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Catalytic C3 Aza-Alkylation of Indoles

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Aza-alkylation reaction at indole C3 position allows the introduction of a differently substituted aminomethyl group, with the formation of a new stereogenic centre. The reaction involves essentially three different partners: indole, aldehyde and an amine. The formation of the reactive iminium specie can be catalyzed by metals, Brønsted acids, Lewis acids or by organocatalysts. The stereoselective reaction is feasible with satisfactory outcomes. This review summarizes the recent (2000-2019) meaningful papers in which the in-depht study and the exploitation of this reactivity are reported.

Introduction

The indole framework is a widespread motif in several natural products (in particular alkaloids of marine, plant or mushroom origins) and pharmaceuticals, characterized by a wide range of biological properties.[1–7] Historically, the most famous members of this family were the anticancer agents vinblastine and vincristine.[8] Intriguing indole reactivity was exploited in many organic syntheses, and is based mainly on its nucleophilicity[9] rather than electrophilicity.[10] The pyrrole-like portion results more reactive than the benzene core toward electrophilic substitutions[11] where indole nitrogen is the hard reactive site and the C3 atom results the soft one. Aza-alkylation of position C3 with an imine-like specie is an attractive synthetic strategy, that allows the introduction of a differently substituted aminomethyl group, with the formation of a new stereogenic center. This reaction is often referred as aza-Friedel-Crafts and will be the topic of this review, that summarizes the meaningful 2000-2019 papers reporting this type of reactivity.

General mechanism.

Indole C3 aza-alkylation is a multicomponent reaction, that involves essentially three different partners: indole, aldehyde and an amine. Aldehyde and amine generate an imine or iminium species, that in turn react with indole. The global result is the alkylation of indole most nucleophilic position, generating a 3-indolyl methanamine. The formation of the iminium species is usually promoted by a catalyst, that could be a metal or a metal-free Lewis acid, or a Brønsted acid, or an organocatalyst.[12,13] If a chiral catalyst is employed, a control over the reaction stereochemistry could be exerted.[14]

The mechanism, depicted in Scheme 1, can occur in one-pot, through the *in-situ* generation of the iminium intermediate, or the imine could be pre-formed and isolated. The catalyst plays a fundamental role also in the stabilization of the iminium moiety and during indole alkylation at C3 position, favouring the re-aromatization process accordingly to the Friedel-Crafts model (Scheme 1).
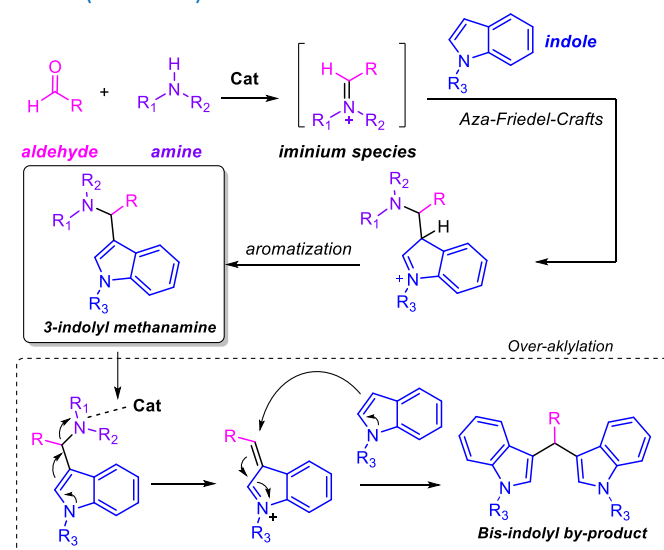
Scheme 1. General mechanism for indole C3 aza-alkylation. Here the catalyst could promote the reaction in several ways, for example favouring the imine formation or the re-aromatization step. In the dashed box, the mechanism of over-alkylation, leading to the generation of the bis-indolyl by-product is represented.

The key iminium intermediate can be also generated from the so-called imine surrogates. Imine surrogates are precursors that could be transformed into imines or iminium species under the reaction conditions. Therefore, the use of these surrogates prevents issues related to imine instability, because the reactive intermediate is generated *in situ* and immediately reacted with

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indole. Common surrogates are *N*-acylimines, convertible into *N*-acyliminium ions,[15] nitrones, aminals, hemiaminals and activated salts of quinolines and isoquinolines. Their use will be disclosed in the following paragraphs of this review.

Notably, C3 aza-alkylation results strategic for the obtainment of polycyclic compounds, in particular when occurs in an intramolecular fashion, with an amine bound on indole C2 position. In this way complex tricyclic tetrahydropyridoindole scaffolds would be easily formed.[16,17]

Nevertheless, the main drawback of indole C3 aza-alkylation concerns the formation of a bis-indolyl by-product, originated through the subsequent alkylation of another unit of indole, as reported in Scheme 1 (dashed box).[18,19] The process is particularly favoured in the presence of aromatic aldehydes and it is often necessary to carefully tune the reaction conditions to avoid this side reaction. Another general limit consists in the challenging application of this reactivity to aliphatic aldehydes, that generates unstable imines.[20]

Review outline

This review aims to give an outline of the recent (2000-2019) advances in the field of indole C3 aza-alkylation. It will be articulated taking into consideration the multitude of catalysts able to promote this kind of reactivity. In fact, metal-catalysed and metal-free-catalysed aza-Friedel-Crafts reactions will be distinguished, and for each case non– stereocontrolled and stereocontrolled methods are going to be considered. A schematic outline is displayed below.

1. Metal-catalysed C3 aza-alkylation.

   1.1. Non-stereocontrolled methods
   Metal-based Lewis acids (In, Sn, Bi, Cu, Fe, Zn, Ag, Au, Pd, Pt, Ir, Ti, Zr, Hf, Sc, Ce, Yb, Sm)
   1.2 Stereocontrolled methods.
   (Cu, Zn, Ag, V and Pd-based chiral complexes)

2. Metal-free C3 aza-alkylation.

   2.1. Non-stereocontrolled methods
   Lewis acids, Brønsted acids, organocatalysis
   2.2 Stereocontrolled methods.
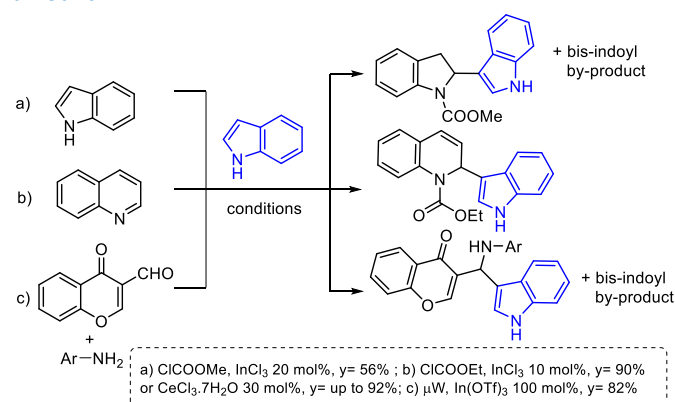   *Chiral phosphoric and sulfonic acids, thioureas, miscellaneous)*

Moreover, to facilitate the reading of this review, each of the four main paragraphs will be concluded by a summary table, reporting all the cited catalysts, the main substituents on the final product, the *ee%* and the corresponding reference number.

1) Metal catalysed C3 aza-alkylation

1.1 Non-stereocontrolled methods

Metal-based catalysis represents a common strategy to drive the C3 indole functionalization with imines or imines surrogates, through the mechanism depicted in Scheme 1. To this extent, several metal- based Lewis acids proved to efficiently promote indoles alkylation. To appreciate the plethora of possibilities, in this section selected examples will be discussed and categorised on the basis of the metal.

Metals belonging to Groups IIIA, IVA and VA of the Periodic Table. Among the metals belonging to group IIIA of the Periodic Table of Elements, indium-based Lewis acids are the most widely exploited to catalyse indoles aza-alkylation. One of the first reported examples date back to 2005. There, Jaisankar and collaborators took advantage of $InCl_3$ to promote the self-addition of indole (Scheme 2a).[18] To this extent, indole was activated with methyl chloroformate, in the presence of a catalytic amount of $InCl_3$ (10 mol%), and then reacted with another indole unit, giving a dimeric compound in which a carbon-carbon bond was formed between the C3 and C2 positions of the two indoles. However, this was only one of three compounds identified in this reaction, because the bis-indolyl by-product and 3-acetylindole were obtained as well in 25% and 10% yield, respectively. A similar activation mechanism was applied few years later to quinolines and isoquinolines. These building blocks were activated with a combination of ethyl chloroformate and $InCl_3$ and then reacted with indole, similarly to the previous example. In these cases, the desired C3 alkylated indoles were afforded in high yields and with a broad scope, considering that substituents such as halides, nitro, methyl, ethyl and cyano groups were well tolerated under reaction conditions (Scheme 2b). Moreover, the formation of the bis-indolyl by-product wasn't observed in appreciable amount.[21,22]

a) ClCOOMe, $InCl_3$ 20 mol%, y= 56% ; b) ClCOOEt, $InCl_3$ 10 mol%, y= 90% or $CeCl_3$.7H$_2$O 30 mol%, y= up to 92%; c) μW, $In(OTf)_3$ 100 mol%, y= 82%

Scheme 2. Indium-catalyzed indole alkylation with indoles, isoquinolines and chromones.

Another indium promoted the three-component-one-pot Mannich-like alkylation of indoles, as reported by Prajapati *et al.* in 2008.[23] In this case, the iminium intermediate was generated *in situ*, reacting 3-formyl chromone and an aromatic amine; then indole and one equivalent of $In(OTf)_3$ were added. The reaction mixture was stirred and irradiated by microwaves. In this way, the desired C3 alkylated indoles were obtained in a rapid, clean and easy manner, with high yields and with only a modest formation of the bis-indolyl by-product. Moreover, the catalyst could be recycled up to three times, with only a slight decreasing in activity. However, the use of sub-stoichiometric or catalytic amounts of indium-based catalysts led to lower yields (Scheme 2c).

Notably, $InCl_3$ was also exploited in a highly diastereoselective protocol, reacting indole with an imine embedding a chiral auxiliary,

as reported by Meng and co-workers. The required aldimines were generated from O-pivaloylated β-D-galactosylamine. Therefore, the desired 3-indolyl methanamines were accessed with a *dr* > 19:1 (Scheme 3).[24] It is noteworthy that the same chiral auxiliary was also exploited by Chen *et al.* In that work, after a screening of catalysts (that didn't consider InCl₃), **tin** chloride proved to be the most performing, giving the desired C3 alkylated indoles, with the best *dr* of 14:1. The minimization of the bis-indolyl by-product formation was guaranteed by the use of tetrabutylammonium iodide (TBAI) as additive, because the interaction between the metal cation and the TBAI iodine atom disfavoured the second undesired aza-alkylation of indole (Scheme 3).[25]
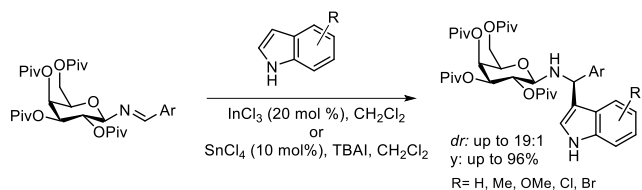
**Scheme 3.** Diastereoselective indole C3-alkylation with pivaloylated imines.

Moving to group VA of the Periodic Table of Elements, **bismuth** -based Lewis acids are worthy of mention. BiCl₃ was exploited to efficiently access a small library of antiproliferative 2,3-dihydro-2,3'-bisindoles[26] through indole dimerization, similarly to the first example reported in Scheme 2.[18] The reaction was characterised by satisfactory yields and could be promoted also by AlCl₃, even though less efficiently. The reaction worked well on indoles substituted on their C5 position with halogens such as Cl and Br and alkyl and O-alkyl groups. Electron-withdrawing groups like COOEt, CN or fluoride led to an evident drop in the yields. However, a similar catalyst (Bi(OTf)₃), failed to afford selectively 3-indolyl methanamines, in a one-pot, three-component Mannich–type reaction between aromatic or heteroaromatic aldimines and indole. In that case, the bis-indolyl by-product was the main component of the reaction mixture.[19] This suggests that a careful and *ad-hoc* screening of reaction conditions is required in every case, to identify the best set, and that is challenging to identify a general protocol applicable to a broad range of substrates.

Transition metal-based catalysts have played a vital role in modern organic and organometallic chemistry due to their inherent properties like variable oxidation state (oxidation number), complex ions formation and catalytic activity. Moreover, when used as nanoparticles, they are able to adsorb other substances on their surface and activate them in the process. Their properties found application in the C3 aza-alkylation of indoles, activating both the electrophile and the nucleophile partners.

Among them, **Copper** –based catalysts are commonly used, and several examples are reported in literature. In 2006 Carretero *et al.* described a broad-scope aza-Friedel-Crafts reaction that allowed the selective preparation of structurally diverse unsymmetrical diaryls, by reaction of indoles and *N*-sulfonyl

aldimines in the presence of Cu(OTf)ₙ/(±)- BINAP (10 mol%).[27] Interestingly, the choice of the catalyst and of the sulfonyl aldimine deeply impacted the reactivity. Thus, while CuOTf promoted the mono aza-Friedel-Crafts reaction, Cu(OTf)₂ selectively favoured the obtainment of the bis-indolyl by-product. Moreover, the employment of 2-pyridylsulfonyl imine led to mono- aza-Friedel-Crafts with both Cu(I) and Cu(II) catalysts, with good yields (70-90%); the protocol can also be applied to aliphatic imines. Electron-rich indoles proved to be very effective, affording the Friedel-Crafts addition product in good yield and as a single regioisomer; the reaction worked also on C2 substituted indoles, that are generally less reactive substrates. A similar approach was exploited by Wu *et al.* (2015), this time using aryl-*N*-Boc aminals as iminium surrogates and Cu(OTf)₂ as the best catalyst.[28] Even though the reaction time was quite long (3 days), a variety of differently substituted aminals and indoles has been used giving moderate to good yields. In particular, electron-rich aminals and indoles showed higher reactivity and gave slightly higher yields than electron-poor ones. The authors didn't mention the formation of any bis-indolyl by-product. Moreover, some attempts aimed at adapting this strategy in an asymmetric fashion were performed, by adding *i*-Pr-Pybox as chiral ligand. A 12% *ee* was appreciated, showing a potential that could be worthy of further studies.

Copper (II) triflate was the catalyst of choice also in the work by Nagarajan and Prakash. They reported a convenient synthesis of polycyclic indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7] naphthyridines *via* copper-catalysed heteroannulation.[29] The general mechanism, reported in Scheme 4a, foresaw the formation of an imine between quinoline alkynyl aldehydes and a differently substituted aniline. In this case, the catalyst played a dual role, activating the triple bond toward the 6-*endo-dig* imino-annulation and then promoting the aza-Friedel-Crafts alkylation between the obtained pyridinium salt and indole. The desired 3-indolyl methanamine was afforded with yields from moderate to excellent, with various anilines and indoles.
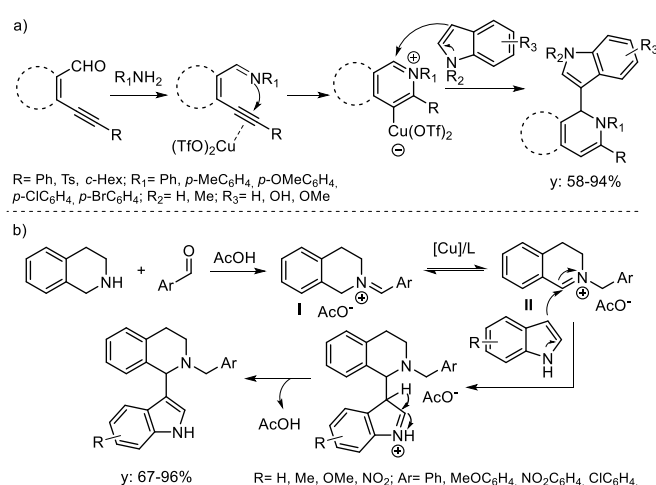
Scheme 4. Copper-catalysed C3-alkylation of indoles.

Notably, an interesting modification to the copper-catalysed indole aza-alkylation was reported two years later by Zhang et al., taking advantage of a mixture of catalysts to promote the one-step direct functionalization of tetrahydroisoquinolines.[30] The reaction mechanism (Scheme 4b) was promoted by the use of CuBr catalyst, PPh3 ligand and AcOH as co-catalysts. AcOH proved to be fundamental to favour the iminium formation between tetrahydroisoquinoline and the aldehyde. However, differently from the previously reported examples, the aza-Friedel-Crafts alkylation of indole didn't occur on iminium I, but on II, formed upon copper-promoted isomerization. The presence of PPh3 ligand was mandatory to suppress the undesired bis-alkylation. The protocol can be applied both to electron-deficient and electron-rich indoles and aldehydes, with good to excellent yields. The use of aliphatic aldehydes gave worse but acceptable results, with a yield of 65%.

