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Indole Chemistry

Catalytic Functionalization of Indoles in a New Dimension

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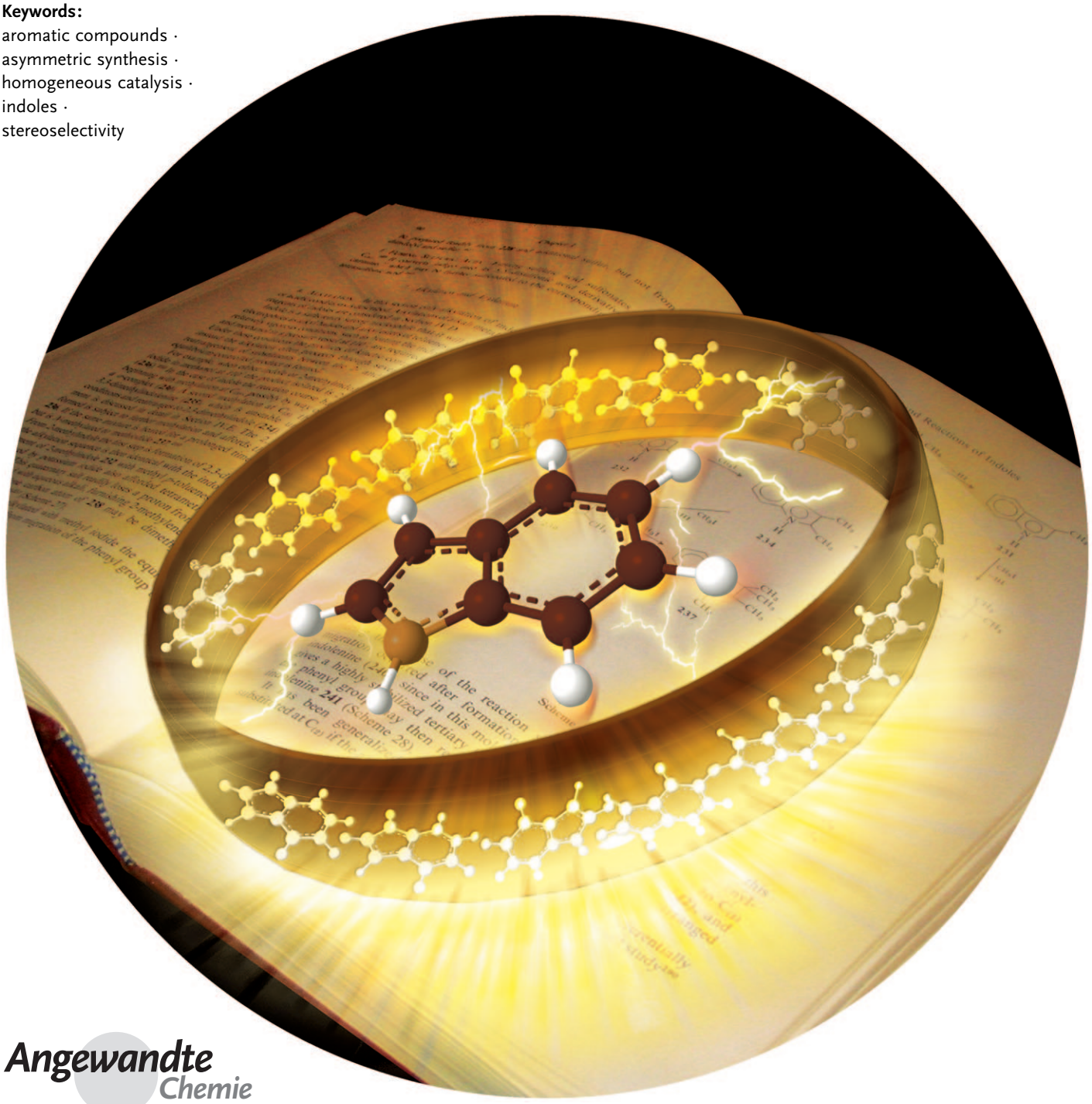
aromatic compounds · asymmetric synthesis · homogeneous catalysis · indoles · stereoselectivity



140 Y*ears ago Adolf von Baeyer proposed the structure of a heteroaromatic compound which revolutionized organic and medical chemistry: indole. After more than a century, indole itself and the complexity of naturally occurring indole derivatives continue to inspire and influence developments in synthetic chemistry. In particular, the ubiquitous presence of indole rings in pharmaceuticals, agrochemicals, and functional materials are testament to the ever increasing interest in the design of mild and efficient synthetic routes to functionalized indole derivatives. This Review emphasizes the achievements in the selective catalytic functionalization of indoles (C–C bond-forming processes) over the last four years.*

From the Contents

1. Introduction

Etymologically, the word indole—the trivial name for benzo[*b*]pyrrole—came from the combination of *ind*igo and *ole*um, as a result of the original methodology for the isolation of the aromatic compound from the natural indigo dye (1869).[1] Since then, indole has become a privileged structure in numerous research areas such as: pharmaceuticals, fragrances, agrochemicals, pigments, and material science.[2] The importance of indole and its broad spectrum of application justifies it being addressed as the "The Lord of the Rings" of aromatic compounds (paraphrasing the novel by J. J. R. Tolkien).

Indole chemistry received particular interest in the mid-1950s, when the alkaloid reserpine[3] was introduced as one of the first drugs for the treatment of diseases of the central nervous system (CNS) such as anxiety and mental disorders. In the 1960s, highly efficient indolyl-based antitumor vincristine was discovered, and later the diverse physiological significance of indolyl alkaloids was expanded to anti-inflammatory, tranquilizing, and antihypertensive activities.

Although all of these areas are still intensively investigated, the most important applications of indole pharmacophores are in drugs that address CNS diseases or manifest anti-inflammatory activity.[4] The current popularity of structurally related carbazole, which is used in organic optoelectronic applications as photoconductive polymeric *N*-vinylcarbazole, is worth mentioning.

Since its discovery, enormous efforts have been devoted to the development of ever more efficient synthetic protocols for the preparation and direct functionalization of this heteroaromatic compound.[5] As a consequence, the resulting research area is extremely extensive and has featured an exponential growth of reports. A survey on SciFinder Scholar (limited to letters and review articles in which indole is present) over the last 112 years clearly shows the ever increasing number of reports targeting indole chemistry (Figure 1).[6] Clearly, such large numbers (more than 80000 publications) originate from extensive studies in the areas of medicinal and agrochemistry; however the synthesis and functionalization of indoles also experienced a significant growth in importance and the number of publications over the past few years (see inset in Figure 1).

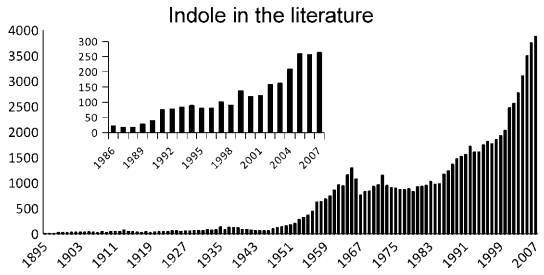


Figure 1. Number of publications (limited to letters and review articles) focusing on indole (SciFinder Scholar). The inset shows the number of publications dealing with the synthesis and/or functionalization of indoles (1986–2007).

During this period we definitively entered a new dimension in the chemical manipulation of indole rings which featured sustainability and efficiency as the main goals. The combination of innovative aspects such as homogeneous and heterogeneous catalysis, alternative reaction media, and uncommon derivatizing agents are essential in pursuing these objectives. The structural diversity and complexity of pharmacologically active indole derivatives constitute a great synthetic challenge for the development of direct and selective syntheses.[7]

Indole is commonly referred to as an electron-rich heteroaromatic system that shows enhanced reactivity, compared to benzene, in electrophilic aromatic substitutions. This

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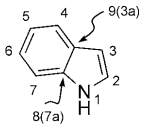
feature should always be considered when working with this type of compound: although the high reactivity can allow organic reactions that are unfeasible for benzene and similar arenes, a careful assessment of the reaction conditions and additives must be carried out to avoid undesired polysubstitution events on the indolyl ring. The most reactive position of indole towards electrophilic substitution is the C3 site (about 10^{13} times more reactive then benzene);[8] however, the N1(pK_a(NH) value ranging from 12.36 to 19.50 in H_2O)[9] and C2-positions must be considered when the whole reactivity is to be defined, particularly when C3-substituted compounds are envisaged (Scheme 1).



Scheme 1. Numbering of the indole system.

The sharp rise in the number of publications since 2000 can also be attributed to the growing interest in catalytic asymmetric Friedel–Crafts alkylations (FCAs) of arenes.[10] In the last few years, the ability of specific chiral catalysts to control the enantiodiscriminating events of aromatic electrophilic substitutions was discovered, which opened direct access to synthetically challenging benzylic stereocenters.[11] In regard to the indole system, a pioneering study addressing enantioselective FCA by means of chiral (tol-binap)–copper(I) complexes was reported by Johannsen in 1999.[12a] Shortly after, the ability of organocatalysis to effect asymmetric Friedel–Crafts reactions was illustrated, and in 2002 Austin and MacMillan elegantly demonstrated the efficiency of chiral imidazolidinones for the enantioselective Michael addition of indoles to enals.[12b] Interest in asymmetric Friedel–Crafts reactions of indoles is currently still accelerating, with more than 30 publications alone in 2008.

Interestingly, although numerous comprehensive review articles have been dedicated to the construction of indole rings,[13] less emphasis has been placed on its functionalization,[14] particularly in terms of catalytic transformations.[15]

This Review aims to highlight the progress in the last few years and the actual state of this thriving area, with particular focus on the construction of new carbon–carbon bonds. Highly important oxidative and reductive processes involving indoles as well as cross-coupling reactions of preactivated indole derivatives (for example, haloindoles)[16] are beyond the scope of this Review. Friedel–Crafts acylation reactions will also not be discussed here.[17]

In some sections, to keep the discussion consistent, the high interdisciplinary nature of the area could result in minor overlap with published monographs/reviews. The Review is deliberately confined to a critical selection of the newest methods. It is not intended to be a comprehensive and exhaustive (encyclopedic) coverage of all the examples present in the literature.

2. Organization of the Review

The chemistry of indole is so extensive that a full coverage of the reactivity of indole would be impracticable. However, some actual trends in modern organic chemistry, such as catalysis, environmental friendliness (greenness), and selectivity will be considered as guidelines for the selection of examples from the literature (Figure 2a).

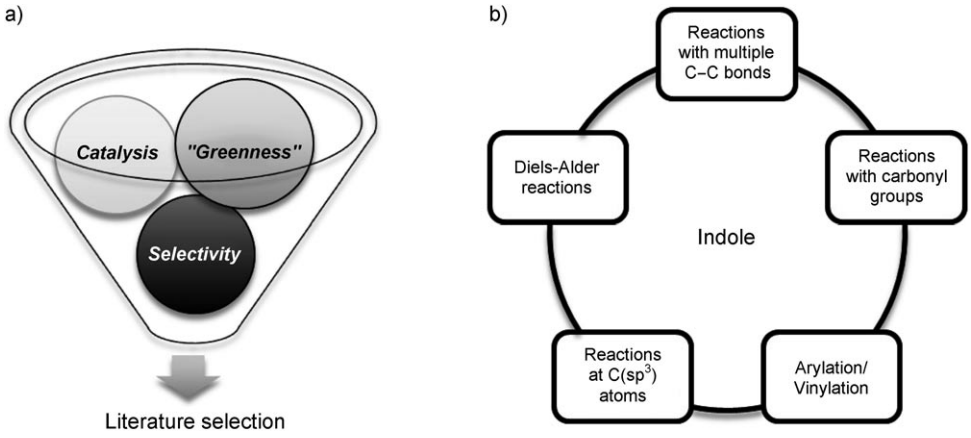


Figure 2. a) "Pass-fail" criteria for the literature selection. b) Reaction types chosen for the Review.

Marco Bandini received his PhD in chemistry in 2000 from the University of Bologna with Prof. Achille Umani-Ronchi. After several periods of research at the University of North Carolina at Chapel Hill (M. R. Gagné) and University of York (D. Macquarrie, Marco Polo Fellowship), he was appointed assistant Professor at the University of Bologna. His research interests include the development of new homogeneous and heterogeneous catalysts for asymmetric transformations.

Astrid Eichholzer was born in Friesach (Austria). She graduated at the University of Graz (Austria) in 2006 and is now carrying out PhD research at the University of Bologna (Italy) under the supervision of Prof. Achille Umani-Ronchi. In 2008, she spent five months at the University of Cambridge (UK) under the supervision of M. J. Gaunt. She is currently developing new inter- and intramolecular cyclization reactions for the synthesis of polyaromatic compounds.

Although a distinct differentiation between these concepts is not always practicable, the following criteria have been used during the preparation of this Review:

- **Catalysis**: The use of chemical additives in substoichiometric amounts (loading ≤ 10 mol%) that are capable of positively affecting both the kinetics and the selectivity of the reaction. Although catalyst amounts above 10 mol% do not strictly fit this definition, reactions requiring additive loadings of up to 20 mol% are generally still considered to be catalytic processes.
- **Environmental friendliness**: This point is determined through reaction parameters which address the minimization of hazardous waste and/or lead to a clear energy saving. These parameters include alternative reaction media, recovery of the catalyst, atom economy, low reaction temperatures, and short reaction times.
- **Selectivity**: Chemo- and regioselectivity are fundamental issues in Friedel–Crafts alkylation reactions, particularly with electron-rich heteroaromatic compounds. Moreover, over the last few years stereochemical aspects have also risen in prominence.

The main purpose of this Review is to serve as a teaching aid for young researchers interested in indole chemistry, with the general aim to provide an overview of the actual potential of catalytic organic reactions in the functionalization of indole rings. Particular emphasis is given to the scope and limitation of the protocols to underline the synthetic tasks still open.

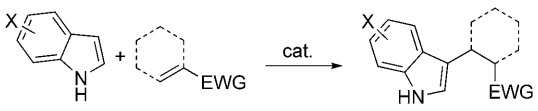
The Review is organized according to five main themes (Figure 2b): additions to C–C multiple bonds (Section 3), additions to carbonyl and similar groups (Section 4), reactions at electrophilic C(sp^3) centers (Section 5), direct arylation/vinylation (Section 6), and Diels–Alder cycloadditions (Section 7).

3. Reactions with C–C Multiple Bonds

3.1. Michael Additions

3.1.1. Introduction

The β-(3-indolyl)carbonyl/(nitro) framework is a valuable structural unit for the synthesis of a plethora of indole derivatives for a wide range of medicinal purposes.[18] The conjugate addition of indoles to electron-deficient carbon–carbon double bonds provides an easy and direct access to such structural units (Scheme 2). The use of catalytic amounts of either Brønsted or Lewis acids generally assists the Friedel–Crafts alkylation through activation of the Michael acceptor. However, when α,β-unsaturated carbonyl compounds are used, particular attention must be paid to the strength of the promoting agent to achieve high regioselectivity (1,4- versus 1,2-addition) and to suppress undesired dimerization and polymerization processes.

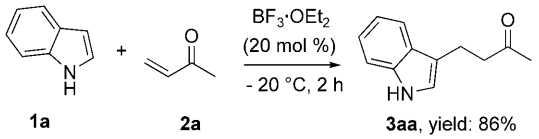


Scheme 2. Catalytic Michael-type Friedel–Crafts alkylation of indoles (EWG: COX, NO_2).

Inter- and intramolecularly Michael-type Friedel–Crafts alkylation[19] is probably the most investigated approach for the catalytic selective functionalization of indoles over the last decade. Among the numerous Michael acceptors, enals and enones have been overwhelmingly adopted for the functionalization of indoles. However, nitroolefins have recently risen to prominence as a result of the synthetic versatility of the resulting β-nitroindolyl compounds in the synthesis of indole alkaloids.

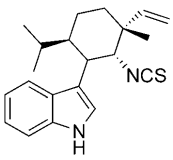
3.1.2. α,β-Unsaturated Ketones

The pioneering investigations addressing the catalytic 1,4-addition of indoles to enones featured the use of clays[20a] and $BF_3{\cdot}OEt_2$.[20b] However, the scope of substrates was quite narrow and mainly confined to methyl vinyl ketone (MVK, **2a**; Scheme 3).



Scheme 3. Pioneering Lewis acid catalyzed conjugate addition of indole to MVK (Ref. [20b]).

A general catalytic Michael-type indole alkylation was subsequently published by Harrington and Kerr in which $Yb(OTf)_3$ (2.5 mol%) was employed as an efficient catalyst in the synthesis of valuable precursors of hapalindole D (**4**).[21]



Hapalindol D (**4**)

Nowadays, the conjugated addition of electron-rich arenes (mainly indoles) to enones has become so popular in organic chemistry that it is commonly employed as a benchmark for new Lewis/Brønsted acid catalysts; several dozens of examples related to this approach have appeared in the literature since 2005. The thermodynamics of the reaction with model substrates (that is, unsubstituted or indoles containing electron-donating groups and alkyl/aryl enones) are generally quite favorable, since both indoles and enones are valuable reaction partners in conjugate additions. In contrast, the reaction is often limited to indoles carrying electron-withdrawing groups such as cyano and nitro. Although the C3-position is the preferred site for electrophilic aromatic substitutions, C2 and N1 functionalizations can become competitive if C3-substituted indoles are involved.[22]

The catalytic systems that have found application in this process range from Lewis acids, homogeneous and heterogeneous Brønsted–Lowry acids, to organic molecular catalysts. A collection of methods is reported in Table 1 in regard to the condensation of indole (**1a**) and MVK (**2a**) as a model reaction.

Table 1: Catalytic Michael-type Friedel–Crafts alkylations of **1a** with **2a**.

