寄稿論文

IDPi Catalysis: Revolutionizing Asymmetric Synthesis

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Introduction

During the last decade, IDPi (iminodiphosphorimidate) catalysis has become almost universal and transformed the landscape of asymmetric organocatalysis into unprecedented ways. This article informs about key guidelines for the effective implementation of the IDPi platform in addressing complex chemical challenges. In contrast to other asymmetric organocatalysts, IDPi stands out with three key features:

1. Modularity

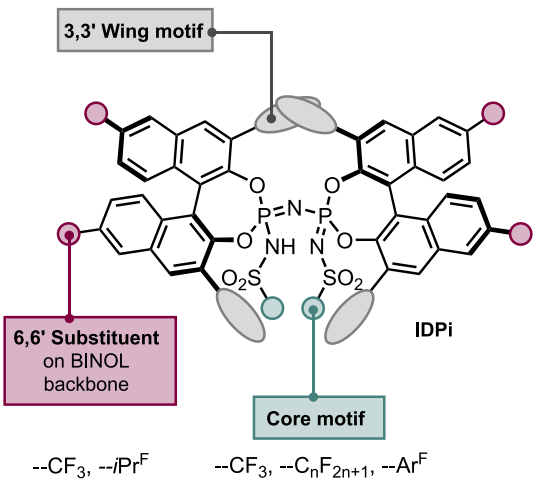


Figure 1: General design elements of IDPi.

Three positions of the IDPi moiety can be varied: The core, the wing, and the 6,6'-position of the BINOL backbone (**Figure 1**). This brings in high modularity and therefore flexibility in catalyst design, compared to other organocatalytic systems, such as chiral phosphoric acids. It enables large arrays of catalysts to be synthesized and screened, as the core, wing, and backbone can be varied independently. This high diversity fosters the design and serendipitous discovery of "impossible reactions". Further, it encourages a catalyst-focused design strategy over a substrate-engineering perspective, making "real-world" applications possible.

2. Confinement

The dimeric nature of IDPis shapes an enzyme-like pocket of the imidodiphosphorimidate core – a design element missing in most other small molecule catalysts. Core and wing tailor the pocket on an atomic scale and allow precise control over substrate-catalyst interactions. IDPis preorganize and confine substrates, thus allowing the differentiation of the smallest possible chemical entities (e.g., methyl vs. ethyl).[1]

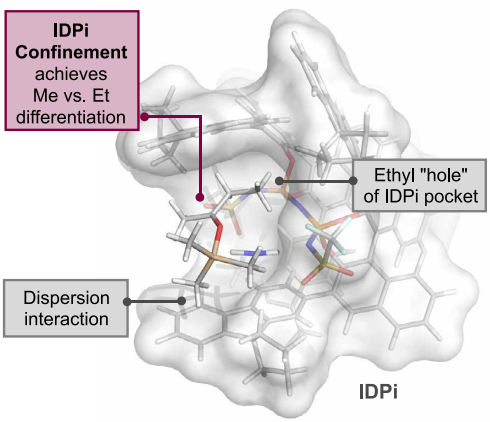


Figure 2: Confinement of IDPis in the cyanosilylation of ethylmethylketone.[1]

Recommendation

Comparing the reactivity of IDPi with that of the achiral, unconfined parent, bistriflimide $HNTf_2$, shows the noticeable effect of IDPi confinement. Whereas $HNTf_2$ often leads to decomposition, IDPis excels in chemoselectivity.

Besides spatial confinement (e.g., sterics of wing and core), dispersion plays a pivotal role in achieving high levels of stereoselectivity.[2] Further, confinement allows substrate- and product-specific binding, inhibiting, for example, decomposition.[3] Admittedly, an entirely rational design strategy has yet to be achieved. As more and more results become available, machine learning will accelerate screening efforts.[4]

3. Acidity

The Yagupolskii principle states that an acidifying effect is achieved upon replacement of O atoms by NTf groups.[5] IDPi's are Yagupolskii-extended IDPs, which possess confinement with high acidities.[6] Through that, the pKA value of IDP ~11 (in MeCN) can be lowered to ~2 for IDPi's (in MeCN, **Figure 3**). High acidity is a prerequisite for accessing more and more nonbasic substrates, such as olefins[7] or cyclopropanes.[8]

Design elements that modulate acidity are the core and wing, albeit they also influence the *Confinement*. In contrast, employing an electron-withdrawing substituent on the 6,6'-BINOL backbone leads to enhanced acidity without changing the IDPi microenvironment.

Recommendation

In cases where high stereoselectivity is achieved, but reactivity requires still enhancement, the incorporation of the 6,6′-substituted BINOL backbone is recommended.

In general, a $-CF_3$ group is more acidifying than, for example, a $-C_6F_5$ group. Importantly, heteroaryl wings, such as benzofurans, have a highly acidifying effect too.[9]

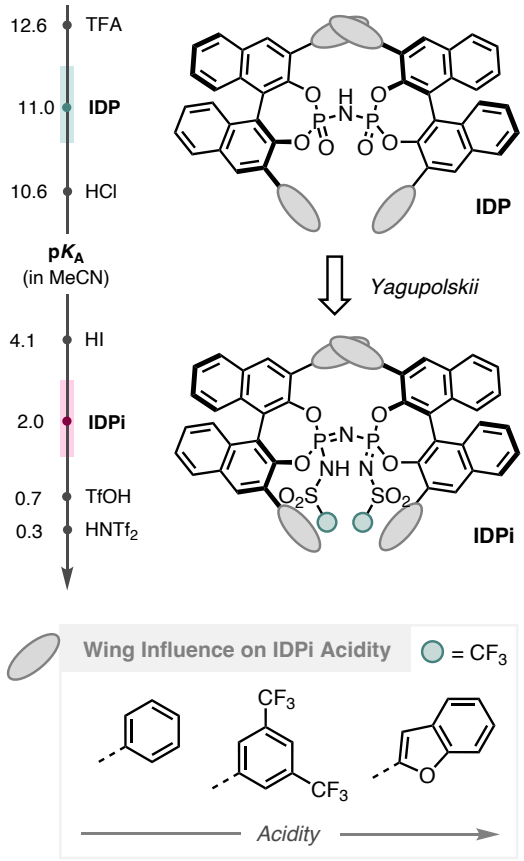


Figure 3: Structure-activity relationship on the acidity of IDPis.

Reactivity Modes of IDPi

So far, three IDPi reactivity modes have been realized: Brønsted-acid catalysis, Lewis-acid silylium-catalysis, and photoredox-catalysis (**Figure 4**).

In Brønsted acid-catalysis, the enantiopure IDPi catalyst activates the substrate via protonation to form an ion pair, facilitated through hydrogen bonding and dispersion interaction. This protonation leads to an attack by an additional reagent or triggers an intramolecular reaction guided by the chiral confinement. Finally, the product complex collapses to regenerate the IDPi (**Figure 4A**).

Recommendation

If the substrate contains a Lewis-affinic site, we recommend practitioners to perform both Brønsted acid and Lewis-acid conditions in initial screening attempts.

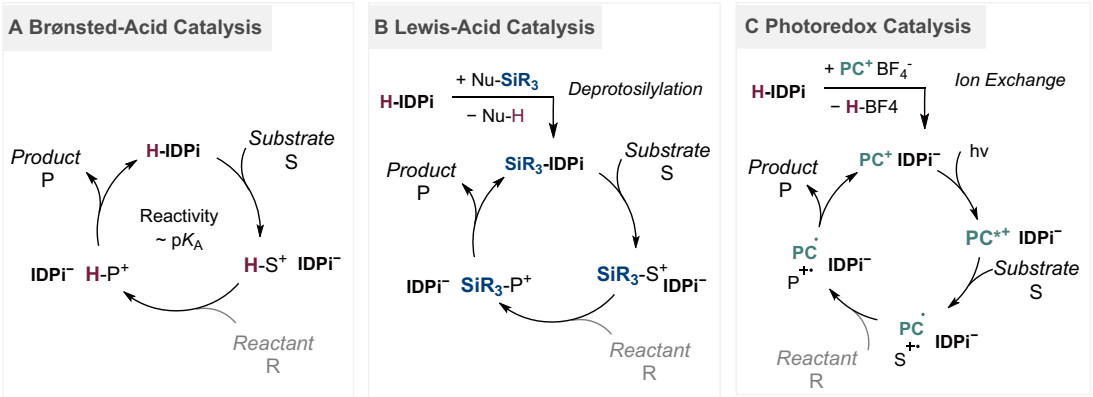


Figure 4: Three catalytic modes of IDPis.

If a suitable silyl source is used in conjunction with an IDPi, deprotosilylation of the catalyst generates a silylium Lewis acid *in situ*. The subsequent steps mirror those observed in Brønsted acid catalysis. Still, silicon's high oxophilicity offers novel activation modes and can disable unproductive reaction pathways (e.g., polymerization), extending the substrate scope where Brønsted acid-catalysis is unsuccessful (**Figure 4B**).

A third concept is photoredox catalysis. Instead of an achiral photoredox catalyst salt counterion, like BF_4^-, an IDPi anion is employed. This chiral counteranion accompanies the photoredox cycle and induces stereoselectivity in the enantiodetermining step, e.g., when a reagent attacks a radical cationic substrate $S^{+\cdot}$ (**Figure 4C**). All three concepts fall into the realm of Asymmetric Counteranion Directed Catalysis (ACDC).[10] As it is a universal concept, applications in other domains of catalysis such as transition metal catalysis are on the horizon.

IDPi Synthesis

Among others,[11] IDPis are primarily accessed through two distinct methods (**Figures 5** and **6**). Typically, IDPis are synthesized following an *in situ* dimerization strategy. In this particular method, BINOLs are treated with the corresponding *N*-sulfonyl-phosphorimidoyl trichloride R-I and subsequently with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) as

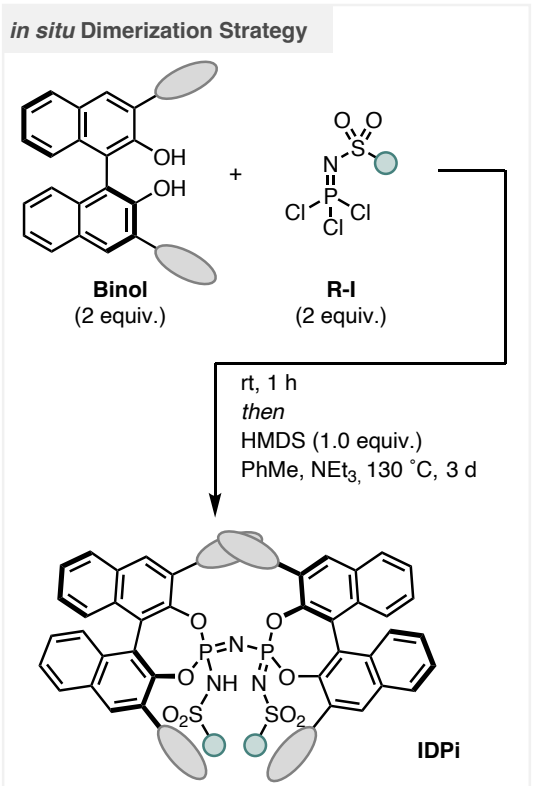


Figure 5: Synthesis of IDPis via the *in situ* dimerization approach.

an ammonia surrogate to furnish the desired IDPi (**Figure 5**). The replacement of HMDS with ammonia may result in a variation of this method.