Another class of widely exploited transition metal catalysts includes **iron**-based Lewis acids, that are abundant and generally cheap. An interesting example was reported by Ji et al. in 2010 and concerned the C3 alkylation of indole with tert-enamides.[31] To this extent, several iron salts were considered as catalysts, and among them, $Fe(NO_3)_3 \cdot 9H_2O$ gave the best results. TBAI was required as additive, since the reaction was performed in water. Moderate to high yields were observed even with N-methylindole, that did not react under Brønsted acid catalysed conditions. However, as justified from the reaction mechanism, this procedure is limited to tert-enamides: other N-vinyl compounds not bearing the carbonyl group did not work under the same conditions, because the coordination of the iron nucleus is mandatory in the catalytic cycle to obtain the active N-acyliminum salt (Scheme 5).
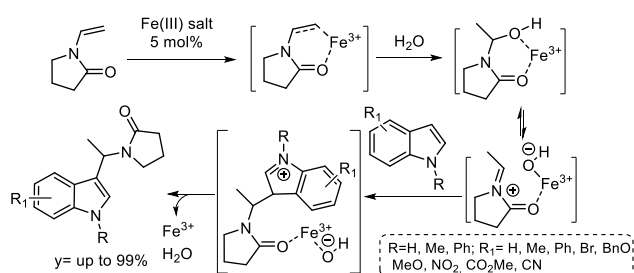
**Scheme 5.** Iron-catalysed alkylation of indoles with N-vinyl lacatms.

The same protocol was exploited one year later by Zhang et al. They screened several metal-based Lewis acids, identifying FeCl3 as the most promising. However, it is necessary to emphasise that in this work the efficient $Fe(NO_3)_3 \cdot 9H_2O$ catalyst exploited by Ji wasn't considered.[32]

Other common iron (III)-based catalysts are ferric hydrogen phosphate and ferric sulphate, as reported in the works by Gholizadeh[33] and Behbahani,[34] respectively.

In the first case a multicomponent reaction between an aromatic aldehyde, an aniline and indole, under solvent-free conditions was considered. Here, $Fe(HSO_4)_3$ proved to be the best catalyst, affording the desired indolyl 3-methanamines with good yields and high tolerability toward several substituents on the three reaction partners, and being recyclable upon 5 times. Interestingly, the use of any solvent, under the same reaction conditions, favoured the formation of the bis-indolylmethane by-product. The same multicomponent strategy, again under neat conditions, was published one year later by Behbahani et al., with similar outcomes, but using $FePO_3$ as catalyst of choice.[34]

Another group of inexpensive catalysts is constituted by **zinc**-based Lewis acids. In this field, Rawat et al. developed a nanocomposite of reduced graphene oxide and zinc oxide (RGO/ZnO) as a heterogeneous catalyst, for the synthesis of various 3-substituted indoles in water.[35] This catalytic system was applied to reactions with various indoles, aromatic aldehydes and secondary amines with excellent yields (83-92%) in short reaction times (15-30 min). Moreover, RGO/ZnO catalyst could be easily recovered from reaction mixtures and recycled at least 6 times without significant loss in catalytic activity. Zinc was also used by Li and Nakamura in 2016 in the synthesis of 2-indolyl tetrahydroquinolines, via an intramolecular hydroarylation-redox cross-dehydrogenative coupling of N-propargylanilines, exploited as unusual imine surrogates, with indoles.[36] The reaction mechanism, involving $Zn(OAc)_2$, is depicted in Scheme 6. There, the Lewis acid activated the triple bond toward the hydroarylation, giving a dihydroquinoline in equilibrium with an iminium salts, that was alkylated by indole.


R=H, Me, OMe, Cl, CO_2Et; R_1=Me, Bn, allyl; R_2= H, n-Bu, Ph; R_3= H, Me, Br, CO_2Me
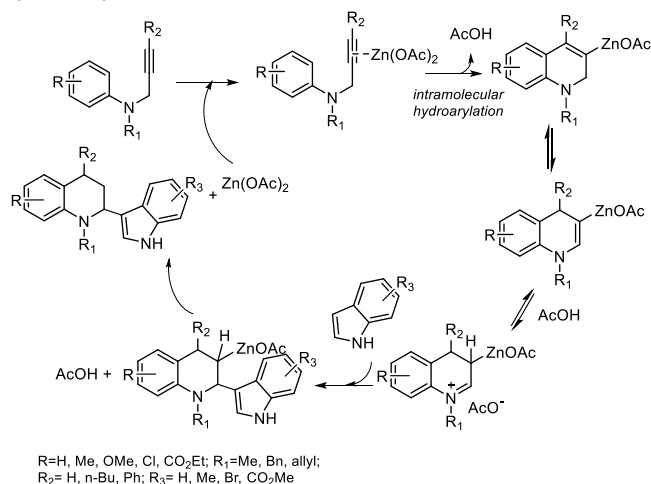
Scheme 6. Zinc-promoted intramolecular hydroarylation-redox cross-dehydrogenative coupling of N-propargylanilines

Moving to the region of the noble metals in the Periodic Table of Elements, several catalysts based on silver, gold, palladium, platinum and iridium efficiently promoted indoles aza-Friedel-Crafts reaction. For example, a **silver** based Lewis acid was exploited by Larock et al. in 2011, for the synthesis of a 105-membered library of 1-(3-indolyl)-1,2-dihydroisoquinolines, using a multicomponent reaction between variously substituted

2-(1-alkynyl)benzaldehydes, amines and indoles, catalysed by AgOTf and L-proline as co-catalyst.[37] Similarly to the previously reported work by Nagarajan and Prakash (Scheme 4a), after the formation of the imine specie, the triple bond was activated toward the cyclization, followed by the aza-Friedel-Crafts alkylation. This procedure was generally functional group-tolerant and allowed the obtainment of diversely substituted 1,2-dihydroisoquinolines in up to 98% yield. On the other hand, its major limitation concerned the detrimental effect of substituents on indole C2 position over the reactivity. A different example about silver, this time involving hetero-nanoparticles, was published in 2016 by Deka *et al.*.[38] They reported the use of bimetallic Ag@Ag$_x$Ni$_y$ core@graded-alloy-shell nanoparticles in the Mannich-type one-pot coupling of aldehydes, imines and indoles to afford C3-substituted indoles with 85-92% yield, in short reaction time (30 min) and under green conditions. The study of the mechanism suggested that the iminium formation occurred on the nanoparticle surface. Interestingly, the nanoparticles can be magnetically recycled and used up to five catalytic runs without loss in activity and in the stability of structure and morphology.

Moving to **gold**-mediated catalysis, it has been widely exploited in cascade reactions, involving indole C3 aza-alkylation as key steps, and originating complex polycyclic scaffolds, on the basis of gold ability to promote different catalytic cycles. A representative example was published in 2012 by Sridhar *et al.*, and concerns a domino intramolecular cycloisomerization/ Pictet-Spengler reaction of 2-(4-aminobut-1-yn-1-yl)anilines with aldehydes.[39] Here, the first step was the gold(I)-catalysed intramolecular hydroamination of 2-(4- aminobut-1-yn-1-yl)aniline, affording isotryptamine. The reaction occurred through the formation of a π-complex between gold and the alkyne. Then, the aldehyde was activated by Au(I) -regenerated at the end of the previous catalytic cycle- toward the formation of the iminium intermediate with isotryptamine. The catalytic cycle is concluded by the Pictect-Spengler intramolecular cyclization, accompanied by the regeneration of the active gold specie (Scheme 7).
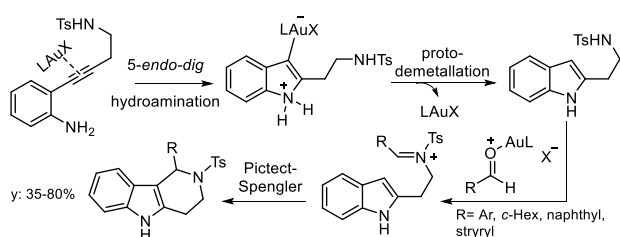
Scheme 7. Gold-catalysed hydroamination – Pictect-Spengler reaction of 2-(4- aminobut-1-yn-1-yl)aniline.

Several gold-based catalysts were able to promote this domino reaction, but the best results were obtained with a AuIPrCl (5 mol %)/AgSbF$_6$ (10 mol %) catalytic system, that guaranteed the formation of tetrahydropyrido indole derivatives in good yields. This approach worked with a wide range of aldehydes, both

aliphatic and aromatic, even though electron-rich ones reacted faster. It has been demonstrated that the role of excess AgSbF$_6$ was to facilitate the Pictet-Spengler cyclization.

A combination of a gold-based catalyst together with a co-catalyst was recently exploited by Qiao and co-workers, in a cascade process involving two catalytic cycles and taking advantage once again of alkyne activation by metal, as in some of the previously reported examples.[40] Here, the two reaction partners were isotryptamine and an alkynoic acid. The role of the first catalytic cycle was the conversion of the alkynoic acid into a cyclic intermediate, able to generate the active iminium specie upon reaction with isotryptamine. To this extent, gold coordinated the alkyne that, in turn, underwent an intramolecular *exo*-cyclization, giving a vinyl-gold intermediate. Upon proto-demetallation, an enol-lactone was formed, and reacted with isotryptamine. The obtained intermediated was the starting point of the second catalytic cycle. Here, the ketone was activated by gold, leading to an acyliminium salt that was intramolecularly alkylated by indole C3 position. Regeneration of the catalyst concluded the process (Scheme 8).
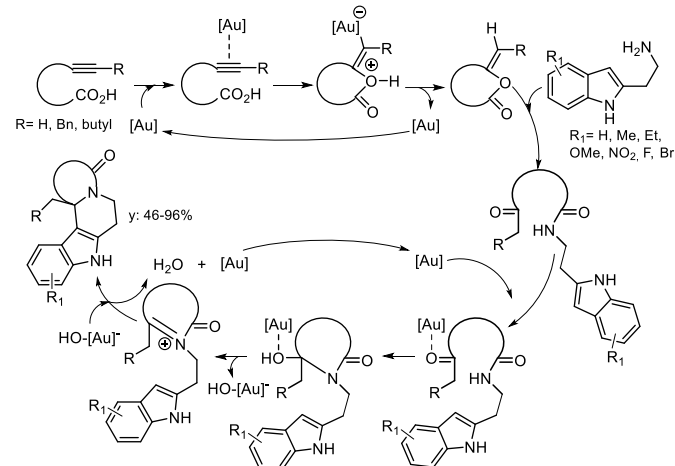
Scheme 8. Catalytic cycle for Qiao's synthesis of nitrogen-containing condensed polycycles.

Notably, both the catalytic cycles were efficiently promoted by Au(PPh$_3$)Cl. The reactivity could be tuned by the action of two co-catalysts. Thus, while trifluoroacetic acid accelerate the cascade process, silver salts such as AgBF$_4$ resulted to increase gold activity, when the reaction was performed on bulky and internal alkynes. Using this strategy, complex indole-fused scaffolds were obtained with high selectivity, broad scope and excellent yields. Interestingly from an ecologic point of view, the process worked quite well also in water as solvent.[41]

Another class of noble metal-based Lewis acids, employable in indoles C3 aza-alkylation, is constituted by **palladium** salts. These catalysts are widely diffused, due to their high tolerance toward several functional groups. In this context, Lu *et al.* developed a Pd(OAc)$_2$-catalysed tandem reaction, for the synthesis of indol-3-yl substituted 1,2-dihydroisoquinolines.[42] They fortuitously discovered that reacting *o-*

alkynylbenzaldimines with substituted indoles in the presence of this catalyst, they could obtain regioselectively the isoquinoline scaffold, substituted with an indole unit in its 1-position. The mechanism, reported in Scheme 9a, is initiated by the formation of the π-complex with the alkyne. This activation induces the cyclization by imine, that in turn is activated toward aza-alkylation by indole. The generated intermediate is converted into the final product after the protonolysis of the vinyl-palladium bond, accompanied by the Pd (II) catalyst regeneration.
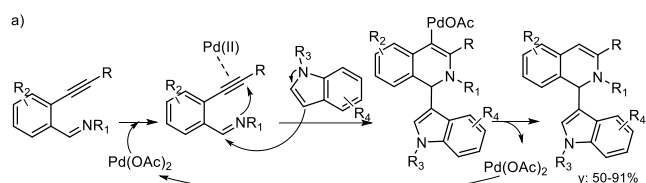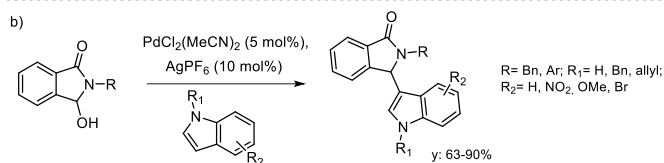

Scheme 9. a) Catalytic cycle for the obtainment of indolyl-substituted 1,2-dihydroisoquinolines, mediated by Pd(OAc)$_2$; b) PdCl$_2$(MeCN)$_2$/AgPF$_6$ catalysis with *in-situ* generated *N*-acyliminium ions reaction.

This protocol was characterized by high tolerability toward different functional groups, but lower yields resulted when the substituent of *o*-alkynylbenzaldimines was an electron-donating group and when the alkyne substituent was changed from phenyl to CH$_2$OMe.

Palladium-based Lewis acids were the catalysts of choice also in the work by Pratihar *et al.*,[43] concerning the reaction of *in-situ* generated *N*-acyliminium ions with several nucleophiles, including indoles (Scheme 9b). After an accurate screening of catalysts, the combination of PdCl$_2$(MeCN)$_2$ and AgPF$_6$ appeared to be the most promising. In fact, the vacant coordination site at Pd^{II} centre was required to bind both the electrophile and the nucleophile close together, favouring the reaction, while AgPF$_6$ was fundamental for the *in-situ* generation of active cationic specie.

To conclude the list of catalysts based on noble metals, two examples dealing with platinum and iridium respectively are going to be considered. Regarding **platinum**, Shi *et al.* reported a domino protocol for the synthesis of substituted 2,3-dihydropyrroles, based on a challenging hetero(aryl)-allenes cyclization.[44] This strategy was developed mainly on thiophenes, but could be applied also to indole, even though with moderate yield. Here PtCl$_2$ played a fundamental dual role: firstly, it is responsible of allene activation toward the

intramolecular cyclization, forming the 2,3-dihydropyrrole motif. Subsequent migration of the (hetero)arylmethylene group originated a carbene intermediate, that underwent 1,2-hydride migration. On the obtained compound, the intramolecular indole C3-aza-alkylation could take place, following either pathways a or b, as reported in Scheme 10.
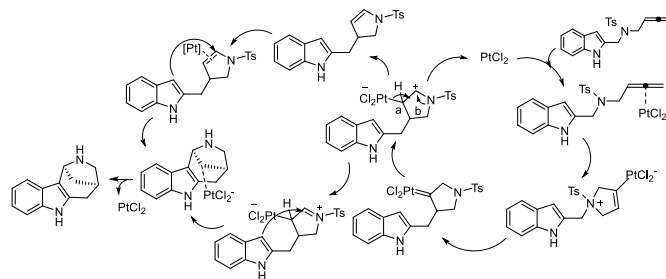

Scheme 10. Pt-catalysed domino protocol for the synthesis of substituted 2,3-dihydropyrroles.

On the other hand, Roy and co-workers exploited an *in-house* produced heterobimetallic **iridium**-tin complex [Ir(COD)(SnCl$_3$)Cl(μ-Cl)]$_2$ to catalysed the aza-Friedel-Crafts reaction of indole with preformed *N*-sulfonyl aldimines. This protocol displayed a decent tolerability towards differently substituted aromatic aldimines, but the formation of the bis-indolyl by-product was observed as well. However, acting on the reaction temperature and on the equivalents of nucleophile, this approach can be tuned, promoting the second Friedel-Crafts alkylation and generating the bis-indolyl scaffold as main product.[45]

Another group of interesting Lewis acids, exploitable for the aza-alkylation of indole C3 position, is based on the elements of group IVB of the Periodic Table of Elements, in particular titanium, zirconium and hafnium.

