Asymmetric Catalytic Transformations of Aza-*ortho*- and Aza-*para*-Quinone Methides

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ASYMMETRIC CATALYTIC TRANSFORMATIONS

aza-*o*-QM   aza-*p*-QM

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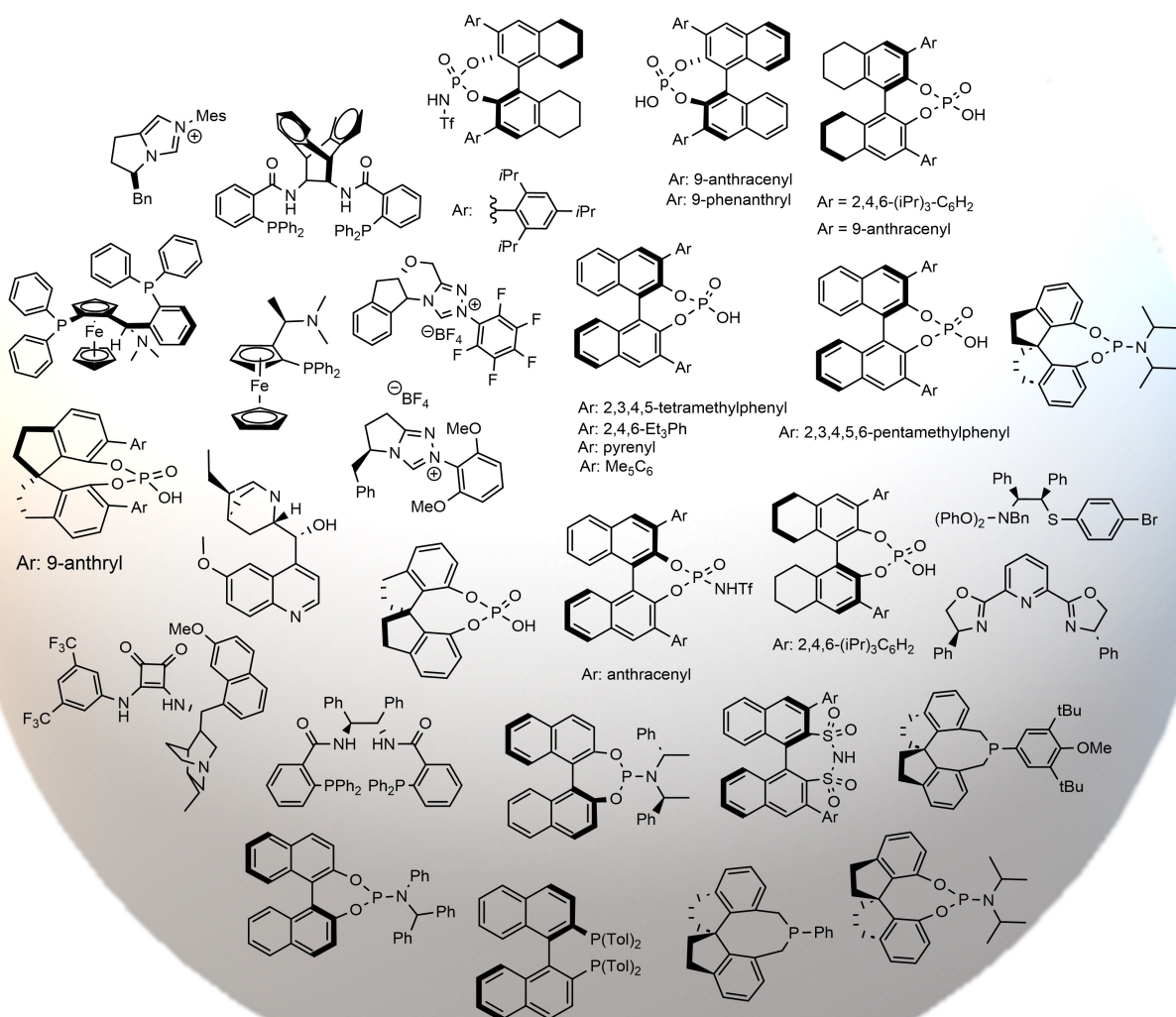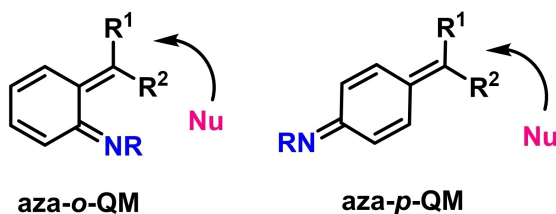
The catalytic methodologies for the derivatization of aza-QM have recently appeared in the literature and involve organo-catalytic and organometallic approaches. This review aims at analyzing the diverse catalytic systems involving chiral NHC carbenes, phosphoric acids, phosphoramidites, phosphine and copper and palladium catalysis showing its applicability for the synthesis of a diverse away of N-containing compounds which in many cases have biological activity.

1. Introduction

Quinone species, such as quinone-imines, quinone methides (QM), and aza-quinone methides (aza-QM), comprise over the 40% of the reactive metabolites. In the organism, cytochromes P450 and peroxidases catalyze the formation of these highly electrophilic species, which either tend to form covalent bonds with nucleophilic sites of the proteins and DNA in cells causing cytotoxicity, immunotoxicity, and carcinogenesis[1] or undergo its deactivation by hydration in water or reaction with glutathione.[2] Many efforts have been made in recent years in order to avoid the formation of these reactive molecules. Recently, a deep learning approach has been developed in order to predict its formation from different drugs, such as acetoamidophen or lumiracoxib.[3]
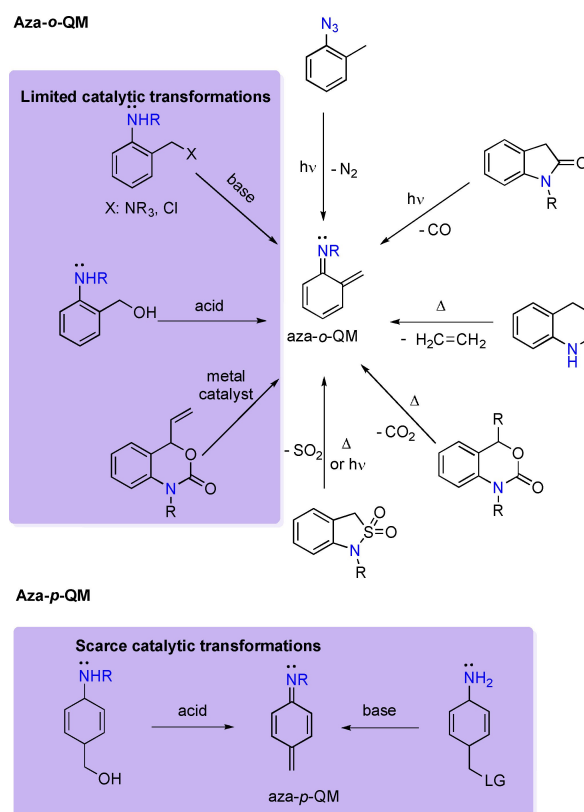
On the other hand, these QMs are intriguing from the point of view of its chemical reactivity. They consist of a prochiral highly conjugated molecule prone to react with nucleophiles at a specific position. In fact, many struggles were directed to develop strategies for the derivatization of these reactive molecules.[4] While QM are known for more than a century,[5] and they have been widely applied for medicinal, biological purposes,[6] the aza-QM have received much less attention.

The aza-QMs or also called quinone methide imines consist of a cyclohexadiene moiety conjugated with an imine group and an exo-methylene component in para-conjugation (aza-p-QM) or ortho-conjugation (aza-o-QM) (Figure 1). They are neutral molecules with an aromatic zwitterionic resonance structure, responsible of its electrophilicity toward the 1,4- and 1,6- position respectively. However, aza-QM are less reactive that the related QM as they bear a less electronegative nitrogen atom compared to the oxygen atom present in the QMs. Consequently, the zwitterionic form is less stabilized.

Despite of this fact, they are difficult to isolate because of their trend to rearomatize. They are always generated *in situ* in the reaction media from an appropriate source. The reactivity of aza-o-QM has been well studied in recent years and a wide variety of starting materials serve as precursors for their synthesis (Scheme 1): (2-aminophenyl)methanol under acidic conditions,[7] 2-(chloromethyl)aniline under basic conditions,[8] thermal or photochemical conditions by extrusion of a labile group (e.g. CO, CO_2, N_2 ethene,).[4] However, if we aim our focus on catalytic transformations of derivatization of aza-o-QM, we can only find basic, acidic or metal catalysis.

On the contrary, the aza-p-QMs have been far less explored, and scarce catalytic methods have been reported to date. The two existing approaches are based either on dehydration under

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Scheme 1. Methods for the generation of aza-o-QM and aza-p-QM.
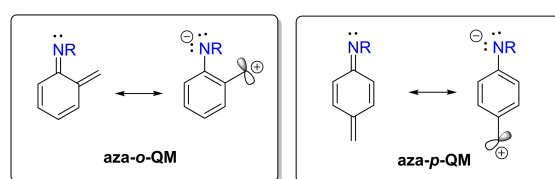
Figure 1. Resonance structures of aza-o-QMs and aza-p-QM.

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acidic conditions from a (4-aminophenyl)methanol derivative, or deprotonation of the aniline to generate the quinone methide.

The aza-QM are also a source of inspiration in medicinal,[9,10] material,[11] or polymer chemistry.[12] In medicinal chemistry, they have been used as aminoferrocene-based prodrugs which are activated in cells in the presence of specific amounts of H_2O_2 leading to the active cancer drug and an aza-QM as a side product.[7] One example as adaptive materials deals with stimulus-responsive supramolecular assemblies, that is a molecule that reacts under a reducing media generating an aza-QM. The aza-QM is deactivated in the aqueous solution, and the target molecule which is able to form supramolecular assemblies.[9]

They are as well decomposition products of, a special kind of polymer that is able to respond to external stimuli: the self-immolative polymers.[13] This unique molecule consists of a polymer chain that it is capped with a protecting group (PG). When the PG is *in situ* removed by a trigger, it generates the decomposition of the polymer from head to tail and the release of the target. During the 1,4- or 1,6-elimination process, reactive aza-QMs are generated and subsequently deactivated by a nucleophile, generally water, to form fluorescent aniline molecules.

Although Rueping and coworkers recently published a review article covering the aza-*o*-QM reactivity in enantioselective transformations and Schneider and coworkers published a review on cycloadditions of *o*-QM including aza-*o*-QM,[14] we believe there is still room for another article as we intend to give a clear overview of the last advances in the asymmetric catalytic transformations that involve the use of aza-*o*-QMs or aza-*p*-QMs for the construction of novel chiral N-heterocyclic structures, giving an special emphasis on the mode of action of the organo and metal catalysts. A chronological order in the different chapters will be followed.

2. Catalytic Asymmetric Reactions of Aza-Quinone Methides

While the catalytic methodologies for the derivatization of *o*-QM and *p*-QM have been extensively developed in the last decades for the synthesis of chiral diarylmethanes and chiral phenols, there is a limited number of catalytic methods that involve aza-*o*-QM, namely 1,4-conjugate additions, or aza-Diels Alder reactions. Moreover, the methods for the derivatization of aza-*p*-QMs are quite scarce, specifically 1,6-conjugate addition or 1,8-conjugate additions, underdeveloped methods in general (Figure 2).[15]

The use of chiral catalysts for the transformation of aza-QM enable the obtaining of enantioenriched N-heterocycles in a more efficient manner. As stated by Anastas in his dodecalogue, one of the twelve principles of the Green Chemistry considers highly desirable the use of catalysts in terms of a higher atom economy and sustainability of a process.[16] Therefore, the use of any catalytic transformation is highly desirable in every synthetic process which needs of activation in order to proceed. From now on, we will describe the recent reports on the generation and derivatization of aza-*o*-QM and aza-*p*-QM by catalytic methodologies.

2.1. Catalytic transformation of aza-ortho-quinone methides (aza-*o*-QM)

Aza-*o*-QMs, also called o-quinone methide imines or as aza-*o*-xylylenes were observed for the first time by Burgess and McCullagh in 1966,[17] who isolated a cycloaddition product arising from aza-*o*-QM intermediates. From that date, a vast number of methodologies have appeared in the literature. Many of these strategies involved aza-*o*-QM as electron-poor dienes which undergo inverse-electron demand Diels-Alder reactions.[18]

A straightforward and efficient method for the generation of an aza-*o*-QM was reported by Corey in 1999.[19] In this seminal work, an amide or sulfonamide derivatives of o-chlorometh-

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Aitor Maestro obtained his PhD (2019) from the University of the Basque Country, where he worked with Prof. Francisco Palacios and Dr. Javier Vicario on the synthesis of amino-phosphonates and asymmetric organocatalysis. After that, he worked as a postdoctoral research associate on enantioselective Cu(I)-catalysis, with Prof. Syuzanna Harutyunyan (University of Groningen, 2020–2021), and on the mechanism and applications of the CuAAC with Prof. Allan J.B. Watson (University of St. Andrews, 2021–2022). He is currently a post-doc in the group of Prof. Oliver Kappe (University of Graz), working on asymmetric catalysis in continuous flow. His research interests include the development of sustainable processes and asymmetric catalysis.
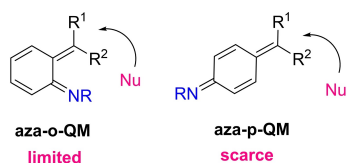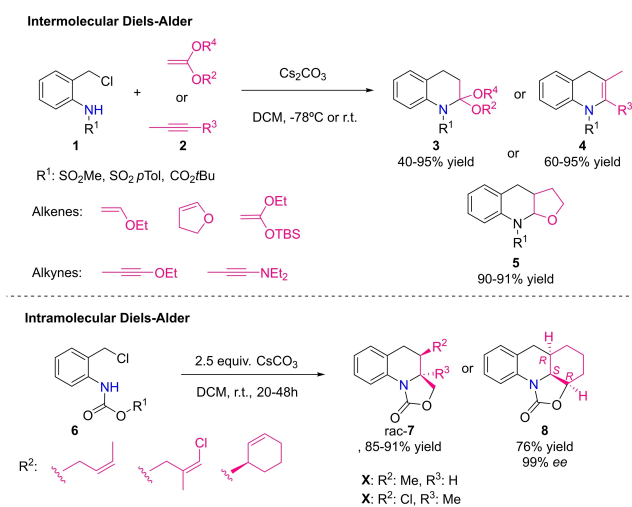
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Figure 2. Catalytic conjugate addition to aza-*o*-QMs and aza-*p*-QMs.

Scheme 3. Enantioselective annulations for dihydroquinolones by in situ generation of azolium enolates.

ylaniline were slowly added to a solution of Cs$_2$CO$_3$ and ethyl vinyl ether in DCM at $-78\,°$C to yield 2-substituted tetrahydroquinolines (Scheme 2). This methodology was applied for the synthesis of diverse tetrahydroquinolines **3** and dihydroquinolines **4** derivatives. The outcome of the reaction can be explained in terms of the formation of a reactive aza-*o*-QM which play the role of diene in the inverse Diels Alder reaction with different dienophiles. Besides, the intramolecular version of this transformation was as well explored (Scheme 2) to yield tricyciclic **7** and tetracyclic tetrahydroquinolines **8**.
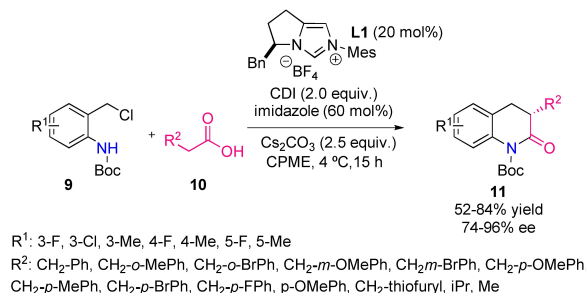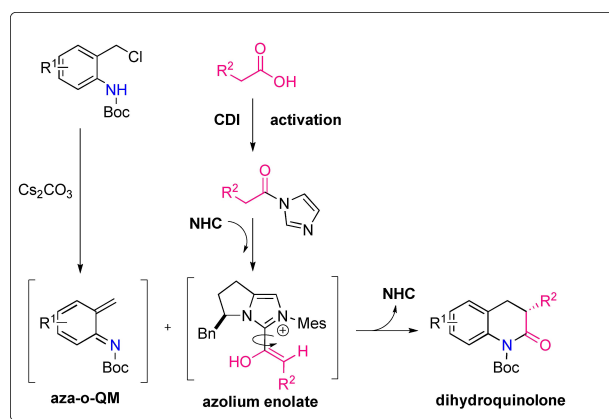
However, the development of enantioselective catalytic methodologies had a posterior development. The first metal catalyzed methodology dates in 2008, while the first organocatalytic methodology dates from 2014. In the next two subsections the enantioselective transformations of aza-*o*-QM will be described in detail.

2.1.1. Organocatalysis

The first catalytic methodology using a base-induced generation of aza-QM was developed by the group of Scheidt in 2014.[20] In this work, an organocatalytic method for the synthesis of chiral dihydroquinolones employing *N*-heterocyclic carbenes (NHCs) was carried out (Scheme 3). For that purpose, *N*-(o-chloromethyl)aryl amide **9** was treated with Cs$_2$CO$_3$, similarly to the seminal work of Corey, forming the reactive aza-
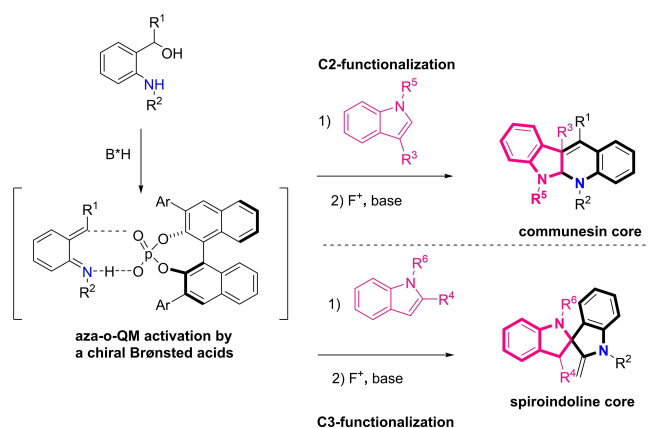
o-QM. Simultaneously, the chiral NHC precatalyst was activated in the presence of Cs$_2$CO$_3$ and consecutively, reacted with an activated acyclic carboxylic acid to generate the stable azolium enolate. This intermediate reacted with the transient aza-*o*-QM following either a 1,4-conjugate addition-acylation pathway or a [4+2] cycloaddition route to yield the chiral dihydroquinolones **11** in an enantioselective fashion (Scheme 3). The judicious choice of a carboxylic acid as nucleophile, avoided dimerization issues typical of aldehydes.

