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Mini-Review

Recent Advances in the Prins Reaction

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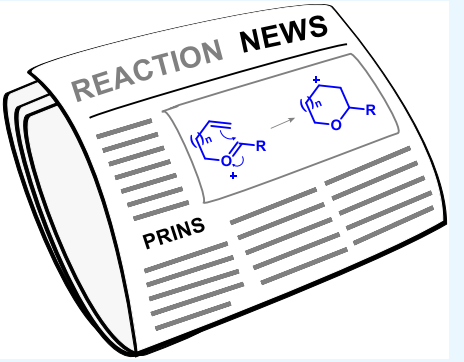
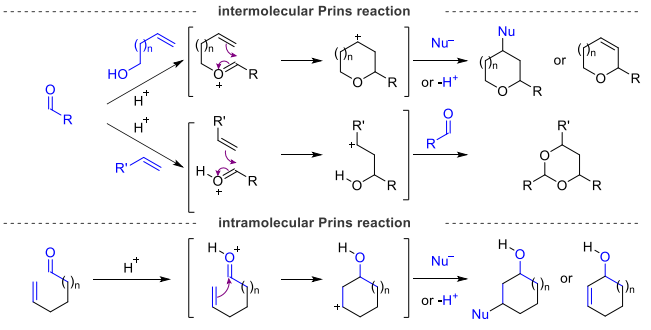
ABSTRACT: The Prins reaction is a very convenient synthetic platform for the preparation of oxygen-containing heterocyclic compounds, especially tetrahydropyrans and tetrahydrofurans. While this reaction has been extensively used by synthetic chemists since its discovery, the last years have witnessed impressive improvements in its performance and scope and especially in the development of new catalytic and enantioselective versions. This mini-review presents these recent advances through selected representative examples.



1. INTRODUCTION

The Prins reaction is a powerful and versatile methodology for the construction of oxygenated heterocyclic compounds.[1−3] This reaction, together with its *N*- and *S*-variants, has been extensively used for the preparation of different-ring-size carbo- or heterocycles in the so-called Prins cyclization, a transformation that requires the use of an aldehyde or a related compound, an alkene (the so-called π-component) and a nucleophile, in a process that is typically promoted by a Lewis or Brønsted acid (Scheme 1). The key step on this reaction is

Scheme 1. General Scheme for the Prins Reaction



the formation of an oxocarbenium ion that reacts with 1 equiv of the π-component in an intermolecular (Scheme 1, top) or intramolecular fashion (Scheme 1, bottom). Depending on the structure of the alkene and the presence/absence of an external nucleophile, this initial carbocationic intermediate can evolve through different pathways, leading to the formation of a variety of substituted oxygen-containing carbo- or heterocycles (typically from five- to seven-membered rings) in a straightforward way.

Due to the high utility of this reaction as a key strategic tool in organic synthesis, the last years have witnessed significant advances, focused on the following aspects that have widened the scope and utility of the Prins reaction: (section 2) the search for new catalytic systems with improved performance, (section 3) the diversification of the components that can be used in the reaction, (section 4) the incorporation of the Prins reaction in complex cascade processes, and (section 5) the development of enantioselective versions. The following sections will cover these advances through a selection of representative examples.

2. NEW CATALYSTS FOR THE PRINS REACTION

In recent years, many efforts have been made in utilizing earth-abundant transition-metal complexes for catalyzing the Prins reaction, also with a focus on performing the reaction under more environmentally friendly conditions. In this sense, Martin and Padron have presented a procedure for the Prins cyclization employing iron halides as catalysts in combination with a stoichiometric amount of trimethylsilyl halides as nucleophilic terminal quenchers of the carbocationic intermediate formed after the addition of the π-component to the