Moving our attention toward **titanium**-based catalysts, Bosch *et al.* reported several examples in which TiCl$_4$ was exploited to favour indoles C3 aza-alkylations, taking advantage of hexacyclic lactams as masked acyliminium salts. Considering that the imine-like partner contained two stereocenters, it behaved as a sort of chiral auxiliary. Therefore, the Friedel-Crafts alkylation on indole occurred on the less hindered face of the metal-coordinated acyl iminium ion. The reaction proceeded under mild conditions, with high yields and good stereoselectivity, and was exploited for the enantioselective synthesis of uleine alkaloids (Scheme 11a).[46,47]

In another interesting example by Gao, the tuning of the titanocene dichloride catalyst allowed a fine control over the reaction mechanism, favouring the formation of the 3-indolyl methanamine or of the bis-indolyl by-product. In particular, phenol derivatives (*e.g.* Cp$_2$TiCl(OC$_6$H$_5$)) were identified as efficient ligands to access the first product with excellent yields, while aminophenols ligands, such as Cp$_2$TiCl(OC$_6$H$_4$NH$_3^+$Cl$^-$), proved to enhance the catalyst reactivity, favouring the second alkylation, leading to the dimeric product (Scheme 11b).[48]
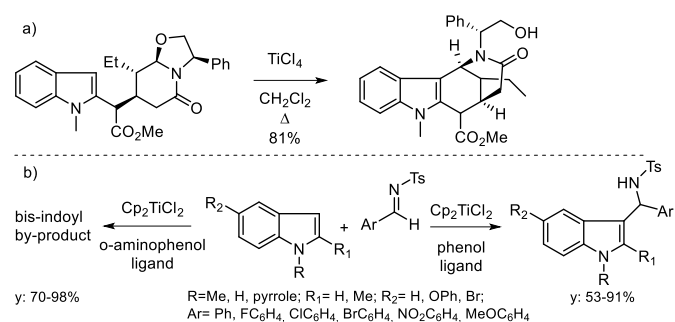
Scheme 11. a) Key step for the synthesis of uleine alkaloids. b) tuneable titanium-promoted synthesis of 3-indolyl methanamines or bis-indolyl by-product.

Environmental-friendly **zirconium**-based catalysts constitute a good alternative to the previously reported ones. A cheap zirconium oxychloride octahydrate catalyst, efficiently promoted the one-pot, three-component condensation between indoles, aromatic aldehydes, and *N*-alkylanilines, under neat conditions. Notably, the same reaction could be efficiently catalysed by $CuCl_2\cdot 2H_2O$ as well.[49] Another common zirconium-based catalyst is the so-called Schwartz reagent (Cp_2ZrHCl). It was employed to a great extent for the synthesis of α-branched amides from indole; in fact, this catalyst is able to activate nitriles and, in the presence of an acylchloride, converts them into *N*-acylimines, that could react with indole, through the reactivity mentioned in several of the previous examples.[50] The same catalyst and the same reactivity were exploited also to build the condensed polycyclic carbon skeleton of the natural alkaloid (-)-gilbertine.[51] Moreover, zirconium-based nanoparticles were used to favour the one-pot three-component synthesis of a library of multi-functionalized 2,3-disubstituted isoindolin-1-ones.[52] Here, ZrO_2 nanoparticles worked as a dual acid–base solid support, under neat conditions.
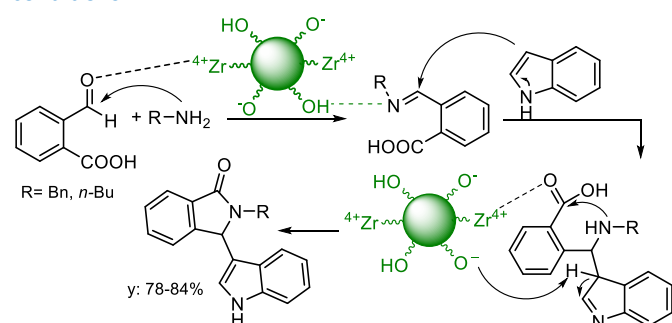

Scheme 12. Synthesis of multi-functionalized 2,3-disubstituted isoindolin-1-ones, mediated by Zr nanoparticles.

The surface of the ZrO_2 nanoparticles, which is embedded with active hydroxyl groups, oxyanions and Zr^{4+} ions, efficiently catalyses the condensation of 2- carboxybenzaldehyde, aliphatic amines and different nucleophiles, including indole. The main advantage of this procedure consisted in the possibility of recycling the catalyst. As shown in Scheme 12, the

aza-Friedel-Crafts alkylation of indole was concluded by the formation of the desired pentacyclic lactam.

In relation with the use of **hafnium**, Sakai and co-workers took advantage of $Hf(OTf)_4$ doped with Me_3SiCl for the synthesis of non-natural indolyl aminoacid derivatives.[53,54] Here, *N,O*-acetals were exploited as efficient imine surrogates. In fact, hafnium coordinated the oxygen atom, favouring the formation of the iminium species upon methoxy elimination. TMSCl trapped the methoxy ion, regenerating the hafnium catalyst. Then, the alkylation of indole occurred as usual.

Lewis acids based on the so-called **rare-earth elements** are worthy of mention, considering that in some cases they were able to efficiently promote indole C3 aza-alkylation, when more common metal-based Lewis acids failed. Interesting possibilities include **scandium**, **ytterbium, cerium** and **samarium** salts. For example, $Sc(OTf)_3$ was exploited in the aza-Friedel-Crafts reaction between donor-acceptor aminocyclopropanes and indoles.[55] When activated with two electron-withdrawing substituents, aminocyclopropanes behave essentially as unusual imine surrogates. The release of the ring strain, combined with bond polarization, generates a reactive synthon that could be attacked by nucleophiles, such as indole. A fine tuning of aminocyclopropane substituents proved to be critical to control the reaction outcome, favouring indole mono-alkylation over the formation of the undesired bis-indolyl by-product. In particular, the use of phthalimide-substituted cyclopropane-trifluoroethanol diesters guaranteed the perfect balance between reactivity and stability, favouring the selective formation of 3-indolyl methanamine. Both electron-withdrawing and electron-rich substituents on the indole partner were well tolerated, as well as *N*-protected and *N*-deprotected indoles. Notably, the obtained scaffolds could be easily converted into γ-aminobutyric acid analogues (interesting bioactive compounds), upon removal of the phthaloyl protecting group and Krapcho decarboxylation (Scheme 13).
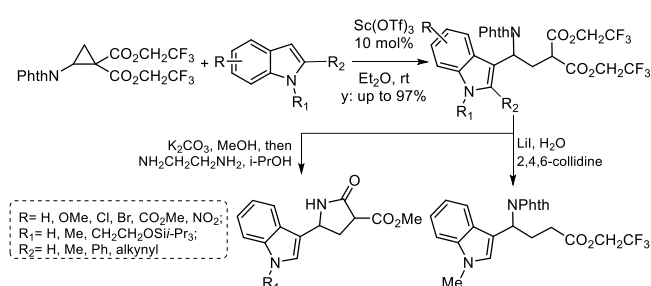
Scheme 13. Sc-catalysed Friedel-Crafts reaction of aminocyclopropanes.

Moreover, the same scandium-based catalyst was employed by Rohde, to promote the condensation of 2-substituted indole with an *O*-acetyl piperidine derivative, as key step in the total synthesis of actinophyllic acid. In this work several other cerium and iron based-catalysts were tested as well, but $Sc(OTf)_3$ prove to be the most efficient one.[56]

For what concern **lanthanides**, Yadav and co-workers, accordingly to their interest in quinolines and isoquinolines alkylation, reported a protocol based on $CeCl_3 \cdot 7H_2O$ (Scheme 2b).[57] The reaction occurred on activated N-acylated quinolines and proved to be completely regioselective. Here, cerium appeared to coordinate the carbonyl of the N-acyliminium ion, favouring the following nucleophilic attack by indole. This approach worked well on both electron-rich and electron-deficient quinolines and on differently substituted indoles. Compared with other lanthanides-based catalysts, $CeCl_3 \cdot 7H_2O$ gave better results in term of conversion and reaction times. Few years later, this protocol was modified using indium salts, as previously reported.[21] Ytterbium triflate was exploited to condense indoles with the imine generated by benzylamine and ethyl glyoxylate, in order to access unnatural tryptophan derivatives.[58] Moreover, the $Yb(OTf)_3$-SiO_2 system efficiently catalysed the one-pot, three-component synthesis of 3-substituted indoles.[59] This approach was tested on N-methyl aniline and differently substituted aromatic aldehydes; both N-protected and deprotected indoles reacted well and high yields were observed also in the presence of electron-donating and electron withdrawing substituents. Other metal-based triflates were tested, including $Ce(OTf)_3$-SiO_2 and $Cu(OTf)_2$–SiO_2, but they resulted to be less efficient than $Yb(OTf)_3$-SiO_2. Finally, in the work by Liu and collaborators, SmI_3, proved to be definitely more active than other Lewis acids such as $ZnCl_2$, $AlCl_3$ and $FeCl_3$, in promoting indoles C3 amidoalkylation.[60] Here, indoles were reacted with N-(α-benzotriazol-1-ylalkyl)amides, exploited as imine surrogates. SmI_3 (20 mol%) afforded the desired alkylated indoles with general good yields, but with some limitations. In fact, bulky substituents on indole C2 position, as well as EWG on its benzene ring, gave longer reaction times and lower yields. Moreover, R_2 must be an aryl group, or the reaction didn't proceed at all. The mechanism is depicted in Scheme 14 and involves the coordination of samarium to the benzotriazole moiety, favouring the formation of the N-acylimine that in turn reacted with indole.
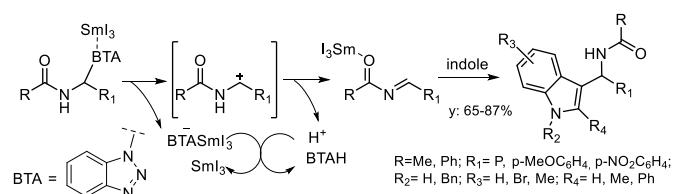
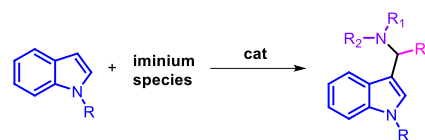**Scheme 14.** Samarium-promoted indoles C3-amidoalkylation.

A summary of the examples cited in this paragraph, including the type of catalysts, the substituents on the final product and the corresponding reference numbers, is reported in **Table 1**.

-1.2 Stereocontrolled methods

In the previous paragraph the main advances in metal-catalysed indole C3 aza-alkylation have been summarised. In this context, it's evident that the development of asymmetric version of this synthetic methodology would open the possibility of obtaining enantioenriched 3-indolyl methanamines, exploitable as key building blocks for the enantioselective synthesis of bioactive compounds.

Table 1

Catalyst	R	R_1	R_2	R_3	Ref
$InCl_3$	H, Me,Ts	Me,Ts	Ar	Styryl	[18]
$InCl_3$	H, Me	CO_2Et	Ar	Vinyl	[21,22]
$In(OTf)_3$	H	H	Ar	Vinyl	[23]
$InCl_3$	H	Alk	H	Ar, Alk	[24]
$SnCl_4$/TBAI	H	Alk	H	Ar	[25]
$BiCl_3$	H, Me	H	Ar	Styryl	[26]
$Bi(OTf)_3$	H	H	Boc	Ar	[19]
$Cu(OTf)_2$	H, Me	SO_2R	H	Ar	[27]
$Cu(OTf)_2$	Boc	Boc	H	Alk, Ar	[28]
$Cu(OTf)_2$	H, Me	Ar	Styryl[a]	Ar	[29]
CuBr	H	Ar	Alk[b]	Bn	[30]
$Fe(NO_3)_3$	H	Acyl	Alk	Alk	[31]
$FeCl_3$	H, Me, Ph	Acyl	H, Alk	Me	[32]
$Fe(HSO_4)_3$	H	Ar	Alk	Ar	[33]
$FePO_4$	H	Ar	Me	Ar	[34]
RGO/ZnO Nanop.	H	Alk, Ar	Alk	Ar	[35]
$Zn(OAc)_2$	H	Ar, Bn	Ar	Alk	[36]
AgOTf	H, Me	Ar	Styryl	Ar	[37]
$Ag@Ag_xNi_y$ Nanop.	H	Alk, Ar	H, Alk	Ar	[38]
AuIPrCl/ $AgSbF_6$	H	Ts	Alk	Alk, Ar, Styryl	[39]
$Au(PPh_3)Cl$	H	Acyl	Alky	Alk, Ar	[40, 41]
$Pd(OAc)_2$	H, Me	t-Bu, Ar	Alkenyl	Ar	[42]
$PdCl_2(MeCN)_2$/ $AgPF_6$	H, Bn, Allyl	Ar, Bn	Acyl	Ar	[43]
$PtCl_2$	Ts	Ts	Alk	Alk	[44]
Ir(III)-$SnCl_3$	H	Ts	H	Ar	[45]
$TiCl_4$	H	Acyl	Ar	Alk	[46, 47]
$CpTiCl_2$	H, Me	Ts	H	Ar	[48]
$ZrOCl_2$	H	Alk	Ar	Ar	[49]
$CpZr(H)Cl_2$/ $ZnBr_2$	H, SO_2Ph	Ac	H	Alk	[50]
$CpZr(H)Cl_2$	H	Alk	Alk	Alk	[51]
ZrO_2-NPS	H	Acyl	Bn, Alk	Ar	[52]
$Hf(OTf)_4$/ Me_3SiCl	H, Me	Alk, H	Alk, H	CN, CO_2H, COOMe	[53, 54]
$Sc(OTf)_3$	H, Me	-	Phth	Alk	[55]
$Sc(OTf)_3$	H	Boc	Alk	Alk	[56]
$CeCl_3$	H, Me, Bn	CO_2Et	Styryl	Ar	[57]
$Yb(OTf)_3$	H, Me	Bn	H	CO_2Et	[58]
$Yb(OTf)_3$ –SiO_2	H, Me	Me	Ar	Ar	[59]
SmI_3	H, Bn	Acyl	H	Ar	[60]

[a] This substitution derives from a heteroannulation that occurs on the substrate.
[b] Migration of the imine double bond during the reaction, R_2 came from the aldehyde and R_3 from the amine.

To this extent, the combined use of metal catalysts and chiral ligands could be an obvious strategy. In this way, the two reaction partners would react in a chiral environment, that would guarantee the control over the stereochemical outcome. In this section, selected interesting examples of the use of chiral organometallic complexes will be disclosed. In Figure 1 the structures of the best catalyst-ligand combinations for each cited work are reported.

Also in this field, **copper**-based catalysts are widely exploited, considering the already mentioned abundance and moderate

cost of copper salts. As chiral ligands, different options could be considered. Some common examples are binaphtyles, bis-oxazolidines and chiral amino alcohol-based Schiff bases.

One of the first enantioselective copper-promoted aza-Friedel-Crafts reaction on indoles, dates back to 1999, as reported by Johannsen.[61] He took advantage of a copper (I) salt (CuPF$_6$) and the commercially available (R)- (+)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl ligand, to originate a complex (**1** in Figure 1) able to catalyse indole alkylation with *N*-tosyliminoesters of ethyl glyoxylate. The reaction, optimised with 1 mol% catalyst loading and with a temperature between -78°C and -40°C, afforded the desired 3-indolyl methanamines in almost quantitative yield and with high enantioselectivity, that could be enhanced through a simple recrystallization, affording impressive *ee*>99%. Notably, the presence of electron-rich or electron-withdrawing substituents on indole didn't impact the enantioselectivity, but in the second situation, the temperature was raised to -20°C to increase the reaction yield.
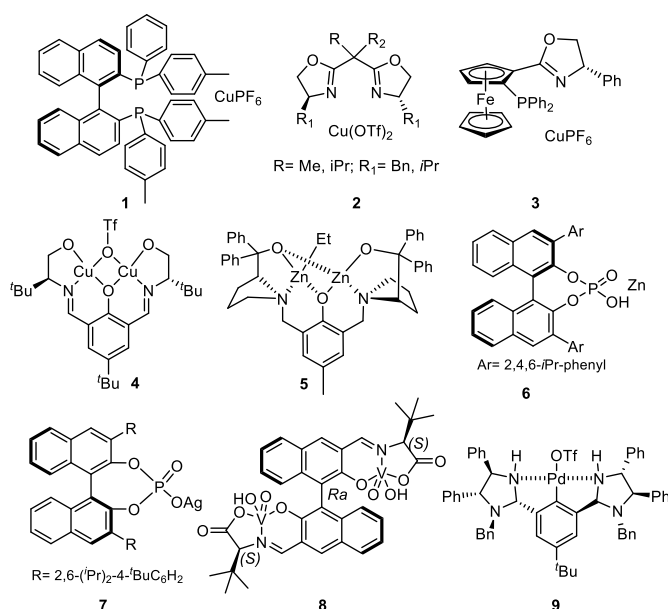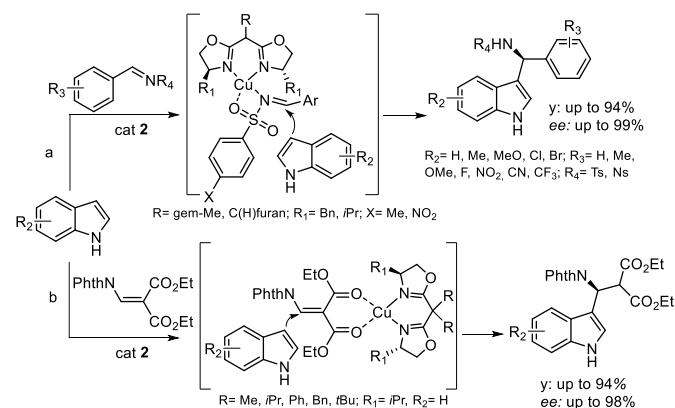
widely exploited substituents. These catalytic complexes were exploited in the works by Zhou,[62] Fu[63] and Beletskaya.[64] Zhou and Fu considered two similar catalysts to promote the reaction between indole and tosyl-protected aryl imines (Scheme 15a). They obtained C3-alkylation with high yields and enantioselectivities (up to 96%), and with only a limited formation of the bis-indolyl by-product, that could be furtherly suppressed lowering the temperature. A mandatory requirement was the presence of an electron-withdrawing group on aldimine aryl moiety. In fact, electron-donating groups led to detrimental effects over the catalytic activity, because they enhanced the electron density on the C=N bond, making it less electrophilic. On the other hand, Beletskaya employed the same kind of catalysts on phthalimidomethylene malonate, exploited as imine surrogate, to synthesise a library of β^3-tryptophan derivatives. Even in absence of the key sulfonyl moiety present in the previously reported examples, a 1,3-coordination mode was guaranteed and secured the obtainment of differently substituted 3-indolyl methanamines with *ee* up to 99% (Scheme 15b).