Even though a multitude of IDPis are accessed using the *in situ* dimerization strategy, a second method has been developed for the synthesis of highly confined IDPis using hexachlorobis-phosphazonium hexachlorophosphate (HCPP). The advantage of this approach is that it circumvents an inefficient dimerization of the two phosphoryl chloride moieties in the first method, which can occur due to steric repulsion. This is facilitated by the preinstalled P-N-P core (**Figure 6**).

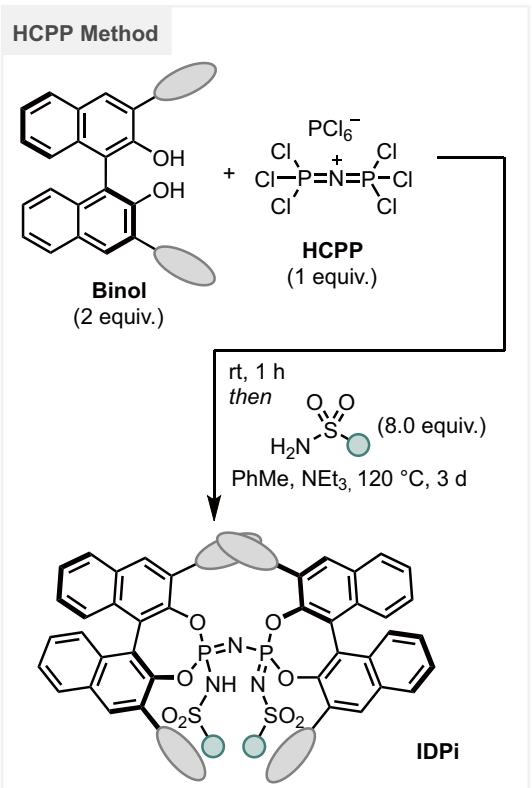


Figure 6: Synthesis of IDPi via the HCPP approach.

Recommendation

The yield of the IDPi synthesis can be improved by adding a catalytic amount of DMAP (4-(Dimethylamino)pyridine).

Reaction Classes of IDPis

The power of highly confined and super acidic IDPis as organocatalysts is demonstrated by their ability to activate a broad range of substances. In the ensuing sections, a complete compendium of IDPi-catalyzed reactions is presented, encompassing the activation of basic imine substrates, the activation of carbonyl compounds, and the conversion of barely basic olefins. Synthetic highlights are emphasized throughout.

Activation of Aldehydes and Ketones

The first reported IDPi-catalyzed reaction was the enantioselective organocatalytic Hosomi–Sakurai reaction, where allyltrimethylsilane was added to aldehydes to yield homoallylic alcohols after protodesilylation (**Figure 7**).[12] The high reactivity of IDPis, despite low catalyst loading, combined with the excellent enantioselectivity in this reaction and the possibility of converting aliphatic, unbiased substrates, forebodes the power of IDPis as valuable organocatalysts. The real power of IDPis was then demonstrated in the following decade on several challenging reactions, some of which were considered “impossible”

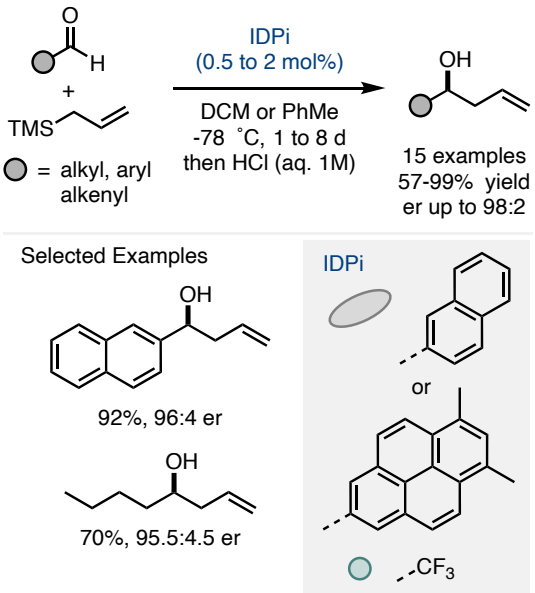


Figure 7: Hosomi-Sakurai reaction.

Staying in the Lewis-acid reactivity mode of IDPis, the single aldolization reaction of acetaldehyde silyl enol ethers was achieved in overall high yields and selectivities (**Figure 8**).

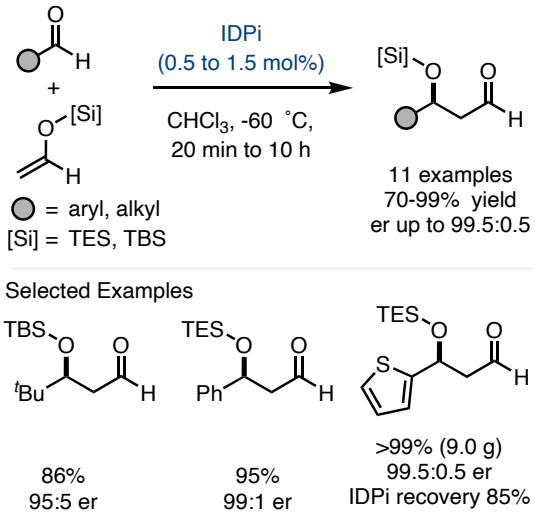


Figure 8: Mukaiyama-aldol reaction.

Remarkably, the confined environment of IDPis prevents oligomerization of the products, an issue often observed when the product contains the same functional group as the starting material. This Mukaiyama-aldol reaction of aldehydes with silyl enol ethers exemplifies the enzyme-like confined environment of IDPis.[13]

Expanding the scope of organocatalytic Mukaiyama-aldol reactions, with the confined IDPi catalysts, it was also possible to control the *syn*- or *anti*-Mukaiyama-aldol reaction of propionaldehyde enolsilanes (**Figure 9**).[14]

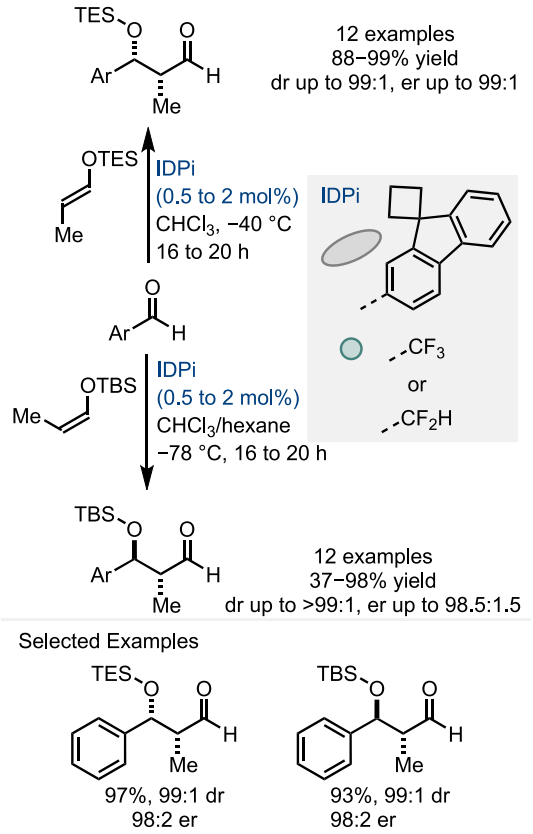


Figure 9: *syn*- and *anti*-selective Mukaiyama-aldol reaction.

Highlight: ppm-catalysis

In general, the catalyst loading of IDPi-catalyzed reactions is low. Exceeding this, the asymmetric Mukaiyama-aldol reaction of ketones with silyl ketene acetal demonstrates the catalytic power of IDPis. In this reaction, sub-ppm catalyst loadings, ranging from 500 ppm to 0.9 ppm, were applied, and a turnover number (TON) of 911,000 could be achieved (**Figure 10**).[56]

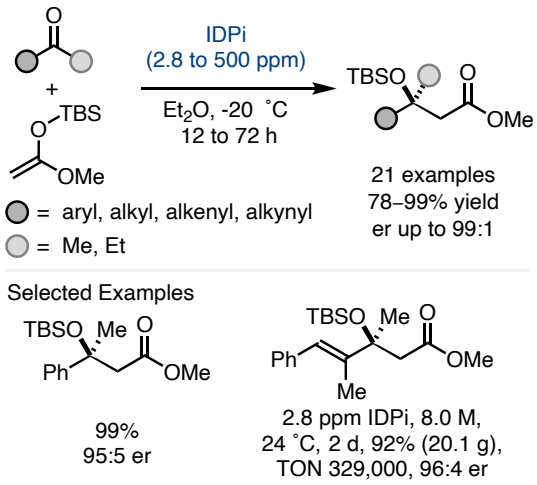


Figure 10: ppm-catalysis of IDPis.

Another 1,2-addition of a nucleophile onto the carbonyl functional group is the formation of cyanohydrines from ketones with TMSCN. Notably, the differentiation of a methyl and ethyl group can be achieved using IDPi catalysts (**Figure 11**).[1]

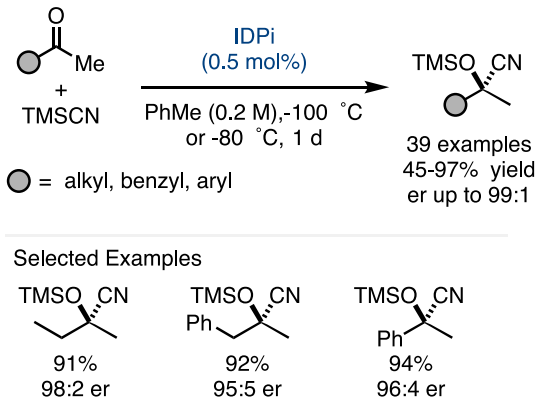


Figure 11: Cyanosilylation of small ketones.

