DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

Asymmetric Oxidative Mannich Reactions

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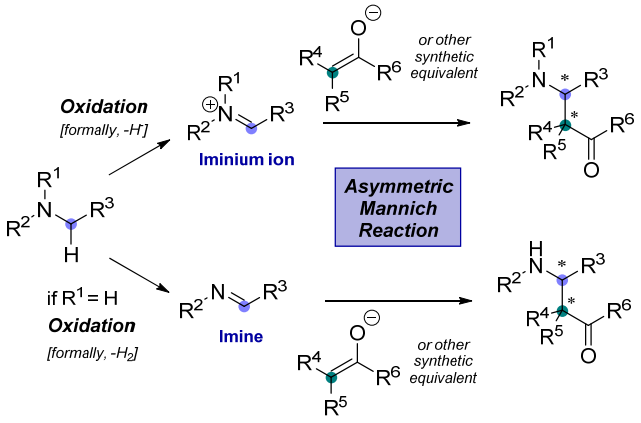
Abstract. The asymmetric Mannich reaction is one of the most straightforward methodologies for the enantioselective synthesis of chiral amines. In general, asymmetric Mannich reactions involve the use of imines as electrophiles. However, in recent years, several asymmetric oxidative Mannich reactions have been reported using amines as electrophiles. This review provides an overview of these recent publications, including the different oxidants used and the scope and limitations of the different catalytic systems.

Keywords: Mannich reaction; asymmetric catalysis; amines; oxidation; cross-dehydrogenative coupling

1 Introduction

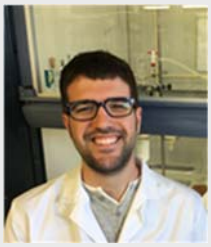
Chiral amines are embodied in many biologically important molecules, like natural products, drugs and drug leads.[1] This kind of compounds are particularly important in pharmaceutical industry and chemical synthesis and countless approaches have been established to prepare them.[2] In this context, the enantioselective addition of enolates (or enolate synthetic equivalents) to electrophilic C=N double bonds (the so-called Mannich reaction) is a straightforward strategy to access to these enantioenriched highly valuable products.[3] However, the asymmetric Mannich reaction has several disadvantages such as the problematic synthesis and instability of some imines, or in the case of alkanal derived imines are rather unstable compounds since the azomethine–azaenol equilibrium generally privileges the enamide tautomer which lacks any electrophilic character. An alternative to avoid these drawbacks of using imines as electrophiles in enantioselective Mannich reactions, is their preparation in situ from readily available amines by simple oxidation.

Organic amines are ubiquitous class or compounds present in nature and they are readily available. Amines bearing alkyl chains can be oxidized in order to generate an electrophilic carbon center, which can be trapped, in an enantioselective way, by distinct nucleophiles. If the nucleophile is an enolate or an enol (or synthetic equivalents), the process could be described as an asymmetric oxidative Mannich reaction (Scheme 1). Recently, several examples of asymmetric oxidative Mannich reactions using secondary and tertiary amines have been described in the literature and have been applied for the synthesis of natural products and pharmaceutically relevant molecules.



Scheme 1. General overview of the methodologies described in this review.

In this review, an exhaustive overview of the whole reaction process is shown, mainly regarding how the oxidation step proceeds, but also focusing on the subsequent catalytic asymmetric induction. With the aim of elaborate a practical guideline that can serve to select a preliminary reaction conditions for a desired transformation, we have categorized this review on the base of the amine oxidation step. The amine can be oxidized directly using either a stoichiometric oxidant or a catalytic cycle coupled with a stoichiometric oxidant, as well as with novel elegant strategies such as electrochemistry or photoredox catalysis.



Jaume Rostoll-Berenguer graduated in chemistry (2017) and received his Master's degree in Organic Chemistry (2018), both from the University of València. Since 2018, he is developing his PhD studies focused on the functionalization of amines using visible-light photocatalysis at the same University under the supervision of Dr. Carlos Vila and Prof. Dr. José Ramón Pedro.

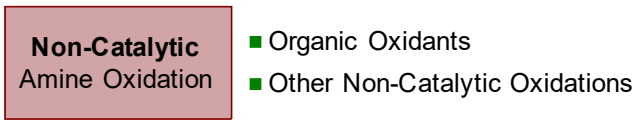
Gonzalo Blay received his degree in chemistry (1987) and his Ph.D. (1992) from the University of València. He has been a Marie Curie postdoctoral fellow at the Agricultural University of Wageningen, The Netherlands, with Professor A. de Groot (1993–94) and visiting researcher at Aarhus University, Denmark, with Professor K. A. Jørgensen (2005). In 1996, he became Associate Professor at the Department of Organic Chemistry of the University of València and was appointed Full Professor in 2012. His research interest includes organic synthesis and the development of catalytic methodologies, in particular asymmetric catalysis.

José R. Pedro graduated in chemistry from the University of València in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at the University of València. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at the University of València (AsymCat, GIUV13).

Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from the University of València. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling reactions with organolithium reagents and asymmetric catalysis. In 2018, he was appointed as a 'Ramón y Cajal' researcher at the Organic Chemistry Department, University of València. His current research interests are asymmetric catalysis and photocatalysis.

2 Non-Catalytic Amine Oxidations

Formally, amine oxidation may refer to the formation of N-O new species from N-H bonds.[4] However, in this context, we refer to amine oxidation as the formation of an electrophilic intermediate through a formal hydride abstraction of the starting amine (Scheme 1). As mentioned in the Introduction, this first chemical transformation could be achieved by many methods but, in this section, we will focus on procedures in which the oxidation is provided by a stochiometric oxidant, without the mediation of any catalyst. Additionally, this section will be split in two subsections, being the first one referred to procedures in which the amine is directly oxidized by the action of a stoichiometric organic oxidant. The second subsection will cover other non-catalytic methodologies in which the oxidation of the amine is accompanied by the reduction of a functional group suitably located in another part of the same molecule (Scheme 2).

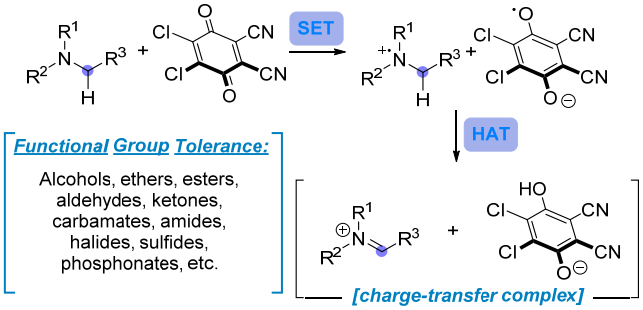


Scheme 2. Summary of the reports that will be reviewed regarding non-catalytic amine oxidation.

2.1. Organic Oxidants

Several organic molecules have been used as organic oxidants to prepare several important molecules. For example, quinones have been extensively used for the direct oxidation of organic compounds, mainly regarding the aromatization of cyclic compounds, as for example in the Hantzsch pyridine synthesis.[5] Among all quinones, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) represents one of the most

versatile organic oxidant, due to its relative stability under a wide variety of reaction conditions and its facility to undergo hydride transfer processes.[6] DDQ have already been used for the deprotection of benzylic ethers in a huge variety of synthetic challenges and reaction conditions. As postulated for benzylic ethers, the hydride transfer step should proceed through an initial Single Electron Transfer (SET) followed by a Hydrogen Atom Transfer (HAT) to give a charge-transfer complex between the electron-rich amine and DDQ (Scheme 3).[7]

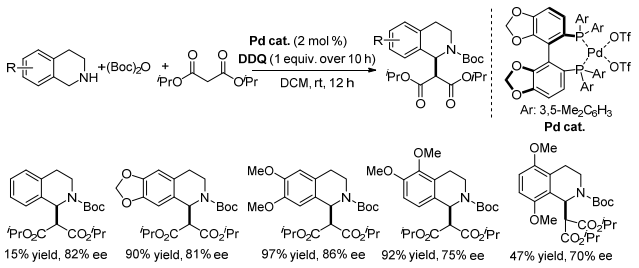


Scheme 3. Plausible oxidation route for amines in the presence of DDQ.

This ability to generate electrophiles from amines smoothly has attracted the attention for the developing of Mannich-type enantioselective procedures, in combination with an asymmetric-inductive catalytic system.

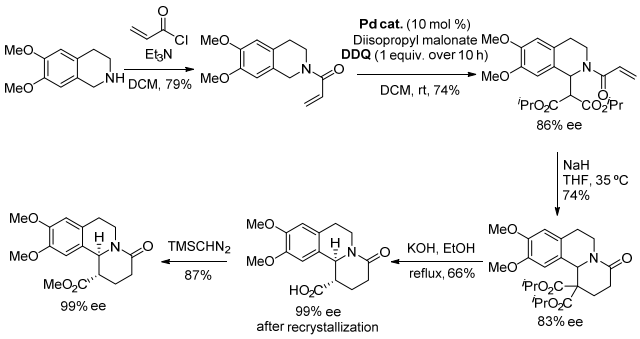
Cyclic amines are an important scaffold in organic synthesis and medicinal chemistry. In this context, an important class of cyclic amines is the tetrahydroisoquinoline skeleton,[8] is present in several natural products and is one of the among top 20 nitrogen heterocycles in drugs.[9] Therefore, synthetic organic chemists have studied the functionalization of these compounds in the last decades.

To the best of our knowledge, the first report in which an amine is oxidized with DDQ with the aim of undergo a subsequent enantioselective Mannich reaction, appeared in 2008 from the Sodeoka laboratory.[10] The authors were capable of coupling *N*-Boc-tetrahydroisoquinolines (*N*-Boc-THIQs) with diisopropyl malonate in an enantioselective way by using a chiral palladium complex, after a DDQ oxidation. The *N*-protection with $(Boc)_2O$ was carried out in situ after the oxidation step. Then, they applied their protection-oxidation-Mannich reaction methodology to other electron-rich THIQs obtaining the corresponding products in poor to excellent yields and moderate enantioselectivities (Scheme 4). The presence of methoxy substituent on the aromatic ring was determined to be crucial for the success of the reaction.



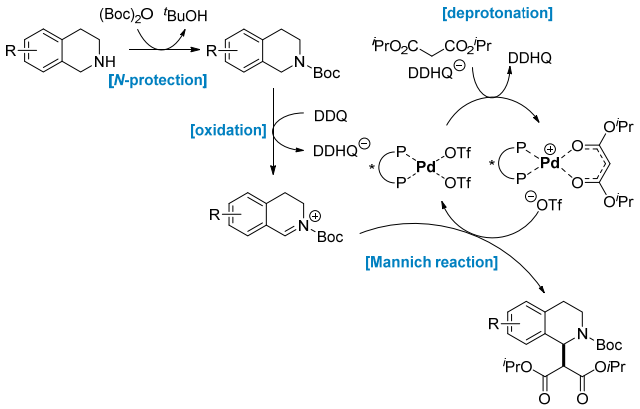
Scheme 4. Enantioselective addition of diisopropyl malonate to THIQs (Sodeoka, 2008).

The researchers also applied their asymmetric oxidative protocol to the synthesis of a chiral tetrahydrobenzo[a]quinolizidine derivative (Scheme 5). First, 6,7-dimethoxy-THIQ was treated with acryloyl chloride to deliver *N*-acylation product. Then, this *N*-protected THIQ was subjected to the enantioselective oxidative Mannich protocol, which provided the desired product in 74% yield and 86% ee. An intramolecular Michael addition was then achieved upon deprotonation of the malonate acidic α-proton with NaH. Finally, after a basic hydrolysis and a subsequent recrystallization, the corresponding enantiopure carboxylic acid was obtained, which was converted into the corresponding methyl ester using $TMSCHN_2$.



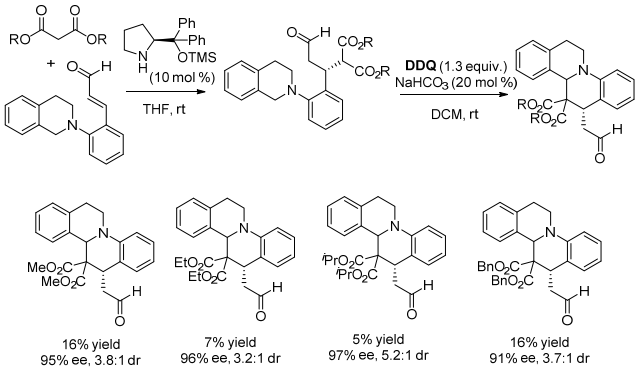
Scheme 5. Synthetic route towards a chiral tetrahydrobenzo[*a*]quinolizidine derivative.

Finally, the authors proposed a tentative mechanism by which the reaction should proceed. First, the corresponding THIQ is *N*-protected by the action of Boc anhydride. The in situ-generated *N*-Boc-THIQ is readily oxidized by DDQ in the same way as depicted in Scheme 3. The last step could be the trapping of the *N*-Boc-THIQs-derived iminium ion by the palladium chiral enolate, which is formed upon coordination and subsequent deprotonation of diisopropyl malonate and the Pd complex (Scheme 6).



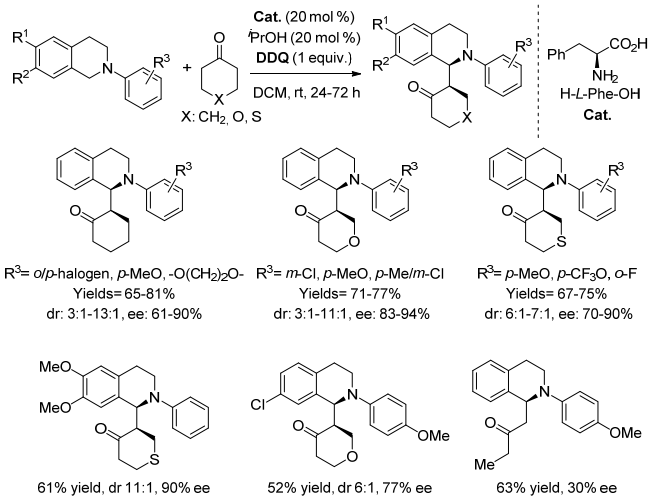
Scheme 6. Mechanistic proposal for the asymmetric diisopropyl malonate addition to THIQ.

Almost four years later, in 2012, Kim and Gwon described a two-step methodology to synthesize chiral fused THIQs.[11] The authors designed a 2-cinnamaldehyde-derived THIQ, on which, first, an enantioselective Michael addition of malonates to the β-position of the cinnamyl moiety was achieved by the action of O-TMS-diphenylprolinol.[12] Then, the corresponding chiral THIQ was subjected to an oxidative intramolecular Mannich reaction using DDQ as stoichiometric oxidant and $NaHCO_3$ as additive. Using their protocol, these researchers were able to synthesize four chiral THIQs with different malonate derivatives in low yields after 2 steps (up to 16%) and moderate diastereoselectivities (up to 5:1), albeit with excellent enantioselectivities (Scheme 7).



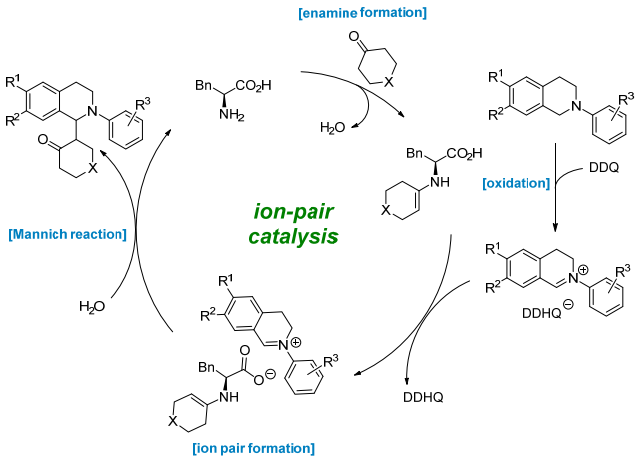
Scheme 7. Enantioselective synthesis of fused THIQs (Kim, 2012).

In 2013 the laboratory of Wang investigated the capability of chiral amino acids to act as bifunctional organocatalysts in an oxidative asymmetric Mannich reaction.[13] The authors envisioned that the iminium cation, formed by oxidation of the corresponding THIQ with DDQ, might form an ion-pair with the carboxylate group of the catalyst, whereas the amine group of the amino acid could form a nucleophilic enamine from the ketone reagent. The formation of this highly organized intermediate could induce the enantioselective addition of the enamine to the iminium cation. Following this approach, they could develop a methodology for the enantioselective Mannich reaction between *N*-aryl-THIQs and ketones using natural phenylalanine as bifunctional ion-pair forming organocatalyst, ^{i}PrOH as additive and DDQ as stoichiometric oxidant (Scheme 8). Under these conditions, they can access 15 differently substituted THIQs bearing a variety of six-membered cyclic ketones in moderate to good yields, high diasteroselectivities and good enantiomeric excesses. However, a substantial drop in the enantiomeric excess (30% ee) was observed when butanone, a linear ketone, was employed.