Figure 1. Structures of the chiral organometallic catalysts exploited to promote enantioselective aza-Friedel-Craft reaction between indoles and imines.

Scheme 15. Stereocontrolled indole C3 aza-alkylation, mediated by copper bis-oxazolines (**2**).

Other interesting chiral ligands, exploitable in combination with Cu(OTf)$_2$, are chiral bisoxazolines, that usually work on *N*-tosylated aldimines. Compared with other complexes, that secure the enantiocontrol through the formation of 1,4- or 1,5-chelating complexes, bisoxazolines-copper catalysts (**2** in Figure 1) promoted a 1,3-binding mode, in which the nitrogen atom of imine and the oxygen atom of the sulfonyl are coordinated to copper. Then, the indole alkylation occurs only on one of the two faces, guaranteeing the enantiocontrol (Scheme 15). Depending on the substituents on the chiral bisoxazoline, *ee* could be from modest to excellent: Bn and *i*-Pr that are the most

Moreover, the oxazolidine ring was one of the key motives in a different copper- Ph-Phosferrox organometallic complex (**3** in Figure 1), as reported by Deng *et al*.[65] There, a library of highly substituted tetrahydro-γ-carboline derivatives was accessed, in moderate to high yields (up to 92%), chemoselectivities (up to 94:6) and excellent levels of stereoselectivities (up to *dr*> 98:2, ee > 99% in most cases). The two reaction partners were azomethine ylides and 2-indolylnitro ethylenes, serving as novel potential dipolarophiles in the reaction mechanism (Scheme 16), that is formally an asymmetric [3+3] cycloaddition, in which the azomethine ylide is generated *in-situ* and then coordinated to the chiral complex. Then, the Michael addition occurred on 2-indolylnitroethylene *Si*-face, due to the steric effect exerted by the oxazolidine substituent and by the PPh$_2$ of the Phosferrox ligand. The obtained Zwitterionic intermediate, is stabilised at its carbanion by the adjacent nitro group. Therefore, the intramolecular Mannich [3+2] cyclization is suppressed, and the aza-Friedel-Crafts alkylation resulted as the favoured pathway. After protonation, the desired [3+3] adduct is afforded and the catalysts

regenerated. Notably, the Mannich pathway is preferential when aliphatic azomethine ylides are employed.
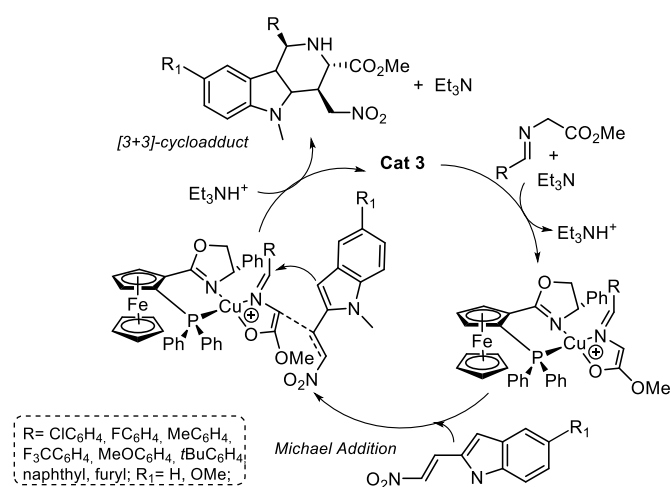
Scheme 16. Catalytic cycle for the obtainment of tetrahydro-γ-carbolines, mediated by copper- Ph-Phosferrox complex **3**.

Finally, dinuclear copper-based chiral complexes (**4** in Figure 1) were reported by Bajaj and co-workers.[66] The required chiral Shiff base ligands were easily accessed reacting aromatic bis-aldehydes with different enantiopure amino alcohols, and were exploited in combination with Cu(OTf)$_2$. This catalyst efficiently promoted the reaction between indoles and *N*-sulfonyl aldimines, with excellent yields and modest to high enantioselectivity. Electron-withdrawing substituents on position 3 and 4 of aldimine aromatic ring gave particularly good results, while electron rich groups in the same positions led to lower yields and selectivity. Indoles reacted well when substituted with both electron-donating and electron-deficient groups.

Dinuclear zinc-based chiral catalysts 5 (Figure 1), promoted aza-Friedel-Crafts indole alkylation as well. Also in these cases, 3-indolyl methanamines were afforded with excellent yields, high tolerability toward several functional groups and with good enantiomeric ratios.[67,68] The reaction mechanism (Scheme 17a) involves the coordination of indole and aldimine to the two contiguous copper or zinc atoms. In this way, the two reaction partners are bound in close proximity and surrounded by a chiral platform. After the C3 alkylation, a new molecule of indole displaces the 3-indolyl methanamines, starting another catalytic cycle. Notably, *N*-methylindoles did not react, suggesting that the free *N*–H is fundamental for the reaction mechanism.

Another possible zinc-ligand combination is based on the use of the already mentioned phosphoric acids, as envisaged for example by Moran *et al.*.[69] Here, an enantioselective multi-catalytic protocol, based on nickel and zinc-containing organometallic complexes, was developed, to react indoles with *N*-Boc allylcarbamates, exploited as iminium surrogates. The first step in this sequence was the isomerization of *N*-allylcarbamate to aliphatic imine, promoted by NiCl$_2$·dme complexed with triphos. Then, the imine underwent indole C3

aza-alkylation; this step was favoured by zinc and (*R*)-TRIP ligand (complex **6**, Figure 1). This reaction could be performed in one-pot, without isolating the imine intermediate (Scheme 17b), and gave good yields and uniformly excellent enantioselectivities, with both electron-rich and electron-withdrawing substituents on the indole partner.
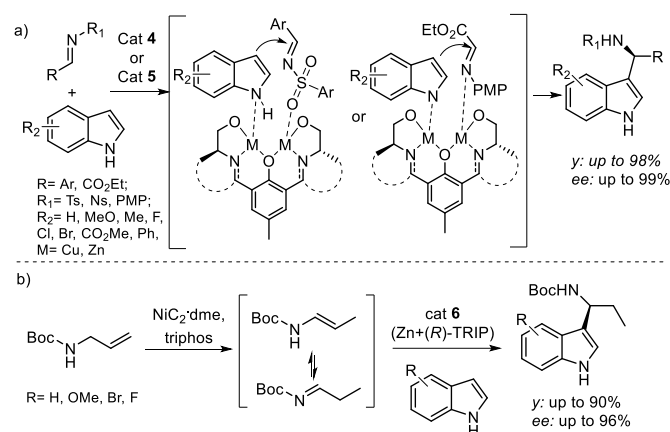

Scheme 17. a) General mechanism for indole C3-aza-alkylation mediated by chiral Schiff base-metal complexes **4** and **5**; b) One-pot functionalization of *N*-Boc allyl carbamates.

The versatility of phosphoric acids as ligands for the generation of chiral organometallic complexes was exploited again in the work by Zhang *et. al.* They developed an enantioselective version of the palladium-catalysed aza-Friedel-Crafts alkylation of o-alkynylbenzaldimines, previously reported by Lu (Scheme 9).[42] Catalysts screening allowed the identification of the best combination, that was constituted by a **silver** (I) salt and a bulky-substituted phosphoric acid as chiral counterion (**7**, Figure 1). Also in this case, a library of indol-3-yl substituted 1,2-dihydroisoquinolines was generated. The major limit of this strategy consisted in the generally modest enantiomeric excesses, improvable only when an electron-withdrawing group such as fluorine was bound on the aldimine.[70]

Furthermore, a binaphthyl unit was one of the key motives in dinuclear **vanadium** catalysts, developed by Sasai and co-workers.[71] The bulky catalyst **8**, reported in Figure 1 proved to be the most efficient in promoting the alkylation of *N*-tosyl arylimines with electron-rich nucleophiles, such as naphthols and indoles. As occurred for the other cited dinuclear organometallic catalysts, the catalytic mechanism involved the simultaneous coordination of both the reaction partners to the two metallic centres, in a chiral environment (Scheme 18). In this way, 3-indolyl methanamines were accessed with high yields and *ee* up to 91%. In particular, the best results were obtained when the aldimine was substituted with an electron-withdrawing group. Obviously, this approach worked only on deprotected indoles, because the formation of a covalent bond between its nitrogen and vanadium is a fundamental

requirement. Notably, no trace of bis-indolyl by-product was detectable.
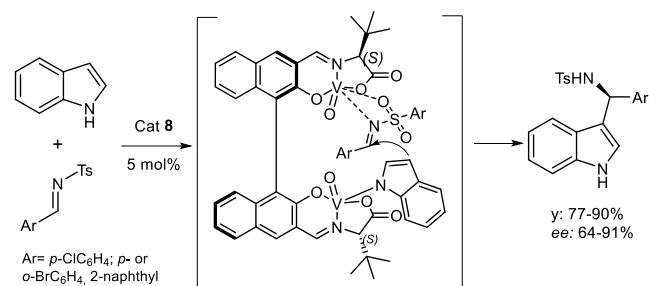
Scheme 18. Indole C3 aza-alkylation mediated by vanadium-based chiral complex **8**.

Finally, the last example that we are going to consider in this section concerns the use of a palladium-based chiral complex, that was reported by Arai and co-workers in 2016. Interestingly, this unusual approach is based on indole *N*-H activation by a chiral base, rather than Lewis or Brønsted acids.[72] Therefore, this methodology could find its optimal application in the alkylation of acid-labile substrates. The catalyst was constituted by a palladium-based imidazolidine-containing NCN-pincer complex (**9** in Figure 1) and K_2CO_3. This combination promoted the alkylation of *N*-deprotected indoles with *N*-Boc imines, generated *in situ* from *N*-Boc sulfinyl amines, to avoid instability issues. The first step in the catalytic cycle was the coordination of indole to palladium. This event was assisted by K_2CO_3 and gave *N*-H bond activation. K_2CO_3 also allowed the conversion of the *N*-Boc sulfinyl amine surrogate into the active imine, that approaches the indole on a preferential face, due to the presence of the chiral complex (Scheme 19).
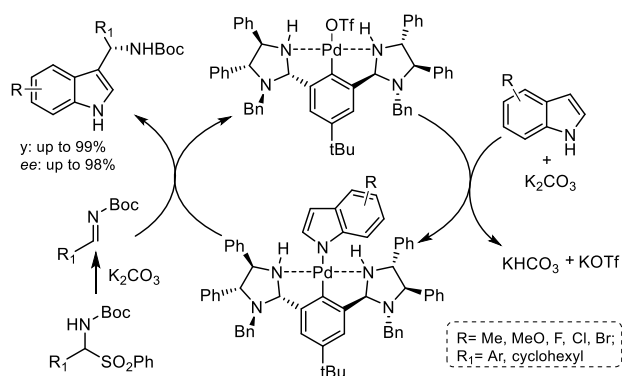
Scheme 19. Plausible mechanism for the alkylation of indoles with *N*-Boc imines, promoted by palladium complex **9**.

This approach worked well with several functionalities on both indoles and imines, giving enantiomeric excesses up to 97% even with aliphatic *N*-Boc sulfinyl amines. As in other previously discussed examples, this strategy is limited to *N*-deprotected indoles.

Before moving to the next chapter, dealing with metal-free indole C3 aza-alkylations, the examples discussed in this section are summarised in Table 2.

Table 2

Catalyst	R	R_1	R_2	R_3	ee %[a]	Ref
1	H	Ts	H	COOEt	>99	[61]
2	H	Ts, Ns, Phth	H	Ar, -CH(CO$_2$Et)$_2$	>99	[62-64]
3	H, Me, Bn, Allyl	CH$_2$-COOMe	H	Ar	>99	[65]
4	H	Ts	H	Ar	97	[66]
5	H	Ts, PMP	H	Ar, CO$_2$Et	>99	[67, 68]
6 + NiCl$_2$·dme	H	Boc	H	Alkyl	96	[69]
7	H	Ts	Alkene	Ar	89	[70]
8	H	Ts	H	Ar	91	[71]
9	H	Boc	H	Ar, Alkyl	97	[72]

[a] The best enantiomeric excess value obtained in the corresponding work, is reported.

2) Metal– free C3 aza-alkylation

The use of Brønsted and Lewis acids, as well as the exploitation of several organocatalysts, constitute a valid alternative to metal-based catalysis, in order to achieve the C3-alkylation of indoles. As main advantage, these approaches overcomes issues like metal contamination, that is quite crucial in the synthesis of bioactive products. Analogously to metal-based Lewis acids, these catalysts work activating imines and aldimines, making them more prone to the nucleophilic attack by indole. The reaction can occur one-pot, or the fundamental imine building block can be preformed; masked imine sources can be exploited as well.

In the following paragraphs, some interesting examples dealing with indoles C3 aza-alkylation promoted by metal-free Lewis acids, Brønsted acids and by organocatalysts will be disclosed, distinguishing also in this case between non-asymmetric and asymmetric methods.

2.1 Non-stereocontrolled methods
2.1.1 Lewis acids- promoted methods
In this paragraph several strategies employing metal-free Lewis acids as catalysts will be presented. This section will be mainly devoted to boranes, that are indeed the most diffused members of this class. Nevertheless, the use of other less common Lewis acids, such as iodide, silica, disulfonamides and sulfonium salts, will be disclosed at the end of the paragraph.

Boranes are strong Lewis acids, due to the presence of only six electrons in boron outer shell, that makes this atom prone to accept an additional electron pair. Among them, BF$_3$·OEt$_2$ complex is widely used, being a convenient and easy to handle source of the gaseous borane trifluoride. This Lewis acid was exploited to a great extent to promote indoles C3-aza alkylation with *N*-acyliminum ions, as reported in the works by Petersen[73],

Vorozhtsov[74] and Ryder.[75] In the first example, a library of 1,4,5-trisubstituted γ-lactams was generated through two different procedures. In the preliminary efforts, the key precursor, bearing an amide and a masked aldehyde was refluxed in the presence of BF₃·OEt₂ and indole (Scheme 20a,i.). The mechanism involved the formation of an *N*-acyliminium ion, that in turn reacted with indole, giving the desired lactam with a modest yield, improvable lowering the temperature to 20°C. Notably, the presence of an aryl substituent in the adjacent position to the reactive centre assured the formation of the racemic *trans* product. The second exploited strategy foresaw the use of acetic acid as catalyst, and will be disclosed in the next paragraph, dealing with the use of Brønsted acid.