After the IDPi-catalyzed activation of the carbonyl group, an enantioselective Friedel-Crafts and semipinacol rearrangement cascade reaction can be initiated from indole starting materials (**Figure 13**).[11]

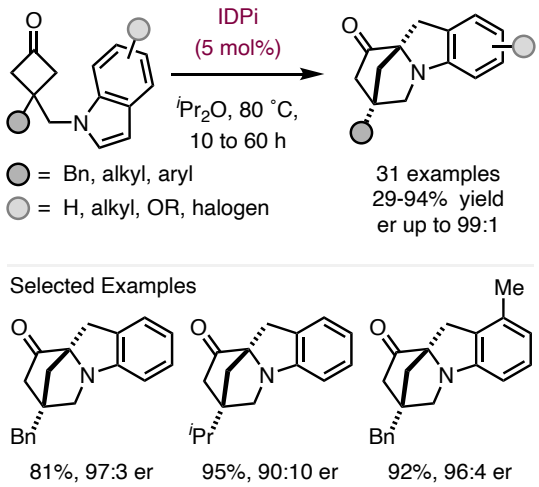


Figure 13: Friedel-Crafts-semi-pinacol cascade.

Pericyclic reactions are potent, atom-economical chemical reactions that can also be catalyzed by Brønsted or Lewis acids. The IDPi-catalyzed hetero-Diels-Alder [4+2] cycloaddition of electronically unbiased dienes with various aldehydes was achieved with overall high yields and excellent selectivities (**Figure 14**).[15] Typical Diels-Alder cycloadditions of dienes with α,β-unsaturated carbonyl compounds as dienophiles are covered in the next section.

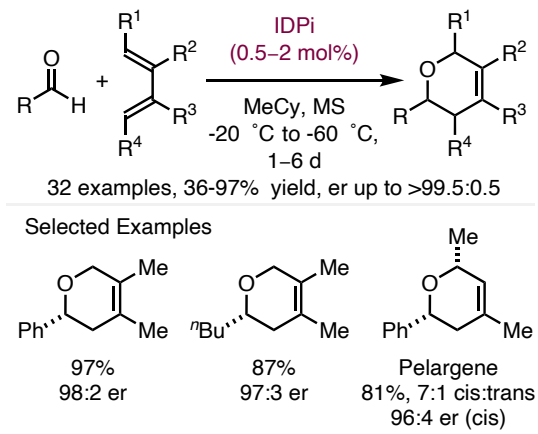


Figure 14: IEDDA reactions between dienes and aldehydes.

Electrocyclizations, another category of pericyclic reactions, such as the Nazarov cyclization of alkyl-substituted divinyl ketones, yielding cyclopentenones, was also realized in an asymmetric catalytic fashion using IDPis (**Figure 15**).[16]

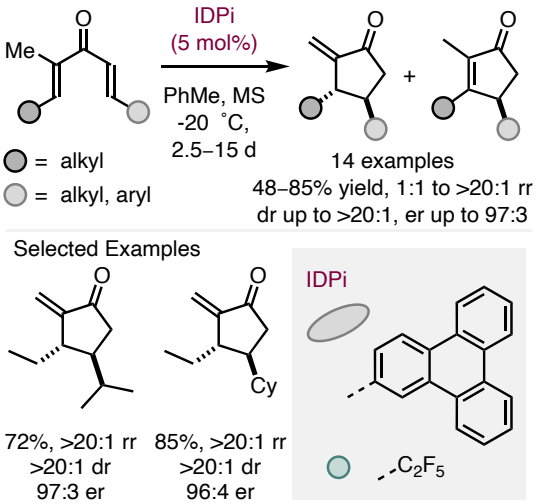


Figure 15: Nazarov cyclization.

Highlight: NCOF-IDPis

[6+4] Cycloadditions offer access to synthetically valuable 10-membered ring systems, but controlling their reactivity and selectivity—especially with simple hydrocarbon substrates—has remained a significant challenge. Recent work reveals that highly acidic IDPi catalysts, while inactive under homogeneous conditions, can self-assemble into an insoluble, double-helix-shaped noncovalent organic framework. This supramolecular structure uniquely enables the stereoselective [6+4] cycloadditions between simple dienes and tropone, opening a new pathway for this elusive transformation (**Figure 12**).[57]

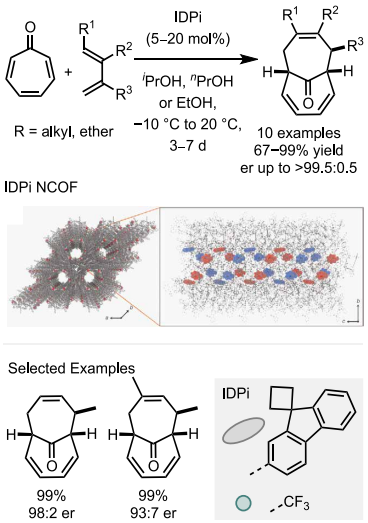


Figure 12: NCOF catalysis of IDPis.

IDPis catalyze the Pictet–Spengler reaction of *N*-carbamoyl-β-arylethylamines with diverse aldehydes. The obtained tetrahydroisoquinoline was used to access naturally occurring alkaloids (**Figure 16**).[17]

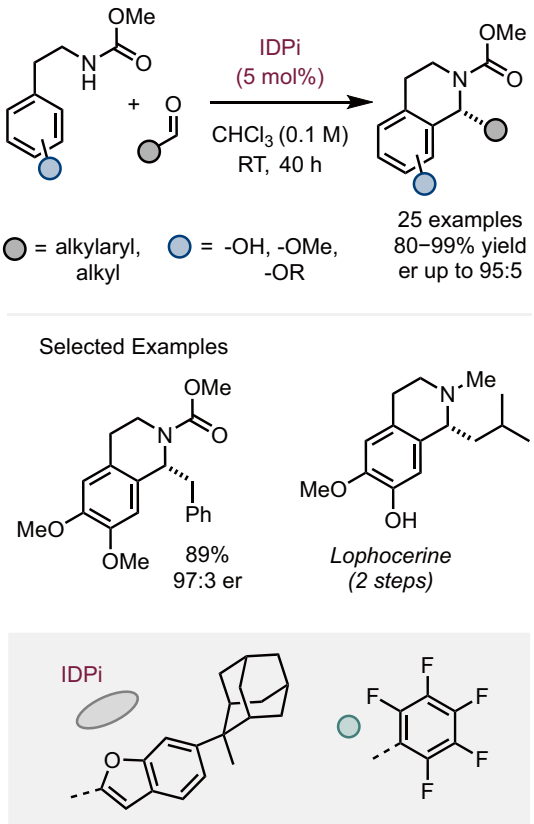


Figure 16: Pictet-Spengler reaction.

Enol silanes are highly useful reagents in fundamental C–C bond-forming reactions, such as the Mukaiyama-aldol, Michael, and Mannich reactions. The use of chiral enol silanes in those reactions has enabled access to enantiopure natural products and biologically active molecules. However, the production of enantiopure enol silanes generally requires the use of stoichiometric amounts of chiral precursors or reagents. Using IDPis, the access to enantiopure enol silanes was achieved in high yields and enantioselectivities in an asymmetric deprotosilylation of ketones, a protodesilylative kinetic resolution of racemic enol silanes, or the kinetic resolution of racemic 2-substituted cyclic ketones (**Figure 17**).[18,19]

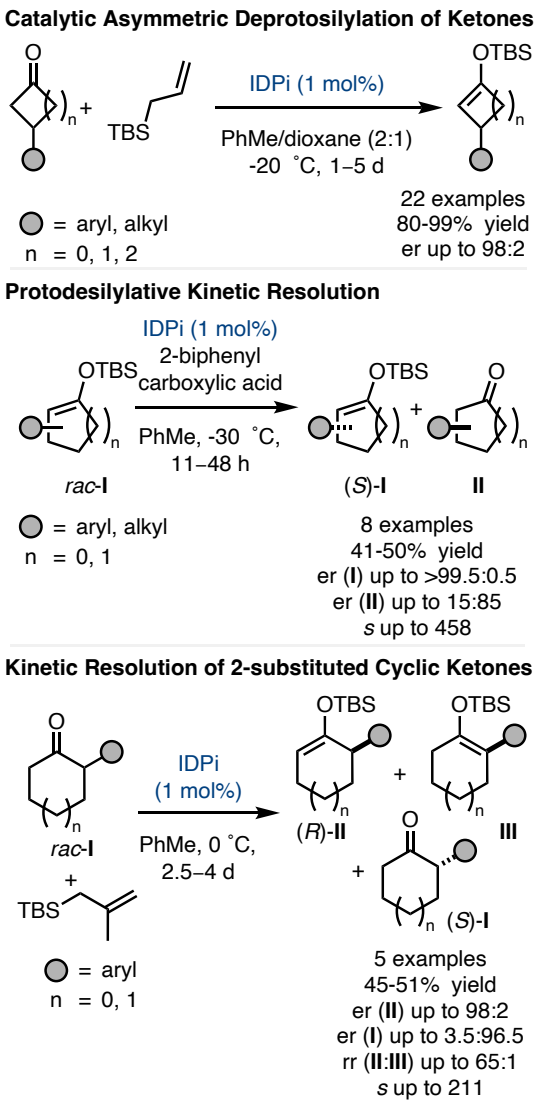


Figure 17: Three syntheses of enantiopure enolsilanes.

Additionally, the creation of chiral compounds through desymmetrization could also be expanded from the asymmetric deprotosilylation of symmetrical ketones to the atroposelective silylation of 1,1'-biaryl-2,6-diols (**Figure 18**).[20]

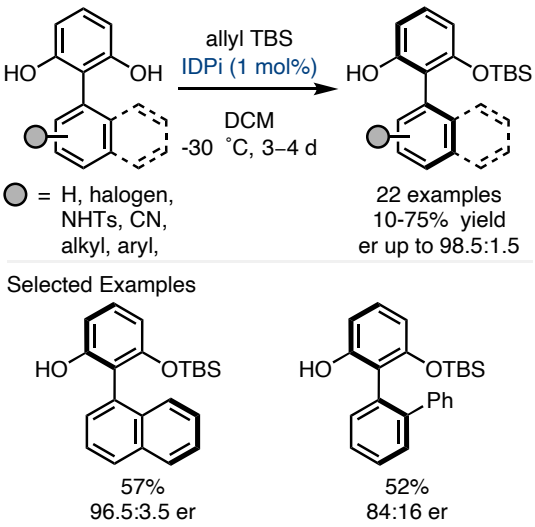


Figure 18: Atroposelective silylation.

