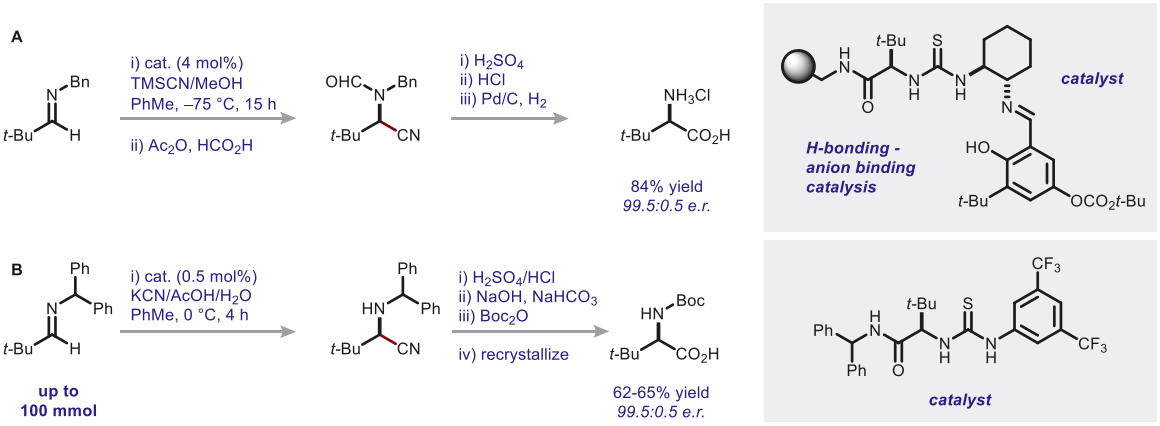
Recyclability

Catalysts need to be highly active and reusable to have long-term capabilities in industrial settings. For these reasons, heterogeneous catalysts have cemented their place in process chemistry, as they are easily recovered and recycled. However, while transition metal-based catalysts are typically immobilized through complexation, this can be detrimental as the metal can leach from the polymer support, which deactivates the catalyst and can contaminate the reaction products. Immobilized organocatalysts on the other hand, have the potential to be far more robust, as they can be covalently-bound to the supporting material, with leaching being a practical impossibility.

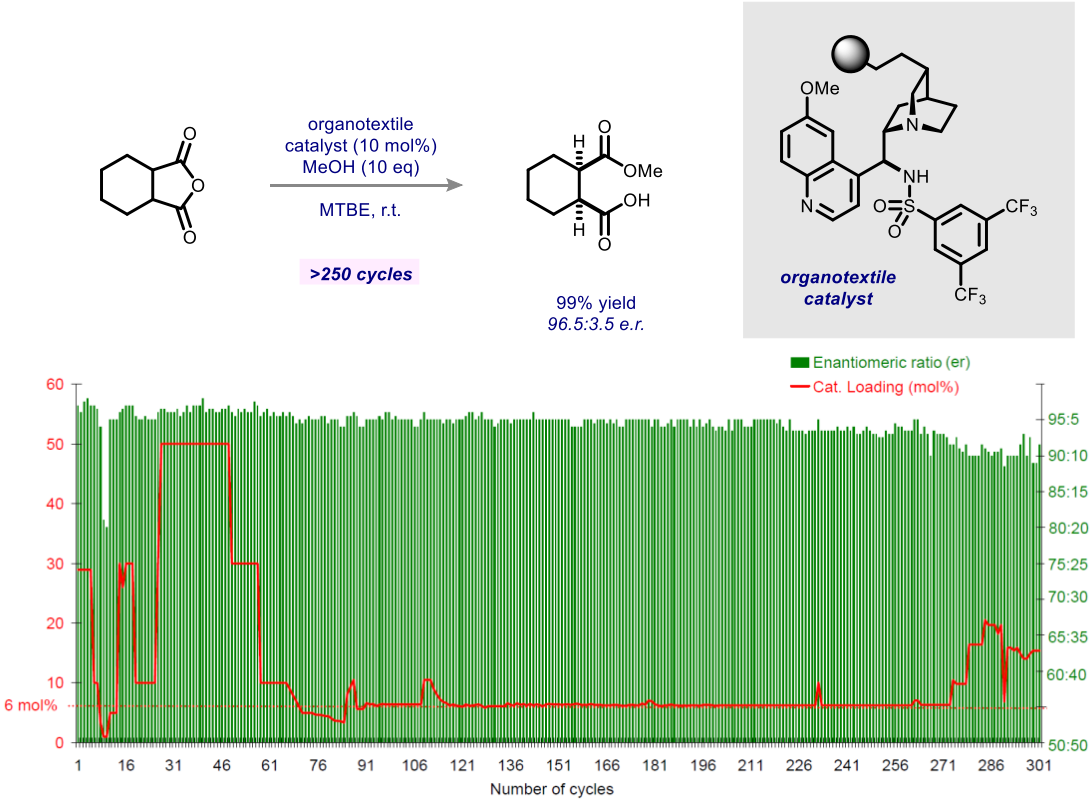
An example from our group that highlights this point is a cinchona alkaloid-derived catalyst bound to a nylon support. This textile-immobilized organocatalyst proved to be incredibly stable and active, as it was recycled more than 250 times for the desymmetrization of anhydrides with no loss in efficiency. Furthermore, neither the catalyst nor the textile material required any prefunctionalization prior to immobilization, which was achieved just using ultraviolet light (Scheme 3) [19].

