Chem Soc Rev

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Journal:	*Chemical Society Reviews*
Manuscript ID:	CS-REV-06-2014-000209.R1
Article Type:	Review Article
Date Submitted by the Author:	20-Jun-2014
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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Strategies for the asymmetric functionalization of indoles: an update

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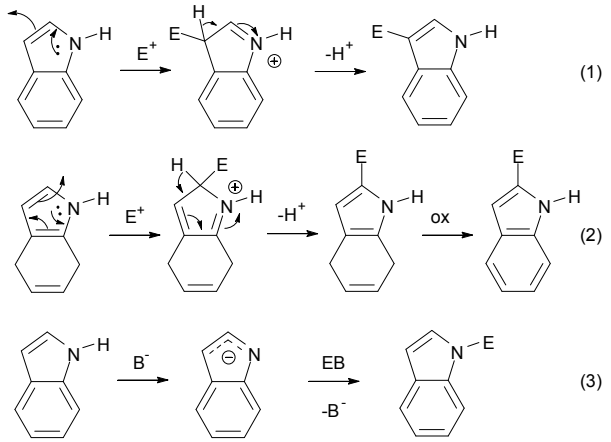
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

During the past four years, the research of new synthetic methodologies for the rapid construction of enantiomerically pure substituted indole has had a fruitful and important growth. This research line continues to produce stunning arrays of enantioselective technologies either metal or organocatalyzed. Thus, an update of our previous review (*Chem. Soc. Rev*., 2010, **39**, 4449–4465) has become necessary and this critical review documents the literature on this topic, until the end of 2013.

1. Introduction

It is estimated that more than 50 % of the published chemical literature contains heterocyclic structures and 70% of all pharmaceutical products possess heterocyclic structural subunits, because of a favourable combination of drug-like properties. In particular, over ten thousand biologically active indole derivatives have been identified to date.[1] Of those, over 200 are currently marked as drugs or undergoing clinical trials.[2] Furthermore, the indole nucleus is not only important in biological systems and in pharmaceutical research,[3] but also it is a common moiety in material science.[4-6] Hence, it is not surprising that this structural motif is the topic of research and reviews that continuously appear in the literature.[7-16]

Functionalization of the indole nucleus takes place by electrophilic aromatic substitution on C-3 (Scheme 1, eq (1)), which is 10^{13} times more reactive than benzene positions.



Scheme 1 Electrophilic attacks to C-3 (1), C-2 followed by oxidation (2), deprotonated N-1 (3).

Electrophilic substitution of the 2-position can occur only if the pyrrole core is electronically isolated: i.e. on 4,7-dihydroderivatives (Scheme 1, eq (2)). Finally, the reduced nucleophilicity of the *N*–H functionality allows *N*-substitution only when the *N*–H proton of indoles is removed to generate a strong charged nucleophile (Scheme 1, eq (3)). Electrophilic substitution of the carbocyclic ring can take place only after N-1, C-2, and C-3 positions are substituted and, owing to this difficulty, benzene-ring functionalization is generally obtained by *de novo* ring syntheses.[17]

In addition, biologically active indoles often carry stereocentres in the α- or β-positions of the ring side-chains. The formation of optically active compounds requires modification of the described procedures either with the employment of an optically active catalyst/mediator or chiral substrates followed by cleavage of the auxiliary. Actually in the last years, application of asymmetric catalysis to enantioenriched indole derivatives rose in importance.[18]

Reviews on asymmetric catalysis explaining the main strategies applied to a large variety of substrates continue to appear in the literature, thus, we refer to those papers for details.[19-25] Organocatalysts can be divided in two main families: covalent and hydrogen-bonding catalysts, and each one in some sub-families (Figures 1-2).

This review aims to collect organocatalyzed functionalizations of the pyrrole moiety of indole core nucleus with a panoramic and critical survey of the literature appeared in the last four years (from the beginning of 2010 to the end of 2013) updating our previous review that covered literature until the end of 2009.[18]

2. Functionalization at C-3

2.1 Friedel-Crafts (F-C) reactions

Unsaturated compounds, such as activated alkenes, or carbonyl compounds and imines found large application as suitable electrophilic reagents for F-C alkylation.[26, 27] In the following sections the functionalization of the 3-position of the indole nucleus by this reaction will be considered.

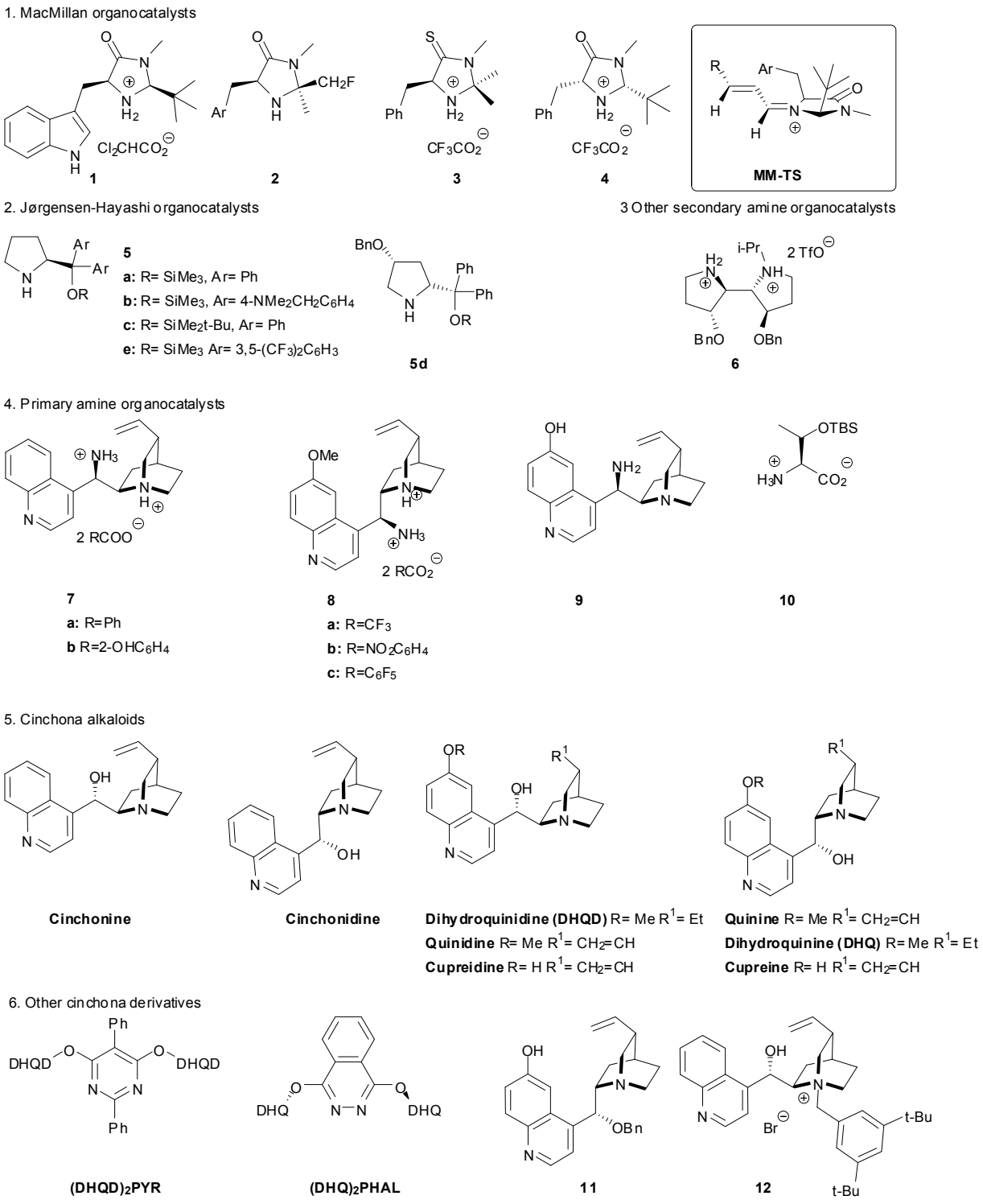


Fig 1 Covalent organocatalysts used in the reactions described in this reviews divided into main families

2.1.1 Conjugate addition of α,β-unsaturated compounds

Since the origin of organocatalytic F–C alkylation of indoles, α,β-unsaturated carbonyl compounds are classical substrates for the synthesis of chiral indole derivatives.

Thus, it is not surprising that new instances are continuing to appear in the literature, in particular, application of classical "iminium ion catalysis" with MacMillan's and Jørgensen–Hayashi's organocatalysts to the F-C alkylation of indoles with α,β-unsaturated aldehydes. Into this research line, Kim's group developed an asymmetric organocatalytic Friedel-Craft reaction to produce enantioenriched 4-substituted chroman-2-ols in 32-85% yields but with low ee (not exceeding 62%, Scheme 2).[28]

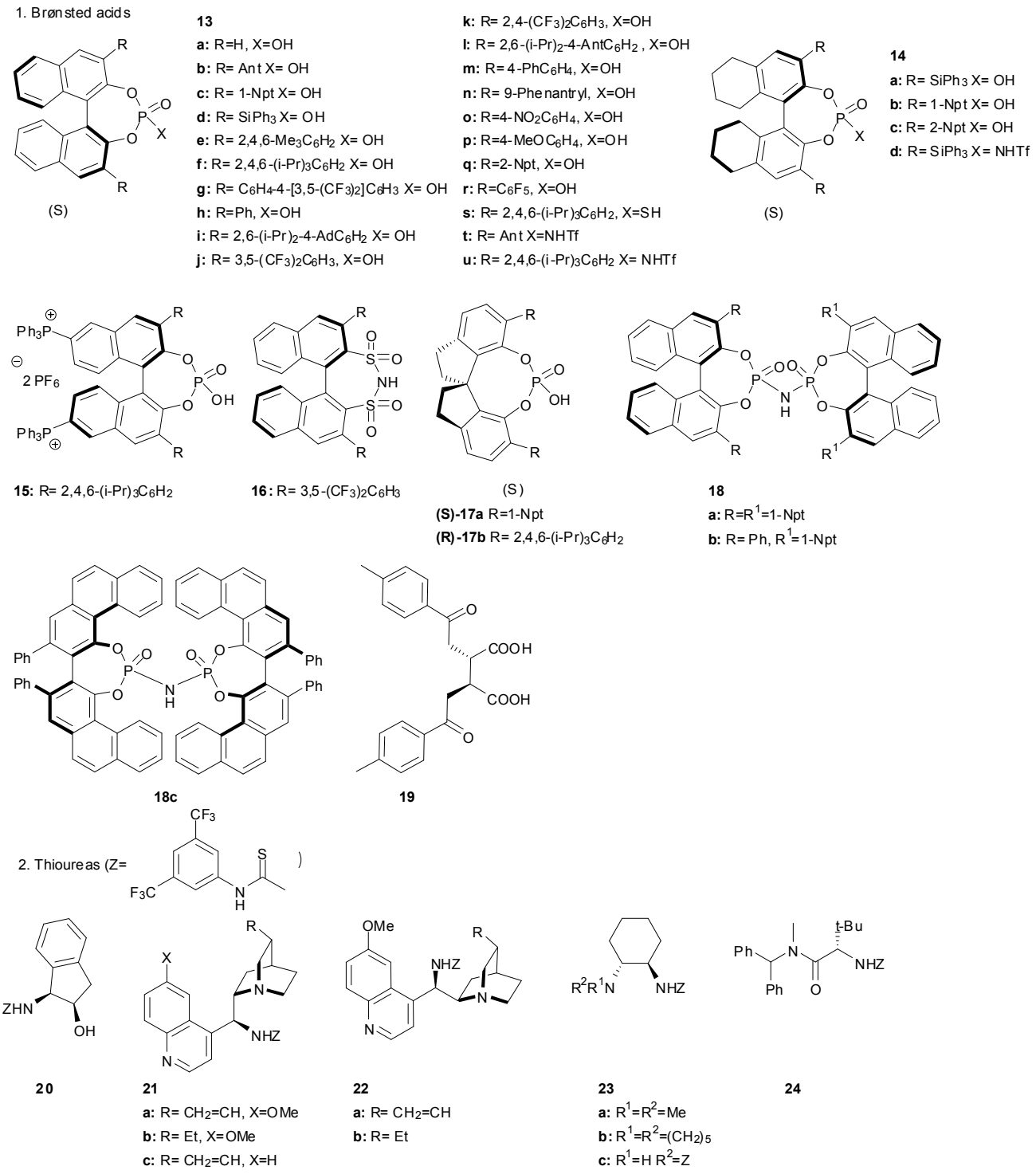


Fig. 2 Hydrogen-bonding organocatalysts used in the reactions described in this reviews divided into main families (for phosphoric acids only one isomer is depicted for simplicity. In the text the configuration descriptors will be mentioned)

Unfortunately, authors did not specify the stereochemistry of the two stereocentres, but we can expect the generally accepted behaviour of the MacMillan's catalysts. In fact, the stereochemical course is now well-established: the (*S*)-iminium ions of (*E*)-configuration are preferentially approached by nucleophiles from the *Si*-diastereotopic face, i.e., *anti* to the $ArCH_2$ and the *t*-butyl substituents on the heterocycle (**MM-TS,** Figure 1).[18]

Recently, Groselj and co-workers observed a "puzzling fluorine effect" when a fluoromethyl group substituted the *t*-butyl in the catalysts (**2,** Figure 1).[29] Surprisingly, these catalysts preferentially gave the (*R*)-enantiomer (up to 86 % ee). Authors reported these results without convincing explanation, although NMR analyses and DFT calculations of the intermediates were made without finding evidence, as to why introduction of an F-atom in the *cis*-methyl group of the MacMillan's catalysts should

lead to topicity reversal.

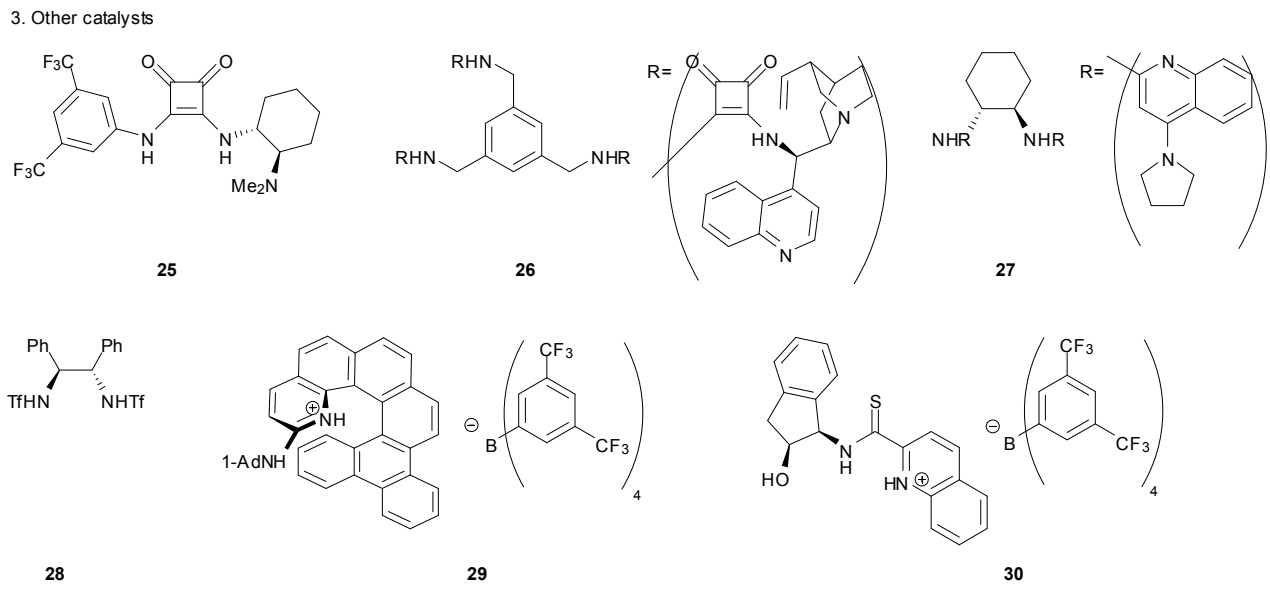
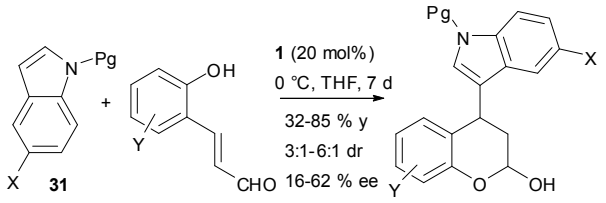
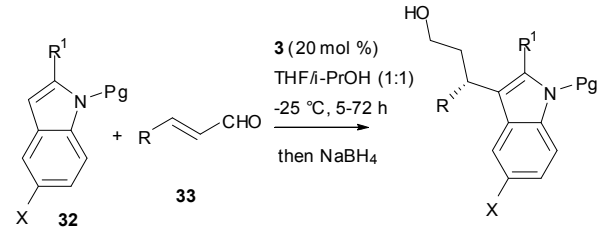


Fig. 2 Continue



Scheme 2 Synthesis of 4-(3-indolyl)chroman-2-ols [28]

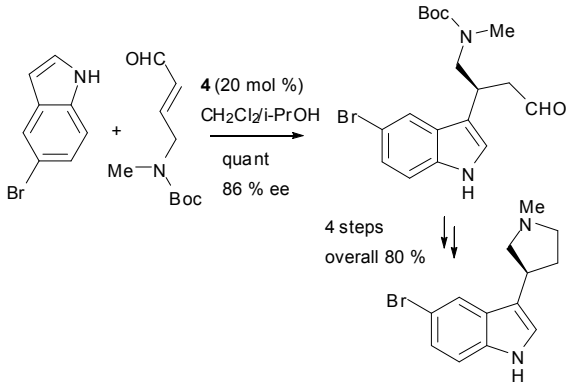


Scheme 3 Sulfur modified MacMillan-type catalyst [30]

In fact, at the thermodynamic equilibrium, the higher populated conformer, with the Ph group over the π-system in the *E*-isomer, seems hindering *Re*-attack, rather than favouring it. In addition, a preferential kinetic formation of the *Z*-isomer with slow *E/Z*-isomerization and trapping by the nucleophile from the *anti-Re*-face did not found NMR evidences.

Imidazolethiones provided a practical method for the preparation of chiral indole derivatives in 77-88% yields and 60-99% ee under less harsh conditions, compared with MacMillan-type catalyst (Scheme 3).[30] *m*-Substituted cinnamaldehyde with unprotected indoles gave the poorest enantioselectivities and authors invoked reversibility and racemization of the reaction to explain the result.

The organocatalytic asymmetric conjugate addition reaction of indoles to α,β-unsaturated aldehydes has been applied to the concise synthesis of an advanced precursor of a drug prototype for the treatment of migraine headaches by Hanessian's group (Scheme 4).[31] The use of the (*R,R*)-enantiomer of the classical MacMillan's organocatalyst should be noted. The scope of the reaction was extended to a variety of *N*-substituents with enantioselectivities, which did not vary significantly with their bulkiness and electronic properties. However, the bulkier bis-protected substrates require longer reaction times, while mono-substituted amine failed to participate to the reaction.

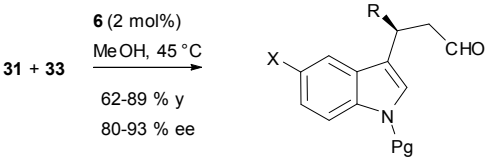


Scheme 4 Synthesis of the precursor of an inhibitor of Nitric Oxide Synthase[31]

A second class of organocatalysts for F–C alkylation of indoles via "iminium ion catalysis" are diarylprolinol silyl ethers, the so-called Jørgensen–Hayashi's organocatalysts. Xu and co-workers demonstrated by ^{29}Si-NMR experiments that silicon moiety not only serves as a bulky group to induce steric repulsion, but also serves as a Lewis acidic promoter to accelerate the reaction between the NH and the α,β-unsaturated aldehyde.[32] Furthermore, the introduction of an amino group on the diarylprolinol silyl ether (such as in **5b**, Figure 1) increases the

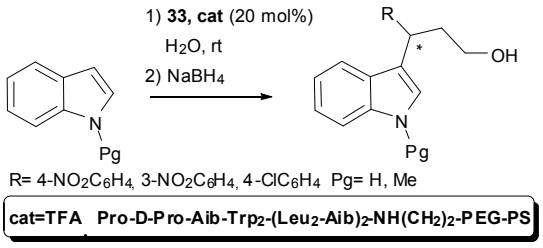
stereoselectivity (98->99% ee) avoiding the use of acids or bases, but products are recovered in unsatisfactory yields (37-65%)

Other organocatalysts were recently employed in the addition of α,β-unsaturated aldehydes to indoles. For instance, Zhang and co-workers presented an *N*-isopropylbipyrrolidine (**6**). This new organocatalyst facilitates the enantioselective alkylation reaction, providing 3-alkylated indoles with opposite stereochemistry respect to classical MacMillan's catalyst in 62–89% yields with 80–93% ee using only 2 mol% of catalyst loading (Scheme 5).[33]



R= Me, Et, Pr, COOEt, $PhCO_2CH_2$ X= H, Br. OMe Pg= H, Bn, CH_2=$CHCH_2$

Scheme 5 *N*-Isopropylbipyrrolidine organocatalyst for addition of unsaturated aldehydes to indoles [33]

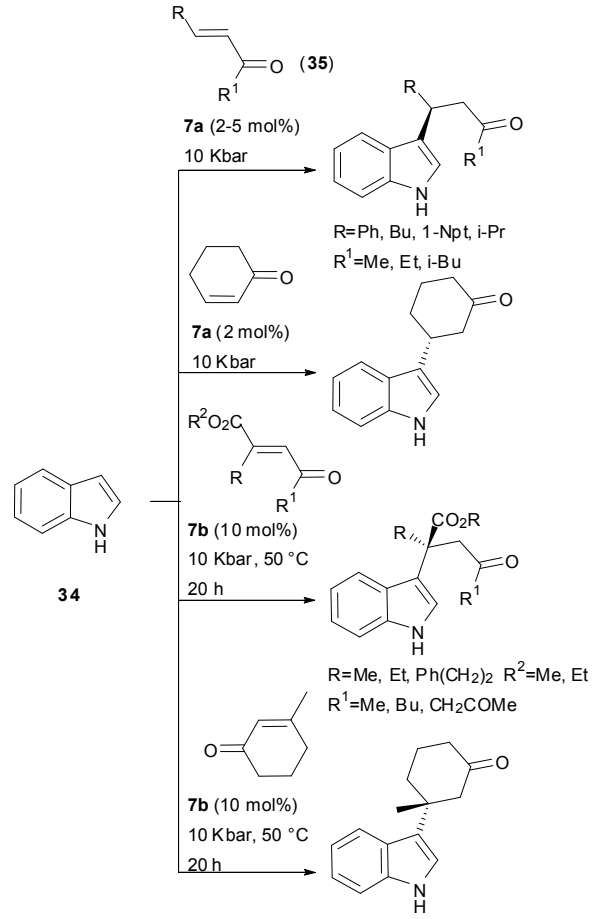


Scheme 6 Peptide catalyst for F-C alkylation of indoles[34]

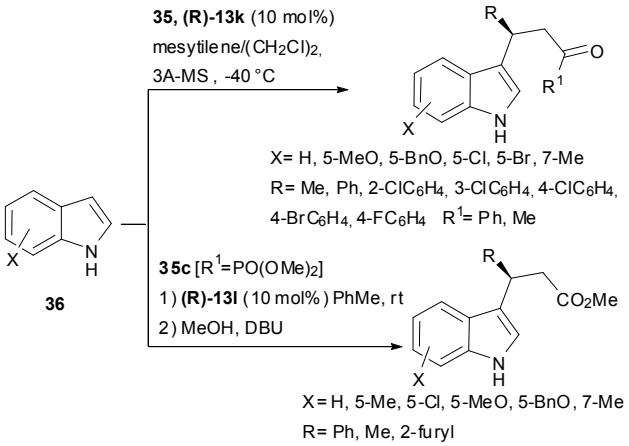
Recently, a PEG-PS-resin supported peptide catalyst, which has both β–turn motif D-Pro-Aib and α–helical motif (Leu-Leu-Aib)$_2$, was developed.[34] This approach mimics enzymatic reactions and opens the way to the utilization of water as a solvent for organic reactions. With the optimum peptides sequence, the addition products were recovered in 76-84% yields and 89-91% ee, but only four examples were reported and stereochemistry was given only in one (Scheme 6).