Activation of Unsaturated Carbonyl Compounds

Besides the activation of carbonyl substrates, IDPis also enhance the reactivity of the olefin group of unsaturated carbonyl compounds for conjugate addition reactions and Diels–Alder reactions. Generally, multiple chiral centers could be formed through both Brønsted acid and Lewis acid catalysis, and IDPi catalysts show excellent stereoselectivity for various transformations, including enantioselectivity, diastereoselectivity, regioselectivity, etc.

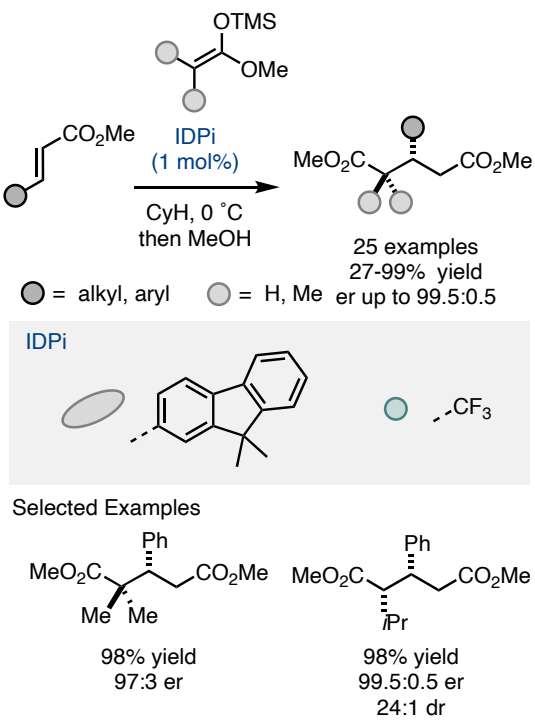


Figure 19: Addition of SKAs to α,β-unsaturated esters.

α,β-Unsaturated esters are readily available but challenging substrates to activate in asymmetric catalysis, considering their poor electrophilicity. The highly acidic, well-defined confined IDPis could activate the α,β-unsaturated esters and catalyze the asymmetric Mukaiyama–Michael reaction of silyl ketene acetals (SKA) with α,β-unsaturated esters. The reaction showed high yield, enantioselectivity, and diastereoselectivity (**Figure 19**).[21] Additionally, IDPi catalysts have reasonable control over 1,4-addition rather than 1,2-addition.

The IDPi activates α,β-unsaturated esters, which can react not only with strong SKA nucleophiles for conjugate addition reactions, but also with weak nucleophiles, like dienes, for Diels–Alder reactions. Based on extremely reactive silylium IDPi Lewis acids, a large variety of α,β-unsaturated esters and different dienes could be applied in the catalytic Diels–Alder reaction (**Figure 20**).[22]

The reactions are scalable and highly diastereo- and enantioselective, and high-level computational calculations revealed the controlling effect of the catalyst via steric and dispersion interactions.[23]

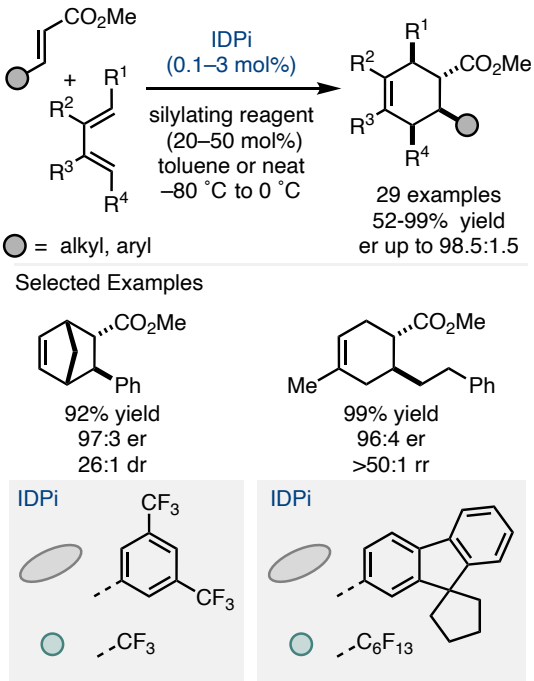


Figure 20: Diels-Alder reactions with α,β-unsaturated esters as dienophiles.

IDPis can also activate enals, and due to the high catalytic activity of IDPi catalysts, a multi-substrate screening approach becomes possible. IDPi was identified as a broadly applicable Diels–Alder catalyst for α-substituted, β-substituted, and α,β-disubstituted enals with excellent selectivities (**Figure 21**).[24]

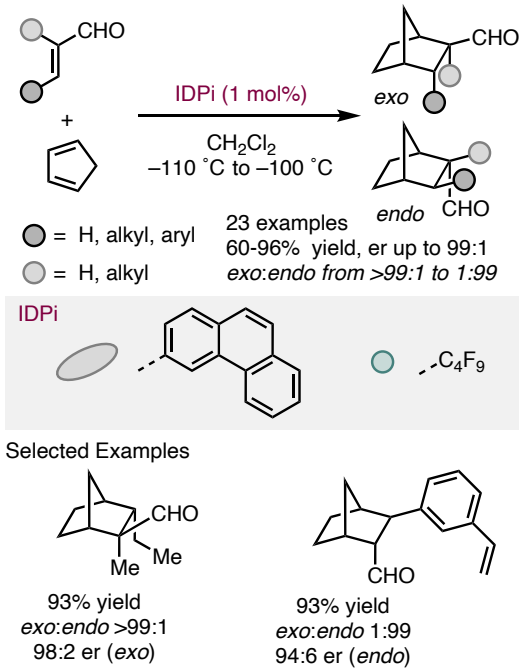


Figure 21: Diels-Alder reactions with enals.

A great example of control over multiple chiral centers is the Diels–Alder reaction of cross-conjugated cyclohexadienones with cyclopentadiene. Five stereogenic centers are effectively controlled by an IDPi catalyst, providing tricyclic products in excellent stereoselectivity (**Figure 22**).[25]

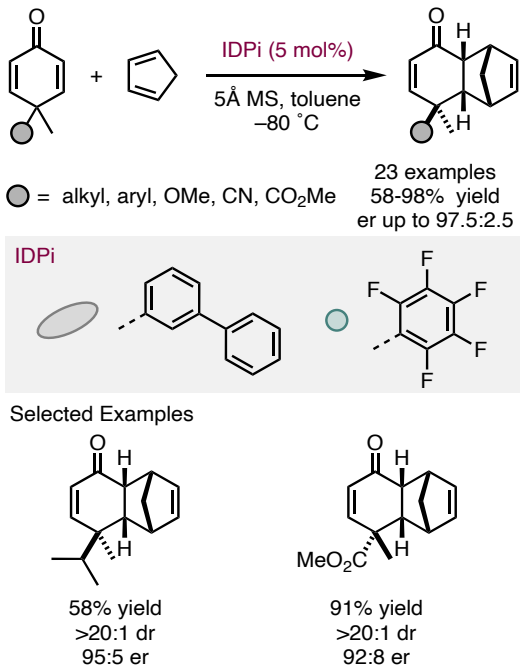


Figure 22: Diels-Alder reactions with cyclohexadienones.

The catalytic enantioselective spirocyclizing Diels–Alder reactions of exo-enones with dienes are attractive due to their unique structural characteristics and biological activities, but are unprecedented. Excitingly, IDPi can catalyze this transformation to give spirocyclanes, which feature highly congested, quaternary stereogenic spirocenters and are used in concise total and formal syntheses of several sesquiterpenes, including α-chamigrene, β-chamigrene, laurencenone C, colletoic acid, and omphalic acid (**Figure 23**).[26] The stereo- and regioselectivities of the spirocyclizing cycloaddition are effectively controlled by strongly acidic and confined IDPi catalysts.

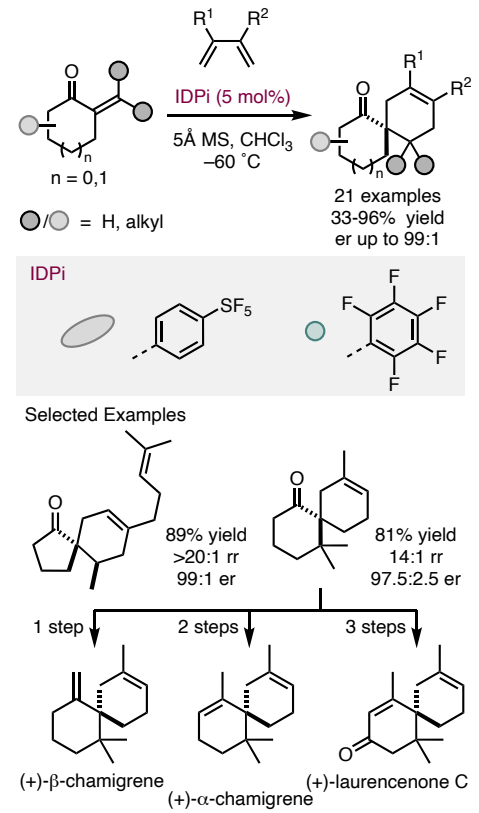


Figure 23: Diels-Alder with *exo*-enones towards a panoply of natural products.

Activation of Carbon–Carbon Double Bonds

Besides the activation of imine and carbonyl substrates, IDPis furthermore enable the activation of less basic olefins. Traditionally, this activation relies on transition metal catalysts; however, using the Brønsted-Acid reactivity mode or the Photocatalysis mode of IDPis, transformations such as hydrofunctionalizations or [2+2] and [2+1] cycloaddition reactions with simple olefins are now organocatalytically possible.

The asymmetric intramolecular hydrolalkoxylation of 1,1-disubstituted olefins represents the first organocatalytic activation of unbiased olefins. To activate these substrates, high acidity is required, and combined with the well-defined confined, enzyme-like microenvironment of IDPis, the products are obtained with excellent selectivity and high yields (**Figure 24**).[7]

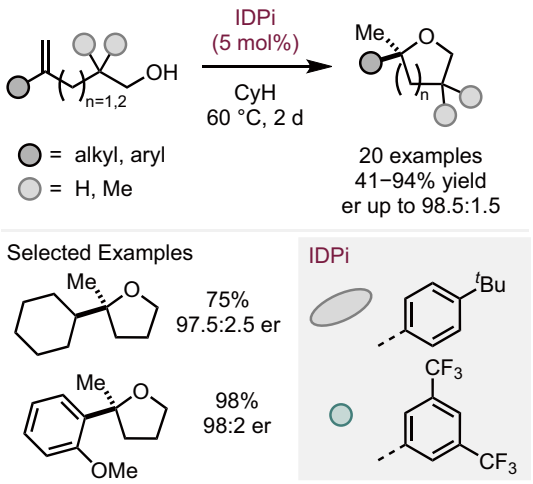


Figure 24: Intramolecular hydroalcoxylation.

