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Recent advances in aza Friedel–Crafts reaction: strategies for achiral and stereoselective synthesis

Ameni Hadj Mohamed and Nicolas Masurier *

The aza-Friedel–Crafts (aza-FC) reaction is a very powerful tool for forming C–C and C–N bonds, based on an acid-catalyzed addition of electron-rich aromatic compounds to imines. This reaction has been particularly useful for synthesizing polysubstituted amines bearing various aromatic groups, as this structural motif is present in many biologically active and pharmacologically relevant compounds. Through representative examples, recent improvements achieved on the aza-FC reaction are presented, classified according to the type of catalyst used. Particular emphasis has been put on the different catalysts used to obtain optically active compounds, as the stereoselective addition of a C(sp²)–H bond to an imine allows access to chiral amines in a completely atom-economical way.

1. Introduction

The aza Friedel–Crafts (aza-FC) reaction is a very powerful tool to form C–C and C–N bonds based on acid-catalysed addition of electron-rich aromatic compounds to imines.^{1–3} Therefore, this reaction involves the use of an amino compound (primary or secondary amine, sulfonamide, primary amide, (thio)urea, etc.), an aldehyde or a ketone and an electron-rich aromatic

compound.⁴ This reaction allows access to polysubstituted amines bearing various aromatic groups, such structural motifs being found in many biologically active and pharmacologically relevant compounds.^{3,5} The importance and efficiency of aza-FC reactions in organic and medicinal chemistry has pushed researchers to perform a tremendous amount of work, seeking to improve their operating conditions in order to decrease toxic waste and to generate the desired product in the highest yields.

Moreover, the stereoselective addition of an sp² C–H bond to an imine allows access to optically active amines in a completely atom-economical way, making this reaction an efficient

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way to access complex chiral molecules. Therefore, controlling and increasing the stereoselectivity of the reaction has become a major concern of many research groups. Thus, a wide variety of catalytic systems have been studied, such as Lewis and Brønsted acids, and chiral organic and organometallic catalysts, with the main objective of accessing polysubstituted amines with excellent enantioselectivity and regioselectivity.^{6–8}

Two types of aza-FC reaction could be considered: intermolecular and intramolecular reactions. In the intermolecular type, electron-rich compounds such as naphthol,^{9–12} indole⁴ and pyrrole^{13,14} are commonly used as aza-FC donors and could react with a variety of imines. Regarding the intramolecular aza-FC reaction, they have been extensively investigated for years.^{15–19} Seminal work describes several types of intramolecular synthesis of tetrahydro- β -carbolines, from tryptamines and various aldehydes or ketones (known as the Pictet Spengler reaction), and this reaction will not be discussed here.^{20–27}

In this current review, we present an overview of the most relevant works and the improvement achieved in the aza-FC reaction, classified in the following sections according to the type of catalyst used. As this reaction led to the formation of a new chiral center, a particular focus will be on the different catalysts used to obtain optically active compounds.

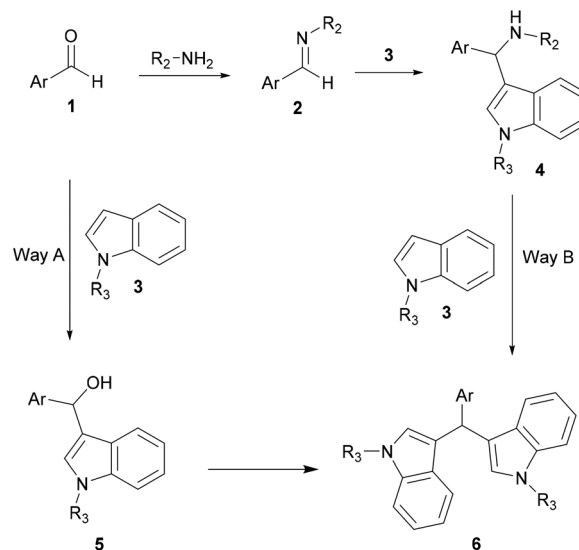
2. Achiral aza Friedel–Crafts reactions

2.1. Brønsted acid catalyzed aza Friedel–Crafts reactions

Acid assistance protons are quite versatile catalysts of organic reactions and several Brønsted acids have been reported to efficiently catalyze aza FC reactions, involving a large variety of electron-rich compounds and imines.

2.1.1. Decanoic acid. Shirakawa and Kobayashi described in 2006 a three-component aza-FC reaction of aldehydes **1**, primary amines, and indoles **3** in water using a carboxylic acid as a catalyst.²⁸ Typically, aza-FC reactions of indoles **3** with an aromatic aldehyde, in the presence of acid, often result in an unwanted bis-indolyl product **6**, which could be formed after the reaction of two indole units with an aromatic aldehyde (way A), or the subsequent nucleophilic attack of **4** by **3** (way B), as shown in Scheme 1.^{29–32}

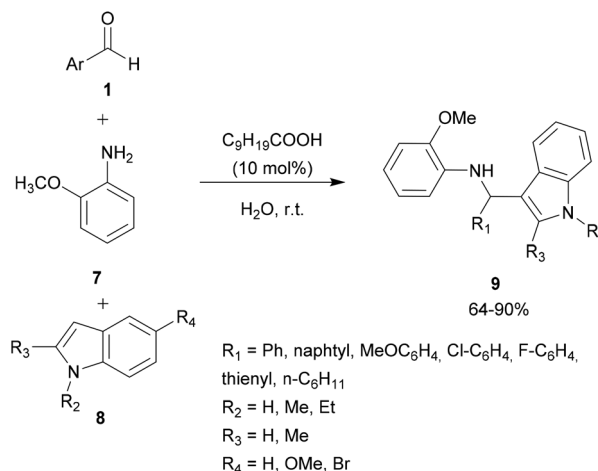
In an attempt to solve these shortcomings, Shirakawa and Kobayashi undertook the search for a suitable carboxylic acid as a catalyst that avoids the formation of the unwanted bis-indolyl product **6**.²⁸ Thus, several carboxylic acids were tested at 5 mol%. The results showed that in the presence of TFA and AcOH, no reaction took place. However, using scandium tris (dodecyl sulfate) and dodecylbenzenesulfonic acid, both the desired product **4** and the undesired product **6** were obtained. Other carboxylic acids containing different lengths of alkyl chains were also studied, showing that the length of the alkyl chains of the carboxylic acids was crucial for this reaction. Interestingly, decanoic acid ($C_9H_{19}COOH$) was found to be the most efficient catalyst, giving a good yield of the expected



Scheme 1 Side pathways of aza-FC leading to bis-indolyl derivatives.

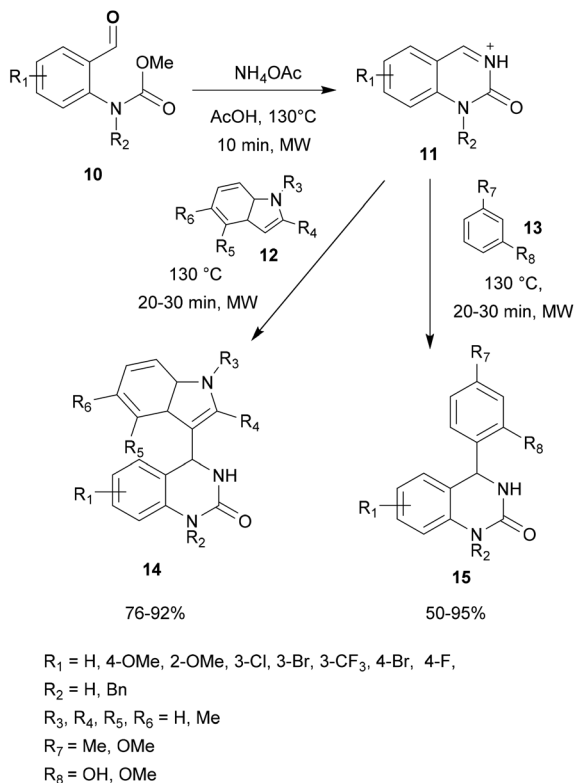
product without any formation of the unwanted product **6**. Optimization of the catalytic amount of the catalyst concluded that 10 mol% afforded the best yield of the expected product, which was recovered by recrystallization. Indeed, it is noteworthy that this strategy constitutes an easy and simple approach for the development of 3-substituted indoles compounds **9** without any need for chromatographic purification (Scheme 2).

2.1.2. Acetic acid. Sawant and co-workers reported in 2018 an efficient and a rapid way giving access to 4-aryl 3,4-dihydroquinazolines using a microwave-assisted aza-FC reaction in the presence of acetic acid (AcOH).³³ A one-pot cascade sequence was explored starting with the generation of cyclic *N*-acyliminium ions, from *O*-formyl carbamates **10** and ammonium acetate (Scheme 3). The *in situ* generated ion **11** could then react with indole **12** using microwaves, thanks to



Scheme 2 Three-component aza-FC reaction catalyzed by decanoic acid in water.



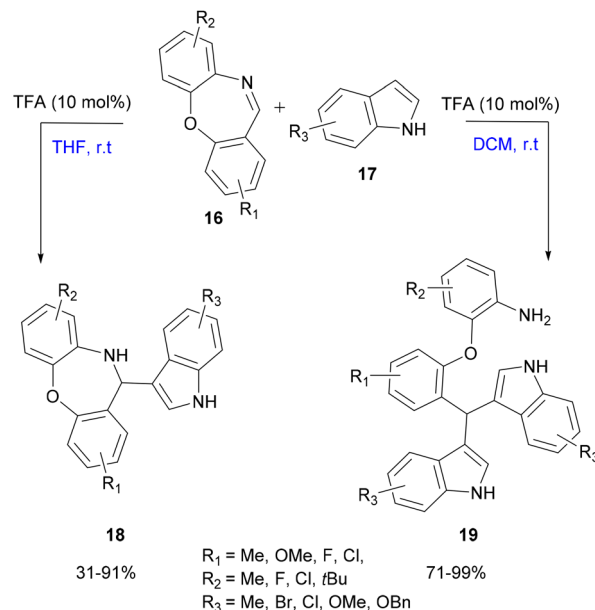


Scheme 3 Microwave-assisted aza-FC reaction.

an aza-FC reaction. As this first attempt proved to be effective and successful, further experiments were carried out by highlighting the influence of introducing electron-donating or electron-withdrawing substituents at different positions in the molecule. Whatever the substituent introduced in the *O*-formyl carbamate or the indole nucleus, the reaction afforded the 4-indolyl 3,4-dihydroquinazolinones **14** in good to excellent yields (76–92%) and in a short reaction time (10–30 min).

The applicability of the microwave-assisted aza-FC arylation of *N*-acyliminium ions was also investigated using substituted electron-rich phenyl derivatives **13**. This study demonstrates that this protocol tolerated a wide range of arenes affording the corresponding desired products **15** with yields up to 95% (Scheme 3).

