2.2 Unprecedented Reactivity and Selectivity: The IDPi Breakthrough

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ABSTRACT: Since moving to the Max-Planck-Institut für Kohlenforschung, a central aim of our research has been to develop high performance organocatalysts that rival the reactivity and selectivity of the very best enzymes and transition metal catalysts available to today's chemists. Over the years our research advanced from proline's combined enamine and Brønsted acid activation to more purely acidic motifs. During this time, we began to realize that high acidity and structural confinement are the pivotal elements in asymmetric acid catalysis. As a consequence, our research recently culminated in the imidodiphosphorimidate (IDPi) catalyst class, introduced already at the end of the previous reporting period. By combining extreme acidity *and* a highly confined active site, IDPi catalysts have met with remarkable success, as powerful Brønsted acid catalysts and as "silylium" Lewis acid precatalysts in several previously inaccessible transformations. Substrates as challenging to activate as simple olefins were readily transformed, ketones were employed as electrophiles in aldolizations allowing sub-ppm level catalysis, whereas enolates of the smallest donor aldehyde, acetaldehyde, did not polymerize but selectively added a single time to a variety of acceptor aldehydes.

1. IDPi in Organic Lewis Acid Catalysis

To overcome barriers concerning reactivity and selectivity in organocatalysis, imidodiphosphorimidate (IDPi) catalysts were designed by combining the high catalytic activity of disulfonimide (DSI) catalysts with the steric confinement of imidodiphosphate (IDP) catalysts. This advancement was enabled by applying the "Yagupolskii trick", consisting of the tremendous acidifying effect upon the replacement of O atoms by NTf groups in benzoic acid, to the IDP motif (Figure 1). The profoundly enhanced acidity [pK_a = 4.5 to ≤2.0 in MeCN (depending on substituents R and R')] of the imidodiphosphorimidates created in this approach made them promising candidates for the exploration of new reactivities in asymmetric organic Lewis acid catalysis.[1]

Asymmetric Catalysis via Cyclic, Aliphatic Oxocarbenium Ions

Substituted oxacycles constitute carbohydrates and occur in numerous other classes of drugs and natural products. This motif is frequently accessed through S_N1-type substitution reactions involving cyclic oxocarbenium ions. Stereoselective intermolecular substitution reactions of this type so far have involved further stabilizing functionalities which additionally facilitate enantiofacial differentiation. Enantioselective nucleophilic addition reactions to simple aliphatic, cyclic oxocarbenium ions affording substituted tetrahydrofurans and -pyrans had remained an unsolved challenge though. This challenge could be solved by IDPi catalysts which not only exhibited exceptionally high catalytic activity even under cryogenic conditions, but further provided tetrahydrofurans in outstanding enantiomeric ratios of up to 99:1 (Scheme 1a).[2]

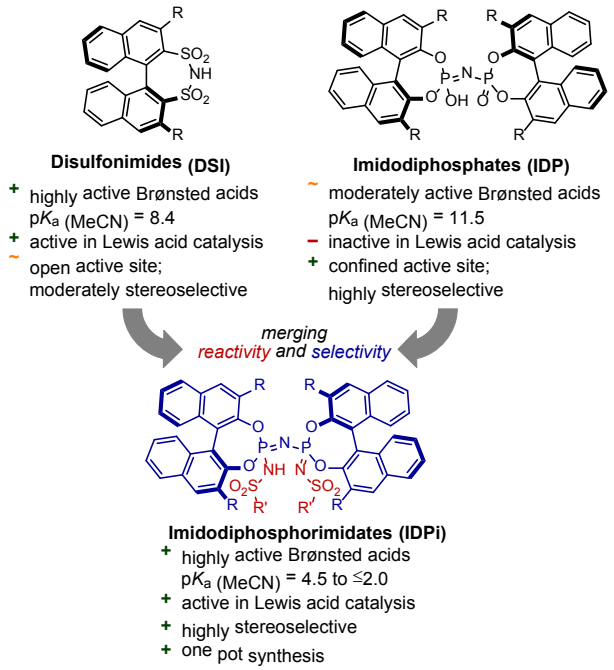
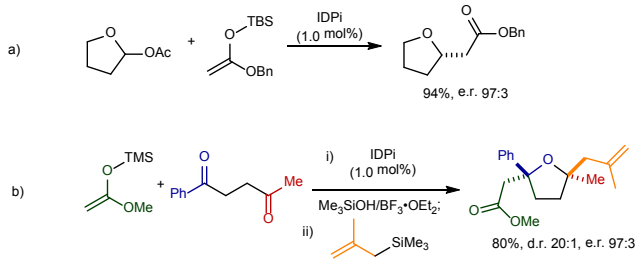