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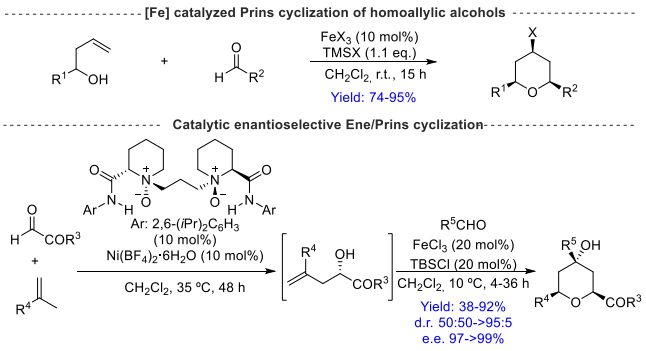
oxonium ion.[4] This reaction provides a direct access to dihydropyrans containing three stereocenters with complete diastereoselectivity (Scheme 2, top).

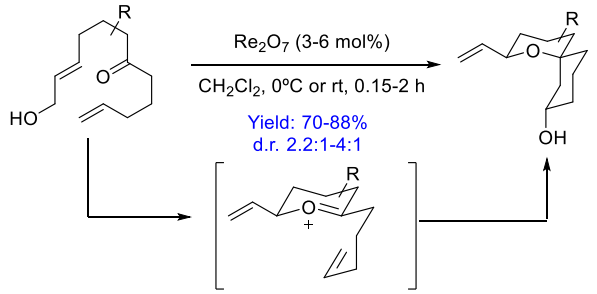
Scheme 2. Two Examples of Fe(III)-Catalyzed Prins Reactions



Moreover, the use of enantiomerically pure homoallylic alcohols provides the final products with complete diastereoselectivity, as shown by Feng in a two-step protocol that capitalized the good performance of an enantioselective Ni-catalyzed ene reaction for the preparation of enantiomerically enriched homoallylic alcohols followed by an iron-catalyzed Prins cyclization under the same conditions shown before (Scheme 2, bottom).[5]

Other less common Lewis acid catalysts such as rhenium(VII) oxide has been utilized to promote the spirocyclization of hydroxydienones such as those shown in Scheme 3.[6] This

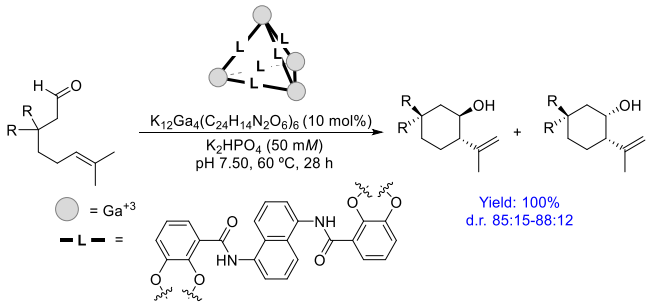
Scheme 3. Re_2O_7-Catalyzed Prins Cyclization



reaction takes place after an initial allylic alcohol isomerization which provides *in situ* a δ-hydroxyketone intermediate able to generate the required oxocarbenium ion that undergoes the Prins-type cyclization. This strategy has been applied to a variety of substrates incorporating a methyl substituent in different positions of the tethering alkyl chain, giving very good yields and moderate diastereoselectivities in all cases tested.

The performance of the Prins reaction can also be improved by using supramolecular catalysts that can confine the reacting substrate in a close environment that stabilizes the intermediates and facilitates the overall process. In this sense, Toste, Bergman, and co-workers have employed a gallium-derived supramolecular architecture that presents cation-stabilizing abilities together with hydrophobic properties in the interior part, conditions highly beneficial for the Prins reaction to occur (Scheme 4).[7] The authors have evaluated the reaction with two citronellal-like aldehydes, observing complete conversion and excellent yield accompanied by very good stereoselectivities. It should be noted that the