The addition of indoles to α,β-unsaturated ketones is a more challenging reaction. The relative bulkiness of secondary amines such as MacMillan or Jørgensen–Hayashi's catalysts is unfavourable for the generation of iminium ions. Thus, chiral less-demanding primary amines *via* "Iminium Ion Catalysis" as well as Brønsted acid catalysis, through hydrogen-bonding mechanism, were used in more ancient papers.[18]

In the last years, "Iminium Ion Catalysis", with primary amines derived from cinchona alkaloids, was improved by increasing the reaction pressure. In fact, F-C alkylation of indoles with simple enones proceeded under 8-10 kbar by 2-5 mol% of catalyst with good enantioselectivity (83-90%) and yields (70-95%) (Scheme 7).[35] This reaction represented the first promising results of the organocatalytic F-C reaction with prochiral sterically hindered β,β–disubstituted *E*-enones, which led to the formation of indole derivatives containing all-carbon quaternary stereogenic centres with 57-78% yields and 48-80% ee when 10 mol% of catalyst is employed. The use of β,β–disubstituted *Z*-enone resulted in the opposite direction of asymmetric induction but in a moderate yield and ee (48 and 44%, respectively, just an example). Compared with classical Melchiorre's[36] and Chen's procedures,[37] products were recovered in comparable and somewhat higher yields and enantioselectivity, but catalyst loading is much lower. On the other hand, equipment for high-pressure reaction is required with respect to the classical glassware.



Scheme 7 F-C reaction with prochiral sterically hindered β,β–disubstituted *E*-enones[35]

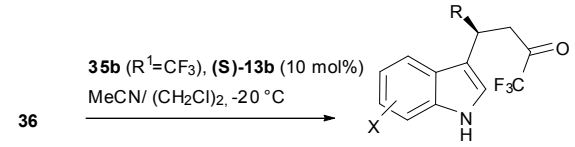


Scheme 8 F–C alkylation of indoles catalysed by chiral phosphoric acid by Akijama [38,39]

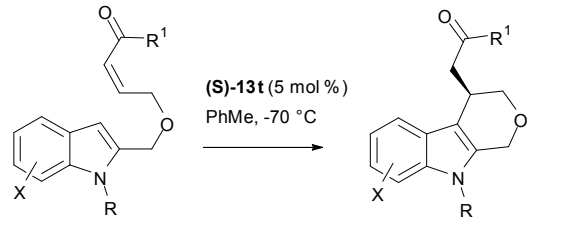
The addition of α,β-unsaturated ketones catalysed by Brønsted acids has been improved in the last years. For instance, Akijama and co-workers set up the asymmetric F–C alkylation of indoles with α,β-unsaturated ketones catalysed by chiral phosphoric acid,

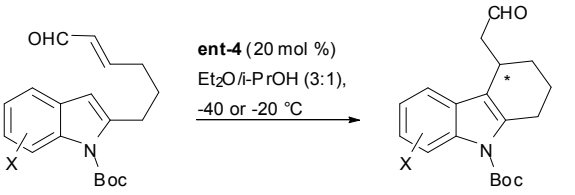
recovering the addition product in 37-98% yields with 58-92% ee (Scheme 8).[38]

Similarly, Ma and co-workers developed an asymmetric addition of α,β-unsaturated trifluoromethyl ketones to indoles in 25-99% yields with 18-88% ee (Scheme 9).[40] Moreover, the products could be transformed into two diastereomeric alcohols with retention of optical purity but without diastereoselectivity.



Scheme 9 F–C alkylation of indoles catalysed by chiral phosphoric acid by Ma[40]





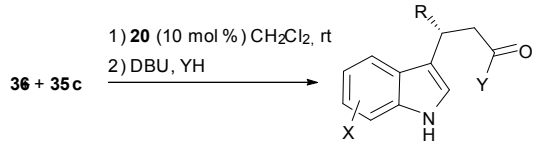
Scheme 10 Intramolecular F–C alkylation reaction [41, 42]

Chiral phosphoric acids are also efficient catalysts for the F–C addition reaction of electron-rich indoles with α,β-unsaturated acyl phosphonates in 52-79% yields and 70-92% ee except for 7-methylindole, in which the ee was 19%.[39] The acyl phosphonates serve as masked ester or amide equivalents, which, upon quenching with methanol or morpholine, generate the final structures *in situ* without loss of optical purity. It should be noted that Ma and co-workers used a (*S*)-configured catalyst,[40] but they obtained product with the same configuration of Akijama.[38,39]

Chiral *N*-triflyl phosphoramide was also an efficient catalyst (5 mol%) for the asymmetric intramolecular F-C alkylation reaction of indolyl enones (Scheme 10, top).[41] The substituted tetrahydro-pyrano[3,4-b]indoles were obtained in 81-99% yields (except for compound in which X=H, R=Me, R^1=4-$MeOC_6H_4$; where the yield was only 49%) and 63-98% ee (except for aliphatic ketone substrates; where the ee was only 16%).

A highly enantioselective intramolecular F-C-type alkylation of ω-indol-2-yl α,β-unsaturated aldehydes has been reported by using **ent-4** (20 mol%) as the catalyst. Functionalized tetrahydrocarbazoles were recovered in 61-89 % yields with 74-91 % ee (Scheme 10, bottom).[42] Unfortunately, the stereochemistry of the new stereocentre is not reported.

Hermeke and Toy surmised that the attachment of phosphonium ion tag to chiral binaphthyl-based phosphoric acid catalysts can aid in the separation and reuse of the catalyst.[43] In fact, this catalyst is soluble in CH_2Cl_2, but not in Et_2O. Placement of the tags at the 3- and 3'-positions of the phosphoric acid failed to produce an active catalyst, while substitution in the 6 and 6' positions produced an efficient and enantioselective catalyst (**15**, Figure 2) for organocatalytic asymmetric F-C reactions of indoles. The chiral catalyst was easily removed at the end of the reactions, and could be reused several times, albeit with somewhat decreased efficiency and enantioselectivity. This reaction was applied to β,γ-unsaturated α-keto esters (89-98% yield and 46-60% ee) and enamides (81-98% yield and 70-90% ee). Stereochemistry was not reported, but could be supposed in analogy with other binaphthyl phosphoric acids.

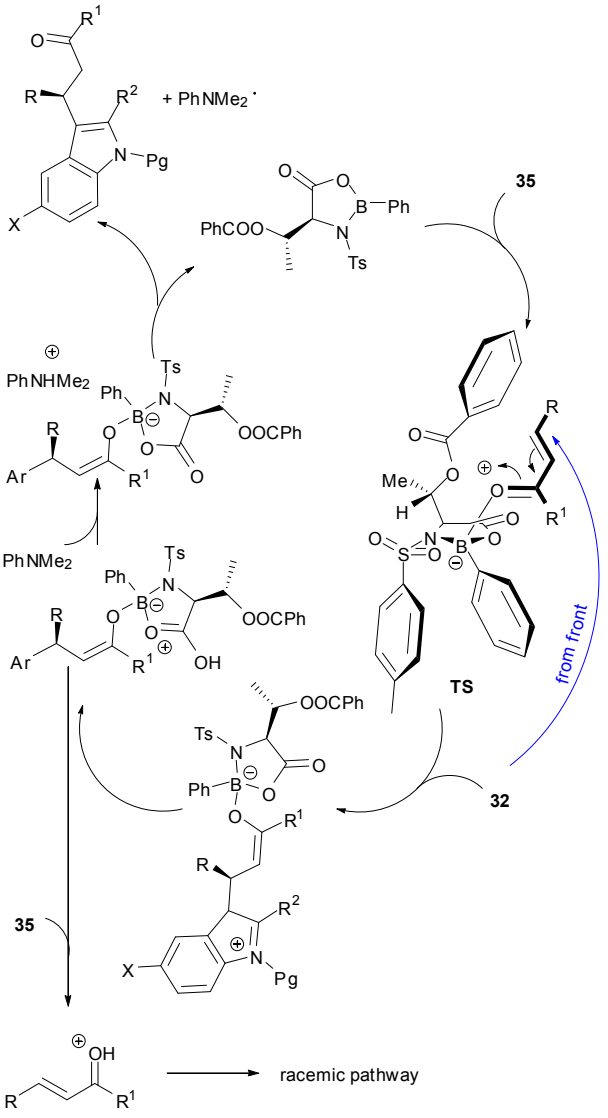


Scheme 11 Additions of α,β–unsaturated acyl phosphonates to indoles[44]

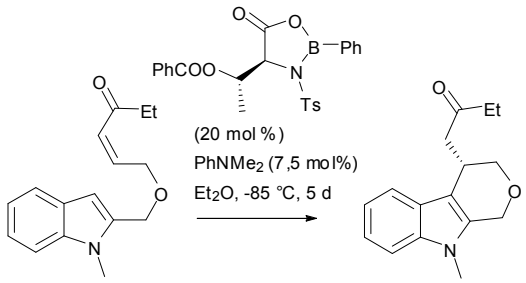
Chiral thioureas as the catalysts performed conjugate additions of α,β–unsaturated acyl phosphonates to indoles 57-92% yields and 72-90 %ee.[44] The achievement of the opposite enantiomer from the reaction with phosphoric acid, and a partial racemization, influenced by the nucleophilicity and basicity of the chosen nucleophile, not-mentioned with phosphoric acid, should be noted (Scheme 11).

allo-Threonine-derived oxazaborolidinone catalysis is effective in the enantioselective F–C alkylation of indoles with α,β-unsaturated ketones (Scheme 12).[45] Products were obtained in 23-96% yields and 37-94% ee, but indole reacts in poor yield (19%) or does not react with ketones bearing a butyl and a phenyl group at the β–position, respectively. The use of *N,N*-dimethyl-aniline (2.5 mol%) as an additive is found to be essential to obtain high enantioselectivity and its effect was rationalized in terms of retardation of a proton-catalysed racemic pathway, which deteriorates the enantioselectivity of the F–C alkylation reaction. The catalyst (20 mol%), in the presence of *N,N*-dimethylaniline (7.5 mol%), can be applied successfully to intramolecular F–C alkylation. In fact, tetrahydropyranoindole was obtained in 60% yield with 90% ee after five days and, significantly, with opposite stereochemistry with respect to the *N*-triflylphosphoramide. The reaction mechanism is quite different from both iminium ion and Brønsted acid catalysis and it is depicted in scheme 12. The enantioselectivities and the absolute stereochemical course of the reactions were rationalized in terms of the **TS**-complex, in which the substrate coordinates to the boron atom in an *s-cis-anti* fashion, allowing the addition of the nucleophile on the open *Si*-face.

Iminochromenes under thiourea organocatalysis are valuable partners in the F–C alkylation of indoles.

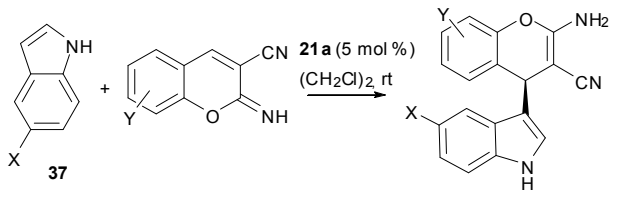


R= Me, Bu, CO_2Et, Ph, 4-FC_6H_4, $BnOCH_2$, $(MeO)_2CH$
R^1= Me, Et, Bu, Ph, C_5H_{11} R-R^1=$(CH_2)_3$
Pg= H, Me, Bn, CH_2=$CHCH_2$ R^2= H, Me, X= H, Me, MeO, Cl, Br



Scheme 12 Oxazaborolidinone catalysis for F-C alkylation of indoles[45]

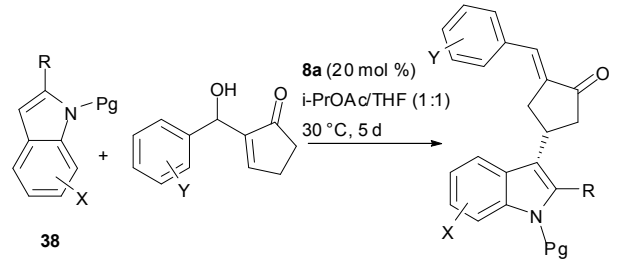
This reaction afforded chiral functionalized 2-amino-4-(indol-3-yl)-4*H*-chromenes in 66-87% yields with 39-86% ee (Scheme 13).[46] The catalyst may act as a bifunctional catalyst, activating indole by hydrogen bonding interaction with the basic nitrogen atom of the cinchona moiety and the iminochromene by the thiourea moiety. Furthermore, the one-pot three-component synthesis of chromene derivatives from indole, salicylaldehyde, and malononitrile has been also reported to provide the desired product in 69% yield with 40% ee (see also section 5 for similar reaction).



X= H, Me, Cl Y= H, 8-EtO, 8-MeO, 6,Cl, 6-Br, 6-MeO, 6,8-Cl_2

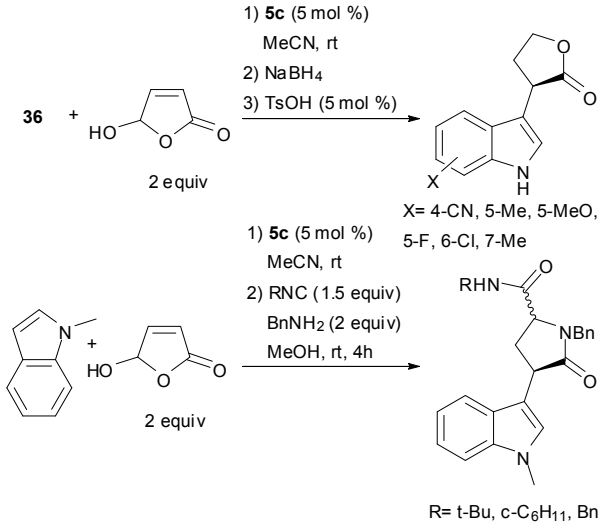
Scheme 13 Synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromenes [46]

Finally, the enantioselective nucleophilic substitution of allyl alcohols should be reported. This reaction is rare and the enantioselective control is a great challenge because free OH may participate in the asymmetric induction and hydoxy group is not a good leaving group. In recent years, Morita–Baylis–Hillman alcohols derived from cyclopent-2-enone were found to enantioselectively react with indoles under catalysis by chiral 9-amino-9-deoxyepiquinine in combination with an acid (Scheme 14).[47] Conjugate addition products were recovered in 68-92% yields with 47-93% ee.



X= H, 5-Br, 5-Me, 5-OMe, 6-Me, Pg= H, Me, R= H, Me, Ph
Y= H, 4-F, 4-Cl, 4-Br, 4-Me, 4-OMe, 4-Ph, 3-OMe, 3-F, 3-Cl, 3-Br

Scheme 14 Asymmetric addition of Morita–Baylis–Hillman alcohols[47]



Scheme 15 Synthesis of enantioenriched indolyl-γ-lactones and γ-lactams [48]

No reaction was observed either with alcohols bearing cyclohexenone moiety or alkyl instead of aryl substituent. Lower

yields and selectivities were observed with *N*-protected indoles. Authors surmised a mechanism in which the primary amine forms an iminium ion in which the *Re*-face is less hindered, and then the protonated tertiary amine moiety assisted the dehydration reaction.

Another unsaturated alcohol used as an electrophile in the F-C alkylation of indoles was 5-hydroxyfuran-2(5*H*)-one.[48] The *in situ* reduction of the F-C adducts afforded indolyl lactones in 85-95% yields with 80-96% ee (Scheme 15). Moreover, the F-C adduct was used also in a three-component Ugi reaction to afford chiral five-membered lactams (74-95% yields, 78-88% ee, but only in about 1.2:1 dr in favour of the *cis* isomer).

2.1.2 Conjugate addition to nitroalkenes

Nitroalkenes are activated alkenes suitable for F-C alkylation with indoles. Moreover, the nitro moiety is very flexible and can be conveniently transformed into numerous molecular motifs. Although this area of research has been more extensively explored using metal catalysis, important organocatalytic enantioselective examples have been appeared in the literature in the last years.[49-54] Hydrogen-bond catalysts are the catalysts of choice for enantioselective reactions.

A DFT calculation to elucidate the reaction mechanism and the origin of the high enantioselectivity was recently carried out with phosphoric acid as the catalyst.[55] The reaction was found to proceed through a cyclic transition state, in which indoles and nitroalkenes are simultaneously activated by Brønsted acidic (proton) and basic sites (phosphoryl oxygen), respectively. The enantioselectivity is entirely controlled by the steric effect between the 3,3'-substituent group on the catalyst and the indole ring. In fact, more sterically demanding groups increase the energy difference between the two diastereomeric transition states that afforded the *S* and *R* products (Figure 3). For instance the energy difference increases from 1.4 Kcal/mol to 2.7 Kcal/mol when the 3,3'-substituent group are 9-anthryl and $SiPh_3$, respectively.

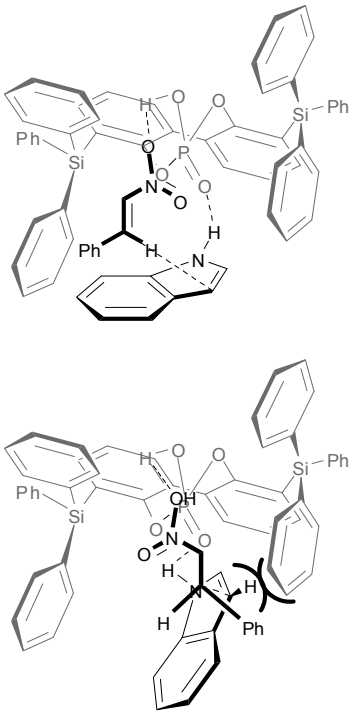
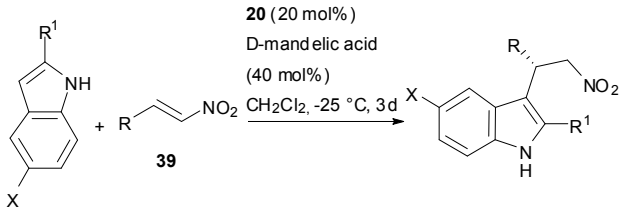


Fig. 3 The two diastereomeric transition states that afforded the *S* and *R* products by DFT calculation [55]



Scheme 16 Thiourea catalysts / Brønsted acids couple for the F-C alkylation of indoles[56]

Moreover, an efficiently modulation of catalyst structure can enhance both the reaction rate and the enantioselectivity when thiourea catalysts are used in these reactions. Recently, Herrera's group showed that a combination of Brønsted acid and thiourea is very effective for the enantioselective F-C reaction of indoles with nitroalkenes.[56] The synergic effect between both species is higher than the effect promoted by each one separately. With the best combination and in the optimum reaction conditions (Scheme 16), adducts were recovered in often unsatisfactory isolated yields (28-94%) but with 82-88% ee except for 2-methylindole adduct (58% ee).

Finally it should be mentioned a recent report about some urea-derived metal-organic frameworks as hydrogen-bond-donating heterogeneous catalysts, which exhibit excellent catalytic activity and very broad substrate scope for the F-C alkylation reactions of indoles with nitroenes, although it is an organocatalyzed non-asymmetric reaction.[57]

2.1.3 Additions to carbonyl derivatives

The addition of indole derivatives to imines, α-ketoesters, and aldehydes provides easy access to the synthesis of enantiopure 3-indolylmethanamine or methanol derivatives, other pivotal structural motifs embedded in numerous natural and unnatural products with significant biological activities. This field has been more widely explored in the year-range covered by this review than in the past.

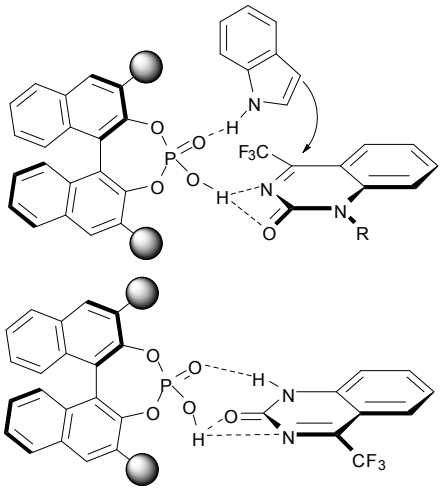
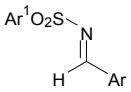
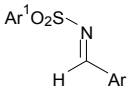
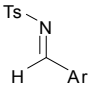
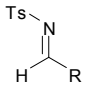
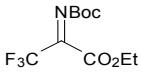
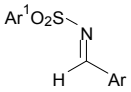
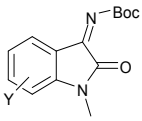
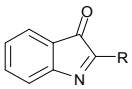
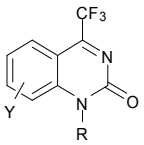
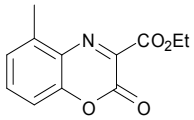
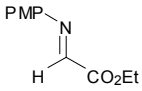


Fig. 4 Surmised transition states for addition of cyclic ketimine s to indoles[58]

Table 1 Organocatalytic synthesis of 3-indolylmethanamines

Entry	Indole	Imine	Catalyst	Yield (%)	ee (%)	Ref
1	**36**		**25** (2.5 mol%) THF 50 °C	85–96 [a] (14 Examples)	84–96 (R)	[59]
2	**36**		**(S)-17a** (10 mol%) PhMe, -60 °C	68-97 [a] (17 examples)	91->99 (S)	[60]
3	**36**		**18a** (2 mol%) DMAP [b] (0.2 mol %) PhMe, rt	90-99 [c] (28 examples)	98->99 (R)	[61]
4	**34**		**18c** (0.25 mol%) DMAP [b] (0.025 mol%) PhMe, -40 °C	88-93 [c] (5 examples)	96->99 (R)	[61]
5	**36**		**(*S*)-13f** (6 mol%) PhMe, -78 °C, 3 h	65-99 [d] (9 examples)	86-96 (R)	[62]
6	**31** (Pg = H)		**16** (5 mol%) PhMe, -60 °C	60-95 [a] (19 examples)	40-95 (R)	[63]
7	**38**		**(*R*)-13m** (5 mol%) Et_2O, 4Å MS, 0 °C, 4 h	92-98 (16 examples)	64-98 (S)	[64]
8	**36**		**14a** (5 mol%) $CHCl_3$/PhMe (3:1) -70 °C	49-98 (15 examples)	79-91 (R)	[65]
9	**36**		**(*R*)-13f** (5 mol%) $(CH_2Cl)_2$, -35 °C	93-98 [e] (20 examples)	85-99 (S)	[58]
10	**36**		**(*S*)-13e** (10 mol%) PhMe, -78 °C	82-99 (9 examples)	94->99 (R)	[66]
11	**36**		**19**·10 H_2O (10-30 mol%) PhMe, -60 or -80 °C	13-99 (6 examples)	14-88 (stereochemistry not reported)	[67]

[a] An item with cyclohexylcarbimine was also reported and lower yields and enantioselectivities were obtained. [b] Addition of DMAP suppressed formation of the side product and the reaction proceeds more chemo-selectively but more slowly. [c] One example was conducted on gram-scale without affect enantioselectivity. [d] An item with *N*-methylindole was also reported to give only 22 % yield and no enantioselectivity. [e] The reaction with 5-cyanoindole gave only 56 % yield after 120 h.

In particular, the addition of *N*-activated imines with electron-withdrawing groups to indoles has been studied. The chiral catalyst should be effective in activating the weakly electrophilic imines to iminium ions, but still compatible with the acid-sensitive 3-indolylmethanamines, to avoid its reaction with indoles to form bisindolylmethanes. In fact, low temperatures are generally requested to suppress bisindolylmethane formation (Table 1). In the years covered by this review, also the reactions with inactivated or cyclic imines were studied.

In most of the reactions reported in table 1, coordination of N-H to the P=O moiety and of imino nitrogen atom to the acidic proton of the catalyst is generally expected to enhance enantioselectivity and forms a chiral environment wherein the indole preferentially attacks the less hindered face of the C=N group (Figure 4, top is an example).

For instance, in the reaction of *3H*-indol-3-one (Table 1, entry 8), the presence of the N-H bond in the indole was found to be crucial in order to obtain high enantioselectivity, because *N*-methylindole afforded the product only with 54% ee.[65] Moreover, the worst results were obtained with the sterically demanding *meta*-substituted imines or 7-substituted indoles, in which the yield was the lowest (49%) and the reaction time the longest (32h), respectively.

However, *N*-H bond have a negative effect on enantioselectivity with iminoisatins, with the result that unprotected indole gave a moderate enantioselectivity (table 1 entry 7).[64]

Trifluoromethyldihydroquinazolines (Table 1, entry 9) have attracted attention, because some derivatives of them are drug candidates as potent HIV non-nucleoside reverse transcriptase inhibitors.[58] In this reaction, *N*-methylindole as well as unprotected cyclic ketimine led to the resulting products with very low enantioselectivity, since protection of indole prevents its coordination, whereas unprotecting the cyclic imine blocks all

coordination sites (Figure 4, bottom).