Cat. (%)	Solvent	*t* [h] (*T* [°C])	Yield **3aa** [%]	Ref.
$Hf(OTf)_4$ (1)	CH_3CN	2 (RT)	90	[23a]
SmI_3 (10)	CH_3CN	1 (80)	95	[23b]
SmI_3-silica gel (10)	CH_3CN	0.02[a]	90	[23c]
I_2 (1)[b]	–	0.1 (RT)	76	[23d]
GaI_3 (10)	CH_2Cl_2	1 (RT)	90	[23e]
hν (350 nm)	CH_2Cl_2	18 (RT)	46	[23f]
$ZnBr_2$-HPA (0.1 g)	CH_3CN	4 (80)	89	[23g]
$ZnBr_2$-FAP (0.2 g)	CH_3CN	4 (80)	94	[23h]
$H_3PW_{12}O_{40}$ (0.5)	H_2O	0.2 (RT)	100	[23i]
nano-TiO_2 (10)	CH_2Cl_2	3 (RT)	92	[23j]
$[PdCl_2(CH_3CN)_2]$ (2)	[bmim]BF_4[c]	5 (100)	94	[23k]
silica-Na (20)[d]	H_2O	24 (30)	96	[23l]
silica-Sc-IL (20)[e]	H_2O	4 (RT)	96	[23m]
$Al(DS)_3 \cdot 3H_2O$ (10)	H_2O	24 (RT)	20	[23n]
pyrrolidine (30)[f]	CH_2Cl_2	6 (RT)	92	[23o]
$AuCl_3$	DCE	0.05 (RT)	95	[23p]
$MgClO_4/FeCl_3$ (10)[c]	MeOH	12 (RT)	96	[23q]

[a] Microwave irradiation at 680 W. [b] 5-Cyanoindole (**1b**) was used. [c] Chalcone (**2b**) was used. [d] In the presence of $[DBIm]SbF_6$. [e] In the presence of $[DBIm]SbF_6$ (20 mol%). [f] With $HClO_4$ (30 mol%) as a co-catalyst. 5-Methyl-3-hexen-2-one (**2c**) was used.

Although seminal examples focused entirely on homogeneous Lewis acid catalysis, the environmental and safety standards required in the production of fine chemicals led to a great deal of effort being devoted to the use of recoverable supported Lewis acids, inorganic solid acids, alternative reaction media (water, ionic liquids), and clean reaction promotors such as UV and microwave irradiation.

The tendency of indoles to couple regioselectively with enones was recently exploited by Florent, Bertounesque, and co-workers in the synthesis of pharmacologically active angular heterocyclic lignans (**8**).[24] The authors elegantly employed a double indium(III)-catalyzed Friedel–Crafts alkylation[25] of variously functionalized indoles with methyl thuriferates such as **5**. High yields and diastereomeric excesses of greater than 95% were achieved (Scheme 4).

Indole derivatives containing stereochemically defined benzylic stereocenters are relevant in numerous natural products and pharmaceutical agents. According to MacMillan: "*… the indole framework has become widely identified as a 'privileged' structure or pharmacaphore, with representation in over 3000 natural isolates and 40 medicinal agents of diverse therapeutic action.*"[12b] Conjugate addition of indoles to α,β-unsaturated ketones represents a stimulating platform for the development of new chiral catalysts. The enantiodiscriminating event of the process is generally assisted by noncovalent (metal and Brønsted acid catalysis) or covalent (amino catalysis)[26] interactions between the catalaphoric unit and the carbonyl unit (Figure 3).

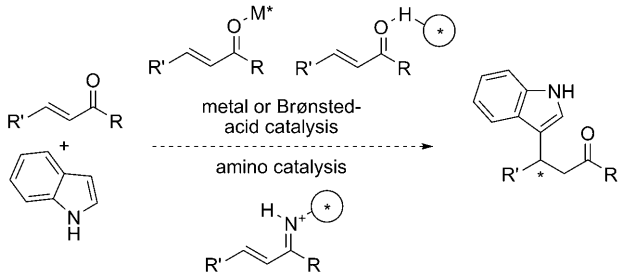
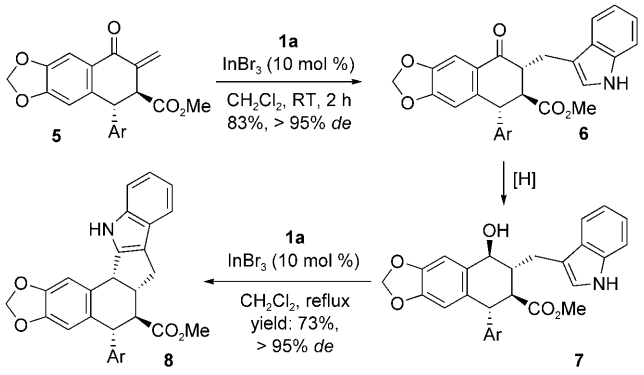


Figure 3. Metal-based and metal-free chiral activation in the Michael addition of indoles to enones. Chiral entities are represented by (*).

Determinant indole–catalyst interactions are less common than carbonyl–catalyst activation interactions, although several cases of bifunctional catalysis have been documented.

Chemoselection (1,2- versus 1,4-addition) is not a relevant issue with enones, because of the generally low tendency of simple keto-carbonyl groups to undergo 1,2-addition with indoles. As a consequence, 1,4-processes are generally favored. The reasons for the relatively late development of efficient catalytic systems for such asymmetric processes can be rationalized in terms of: 1) the challenging stereodifferentiation of the enantiotopic faces of the Michael acceptor, as a consequence of the steric similarity of the carbonyl substituents (metal catalysis); 2) the difficult generation of congested catalyst–substrate intermediates (organocatalysis, Figure 4).

Asymmetric conjugate addition of indoles to simple enones was pioneered in 2003 by Bandini, Umani-Ronchi et al., who uses the organometallic catalyst [Al(salen)Cl]/lut.[27] Only Pedro and co-workers have since addressed this challenging task, by investigating the activity of (*R*)-3,3′-Br_2-binol/$Zr(OtBu)_4$ (20 mol%) in the Michael addition of indoles and 4,7-dihydroindoles (**9**) with enones.[28] The latter



Scheme 4. Indium-catalyzed Friedel–Crafts alkylations as key steps in the synthesis of angular lignan **8**. Ar = 3,4,5-$(MeO)_3C_6H_2$.

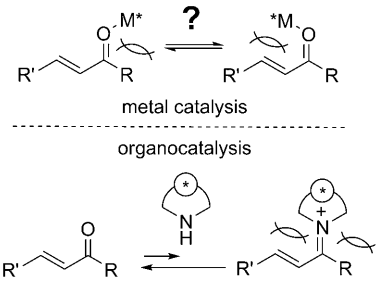
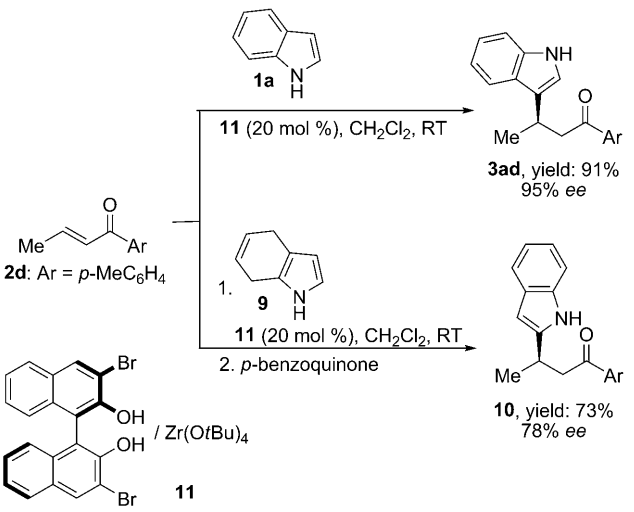


Figure 4. Which catalyst is suitable for asymmetric indole/enone condensations?

case represents an indirect method to access the C2-alkylated indole nucleus **10**. Good to excellent enantiomeric excesses (up to 97% *ee* for C3 alkylation and up to 78% *ee* for the C2-alkylation) were obtained. However, severe limitations in the scope of the substrates occurred, with restriction to acyclic α,β-unsaturated aryl ketones (Scheme 5).



Scheme 5. Zirconium(IV)–binol-catalyzed enantioselective synthesis of 2- and 3-functionalized indoles by Michael addition with ketone **2d**.

In contrast to simple enones, bidentate α,β-unsaturated ketones gained great attention and popularity for the stereospecific alkylation of indoles. The major advantage in using such an electrophile, rather than a monodentate one, lies in the possibility to bind rigidly to dicationic chiral Lewis acids, thereby leading to higher stereodifferentiation.

Historically, this area was opened up by a contribution by Jørgensen and co-workers (2001) in which they combined β,γ-unsaturated α-ketoesters and *t*Bu-box/copper(II) triflate (2–10 mol%) to obtain β-indolyl ketosters in a highly stereoselective manner.[29]

The combination of copper(II) triflate and box ligands (**12**) largely dominated in this area, although some relevant studies with chiral scandium(III)–box complexes have been reported. Here, efforts have primarily addressed the discovery of innovative and synthetically flexible bidentate (O,O and O,N) electrophiles (**13**–**18**) that are capable of guaranteeing high enantiocontrol with a broad range of substrates. In Figure 5 a collection of Michael acceptors as well as the corresponding chiral Lewis acids for stereoselective Michael-type Friedel–Crafts alkylations have been summarized. Investigations with copper catalysis were reported by Palomo et al. (**12a**/**13**),[30a] Kim and co-workers (**12b**/**14**),[30b] and Singh and Singh (**12c**/**15**),[30c] whereby variable catalyst loadings (5–20 mol%) provided excellent enantiocontrol (> 90% *ee*). Comparable efficiency was also found with chiral scandium(III)–box (**12d,e**) catalysts (10 mol%) in combination with α,β-unsaturated acyl phosphonates **16**,[31a,b] α,β-unsaturated 1-acylimidazoles **17**,[31c] and β,γ-unsaturated α-keto esters (**18**).[31d]

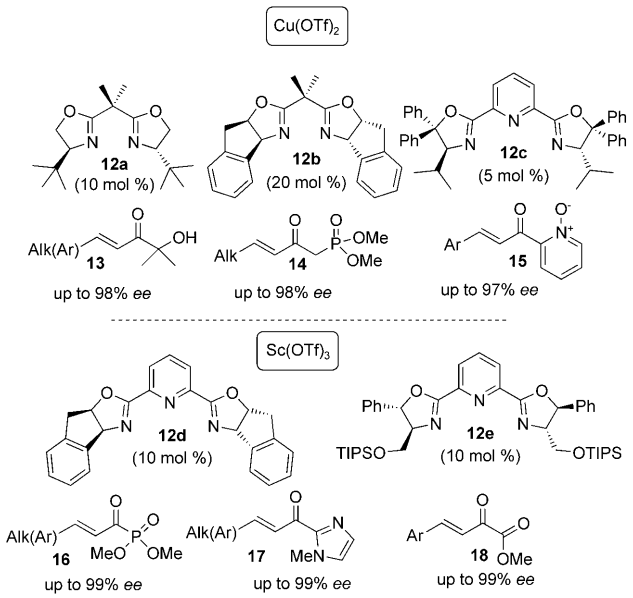


Figure 5. Copper(II) and scandium(III) complexes for enantioselective Friedel–Crafts alkylations of indoles.

To date, the search for asymmetric metal-catalyzed Michael additions of indoles to nonchelating ketones has produced only a handful of examples because of the intrinsic difficulties (Figure 4). Organocatalytic methods appeared to be even less suitable for this purpose, in fact the classic LUMO-lowering activation, via formation of an iminium ion, is unfavorable in the case of ketones because of steric hindrance (Figure 4, bottom).[23o]

A breakthrough in the field occurred when the research groups of Melchiorre[32a] and Chen[32b] addressed the use of chiral primary amine salts as suitable candidates for asymmetric organocatalyzed 1,4-addition of indoles to enones, because of their reduced steric requirements (Figure 6).

The key role played by the counterions in asymmetric amino catalysis is well documented. In fact, asymmetric counteranion-directed catalysis (ACDC) was recently introduced by List and co-workers[33] and successfully adopted by Melchiorre and co-workers. They combined 9-amino-9-deoxyepihydroquinine (**19a**; 20 mol%) with D-*N*-Boc-Phg (40 mol%) to afford a powerful catalytic salt for a range of indole/enone combinations.[32a] The use of *N*-protected amino acids as Brønsted acid co-catalysts decreased the turnover

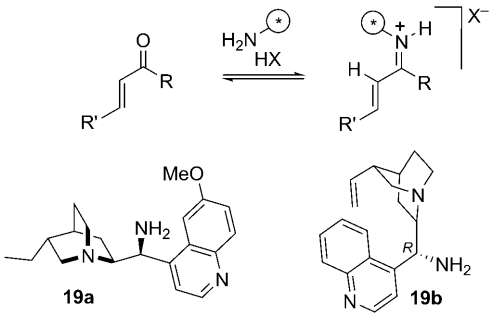
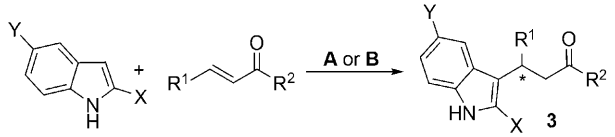


Figure 6. Minimization of steric factors in the iminium activation of enones by using primary amines as catalysts.

frequency of the process (at 70 °C) with respect to that with CF_3SO_3H, as used by Chen (−20 °C→0 °C),[32b] but resulted in higher *ee* values (Table 2).

Table 2: Amino catalysis in the enantioselective alkylation of indoles with α,β-unsaturated ketones.



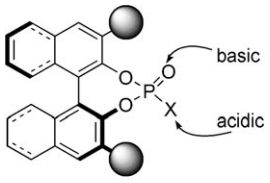
1a: X = Y = H
1c: X = H, Y = OMe
2e: R^1 = Ph, R^2 = Me
2f: R^1 = *p*-ClC_6H_4, R^2 = Me
2g: R^1 = $(CH_2)_4CH_3$, R^2 = Me
2h: R^1 = $(CH_2)_2CH_3$, R^2 = Me

Indole	Ketone	Method[a]	Yield [%]	*ee* [%]
1a	**2e**	A	>95	87
1a	**2e**	B	72	62
1a	**2f**	A	92	89
1b	**2f**	B	99	70
1a	**2g**	A	91	93
1a	**2h**	B	74	78

[a] Method A: **19a**/Boc-D-Phg-OH (20/40 mol%), toluene, 70 °C. Method B: **19b**/TfOH (30/60 mol%), CH_2Cl_2/*i*PrOH.

Over the last few years, the use of weak catalyst–substrate interactions have also become predominant in organocatalysis, because of the wide range of chiral Brønsted acids available.[34] After the seminal paper by Sigman and Jacobsen in 1998,[35] new chiral Brønsted acids have been applied in challenging stereoselective transformations.

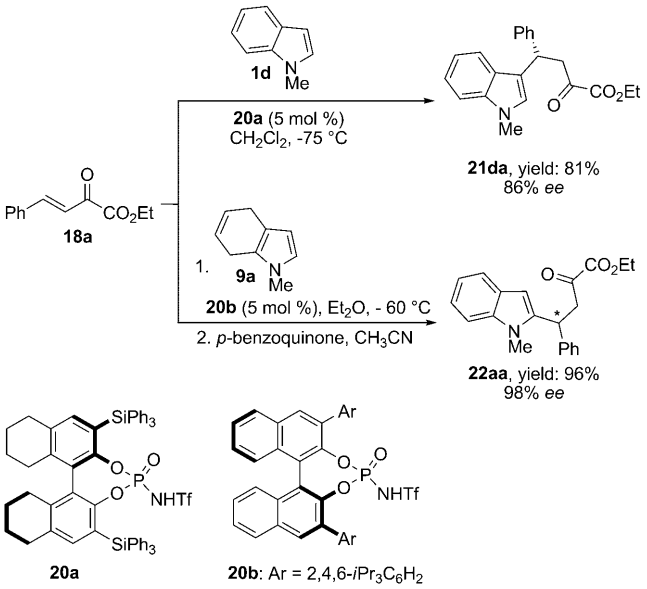
As will be evident from this Review, Brønsted catalysis (for example, chiral binaphthol-derived phosphoric acids **20**)[36] has frequently been exploited in indole chemistry to



20: X = OH, NHTf

synthesize alkylated compounds in a highly enantiomerically pure form. The introduction of sterically demanding bulky groups (such as arenes or -SiR_3) at the 3- and 3′-positions of the binol skeleton lead to the creation of a chiral environment close to the reaction partners, which are generally placed in a favorable spatial arrangement by the dual function (Brønsted acid and base) exerted by the phosphoric unit. Such an approach has been applied with variable success to the stereoselective condensation of indoles with structurally different enones. Simple α,β-unsaturated ketones still proved to be challenging Michael acceptors for indole alkylations, and only moderate *ee* values (up to 56% *ee*) were recorded by Zhou, He, and co-workers by using octahydrobinaphthol (H_8-binol) phosphoric acid (2 mol%).[37,38]

In contrast, activated β,γ-unsaturated α-keto esters **18** served as straightforward electrophilic agents under catalysis by chiral Brønsted acids, as shown by Rueping et al.[39a] and You and co-workers.[39b] They performed the C3-alkylation of indoles and C2 functionalization of 4,7-dihydroindoles in a highly stereocontrolled fashion by using binol-based *N*-triflylphosphoramides **20a**,**b** (Scheme 6).

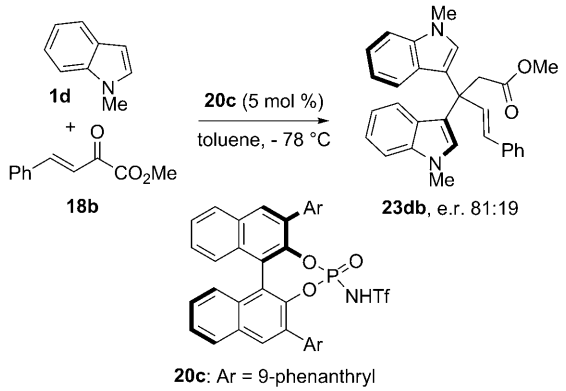


Scheme 6. Asymmetric alkylation of indoles and 4,7-dihydroindoles in the presence of chiral Brønsted acids.