Highlight

One highlight of IDPi catalysis is the polyene cyclization of the acyclic (*3E*,*7E*)-homofarnesol to (−)-Ambrox, a valuable, rare, naturally occurring ambergris odorant. In this complex cyclization reaction, the IDPi catalyst takes control over the formation of multiple carbon-carbon bonds and the construction of four stereogenic centers in a single reaction step. This transformation demonstrates the power of IDPis as catalysts and their enzyme-like nature, achieving excellent selectivities in challenging reactions. This reaction was successfully scaled up with recycling of the catalyst and the solvent.

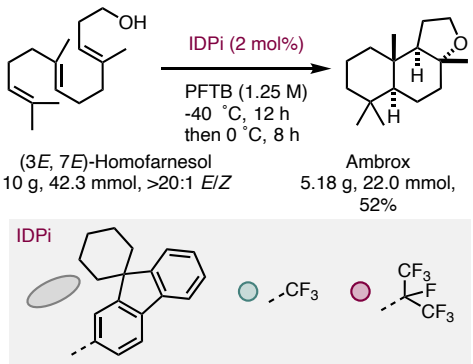


Figure 25: IDPi catalyzed cyclization of (*3E*,*7E*)-homofarnesol to (–)-Ambrox.

The previously described methodology is not only applicable for the hydroalkoxylations of 1,1-disubstituted olefins to generate tetrahydrofuranes, but also for the intramolecular hydrolactonization of similar substrates. With a simple change of the core of the IDPi catalyst, the desired γ- and δ-lactones are obtained with comparable high yields and enantioselectivities. In both methods, alkyl- and aryl-substituted olefins are well tolerated. Besides the formation of a five-membered heterocyclic system, the expansion to the formation of six-membered heterocycles was also achieved. Both structural motifs, 1,1-disubstituted tetrahydrofurans and γ,γ-disubstituted lactones, are common motifs of biologically active molecules, like Boivinianin A (**Figure 26**).[27] Mechanistically, in both described methods, the reaction proceeds via an asynchronous concerted mechanism, where alkene protonation precedes ring-closure.

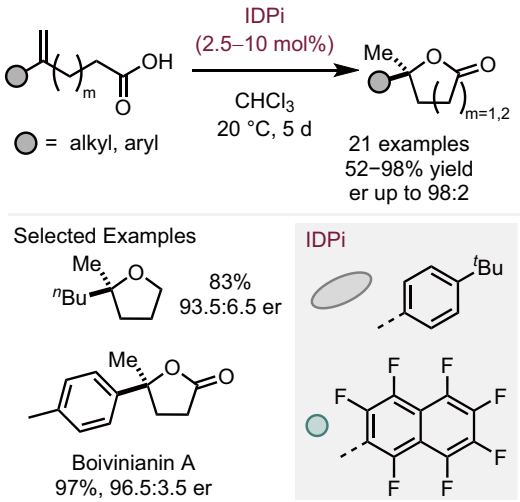


Figure 26: Intramolecular lactonization.

A few years later, the asymmetric intramolecular hydroamination of 1,1-disubstituted olefins with nosyl-protected amines could be realized to afford pyrrolidines in high yields and enantioselectivities (**Figure 27**).[28]

While the presented asymmetric intramolecular hydroalkoxylation, hydrolactonization, and hydroamination reactions form carbon-oxygen or carbon-nitrogen bonds, the following example of an asymmetric intramolecular hydroarylation demonstrates the formation of C-C bonds. In this asymmetric Friedel-Crafts arylation, the activated aliphatic 1,1-disubstituted olefin is attacked by the electron-rich indole, yielding a spirocyclic intermediate first, which aromatizes through an alkyl migration. High enantioselectivity and yield are obtained after a change of the IDPi-wing substituent, creating the necessary confined environment for this transformation (**Figure 28**). [29]

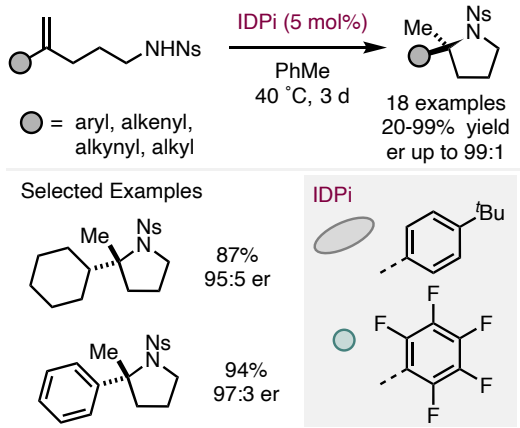


Figure 27: Intramolecular hydroamination.

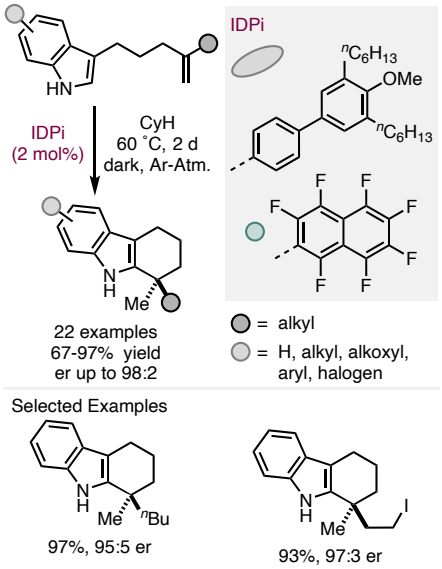


Figure 28: Friedel-Crafts arylation.

As mentioned in the "Reactivity Modes of IDPis" section, IDPi anions can also be used as chiral counterions to a cationic photocatalyst. This ACPC concept (asymmetric counteranion-directed photocatalysis) was first reported in an asymmetric photocatalytic [2+2] cycloaddition reaction (**Figure 29**).[30]

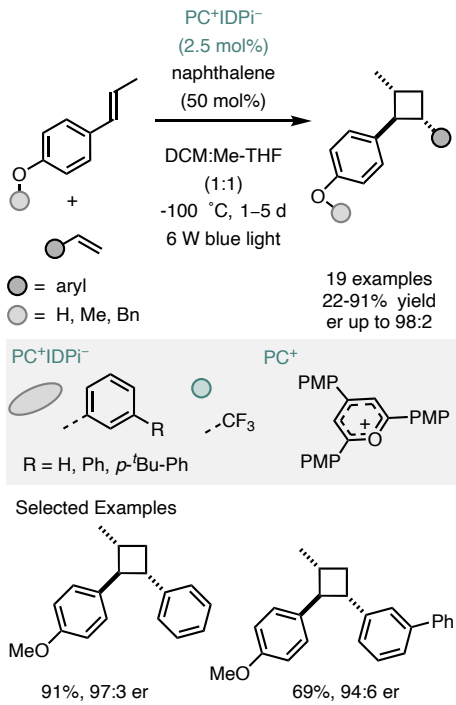


Figure 29: Photoredox-catalyzed [2+2]-cycloadition aided by Asymmetric Counteranion Photocatalysis (ACPC).

This ACPC concept has also been successfully applied to the asymmetric [2+1] cycloaddition of olefins and diazocompounds (**Figure 30**). In this example, polyolefins were successfully differentiated by IDPis, delivering excellent regioselectivities. In contrast, Rhodium-catalyzed carbene-addition resulted in complex regioisomeric mixtures. [31]

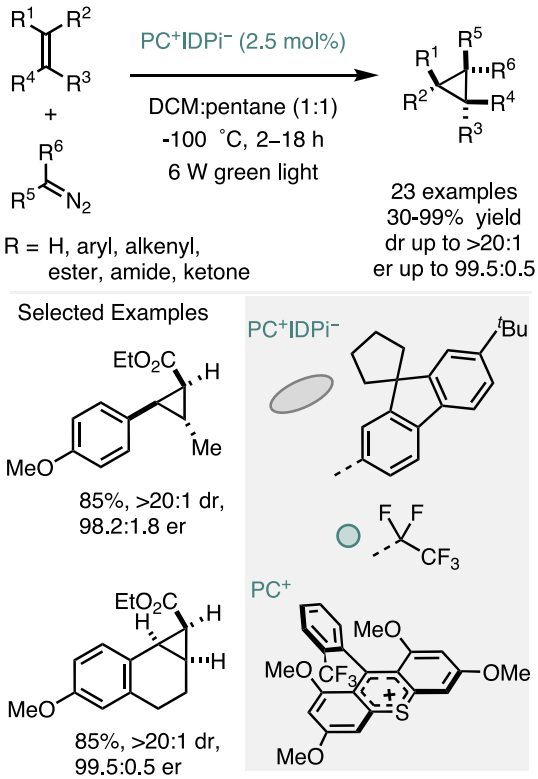


Figure 30: Photoredox-catalyzed [2+1]-cycloaddition.

Carbocations, Non-Classical Carbocations and Ring-Strain

Benzylic stereogenic centers are ubiquitous in natural products and pharmaceuticals. A potentially general, though challenging, approach toward their selective creation would be the asymmetric S_N1 reactions that proceed through highly reactive benzylic cations. A broadly applicable solution was found in identifying IDPi chiral counteranions that pair with secondary benzylic cations to engage in catalytic asymmetric C–C-, C–O- and C–N-bond forming reactions with excellent enantioselectivity (**Figure 31**).[32] The critical cationic intermediate can be accessed from different precursors via Lewis- or Brønsted acid catalysis. Key to this strategy is the use of only weakly basic, confined IDPi counteranions that are posited to prolong the lifetime of the carbocation, avoiding non-productive deprotonation pathways to the corresponding styrene.