2.1.3. Trifluoroacetic acid. Wu and co-workers investigated the trifluoroacetic (TFA)-catalyzed aza-FC reaction performed on seven-membered cyclic imine dibenzo-1,4-oxazepines **16** with various indoles **17** (Scheme 4).³⁴ When the reaction was carried out in tetrahydrofuran (THF) with 10 mol% of TFA, the mono-indole substituted product **18** was obtained selectively in 31 to 91% yields. It was also reported that a double aza-FC occurred, when dichloromethane (DCM) was used as the solvent, providing the bis-indole substituted aniline derivatives **19** in 71% to 99% yields. The authors suggested that the selectivity between the single or the double aza-FC is presumably due to the presence of THF forming hydrogen bonds with the TFA, thus weakening the Brønsted activity to suppress



Scheme 4 Selectivity difference depending on the solvent in the TFA-catalyzed aza-FC reaction of cyclic imine and indole.

further alkylation with another indole, allowing only a single addition. Using DCM, no-hydrogen bond with the catalyst could be formed and a double indole addition is obtained.

Structurally diverse indole derivatives and cyclic imines as the substrates provided the targeted compounds in high yields, using mild conditions, solvent-controlled efficient selectivity and easily accessible TFA (10 mol%) as a catalyst.³⁵

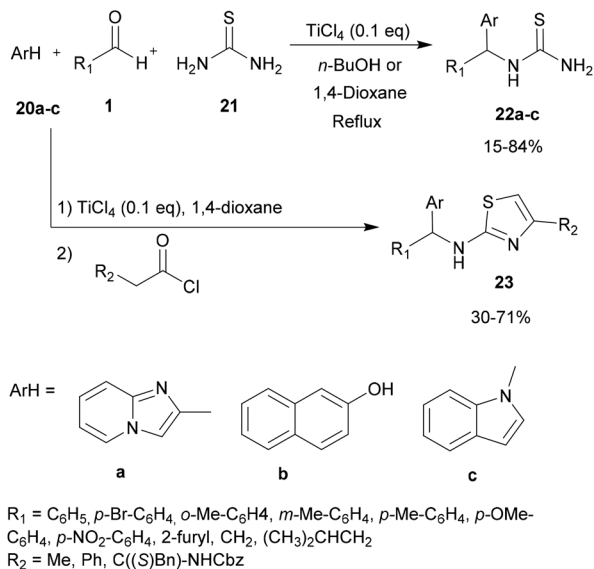
2.2. Lewis acid catalyzed aza Friedel–Crafts reactions

For a long time, transition metal-catalyzed multi-component reactions (MCRs) have attracted great interest because of their ability to achieve many difficult transformations using a one-pot method. In particular, metal catalysts which are derived from the VIII–X group show remarkable efficiency for the formation of carbon–carbon and carbon–heteroatom bonds. Specifically, transition metals have been shown to be effective and widely used, especially in aza-FC coupling.¹⁶

2.2.1 Titanium tetrachloride. Titanium tetrachloride (TiCl_4) catalyst is broadly used as an efficient Lewis catalyst for aza-FC coupling. Chaubet and co-workers reported the synthesis of aminothiazole compounds *via* a one-pot reaction between an electron rich aromatic-ring (2-methylimidazo[1,2-*a*]pyridine **20a**, β -naphthol **20b** or *N*-methylindole **20c**, thiourea **21** and aldehydes **1** as the key step of the synthesis (Scheme 5).¹²

The development of the experimental protocol involved several optimizations of the catalyst, the solvent, the reaction concentration and the temperature used. The aza-FC reaction was first optimized with **20a** as the electron-rich aromatic ring. Several Brønsted and Lewis acids were tested and TiCl_4 (0.1 eq.) in 1,4-dioxane or in *n*-butanol was shown to be the most efficient condition to access mono-substituted thiourea deriva-



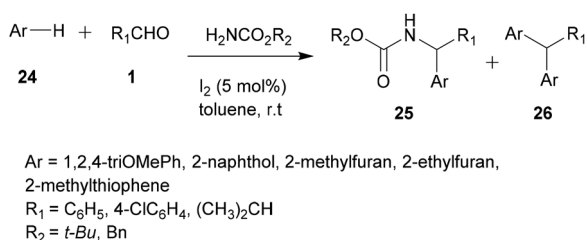


Scheme 5 TiCl₄-catalyzed aza-FC reaction of aromatic compounds with an aldehyde and thiourea.

tives **22**, in 15 to 84% yields, depending on the aldehyde used. These conditions proved to be compatible to further involve the monosubstituted thiourea in a one-pot tandem Hantzsch cyclization with an α -chloromethylketone, leading to the formation of the polysubstituted aminothiazole derivatives **23** in 30 to 71% isolated yields.

2.2.2 Iodine catalyzed aza-FC reaction. Molecular iodine is a simple, inexpensive, and less toxic reagent alternative that proved to be an effective catalyst for several types of chemical transformation. In 2012, Reutrakul and co-workers reported an iodine-catalyzed one-step three component aza-FC reaction of activated arenes or heteroarenes with carbamates in combination with a variety of aldehydes (Scheme 6).³⁶ Several reaction parameters, such as the amount of the catalyst required, and the solvent and temperature used were optimized. Accordingly, the reaction proceeded efficiently in toluene at room temperature using only 5 mol% iodine catalyst.³⁷

In order to study the scope of this reaction, a variety of substituted aliphatic and aromatic aldehydes, as well as several arenes and heteroarenes, were tested. Results showed that, using the conditions described above, the corresponding

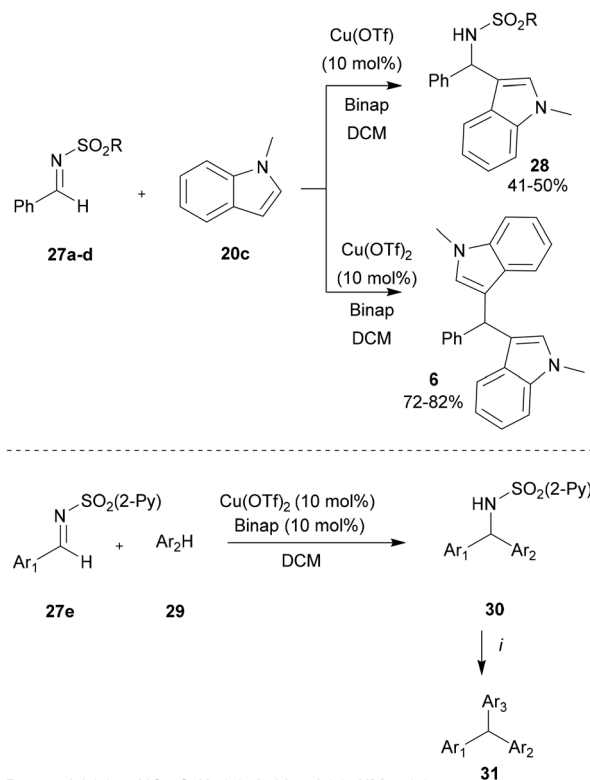


Scheme 6 One-pot three-component aza-FC reaction catalyzed by iodine.

expected products **25** were recovered in good yields, up to 90% (Scheme 6). However, the reaction leads to a second final product **26** resulting from a double addition of the arene/heteroarene, which is still recovered in a minor quantity.

2.2.3 Copper-catalyzed aza Friedel-Crafts reaction. Copper-based catalysts have for years been shown to be pivotal in the formation of carbon–nitrogen bonds by aza-FC reactions involving amine reagents.^{38–42}

In 2006, Carretero and co-workers performed the development of symmetric and asymmetric diarylmethanes and triarylmethanes using the aza-FC reaction. In their works, the authors highlighted the use of copper-based catalysts and stated the influence of the source of the copper catalyst as well as the nature of the sulfonyl imines used on the proceeding of the reaction.⁴³ Using phenyl-derived, thienyl or dimethylamine sulfonyl imines **27a–d**, *N*-methylindole and Cu(OTf) as the catalyst, the aza-FC reaction proceeded smoothly and led selectively to the monosubstituted product **28**, whereas the use of the more reactive Cu(OTf)₂ led to bis-indole **6** (Scheme 7). Interestingly, when 2-pyridylsulfonyl imines **27e** were used with indoles **29**, both catalysts led only to the mono-Friedel-Crafts products **30** and no bis-indoles **6** were formed. The most electrophilic Cu^{II} system provided **30** in good yields



Scheme 7 One-pot synthesis of unsymmetrical triarylmethanes through a copper-catalyzed aza-FC reaction.



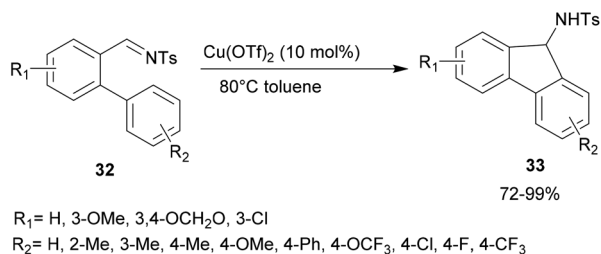
(70–90%), with very short reaction times (5 to 25 min). Finally, the further addition of another electron-rich arene allowed the preparation of various triarylmethanes **31** in good yields (72–85%). However, it was observed that the one-pot reaction occurred only when Ar₂ was a highly reactive indolyl derivative. To access more diversity, the second aromatic electrophilic substitution could be performed on isolated sulfonamides in the presence of Sc(OTf)₃ (10 mol%) in ACN at 60 °C.

This study showed that the copper catalyst system Cu(OTf)₂ applied in a sequential one-pot synthesis promotes a controlled double electrophilic aromatic substitution which provides access to unsymmetrical triarylmethanes with wide structural diversity and good yields (Scheme 7).