An interesting case of atropisomerism occurred in the chiral Brønsted acid catalyzed alkylation of indoles presented by Rueping et al. Here, the chemoselectivity of the reaction (1,2- versus 1,4-addition) was controlled by fine-tuning the stereoelectronic properties of the catalysts. In particular, sterically congested phosphoric amide **20c** enabled the chemoselective 1,2-addition of **1d** to **18b**. Interestingly, the product **23 db** was isolated as an atropoisomeric mixture in a ratio of 81:19. A mechanistic explanation for the observed stereoinduction is related to the formation of a tight ion pair between the anion of the catalyst and the positively charged species originating after elimination of the hydroxy group from the 1,2-addition adduct (Scheme 7).

3.1.3. α,β-Unsaturated Aldehydes

Enals are intriguing electrophilc reaction partners for the catalytic alkylation of indoles. The remarkably higher reactivity of the carbonyl unit, compared to the enone counterpart, makes the chemoselective 1,4-addition a still partially unsolved task. In fact, bi-, tri-, and multiple alkylation processes generally occur simultaneously, thereby leading to useless chemical outcomes for synthetic applications (Figure 7).[40] The absence of metal-promoted chemoselective Michael additions of indoles to enals in the literature illustrates the intrinsic difficulties of such a transformation.



Scheme 7. Organocatalyzed enantioselective synthesis of atropoisomeric bisindole **23db**.

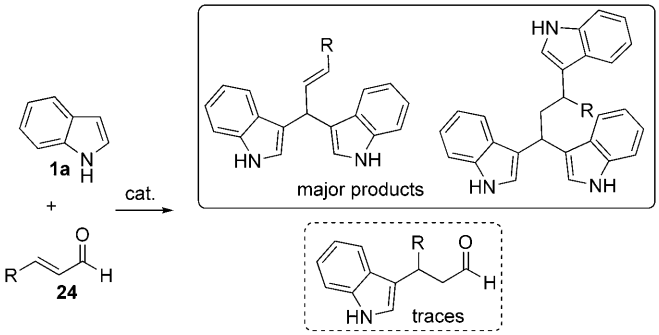


Figure 7. Chemoselectivity in the conjugate addition of indoles to enals.

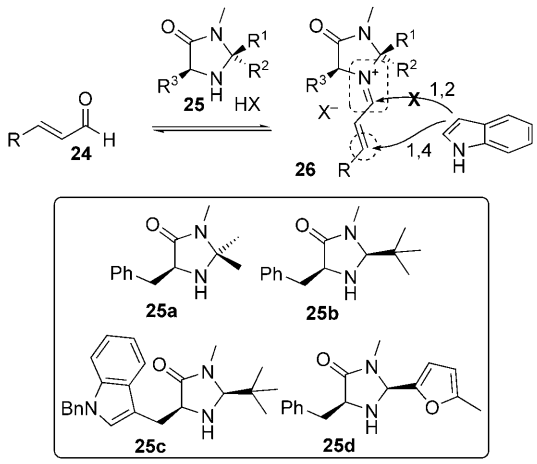
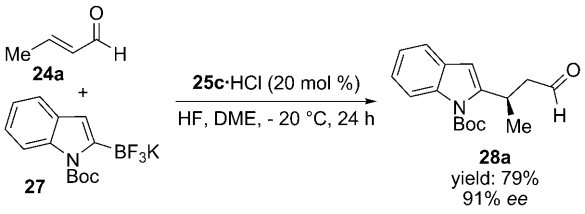


Figure 8. The use of chiral imidazolidinones **25a–d** results in 1,4-addition of indoles to enals being favored over 1,2.addition.



Scheme 8. Enantioselective organocatalyzed C2-alkylation of indoles by using trifluoroborate salts.

A reliable and innovative solution to these drawbacks came with the enlightened use of readily available chiral imidazolidinones **25** as LUMO-lowering activators of α,β-unsaturated aldehydes.[12b,41] Here, the formation of intermediate chiral iminium ions **26** guaranteed: 1) electrophilic activation of the β position; 2) prevention of nucleophilic attack to the carbonyl unit (steric congestion); and 3) efficient stereodifferentiation of the diastereotopic faces of **26** because of the stereochemical orientation of the groups R^1–R^3 (Figure 8).

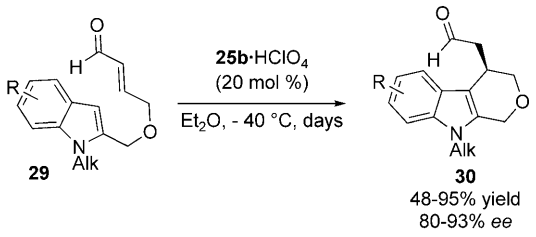
After this seminal publication, the scope of the reaction was further expanded by the same research group to an organocatalytic cascade process (with **25c**)[42a] and to the C2-selective functionalization of an electron-deactivated *N*-Boc-protected indole derivative in the presence of the corresponding trifluoroborate salt **27** and crotonaldehyde **24a**.[42b] Here, the combination of tryptophan-derived catalyst **25c** and hydrofluoric acid (1 equiv) succeeded in furnishing **28a** in 79% yield and 91% *ee* (Scheme 8).

Over the last four years, growing interest has been shown to the enantioselective organocatalyzed alkylation of indoles by 1,4-addition to enals[43] because of its utility in preparing valuable intermediates for biologically active components. As an example, Dalton King, Meng et al. used the conditions developed by MacMillan and co-workers for the functionalization of substituted indoles with new α-branched cyclic enals.[44a] The resulting alkylated compounds were readily converted into potential candidates for selective serotonin reuptake inhibitors (SSRIs). Moreover, Fréchet and co-workers explored the combined use of encapsulated organocatalysts (**25b**, pyrrolidine derivative) in soluble hyperbranched polymers for the one-pot stereoselective iminium and enamine catalysis. Here, a sophisticated multistep Friedel–Crafts alkylation sequence on **1d** occurred in a highly stereoselective manner.[44b]

More recently, intramolecular conjugate addition of indoles to enals was elegantly demonstrated by Xiao and co-workers with a tandem ruthenium-catalyzed cross-metathesis/intramolecular hydroarylation sequence.[45a] The key step was the enantioselective organocatalyzed cyclization of indolyl α,β-unsaturated aldehydes **29** in the presence of catalyst **25b**·$HClO_4$ (20 mol%) for the construction of polycyclic tetrahydropyrano[3,4-*b*]indoles (THPIs, **30**).[45b] Outstanding levels of enantioselection (80–93% *ee*) were obtained even if long reaction times (days) were required (Scheme 9). Furthermore, the same authors also obtained similar results for the intermolecular Michael addition of indoles to dialkyl 3-oxoprop-1-enylphosphonates (**25b**·TFA as catalyst).[45c]

3.1.4. α,β-Unsaturated Carboxylic Compounds

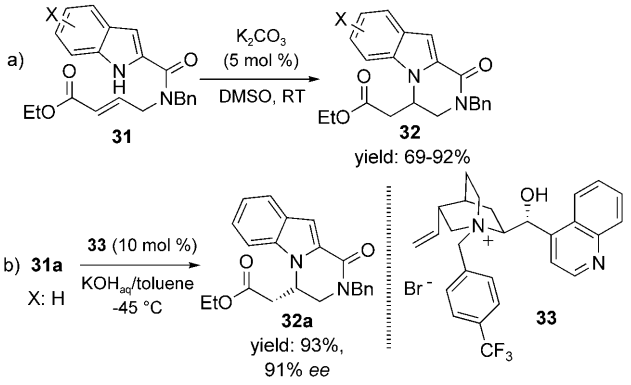
Carboxylic acid derivatives with indol systems are important chemical architectures in medicinal chemistry and agrochemicals.[46] Unfortunately, direct access to these molecular motifs by conventional catalytic Michael additions is fre-



Scheme 9. Enantioselective synthesis of THPIs **30** by organocatalyzed intramolecular Michael addition of indoles to enals.

quently not possible because of the intrinsic reluctance of common unsaturated carboxylic derivatives to undergo 1,4-additions with indoles.[47]

The intramolecular conjugate addition of the indole nitrogen atom (hydroamination) to α,β-unsaturated esters was recently described.[48a] By using basic catalysis (5 mol% K_2CO_3, DMSO, RT, minutes), readily accessible indolyl esters **31** underwent rapid, high-yielding, and regioselective ring closure to the corresponding 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones **32** (Scheme 10a). An enantioselective variant



Scheme 10. Intramolecular aza-Michael addition of indoles under base catalysis (a) and a stereoselective variant (b).

of this aza-Michael-type alkylation of indoles, under phase-transfer conditions, was reported shortly after. In this example, the acidity of the N–H proton in **31** was used to enhance the reactivity of the indole system under basic conditions. Deprotonation led to the subsequent formation of tight and conformationally rigid ion pairs with chiral cinchona-based ammonium salt **33** (10 mol%), which enabled high enantiocontrol to be obtained (up to 91% *ee*, Scheme 10b).[48b]

The low reactivity of simple α,β-unsaturated carboxylic acid derivatives in acid-catalyzed Michael-type Friedel–Crafts indole alkylations has been circumvented by the use of benzylidene malonates **34** as highly reactive Michael acceptors. The efficiency of this class of electron-deficient C–C double bonds in enantioselective alkylation of indoles was demonstrated by Jørgensen and co-workers (2001) by using chiral copper(II)–box complexes.[49] The bidentate nature of the malonate derivatives perfectly matched the coordinating vacancies of the bicationic copper(II) complexes (see Figure 5), thus leading to conformationally rigid Lewis acid/base adducts **35a** and consequently efficient stereodifferentiation (Figure 9).

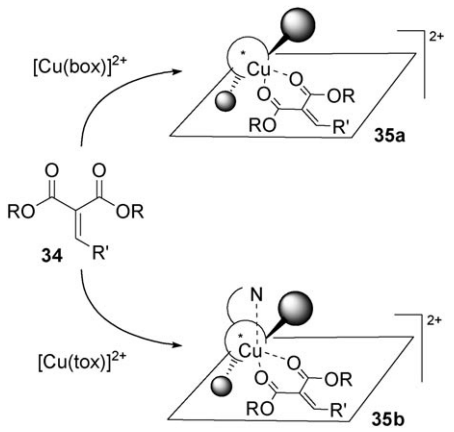
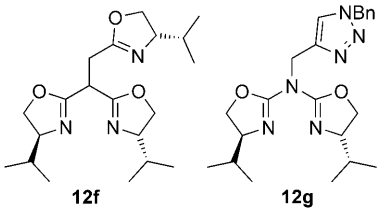


Figure 9. Coordination of [Cu^{II}(box)] and [Cu^{II}(tox)] complexes with Michael acceptors **34**.

Further developments led to the discovery that the tridentate trisoxazoline (tox) **12f**[50a,b] and azabis(oxazoline) **12g** dramatically improved the enantioselectivity (up to



69% *ee*)[49] through the hypothetical formation of highly stereodiscriminating pentacoordinated copper complexes (**35b**). Evidence of the role of the extra coordination sites came from Reiser and co-workers,[50c,d] who emphasized the effect of the ligand/metal ratio on the final outcome of the Michael addition. The reaction is unfortunately restricted to the use of aromatic malonate derivatives (**34**, R′ = Ar); the corresponding aliphatic analogues (for example, R′ = Me) led to markedly lower enantiomeric excesses. The application of such a protocol to ethenetricarboxylates was also reported.[50e]

3.1.5. Nitroolefins

The nucleophilic conjugate addition of indoles to nitroolefins **36** has been known for a long time.[51] This reaction offers considerable synthetic utility, by opening up access to versatile building blocks for the preparation of indole-based alkaloids. For example, the resulting β-indolylnitroalkanes **37** can be easily transformed into melatonin analogues **38a**, 1,2,3,4-tetrahydro-β-carbolines (THBCs, **38b**), and "triptans" **38c** (Figure 10).

Despite the ability of nitroolefins to act as Michael acceptors,[52] the uncatalyzed reaction proceeds sluggishly and

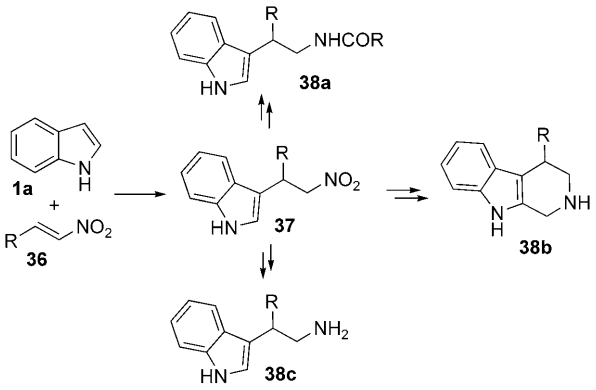
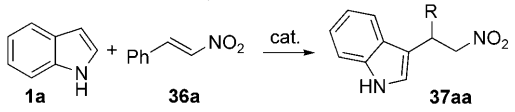


Figure 10. Indolylnitroalkanes: versatile intermediates in organic synthesis.

leads to relatively poor conversions. Therefore, in analogy to the scenario involving enones, special effort has been devoted to the discovery of efficient and selective catalytic species. A collection of recent Friedel–Crafts alkylations by the Michael addition of indoles to nitroalkanes is shown in Table 3, with the condensation of **1a** and (*E*)-nitrostyrene (**36a**) selected as a model reaction.

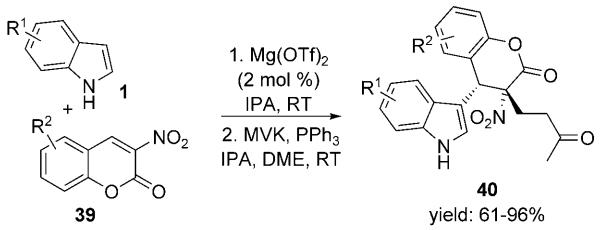
Table 3: Advances in the catalytic Michael addition of indole to **36a**.



Cat. (%)	Solvent	*t* [h] (*T* [°C])	Yield **37aa** [%]	Ref.
I_2 (30)	Et_2O	2 (RT)	99	[53a]
$H_4[Si(W_3O_{10})_3]$ (20)	CH_3CN	0.25 (RT)	90	[53b]
SmI_3 (10)	CH_3CN	1 (RT)	95	[23b]
$CeCl_3 \cdot 7H_2O$-SiO_2 (30)	–[a,b]	8 (RT)	96	[53c]
SA (10)	–[a]	0.5 (60)	96	[53d]
Selectfluor (10)	CH_3CN	3 (RT)	92	[53e]
$NaHSO_4$-SiO_2 (10)	CH_3CN	2 (RT)	92	[53f]
SiO_2, MW	–	0.02 (–[c])	95	[53g]
–[d]	H_2O	5 (100)	85	[53h]
CTH (10)	H_2O	14 (RT)	93	[53i]
$BiOClO_4$ (9)	CH_3CN	1.5 (RT)	88	[53j]
H_3PW_{40} (–[c])	H_2O	18 (RT)	82	[23k]

[a] Solvent-free conditions. [b] In the presence of silica-supported NaI (30 mol%). [c] Not available. [d] No additive.

From the examples listed in Table 3, the ongoing tendency toward the use of alternative reaction media (mainly water) and heterogeneous acid catalysis clearly emerges. An interesting synthetic application of the catalytic Michael addition of indoles to nitroolefins was described for the synthesis of multifunctionalized 3,4-dihydrocoumarins in a diastereoselective manner.[54] Here, the one-pot tandem $Mg(OTf)_2$-catalyzed conjugate addition of indoles to 3-nitrocoumarin derivatives **39** and MVK led to polyfunctionalized products **40** in high yield (61–96%) and with a high selectivity for the *cis* isomers (Scheme 11).



Scheme 11. Sequential Michael additions for the synthesis of indole-containing hydrocoumarins.

Enantioselective condensations of indole with nitroalkanes appeared only recently with [Al(salen)Cl]/py used as the chiral catalyst (10 mol%).[55] Moderate enantioselectivity (up to 63% *ee*) was obtained with 2-aryl indoles. Moving from single- to two-site-binding substrate–catalyst interactions caused a marked improvement in the reaction rate and enantiocontrol (Figure 11). In this context, bicationic metal catalysis (with chiral M^{2+}–box complexes; M = Zn, Cu)[56] and hydrogen-bond-based organocatalysis (through chiral thioureas)[57] has developed in parallel.

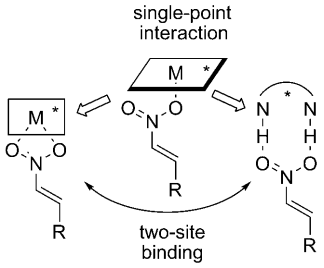
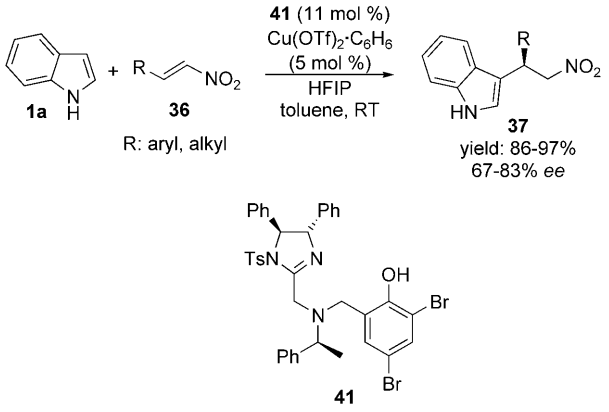


Figure 11. Catalyst–substrate coordination modes in the asymmetric Michael addition of indoles to nitroalkenes.