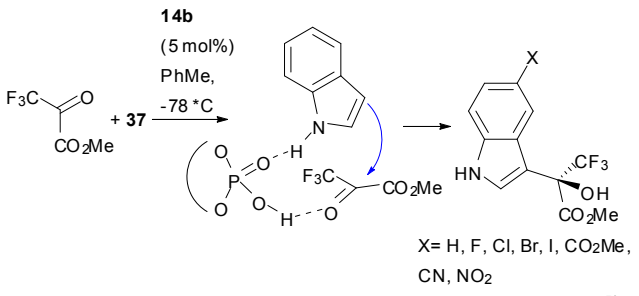
The adducts from the reaction described in table 1, entry 10 can be versatile intermediates in organic synthesis.[66] In fact, authors converted them to important chiral building blocks, such as amino diols, without loss of optical purity.

Other asymmetric acids as the catalysts revealed less efficient (Table 1, entry 11), but coordination of *N*-H to the catalyst is found to be crucial for enantioselectivity, once more. In fact, *N*-methylindole afforded a racemic product. [67]

An organocatalytic F-C reaction of simple ketimines has yet to be reported. In fact, the *E/Z* relative stability of the imine substrate is an important factor for deciding the stereochemical outcome of the reaction, since reaction with the *Z*- and *E*-isomers yields the opposite enantiomers and the little difference in steric effect often do not allow the predominant formation of one imine isomer over the other. However, chiral phosphoric acids were tested as the catalyst for the F-C addition of dehydroalanine esters to indoles. The reaction worked well in non-asymmetric fashion, whereas with chiral catalysts the enantiomeric excess was always low (16-66% being the best results with only 20% yield).[68] Moreover, other organic Brønsted acid catalysed the same reaction allowing for the synthesis of achiral bis(indolyl)alkanes or, when 2- or 4-bulky substituted indoles were used, indolyl acrylates by elimination, both achiral compounds.[69]

Trifluoropyruvates are another largely used carbonyl derivative for F-C alkylation reaction of indoles, because generally the trifluoromethyl group changes the physical, chemical, and biological properties of the molecules owing to its strong electron-withdrawing property.

Phosphoric acids catalysed the reaction leading to 95-100% yields of the adducts with 80-98% ee (Scheme 17).[70] Dilution enhanced enantioselectivity, depressing the racemic background reaction. Also in this reaction, the presence of the N-H moiety of the indole ring is essential to attain high enantioselectivity, thus phosphoric acid is assumed to activate the carbonyl group and, at the same time, the phosphoryl oxygen atom forms a hydrogen bond with the N-H moiety.



Scheme 17 Asymmetric addition of trifluoropyruvate to indoles [70]

The F-C reaction of indoles (**32**) with trifluoropyruvates was also performed with 5 mol% of C3-symmetric cinchonine-squaramide (**26**).[71] Enantioenriched trifluoromethylindoles (14 examples) were prepared in 75-99% yields with 80->99% ee. The stereochemistry was the same as with **14b**. Ethyl trifluoropyruvate generally gave a higher ee than methyl trifluoropyruvate. The poor solubility of the catalyst allowed its recycling up to five times without loss of efficiency.

The reaction was also attempted in Solkane® 365mfc in the presence of the 4-(perfluorooctyl)benzyl ether of cupreidine and cupreine (10 mol%).[72] These new catalysts were prepared in order to improve solubility of cinchona alkaloids into hydrofluorocarbon solvent. Nine different adducts in both enantiomeric forms were obtained in 17-99% yields and 43-85% ee.

The adduct of the addition of 6-cyanoindole to ethyl trifluoropyruvate (Figure 5) was prepared in both enantiomeric forms by employing cinchonidine and cinchonine as the catalyst for the (+) and the (-)-isomers, respectively.[73] This compound was the key intermediate for the synthesis of non-steroidal glucocorticoid receptor modulators. The optimized method can be applied to 100-g scale synthesis with 90% ee, in 84% yield. The catalyst can be separated and reused.

The same research group described the asymmetric synthesis of [^{14}C]-labelled glucocorticoid receptor modulator (-)-piperidin-4-yl)oxy]-3-methoxyphenyl}acetic acid, based on optimization of the cinchonidine catalysed addition of 6-bromoindole to ethyl trifluoropyruvate with high enantioselectivity (>99% ee) and 99.5% radiochemical purity.[74] The change of the optical rotation during the synthesis should be noted.

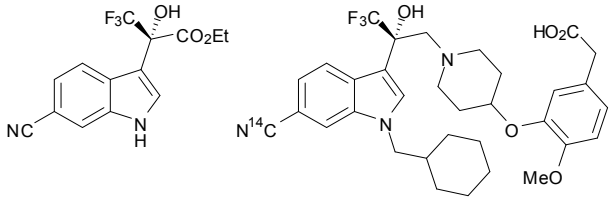
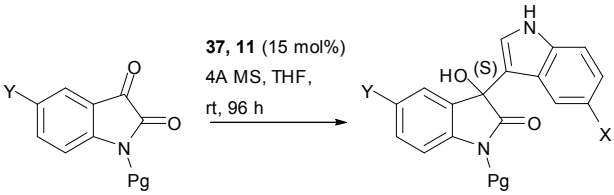


Fig. 5 (+) 6-cyano-3-[3-ethoxycarbonyl-1,1,1-trifluoro-2-hydroxy-propan-2-yl]-1*H*-indole and (-)-{4-[(1-{2-[6-cyano-1-(cyclohexylmethyl)-1H-indol-3-yl]-3,3,3-trifluoro-2-hydroxypropyl}piperidin-4-yl)oxy]-3-methoxyphenyl}acetic acid(the stereochemistry is not reported in ref [73, 74], but positive rotation was observed for compounds with the reported stereochemistry in ref [71]

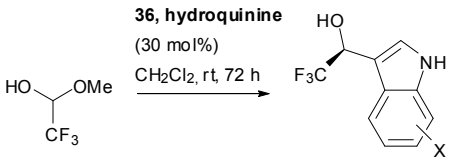


Scheme 18 Asymmetric addition of indoles to isatins [75]

The organocatalytic F-C addition of isatin to indole was performed with **11** as the catalyst in 88-99% yield with 80-99% ee (Scheme 18).[75] The reaction is scalable until gram-scale in 91% yield and 95% ee. After a single recrystallization 81% product was isolated with >99% ee. From observation of the reaction course with quinuclidine quaternary salts or 6'-O-protected catalysts and N-protected indoles, a transition state involving a ternary complex between the catalyst, isatin, and indole has been proposed by authors. The 6'-hydroxy group of the cinchona alkaloid activates the carbonyl group of isatin through hydrogen bonding, the quinuclidine *N*-group binds and orients the indole through the formation of a hydrogen bond with N-H.

Another class of carbonyl derivatives often used as reagents for F-C alkylation of indoles are hemiacetals and hemiaminals.

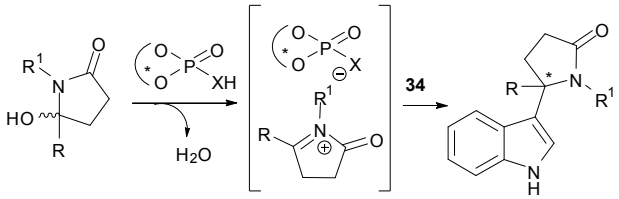
For instance, enantioenriched trifluoro-1-(indol-3-yl)ethanols were prepared in 92-98% yields with moderate enantioselectivities (30-75% ee) from indoles and inexpensive trifluoroacetaldehyde methyl hemiacetal. The reaction is catalysed by hydroquinine at room temperature (Scheme 19). The enantioselectivity is strongly dependent on the concentration of substrates and catalyst due to the competitive non-catalysed reaction.[76] The mechanism proposed by authors involved two hydrogen bonds through the weakly acidic indole N-H and quinuclidine N, and through the OH of hydroquinine and the carbonyl of trifluoroacetaldehyde. This cyclic arrangement provides the chiral environment for enantio-differentiation leading to the favoured formation of (*S*)-isomer. The presence of substituents in the N-1 or C-2 positions of indole would disrupt this cycle and, actually, result in racemic or no product, respectively.



X= H, 5-F, 5-Cl, 5-Br, 5-I, 5-MeO, 5-BnO, 5-Me, 7-Et

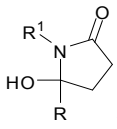
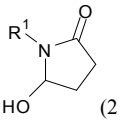
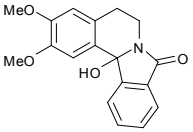
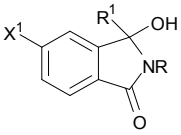
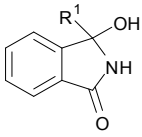
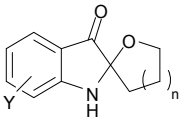
Scheme 19 Synthesis of trifluoro-1-(indol-3-yl)ethanols [76]

Hemiaminals, especially hydroxylactams, were employed as synthetic equivalents of iminium ion. Then, asymmetric organocatalytic addition of a nucleophile such as indole allows for the preparation of enantioenriched adducts. The concept of "asymmetric counteranion-directed" catalysis has been invoked to explain the enantioselection in these reactions. The acid generates a chiral ion pair (Scheme 20) by protonation of the hydroxylactam and forms a hydrogen bond with the indole *N*−H moiety. The steric interaction between the *N*-acyliminium ion and the congested catalyst would determine the orientation inside the chiral pocket of the catalyst. It should be noted that although stoichiometric amounts of water are released during the reaction, addition of molecular sieves did not generally result in an enhanced reactivity or in a significant drop of enantioselectivities.



Scheme 20 Surmised mechanism for α-amidoalkylation of indoles with *N*-acyliminium ions

Table 2 α-Amidoalkylation of indoles with *N*-acyliminium ions formed in situ from cyclic hydroxylactams.

Entry	Indole	Hydroxylactam	Catalyst	Yield (%)	ee (%)	Ref
1	**34**	 (2 equiv) [a]	**14d** (5 mol%) CH_2Cl_2, -65 or 20 °C, 48 h	20-93 (10 examples)	53-86 (stereochemistry not reported)	[77]
2	**34**	 (2 equiv)	**(*R*)-13n** (5 mol%) $(CH_2Cl)_2$, rt 18 h	60-99 (16 examples)	10-99 [b] (S)	[78]
3	**37**		**(*R*)-13f** (20 mol%) THF, rt, 24 h	70-79 (3 examples)	58-74 (R)	[79]
4	**36**		**14c** (5 mol%) $CHCl_3$, rt	46-99 (16 examples)	24-83 [c] (R)	[80]
5	**36**		**14c** (5 mol%) MeCN, 20 °C	59-99 (25 examples)	56-95 (R)	[81]
6	**36**		**(*S*)-13f** (5mol%) 4Å MS CH_2Cl_2, -70 °C	88-98 (15 examples)	88-99 (S)	[82]

[a] Prepared in two steps from succinic anhydride. [b] The lowest ee was observed with 2-arylindole. [c] Only 2% ee for N-substituted isoindolines.

The examples of this reaction collected in table 2 appeared in the literature in the time-range of this review.

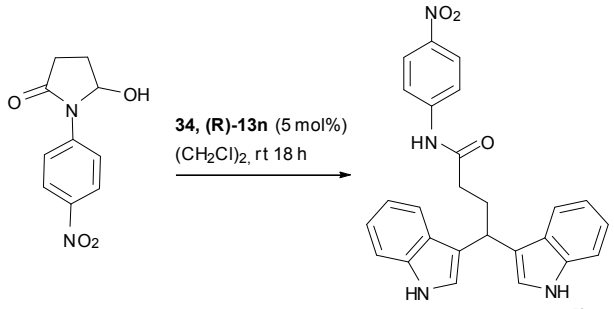
Masson and co-workers (Table 2, entry 2) found that, when a C-3-substituted indole was employed, the *N*-alkylated regioisomer was recovered with 20% ee.[78] When *N*-(4-nitrophenyl)hydroxylactam was used, a double alkylation product with the lactam ring being opened was obtained solely (Scheme 21).

During setting up the best condition for the reaction described in Table 2 entry 4, Wang and Zhou found that, the product was

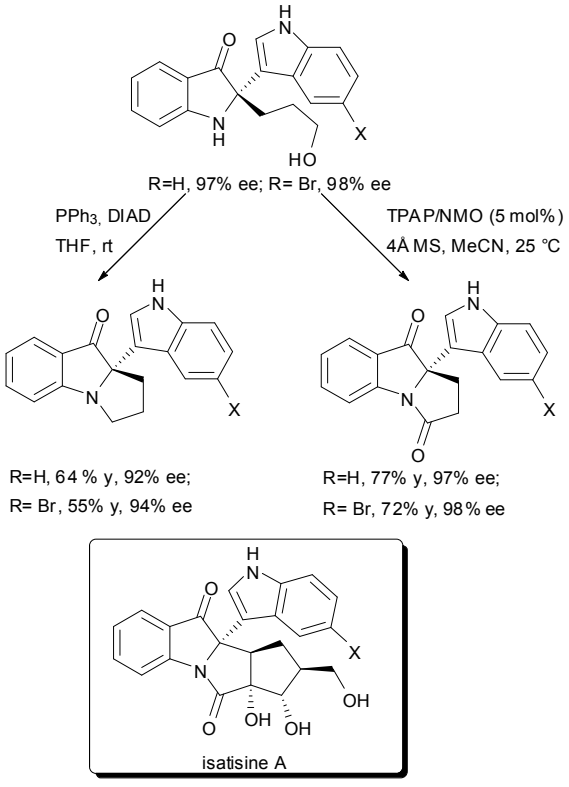
recovered with opposite optical rotation simply by changing the 3,3'-substitutent of (*S*)-phosphoric acid from R = Ph to R = 4-MeC_6H_4.[80] Then, they optimized the conditions for the formation of quaternary stereogenic compounds (Table 2 entry 5).[81]

The adducts from the racemic spiro indolin-3-ones (Table 2, entry 6) contain a free hydroxyl group that provides a versatile handle for performing subsequent transformations (Scheme 22).[82] For instance, treatment with PPh_3/DIAD or under Ley oxidation conditions a tricyclic compound was obtained with good stereochemical integrity. The latter tricyclic motif exists in isatisine A, thus potentially it could be a key intermediate for its synthesis or for related compounds.

Reactions with simple aldehydes or ketones are rarer. In the time-range covered by this review, three examples appeared in the literature.



Scheme 21 Unexpected bis-alkylation with hydoxylactams[78]

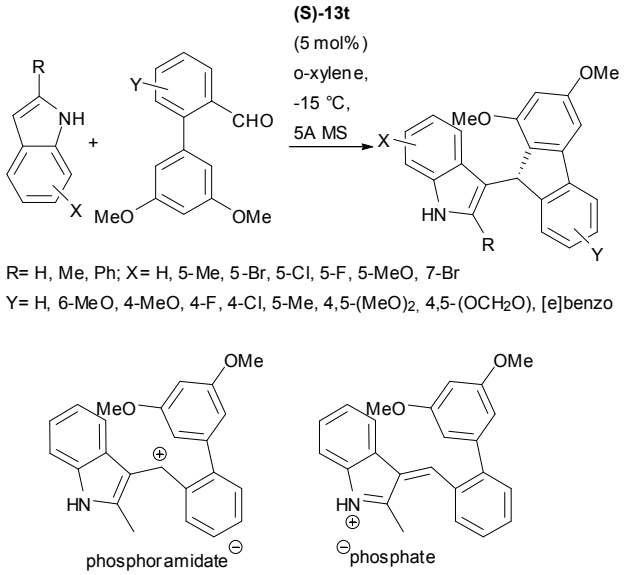


Scheme 22 Synthesis of potential key intermediates of isatisine A[82]

Indoles and 2-formylbiphenyl derivatives undergo double Friedel–Crafts reaction to 9-(3-indolyl)fluorene derivatives in 35-98% yields, with 2-94 % ee under **(*S*)-13t** catalysis (Scheme 23).[83] The worst results were obtained with indole and 2-phenylindole, thus indicating that 2-methylindoles are the best substrates for this reaction. Protection of the indole with methyl group led to complete conversion to fluorene but only in 34% ee.

With less electron-activated biphenyls (only a MeO group in a conjugate position), reaction has to be run at room temperature, otherwise bisindole derivatives are recovered. Finally, comparing to its corresponding chiral phosphoric acid **(*S*)-13b**,[84] phosphoramide **(*S*)-13t** catalysed reactions led to products with opposite absolute configuration. A plausible reaction mechanism was proposed by authors: after the first Friedel–Crafts reaction, the secondary alcohol is converted into a cation, where the close counteranion creates a chiral environment to control the enantioselectivity over the second Friedel–Crafts alkylation reaction.

The reaction with chiral *N*-triflylphosphoramide might form different type of counterion comparing to chiral phosphoric acid (carbon versus nitrogen, Scheme 23), which likely contributes to reverse the absolute configuration of the product.



Scheme 23 Synthesis of 9-(3-indolyl)fluorene derivatives [83]

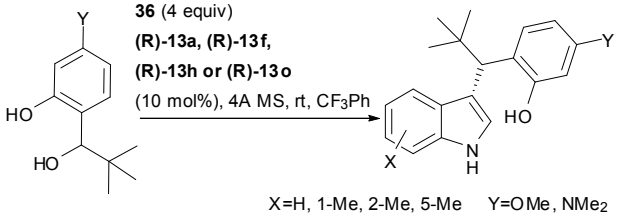
2.1.4 Other F-C reactions

As the only example in this section, we mention the reaction of methyl-substituted indoles with secondary *ortho*-hydroxybenzylic alcohols in the presence of chiral phosphoric acids, by a close counteranion catalysis, thus reinforcing the mechanism envisaged with hemiaminals and hemiacetals (Scheme 24).[85] While yields are generally high (>90%), every substrate needs of a particular catalyst and significant enantioselectivity (77% ee) is only achieved for the substrate–catalyst combination affording the lowest yield (23% of the reacted starting material). It should be noted that in some incomplete reactions, a kinetic resolution of the starting material was observed. The presence of a close contact ion pair and no direct SN2-type substitution was confirmed by the reaction of such enriched starting materials with racemic phosphoric acid, which led to a racemate.

2.2 Addition to 3-substituted indoles

In the previous sections, we considered the catalytic asymmetric addition of indoles to various electrophiles, but there is another

main method for preparing chiral 3-substituted indoles to be used especially in the absence of an appropriate electrophile: the catalytic asymmetric addition of various nucleophiles to achiral 3-functionalized indoles. These sections are devoted to these reactions.



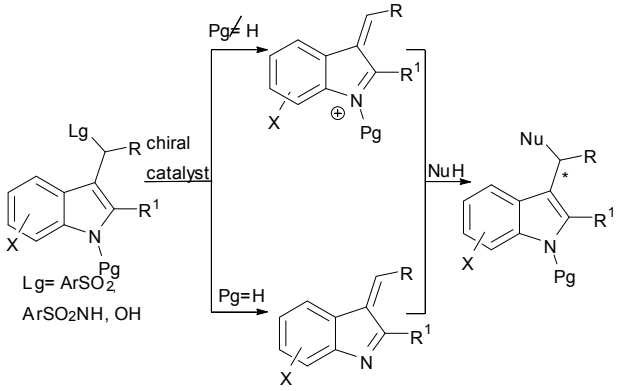
Scheme 24 Reaction of indoles with *o*-hydroxybenzylic alcohols[85]

2.2.1 Via vinyliminium or imine intermediates

In recent years, a formal nucleophilic substitution of a leaving group (L_g) such as an arylsulfonyl, hydroxy, or sulfonamido group at the "benzylic" 1'-position of achiral 3-substituted indoles has emerged as an alternative approach for introducing a chiral side chain (Scheme 25). This approach was introduced by Petrini's group in 2006 in racemic form [86] and found to pass through the formation of vinylimine (or iminium) intermediates. Recently, enantioselective catalysis was introduced and these reactions are collected in table 3. Generally, the reaction works better with 2-substituted indoles.

The direct organocatalytic coupling of substituted diketopiperazines with indolenins from 3-(-1-arylsulfonyl-alkyl)indoles has been developed by some cinchona alkaloid derivatives as organocatalysts. However, although organocatalyst are chiral, authors do not report enantiomeric excesses of their reactions. [87]

The reaction between 2-unsubstituted indole and nitroalkanes was unsuccessfully attempted by Dobish-Johnston (65% yield, with 40 % ee (*1'S,2'S*) and racemic diastereomer)[88] and by Bernardi-Petrini's group [60 (4 % ee) : 40 (18 % ee)].[89]

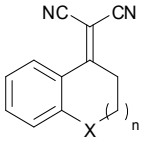
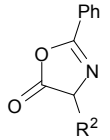


Scheme 25 Nucleophilic asymmetric substitution of a leaving group at the 1'-position of 3-substituted indoles

Dobish-Johnston also carried out the reaction in toluene/water mixtures without significant variations in yields and selectivities.[88] Finally they reduced adducts by denitration and the diastereomeric mixture led to the convergent reduced product in comparable enantioselectivity.

Bernardi-Petrini's group carried out the reaction in solvent-free conditions (a slight excess of nitroalkane is enough to ensure homogeneity) and adducts are easily and efficiently reduced to tryptamines without loss of enantiopurity.[89]

Table 3 Asymmetric nucleophilic substitution of p-Ts group from racemic 3-substituted indoles

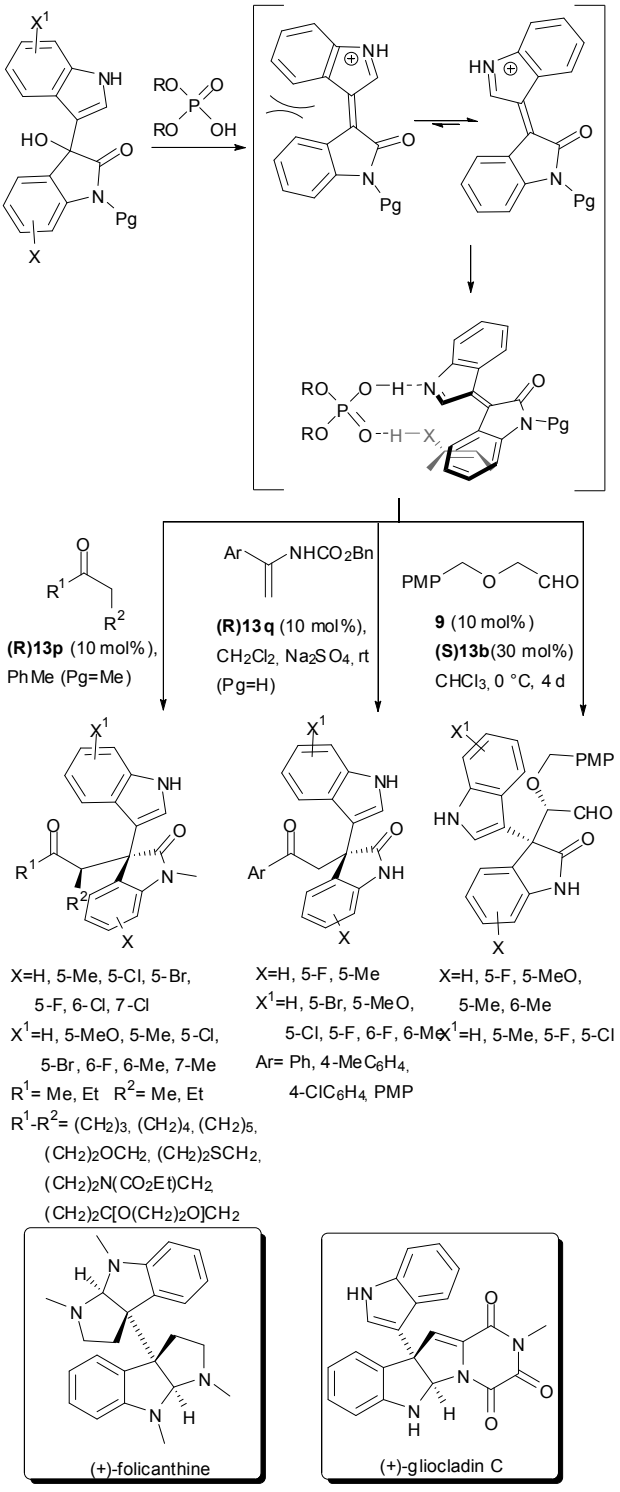
Entry	NuH	Catalyst	Yield (%)	ee (%)	Ref
1	$R^2CH_2NO_2$	**27** (10 mol%), K_2CO_3, PhMe, rt, 22 h	47-78 (14 examples)	37-89 [a]	88
2	$R^2CH_2NO_2$	**21b** (10 mol%), K_3PO_4, rt, 60 h	60-97 (19 examples)	62->99[b]	89
3	$CNCH_2CN$	**22a** (10 mol%), K_3PO_4 PhMe, 30 °C, 24 h	70-95 (13 examples)	65->99 (S)	90
4		**23a** (20 mol%), K_2CO_3. PhMe, 30 °C, 16 h	60-93 (20 examples)	71->99 [c]	91
5		**21c** (20 mol%), K_3PO_4, PhMe, 30 °C, 2 h	40-88 (19 examples)	50-97[d]	92
6	$CHF(SO_2Ph)_2$	**12** (10 mol%), Cs_2CO_3, PhMe, -10 °C, 3-5 d	54-99 (13 examples)[e]	17-97 (R)	93
7	2-naphthols	**22a** (10 mol%), K_3PO_4, PhMe, 30 °C, 24 h	64-96 (22 examples)	65-98 (R)[f]	94

[a] dr from 50:50 to 60 (*1'S,2'S*):40 (*1'S,2'R*). [b] Three examples are also reported with **22b** and enantiomers are obtained in comparable yields and selectivity; dr about 60:40 when appropriate, being (*1'S,2'S*) the major isomer. [c] dr from 52:48 to 99:1 being (*1'S,2'R*) the major isomer. [d] dr from 58:42 to 90:10 being (*1'R,2'S*) the major isomer. [e] Cinchonidine derivative afforded the enantiomer in comparable yield and selectivity; 2-unsubstituted indole gave a racemate. [f] When R = t-Bu and i-Bu only racemate and 13% ee were obtained, respectively; 2-unsubstituted indole gave 26% ee.