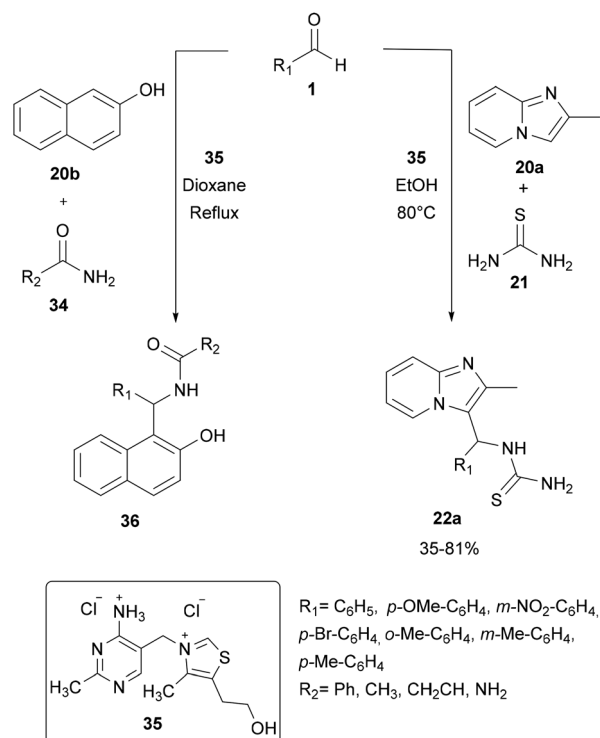
In 2011, Lu and co-workers studied a variety of Lewis acids to perform an intramolecular aza-FC reaction on *O*-arylated *N*-tosylbenzaldimines **32** (Scheme 8).⁴⁴ Whereas palladium or iron complexes did not show any catalytic activity, the use of 10 mol% of Cu(OTf)₂ as the catalyst, in toluene at 80 °C, was shown to be the most efficient condition for the intramolecular aza-FC reaction. The expected product **33** was obtained in high yield (Scheme 8). Interestingly, this reaction occurred smoothly with electron-donating or withdrawing groups at R₂.

2.3. Organocatalysts for achiral aza Friedel–Crafts reactions

2.3.1 Thiamine (vitamin B1). A study reported by Hu and co-workers described an efficient and practical multicomponent aza-FC reaction involving the use of vitamin B1, known as thiamine hydrochloride, as an efficient catalyst for this reaction (Scheme 9).^{44,45} The reaction of β-naphthol **20b**, benzaldehyde **1** and benzamide **34** was carried out in the presence of 10 mol% of vitamin B1 **35** in ethanol at 80 °C to afford the desired product **36** with an excellent yield (93%). The feasibility and the generality of this protocol were investigated by using these conditions for the synthesis of a series of amidoalkyl naphthols. Aromatic aldehydes bearing electron-donating or withdrawing substituents were reacted efficiently, giving excellent yields (85 to 93%). Using unsubstituted amides as well as urea derivatives, this protocol was also effective and led to good yields. On the other hand, this protocol was inefficient and not compatible either with aliphatic aldehydes and α,β-unsaturated aldehydes or with hindered and *N*-substituted amides.



Scheme 8 Substrate scope for a Cu(OTf)₂-catalyzed intramolecular aza-FC reaction.



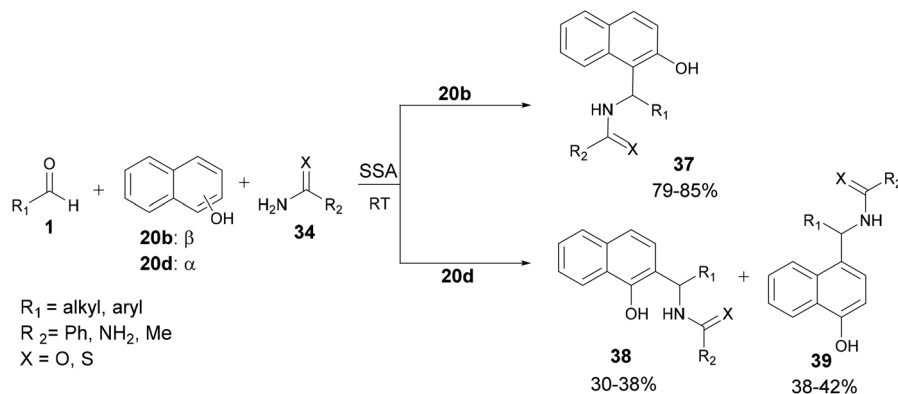
Scheme 9 One pot aza-FC reaction catalyzed by vitamin B1.

The use of thiamine-HCl **35** as a catalyst in 1,4-dioxane was also explored by Chaubet and co-workers in 2011.¹² This catalyst proved to be efficient as an alternative of titanium tetrachloride (see part 2.2.1) to promote the aza-FC reaction between thiourea, an aromatic aldehyde and imidazo[1,2-*a*]pyridine **20a**. This process allows the generation of the expected mono-substituted thiourea **22a** with moderate to good yields (Scheme 9). However, some aldehydes such as 4-nitrobenzaldehyde or isovaleraldehyde were unreactive under these conditions, while titanium tetrachloride led to the desired product, suggesting that this catalyst is less effective than Lewis acids to catalyse aza-FC reactions.

2.3.2 Solid supported catalysts for aza-FC reactions. The heterogeneous catalyzed aza-FC reaction was explored by Murthy and co-workers in 2007.⁴⁶ This strategy provided various amidoalkyl naphthols which were synthesized in high yields from aromatic or aliphatic aldehydes, α- or β-naphthols, and (thio)amides or (thio)urea under silica-supported sulfuric acid (SSA) catalysis. This reaction was performed under solvent-free conditions at room temperature and proved to be very efficient with β-naphthol **20b**, affording compounds **37** in good yields. When α-naphthol **20d** was used, a mixture of products **38** and **39** was obtained, resulting from a substitution in positions 2 and 4 respectively (Scheme 10).

Unlike some other catalytic systems, this strategy proves effective even with aliphatic aldehydes and appears to be suitable for large-scale operations as well.



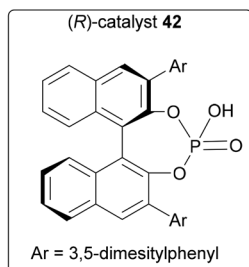
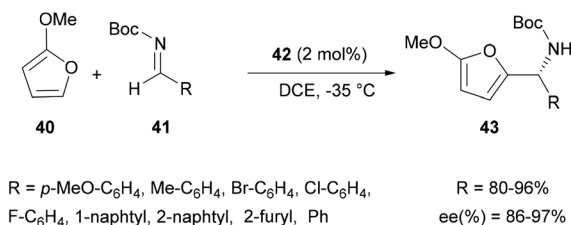


Scheme 10 Aza-FC reaction between aldehydes, α - or β -naphthols, and (thio)amides (thio)urea under silica supported sulfuric acid (SSA) catalysis.

3. Stereoselective aza Friedel–Crafts reactions

3.1. Brønsted acid-catalyzed aza-FC reactions

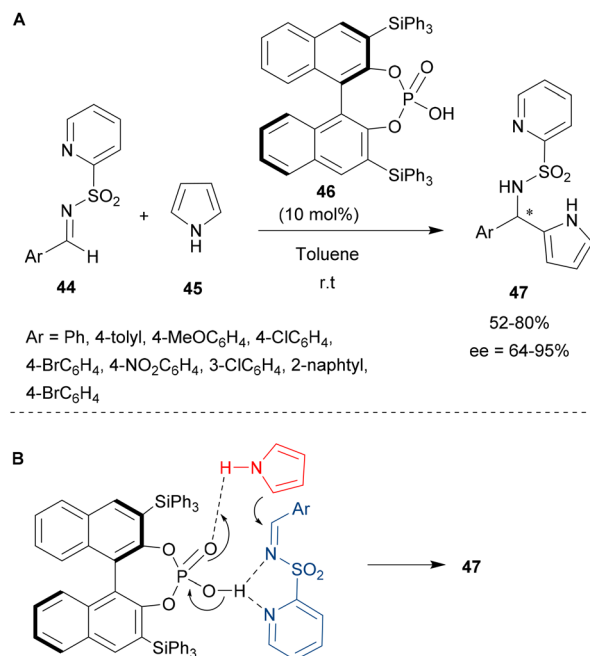
3.1.1. Chiral phosphoric acids for aza-FC reactions. Phosphoric acid-based catalysts were extensively employed for the catalysis of aza-FC reactions due to their ability to activate a large spectrum of substrates and their high efficiency to induce enantioselectivity.^{47–57} The first asymmetric aza-FC reaction catalyzed by chiral Brønsted acids was reported by Terada and co-workers in 2004² using 2-methoxyfuran **40** with *N*-Boc aldimines **41** and 2 mol% of the chiral phosphoric acid **42** (Scheme 11). This synthesis has been shown to be effective, even on substituted aldimines containing various alkylated and halogenated aromatic groups, with good yields and high ee (up to 97%). Since this first report, many teams have developed such catalysts to access chiral amines, using the aza-FC reaction. These works have been the subject of excellent reviews,^{3,58} and we only report the most recent developments in this field.



Scheme 11 Organocatalyzed asymmetric aza-FC reaction of 2-methoxyfuran.

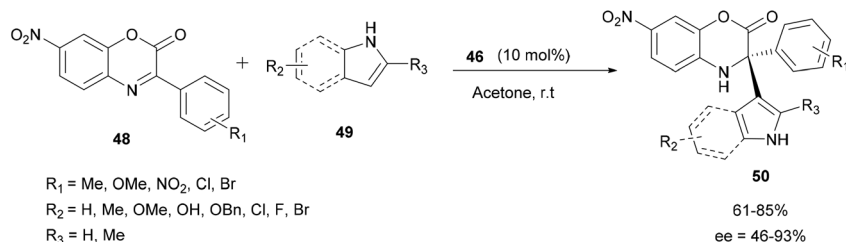
In 2009, Nakamura's team reported the enantioselective organocatalytic aza-FC reaction of unprotected pyrrole **45** with imines containing an heteroaryl-sulfonyl group **44** (Scheme 12A).⁵⁹ Interestingly, the imine bearing a 2-pyridinyl-sulfonyl group has two points of coordination with the catalyst, which can effectively enhance the reactivity and enantioselectivity of the reaction by controlling the transition states or intermediates by chelation (Scheme 12B). The catalyst **46** employed was a monophosphoric binaphthol which led to high enantioselectivity up to 95%.

In 2017, Zhao and co-workers described the enantioselective reaction of aza-FC of indoles with hindered cyclic aryl α -ketimino esters **48** catalyzed by the same chiral silylated phosphoric acid **46**, to access chiral α,α -disubstituted derivatives of unnatural



Scheme 12 Enantioselective aza-FC reaction of *N*-(2-pyridinylsulfonyl) imines with unprotected pyrrole. Scope of the reaction (A) and assumed transition state of the reaction (B).





Scheme 13 Aza-FC reaction of cyclic α -ketimino ester and indole or pyrrole derivatives.

α -amino esters (Scheme 13).⁶⁰ Despite the steric hindrance of the imine used, this reaction carried out in acetone at room temperature efficiently gave access to the corresponding products **50** with a tetrasubstituted α -stereogenic center in moderate to high yields (up to 85%) and with high enantioselectivities (up to 93% ee). This methodology was also applied to unprotected pyrroles, and it provided the expected products in good yields, but this time with moderate enantioselectivities. Using *N*-methylindole or *N*-substituted pyrroles, no reaction was achieved under the same conditions used. This result demonstrated that in this reaction, the presence of a N–H bond was crucial for the success of the process.