Among the number of C_1- and C_2-symmetric metal complexes that have proved to be efficient stereodifferentiating agents in the 1,4-addition of indoles to nitroalkenes, special mention must be made to the system recently proposed by Arai et al.[56a] The novelty lies in the combination of a high-throughput screening method with circular dichroism for the rapid investigation of multiple ligand–metal combinations. A survey of 32 compounds showed chiral imidazoline-aminophenol **41** to be the ligand of choice for $Cu(OTf)_2 \cdot C_6H_6$ (Scheme 12).

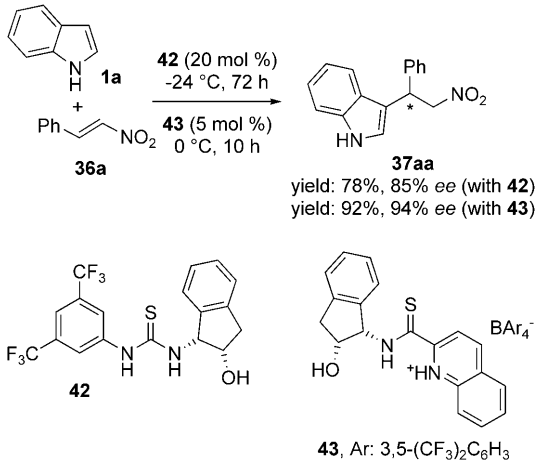
Chiral thioureas have become important structural units in enantioselective organocatalysis.[34,58] They enable the simultaneous formation of two hydrogen bonds to a substrate with consequent electrophilic activation. The two-site hydrogen-bonding arrangement generally guarantees higher directionality than a single hydrogen-bonding interaction. For these reasons, chiral thioureas are frequently utilized for the activation of bidentate nitroolefins in asymmetric transformations.

In this context, Ricci and co-workers pioneered the use of chiral thioureas for the enantioselective organocatalyzed addition of indoles to nitroalkenes.[57b] The C_1-symmetric thiourea **42**, derived from enantiomerically pure (1*R*,2*S*)-*cis*-



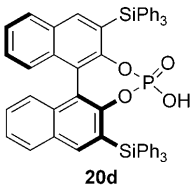
Scheme 12. High-throughput, solid-phase catalysis with CD detection leading to the new chiral catalyst **41** for asymmetric indole alkylation.

1-amino-2-indanol, was found to be a good catalyst for the regioselective functionalization of indoles at C3. A dual catalytic activity of **42** was finally proposed on the basis of mechanistic investigations. More recently, Ganesh and Seidel modified the thiourea skeleton, which led to the discovery of quinolinium thioamide **43** as an efficient catalyst.[57d] The stronger interaction between the protonated pyridyl unit and the substrate markedly increased the reaction rates (catalyst loading as low as 5 mol%), thus allowing large-scale experiments (20 mmol of **36a**) to be carried out in reasonable reaction times and with high enantiomeric excess (Scheme 13).



Scheme 13. Enantioselective thiourea-catalyzed conjugate addition of indoles to nitroalkenes.

Although chiral phosphoric acids have predominantly found applications in asymmetric catalysis with monodentate electrophilies, Akiyama and co-workers reported on the efficiency of chiral Brønsted acid **20d** (10 mol%) in controlling the stereodselective 1,4-addition of the indole nucleus to aliphatic as well as aromatic nitroolefins. The beneficial role of activated molecular sieves for both the reaction rate and stereoselection (88–94% *ee*) was also outlined by the authors.[59]



3.2. Metal-Catalyzed Hydroarylation Reactions

3.2.1. Introduction

The direct catalytic addition of arenes to unactivated multiple bonds (for example, alkenes, alkynes, and allenes), commonly referred as the hydroarylation reaction, is an efficient atom-economical route for the preparation of functionalized aromatic compounds. However, practical examples of such an approach remained scarce until recently and was limited to arenes possessing adequate directing groups.[60]

Some of the difficulties that have for a long time made the hydroarylation of π bonds unsuitable for large-scale preparations are the need for a large excess of the arenes, stoichiometric amounts of metal promoters, and forcing reaction conditions. However, the introduction of π-acidic late-transition metals (for example, Pt, Pd, Au, Rh) allowed both the direct inter- and intramolecular addition of aromatic C–H bonds to unactivated π systems with a remarkable functional-group compatibility.

Two distinct mechanistic pathways can be recognized from the electronic properties of the aromatic compound (electron-rich or electron-deficient) and the type of metal catalyst (oxidation state, type of ligands). Here, cationic metal species in high oxidation states combined with arenes carrying electron-donating groups generally undergo addition reactions through activation of the multiple bonds by π acids. In contrast, hydroarylation with electron-poor aromatic compounds catalyzed by nucleophilic metal complexes can involve the preliminary activation of C–H bonds of the arene by oxidative insertion of the metal species. In the latter case, the introduction of directing groups on the aromatic ring assists the C–H activation event that controls the regiochemistry. The opposite addition modes of the aromatic C–H bonds to alkynes in the two mechanisms (namely, *trans* for π-acid activation of the multiple bond and *cis* for metal C–H activation) is reflected in the stereochemistry of the final product (Figure 12).

Finally, hydroarylation of alkenes and allenes involving indoles represent a valuable shortcut for the construction of benzylic stereocenters. Efforts toward the development of catalytic and enantioselective variants of indolyl C–H addi-

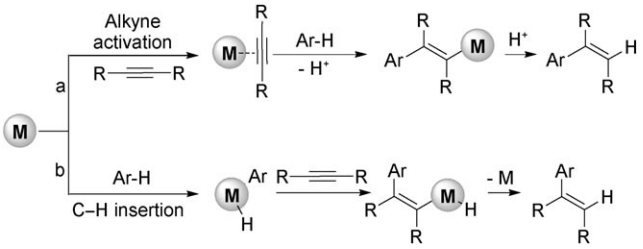
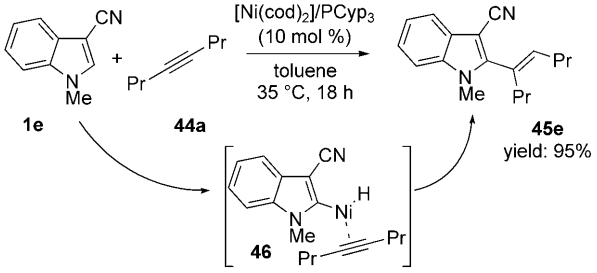


Figure 12. Metal-catalyzed hydroarylation of triple C–C bonds: alkyne activation versus C–H activation.

tion to olefins have recently been documented (see Section 3.2.3).

3.2.2. *Hydroarylation of Alkynes*

The use of indoles in the hydroarylation reactions of alkynes allowed the synthesis of functionalized indolylalkenes in a stereochemically defined fashion, without the need for prefunctionalized haloindoles in Heck-type cross-coupling processes.[61] Although the electron-rich nature of the indole system makes alkyne activation the predominant pathway, examples of hydroarylation by C–H bond activation on the indole has also been reported. As an example, Nakao, Hiyama et al. reported on the catalytic efficiency of the Ni^0/$PCyp_3$ complex for the regioselective C2-addition of indoles to internal alkynes.[62] Here, the presence of electron-withdrawing groups (for example, CN, CO_2R, CHO) guaranteed the chemoselective C2-H activation under mild reaction conditions (35 °C, Scheme 14).



Scheme 14. Nickel(0)-catalyzed hydroarylation of indol **1e**.

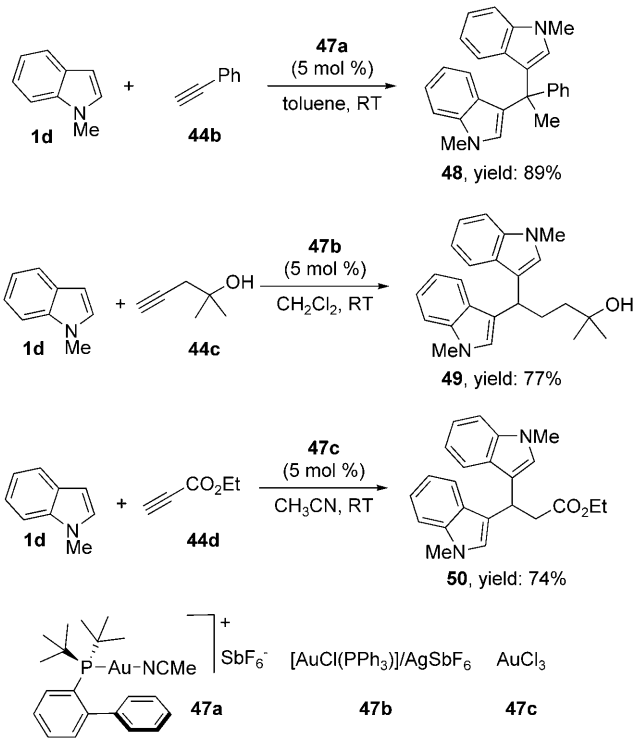
Nowadays, gold(I) and gold(III) species are capturing the attention of the chemical community because of their unique catalytic properties,[63] which have been elegantly rationalized in terms of relativistic effects.[64] Electrophilic activation of multiple C–C bonds toward the addition of C, O, and N nucleophiles is one on the main goals in organic chemistry.

The role of gold catalysts in the condensation of arenes with alkynes was pioneered independently by the research groups of Reetz,[65a] Dyker,[65b] and He.[65c] Mechanistically, although direct auration of unfunctionalized aromatic compounds is long since known,[66] the activation of the triple bond by the "soft" Lewis acid character of the gold species is suggested to operate during the Ar–H addition process.

Intermolecular gold-catalyzed hydroarylation of triple bonds is a straightforward approach for the synthesis of bis(indolyl)alkanes. Several research groups exploited the activity of gold(I) and gold(III) complexes in promoting the double addition of indoles to terminal alkynes.[67] The regioselectivity of the process was demonstrated to be highly affected by the oxidation state and coordination sphere of the catalysts (Scheme 15).

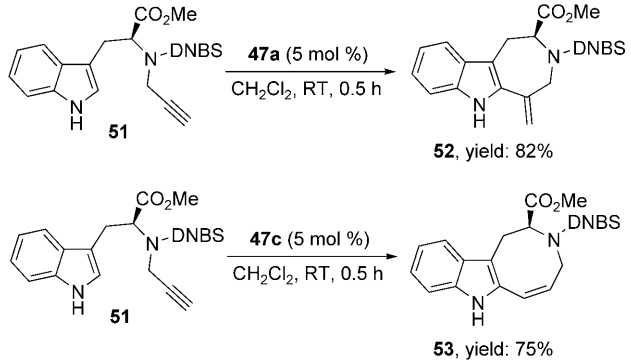
The use of C3-substituted indoles (for example, scatole) activates the C2-position toward nucleophilic addition, thereby allowing the construction of structurally more complex polycyclic bis(indolyl) compounds.[67b]

Six- seven-, and eight-membered rings bearing a fused indolyl nucleus have also been realized by the intramolecular



Scheme 15. Gold-catalyzed addition of **1d** to terminal alkynes.

gold-catalyzed reaction of indoles with alkynes. Echavarren and co-workers demonstrated that the 7-*exo*-dig versus 8-*endo*-dig cyclization could be fine-tuned simply by proper choice of the gold catalyst. This allowed the selective synthesis of azepinoindole **52** or indoloazocine **53** from the same precursor **51** (Scheme 16).[68]

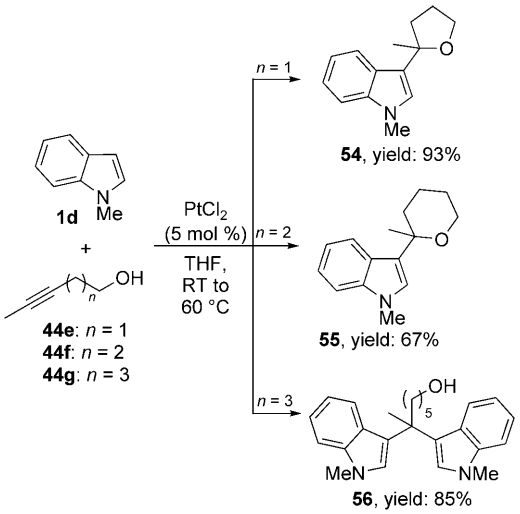


Scheme 16. Synthesis of azepinoindole **52** and indoloazocine **53** by intramolecular gold-catalyzed addition of indoles to alkynes.

Lavendamycin[69a] and analogous compounds are functionalized carboline derivatives known for their potent antitumor and antibiotic activities. England and Padwa recently proposed a facile route to this class of compounds which involved a high-yielding gold(I)-promoted cycloisomerization of propargylindole derivatives.[69b]

The intramolecular addition of indoles to internal and terminal alkynyl alcohols **44e–g**, catalyzed by $PtCl_2$ (5 mol %), was also reported recently.[70] Here, depending

on the chain length of the alkyne, five-membered tetrahydrofuran, six-membered tetrahydro-2*H*-pyran, or bis(indolyl)alkane derivatives were obtained in excellent yields (Scheme 17). The reaction is believed to evolve through regioselective addition of the indole to cyclic enol ether intermediates.



Scheme 17. Platinum(II)-catalyzed reaction of indole **1d** with alkynyl alcohols **44e–g**.

3.2.3. *Hydroarylation of Alkenes and Allenes*

The nucleophilic addition of indoles to unfuntionalized alkenes and allenes has only recently received significant attention. Analogous to the reactions of alkynes, the activation of the multiple bonds is generally achieved by using a π-acidic metal center. Cationic platinum complexes could be used successfully for this; in fact, the relatively high kinetic and thermodynamic stability of σ-alkyl–platinum(II) intermediates[71] enables a protonation as the final step of the catalytic cycle (Figure 13). The method is generally addressed as an "outer-sphere" nucleophilic attack of the indole on the metal-activated alkenes. In contrast, electrophilic activation of C–C double bonds by Pd^{II} centers generates poorly stable σ-alkyl–palladium(II) species that generally evolve to the unsaturated product through β-hydride elimination (vinylation; see Section 6.3.3).[72]

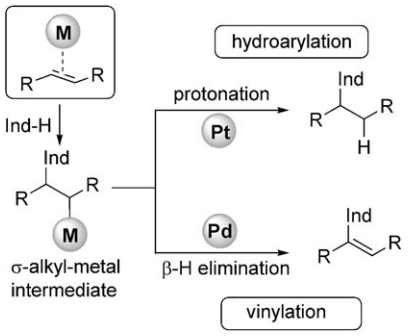
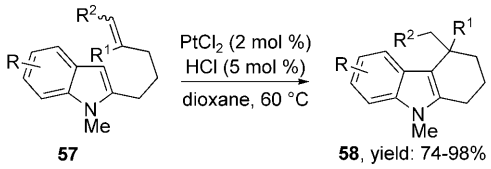


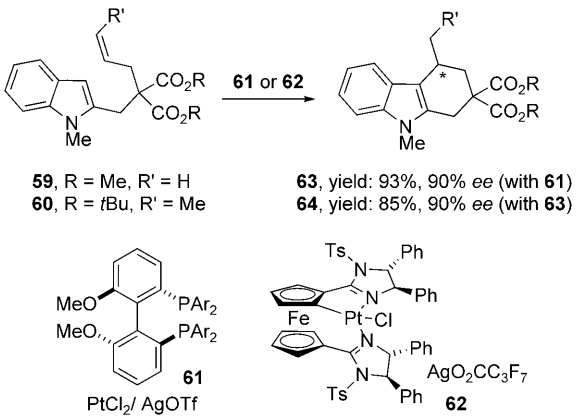
Figure 13. Platinum- and palladium-catalyzed reactions of indoles with unactivated alkenes.

Platinum catalysis was extensively investigated by Widenhoefer and co-workers. They presented several elegant inter-[73a] as well as intramolecular[73b] hydroarylations of olefins with indoles. Of particular synthetic relevance is the $PtCl_2$-catalyzed (2 mol%) ring closure that led to a variety of 4-substituted tetrahydrocarbazoles (**58**) in 74–98% yield (Scheme 18). Insight into the mechanism was obtained by subjecting deuterated compounds to the hydroarylation reaction, which showed an exclusive 6-*endo*-trig regioselection combined with an "outer-sphere" pathway.



Scheme 18. $PtCl_2$-promoted synthesis of substituted tetrahydrocarbazoles **58** by intramolecular hydroarylation of alkenes.

The possibility to control the stereochemistry of the process through the complexation of the platinum center with chiral ligands was demonstrated by the same research group. The scope of the reaction was expanded further by employing (*S*)-3,5-*t*Bu_2-4-MeO-biphep (**61**) as the ligand of choice, which led to *ee* values of up to 90% *ee* with terminal olefins.[74a] A key factor for the successful stereoinduction was the increased steric bulk of ligand **61** around the phosphorus atoms (Scheme 19). The use of challenging internal alkenes in



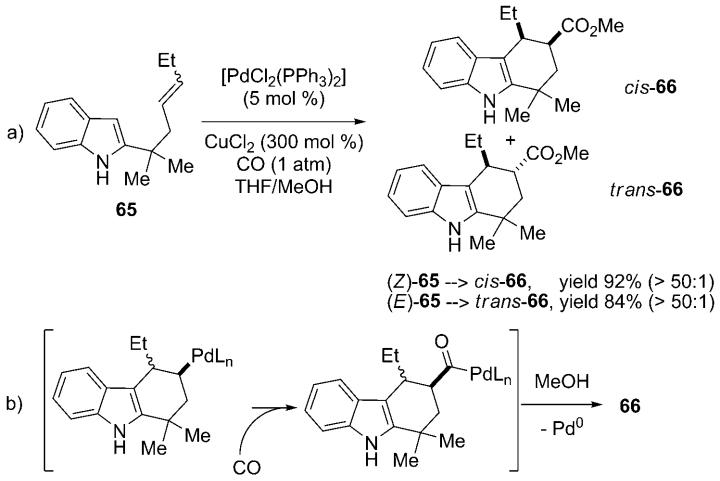
Scheme 19. Enantioselective intramolecular addition of indoles to terminal and internal alkenes in the presence of a platinum catalyst. Ar: 3,5-*t*Bu_2-4-$OMeC_6H_2$.

the enantioselective intramolecular alkylation of indoles was very recently addressed by using a strained planar platinum–ferrocenylbis(imidazoline) complex **62** (5 mol%) as the chiral catalyst.[74b] Huang and Peters predicted that forcing the platinum(II) center into a highly distorted square-planar geometry (ground-state destabilization) would increase the catalytic activity. Excellent yields and selectivities were

observed for a wide range of internal alkenes, regardless of the indole and olefin substitution (Scheme 19).