In the addition of cyanoolefins, the use of **22a** afforded the enantioenriched adduct in 60% yield with 99:1 dr and 90% ee. Furthermore, an instance with non-cyclic dicyanoolefin also furnished the vinylogous Michael addition product in 74% yield, 80:20 dr and 96% ee.[91]

Recently, 3-hydroxy-3-indolyoxindoles emerged as precursors of stable carbocations or vinylogous imino intermediates (L_g = OH and R = 2-oxyndol-3-yl, Scheme 25) in the nucleophilic substitution reaction with various nucleophiles, thus providing 3,3'-disubstituted oxindoles with the creation of a quaternary all-carbon stereogenic centre at C-3. The reaction proceeds through a sequential dehydration/Michael addition reaction with the

phosphoric acid activating the unsaturated iminium species through hydrogen-bonding interactions.



Scheme 26 Asymmetric nucleophilic substitution of 3-hydroxy-3-indolyoxindoles with ketones[95], enecarbamates [96] and aldehyde[97] (in the mechanism ring-substituents are omitted for simplicity)

Both speculative mechanistic hypothesis (favouring a *trans*-vinylogous imino intermediate for lower steric interactions, Scheme 26)[95] and theoretical studies using DFT calculations (favouring by approximately 1 kcal/mol^{-1} a tilted *cis*-vinylogous imino intermediate)[96] suggested that nucleophile attacks from the less sterically demanding *Re*-face.

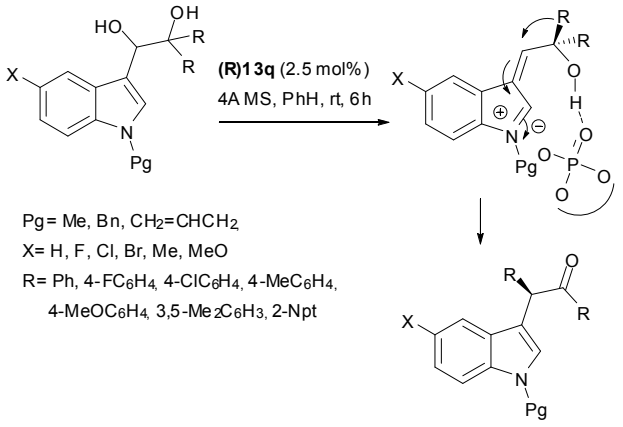
The reaction with ketones afforded (*R,R*)-adducts in 27-98 % yields (the lower values for acyclic ketones) with 78:22-99:1 dr and 74-97% ee.[95] Unfortunately, reaction temperature and reaction times have to be adjusted for each substrate.

The reaction with enecarbamates afforded (*R*)-adducts in 70-92% yields with 90-96% ee. The importance of this reaction was showed in the construction of the 3a,3a'-bispyrrolidino[2,3-b]indoline core of (+)-folicanthine.[96]

Then the reaction was extended to 2-alkyloxyacetaldehyde. The cinchona-based primary amines were chosen for their success in the control of stereoselectivity in either enamine or iminium catalysis.[97] However, the classical couple (cinchona alkaloid-based amines and TFA) was ineffective, while the presence of a chiral phosphoric acid as a cocatalyst dramatically enhances the stereochemical control. In particular, the (*S*)-phosphoric acid was proven a matched cocatalyst, whereas the *R*-enantiomer was ineffective. In addition, p-methoxybenzyl framework was found to be the protecting group ensuring the best results. Actually, products were recovered in 53-89% yield with 86:14-91:9 dr and 94-97% ee (*R,S*-isomer).

This procedure was also applied in a 12-steps enantioselective total synthesis of (+)-gliocladin C in 19% overall yield from 3-hydroxyoxindole.

Another reaction involving a carbocation is the pinacol rearrangement of 1',2'-diols to chiral (*R*)-α-indolyl ketones with 83-99% yields and 91-96% ee (Scheme 27).[98] the chiral phosphoric acid was envisaged to induce dehydration to an iminium intermediate with two-point binding (hydrogen-bonding and electrostatic interactions) with the catalyst. Thus, a face is shielded and subsequently only the aryl group on the less hindered face could rearrange.

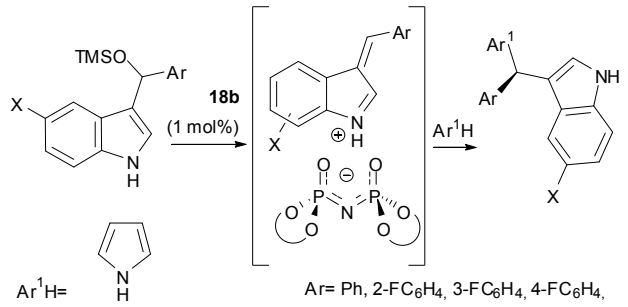


Scheme 27 Pinacol rearrangement[98]

p-Phenyl-substituted bisindolylmethanes are very effective drugs in the treatment of cancer. Thus, the development of high enantiocontrol in the synthesis of triarylmethane molecules becomes important in the last years.

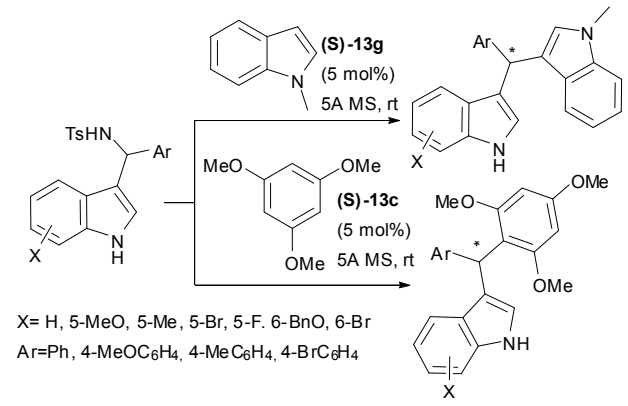
For instance, chiral imidodiphosphoric acids with different

3,3'-substituents catalysed highly efficient and enantioselective F-C-type alkylations for the construction of bisindolyl- and pyrrolylindolylmethanes with a low catalyst loading (1 mol %).[99] This reaction is issued in this section and not in sections above, because the staring material is a formal indolylcarbocation. Triarylmethanes were synthesized in 62- 99% yields with 77-96% ee (Scheme 28). Configuration of the stereocentre was only defined as (R) for bisindoles, whereas no information was given for pyrrolylindoles.



Scheme 28 Synthesis of triarylmethanes from diarylmethanols[99]

On the other hand, during the studies on the chiral phosphoric acid catalysed F-C reaction of indole with imines (see Table 1) a side reaction affording triarylmethane by-products with two indole groups was sometimes observed. This fact prompted You and co-workers to explore the alkylation of a (3-indolyl)methanamine with another electron-rich arene. Actually, in the presence of a chiral phosphoric [**(*S*)-13j** or **(*S*)-13c**], the unsymmetrical triarylmethanes were obtained in 19-91% yields and 45-65% ee (Scheme 29). [100]



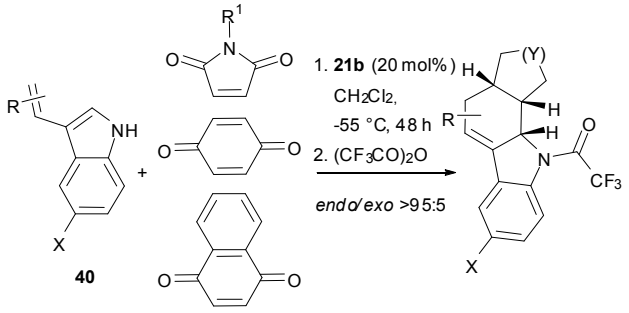
Scheme 29 Synthesis of triarylmethanes from diarylmethanamine

When 1,3,5-trimethoxybenzene was tested the two prepared triarylmethanes were obtained in 64% ee and 91% ee, respectively. However, the yields remained very poor due to the formation of dialkylation by-products. Another interesting feature of this reaction is the possibility of kinetic resolution of the starting methanamines. In fact, carrying out the reaction with a ratio of 1:0.6 for methanamine/arene, (*R*)-methanamine was recovered in 49% yield with 35% ee. However, the configuration of the triarylmethane is not given. Moreover, no product is superimposable with those reported in Scheme 28 and optical rotation does not help because some products have positive other negative α_D.

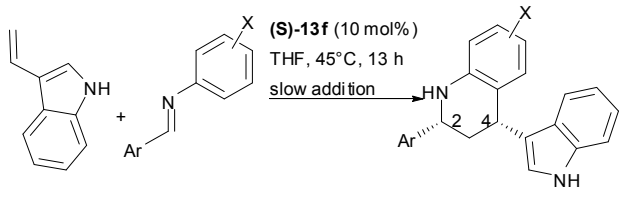
2.2.2 Cycloaddition reactions

The enantioselective Diels-Alder (D-A) and hetero-D-A reactions of 3-vinylindole derivatives using H-bond driven organocatalysis have attracted great attention.

The reaction of maleimide and benzoquinone with 3-vinylindoles proceeds under mild conditions to give optically enriched *endo*-tetrahydrocarbazoles in 51-98% yields and 52->99% ee (Scheme 30).[101] The enantiomeric product was recovered in comparable yields and enantioselectivity with the pseudoenantiomeric catalyst **22b**. Although an *E*/*Z* mixture (1:1) was employed as the starting material, only (*E*)-3-(propen-1-yl)indole noteworthy underwent the cycloaddition reaction, giving the expected product as a single diastereoisomer. Partially based on experimental evidences and partially speculative, the operational mode of the catalysis was established by authors according to HOMO and LUMO activation by the Brønsted basic and acidic sites of the organocatalyst, respectively, in a highly organized hydrogen bond network.



Scheme 30 Optically enriched tetrahydrocarbazoles by D-A reaction[101]

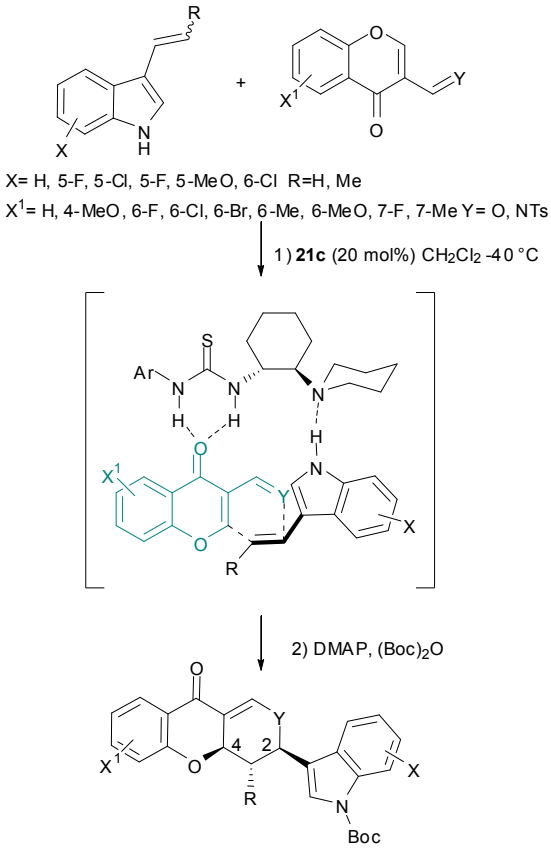


Scheme 31 Optically enriched tetraquinoline by D-A reaction[102]

The Povarov reaction is an inverse-electron-demand [4+2] cycloaddition between an *N*-arylimine (diene) and an electron rich olefin (dienophile), which is the vinylindole in this case. Catalyst **(*S*)-13f** was found efficient in a wide range of arylimines.[102] The cycloadducts were obtained in 44-98% yields, 90:10->98:2 *cis : trans* ratio and 73-98% ee (*2R,4R*-isomer, Scheme 31). Using a three-component procedure involving the formation of the imine in situ, even unstable imines could be successfully engaged.

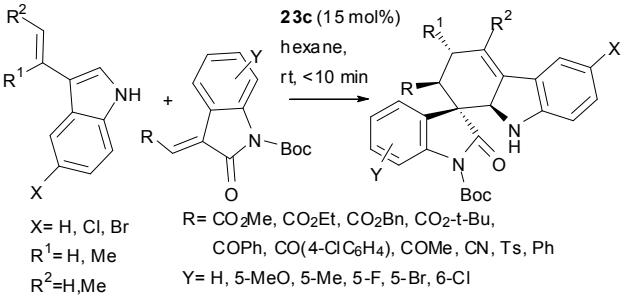
Structurally and biologically interesting chiral flavonoids incorporating chromanone, dihydropyran, and indole structures

have been constructed through catalytic asymmetric inverse-electron-demand [4+2] cycloaddition of chromone oxadienes and 3-vinylindoles (Scheme 32). The reaction proceeded smoothly to afford the adducts with 42-91% yields, 12-94% and 67-97% ee for the (*2R,4R*)-*endo* and (*2R,4S*)-*exo* products, respectively, although the *endo/exo* ratios of the product are moderate (not exceeding 79:31 dr).[103] However, the two diastereoisomers could be easily separated by flash chromatography and the reaction can be performed on the gram-scale without loss of enantioselectivity. Also in this reaction, only (*E*)-3-(propen-1-yl)indole underwent the reaction from 1/1 *E/Z* mixture, giving the *endo* product with only 12% ee and unfavourable ratio with *exo* isomer (38:62 dr).



Scheme 32 Reaction of chromone heterodienes with 3-vinylindoles[103]

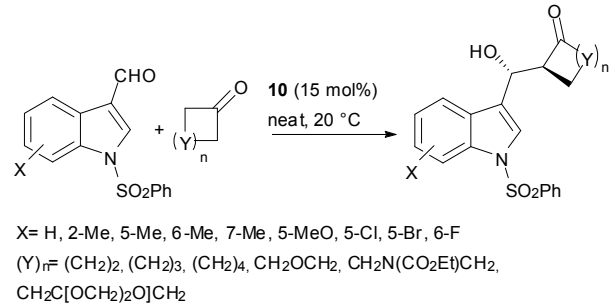
Carbazolespirooxindole derivatives were synthesized in 75-99% yields with 88-99% ee of an almost single diastereomer by stereocontrolled D-A reaction of 3-vinylindoles and alkylideneoxindoles, catalysed by **23c** (Scheme 33).[104] Recycling of the organocatalyst is favoured by the difference in the solubilities of the D-A adduct and the catalyst. The former precipitates from the reaction mixture, whereas the latter remained in solution, which is used for the next cycle of the D-A reaction. This procedure can be repeated several times with only a marginal loss of performance. Moreover, the reaction was scaled-up to gram-scale. Although the mechanism of this reaction has not been completely elucidated, some features were described: strong interactions between catalyst and the methyleneindolinone were observed in the ^{13}C NMR spectra. No evidence of catalyst interactions with 3-vinylindole was found by NMR, but the reaction with 1-methyl-3-vinylindole indicated that the N-H group of the vinylindole is essential. On the other hand, only Boc-protected 3-methyleneoxindole derivatives provided a stereocontrolled product. The unusual *exo*-selectivity suggested that interactions additional to H-bonds between the oxindole and vinylindole such as π–π bonding interactions.



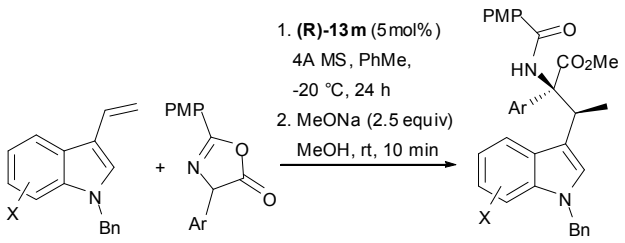
Scheme 33 D-A reaction of 3-vinylindoles and methyleneindolinones).[104]

2.2.3 Other reactions

An efficient aldol reaction of *N*-benzenesulfonyl-protected indole-3-carbaldehydes with cyclic ketones afforded 3-indolylmethanols in 28-96% yields with 54:46-97:3 *anti*-stereoselectivities, and 92->99% ee (Scheme 34).[105] Among aliphatic ketones, 2-butanone reacted in 36% yield, with 60:40 *syn*-stereoselectivity (reversed with respect cyclic ketones), with 94% ee of the major isomer, while acetone and 3-pentanone did not react. In addition, *N*-benzenesulfonyl indole-2-carbaldehyde was tested with cyclohexanone, and adduct was recovered in 88% yield, 90:10 *anti*-stereoselectivity and 96% ee at 0 °C.



Scheme 34 Organocatalytic aldol reaction of indole-3-carbaldehydes with ketones[105]



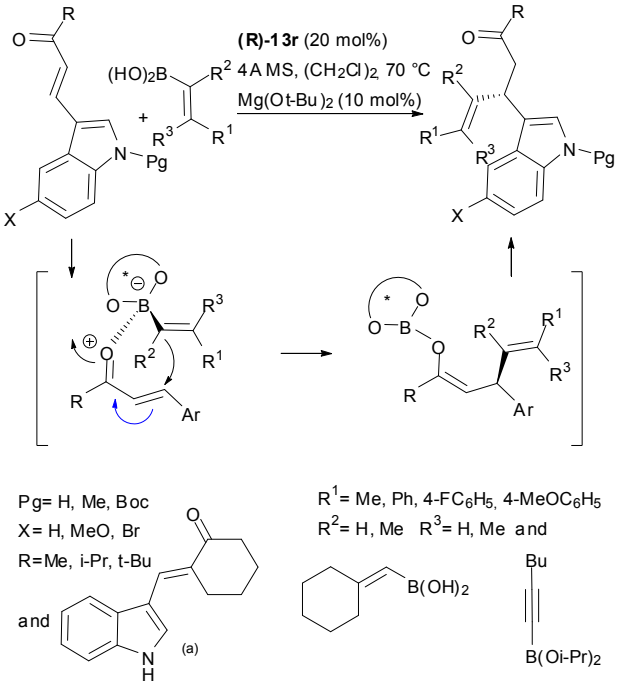
Scheme 35 Synthesis of enantioenriched tryptophan derivatives[106]

Moreover, the enantioselective addition of a nucleophile to the double bond of 3-vinylindoles catalysed by phosphoric acid has

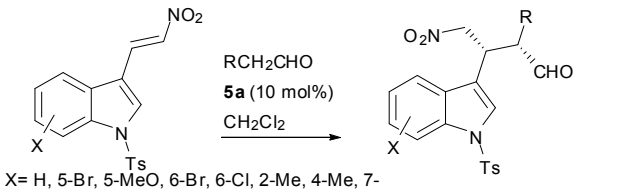
been proposed by Terada and co-workers. [106] In the presence of **(*R*)-13m**, the addition of oxazol-5(4*H*)-ones to 3-vinylindoles was performed and tryptophan derivatives with adjacent quaternary and tertiary stereogenic centres were obtained in 35-87% yields, 91:9 to 98:2 *syn*-selectivity and 75-95% ee (Scheme 35). Such derivatives are potentially useful for the preparation of conformationally restricted peptides. Once more, the reaction with (*E*)- and (*Z*)-3-(prop-1-enyl)indoles showed marked differences in the reactivity, and the *E*-isomer led again to better results (69% yield, 86 (74% ee) : 14 (22% ee) *syn*-selectivity).

The addition of a nucleophile to 3-(1'-2'-unsaturated)indoles is another explored strategy for the creation of chiral stereocentres at the indole 3-position.

For instance, this stereocentre has been created at the benzylic position of the indole by the addition of alkenyl and alkynyl boronic acids to β-(indol-3-yl)-α,β-unsaturated ketones catalysed by a chiral phosphoric acid catalyst (Scheme 36).[107] Addition of 10 mol% of $Mg(Ot\text{-}Bu)_2$ as an additive increased the yield and products were recovered in 70-91% yields with 87-99 % ee. The reaction is supposed to occur with formation of a "ate complex" between catalyst, boronic acid and indolyl chalcone. Next, the alkenyl group intramolecularly transfers from the boron "ate complex" in the *s-cis* conformation to form an enol borate. This protocol was then applied in an enantioselective synthesis of antimalarial compounds flinderoles and borreverines.[108]



Scheme 36 Addition of alkenyl and akynylboronic acids to β-(indol-3-yl)-α,β-unsaturated ketones)[107, 108]
[(a)] dr 55:45 but stereochemistry is not specified



Scheme 37 Addition of aldehydes to indolylnitroalkenes[109]

The Michael addition of aliphatic aldehydes to indolylnitroalkenes has been developed using **5a** as the organocatalyst. The desired optically enriched *syn*-derivatives was recovered in in 90-98% yield in 97:3–>99:1 dr and always >99% ee (Scheme 37).[109] Authors claimed (*1'R,2'S*) stereochemistry for the products but they did not report experimental evidence of how this stereochemistry was elucidated. In addition, isobutyraldehyde was also used, but only 26% yield and 87% ee of the desired product were obtained. Moreover, (±)-citronellal afforded a diastereomeric couple of products in 52% and 31% yields with >99% ee, once more, the exact stereochemistry of each one was not reported. The obtained products were then converted into 1,4-amino alcohols, γ-amino acids, and tryptamine derivatives without affecting diastereo and enantioselectivities.

3. Functionalization at C-2

2-Substituted indoles are potential intermediates for many alkaloids and pharmacologically important substances. If indole undergoes electrophilic substitution preferentially at C-3-position, pyrrole gives reaction at C-2-position, as well explained by the stability of the Wheland intermediates for the electrophilic substitution. Based on these features, 4,7-dihydroindoles are good intermediates for the synthesis of 2-substituted indoles. In fact, they are pyrroles in nature, but they can easily be converted into indoles by oxidation.

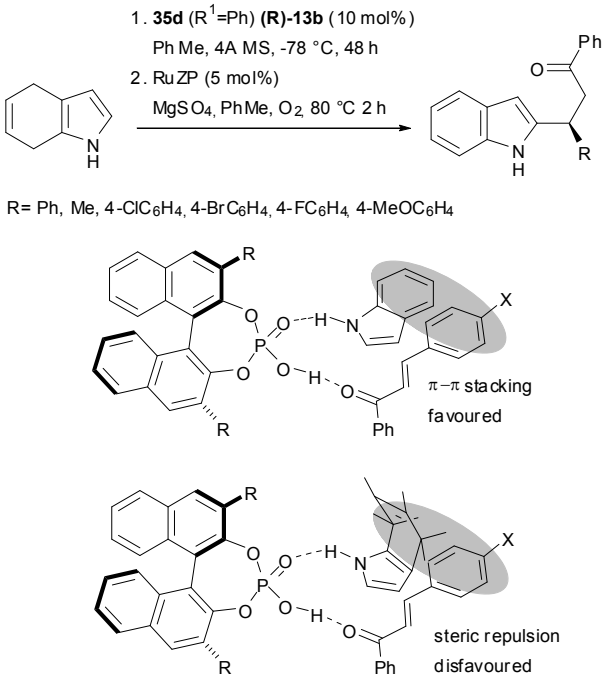
Other interesting indole derivatives are compounds containing the tetrahydro-β-carboline core, because of their inherent biological activity. These compounds are generally obtained via the P-S reaction that allows cyclization on the C-2-position of the indole core of tryptamine with a variety of aromatic and aliphatic carbonyl compounds in the presence of a Brønsted acid.

