Enantioselective Organocatalysis and Superacid Activation: Challenges and Opportunities

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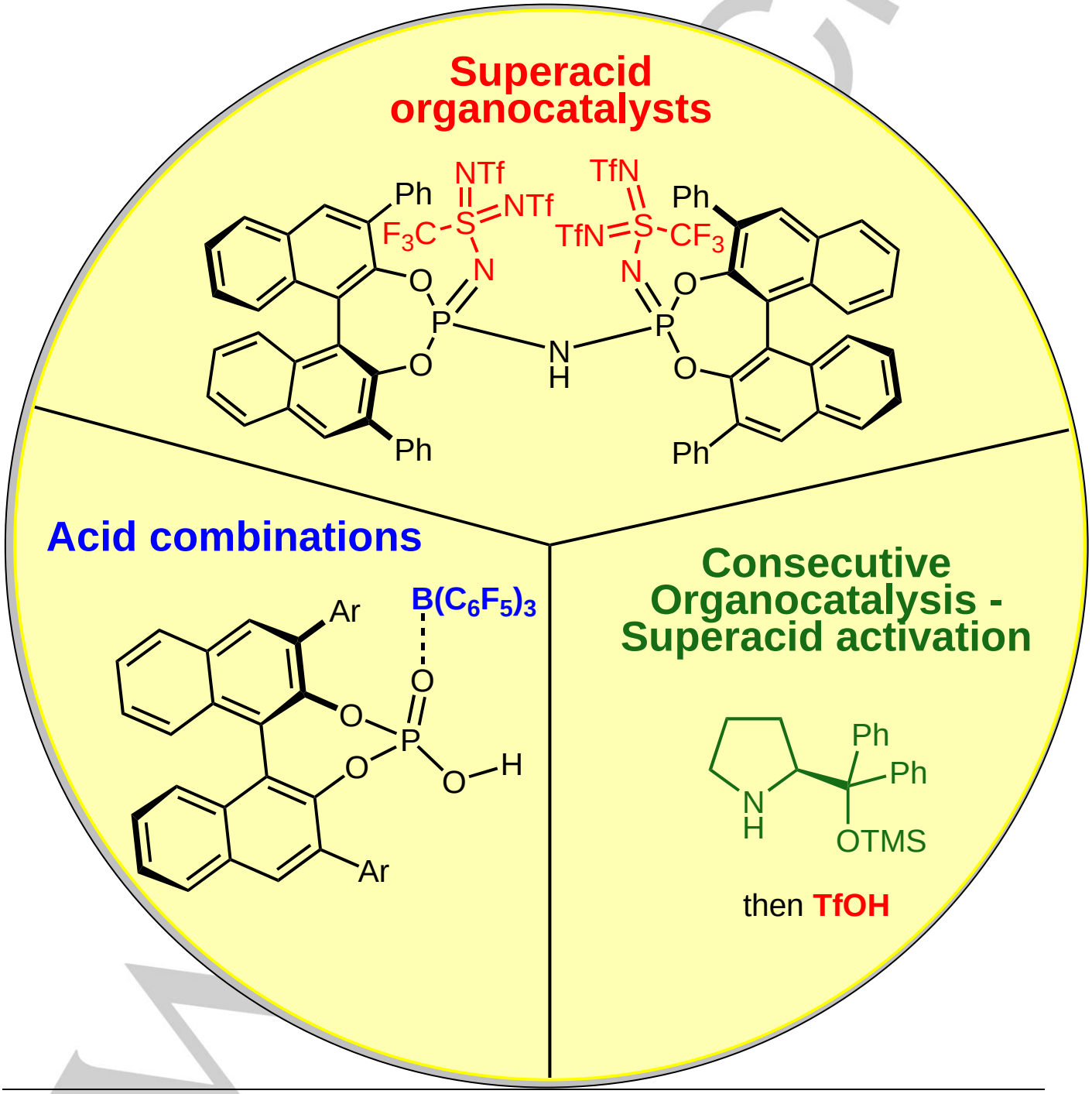
CONCEPT

Enantioselective Organocatalysis and Superacid Activation: Challenges and Opportunities

Bastien Michelet,[a] Agnès Martin-Mingot,[a] Jean Rodriguez, [b] Sébastien Thibaudeau*[a] and Damien Bonne*[b]