This methodology was utilised on a variety of carboxylic derivatives bearing aryl and alkyl substituents (R^2), and electron-rich and electron-poor aza-QM precursors, affording excellent enantioselectivities and yields (Scheme 3).

In 2004 Akiyama[21] and Terada,[22] made a breakthrough discovery when they found out that chiral binaphthol-derived phosphoric acids performed as efficient chiral Brønsted acids for asymmetric Mannich type reactions. Since then, many other enantioselective transformations using chiral phosphoric acids have been reported until today.[23] In 2015, the group of Rueping conceived a methodology for the generation of a transient aza-*o*-QM happening through a dehydration reaction of a 2-aminobenzyl alcohol with a chiral Brønsted acid as organocatalyst (Scheme 4).

The reaction with 3-substituted indoles afforded the formation of chiral communesin derivatives, while the reaction with a 2-substituted indole enables the obtaining of chiral spiroindoline derivatives (Scheme 4). Both compounds are motifs present in many drugs and pharmaceuticals.[24,25]

Scheme 2. Synthesis of tetrahydroquinolines through intermolecular and intramolecular aza-Diels-Alder of aza-*o*-QM and electron riched alkenes.

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Scheme 4. Generation of aza-o-QM through BINOL derived phosphoric acid catalysis for the synthesis of communesin alkaloids and spiroindolines.

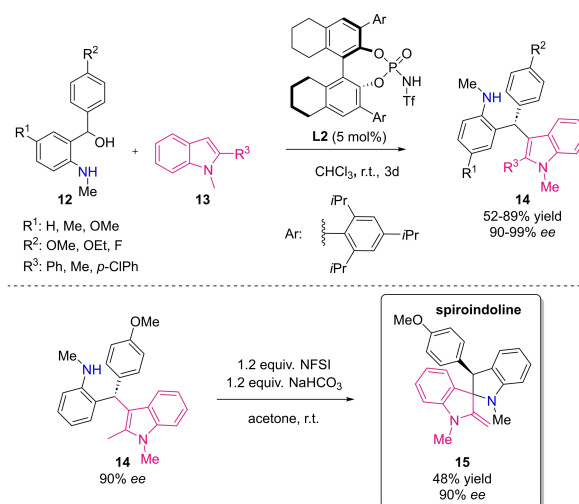**Scheme 5.** Asymmetric Brønsted acid catalyzed synthesis of triarylmethanes – construction of spiroindoline scaffolds.

The combination of Brønsted acid catalysis and aza-o-QMs have been stablished as a good match for the development of asymmetric transformations involving these reactive intermediates.[26] The mechanism of action is depicted in Scheme 4: the phosphoric acid (or the amide derivative) acts as a bifunctional catalyst. The acidic H of the phosphoric acid lower the LUMO orbital of the N in the aza-o-QM through hydrogen bonding or ion pairing and at the same time, the oxygen atom of the phosphoryl group coordinates to the electrophilic exo-methylene moiety forming a chiral transition state, which will procure a preferred pathway for the addition of a nucleophile.

The reaction of 2-aminobenzyl alcohols with 2-substituted indoles enabled the C3-functionalization. The ortho-amino benzyl alcohol **12** was chosen as the substrate in the presence of 5 mol% of N-triflylphosphoramide **L2** led to the obtaining of **14** in good yields and enantioselectivities. The treatment of derivative **14** with N-fluorobenzenesulfonimide (NFSI) in the presence of NaHCO₃ led to the obtaining of spiroindoline **15** (Scheme 5).

The reaction of **16** with 3-substituted indoles enabled the C2-functionalization due to the blocking of the C3-position. A wide variety of substrates with different substitution patterns and EWG and EDG provided the desired triarylmethanes **18** in good yields and excellent enantioselectivities (Scheme 6). Furthermore, the synthesis of communesin framework **19** with quaternary stereocenters was performed in a one-pot addition/ spirocyclization sequence reaction for a variety of substrates (Scheme 6).

In the same year 2015, the group of Tang carried out for the first time the generation of a quinolinium salt (aza-o-QM) by abstraction of a hydrogen of a 1,2-dihydroquinoline derivative by means of a chiral phosphoric acid.[27] The formed chiral phosphonium salt intermediate was *in situ* reduced by using Hantzsch ester yielding a chiral tetrahydroquinoline (Scheme 7).

This novel methodology allows to form an aza-o-QM intermediates under mild reaction conditions by using chiral Brønsted acid **L4** and Hantzsch ester as a hydrogen source. Besides, using this methodology chiral tetrahydroisoquinolines
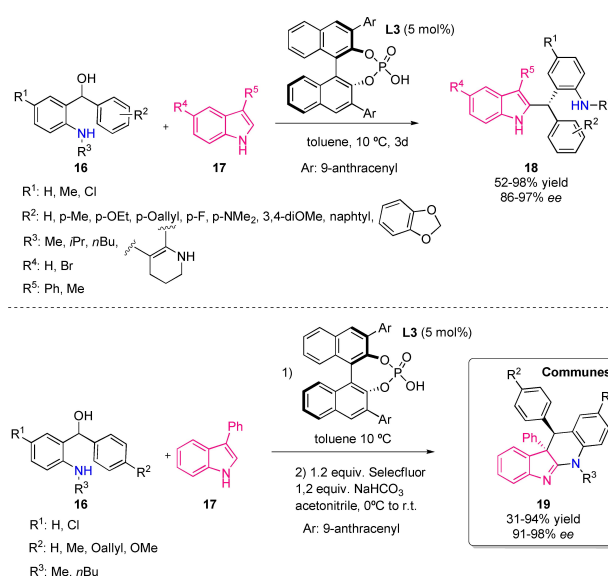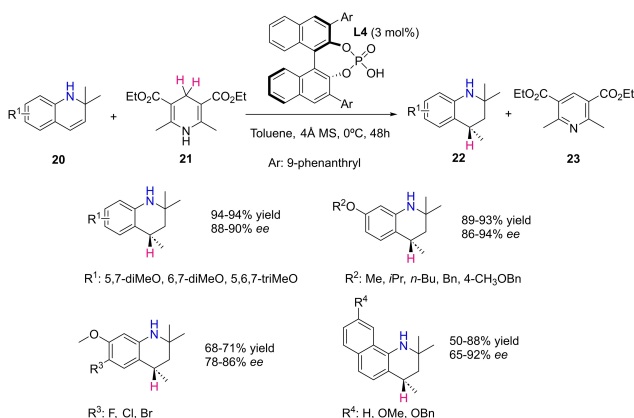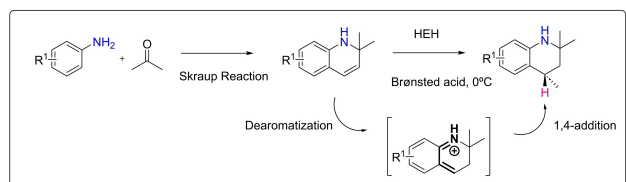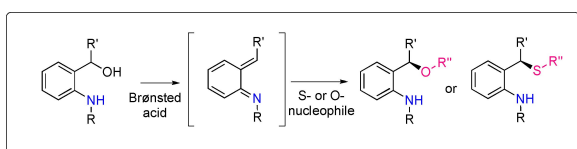

Scheme 6. Asymmetric Brønsted acid catalyzed synthesis of triarylmethanes – one-pot reaction for the construction of communesin scaffolds.

22 were obtained in high yields and enantioselectivities (*ee* up to 94%). The limitation of this methodology relies on its need to use electronriched dihydroquinolines bearing O-alkyl substituents.
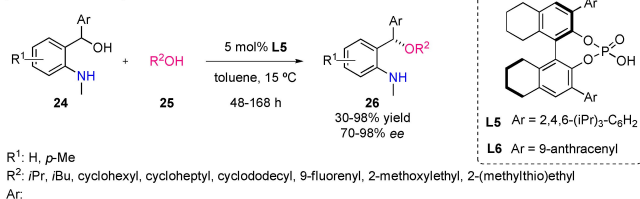
In 2016, the group of Rueping reported a novel methodology for the reaction of aza-o-QM with different O and S nucleophiles (Scheme 8).[28] For that purpose, their precedent strategy consisting of the generation of an aza-o-QM intermediate from the corresponding alcohol by using a chiral phosphoric acid was followed. The aza-o-QM was next reacted with the nucleophile affording the product in an enantioselective fashion The optically active ethers and thioethers synthesized with this methodology are valuable products as they are present in
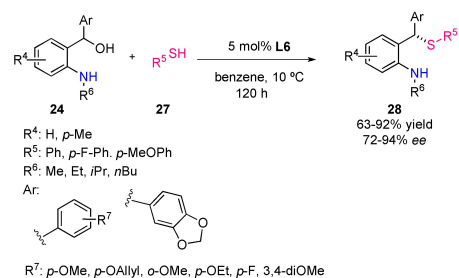
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Scheme 7. Asymmetric Brønsted acid catalyzed hydrogenation of 1,2-dihydroquinoline.

Scheme 8. Asymmetric Brønsted acid catalyzed substitution of diaryl methanols with thiols and alcohols for the synthesis of chiral thioethers and ethers.

The optimization of the reaction conditions revealed that phosphoric acids **L5** and **L6** showed the best performance in the Brønsted acid catalyzed enantioselective sulfa- and oxa-Michael additions to **24** affording the corresponding chiral ether **26** and thioether **28** in enantioselectivities up to 98 % and 94 % ee respectively (Scheme 8).

Also, in 2016, the group of Schneider published a direct and highly enantioselective synthesis of tetrahydroacridines using phosphoric acids as chiral catalysts (Scheme 9).[29] The phosphoric acid acts as a bifunctional catalyst promoting the generation of a reactive aza-*o*-QM intermediate. Next, the activation of an enamide makes it more reactive toward a Diels-Alder reaction with the aza-*o*-QM. Finally, the product formed suffers spontaneously an elimination of acetamide to yield the tetrahydrobenzo[c]acridine product (Scheme 9).
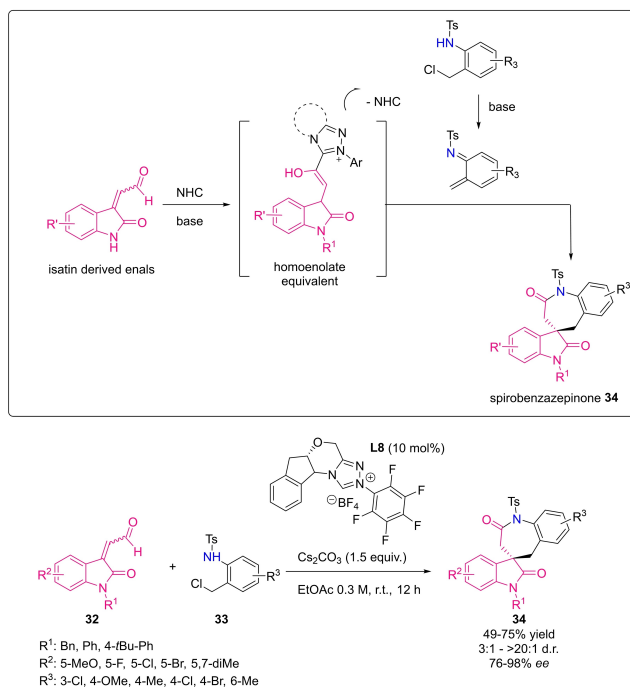
The optimized reaction conditions revealed that *N-p*-methyoxybenzyl-(PMB)-protected ortho-aminobenzhydryl alcohol **29**, tetralone-based enamide **30**, and 10 mol% of chiral BINOL-based phosphoric acid **L7** yielded the tetrahydrobenzo[c]acridine derivatives **31** in high yield and excellent selectivities. Besides, this methodology could be scaled-up to grams observing a retaining of the enantioselectivity and yield.

In order to exploit the different reactivities of aza-o-QMs and azolium enolates, the group of Enders developed in 2016 a strategy for the NHC-catalyzed asymmetric synthesis of spiro-benzazepinones, spiro-1,2-diazepinones, and spiro-1,2-oxazepinones (Scheme 10).[30] This methodology consisted of the combination of isatin-derived enals **32** and NHC-catalysis together with aza-o-quinone methides or azoalkenes, which can be readily generated in situ from N-(ortho-chloromethyl)aryl amides **33** (Scheme 10).

After the screening of different triazolium precatalyst, they found that **L8** bearing the perfluorobenzene substituent
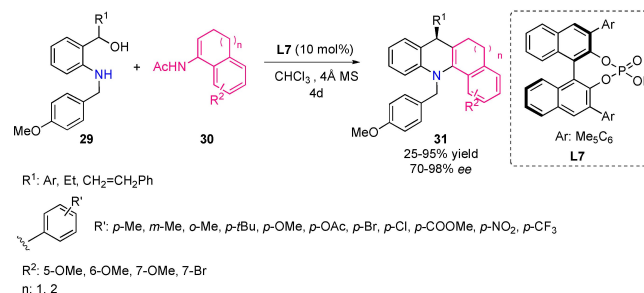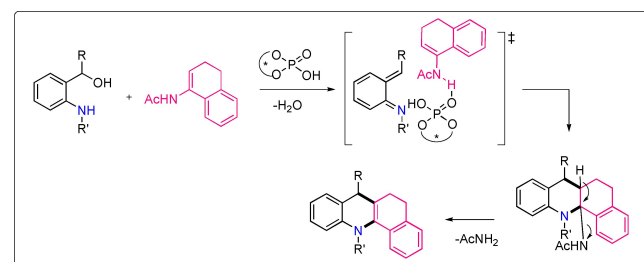
Scheme 9. Brønsted acid catalyzed addition of enamides to aza- *o*-QM for the synthesis of chiral tetrahydroacridines.

ligands in metal-catalyzed reactions, chiral auxiliaries, and organocatalysts.

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Scheme 10. NHC-catalyzed asymmetric synthesis of spirobenzazepinones, spiro-1,2-diazepinones, and spiro-1,2-oxazepinones.

Scheme 11. Catalytic cycle for the NHC-catalyzed asymmetric synthesis of spirobenzazepinones.

afforded the highest enantioselectivity in the reaction when using Cs$_2$CO$_3$ as base and EtOAc as solvent. The scope of the reaction covered a variety of spirobenzapinones in moderate to excellent diastereoselectivities and very good enantioselectivities (Scheme 10).

A plausible mechanism for the synthesis of spirobenzapinone is depicted in the Scheme 11: In a first step, the triazolium precatalyst is activated through deprotonation with the base leading to the active catalyst **A**, which then reacts with the aldehyde of the isatine derivative forming the Breslow intermediate **B**, which can evolve towards the more reactive mesomeric form **C**, which then react through Michael addition with the in situ formed aza-*o*-QM giving the reactive intermediate **D** which deliver the chiral spiro benzopinone regenerating the NHC catalyst **A**.

In 2017, Schneider and coworkers published another work on phosphoric acid catalysis for the synthesis of 1,4-dihydroquinoline-3-carboxylates, consisting of the same principle that in their previous work (Scheme 12).[31] In this article, the *in situ* formed aza-*o*-QM through dehydration is reacted with a 1,3-dicarbonyl compound affording the 1,4-dihydroxiquinoline derivative in a stereoselective fashion. The chiral phosphoric acid acts both as a bifunctional catalyst activating the aza-*o*-QM and the enol form of the β-keto ester (Figure 3).

The transformation could be extended to different ortho-aminobenzhydryl alcohols **35** and a wide variety of β-keto esters **36** and by using the chiral phosphoric acid **L9** bearing a 2,3,4,5,6-pentamethylphenyl group or **L10** bearing 2,4,6-Et$_3$Ph at the 3,3'-position and affording the 1,4-dihydroquinolines **37** in enantioselectivities up to 88% *ee* (Scheme 12).
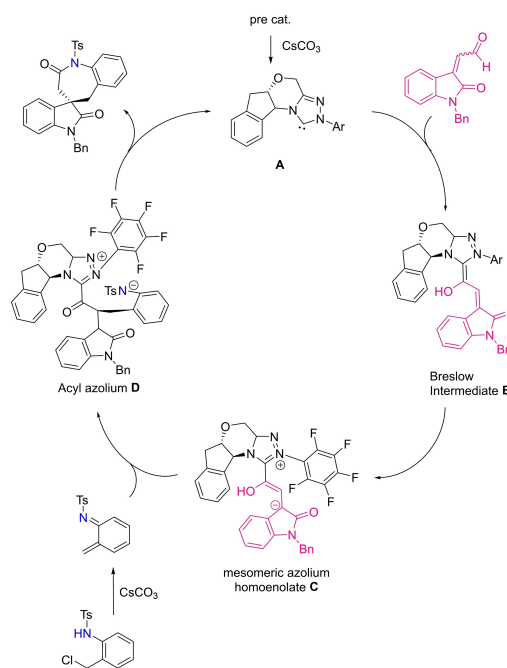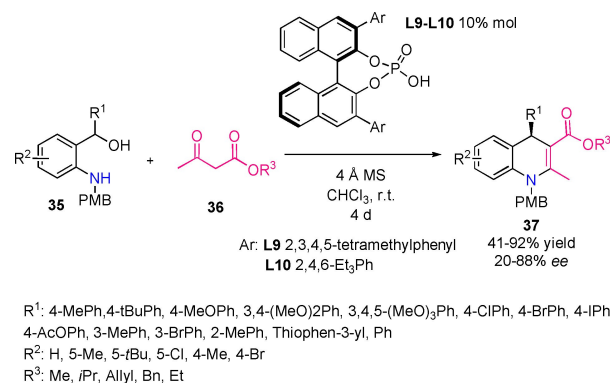
Scheme 12. Brønsted acid-catalyzed, enantioselective synthesis of 1,4-dihydroquinoline-3-carboxylates via in situ generated ortho-quinone methide imines.
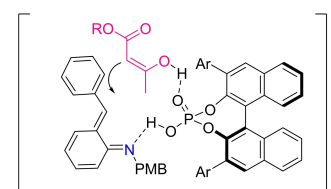
Figure 3. Proposed transition state of the chiral phosphoric acid: o-aza QM and the enol form of the β-keto ester.