Although metal-catalyzed processes[75] dominate in the hydroarylation reactions of indoles, interesting examples of two- or three-component Brønsted acid (*p*TsOH, TfOH) catalyzed alkylations of indoles have also been reported.[76]

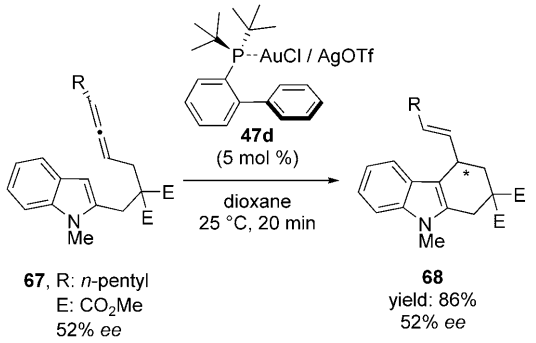
The reactivity of indoles toward unactivated alkenes under palladium catalysis and oxidative conditions[77a] prompted Liu and Widenhoefer to investigate the mechanism of the related inter- and intramolecular carboalkoxylation of alkenylindoles. After a preliminary report in 2004,[77b] they screened a number of reaction parameters of this process.[77c] The intramolecular ring closure showed a direct correlation between the configuration of the final product **66** and that of the C–C double bond in the starting material **65** (Scheme 20a). This finding is indicative of the stereospecific insertion (with retention of the configuration) of a CO molecule into the carbon–palladium bond, thereby leading to an acylpalladium species that can finally be trapped by MeOH to give **66** (Scheme 20b).



Scheme 20. a) Stereospecific cyclization/carboxyalkylation of **65**. b) Insertion of CO into the Pd–C bond.

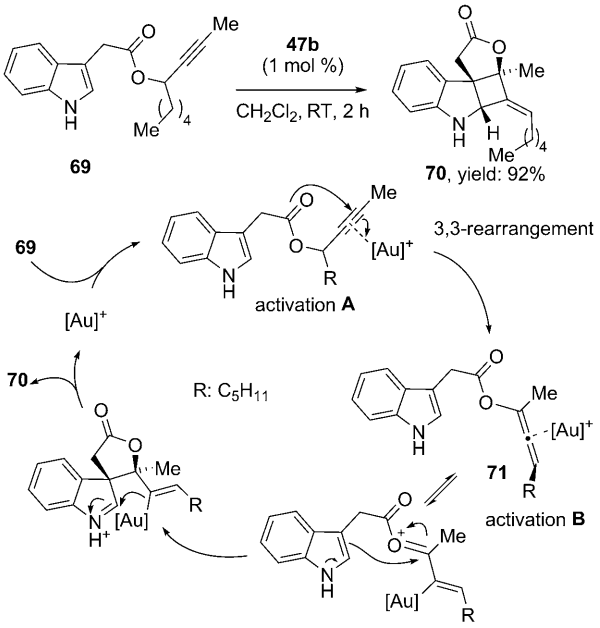
On the basis of these examples, allenes should also be considered as suitable candidates for the functionalization of indoles. In fact allenes have shown higher reactivity than alkenes in metal-based nucleophilic additions.[78] As a proof of concept, an efficient intramolecular hydroarylation of 2-allenylindoles (**67**) catalyzed by the Echavarren gold(I) complex **47d** was reported.[79] Exclusive 6-*exo* selectivity was observed in the ring closure, with complete transfer of axial chirality to the newly formed stereocenter. As an example, when enantiomerically enriched 2-allenylindole **67** (52% *ee*) was allowed to cyclize in the presence of **47d** (5 mol%), the corresponding tetrahydrocarbazole **68** was isolated with the original enantiomeric excess of **67** (Scheme 21).

Alternatively, stereocontrol can be introduced by external sources such as the gold catalyst. Chiral gold complexes of general structure [(P-P)Au_2Cl_2] in the presence of AgOTf led to efficient electrophilic activation.[80]



Scheme 21. Transfer of the axial chirality of the allene unit to a stereocenter by the gold(I)-catalyzed intramolecular hydroarylation of allenyl indoles.

The greatest shortcomings in the use of organoallenes are their elaborate syntheses and relative poor stability. Thus, a convenient alternative would be to generate these highly reactive frameworks in situ. The study presented by Zhang[81] nicely addresses such an issue; in this case the ability of **47b** (1 mol%) to promote a tandem electrophilic activation of functionalized indole-3-acetate **69** was exploited for the synthesis of 2,3-indoline-fused cyclobutane **70**. Here, the initial nucleophilic attack of the ester group on the activated triple bond (**A**) led to an unstable cationic species (not shown) that underwent a 3,3-rearrangement to give the allenyl indole **71**. The gold complex then promoted the second electrophilic activation (**B**) of the allenyl unit for nucleophilic addition of the indole at the C3-position. Finally, an intramolecular trapping of the iminium adduct with the alkyenylgold unit led to the formation of the tetracyclic compound **70** (Scheme 22).



Scheme 22. Tandem electrophilic activation in the gold-catalyzed synthesis of 2,3-indolinocyclobutane **70**.

4. Reaction with C=X Bonds

4.1. Aldehydes and Ketones

Indole reacts smoothly with aldehydes and ketones in the presence of Lewis or Brønsted acids.[19] The initially formed indole-3-carbynol **73** is generally not sufficiently stable and, after elimination of one molecule of water, it generates a highly reactive 3-alkylidene-3*H*-indolinium cation **74** that can condense with a second molecule of indole (for example, through a Michael-type addition). The resulting bis(indolyl)alkanes **75** constitute a class of structures commonly isolated from numerous terrestrial and marine sources.[82] Important pharmacological activities have even been recognized in simple bis(indolyl)alkanes[83] such as **75aa** (anticarcinogenic properties) and **75ab** (Vibrindole A; antibacterial properties; Figure 14).[83b]

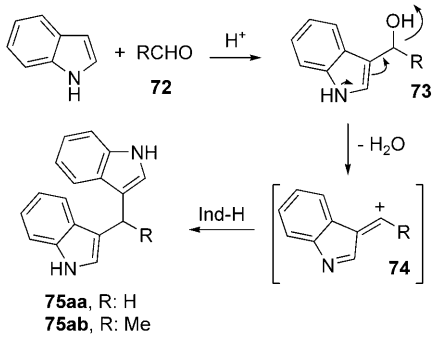
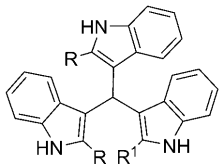


Figure 14. Proposed mechanism for the acid-promoted condensation of indoles with carbonyl compounds to give the natural occurring bis(indolyl)alkanes **75aa** and **75ab**.

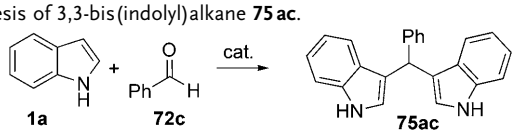
As a consequence of the growing demand for environmentally friendly processes, many new methods for the preparation of bis(indolyl)alkanes have been developed. At present, a large number of acid promoters is known, including organic and metal catalysts that operate both in conventional and alternative reaction media (H_2O, ionic liquids). Over the last few years the search for environmentally friendly and highly efficient catalytic systems has continued; some representative examples for the model reaction between **1a** and benzaldehyde (**72c**) are reported in Table 4.

Higher catalyst loadings, higher temperatures, and longer reaction times are generally required for simple ketones compared to aldehydes. Among the examples listed in Table 4, only the methods based on benzoic hydrazide (BH)[84j] have addressed an exhaustive screening of ketones. Triindolylmethanes (**76**, TRIMs) have received considerable attention because of their pharmacological and biological activities[85a] as well as their application as dyes.[85b] The synthesis of symmetric TRIMs (with three molecules of the same indole) has been known for a long time and involves the condensation of an excess of indole with orthoformate under strongly acidic conditions (HCl in EtOH).[86a] Many different approaches have been reported for the construction of symmetric TRIMs.[86b]



76, R^1 = H, R

Table 4: Catalytic condensation of indole (**1a**) with benzaldehyde **72c**: Synthesis of 3,3-bis(indolyl)alkane **75ac**.



Cat. (%)	Solvent	*t* [h] (*T* [°C])	Yield **75ac** [%]	Ref.
$CuBr_2$ (5)	CH_3CN	0.4 (RT)	95	[84a]
Amberlyst	CH_3CN	12 (RT)	99	[84b]
$NaBAr^F_4$ (0.2)	H_2O	5 (30)	99	[84c]
SA (50)	MeOH	3 (RT)	90	[84d]
$La(PFO)_3$ (5)	EtOH	1.5 (RT)	96	[84e]
[hmim][HSO_4] (5)	EtOH	1 (RT)	97	[84f]
ILIS-SO_2Cl (10)	MeCN	5.5 (RT)	97	[84g]
carbohydrate derivatives[a] (10)	H_2O	12 (RT)	84	[84h]
[bmim][$MeSO_4$] (5)	—[b]	0.4 (RT)	92	[84i]
BH[c] (1)	MeOH	32 (RT)	84	[84j]
NH_4Cl (50)	—[b]	2 (90)	96	[84k]

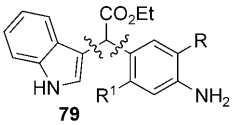
[a] Carbohydrate-based tolylsulfonylhydrazine. [b] Solvent-free conditions. [c] Benzoic hydrazine derivative.

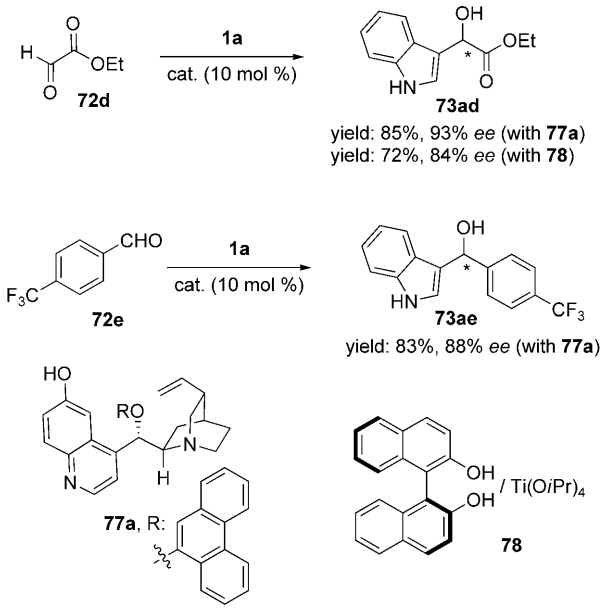
More recently, attention turned to the preparation of asymmetric TRIMs that can be conveniently obtained through the condensation of thr indolyl nucleus with indolecarbaldehydes (mainly indole-3-carbaldehyde). Lewis acids and I_2 proved to be good promoting agents for this transformation, but were restricted to electron-neutral and electron-rich indole compounds.[87]

As expected, the enantioselective condensation of indoles to aldehydes with effective isolation of the indolylmethanol derivative **73** has rarely been reported. An exception is the asymmetric 1,2-addition of ethyl glyoxalate **72d** to a variety of indoles in the presence of the bifunctional cinchona alkaloid **77a**.[88] Here, high *ee* values (82–93%) were recorded for a range of substrate combinations. The process was extended to simple aromatic aldehydes, but longer reaction times and higher temperatures were required (Scheme 23).

Shortly after, the reaction of variously substituted indoles with **72d** in the presence of catalytic amounts of binol/$Ti(OiPr)_4$ complex **78** (10 mol%) was reported.[89] After optimization of the reaction parameters, very high enantioselectivity were reached (up to 96% *ee*); however, the method appeared to be limited to the glyoxylate derivative **72d**. The formation of a hydrogen bond between the formyl group and an oxygen atom of the binol unit was proposed to explain the reactivity.

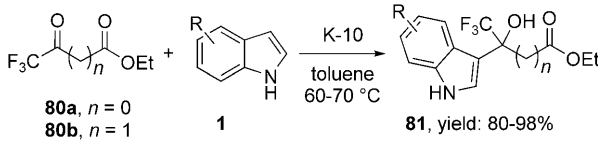
The condensation of indoles with ethyl glyoxylate **72d** was also used in a multicomponent transformation. Desimoni et al. demonstrated the role of Sc(OTf)$_3$ (5 mol%) in controlling the chemoselectivity of a Passerini reaction. α,α′-Bisaryl acetates **79** were obtained in good yields under the optimized conditions.[90]





Scheme 23. Organo- and metal-catalyzed enantioselective addition of **1a** to aldehydes.

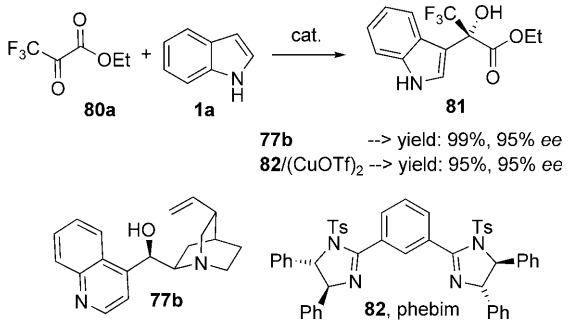
In analogy to aldehydes, reports of the 1:1 addition of indoles to simple methyl ketones are very rare in the literature, since the addition product **73** could not be isolated under the harsh reaction conditions. In contrast, activated β-ketoesters (pyruvates) have shown to be suitable for the preparation of indolyl(hydroxy)alkane carboxylic acid derivatives, even in enantiomerically enriched form.[91] A very interesting study along these lines was reported by Abid and Török, who used K10-montmorillonite as a solid acid in the addition of indoles to ethyl 3,3,3-trifluoromethylpyruvate (**80a**) as well as the considerably less-reactive β-keto ester analogues **80b**.[92] The corresponding trifluoromethylated indolylalkanecarboxylic acid derivatives **81** were isolated in excellent yields, regardless of the substitution pattern of the indole nucleus (Scheme 24).



Scheme 24. Heterogeneously catalyzed hydroalkylation of indoles with trifluomethylpyruvate derivatives.

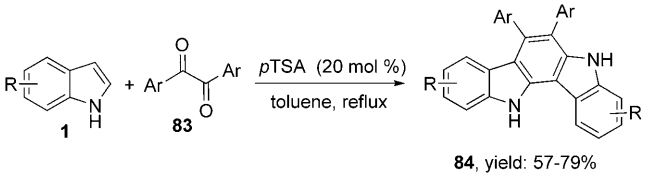
After the pioneering studies by Jørgensen and co-workers,[91] the search for mild and efficient enantioselective hydroalkylations of indoles with trifluoromethyl pyruvates attracted much attention because of their importance in medicinal chemistry[93] and their application as reagents for chiral resolution.

The research groups of Török and Toru reported on the possibility of performing the enantioselective hydroalkylation of indoles with **80a** under organo-[94a] and metal catalysis.[94b] In the first example natural occurring alkaloids (cinchonidine and cinchonine) were used, while in the second approach copper(II) complexes with chiral bis(imidazoline) ligands **82** (10 mol%) were used. Exceptionally high enantioselectivities were obtained in the two cases—up to 95% *ee* with cinchonidine catalysis and up to 96% *ee* with Cu^{II} catalysis—and, although conceptually different, both approaches are based on dual activation modes (Scheme 25). In fact, both experimental and spectroscopic evidence required a simultaneous activation of the indole and pyruvate by the chiral catalysts. It is noteworthy that 0.2 mol% of the Cu^{II}–**82** system resulted in a turnover number of approximately 200.



Scheme 25. Metal catalysis and metal-free catalysis in the asymmetric alkylation of indoles with **80a**.

Finally, we would like to highlight a recent example: the Brønsted acid catalyzed synthesis of indolo[3,2-*a*]carbazoles **84**. This class of polycyclic compounds, besides having most of the biological properties (antitumor activity, antihistaminic, etc.) of indolyl analogues, also shows intense luminescent properties for applications in optoelectronics.[95] The protocol is very simple and involves a sequence of condensation events between indoles and benzil derivatives (**83**) in the presence of *p*TSA (Scheme 26).[96]



Scheme 26. Synthesis of indolo[3,2-*a*]carbazoles **84** by catalytic condensation of indoles with benzils.

4.2. Imines

3-Indolylmethanamines **86** are key motifs[97] of wide interest that can be conveniently synthesized by condensing an indole with the desired aldo- of ketoimine.[98] In contrast to 3-indolylglycinols **73**, indolylmethanamines are sufficiently stable to be isolated. In general, an electrophilic activation of the imine precursor by an acid catalyst is required to shorten the reaction time and to guarantee satisfying levels of selectivities in the reactions (Figure 15).