Scheme 4. Ga(III)-Catalyzed Encapsulated Prins Cyclization

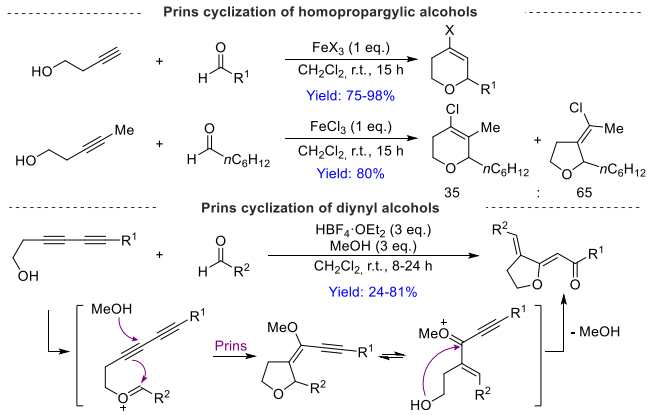


reaction in the absence of this catalyst results in the nonselective formation of a mixture of alkene hydration byproducts. Importantly, this reaction is performed in a slightly basic pH solution, representing a good alternative for other methodologies carried out in highly acidic solutions.

3. PRINS CYCLIZATION USING LESS CONVENTIONAL SUBSTRATES

Although the Prins cyclization has been typically carried out by using an alkene moiety as the π-donor, together with an alcohol and an aldehyde, one of these three components can be replaced by some other modified reactants, widening the scope of the Prins reaction to provide products of different natures. In this sense, although simple alkenes are the most used π-components, alkynes[8] or diynes[9] can be used in the reaction. For instance, when unsubstituted 3-alkynols are employed in the FeX_3-promoted Prins reaction with aldehydes, the expected halogenated dihydropyrans are obtained as the final products, with the iron halide acting as both a Lewis acid and nucleophilic halide source that terminates the reaction (Scheme 5, top). However, when an internal alkyne was

Scheme 5. Prins Cyclization of Alkynols



placed at the substrate, the pyran adduct was obtained as a minor product, with the preferential formation of the regioisomeric alkylidenetetrahydrofuran that arises from the corresponding *5-exo-dig* cyclization on the oxocarbenium intermediate. This behavior is also illustrated in the reaction with homopropargyldiynes (Scheme 5, bottom), in which bis-alkylidenetetrahydofurans are obtained as a consequence of the structure of the intermediate generated during the Prins cyclization that undergoes a molecular reorganization, which

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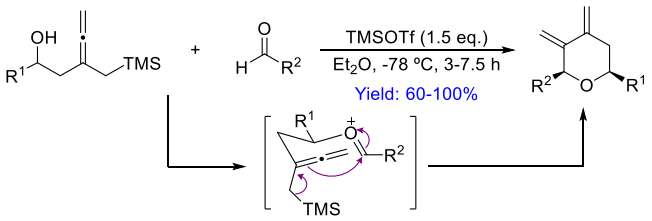
forms an open-chain oxocarbenioum ion, the latter cyclizing to the final product.

Chiral homoallenyl alcohols have been also studied in one example of a TMSOTf-promoted Prins cyclization (Scheme 6).[10] In this particular case, the presence of a trimethylsilyl

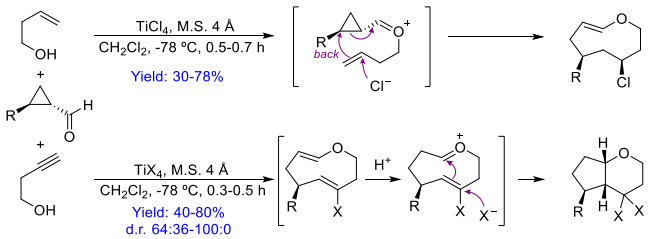
Scheme 6. Prins Cyclization of Chiral Allenyl Alcohols



group at an allylic position with respect to the allene moiety was necessary for initiating the cyclization step. This strategy allowed the preparation of dimethylidenetetrahydropyrans in good to excellent yields and as a single diastereoisomer.