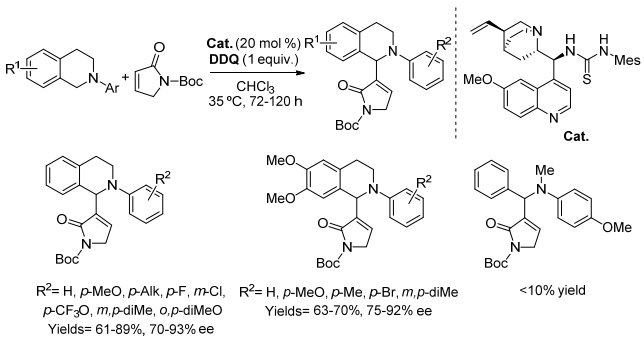
Scheme 8. Catalytic enantioselective oxidative coupling of THIQs with ketones (Wang, 2013).

The absolute configuration of the two contiguous stereocenters was established by single-crystal X-Ray diffraction. Finally, these researchers proposed a mechanistic pathway by which the reaction should proceed (Scheme 9). First, DDQ was able to oxidize the proper THIQ to its corresponding iminium ion with the concomitant formation of the DDHQ ion. Then, this electrophile can form an ion-pair with the chiral enamine derived from the condensation between H-*L*-Phe-OH and the corresponding cyclic ketone, upon deprotonation of the carboxylic acid. The formation of this ion-pair allows the enamine to react with the iminium cation in an enantioselective manner, providing, after hydrolysis, the enantioenriched desired product.



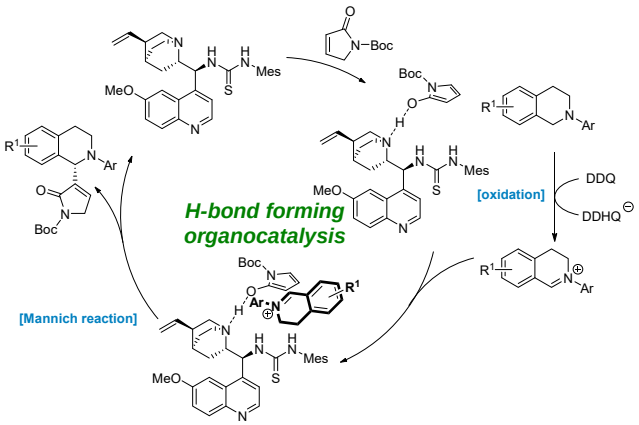
Scheme 9. Mechanistic proposal for the oxidative Mannich reaction enabled by ion-pair catalysis.

One year later, in 2014, the same research group reported an asymmetric oxidative coupling between THIQs and α,β-unsaturated γ-butyrolactams.[14] Although formally this transformation seems a Morita-Baylis-Hillman reaction, it does not involve a nucleophilic β attack of the catalyst to generate a chiral enolate. In contrast, the enolate is formed after a deprotonation in the vinylogous position and, therefore this transformation can be considered as a Mannich reaction and consequently it is included in this review. These researchers anticipated that, after the oxidation of THIQ by DDQ, a chiral hydrogen-bond forming organocatalyst could deprotonate γ-butyrolactames in its vinylogous position to generate a highly stabilized aromatic enolate, which would be capable of reacting with THIQ iminium cation. Based on these considerations, they screened several hydrogen bonding catalyst, being the best catalyst a thiourea derived from quinine alkaloid.[15] Using their optimal reaction conditions, they explored the scope of the reaction with differently substituted N-aryl THIQs, obtaining the desired products in good yields and good to high enantiomeric excesses (Scheme 10).



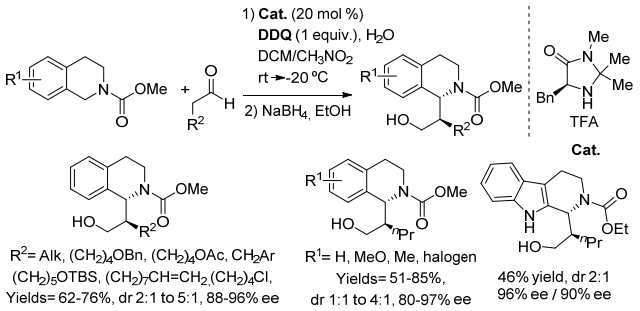
Scheme 10. Organocatalytic asymmetric oxidative addition of γ-butyrolactames to THIQs (Wang, 2014).

The authors proposed a possible reaction pathway outlined in Scheme 11. DDQ oxidize the tertiary amine (THIQ) to its corresponding iminium cation. Meanwhile, the thiourea catalyst activated α,β-unsaturated γ-butyrolactam through a hydrogen bond, generating the *tert*-butyl 2-hydroxy-1*H*-pyrrole-1-carboxylate, which attacks the iminium cation to afford the final product.



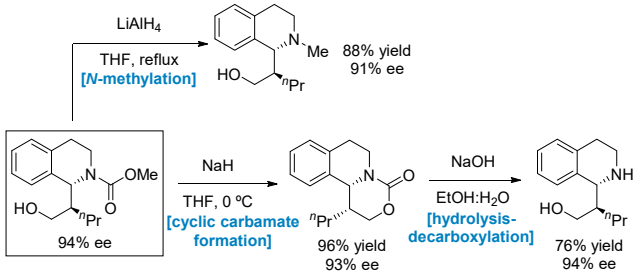
Scheme 11. Mechanistic hypothesis for the enantioselective addition of γ-butyrolactames to THIQs.

In 2016, Liu and collaborators reported an enantioselective oxidative Mannich reaction between *N*-carbamoyl THIQs and aldehydes.[16] Their approach is based on the capability of chiral imidazolidinones derived from natural amino acids to act as organocatalysts through the formation of chiral enamines.[17] The authors selected the imidazolidinone derived from *L*-Phe, developed by MacMillan,[18] as the optimal organocatalyst, in combination with DDQ as oxidant and water as additive. To facilitate the isolation and the determination of the enantiomeric excess by chiral HPLC, the aldehyde moiety in the final product was reduced with $NaBH_4$. Using the optimal reaction conditions, they could generate a set of seventeen enantioenriched alcohols in moderate to good global yields (up to 86%), moderate diastereomeric ratios (up to 4:1) and excellent enantioselectivities (up to 96%) (Scheme 12). This methodology exhibited high functional group tolerance in the aldehyde partner. Several groups such as alkenes, benzyl ethers, acetate, silyl ethers or halides are tolerated without negatively affecting efficiency as well as the enantioselectivity of the reaction. A *N*-carbamoyl tetrahydro-β-carboline was also a suitable substrate for this asymmetric protocol.



Scheme 12. Enantioselective oxidative Mannich reaction between THIQs and aldehydes (Liu, 2016).

To showcase the utility of the enantioenriched Mannich products, several synthetic transformations were carried out (Scheme 13). The treatment of the chiral carbamate with $LiAlH_4$ at reflux temperature generated the corresponding *N*-methylamine in high yield and without any erosion of the enantiomeric excess. Additionally, primary alcohol could be engaged in an intramolecular transcarbamylation reaction in the presence of NaH, affording the desired product in 96% yield and maintaining the enantiomeric excess. Finally, the hydrolysis of cyclic carbamate with the spontaneous decarboxylation generated the corresponding 1,3-aminoalcohol, an interesting synthetic building block.

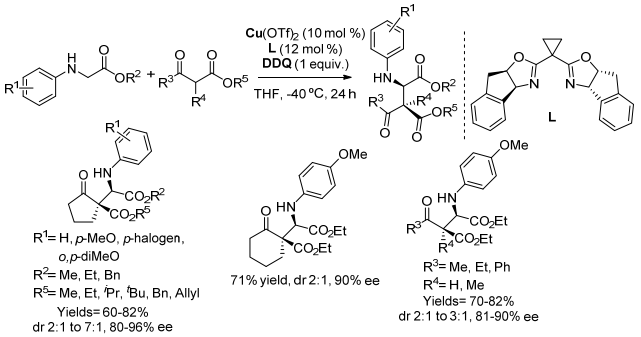


Scheme 13. Synthetic modifications of the Mannich products.

It has been proved that tetrahydroisoquinolines are privileged substrates in direct oxidative Mannich reactions. The last five reviewed examples constitute a perfect exemplification of how this kind of cyclic amines can be directly oxidized using DDQ and then enantioselectively functionalized with a variety of enolate precursors, such as malonates, ketones and aldehydes, including an intramolecular version.

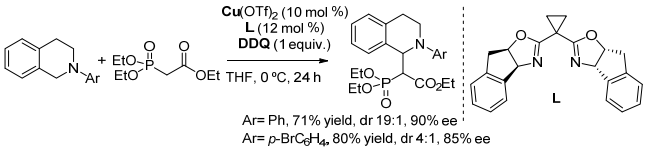
On the other hand, glycine derivatives have also attracted the attention in this field of organic chemistry, mainly due to their availability and the interest of their reaction products, as they could be easily transformed in enantioenriched non-natural α-amino acid derivatives.

It was the research group of Wang who, in 2011, combined the oxidant ability of DDQ with a chiral Cu(II)-BOX complex to efficiently couple β-ketoesters with glycine esters in an enantioselective manner.[19] After testing some Cu(II)-BOX complexes,[20] they realized that the BOX ligand derived from indane (IndaBOX) was the optimal one to perform the desired transformation in combination with $Cu(OTf)_2$. With these optimal reaction conditions, the authors studied the scope of the reaction using several β-ketoesters as well as several glycine esters derivatives, obtaining the desired products in good to high yields, low diastereoselectivities and high enantiomeric excesses (Scheme 14).



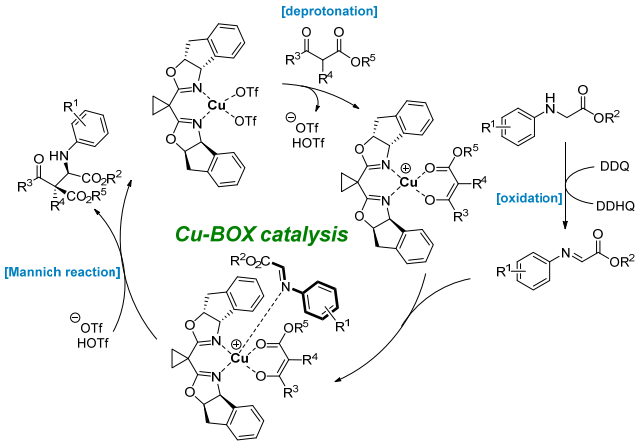
Scheme 14. Asymmetric oxidative Mannich reaction between glycine esters and β-ketoesters (Wang, 2011).

Additionally, these researchers extended their methodology to the functionalization of *N*-aryl-THIQs with Horner-Wadsworth–Emmons phosphonates. Fortunately, they were able to obtain two examples in good yields, excellent diastereoselectivities and high enantiomeric inductions (Scheme 15).



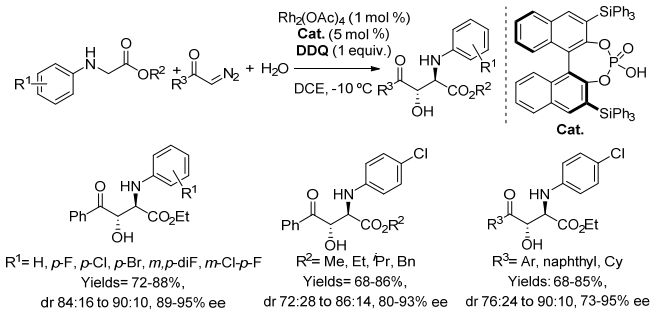
Scheme 15. Oxidative Mannich reaction with THIQs and HWE phosphonates (Wang, 2011).

Lastly, the authors proposed a mechanism to rationalize their transformation and the absolute configuration of the newly formed stereocenters (Scheme 16). First, DDQ is oxidant enough to transform the proper glycine ester into the corresponding *N*-aryl imine. The combination of $Cu(OTf)_2$ and enantiopure IndaBOX ligand resulted in the formation of the chiral Cu(II)-IndaBOX complex, which can participate in a ligand exchange process with the corresponding β-ketoester to yield, through a deprotonation, a chiral copper enolate. The metallic center is also capable of coordinate the glycine imine though its nitrogen atom, providing this way a preferential nucleophilic attack of the chiral enolate to the *Si* face of the imine.



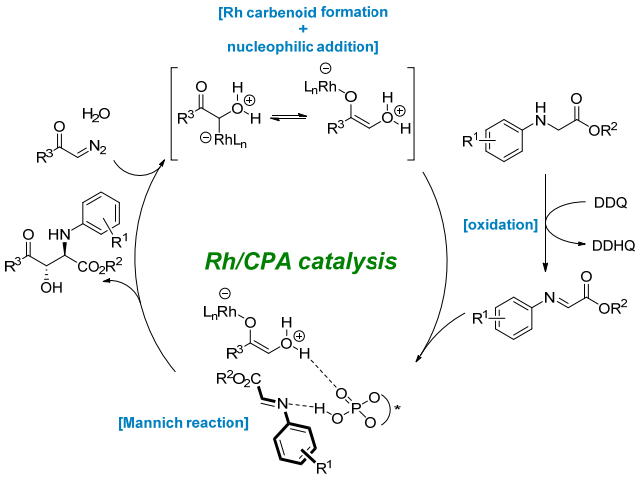
Scheme 16. Mechanistic proposal for the copper-catalyzed addition of β-ketoesters to glycine esters.

Continuing with the reports on the functionalization of glycine derivatives through an asymmetric oxidative Mannich reaction, the research group of Liu and Hu described in 2016 an interesting tricomponent protocol to asymmetrically couple *N*-aryl glycine esters, α-diazoketones and water.[21] After assaying several reaction conditions, the authors described as an optimized catalytic conditions a catalytic system formed by $Rh_2(OAc)_4$ and a chiral phosphoric acid with $SiPh_3$ substituents, in combination with DDQ as oxidant. With these optimal conditions, they could extend the scope of the reaction to other aromatic and aliphatic α-diazoketones, as well as other *N*-aryl glycine esters, obtaining the desired products in moderate to good yields, high diastereoselectivities towards the anti-isomer, and good to high enantiomeric excesses (Scheme 17).



Scheme 17. Enantioselective oxidative tricomponent Mannich reaction between glycine esters, α-diazoketones and water (Liu and Hu, 2016).

To rationalize the transformation, the authors proposed a mechanism by which the reaction might proceed. The ability of Rh(II) to form carbenoids through the displacement of N_2 in α-diazoketones is well known.[22] In fact, these carbenoids are electrophilic enough to be attacked by several nucleophiles, such as water, resulting in formal atom insertions. However, in this report, after the nucleophilic attack of water, the resulting intermediate can tautomerize towards a rhodium enolate and therefore it can participate in further reaction steps. To sum up, α-diazoketone reacted with rhodium(II) acetate to form the corresponding carbenoid with the concomitant release of N_2. This carbenoid suffered the nucleophilic attack of water, resulting in the formation of an oxonium rhodium enolate, which is able to react with the corresponding *N*-aryl imine (formed by oxidation of the proper *N*-aryl glycine ester) in an enantioselective way through a transition state where the chiral phosphoric acid acts as a bifunctional organocatalyst (Scheme 18).

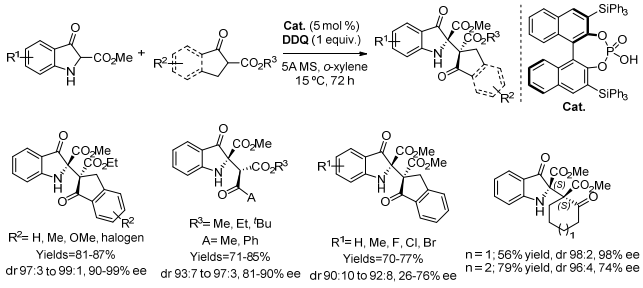


Scheme 18. Mechanistic proposal for the enantioselective tricomponent Mannich reaction.