Catalytic activity

The low reactivity and consequential high loadings of catalysts required in the early days of organocatalysis has been considered a significant pitfall when compared to certain high-performance transition metal- or



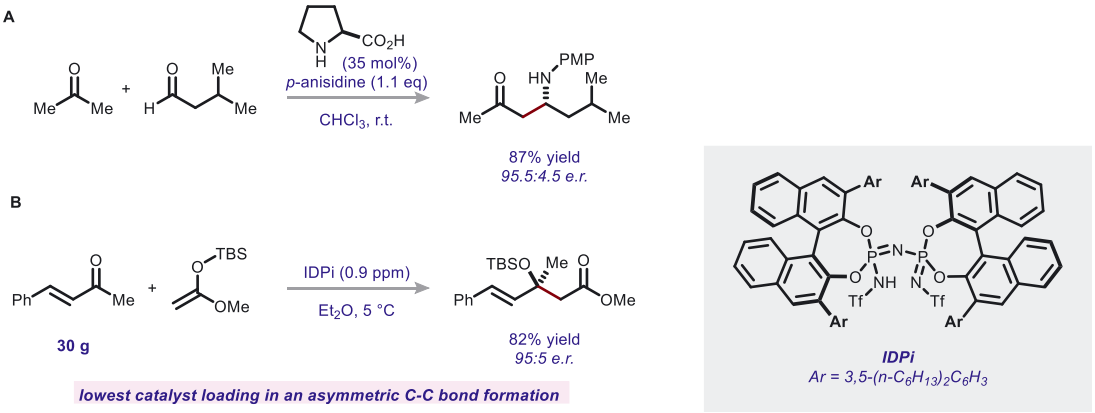
Scheme 2: Chiral thiourea-catalyzed Strecker synthesis.



Scheme 3: Desymmetrization of anhydrides using a textile-supported catalyst.

enzyme catalysts. As the field has grown over the past 20 years however, there have been substantial improvements and now there are some organic molecules that outperform even some of the most reactive metal- and biocatalysts.

At the dawn of the field, loadings from 10 to 30 mol% were typical for proline-catalyzed reactions, to enhance the rate of condensation with the substrate and reduce side reactions [20]. As new activation modes have been realized, however, novel catalysts have been constructed that exploit them with ever-increasing efficiency; the progression from enamine catalysis to asymmetric counteranion-directed catalysis (ACDC) for enantioselective Mukaiyama aldolizations circumvents the covalent activation path and utilizes strong ionic