Very recently, Banerjee and co-workers have studied the behavior of cyclopropanecarbaldehydes as substrates in the Prins type reaction.[11] The particular nature of the cyclopropane ring attached to the aldehyde moiety makes this transformation very interesting from a synthetic point of view, since it represents a straightforward methodology for accessing oxygen-containing medium-sized rings by the concomitant ring opening of the cyclopropane (Scheme 7). In this reaction, the

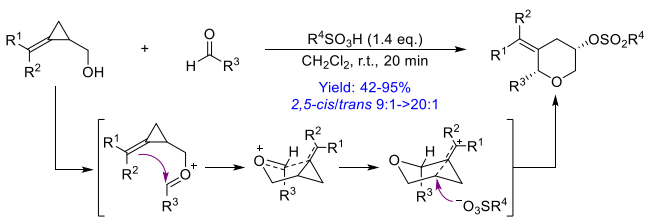
Scheme 7. Prins Reaction of Cyclopropanecarbaldehydes



use of an alkyne as the π-donor in the reaction implies the addition of a second halide in a subsequent transannular Prins-type reaction, leading to the formation of a bicyclic core in moderate to good yield.

Similarly, methylenecyclopropanecarbynols have been evaluated in a Prins cyclization promoted by a Brønsted acid such as MsOH or *p*-TsOH (Scheme 8).[12] This reaction generates alkylidenetetrahydropyrans with almost complete 2,5-*cis* stereoselection and also retaining the configuration of the alkylidene substituent of the starting material. The mechanism proposed by the authors is based on a Prins reaction that

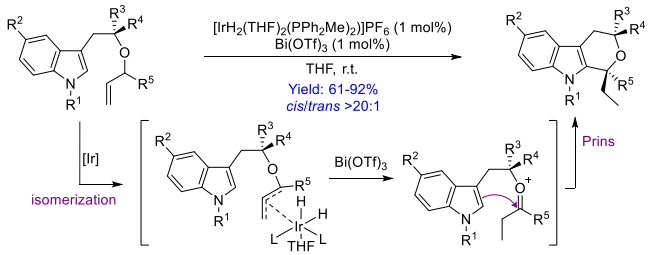
Scheme 8. Prins Cyclization of Methylenecyclopropanecarbynols



occurs through a six-membered transition state in a chairlike conformation. Interestingly, the reaction was also demonstrated to be fully enantiospecific, showing complete transfer of enantiomeric excess from the substrate to the product when an enantiomerically enriched carbinol was employed as the starting material.

There has also been intense research directed toward the identification of alternative reagents that can be employed as the source of the aldehyde/ketone electrophilic reagent. This enables the use of substrates that are not compatible with the typically strong Lewis/Brønsted acids employed to promote the Prins reaction or that fail to generate the required oxocarbenium ion. This is the case when ketones are employed as substrates, due to their poor ability to condense with the homoallylic alcohol because of their poorer electrophilicity compared to that of aldehydes. A solution to this problem involves the possibility of employing allylic alcohols together with a transition-metal catalyst, the latter being involved in the isomerization of the allylic alcohol to generate a thermodynamically more stable enol intermediate. Next, this intermediate undergoes a Prins reaction in the presence of a Lewis acid used as a second catalyst that generates the reactive oxocarbenium ion intermediate. A good example of this approach is shown in Scheme 9, in which Scheidt and co-

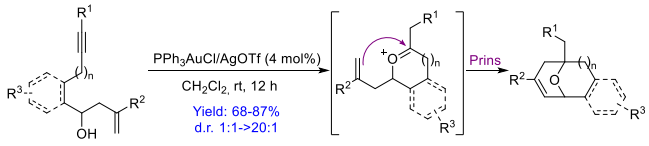
Scheme 9. [Ir]/Bi(OTf)$_3$-Catalyzed Prins Cyclization on Allylic Ethers



workers employed a combination of an iridium-based catalyst with bismuth triflate for the Prins cyclization of indolyl-substituted allylic ethers to obtain a variety of fused pyranoindoles in good yields.[13]

Another important methodology for the easy formation of oxonium ions has been introduced by Wang and co-workers employing Au(I) as a catalyst (Scheme 10).[14] In this example,

Scheme 10. Au(I)-Catalyzed Prins Cyclization



homoallylic alcohols containing an alkyne lateral chain underwent cyclization in the presence of a catalytic amount of cationic gold catalyst, the latter being involved in the activation of the alkyne moiety. This generated a cyclic oxonium ion that subsequently experienced an intramolecular Prins-type reaction that delivered the final oxabicyclo[3.3.1]-alkane adducts.