To further demonstrate the synthetic applicability of the prepared 1,4-dihydroquinolines, they were subjected to hydrogenation (Scheme 13). Firstly, using chemoselective hydrogenation of the enolate double bond afforded product **38** in 91%

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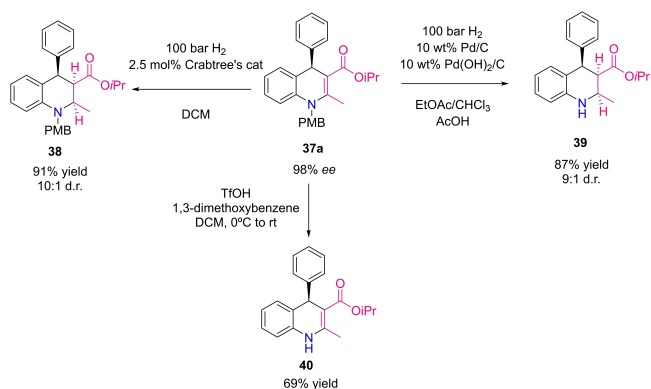
Scheme 13. Synthetic applicability of 1,4-dihydroquinoline **37 a**.

yield and 10:1 d.r. Secondly, the derivative **37 a** was hydrogenated and deprotected using both palladium on charcoal and Pearlman's catalyst in combination with molecular hydrogen to afford derivative **39** in 87 % yield. Finally, deprotection of the *N*-atom using acidic conditions afforded product **40** in 69 % yield,

In 2018, the group of Schneider went forward with their research program on development of asymmetric transformations catalyzed by chiral organocatalysts using aza-*o*-QM as reactive intermediates. Firstly, in early 2018, a work on intramolecular aza-Diels-Alder reactions (ADAR) of ortho-quinone methide imines was reported (Scheme 14).[32] In this article, an intramolecular version of an aza-Diels-Alder reaction was developed. For this purpose, a screening of chiral BINOL-derived phosphoric acids was carried out, observing in all cases low conversions were reached. On contrast, if more reactive chiral
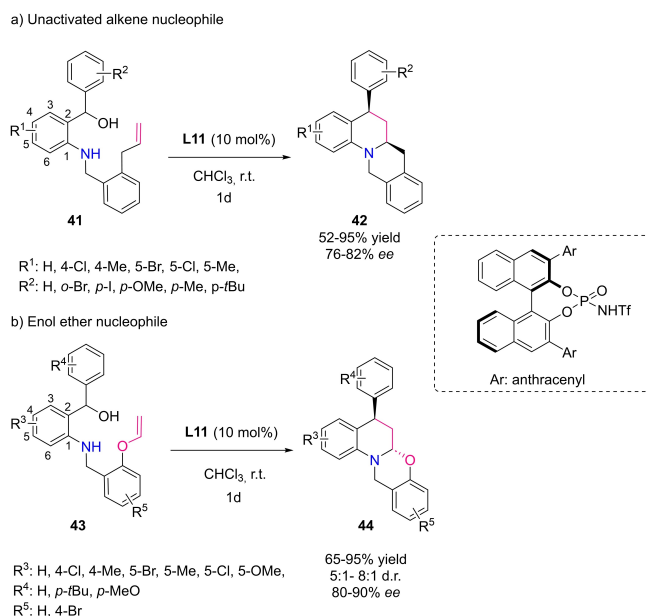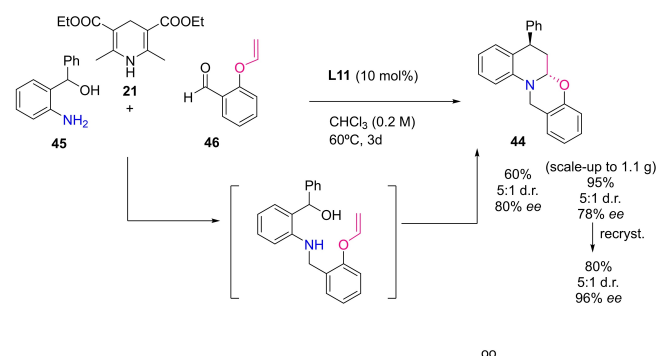
N-triflyl phosphoric acid amide catalysts were tested, higher conversions were reached, and catalyst **L11** substituted with 9-anthracenyl group at 3,3′-positions of the BINOL backbone without the need of molecular sieves afforded the highest enantioselectivity in the reaction (Scheme 14).

In order to broaden the scope of the transformation, the catalytic reaction was performed using amino alcohol derivatives with an electronically activated enol ether as the dienophile **43**. As expected, this structural change contributed to a significant rate enhancement. Contrary to quinolizidines, the major diastereomer of oxazinoquinolines **44** was 2,4-trans-configured, and the diastereoselectivity remained constant over the course of the reaction. Oxazinoquinolines **44** were obtained in good yields, with up to 8:1 d.r. and up to 90 % *ee*. (Scheme 14).

Furthermore, a domino reaction consisting in the synthesis of the substrate followed by cycloaddition was performed (Scheme 15). Starting from free amino alcohol **45**, and aldehyde **46**, by reductive amination in the presence of the organocatalyst *N*-triflyl phosphoric acid amide **L11** and Hantzsch ester, led to the intermediate, which then served as the substrate for the ADAR affording the oxazinoquinoline **44** in a 60 % yield and with good diastereo- and enantioselectivity. In order to show the applicabiblity of the reaction on a large scale with a mínimum catalyst loading (1 mol%). This scaled-up reaction afforded 1.1 g of the product **44** in good yields and selectivities (Scheme 15).

Later in 2018, Schneider and coworkers reported a work on synthesis of spirocyclic dihydroquinolones via domino Michael addition-lactamization of aza-*o*-QM (Scheme 16).[33]

The use of the additive MgSO$_4$ provokes the formation of a chiral magnesium phosphate salt Mg (CPA)$_2$ which has been determined through control experiments to be more reactive catalyst for this reaction than the free phosphoric acid. However, MgSO$_4$ has only influence in a rate enhancement and yield improvement but doesn't affect on the enantioselectivity of the reaction. The reaction between different substituted alkyne derivatives **47** and β-ketoesters **48** using phosphoric acid **L12** and in the presence of MgSO$_4$ afforded the spirocyclic dihydroquinolones **49** in high yields and selectivities.

Scheme 14. Intramolecular aza-Diels-Alder reactions of aza-*o*-QM: enantioselective synthesis of benzannulated quinolizidines.


Scheme 15. Scale-up of the intramolecular aza-Diels-Alder reactions of aza-*o*-QM.
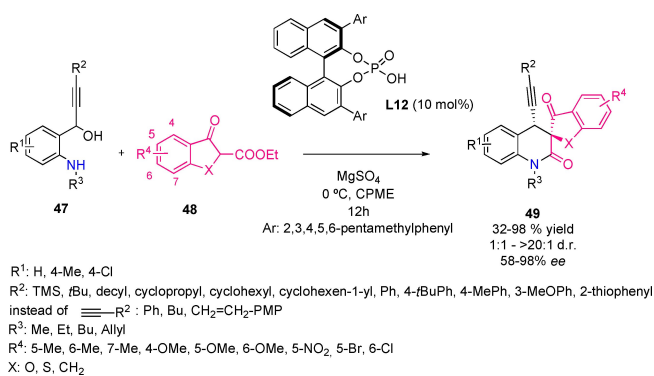
Scheme 16. Enantio- and diastereoselective synthesis of spirocyclic dihydro-quinolones via domino Michael addition-lactamization of aza-o-QM.

With this one-step domino Michael addition-lactamization process, two contiguous chiral centers (a tertiary and a quaternary carbon center) can be created with almost perfect selectivity, in a high yielding. The quinolone architecture built using this methodology is present in a wide number of drugs, as common antibiotics (e.g., ciprofloxacin) as well as some antiviral agents (e.g., HIV-1 reverse transcriptase inhibitors).

In early 2019, a carbene-catalyzed enantioselective decarboxylative annulations for the synthesis of dihydrobenzoxazinones and quinolones was reported by Cheong, Scheidt and coworkers (Scheme 17).[34] In this work, a novel methodology consisting of direct decarboxylative strategy for the generation of aza-o-quinone methides (aza-o-QMs) by a N-heterocyclic carbene was developed. The released of CO_2 enable the generation of the reactive aza-o-QM, which implies that no external oxidants or stoichiometric bases are required and represents the first use of NHC-bound aza-o-QMs as nucleophilic partners in asymmetric catalysis. After a wide screening of triazolium salts, **L13** was identified as the one which provide the highest enantioselectivities, while KHMDS was selected as a
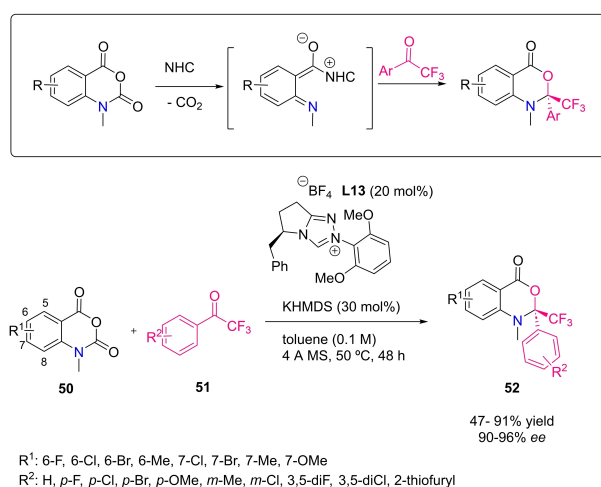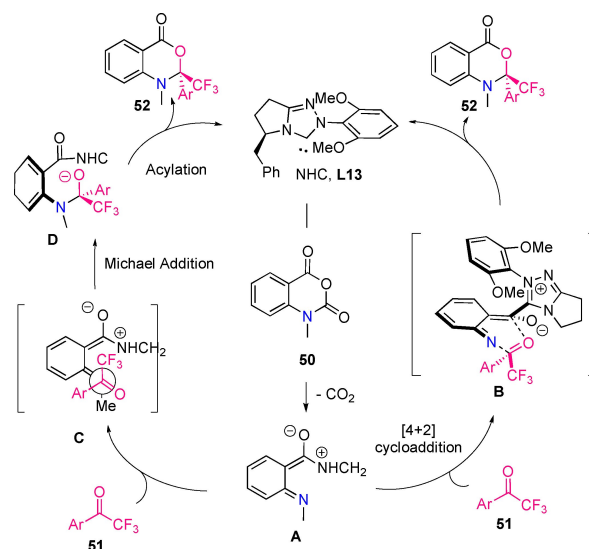
non-nucleophilic strong base. After 48 h of reaction the product **52** was obtained in yields up to 91% and enantioselectivities up to 96 ee.

The addition of carbene catalyst to anhydride substrate **50** and subsequent release of CO_2 generates NHC bound aza-o-QM intermediate **A** (Scheme 18), which was identified by HRMS. Then intermediate **A** can undergo either a concerted [4+2] pathway or a stepwise Michael addition-acylation route. In the [4+2] pathway, concerted addition of trifluoromethyl ketone **51** occurs provoking the evolution of the intermediate **A** towards **B**, which finally release the product **52**. While, in the Michael addition-acylation pathway, a carbon—nitrogen bond is formed via **C** to generate intermediate **D**, which then produce the O-acylation to regenerate the NHC **L13**.
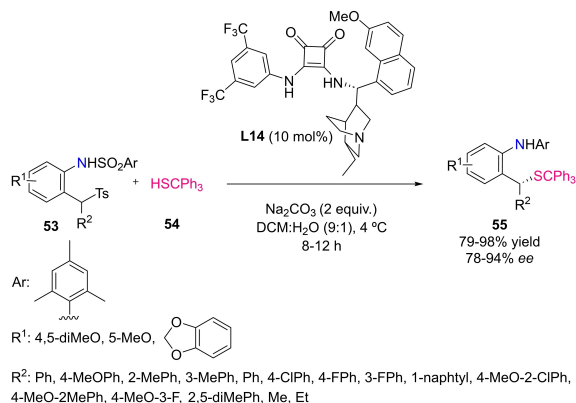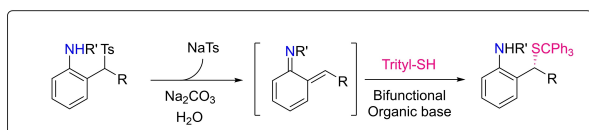
In order to find out which pathway is the most favorable, potential energy surface around the Major-TS, (S)-**B** was computed observing only one saddle point which suggest the existence of a concerted process with no intervening intermediates.

Later, in 2019 an enantioselective methodology using phase transfer conditions consisting on 1,4-addition of tritylthiol to in situ generated aza-o-quinone methides was reported by Liu and Li and coworkers (Scheme 19).[35] In this work, a 2-(tosylmethyl)aniline **53** serves as a precursor for the *in situ* generation of the aza-o-QM under basic conditions. Then, the 1,4-addition of the sulfur nucleophile **54** happens in an enantioselective fashion in the presence of the bifunctional organic base **L14**. The function of the catalyst is enabling the activation of both the nucleophile by deprotonation with the basic site and aza-o-QMs via hydrogen-bonding interactions, creating a well-organized transition state.

Squaramide **L14** and a mixture of DCM: H_2O (9:1) led to the best results in terms of yield and enantioselectivity. The substitution at the *N*-atom played a decisive role as well, the 2,4,6-trimethyl benzene substituent afforded the best results.


Scheme 17. Carbene-catalyzed enantioselective decarboxylative annulations to access dihydrobenzoxazinones and quinolones.

Scheme 18. Alternative pathways: [4+2] cycloaddition vs. Michael addition/acylation.

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Scheme 19. Bifunctional squarimide catalyzed 1,4-addition of tritylthiol to in situ generated aza-*o*-QM.
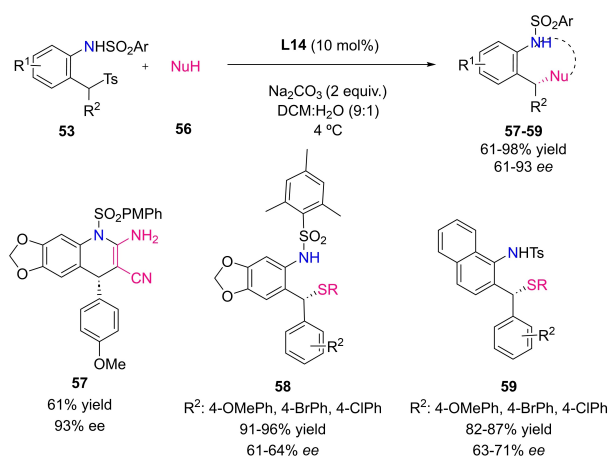
Scheme 20. Bifunctional squarimide catalyzed 1,4-addition of malononitrile and benzyl thiols to *in situ* generated o-aza-QM.
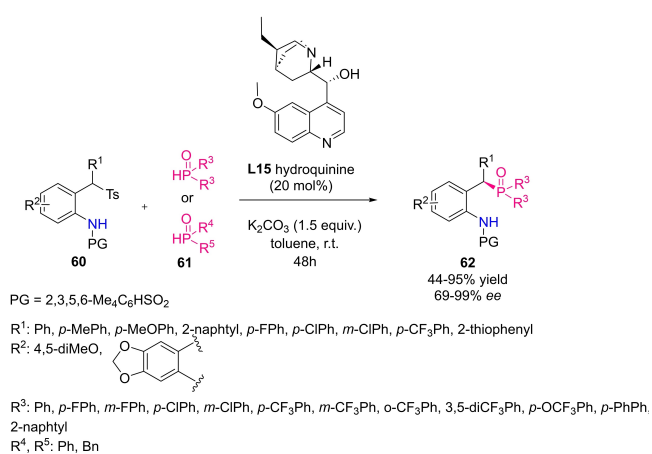
Scheme 21. Hydroquinine-catalyzed asymmetric 1,4-hydrophosphination of in situ generated aza-*o*-QM with H-phosphine oxides.

A wide scope of 2-(tosylmethyl)anilines **53** were subjected to reaction affording a diverse range of chiral ortho-amino substituted benzyl mercaptans **55**.

Furthermore, other nucleophiles such as malononitrile and different substituted benzyl thiols were employed as nucleophiles, obtaining the corresponding product **57–59** in excellent (93% *ee*) and moderate enantioselectivities (61–71% *ee*) respectively (Scheme 20).

In 2021, as a followed-up work Wang, Yiang and coworkers developed an enantioselective hydroquinine-catalyzed hydrophosphination reaction of *in situ* generated aza-*o*-QM (Scheme 21).[36]

After the screening of different organocatalysts including squarimides, thioureas and quinine derivatives on substrate **60**, hydroquine **L15** was chosen as the suitable catalyst, using as well K_2CO_3 as a base and toluene as solvent. A substrate and nucleophile screening were carried out observing how a variety of hydrophosphine oxides derivatives were synthesized in enantioselectivities up to 99% *ee* and 95% yield (Scheme 21).
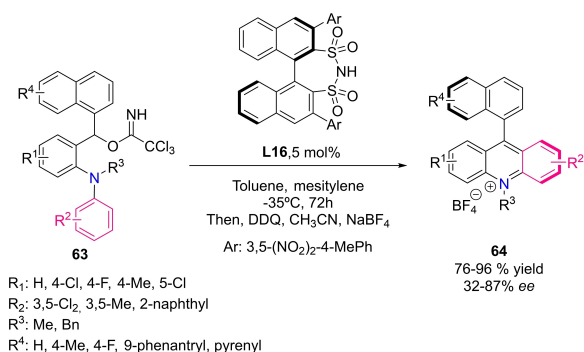
As it is depicted in the proposed mechanism (Scheme 22), the treatment of the substrate **60** with a base led to the formation of a reactive aza-*o*-QM intermediate, which is activated by hydroquinine catalyst through hydrogen bonding. This catalyst acts as a bifunctional catalyst, stabilizing also the enol form of the phosphine oxide nucleophile. Therefore, it is created a stable transition state (TS), which favor the 1,4-addition, and finally leads to the chiral phosphine oxide aniline **62**.

In early 2022, Sparr and coworkers published an atroposelective synthesis of acridine derivatives **63** through an *in situ* generated aza-*o*-QM (Scheme 23).[37] The initial intramolecular disulfonamide-catalyzed cyclization leads to the formation highly enantioenriched of dihydroacridine derivatives, then, a subsequent oxidation affords the corresponding acridines in high yields and moderate to high enantiocontrol. The use of 3,5-disubstituted aryl amines was found determinant in order to obtain high stereocontrol.
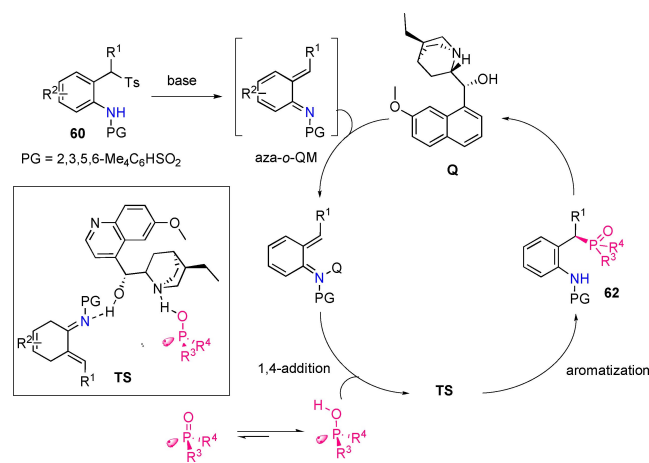
Scheme 22. Catalytic cycle for the hydroquinine-catalyzed hydrophosphine conjugate addition to aza-*o*-QM.