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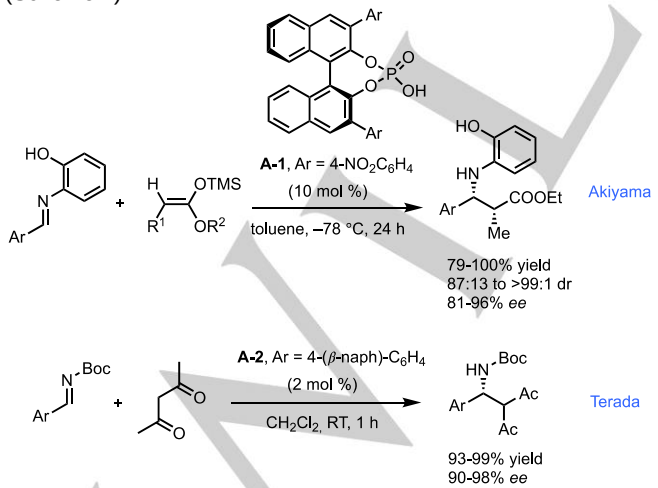
Abstract: Since the pioneer reports of Akiyama and Terada groups on Brønsted acid organocatalysis, this field never stopped growing with the development of ingenious strategies for the activation of challenging poorly reactive substrates. The development of superacidic organocatalysts is an important way to selectively functionalize reluctant electrophiles and other approaches have also emerged such as the combination of Lewis and Brønsted acids as well as the consecutive organocatalysis and superacid activation. This concept aims to highlight these different strategies and demonstrate their complementarity.

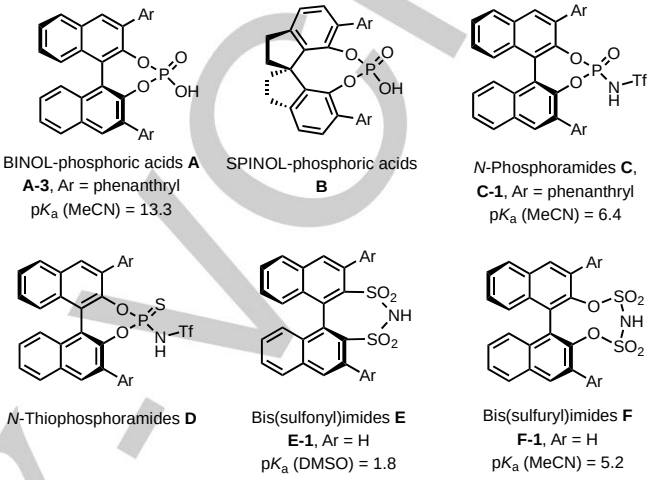
1. Introduction

While nature is able to generate highly complex molecules from simple substrates,[1] this challenge is still faced by chemists, despite the growing demand. In this context, producing enantioenriched molecules from simple substrates is especially appealing and enantioselective catalysis is the most attractive way to attain this objective. Over the past decades, enantioselective catalysis by small organic molecules (so-called organocatalysis) confirmed its synthetic potential and emerged as a powerful strategy offering operational simplicity and overcoming difficulties encountered by other strategies in this domain (mild reaction conditions, environmentally benign, low cost, accessibility of organocatalysts).[2] Since several years, this domain has become one major pillar of enantioselective catalysis and has been recently highlighted with the Nobel Prize attribution to MacMillan and List in 2021.[3] Among the different activation modes that appeared throughout the years, Akiyama and Terada lay the foundation of Brønsted acid organocatalysis in 2004 by separate reports on enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid, which constitute the first examples of chiral phosphoric acid-catalyzed organic reactions and opened a new avenue in enantioselective organocatalysis (Scheme 1).[4,5]



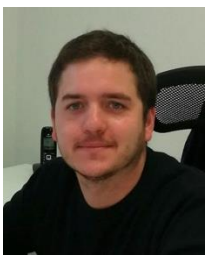
Scheme 1. Pioneer reports on the Brønsted acid organocatalysis.