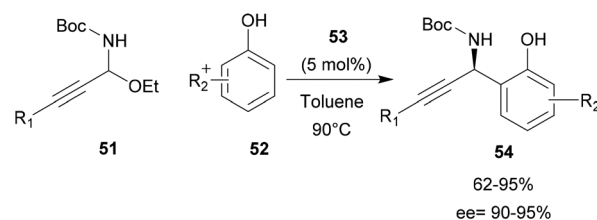
Chiral phosphoric acids have also proved to be efficient for the synthesis of non-poly-aromatic compounds. Shao and co-workers described an unusual synthesis of chiral propargylamine compounds **51** using low electron starting compounds such as phenol derivatives **52**.⁶¹ However, the use of electron-neutral phenols in the asymmetric aza-FC reaction remained elusive due to its lower nucleophilicity compared with naphthols and indoles. Herein the reaction could occur at two different reaction sites (*ortho* and *para* positions).

In the presence of the chiral phosphoric acid catalyst **53** ((*R*)-TRIP), the reaction between propargyl derivative **51** and substituted phenol **52** proceeded successfully, providing the desired 1,2-addition aza-FC product **54** with good yields (up to 95%). This study has shown that the aza-FC reaction can be applied to non-electron-rich aromatic reagents, thus opening up perspectives for this reaction (Scheme 14).

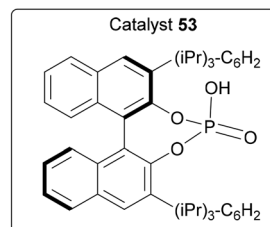
Some authors have further explored and developed the range of applications of phosphoric acid catalysts on the aza-FC reaction, using chiral imidazoline-phosphoric acid derivatives. These catalysts were developed to act as dual activating organocatalysts, by enhancing the electrophilicity of the imine and the nucleophilicity of the unprotected indole or pyrrole by hydrogen bonding (Scheme 15).^{62,63}

Thus in 2016, Nakamura's group studied such catalysts in the enantioselective aza-FC reaction of 2-substituted 3*H*-indol-3-ones **55** with unprotected pyrrole **45** (Scheme 16A). Several organocatalytic catalysts have been screened to address the difficulty of this reaction and the bis(imidazoline)phosphoric acid catalyst **56** offered the highest yield and enantioselectivity, even when only 2 mol% of the catalyst were used.⁶³

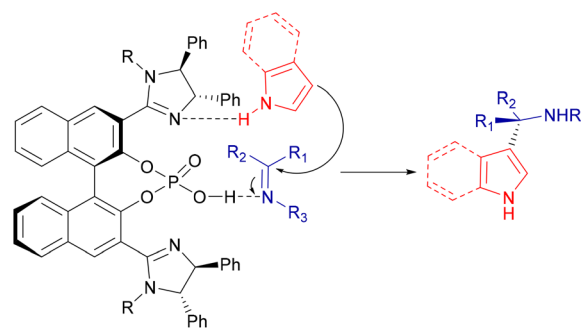
In 2018, they also demonstrated that the imidazoline-phosphoric acid derivative **60** can efficiently catalyze the aza-FC reaction between indoles **59** and 4-aryl-3-oxo-1,2,5-thiadiazol-



$R_1 = \text{Ph, Bn, Me}_3\text{Si, CF}_3, \text{Me-C}_6\text{H}_4, \text{Ph-CH}_2\text{CH}_2$
 $R_2 = \text{F, Cl, Br, I, Ac, COPh, CO}_2\text{Et, COH, morpholine}$



Scheme 14 Asymmetric aza-FC-type arylation strategy for the synthesis of chiral propargylamines.

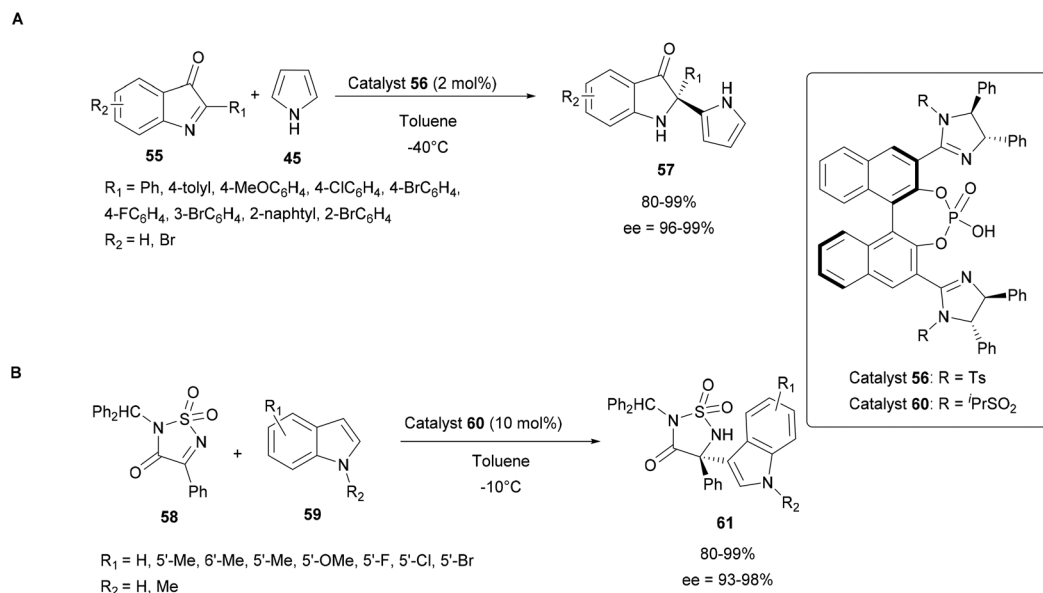


Scheme 15 Possible interactions between imidazoline-phosphoric acid derivatives and substrates of the aza-FC reaction.

1,1-oxides **58** as cyclic ketimines (Scheme 16B). Here, it was found that the reaction proved to be efficient, which opens up prospects for the use of this catalyst with more complex substrates.⁶²

Since their development in 2012 by Čorić and List,⁶⁴ imido-diphosphoric acids have been extensively used by Zhang's group to catalyze a range of reactions including aza-FC reactions.⁶⁵⁻⁶⁷





Scheme 16 Organocatalytic enantioselective aza-FC reactions using imidazoline/phosphoric acids and 3*H*-indol-3-ones (A) or cyclic ketimines (B).

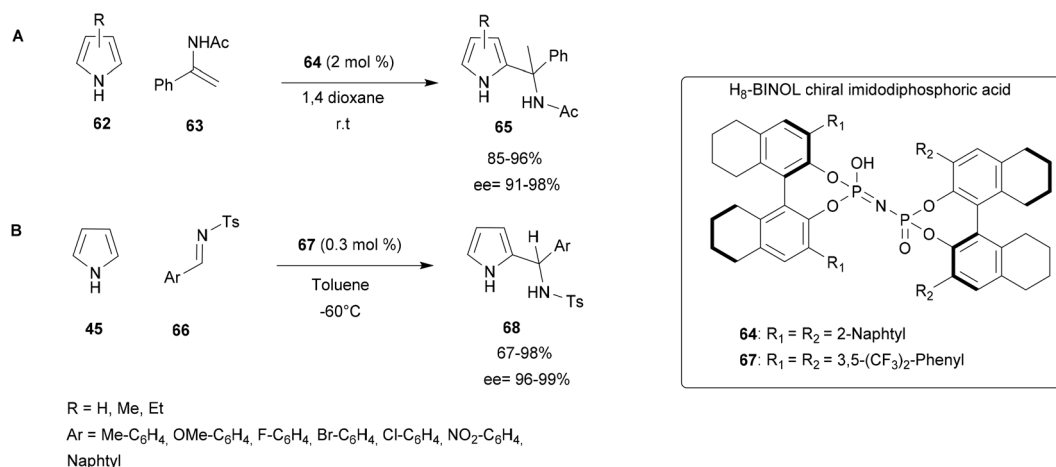
Since 2014, this group has been working on chemo-, regio- and enantioselective aza-FC reactions catalysed by H_8 -BINOL-type chiral imidodiphosphoric acid.^{65,67} In 2015, this catalyst was investigated in an aza-FC reaction between pyrroles and imines/enamides. A multiparametric optimization of this reaction (solvent, amount of catalyst, temperature, ...) concluded that the reaction proceeds successfully in the presence of 2 mol% of the catalyst in dioxane at room temperature. These conditions were applied to a range of substrates. First α -phenyl substituted enamides **63** with electron-withdrawing or electron-donating groups at the *ortho*, *meta* or *para* position of the phenyl ring (Scheme 17A) led to compounds **65** with high yields and excellent enantioselectivity (85–96% yield, 91–98% ee).⁶⁶

Encouraged by these successful results, the procedure was then applied to the reaction between pyrroles **45** and imines

66. During this process, a range of enantio-enriched substituted aryl-(2-pyrrolyl)methanamine scaffolds **68** were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 99% ee) using lower catalyst loadings of 0.3 mol% (Scheme 17B).⁶⁷

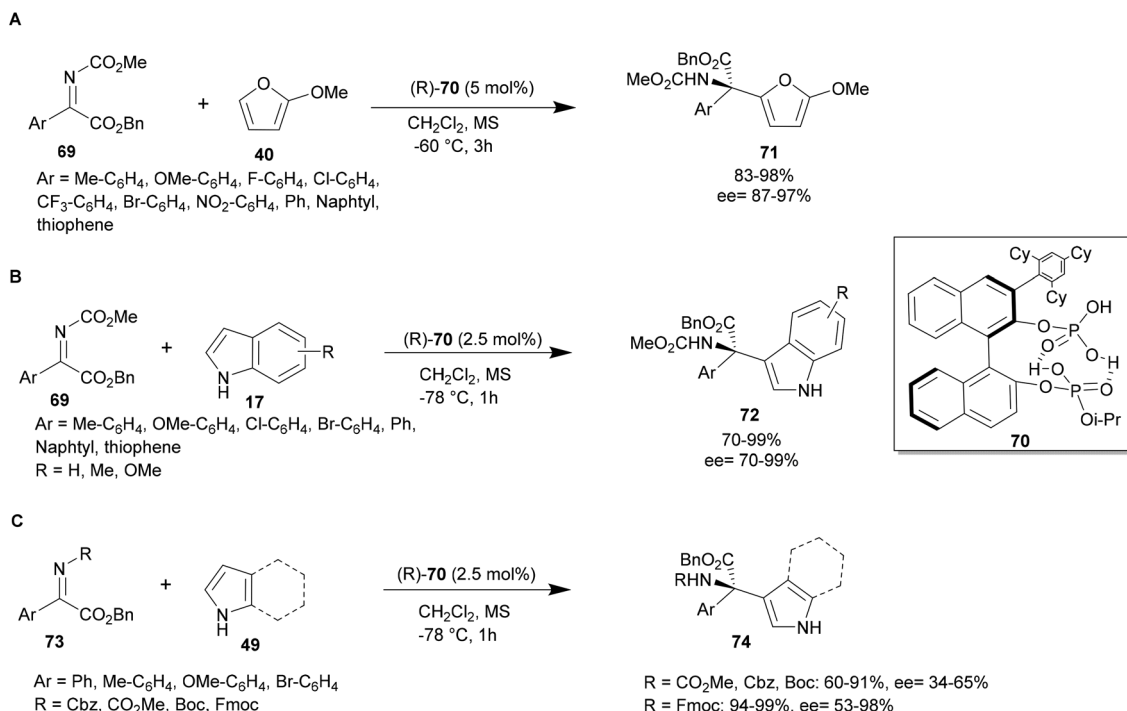
Bis(phosphoric acid) derivatives have recently been designed and reported in the literature as multiprotic acids. These catalysts containing a hydrogen bonding network are found to be important not only for the enhancement of catalytic activity, but also for the fine control of the conformation of substrates, reactants and catalysts due to acid–base cooperative interactions.