Moreover, N-activated imines (**85**) with electron-withdrawing substituents (for example, FG = SO_2R, CO_2R,

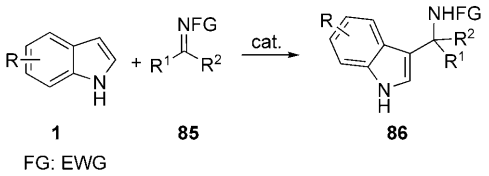
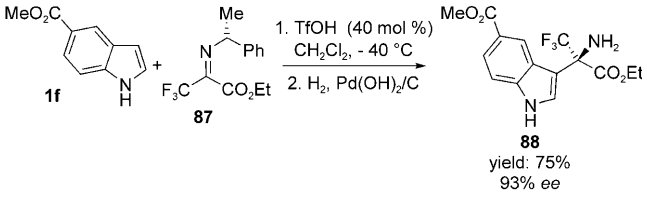


Figure 15. Synthesis of 3-indolylalkylamine derivatives.

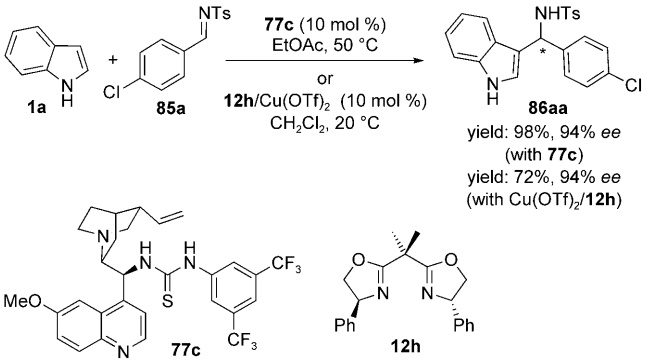
$PO(OR)_2$) are generally employed, thereby enabling mild reaction conditions to be used.

α-(3-Indolyl)glycines (**86**; R^1: H, R^2: CO_2R) are an important family of synthetic intermediates for the preparation of nonproteinogenic amino acids.[97c,d,f] Indolylglycines can be conveniently obtained as a racemic mixture by spontaneous[98,99a,b] or catalyzed[99c] Friedel–Crafts alkylation of indoles with preformed or in situ prepared glyoxylate imines. Good levels of diastereoselectivity can be achieved when preformed alkylating agents are used by introducing a chiral auxiliary on the imine.[98a] Very recently, the use of superacidic trifluoromethanesulfonic acid (TfOH, triflic acid)[100] as the promoter for the regioselective C3-addition of indoles to enantiopure 3,3,3-trifluoropyruvate-α-methylbenzylimine (**87**) was reported.[101] The method was extremely stereoselective (up to 99% *de*) and both electron-withdrawing and electron-donating groups were tolerated on the indolyl core. The chiral auxiliary could be selectively removed under mild reaction conditions (H_2, $Pd(OH)_2$; Scheme 27).



Scheme 27. Diastereoselective aminoalkylation of indole **1f** promoted by TfOH.

Interestingly, although the asymmetric synthesis of indolylglycines represents one of the seminal examples of catalytic enantioselective Friedel–Crafts alkylation,[12a] it took several years before the problems of the scope, stereoselectivity, and catalyst loading were successfully addressed. In 2005, Leighton and co-workers reported on the use of chiral silacycles in the enantioselective alkylation of electron-rich arenes with benzoylhydrazones.[102] The research groups of Zhou[103a] and Deng[103b] independently highlighted in 2006 the efficiency of copper(II)–box complexes and cinchona alkaloids with a thiourea group in the 9-position for the enantioselective alkylation of indoles with aldoimines. Both methods worked exceptionally well with aromatic aldoimines, while only the organocatalytic approach was successful with aliphatic substrates. *N*-sulfonyl protecting groups were essential for the copper-catalyzed process, and a dramatic drop in enantioselection was observed when they were replaced with phenyl groups. These results led the authors to suggest a 1,3-binding mode between the alkylating agent (N,O) and the copper center. The bifunctional activity of the cinchona alkaloid was also demonstrated by the inertness of *N*-methylindole under the optimized reaction conditions (Scheme 28).

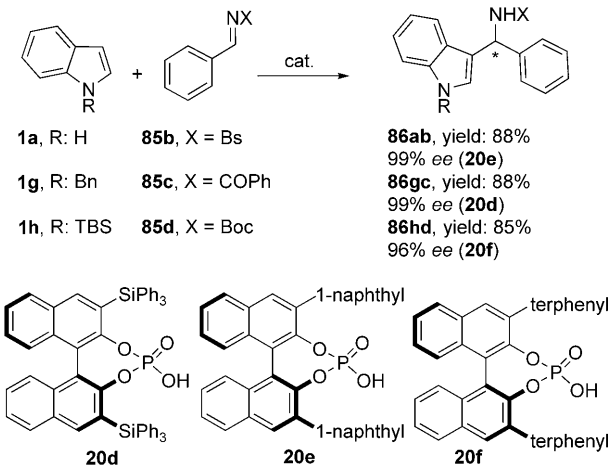


Scheme 28. Enantioselective synthesis of 3-indolyl(aryl) methanamines by metal-free and copper catalysis.

Shortly after, the research groups of You,[104a,b] Antilla,[104c] and Terada[104d] reported almost simultaneously three phosphoric acid catalyzed variants of the enantioselective aminoalkylation of indoles. These approaches differed in the substituents at the 3,3′-positions of the binol skeleton as well as the structure of **85**, but gave products with excellent enantiomeric excess. Although mechanistic details have not been reported, bifunctional catalysis, which generally operates with chiral phosphoric acids, can be ruled out since the research groups of Antilla and Terada studied *N*-protected indoles exclusively (Scheme 29).[105]

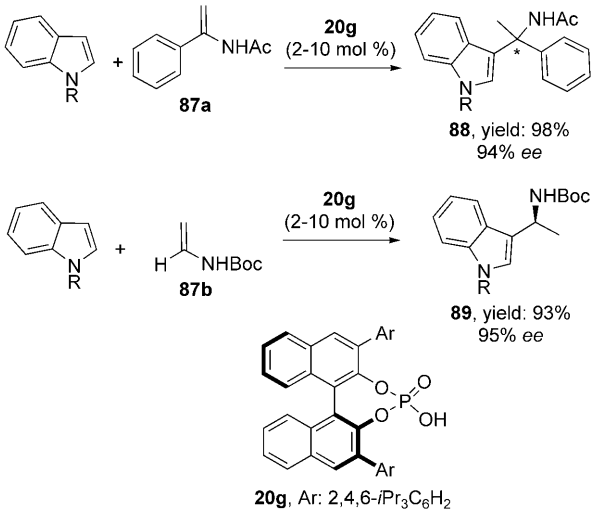
An analogous strategy was also reported by Hiemstra and co-workers for the synthesis of enantiopure indolylglycines by means of *N*-sulfenyl-protected aldoimines.[104e]

Despite the excellent yields and enantiomeric excesses obtained with the previous methods, two main challenges still remained to be solved in the asymmetric amino alkylation of indoles: 1) the use of aliphatic aldoimines, and 2) the use of ketoimines. The lack of examples addressing aliphatic alky-



Scheme 29. Use of chiral monophosphoric acids **20d–f** in the addition of indoles to aldoimines.

lating agents can mainly be ascribed to their poor stability and difficult handling. The use of keto derivatives is generally limited by their poor reactivity and difficult stereodiscrimination. Both aspects were brilliantly overcome by the research groups of Zhou[106a] and Terada,[106b] who used Brønsted acid catalysts with unusual alkylating substrates such as α-aryl enamide **87a** and enecarbamate **87b** (Scheme 30).

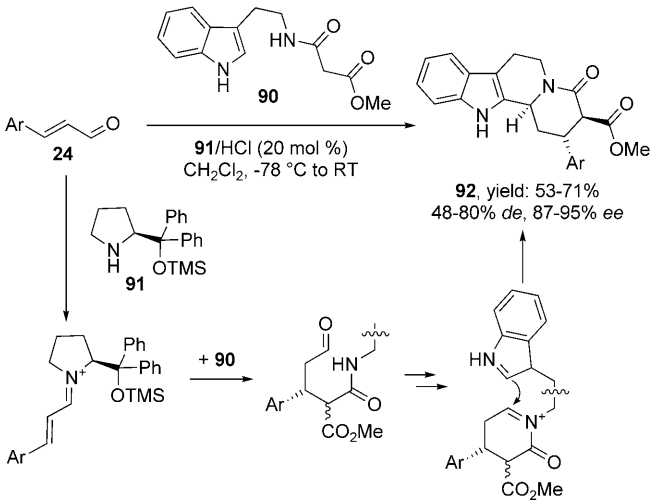


Scheme 30. Representative examples of the alkylation of indoles with electron-rich alkenes in the presence of a chiral monophosphoric acid as the catalyst.

Investigation into the reaction mechanisms revealed that the protonation of nucleophilic enamides/enecarbamates **87** favored the formation of highly electrophilic iminium salts, which smoothly underwent a condensation reaction with indole.

Chiral binol-phosphoric acids were also efficiently adopted by Ma and co-workers in the enantioselective (up to 98% *ee*) alkylation of indoles. In this three-component indole alkylation, indole, aniline, and (di)trifluoroacetaldehyde hemiacetal reacted to form (di)trifluoromethyl-3-indolylmethanamine.[107]

To conclude this section we would like to point out a recent investigation based on an asymmetric organocatalytic cascade sequence to generate polycyclic precursors of quinolizidines.[108] The diphenylprolinol derivative **91** (20 mol%) took part in the formation of the first stereocenter generated by the Michael addition of an enol amidoester to an enal. Two consecutive ring-closing reactions (with the latter being a formal intramolecular alkylation at the C2-position of the indole system) finally led to tetracyclic compounds **92** with three stereocenters (Scheme 31).



Scheme 31. Synthesis of quinolizidine derivatives by organocatalyzed cascade reactions.

4.3. Pictet–Spengler Reaction

In 1911 Pictet and Spengler reported the first example of a Brønsted acid promoted intramolecular condensation of electron-rich arenes and imines that would revolutionize the way of generating polycyclic nitrogen-containing aromatic compounds.[109] Following the general scheme reported in Figure 16, a virtually unlimited number of tetrahydroisoquinoline (THIQ) and tetrahydro-β-carbonline (THBC) scaffolds can be conveniently synthesized in high yields.[110] Over the past century, Pictet–Spengler reactions continued to have a large impact on the preparation of natural and unnatural pharmacologically active compounds. Moreover, traditional approaches have been complemented by new concepts such as catalysis, stereoselectivity, alternative reaction media, and solid-phase synthesis.

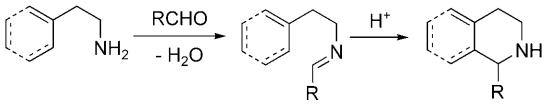
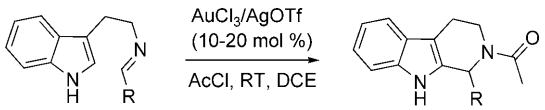


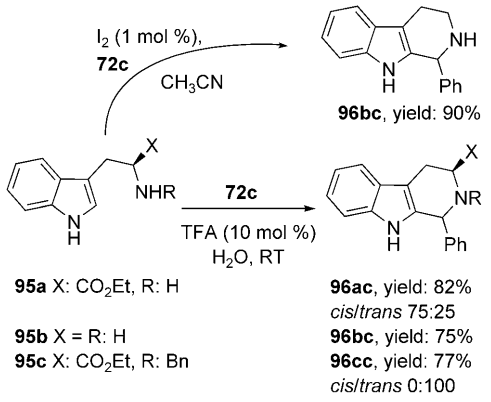
Figure 16. The Pictet–Spengler condensation.

The electron-rich indole even reacted under mild reaction conditions in the presence of catalytic amounts of acid additives. In this context, Youn reported on the efficiency of the $AuCl_3$/AgOTf catalytic system (10 mol% relative to gold) in promoting the acyl-Pictet–Spengler condensation of preformed imines of tryptamine (**93**) with aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes.[111] The addition of an equimolar amount of acetyl chloride speeded up the reaction through the formation of highly activated *N*-acyliminium ion intermediates (Scheme 32).



Scheme 32. Gold-catalyzed acyl-Pictet–Spengler reaction.

The replacement of conventional organic solvents with water or with solvent-free protocols is also an important topic in regard to the Pictet–Spengler reaction. In particular, Kundu and co-workers reported a Pictet–Spengler reaction in pure water in the presence of a catalytic amount of TFA (10 mol%).[112a] In this example, the indole was alkylated with imines formed in situ from L-Trp-OMe **95a**, tryptamine **95b**, or *N*-Bn-L-Trp-OMe **95c** and a series of aromatic aldehydes. The resulting THBCs **96** were obtained in moderate to good yields, with the level of diastereoselectivity directly related to the substitution on nitrogen atom of the Trp (Scheme 33).



Scheme 33. Recent examples of catalytic Pictet–Spengler reactions.

Analogously, molecular iodine was reported to be a good additive for the efficient condensation of tryptamine and aromatic aldehydes at a loading as low as 0.5 mol%.[112b] The reactions are normally carried out in CH_3CN, but the ring closure can also be carried out under solvent-free conditions.

The chemoselective synthesis of tetrahydro-β-carbolines by a tandem hydroformylation Pictet–Spengler reaction was also investigated. Such an approach was firstly reported by Taddei and co-workers as part of a solid-phase synthesis,[113a] and was recently demonstrated in solution by Bondzic and Eilbracht.[113b] The protocol allowed the introduction of unusual substituents at the C1-position of the THBC skeleton without the need for costly and sensitive aldehydes. In fact, the combined use of disubstituted terminal and internal olefins with $[Rh(acac)CO_2]$ (1 mol%) under CO/H_2 pressure (40–80 bar) furnished the desired THBCs in moderate to good yields. Also in this case, a Brønsted acid catalysis was applied to address the intrinsic inertness of tryptamine.

Catalytic enantioselective Pictet–Spengler reactions were pioneered by Jacobsen and co-workers in 2004. They used chiral pyrrole thiourea **97a** to activate *N*-acyliminium anion intermediates (Figure 17).[114a] With the aim of broadening the scope of this approach, the same research group later discovered the suitability of the hydrogen-bond donor thiourea **97b** in promoting the Pictet–Spengler cyclization of readily available β-indolyl ethyl hydroxylactams **98** in a highly enantioselective manner.[114b]

Mechanistically, these findings can be explained in terms of counterion-directed enantioselective catalysis (CDEC), with the postulated formation of the tight complex **100** from between *N*-acyliminium chloride and thiourea. Such a conclusion is supported by the following observations: 1) spectroscopic investigation revealed the rapid and irreversible formation of chlorolactam **99** as the key step of the catalytic cycle (an S_N1 is favored over an S_N2 mechanism), 2) no effective enantiodiscriminating interactions could be identified between **97b** and the plausible reaction intermediates **101a** and **101b** (Scheme 34).

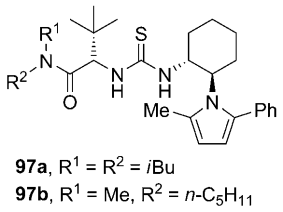
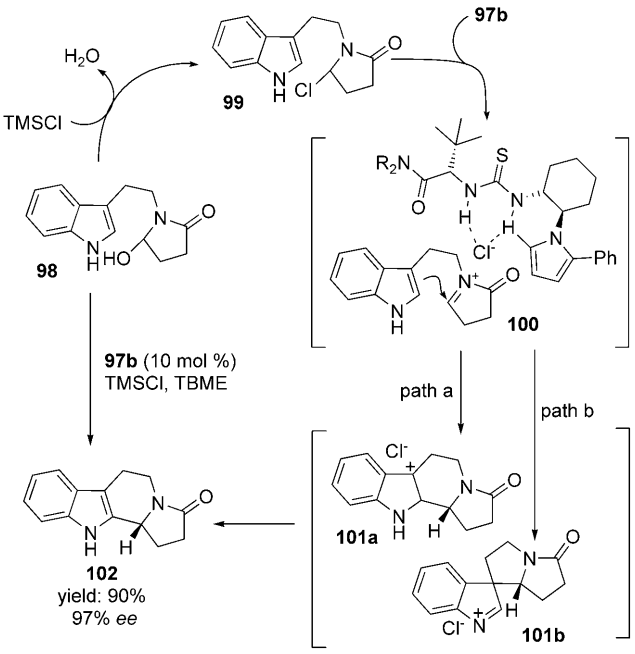


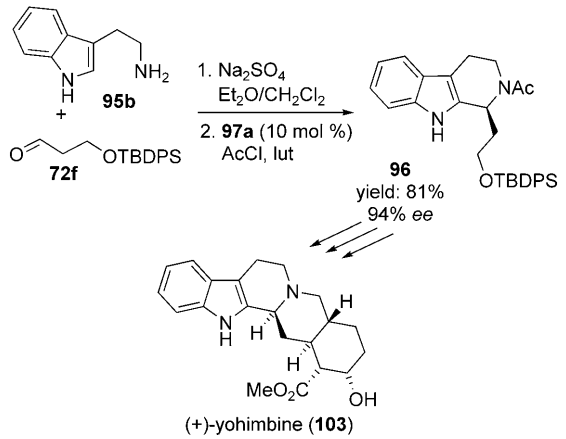
Figure 17. Jacobsen's chiral thioureas for enantioselective hydrogen-bond catalysis.



Scheme 34. Enantioselective Pictet–Spengler reaction by hydrogen-bond-donor catalysis through anion binding.