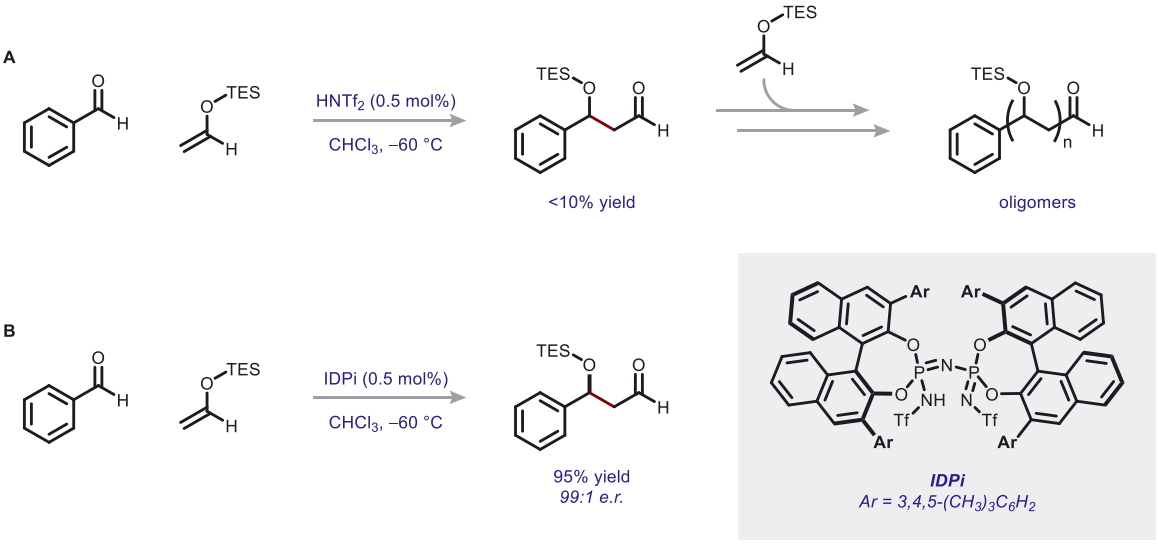
Scheme 4: Comparison of catalyst efficiency for selective transformations of carbonyl compounds.

and other interactions to promote reactivity and selectivity. Strongly acidic imidodiphosphorimidates (IDPi) are now available that can catalyze challenging carbon–carbon bond forming reactions at approaching sub-ppm loadings (Scheme 4) [21].

These catalysts have been rationally designed so that the acidic active site is contained within the highly confined dimeric BINOL scaffold. This in turn has facilitated some unprecedented selectivities, such as the single aldolizations of acetaldehyde enolates (Scheme 5) [22].

"New" reactivity

In a relatively short period of time the field of organocatalysis has grown from an academic curiosity to one of the key pillars of asymmetric synthesis. This rapid expansion is largely attributed to the discovery of new substrate activation modes, which in turn has facilitated the development of novel processes. Additionally, the merger of organocatalysis with other catalytic methods has solved some of the long-standing problems in enantioselective synthesis [23–26].