In 2018, Ishihara and co-workers developed the chiral C_1 -symmetric BINOL-derived bis(phosphoric acid) catalyst (*R*)-**70**, which has OP(=O)(OH)_2 and OP(=O)(OH)(Oi-Pr) moieties at



Scheme 17 Enantioselective aza-FC reaction of pyrroles and imines/enamides.





Scheme 18 Bis(phosphoric acid)-catalyzed aza-FC type reaction of α -ketimino esters with furan, indole and pyrrole.

the 2,2'-positions. This catalyst was investigated in an aza-FC reaction between 2-methoxyfuran and various substituted aryl α -ketimino esters using 5 mol% of catalyst **70**, in dichloromethane at -78°C . The scope of this reaction has been studied and these conditions revealed to be suitable for electron-withdrawing and electron-donating substituted aryl α -ketimino esters. Targeted compounds **71** were obtained with excellent yields and enantioselectivity up to 99% (Scheme 18A).⁶⁸

In 2020, the team of Ishihara and co-workers studied the bis-(phosphoric) catalyst **70** with pyrroles and indoles as substrates. An aza-FC reaction of indole **17** with aryl- α -ketimino ester **69** was performed in dichloromethane using only 2.5 mol% of catalyst **70** at -78°C . Various substituted aryl or heteroaryl- α -ketimino esters **69**, bearing electron-donating or electro-withdrawing groups, are tolerated and give access to the desired compound in high yields and ee (up to 99%) (Scheme 18B). Aza-FC on pyrroles was also achieved using α -ketimino esters protected by a methylester, a benzylcarbonyl or a Boc group in the same conditions. With these substrates, the reaction led to moderate yields and enantioselectivity, which were improved when an Fmoc-group was used as a protective group (yields up to 99% and ee up to 98%, Scheme 18C).⁴⁸ Interestingly, using either indole or pyrrole, the catalyst is effectively recovered after column chromatography in 99% yield. However, this reaction is limited to aromatic α -ketimino esters and is not applicable to non-aromatic imines, probably due to a lack of attractive hydrogen bonding and/or π - π stacking interactions among the substrates and catalyst **70**.

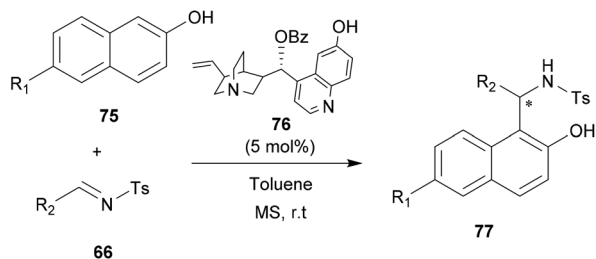
3.2. Organocatalytic catalysis of aza Friedel-Crafts reactions

Asymmetric organocatalysis has emerged as an effective and safe alternative to synthesize optically pure compounds without using any precious or toxic metals.⁶⁹ Organocatalysis offers several notable advantages over their metal homologue processes. For example, catalysis can be environmentally harmless, reactions can be operated under aerobic conditions and the catalysts are generally inexpensive. Organocatalytic and metal-free catalysis proved to be able to catalyze several types of C-C and C-X bond-forming reactions with high chemical and stereochemical efficiency, thereby complementing other major organocatalytic asymmetric approaches. Due to their unique molecular recognition ability, several organocatalysts attracted much attention in asymmetric aza-FC reactions.^{10,70-74} In this section, we report the most outstanding examples of organocatalyzed aza-FC reactions.

3.2.1. Cinchona alkaloid derivatives for the catalysis of aza-FC reactions. *Cinchona* alkaloids and their modified derivatives have been described for years as very useful catalysts for a variety of fundamental organic transformations that have given rise to interestingly enantioselective aza-FC reactions.⁷⁵⁻⁸²

In 2011, Chimni and co-workers have explored the catalytic potential of 6'-OH *Cinchona* alkaloids for an aza-FC reaction of naphthol with *N*-sulfonyl aldimines.¹⁰ Substituted 2-naphthols **75** with electron-donating or electron-withdrawing groups at C6 were successfully reacted with aromatic *N*-tosylimine **66** derivatives to give aza-FC adducts **77** with good to excellent ee, using only 5 mol% of the catalyst **76** (Scheme 19). This reac-



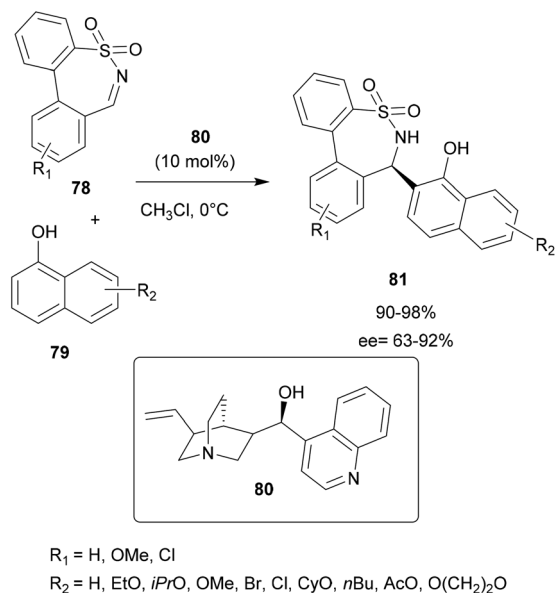


Scheme 19 Alkaloid-modified derivatives-catalyzed aza-FC type reaction of naphthol derivatives with *N*-tosylimines.

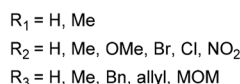
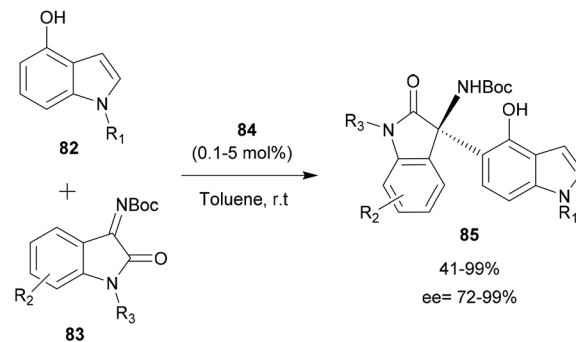
tion is also suitable for scale-up. Thus, the gram scale carried out under the same conditions on unsubstituted β -naphthol proved to be efficient and led to the expected product in good yield (86%) and good enantiomeric excess (91%).

In 2019, Zhou and co-workers employed *Cinchona* alkaloid-based organocatalysts for asymmetric aza-FC reactions between seven-membered cyclic *N*-sulfonylimines **78** and α -naphthols **79** in order to access chiral seven-membered cyclic sulfonamides (ϵ -sultams) **81**,⁸⁰ compounds known for their attractive biological activities.⁸³ In this work, several conditions were evaluated, such as the solvent, the alkaloid derivative catalyst used and the temperature. Among several alkaloid derivatives tested, it was found that the catalyst **80** in chloroform allowed the efficient synthesis of cyclic sulfonamide derivatives **81** in 90–98% yields with ee up to 92% (Scheme 20).⁸⁰

Pedro and co-workers presented in 2016 a regio- and enantioselective aza-FC reaction to functionalize hydroxy-substituted indoles (Scheme 21).⁸² Interestingly, this method allowed the functionalization of the carbocyclic ring instead of



Scheme 20 The alkaloid derivative-catalyzed asymmetric aza-FC reaction of *N*-sulfonylimines with naphthols.



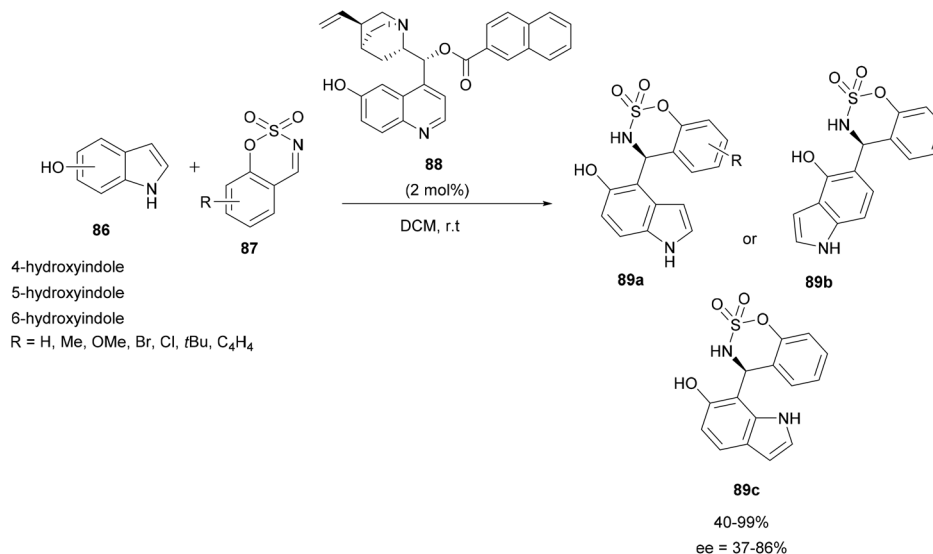
Scheme 21 Regio and enantioselective aza-FC catalyzed by a quinine skeleton as a bifunctional organocatalyst.

the “classical” C-3 position of the indole. The reaction was performed on hydroxyindoles **82** with isatin-derived ketimines **83**, using a squaramide-based quinine derivative **84** as a bifunctional organocatalyst (catalyst amount 0.1–5 mol%). In toluene at room temperature, the reaction led to highly enantio-enriched tetrasubstituted 3-aminooxindoles **85** in high yields and ee. Interestingly, this strategy allows the introduction of substituents in all positions of the indole carbocyclic ring in a regioselective manner, by simply switching the position of the hydroxy group activating/directing the regioselectivity. Moreover, the authors showed that, after functionalization, the activating/directing hydroxy group could be removed or used for further transformations. Thus, this approach enables structural diversity to be achieved according to research needs.