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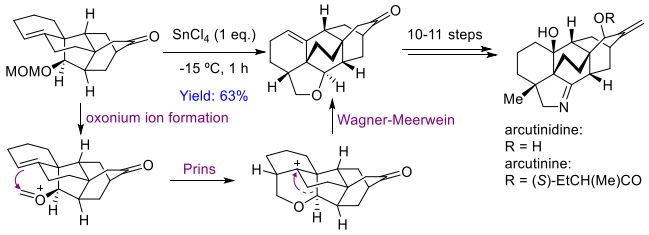
4. PRINS REACTION IN CASCADE PROCCESSES

The inherent mechanistic profile of the Prins reaction makes it very appropriate for the implementation of a cascade process, through the design of a functionalized starting material in which there is a secondary functionality ready to interact with the carbocation intermediate formed after the initial addition of the π-component to the oxicarbenium ion.[15] Scheme 11

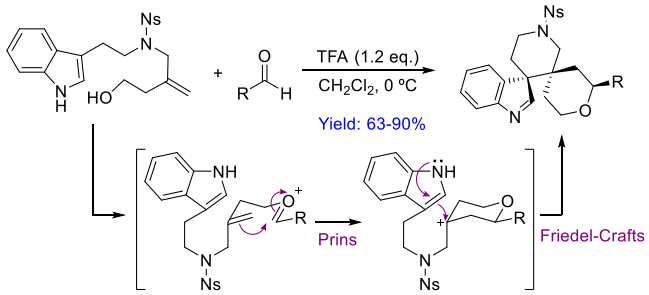
Scheme 11. Total Synthesis of Arcutinidine and Arcutinine through Cascade Prins/Wagner−Meerwein



shows a representative example of this strategy in total synthesis. In their report, Li and co-workers have used a Prins cyclization followed by a Wagner−Meerwein rearrangement that enables the construction of the central core of arcutinidine and arcutinine natural products.[16] Under the optimized reaction conditions, the reaction proceeded with complete diastereocontrol during the cyclization step which, in combination with the stereospecific nature of the subsequent Wagner−Meerwein rearrangement, led to the target compound with complete stereocontrol. Remarkably, this transformation could also be carried out on a gram scale, which facilitated its application to the total synthesis of both natural products through an additional 10 and 11 steps, respectively.

The carbocation that is formed after the initial Prins cyclization can also serve as a reactive center for initiating other types of cascades. For instance, Scheme 12 shows one

Scheme 12. TFA-Promoted Cascade Prins/Friedel−Crafts Reaction

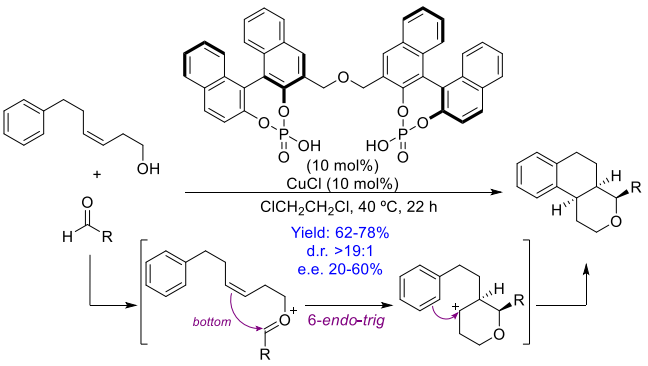


example in which a nucleophilic functional group present in the starting material can undergo addition to the carbocation, leading to more complex structures.[17] In this case, an indole moiety was incorporated as the nucleophilic site, which is involved in a Friedel−Crafts cyclization that followed the Prins reaction. The overall process occurred with complete diastereoselectivity.