Figure 1. Imidodiphosphorimidate (IDPi) catalysts: merging reactivity and selectivity.

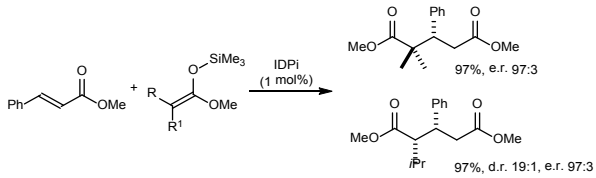
We also expanded enantioselective addition reactions to cyclic oxocarbenium ions to the synthesis of difficult to access 2,2-disubstituted and higher decorated tetrahydrofuranes and tetrahydropyrans, starting from 1,4- and 1,5-ketoaldehydes or diketones (Scheme 1b).[3]



Scheme 1. Examples for the IDPi-catalyzed synthesis of substituted tetrahydrofuranes.

A General Mukaiyama–Michael Reaction of Silyl Ketene Acetals with α,β-Unsaturated Methyl Esters

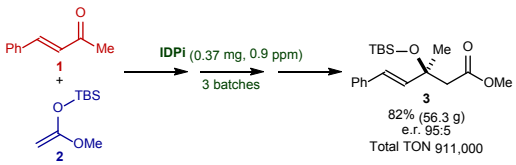
α,β-Unsaturated esters as electrophiles in enantioselective Mukaiyama–Michael reactions not only suffer from difficult enantiofacial discriminations but also from an inherently low electrophilicity. As a consequence, asymmetric Michael reactions have thus far been largely limited to enals and enones as electrophiles, or to alkylidene malonates. In contrast, examples with simple α,β-unsaturated esters have remained rare, and more commonly the critical ester moiety has been replaced by more electrophilic analogues, thereby significantly diminishing the step- and atom economy. Catalytic asymmetric Mukaiyama–Michael additions to alkyl cinnamates have to our knowledge been unprecedented. Intriguingly, IDPi catalysts afforded various diesters in reactions of SKAs with alkyl cinnamates in excellent yields and enantiomeric ratios of up to 99:1., using as little as 1.0 mol% catalyst loading (Scheme 2). Other α,β-unsaturated esters were well tolerated and furnished the desired products in high yields and enantioselectivities.[4]



Scheme 2. Examples for the IDPi-catalyzed Mukaiyama–Michael addition to methyl esters.

Approaching sub-ppm-level Asymmetric Organocatalysis With A Mukaiyama Aldol Addition