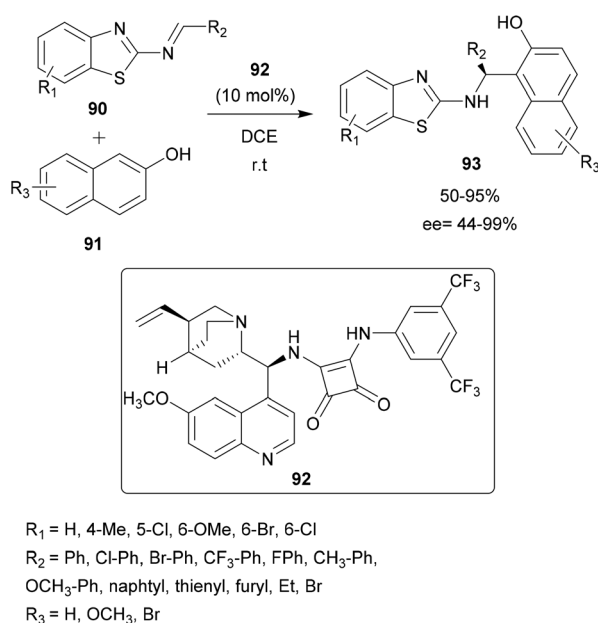
In 2019, the same team applied a similar strategy with cyclic electrophilic imines, benzoxathiazine 2,2-dioxide derivatives **87** and 4- to 6-hydroxyindoles **86** to prepare chiral indolyl sulfamidates **89a–c**. The aza-FC reaction was realized in DCM in the presence of a small amount of quinine-derived bifunctional organocatalyst **88** (2 mol%) (Scheme 22).⁸⁴ The substitution occurred in the α -position of the hydroxyl group and compounds **89** were obtained in moderate to good yields and enantioselectivities.

Using the *Cinchona*-derived squaramide organocatalyst **92**, Wang and co-workers described the enantioselective aza-FC reaction between benzothiazolylimines **90** and 2-naphthols **91**.⁸⁵ 25 examples of 2'-aminobenzothiazolomethyl naphthols **93** with potential antiproliferative and anthelmintic activities were obtained with moderate to high yields and enantioselectivity (Scheme 23). The induction is explained by the spatial conformation of the catalyst which allows the for-





Scheme 22 Aza-FC catalyzed by bifunctional organocatalyst for the development of chiral indolyl sulfamides.



Scheme 23 Bifunctional squaramide-catalyzed enantioselective aza-FC reaction between naphthols and benzothiazolimine derivatives.

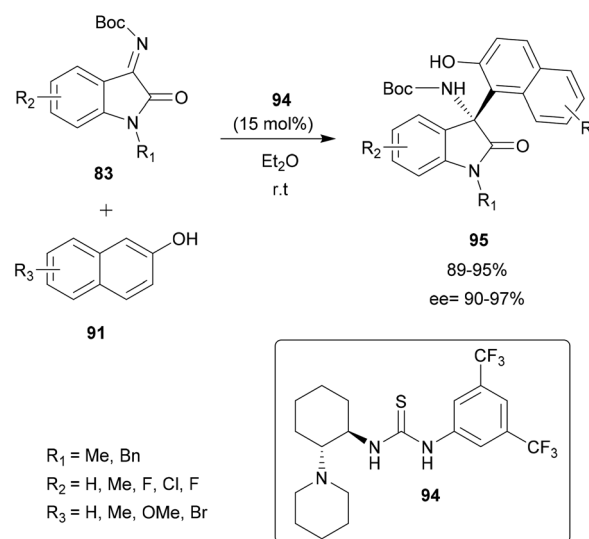
mation of hydrogen bonds between the two NH groups of the squaramide catalyst and the two nitrogen atoms of the benzothiazolimine derivative, allowing the stereo-controlled nucleophilic attack of the β -naphthol.⁸⁵

3.2.2. Takemoto-type catalysts for the catalysis of aza-FC reactions. In order to develop aza-FC reactions using new catalytic systems, Jin and co-workers described for the first time in 2021 the reaction between β -naphthols **91** and isatin-derived ketimines **83**, using a Takemoto-type catalyst **94**, an organic catalyst containing piperidine and tertiary (thio)urea-amine groups. The use of 15 mol% of this catalyst, in diethyl ether at

room temperature, gave the desired products **95** with high yields and enantioselectivities (Scheme 24).⁸⁶

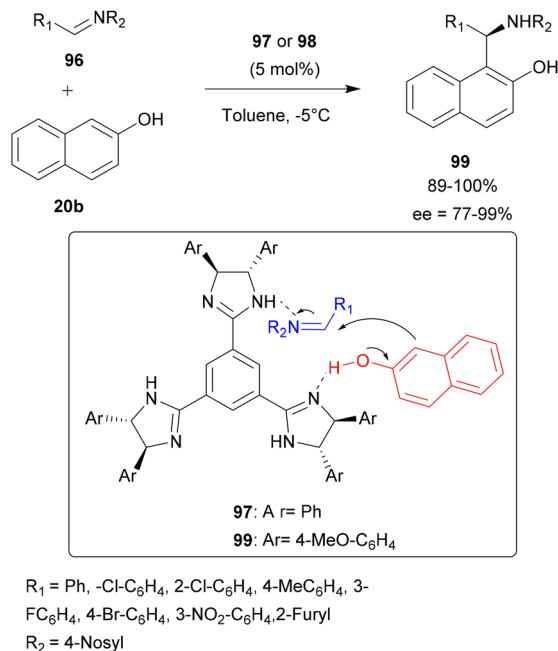
3.2.3. Chiral trisimidazoline-catalyzed aza-FC reactions. Imidazoline-derived chiral organocatalysts are known to have great potential as reaction-promoting units because of the Brønsted acidity of their corresponding salts.

Sasai and co-workers have reported the first imidazoline-mediated aza-FC type reaction between nosyl-aldimines **96** and β -naphthol **20b**. The choice of chiral trisimidazoline was related to the assumption that one imidazoline group could function as a Brønsted base interacting with the hydroxyl group of **20b**, while the other imidazoline could give its proton to the imine derivative **96** (Scheme 25). The reaction was



Scheme 24 Enantioselective aza-FC reaction of β -naphthol with ketamine using a Takemoto catalyst.





Scheme 25 Chiral trisimidazoline-catalyzed aza-FC reaction of aldimines and β -naphthol and the proposed transition state.

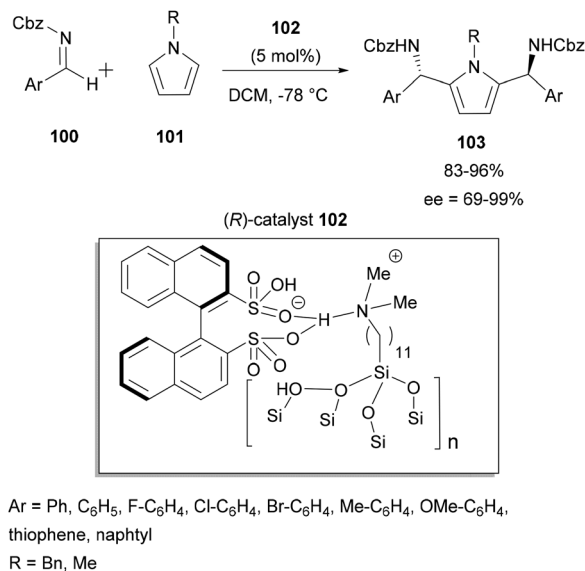
carried out in the presence of 5 mol% of chiral trisimidazoline **97** or **98** in toluene at -5°C to give sulfonamides **99** with good yields and moderate to high enantioselectivities (72 to 99%), depending on the aldimine used.⁸⁷

3.3. Solid-supported acid for aza-FC catalysis

The immobilization of both of chiral and achiral catalysts on a solid support has made significant progress in recent years and it represents an attractive approach to increase the durability of organic synthesis. This immobilization approach of chiral catalysts is increasingly important in the catalysis of asymmetric reactions.^{88–90}

In order to reduce the conformational flexibility of immobilized chiral or achiral Brønsted acid catalysts, some researchers adopted a simple adsorption of an acid molecule by an immobilized base through acid–base interactions. In most of the cases, the immobilized support adopted is silica because of its structural characteristics such as a large surface area and abundant silanol groups that allows chemical interactions and the easy adsorption of various compounds at its surface. Moreover, this type of catalyst immobilized on a solid support often has the advantage of easy removal and reuse.⁹¹

3.3.1. Silica-supported chiral phosphoric acid derivative. Because of the great utility of heterogeneous catalysts in terms of ease of recovery and reusability, a strong silica-supported ammonium (*R*)-BINsate, easily recovered and reusable, has been described by Ishihara and co-workers to catalyze an enantio- and diastereoselective aza-FC double aminoalkylation reaction of *N*-benzyl- or *N*-methylpyrroles **101** with aldimines (Scheme 26). The heterogeneous supported silica catalyst **102** was shown to have a high catalytic activity for the enantio-



Scheme 26 Enantioselective aza-FC reaction catalyzed by silica-immobilized chiral phosphoric acid.

selective FC-type double aminoalkylation of *N*-benzyl- or *N*-methylpyrrole **101** with aldimines **100**. Moreover, the catalyst could be easily recovered and reused up to three times without any reduction of catalytic activity or enantiocontrol, achieving up to 83% yield and 99% after 3 uses, while the homogenous catalyst is reactive only for a single aminoalkylation.⁹²

3.3.2. Thiourea cinchona alkaloid supported on mesoporous silica. As described in the section of organocatalytic catalysts (see part 3.2.1), alkaloids have an essential place in the enantioselective catalysis of aza-FC reactions. Because of their significance Guo and co-workers have performed an improvement of these alkaloid-based organic catalysts by immobilizing 9-thiourea *epi*-quinine on a mesoporous silica (SBA-15) by covalent linkage. The solid catalyst was thereby employed for the heterogeneous catalysis of the aza-FC reaction between indoles **17** and imines **103** (Scheme 27). The reaction carried out in ethyl acetate (EtOAc) in the presence of a small amount of catalyst (only 1 mol%) gave access to the expected products **105** with good yields and high enantioselectivity.⁹³

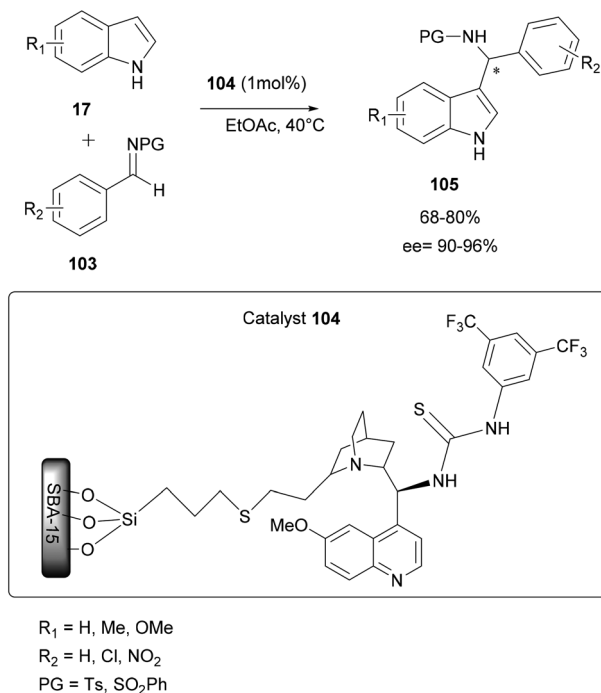
In addition, this heterogeneous catalyst **104** has the advantage of being easily removable from the reaction medium by simple filtration and it can be regenerated just by washing with an organic solvent and reused up to 4 times without any loss of enantioselectivity (ee up to 96%).