6. ENANTIOSELECTIVE PRINS CYCLIZATION

In the particular case of the Prins cyclization, several methodologies based on chiral auxiliaries have been recently developed for accessing enantioenriched cyclic compounds in an asymmetric way. In this sense, strategies that use asymmetric catalysis are scarce. One of the first catalytic enantioselective version of the Prins cyclization was reported only few years ago by Lalli and van de Weghe (Scheme 13).[18]

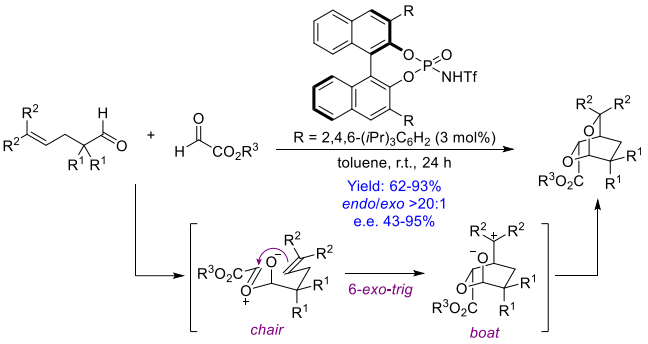
Scheme 13. CuCl/BINOL-Derived Diphosphoric Acid Catalyzed Prins Cyclization



In this report, a combination of a Lewis acid (CuCl) together with a chiral Brønsted bis-phosphoric acid derived from BINOL was identified as the best catalyst system. The overall process consists of a cascade Prins/intramolecular Friedel−Crafts type alkylation, leading to a family of benzo[*f*]-isochromenes in good yield and diastereoselectivities and moderate enantioselectivities.

Chiral *N*-triflylphosphoramides have been also evaluated as catalysts for the enantioselective Prins cyclization between different enals and glyoxylates (Scheme 14).[19] In this reaction,

Scheme 14. *N*-Triflylphosphoramide Catalyzed Enantioselective Prins Cyclization



the oxocarbenium ion is generated by the addition of the glyoxylate aldehyde oxygen to the enal substrate in the presence of the Brønsted acid and is followed by the Prins cyclization and final carbocationic quench by the remaining hemiacetal moiety, ending up in the formation of a bicyclic compound. The selectivity observed in this process can be explained by the initial attack of the alkene moiety to the *E*-configured carbenium ion under stereochemical control by the chiral acid catalyst followed by a 6-*exo*-*trig* cyclization and the final nucleophilic addition of the hemiacetal through a boatlike conformation, producing the 2,6-dioxabicyclo[2.2.2]octane in good yields and excellent enantioselectivities in almost all cases.

A more general strategy for performing a catalytic enantioselective Prins cyclization has been presented by List and co-workers, enabling the straightforward synthesis of

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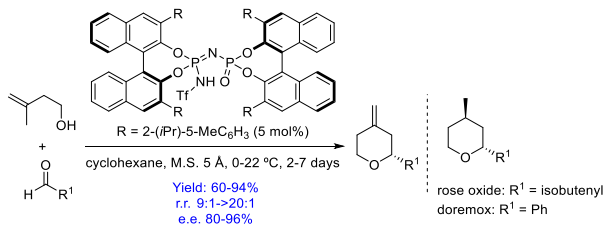
tetrahydropyrans through the reaction between a simple homoallylic alcohol and an aliphatic or an (hetero)aromatic aldehyde (Scheme 15).[20] In this particular case, the imino-