As we have seen in the previous examples, DDQ is a useful organic oxidant for the dehydrogenation of various amines, such as THIQs and glycine derivatives. On the other hand, indoles bearing a substituent in its C-2 position can be subjected to an oxidative dearomatization process to generate indol-3-ones. This process requires the formal transfer of an oxygen atom to the C-3 position of the indole. However, this particular kind of oxidation cannot be carried out with DDQ or other HAT oxidants. In this context, *N*-oxoammonium salts have emerged as efficient oxygen atom transfer agents, although they were already known as alcohol to ketone/aldehyde oxidants in both stoichiometric and catalytic forms.[23]

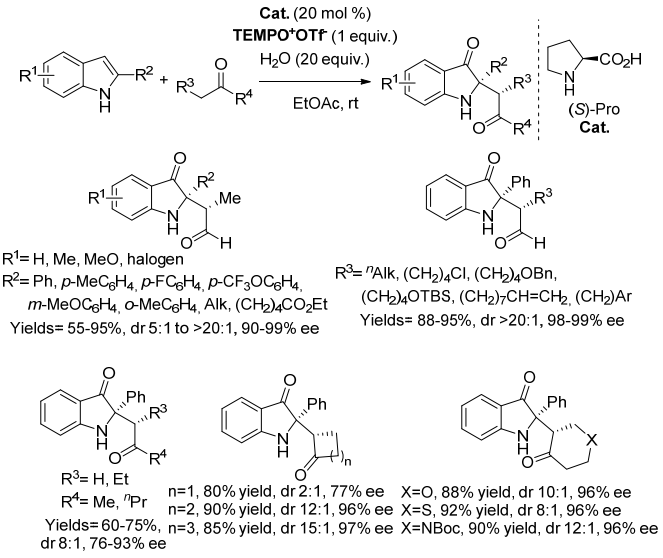
In 2009, the group led by Subba Reddy described the asymmetric oxidative Mannich reaction between β-ketoesters and 3-indanone-2-carboxylates, which were converted to the corresponding imines using DDQ as oxidant. After an optimization process, they selected a chiral phosphoric acid bearing triphenylsilyl groups in both the 3 and the 3' positions as the best organocatalyst to achieve high enantiocontrol, in combination with *o*-xylene as solvent in the presence of 5Å MS[24]. The authors were able to obtain several Mannich products with different substitution patterns in the aromatic ring of the β-ketoesters in high yield

(81-87%) and excellent stereocontrol (from 97:3 to 99:1 dr and from 90 to 99% ee). The reaction was also satisfactory when simpler β-ketoesters were employed as substrates, obtaining the desired products in good yield (71-85%), high diastereoselectivities (from 93:7 to 97:3) and good enantiomeric excesses (81-90% ee). However, the use of differently-substituted 3-indanone-2-carboxylates led to low enantioenriched products (26-76% ee), albeit with good yields (70-77%) and excellent diastereoselectivities (from 90:10 to 92:8). Two cyclic β-ketoesters were also tested under the optimal reaction conditions and the corresponding products were obtained with high stereocontrol but with a moderate yield (Scheme 19). The authors did not provide a mechanistic hypothesis.



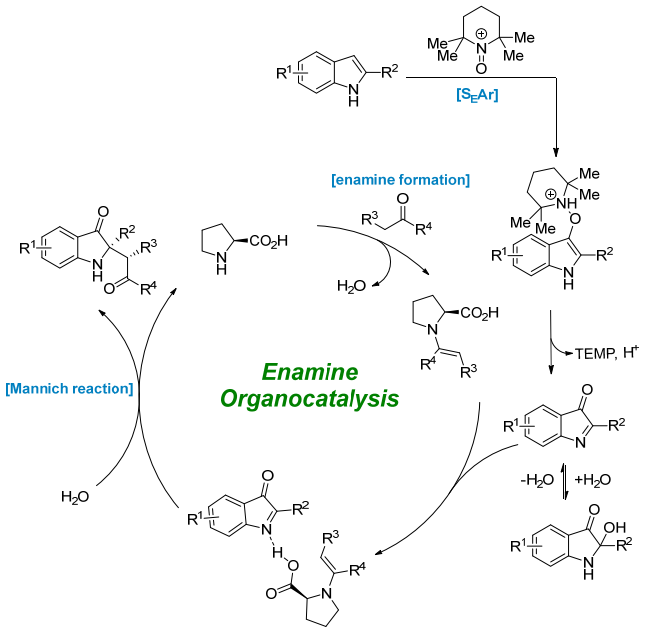
Scheme 19. Oxidative Mannich reaction between β-ketoesters and 3-indanone-2-carboxylates (Subba Reddy, 2019).

Also in 2019, the Zhang's laboratory reported an enantioselective oxidative Mannich reaction between aldehydes or ketones and indolones, which were generated in situ through an oxygen atom transfer from a N-oxoammonium salt to a 2-substituted indole.[25] After an optimization process, they were able to select TEMPO+OTf- as the best *N*-oxoammonium salt to accomplish the in situ oxidation of C-2-substituted indole in 12 hours. Then, the addition of the corresponding carbonyl compound along with (*S*)-proline allowed the authors to obtain the desired product in excellent stereocontrol through an asymmetric Mannich alkylation. With these conditions, they explored the scope of this transformation using differently substituted indoles, aldehydes and ketones. These researchers could obtain the desired products in high to excellent yields, diastereomeric ratios and enantiomeric excesses. The reaction tolerates aldehydes with a wide range of functional groups such as electronically varied aryl moieties, benzyl ethers, alkenes, halides or silyl ethers. Regarding the ketones, the reaction could be applied to four, five and six membered cyclic ketones as well as heterocyclic rings, although with cyclobutanone the stereoselectivity is lower. Concerning the indole substitution pattern, the reaction allowed the use of 2-aryl or 2-alkyl indoles as well as differently substituted indoles in the diffent positions of the homocyclic ring of the indole (Scheme 20).



Scheme 20. Enantioselective dearomative oxyalkylation of indoles with aldehydes and ketones (Zhang, 2019).

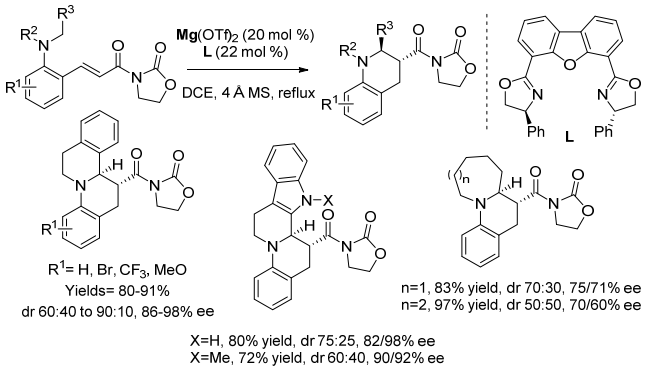
To gain insight into the reaction mechanism, the authors conducted several assays. They realized that 2-phenylindole is efficiently converted into the corresponding 3-oxo-2-phenylindolenine, along with the corresponding hydrated form (the hemiaminal). Furthermore, isolated indol-3-one reacted with propionaldehyde in the presence of (*S*)-proline to give the desired product in 96% yield, dr >20:1 and 99% ee. Interestingly, *N*-methyl-2-phenylindole reacted with propionaldehyde under the optimized conditions, but the corresponding product in obtained was only 65% yield, a low dr of 3:2 and as a racemate, suggesting the implication of azomethinic nitrogen in the organocatalytic cycle. Based on these observations, the authors proposed a mechanism to rationalize the transformation (Scheme 21). First, the electrophilic character of $TEMPO^+$ allows the C-3 nucleophilic addition of the corresponding 2-substituted indole (S_EAr). This oxidized intermediate is able to expel TEMP (tetramethyl piperidine) with the concomitant formation of the corresponding indolone, which exists in equilibrium with its hydrated form. Then, the azomethinic nitrogen can be coordinated through the carboxylic acid of the chiral enamine, formed by condensation between (*S*)-Pro catalyst and the corresponding carbonyl compound. (*S*)-Proline can favour the nucleophilic attack of the enamine to one face of the imine, leading to an enantioenriched Mannich product after the hydrolysis.



Scheme 21. Mechanistic proposal for the asymmetric oxidative Mannich reaction of 2-substituted indoles and aldehydes or ketones.

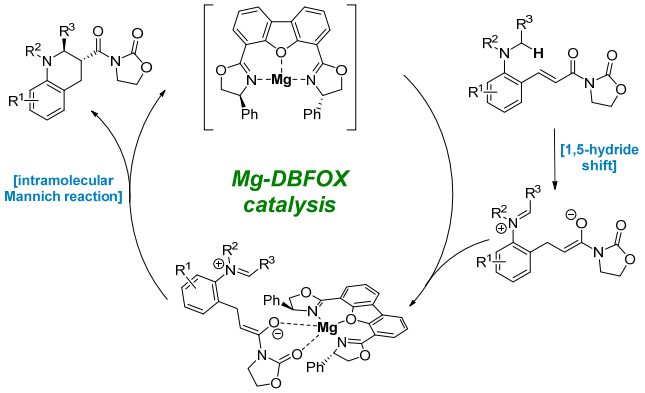
2.2. Other Non-Catalytic Oxidations

In all these last eight described examples, the corresponding amine (THIQ, glycine ester or 2-substituted indole) is directly oxidized by an organic oxidant. In this section, we will show other methodologies in which the amine is also oxidized by an oxidizing agent but, in these cases, the oxidation does not take place through a direct interaction of the amine and the oxidant. For example, the research group of Seidel in 2009 described an elegant method to access iminium cations through an intramolecular 1,5-hydride shift.[26] This redox-neutral process is based on the transfer of a hydride to an oxidized functionality, as for example in this case, an alkenyl substituent.[27] Within this approach, there is no need for an external oxidant. These researchers took advantage of this strategy and were able to design cyclic amines bearing an α,β-unsaturated system in the proper position to ensure an intramolecular 1,5-hydride shift, with the concomitant formation of both an iminium cation and an enolate. This zwitterionic intermediate can experiment an intramolecular cyclization assisted by a chiral Mg(II) complex to yield enantioenriched ring-fused tetrahydroquinolines (THQs). Specifically, they generated a complex between $Mg(OTf)_2$ and DBFOX ligand, using 4Å MS and DCE as solvent. Using these optimal conditions, they could obtain nine ring-fused THQs, β-carbolines, azepane and azocane derivatives in good yields, moderate diastereoselectivities and high enantiomeric excesses (Scheme 22).



Scheme 22. Enantioselective synthesis of fused THIQs through a 1,5-hydride shift (Seidel, 2009).

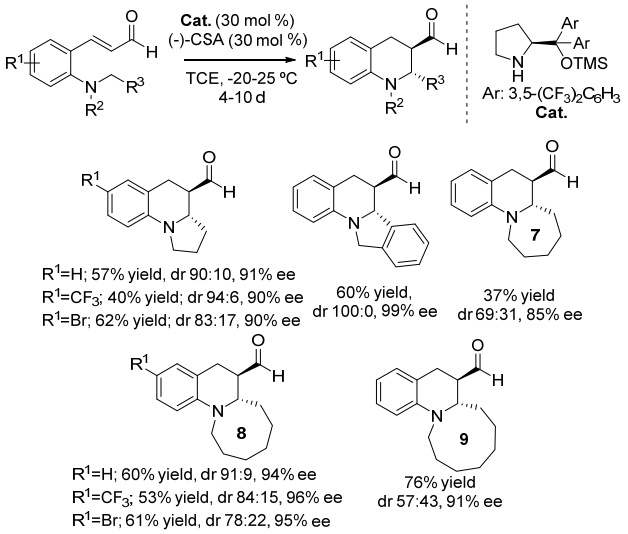
Finally, the authors proposed a reaction mechanism by which the transformation should proceed (Scheme 23). First, due to high temperature an intramolecular sigmatropic 1,5-hydride shift occurs to generate a zwitterionic intermediate, which bears an electrophilic iminium cation and a nucleophilic amide enolate. Then, the enolate moiety acts as a bidentate ligand for the chiral Mg-DBFOX complex assisted by the presence of the oxazolidinone nucleus. This coordination allows the enolate to attack the iminium cation in an asymmetric fashion, providing the desired enantioenriched fused amines.



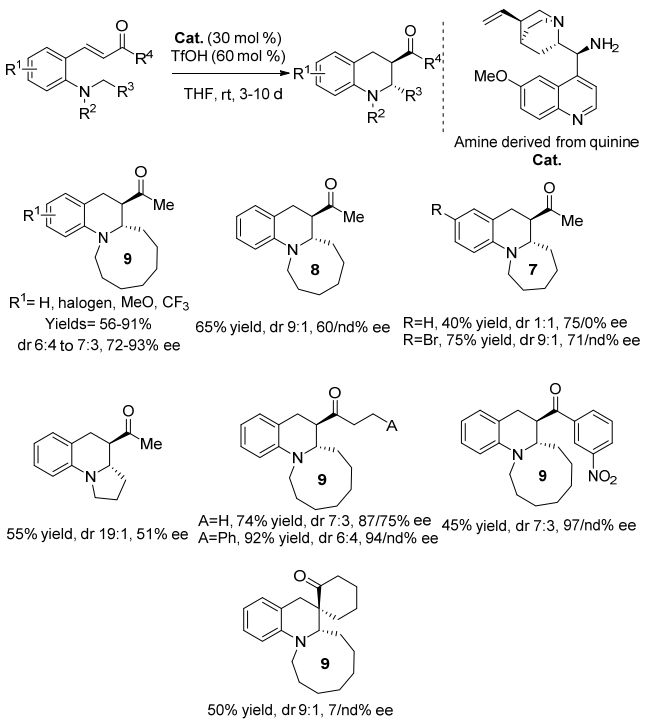
Scheme 23. Proposed mechanism for the asymmetric construction of fused THQs through an 1,5-hydride shift.

In 2010, the research group of Kim took advantage of the same strategy to synthetize chiral THQs bearing a free aldehyde moiety.[28] In this case, the formation of the enamine between the corresponding 2-aminocinnamaldehyde and the chiral *O*-protected prolinol triggers a 1,5-hydride shift to generate an iminium cation along with a chiral enamine, which can undergo an intramolecular Mannich reaction to furnish the corresponding enantioenriched THQ products (Scheme 24). After an optimization process, they realized that a 30 mol% of (-)-CSA was necessary to conduct the reaction, along with trichloroethylene as solvent. They were able to generate a small collection of chiral THQs bearing different substituents in the

aromatic ring and with different amine ring sizes in moderate yields (37-75%) and high both diastereomeric ratios (from 57:43 to 100:0) and enantioselectivities (85-99% ee).



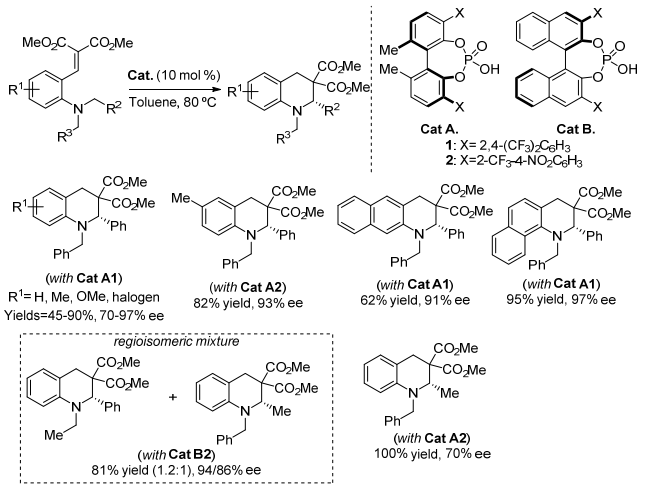
Scheme 24. Enantioselective synthesis of THQs from 2-substituted cinammaldehydes (Kim, 2010).



Scheme 25. Enantioselective synthesis of THQs through a 1,5-hydride shift from aryl-3-buten-2-one (Kim, 2013).

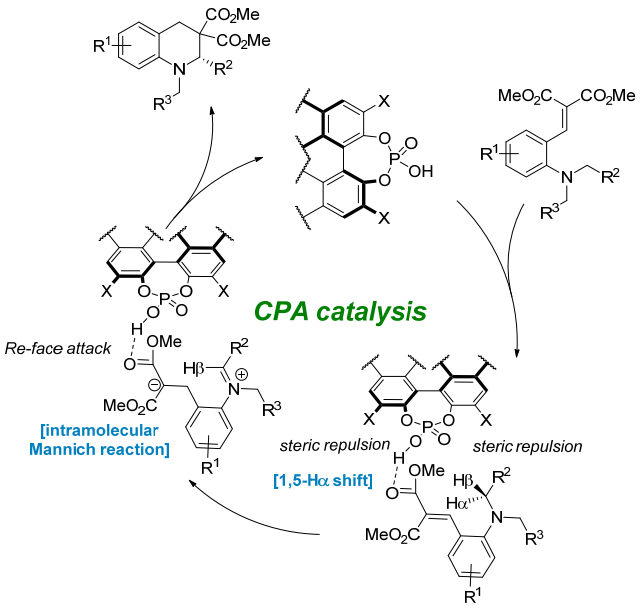
Three years later, in 2013 the same laboratory published a similar strategy to synthetize chiral THQs.[29] These researchers designed an aryl-3-buten-2-one with a cyclic amine at its *ortho* position, which should undergo a 1,5-hydride shift upon the formation of a chiral imine. They selected amine derived from quinine as the best organocatalyst for imine formation and triflic acid as substoichiometric additive. Using these conditions, they could synthesize fourteen ring-fused THQs in moderate to good yields, diastereomeric ratios and enantioselectivities (Scheme 25).[30] The authors tested substrates containing an acyclic amino group as *ortho*-substituent of the aryl group of the enone, but the intramoecular redox-neutral Mannich reaction did not take place.