Recently also asymmetric cycloaddition reactions of quinidomethanes and 2-vinylindoles have been employed to build enantio-enriched 2-substituted indoles.

3.1 F–C of 4,7-dihydroindoles

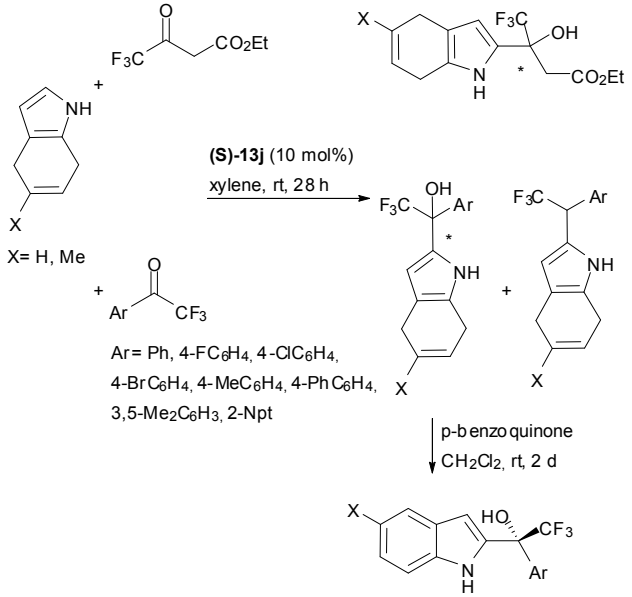
The origin of the enantioselectivity of the chiral phosphoric acid-catalysed Friedel–Crafts reactions between 4,7-dihydroindoles and nitroolefins has been studied by DFT calculation using complete models on PBE1PBE/[6-311+G(d,p), 6-31G(d,p)] level. Depending on the catalyst, the enantioselectivity of the reaction is controlled either by the steric effect between the catalyst and the substrate or by the solvent effect.[110]

In section 2.1 we already reported asymmetric F–C alkylation of indoles with α,β-unsaturated ketones catalysed by chiral phosphoric acid, set up by Akijama and co-workers.[38] This method could also be applied to the asymmetric synthesis of 2-substituted indole, starting from 4,7-dihydroindole. The asymmetric F–C alkylation reaction with α,β-unsaturated ketones and the subsequent oxidation with 5 mol% of RuZrP® afforded products in 51-90 % yield with 79-87 % ee (Scheme 38).



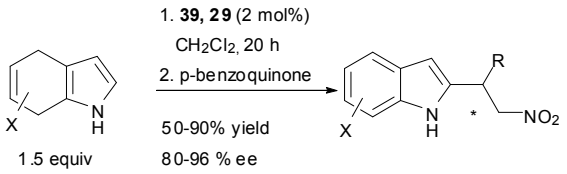
Scheme 38 Addition of α,β unsaturated ketones to 4,7-dihydroindoles and surmised transition states (see also scheme 8)[38]

Interestingly, although in both F–C reactions (the present and that described in section 2.1) an (*R*)-phosphoric acid catalyst was employed, the absolute configuration of the corresponding adducts was switched. In the case of dihydroindole, the enriched enantiomer was the *S*-enantiomer, while the *R*-isomer was the prevalent in the F–C reaction at C-3. This behaviour was explained by authors surmising the transition states pictured in Scheme 37, in which π–π stacking favours, while steric repulsion disfavours, the transition state leading to the *R*-isomer.

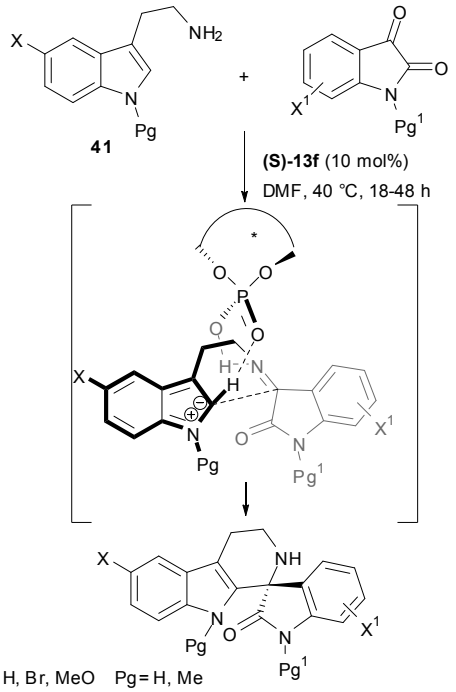


Scheme 39 Reaction of 4,7-dihydroindoles with trifluoromethyl derivatives[111]

An enantioselective F–C reaction of 4,7-dihydroindoles with aromatic trifluoromethyl ketones has been realized leading to 2-substituted 4,7-dihydroindoles with a trifluoromethylated tertiary alcohol moiety in 45–69% yields with 60–93% ee (Scheme 39).[111] Furthermore, 2-functionalized indole derivatives could be produced through a two-step one-pot process by oxidation with p-benzoquinone. The absolute configuration of 4,7-dihydroindoles was not reported, but configuration of the indole (X = H, R = Ph) was assigned by comparison of retention time and specific rotation with the known compound. Unfortunately, a racemic dehydrated by-product was observed with prolonged reaction times in comparable yield (30-51%) with the expected trifluoromethylated tertiary alcohol. On the other hand, the same reaction with ethyl 4,4,4-trifluoroacetoacetate afforded products in 80-95% yield with 83-93% ee and no by-product was recovered.



Scheme 40 Helical chiral 2-aminopyridinium ions for asymmetric addition of nitroenes to 4,7-dihyidroindoles. [112]



Scheme 41 Chiral Brønsted acid-catalysed P-S reaction of isatins[113]

More recently, a new class of H-bond donor catalysts prepared from 1-azahelicene *N*-oxides have been evaluated in the additions of 4,7-dihydroindoles to nitroalkenes (Scheme 40).[112] Catalyst **29** displayed high levels of asymmetric induction, strongly supporting that the 2-aminopyridinium ion can function as a dual H-bonding catalyst and that the bottom half of the helicene

framework effectively covers the space beneath the two H-bonds. However, the best results are obtained with an excess of dihydroindole.

3.2 Pictet–Spengler (P-S) reaction

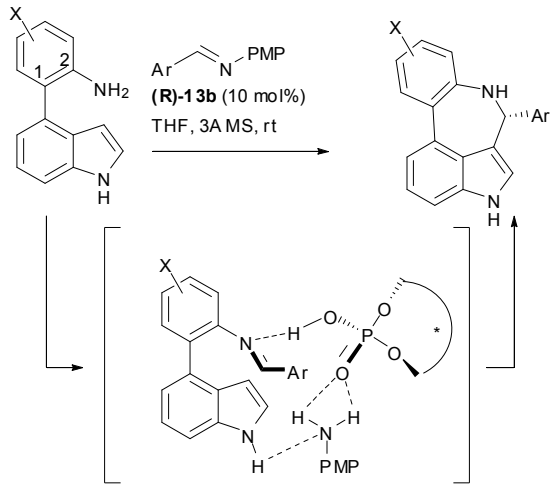
Tetrahydro-β-carboline spiroxindoles are the core of some potent anti-malarial agents showing very good pharmacokinetic properties. They can be prepared by catalytic asymmetric P-S reaction of isatins and tryptamines under phosphoric acids catalysis. Actually, this reaction afforded desired products in 68-97% yields with 71-95% ee (*S*-isomer, Scheme 41). [113]

A possible interaction with the isatin and indole NH's of the phosphoric acid in the transition state was excluded, because both *N*-protected derivatives did not significantly decrease enantioselectivity. Rather, an eventual interaction between the P=O moiety of the catalyst with the proton at the 2-position of the indole nucleus might instead be envisioned, assisting the hydrogen transfer process. Moreover, steric constraints of the catalyst force the activated ketimine into a conformation in which the *Si*-face is less hindered. The surprising tolerance of this reaction to small amounts of water is worth of note. Authors ascribed to the hindered aryl groups of phosphoric acid the ability to wrap the active site of the catalyst in a hydrophobic pocket, avoiding external hydrogen bond donors or acceptors to approach the substrate.

Approximately at the same time, a strictly related reaction appeared in the literature.[114] Both enantiomers of the tetrahydro-β-carboline spiroxindoles from 5-methoxytryptamine were obtained with **(*S*)-13f** and **(*R*)-13b**, respectively in 44-99% yields with 16-90% ee. One exception of this method is represented by N-acetyl isatin, which afforded only the imine product with trace amount of spirocyclization The reaction conditions for **(*S*)-13f** are superimposable with those reported in Scheme 41,[113] while for **(*R*)-13b** dichloromethane was used as the solvents at lower temperature (23 °C) but with prolonged times (72-96 h).

A P-S-type reaction has been envisioned for the asymmetric synthesis of optically active 3,4-fused indole derivatives.[115] Conversely from classical P-S reaction, in this case, a seven-membered ring is formed from the 3 and 4 positions of the indole nucleus. Moreover, the aldehyde was replaced with an imine and the precursor for cyclization was generated through transimination under acidic conditions. Under the optimized reaction conditions (Scheme 42), a range of 4-(2-aminoaryl)indoles smoothly gave structurally diverse indolo[3,4-cd]-1-benzazepines in 70-99% yields and 84-91% ee. Under the same reaction conditions, 4-(2-aminophenyl)-7-azaindole did not react, whereas with the corresponding aldehyde the benzazepine product was recovered in 77% yield with 90% ee. Moreover, indole NH moiety was found to be essential for high enantioselectivity. These findings suggested authors that the arylamine by-product and the indole NH moiety should play important roles in assembling the cyclization precursor, the chiral phosphoric acid, and the arylamine by-product through hydrogen bonding interactions, and such an organization should facilitate the cyclization step in a highly enantioselective manner.

The **14a**-catalyzed P-S reaction of an N_β-(5-oxy-2,4-pentadienyl)tryptamine derivative with methyl 5-oxo-2-(phenylseleno)pentanoate (84% ee) constitutes the basis for a nine-step total synthesis of (+)-yohimbine (Figure 6).[116]



X= H, 5-Me, 5-MeO, 5-PhO, 5-CF_3O, 3,5-Me_2, 3,4-benzo
Ar= Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$TsOC_6H_4$, 4-MeC_6H_4 3-ClC_6H_4 4-$MeO_2CC_6H_4$, 2-Npt

Scheme 42 Synthesis of optically active indolo[3,4-cd]-1-benzazepines[115]

Finally, chiral SPINOL-phosphoric acid [**(*S*)-17a**] has been found highly enantioselective catalysts for the asymmetric P–S reaction of N_β-protected tryptamines with a series of aliphatic and aromatic aldehydes, affording (*S*)-tetrahydro-β-carbolines in 35-99 % yields and 30-98% ee. This protocol has been applied in the asymmetric total synthesis of (-)-harmicine (Figure 6).[117]

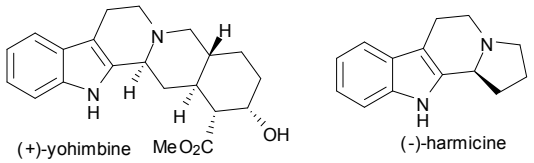
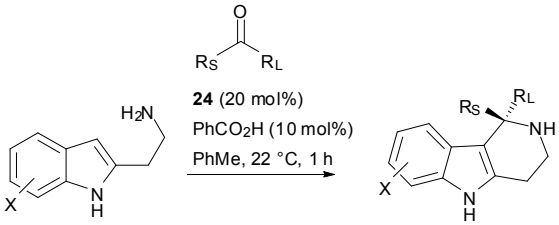


Figure 6



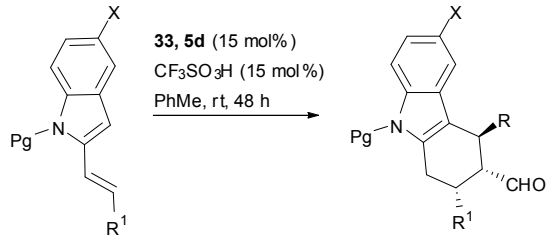
Rs= H, Me
R_L= i-Pr, i-Bu, n-C_5H_{11}, c-C_6H_{11}, $(Et)_2CH$, t-Bu, Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 1-Npt
X= 8-F, 8-MeO, 8-Me, 8-CH_2=CH, 7-F, 7-MeO

Scheme 43 Enantioselective iso-P-S reaction [118]

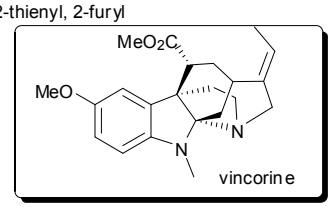
An enantioselective iso-P-S cyclization which involves the introduction of a asymmetric carbon on C-3 by reaction of condensation of isotryptamines and aldehydes or ketones was also reported.[118] The reaction was induced by a chiral thiourea/benzoic acid dual catalyst system that afforded enantiomerically enriched 4-substituted tetrahydro-γ-carbolines (45-81% yields, 98->99% ee) (Scheme 43). If products are N_β-Boc protected, they are solids that after trituration or crystallization allowed a scalable procedure.

3.3 Cycloaddition reactions

In section 2.2.2, we described the cycloaddition reactions of 3-vinylindoles. The same reactions can be carried out on 2-vinylindoles. However, under the reaction conditions described in Scheme 30 and even at higher temperature, the reaction of maleimide with 2-vinylindoles exhibits poor reactivity and the expected cycloadducts are obtained in low yields, though with substantial enantioselectivity.[101]



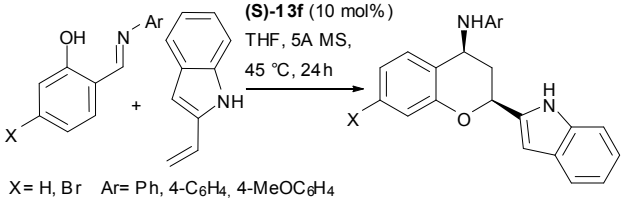
R= H, Et, Pr, CO_2Et, Ph, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 2-thienyl, 2-furyl
X= H, OMe
Pg= H, Me, Bn, CH_2=CH
R^1= H, Me, Ph, 4-BrC_6H_4



Scheme 44 Enantioselective synthesis of functionalized tetrahydrocarbazoles [119]

The enantioselective D-A reaction between *N*-protected-2-vinylindoles and α,β-unsaturated aldehydes was instead promoted by prolinol catalyst. Enantioenriched tetrahydro-carbazoles were recovered in 56-83% yields with 75:25-95:5 *endo/exo* ratio and 94-99% ee except for N-allyl and N-benzylindoles in which enantiomeric excess was only 68 and 23%, respectively (Scheme 44).[119] The low enantioselectivity was attributed to the increased steric hindrance of the protecting group. In fact, *N*-Boc and *N*-Cbz indoles did not react at all. When R^1 = Me, the reaction proceeded slowly and trace amounts of products were observed. Authors speculate that a concerted mechanism is more convincing, thus we report here the reaction and not in the cascade reaction section. The absolute configuration of the *endo*-product was determined to be *2R,3R,4R* by X-ray analysis. The synthesis was applied to the core structure of vincorine.

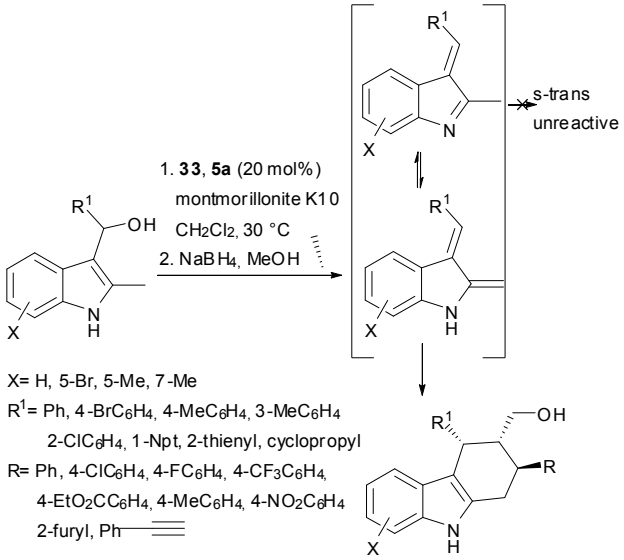
The Povarov reaction of *N*-arylimine and 2-vinylindoles provided cycloadducts in higher efficiency than the 3-vinyl-counterpart (66-98% yields, 90:10->98:2 *cis : trans* ratio and 90->99% ee) under the same experimental conditions described in Scheme 31.[102] Moreover, the use of salicylaldehyde-derived N-arylimines allowed optically active 4-aminobenzopyran derivatives to be obtained in 30-60% yields, with 67:33->98:2 *cis/trans* ratio and 50-80% ee (*2S,4S*, Scheme 45).[120]



X= H, Br Ar= Ph, 4-C_6H_4, 4-$MeOC_6H_4$

Scheme 45 Synthesis of optically active 4-aminobenzopyran derivatives [120]

Indole-based *ortho*-quinodimethanes are reactive diene species, which can be *in situ* generated from 2,3-disubstituted indoles. They provided straightforward access to polycyclic heteroaromatic compounds through a new synthetic pathway. Asymmetric amino catalysis is the enabling strategy to induce the transient generation of quinodimethanes, while directing the pericyclic reactions with dienes toward a highly stereoselective pathway. *N*-Unprotected indole derivatives remain unchanged under these reaction conditions owing to the proton transfer from the free NH moiety, which generates a diene in a *trans* disposition, unable for D-A reaction (see Scheme 47).



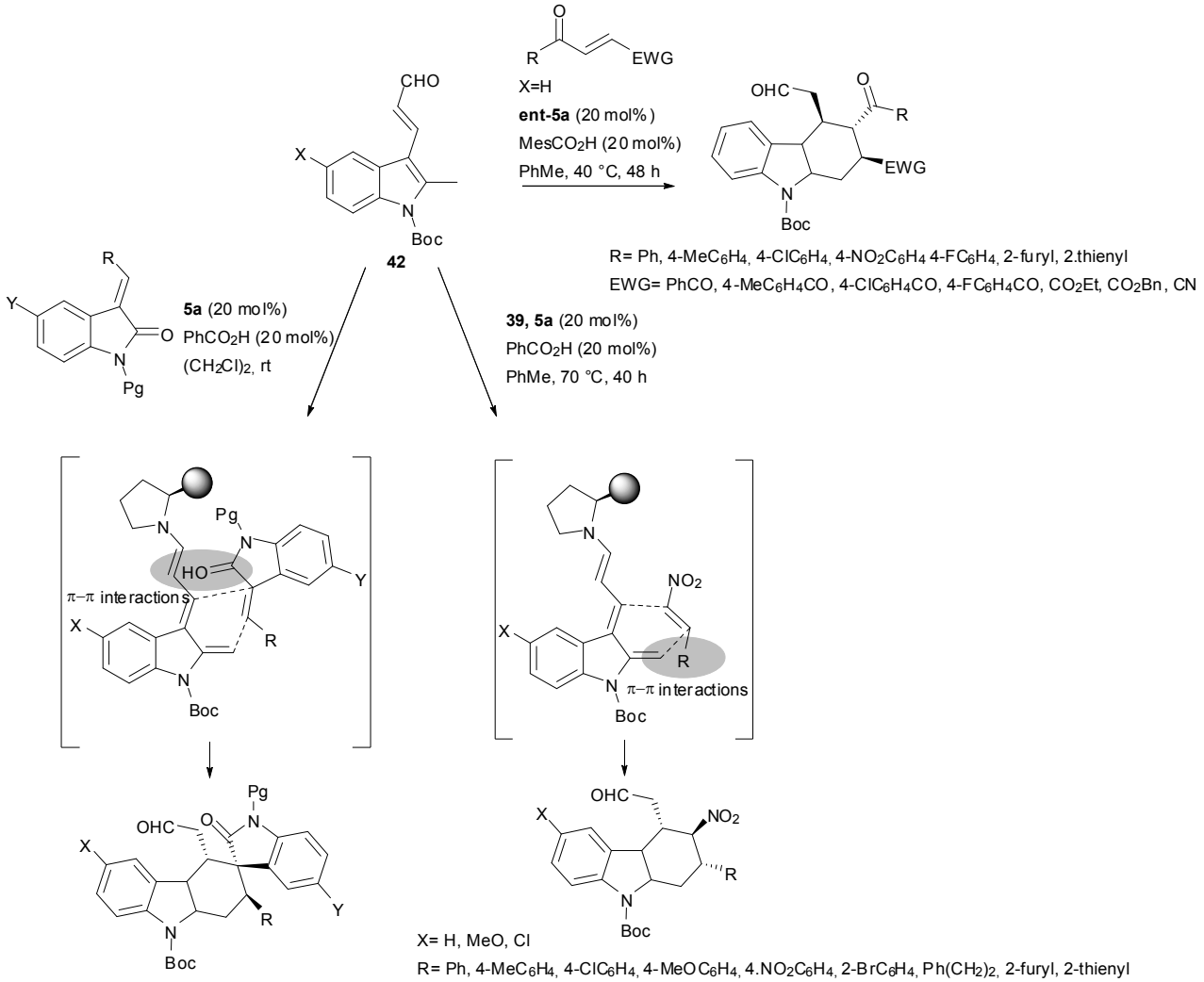
Scheme 47 Asymmetric D-A reaction from in situ generated *o*-quinodimethanes[121]

The reaction with nitroenes afforded *exo*-D-A adducts in 22-96% yields, with 91:9-95:5 dr and 90-93% ee (Scheme 46).[122]

The stereochemical outcome was explained by unfavourable electrostatic repulsion between the nitro group and the silyloxy group of the diene. On the other hand, the reaction with methyleneindolinones gave *endo*-D-A adducts in 53-98% yields, with 89:11-95:5 dr (except for R^2 = 4-$NO_2C_6H_4$ in which dr = 1:1) and 94-99% ee (Scheme 46).[122] The selectivity pattern to the endo approach was explained by favourable π(C=O) - π(diene) interactions. The reaction was also extended to keto-containing dienophiles by using the enantiomer of the classical diaryl prolinol as the catalyst. The D-A adducts were obtained in 64-92% yields, with 78:12-95:5 dr and 97-99% ee.[123] The stereochemistry of the cycloadducts appears to be insensitive to the double bond geometry of dienophile. In fact, starting from both *trans*- and *cis*-isomers, the same tetrahydrocarbazole was forged. Melchiorre explained this behaviour by a scrambling of the double bond occurring prior to the cycloaddition, supporting this with NMR evidence. However, in our opinion, a cascade reaction, with a reversible first stage disrupting the double bond, cannot be discarded.

Chen's group envisaged the in situ formation of *ortho*-quinodimethanes by acidic dehydration of indol-3-ylmethanols. The reactions were catalysed by prolinol **5a** (20 mol%) in the

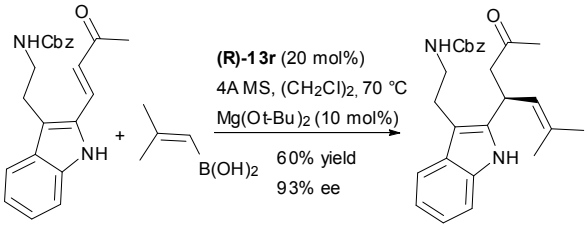
presence of montmorillonite K10 as the dehydrating agent at 30 °C, followed by reduction with $NaBH_4$; *endo*-D-A adducts were recovered in 30-73% yields, with 86:14-95:5 dr and 90-99% ee (Scheme 47). [121]



Scheme 46 Indole-based *ortho*-quinodimethanes as reactive diene species[122, 123]

3.4 Other reactions

In section 2.2.3, we already described the reaction of alkenylboronic acids to β-(indol-3-yl)-α,β-unsaturated ketones. In that paper, [107] an instance with β-(indol-2-yl)-α,β-unsaturated ketones has been also reported under the same experimental conditions (Scheme 48).