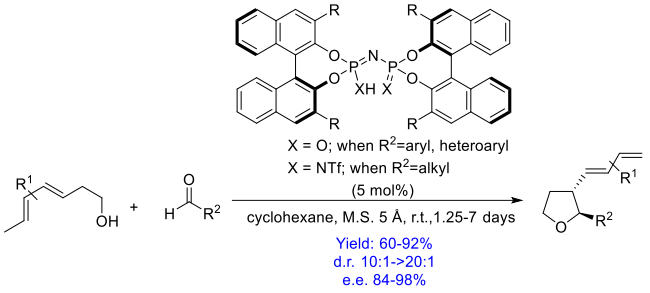
Scheme 15. BINOL-Derived Imino-Imidodiphosphate Catalyzed Prins Cyclization



imidodiphosphate catalyst participates in the reaction by catalyzing the process in a confined environment that enables a very efficient transfer of stereochemical information from the catalyst to the product. This methodology has been applied for the synthesis of several fragrances by simple hydrogenation of the exocyclic double bond.

Similar reaction conditions were also used for the preparation of enantioenriched tetrahydrofurans, in this case involving a 5-*exo-trig* cyclization in the intramolecular addition to the oxocarbenium ion (Scheme 16).[21] In this particular case,

Scheme 16. BINOL-Derived Imino-Imidodiphosphate-Catalyzed Prins Cyclization

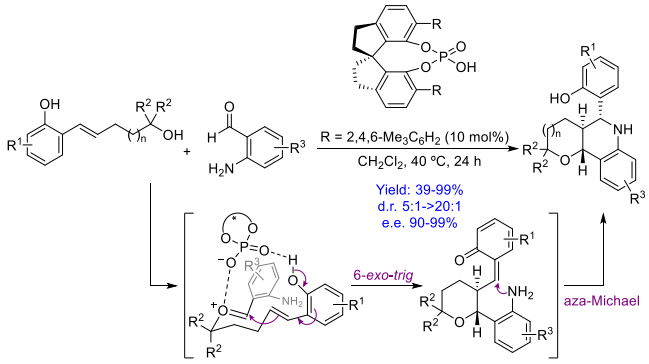


a less acidic chiral imidodiphosphate catalyst was found to be the most efficient one when the reaction was performed using aromatic or heteroaromatic aldehydes, while a more acidic imidodiphosphorimidate was necessary when aliphatic aldehydes were used. This methodology allows the preparation of 2,3-disubstituted tetrahydrofurans in excellent *trans*-selectivity with enantioselectivities in the range of 84−98%.

Very recently, these two last strategies have been used for performing an enantioselective cascade Prins cyclization/aza-Michael process (Scheme 17).[22] For this reaction, 3- or 4-enols bearing a 2-hydroxyphenyl substituent were combined with substituted anthranilic aldehydes, both reagents condensing under phosphoric acid catalysis to generate the oxocarbenium ion. After the Prins cyclization took place in an *exo-trig* mode, a *o*-quinone methide was generated, which underwent an aza-Michael reaction. The overall process produced a single diastereoisomer in good yields and excellent enantioselectivities in the presence of a chiral phosphoric acid catalyst, which not only provided enantiocontrol to the Prins cyclization but also assisted the dearomatization of the phenol that initiated the process through a rigid chairlike transition state.

In conclusion, impressive advances have been made in the past few years that have improved the potential of the Prins

Scheme 17. SPINOL-Derived Phosphoric Acid Catalyzed Cascade Prins/Aza-Michael Cyclization



reaction as a general tool in synthesis. Not only have new catalytic systems been developed that enable carrying out the reaction using more accessible reagents/catalysts or under environmentally friendly conditions but also the reaction has significantly widened its scope through the use of complex starting materials that have unveiled previously untrodden reactivity profiles. In addition, the recently reported catalytic and enantioselective versions of this venerable reaction have contributed to solve a longstanding problem in trying to apply this reaction for the synthesis of a chiral compound in an enantioenriched form. Despite such enormous advances, this is still a highly active field and future improvements are also expected in the coming years, especially focused on potential applications of these new variants in high scale, directed toward chemical production at an industrial level.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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Biographies