Chiral phosphoric acids (CPA) were examined as suitable catalysts in the synthesis of THQs through 1,5-hydride shift independently by the groups of Akiyama[31] and Luo[32] in 2011 and 2012, respectively. The group of Akiyama designed an arylidene malonate bearing a dibenzylamine group at its *ortho* position as a model substrate. After the optimization of the reaction conditions, they selected three different chiral phosphoric acids to perform the reaction depending on the starting material. The corresponding chiral THQs were obtained in moderate to good yields (45-100%) and high enantioselectivities (70-97% ee) (Scheme 26).



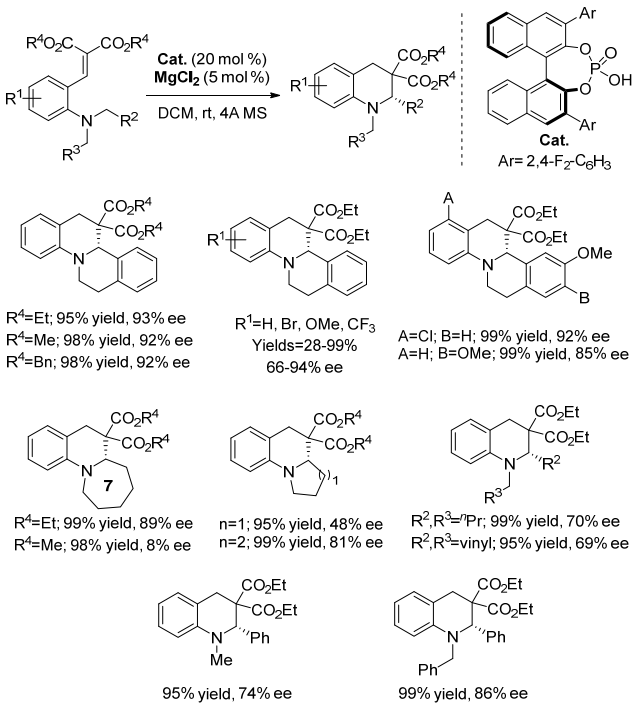
Scheme 26. Enantioselective synthesis of THQs catalyzed by chiral phosphoric acids (Akiyama, 2010).

To gain insight into the reaction mechanism, the authors carried out several experiments using isotopically labelled substrates as well as an achiral acid catalyst. Then, they realized that the 1,5-hydride shift of one of the enantiotopic hydrogens occurs in a stereoselective manner due to the binding of the CPA to the substrate. After that, the asymmetric intramolecular Mannich reaction between the previously formed enolate and the iminium ion provides the desired product (Scheme 27).



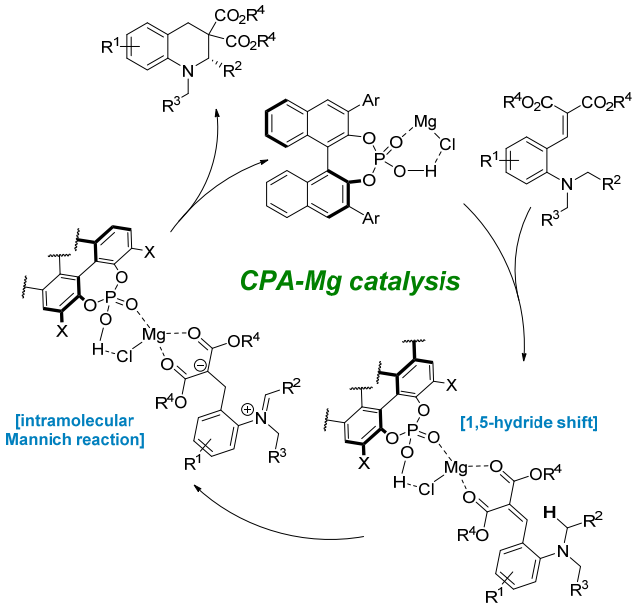
Scheme 27. Mechanism for the enantioselective synthesis of THQs catalyzed by chiral phosphoric acids.

On the other hand, the research group of Luo developed a CSA-based catalytic methodology to construct chiral THQs through an intramolecular Mannich reaction of arylidene malonates bearing either a cyclic or acyclic tertiary amine at its *ortho* position. The presence of $MgCl_2$ as a co-acidic catalyst was crucial for the success of the transformation, along with dichloromethane as solvent and 4Å MS. Under the optimized reaction conditions, the researchers were capable of synthetizing a set of differently substituted THQs with either electro-donating or electro-withdrawing groups in excellent yields (up to 99%) and moderate to good enantiomeric excesses (48-94% ee) (Scheme 28).



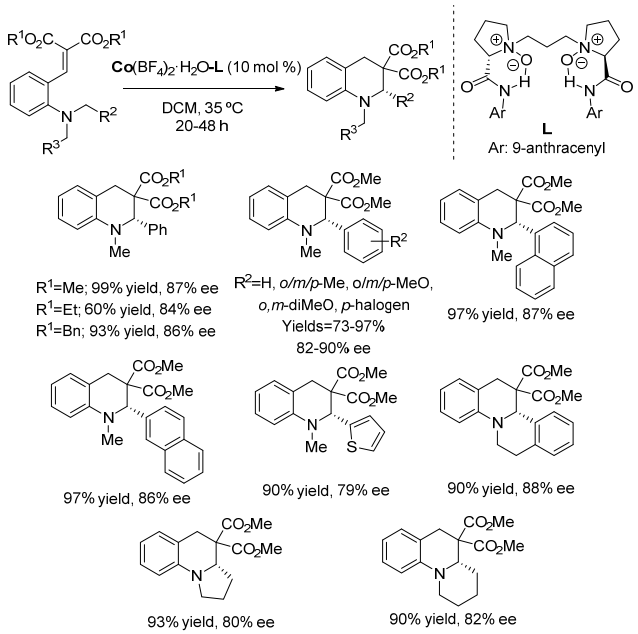
Scheme 28. Enantioselective synthesis of THQs enabled by CPA-Mg(II) catalysis (Luo, 2010).

According to the researchers, Mg(II) serves as a union bridge between CPA and both carbonyl groups of the starting material. As previously mentioned, the initial 1,5-hydride shift triggers the subsequent enantioselective intramolecular Mannich reaction in order to generate the corresponding chiral THQ product (Scheme 29).



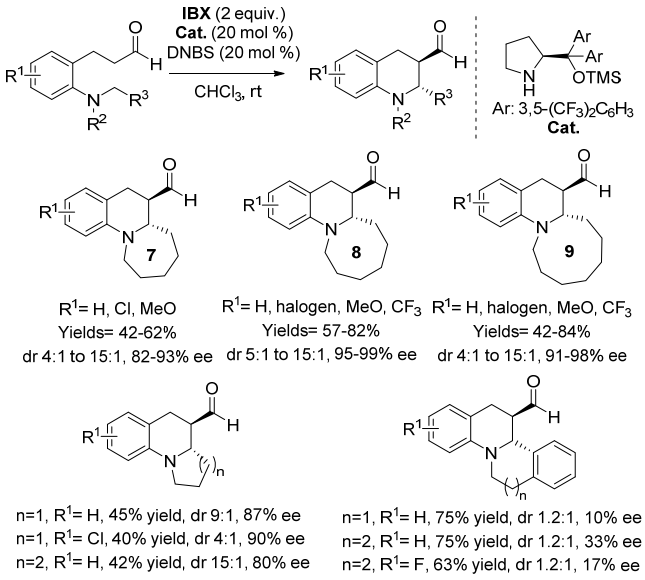
Scheme 29. Mechanism for the dual CPA/Mg(II) catalytic protocol for the synthesis of chiral THQs.

A similar reaction was described in 2011 by the research group of Feng.[33] In their approach, the use of a chiral complex from a Co(III) salt and a *N*,*N*'-dioxide chiral ligand allowed them to obtain a library of THQs. Both cyclic and acyclic aliphatic residues at the nitrogen were tolerated, obtaining the corresponding chiral THQs with high yields (73-99%) and moderate enantioselectivities (79-90% ee) (Scheme 30).



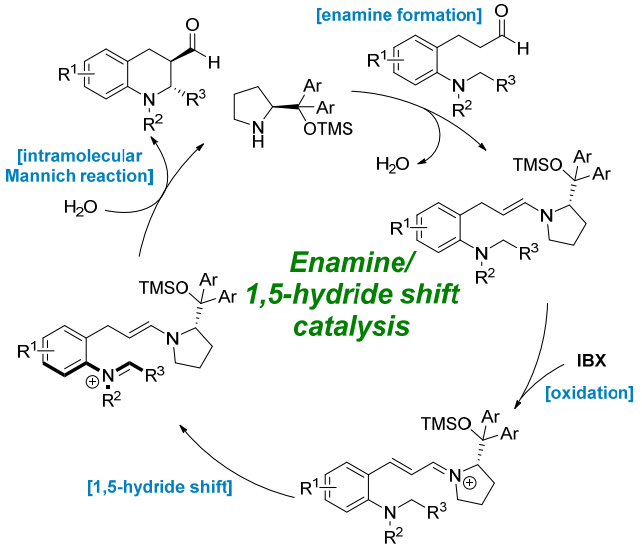
Scheme 30. Asymmetric synthesis of THQs provided by Co(III)-*N*,*N*'-dioxide complex (Feng, 2011).

In 2014, Kim's research group reported an approach towards fused tetrahydroquinolines (THQs) also taking advantage of 1,5-hydride transfer.[34] This time, a dihydrocinnamaldehyde moiety bearing a cyclic amine at its ortho position is presented as a model substrate. The authors envisioned that the dihydrocinnamaldehyde moiety could form a chiral enamine through a condensation with a chiral secondary amine, which might be oxidized to the corresponding α,β-unsaturated iminium by the assistance of an external oxidant. As postulated for the previous example, this last step should trigger a 1,5-hydride transfer to generate an iminium cation with the concomitant generation of the chiral enamine, providing this way a perfect scenario for an intramolecular asymmetric Mannich reaction. Again, the iminium cation is generated indirectly from an oxidized part of the molecule. After conducting an optimization process, they were able to select the Hayashi-Jørgensen catalyst as the best one to induce enantioselectivity in the intramolecular cyclization, in combination with IBX (2-iodoxybenzoic acid)[35] as stoichiometric oxidant and 2,4-dinitrobenzensulfonic acid (DNBS) as additive. Using these conditions, they were able to access a library of twenty fused THQs in moderate to good yields, good diastereomeric ratios and excellent enantioselectivities in most of the cases (Scheme 31).



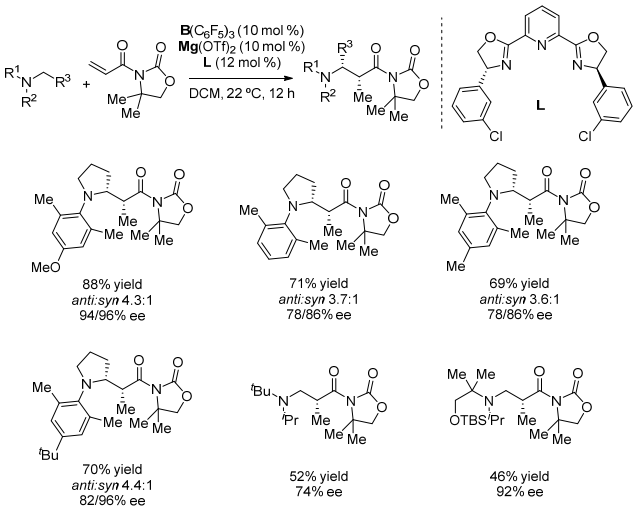
Scheme 31. Enantioselective organocatalytic synthesis of fused THIQs (Kim, 2014).

According to the authors, this straightforward approach towards enantioenriched THQs bearing large saturated cycles should proceed through an enamine oxidation, an intramolecular redox reaction (1,5-hydride shift) and an intramolecular final Mannich-type reaction (Scheme 32). First, the corresponding chiral enamine is formed through a condensation reaction between the aldehyde and the Hayashi-Jørgensen catalyst. Then, IBX is capable of oxidizing this chiral enamine to give an α,β-unsaturated iminium cation, which could experiment a sigmatropic 1,5-hydride shift to yield the proper iminium cation and the chiral enamine. Finally, the chiral enamine is able to participate in an asymmetric intramolecular Mannich reaction to generate the target chiral THQs in an enantioenriched form.



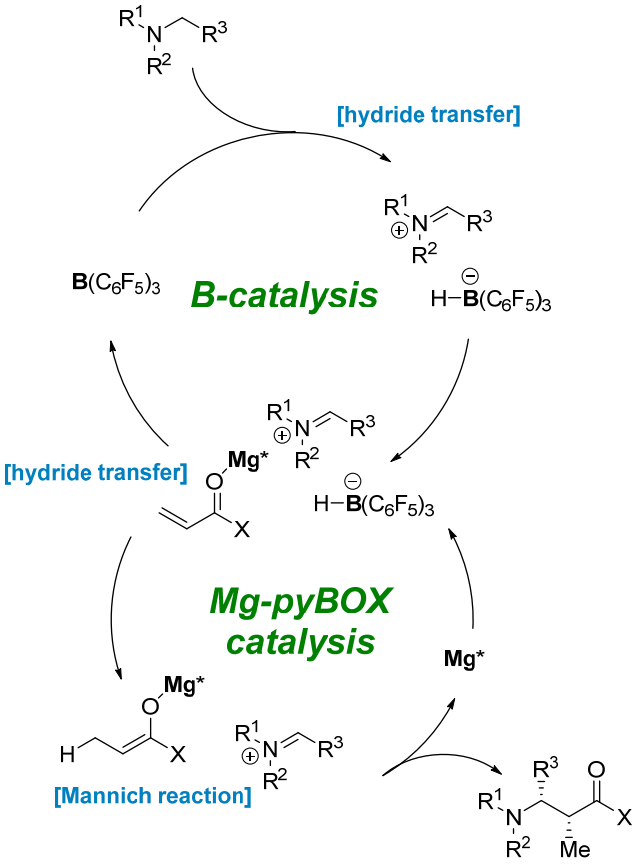
Scheme 32. Mechanistic proposal for the enantioselective construction of THIQs through a 1,5-hydride shift.

All the examples reviewed here on hydride transfer mechanisms are based on an intramolecular process. However, this kind of reactivity can also be achieved intermolecularly by the synergistic action of both a chiral and achiral Lewis acid, as the laboratory of Wasa described in 2018.[36] $B(C_6F_5)_3$ showed excellent activity in α-hydride transfer from several tertiary amines to many electron-poor alkenes. The subsequent Mannich reaction between both ionic species (the iminium cation and the enolate) provided a collection of functionalized tertiary amines with high functional group tolerance. After that, the authors were interested in developing an enantioselective protocol for the abovementioned transformation. For which, they centered the attention in an acryloyl oxazolidinone bearing two methyl substituents and *N*-arylpyrrolidines as model substrates. The only use of $B(C_6F_5)_3$ did not provide the desired product but, when $Mg(OTf)_2$ was also added, the expected product was obtained due to the activation of the carbonyl. This result suggested the authors to employ a chiral Mg(II) complex to drive the reaction asymmetrically. Several bisoxazoline ligands were evaluated, of which pyBOX showed superior performances. Using this dual catalytic system, they could obtain six chiral tertiary amines in moderate yields and good stereocontrol (Scheme 33).



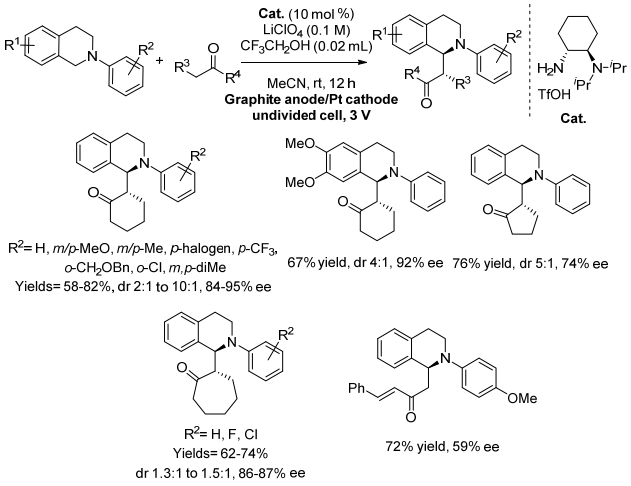
Scheme 33. Catalytic Enantioselective C-H functionalization of tertiary amines with α,β-unsaturated compounds (Wasa, 2018).