Strong chiral Brønsted organoacids have proven themselves to be highly powerful catalysts for a wide array of synthetic transformations,[6] also efficient in the field of total synthesis.[7] Excellent contributions from different groups offer now a powerful collection of Brønsted acid organocatalysts going from BINOL-phosphoric acids **A**,[8] SPINOL-phosphoric acids **B**,[9] *N*-(thio)phosphoramides **C** and **D**,[10] bis(sulfonyl)imides **E**[11] and bis(sulfuryl)imides **F**[12] for the main representatives (Scheme 2). Increasing the acidity of the catalyst allows the activation of less basic substrates with increased catalytic activity.[13]



Scheme 2. Main Brønsted acid organocatalysts and reported associated pK_a values.

Despite their effectiveness, owing to their acidity[14] they are mainly used to activate basic substrates (imines, enol ethers, certain carbonyl compounds).[15] The activation of poorly basic substrates remains more challenging and the ultimate goal would be to efficiently activate non-polarized C=C bonds such as olefins or arenes, delivering elaborated enantioenriched products from the simplest non-functionalized substrates. As a result, to overcome the existing barriers related with selectivity and reactivity, new perspectives have been opened recently. This article highlights recent developments of organocatalysts that overcome the reactivity of commonly employed Brønsted superacids and capitalize on specific confinement properties, as well as new strategies combining organocatalysts and (super)acids.



Bastien Michelet obtained his PhD from the Paris-Saclay University in 2015 under the supervision of Prof. Vincent Gandon. After postdoctoral studies with Prof. Gwilherm Evano at Université Libre de Bruxelles, he joined the group of Prof. Sébastien Thibaudeau in 2017. In 2018, he was appointed as Chargé de Recherche CNRS at the Institut de Chimie des Milieux et Matériaux de Poitiers. His main scientific interests include organic synthesis and superacid chemistry with particular emphasis on the development of new synthetic methods and mechanistic studies.

Agnès Martin-Mingot received her PhD from the Poitiers University (France) in 1996. She was appointed as professor assistant in 1997 at the university of Poitiers and collaborates with Sébastien Thibaudeau in the field of superacid chemistry at the Institute of Chemistry of Poitiers (IC2MP). She focuses her research on the development of synthetic methods in superacidic media and on their mechanistic aspects especially via in situ NMR analysis.

Jean Rodriguez was born in Cieza (Spain) in 1958 and in 1959 his family emigrated to France. After studying chemistry at the University of Aix-Marseille (France), he completed his Ph.D. as a CNRS researcher with Prof. B. Waegell and Prof. P. Brun in 1987. He completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-7313-iSm2. His research interests include the development of multiple bond-forming transformations including domino and multicomponent reactions, and their application in stereoselective organocatalyzed synthesis. In 1998, he was awarded the ACROS prize in Organic Chemistry, in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society and in 2013 became “Distinguished member” of the French Chemical Society.

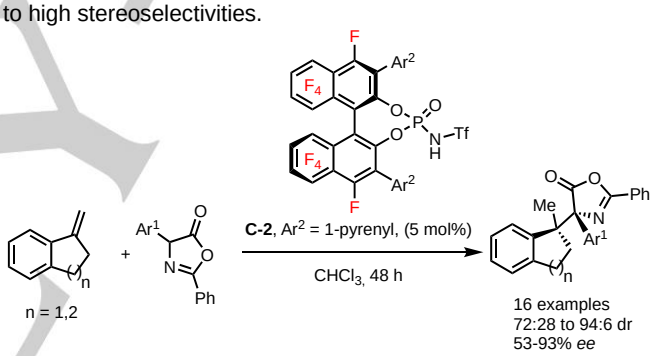
Sébastien Thibaudeau was born in France, in 1975. He received a B.A. with a major in Chemistry in 1999 followed by his Ph.D. in Chemistry from the University of Poitiers, in 2002. After a Marie-Curie postdoctoral fellowship at the University of Oxford under the guidance of Prof. Véronique Gouverneur, he joined the faculty in the Department of Chemistry at the University of Poitiers in 2004, where he is currently Professor. His research interests include carbocation chemistry and (super)acid-promoted reaction development.