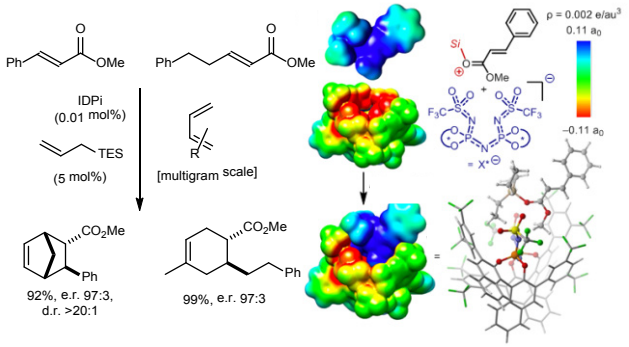
Few reactions have caught as much attention by organic chemists as the aldol reaction, judged by the myriad of auxiliary- and catalyst-based stereoselective methods developed in the past decades. Ketone acceptors have however remained a challenging class of substrates in catalytic enantioselective variants of this transformation due to the reduced steric dissimilarity of the carbonyl-bound substituents in ketones as compared to aldehydes and the generally lower reactivity of ketones as electrophiles (as compared to aldehydes). The List group showed that IDPi catalysts successfully overcame previous limitations. Aldol products were obtained rapidly in >90% yield and with an e.r. of >95:5 by using only 0.05 mol% (= 500 ppm) catalyst loading. A range of aryl alkyl ketones, dialkyl ketones and enones were shown to perform very well with IDPi catalysts, with catalyst loadings as low as 50–500 ppm.[5] Moreover, to explore the limits of organocatalysis, the reaction furnishing aldol **3** was performed on a multidecagram scale (Scheme 3). As little as 0.37 mg ($1.9 \cdot 10^{-4}$ mmol, 0.9 ppm) of IDPi catalyst fully converted three batches of ketone **1** (each 10.0 g, 68.4 mmol) and silyl ketene acetal **2** (14.2 g, 75.2 mmol, 1.1 equiv) in Et_2O (8.55 mL), ultimately reaching 95% conversion of all subjected ketone **1** and allowing for the isolation of aldol **3** in 82% yield and an e.r. of 95:5, corresponding to an outstanding total turnover number (TON) of $9.11 \cdot 10^5$.[5] Such low catalyst loadings have been unprecedented in asymmetric, catalytic C–C bond forming reactions.



Scheme 3. Sub-ppm level catalysis in the aldolization of ketone **1**.

Diels–Alder Reaction of α,β-Unsaturated Methyl Esters

Despite tremendous advances in enantioselective catalysis of the Diels–Alder reaction, the employment of simple α,β-unsaturated esters, one of the most abundant and useful classes of dienophiles, has been severely limited in scope due to their low reactivity. IDPi catalysts offer a solution to this problem by converting a large variety of poorly reactive α,β-unsaturated methyl esters with different dienes to the cycloaddition products in excellent yields, enantio- and diastereoselectivities using very low catalyst loadings of only 0.1–3 mol%. In collaboration with the Neese group the reaction profile and the chiral ion pair were also investigated computationally to understand the origin of enantioselectivity (Scheme 4).[6]

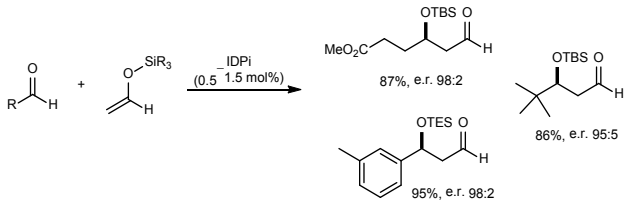


Scheme 4. IDPi-catalyzed Diels–Alder reaction.

Asymmetric Aldolizations of Vinyloxysilanes

The most challenging donors are undoubtedly those that produce another reactive acceptor unit in the course of the reaction, i.e. aldehydes, as these processes tend to yield oligomers and feature limited stability of the aldol

products. The employment of the smallest donor aldehyde, acetaldehyde, however has remained problematic and an enantioselective variant of single and double aldolizations of aromatic and aliphatic acceptor aldehydes so far elusive. IDPi catalysts cleanly converted benzaldehyde and derivatives thereof, such as *o*-tolualdehyde and *m*-anisaldehyde, with the simple TES or TBS enolates of acetaldehyde into the aldol products in very high yields and at remarkable enantiomeric ratios. Intriguingly, even aliphatic aldehydes were efficiently transformed and furnished the desired single aldolization products in high yields and good to excellent e.r. (Scheme 5).[7]



Scheme 5. Examples for the IDPi-catalyzed Mukaiyama aldol reaction with acetaldehyde enolsilanes.