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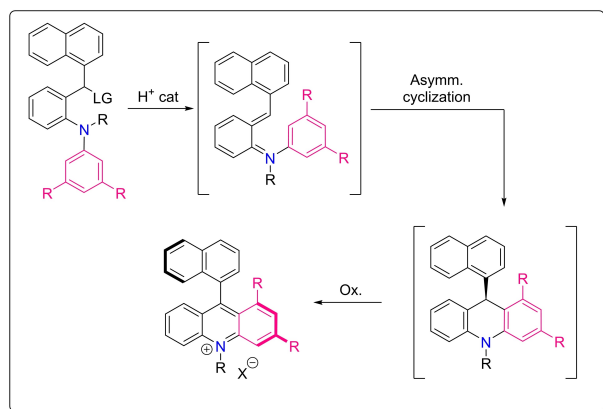
Scheme 23. Asymmetric one-pot cyclization/oxidation process with *in situ* generated aza-*o*-QM.

A late-stage diversification of **65** was carried out, providing the amino substituted atropisomeric acridiniums **66** and **67** with 84% *ee* and 86% *ee*, respectively (Scheme 24).

More recently, Li's group reported the first example of phosphine-catalyzed reaction with aza-*o*-QM (Scheme 25).[38] The reaction consists of the initial 1,4-phospha Michael reaction to the acrylate moiety of **68** to generate the polarized aza-*o*-QM intermediate. Then, this intermediate is trapped with isocya-
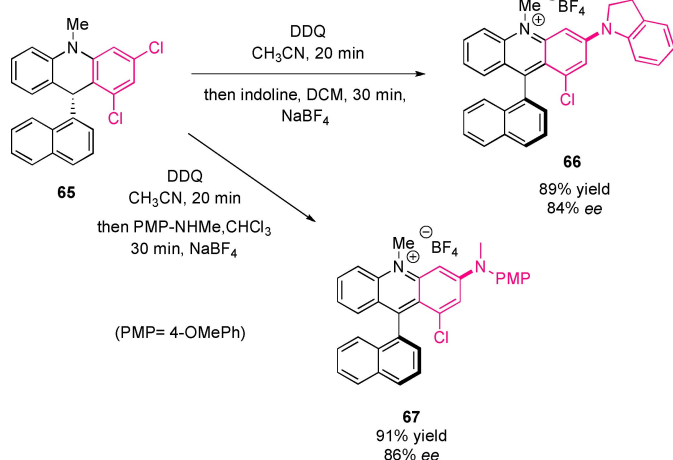
Scheme 24. Late-stage diversification of product **65**.
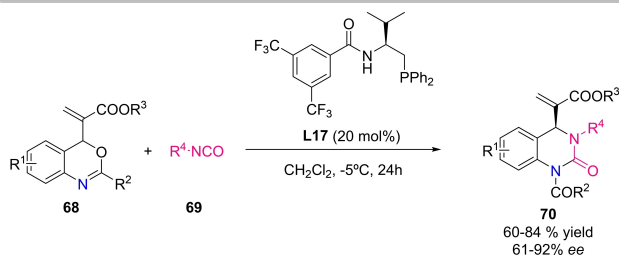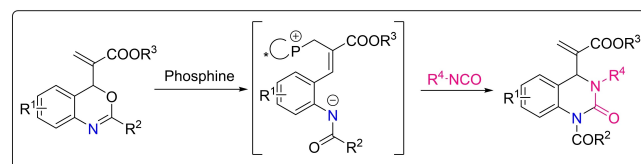
Scheme 25. Asymmetric phosphine catalyzed reaction with aza-*o*-QM intermediates.

nates **69** through a formal [4+2] cycloaddition, leading to the formation of dihydroquinazolin-2-ones **70** with good yield and enantiomeric excesses. Remarkably, this type of transformations involving polarized aza-*o*-QM derivatives are typically catalyzed by transition metals, as later will be described, which open new directions for future research in the field.

To further demonstrate the synthetic applicability of the dihydroquinazolin-2-ones **70**, the derivatization of the products was carried out (Scheme 26). Firstly, the treatment of **70a** with diisobutylaluminum hydride (DIBAL−H) afforded the corresponding alcohol **71** in a 64% yield. Secondly, the treatment with SmI$_2$ of **70b** led to the obtaining of 3,4- dihydroquinazolin-
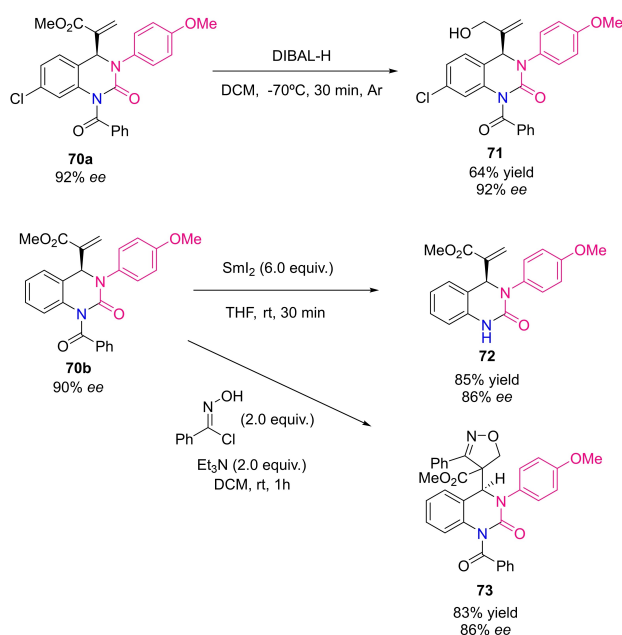
Scheme 26. Synthetic applicability of the dihydroquinazolin-2-ones **70**.

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2-one **72** in 85% yield. Lastly, a [3+2] dipolar cycloaddition between *N*-hydroxybenzimidoyl chloride and **70b** provided the product **73** in an 83% yield.

2.1.2. Metal catalysis

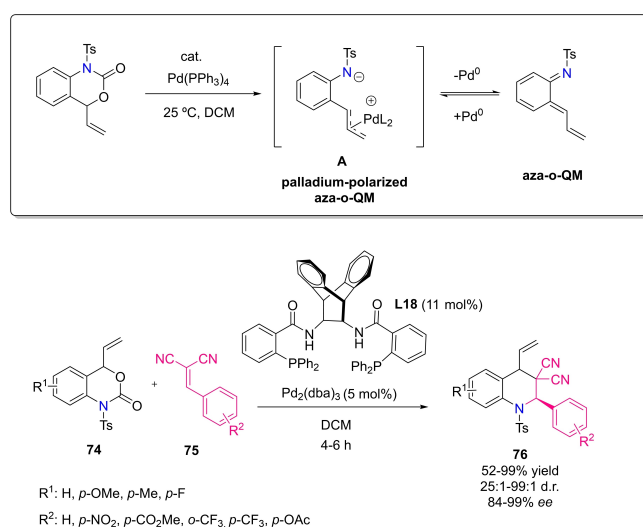Many of the methodologies for the transformation of aza-*o*-QM involved inverse-electron demand Diels-Alder reactions where the aza-*o*-QM react with electron-poor dienes.[18] However, the first catalytic metal-catalysed asymmetric [4+2] cycloadditions of aza-*o*-QMs with electron deficient alkenes was not developed until 2008 by Tunge and coworkers (Scheme 27).[39]

From the appropriate cyclic carbamate **74**, in the presence of Pd(0) catalyst, an allyl π complex was formed causing the formation of the zwitterionic intermediate (**A**) that could evolve expelling Pd(0) to generate a free aza-*o*-xylylene. After DFT calculations, Tunge *et al* concluded that the palladium polarized aza-*o*-xylylene **A** was the reactive intermediate in the cycloaddition reaction. It was carried out a screening of Trost ligands, finding that **L18** provided the highest enantioinductions. The scope of the reaction revealed that a variety of carbamates reacted with electron deficient alkenes generating tetrahydroisoquinoline derivatives **76** with up to 99:1 d.r. and 99% *ee* (Scheme 27).

After the pioneering work of Tunge, many different asymmetric transformations based on the reaction of Pd-catalyzed decarboxylation of vinyl benzoxazinones have been developed. In 2014, Tan, Li and coworkers developed an asymmetric [4+1] cycloaddition of aza-*o*-QM and sulphur ylides via a palladium-catalysed decarboxylation-cycloaddition sequence (Scheme 28).[40] Following the strategy developed by the group of Tunge, trapping of Pd-stabilized aza-*o*-xylylenes by a nucleophile, a number of 3-vinyl indolines were rapidly assembled: the use of a palladium catalyst Pd₂(dba)₃·CHCl₃ in a 5 mol% and phosphoramidite ligand **L19** (6 mol%) with a vinyl

benzoxazinanone **74**, and a sulphur ylide **77** at −40 °C led to a variety of 3-vinyl indolines in good to excellent yields and excellent diastereo- and enantioselectivities (Scheme 28).

A possible mechanism for the reaction is depicted in Scheme 29. Firstly, Pd-polarized aza-*o*-xylylene **A** was obtained from vinyl benzoxazinanone through a decarboxylation reaction promoted by the chiral Pd⁰ catalyst. Next, this species reacted with sulphur ylide to form Pd complex **B** through electronic interaction. A new C—C bond was formed irreversibly via an intramolecular asymmetric allylation reaction to lead to intermediate **C** in good diastereo and enantioselectivity. Then, the palladium catalyst is decoordinated to yield zwitterionic species **D**. And finally, the desired chiral indoline product was achieved by N-alkylation.

To further demonstrate the synthetic potential of this approach, the indoline product **78a** was derivatized into different compounds (Scheme 30). Firstly, reduction with sodium borohydride followed by propargylation, and a Pauson-
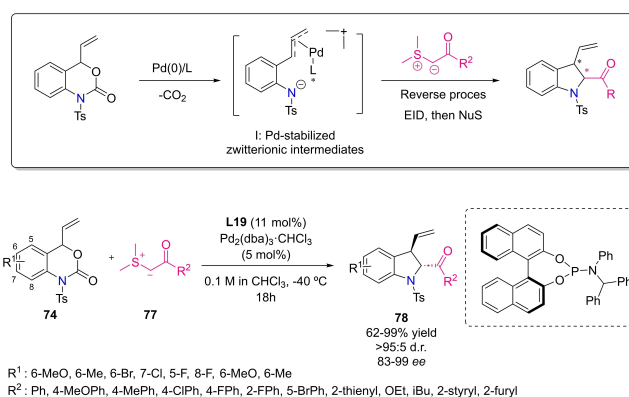
Scheme 28. Asymmetric trapping of zwitterionic intermediates by sulphur ylides in a palladium-catalysed decarboxylation-cycloaddition sequence.

Scheme 27. Asymmetric cycloadditions of palladium-polarized aza-*o*-xylylenes.
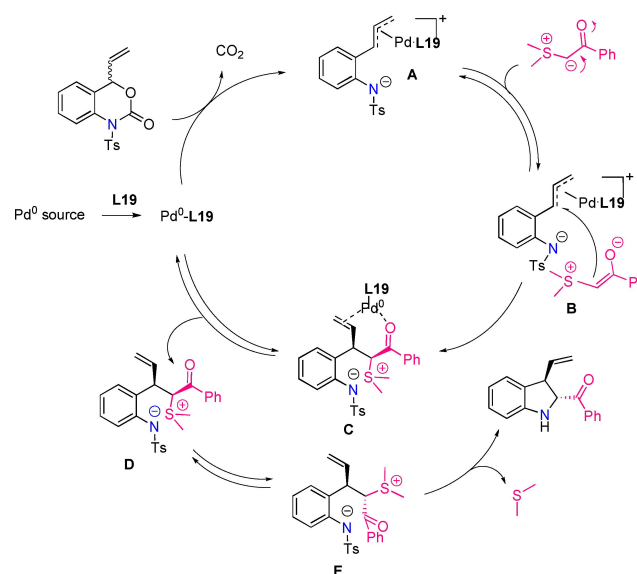
Scheme 29. Asymmetric cycloadditions of palladium-polarized aza-*o*-xylylenes.

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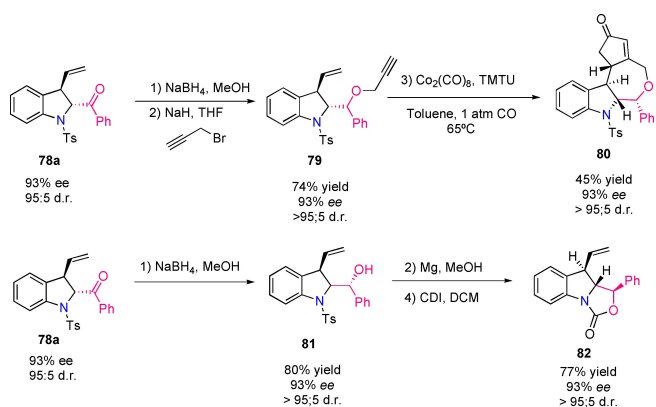
Scheme 30. Derivatization of **78 a** into useful heterocyclic compounds.

Khand reaction with a cobalt catalyst under a CO atmosphere afforded a fused carbo-/heterocyclic architecture **80** bearing a seven membered ring. Besides, the reduction of chiral indoline **78 a** followed by deprotection of the tosyl group and treatment with CDI provided an oxazolo[3,4-a]indol-3-one core **82**. This class of compounds exhibit a potent antibacterial agents and they are important intermediates in the synthesis of natural indoline alkaloids.

In 2017, Guo and coworkers reported the enantioselective synthesis of imidazolidine derivatives through a tandem [3+2] cycloaddition/1,4-addition reaction of azomethine ylides and aza-*o*-QM.[41] The initial motivation in order to develop this tandem reaction has its basis on the reversibility of the cycloaddition reaction between azomethine ylides and carbon nitrogen bond, which caused a low yield in the reaction. A possible way to overcome this issue deals with the capture of the imidazolidinone derivative *in situ*, by reaction with a reactive aza-*o*-QM. After a thorough screening of ferrocenyl ligands and Ag(I) salts, they found that the use of AgOTs and ligand **L20** afforded the best enantioselectivity and diastereomeric ratio in the reaction (Scheme 31). In order to form *in situ* the aza-*o*-QM intermediate 2 equivalents of KOH as a base and a crown ether (20 mol%) were used to facilitate the deprotonation event. The imidazoline products **84** were obtained in good
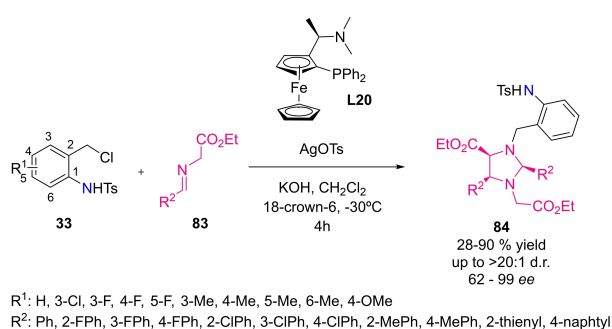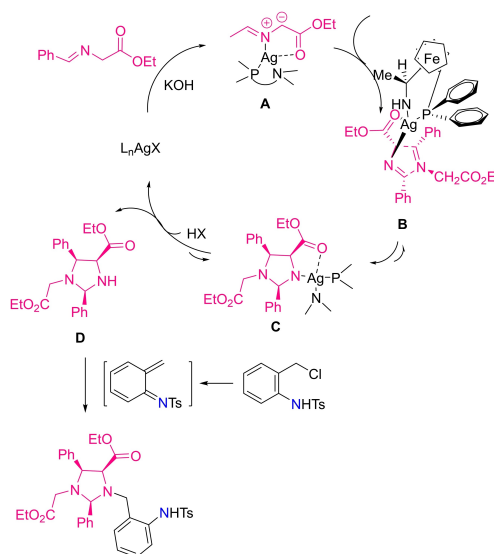
yields and enantioselectivities up to 99% *ee* with a variety of electron rich and electron poor derivatives (Scheme 31).

The plausible mechanism is depicted in Scheme 32. In the first place, the treatment of the azomethine with a base in the presence of the silver(I) salt lead to the formation of the metalloazomethine ylide **A** as an active species. Next, a second equivalent of the azomethine ylide reacts through a regioselective [3+2] cycloaddition. The depicted transition state **B** is the more thermodynamically stable intermediate which then leads to imidazolidine complex **C** which is next protonated to generate **D**, and then captured by a in situ generated aza-*o*-QM affording the the final product.

Also in 2017, Shi, Mei and coworkers reported a palladium(0)/chiral ligand-catalyzed enantioselective decarboxylative [4+2] cyclization of vinyl benzoxazinanones with isatins to build the tryptanthrin skeleton privileged scaffold widely found in bioactive natural alkaloids and synthetic compounds (Scheme 33).[42]
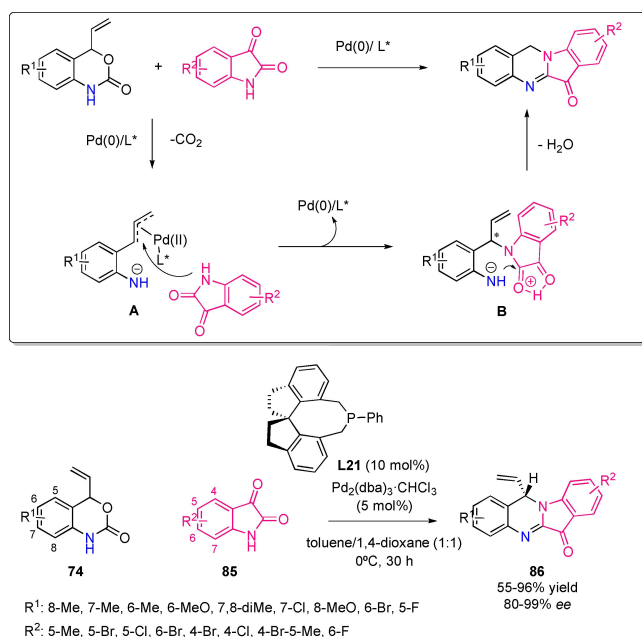
Firstly, benzoxazinanone **74** is converted into Pd-stabilized zwitterionic intermediates **A**, followed by attack of the amide N—H group of isatins to intermediate **A**, which then underwent the intramolecular attack of the negatively charged *N* atom to the carbonyl group of the isatin moiety leading to enantioenriched tryptanthrin derivative. The methodology was applied for a wide variety of isatin derivatives **85** and vinyl benzoxazinanone **74** obtaining yields up to 96% and >99% *ee*.