Damien Bonne was born in Epinal (France) in 1979. After studying chemistry at the Ecole Supérieure de Chimie de Lyon (CPE Lyon, France), he completed his Ph.D. in 2006 under the supervision of Prof. J. Zhu working on isocyanide-based multicomponent reactions. He then moved to the University of Bristol (UK) to join the group of Prof. V. A. Aggarwal as a postdoctoral associate. Since 2007 he has been working at Aix-Marseille University (France). He was promoted to full professor in 2022 and his research interests include the development of new organocatalyzed methodologies and their application in stereoselective synthesis.

2. Ultimately pushing the Yagupolskii principle toward superacidic organocatalysts

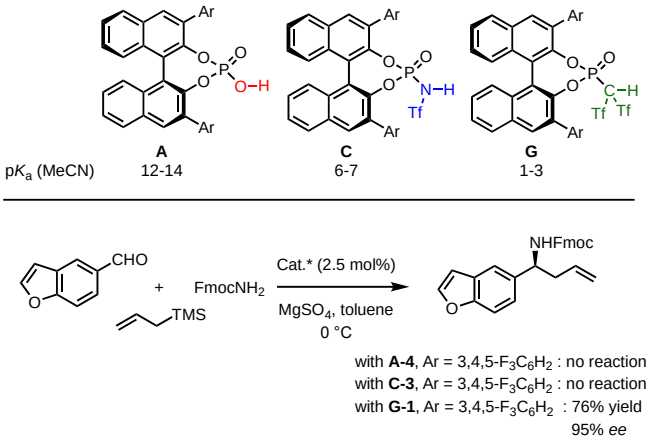
Aiming at activating small unbiased substrates, recent efforts were especially conducted through the development of designed catalysts that could reach acidities realm of TfOH or Tf_2NH superacids.[16] The replacement of oxygen atoms with strongly electron withdrawing groups, the so-called Yagupolskii principle[17] led to promising organocatalysts that borders on molecular superacids. Krossing and Leito recently distinguished solid molecular superacids from primary superacids and conjugate Brønsted-Lewis strongest superacidic media.[18] The proton bound in neutral molecular superacid is in equilibrium with the solvated proton in solution (at least in dichloroethane). Derived from weakly coordinating counter anions some of them were shown to be able to generate electrophilic silylium ions,[19] as shown by some recently developed C-H binaphthyl-allyl-tetrasulfones organocatalysts.[20]

Hence, the group of Terada designed new catalysts based on a F_{10}BINOL skeleton, allowing to reach very high acidities, in particular for the *N*-triflyl phosphoramide **C-2** whose pK_a was calculated by DFT at –4.95 in DMSO (Scheme 3).[21] This property was exploited for the functionalization of non-activated alkenes and they reported the possible enantioselective intermolecular addition of azalactones to styrene derivatives affording a product with two vicinal stereogenic centers in good yields and moderate to high stereoselectivities.



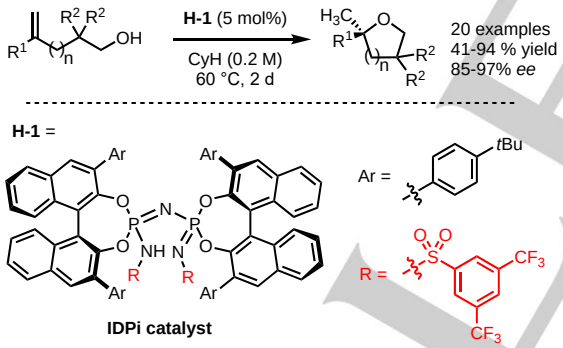
Scheme 3. Functionalization of non-activated alkenes.

Recently, the groups of Chen, Ding and Zhao reported the preparation of the chiral super Brønsted acid **G** bearing a bis((trifluoromethyl)sulfonyl) methane group and compared its catalytic properties with other classical organocatalysts **A** and **C** (Scheme 4).[22] The superacidic properties of catalyst **G-1** allows its uses in difficult reactions such as enantioselective Mukaiyama-Mannich reactions, allylic amination, three-component coupling between arylaldehyde, allyltrimethyl silane and Fmoc-NH_2 for the preparation of optically active homoallylamines as well as protonation of silyl enol ethers. In general, shorter reaction times are observed with catalysts **G** which also surpass **A** and **C** both in terms of reactivity and enantiocontrol.