2. IDPi in Brønsted Acid Catalysis

The design of ever more acidic chiral Brønsted acids for both enantioselective Brønsted and "silylium" Lewis acid catalysis has been key to expanding the scope of substrate classes to more challenging and less basic ones.

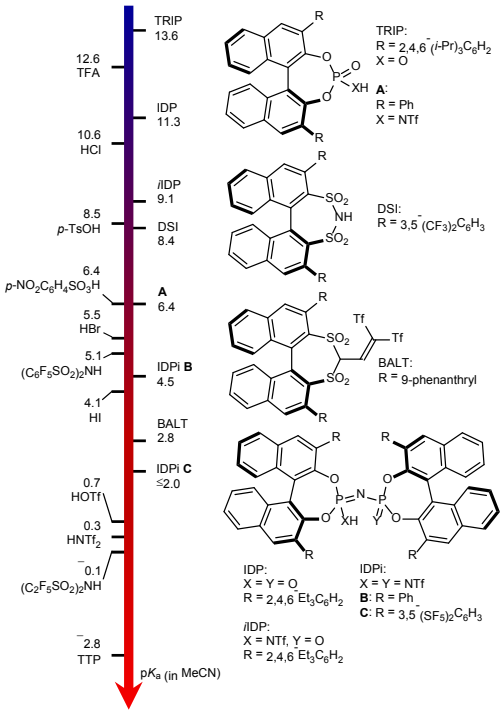
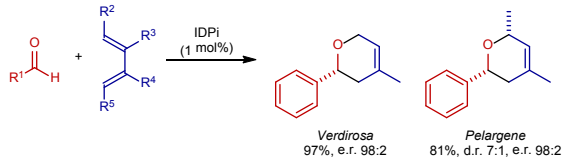


Figure 2. Experimental pK_a values of chiral and achiral Brønsted acids in MeCN.[1] TTP = 1,1,3,3-tetratriflylpropene.

While phosphoric acids like TRIP (pK_a = 13.6 in MeCN) are widely limited to readily activated imines, the significantly more acidic disulfonimides (DSI, pK_a = 8.4 in MeCN; cf. pK_a (*p*-TsOH) = 8.5 in MeCN; Figure 2) expanded the boundaries to the activation of aldehydes for numerous C–C bond-forming addition reactions.[8] For the addition of particularly unreactive nucleophiles or the activation of even less basic substrates, including olefins,[9] no sufficiently active catalyst class existed so far, resulting either in low substrate conversion and/or in undesired side-reactions driven by the Brønsted basicity of the counteranion.[5,10] By comparison, the basicities of the newly developed binaphthyl-allyl-tetrasulfones (BALT; pK_a = 2.8 in MeCN) and IDPis (pK_a (**B**) = 4.5, pK_a (**C**) ≤ 2.0 in MeCN) are profoundly reduced, allowing the selective conversion of such unreactive substrates as α,β-unsaturated esters,[11] readily enolizable ketones as electrophile[5] and even simple olefins.[9]

A General Catalytic Asymmetric [4+2]-Cycloaddition of Dienes with Aldehydes

The [4+2]-cycloaddition of dienes with aldehydes gained influence over decades for its efficiency and synthetic utility in the quick assembly of pyran substructures and the possibility to generate contiguous stereogenic centers, granting access to valuable enantiopure compounds. We recently found that IDPi catalysts possess appropriate features to catalyze this transformation using aromatic and even simple aliphatic aldehydes with high reactivity and selectivity.[12] The superior acidity and enhanced confinement of IDPi enabled simple 2,3-dimethyl-1,3-butadiene to react with aromatic and even simple aliphatic aldehydes that proved inaccessible even with TfOH.[13] Examples displaying the reactivity of other simple and in this transformation previously unprecedented dienes with a range of aldehydes were also reported (Scheme 6).[12]



Scheme 6. IDPi-catalyzed [4+2]-cycloaddition reaction of simple dienes with aromatic and aliphatic aldehydes.