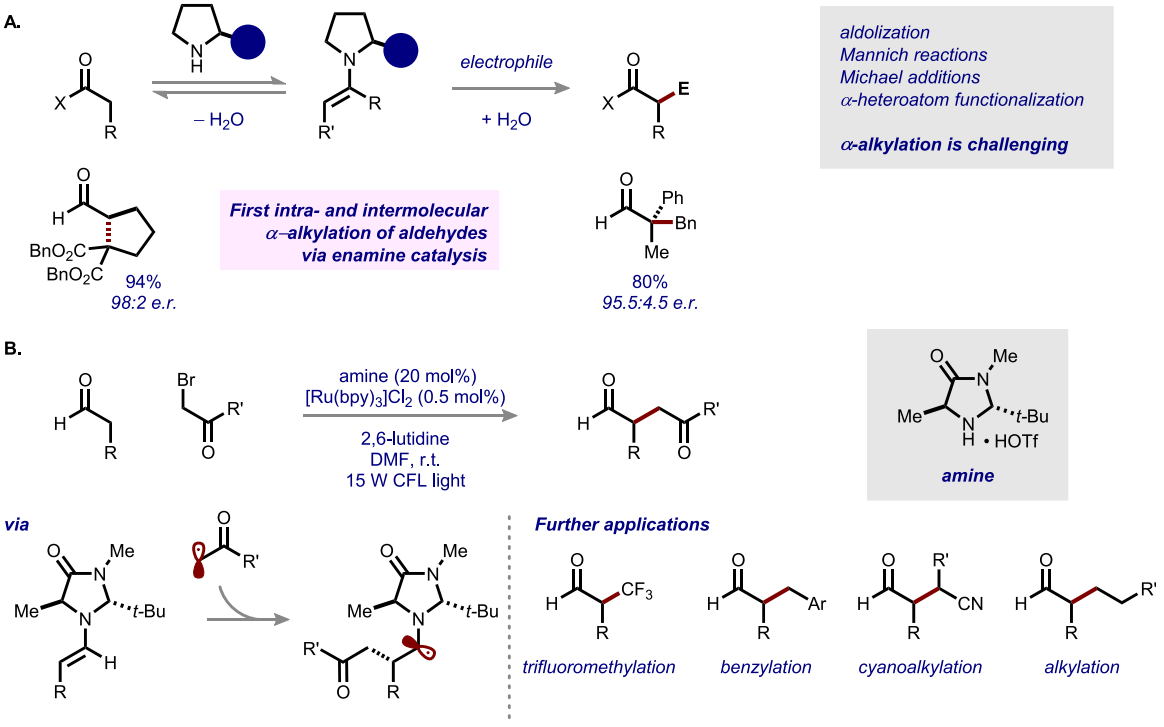
Scheme 5: The development of organocatalysts with confined active sites enable selective single aldolizations of acetaldehyde enolates.

At the heart of this revolution was the use of amines such as proline to activate carbonyl-containing compounds through ionic, two-electron processes [27]. Whilst enamine catalysis addressed many difficult transformations, from aldolizations and Mannich reactions, to the selective introduction of heteroatoms, enantioselective α-alkylation of aldehydes was one challenge that remained troublesome for a long time. Due to the modest reactivity of alkyl halides, the reactions are commonly hampered with unwanted side processes such as self aldolization or direct *N*-alkylation of the amine catalyst (Scheme 6A). As a consequence, the development of the first intra- and intermolecular aldehyde α-alkylations *via* enamine catalysis proved to be extremely difficult and required special substrates [28, 29].

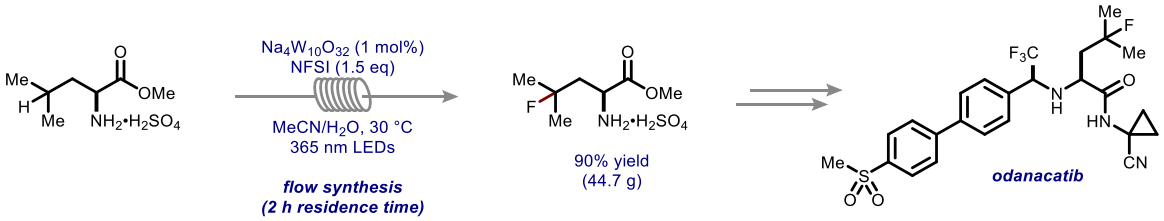
An incredibly powerful solution was realized, however, by treating alkyl halides not as electrophiles, but as radical precursors, which could then be trapped by an electron rich olefin, *the enamine*. Using photoredox catalysis to selectively generate the radical species under mild conditions, this approach provides an answer to the problems inherent to ionic alkylations and could be exploited for a range of transformations [30–32]. Most recently, the α-alkylation of aldehydes using simple olefins has been achieved by incorporating a catalytic hydrogen atom transfer (HAT) cycle (Scheme 6.B) [33].

Developments in some additional dual organocatalytic/photoredox transformations have also shown that organic photosensitizers can be employed, avoiding the use of traditional precious metal catalysts. In some specific cases, the photocatalyst can be left out altogether, as the substrate is directly excited by light [32].