A similar protocol was employed by Vorozhtsov, in which α-hydroxy lactams were converted into *N*-acyliminium ions upon treatment with BF₃·OEt₂ and then underwent aza-Friedel-Crafts reaction with indoles (Scheme 20a,ii.).[74] Recently, Ryder and co-workers took advantage of α-cyclopropyl *N*-acyliminium ions, analogously generated from the corresponding α-cyclopropyl hemiaminals (Scheme 20a,iii.).[75] These building blocks could react with indole, in the presence of a borane, either giving the aza-Friedel-Crafts reaction or a sequential homo-conjugate- and 1,2-addition. In both cases, the use of a chiral precursor, allowed a control over the diastereoselectivity in the formation of the new quaternary stereocenter. As supported by experimental evidences and by computational studies, the C3-aza-alkylation of indole was kinetically controlled and occurred *syn* to the alkoxy substituent through an early transition state. When the indole ring is less nucleophilic (*i.e.* in the presence of electron-withdrawing substituents), the reaction was reversible and the thermodynamically favoured homoconjugate addition afforded the spirocyclic compound.
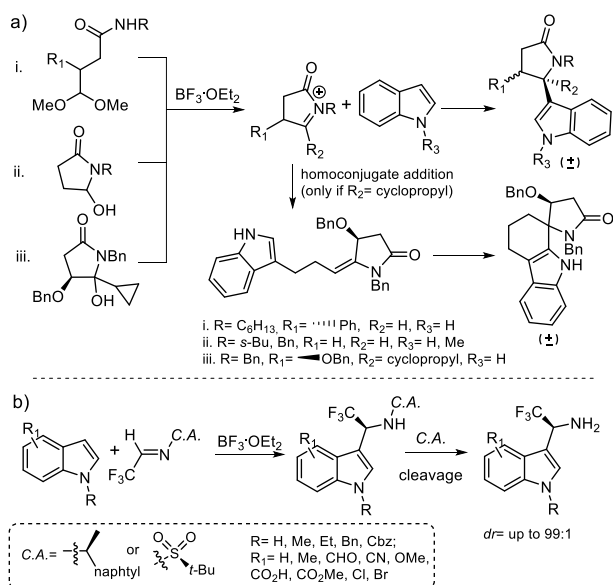
Furthermore, several research groups reported the use of boron trifluoride to achieve the functionalization of indoles C3 position with a CF₃ containing substituent, giving a scaffold containing a key motif in medicinal chemistry. This result could be obviously accessed exploiting an α-trifluoromethylimine, or its surrogates, such as hemiaminals, as published by Gong and co-workers (Scheme 20b).[76,77] It is noteworthy that this strategy was adapted in a stereoselective fashion, simply exploiting imines bearing a chiral auxiliary. The diastereoselectivity was influenced essentially by steric factors, with the higher *dr* (99:1 for the *syn* compound) accessed when a bulky imine was exploited. Interestingly, catalytic hydrogenation allowed the efficient cleavage of the chiral auxiliary. A similar approach, involving different chiral auxiliary-containing α-trifluoromethylimines (specifically (S)-*N*-tert-butylsulfinyl-3,3,3-trifluoro acetaldimine), and once again BF₃·Et₂O as catalyst, was developed by Pan and co-workers.[78] The reaction occurred well on *N*-substituted indoles, but required the use of a stoichiometric amount of catalyst to secure high yields and diastereoselectivity, because the sulfoxide oxygen in the imine partner acts as a Lewis base, neutralizing the catalytic effect. Moreover, electron rich indoles gave better results than electron-withdrawing-substituted ones, with an effected more marked when the substituent was in position 2 of the benzene ring. Also in this case, the chiral auxiliary could be cleaved, giving the free amine, without appreciable racemization.

In addition to boron trifluoride, other boranes that could be considered as catalysts are B(C₆F₅)₃ and PhBCl₂, as reported in the examples in Scheme 21.
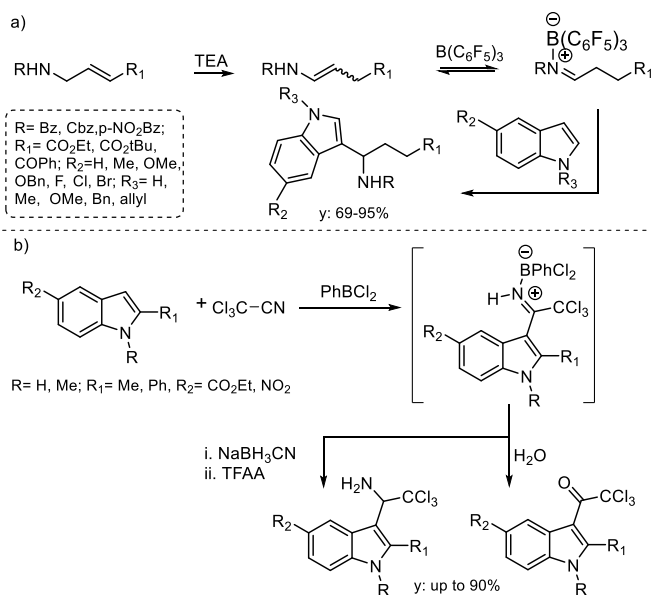
Scheme 21. Borane-promoted aza-Friedel-Crafts reaction of indoles with aminocrotonate (a) and nitriles (b).

The first was exploited in an efficient one-pot, two-steps sequential approach, aimed at accessing some biologically

Scheme 20. BF₃-promoted indole C3-aza alkylation.

attractive 8,9-dihydropyrido[1,2-a]indoles, containing the well-known GABA scaffold.[79] The tandem protocol was initiated by the triethylamine-mediated π-isomerization of a *N*-protected γ-aminocrotonate to enamine. In the presence of B(C$_6$F$_5$)$_3$, the enamine was converted into an iminium salt, that reacted with several indoles. Optimization of reaction conditions allowed the obtainment of the desired scaffold in high yields, avoiding the formation of the bis-indolyl adduct. (Scheme 21a).

PhBCl$_2$, it was exploited as catalyst of choice by Hamana *et al*., to afford C3 substituted indoles.[80] Interestingly, in this work the reaction partner was a nitrile that, upon reaction with indole, gave an iminium intermediate whose fate was decided by the reaction conditions. In fact, while hydrolysis generated 3-acylindoles, reduction in the presence of NaBH$_3$CN led to 1-(1H-indol-3-yl) alkylamines (Scheme 21b). In this context, electron-poor nitriles gave higher yields than electron-rich ones and *N*-methyl indoles behaved better than *N*-deprotected ones, affording the final product with higher yields.

Moreover, also boronic acids such as 3-chlorophenylboronic acid, could promote in a similar way the one-pot multicomponent alkylation of indole. Also in this case, the boron atom coordinates the aldehyde oxygen, favouring the formation of an iminium ion, and assists the indole nitrogen during the re-aromatization process.[12]

As already mentioned, the use of other metal-free Lewis acids as catalysts is quite rare. Some examples include iodide, disulfonamides and silica.

Iodide was exploited to favour the C3-alkylation of indole with imines generated by the reaction between aromatic aldehydes and anilines,[81] or from lactams (Scheme 22a).[82,83] In the first case, the reaction mildly occurred as a one-pot, three-component coupling, characterised by broad scope and modest to excellent yields. On the other hand, Ji *et al*. took advantage of iodine-mediated catalysis to promote indole alkylation with an acyliminium ion, generated *in situ* starting from 1-[ethoxy(4-nitrophenyl)- methyl]pyrrolidin-2-one or 1-vinylpyrrolidin-2-one and congeners. In this way, two libraries of 3-indolyl methanamines were obtained, with high yields and broad scope, considering that both electron-rich and electron-poor substituents were well tolerated on the indole partner, as well as substituents on its C2 position.

Disulfonamides and sulfonium salts have been used too. Toghraei-Semiromi and co-workers used poly(*N*-bromo-*N*-ethyl-benzene-1,3- disulfonamide) [PBBS] and *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide [TBBDA] as efficient solid phase catalysts.[84] They can be easily synthesised and recycled several times without efficacy loss. The reaction mechanism involved the generation of a Br$^+$ ion, able to promote the activation of the imines resulting from aromatic aldehydes an heteroaromatic amines, such as amino-pyridines and amino-pyrimidines. The subsequent indole alkylation occurred with high yields, tolerating several substituents on the aldehyde partner (Scheme 22b). Analogously, sulfonium salts like bromodimethylsulfonium bromide (BDMS)[85] resulted cheap and effective catalysts in multicomponent reactions aimed at

accessing substituted 3-aminoalkylated indoles. The protocol was tested with good results on differently substituted indoles, aromatic aldehydes and anilines (Scheme 22c).
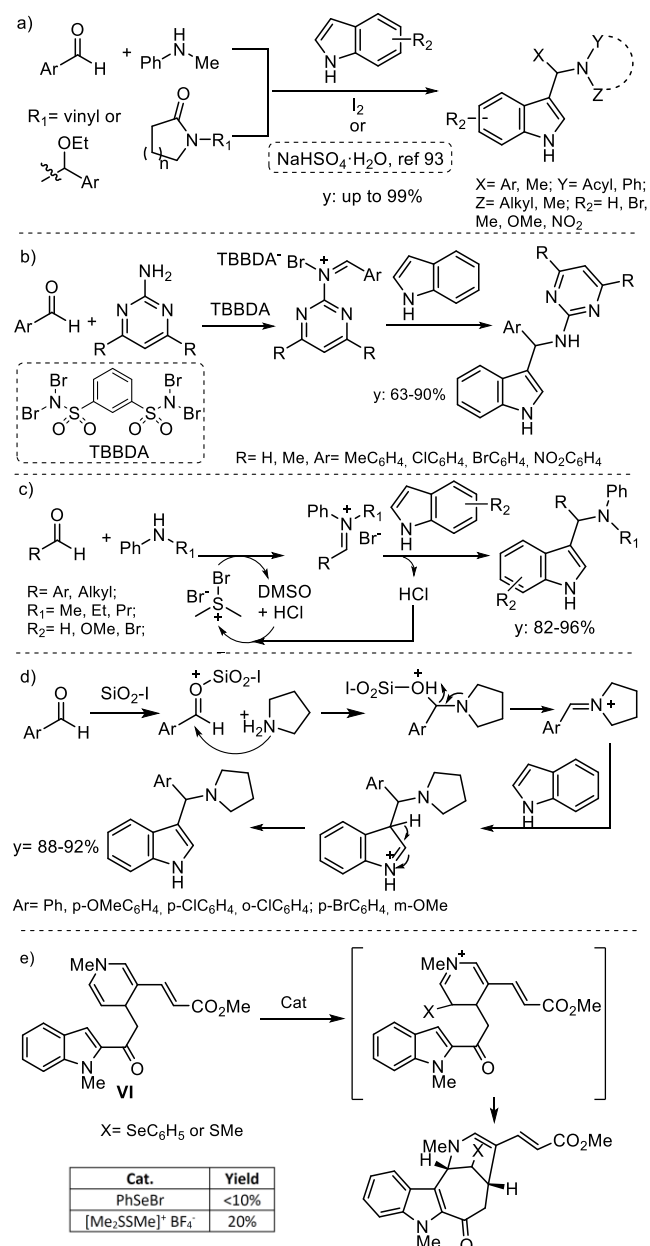
Scheme 22. Examples of indole C3 aza-alkylation, mediated by Lewis acid different from boranes, such as iodide (a), TBBDA (b), BDMS (c), SiO$_2$-I (d), [Me$_2$SSMe]$^+$BF$_4^-$ and C$_6$H$_5$SeBr (e).

Silica emerged an effective catalyst as well. Interestingly, Farooqui and Ahad exploited an innovative SiO$_2$-I system to favour the reaction between indole, pyrrolidine and a differently substituted aromatic aldehyde. Yields were high with both electronrich and electron-deficient aldehydes. Notably, under the same reaction conditions, iodide alone led to the preferential formation of the undesired bis-indolyl by-product. As other heterogeneous solid catalysts, SiO$_2$-I can be easily

recovered and reused several times without significant activity loss (Scheme 22d).[13] Moreover, silica was the catalysts of choice also in a key step of the total synthesis of an analogue of Marbostat-100, a potent anti-inflammatory and antirheumatic histone deacetylase 6 inhibitor, promoting the formation of the required tricyclic core.[86] Finally, in the pioneering work by Bosch et al., two different sulfur and selenium derivatives ([Me$_2$SSMe]$^+$BF$_4^-$ and C$_6$H$_5$SeBr) were employed to promote the cyclisation of VI, a fundamental intermediate in the total synthesis of N(a)-methylervitsine (Scheme 22e); the latter assured an higher yield. [87]

2.1.2 Brønsted acids- promoted methods

Brønsted acids are probably the most intuitive and simple catalysts to promote aza-Friedel Crafts-type alkylation of indoles.

The catalytic mechanism is based on the protonation of the aldehyde oxygen, favouring the formation of the imine intermediate. The vastness of this topic precludes the possibility to be exhaustive. Therefore, in this section different categories of Brønsted acids will be presented and few examples for each of them will be described.

Mineral acids and acidic salts. Aza-Friedel-Crafts alkylation of indoles can be catalysed by mineral acids and acidic salts. In this context, the most common acid is the HCl. A typical approach involves the use of nitrones as imine surrogate. After the aza-Friedel-Crafts reaction with indole, indolyl-N-hydroxylamines could be accessed.

R= Me, iBu, CH$_2$NHBoc, R$_1$= H, halogen
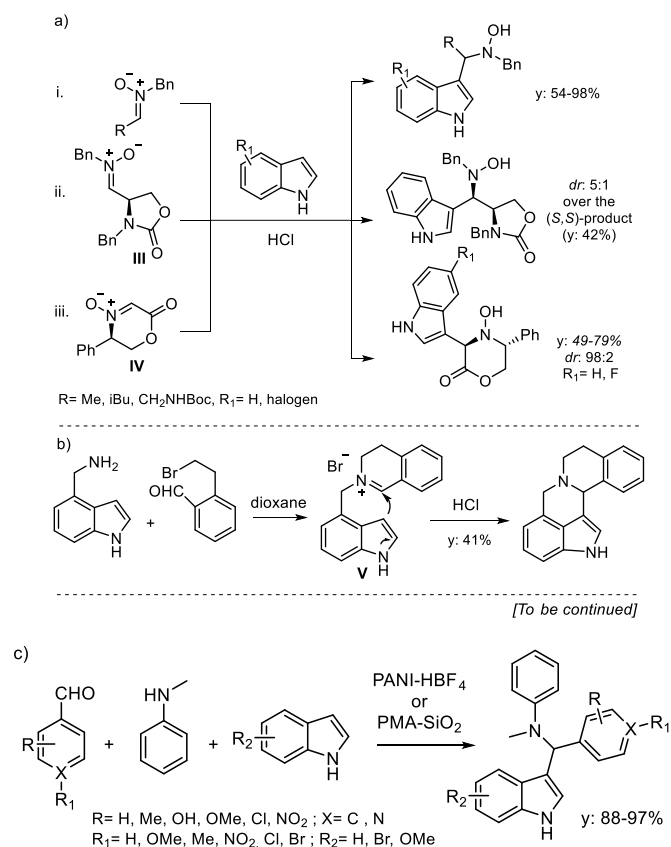
Scheme 23. Representative examples of indole C3 aza-alkylation promoted by mineral acids, such as HCl, and acidic salts.

Notably, this strategy is applicable on aliphatic nitrones, as reported by Jolivalt and collaborators, that exploited HCl catalysis to obtain a library of antibiotic co-adjuvants (Scheme 23a,i.).[88] Interestingly, the same procedure is easily adaptable in a diastereoselective fashion, simply employing a chiral nitrone, as appreciable in the works published by Denìs[89] and Pelloux-Léon.[90] In the first case, chiral nitrone III was reacted with indole in the presence of HCl. In this way, a mixture of diastereomers in 5:1 ratio was accessed (Scheme 23a,ii.). The major one was then exploited as key building block to synthesise an analogue of azaelliptitoxin. Better results in term of diastereoselectivity were secured using the chiral nitrone IV, that reacted with indole or 5-fluoroindole, giving the corresponding indolyl hydroxylamines with excellent dr > 98:2, even though with higher yield for unsubstituted indole (Scheme 23a,iii.).[90]

However, HCl-mediated catalysis can be applied also to iminium ions and not only to nitrones, as reported for example by Robaa et al..[16] There, the intramolecular aza-Friedel-Crafts reaction of iminium salt V, led to a complex pentacyclic scaffold, useful for the synthesis of some selective dopamine antagonists (Scheme 23b).

In the previously described examples, concentrated aqueous solutions of HCl were employed. However, when milder conditions are required, HCl can be generated in situ, from acetylchloride in methanol [91] or from the hydrolysis of 2,4,6-trichloro-1,3,5-triazine (TCT).[92]

An alternative to the use of mineral acids such as HCl is constituted by acidic salts. NaHSO$_4$·H$_2$O emerged as a metal-free, green, efficient and recyclable catalyst in the protocol developed by Ji, aimed at the alkylation indoles with tert-enamides with indoles, as previously described in Scheme 22a.[93]

In this project, catalysts screening was performed for the reaction between 1-vinylpyrrolidin-2-one and indole and the HSO$_4^-$ moiety resulted the most efficient counteranion. This methodology was characterized by a broad scope and could be useful for the synthesis of pharmaceutically active γ-butyrolactam analogues.