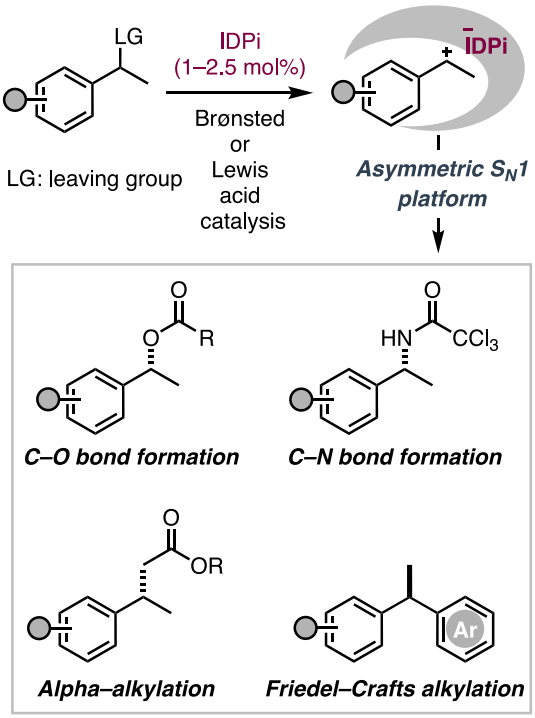


Figure 31: "Taming" the benzylic carbocation.

Asymmetric cycloadditions are prominently sought-after disconnection strategies and immensely valuable for the rapid construction of stereochemical complexity. Yet, to date, asymmetric [4+3] cycloadditions are underdeveloped. The strong and confined IDPi Lewis acids could enable a highly enantioselective, catalytic [4+3] cycloaddition of *gem*-dialkyl 2-indolyl alcohols and dienolsilanes, furnishing novel bicyclo[3.2.2]cyclohepta-[*b*]indoles with up to three stereogenic centers (**Figure 32**).[33] This transformation reveals IDPis could overcome major limitations of previously investigated systems and be valuable for the rapid and efficient asymmetric synthesis of several potentially biologically active natural products.

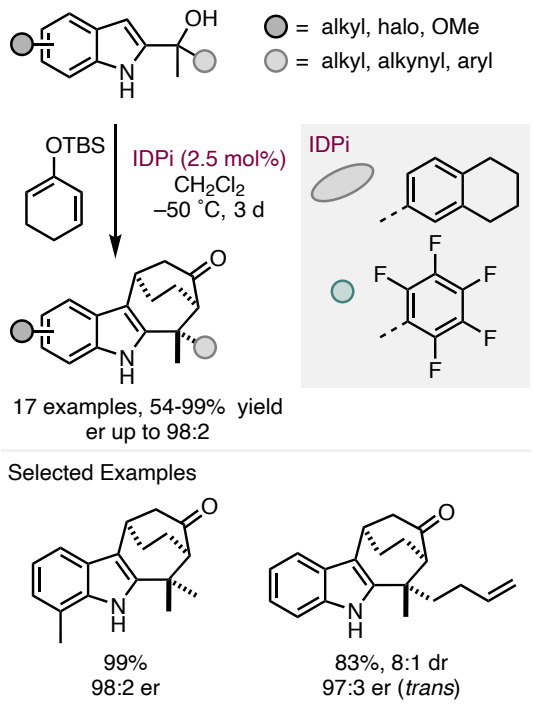


Figure 32: (3+2) cycloadditions.

Asymmetric allylic substitution reactions have become a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds. This field has long been dominated by transition-metal catalysis. Cheng, You and co-workers report that IDPi catalyzes intramolecular asymmetric allylic alkylation of indoles with allylic primary alcohols (**Figure 33**), broadening the scope of the asymmetric allylic substitution reaction.[34]

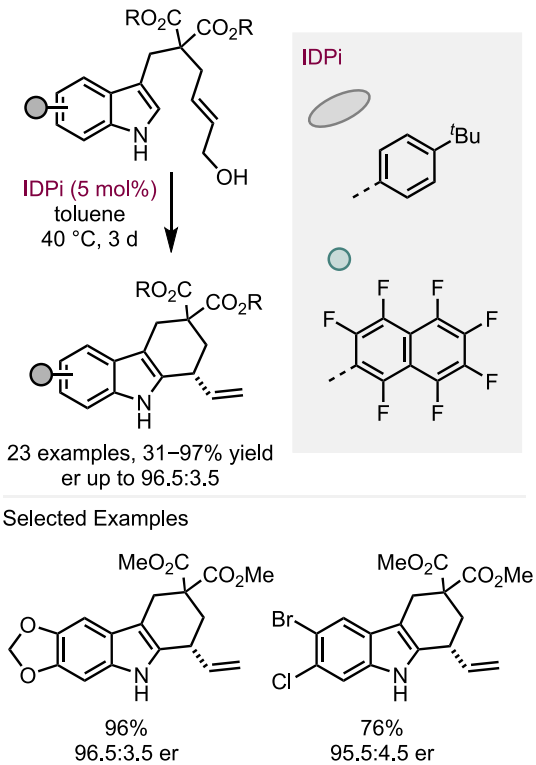


Figure 33: Asymmetric allylic alkylation.

Vinyl cations tend to react extremely quickly and indiscriminately with any other bond in the vicinity. Therefore, aryl and vinyl carbocations have not been applied in catalytic enantioselective reactions. Sigman, Houk, Nelson and co-workers report that IDPi catalyst can engage a vinyl cation just tightly enough to steer an ensuing highly enantioselective intramolecular vinyl carbon–hydrogen insertion reaction (**Figure 34**).[35] Active site confinement of IDPi catalyst not only enables effective enantiocontrol but also expands the scope of vinyl cation C–H insertion chemistry, which broadens the utility of this transition metal–free C(sp^3)–H functionalization platform.

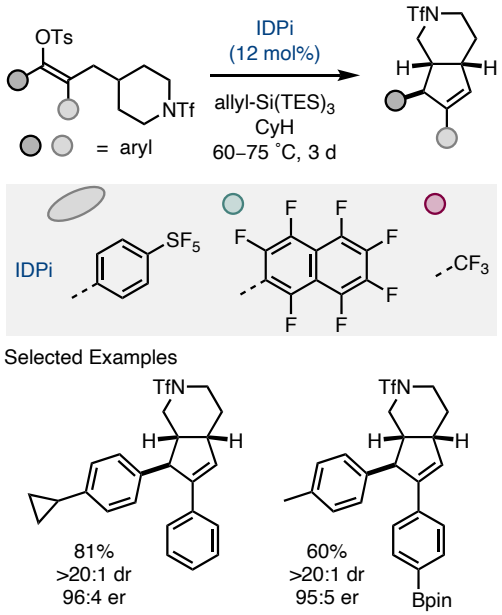


Figure 34: Vinylcarbocation activation.

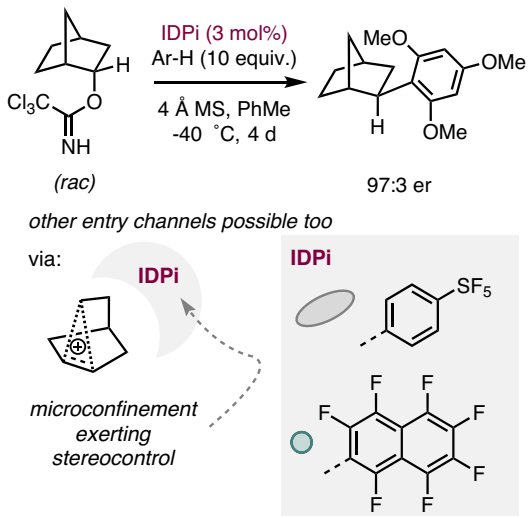
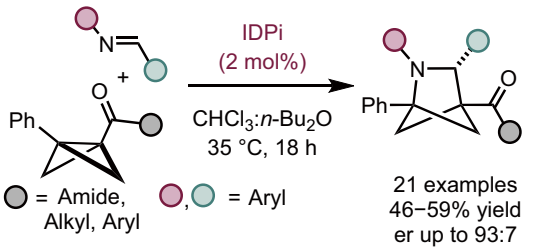


Figure 35: IDPi controls non-classical carbocations.

Since the seminal dispute about the non-classical nature of the 2-norbornyl cation, chemists became intrigued by taming such non-classical carbocations in organic synthesis.

IDPi showed how exquisite enantioselective control over the 2-norbornyl cation is possible through non-covalent stabilization of the non-classical cation. [36]

The reaction between imines and bicyclo[1.1.0] butanes (BCB) shows how IDPi can "tame" strain-release channels successfully towards enantioenriched azabicyclo[2.1.1]hexane without any directing groups installed on the BCB precursors, as Lewis-catalysis previously necessitates (**Figure 36**).[37]



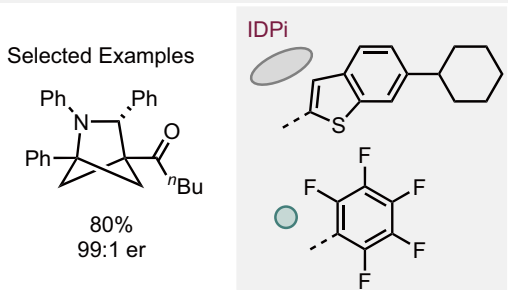


Figure 36: Addition of Imines to bicyclo[1.1.0]butanes (BCBs).

In a landmark paper, the activation of unbiased cyclopropanes was demonstrated utilizing IDPis. The high acidity and the microcontrol of IDPis made stereocontrol over those alkane-fragmentations possible (**Figure 37**).[8]

Another example of pure hydrocarbon activation was demonstrated in the catalytic asymmetric Wagner–Meerwein shifts of aliphatic hydrocarbons (**Figure 38**).[38]

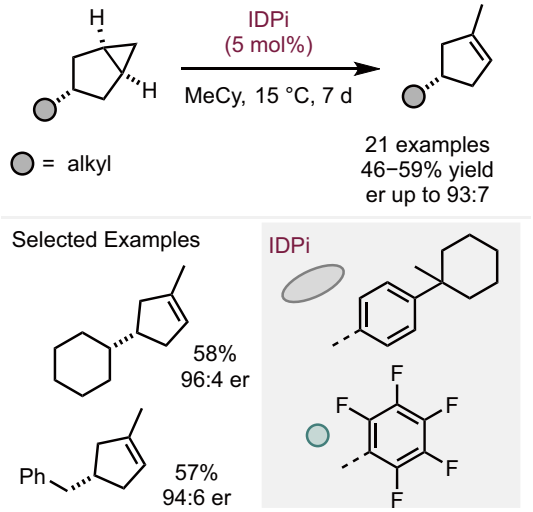


Figure 37: "Cracking" of cyclopropanes.