Finally, the authors provided a mechanism by which their transformation should proceed (Scheme 34). First, boron Lewis acid can abstract an α-hydrogen from the corresponding tertiary amine to generate an iminium ion and a borohydride specie. Then, the proper electron-poor alkene can suffer a hydride addition from the borohydride upon the coordination of the Mg(II)-pyBOX complex. Finally, the intermolecular Mannich reaction between the iminium cation and the chiral Mg(II) enolate furnishes the desired product.



Scheme 34. Mechanism for the dual Lewis acid catalyzed Mannich Reaction.

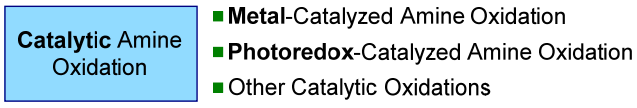
The last example on non-catalyzed amine oxidation comes from the research group of Luo in 2017.[37] The authors employed an undivided cell on which a potential of 4 V over C and Pt electrodes was applied to oxidize *N*-aryl-THIQs to their corresponding iminiums cations. In the electrochemical methods electrons are used as redox reagents and consequently these methods match well with the criteria of green chemistry.[38] The electrochemically formed *N*-aryl-THIQs iminium cations were efficiently trapped by several ketones through the formation of a chiral enamine with a chiral bifunctional diamine organocatalyst derived from chiral *trans*-*N*,*N*-diaminocyclohexane, obtaining the target Mannich products in good yields and high stereocontrol (up to 10:1 dr and 95% ee). CF_3CH_2OH was used as additive because it is believed that protonic additives have beneficial effects in this kind of transformations due to the formation of THIQs hemiaminals and to the increase of the conductivity in the reaction mixture (Scheme 35).[39]



Scheme 35. Catalytic Enantioselective Electrochemical Oxidative Coupling of THIQs with ketones (Luo, 2017).

3 Catalytic Amine Oxidation

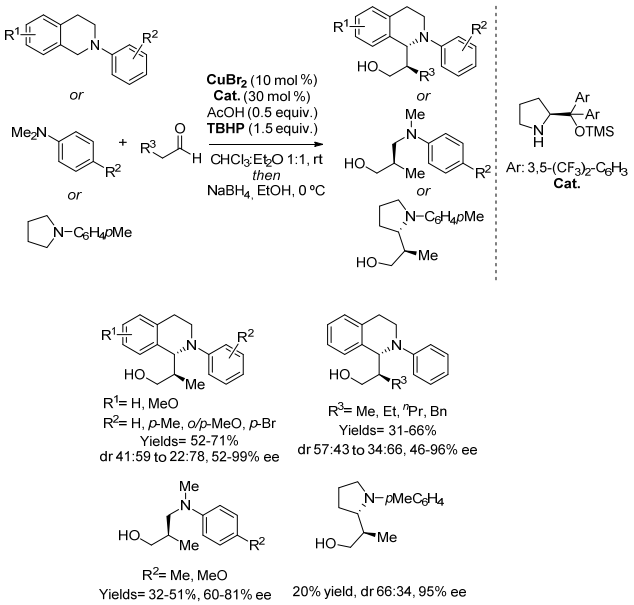
In this section, the catalytic amine oxidation for enantioselective Mannich reactions will be discussed (Scheme 36). Catalytic methods for amine oxidation include metal-catalyzed methods, in which a metal or a metal complex is the responsible for the oxidation of the amine, and photocatalytic methods based on Single Electron Transfer (SET) events between a photocatalyst in the excited state and the amine. Additionally, indirect amine oxidation through a catalytic method will also be discussed.



Scheme 36. Summary of the reports that will be discussed regarding catalytic amine oxidation.

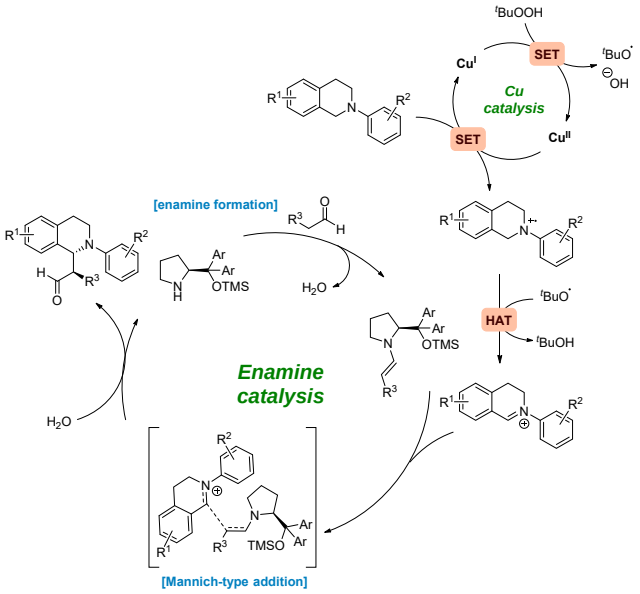
3.1. Metal-Catalyzed Amine Oxidation

In this section, two reports on enantioselective functionalization of amines through a Mannich reaction enabled by metal-catalyzed iminium cation generation are presented. First, the research group of Chi reported, in 2012, an enantioselective protocol to couple *N*-aryl-THIQs and other tertiary amines with aldehydes using $CuBr_2$/^{t}BuOOH as oxidizing system and the Hayashi-Jørgensen organocatalyst for the asymmetric induction.[40] Using these optimal conditions, they were capable of generating a collection of enantioenriched THIQs as well as *N*,*N*-dialkylanilines and *N*-*p*MeC$_6$H$_4$-pyrrolidine in moderate yields (20-71%), modest syn/anti selectivity (up to 78:22 dr) and good enantiomeric excesses (up to 99% ee) (Scheme 37). The reaction tolerates several electron-donating and electron-withdrawing groups in the *N*-aryl group of the THIQs, however only *N*,*N*-dimethylanilines with electron-donating groups (Me or MeO) at para-position afforded the corresponding Mannich products in this methodology.



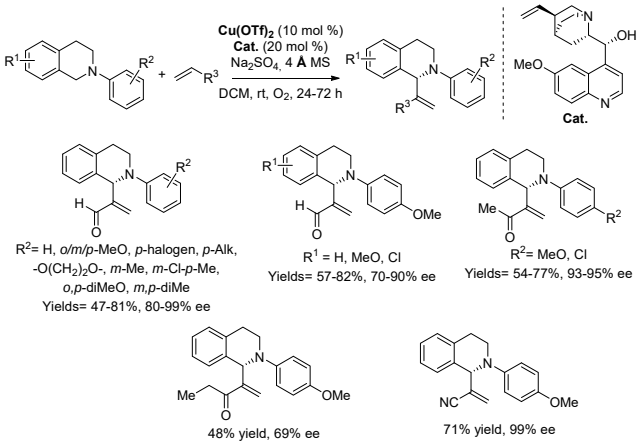
Scheme 37. Enantioselective oxidative Mannich reaction between tertiary amines and aldehydes (Chi, 2012).

The authors also provided a mechanistic hypothesis for the transformation, which is based in the combination of two independent catalytic cycles. The Cu(II)-Cu(I) domain, by which the iminium cation is formed, and the enamine asymmetric catalytic cycle, where the enantiodifferentiation between the two faces of the iminium cation takes place (Scheme 38). First, the nitrogen of THIQ is one-electron oxidized through a Single Electron Transfer (SET) from Cu(II), releasing the corresponding radical cation along with Cu(I). In this proposed mechanistic pathway, Cu(II) acts as an electron relay catalyst between THIQ and TBHP (^{t}BuOOH). Because of this, Cu(II) is regenerated after another SET between TBHP and Cu(I), which also produces tert-butoxyl radical. The corresponding iminium cation is finally formed upon a Hydrogen Atom Transfer (HAT) from the radical cation and *tert*-butoxyl radical.[41] Subsequently, the chiral enamine formed through a condensation between Hayashi-Jørgensen catalyst and the corresponding aldehyde is able to react with the iminium cation in an enantioselective manner to afford the desired Mannich product.



Scheme 38. Mechanistic hypothesis for the enantioselective cross dehydrogenative coupling between tertiary amines and aldehydes.

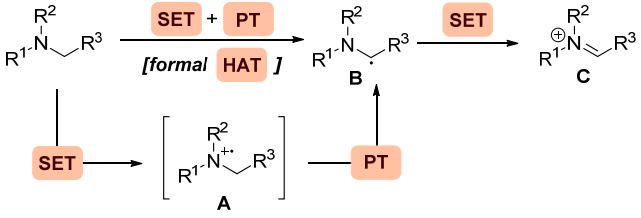
The second example regarding the use of a metal-based catalytic system to oxidize amines was reported by Wang also in 2012.[42] His research team was able to combine $Cu(OTf)_2$ and quinine for the enantioselective addition of α,β-unsaturated carbonyl or related compounds to *N*-aryl-THIQs. Once again, copper species could act as a redox mediator between THIQ and the stoichiometric oxidant, being in this case, molecular oxygen. Meanwhile, quinine should act as a nucleophilic catalyst through its tertiary amine group for the generation of a chiral enolate after the conjugate addition to the corresponding α,β-unsaturated carbonyl compound. Again, formally this transformation is classified as a Morita-Baylis-Hillman reaction, but it involves the addition of a chiral enolate to an electrophilic C=N double bond. As a result, this transformation can be considered as a Mannich reaction and therefore it is included in this review. The researchers were able to obtain a library of twenty-one differently substituted THIQs with several Michael acceptors with moderate to good yields, and high enantioselectivities (Scheme 39).



Scheme 39. Enantioselective Cu/quinine-catalyzed aerobic oxidative olefination of THIQs (Wang, 2012).

3.2. Photoredox-Catalyzed Amine Oxidation

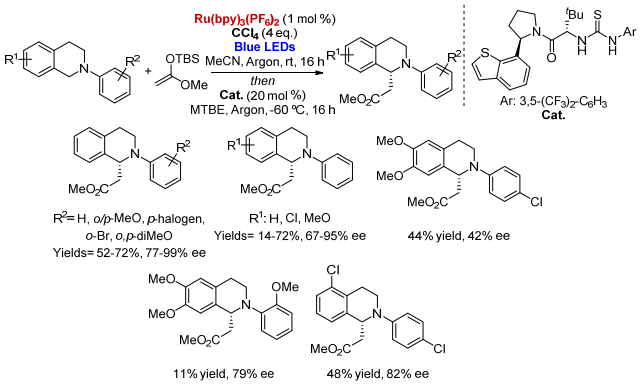
In the last decade, visible-light photoredox catalysis has attracted significant attention in synthetic organic chemistry due to the enormous possibilities and its valuable advantages from the point of view of sustainable and green chemistry.[43] In this context, amines often act as single-electron donors in photoredox processes and are subsequently oxidized to nitrogen radical cations **A**. This nitrogen radical cation **A**, after a Proton Transfer is transformed into the α-amino radical **B**) which can undergo another SET event generating an iminium ion **C**, when a good hydrogen atom acceptor is present in the reaction (Scheme 40). Once the iminium ion **C** is formed it can react with nucleophiles, affording the amine functionalized in α-position to the nitrogen. This strategy has been used extensively to functionalize amines forming a number of important bonds such as C–C, C–N, C–O, C-S and C–P.[44] In this regard, carbonyl compounds are suitable nucleophiles and several examples of asymmetric photoxidative Mannich reactions have been reported in the literature.



Scheme 40. Overview of the redox behaviour of amines under photoredox catalysis.

The first example on the enantioselective Mannich reaction through the oxidation of an amine using visible-light photoredox catalysis comes from the collaborative work of Jacobsen and Stephenson in 2014. They were interested in the asymmetric Mukaiyama-Mannich addition of silyl enol ethers to *N*-aryl-THIQs merging anion binding organocatalysis

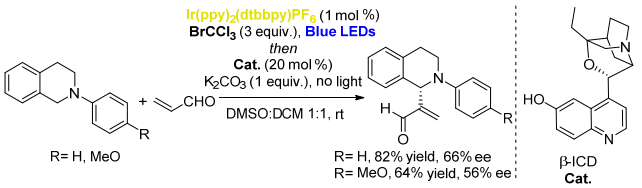
and photoredox catalysis.[45] After an optimization process, they realized that the best conditions involve a two-step protocol, in which, first, THIQ is oxidized by the action of $Ru(bpy)_3(PF_6)_2$ and CCl_4 as stoichiometric oxidant under the irradiation of Blue LEDs. Then, the asymmetric Mannich reaction was achieved when a chiral thiourea organocatalyst and the silyl enol ether were added to the reaction mixture. With the optimized reaction conditions, the authors studied the scope and limitations of the reaction using THIQs with different substitutions patterns in both aromatic rings. They were able to obtain target compounds in moderate yields and good to high enantiomeric excesses (Scheme 41).



Scheme 41. A combination of photoredox catalysis and anion binding organocatalysis for the enantioselective Mukaiyama-Mannich reaction (Jacobsen and Stephenson, 2014).

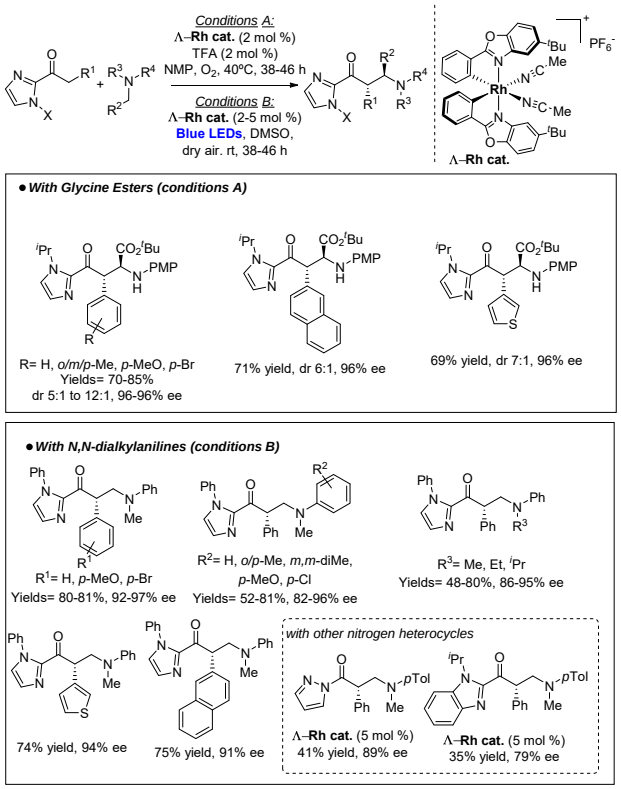
Although the authors did not provide any specific mechanistic hypothesis, the reaction should proceed through the photoredox-mediated formation of THIQ iminium ion and, the enantioselective induction might be achieved by the formation of a chiral ion pair through the coordination of chloride with the NH acidic protons of the thiourea.[46] Indeed, the formation of the iminium cation of THIQs using visible-light photoredox catalysis and CCl_4 as oxidant as well as the use of chiral thioureas as anion binding catalysts are already known.[47]

In the same year, the laboratory of Xiao reported a methodology in which THIQs are alkenylated with acrolein through a similar two-step synthetic route.[48] First, quantitative generation of THIQ-iminium cation was achieved using $Ir(ppy)_2(dtbbpy)PF_6$ as photoredox catalyst and $BrCCl_3$ as final oxidant under the irradiation of Blue LEDs. Then, in dark, the addition of acrolein along with DABCO as nucleophilic catalyst allowed the formation of the corresponding products as a racemates. Nonetheless, an initial attempt towards an asymmetric acroleination of THIQs was also investigated by the authors. They tested the reaction with two THIQ iminium ions using β-isocupreidine (β-ICD) as the nucleophilic catalyst instead of DABCO, obtaining the desired products in good yields but moderate stereocontrol (Scheme 42).