Finally, heterogeneous solid acid catalysts can be used as well, taking advantage of the possibility of an easy recovery and recycling. This is the case of phosphomolybdic acid (PMA) together with silica (SiO$_2$)[94] and of polymeric PANI (polyaniline)-HBF$_4$, that promoted the one-pot three-component synthesis of 3-indolyl methanamines. [95] Both these methodologies exploited mild reaction conditions and were characterized by a wide scope, considering that differently 5-functionalized indoles and substituted aromatic and heteroaromatic aldehydes smoothly reacted with N-methylaniline, giving the final products in high yields (Scheme 23c).

Interestingly, PMA-SiO$_2$ was the only catalyst that allowed the obtainment of the desired alkylated indoles as single products, while the use of PMA alone gave a mixture with the bis-indolyl by-product. Moreover, this protocol was efficiently applied to aliphatic aldehydes.

[To be continued]

R= H, Me, OH, OMe, Cl, NO$_2$; X= C , N
R$_1$= H, OMe, Me, NO$_2$, Cl, Br ; R$_2$= H, Br, OMe

Sulfonic acids. Several sulfonic acids are well known catalysts to achieve indoles C3 aza-alkylation. In this field, Xie and co-workers reported the efficient C3 alkylation of indoles with aliphatic imines derived from piperidine.[96] There, a depth catalyst screening revealed that this reaction could be efficiently promoted by Brønsted acids. Methanesulfonic acid proved to be the most performant, possessing the perfect acidity to protonate the imine. In fact, both stronger (CF$_3$SO$_3$H) and weaker acids (CH$_3$COOH, PhCOOH) led to lower yields. The reaction could be performed in water, using TBAI as transfer phase catalyst, and tolerated several functional groups on indole, although lower yields were observed in the presence of halogen substituents. On the other hand, the cyclic imine could be functionalised with a methyl group or with an additional condensed six-member ring, affording an isoquinoline-like motif, without impacting the reactivity (Scheme 24a). Another interesting example was published by de Almeida and involved an aza-Nazarov intramolecular cyclization on *N*-acyliminium salts with several heteroaromatic arenes, including indoles.[97] The reaction was promoted by a super-acid catalyst such as trifluoromethanesulfonic acid, that indirectly further activated the iminium salt, through the coordination on the acyl group. In this way, the acyliminium salt was destabilised and became more prone to react in the following steps, namely the intramolecular Nazarov cyclization, affording a pentacyclic scaffold (Scheme 24b).
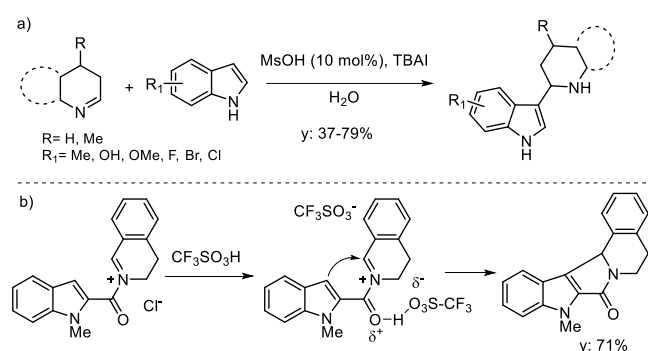

Scheme 24. Examples of sulfonic acids-mediated indole C3 aza-alkylation.

As occurred for several of the previously reported examples, the possibility of an easy recovery and recycling of the catalyst represents an undeniable advantage. Thus, is not surprising that also different supported sulfonic acids-based catalysts have been developed in the last years, including Fe$_3$O$_4$-OSO$_3$H nanoparticles[98] and cellulose-based sulfonic acid.[99] The main advantage of the first methodology is indeed the possible catalyst recovery using a magnetic stick. Notably, the use of Fe$_3$O$_4$ nanoparticles or sulfonic acids alone favoured the formation of the bis-indolyl by-product, while the use Fe$_3$O$_4$-OSO$_3$H nanoparticles guaranteed the perfect combination of a Lewis and a Brønsted acid, promoting the formation of the mono-alkylated product. This methodology allowed the one-pot reaction between indole, dimethyl aniline and differently substituted aromatic aldehydes under neat conditions, giving the C3 alkylated indole with high yields. The nanoparticles can

be recycled up to 5 times without efficacy loss. On the other hand, the cellulose-based catalyst is biodegradable, stable to air, water, and light and is easily recoverable and reusable up to four times.[99] From the first catalysts screening, cellulose-SO$_3$H emerged as the most promising to promote the one-pot, three-component reaction between indoles, *N*—alkyl anilines and aromatic aldehydes. Other metal-based and metal-free Lewis acids resulted the less efficient.

Carboxylic acids. Carboxylic acids are common Brønsted acids-based catalysts, that easily found application in indole C3 aza-alkylation. In this context, acetic and trifluoroacetic acid are the most widely employed and a high number of examples is present in literature. Here, we are going to disclose only few representative cases.
Acetic acid was exploited by Odell *et al*.[17] to synthesise a wide library of 3,4- dihydroquinazolinone-embedded polyheterocyclic scaffolds, reacting o-formyl carbamates with various amines. The reaction mechanism was based on the formation of a cyclic *N*-acyliminium ion, upon treatment of the carbamate with AcOH and microwaves. This kind of intermediate could be then reacted with several nucleophiles. Particularly good results were accessed using 4-(aminomethyl) indole (Scheme 25).
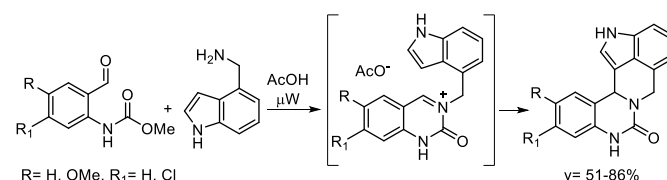
Scheme 25. AcOH-promoted synthesis of 3,4- dihydroquinazolinone-embedded polyheterocyclic scaffolds.

Acetic acid was the catalyst of choice also in the work by Gosselin and co-workers, based on the mild one-pot reaction between ethyl-glyoxylate, a primary carbamate and indole,[100] and in the already mentioned work by Petersen, were AcOH promoted the three-component, one-pot version of the reaction reported in Scheme 20a,i.[73] TFA efficiently catalysed the synthesis of polycyclic compounds such as pyrimidine-fused indolodiazocines[101] and indolyl-benzazepine,[102] as reported by Bai and Kundu, respectively. In detail, in the work by Bai, the required polycyclic scaffolds were originated from the indolyl-pyrimidine intermediate **VII**, that, in the presence of TFA, generated an iminium specie with electron-poor aromatic and aliphatic aldehydes, and then underwent aza-Friedel-Crafts alkylation of indole C3 position, originating a 8-membered ring (Scheme 26a). The same approach was exploited by Kundu: also there an amino-functionalised indole was converted into an iminium ion upon treatment with TFA and then underwent the intramolecular cyclization promote by indole C3 atom (Scheme 26b).
Furthermore, a different cascade approach, exploiting again TFA catalysis, was recently published by Wang *et al*., involving a one-pot dearomative double nucleophilic addition to quinoline or pyridine (Scheme 26c).[103] This protocol required two different catalysts. In the first step, the reaction of quinoline with a Grignard reagent,

mediated by $BF_3\cdot OEt_2$, led to quinoline (or pyridine) dearomatization, accompanied by alkylation in C4 position. The obtained enamine, upon treatment with TFA, was converted into an iminium salt, that reacted with indole through an aza-Friedel-Crafts alkylation, that occurred on quinoline C2 position. The reaction was characterised by a wide scope, considering that differently substituted N-Me indoles are well tolerated, as well as diverse Grignard reagents.
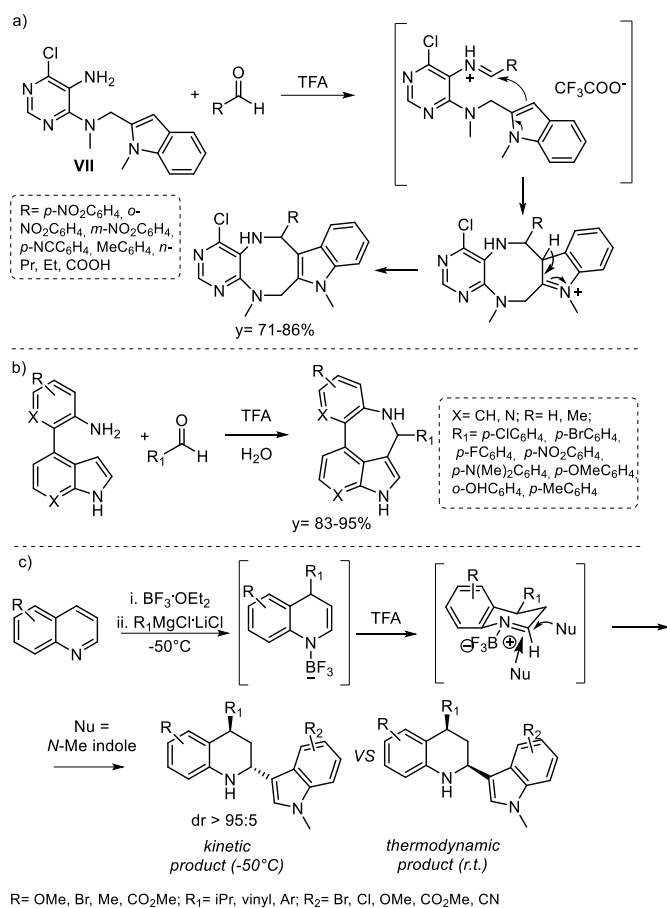
Scheme 26. TFA-promoted indole C3 aza-alkylation, leading to the formation of complex polycyclic systems.

The adoption of a chair-like transition state guaranteed a good diastereoselectivity, with the preferential *anti*-position of the two substituents, when the reaction was performed at -50°C. In contrast, at higher temperature, a mixture of diastereomers was obtained with the *syn* one as main product. Other efficient carboxylic acids catalysts include benzoic acids and long-chain aliphatic acids. For example, Xiao and collaborators realized that 3,5-dinitrobenzoic acid (DNBA) was the perfect catalyst to promote the one-pot multicomponent reaction between N-protected-2-vinyl indoles, aromatic aldehydes and p-methoxy aniline.[104] In this way a library of tetrahydro-γ-carbolines was afforded, with high yields, high tolerance of electron-rich and electron-withdrawing substituents on both aldehyde and indole reaction partners and suppressing the formation of the bis-indolyl by-product. It is noteworthy that an unprecedent chemo- and regio-selectivity switch was observed when

the protocol was applied to N-H-2-vinylindoles; in that case the formation of a tetrahydroquinoline product was appreciable, in high yield and excellent diastereoselectivity (>95:5), as the result of a formal inverse-electron-demand aza-Diels–Alder process, favoured by hydrogen bonding between DNBA and the N-H- 2-vinylindole (Scheme 27).
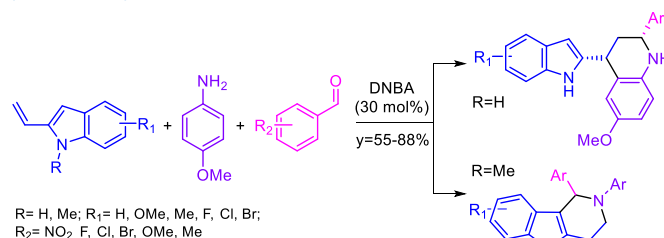

Scheme 27. DNBA-catalysed multicomponent reaction between 2-vinylindoles, anilines and aldehydes, resulting in a formal inverse-electron-demand aza-Diels–Alder reaction when R=H, or in the aza-Friedel-Crafts reaction if R=Me.

Regarding long-chain aliphatic acids, they can be considered as green-catalysts, in particular for reactions conducted in water. In the pioneering work by Shirakawa and Kobayashi (2006),[105] this class of carboxylic acids was used to favour the one-pot reaction between indoles, aromatic aldehydes and primary amines. Interestingly, acetic and trifluoroacetic acids did not show any catalytic activity, while other catalysts, such as scandium tris(dodecylsulfate) and dodecylbenzenesulfonic acid afforded the desired 3-indolyl methanamine in low yield and accompanied by the formation of the bis-indolyl by-product. In contrast, decanoic acid promoted the mono-aza-Friedel-Crafts reaction, giving the required product in high yields (up to 91%), also compared with other carboxylic acids bearing longer or shorter side chains. It's important to underline that this was one of the first cases in which the formation of the dimeric by-product was efficiently suppressed. Furthermore, to demonstrate the synthetic utility of this approach, several post-functionalizations were accessed, taking advantage of the reactivity of the C-N bond resulting from the imine formation.

Finally, among carboxylic acid catalysts, a particular mention is due to L-proline, a natural aminoacid that in the last decades was widely exploited as an efficient green organocatalyst.[106] L-proline behaves as a bifunctional catalyst, considering that it possesses two reactive chemical handles (the amine and the carboxylic acid), that can participate to the catalytic cycle. Due to its defined stereochemistry, it is usually employed to promote asymmetric reaction. Nevertheless, in this section a not-stereocontrolled example by Kumar *et al.* will be cited, because it constituted an interesting variant to the previously described reactivity between indoles and imines.[107] In this paper, L-proline catalysed the multicomponent synthesis of 3-amino alkylated indoles, through a Mannich-type reaction in solvent-free conditions. There, common Brønsted and Lewis acids were tested, but in most of the cases they induced the formation of the undesired

bis-indolyl by-product. In this case, no formation of the by-product was appreciated. Study of the reaction scope revealed that *N*-H, *N*-protected and 5-substituted indoles were tolerated, as well as differently substituted aromatic aldehydes. As amine partner, pyrrolidine and piperidine were the most widely used. Lower yields were observed only in the case of aliphatic aldehydes. The main advantage of this methodology consists in the amphoteric nature of the catalyst, that favours a slightly different mechanism: in fact, the first event of the catalytic cycle seems to be the formation of an imine between aldehyde and L- proline (stabilized by the presence of the proline carboxylic acid), rather than between aldehyde and pyrrolidine. Then, the imine is alkylated by indole, generating an intermediate susceptible of nucleophilic attack by the secondary amine, that displaces the proline, regenerating the active catalysts. The mechanism is reported in Scheme 28.
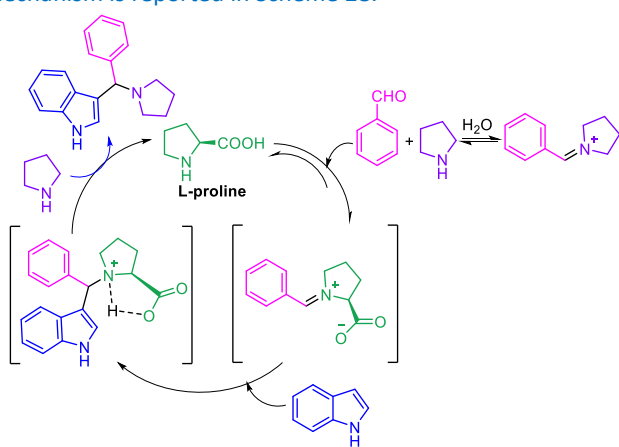
**Scheme 28.** Mechanism of the Mannich-type reaction catalysed by L- Proline.

2.1.3   *Other organocatalysts*

Following the aforementioned case of L-proline, it's clear that the synthesis of 3-amino-alkylated indoles can be promoted by a wide range of other organocatalysts. In this paragraph, few selected examples concerning their use in non-asymmetric procedures will be disclosed, to show the inspiring diversity of the catalysts that can be considered.

An interesting example involved sodium dodecyl sulfate (SDS)-promoted Mannich-like three-component reaction, as reported by Kumar and co-workers.[108] The surfactant, constituted by a hydrophobic tail and by and hydrophilic head (the SO₄⁻ groups), tends to form micelles in water. Its employment as catalyst derives by a dual action: the imine intermediate is stabilized by the micelle, while the SDS head interacts with the indole N-H through a hydrogen bond, increasing the electron density at the C3 position and favouring nucleophilic addition (Scheme 29a).

It is noteworthy that different other surfactants were tested, but all of them gave poor yields. Different 5- and *N*-substituted indoles and several aromatic and aliphatic aldehydes were well tolerated and reacted giving generally high yields (78-94%).