Efraim Reyes was born in Galdakao (Bizkaia, Spain) in 1978. He graduated from the University of the Basque Country (UPV/EHU) in 2001 and received his Ph.D. in 2006, under the direction of Prof. Dr. D. Badia and Prof. Jose L. Vicario. During his Ph.D. studies, he had a short stay at the University of Stockholm (Sweden) to obtain the "international doctor" distinction. After postdoctoral studies in 2007−2008 at the Center for Catalysis of the University of Aarhus (Denmark) under the supervision of Prof. Dr. K. A. Jørgensen, he returned to the Research Group of Asymmetric Synthesis (UPV/EHU), where he is currently working as an Associate Professor. Recently (2022), he has moved to the Georg August University in Göttingen (Germany) as a visiting Professor in the group of Prof. Lutz Ackermann to develop new electrocatalytic C−H functionalizations under metal catalysis. His current research is focused on asymmetric catalysis.

Liher Prieto obtained his degree in chemistry in 2012 and the Ph.D. in 2017 under de supervision of Prof. Jose L. Vicario at the University of the Basque Country (UPV/EHU). During his career, he has had several research stays at different universities: Erasmus student exchange at the University of Strathclyde (Glasgow, UK) under the supervision of Prof. Craig Jamieson, predoctoral stay at The Scripps Research Institute (La Jolla, CA, USA) in the group of Prof. Phil S. Baran, and postdoctoral studies at the University of Toronto (Canada) under the supervision of Prof. Mark Lautens. In 2018, Liher was appointed Assistant Professor at UPV/EHU. In 2019, Liher moved to the University of Toronto (Canada) as Visiting Professor in the group of Prof. Mark Lautens for 9 months. Now Liher's research is focused on the development of multicatalytic asymmetric transformations merging metallo- and organocatalysis.

Uxue Uria was born in Sopela (Bizkaia) in 1982. She graduated from the University of the Basque Country, Basque Country, Spain, in 2005 and received her Ph.D. in 2009, working in the development of organocatalytic conjugate additions under the direction of Prof. Dr. D. Badia and Prof. Jose L. Vicario. After postdoctoral studies with the group of Magnus Rueping in the RWTH Aachen (Germany) from 2010 to 2012, working in the use of chiral Brønsted acid catalysts, she returned to Bilbao first as a postdoctoral associate (Juan de la Cierva) and now as an Associate Professor. Her current research activity focuses on the application of organocatalysis to trigger challenging organic reactions and their application to the synthesis of natural products.

Luisa Carrillo was born in Bilbao in 1965. She graduated from the University of the Basque Country in 1988 and received her Ph.D. in 1998, working in the Department of Organic Chemistry for the Faculty of Science at the same University. Next she joined the Group of Asymmetric Synthesis under the direction of Prof. Dr. Badia. Her current research interests focus on the design of new methodologies in asymmetric synthesis and their application in the synthesis of pharmacologically active compounds.

Jose L. Vicario was born in Elda (Alicante, Spain) in 1973. He graduated from the University of the Basque Country in 1996 and received his Ph.D. in 2000 at the same University. After postdoctoral studies in 2002 at the RWTH Aachen (Germany), under the supervision of Prof. Dieter Enders, he returned to the Department of Organic and Inorganic Chemistry of the University of the Basque Country to start his independent career, where he is currently Full Professor. Current research interests focus on the design of new methodologies in asymmetric synthesis, especially asymmetric organocatalysis, and the stereocontrolled synthesis of pharmacologically active compounds.

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■ ABBREVIATIONS

BINOL,1,1′-bi-2-naphthol; Ms,mesyl; MS,molecular sieves; Ns,nosyl; SPINOL,1,1′-spirobiindane-7,7′-diol; Tf,triflyl; THF,tetrahydrofuran; TMS,trimethylsilyl; Ts,toluenesulfonyl

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