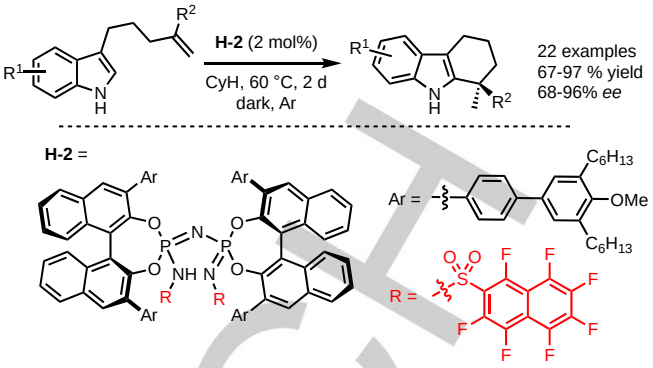
Scheme 4. Development of a chiral super Brønsted acid.

In 2018, List reported the intermolecular etherification of non-activated olefins using highly acidic imidodiphosphorimidate (IDPi) organocatalyst **H** (Scheme 5).[23] This catalyst also provides a confined enzyme-like environment responsible of the very high selectivities that are usually difficult to reach for such transformation. This concept of confinement was further exploited to answer the challenging enantioselective Nazarov cyclization of simple acyclic alkyl-substituted divinyl ketones. [24] In this transformation, the confinement not only increases the catalytic activity but it also allows the growth of the population of reactive *s-trans/s-trans* conformation of the divinyl ketone substrate. Here, the confinement can be considered as much important as acidity to attain ultimate level of reactivity and efficiency, as a unified element in selective catalysis.[25]



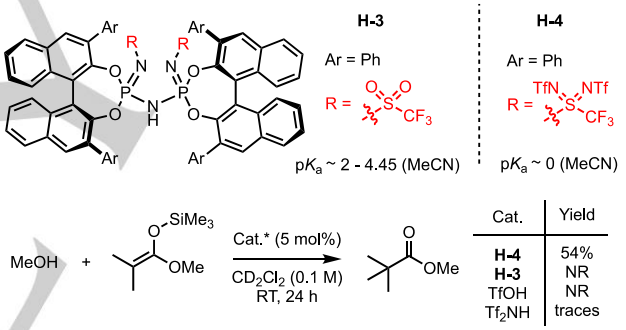
Scheme 5. Highly acidic and confined IDPi organocatalysts.

Following this strategy, List recently reported the especially efficient IDPi organocatalyst **H-2** that was rationally designed to activate *gem*-disubstituted olefins (Scheme 6).[26] This favors the intramolecular cation-promoted hydroarylation to quaternary stereogenic center-bearing products in excellent enantioselectivity. Here, the activity and selectivity of the catalyst are especially favored by the presence of strong electron-withdrawing perfluoronaphtalene-2-sulfonyl motifs that increase the acidity of the IDPi catalyst while the diphenyl substituents in 3,3' positions of the BINOL backbone maximize π–π interactions between the catalyst and the substrate.



Scheme 6. IDPi-catalyzed functionalization of indoles.

Capitalizing on an efficient and operationally simpler synthesis of imidodiphosphate, List ultimately challenged superacid organocatalysts synthesis and reactivity by developing an even more acidic IDPii catalyst **H-4** (Scheme 7). [27] Here, the Yagupolskii concept [28] is followed by substituting the trifluoromethanesulfonyl group in **H-3** by a *N,N'*-bis(trifluoromethylsulfonyl)phenyl sulfonodiimidoyl group, that significantly enhanced the acidic character of the catalyst **H-4** (estimated pK_a ~ 0 in MeCN). Applied to α-methylation of a silyl ketene acetal,[29] its unique reactivity overcomes the reactivity of TfOH and Tf_2NH superacids.



Scheme 7. Highly acidic and confined IDPii organocatalysts.