A similar mechanism was observed in the cases of zwitterionic molten salts, such as 4-(1-imidazolium)-butane sulfonate

(IBS),[109] and ionic liquids like [Hmim]HSO₄.[110] Both the catalysts contain an imidazolium portion, responsible of aldehyde activation toward the formation of the iminium species, while the sulfonate and the hydrogen sulphate ions activate the indole as reported in the SDS example. Both the procedures proved to be mild and efficiently afforded the desired C3 amino-alkylated indoles. IBS-mediated catalysis was applied to a wide combination of 5-substituted indoles, differently functionalized aromatic and aliphatic aldehydes and amines such as *N*-methylaniline and morpholine, affording the final products in yields >80% and without trace of the bis-indolyl by-product. In the case of [Hmim]HSO₄, several aromatic aldehydes were well tolerated (Scheme 29b).
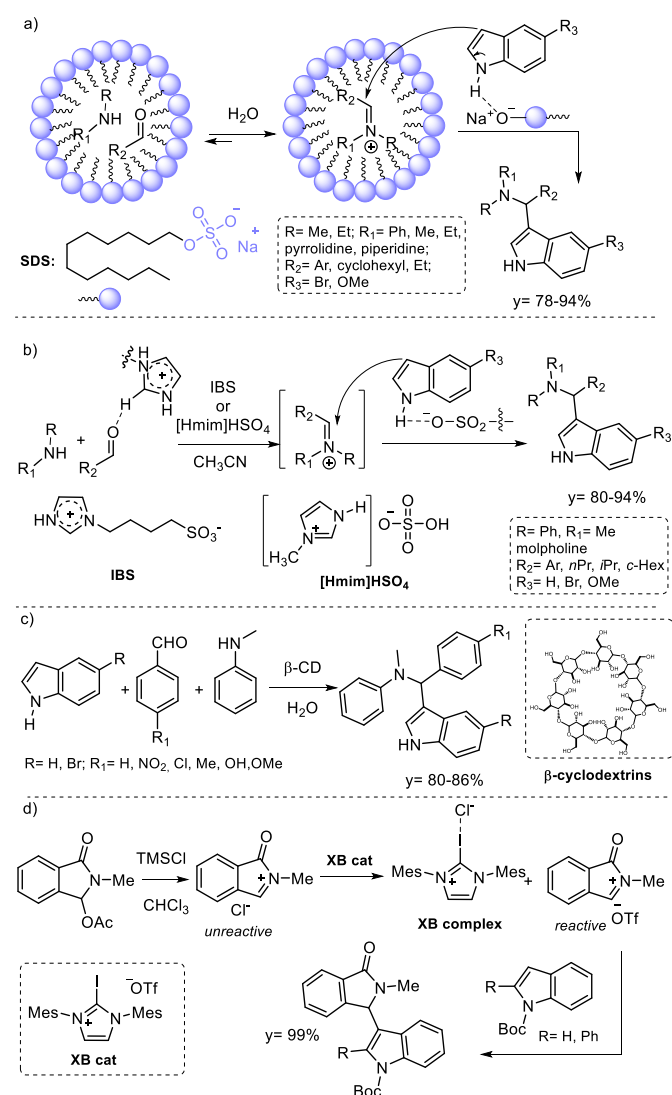
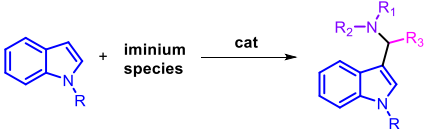**Scheme 29.** Representative examples of organocatalysed not-stereocontrolled C3-aza-alkylation of indoles.

Another class of useful organocatalysts is constituted by β-cyclodextrines, which are cyclic oligosaccharides presenting hydrophobic cavities.[111] The catalytic mechanism is based on aldehyde complexation by cyclodextrine through hydrogen bonding, favouring the formation of the iminium species with

N-methylaniline. The reaction was carried out in water and β-cyclodextrins were easily recovered and reused several times without loss in efficiency. Notably, no formation of bis-indolyl by-products was observed (scheme 29c).

A different activation mechanism takes advantage of the combination of a halogen-bond catalyst and TMSCl, exploited to favour the reaction between *in situ*-generated *N*-acyliminium salts and different nucleophiles, including *N*-Boc indole and *N*-Boc-2-phenylindole.[112] In detail, TMSCl initially converts the *N,O*-aminal into the pre-activated *N*-acyliminium chloride. Then, the halogen-bond catalyst interacts with the chloride anion, undergoing an anion metathesis and affording the highly reactive *N*-acyliminium triflate. At this point, indole C3 aza-alkylation can easily occur, affording the 3-indolyl methanamines in quantitative yield (Scheme 29d).

Examples about the employment of organocatalysis in a stereocontrolled fashion, are reported in the final chapter of this review. This section is concluded by the summarizing Table 3, reporting the examples previously disclosed.

Table 3.

Catalyst	R	R$_1$	R$_2$	R$_3$	Ref
BF$_3$·Et$_2$O	H, Me	Alk, Bn	Acyl	Alk	[73-75]
BF$_3$·Et$_2$O	H	H	H	CF$_3$	[76]
BF$_3$·Et$_2$O	H	H	Alk	CF$_3$	[77]
BF$_3$·Et$_2$O	Me	H	SO*t*Bu	CF$_3$	[78]
B(C$_6$F$_5$)$_3$	H, Alk	H	Bz, Cbz	Alk	[79]
PhBCl$_2$	H, Me	H	COCF$_3$	CCl$_3$	[80]
Boronic acid	H	Ar	H	Ar	[12]
I$_2$	H	Ar	Me	Ar	[81]
I$_2$	H, Me	Alk	Acyl	Me	[82]
I$_2$	H	Alk	Acyl	Ar	[83]
TBBDA/ PBBS	H	H	Ar	Ar	[84]
BDMS	H	Alk	Ar	Ar	[85]
SiO$_2$	Alk	H	Alk	Acyl	[86]
SiO$_2$-I	H	Alk	Alk	Ar	[13]
HCl	H	Bn	OH	Alk	[87]
HCl or AcCl/MeOH	H	Bn	OH	Alk	[88]
HCl	H	Alk	OH	Acyl	[89]
HCl	H	Alk	Alk	Ar	[16]
AcCl/MeOH	H	Alk	OH	Alk	[90]
TCT	H	Alk	Ar	Ar	[91]
DMTSF/ C$_6$H$_5$SeBr	Me	Alk	Vinyl	Alk	[92]
NaHSO$_4$·H$_2$O	H	Alk	Acyl	Me	[93]
PMA–SiO$_2$	H, Me	Ar	Me	Ar, Alk	[94]
PANI-HBF$_4$	H	Ar	Me	Ar	[95]
CH$_3$SO$_3$H	H, Me	Alk	H	Ar, Alk	[96]
CF$_3$SO$_3$H	Me	Acyl	Alk	Ar	[97]
Fe$_3$O$_4$–OSO$_3$H	H	Ar	Me	Ar	[98]
Cellulose-SO$_3$H	H, Me	Alk	Ar	Ar	[99]
AcOH	H	Alk	Acyl	Ar	[17]
AcOH/AcCl	H, Me	Cbz	H	COOEt	[100]
AcOH	H, Me	Alk	Acyl	Bn	[73]
TFA	Me	Ar	H	Ar, Alk	[101]
TFA	H	Ar	H	Ar	[102]
TFA	H, Me	Ar	H	Alk	[103]
DNBA	Bn	Ar	Alk	Ar	[104]
C$_9$H$_{19}$COOH	H, Me, Et	Ar	Ar	Ar	[105]
L-proline	H	Alk	Alk	Ar	[107]
SDS	H, Me, Bn	Alk, Ar	Alk	Ar, Alk	[108]
IBS	H	Alk, Ar	Alk	Ar, Alk	[109]
[Hmim]HSO$_4$	H	Ar	Me	Ar	[110]
β-CD	H	Ar	Me	Ar	[111]
XB-catalyst	Boc	Acyl	Me	Ar	[112]

-2.2. Stereocontrolled methods

The benefit of using a metal-free catalyst, shown in the previous section, has brought as an obvious consequence the development of the enantioselective version of the metal-free aza-Friedel-Crafts alkylation of indoles. In the next paragraphs some examples dealing with the use of chiral organocatalysts are displayed: here, chiral Brønsted acids, in particular phosphoric acids, are the most represented class, followed by thioureas.

Chiral phosphoric acids and phosphorylimides.

10a R = 1-naphthyl
(S)-10b R = SiPh$_3$
(S)-10c R = 9-phenanthryl

10d R = 3,5 diPh-C$_6$H$_3$
10e R = 9-anthracenyl
(R)-10c R = 9-phenanthryl
(R)-10b R = SiPh$_3$
10f R = 2,4,6 tri-i-Pr-C$_6$H$_2$

11 R = 3,5-di-CF$_3$-C$_6$H$_3$

12 R = 1-naphthyl

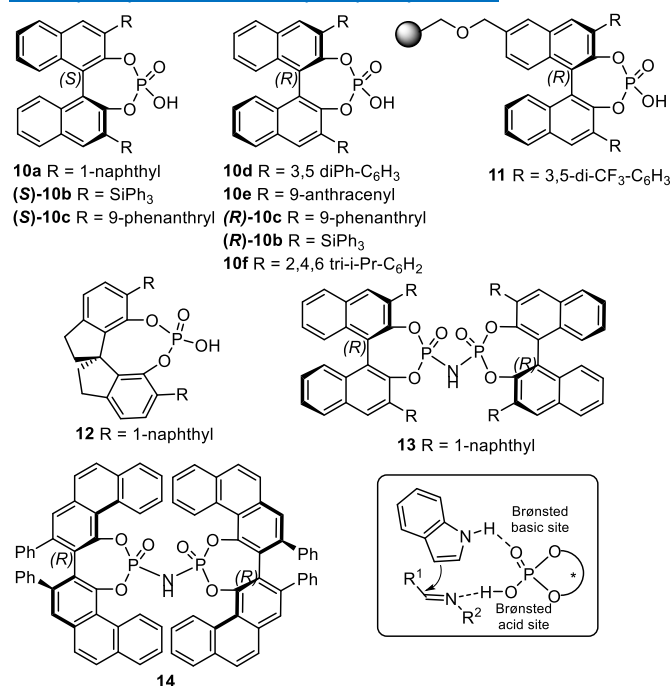**13** R = 1-naphthyl

14

Figure 2. Structure of the chiral phosphoric acids cited in this paragraph and the coordination mechanism (in the box).

As already mentioned, chiral phosphoric acids play a key role in asymmetric organocatalysis, due to their availability and versatility in promoting several organic transformations.[113,114] The catalytic activity depends on the simultaneous presence of an acid and a basic Brønsted sites, that allows the dual coordination of an electrophile and a nucleophile moiety. The presence of a cyclic structure, as well as of bulky, chiral substituents, restricts the possible catalyst conformations and generates a chiral environment in which the transformation could occur in an enantioselective fashion. In Figure 2, the chiral phosphoric acids cited in this paragraph can be appreciated, together with a schematic representation of the binding mode in indoles C3 aza-alkylation, involving the simultaneous interaction with the imine and the indole, by hydrogen bonding (box in Figure 2).[115] As consequence, in almost all the described

reactions a free *N*-H indole is fundamental to secure high enantioselectivity.

In this field, axially chiral biaryls such as BINOL derivatives, are the most widely exploited catalysts. Several of them were designed by varying the bulky substituents at the 3- and 3'-positions of the binaphthyl scaffold, to optimize the final enantiomeric excess. Some representative cases will be disclosed below, starting with the work by You *et al.* (Scheme 30a).[116] There, the naphthyl-functionalised catalyst (**10a** in Figure 2) effectively promoted the reaction between indoles and *N*-Ts or *N*-Bs aromatic imines, giving high yields and enantiomeric excesses (*ee*=94% and >99% respectively, in the best conditions set). The main limitation of this approach consisted in the lower *ee* observed when *N*-Ts alkyl imine were employed.
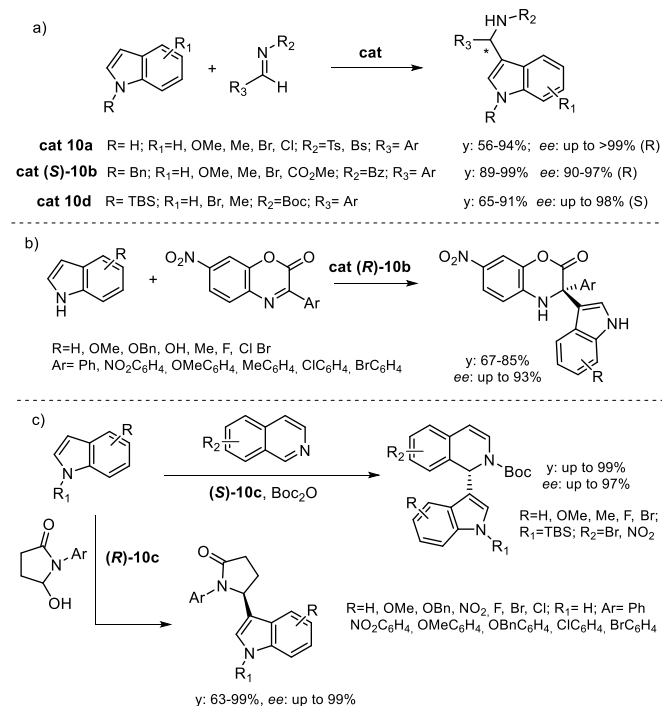
Scheme 30. Representative examples of indole alkylation in the presence of chiral phosphoric acids characterised by the general structure **10** (in Figure 2).

Compound **(S)-10b**, based on the same core structure, but with two SiPh$_3$ substituents, resulted to be the best catalysts for the reaction between indoles and *N*-acylimines. However, in this case enantioselectivity was high only when the nitrogen of indoles was protected. The best results (*ee* up to 97%) were obtained reacting *N*-benzoyl aryl imines and indoles protected as *N*-benzyl (Scheme 30a). Electron-rich and electron-withdrawing substituents were well tolerated on both the indole and the imine partners, while even the presence of a small methyl group on indole C-2 position was detrimental, leading to lower *ee* (64%) due to unfavoured steric interactions.[117] The opposite enantiomer of this catalyst (**(R)-10b** in Figure 2) was exploited by Zaho and co-workers, to react

cyclic aryl α-ketimino esters with indoles (Scheme 30b).[118] Here, the presence of an α-carboxyl moiety was mandatory to activate the poorly reactive ketimine. The mechanism required the use of deprotected indoles and generated a quaternary stereocenter in a stereoselective fashion. The enantioselectivity decreased when electron-withdrawing functionalized- and C2 substituted indoles were used, while different aryl moieties on the ketimine were well tolerated.

The bulkier catalyst **10d** (in Figure 2) was successfully exploited by Uraguchi *et al.*, to favour the reaction between *N*-Boc aryl imines and *N*-tert-butyldimethylsilyl-protected indoles. A low catalyst loading (2-3 mol % for the most part of the examples), a limited excess of imine used, good yields and excellent *ee* were the merits of the method (Scheme 30a).[113]

The two enantiomers of a phenanthryl-substituted binol-based chiral phosphoric acid **(S)-10c** and **(R)-10c** (in Figure 2), promoted the indole alkylation with isoquinolines[119] and γ-hydroxy-γ-lactams,[120] respectively (Scheme 30c). In the first case, the reaction occurred on *N*-Boc-activated isoquinolines, providing chiral dihydroisoquinolines with indole substituents at the C1 position in excellent yields and enantioselectivities. On the other hand, catalyst **(R)-10c** favoured the conversion of the γ-hydroxy-γ-lactam surrogate into an iminium ion, upon water elimination. In this way, a tied pair between the cationic acyl iminium and the chiral phosphate counteranion was established, and the following alkylation of indole could occur stereoselectively. Excellent results were achieved with differently substituted indoles. The only requirements concerned the use of *N*-free indole, to guarantee the formation of a hydrogen bond with the catalyst (box in Figure 2) and the lack of substituents on indole C2 position. In fact, as occurred in some of the previously described example, the presence of bulky groups in C2 position could be detrimental for the stereocontrol.
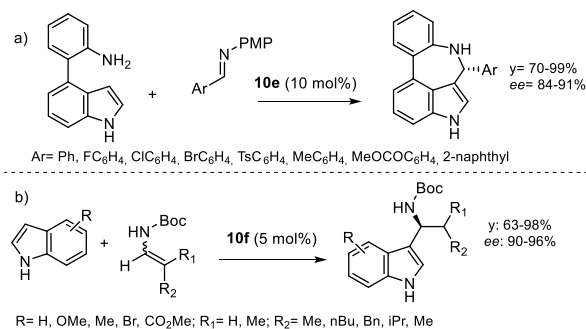
Scheme 31. a) enantioselective Pictet-Spengler reaction promoted by catalysts **10e**. b) Indole enantioselective alkylation with enecarbamates, in the presence of **10f**.