Multi-Substrate-Screening Identifies Catalysts for Diels–Alder Reactions of α,β-Unsaturated Aldehydes

Another difficult, but due to its wide synthetic applicability highly desirable substrate class for the Diels–Alder reaction comprises structurally diverse aldehydes. These were reacted with cyclopentadiene using a multi-substrate screening approach (Figure 3) to identify a suitable catalyst. Gratifyingly, highly general IDPi catalysts could be discovered, showing that multi-substrate screenings can aid in identifying broadly useful and highly stereoselective catalysts of challenging carbon–carbon bond forming reactions.[14]

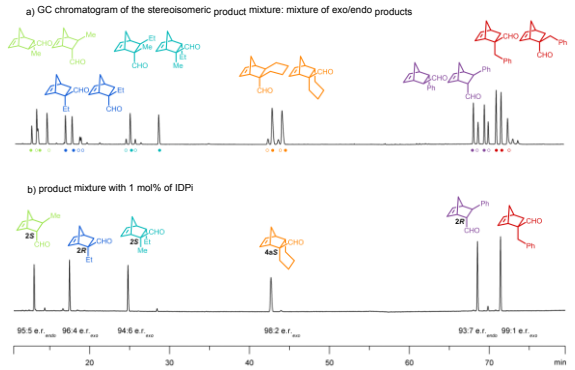
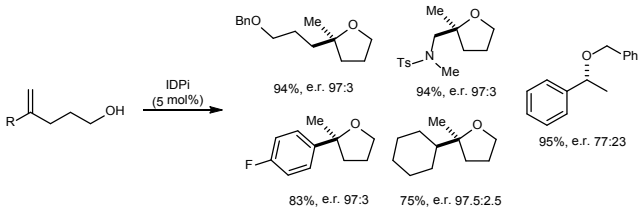


Figure 3. Multi-substrate screening of Diels–Alder reactions of α,β-unsaturated aldehydes and cyclopentadiene.

Hydroalkoxylation of Simple Olefins

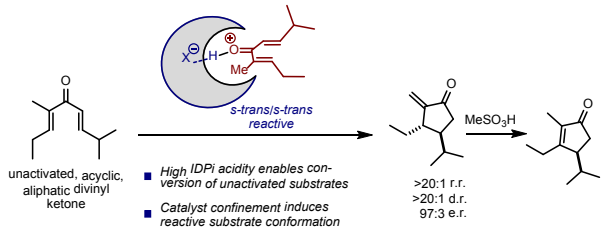
A great challenge in organocatalysis has been the application of simple olefins as electrophiles in hydrofunctionalizations, owed to their inherent low Brønsted basicity. Yet, the intrinsic simplicity, perfect atom economy and the abundant substrate availability renders such hydrofunctionalizations highly desirable. The employment of unactivated olefins as electrophiles in asymmetric hydroalkoxylations, however, has remained elusive in Brønsted acid catalysis. Intriguingly, IDPi catalysts exhibited high catalytic activity toward the desired hydroalkoxylation. A variety of functionalized and unfunctionalized alkenols were successfully converted under the optimized reaction conditions, providing the desired THFs in good yields and excellent enantioselectivities. Diene- and styrene-derived substrates were also well tolerated (Scheme 7).[9]



Scheme 7. Examples for the IDPi-catalyzed hydroalkoxylation of simple olefins.

Nazarov Cyclization of Simple Divinyl Ketones

Despite being considered one of the most direct and atom-economical transformations for the synthesis of cyclopentenones, the asymmetric Nazarov cyclization is arguably one of the least employed methods toward chiral cyclopentenones.