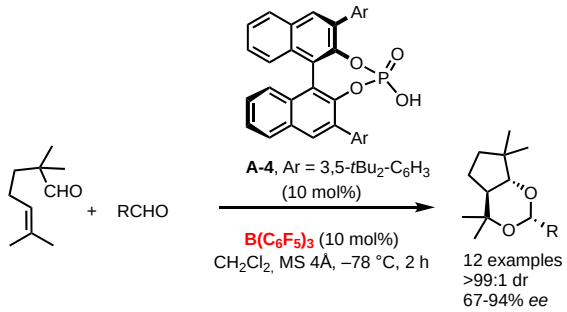
3. Combining acids to enhance catalytic activity

A distinct concept to increase the catalytic activity of organocatalysts is to combine acids through LBA (Lewis acid-assisted chiral Brønsted Acid catalysis), LBBA (chiral Lewis Base assisted Brønsted Acid catalysis) or BBA strategy[30] (Brønsted acid-assisted chiral Brønsted Acid catalysis).

LBA strategy proved its efficiency in catalyzing reactions that are inherent to biocatalytic domain, as for example, the lanosterol biosynthesis which remained challenging to synthetic chemists. This concept has been pioneered by Yamamoto by combining BINOL and tin tetrachloride for the enantioselective protonation of cyclic silyl enol ethers and acyclic ketene bis(trialkylsilyl) acetals. [31] This approach was then successfully improved by Toste by using chiral Brønsted acid from a cationic gold(I) complex affording higher levels of enantioselectivity for a large array of cyclic and acyclic silyl enol ethers.[32] Looking for a strong acidic chiral proton source for this C=C double bond activation initiated polycyclization, Corey showed that a combination of dichloro-BINOL and Lewis acid $SbCl_5$ allowed the cyclization that

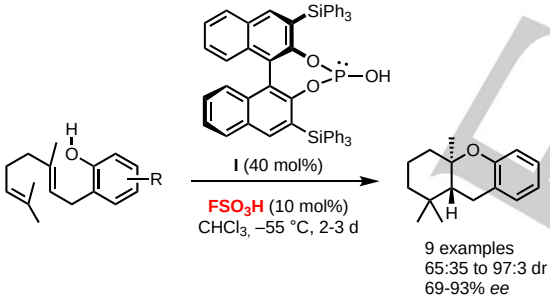
is initiated by enantioselective protonation of non-activated alkenes.[33]

Following this strategy with tris(pentafluorophenyl)borane, the activation of 3,3'-Ar_2-BINOL-derived phosphoric acid **A-4** allowed the enantioselective and diastereoselective carbonyl-ene cyclization to generate functionalized unsaturated piperidines, tetrahydropyranes or cycloalkanes (Scheme 8).[34] In this recent significant contribution, Ishihara confirms the potential of this strategy for other enantioselective carbocation-based cyclization from alkenes.



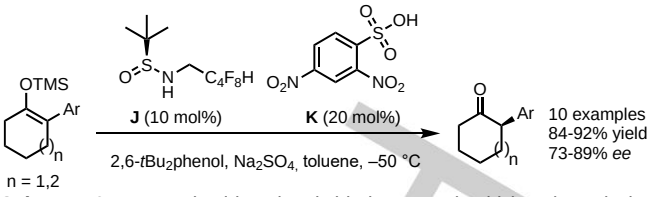
Scheme 8. Enantioselective LBA-catalyzed carbonyl-ene cyclization.

Ishihara also developed Lewis base-assisted Brønsted acids (LBBA) that efficiently catalyzes the biomimetic enantioselective cyclization of 2-geranylphenols to give the desired *trans*-fused cyclic products (Scheme 9).[35] Here, the reaction between Lewis base **I** and fluorosulfonic acid gives a fluorosulfonate salt of a chiral BINOL-phosphonium ion. This allows for the diastereo- and enantioselective approach of the terminal isoprenyl group toward the very reactive phosphonium proton.



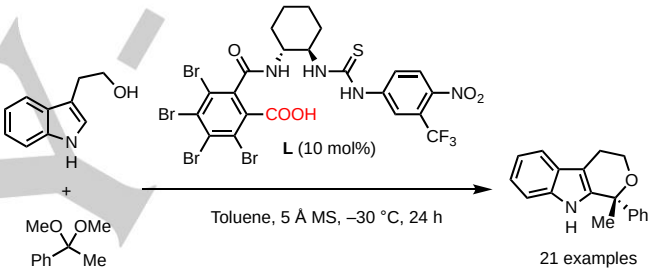
Scheme 9. LBBA-catalyzed cyclization.