Whereas asymmetric organocatalytic transformations are beginning to emerge across industry [34, 35], the application of photoredox catalysis is still relatively rarely seen. Optimal light penetration is crucial for a high yielding reaction and so these methods cannot be scaled-up using traditional batch techniques. Operating in flow reactors has provided a promising solution to this; however, the infrastructure is still not there on process-scale. Nevertheless, potential for photoredox catalysis to streamline syntheses is beginning to be appreciated. One example is in the synthesis of Merck's promising osteoporosis drug Odanacatib (Scheme 7). Preparation of the key γ-fluoroleucine derivative had previously required multiple steps using hazardous reagents, such as hydrofluoric acid. Through photocatalysis the route could be shortened to a single step, where the key intermediate was produced *via* a C–H fluorination of the unprotected leucine derivative [36].



Scheme 6: The combination of enamine- and photoredox catalysis enables the asymmetric α-alkylation of aldehydes.



Scheme 7: Large-scale photocatalytic C–H fluorination of leucine in flow.

Universality

Acid catalysis is perhaps the most general approach to catalysis there is. It is not unlikely that the majority of all catalyzable transformations can be catalyzed by acids. The concept of using chiral, enantiomerically pure Brønsted acids has not quite penetrated the arsenal of asymmetric, catalytic methodology during the last century, despite early attempts with chiral metal complexes [37]. The asymmetric Brønsted acid catalysis displayed by proline and Akiyama's pioneering studies on BINOL-derived Brønsted acid catalysts have led to a rather drastic change [6, 38]. Acid organocatalysis is a growing area with significant potential for industrial applications. While BINOL-derived phosphates are frequently used, their reactivity and ability to activate less basic substrates is limited by their acidity. For example, the popular phosphoric acid TRIP has a pKa of 13.6 in acetonitrile. This acidity is certainly sufficient to catalyze various additions to imines and also to certain oxygenous substrates. However, to enable activation of simple aldehydes, for example, requires much stronger acids. Similarly, olefin activation *via* protonation has been beyond reach of this catalyst class. Also, higher Brønsted acidity should enable higher rates and turnover frequencies. Last but not least, anions derived from stronger acids display a significant potential as counteranions in asymmetric Lewis acid catalysis with cationic Lewis acids.

In 2012, we have introduced a new catalyst design, in which two phosphates are bridged *via* an imido nitrogen group. The resulting imidodiphosphate (IDP) catalysts, because of the now four substituents in the corresponding 3- and 3′-positions, all pointing toward the active site, create significant confinement, while still displaying relatively strong acidity (pKa = 11.3, CH_3CN) [39]. By carefully choosing appropriate substituents, the confinement can be easily fine-tuned. Furthermore, successive replacement of oxygen atoms with NTf-groups, can massively enhance the acidity. The resulting imino imidodiphosphates (*i*IDP) and IDPi [40, 41], with more or less electron neutral aryl substituents, display pKa's of around 9 and 4.5. With fluorinated substituents, the acidity can be further enhanced, reaching a level displayed by common "magic acids" such as triflic acid and triflimide (Fig. 2) [42].