Scheme 8. IDPi-catalyzed Nazarov cyclization.

The limited application is likely an effect of systematic substrate specificity for given variants and, therefore, a lack of generality. Using IDPi catalysts, a powerful catalytic, asymmetric Nazarov cyclization of simple, acyclic, aliphatic-substituted divinyl ketones could be developed (Scheme 8).[15]

3. Conclusion

Imidodiphosphorimidates (IDPis) have opened doors to unprecedented reactivities in catalysis, while providing outstanding stereocontrol in a series of challenging inter- and intramolecular C–C and C–O bond-forming reactions.[1] Small organic molecules such as proline are capable of catalyzing transformations with high enantioselectivities through the presence of covalent and strong non-covalent (H-bonding) interactions with the reacting substrates.[16] In contrast, IDPis, mimicking enzymes, effect excellent enantiofacial discrimination through the confined chiral microenvironment of their substrate binding sites. The immense potential of IDPi catalysts has been amply illustrated in only a short period of time, and various further applications and mechanistic insights can be expected in the future.

REFERENCES

(1) L. Schreyer; R. Properzi; B. List, *Angew. Chem. Int. Ed.* **2019**, *58*, 12761–12777.
(2) S. Lee; P. S. J. Kaib; B. List, *J. Am. Chem. Soc.* **2017**, *139*, 2156–2159.
(3) S. Lee; H. Y. Bae; B. List, *Angew. Chem. Int. Ed.* **2018**, *57*, 12162–12166.
(4) T. Gatzenmeier; P. S. J. Kaib; J. B. Lingnau; R. Goddard; B. List, *Angew. Chem. Int. Ed.* **2018**, *57*, 2464–2468.
(5) H. Y. Bae; D. Höfler; P. S. J. Kaib; P. Kasaplar; C. K. De; A. Döhring; S. Lee; K. Kaupmees; I. Leito; B. List, *Nat. Chem.* **2018**, *10*, 888–894.
(6) T. Gatzenmeier; M. Turberg; D. Yepes, Y. Xie; F. Neese; G. Bistoni; B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12371–12676 and unpublished work.
(7) L. Schreyer; P. S. J. Kaib; V. N. Wakchaure; C. Obradors; R. Properzi; S. Lee; B. List, *Science* **2018**, *362*, 216–219.
(8) T. James; M. van Gemmeren; B. List, *Chem. Rev.* **2015**, *115*, 9388–9409.
(9) N. Tsuji; J. L. Kennemur; T. Buyck; S. Lee; S. Prévost; P. S. J. Kaib; D. Bykov; C. Farès; B. List, *Science* **2018**, *359*, 1501–1505.
(10) M. Mahlau; P. García-García; B. List, *Chem. A Eur. J.* **2012**, *18*, 16283-16287.
(11) T. Gatzenmeier; M. van Gemmeren; Y. Xie; D. Höfler; M. Leutzsch; B. List, *Science* **2016**, *351*, 949–952.
(12) L. Liu; H. Kim; Y. Xie; C. Farès; P. S. J. Kaib; R. Goddard; B. List, *J. Am. Chem. Soc.* **2017**, *139*, 13656-13659.
(13) J. Guin; C. Rabalakos; B. List, *Angew. Chem. Int. Ed.* **2012**, *51*, 8859–8863.
(14) H. Kim; G. Gerosa; J. Aronow; P. Kasaplar; J. Ouyang; J. B. Lingnau; P. Guerry; C. Farès; B. List, *Nat. Commun.* **2019**, *10*, 770.
(15) J. Ouyang; J. L. Kennemur; C. K. De; C. Farès; B. List, *J. Am. Chem. Soc.* **2019**, *141*, 3414–3418.
(16) a) B. List; R. A. Lerner; C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. b) S. Bahmanyar; K. N. Houk; H. J. Martin; B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.