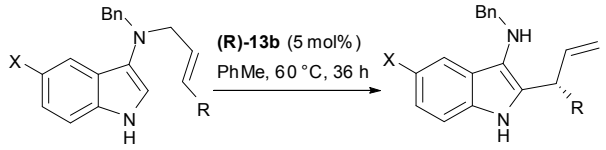


Scheme 48 Addition of alkenyl boronic acids to β-(indol-2-yl)-α,β-unsaturated ketones)[107]

Moreover, in section 2.1.1 (Scheme 10 bottom) we already reported the reaction of ω-indol-2-yl α,β-unsaturated aldehydes. If indol-3-yl derivetives are prepared, cyclization occurs at the C-2 position allowing the synthesis of (1R)-(tetrahydrocarbazol-1-yl)acetaldehydes.[42] By using **5e** (20 mol%) in the presence of 3,5-dinitrobenzoic acid (20 mol%), products are recovered in 40-95 % yields with 84-98 % ee. It should be noted that the absolute configuration is now reported, differently from what described in scheme 10 bottom.

3-Aminoindoles, which can be transformed into synthetically useful chiral products, have been obtained by Brønsted acid catalysed enantioselective indole aza-Claisen rearrangement (Scheme 49).[124] Yields ranged from 81 to 93% and ee from 22 to 96 %. Authors calculated the most stable transition-state structure at the B3LYP/6-31G(d) level and found CH−O and NH−O interactions that organize such that 9-anthracenyl group blocks the *Si*-face of the substrate, favouring the allyl shift on the *Re*-

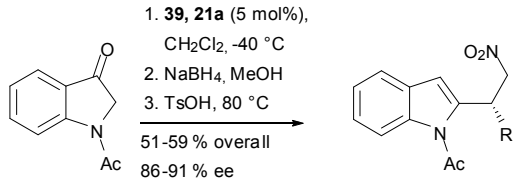
face.



R= Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-BrC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, Ph(CH$_2$)$_2$, 2-Npt, 3-furyl, 3-(NTs)pyrrolyl
X= H, Cl, MeO

Scheme 49 Enantioselective indole aza-Claisen rearrangement[124]

Finally, the asymmetric Michael addition of 1-acetylindolin-3-ones to β-nitrostyrenes has been reported. A series of (*S,S*)-2-substituted indolin-3-one derivatives were obtained up to 99% yields and 92% ee, then four of these examples were transformed into 2-functionalized indoles without racemization of the remaining stereocentre (Scheme 50).[125] The hydrogen bonding of the thiourea moiety with the nitro group adducts, while the tertiary quinuclidine nitrogen deprotonates an acidic proton of 1-acetylindolin-3-one, accounts for the stereochemical outcome of the Michael addition.



R= Ph, 2-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$

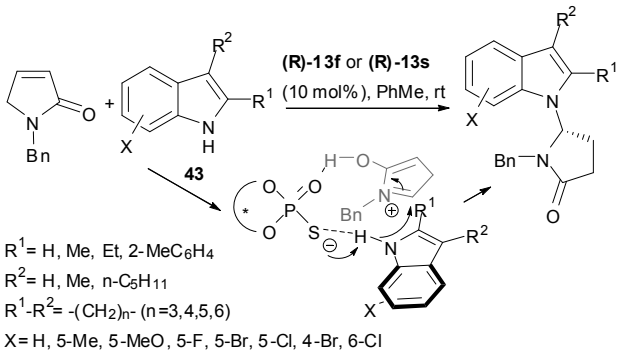
Scheme 50 Asymmetric Michael addition of 1-acetylindolin-3-ones to β-nitrostyrenes[125]

Although not an asymmetric synthesis, the biphenyl-2,2'-diol derived phosphoric acid catalysed F–C alkylation of 3-substituted indoles with α-amidosulfides (N,S-acetals) should be mentioned.[126] 2,3-Disubstitued indoles were recovered in 60-87% yield.

4. Functionalization at N-1

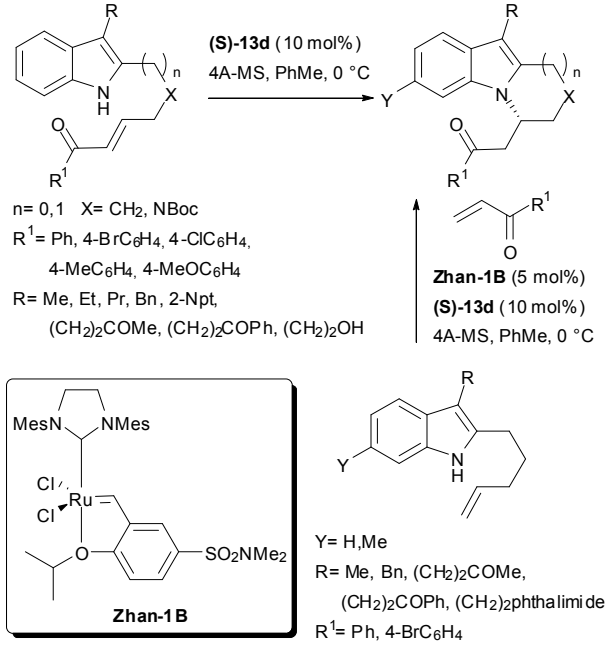
In sharp contrast to the progress in enantioselective alkylation at the C-3 or C-2 positions of indoles, the asymmetric *N*-alkylation remains underdeveloped: probably because the NH proton of indoles must be removed to generate the nucleophile. One way to circumvent this problem is to use a base as a catalyst to facilitate the cleavage of the acidic proton on the N atom and make the N atom prone to alkylation, but amines are generally too weak base. On the other hand, Brønsted acids cannot be obviously employed, but the conjugate base of a chiral phosphoric acid could be produced by the abstraction of the acidic proton by another substrate and then it would function as a catalyst to promote the *N*-alkylation of an indole under the appropriate reaction conditions. Alternatively, the pKa value of the NH proton can be reduced by introducing an electron-withdrawing substituent.

The Brønsted acid catalysed intermolecular enantioselective *N*-alkylation of indoles with α,β-unsaturated γ-lactams as electrophiles provides a method for the synthesis of chiral pyrrolidinones containing indole nucleus, useful precursors to more complex product targets. The reactivity of Brønsted acid **(*R*)-13s**, which contains the larger SH moiety was compared on eight substrates with that of **(*R*)-13f**. The sulfur should lead to a more rigid ion pair. Actually, **(*R*)-13s** gave relatively higher enantioselectivities (86-93% *vs* 80-93% ee), but generally lower yields (24-65% *vs* 65-87%), with respect to **(*R*)-13f**. Catalyst **(*R*)-13s** was used in other 12 examples with 24-98% yields, 82-95% ee overall the 20 examples (Scheme 51).[127]

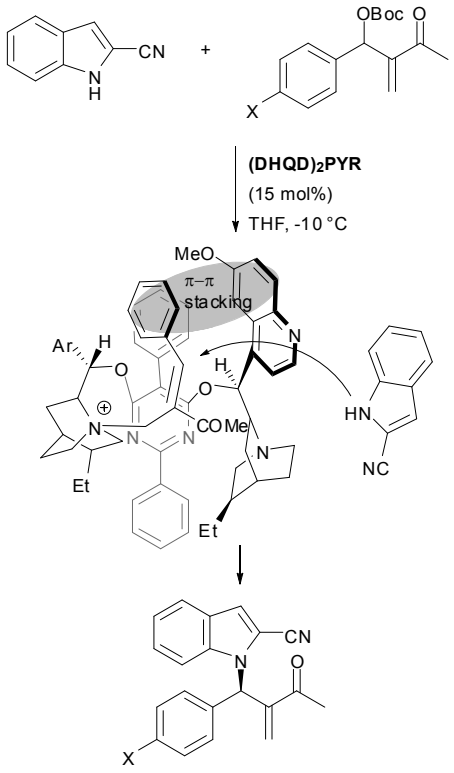


Scheme 51 Enantioselective N–H functionalization of indoles by chiral Brønsted acids[127]

To rationalize the reaction pathway, authors carried out labelling and FTIR experiments. From this evidence, they surmised that the free hydroxyl group in the enol-type cyclic *N*-acyliminium ion captures the conjugate base of the phosphoric acid in a contact ion pair, presumably by intermolecular hydrogen bonding. Assisted by the conjugate base, the acidic NH group of the indole is prone to nucleophilic addition to the cyclic *N*-acyliminium ion. The chiral environment created by the catalyst causes the indole to approach from the *Re*-face of the *N*-acyliminium ion to furnish the *S*-configured product.



Scheme 52 Intramolecular aza-Michael addition of 3-substitued indolyl α,β-unsaturated ketones[128]



Scheme 53 Asymmetric substitutions of MBH-adducts with 2-cyanoindole[129]

The intramolecular aza-Michael addition of 3-substitued indolyl α,β-unsaturated ketones has been realized using catalyst **(*S*)-13d** to provide the heterocyclic products in 72-98% yield and with 69-93% ee (S-isomer, Scheme 52).[128] The polycyclic indoles were also constructed using an olefin cross-metathesis / intramolecular aza-Michael addition sequence in comparable overall yields (45-94 %) little lower ee (87-90%) (see section 5.3 for other N-1 cascade reactions). It should be noted that DFT calculations suggests that the N-1 than C-3 cyclization is thermodynamically more favourable. However, in some cases mixture of N-1 and C-3 adducts were found. Authors explained this finding by stabilization of a final product-catalyst complex by hydrogen bonds with the imine nitrogen atom. However, the C-3 adducts easy isomerize into the N-1 adducts by increasing temperature.

An efficient asymmetric substitution of O-Boc-protected Morita–Baylis–Hillman (MBH) adducts with 1*H*-indole-2-carbonitrile in the presence of $(DHQD)_2PYR$. The products were obtained in 67-99% yields and 92-96% ee (Scheme 53).[129] Authors envisaged that, after addition of the $(DHQD)_2PYR$ to the MBH adduct, the rear face of the such formed E-configured alkene is blocked. Moreover, the aromatic ring of MBH substrate is stabilized through π–π stacking with the linker. Subsequently the attack of the incoming nucleophile takes place on the *Re*-face.

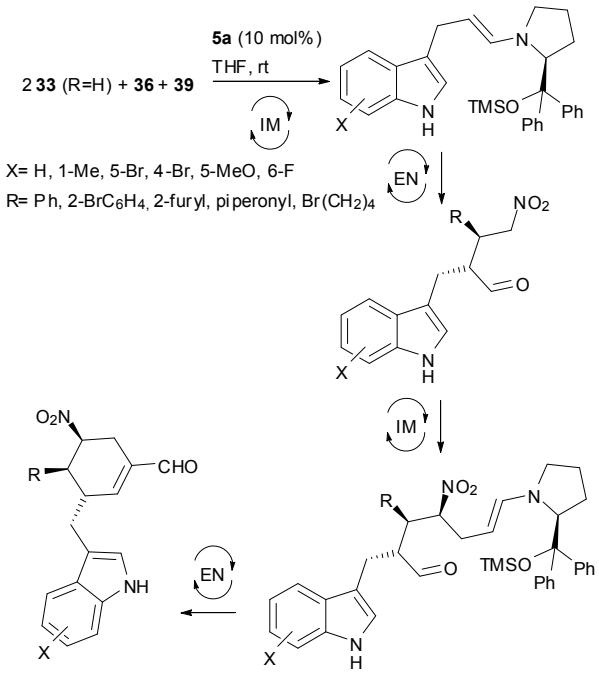
5. Cascade and Multi-Component Reactions

Enantioselective reactions dramatically grew up their importance when some intermediates of the catalytic cycle can undergo further manipulations (the so-called cascade or domino reactions) or when more than two reagents can be added in a one-pot reaction allowing multi-step reactions (multi-component reactions, MCR). In such a manner, complex molecules are built from simple precursors in one single operation, thereby avoiding the isolation of reaction intermediates and time-consuming protecting group manipulations. For instance, organocascade catalysis and collective natural product synthesis, can facilitate the preparation of useful quantities of a range of structurally diverse natural products from a common molecular scaffold.[130,131] These techniques had pioneering instances in our previous review, but in recent years, they have shone in all their synthetic potential. Thus, this separate section will be devoted, scheduled into ring position firstly involved.

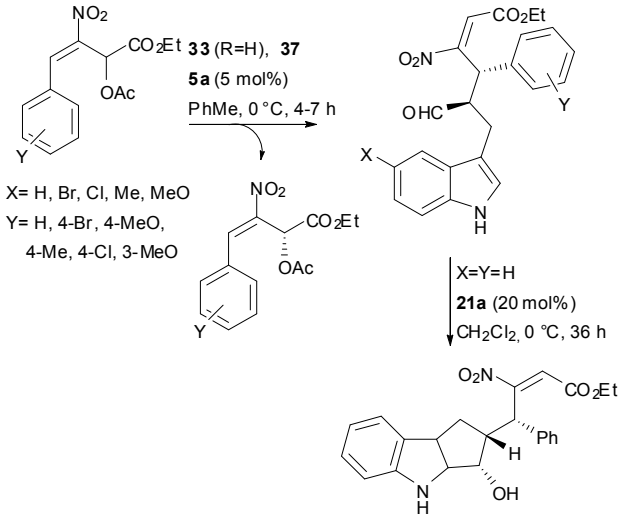
5.1 Reaction at C-3

In 2010, Enders' group envisaged a quadruple cascade using indoles, acrolein, and nitroalkenes as components to afford polysubstituted functionalized 3-(cyclohexenylmethyl)-1*H*-indoles bearing three stereogenic centres in 23-82% yields with 91:9->95:5 dr and 94->99% ee (Scheme 54).[132] This cascade is initiated by an F–C reaction on the indole after an iminium activation mode by catalyst **5a**, followed by two Michael additions and finally by an aldol condensation.

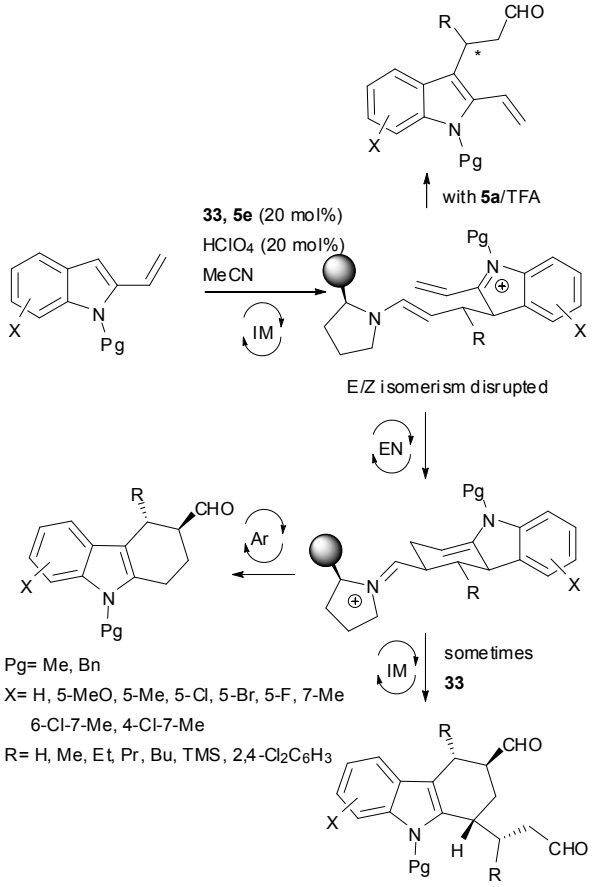
The substitution of simple nitroalkenes with nitroallylic acetates and little modification in the reaction conditions (toluene at 0 °C) allowed an interesting multicomponent organocascade kinetic resolution. Low catalyst loading of **5a** was enough for obtaining enantioenriched 3-alkylated indoles (29-47% yields with 83-99% ee of an almost single diastereoisomer) and enantioenriched nitroallylic acetates (24-44% yields with 79-95% ee) at about 60% of nitroallylic acetate conversion.[133] The reaction proceeds via a sequential iminium/enamine catalytic cycle (Scheme 55). The reaction can be easily scaled up on gram-scale, and adducts can be cyclized, using the quinine-based thiourea catalyst **21a**, to obtain tetrahydrocyclopenta[b]indole derivatives with 40% yield and >99% ee.



Scheme 54 Functionalized 3-(cyclohexenylmethyl)-1H-indoles from quadruple cascade reaction[132]



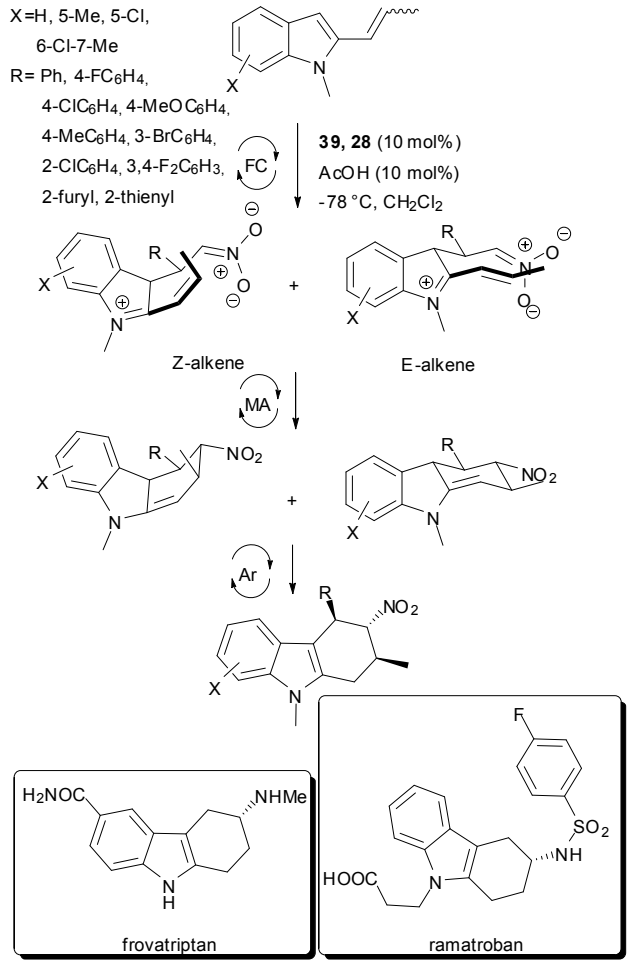
Scheme 55 Three-component organocascade kinetic resolution[133]



Scheme 56 Highly substituted tetrahydrocarbazoles through iminium/enamine cascade reactions[134]

Chen and co-workers generated tetrahydrocarbazole derivatives with two or more stereocentres by reaction cascade of 2-vinylindoles. Using an "iminium" and then "iminium/enamine" activation strategy, authors were able to prepare tetrahydrocarbazole carbaldehydes from 2-vinylindoles and enals in 44-97% yields with 99:1 dr (except for 1-benzyl-2-vinylindole and 2-butenal in which dr was 76:24) and 56-99 % ee (acrolein gave the worst enantioselectivity) (Scheme 56).[134] The inherent steric interference of the catalyst was found to be able to prevent the cyclization step, thus a number of diarylprolinol silyl ethers-acid couples were tested, and **5e**/$HClO_4$ was found the best one. Moreover, both (*E*) and (*Z*)-hex-2-enal gave the desired product with the same configuration, thus indicating that the cascade pathway is more favourable than the alternative D-A cycloaddition route.

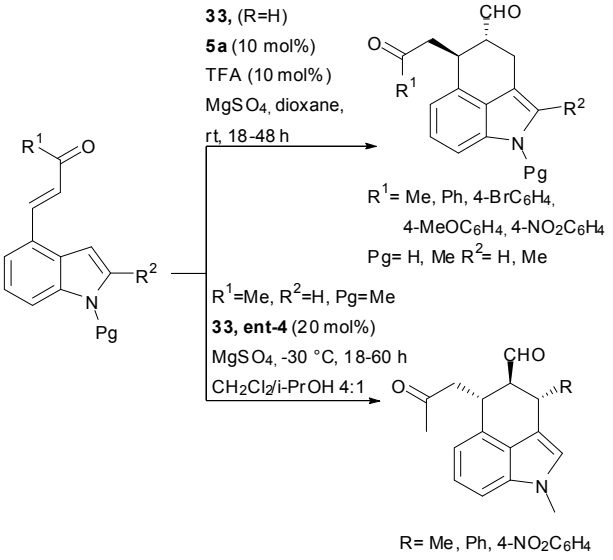
The same research group prepared tetrahydrocarbazoles in 42-86% yields with 80:20-99:1 dr and 82-98% ee under **28** catalysis by a F-C reaction/Michael addition/aromatization reaction cascade of 2-propenylindoles with nitroolefins (Scheme 57).[135] Differently from the previous, this is a prominent example of asymmetric cascade reactions catalysed only by a hydrogen-bonding donor. The reaction can be carried out on a gram-scale and it is applied to the preparation of frovatriptan and ramatroban analogues.



Scheme 57 Highly substituted tetrahydrocarbazoles through hydrogen-bonding-catalysed cascade reactions [135]

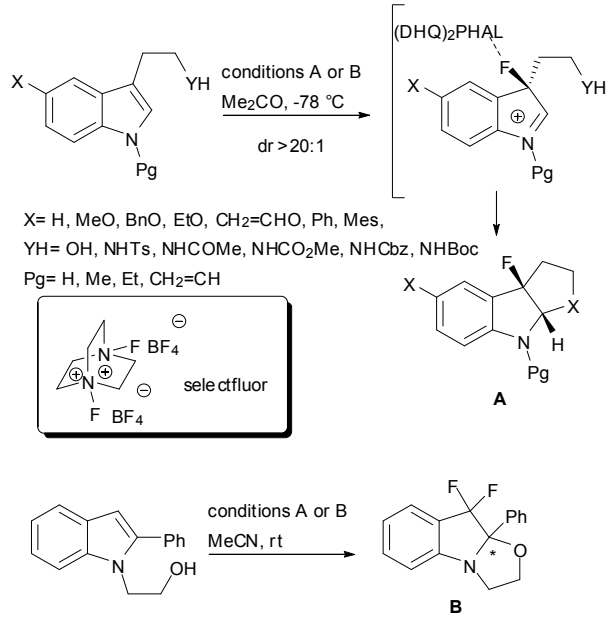
Bernardi's group reported a new synthetic route to 3,4-annulated indoles (1,3,4,5-tetrahydrobenzo[cd]indole) by organocatalytic iminium/enamine cascade reaction from 4-substituted indoles and enals. The main problem to be overcome was the diminished nucleophilicity of the C-3, caused mainly by conjugation of this

carbon with the electron withdrawing C-4-acceptor necessary for the intramolecular Michael addition of the enamine in the cascade. α,β-Unsaturated ketones were found as a good compromise; in fact, a nitroalkene moiety did not give the F-C product, while a α,β-unsaturated ester provided exclusively the open product. Under **5a** catalysis (**5e** for R^1 = 4-MeOC_6H_4), the reaction with acrolein afforded the expected products in 67-81 yields, with 91-99% ee as a single diastereoisomer (Scheme 58); *N*–Me indole needed 20 mol% catalyst loading.[136] Prolinols were unable in promoting the reaction with β-substituted enals, thus a more electrophilic MacMillan's second-generation catalyst (**ent-4**) had to be used. However, considerable amounts of *N*-alkylated products were recovered and only with *N*–Me indole products were obtained in satisfactory 71-77% yields and 83-95% ee as a single diastereoisomer.



Scheme 58 Asymmetric synthesis of 3,4-annulated indoles [136]

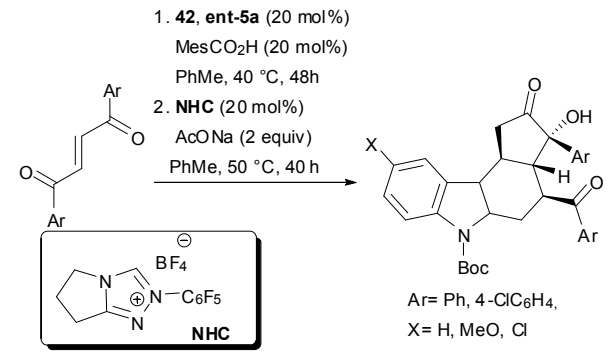
Asymmetric fluorocyclization are rare owing to the scarce availability of electrophilic fluorinating reagents. This fact represents a significant gap since enantiopure fluorinated heterocycles are a class of important compounds in medicinal chemistry Recently, Gouverneur and co-workers disclosed a process that delivers enantioenriched fluorinated indole derivatives, namely hexahydropyrrolo[2,3-b]indoles or tetrahydro-2H-furo-[2,3-b]indoles.[137] The reaction was carried out in both stoichiometric [Selectfluor/$(DHQ)_2$PHAL] and catalytic conditions [NFSI//$(DHQ)_2$PHAL (20 mol%)]. When an equimolar amount of catalyst was used, yields are generally lower (33-90% *vs* 47-95%), and enantiomeric excesses slightly higher (40-90% *vs* 62-84%) than under catalytic conditions (Scheme 59). Authors envisaged that the process starts from an irreversible fluoroquaternization at C-3 followed by the intramolecular capture of the transient iminium intermediate. A series of observations at ^{19}F-NMR allowed speculating that the *N*-fluoroammonium salt of the cinchona alkaloid is responsible for the enantiocontrol. Finally, an indole derivative, which bears an oxygen nucleophile at the nitrogen atom, was also subjected to fluorocyclization using equimolar amounts of Selectfluor and $(DHQ)_2$PHAL. The difluorinated tricyclic tetrahydrooxazolo[3,2-a]indole was delivered in 50% yield and with 68% ee.



