# **ORGANIC** CHEMISTRY







**FRONTIERS** 

**View Article Online REVIEW** View Journal | View Issue



Cite this: Org. Chem. Front., 2023, **10**, 1847

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

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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(sp<sup>2</sup>)-H bond to an imine allows access to chiral amines in a completely atom-economical way.

Received 21st December 2022. Accepted 28th February 2023 DOI: 10.1039/d2qo02018a

rsc.li/frontiers-organic

## 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

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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 sp<sup>2</sup> 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<sup>13,14</sup> 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.

## 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 bisindolyl 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<sub>9</sub>H<sub>19</sub>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).<sup>33</sup> 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

OMe 
$$R_1$$
 OMe  $R_2$  OMe  $R_1$  OMe  $R_2$  OMe  $R_3$  OMe  $R_4$  ON  $R_5$  OMe  $R_5$  OMe  $R_6$  OMe  $R_7$  OMe  $R_8$  Ome  $R$ 

R<sub>1</sub> = H, 4-OMe, 2-OMe, 3-Cl, 3-Br, 3-CF<sub>3</sub>, 4-Br, 4-F,

 $R_2 = H, Bn$ 

 $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  = H, Me

 $R_7$  = Me, OMe

R<sub>8</sub> = OH, OMe

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).<sup>34</sup> 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

TFA (10 mol%)

THF, r.t

$$R_{3}$$
 $R_{3}$ 
 $R_{4}$ 
 $R_{1}$ 
 $R_{2}$ 
 $R_{3}$ 
 $R_{3}$ 
 $R_{4}$ 
 $R_{5}$ 
 $R_{1}$ 
 $R_{2}$ 
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 $R_{1}$ 
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 $R_{3}$ 
 $R_{4}$ 
 $R_{5}$ 
 $R_{$ 

**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.<sup>35</sup>

## 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.<sup>16</sup>

**2.2.1 Titanium tetrachloride.** Titanium tetrachloride (TiCl<sub>4</sub>) 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- $\alpha$ ]pyridine **20a**, β-naphthol **20b** or *N*-methylindole **20c**, thiourea **21** and aldehydes **1** as the key step of the synthesis (Scheme 5).<sup>12</sup>

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  $\bf 20a$  as the electron-rich aromatic ring. Several Brønsted and Lewis acids were tested and  $\rm TiCl_4$  (0.1 eq.) in 1,4-dioxane or in  $\it n$ -butanol was shown to be the most efficient condition to access mono-substituted thiourea deriva-

ArH + 
$$R_1$$
 H +  $R_2$  N +  $R_2$  N +  $R_2$  N +  $R_3$  N +  $R_4$  N +

 $R_1 = C_6H_5$ , p-Br- $C_6H_4$ , o-Me- $C_6H_4$ , m-Me- $C_6H_4$ , p-Me- $C_6H_4$ , p-OMe- $C_6H_4$ , p-NO<sub>2</sub>- $C_6H_4$ , 2-furyl,  $CH_2$ ,  $(CH_3)_2CHCH_2$  $R_2$  = Me, Ph, C((S)Bn)-NHCbz

Scheme 5 TiCl<sub>4</sub>-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.<sup>37</sup>

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

Ar = 1,2,4-triOMePh, 2-naphthol, 2-methylfuran, 2-ethylfuran, 2-methylthiophene  $R_1 = C_6H_5$ , 4-CIC<sub>6</sub>H<sub>4</sub>, (CH<sub>3</sub>)<sub>2</sub>CH

 $R_2 = t-Bu$ . Bn

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. Copperbased 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)<sub>2</sub> 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 CuII system provided 30 in good yields

$$SO_2(2-Py)$$
  $Cu(OTf)_2$  (10 mol%)  $OCM$   $OCM$ 

R = p-tolyl (a), p-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> (b), 2-thienyl (c), NMe<sub>2</sub> (d)

Ar<sub>1</sub>, Ar<sub>2</sub>, Ar<sub>3</sub> = indolyl, (5-OMe)-N-methylindolyl, 2,4,6-triOMePh, 2-OMe-thiophenyl... i: if Ar<sub>2</sub> = indolyl: Ar<sub>3</sub>H, 40°C (one-pot); for other aromatic groups: Ar<sub>3</sub>H, Sc(OTf)<sub>3</sub> 10 mol%, ACN, 60°C

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 Ar<sub>2</sub> 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)<sub>3</sub> (10 mol%) in ACN at 60 °C.