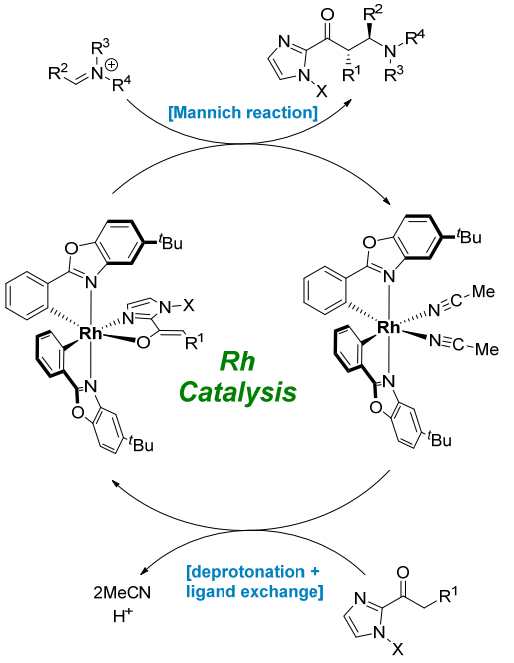
Scheme 42. Enantioselective acroleination through a photoredox-catalyzed THIQ oxidation (Lu and Xiao, 2014).

In 2015, the research group of Meggers reported an elegant protocol using 2-acylimidazoles as enolate precursors in an enantioselective oxidative Mannich reaction promoted by a chiral-at-rhodium complex.[49,50] Initially, the authors optimized the reaction conditions between 2-acylimidazoles and α-iminoesters but, then, they realized that these imines could be accessible by oxidation of the corresponding glycine esters. Keeping that in mind, they were able to establish the optimal conditions for the formal enantioselective cross dehydrogenative coupling between 2-acylimidazoles and glycine esters though an oxidation-Mannich reaction tandem process. The researchers were able to prepare an assortment of differently substituted chiral 2-acylimidazoles bearing an aminoester moiety in good yields and excellent stereocontrol using a chiral-at-rhodium complex as catalyst, TFA as additive under an O_2 atmosphere (Scheme 43). Additionally, these researchers could extend their methodology to tertiary N, cations. As checked by both cyclic voltammetry and UV-Vis spectroscopy, the abovementioned chiral-at-rhodium catalyst did not only serve as a catalyst for the formation of a chiral enolate, but also is able to act as photocatalyst for the iminium cation generation. After an optimization process, they found out that the same Rh catalyst was able to oxidize *N*,*N*-dimethylanilines under Blue LEDs irradiation and air atmosphere, and the same rodhium catalyst is able to perform the asymmetric Mannich reaction of 2-acylimidazoles to the corresponding photogenerated iminium ions. With these conditions, they could extend the scope of the reaction to 2-acylimidazoles and *N*,*N*-dimethylanilines bearing multiple substitution patterns, obtaining the desired products in good to high yields and excellent enantiomeric excesses (Scheme 34).



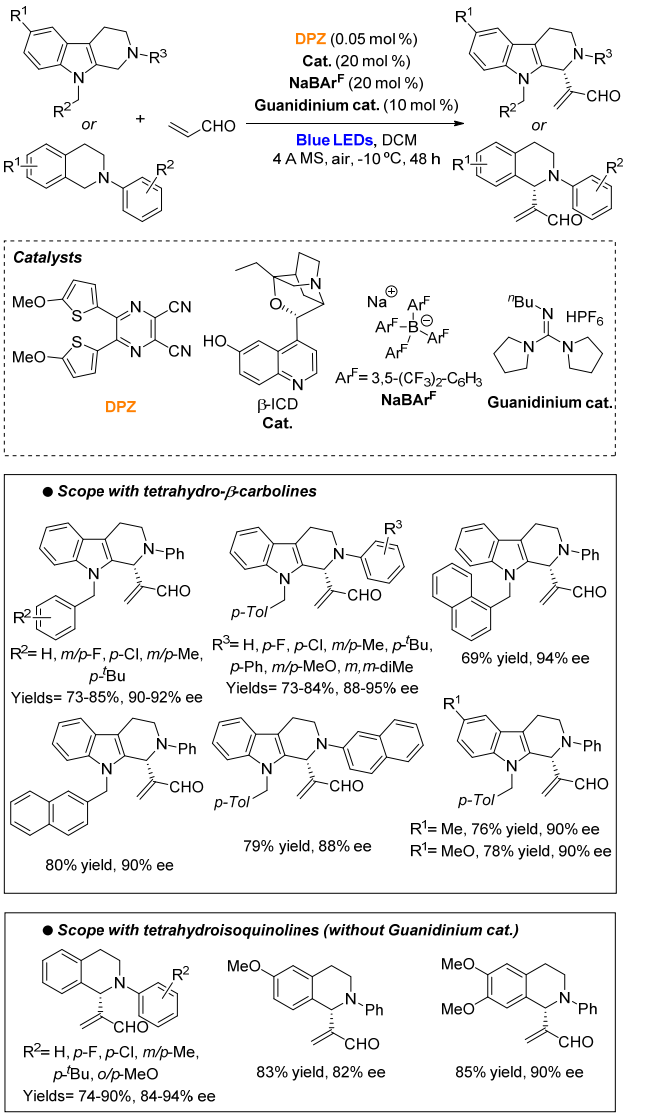
Scheme 43. Enantioselective oxidative Mannich reaction between 2-acylimidazoles and amines (Meggers, 2015).

The researchers postulated a chiral Rh complex bearing the enolate derived from 2-acylimidazole, which seems to be responsible for the asymmetric induction in the attack to either the glycine-derived imine or the *N*,*N*-dimethylaniline iminium cation (Scheme 44).



Scheme 44. Mechanistic approach for the rhodium catalyzed Mannich reaction.

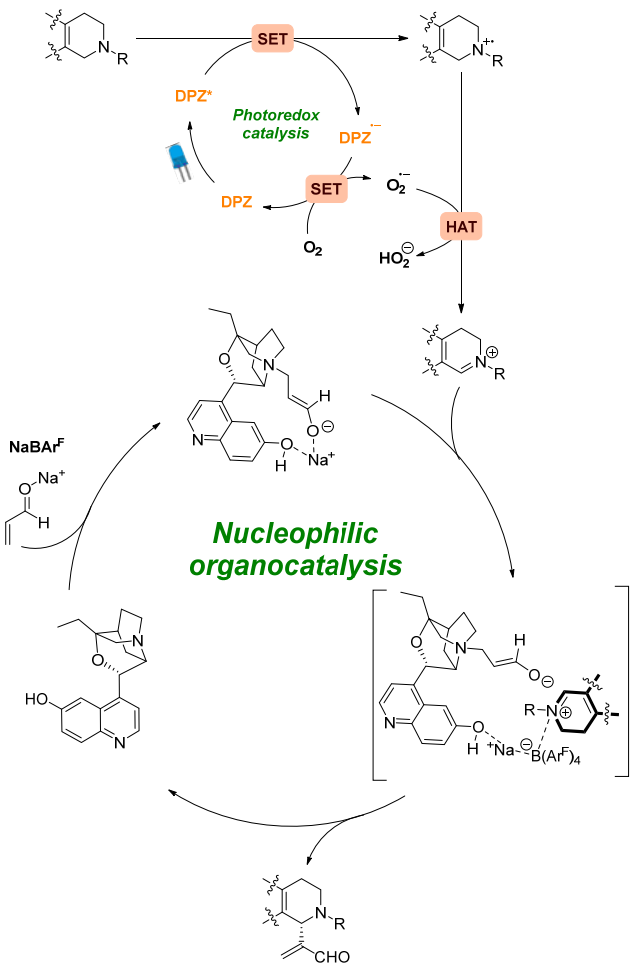
In 2016 the research group of Jiang published a methodology for the oxidative asymmetric functionalization of tetrahydro-β-carbolines (THCs) and THIQs with electron-poor alkenes using a multicatalytic system under visible-light irradiation.[51] Dicyanopyrazine-derived[52] (DPZ) chromophore was chosen as photocatalyst, along with β-isocupreidine as nucleophilic catalyst and $NaBAr^F$ as cocatalyst under the irradiation of Blue LEDs. With these conditions in hand, the authors were able to extend this protocol to other differently substituted THCs and THIQs using acrolein as enolate precursor. The desired products were obtained in high yields and enantiomeric excesses (Scheme 45). It is important to remark that acrolein was the only suitable electron-poor alkene for the catalytic system, whereas with acrylonitrile, no conversion was observed towards the desired product.



Scheme 45. Enantioselective olefination of tertiary amines via cooperative photoredox and asymmetric catalysis (Jiang, 2016).

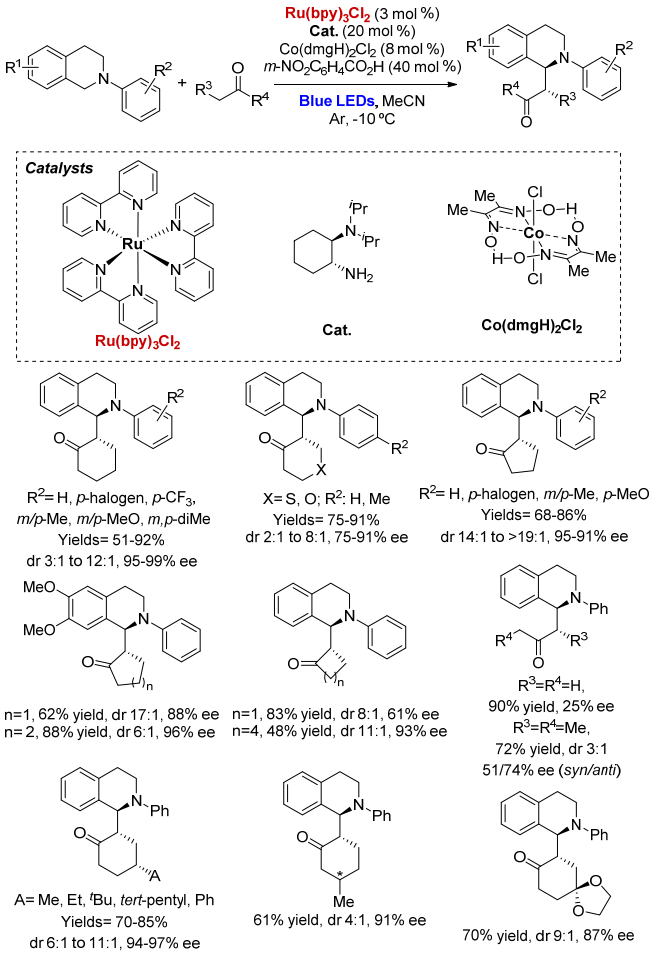
Finally, with the aim of rationalize the transformation and to give an explanation about the need of all

catalysts, the authors proposed a putative mechanistic pathway (Scheme 46). First, DPZ photocatalyst is transferred to its excited state through the absorption of visible-light to generate a highly oxidizing species, which is capable of engaging the corresponding tertiary amine in a SET process with the concomitant formation of the corresponding radical cation along with reduced DPZ. The photocatalyst can be regenerated through a SET with molecular oxygen, also providing superoxide radical anion, which can undergo a HAT to finally generate the iminium cation. This highly electrophilic species is now able to participate in the organocatalytic cycle. β-ICD can attack the β position of acrolein by virtue of its tertiary amine moiety to generate a chiral enolate, which resulted stabilized by the coordinating ability of the sodium salt. Then, BAr^F- acts as a stabilizing agent for the iminium, also facilitating the approach to the nucleophilic enolate. Finally, after the Mannich-type addition, the expected product is obtained as an enantioenriched mixture.



Scheme 46. Putative mechanism for the enantioselective addition of acrolein to THCs and THQs.

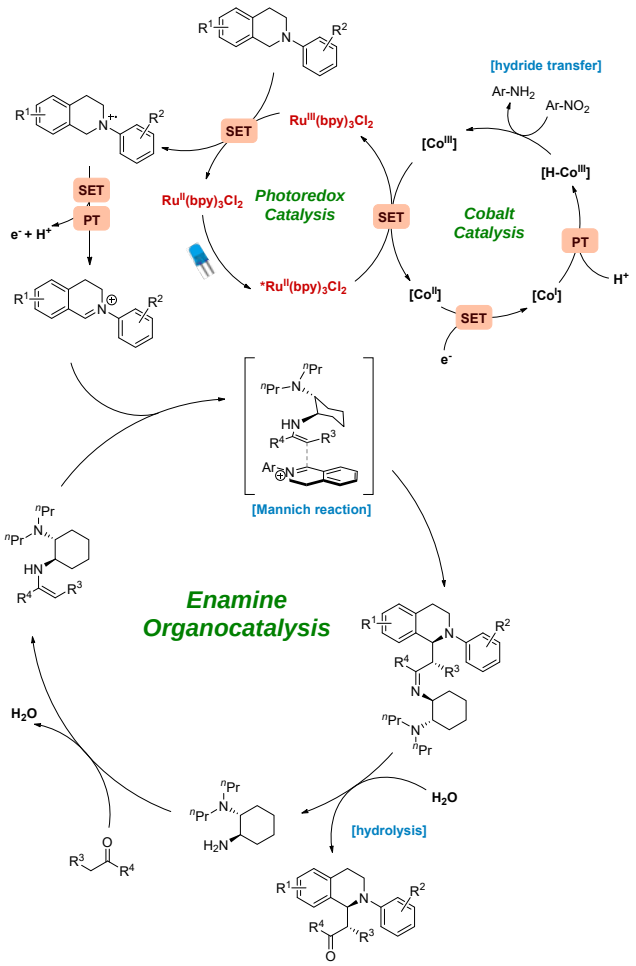
The research laboratory of Luo and Wu reported in 2017 an efficient combination of three catalysts for the asymmetric oxidative Mannich reaction between *N*-aryl-THIQs and cyclic ketones (Scheme 47).[53] The synergy between $Ru(bpy)_3Cl_2$ as photoredox catalyst, $Co(dmgH)_2Cl_2$ as hydrogen relay catalyst and a chiral primary 1,2-diamine derivative allows the authors to prepare a huge variety of enantioenriched keto-THIQs with high yields (up to 92%), moderate to good diastereoselectivities (from 2:1 to > 20:1) and high enantiomeric excesses (up to 99% ee). Remarkably, this protocol resulted efficient in the desymetrization of substituted cyclohexanones, as well as in the scalability of the reaction to 2 mmol scale. However, when acyclic ketones were used as nucleophiles the stereoselectivity was much lower.



Scheme 47. Asymmetric oxidative Mannich reaction of THIQs and ketones by multiple catalysis (Luo and Wu, 2017).

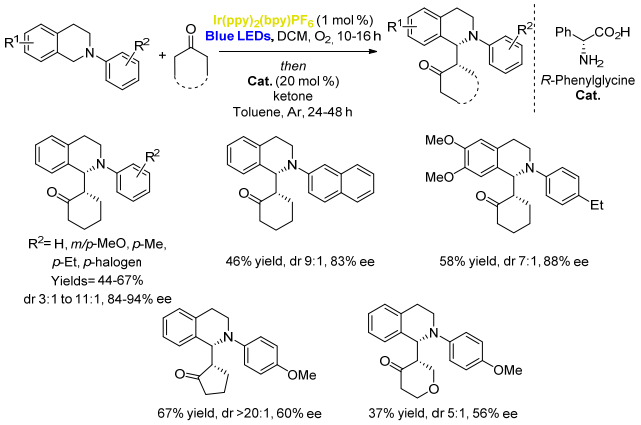
To gain some insight into the reaction mechanism, the authors conducted the model reaction adding 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) or TEMPO as radical scavengers. The presence of these radical trapping agents slightly inhibited the reaction, suggesting a fast electron transfer in the formation of the iminium cation. They also observed the generation of the iminium cation by HRMS in a two-step experiment in which, first, THIQ is oxidized in the presence of Ru, Co and nitroaryl catalyst and then, in the dark, chiral amine organocatalyst along with cyclohexanone were added to finally yield the desired

product in 81% yield, dr 8:1 and 98% ee. This result suggested the implication of two independent catalytic domains in the mechanism: the enamine organocatalytic domain (chiral amine) and the oxidation domain (Ru, Co, nitroaryl). All these results were put together in a mechanistic pathway (Scheme 48). Focusing on the oxidation domain, after the excitation of the Ru photocatalyst, a SET with the Co(III) occurs to generate a highly oxidizing Ru(III) species, which is able to undergo a SET with the corresponding THIQ to generate the radical cation. The radical cation can suffer both a SET and a Proton Transfer (PT) with Co(II) complex to release the desired iminium cation along with protonated Co(I) complex. This Co(I) complex can be interpreted as a Co(III) hydride and therefore is able to trigger a nitro reduction through a hydride transfer process. On the other hand, in the enamine organocatalysis domain, a chiral enamine has been formed upon the condensation between the starting ketone and the chiral catalyst derived from 1,2-cyclohexyldiamine. Then, this chiral nucleophilic enamine reacts with the previously photogenerated iminium cation in an enantioselective manner to afford (after hydrolysis) the target Mannich product.