3.4. Organometallic complex catalysts for the aza Friedel–Crafts reaction

3.4.1. Palladium-based complexes. Organometallic complexes based on palladium are also used as catalysts in the enantioselective aza-FC reaction and several studies have shown their effectiveness.

In 2019, Kakino and co-workers described the aza-FC reaction of indoles with isatin-derived *N*-Cbz-ketimines **106** using





Scheme 27 Asymmetric aza-FC reaction of indoles with imines using 9-thiourea *epi*-quinine immobilized on mesoporous silica (SBA-15).

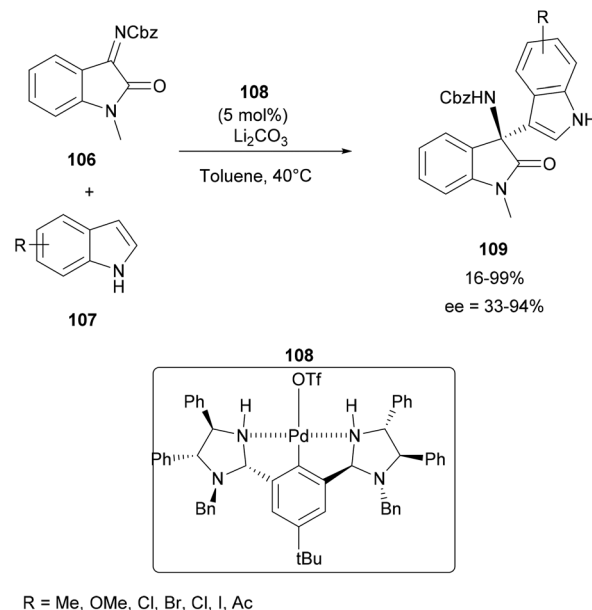
a chiral bis(imidazolidine)-containing NCN-pincer palladium catalyst **108**. In the presence of lithium carbonate in toluene at 40 °C, this asymmetric optimized synthesis pathway leads to several indolyl-amino-2-oxindoles **109**, substituted by electron-withdrawing or donating groups, with yields in the range of 16–99% and a moderate to good enantioselectivity between 33–94% (Scheme 28).^{94,95}

3.4.2. Zinc-based complexes. Zinc-based complexes have been used and described for the catalysis of the highly enantioselective aza-FC reaction.^{9,96,97}

A dinuclear zinc complex-catalyzed aza-FC (Fig. 1) was investigated by Hui and co-workers in 2010 (Fig. 1).⁹ In this study, three chiral zinc-based complexes **110**, **111** and **112** were tested with 2-naphthol and tosylimines (Scheme 29).

The reaction between *N*-tosyl-phenyl-1-imine and β -naphthol in the presence of dinuclear zinc complexes **110** or **112** led to **114** with low enantioselectivities (85% and 54% respectively). Using the complex **111**, the desired product was obtained in a good 90% yield and with high enantioselectivity (ee = 96%) in toluene at 30 °C, but only when using 1 equivalent of catalyst. This reaction is also efficient with *N*-Boc phenyl-1-imine and the corresponding aza-FC product **114** was obtained in 88% yields and 91% ee.

Then, the efficacy of catalyst **111** was evaluated using a wide variety of aliphatic or aryl-alimine substrates, possessing either electron-withdrawing or electron-donating groups. With all compounds **113**, the reaction was successful and the highest enantioselectivities (90 to 98%) were obtained with sterically hindered 4-substituted arylimines.



Scheme 28 Enantioselective aza-FC reaction catalyzed by a chiral palladium complex.

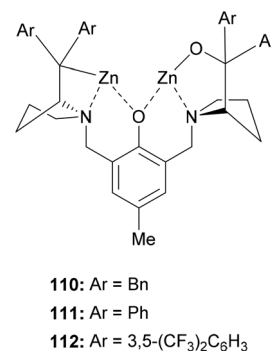
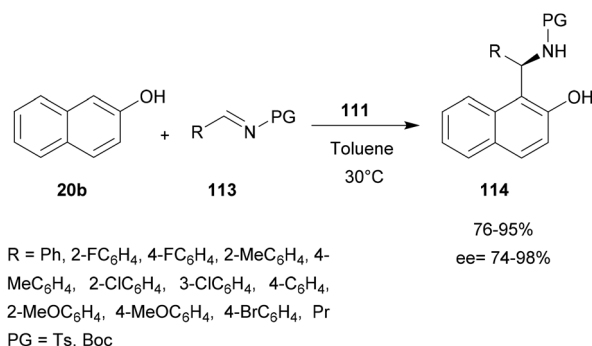


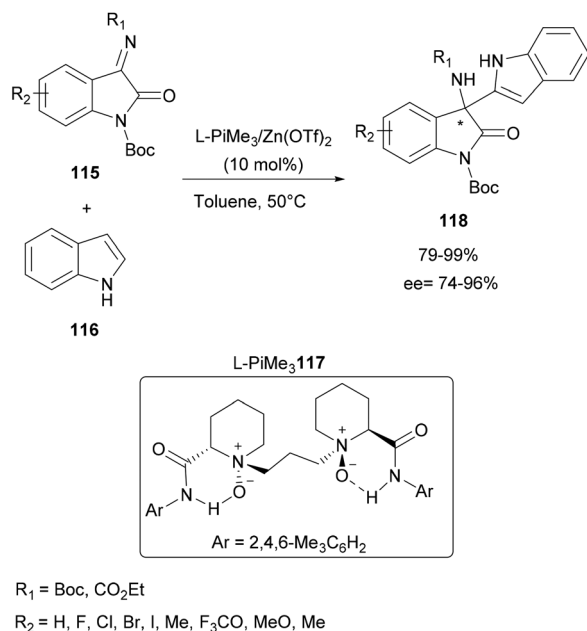
Fig. 1 Organozinc complexes developed and used for aza-FC catalysis.



Scheme 29 Zinc complex-catalyzed enantioselective aza-FC of β -naphthol and imines.

Another study using an organozinc complex has been reported by Feng and co-workers in 2016. This time, the aza-FC reaction between isatin-derived ketimines and free pro-





Scheme 30 Organozinc-catalyzed aza-FC addition of substituted isatin-derived ketimines.

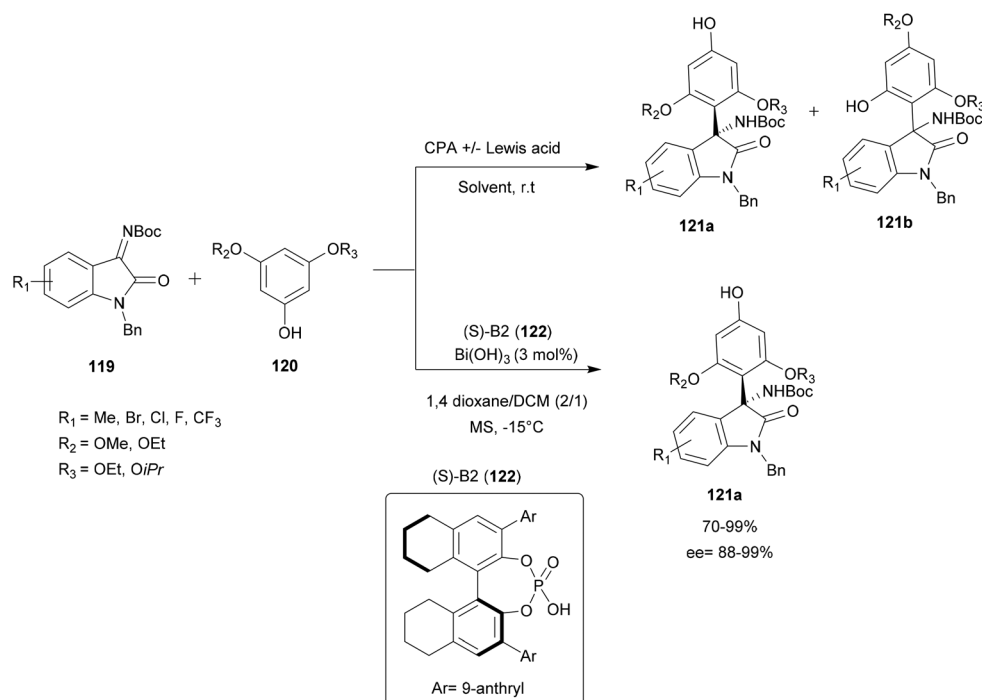
tected indoles was investigated in the presence of a N,N' -dioxides-zinc(II) complex catalytic system (Scheme 30).⁹⁷ Initially, several metals were screened to catalyze this aza-FC coupling reaction in the presence of various chiral N,N' -dioxide ligands. Complexes containing $\text{Sc}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$ and $\text{Ni}(\text{OTf})_2$ allowed obtaining of the expected products with average yields

but with low ee. Fortunately, the use of $\text{Zn}(\text{OTf})_2$ allowed good results. This study is followed by the optimization of the chiral ligand in order to improve the ee. It was found that $L\text{-PiMe}_3$ **117** improved considerably the enantioselectivity. These conditions are then retained to prepare a series of final enantiomerically enriched 3-indolyl-3-amino-oxindoles **118** containing different electron-withdrawing and electron-donating groups in up to 99% yield and 96% ee.