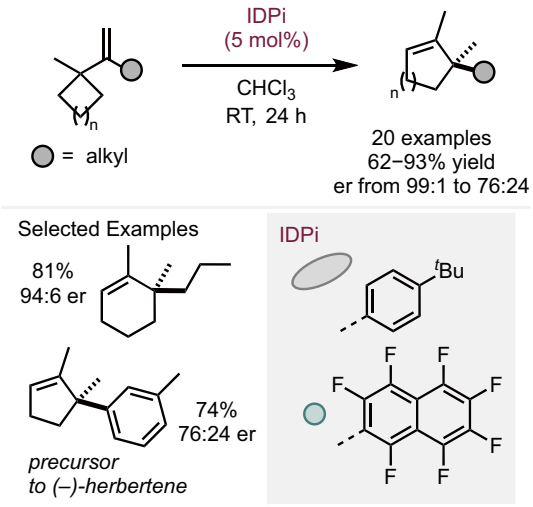


Figure 38: Enantioselective Wagner-Meerwein shift.

Heteroatom-stabilized Carbocations

Even though acid catalysis is often incompatible with substrates bearing basic nitrogen moieties, a suitable protecting group strategy usually enables the successful implementation of *N*-functionalities with the IDPi platform, as shown in the following examples.

Enantiopure and unmodified β^2-amino acids can be obtained through reaction of a panoply of bis-silyl ketene acetals with silylated aminomethyl ethers, after a hydrolytic workup. This reaction was achieved by employing IDPis under silyation conditions (**Figure 39**).[39]

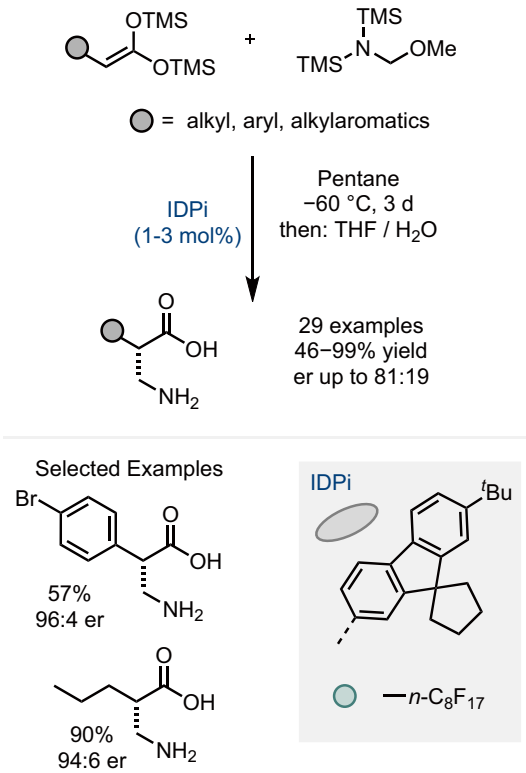


Figure 39: Synthesis of enantiopure β2-amino acids.

Similarly, aliphatic β^3-amino acid derivatives can be synthesized employing silyl nitronates. This report constitutes the first asymmetric example, in which silyl nitronates react in an electrophilic fashion at their carbon atom (being amphiphilic). Notably, a multi-substrate screening was used to rapidly identify suitable IDPi catalysts (**Figure 40**).[40]

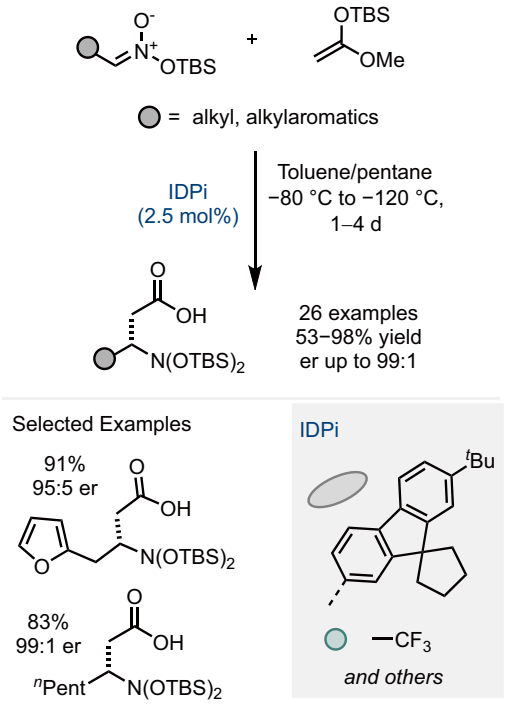


Figure 40: Synthesis of enantiopure aliphatic β3-amino acid.

Further, IDPis enable the *in situ* generation of *N*-Boc-formaldimine from *tert*-butyl (hydroxymethyl) carbamate, which participates in an enantioselective, inverse-electron demand hetero-Diels-Alder [4+2] cycloaddition reaction with terminal and 1,1-disubstituted olefins. With this asymmetric oxy-aminoalkoxylation, valuable 1,3-aminoalcohols can be obtained, as demonstrated in the synthesis of the antidepressant (*R*)-fluoxetine hydrochloride on a multigram scale (**Figure 41**).[41]

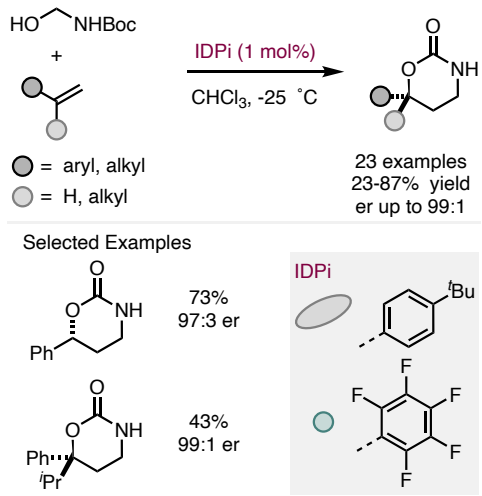


Figure 41: Asymmetric oxy-aminoalkoxylation of olefins.

The Friedel–Crafts reaction is a powerful method for the introduction of carbon substituents to arenes. However, the scope of the reaction is intrinsically limited by the arene's nucleophilicity, which has previously restrained the applicability of asymmetric variants to activated substrates. A strong and confined acid was demanded to enable the asymmetric catalytic Friedel–Crafts reaction of simple alkylbenzenes. IDPis were poised to overcome these previous fundamental limitations. IDPis can catalyze the asymmetric Friedel–Crafts reaction of unactivated, purely hydrocarbon arenes, alkoxybenzenes, and heteroarenes with *N*,*O*-acetals to give enantioenriched arylglycine esters with high regio- and stereoselectivity (**Figure 42**).[41]

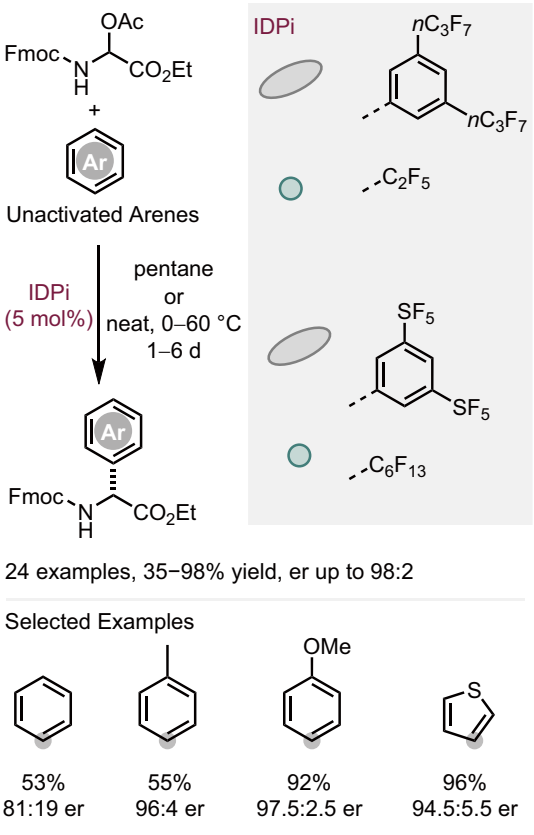


Figure 42: Asymmetric Friedel–Crafts reactions of unactivated arenes.

IDPi catalysis can also be applied in enantioselective synthesis of 1,4-(hetero) dicarbonyl compounds through α-carbonyl umpolung. Schneider and co-workers report the highly enantio- and diastereoselective addition of silyl ketene acetals toward electrophilic 1-azaallyl cations to furnish chiral 4-hydrazonoesters, which are masked 1,4-dicarbonyl compounds (**Figure 43**).[42] α-Acetoxy hydrazone was employed and ionized with a strongly Lewis acidic, chiral silylium IDPi catalyst, forming the key ion pair intermediates for the high enantio- and diastereoselectivity, characterized with NMR and mass spectroscopy, revealing the excellent stereochemical control of IDPi over the stereogenic centers.

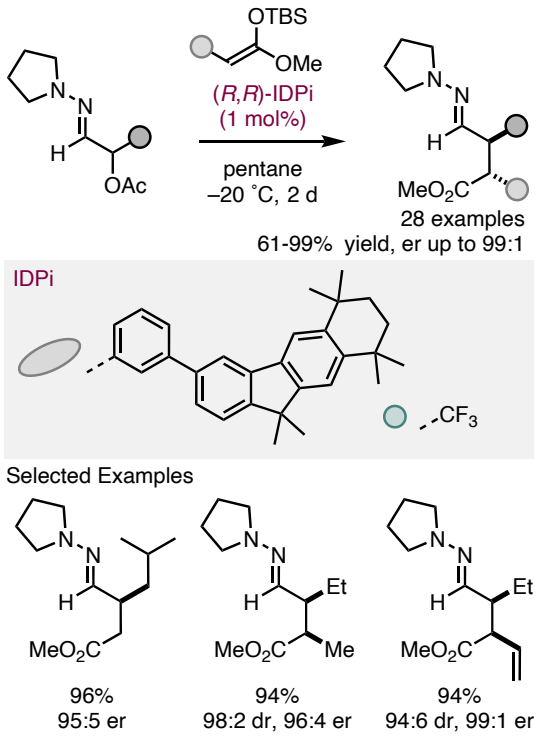


Figure 43: Asymmetric assembly of 1,4-(hetero) dicarbonyl compounds by IDPis.