An analogous catalyst **10e** (in Figure 2), bearing anthracenyl substituents instead of phenanthryl ones found employment in an enantioselective Pictet-Spengler reaction aimed at generating complex and diverse indolo[3,4-*cd*][1]benzazepines from of 4-(2- aminoaryl)indoles, with satisfactory yields and *ee*

(Scheme 31a).[121] Furthermore, another BINOL-based chiral phosphoric acid **10f** (Figure 2) was efficiently used in a protocol applicable to the challenging aliphatic imines.[122]

These labile intermediates were generated *in situ* by protonation of enecarbamates, mediated by the catalyst. Notably, in this phase of the mechanism, *Z*-enecarbamates reacted faster than the *E*-ones. Then, indole approached the ionic intermediate on a preferential face, on the basis of the steric interactions exerted by the phosphoric acid. In this way, the desired C3-alkylated indoles were generated in moderate to high yields and satisfactory *ee* (Scheme 31b).

An interesting improvement to this kind of reactivity was accessed exploiting polystyrene-supported chiral phosphoric acids, such as **11** (structure in Figure 2), that found perfect application in the convenient and rapid generation of a library of enantiopure 3-indolyl methanamines through flow-chemistry.[123]

So far, chiral catalysts based on BINOL-phosphoric acids were presented, being the most commonly employed. However, other kind of chiral scaffolds could be considered as well, as demonstrated by Wang and collaborators, that took advantage of a phosphoric acid built upon a spirobiindane backbone (**12**, Figure 2). In this way, they accessed the efficient enantioselective C3 aza-alkylation of indoles with *N*-tosyl- and *N*-*p*-bromobenzene sulfonylimines, in moderate to good yields and high *ee*, as reported in Scheme 32a. [124]
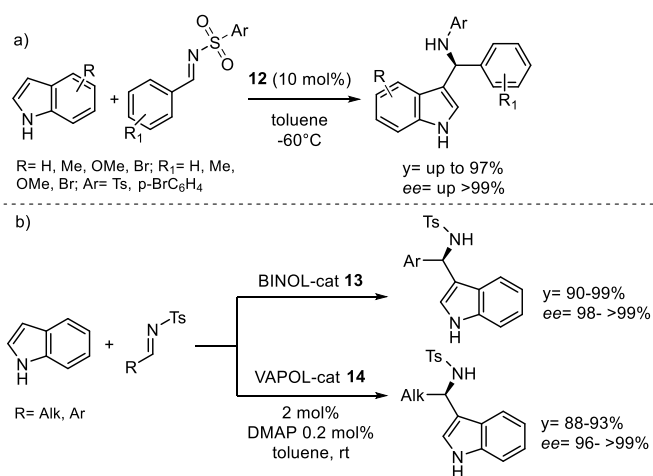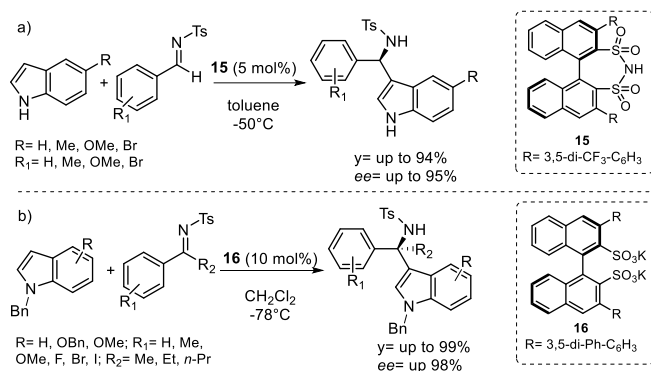

Scheme 32. Indole C3 aza-alkylation with aromatic and aliphatic imines, catalysed by bulky chiral phosphoric acids **12** (a) and **13**-**14** (b). As appreciable in b), catalysts **14** gave impressive results with alkylimines.

Notably, a huge breakthrough in this kind of chemistry was achieved by Wu and co-workers,[125] through the design of the double axially chiral bisphosphorylimides, such as **13** and **14** in Figure 2, that gave impressive results in terms of activity, yields and *ee*, not only on *N*-Ts aryl imines but also on *N*-Ts alkyl imines (Scheme 32b). **14** proved to be particularly feasible in catalysing indole alkylation with aliphatic imines, leading to 3-indolyl

methanamines with yields and enantiomeric excesses comparable with aryl imines (*ee* up to 99%). Moreover, the use of DMAP as co-catalyst resulted a good strategy to suppress the formation of the undesired bis-indolyl by-product.

Chiral sulfonic acids and sulfonimides. Closely related to the previous class of catalysts, sulfonic acids and sulfonimides are strong Brønsted acids, catalytically active at low temperature, suggesting a reasonable better stereoselectivity. Two interesting examples were reported by Lee[126] and Ishihara[14] (Scheme 33).


Scheme 33. Structures of the chiral sulfonic acids and sulfonimides cited in this section and schematic representations of their reactivity, to favour indole C3 aza-alkylation with aromatic imines.

In the first case, sulfonimide **15** (5 mol %) was an effective catalyst in the reaction of indoles with *N*-sulfonylarylimines. The first catalyst screening was discouraging, considering that even at 60°C, the reaction proceeded quite slowly, with moderate yields and enantioselectivities, and accompanied by the formation of the undesired bis-indolyl by-product. Washing the sulfonimide with diluted HCl was fundamental to obtain a fully active catalyst. In this way, it was possible to decrease the catalyst loading to 5 mol%, and the alkylated indoles were efficiently accessed (yields and *ee* up to 94% and 95%, respectively), at -50°C and in only 1.5 hours (Scheme 33a). The stereo-electronic properties of the imines didn't particularly impact the reactivity, while electron-deficient indoles gave lower enantioselectivity levels. The main limit of this protocol was the lack of applicability on aliphatic imines.[126] In the second example, Ishihara took advantage of chiral potassium binaphthyldisulfonates, such as **16**, to promote the challenging reaction between *N*-Bn indoles and low-reactive *N*-tosyl ketimines. The protecting groups choice was oriented by the necessity of increasing indole nucleophilicity and iminocarbon electrophilicity. A catalysts screening revealed that the use of potassium as counterion led to the higher yields. The use of acetic acid as additive guaranteed a successful reaction on a broad substrate scope, with high yields and enantioselectivities, employing a particularly low catalyst loading (0.3 mol %) (Scheme 33b). AcOH could coordinate to the K⁺ centre, leading

to a possible monomeric active catalyst, or could act as a H+ carrier, favouring product release and catalysts regeneration. This approach could also be applied to aliphatic ketimines, even though with lower yields and stereoselectivities.[14]

Thioureas. Thioureas are common bifunctional chiral organocatalysts, able to promote asymmetric reactions through the formation of a network of hydrogen bonding interactions with the reacting nucleophiles and electrophiles. Therefore, it's easily deducible that they could find application in the aza-Friedel-Crafts alkylation of indoles. Some interesting examples will be disclosed in this paragraph, involving the catalysts **17**, **18** and **19**, represented in Scheme 34.

In 2006, Deng and co-workers developed a class of hybrid catalysts, in which thioureas and cinchona alkaloids were merged to generate chiral scaffolds, such as **17** (Scheme 34a).[127] This organocatalyst promoted the reaction between indoles and *N*-Ts and *N*-Bs imides, giving impressive enantioselectivity even at higher temperature (50°C). Under these conditions, the reaction occurred also on poorly reactive substrates, such as electron-rich imines and electron-deficient indoles. Excellent results in term of yields and *ee* were observed on alkylimines.

Another interesting thiourea-based chiral catalyst (**18**) was developed by Peterson and Jacobsen, to couple indoles with acyliminium salts, *in situ* generated from acetoxylactams (Scheme 34b).[128]
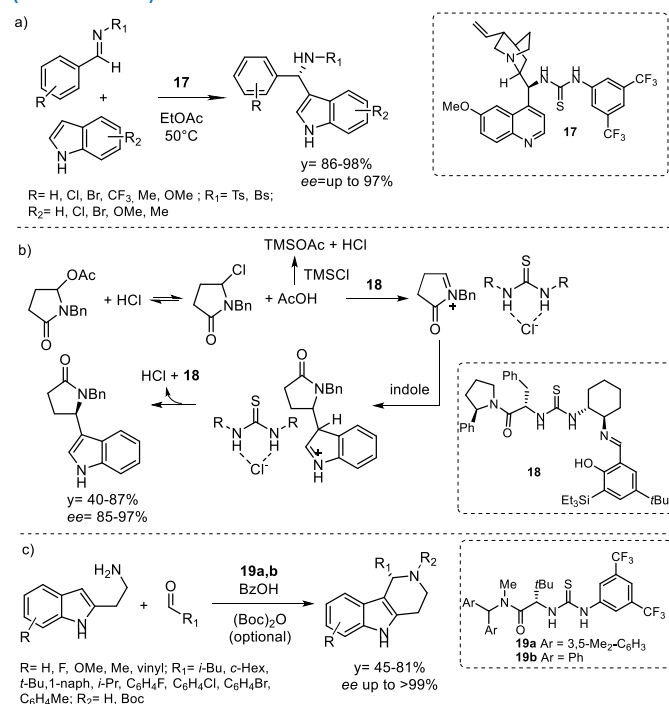
through a highly selective anion-binding mechanism, that required the presence of TMSCl and water as additives. This suggested that the acetoxylactam reacts with HCl (generated *in situ*) to form a chlorolactam, that then interact with **18**, forming the reactive acyliminium ion. This equilibrium seemed driven by trapping of the acetic acid by-product with TMSCl, as appreciable in Scheme 34b. High enantioselectivies were observed on both electron-rich and electron-deficient indoles, but in the latter case yields were definitely lower. A similar strategy was then adapted to a one-pot enantioselective iso-Pictet-Spengler reaction, as reported few years later, again by Jacobsen (Scheme 34c).[129] Here, functionalised iso-tryptamines interacted with both aromatic and aliphatic aldehydes, forming an iminium specie that then underwent the iso-Pictet-Spengler cyclization. In this case the best catalytic system was constituted by thiourea **19a** and benzoic acid, that led to the generation of a library of differently substituted tetrahydro-γ-carbolines, with high yields and stereoselectivity. An interesting modification to this protocol took advantage of the less enantioselective but cheaper catalyst **19b**. In fact, treatment of the crude product deriving from the iso-Pictet-Spengler reaction with Boc₂O generated a *N*-Boc tetrahydro-γ-carboline, whose enantiomeric composition could be upgraded to >99% *ee* in the most part of the cases, simply by direct crystallization or trituration (Scheme 34c).

Miscellaneous. In this section two examples that cannot be included in the previous paragraphs are reported. The first one deals with squaramides, organocatalysts closely related to chiral thioureas. Catalyst **20**, easily accessible in few steps from the commercially available dimethyl squarate, contains a basic site, that can coordinate indoles and an acidic site that can activate *N*-Ts imines [130] In this way, the efficient C3 indole aza-alkylation was accessed, with good yields and enantioselectivity, even with *N*-tosylalkyl imines (Scheme 35a). The second example concerns chiral polyethers, such as **21**, that promoted aza-Friedel-Crafts alkylation of indoles through a mechanism requiring the presence of a fluoride ion and involving the formation of a sort of chiral cage, similarly to the concept of the active site in enzymes (Scheme 35b).[131]

First of all, catalyst **21** needs to be complexed with a unit of KF. Then, α-amidosulfones, used as imine surrogates, are coordinated to the chiral complex. Elimination of the sulfinate group affords the imine, that reacts with the activated indole. Notably, **21** was properly designed, to possess: 1) phenolic groups as acid sites; 2) a polyether chain that can bind KF (the basic site); 3) iodines that tune the acidity of the catalyst, in order to disfavour the formation of the undesired bis-indolylmethane. A considerable effort was devoted to the exploration of reaction scope, with several examples; it emerged that electron-rich and electron-withdrawing substituents were tolerated on the indole phenyl ring, as well as the presence of a methyl group on C2 position. Electron-rich aromatic imines and aliphatic imines led to lower but

Scheme 34. Schematic representation of the approaches based on the use of thioureas-based catalysts.
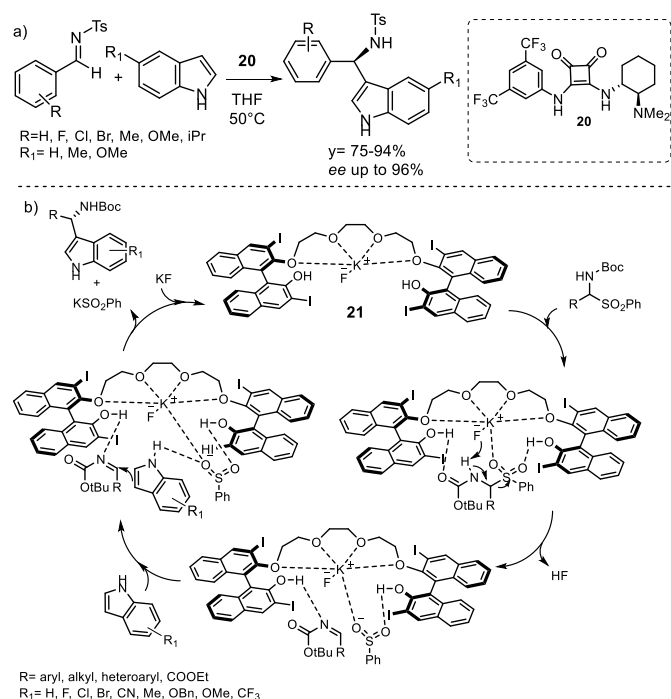
Catalyst **18** was carefully designed to access the higher level of stereoselectivity, optimizing the Schiff base, the amide, and the amino acid side-chain components. The reaction occurred

acceptable yields, while the *ee* remained high in most of the cases.

R=H, F, Cl, Br, Me, OMe, iPr
R$_1$= H, Me, OMe
y= 75-94%
ee up to 96%

R= aryl, alkyl, heteroaryl, COOEt
R$_1$= H, F, Cl, Br, CN, Me, OBn, OMe, CF$_3$

Scheme 35. a) general scheme for indole C3 aza-alylation mediated by **20**; b) catalytic cycle for the C3 aza-alkylation of indoles promoted by **21**.

The examples discussed in section 2.2 are summarised in Table 4, which reports the catalysts, the type of substituents on the final scaffold, the best *ee%* and the corresponding reference number.

Table 4
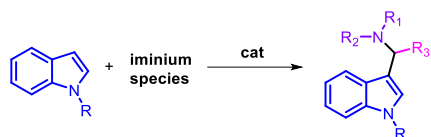
Catalyst	R	R1	R2	R3	ee%^{a}	Ref
10a	H	Ts, Bs	H	Ar	>99	[116]
(S)-10b	Bn	Acyl	H	Ar	97	[117]
(R)-10b	H	Ar	H	Ar, COOH^b	93	[118]
10d	TBS	Boc	H	Ar	98	[113]
(S)-10c	TBS	Boc	Styr	Ar	97	[119]
(R)-10c	H	Acyl	Ar	Alkyl	>99	[120]
10e	H	Ar	H	Ar	91	[121]
10f	H	Boc	H	Alkyl	96	[122]
11	H	Ts	H	Ar	98	[123]
12	H	Ts	H	Ar	>99	[124]
13	H	Ts	H	Ar	>99	[125]
14	H	Ts	H	Alkyl	>99	[125]
15	H	SO$_2$R	H	Ar	95	[126]
16	Bn	Ts	H	Ar, Alkyl^b	98	[14]
17	H	Ts, Bs	H	Ar	97	[127]
18	H	Bn, Me	Acyl	Alkyl	97	[128]
19a,b	H	H, Boc	Alkyl	Ar, Alkyl	>99	[129]
32	H	Ts	H	Ar, Alkyl	96	[130]
33	H	Boc	H	Ar, Alkyl, CO$_2$R	>99	[131]

^{a} The best enantiomeric excess value obtained in the corresponding work, is reported. ^{b} in these works the reaction is performed on a ketamine or a ketamine ester. In this way quaternary stereocenters are generated.

Conclusions

In summary, the main advancements in the field of the aza-alkylation reaction at position 3 of the indole scaffold have been presented in this review. Various catalytic systems based on metals-based catalysts, Brønsted acids, Lewis acids or organocatalysts have been presented and discussed. The availability of diversified conditions to adapt the reaction toward different and complementary aims makes this approach tactical and fruitful. The presence of different functional groups on the indole scaffold sounds not limiting for the reaction outcome, while the position of the substituents could cause a less flexible applicability. The aromatic aldehydes are largely used with different substituents while the use of the aliphatic ones is more challenging, even if excellent results were accessed in some of the cited works. Stereoselectivity is easily controlled through metal catalysts combined with chiral ligands, as well as under metal-free conditions. The use of surfactants appears intriguing in terms of sustainability and it's worthy of further investigation. We are confident that the fascinating reactivity of the indole nucleus and the relevance of many interesting natural and pharmaceutical indole-containing compounds will stimulate further applications and exploitations of the presented synthetic strategies.

Conflicts of interest

The authors declare no conflict of interest.

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