Scheme 59 Asymmetric fluorocyclization of indole derivatives[137]

A great challenge in asymmetric catalysis is the development of new binary systems that can realize the compatibility of two characteristically distinct catalysts.

In scheme 46, we already described the aminocatalytic asymmetric indole-2,3-quinodimethane strategy developed by Melchiorre's group. They designed also a one-pot D-A/benzoin reaction sequence to stereoselectively access *trans*-fused tetracyclic indole-based compounds having four stereogenic centres.[123] Given the compatibility of **ent-5a** and *N*-heterocyclic carbenes, combining these two catalysts, the expected tetracyclic compounds were recovered in 40-66% yields, with 86:14-88-12 dr and 97-99% ee (Scheme 60).

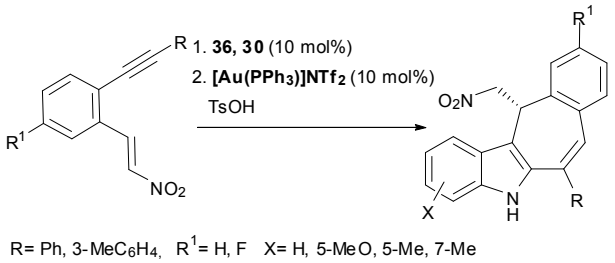


Scheme 60 Asymmetric D-A/benzoin reaction sequence[123]

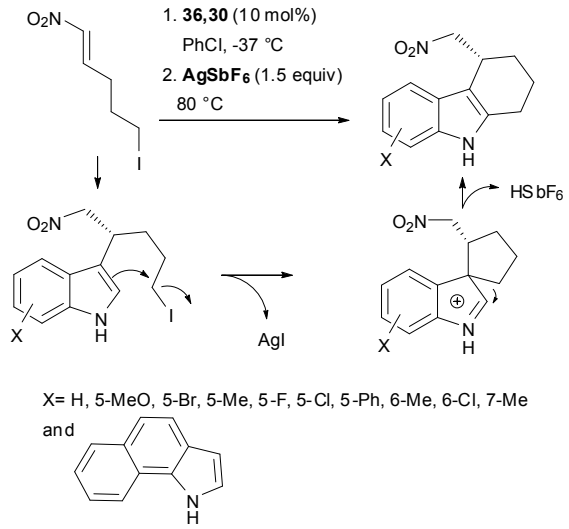
The sequential combination of two catalysts was also attempted combining organocatalysis and metal catalysis. An example has been already described in Scheme 52.

Moreover, Enders' group mixed organocatalysis and gold catalysis on C-2,C-3-unsubstituted indoles providing an efficient one-pot access to (*R*)-tetracyclic indole derivatives in 51-96%

yields and 95-99% ee (Scheme 61)[138]. The organocatalyst allowed F–C type reaction of nitroene, and then the gold catalyst promoted a 7-*endo-dig* cyclisation.



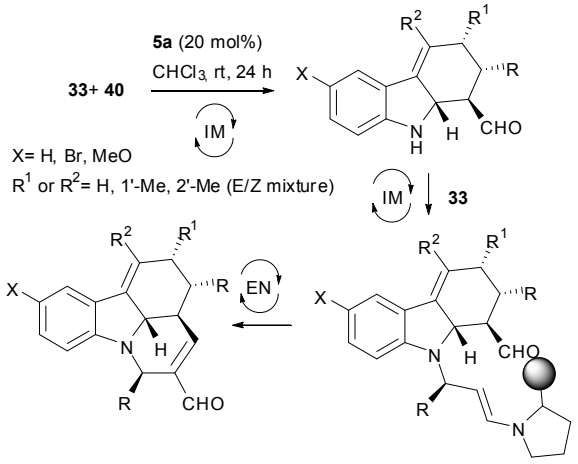
Scheme 61 Enantioselective synthesis of tetracyclic indole derivatives [138]



Scheme 62 Asymmetric Michael addition/Ciamician–Plancher rearrangement sequence [139]

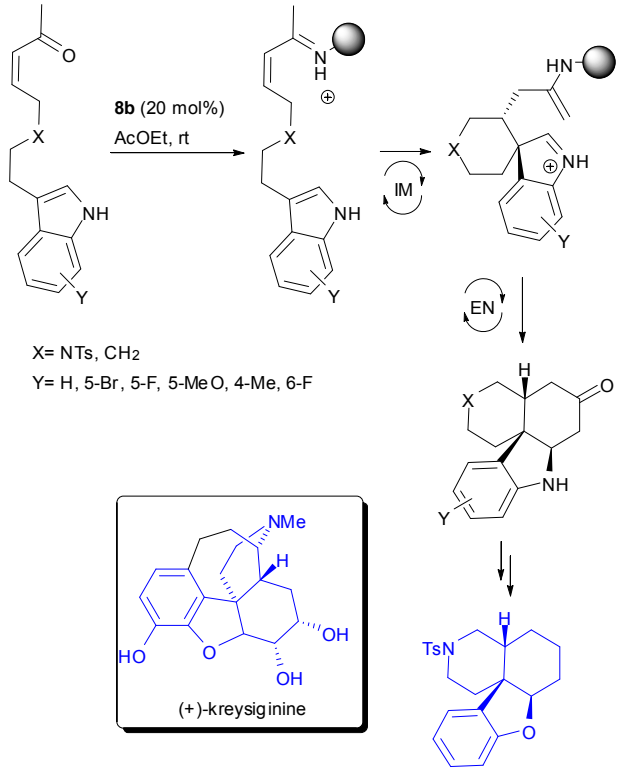
The same research group set up the synthesis of 1,2,3,4-tetrahydrocarbazole analogue by a Michael addition of indoles on a haloalkane-substituted nitroolefin followed by AgI-mediated Ciamician–Plancher rearrangement.[139] R-Configured products were isolated in 33-81% yields and 86-96 % ee (Scheme 62). Both products from reactions described in Schemes 61 and 62 were further manipulated to afford drug analogues.

A three-component triple cascade of 3-vinylindoles with α,β-unsaturated aldehydes following an "iminium–iminium–enamine" activation sequence was recently developed.[140] Partially unsaturated tetracyclic pyridocarbazole derivatives were recovered as a single diastereoisomer in 14-84% yields with 96-99% ee [not determined only for 3-(2-furyl)propenal, because of the low yield (14%)]. With **5a**, the enantiomeric products were noteworthy recovered in comparable yield and selectivity. When a mixture 1:1 *E/Z* of the vinylindole was used only the *E* isomer undergoes the cycloaddition even in the presence of a two-fold amount of the vinylindole, in agreement with similar reactions already described in Schemes 30 and 35. Moreover, a substituent on the C-2 of the indole totally prevents the reaction. The organocatalytic triple cascade is initiated by the asymmetric D-A reaction of the 3-vinylindole, leading to a tetrahydrocarbazole intermediate. The indole nitrogen atom can then act as a nucleophile in an aza-Michael addition, affording an *N*-alkylated intermediate, which is a suitable substrate for the final intramolecular aldol condensation (Scheme 63).



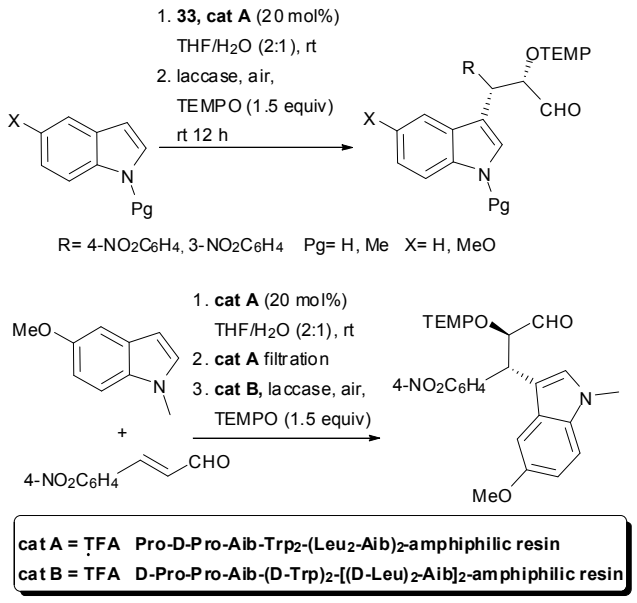
Scheme 63 D-A/aza-Michael/aldol condensation domino reaction[140]

Indolyl methyl enones from tryptamine can be assembled through a nucleophilic polycyclization to the tetracyclic derivatives in a cascade process with a chiral primary amine catalyst.[141] The intramolecular Michael addition generates a spirocyclic indolenine intermediate through iminium catalysis, followed by intramolecular Mannich reaction by enamine catalysis (Scheme 64). The final products are recovered in 54-94% yields, 80:20-95:5 dr and 95-99% ee. The pseudoenantiomeric catalysts afforded the enantiomer in comparable yields and selectivity. With this methodology, an analogue of (+)-kreysiginine was also synthesized.



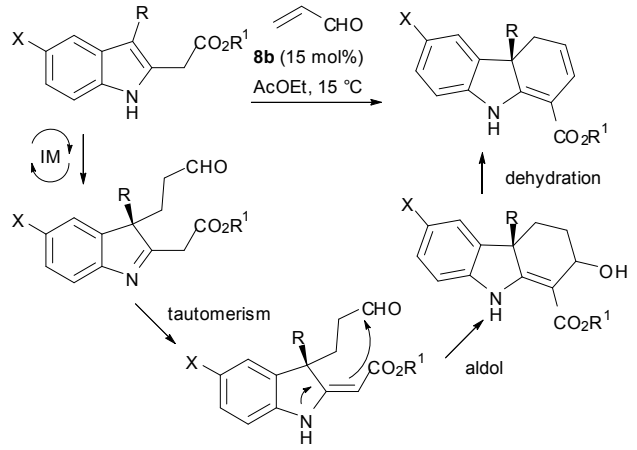
Scheme 64 Intramolecular Michael addition/ Mannich reaction.[141]

In Scheme 6, we already showed an instance of F-C type reaction in the presence of a resin-supported peptide catalyst. A similar procedure, when followed by oxidation with the enzyme laccase, allowed to realize an asymmetric one-pot alkylation and α-oxyamination sequential reaction in aqueous medium (Scheme 65).[142] The increase in the ee value of the major diastereomer in the one-pot sequence with respect to that of each single reaction should be noted. Removal of the peptide catalyst **A** after the F-C step and addition of peptide catalyst **B**, which is the enantiomer of **A** allowed the *anti*-isomer to be obtained as the major diastereomer [*anti : syn* 77 (96% ee) : 23 (69% ee)].

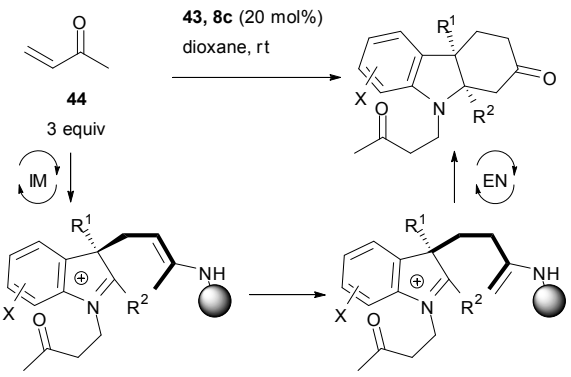


Scheme 65 Asymmetric one-pot sequential F-C alkylation and α-oxyamination[142]

Finally, we describe two reactions that, at a first sight, are cycloadditions, but, after in-depth investigation of the reaction course, demonstrate to be cascade reactions.



Scheme 66 Addition of 2,3-disubstituted indole to acrolein [143]

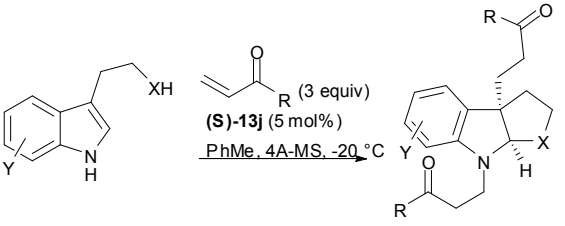


Scheme 67 Addition of 2,3-disubstituted indole to methyl vinyl ketone[144]

The first example uses acrolein realizing the formation of highly substituted hydrocarbazoles by a formal [3+3] cycloaddition between acrolein and 2,3-disubstituted indoles (Scheme 66). The actual mechanism passes through condensation of indole derivative with acrolein *via* iminium catalysis to afford an indolenine intermediate. It undergoes isomerization to enamino-ester, which affords hydrocarbazoles in 63-99% yields and 90-99% ee (4a*R*-isomer) after cyclization and dehydration.[143]

The second one is a formal [4+2] cycloaddition of 2,3-disubstituted indoles with vinyl methyl ketone in the presence of a catalytic amount of **8c**. Actually, the reaction course goes through a Michael and Mannich cascade process, *via* iminium-enamine catalysis. This method provides bridged-ring indoline scaffolds containing two quaternary carbon centres with 54-98% yields and 81-98% ee. (Scheme 67).[144] N-Alkylation cannot be avoided, so that a three-fold excess of ketone is always added.

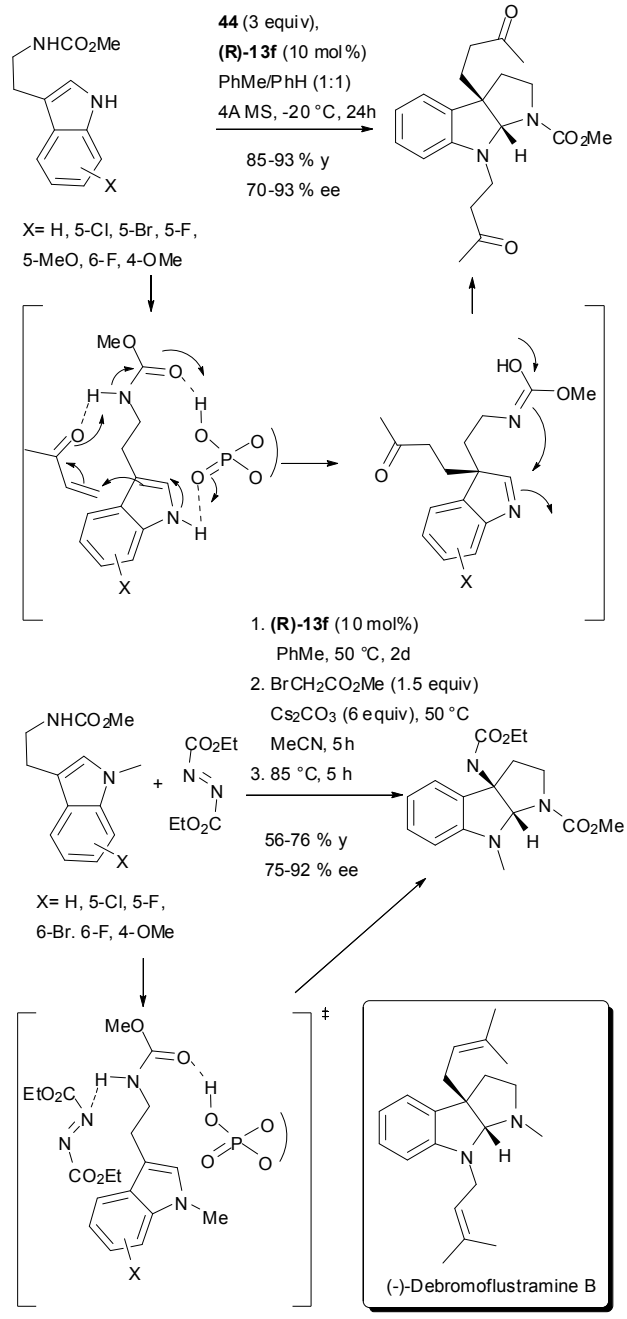
Then Cai and co-workers extended this methodology to tryptamines and (3-indolyl)ethanol leading to pyrrolo- or furo-indoline derivatives in 33-97% yields with 50-84% ee., through a chiral phosphoric acid catalysed Michael addition-cyclization cascade reaction (Scheme 68).[145]



Scheme 68 Synthesis of enantioenriched pyrrolo- and furo-indoline derivatives [145]

Other two important kinds of pyrroloindolines, with either carbon-carbon or carbon-nitrogen linkages, were accessed by Michael addition of methyl vinyl ketone or DEAD to tryptamine, respectively (Scheme 69).[146] With DEAD, 10-carbomethoxy-1-methyltryptamine was found the substrate with higher selectivity. This synthetic approach has been applied in the concise asymmetric total synthesis of (-)-debromoflustramine B, an

alkaloid isolated from bryozoa *Flusta foliacea* with promising bioactivity.



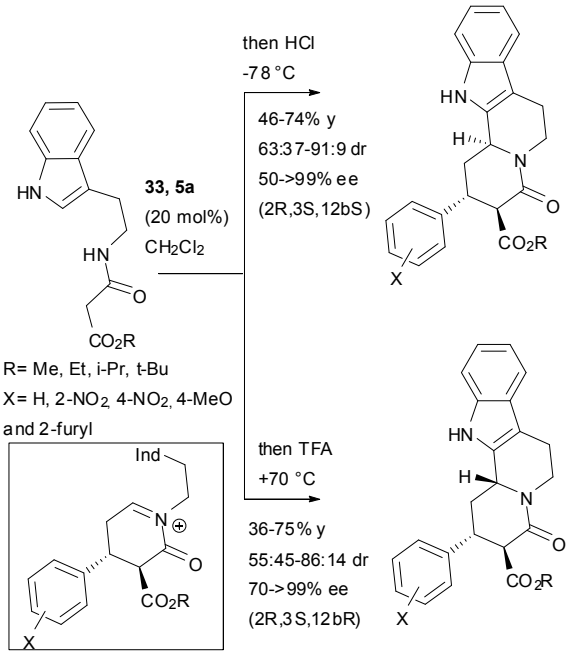
Scheme 69 Enantioselective formation of pyrroloindolines[146]

Finally, Hong's group recently described a cascade reaction with formation of a stereocentre between the C-2 of an indole nucleus and the C-3 of another. We decided to give the preference to the C-2, therefore this reaction will be described in the next section (see Scheme 82). [147]

5.2 Reaction at C-2

Most of the cascade or multi-component reactions involving the initial alkylation of the C-2 result from P-S reactions. In particular, great attention has been paid to the synthesis of indoloquinolizidine that constitutes one key structural backbone of a large number of medicinally interesting natural indole alkaloids.

Franzèn and co-workers, in a wider organocatalytic addition/cyclization/annulation sequence for the synthesis of optically enriched quinolizidines reported the synthesis of some indole derivatives (Scheme 70).[148] The one-pot sequence relies on **5a**-catalyzed enantioselective conjugate addition of electron-deficient amide to α,β−unsaturated aldehydes, directed to the sterically less hindered *Si*-face by shielding of the *Re*-face of the iminium intermediate by the bulky aryl groups on catalyst. Then spontaneous formation of the thermodynamically more stable *trans*-hemiaminal establishes the second stereocentre. However, reaction time and temperature has to be set-up for each reaction thus a general procedure is not available. Finally, addition of acid to the reaction mixture leads to elimination of water and formation of an *N*-acyliminium ion, which undergo F-C-type reaction giving the α- or β-epimer depending on the reaction conditions.

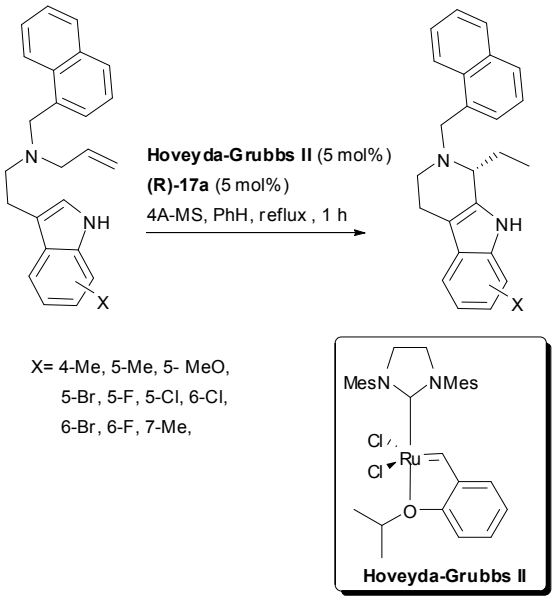


Scheme 70 Asymmetric indoloquinolizidine synthesis

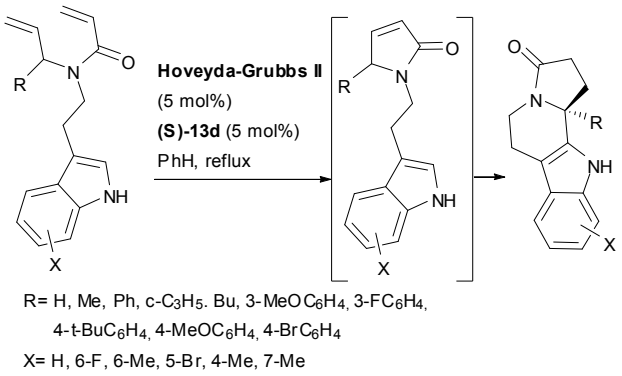
Other cascade reactions involving a P-S cyclization step are applications of binary organo/metal catalyst systems. For instance, an olefin isomerization/P-S cascade reaction by the sequential catalysis of **Hoveyda-Grubbs II** and chiral phosphoric acid afforded carbolines in 57-94% yields with 83-87% ee (Scheme 71).[149] Differently from *N*-allyl tryptamines, the Grubbs type catalysts are ineffective in promoting the isomerization of internal olefin. However, being a ruthenium hydride, generated in situ, the species responsible for the isomerization stage, the addition vinyl ethyl ether promoted the decomposition of Grubbs catalyst to hydride. Thus, *N*-crotyl, *N*-cynnamyl and *N*-(4-bromocynnamyl)tryptamine underwent the reaction in 72-75% yields with 85-87% ee.[149]

The same research group reported also a highly efficient synthesis of enantioenriched indolizinoindoles (82-98% yields, 22-99% ee) through a RCM/isomerization/P-S cascade reaction always *via* **Hoveyda-Grubbs II**/(***S***)**-13d** sequential catalysis

(Scheme 72).[150] The reaction was found to proceed via lactam, because one of such lactams was independently prepared and then submitted to **(*S*)-13d** catalysis, affording the indolizino-indole in comparable yields and selectivity.



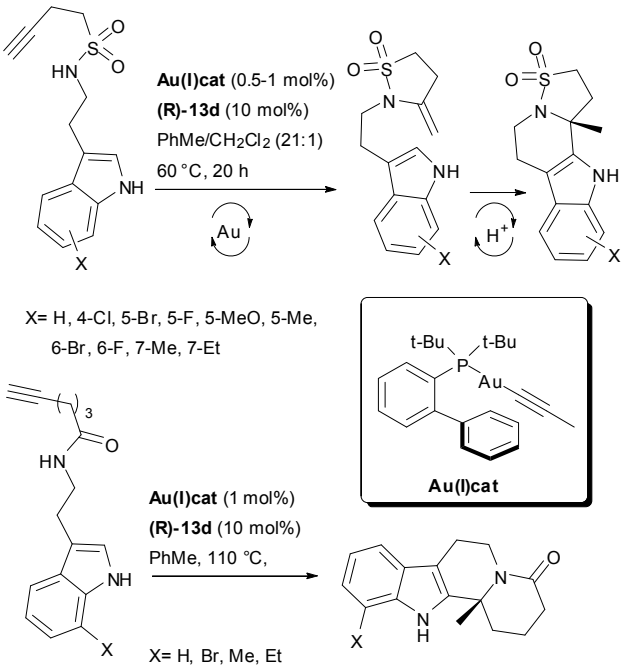
Scheme 71 Olefin isomerization/asymmetric P-S cascade[149]



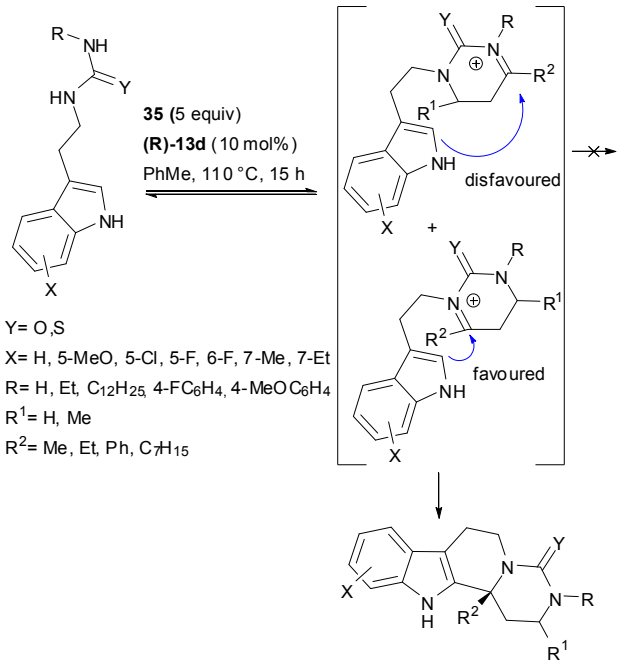
Scheme 72 RCM/olefin isomerization/P-S cascade[150]

Dixon and co-workers reported a cyclization cascade using another binary organo/metal catalyst system, that is a combination of gold(I) and **(*R*)-13d** catalysts.[151] An initial 5-exo-dig hydroamination and a subsequent phosphoric acid catalysed cyclization process provided sulfonamides in 60-85% yields and 81-95% ee. The method can be extended to lactam derivatives, with 60-99% yields and 66-93% ee (Scheme 73).