3.4.3. Bismuth-based catalytic complexes. The reactivity of isatin-derived ketimines was also studied with unsymmetrical electron-rich phenols. In this case, the aza-FC reaction could lead to the formation of several regioisomers, when chiral phosphoric acid (CPA) **122** was used, as depicted in Scheme 31. Attempting to improve the regioselectivity and the enantioselectivity of this reaction, Cheng's team improved the regioselectivity and enantioselectivity of the reaction by adding a Lewis acid.⁹⁸

A screening of several Lewis acids in the presence of CPA with different solvents was performed. Under most conditions tested, the improvement in regioselectivity of this reaction is not significant. However, using $\text{Bi}(\text{OH})_3/(S)\text{-B2}$ **122** catalyst, in dioxane/DCM (2/1) with 5 Å molecular sieves at -15°C , provides a series of 3-substituted functional 3-amino-2-oxindoles **121a** with good yield (up to 99%), excellent enantioselectivity (ee up to 99%) and moderate to very good regioselectivity (p/o up to 25/1) (Scheme 31).

3.4.4. Au/Pd-chiral phosphoric acid nanoparticles. A new class of chiral bifunctional heterogeneous materials composed of Au/Pd nanoparticles and chiral phosphoric acids as active orthogonal catalysts (IOC-PI/CB(Au/Pt)) **124** was prepared and described by Kobayashi and co-workers in 2017.⁹⁹



Scheme 31 Bismuth-catalyzed enantio and regioselective aza-FC of phenol and isatin-derived ketimines.



After its synthesis, this catalyst was able to catalyze a succession of one-pot reactions: aerobic oxidation reactions of benzyl alcohols **123** to the corresponding aldehyde **125**, followed by an intramolecular aza-FC reaction with *N*-aminoethylpyrroles **126**. The reaction was carried out with 4-substituted benzyl alcohols with a wide range of functional groups, such as F, Cl, CF₃, CO₂Me and CN, to provide the corresponding chiral pyrrolo-piperazines **127** in good yields and enantioselectivities (Scheme 32).

Moreover, the designed chiral heterogeneous catalyst could be recovered and reused several times without significant loss of activity or enantioselectivity.

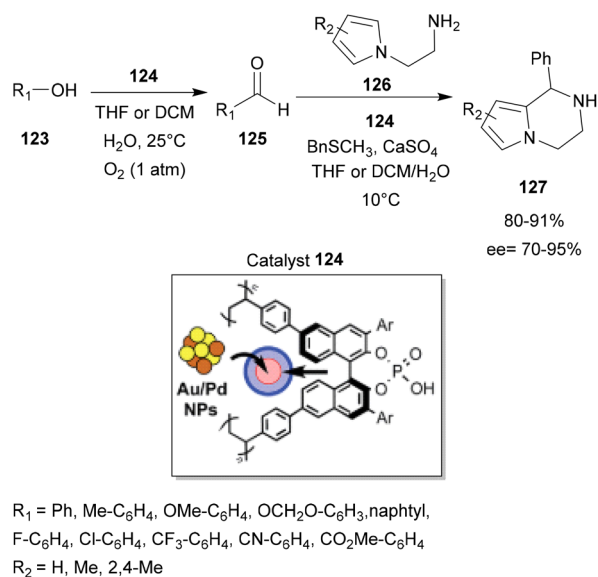
3.4.5. Copper dinuclear catalysts. In 2018, Chemlar and co-workers explored enantioselective phenol additions to alkyl aldi-

mines **131**, trying several catalytic systems to promote an efficient addition of mildly activated phenols to imine derivatives.¹⁰⁰

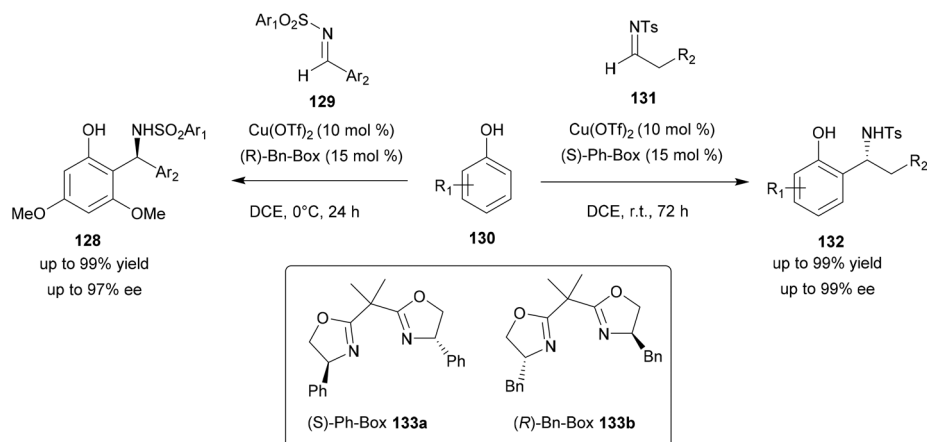
Using Cu(OTf)₂, several conditions were evaluated such as the chiral ligands as well as the solvent used. Thus, Cu(OTf)₂ associated with various chiral bis(oxazoline) ligands was screened for the reactivity and enantioselectivity. Among all tested ligands, the (*S*)-Ph-Box ligand **133a** afforded the best reactivity and enantiomeric excess. Several solvents such as DCM, dichloroethane (DCE), THF, ethyl acetate, xylene and toluene were also screened and DCE led to the best yield and enantiomeric excess. These conditions were then tested with *N*-tosyl arylimines **129** but led to poor regioselectivity and enantioselectivity. With these substrates, (*R*)-Bn-Box **133b** with Cu(OTf)₂ in DCE was found to be effective and led to compounds **128** with significant yields and ee (up to 99%) (Scheme 33). The scope of these two reactions was studied with compounds containing electron-withdrawing or electron-donating groups. In all cases, the aza-FC product was obtained in high yield and ee (>99%).

In order to generate a catalyst with eco-compatible, easily recoverable and recyclable properties while retaining its role in enantioselective catalysis, Bajaj and co-workers designed and synthesized recyclable chiral tridentate Schiff base ligands incorporating donor atoms and different (achiral and chiral) linkers (trigol, piperazine and diethyl D-(–)-tartrate).¹⁰¹ Several sources of copper were also tested and Cu(OTf)₂ was found to be the most reliable. Among all the tested copper catalysts, the dinuclear copper catalyst derived from ligand **136**, containing a chiral diphenyl amino-alcohol moiety and diethyl D-tartrate as a chiral linker was found to be the most effective catalyst for the asymmetric aza-FC reaction of tosyl aldimine **135** with 1-naphthol.

The reaction was carried out in DCM using only 2.5 mol% Cu(OTf)₂ catalyst coupled to the ligand **136** under anhydrous conditions. The conditions proved to be efficient and applicable using various substituted tosyl imines **135** and several substituted α - or β -naphthols **134**. The expected products **137** or **138** were obtained in high yields (up to 98%) and high enantioselectivity up to 99% (Scheme 34).

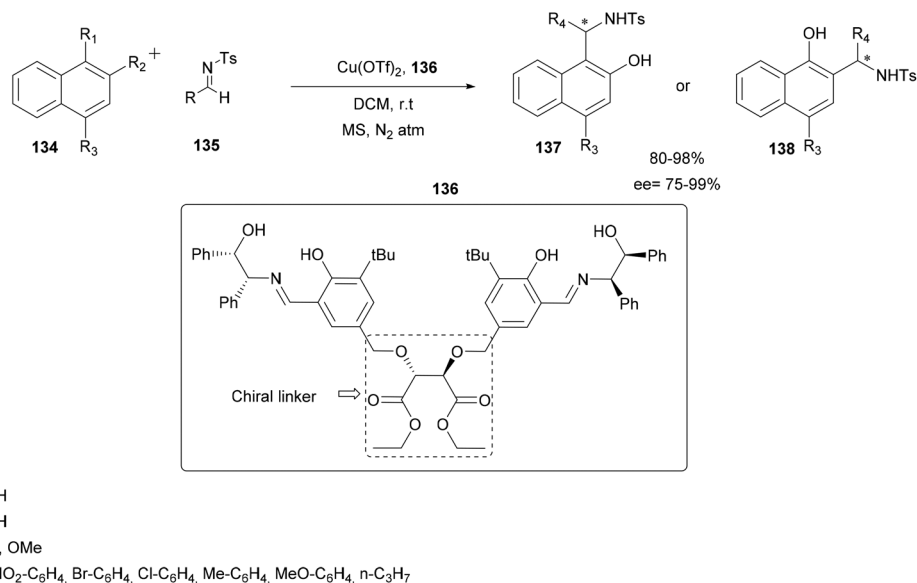


Scheme 32 Sequential aerobic oxidation of benzyl alcohol and asymmetric aza-FC reaction catalyzed by chiral bifunctional heterogeneous catalysts Au/Pd.



Scheme 33 Copper-catalyzed enantioselective aza-FC reaction.





Scheme 34 Enantioselective addition of 1- or 2-naphthol with tosyl aldimine with a dinuclear Cu(II) complex catalyst.

Usually, under homogeneous conditions, catalysts are not recyclable due to their inherent problem of solubility and thus their separation during post-catalytic processing. However, in this work, the authors recovered the catalyst according to the following process. After the first catalytic run, the amount of solvent was reduced and an excessive amount of *n*-hexane:ethyl acetate (9 : 1) was added to the reaction mixture. The catalyst precipitated out of the reaction mixture, and the unreacted substrate and product remained in the solvent supernatant, which was then removed by centrifugation. At each catalyst recycling post-treatment step, 98–99% of the initial amount of catalyst is recovered. The recovered catalyst retains its catalytic efficiency for the asymmetric aza-FC reaction of naphthols **134** with tosyl aldimines **135** without any noticeable decrease of its reactivity and enantioselectivity up to six cycles.

4. Conclusion

The rich variety of aromatic organic compounds being compatible with the aza-FC reaction has made it one of the most important C–N–C bond-forming reactions in synthetic organic chemistry, allowing the synthesis of polyfunctionalized amines.

Several Lewis acids, Brønsted acids and organic catalysts have been employed for the synthesis of achiral compounds *via* relatively affordable synthesis routes that we have reported in the first part of this review.

Despite the success of this reaction, some limitations such as the selectivity of the aza-FC-derived products could be a constraining feature. For this reason, great progress has been made in the design and the applications of new catalysts and ligands to overcome the regio- and stereoselectivity of the aza-FC reaction. A large variety of chiral catalysts have been then

developed, including binaphthyl phosphoric acids, *Cinchona*-derived catalysts, and thiourea or imidazoline compounds. The novelty of the catalyst, its suitability for applications and its potential to generate excellent selectivity are among the most attractive requirements. The influence of the architecture and the nature of the ligand on the outcome of the aza-FC was the major discussion point in this review.

Whether achiral or chiral, the aza-FC reaction is compatible with a wide variety of electron-rich aromatic groups and has a high tolerance for different substituents, such as halogens, and electron-withdrawing and electron-donating groups. This makes this reaction crucial in the synthesis of complex compounds or in the preparation of biologically relevant molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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