Cyclic, aliphatic hemiaminal ethers can be substituted with enol silanes guided by IDPi catalysis. It allows the synthesis of 2-substituted pyrrolidines, piperidines, and azepanes, motifs prevalent in numerous alkaloids (**Figure 44**).[43]

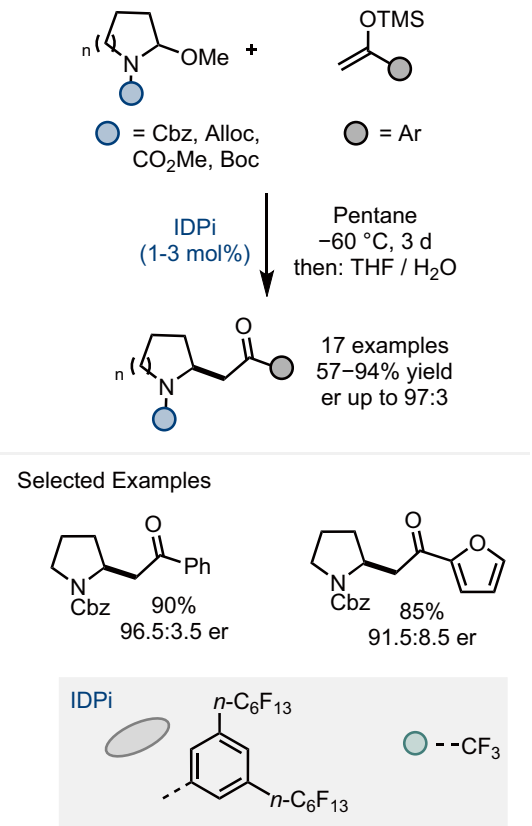


Figure 44: Synthesis of 2-substituted chiral pyrrolidines, piperidines, and azepanes.

Similar to the previous example, where an iminium ion is generated, the generation of analogous oxocarbenium ions is also possible from the respective lactol starting materials (**Figure 45**).[44] Additionally, these oxocarbenium ions could also be generated from dicarbonyl compounds in an intramolecular fashion (**Figure 46**).[45]

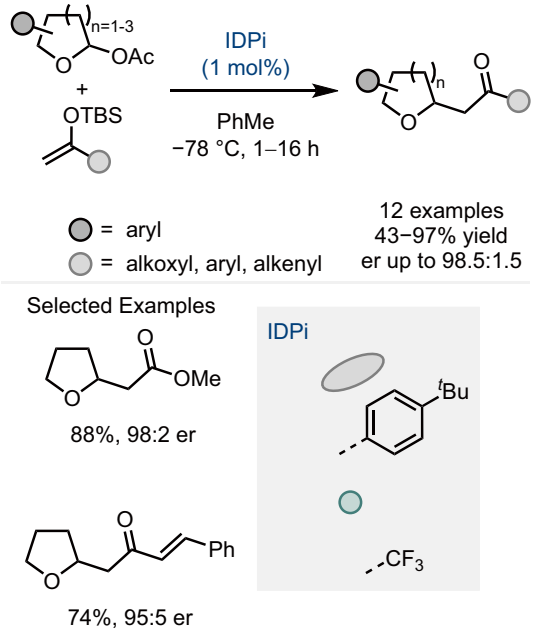


Figure 45: Synthesis of 2-substituted tetrahydrofurans from lactol acetates.

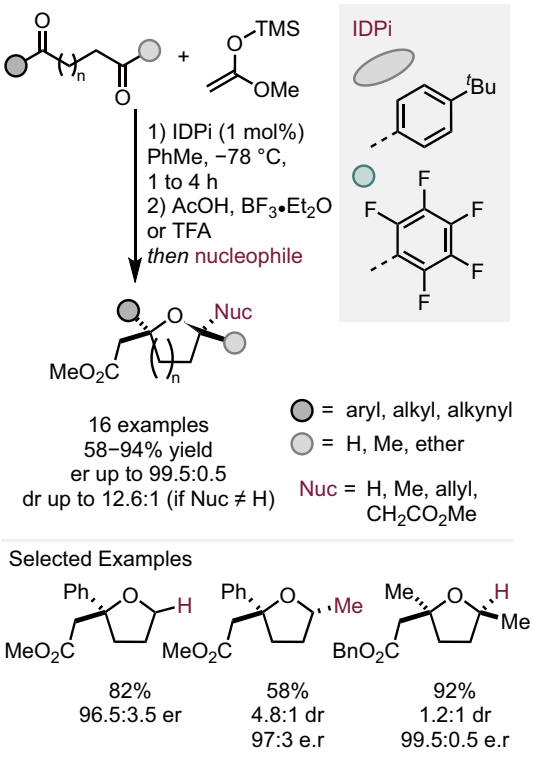


Figure 46: Generation of chiral tetrahydrofuran derivatives from 1,4-dicarbonyls.

The intermolecular generation of oxocarbenium ions and their participation in the Prins-semipinacol rearrangement reaction was also demonstrated (**Figure 47**).[46]

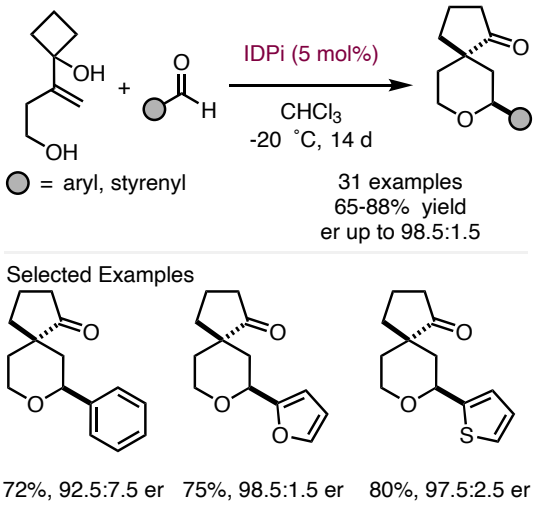


Figure 47: Prins-semipinacol rearrangement reaction.

Si-stereogenic centers

Enantiopure organosilanes are increasingly important, making new synthetic methods highly desirable. Organocatalytic asymmetric access to enantiopure silanes was unprecedented until IDPi demonstrated efficient synthesis of *Si*-stereogenic silyl ethers and *Si*-stereogenic silacycles.

First, silyl ethers can be prepared from achiral bis(methallyl)silanes via a C–C bond-forming desymmetrization enabled by an IDPi catalyst.[47] Additionally, a dynamic kinetic asymmetric transformation (DYKAT) of racemic silanes and allylsilanes was realized (not shown).[48] If no external nucleophile, like 2,6-dimethylphenol, is present, a *Si*-stereogenic silacycle is formed in the presence of acetic acid (**Figure 48**).[49]

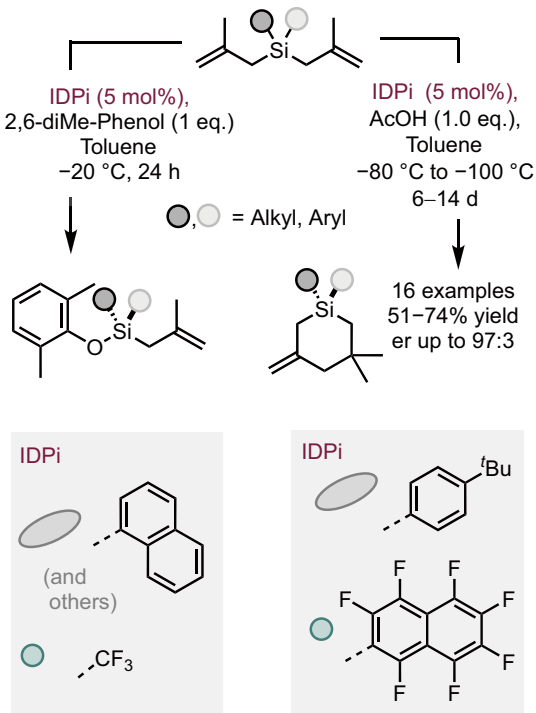


Figure 48: Synthesis of Si-stereogenic centres by IDPi.

Polymerization

High acidity in combination with confinement proved to advance polymer science equally - enabling high control over tacticity of polymers. For example, IDPi catalyzes the polymerization of vinyl ether monomers towards high molecular weight isotactic polyvinylethers (PVEs).[50,51] This reaction was also applied in the synthesis of a stable persistent radical in well-defined molecular polymers that enables the long-range order necessary for spin transport.[52]

A similar cationic copolymerization from biorenewable isobutyl vinyl ether (^{i}BVE) and 2,3-dihydrofuran (DHF) monomer mixtures was demonstrated, too.[53]

Further, IDPi's delivered poly(δ-valerolactone) and poly(ε-caprolactone) through controlled/living ring-opening polymerization of lactones, albeit no chiral BINOL backbone was needed in the IDPi structure.[54]

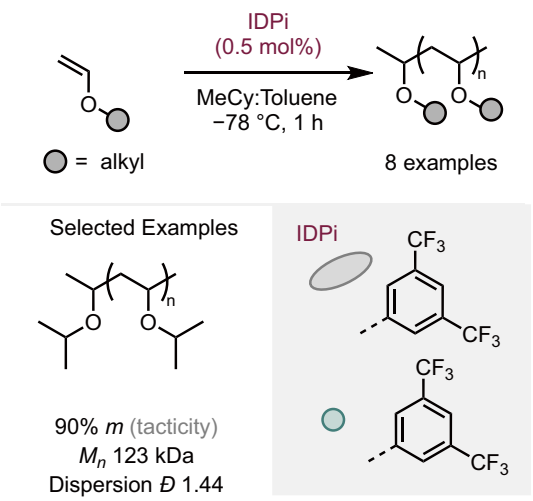


Figure 49: IDPi-controlled polymerization.

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Nils Frank received his BSc degree from the Karlsruhe Institute of Technology (Germany) in 2020. He obtained a MRes degree from the University of Oxford (UK) in the group of Professor Edward Anderson and Professor Fernanda Duarte from 2020 to 2022, where he worked on [3.1.1]propellane synthesis and reactivity. In 2022-2023, he joined F. Hoffmann-La Roche AG (Basel, Switzerland) for a one-year internship in medicinal chemistry. He is currently undertaking his doctoral studies in the laboratories of Prof. Benjamin List (Max-Planck-Institut für Kohlenforschung in Mülheim).

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Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from the Freie University Berlin (1993) and received his Ph.D. (1997) from the University of Frankfurt under the supervision of Prof. J. Mulzer. After postdoctoral studies (1997−1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute with Prof. R. A. Lerner, he became a Tenure Track Assistant Professor there in January 1999. In 2003, he moved to the Max-Planck-Institut für Kohlenforschung, where he has been a director since 2005. From 2012 until 2014, he has been the managing director of the institute. Since 2004, he has served as an honorary professor at the University of Cologne, and since 2020 he has been a Specially Appointed Professor at Hokkaido University, Japan. His research interests are new catalysis concepts and chemical synthesis in general. He has developed several concepts, including aminocatalysis, enamine catalysis, and asymmetric counteranion-directed catalysis (ACDC). He was the recipient of the 2021 Nobel Prize in Chemistry for his pioneering work in asymmetric organocatalysis.

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