This study showed that the copper catalyst system Cu(OTf)<sub>2</sub> 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.

R<sub>1</sub>= H, 3-OMe, 3,4-OCH<sub>2</sub>O, 3-CI R<sub>2</sub>= H, 2-Me, 3-Me, 4-Me, 4-OMe, 4-Ph, 4-OCF<sub>3</sub>, 4-Cl, 4-F, 4-CF<sub>3</sub>

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 heterogenous 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  $\beta$ -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,  $\alpha$ -or  $\beta$ -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. The first asymmetric aza-FC reaction catalyzed by chiral Brønsted acids was reported by Terada and coworkers in 2004 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.

$$R = \rho - MeO - C_6H_4, Me - C_6H_4, Br - C_6H_4, Cl - C_6H_4, Fr - C_6H_4, 1-naphtyl, 2-naphtyl, 2-furyl, Ph$$

$$R = \frac{42 (2 \text{ mol}\%)}{DCE, -35 °C}$$

$$R = \frac{43}{R}$$

$$R = 80 - 96\%$$

$$ee(\%) = 86 - 97\%$$

**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).<sup>59</sup> 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  $\alpha$ -ketimino esters 48 catalyzed by the same chiral silylated phosphoric acid 46, to access chiral  $\alpha$ , $\alpha$ -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  $\alpha$ -ketimino ester and indole or pyrrole derivatives.

α-amino esters (Scheme 13).<sup>60</sup> 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 coworkers described an unusual synthesis of chiral propargylimine compounds 51 using low electron starting compounds such as phenol derivatives 52.61 However, the use of electronneutral 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 3H-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-

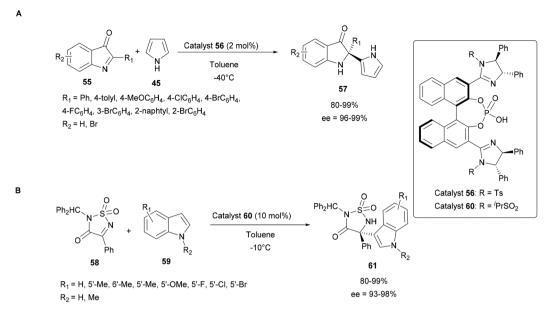
 $R_1$  = Ph, Bn, Me<sub>3</sub>Si, CF<sub>3</sub>, Me-C<sub>6</sub>H<sub>4</sub>, Ph-CH<sub>2</sub>CH<sub>2</sub> R<sub>2</sub> = F, Cl, Br, I, Ac, COPh, CO<sub>2</sub>Et, COH, morpholine

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 imidodiphosphoric acids have been extensively used by Zhang's group to catalyse a range of reactions including aza-FC reactions.65-67



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

Since 2014, this group has been working on chemo-, regioand enantioselective aza-FC reactions catalysed by H8-BINOLtype 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  $\alpha$ -phenyl substituted enamides 63 with electron-withdrawing or electrondonating 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

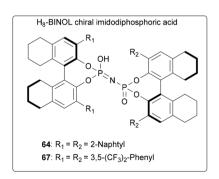
Encouraged by these successful results, the procedure was then applied to the reaction between pyrroles 45 and imines 66. During this process, a range of enantio-enriched substituted aryl-(2-pyrrolyl)methanamine scaffolds 68 were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 99% ee) using lower catalyst loadings of 0.3 mol% (Scheme 17B).67

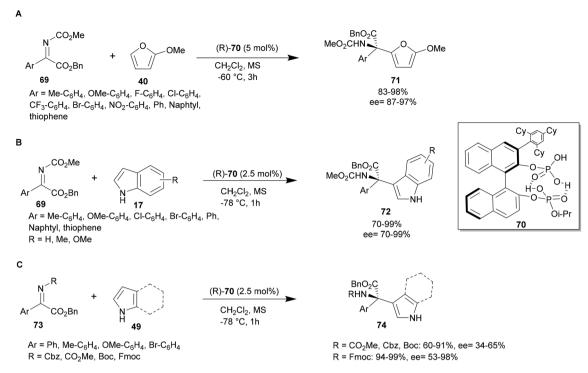
Bis(phosphoric acid) derivatives have recently been designed and reported in the literature as multiprotic acids. These catalysts containing a hydrogen bonding network are found to be important not only for the enhancement of catalytic activity, but also for the fine control of the conformation of substrates, 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)<sub>2</sub> and OP(=O)(OH)(Oi-Pr) moieties at

 $Ar = Me-C_6H_4$ ,  $OMe-C_6H_4$ ,  $F-C_6H_4$ ,  $Br-C_6H_4$ ,  $Cl-C_6H_4$ ,  $NO_2-C_6H_4$ 

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





Scheme 18 Bis(phosphoric acid)-catalyzed aza-FC type reaction of  $\alpha$ -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  $\alpha$ -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  $\alpha$ -ketimino esters. Targeted compounds 71 were obtained with excellent yields and enantioselectivity up to 99% (Scheme 18A).