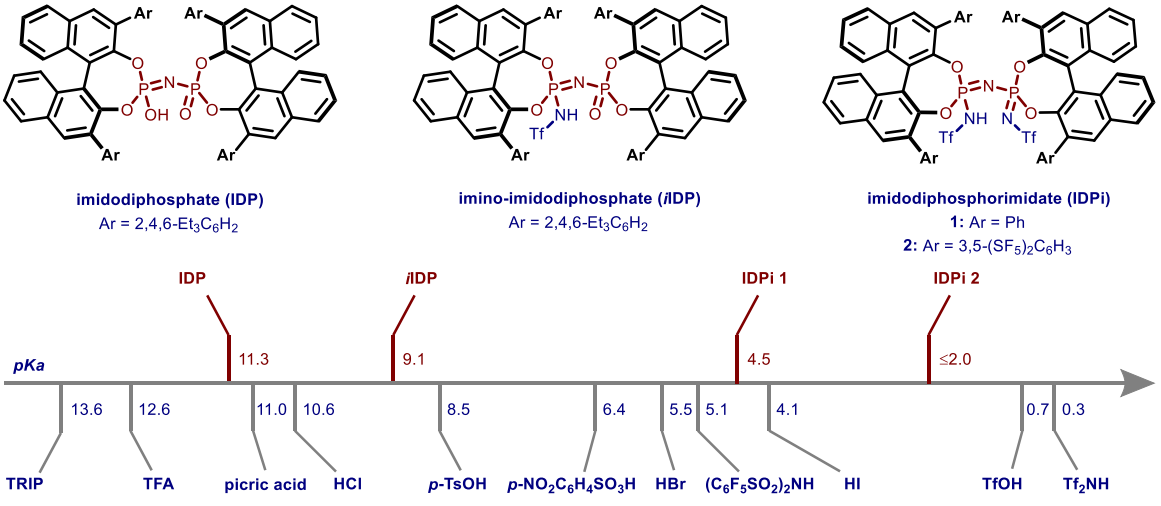
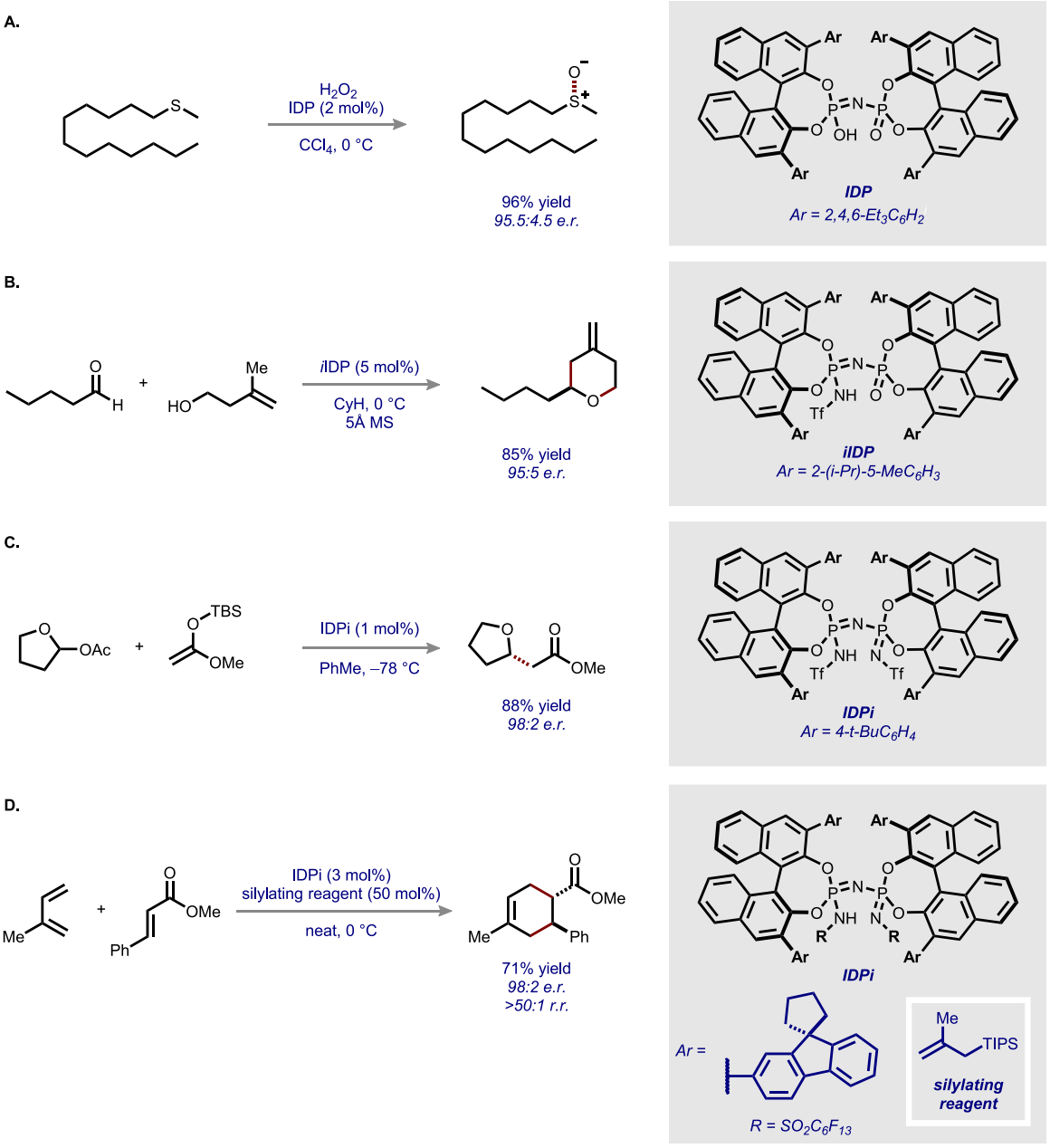