Next, Shi, Mei and coworkers extended the methodology to build tetrahydroquinoline-based spirooxindoles, stablishing a catalytic asymmetric decarboxylative [4+2] cycloaddition of vinyl benzoxazinanones with methyleneindolinones (Scheme 34).[43] After the generation of the Pd-stabilized zwitterionic intermediate, the charged N atom of the aza-*o*-QM attacked the methylene group generating an enolate intermediate which undergoes intramolecular asymmetric allylic alkylation (AAA) of intermediate **B** leading to the construction of the

R[1]: H, 3-Cl, 3-F, 4-F, 5-F, 3-Me, 4-Me, 5-Me, 6-Me, 4-OMe
R[2]: Ph, 2-FPh, 3-FPh, 4-FPh, 2-ClPh, 3-ClPh, 4-ClPh, 2-MePh, 4-MePh, 2-thienyl, 4-naphtyl

Scheme 31. Tandem [3+2] cycloaddition/1,4-addition reaction of azomethine ylides and aza-*o*-QM for asymmetric synthesis of imidazolidines.

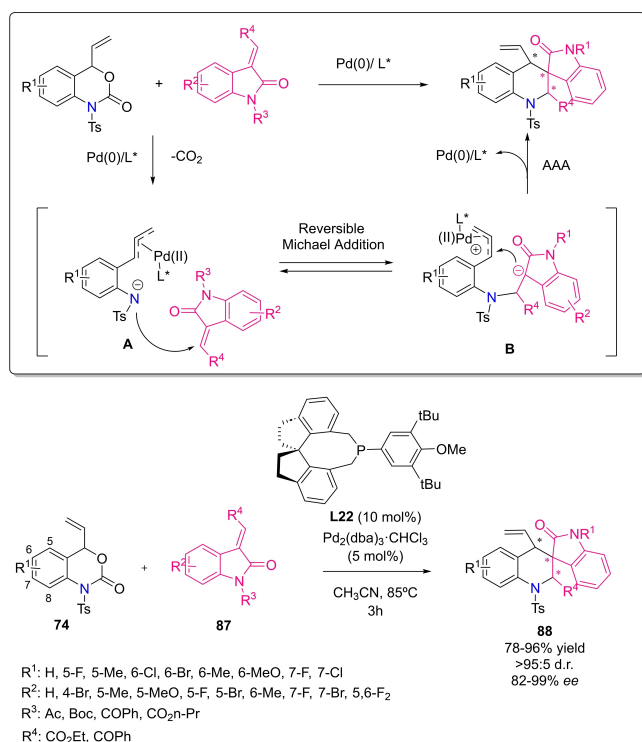**Scheme 32.** Ag(I) catalytic cycle for the tandem [3+2] cycloaddition/1,4-addition reaction of azomethine ylides and aza-*o*-QM.

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Scheme 33. Palladium(0)/phosphine-catalyzed enantioselective decarboxylative [4+2] cyclization of vinyl benzoxazinanones with isatins.

yleneindolinones derivatives **87** to yield 3,3′-spirooxindoles **88** in up to 96% yield and 99% *ee*.

Also in 2017, Lu, Xiao and coworkers reported a Pd-catalysed methodology involving the formation of a reactive aza-*o*-QM, while a simultaneous photochemical generation of a ketene reactive intermediate from a α-diazo ketone is taking place. The aza-*o*-QM and the ketene reacted through a [4+2] cycloaddition to build chiral quinolones (Scheme 35).[44] A bidentate P,S ligand **L23** and a Pd₂(dba)₃·CHCl₃ as palladium catalyst were selected, and the reaction between **74** and **89** was performed at 0 °C and under blue light irradiation to yield a great variety of quinolone derivatives **90** in excellent enantio- and diastereoselectivities (Scheme 35).

In order to explain the enantioselectivity in the reaction in Figure 4 is shown the proposed asymmetric induction modes. The π-allyl–Pd complex determines the most favorable face of the alkene (matched pair) for the attack of the nucleophile in the intramolecular addition, where is minimized the steric hindrance.

Furthermore, the methodology could be implemented at a gram-scale flow reaction demonstrating its synthetic practicability. Sunlight could be used as source of light and only a

Scheme 34. Palladium(0)/phosphine-catalyzed asymmetric decarboxylative [4+2] cycloaddition of vinyl benzoxazinanones with methyleneindolinones.

Scheme 35. Asymmetric Pd-catalyzed photochemical [4+2] cycloadditions of ketenes and aza-*o*-QM.

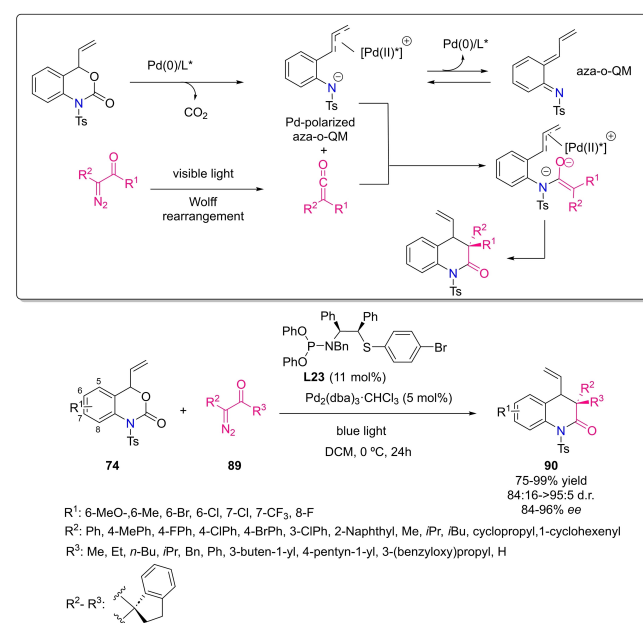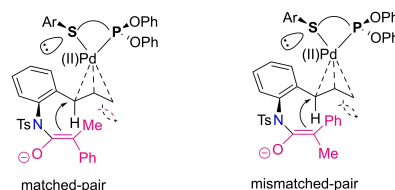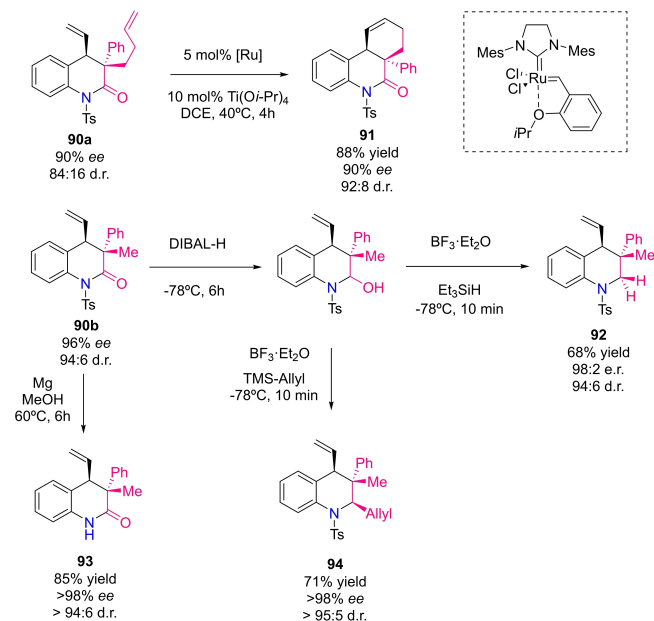**Figure 4.** Proposed asymmetric induction modes in the intramolecular nucleophilic addition.

desired chiral tetrahydroquinoline-based 3,3′-spirooxindole framework (Scheme 34). The methodology was applied for a wide variety of vinyl benzoxazinanones **74** and meth-

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1 mol% of palladium catalyst was needed, producing the enantioenriched quinolinone in good yields and enantio and diastereoselectivities (97% yield, 92% *ee*). Also, to demonstrate the synthetic applicability of the quinolone derivatives further transformations were carried out (Scheme 36). Firstly, a ring-closing metathesis (RCM) reaction of **90a** led to phenanthridin-6(5H)-one **91** in 88% yield. The reduction of **90b** using diisobutylaluminum hydride (DIBAL—H) and triethylsilane provided chiral tetrahydroquinoline **92** in 68% yield. The tosyl group removal led to **93** in 85% yield. While the sequential

reduction/allylation of **90b** afforded chiral tetrahydroquinoline **94** in 71% yield.

In 2017, Lu and coworkers reported a palladium-catalyzed branch- and enantioselective allylic amination of vinyl benzox-azinones (Scheme 37).[45] The authors propose that the H bonding between the negatively charged atom of aza-*o*-QM intermediates can act as a base favoring the approaching to the benzylic position, while at the same time the chiral palladium complex induce the enantioselectivity in the reaction. Vinyl benzoxazinone **95** and amine **96** together with Pd$_2$(dba)$_3$·CHCl$_3$ and phosphoramidite ligand **L24** afforded a wide variety of chiral allyl amines **97** in yields up to 99% and 98% *ee*.

Furthermore, the synthetic utility of the reaction was demonstrated in one-pot syntheses of chiral azaheterocycles, which avoided the isolation of amino alkene intermediates. (Scheme 38). On one hand, the in situ formed amine adduct was further derivatized into a chiral indoline **98**. On the other hand, the allylic amine derivative was subjected to photoredox catalysis obtaining the chiral fused *N*-heterocycle **99**.

In 2018, Guo and coworkers reported an enantioselective palladium-catalyzed [4+2] cycloaddition of vinyl benzoxazi-nones **74** and sulfamate-derived cyclic imines **100** (Scheme 39).[46] This methodology allows the obtaining of chiral tetrahydroquinazoline derivatives **101** in excellent yields and

Scheme 36. Synthetic applicability of quinolone derivatives **90**.

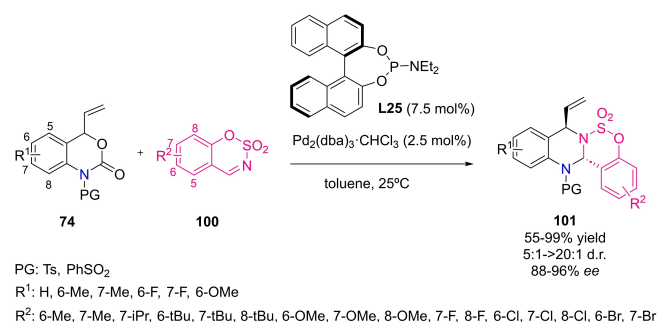**Scheme 38.** Derivatization strategies based on dual Pd-catalysis and Pd with photoredox catalysis.
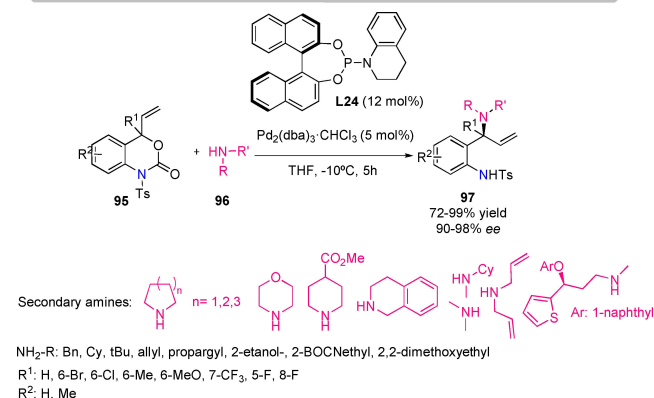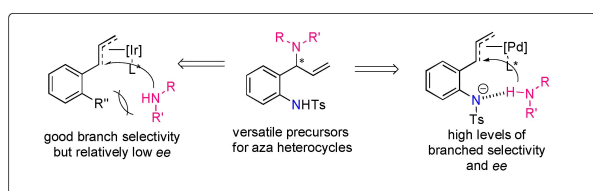
Scheme 37. Palladium-catalyzed branch- and enantioselective allylic amination of vinyl benzoxazinones.
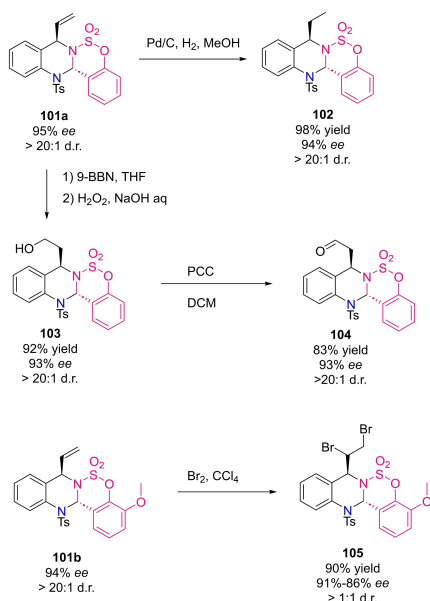

Scheme 39. Enantioselective palladium-catalyzed [4+2] cycloaddition of vinyl benzoxazinones with sulfamate-derived cyclic imines.
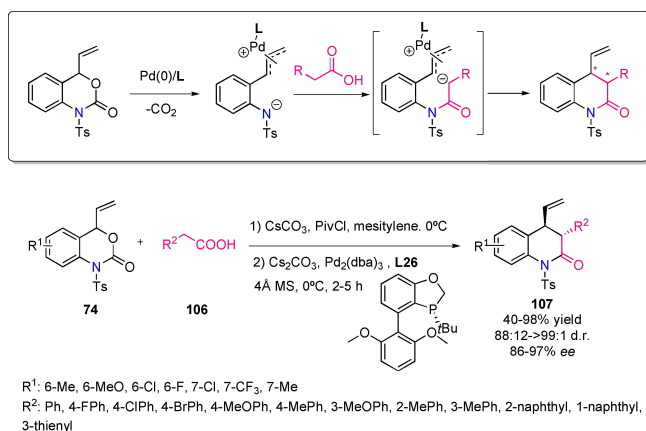
enantioselectivities using as ligand a phosphoramidite **L25** and Pd(dba)$_3$ as catalytic system.

To demonstrate the synthetic utility of the tetrahydroquinazolines derivatives **101**, further transformations were carried out (Scheme 40). Firstly, hydrogenation with palladium on carbon led to product **102** in 98% yield. The treatment of the product **101a** with 9-BBN followed by H$_2$O$_2$ afforded the alcohol product **103** in 92% yield and 93% ee. Further oxidation of **103** with PCC provided the aldehyde **104** in 83% yield, 93% ee. Finally, bromination of the product **101b** led to the dibromo derivative **105** in 90% yield and 1:1 dr.

Also in 2018, Tang, Deng and coworkers reported an asymmetric synthesis of 3,4-dihydroquinolin-2-ones via a stereoselective palladium-catalyzed decarboxylative [4+2]-cycloaddition of vinyl benzoxazinones **74** with carboxylic acids **106** (Scheme 41).[47] The carboxylic acid reacts with pivaloyl chloride
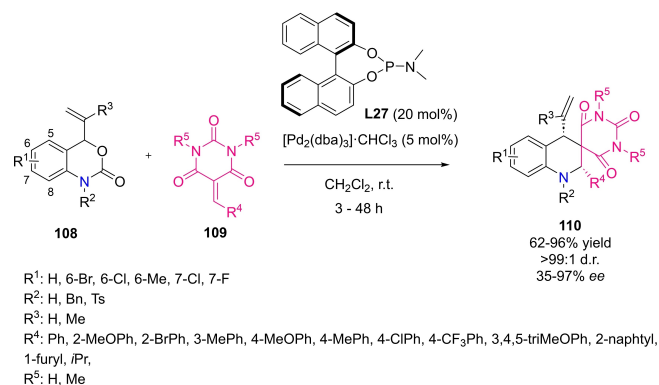
to form a reactive mixed anhydride intermediate which reacts with the *in situ* formed Pd-polarized aza-*o*-QM leading to the 3,4-dihydroquinolin-2-ones **107** in good yields and selectivities.

Additionally, in 2018 Zhao and coworkers reported a different enantioselective synthesis of barbiturate-fused spirotetrahydroquinolines via chiral palladium(0)/ligand complex catalyzed [4+2] cycloaddition of vinyl benzoxazinanones **108** with barbiturate-based olefins **109** (Scheme 42).[48]
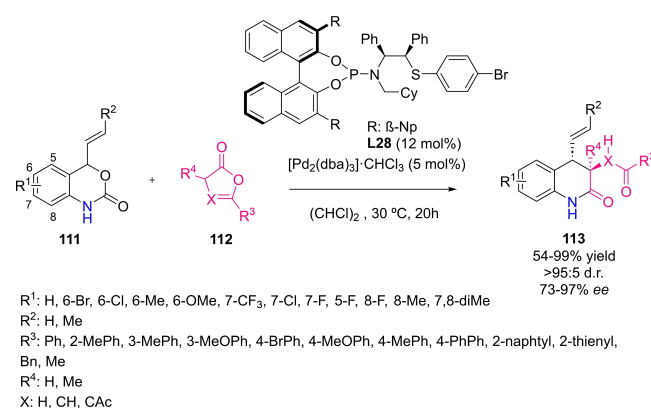
In 2019 Xiao and coworkers reported the use of a P, S ligand **L28** in the palladium-catalyzed [4+2] cycloaddition reaction of benzoxazinones **111** with deconjugated butenolides **112** (Scheme 43).[49] Moreover, they also evaluated the use of azlactones as nucleophiles, obtaining the corresponding hydroquinolin-2-ones **113**.

The same year, Wang and coworkers reported a similar reaction with between alkynyl benzoxazinones **114** and azlactones **115** in order to obtain chiral derivatives **116** (Scheme 44).[50] In contrast to the previous examples in which a palladium catalyst was required, in this case, the reaction was catalyzed by copper iodide, using a PyBox type chiral ligand **L29**.

In 2020 Ashfeld and coworkers reported a different enantioselective synthesis chiral indolines via palladium(0)

Scheme 40. Synthetic applicability of chiral tetrahydroquinazoline derivatives **101**.

R^1: 6-Me, 6-MeO, 6-Cl, 6-F, 7-Cl, 7-CF$_3$, 7-Me
R^2: Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-MeOPh, 4-MePh, 3-MeOPh, 2-MePh, 3-MePh, 2-naphthyl, 1-naphthyl, 3-thienyl

Scheme 41. Enantioselective palladium-catalyzed decarboxylative [4+2]-cycloaddition.of vinyl benzoxazinones with carboxylic acids.

R^1: H, 6-Br, 6-Cl, 6-Me, 7-Cl, 7-F
R^2: H, Bn, Ts
R^3: H, Me
R^4: Ph, 2-MeOPh, 2-BrPh, 3-MePh, 4-MeOPh, 4-MePh, 4-ClPh, 4-CF$_3$Ph, 3,4,5-triMeOPh, 2-naphtyl, 1-furyl, *i*Pr,
R^5: H, Me

Scheme 42. Enantioselective palladium(0)/ligand complex catalyzed [4+2] cycloaddition of vinyl benzoxazinanones.