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  $\pi$ - $\pi$  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. 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. <sup>75–82</sup>

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.<sup>10</sup> 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 alkaloidbased 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,**<sup>80</sup> compounds known for their attractive biological activities.<sup>83</sup> 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 (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

R<sub>1</sub> = H, OMe, CI  $R_2$  = H, EtO, *iPr*O, OMe, Br, CI, CyO, *n*Bu, AcO, O(CH<sub>2</sub>)<sub>2</sub>O

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.

R<sub>3</sub> = H, Me, Bn, allyl, MOM

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 enantioenriched 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 hvdroxv 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 benzothiazolimines 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 chiral indolyl sulfamidates.

R<sub>1</sub> = H, 4-Me, 5-Cl, 6-OMe, 6-Br, 6-Cl R<sub>2</sub> = Ph, Cl-Ph, Br-Ph, CF<sub>3</sub>-Ph, FPh, CH<sub>3</sub>-Ph, OCH3-Ph, naphtyl, thienyl, furyl, Et, Br  $R_3 = H$ , OCH<sub>3</sub>, Br

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.<sup>85</sup>

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 imidazolinemediated 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

Boc N Boc NH Boc NH Boc NH R<sub>1</sub> 
$$R_1$$
  $R_1$   $R_2$   $R_2$   $R_3$   $R_4$   $R_5$   $R_5$   $R_6$   $R_7$   $R_8$   $R_8$   $R_9$   $R_$ 

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

 $R_2 = 4$ -Nosyl

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 silicaimmobilized 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

 $R_1 = H$ , Me, OMe  $R_2 = H, CI, NO_2$ PG = Ts, SO<sub>2</sub>Ph

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 electronwithdrawing 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 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-aldimine 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.

R = Me, OMe, CI, Br, CI, I, Ac

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

Scheme 29 Zinc complex-catalyzed enantioselective  $\beta$ -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-

 $R_1 = Boc, CO_2Et$ R<sub>2</sub> = H, F, Cl, Br, I, Me, F<sub>3</sub>CO, MeO, Me

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 Sc(OTf)3, Cu(OTf)2 and Ni(OTf)2 allowed obtaining of the expected products with average yields

but with low ee. Fortunately, the use of Zn(OTf)<sub>2</sub> 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-PiMe<sub>3</sub> 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 Bi(OH)3/(S)-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, folan intramolecular aza-FC lowed by reaction N-aminoethylpyrroles 126. The reaction was carried out with 4-substituted benzyl alcohols with a wide range of functional groups, such as F, Cl, CF<sub>3</sub>, CO<sub>2</sub>Me and CN, to provide the corresponding chiral pyrrolopiperazines 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 coworkers explored enantioselective phenol additions to alkyl aldi-

 $R_1 = Ph$ ,  $Me-C_6H_4$ ,  $OMe-C_6H_4$ ,  $OCH_2O-C_6H_3$ , naphtyl, F-C<sub>6</sub>H<sub>4</sub>, Cl-C<sub>6</sub>H<sub>4</sub>, CF<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, CN-C<sub>6</sub>H<sub>4</sub>, CO<sub>2</sub>Me-C<sub>6</sub>H<sub>4</sub>  $R_2 = H$ , Me, 2,4-Me

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

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)<sub>2</sub> 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 electrondonating 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 p-(-)-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 p-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)<sub>2</sub> 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 33 Copper-catalyzed enantioselective aza-FC reaction.

R<sub>1</sub> = H, OH

 $R_2 = OH, H$ 

R<sub>3</sub> = H, CI, OMe

 $R_4 = Ph, NO_2-C_6H_4, Br-C_6H_4, Cl-C_6H_4, Me-C_6H_4, MeO-C_6H_4, n-C_3H_7$ 

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.

## 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**

This research was funded by a grant from the Agence Nationale de la Recherche (ANR-16-IDEX-0006).

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