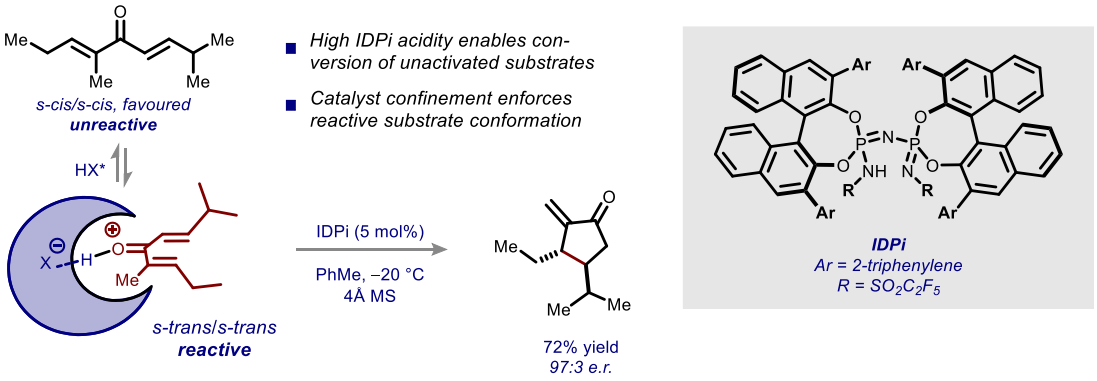
Fig. 2: Confined acids cover a broad range of acidity and can be easily fine-tuned.

The three catalyst classes, thanks to high acidity and confinement enable the handling of unreactive and unbiased substrates. For example, one IDP catalyst has been developed that not only enables acetalization reactions of simple aliphatic substrates [40], but also unprecedented sulfoxidations of aromatic *and* aliphatic sulfides with hydrogen peroxide (Scheme 8.A) [43]. The somewhat stronger *i*IDP catalysts have proven to be general in various Prins cyclizations [44], once again including those involving purely aliphatic substrates (Scheme 8.B). The yet again stronger acidic IDPi catalysts can handle cyclic, aliphatic oxocarbenium ions [45], which previously had been out of reach for any type of chiral catalyst (Scheme 8.C).