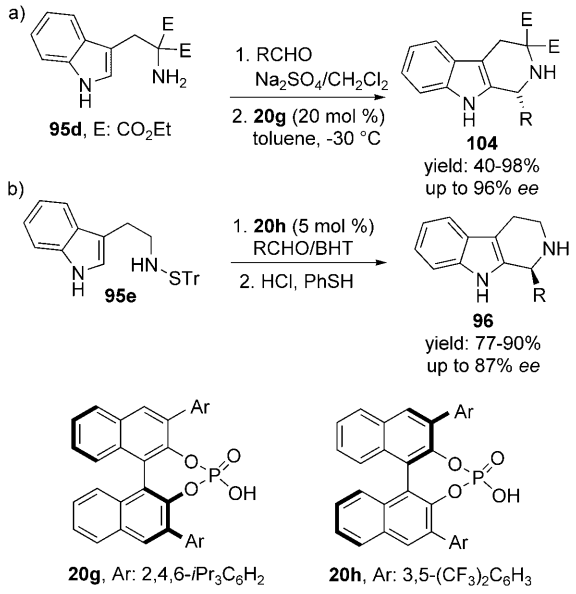
The method found applications in the total syntheses of indolyl alkaloids such as (+)-harmicine and (+)-yohimbine (**103**). In the former case, the natural compound was obtained in only four steps starting from tryptamine **95b** (62% overall yield), with a Pictet–Spengler cyclization of hydrolactams as the stereodiscriminating step. Analogously, hydrogen-bond donor catalysis was employed by Jacobsen and co-workers in the initial stage of the 11-step procedure that led to the monoterpenoid indole alkaloid (+)-yohimbine (**103**) in 14% overall yield (Scheme 35).[114c]

The efficiency of Brønsted acid catalysis in Pictet–Spengler condensation also inspired the research groups of List and later Hiemstra to utilize chiral binaphthol-derived phosphoric acids **20** for the development of enantioselective



Scheme 35. Organocatalyzed enantioselective Pictet–Spengler reaction in the total synthesis of (+)-yohimbine.

variants. List and co-workers combined chiral phosphoric acid **20g** (20 mol%) and readily available geminal substituted tryptamine derivatives **95d** to prepare a library of functionalized THBCs (up to 96% *ee*) with aliphatic and aromatic aldehydes (Scheme 36a).[115] Shortly after, Hiemstra and co-



Scheme 36. Catalytic enantioselective Pictet–Spengler reactions promoted by chiral binol-phosphoric acids.

workers described an alternative catalytic enantioselective Pictet–Spengler reaction in which, the restriction to using geminal ester moieties (Thorpe–Ingold effect) encountered by List and co-workers was overcome by adopting a properly designed *N*-sulfenyltryptamine **95e** in combination with chiral binol-phosphoric acid **20h** (5 mol%). Although accompanied by a slightly lower enantioselectivity (up to 87% *ee*), the tritylsulfenyl group could be efficiently removed directly after the cyclization (Scheme 36b).[116a] The same research group later extended the protocol to challenging *N*-benzyltryptamines by using enantioselective binol-PA catalysis.[116b]

5. Reaction with C(sp^3)-Based Alkylating Agents

5.1. Introduction

It is noteworthy that although alkylating agents with C(sp^3)–X bonds (X = leaving group) were used early on in Friedel–Crafts reactions, organo halides are nowadays only employed in very few catalytic processes.

The recent guidelines relating to sustainability (catalytic protocols, atom economy) and selectivity (chemo-, regio-, and stereocontrol) strongly limited the development of classic alkylating agents, such as alkyl halides, in modern Friedel–Crafts chemistry. In the case of indoles, C3 versus N1 regiochemistry and mono- versus polyalkylation represent severe obstacles in alkylation reactions with reactive organo halides. In this context, the use of preformed indolylmagnesium compounds has frequently been adopted as an alternative to direct alkylations of unfunctionalized indoles.[117a] Examples of regioselective alkylation of electronically neutral indoles with prenyl electrophiles and 1-bromo-3-phenylpropane were reported; however, an excess of $Zn(OTf)_2$[117b] or K_2CO_3/IL[117c] were necessary. Interestingly, uncatalyzed electrophilic allylation and benzylation of indoles with the corresponding organo halides was recently reported by Westermaier and Mayr through the assistance of neutral aqueous or alcoholic solutions.[117d] Moreover, the stereoselective C-glycosidation of substituted indoles with glycosyl bromides was reported to be efficiently catalyzed by $InCl_3$ (10 mol%).[117e]

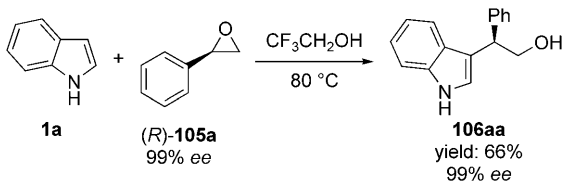
The aforementioned aspects, in combination with the formation of large amounts of metal salts as by-products, prompted chemists to find alternatives to organo halides in Friedel–Crafts alkylations. Epoxides/aziridines, π-activated alcohols, and allylic acetates/carbonates can be considered as electrophilic C(sp^3) reagents for catalytic Friedel–Crafts alkylations.

5.2. Epoxides and Aziridines

In general, Friedel–Crafts alkylation with oxygen-containing compounds such as alcohols and ethers require higher catalyst loadings than processes with alkyl halides and alkenes.[19] This trend can be ascribed to the higher coordinating capability of the oxygen-containing compounds, which would strongly interact with the promoting agents and thereby hinder the catalytic process. Epoxides have for a long time also been investigated in Friedel–Crafts alkylations, and have led to stimulating mechanistic discussions.[118]

After the preliminary studies in the 1960s and 1970s on the use of stoichiometric amounts of Lewis acids such as $AlCl_3$, $SnCl_4$, and BF_3,[119] the discovery over the last decade of unusual Lewis acids such as lanthanide triflates[120a] and indium(III) salts[120b–d] opened up access to the catalytic ring-opening of epoxides with indoles. Moreover, high pressures[120e] and silica gel[120f] were found to assist the regioselective C3-alkylation of indoles with both racemic and enantiomerically pure epoxides.

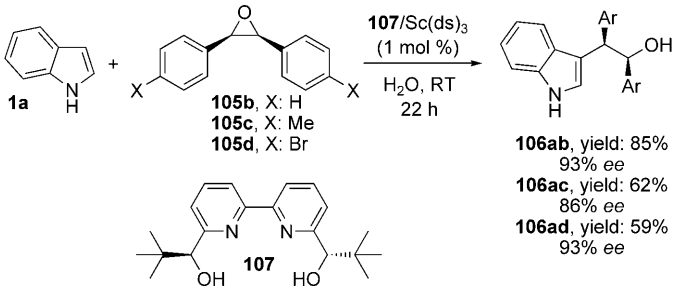
In regard to new reaction media, the efficiency of solvent-free conditions ($RuCl_3$ catalysis),[121a,b] the use of ionic liquids,[121c] or 2,2,2-trifluoroethanol[121d] in the Friedel–Crafts alkylation of indoles with oxiranes is worth mentioning. In the latter case, the ionizing power of the fluorinated solvent CF_3CH_2OH assisted the ring-opening of enantiomerically pure aromatic epoxides through a rigorous S_N2 pathway (Scheme 37).



Scheme 37. Stereoselective ring opening of (*R*)-styrene oxide (**105a**) with **1a** in CF_3CH_2OH.

Heterogeneous catalysis offers the advantages of recoverability, ease of handling, and facilitated work-up of the reaction. For example, nanocrystalline TiO_2 (10 mol%)[122a] and the supported catalyst HBF_4-SiO_2 (2 mol%)[122b] proved to be valuable heterogeneous promoters for indole alkylations with racemic aromatic oxiranes.

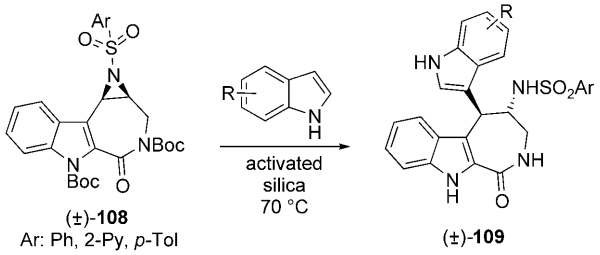
Asymmetric resolution of racemic epoxides and desymmetrization of *meso* epoxides with indoles still remain almost unexplored. After the seminal paper by Cozzi and Umani-Ronchi on chiral [Cr^{III}(salen)X] Lewis acids,[123] only one further example of desymmetrization of *meso*-oxiranes was reported. Scandium(III) dodecyl sulfate (5 mol%) combined with chiral bipyridine **107** (6 mol%) efficiently promoted the desymmetrization of stilbene oxides **105b–d** with indoles in water. The resulting alcohols **106** were obtained in good yields and high enantiomeric excess (Scheme 38).[124]



Scheme 38. Scandium-catalyzed enantioselective alkylation of **1a** through desymmetrization of *meso*-epoxides **105b–d**.

The Friedel–Crafts alkylation of indoles through ring opening of aziridines represents a formidable synthetic route to a plethora of pharmacologically active compounds,[125] and numerous target-oriented syntheses with such a transformation as the key step have been proposed.[120f,126] The usual lower reactivity of aziridines, compared to epoxides, and the poisoning effect exerted by the final products on the promoters lead to the requirement for large amounts of additives.[127] As a result, only a few examples of catalytic ($InCl_3$, $LiClO_4$) ring opening of aziridines with indoles are known.[128] Moreover, the regiochemistry in the nucleophilic attack on terminal arylaziridines can become an issue, and the process is generally limited to strongly activated *N*-tosylaziridines.

A recent application of such a methodology for the construction of highly functionalized polycycles with two indole units has been reported by Tse and co-workers.[129] In this approach, activated silica gel assisted the regioselective ring opening (benzylic position) of presynthesized *N*-arylsulfonamide aziridine **108**. In this way, a variety of indoles could be transformed to give product **109** as a single diastereomer and in good yield (Scheme 39).



Scheme 39. Synthesis of stereochemically defined bis(indolyl)alkanes through heterogeneously catalyzed ring opening of aziridines with indoles.

5.3. π-Activated Alcohols and Acetates

5.3.1. Benzylic Alcohols

The use of readily available and environmentally benign alcohols as alkylating agents (water is the only by-product) in catalytic Friedel–Crafts reactions has been known for a long time.[130] However, the poor leaving-group character of the hydroxy moiety precludes the use of mild reaction conditions, such as low temperatures and mild additives. Large excesses of additives are routinely required because of the deactivation of the catalyst by either irreversible coordination to the hydroxy group or hydrolysis by the water produced during the process. Over the last few years, these problems have been solved by using π-activated alcohols in combination with late-transition-metal catalysts.[131]

The term "π-activated alcohol" is commonly referred to organic molecules with π systems (for example, carbon–carbon multiple bonds, aromatic groups) adjacent to the hydroxy group (Figure 18). These structural units generally favor the direct activation of the C–OH bond through the

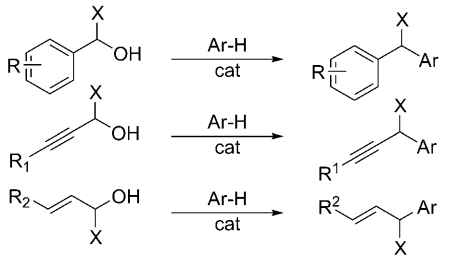
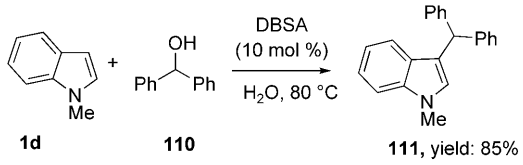


Figure 18. π-Activated alcohols in catalytic Friedel–Crafts reactions.

formation of stabilized positively charged intermediates. Their combination with π-activating elements in the same molecule (X = Ar) can be used to further increase the reactivity in Friedel–Crafts alkylations.

The benzylation of arenes is a classical and industrially useful Friedel–Crafts reaction for the synthesis of di- and triarylalkanes. An ever-increasing number of catalytic direct activations of benzyl alcohols and benzyl acetates are nowadays being recorded.[132]

In this sense, Rueping and co-workers reported on the use of mild and water-tolerant $Bi(OTf)_3$ (1 mol%) in the condensation of several arenes and heteroarenes (for example, scatole) with primary, secondary, and tertiary benzyl alcohols.[133] Interesting examples of the efficient coupling of indoles with benzylic alcohols in water have been reported independently by the research groups of Kobayashi[134a] and Cozzi.[134b,c] In the first case, the use of long-chain dodecylbenzenesulfonic acid (DBSA, 10 mol%) allowed the direct activation of benzhydrol **110** for the regioselective functionalization of the *N*-methylindole in high yield (Scheme 40).



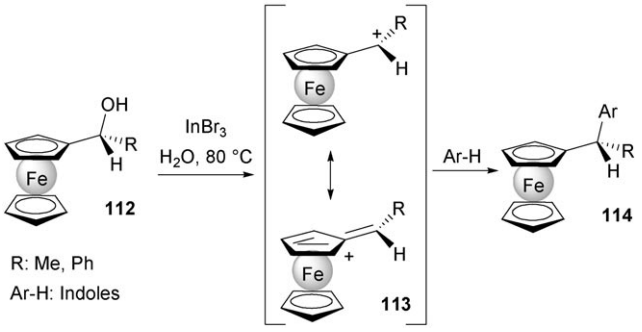
1d **110** **111**, yield: 85%

Scheme 40. Catalytic benzhydrylation in water.

Indole **1d** was also reacted efficiently with a plethora of primary and secondary benzylic alcohols in pure water at 80 °C by exploiting the simultaneous strong Brønsted acidity and surfactant properties of DBSA.

The investigations proposed by Cozzi and co-workers stressed the possibility to alkylate indoles with enantiomerically pure (1-hydroxyalkyl)ferrocenes **112** in the presence of indium(III) Lewis acids[134b] or without additives.[134c] Interestingly, products **114** were isolated in diastereomerically pure form through stereoselective alkylation of indoles with the cationic intermediates **113** originating from dehydratation of **112** (Scheme 41).

Stereoselective benzylation of indoles is still largely unexplored—except for ferrocenyl derivatives—because of the loss of stereochemical information through formation of planar carbocationic species (S_N1 versus S_N2 mechanism favored). The direct synthesis of challenging enantiopure polyaromatic systems has been accomplished by Chung and co-workers through the diastereoselective Friedel–Crafts alkylation of indoles with chiral α-branched benzylic alcohols in the presence of stoichiometric amounts of TFA or $BF_3{\cdot}OEt_2$.[135]



112 **113** **114**

R: Me, Ph
Ar-H: Indoles

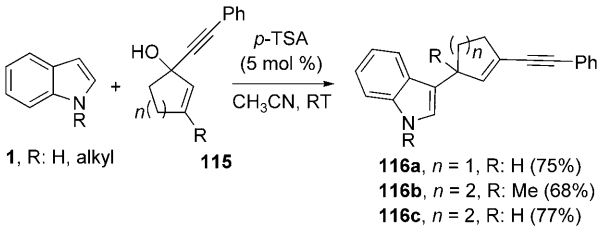
Scheme 41. Stereoselective benzylation of indoles with enantiopure ferrocenyl alcohols.

5.3.2. *Propargylic Alcohols*

The importance of persistent propargyl cations for Friedel–Crafts reactions has been known for a long time.[136] Propargyl cations (better represented as propargylium and allenylium resonance structures) can be conveniently obtained from the corresponding alcohols by treatment with Lewis or Brønsted acids. Highly unstable unsubstituted propargylic cations generally form polymeric compounds; as a consequence 1-aryl-2-propyn-1-ol derivatives (**122**, Scheme 44) are frequently employed in Friedel–Crafts substitutions.

Propargylation of indoles with internal aromatic alkynyl alcohols has nowadays become a benchmark for new catalytic systems with potential applications in Friedel–Crafts chemistry. In line with this, Yadav and co-workers have coupled 1,3-diphenylprop-2-yn-1-ol with a range of indoles under catalytic conditions.[137] All the protocols are characterized by short reaction times (20–30 min), mild reaction conditions, and compatibility for strong electron-withdrawing groups on the indoles.

A particular mention is made to the recent report by Sanz et al., who described the efficiency of *p*TSA (5 mol%) in the construction of benzylic quaternary stereocenters through the condensation of variously substituted indoles with tertiary alkynols.[138] The protocol was also applied to vinyl-substituted alkynols **115**, which reacted by a S_N2' mechanism to give product **116** in high yields (Scheme 42).

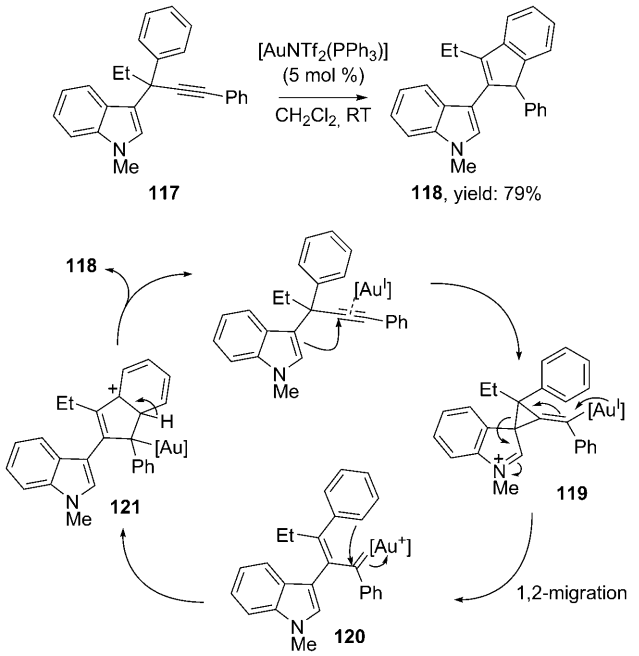


1, R: H, alkyl **115**

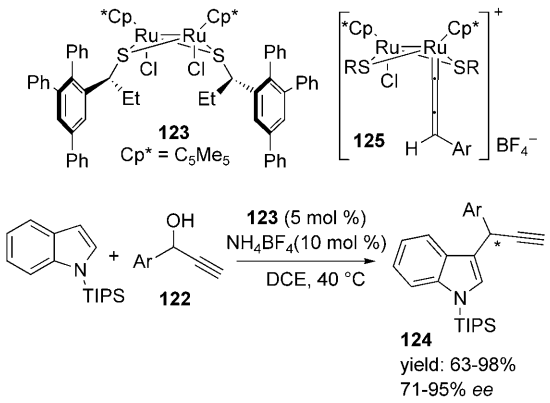
116a, *n* = 1, R: H (75%)
116b, *n* = 2, R: Me (68%)
116c, *n* = 2, R: H (77%)

Scheme 42. Brønsted acid catalyzed alkylation of indoles with vinyl-substituted alkynols.