R^1: H, 6-Br, 6-Cl, 6-Me, 6-OMe, 7-CF$_3$, 7-Cl, 7-F, 5-F, 8-F, 8-Me, 7,8-diMe
R^2: H, Me
R^3: Ph, 2-MePh, 3-MePh, 3-MeOPh, 4-BrPh, 4-MeOPh, 4-MePh, 4-PhPh, 2-naphtyl, 2-thienyl, Bn, Me
R^4: H, Me
X: H, CH, CAc

Scheme 43. Enantioselective palladium(0)/ligand complex catalyzed [4+2] cycloaddition of vinyl benzoxazinanones using P,S ligands.

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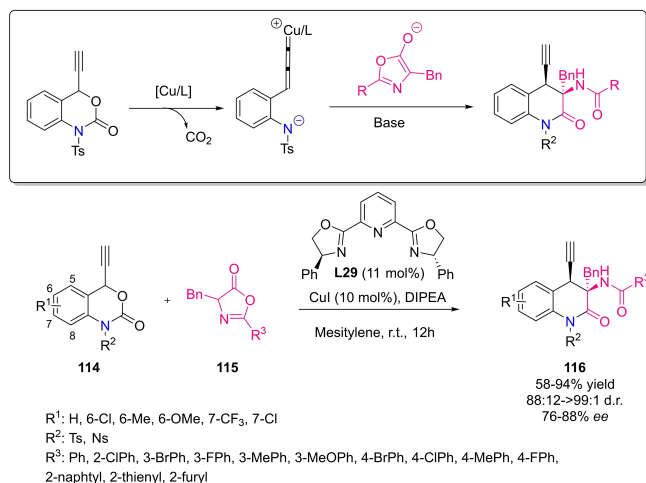
Scheme 44. Enantioselective CuI/PyBox complex catalyzed [4+2] cycloaddition of vinyl benzoxazinanones and azlactones.

catalyzed [4+1] cycloaddition of vinyl benzoxazinanones **74** with *in situ* formed carbenes (Scheme 45).[51] The reaction uses tosylhydrazones **117** as precursors of diazocompounds, which are used as precursors of the palladium carbene nucleophiles. Although the reaction works with high diastereocontrol, the incorporation of a chiral ligand only afforded moderate enantioselectivity.

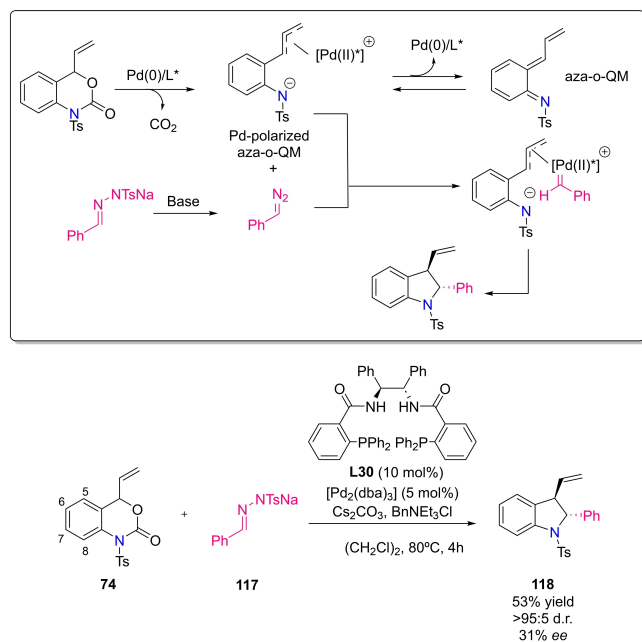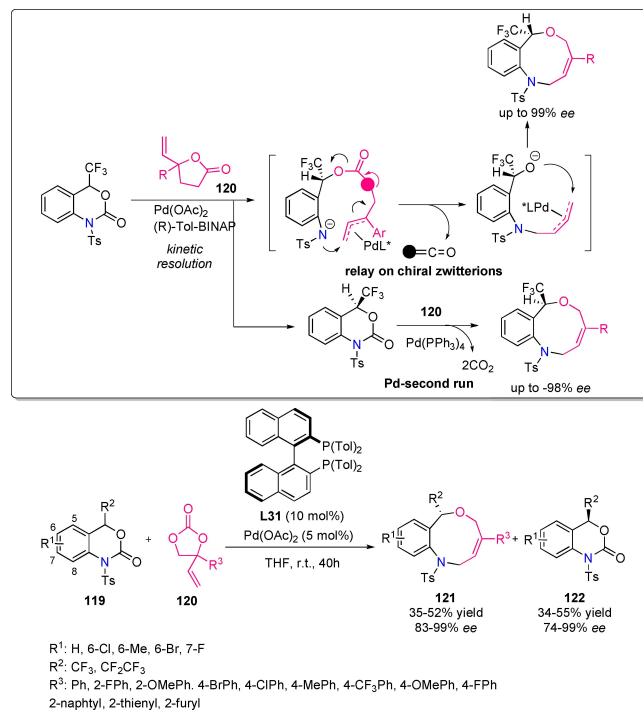The same year, Shibata and coworkers reported kinetic resolution of benzoxazinones **119** with vinyl ethylene carbonates (VECs) **120** using a palladium catalyzed ring opening reaction (Scheme 46).[52] The reaction afforded the corresponding nine-membered heterocycles **121** in high yield and

enantiocontrol when using BINAP ligand **L31** and Pd(AcO)₂. Moreover, they also reported the ring-expansion reaction with the recovered enantioenriched benzoxazinones **122** by simply applying the same reaction conditions in absence of a chiral ligand. This methodology provides a novel method for the construction of enantiomerically enriched 9-membered trifluoromethyl-benzo[*c*][1,5]oxazonines **121**.

To further demonstrate the synthetic potential of this methodology, the chiral nine membered ring derivatives **121** were subjected to different reactions (Scheme 47). Firstly, the oxidation with *m*-CPBA afforded the desired epoxide **123**, in 57% yield and high diastereoselectivity (10:1 dr). Secondly, the

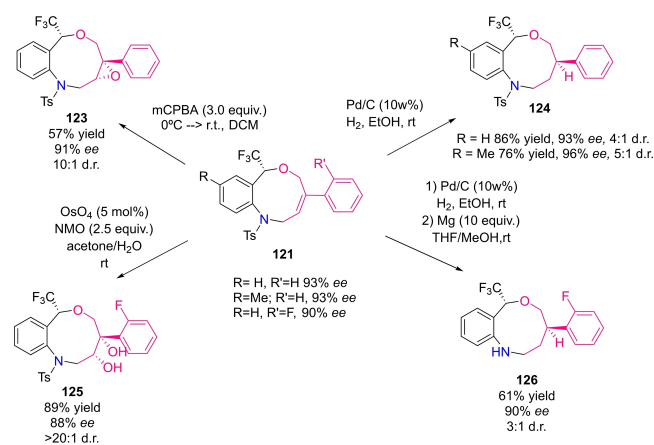**Scheme 46.** Enantioselective palladium(0)/ligand complex catalyzed kinetic resolution of benzoxazinanones.

Scheme 45. Enantioselective palladium(0)/ligand complex catalyzed [4+1] cycloaddition of vinyl benzoxazinanones.
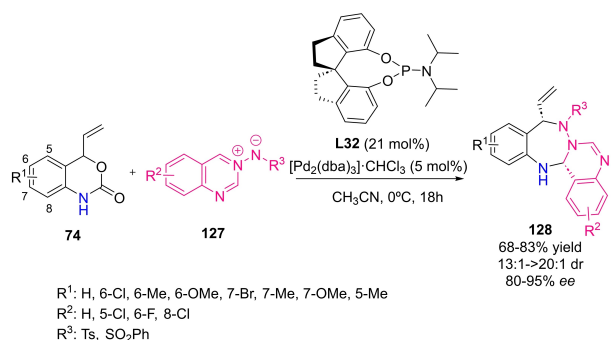

Scheme 47. Synthetic applicability of derivatives 9-membered trifluoromethyl-benzo[*c*][1,5]oxazonines **121**.
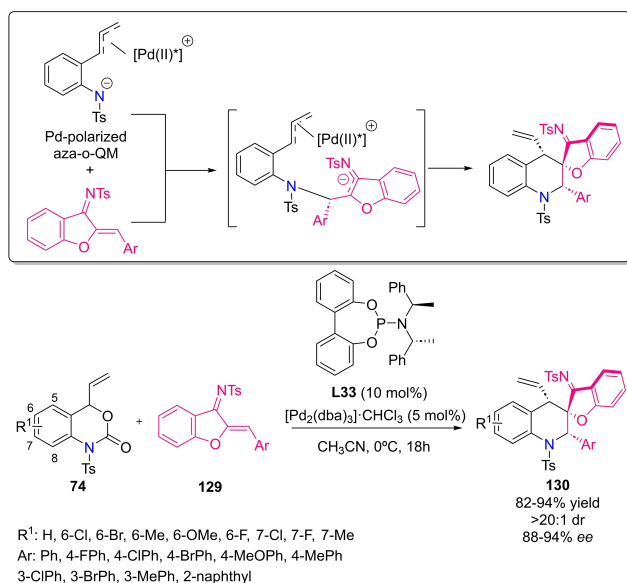
hydrogenation of **121** with Pd/C delivered the corresponding saturated derivatives **124** in good yields and diastereoselectivity. Next, the dihydroxylation using a catalytic amount of OsO_4 afforded the diol **125** in 89% yield and >20:1 dr. F-containing derivative **121** was converted into **126** by the hydrogenation under H_2–Pd/C followed by the treatment with Mg in THF/MeOH in 61% yield.

More recently, Miao and coworkers reported the palladium catalyzed synthesis of benzotriazepine skeleton (Scheme 48).[53] The reaction afforded the seven-membered nitrogen-containing heterocycles **128** in high yield and enantiocontrol using a SPINOL derived phosphoramidite ligand **L32**.

In 2021, Miao and coworkers reported the palladium catalyzed [4+2] cycloaddition of Pd-polarized aza-*o*-quinone methide and benzofuran derived azadienes **129** (Scheme 49).[54] The reaction consists of the initial 1,4-addition of the nitrogen anion, followed by the intramolecular trapping of the formed enamine derivative with the allyl cation, affording chiral spiro-

cycles **130** containing three contiguous stereocenters in high yield and stereocontrol.

In 2021, Zhao's group reported the palladium catalyzed [4+2] cycloaddition of benzoxazinanones **74** and pyrazolone derivatives **131** (Scheme 50).[55] Similarly to the previous example, after the initial asymmetric 1,4-addition, the formed enolate is intramolecularly trapped to afford a single diastereomer of the enantioenriched spirocycles **132** in high yield.

The proposed reaction mechanism is depicted in Scheme 51. The chiral Pd(0)Ln complex formed *in situ*, reacts with substrate **74** to generate a chiral palladium-stabilized zwitterionic intermediate (aza-*o*-QM) by release of carbon dioxide. Next, it undergoes the reversible aza-Michael addition with **131** affording two possible intermediates **A** and **B**. **A** is more stabilized than **B**, which suffers steric repulsions. **A** and **B**

R[1]: H, 6-Cl, 6-Br, 6-Me, 7-Cl, 7-F
R[2]: Ph, 2-OMePh, 2-BrPh, 3-MeBr, 3-ClPh, 4-OMePh, 4-ClPh, 4-BrPh
4-NO_2Ph, 4-CF_3Ph, 2-naphthyl, [i]Pr
Ar: Ph, 4-ClPh, 4-MePh

Scheme 50. Enantioselective palladium(0)/ligand complex catalyzed [4+2] cyclization of benzoxazinanones and alkylidene pyrazolones.

R[1]: H, 6-Cl, 6-Me, 6-OMe, 7-Br, 7-Me, 7-OMe, 5-Me
R[2]: H, 5-Cl, 6-F, 8-Cl
R[3]: Ts, SO_2Ph

Scheme 48. Enantioselective palladium(0)/ligand complex catalyzed [4+3] cyclization.

R[1]: H, 6-Cl, 6-Br, 6-Me, 6-OMe, 6-F, 7-Cl, 7-F, 7-Me
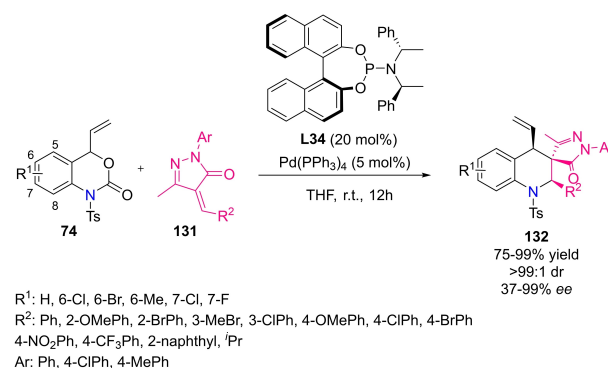Ar: Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-MeOPh, 4-MePh
3-ClPh, 3-BrPh, 3-MePh, 2-naphthyl

Scheme 49. Enantioselective palladium(0)/ligand complex catalyzed [4+2] cyclization of benzoxazinanones and azadienes.
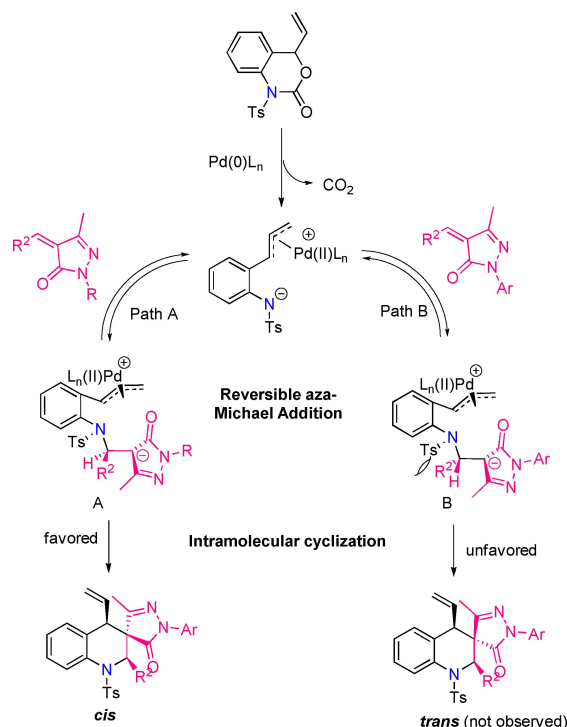

Scheme 51. Mechanism proposed for the [4+2] cycloaddition.

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react by intramolecular cyclization toward the formation of the favored *cis* and unfavored *trans* diastereomers, respectively.

2.1.3. Dual catalysis

In 2016, Glorius' group developed a new methodology which combines transition metal and NHC organocatalysis for the intermolecular reaction between an enal substrate and benzoxazinanones (Scheme 52).[56] This work shows the first asymmetric cooperative system which combines transition metal/NHC organocatalysis. Little research had been previously done as the NHC ligands could coordinate to a transition metal avoiding its use as organocatalyst.

The use of a NHC precatalyst **L35**, and Pd(PPh₃)₄ as Pd⁰ catalyst, and Cs₂CO₃ as a base, α,β-unsaturated aldehyde **133** and a vinyl benzoxazinanones derivative **74** led to the obtaining of a variety of benzazepine derivatives **134** in good yields with excellent enantioselectivities (up to 99% *ee*) (Scheme 52).

Further research was then done in order to unveil the mechanism of the reaction.[57] In this study, applying a combined approach of ESI-MS, in situ NMR, and X-ray investigations as well as extensive mechanistic experiments, a novel mixed NHC/phosphine catalyst [Pd(NHC)(PR₃)] was identified as the active transition metal catalyst in this type of reaction.
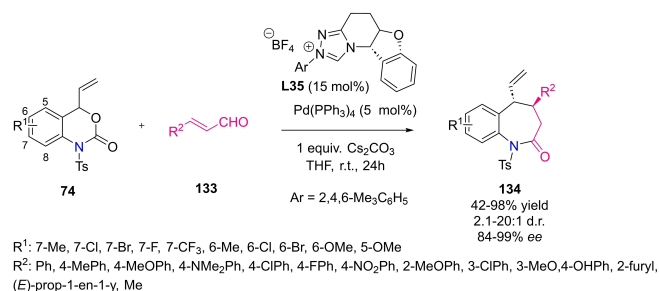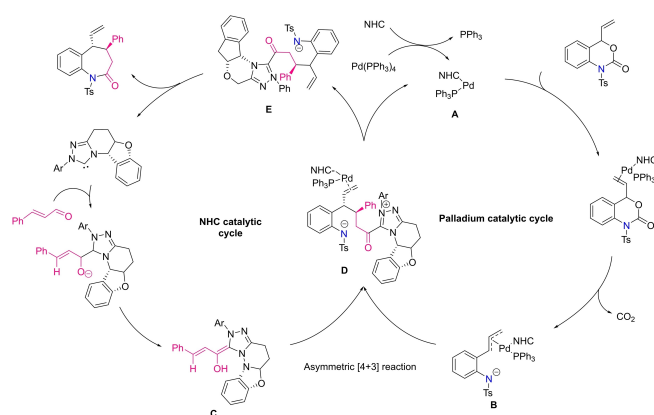
The proposed catalytic cycle depicted in Scheme 53. implies the activation of the NHC carbene by reaction with the Pd⁰ catalyst **A** which then reacts with the vinyl benzoxazinanone derivative to form a palladium complex which provokes the release of CO₂ to form the corresponding Pd polarized aza-*o*-QM **B**.
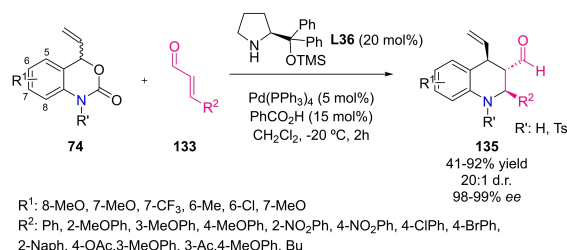
At the same time, the activation of the aldehyde by means of the active carbene to form a homo enolate **C** is happening. This intermediate reacts with the Pd polarized aza-*o*-QM leading to the adduct **D**, which release the [Pd(NHC)(PPh₃)] complex to form Intermediate **E** which subsequently undergoes a cyclization to form the benzazepine derivative.

Also in 2016, the group of Jørgensen developed a method for the synthesis of vinyl tetrahydroquinolines through a synergistic palladium and organocatalyzed [4+2] cycloaddition reaction (Scheme 54).[58] The use of Jorgensen-Hayashi organocatalyst **L36** and Pd(PPh₃)₄ with benzoic acid in the reaction of a vinyl benzoxazinanone substrate **74** and α,β-unsaturated aldehyde **133** leads to a variety of tetrahydroquinolines **135** in good to high yields, and excellent enantio- and diastereoselectivities (>99% ee and >20:1 d.r.).