The same research group has also developed a Michael addition/iminium ion cyclization cascade of tryptamine-derived ureas and enones.[152] The reaction is broad in scope and provides the desired tetracycles in 54-78% yields and 31-96% ee (Scheme 74). Unfortunately, large excess of ketone is necessary. It is worth of note that the cascade affords the tetracyclic products despite the presence of two potentially nucleophilic urea nitrogen atoms. Authors envisaged a rapid and reversible Michael addition step to both nitrogen atoms, followed by iminium ion formation. However, in one case the iminium ion would need to undergo an 8-membered ring cyclization, while, in the other case, a more favourable 6-endo-trig cyclization. Consequently, the reaction course follows this latter pathway.



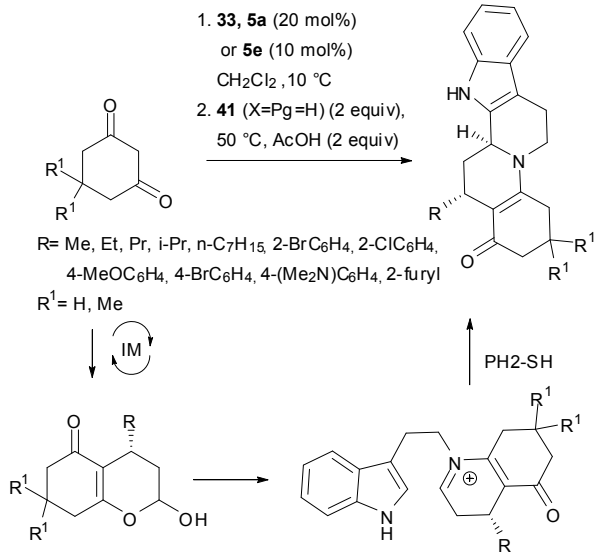
Scheme 73 Enantioselective hydroamination/*N*-sulfonyliminium cyclization cascade [151]



Scheme 74 Enantioselective Michael addition/iminium ion cyclization cascade [152]

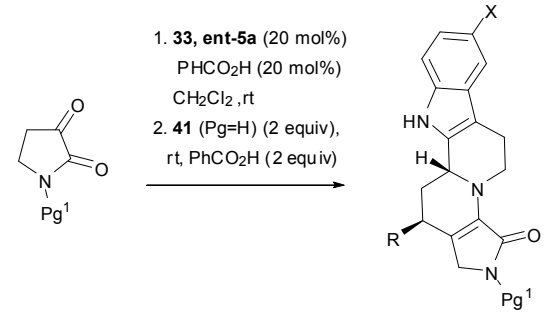
Then, Rueping and co-workers prepared optically active indoloquinolizidines with a quite different strategy. Instead of tedious preparation of the tryptamine derivatives suitable for P-S cyclization, they envisaged a reaction sequence involving a Michael addition of various 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes via "iminium ion activation" to deliver a chiral hemiacetal. This hemiacetal reacts with tryptamine to generate an iminium ion, which then performs diastereoselective

P-S cyclization to afford indoloquinolizidine owing to the steric hindrance of the R group. The reaction proceeded successfully (64-85% yields with 78->99% ee), affording the final products as single diastereomers with 1,3-*anti*-(12b*R*,14*S*)-relationship (Scheme 75).[153] It should be noted that this procedure is a multi-component-reaction only for aliphatic aldehydes; in fact, when aromatic and heteroaromatic substituted aldehydes were employed, purification of the chromenones after the first step was crucial in order to obtain good yields for the final products. Moreover, a switch from catalyst **5e** to **5a** and an increase of catalyst loading from 10 to 20 mol% are also necessary in these last cases.



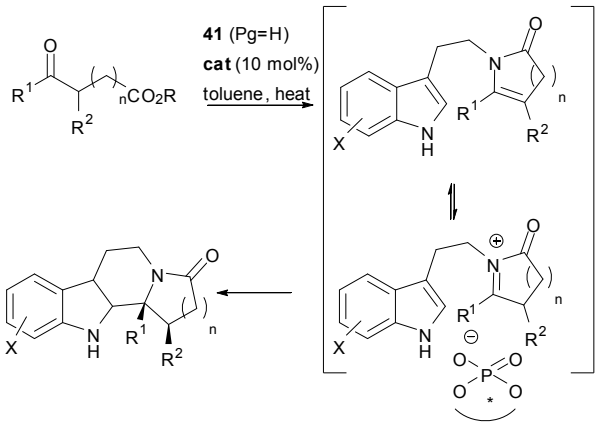
Scheme 75 One-pot Michael addition-cyclization-P-S reaction for the synthesis of indoloquinolizidines[153]

Other indoloquinolizidines can be efficiently constructed [(53-87% yield, 67:33-95:5 dr, 90-97% ee (2*R*,13b*R*)] by the use of α-oxo-γ-butyrolactam as the dicarbonyl derivative (Scheme 76).[154] It should be noted the use of **ent-5a** as the catalyst, which, as expected, afforded the enantiomeric configuration of the asymmetric carbons (pay attention to the different priority order in products depicted in schemes 75 and 76) and the employ of an 1,2- instead of an 1,3-dicarbonyl derivative.



R= Ph 4-MeOC6H4, 4-MeC6H4, 4-BrC6H4, 4-ClC6H4, 4-FC6H4, 4-CNC6H4, 2-MeC6H4, 3-ClC6H4, 2,4Cl2C6H3, 2-furyl
Pg1= Bn, CH2=CHCH2
X= H. OMe

Scheme 76 Other one-pot Michael addition-cyclization-P-S reaction for the synthesis of indoloquinolizidines).[154]



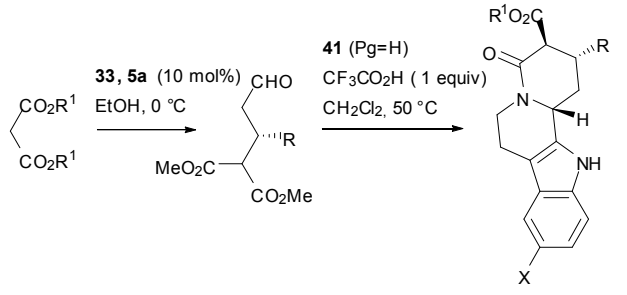
cat= 14a R^1-R^2= $(CH_2)_4$, $(CH_2)_5$, R^1=Me, R^2= Bu, Et, Me
X= H, 5-Br, 5-MeO, 7-Me, n= 1,2 R= H,Et
cat= (R)-13j R^1-R^2= $(CH_2)_3$ X= H, n= 1 R= H
cat= (R)-13d R^1= Me R^2=Me, CO_2Me X= H, 7-Me n= 1 R= H, Me
cat= (R)-13f R^1= Me R^2= SO_2Ph X= 7-Me, n= 1 R= t-Bu

Scheme 77 Enantioselective Brønsted acid catalysed cyclization cascade of tryptamines and ketoacids [155]

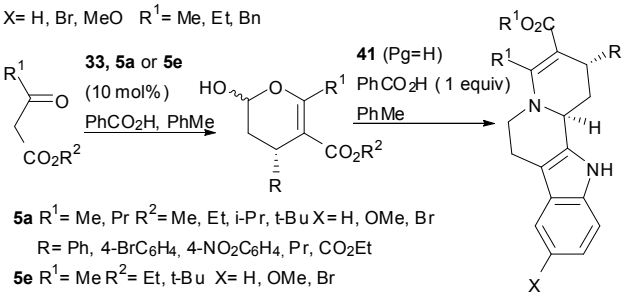
Moreover, direct enantio- and diastereoselective N-acyliminium cyclization cascade through chiral phosphoric acid catalysed condensation of tryptamines with γ- and δ-ketoacid derivatives provided tetracyclic products in 53-99% yields and 68-98% ee (Scheme 77). [155] The most relevant feature and drawback of this reaction is the different catalysts required for each reaction, although **14a** revealed the most general.

Zhao and co-workers reported almost at the same time two very similar reactions for the synthesis of indolo[2,3-a]quinolizidines.[156, 157] We decided to report these reactions, although they are not strictly organocatalyzed P-S reactions. In fact, the absolute stereochemistry was governed by the chirality of the Michael adduct created by the prolinol organocatalyzed conjugate addition of dicarbonyls to α,β−unsaturated aldehydes. Thus, the P-S/lactamization cascade is actually a chiral-pool governed reaction, because the crude Michael adduct was isolated from its reaction mixture and then submitted to P-S/lactamization. It should be noted that the addition of δ-oxomalonates and β-ketoesters afforded products with *cis* [156]and *trans*[157] H2/H12b geometry, respectively. (2*S*,3*S*,12b*R*)-Products were recovered in 27-86% overall yield and 77-99% ee (Scheme 78 top) from reaction of malonates. [156] (2*S*,12b*S*)-Products were recovered in 51-95% overall yields with 67-96 % ee from reaction of ketoesters (Scheme 78 bottom).[157]

Alternatively, Rueping set up a true organocatalytic sequence. Unfortunately, together with many examples of the racemic version, only one instance was reported for the organocatalytic counterpart. Tryptamine was condensed with ethyl acetoacetate to form an enaminone that can undergo a **14a** (5 mol%) catalysed intermolecular Michael reaction with cinnamaldehyde generating a new enantioenriched chiral centre. Subsequent tautomerization yields an iminium ion by the reaction of the secondary amine and the aldehyde moiety. Finally this iminium ion underwent a **14a** catalysed P-S cyclization to form the indolo[2,3-a]quinolizidine structure in 68% yield and 49% ee after 4 days (Scheme 79).[158]

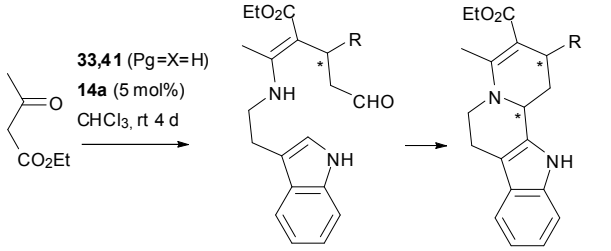


R= 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$
2-BrC$_6$H$_4$CH=CH, 4-FC$_6$H$_4$CH=CH, Me, Et, Pr
X= H, Br, MeO R^1= Me, Et, Bn

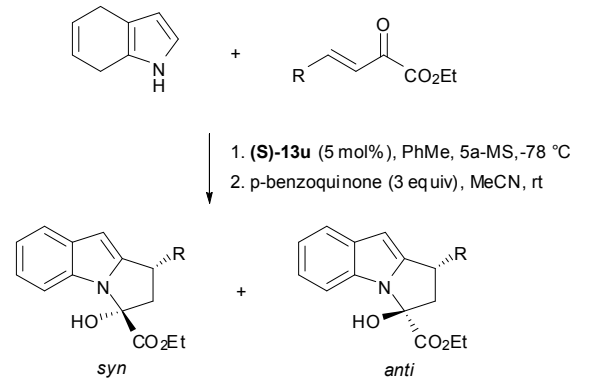


5a R^1= Me, Pr R^2= Me, Et, i-Pr, t-Bu X= H, OMe, Br
R= Ph, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, Pr, CO$_2$Et
5e R^1= Me R^2= Et, t-Bu X= H, OMe, Br
R= Me, Pr, CO$_2$Et, Ph, 4-NO$_2$C$_6$H$_4$, 2-furyl, 2,4-Cl$_2$C$_6$H$_3$

Scheme 78 Syntheses of indoloquinolizidines by a P-S/lactamization cascade[156, 157]



Scheme 79 Rueping's reaction (stereochemistry is not given but *trans* relationship can be deduced from racemic version)[158]

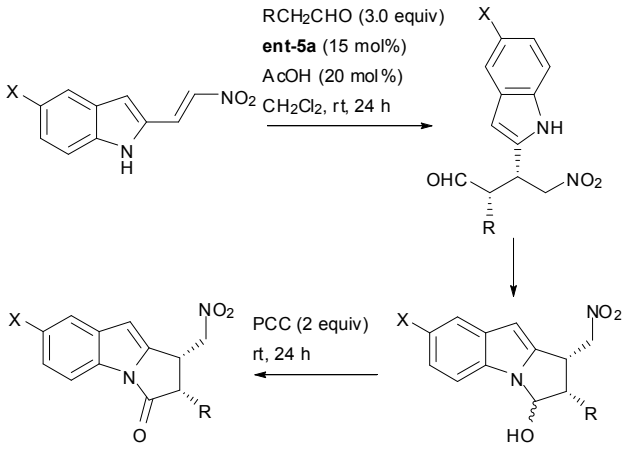


R= Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$
3,4-(OCH$_2$O)C$_6$H$_3$, 1-Npt, 2-Npt, 2-furyl, 2-thienyl

Scheme 80 Synthesis of enantioenriched pyrrolo[1,2-a]indoles[159]

Other cascade reactions involve the C-2. For instance, chiral *N*-triflylphosphoramide (5 mol%) was found an efficient catalyst for the enantioselective F-C alkylation reaction of 4,7-dihydroindole with β,γ-unsaturated α-keto esters. Surprisingly, during the following p-benzoquinone oxidation step, various pyrrolo[1,2-a]-indoles were obtained in 75-96% ee, 48-87% yields and up to 3:1 *anti* : *syn* diastereoselectivity in a two-step one- sequence (Scheme 80).[159]

Another organocatalytic one-pot asymmetric synthesis of almost stereoisomerically pure (>98% de, >99% ee) 1*H*-pyrrolo[1,2*a*]indol-3(2*H*)-ones in 49-68% yields was reported by Enders. The reaction occurs through a Michael–hemiaminalization–oxidation sequence (Scheme 81).[160]



X= H, MeO, Me, Cl
R= Pr, Bu, Bn, CH$_2$=CHCH$_2$

Scheme 81 Michael–hemiaminalization–oxidation sequence[160]

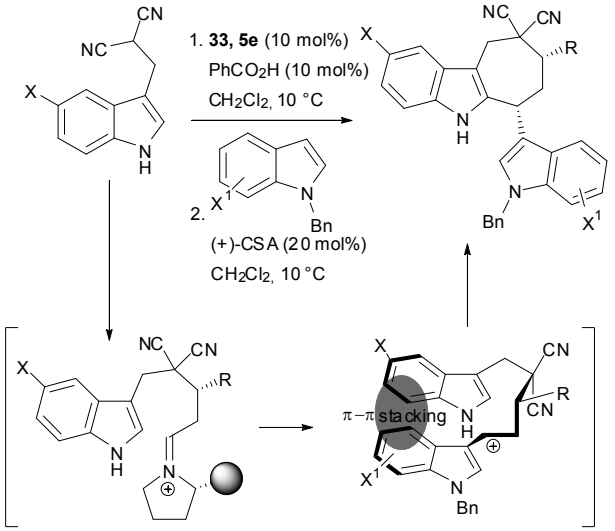
The following reaction creates a stereocentre between the C-2 of an indole nucleus and the C-3 of another. As already mentioned in the previous section, we decided to give the preference to the C-2, since the second indole nucleus behaves as aldehydes in the reaction described in this section.[147] This method allowed the enantioselective synthesis of highly functionalized cyclohepta[b]indoles in 50-72 % yields with 70:30-89:11 dr and 87-96% ee (Scheme 82). The process combines an enantioselective organocatalytic Michael addition and a highly efficient double F-C reaction sequence. In fact, the iminium-activated α,β–unsaturated aldehyde is attacked by indolemalononitrile from the *Re*-face. Then, treatment of this adduct with 1-benzyl-1*H*-indole and (+)-CSA provided the iminium-activated cation intermediate, which underwent cyclization in a half-chair cycloheptane conformer stabilized by π–π stacking.

5.3 Reaction at N-1

As well as the reaction alkylation at N-1 are rarer than other indole alkylation, few examples of cascade reactions involving N-1 are reported.

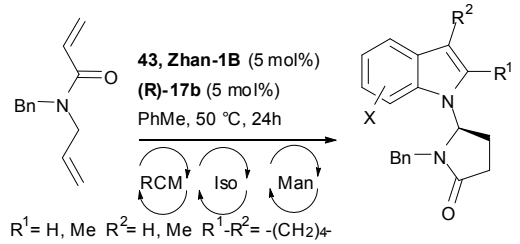
For instance, You and co-workers set-up a synthesis of 5-(1*H*-indol-1-yl)pyrrolidin-2-one derivatives (33-92% yield, 85-95% ee) through a ring-close-metathesis/isomerization/Mannich reaction cascade in the presence of a mixture of **Zhan-1B** and **(*R*)-17b** (5 mol% each) (Scheme 83).[161] The cascade reaction was found more efficient that the stepwise reaction. It should be noted that the sign of the optical rotation of these derivatives is opposite with respect to that reported by Huang (see Scheme 51),[127] thus the *R*-configuration was assigned. However, both research groups used an *R*-configured chiral phosphoric acid as the catalyst. You's group did not report mechanistic hypothesis in order to

explain this different reaction outcome. However, in this review, other examples of products with different configuration obtained from catalysts with the same configuration are reported as well as instances of products with the same configuration arising from catalysts with opposite configuration.



X= H, OMe, Br X^1= H, 4-Br, 5-Cl, 5-Br, 5-CN, 5-OMe, 5-Me, 6-Cl, 7-Br
R= Pr, Bu, (Z)-MeCH2CH=CH(CH2)2, n-C5H11

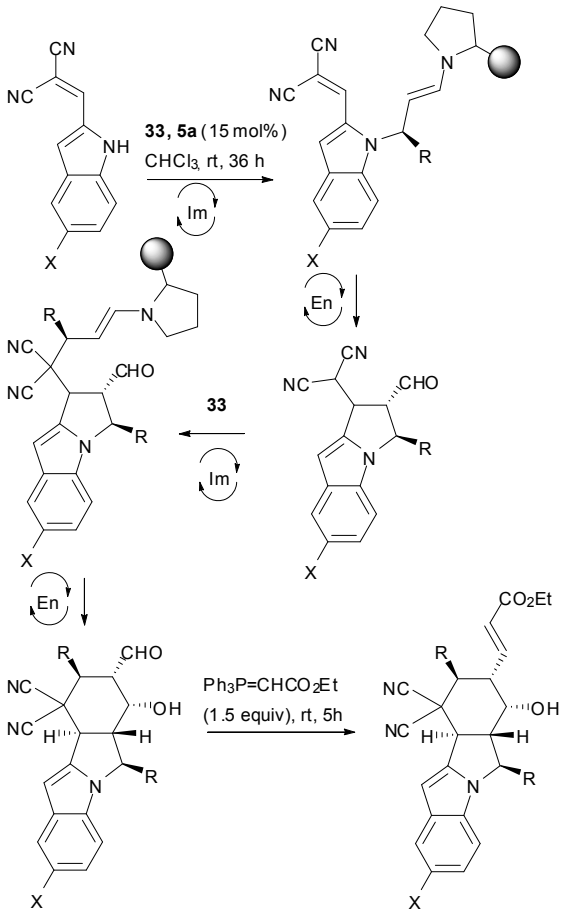
Scheme 82 Sequential organocatalytic Michael/double F-C alkylation reaction[147]



R^1= H, Me R^2= H, Me R^1-R^2= -(CH2)4-
X= H, 5-Me, 5-MeO, 5-Br, 4-Br, 6-Cl

Scheme 83 Enantioselective N–H functionalization of indoles by chiral Brønsted acids by cascade reaction [161]

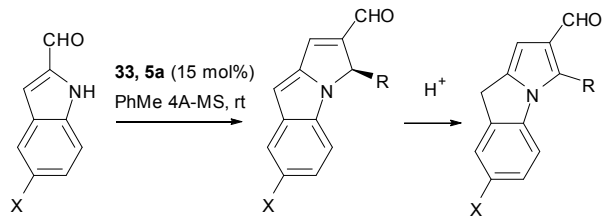
Ender's group reported a quadruple cascade reaction, which employs a sequential iminium–enamine–iminium–enamine activation catalysed by **5a**. The cascade is initiated by the asymmetric *N*-addition of indole-2-methylene malononitrile derivatives to α,β-unsaturated aldehydes, followed Michael addition to the methylene malononitrile to give tricyclic malononitrile derivatives. Again, they act as nucleophiles to another equivalent of the activated α,β-unsaturated aldehyde affording suitable substrates for an intramolecular aldol reaction to give tetracyclic aldehydes. Finally, a Wadsworth-Emmons reaction led to products in 33-70% yields, with >95:5 dr 78-99% ee (Scheme 84).[162] Alternatively, reduction and acetalisation was performed.



X= H, Me, OMe, Br
R= Ph, 4-MeOC6H4, 4-FC6H4, 4-NMe2C6H4, 4-PhC6H4, 2-furyl, 3,4-(OCH2O)C6H3

Scheme 84 Asymmetric aza-Michael/Michael/Michael/Aldol reaction to tetracyclic indoles with six stereocentres[162]

In the previous section the unexpected synthesis of pyrrolo[1,2-a]indoles has been reported (Scheme 80, 81).[159] Other compounds of this family were obtained after the aza-Michael addition, and intramolecular aldol reaction of indole-2-carbaldehydes with α,β-unsaturated aldehydes (Scheme 85).[163] The products were obtained in 57-84% yields, with 81-92% ee. Conversion of these compounds into their achiral tautomers was found to take place spontaneously in weakly acidic media. In particular, 2-furyl derivative was only recovered in 51% yield as the achiral tautomer.



X= H, MeO, F, Cl
R= Ph, 2-MeOC6H4, 2-FC6H4, 2-ClC6H4, 3-MeOC6H4, 4-MeOC6H4 4-FC6H4, 4-ClC6H4 4BrC6H4

Scheme 85 Cascade synthesis of pyrrolo[1,2-a]indole-2-carbaldehydes[163]

6. Conclusion

The functionalization of the indole nucleus is a fascinating area that still has a tremendous impact on organic synthesis. The progress in the development of new organocatalytic reactions allows keeping to a minimum all those ancillary reactions such as functional group manipulation, preactivation of the aromatic ring and protecting–deprotecting group derivatizations. Thus, the sustainability and efficiency of the syntheses is increased as well as they can be applied in the synthesis of natural products and other biologically active compounds, such as pharmaceuticals and agrochemicals. This research area has had an extremely rapid development and today it is still increasing. In fact, in the first months of 2014 a lot of other reactions appeared in the literature.

Moreover, in the year range covered by this review, the same of similar asymmetric indole functionalization were also performed with chiral metal complexes.

7. Abbreviations

Ac	Acetyl
Ant	9-Anthryl
Bn	Benzyl
Boc	t-Butoxycarbonyl
Cbz	Benzyloxycarbonyl
CSA	Camphor sulfonic acid
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
Mes	2,4,6-trimethylphenyl
MS	Molecular sieves
NFSI	N-fluorobenzenesulfonimide
NMO	4-Methtylmorpholine-N-oxide
Npt	Naphthyl
PEG	Polyethyleneglicol
PMP	4-Methoxyphenyl
PS	Polystyrene
TBS	tert-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TPAP	Tetrapropylammonium perruthenate
Ts	4-Methylphenylsulfonyl

Acknowledgments

Dr. Giorgio Bencivenni is gratefully acknowledged for useful discussion and criticisms.

Notes and References

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