Capitalizing on the strong acidity of 2-bis(triflyl)methyl-2'-hydroxy-1,1'-binaphtyl derivatives, their combination with a Brønsted acid to catalyze Mannich type reaction was explored successfully by Yamamoto.[36] Even if such a Brønsted acid-assisted chiral Brønsted acid catalysis (BBA) was less explored, an example from Jacobsen's group is appealing (Scheme 10). The enantioselective protonation of silylenol ethers was shown to occur in good yields in the presence of a co-catalytic system combining chiral sulfinamide **J** and sulfonic acid **K**.[37] It is suggested here that the combination of the strong acid and the chiral sulfonamide allows for enhancing the activity of the catalyst. In addition, the structurally simple sulfinamide catalysts seem engaged in non-covalent attractive interactions (NH–π, CH–π, or hydrogen bonding interactions) that might play a critical role in the transition state organization. TfOH generated proto-iminium ions were also proven to tightly interact with sulfinamide-containing chiral ureas, thus promoting an efficient cooperative catalyst system for enantioselective Povarov reactions.[38]



Scheme 10. Brønsted acid-assisted chiral Brønsted acid (BBA) catalysis.

Another alternative strategy to enhance the catalyst acidity, is to stabilize its conjugate base through intramolecular anion-binding with an intramolecular thiourea receptor.[39] This has been described notably by Seidel's group who developed the highly acidic conjugate-base stabilized carboxylic acid **L** (pKa = 12.7 in MeCN), exceeding that of chiral phosphoric acid **A** (Scheme 11). Catalyst **L** was found to catalyze efficiently the enantioselective oxa-Pictet–Spengler reaction, via intramolecular trapping of a trisubstituted oxocarbenium ion. The enhancement of the acidity of the carboxylic acid function has also been realized by Maruoka though *in situ* formation of a boronate ester by reaction between a chiral diol, and 2-boronobenzoic acid. This strategy was successfully applied to enantioselective *trans*-aziridination.[40]



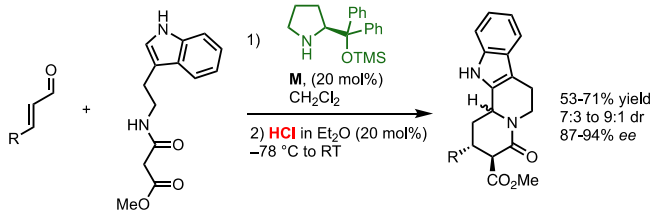
Scheme 11. Highly acidic conjugate-base-stabilized carboxylic acid.

4. Consecutive organocatalysis / superacid activation

An alternative and complementary approach has emerged in recent years, consisting in the consecutive organocatalysis / superacid activation. In this strategy, an organocatalyzed domino transformation allows the elaboration of a complex enantioenriched molecule, which is then originally functionalized thanks to superacid activation. This methodology has the advantage to widen the application scope in the sense that the initial domino transformation is not limited to acid-catalyzed transformations and can be applied to most organocatalytic activation modes. The stereoselectivity is controlled in the initial step, while the superacid functionalization may create additional stereogenic elements in diastereoselective fashion.

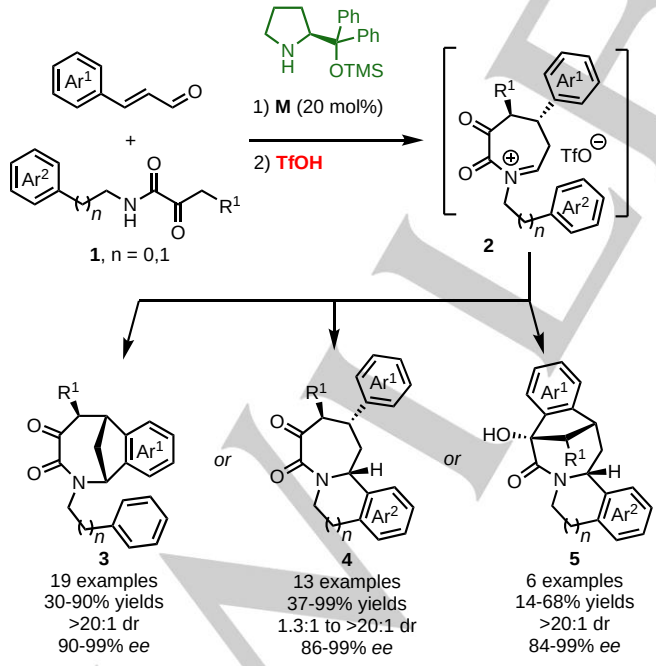
One of the first application of this concept was described by Franzén and co-workers in 2009, who reported the fast construction of the quinolizidine skeleton bearing three new stereocenters with high enantioselectivity but moderate diastereoselectivity (Scheme 12).[41] In the presence of Hayashi-Jørgensen catalyst **M**, the sequence includes an organocatalyzed-enantioselective Michael addition of the 1,3-ketoamide on an enal followed by an acid-catalyzed cyclization of the *N*-acyliminium ion formed *in situ*.[42] This transformation was