The palladium catalyst activates vinyl benzoxazinanones generating **A** which undergoes a decarboxylation to obtain intermediate **B**, which then undergo a [4+2] cycloaddition with iminium-ion activated α,β-unsaturated aldehyde (**C**), generating intermediate **D** upon addition of negatively charged palladium complex **B** to **C**, which then release the cycloaddition product recovering Pd⁰ catalyst and Jorgensen-Hayashi organocatalyst which re-enter in their respective cycles (Scheme 55).

2.2. Catalytic Transformation of aza-para-quinone methides (aza-p-QM)

The study of asymmetric transformation on aza-*p*-QM had a posterior development to the aza-*o*-QM. The difficulty of controlling the enantioselectivity on these substrates rely on the necessity of a remote stereocontrol as the reactive center is much further from the *N*-atom of the substrate than in the aza-*o*-QM.

R¹: 7-Me, 7-Cl, 7-Br, 7-F, 7-CF₃, 6-Me, 6-Cl, 6-Br, 6-OMe, 5-OMe
R²: Ph, 4-MePh, 4-MeOPh, 4-NMe₂Ph, 4-ClPh, 4-FPh, 4-NO₂Ph, 2-MeOPh, 3-ClPh, 3-MeO,4-OHPh, 2-furyl, (*E*)-prop-1-en-1-y, Me

Scheme 52. Cooperative *N*-heterocyclic carbene/palladium-catalyzed enantioselective *umpolung* annulations.

Scheme 53. Proposed catalytic cycle for the *N*-heterocyclic carbene/palladium-catalyzed enantioselective *umpolung* annulations.

R¹: 8-MeO, 7-MeO, 7-CF₃, 6-Me, 6-Cl, 7-MeO
R²: Ph, 2-MeOPh, 3-MeOPh, 4-MeOPh, 2-NO₂Ph, 4-NO₂Ph, 4-ClPh, 4-BrPh, 2-Naph, 4-OAc,3-MeOPh, 3-Ac,4-MeOPh, Bu

Scheme 54. Synergistic palladium- and organo-catalyzed formation of vinyl tetrahydroquinolines in a [4+2] cycloaddition by a palladium decarboxylative activated intermediate and an α,β-unsaturated aldehyde activated by aminocatalysis.
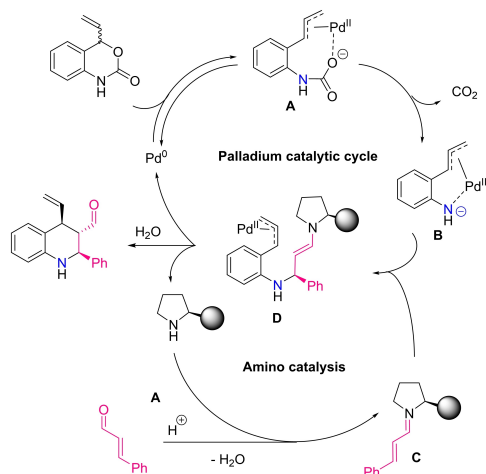
Scheme 55. Proposed catalytic cycle for the palladium- and organo-catalyzed formation of vinyl tetrahydroquinolines via [4 + 2] cycloaddition reaction.
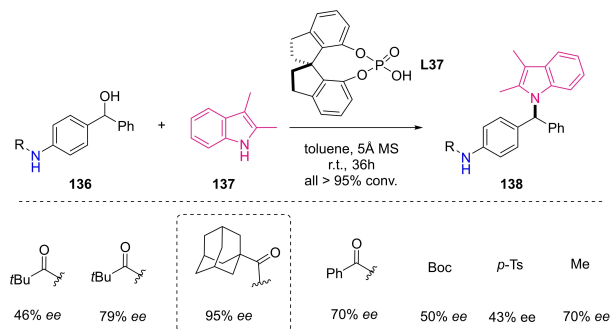
2.2.1. Organocatalysis

The first asymmetric methodology for the derivatization of aza-*p*-QM is dated in the year 2017. The group of Sun developed an enantioselective 1,6-conjugate addition of aza-*p*-QM for the *N*-alkylation of indoles and carbazoles.[59] The authors envisioned that the reactive aza-*p*-QM could serve as reactive nucleophiles for the *N*-alkylation of indoles and carbazoles in an asymmetric fashion by the use of a suitable chiral catalyst. Firstly, to prevent side reactions, the *N*-atom of the model *p*-aminobenzyl alcohol substrate was protected with an acetyl group, and different chiral phosphoric acids based on BINOL and SPINOL backbones were evaluated as potential catalysts to catalyze the dehydration of the alcohol to generate the aza-*p*-QM intermediate, and the subsequent asymmetric alkylation with an indole nucleophile. The SPINOL derivative **L37** was found to be the best organocatalyst affording a 46% *ee* in the reaction.

The influence of the protecting group on the enantioselectivity of the reaction was evaluated: an array of protecting groups were screened: while methyl, sulfonyl groups led to moderate enantioselectivities, the bulky adamantane carbonyl group afforded an excellent enantioselectivity and it was chosen as the protecting group of election (95% ee) (Scheme 56).

Then, different 2,3-substituted indoles **137** and carbazoles **139** were subjected under the optimized reaction conditions affording the enantioenriched products **138** and **140** respectively in excellent enantioselectivities and yields (Scheme 57). The mild reaction conditions allowed that a wide range of functional groups. The product absolute configuration was confirmed by X-ray crystallography.

Next, it was also evaluated whether 2-substituted indoles **141** could serve as *N*-nucleophiles, but instead the reaction with the reaction with 2-phenylindole afforded exclusive reaction at the 3-position, leading to the addition product with diminished enantioselectivity (75% *ee*). A further optimization

led to improved enantioselectivity using dichloromethane as solvent and 3 Å molecular sieves as additive (Scheme 58).

Finally, they performed some control experiments which corroborates that only one phosphoric acid catalyst is involved into the enantiodetermining transition state of the reaction acting as a bifunctional catalyst (Figure 5). Firstly, the *N*-
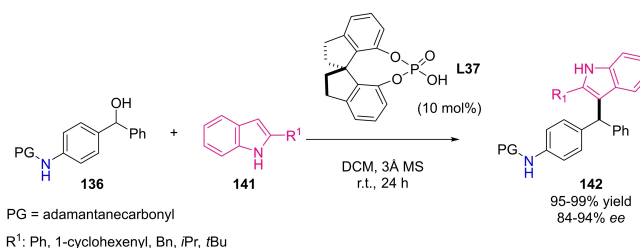

Scheme 56. Protecting group scope for the enantioselective 1,6-conjugate addition of aza-*p*-QM for the *N*-alkylation of indoles.
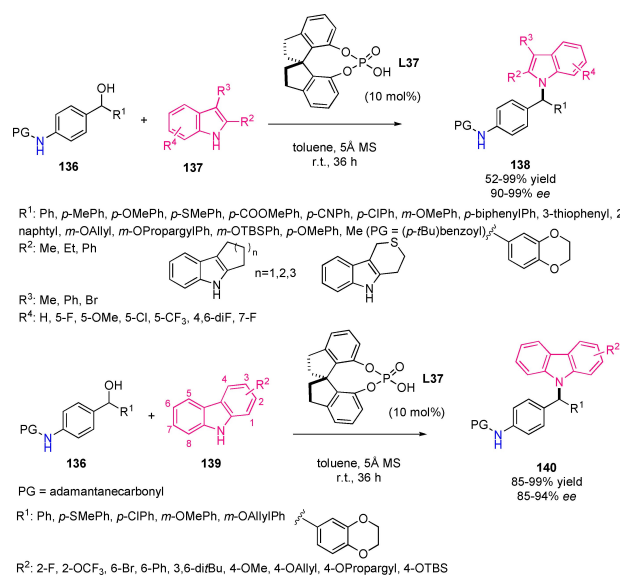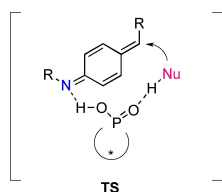

Scheme 57. Enantioselective 1,6-conjugate addition of aza-*p*-QM for the *N*-alkylation of indoles and carbazoles.

Scheme 58. Enantioselective 1,6-conjugate addition of 2-substituted Indole to aza-p-QM

Figure 5. Proposed transition state for chiral phosphoric acid catalytic addition of nucleophiles to aza-*p*-QM.

substituted aniline doesn't react, and secondly non-linear effects are observed.

A follow-up work of Sun of coworkers dealt with an enantioselective 1,8-addition to aza-*p*-quinone methides for the synthesis of tetrasubstituted chiral allenes, a long-standing hurdle on synthetic chemistry (Scheme 59).[60] Taking into account previous work developed in the group on 1,8-addition of para-QMs,[61] it was proposed to study the dehydration of racemic *p*-aminobenzyl propargylic alcohol **143** to generate the corresponding aza-*p*-QM conjugated with a triple bond which would then further react in an enantioselective fashion in the presence of a chiral Brønsted acid and a suitable nucleophile (Scheme 59).

The *N*-atom was protected of the aminobenzyl propargylic alcohol with pivaloyl group (Piv) (**143**) and a β-ketoesters, β-ketoamide and 1,3-diketones or acyclic nucleophile acetylacetone **144** was used as nucleophile chiral phosphoric acid **L38** and using toluene as solvent afforded the enantioenriched product in good to excellent enantioselectivities (Scheme 59).

In this work, the remote control of the chiral phosphoric acid is remarkable, as demonstrated by the high enantioselectivity and diastereoselectivity. The catalyst acts as a bifunctional catalyst activating the nucleophile and the substrate, and there
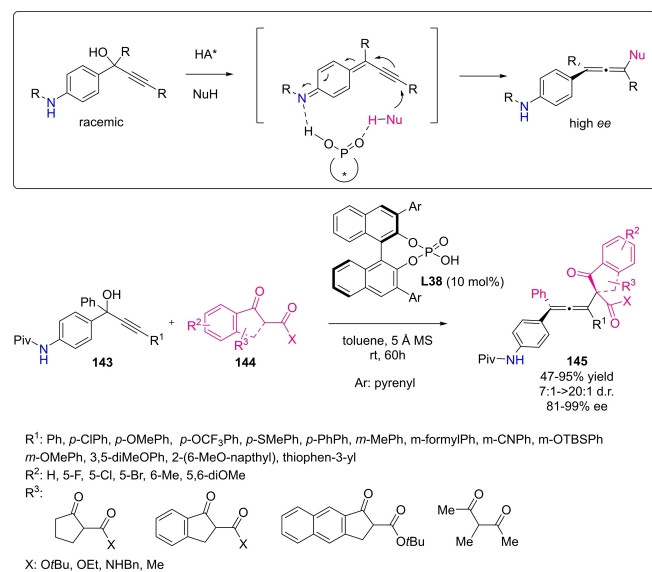
are two possible configurations for the planar aza-*p*-QM intermediate (*Z* or *E* alkene). While both should be formed initially and coexist in equilibrium, and the *E* form might be more reactive toward subsequent C—C bond formation, as it forms a favored transition state.

At the same time, another work appeared on enantioselective 1,8-addition of aza-*p*-QM by the group of Li for the preparation of chiral tetrasubstituted allenes and sulfur-containing quaternary centers possessing adjacent axially stereocenters (Scheme 60).[62] For this purpose, a *N*-triflylphosphoramide **L39** was used as chiral catalyst and 5-methyl-2-phenylthiazol-4(5H)-one **147** as nucleophile.

Firstly, a screening of different BINOL derived phosphoric acids and *N*-triflylphosphoramides was carried out in different solvents, observing that the catalyst **L39** led to the highest enantioselectivity when chlorobenzene was used as solvent and adamantylcarbonyl was the protecting group at the *N*-atom of propargylic alcohol **146** (Scheme 60).
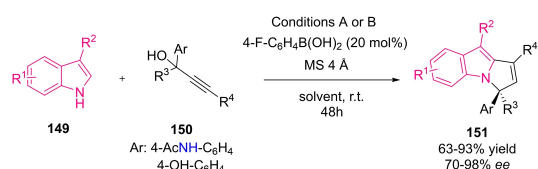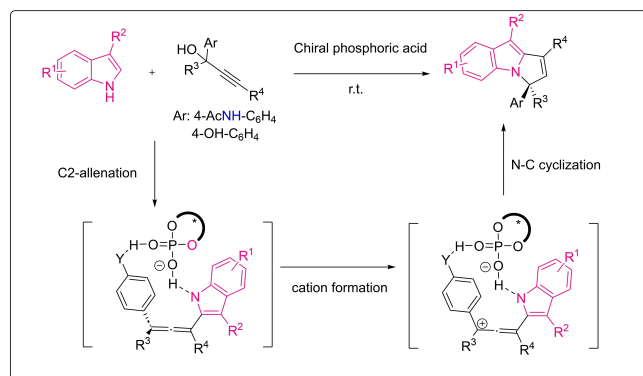
The scope of the propargyl alcohol **146** and 5-methyl-2-phenylthiazol-4(5H)-one **147** revealed that chiral tetrasubstituted allenes **148** could be obtained in excellent diastereoselectivities and enantioselectivities. Finally, control experiments were carried out in order to gain insight into the reaction mechanism. The generation of the aza-*p*-QM could be confirmed by ESI-MS spectrum. From a mixture of propargylic alcohol and acidic organocatalyst **L39** could be detected the intermediate, corroborating the instability and reactivity of these transient intermediates.

In 2020, Li and coworkers reported a chiral phosphoric acid catalyzed formal (3+2) cycloaddition of 3-substituted 1*H*-indoles and propargylic alcohols containing a functional directing group (*p*-NHAc or *p*-OH) (Scheme 61).[63] Despite the difficulty of controlling the enantioselectivity in cation species which are generated *in situ* by elimination of the hydroxy group, the group of Sun and Li had been able to generate chiral
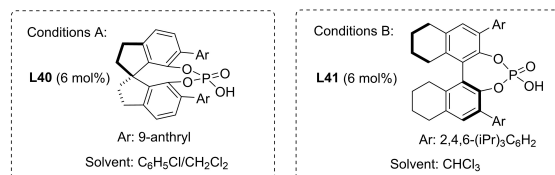

Scheme 59. Brønsted acid catalyzed enantioselective 1,8-addition of 1,3-dicarbonyl compounds to aza-*p*-QM.
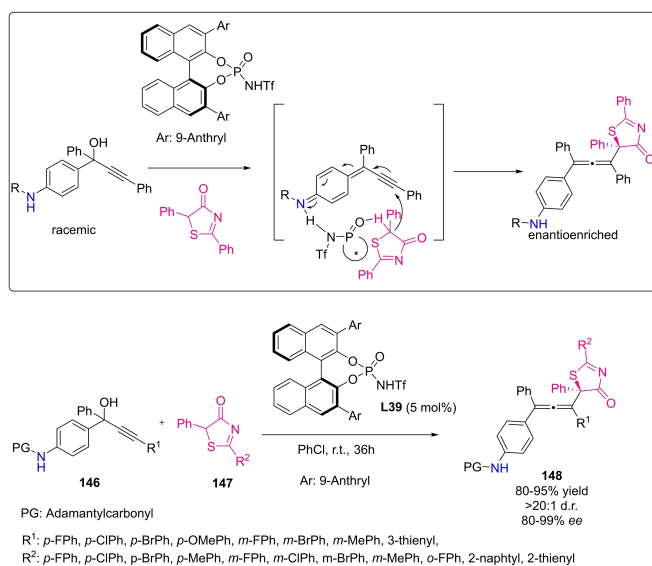
Scheme 60. Organocatalytic remote stereocontrolled 1,8-additions of thiazolones to propargylic aza-*p*-QM.

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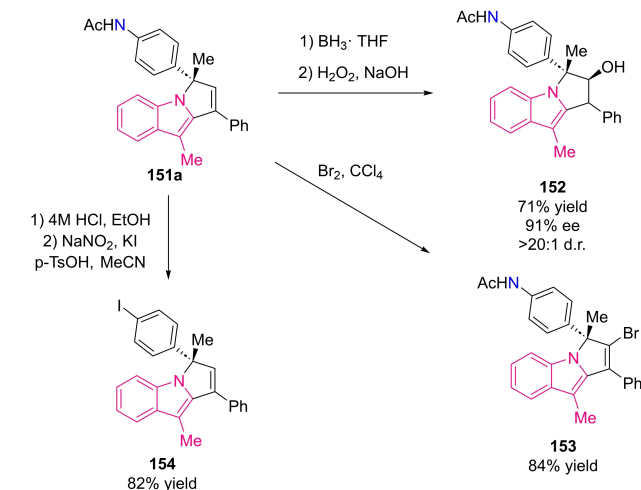Review
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Scheme 61. Chiral phosphoric acid catalyzed formal $(3+2)$ cycloaddition of 3-substituted 1H-indoles and propargylic alcohols.

Scheme 62. Synthetic application of pyrrolo[1,2-a]indole derivatives 151 a.

allenes through 1,8-addition of thiazolones and 1,3-dicarbonyl compounds respectively. In this work, using 2-substituted indole as nucleophile 149 and a propargylic alcohol 150 and instead of happening a 1,8-addition as in previous work, a $(3+2)$ cycloaddition is taking place. A screening of chiral phosphoric acid catalysts and reaction conditions revealed the use of an acidic additive improved the yield, either the use of SPINOL derived phosphoric acid L40 (5 mol%) as catalyst, 4-fluorophenylboronic acid (20 mol%), and 4 Å molecular sieves in PhCl/DCM mixed solvents or H8-BINOL-derived catalyst L41 in CHCl3 led to similar yield and enantioselectivity. The scope of the reaction allowed the obtaining of different derivatives bearing EWG or EDW in their structures (Scheme 61). This methodology represent a straightforward methodology for the synthesis chiral pyrrolo[1,2-a]indoles 151, core present in natural and biologically active products in a straightforward manner.

To demonstrate the synthetic applicability of pyrrolo[1,2-a]indole derivatives 151, further transformations were carried out (Scheme 62). The hydroboration/oxidation reaction afforded dihydropyrroloindole 152 in 71% and d.r. $>20:1$. The bromination of 151 a afforded product 153 in 84% yield, a versatile intermediate for further modifications. Finally, the acetamido group of 151 a was hydrolyzed to an amino group followed by iodination affording derivative 153 in 82% yield.