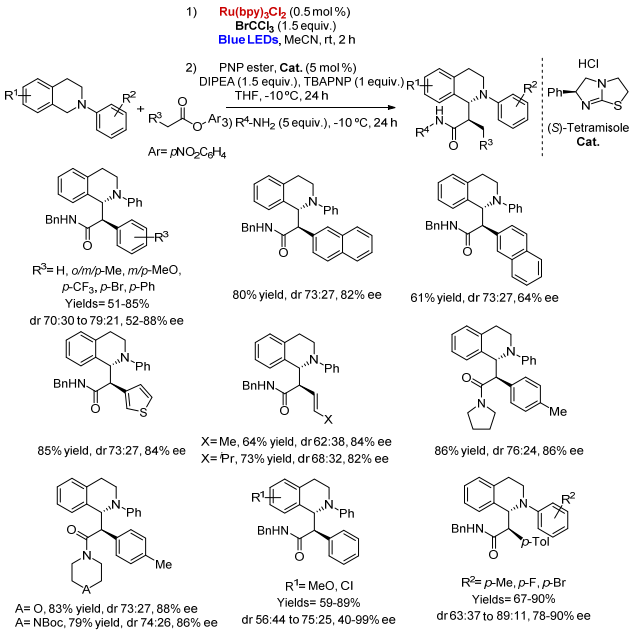
Scheme 48. Mechanistic pathway for the asymmetric oxidative Mannich reaction using a multicatalytic reaction protocol.

Shortly after, in 2018, the research group of Rueping developed a more practical methodology to couple *N*-aryl-THIQs with cyclic ketones through an asymmetric oxidative Mannich reaction triggered by visible light photoredox catalysis.[54] The authors realized that this transformation could be achieved using $Ir(ppy)_2(bpy)PF_6$ as photoredox catalyst in combination with simply (*R*)-phenylglycine as organocatalyst using a two-step procedure. First, the oxidation of THIQ was conducted under visible-light irradiation, and, then the organocatalyst and the starting ketone were added to the reaction mixture to carried out the enantioselective Mannich addition. With these optimal conditions, the authors were capable of synthesize a collection of twelve THIQs bearing a cyclic ketone moiety in moderate yields, good diastereoselectivities and good to high enantiomeric induction (Scheme 49).



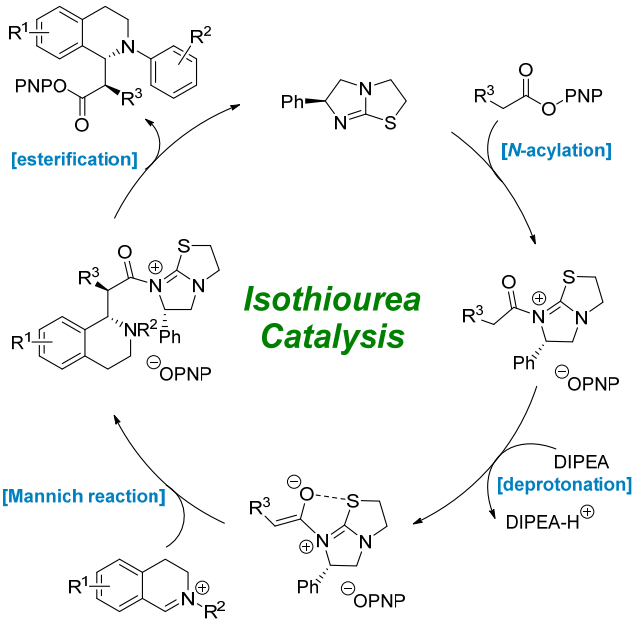
Scheme 49. Cross dehydrogenative coupling between THIQs and cyclic ketones through an oxidative enantioselective Mannich reaction (Rueping, 2018).

Other efforts on enantioselective functionalization of THIQs through an asymmetric oxidative Mannich reaction was reported by Smith and collaborators in 2018, who employed a sequential oxidation-Mannich addition-amidation protocol to generate chiral THIQs bearing an amide moiety.[55] After the evaluation of multiple reaction parameters, such as the organocatalyst, the photocatalyst, the oxidant and the most suitable benzylic ester, the authors were able to select (*S*)-tetramisole as organocatalyst, $Ru(bpy)_3Cl_2$ as photocatalyst, $BrCCl_3$ as oxidant and *p*-NO_2-C_6H_4-ester (PNP ester) as enolate precursor under the irradiation of Blue LEDs. To avoid product decomposition, the authors had to perform an amidation with $BnNH_2$ in order to form a stable and isolable amide product. Using this three-step protocol, the authors were capable to obtain a set of twenty-four chiral amido *N*-aryl-THIQs in moderate to good yields, moderate diastereoselectivity, and moderate to good enantiomeric excesses (Scheme 50).



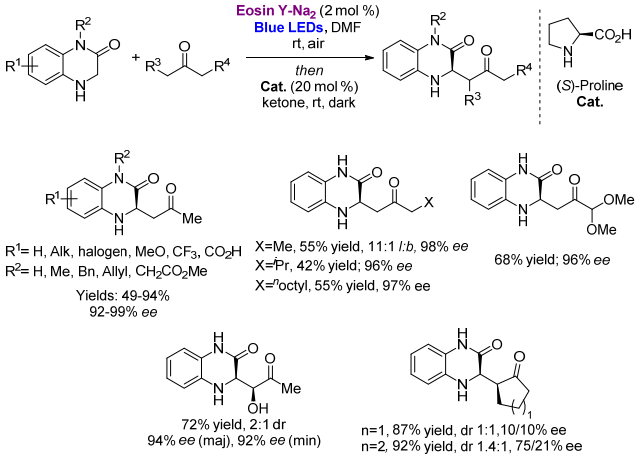
Scheme 50. Isothiourea-catalyzed enantioselective Mannich reaction between THQs and PNP esters (Smith, 2018).

The authors showed how the enantioselective Mannich reaction proceeds after the oxidation of THIQs by means of photoredox catalysis. Although the photoredox-enabled oxidation mechanism was omitted, the isothiourea organocatalytic cycle is depicted in Scheme 51. The iminium nitrogen of the (*S*)-tetramisole is nucleophilic enough to attack the ester moiety generating *N*-acyl isothiourea ion pair, which suffers a deprotonation giving the corresponding enolate. The formation of the enolate is favoured due to the *S*-*O* intramolecular interaction, also providing a fixed and oriented chiral nucleophile. Finally, the Mannich-type addition to the THIQ iminium cation yields (after an esterification) the desired product in an enantioselective way.



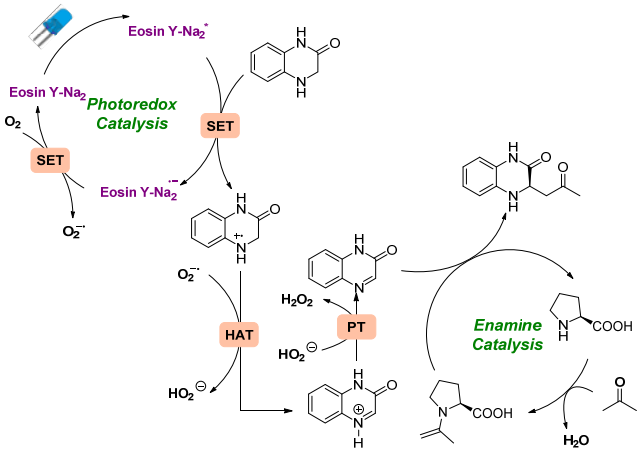
Scheme 51. Reaction mechanism for the enantioselective Mannich reaction enabled by isothiourea organocatalysis.

In 2019, our research group developed a dual catalytic protocol to functionalize, enantioselectively, the C-3 position of 3,4-dihydroquinoxalin-2-ones with ketones using as organocatalyst (*S*)-proline.[56] The structural motif of 3,4-dihydroquinoxalin-2-one is present in several molecules with biological activity and therefore have attracted the attention of the synthetic chemistry community.[57] First, 3,4-dihydroquinoxalin-2-one is oxidized to corresponding quinoxalin-2-one using visible-light photoredox catalysis and then, the generated electrophilic C=N double bond was trapped by a ketone using enamine organocatalysis. After an optimization process, we realized the best way to perform the desired transformation is through a stepwise procedure in which, first, 3,4-dihydroquinoxalin-2-one is oxidized using Eosin Y as photocatalyst under the irradiation of Blue LEDs. Then, the addition of (*S*)-Proline along with the starting ketone enabled the enantioselective Mannich reaction (Scheme 52).



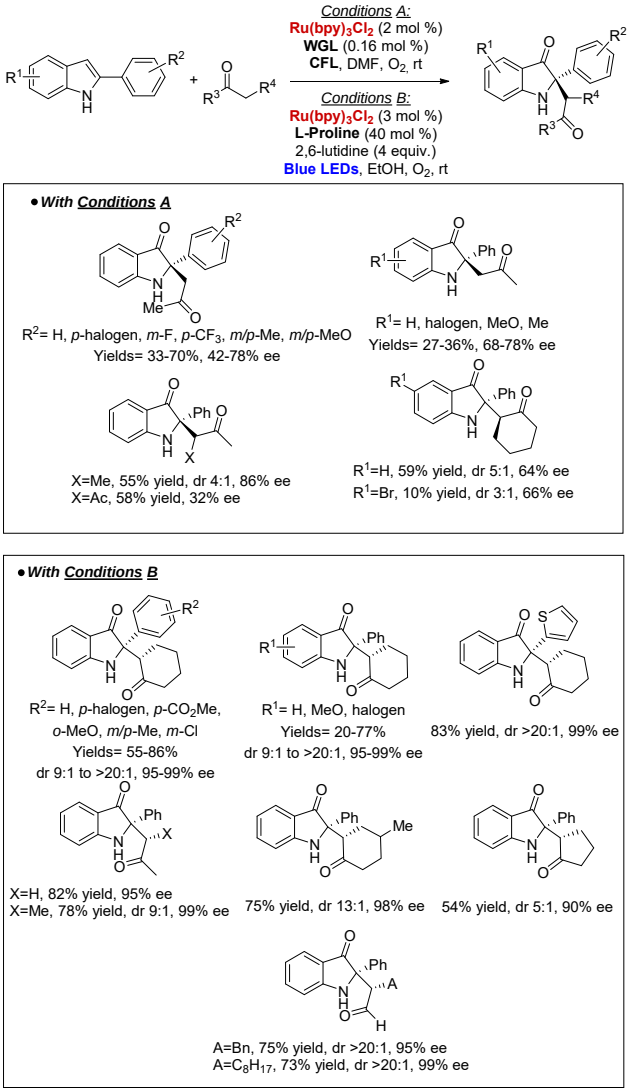
Scheme 52. Enantioselective oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones and ketones (Pedro and Vila, 2019).

After conducting several control experiments, and due to the strong fluorescence emission quenching of Eosin Y in the presence of 3,4-dihydroquinoxalin-2-one, we proposed that the excited state of Eosin Y is deactivated by 3,4-dihydroquinoxalin-2-one through a SET. The resulting radical cation can be converted to protonated quinoxalin-2-one through a HAT with superoxide anion. After deprotonation, quinoxalin-2-one can react in an enantioselective fashion with the chiral enamine formed through a condensation between the corresponding ketone and (*S*)-proline (Scheme 53). The stereogenic assignation of the chiral center was established by means of X-Ray Crystallography as well as by theoretical models.



Scheme 53. Mechanistic pathyway for the enantioselective Mannich reaction between 3,4-dihydroquinoxalin-2-ones and ketones through a combination of photoredox catalysis and organocatalysis.

Shortly after, the research group of Guan and He developed two methodologies to access chiral 2,2-disubstituted indol-3-ones through a tandem oxidation-Mannich reaction. The first report on this transformation was published in 2019, in which 2-arylindoles were efficiently oxidized by $Ru(bpy)_3Cl_2$ in an aerobic atmosphere to the corresponding indolones, over which a Mannich reaction with either linear and cyclic ketones was performed using a lipase from wheat germ (WGL).[58] This protocol constituted an important landmark in the field due to the effective combination of photoredox catalysis and biocatalysis. One year later, in 2020, they could conduct the same transformation but using now proline as organocatalyst instead of WGL.[59] With these more practical conditions, the authors could synthesize similar products but with an enhanced stereocontrol. An illustrated comparation of the performance between these two methodologies is showed in Scheme 54. It is important to note that while the biocatalytic method worked better for linear ketones, the organocatalytic approach seems more efficient for both linear and cyclic ketones. In both methodologies, the final oxidant is O_2.

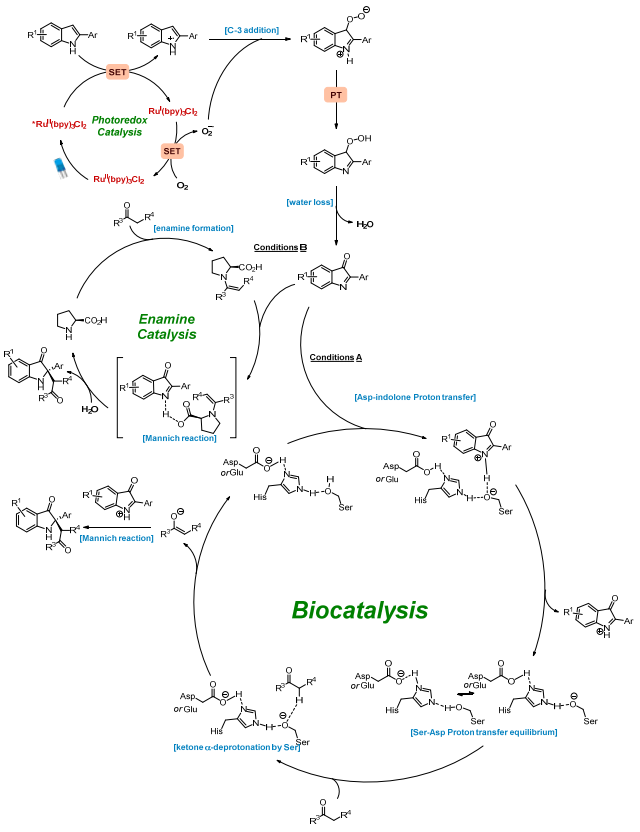


Scheme 54. A comparison between two methodologies (biocatalysis vs organocatalysis) in the oxidation-Mannich reaction between 2-arylindoles and ketones (Guan and He, 2019 and 2020).

A general overview of the catalytic cycles which operate in both biocatalytic and organocatalytic approaches is showed in Scheme 55. The formation of the corresponding indolone by means of photoredox catalysis is the only common element in both strategies. Upon the excitation of $Ru(bpy)_3Cl_2$ by visible-light, a SET with the 2-aryl indole occurs in order to form the corresponding radical cation along with Ru(I) complex, which is reoxidized by the assistance of molecular oxygen. The superoxide anion that has been generated in this last step is able to attack the electron-poor 2-arylindole at its C-3 position to generate, after an intramolecular PT, an hydroperoxide intermediate,

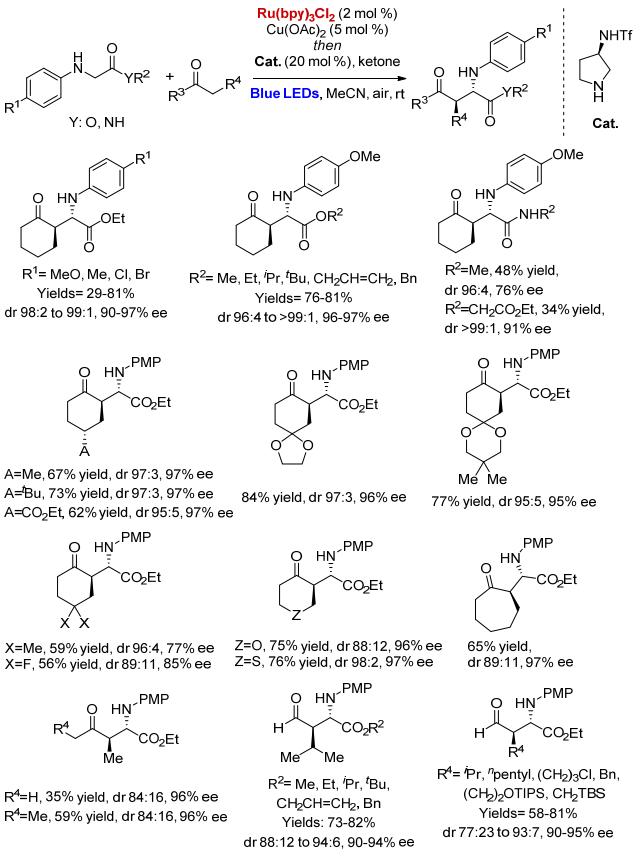
which experiments a spontaneous loss of water to finally generate the corresponding indolone.