later applied to the preparation of corynantheine and ipecac alkaloids.[43]



Scheme 12. Enantioselective synthesis of the quinolizidine skeleton.

Recently, our groups have exploited this strategy for the easy access to enantioenriched complex fused-tricyclic azocanes **3** and **5** or azepanes **4**, by a two-step sequence involving an enantioselective organocascade between 1,2-ketoamide **1** and enal,[44] followed by superacid activation with triflic acid of the domino adduct (Scheme 13). The activated oxa-bridged azepane intermediate acts as a key hidden heptacyclic chiral *N*-acyl iminium ion **2** triggering a chemo- and diastereoselective intramolecular mono- or di-arylation. By careful choice of the Ar^1, Ar^2 and n, the superacid-promoted intramolecular Pictet-Spengler[45] reaction can involve Ar^1, generating optically-enriched methylene-bridged benzazocanes **3** closely related to bioactive morphinan and benzomorphan scaffolds.[46] Alternatively, the cyclization can also involve Ar^2 to afford the enantioenriched pyrido[1,2-a]azepane ring system **4**,[47] which is found in many biologically relevant molecules, such as banistenoside A and B.[48] Finally, a cascade cyclization involving successively Ar^1 and Ar^2 was found possible to give the complex fused-polycyclic azocanes **5**.



Scheme 13. Synthetic strategies to enantioenriched polycyclic azepanes.

5. Conclusion / Perspectives

In conclusion, the field of Brønsted acid organocatalysis never stopped growing since the seminal reports of Terada and Akiyama in 2004 on chiral phosphoric acids. These catalysts are indeed very efficient for the selective activation of basic substrates such as imines or carbonyl compounds. The functionalization of non-polarized C=C bonds such as olefins or arenes remained a challenging goal for many years, which was solved with the development of various creative synthetic strategies. The synthesis of superacid organocatalysts is the most encountered one, reaching very high acidities with pK_a as low as 1 (estimated in MeCN) for the List's IDPii confined organocatalysts. Alternatively, the catalytic activity can be greatly enhanced by the use of combinations of acids, allowing for the efficient functionalization of alkenes. Finally, consecutive organocatalysis and superacid activation is a complementary and attractive alternative since it is not restricted to Brønsted acid activation mode. Although many progresses have been accomplished, many challenges remain, as for example the simple atom-economical enantioselective hydration of alkenes. We anticipate that these three complementary approaches will allow to give new answers to yet unsolved synthetic challenges.

Acknowledgements

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Keywords: Enantioselective synthesis • Organocatalysis Superacid activation

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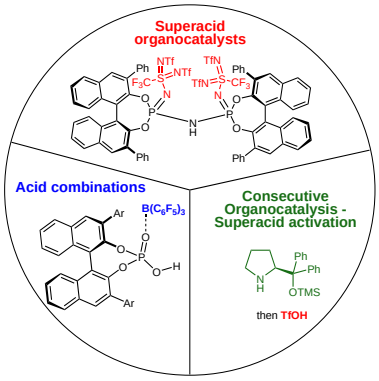

Enantioselective Organocatalysis and Superacid Activation: Challenges and Opportunities

If chiral phosphoric acids catalyst are very efficient for the selective activation of basic substrates such as imines or carbonyl compounds, the functionalization of non-polarized C=C bonds such as olefins or arenes remained a stimulating goal for many years. This concept present the different smart strategies that have appeared throughout the years for the efficient functionalization of these challenging substrates.

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