Also in 2020, the group of Li developed the first example of 1,6-addition of propargylic aza-p-QMs using N-aryl-3-oxobutanamides as nucleophiles (Scheme 63).[64] This methodology allowed controlling the regioselectivity towards the 1,6-addition instead of 1,8-addition as in previous work of Li's group. The use of a 9-anthryl substituted chiral phosphoric acid L42 in 1 mol% catalyst, PhCF3 as solvent and an adamantyl protected aza-p-QM precursor 146 and a N-aryl-3-oxobutanamide 155 as nucleophile led to a variety of 1,6-addition derivatives in enantioselectivities up to 95% ee (Scheme 63). The importance of this transformation lies on the regioselectivity and stereoselectivity of the reaction for the formation of quaternary centers.
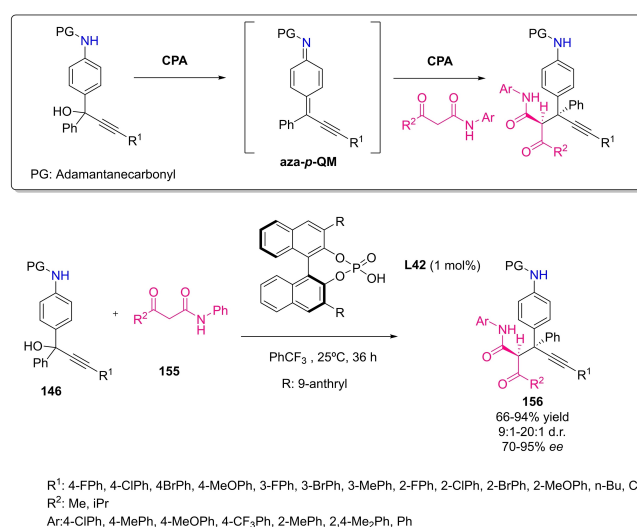
Scheme 63. Chiral phosphoric acid catalyzed 1,6-additions of N-aryl-3-oxobutanamides to propargylic aza-p-quinone methides.

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2. 2. 2. Metal catalysis

Very recently, the Harutyunyan group published the first work on enantioselective 1,6-addition of Grignard reagents to aza-*p*-QM (Scheme 64).[65] For this purpose, they developed a novel methodology to generate aza-*p*-QMs using a Grignard reagent as a base to generate the transient intermediate aza-*p*-QM as well as a nucleophile which reacts with the unstable intermediate leading to the chiral *sec*-alkyl aniline.

Taniaphos ligand **L43** in combination with CuBr was chosen as best catalytic system, and the reaction of aniline derivative **157** and alkyl Grignard reagents **158** as a nucleophile afforded chiral *sec*-alkylaniline derivatives **159** in up to 76% ee and 92% yield (Scheme 64).This works reflects the first example of catalytic derivatization of aza-*p*-QM through metal catalysis and it shows as an advantage that there is no need to protect the N-atom in order to obtain enantioselectivities in the catalytic reaction.

3. Conclusions and Outlook

The N-containing compounds are present in many drugs or biologically active compounds. To this end the study of the reactive aza-QM has attracted attention in the last years as a fruitful strategy for the synthesis of chiral aniline and N-heterocyclic derivatives such as tetrahydroisoquinolines, quinolones, tetrahydroacridines, spirobenzazepinones, indoles etc. Along this review the recent advances concerning the asymmetric catalytic addition of different nucleophiles to aza-QMs has been covered with a special emphasis on the mode of action of the metal and organocatalysts. While the methods which involve the use of aza-*o*-QM have been more developed,

the catalytic methodologies involving aza-*p*-QM are quite scarce, reduced to a number of seven different catalytic approaches to the best of our knowledge.

Overall, most of the catalytic transformations for the derivatization of aza-QM involve the use of organocatalysts: namely chiral phosphoric acids and phosphoramides derived from BINOL and SPINOL, NHC carbenes or bifunctional thiourea catalysts. Furthermore, several transformations involving metal catalysis (palladium and copper) have been reported affording novel chiral *N*-heterocycles. A wide variety of transformations involving the addition of N, O, S, P and C nucleophiles have been discussed in this review.

To sum up, the study of these reactive intermediates on asymmetric transformations has been developed very recently and we expect novel transformations to appear soon in the literature. Mainly on organometallic chemistry, as it would allow the obtaining of chiral N-heterocyclic structures as anilines difficult to access by other synthetic routes with a variety of C-nucleophiles, but also, using photoredox and electrocatalysis which would make possible to access novel N-containing compounds, increasing the chemical diversity.
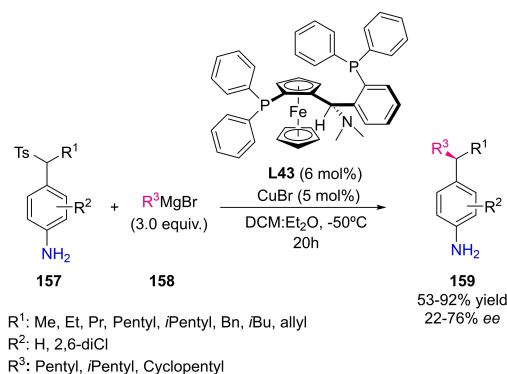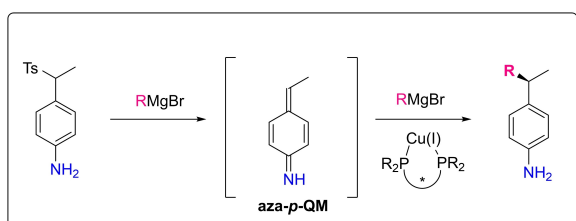
Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

There is no public repository.

Scheme 64. Enantioselective Cu(I)-catalyzed 1,6-addition of Grignard reagents to in situ generated aza-*p*-QM.

R^1: Me, Et, Pr, Pentyl, *i*Pentyl, Bn, *i*Bu, allyl
R^2: H, 2,6-diCl
R^3: Pentyl, *i*Pentyl, Cyclopentyl

157 **158** **159**
53-92% yield
22-76% ee

[1] I. Klopčič, M. Sollner Dolenc, *Chem. Res. Toxicol.* **2019**, *32*, 1–34. DOI: 10.1021/acs.chemrestox.8b00213.

[2] T.-H. Wu, Z.-S. Su, R. Sung, K. Sung, *ChemPhysChem* **2020**, *21*, 307–312. DOI: 10.1002/cphc.201901133.

[3] T. B. Hughes, S. J. Swamidass *Chem. Res. Toxicol.* **2017**, *30*, 642–656. DOI: 10.1021/acs.chemrestox.6b00385.

[4] K. Wojciechowski, *Eur. J. Org. Chem.* **2001**, *19*, 3587–3605.

[5] "Quinone Methides": H.-U. Wagner, R. Gompper in The Chemistry of the Quinonoid Compounds, Vol. 2 (Ed.: S. Patai), Wiley, New York, 1974, chap. 18, pp. 1145–1178.

[6] M. Freccero, *Mini-Rev. Org. Chem.* **2004**, *1*, 403–415. DOI: 10.2174/1570193043403091.

[7] C. Yang, W. Peter, *J. Photochem. Photobiol. A* **1994**, *80*, 227–232. SSDI 1010.6030(93)01001-I.

[8] D. M. Walden, A. A. Jaworski, R. C. Johnston, M. Todd Hovey, H. V. Baker, M. P. Meyer, K. A. Scheidt, P. Ha-Yeon Cheong, *J. Org. Chem.* **2017**, *82*, 7183–7189. DOI: 10.1021/acs.joc.7b00697.

[9] E. Kinski, P. Marzenell, W. Hofer, H. Hagen, J. A. Raskatov, K. X. Knaup, E. M. Zolnhofer, K. Meyer, A. Mokhir, *J. Inorg. Biochem.* **2016**, *160*, 218–224. DOI: 10.1016/j.jinorgbio.2016.02.023.

[10] P. K. Mishra, T. Saha, P. Talukdar *Org. Biomol. Chem.* **2015**, *13*, 7430–7436. DOI: 10.1039/c5ob00785b.

[11] H. Shigemitsu, T. Fujisaku, W. Tanaka, R. Kubota, S. Minami, K. Urayama, I. Hamachi, *Nat. Nanotechnol.* **2018**, *13*, 165–172. https://doi.org/10.1038/s41565-017-0026-6.

[12] S. Gnaim, D. Shabat, *Acc. Chem. Res.* **2014**, *47*, 2970–2984. 10.1021/ar500179y.

[13] O. Shelef, S. Gnaim, D. Shabat *J. Am. Chem. Soc.* **2021**, *143*, 21177–21188. DOI: 10.1021/jacs.1c11410.

[14] a) H.-H. Liao, S. Miñoza, S.-C. Lee, M. Rueping, *Chem. Eur. J.* **2022**, *28*, e202201112. DOI: 10.1002/chem.202201112; b) C. Dorsch, C. Schneider, *Synthesis* **2022**, *54*, 3125–3141. DOI: 10.1055/a-1781-6538.

[15] E. M. P. Silva, A. M. S. Silva *Synthesis* **2012**, *44*, 3109–3128. DOI: 10.1055/s-0032-1316778.

[16] P. Anastas, N. Eghbali, Green Chemistry: Principles and Practice, *Chem. Soc. Rev.*, **2010**, *39*, 301–312. https://doi.org/10.1039/B918763B.

[17] E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, *88*, 1580–1581.

[18] B. Yanga, S. Gao *Chem. Soc. Rev.* **2018**, *47*, 7926–7953. https://doi.org/10.1021/ja00959a066.

[19] H. Steinhagen, E. J. Corey, *Angew. Chem. Int. Ed.* **1999**, *38*, 1928–1931. https://doi.org/10.1002/(SICI)1521-.

[20] A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 10589–10592. DOI: 10.1021/ja505880r.

[21] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568. DOI: 10.1002/anie.200353240.

[22] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. DOI: 10.1021/ja0491533.

[23] a) D. Kampen, C. M. Reisinger, B. List (2010) Chiral Brønsted Acids for Asymmetric Organocatalysis. In: List B. (eds) Asymmetric Organocatalysis. Topics in Current Chemistry, vol 291. Springer, Berlin, Heidelberg; b) X. del Corte, E. Martínez de Marigorta, F. Palacios, J. Vicario, A. Maestro, *Org. Chem. Front.* **2022**, *9*, 6331–6399 DOI: 10.1039/D2QO01209J; c) E. l. Jiménez, *Org. Biomol. Chem.* **2023**, *21*, 3477–3502. DOI: 10.1039/D3OB00212H; d) B.-C. Da, S.-H. Xiang, S. Li, B. Tan *Chin. J. Chem.* **2021**, *39*, 1787–1796. DOI: 10.1002/cjoc.202000751; For recent examples: e) F.-T. Sheng, S. Yang, S.-F. Wu, Y.-C. Zhang, F. Shi *Chin. J. Chem.* **2022**, *40*, 2151–2160 DOI: 10.1002/cjoc.202200327; f) J.-Y. Wang, M. Sun, X.-Y. Yu, Y.-C. Zhang, W. Tan, F. Shi *Chin. J. Chem.* **2021**, *39*, 2163–2171 DOI: 10.1002/cjoc.202100214; For a highlight: g) W. Tan, F. Shi, *Chem. Synth.* **2022**, *2*, 11. DOI: 10.20517/cs.2022.14.

[24] C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758. DOI: 10.1002/anie.200701342.

[25] P. Siengalewicz, T. Gaich, J. Mulzer, *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–817. https://doi.org/10.1002/anie.200801735.

[26] H.-H. Liao, A. Chatupheeraphat, C.-C. Hsiao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 15540–15544. DOI: 10.1002/anie.201505981.

[27] G. Li, H. Liu, G. Lv, Y. Wang, Q. Fu, Z. Tang, *Org. Lett.* **2015**, *17*, 4125–4127. DOI: 10.1021/acs.orglett.5b02025.

[28] A. Chatupheeraphat, H.-H. Liao, S. Mader, M. Sako, H. Sasai, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 4803–4807. DOI: 10.1002/anie.201511179.

[29] M. Kretzschmar, T. Hodík, C. Schneider, *Angew. Chem. Int. Ed.* **2016**, *55*, 9788–9792. DOI: 10.1002/anie.201604201.

[30] L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 11110–11114. DOI: 10.1002/anie.201604819.

[31] T. Hodík, C. Schneider, *Org. Biomol. Chem.* **2017**, *15*, 3706–3716. DOI 10.1002/chem.201803886.

[32] M. Kretzschmar, F. Hofmann, D. Moock, C. Schneider, *Angew. Chem. Int. Ed.* **2018**, *57*, 4774–4778. DOI: 10.1002/anie.201800787.

[33] T. Hodík, C. Schneider, *Chem. Eur. J.* **2018**, *24*, 18082–18088. DOI: 10.1002/chem.201803886.

[34] A. Lee, J. L. Zhu, T. Feoktistova, A. C. Brueckner, P. H.-Y. Cheong, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2019**, *58*, 5941–5945. DOI: 10.1002/anie.201900600.

[35] X. Liu, K. Wang, W. Guo, Y. Liu, C. Li *Chem. Commun.* **2019**, *55*, 2668–2671. DOI: 10.1039/c8cc09382b.

[36] F. Yang, X. Zhou, Y. Wei, L. Wang, J. Jiang, *Org. Chem. Front.* **2021**, *21*, 3477–3502. DOI: 10.1039/d1qo00823d.

[37] X. Wu, C. Sparr *Angew. Chem. Int. Ed.* **2022**, *61*, e202201424. DOI: 10.1002/anie.202201424.

[38] X. Chen, T. Wang, Z. Lu, P. Li, *Org. Lett.* **2022**, *24*, 3102–3106. DOI: 10.1021/acs.orglett.2c01154.

[39] C. Wang, J. A. Tunge, *J. Am. Chem. Soc.* **2008**, *130*, 8118–8119. https://doi.org/10.1021/ja801742h.

[40] T.-R. Li, F. Tan, L.-Q. Lu, Y. Wei, Y.-N. Wang, Y.-Y. Liu, Q.-Q. Yang, J.-R. Chen, D.-Q. Shi, W.-J. Xiao, *Nat. Commun.* **2014**, *5*, 5500 DOI: 10.1038/ncomms6500.

[41] H. Jia, H. Liu, Z. Guo, J. Huang, H. Guo, *Org. Lett.* **2017**, *19*, 5236–5239. DOI: 10.1021/acs.orglett.7b02512.

[42] G.-J. Mei, C.-Y. Bian, G.-H. Li, S.-L. Xu, W.-Q. Zheng, Feng Shi, *Org. Lett.* **2017**, *19*, 3219–3222. DOI: 10.1021/acs.orglett.7b01336.

[43] G.-J. Mei, D. Li, G.-X. Zhou, Q. Shi, Z. Cao, Feng Shi, *Chem. Commun.* **2017**, *53*, 10030–10033. DOI: 10.1039/c7cc05595.

[44] M.-M. Li, Y. Wei, J. Liu, H.-W. Chen, L.-Q. Lu, W.-J. Xiao *J. Am. Chem. Soc.* **2017**, *139*, 14707–14713.

[45] Y.-N. Wang, B.-C. Wang, M.-M. Zhang, X.-W. Gao, T.-R. Li, L.-Q. Lu, W.-J. Xiao, *Org. Lett.* **2017**, *19*, 4094–4097. DOI: 10.1021/acs.orglett.7b01794.

[46] C. Wang, Y. Li, Y. Wu, Q. Wang, W. Shi, C. Yuan, L. Zhou, Y. Xiao, H. Guo, *Org. Lett.* **2018**, *20*, 2880–2883. DOI: 10.1021/acs.orglett.8b00905.

[47] J.-H. Jin, H. Wang, Z.-T. Yang, W.-L. Yang, W. Tang, W.-P. Deng *Org. Lett.* **2018**, *20*, 104–107. DOI: 10.1021/acs.orglett.7b03467.

[48] H.-W. Zhao, N.-N. Feng, J.-M. Guo, J. Du, W.-Q. Ding, L.-R. Wang, Xiu-Qing Song *J. Org. Chem.* **2018**, *83*, 9291–9299. DOI: 10.1021/acs.joc.8b01268.

[49] Y.-N. Wang, Q. Xiong, L.-Q. Lu, Q.-L. Zhang, Y. Wang, Y. Lan, W.-J. Xiao *Angew. Chem. Int. Ed.* **2019**, *58*, 11013–11017. DOI: 10.1002/anie.201905993.

[50] B.-B. Sun, Q.-X. Hu, J.-M. Hu, J.-Q. Yu, J. Jia, X.-W. Wang *Tetrahedron Lett.* **2019**, *60*, 1967–19700. DOI: 10.1016/j.tetlet.2019.06.041.

[51] Z. D. Tucker, H. M. Hill, A. L. Smith, *Org. Lett.* **2020**, *22*, 6605–6609. DOI: 10.1021/acs.orglett.0c02374.

[52] H. Uno, N. Punna, E. Tokunaga, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2020**, *59*, 8187–8194. DOI: 10.1002/anie.201915021.

[53] Y. Gao, X. Zhang, X. Zhang, Z. Miao *Org. Lett.* **2021**, *23*, 2415–2420. DOI: 10.1021/acs.orglett.1c00073.

[54] S. N. F. B. S. Ismail, B. Yang, Y. Zhao *Org. Lett.* **2021**, *23*, 2884–2889. DOI: 10.1021/acs.orglett.1c00505.

[55] J.-M. Guo, X.-Z. Fan, H.-H. Wu, Z. Tang, X.-F. Bi, H. Zhang, L.-Y. Cai, H.-W. Zhao, Q.-D. Zhong *J. Org. Chem.* **2021**, *86*, 1712–1720. DOI: 10.1021/acs.joc.0c02524.

[56] C. Guo, M. Fleige, D. J. -Müller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 7840–7843. DOI: 10.1021/jacs.6b04364.

[57] C. Guo, D. Janssen-Müller, M. Fleige, A. Lerchen, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2017**, *139*, 4443–4451. DOI: 10.1021/jacs.7b00462.

[58] L. A. Leth, F. Glaus, M. Meazza, L. Fu, M. K. Thøgersen, E. A. Bitsch, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15272–15276. DOI: 10.1002/anie.201607788.

[59] M. Chen, J. Sun, *Angew. Chem. Int. Ed.* **2017**, *56*, 4583–4587. DOI: 10.1002/anie.201701947.

[60] M. Chen, D. Qian, J. Sun, *Org. Lett.* **2019**, *21*, 8127–8131. DOI: 10.1021/acs.orglett.9b03224.

[61] D. Qian, L. Wu, Z. Lin, J. Sun, *Nat. Commun.* **2017**, *8*, 567. DOI: 10.1038/s41467-017-00251-x.

[62] L. Zhang, Y. Han, A. Huang, P. Zhang, P. Li, W. Li, *Org. Lett.* **2019**, *21*, 7415–7419. DOI: 10.1021/acs.orglett.9b03224.

[63] J.-F. Bai, L. Zhao, F. Wang, F. Yan, T. Kano, K. Maruoka, Y. Li, *Org. Lett.* **2020**, *22*, 5439–5445, DOI: 10.1021/acs.orglett.0c01812?ref=pdf.

[64] F. Li, X. Chen, S. Liang, Z. Shi, P. Li, W. Li, *Org. Chem. Front.* **2020**,*7*, 3446–3451, DOI: 10.1039/D0QO00888E.

[65] M. Zurro, L. Ge, S. R. Harutyunyan, *Org. Lett.* **2022**, *24*, 6686–6691 DOI: 10.1021/acs.orglett.2c02786.