Despite the 3D structure of WGL has not been stablished by X-Ray diffraction, it is known that its active site is formed by the carboxylic group of either Asp or Glu, the imidazole of a His and the hydroxyl moiety of a Ser. This composition of the active group is frequently found in lipases and therefore the Asp(Glu)-His-Ser triad must play an important role in the catalytic Mannich reaction.[60] According to the literature, the carboxyl group of Asp (or Glu) and the hydroxyl group are connected via a framework of hydrogen bonds through an imidazole (His) group. Thus, the acidic proton of Asp (or Glu) can be transferred to indolone through this framework, being the Ser the final donor. This process generates the protonated form of the indolone as well as the deprotonated form of the triad, in which the negative charge is delocalized along the hydrogen bonding framework. Then, the Ser alkoxide is able to abstract a proton from the starting ketone to form a nucleophilic enolate, which can react with protonated indolone to yield the enantioenriched Mannich addition product. The organocatalytic approach operates as usually through the formation of the corresponding chiral enamine from (*S*)-proline and the starting ketone. Thus, the organocatalyst can form a pre-oriented transition state that allows the enantioselective Mannich-type addition to the indolone.



Scheme 55. Mechanistic overview for the enantioselective asymmetric oxidative Mannich reaction of 2-arylindoles an ketones.

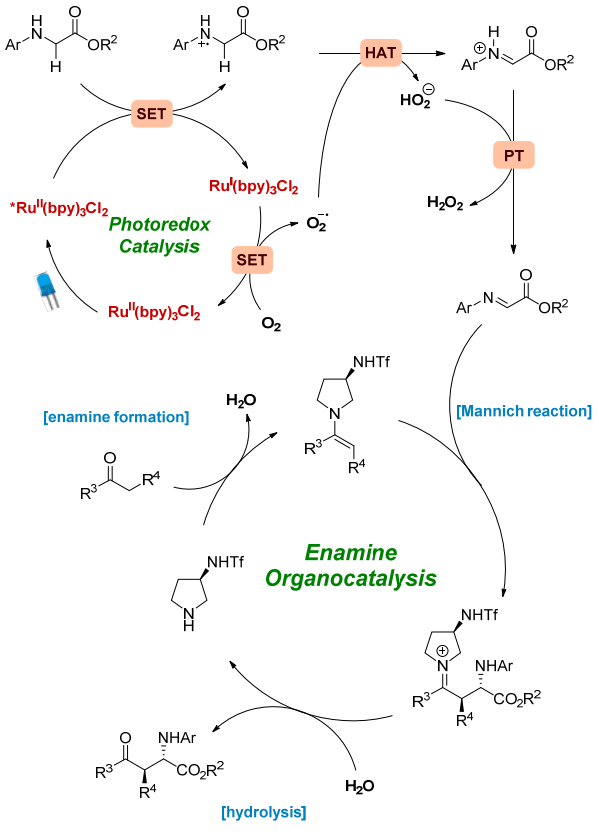
To finish on photocatalytic generation of imines or iminium cations it is important to comment a last report, which came from the Zhang research group in 2020.[61] They were interested in the asymmetric functionalization of glycine esters with ketones, and therefore developed an asymmetric photooxidative Mannich reaction approach. After an exhaustive optimization process, the authors selected $Ru(bpy)_3Cl_2$ as photoredox catalyst and a triflimide-derived chiral secondary amine as the responsible for the asymmetric induction.[62] Additionally, the presence of $Cu(OAc)_2$ was found to be crucial for the success of the transformation. Although the authors were interested on the development of a tandem procedure, they realized that a stepwise procedure was beneficial for the performance of their transformation. Once determined the optimal reaction conditions, the researchers explored the scope of the reaction using both differently substituted glycine esters and ketones. Their catalytic method was robust enough to tolerate cyclic and linear ketones, as well as aldehydes with sophisticated substitution patterns. Generally, the desired products were obtained in good to high yields, excellent diastereoselectivities (selective to the anti isomer) and enantioselectivities (Scheme 56).



Scheme 56. Asymmetric oxidative Mannich reaction between glycine esters and ketones and aldehydes (Zhang, 2020).

To gain insight into the mechanism by which this reaction should proceed, several control experiments

were carried out. Although the addition of TEMPO did not produce any effect in the performance, BHT completely inhibited the reaction, suggesting a radical process. Furthermore, glycine ester was smoothly transformed into the corresponding imine under Ru(II)/Cu(II) and Blue LEDs irradiation. However, the same conditions, but without Cu(II), yielded the amide instead of the imine as the sole product. These experiments suggested that Cu(II) favours the formation of the imine while suppressing the addition of oxygen. But it does not have any implication in the photoredox cycle, as no bathochromic shift was observed when Cu(II) and glycine ester were mixed together. Finally, the reaction of the corresponding imine with cyclohexanone in the presence of triflimide-derived chiral secondary amine produced the target *anti*-Mannich product in 91% yield, dr 98:2 and 98% ee, showing imine as the key intermediate. All these conclusions were put together in a reaction mechanism (Scheme 57). The excited state of Ru(II) photoredox catalyst is oxidant enough to promote a SET with the glycine ester to generate the corresponding radical cation. Molecular oxygen regenerates Ru(II) complex through a SET also forming superoxide anion, which is able to trigger a HAT with the radical cation to obtain the corresponding α-iminoester (after deprotonation). The chiral nucleophilic enamine, which is formed through the condensation of the starting ketone (or aldehyde) and the chiral catalyst, react with the α-iminoester via a diastereomeric transition state, providing after hydrolysis the desired product in an enantioenriched form.



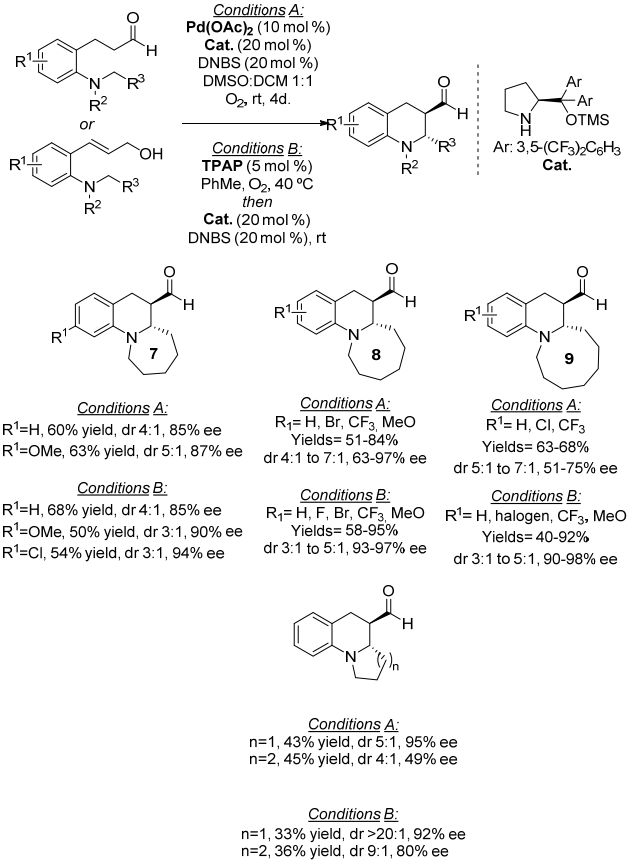
Scheme 57. Mechanistic hypothesis for the asymmetric oxidative Mannich reaction of glycine esters and ketones and aldehydes.

3.3 Other Catalytic Oxidations

In the last section, all reports regarding catalytic oxidations of amines that cannot be categorized in any previous statement are discussed. For example, in 2014, the laboratory of Kim reported two catalytic alternative approaches towards the synthesis of chiral THQs, similar to the ones previously reported by them. This time, the ortho-substituted anilines are catalytically oxidized to the corresponding α,β-unsaturated system, using either $Pd(OAc)_2$ or tetrabutylammonium perruthenate (TPAP) under an aerobic atmosphere, instead of using IBX as stoichiometric oxidant.

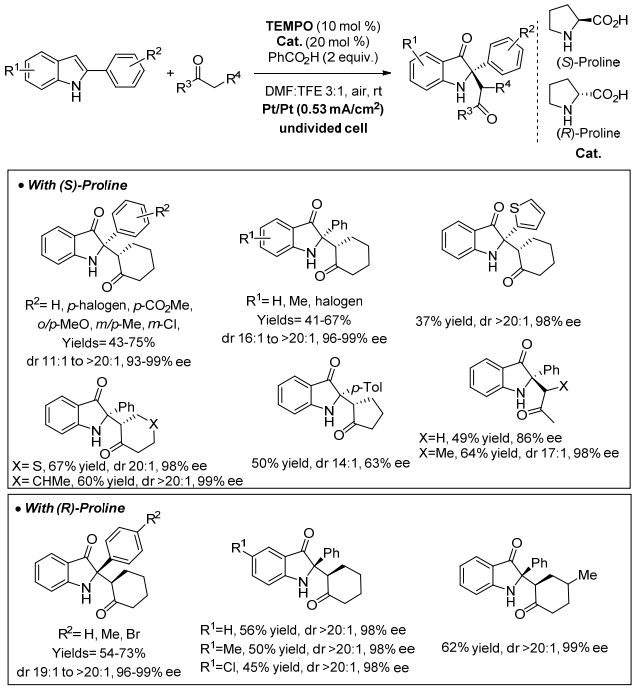
First, in early 2014, the authors used the same ortho-aminosubstituted dihydrocinnamaldehyde as they did before, but now, they could access the α,β-unsaturated system through a $Pd(OAc)_2$-catalyzed oxidation.[63] As before, this oxidation step triggered a sigmatropic 1,5-hydride shift, obtaining the iminium cation as well as the enamine. A final 6-endo cyclization generated the desired product. Using this approach and after an optimization process, they selected the Hayashi-Jørgensen catalyst as the best organocatalyst, along with a mixture of DMSO and DCM as solvent. They were able to synthetize eleven ring-fused THQs in moderate to good yields, moderate diastereoselectivities and moderate to high enantiomeric excesses (Scheme 58). Unfortunately, these reaction conditions failed when a proper aliphatic amine was employed as substrate.

The two last approaches of the authors were based on the oxidation of an aliphatic moiety to generate an α,β-unsaturated system. Shortly after, also in 2014, they envisioned that the same unsaturated system could be obtained by an oxidation reaction with the proper ortho-aminosubstituted primary allylic alcohol.[64] They selected TPAP as catalyst for the oxidation and using molecular oxygen as stoichiometric oxidant. TPAP has shown a wide application in the mild oxidation of primary alcohols to aldehydes.[65] Although they tried to develop a tandem synthetic protocol, the better results were obtained when the generation of the cinnamaldehyde moiety by oxidation took place first at 40 ºC. As usual for this transformation, the asymmetric step was effectively granted by the action of the Hayashi-Jørgensen catalyst. A visual comparison between these two strategies is shown in (Scheme 58). Generally, the two-step TPAP-based approach is more convenient in both diastereomeric induction and enantioselectivity. However, higher yields were obtained with the Pd-catalyzed oxidation method.



Scheme 58. A comparison between a Pd-based oxidation protocol and a TPAP-enabled one for the synthesis of enantioenriched THQs. (Kim, 2014).

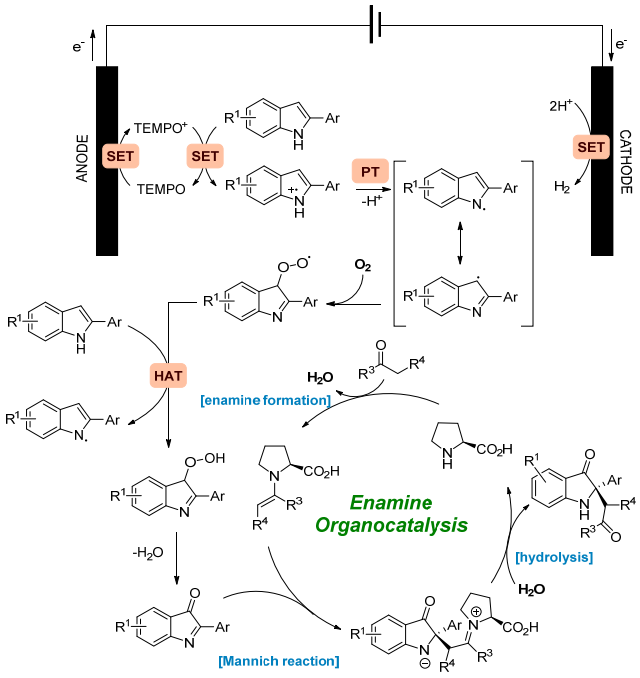
The last example on catalytic oxidation of amines comes from the Guan and He laboratory in 2020.[66] As has said before, this research group was deeply interested in the oxidation of 2-arylindoles to the corresponding indolones. Once formed, they were capable of trapping these intermediate with ketones in an enantioselective way, facilitated by either biocatalysis or (*S*)-Proline enamine catalysis. The abovementioned protocols for the synthesis of C-2 quaternary indolinones were facilitated by a photoredox-catalyzed oxidation of the corresponding 2-arylindoles but, in the present report, they developed an electrosynthetic method for the generation of these common intermediates. The authors envisioned that this redox reaction could be performed by applying the correct potential in the presence of molecular oxygen. After the optimization of the reaction conditions they realized that the addition of TEMPO as an electron mediator increased the performance of the reaction. Additionally, Pt electrodes between which a current of 0.8 mA was applied (current density 0.53 mA/cm2) in an undivided cell are selected. Again, the best organocatalyst to perform the reaction was (*S*)-Proline. With the optimal conditions in hand, they were able to explore the scope of the reaction using differently substituted 2-arylindoles as well as several ketones, including linear ketones. The substitution at both aromatic rings of the indole was well-tolerated (yields up to 75%, dr up to >20:1 and ee up to 99%). Regarding the scope of ketones, the use of both cyclic and linear was also successful, including the desymetrization of substituted cyclohexanones (yields up to 67%, dr up to >20:1, ee up to 99%). For selected substrates, the opposite enantiomer was obtained using (*R*)-proline as catalyst (Scheme 59).



Scheme 59. Electrochemical oxidation of 2-arylindoles and subsequent Mannich reaction with proline (Guan and He, 2020).

To gain some insight into the reaction mechanism, the researchers carried out several control experiments. The absence of either the (*S*)-Proline or the electrical current did not provide the desired product. However, when the reaction was performed in the absence of TEMPO, the target compound was obtained in 50% yield, >20:1 dr and 98% ee, demonstrating that the SET could come directly from the anode, albeit the product was obtained in lower yield. Additionally, the addition of BHT partially inhibited the reaction, and the trapped indolone was detected by HRMS analysis. The origin of the oxygen atom was tracked by the addition of either $H_2{}^{18}O$ or $^{18}O_2$, showing that the labelled oxygen atom was incorporated to the C-3 position of indole, only, when $^{18}O_2$ was employed. With these experimental results, the authors were able to propose a reaction mechanism by which the reaction might proceed (Scheme 60). First, TEMPO can be anodically oxidized to form TEMPO+, which is able to engage a SET event with the corresponding 2-arylindole to generate a radical cation. This last open-shell species can lose a proton to give a *N*-centered radical, which exhibits a partial delocalization to the C-3 position. The addition of molecular oxygen to C-3 provides the corresponding hydroperoxide through a HAT with another molecule of 2-arylindole. The

dehydration of the hydroperoxide finally provides the corresponding indolone, which can participate in the organocatalytic cycle by reacting with the chiral enamine formed after a condensation between (*S*)-proline and the starting ketone. Finally, the hydrolysis of the iminium cation releases the desired enantioenriched chiral Mannich product.



Scheme 60. Mechanistic proposal for the electrochemical-enabled Mannich reaction between 2-arylindoles and ketones.

4 Conclusions

In this review we presented an overview of the asymmetric oxidative Mannich reaction that have been reported in the last years. Several methodologies have been described to transform amines to the corresponding imines or iminium ions, that have been reacted with carbonyl compounds in an enantioselective way in order to obtain enantioenriched chiral amines. This review covers the stoichiometric as well as catalytic oxidative procedures, as well as visible-light photoredox and electrochemical examples, showing the different and successfully approaches for the development of oxidative Mannich reactions. Deeper efforts should be made by the synthetic community in order to expand the methodologies to other class of amines as well as other carbonyl nucleophiles, in order to increase the great potential of this class of reaction. We hope this review serves as a handy reference for synthetic chemists interested in developing new protocols for asymmetric oxidative Mannich reactions.

Acknowledgements

Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (CTQ2017-84900-P) is acknowledged. J. R-B thanks the Ministerio de Ciencia, Innovación y Universidades for an FPU predoctoral contract and C. V. thanks the Agencia Estatal de Investigación (AEI, Spanish Government) for RyC contract (RYC-2016-20187).

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REVIEW

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