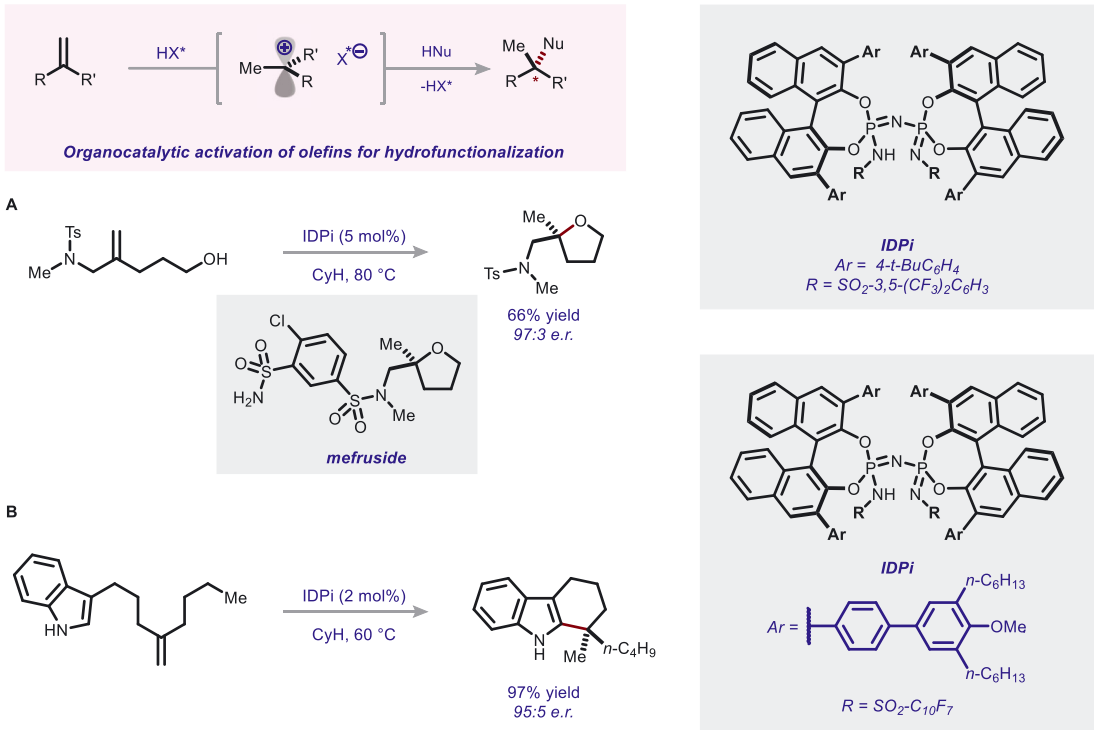
The latter reactivity is enabled through a special type of Lewis acid catalysis. Accordingly, IDPi catalysts, upon treatment with silylated compounds can engage in deprotosilylations. The resulting silylated IDPi catalysts are extremely reactive, possibly among the most reactive chiral, enantiopure Lewis acid catalysts



Scheme 8: Confined IDP, *i*IDP, and IDPi catalysts are privileged for handling unbiased and unreactive substrates.



Scheme 9: A highly enantioselective Nazarov cyclization of unactivated substrates is enabled by an induced fit mechanism.



Scheme 10: The general potential of IDPi-catalyzed hydrofunctionalization reactions of olefins and two recently realized examples.

made to date. This type of silylium-based asymmetric counteranion-directed catalysis (Si-ACDC) has proven to enable several unprecedented reactions, including Diels–Alder reactions, combining moderately reactive dienes with moderately reactive dieneophiles (Scheme 8.D) [46, 47], challenging Michael additions [48], and previously "impossible" Mukaiyama aldolizations [21, 22].

As probably the most acidic chiral catalysts available, IDPi catalysts enable unique and highly challenging Brønsted acid-catalyzed transformations. For example, an IDPi catalyst has been developed that, because of its unique confined active site, catalyzes an unprecedented Nazarov cyclization of simple aliphatic substrates by utilizing an "induced fit" mechanism [49]. The catalyst enforces the highly reactive, though thermodynamically highly disfavored, *s-trans/s-trans* conformation of the dienone substrate (Scheme 9).

Finally yet importantly, the high acidity of IDPi's enables an approach toward what had been considered one of the holy grails of organocatalysis: the activation, *via* protonation, of olefins. This activation mode

generates carbocations that among other things can engage in multiple reactions with nucleophiles. Such hydrofunctionalization reactions are uniquely relevant to chemical synthesis and catalysis because of the prevalence of olefins. So far, this concept found fruition in highly enantioselective intramolecular hydroetherification and hydroarylation reactions (Scheme 10) [50, 51]. But the sky may be the limit for this unique activation mode; many common and inexpensive materials can be considered as nucleophiles in such transformations, generating highly valuable enantioenriched compounds from abundant olefins.

Concluding remarks

In this personal view on the development of organocatalysis during the last two decades, we hope to have conveyed some of the excitement we currently experience, when we realize how drastic and perhaps surprising this field has advanced. From the proof of principle studies of the early days, to more recently designed systems that help in addressing some of the most challenging unsolved problems in current chemical synthesis and catalysis, organocatalysis has come a long way. Asymmetric organocatalysis is ripe to become a broadly applied technology. This transition may take some time but we would be very surprised to find a future in which organocatalysis would not play a major role in large-scale processes in fine chemical, pharmaceutical, and chemical industries.

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