Although not strictly related to indole alkynylation, the following study caught our attention as the first example of catalytic 1,2-indole migration to propargylic derivatives. Here, the unexpected formation of indenylindole compounds **118** was obtained by treating propargylic compound **117** with cationic gold(I) bis(trifluoromethanesulfonyl)imidate (Scheme 43).[139] Mechanistically, the activation of the triple bonds by the gold catalyst accelerated the nucleophilic indole attack, with formation of vinyl–gold species **119**. The authors



Scheme 43. Gold-catalyzed 1,2-migration of indoles in propargylic compound **117**: direct entry to 2-indenylindole **118.**



Scheme 44. Catalytic enantioselective propargylation of indoles via ruthenium–allenylidene intermediates.

suggested that the ensuing 1,2-migration together with a formal cleavage of a C–C bond would be favored by the stabilization of **120** through resonance (not shown). Further intramolecular arene alkylation will lead to the final compound **118**.

Nishibayashi and co-workers pioneered the enantioselective ruthenium-catalyzed propargylation of arenes with aromatic 2-propyn-1-ols **122** by using chiral thiolate-bridged diruthenium complex **123**.[140a] The protocol was further extended by the same research group to *N*-TIPS-protected indoles, which provided the desired propargylated compounds **124** in high yields and enantiomeric excesses (up to 95% *ee*).[140b,c] A closer look at the reaction mechanism shed light on the high levels of stereocontrol achieved. Here, the starting material, 2-propyn-1-ol, interacts with precatalyst **123** to form a ruthenium–allenylidene intermediate **125**, in which the stereodiscrimination of the diastereotopic faces of the allenyl unit is exerted by the aryl pendants of the chiral thiolate ligands. Stacking interactions between the π units of the catalyst and the aromatic ring of **122** were also invoked as the stereodifferentiating element (Scheme 44).

5.3.3. Allylic Alcohols, Acetate, and Carbonates

The regiochemical introduction of allyl moieties into arenes is a straightforward synthetic approach to generate chemical diversity in aromatic compounds.[141] In particular, the regioselective C3-allylation of indoles is a direct approach for the preparation of naturally occurring indole alkaloids and potent HIV inhibitors.[142]

The use of allylic alcohols, acetates, and carbonates in the regioselective catalytic alkylation of indoles can be divided into two main areas on the basis of mechanistic considerations. Allylic alcohols have been used predominantly with classical Lewis or Brønsted acid catalysts to form incipient positively charged intermediates (S_N1 mechanism). On the other hand, the ability of allylic acetates and carbonates to form electrophilic η^3 species with low-valent late-transition metals (such as in the Tsuji–Trost coupling)[143] has also been exploited in selective allylic Friedel–Crafts alkylation of indoles (Figure 19).

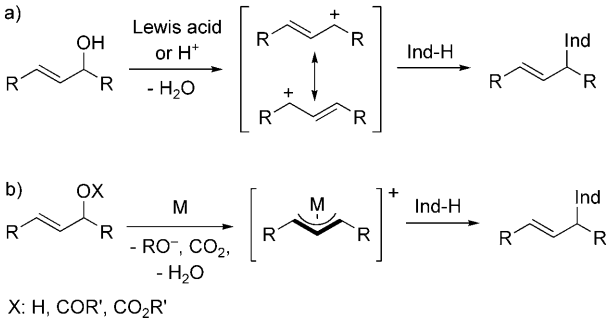
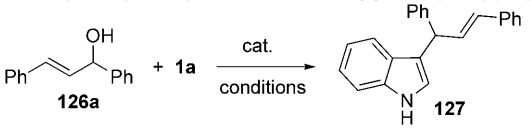


Figure 19. Catalytic allylic alkylation of indoles: mechanistic aspects.

Secondary aromatic allylic alcohols are frequently used in combination with Lewis and Brønsted acids for the direct functionalization of indoles. After preliminary results by Baba and co-workers, who performed the condensation of (*E*)-1,3-diphenylpropenol (**126a**) with **1a** in the presence of $InCl_3$ (5 mol%; Table 5, entry 1),[144a] much attention has been paid toward the discovery of more-efficient catalytic systems. The use of **126a** as the model substrate ensures more energetically feasible C–OH bond cleavages because of the relative stability of the corresponding carbocationic species (Figure 19a). In some cases, the replacement of the OH group through an S_N2' mechanism is suggested, even though there is an absence of concrete experimental evidence.

Less-reactive monosubstituted allyl alcohols are challenging reagents for the allylic alkylation of indoles. In fact, the relatively unstable resulting carbocationic species tend to react preferentially with water or to self-condense instead of being trapped by the aromatic ring.

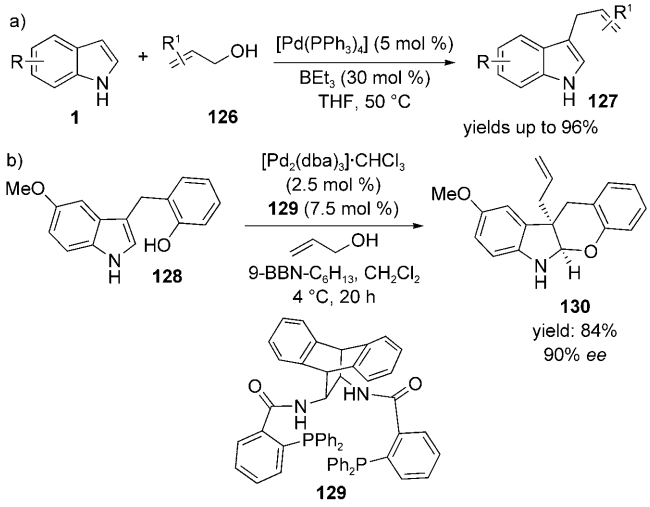
Table 5: Catalytic allylic alkylation of **1a** with (*E*)-1,3-diphenylpropenol.



Cat (%)	Solvent	*t* [h] (*T* [°C])	Yield **127** [%]	Ref.
$InCl_3$ (5)	toluene	6 (80)	64	[144a]
*p*TSA (5)	CH_3CN	–[c] (20)	74	[144b]
$InBr_3$ (10)	DCE	0.5 (RT)	91	[144c]
*p*TSA (5)	CH_2Cl_2	2 (50)	95	[144d]
$FeCl_3$ (10)	$MeNO_2$	1 (55)	58	[144e]
calix-SO_3H[a] (1)	H_2O	18 (RT)	83	[144f]
$AuCl_3$[b] (5)	CH_2Cl_2	–[c] (RT)	95	[144g]

[a] Calix[6]arene-SO_3H. [b] *N*-Methylindole (**1d**) was used in combination with (*E*)-1,3-bis(4-bromophenyl)prop-2-en-1-ol. [c] Not available.

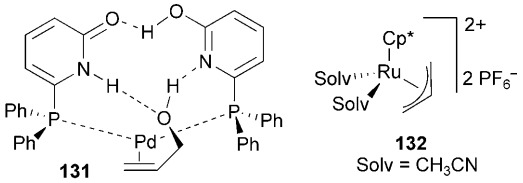
Tamaru and co-workers demonstrated in 2005 the efficiency of $[Pd(PPh_3)_4]$ (5 mol%) in catalyzing the C3-alkylation of variously functionalized indoles with α,γ-methyl- and α,γ-phenyl-substituted allyl alcohols **126**. The addition of triethylborane (30 mol%) resulted in coordination to the hydroxy group, thus favoring the oxidative addition to the palladium(0) center (Scheme 45a).[142] This method was applicable for a wide range of alcohols and indoles, thus allowing the synthesis of complex polycyclic indolyl alkaloids.



Scheme 45. Palladium(0)-catalyzed enantioselective allylic alkylation of indoles with alcohols.

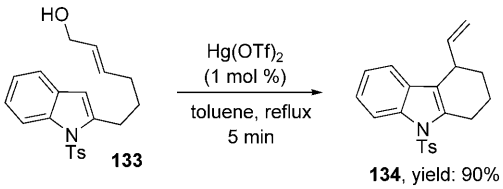
A related enantioselective palladium-catalyzed variant was developed by Trost and Quancard which targeted C3-substituted indoles.[145] Here, a range of indolenine and indoline derivatives with quaternary stereocenters were synthesized efficiently by using $[Pd_2(dba)_3]\cdot CHCl_3$ and chiral dppba ligand **129**. A survey of several additives demonstrated the superiority of 9-BBN-C_6H_{13} in controlling the chemoselectivity (C3 versus N1; Scheme 45b).

The potential of using late-transition metals in this process were subsequently renewed independently, without the need for external additives, by the research groups of Breit[146] and Pregosin.[147] In the former case, the controlled self-assembly of monodentate P ligands into a hydrogen-bonding network generated diphosphines that were highly efficient in promoting the palladium-catalyzed allylation of indoles by directly assisting in the C–OH cleavage at 50–90°C. Very mild reaction conditions were also reported by Pregosin and coworkers in the regioselective functionalization of indoles with simple allylic alcohol by using the ruthenium(IV) catalyst **132** (Scheme 46) at room temperature. The HPF_6 liberated during the course of the reaction accounts for the activation of the alkylating agents toward oxidative addition reaction. Selective single or N,C double allylation of indoles was achieved by the ruthenium catalysis.



Scheme 46. Palladium and ruthenium complexes for direct allylic alkylation of indoles with alcohols.

At present only one example of catalytic intramolecular allylic alkylation of indoles with alcohols has been reported.[148] The method made use of the astonishing ability of $Hg(OTf)_2$ salts (1 mol%) to activate double and triple C–C bonds and so furnish *N*-tosyl-4-vinyltetrahydrocarbazole (**134**), which was isolated in almost quantitative yield (Scheme 47).



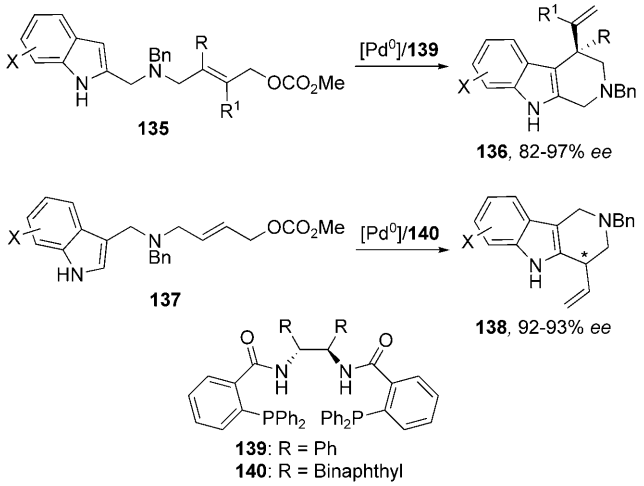
Scheme 47. Synthesis of tetrahydrocarbazole **134** by intramolecular allylic alkylation of indole **133** in the presence of a mercury(II) catalyst.

Allylic acetates and carbonates are extraordinary components of the catalytic Tsuji–Trost condensation, which leads to a virtually unlimited number of functionalized compounds through formation of new C–C, C–N, C–O, and C–S bonds.[141] The use of aromatic compounds as partners of nucleophilic allylic substitution was introduced by Billups et al. in the early 1980s.[149a] In 1999, Kočovský and co-workers used $[\{Mo(CO)_4Br_2\}_2]$ (5 mol%) to promote the condensation of electron-rich arenes and heteroarenes to mono- and disubstituted allylic acetates.[149b] Several years later the scope of the method was expanded significantly by Bandini et al., who used more accessible and easily handled palladium catalysts and allylic carbonates.[150a] The control over N1- versus C3-alkylation was obtained simply through the control over the reaction conditions (solvent, temperature, base). The potential of the protocol in the preparation of TBHCs

through intramolecular allylic alkylation of indoles was also demonstrated.

Ma and co-workers also reported a series of studies that focused on the palladium(0)- and palladium(II)-catalyzed allylic alkylations of indoles with 2-acetoxymethyl-substituted electron-deficient alkenes. The palladium(0)-catalyzed approach[151a] resulted in a wider scope of indoles than that of the corresponding Heck-type protocol (with Pd^{II}).[151b] Not only palladium, but also silver-[152a] and scandium-based[152b] Lewis acids were reported to efficiently catalyze the allylic alkylation of indoles with a range of functionalized allylic acetates.

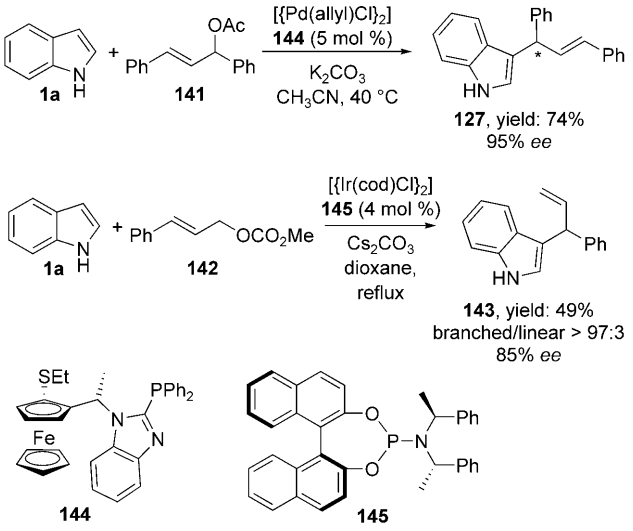
An enantioselective variant of the intramolecular allylic alkylation of functionalized indoles was developed by using chiral ligands on the palladium complex.[150b] The combination of chiral dppba ligands **139** and **140** and $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%) allowed THBCs (**136**) and THGCs (**138**) to be isolated regioselectively, in high yields and enantiomeric excesses. A wide range of substrates was tolerated, with the possibility to introduce quaternary stereocenters at the δ position of the THBC framework in a highly stereoselective manner (Scheme 48).



Scheme 48. Palladium-catalyzed synthesis of THBCs and THGCs by intramolecular AAA of indoles.

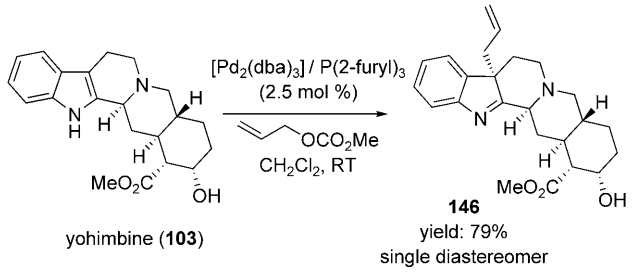
Catalytic and enantioselective intermolecular allylic alkylations of indoles were subsequently reported by the research groups of Chan[153a] and You,[153b] who used chiral palladium and iridium complexes, respectively. While the palladium catalysis required the use of symmetrically substituted allylic acetate precursors (preferential formation of a linear alkylation product), the use of iridium(I) complexes allowed for unsymmetrical 1,3-substituted allyl precursors to be employed, with regioselective formation of the branched alkylated product (Scheme 49).

As outlined previously,[145] the allylic substitutions of C3-substituted indoles led to dearomatization of the indolyl system, with concomitant formation of quaternary stereocenters. In this context, Rawal and co-workers reported an intermolecular palladium-catalyzed alkylation of 2,3-disubstituted indoles with allylic carbonates.[154] Selective C3-



Scheme 49. Intermolecular enantioselective allylic alkylation of indoles catalyzed by chiral palladium and iridium complexes.

alkylation was obtained even in the absence of preventive protecting groups on the nitrogen atom, and led to a library of indolenines with quaternary stereocenters in high yields. The synthetic utility and functional group tolerance of the method were verified by carrying out the allylic alkylation on polyfunctionalized indolyl alkaloids such as (±)-geissoschizol, yohimbine (**103**), and reserpine (Scheme 50).



Scheme 50. Diastereoselective allylic alkylation at C3 of the indole core in yohimbine.

The palladium-catalyzed AAA was successfully applied to *O*-TIPS-protected oxindoles, as illustrated by the total synthesis of horsfiline.[155]

6. Arylation and Vinylation Reactions

6.1. Introduction

This section deals with catalytic cross-coupling reactions of unactivated indole rings.[15b] The importance of direct coupling reactions with unactivated aryl compounds is beyond doubt. The low level of functionalization of the reaction partners results in reduced waste and number of reaction steps in the synthesis of biaryl compounds.[156] The main developments during the last four years are highlighted, with a focus also on C- and N-vinylation reactions.

The electronic nature of the indole core is reflected in its main three reactive sides (N1, C2, C3). Therefore, this section is organized according to the type of bond formed in the coupling reaction: C–N bond formation (at N1) and C–C bond formation (at C2 and C3; Figure 20).

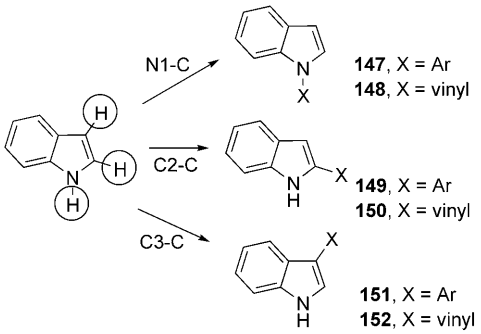


Figure 20. The most reactive positions of indoles in cross-coupling reactions.

6.2. C–N Bond Formation

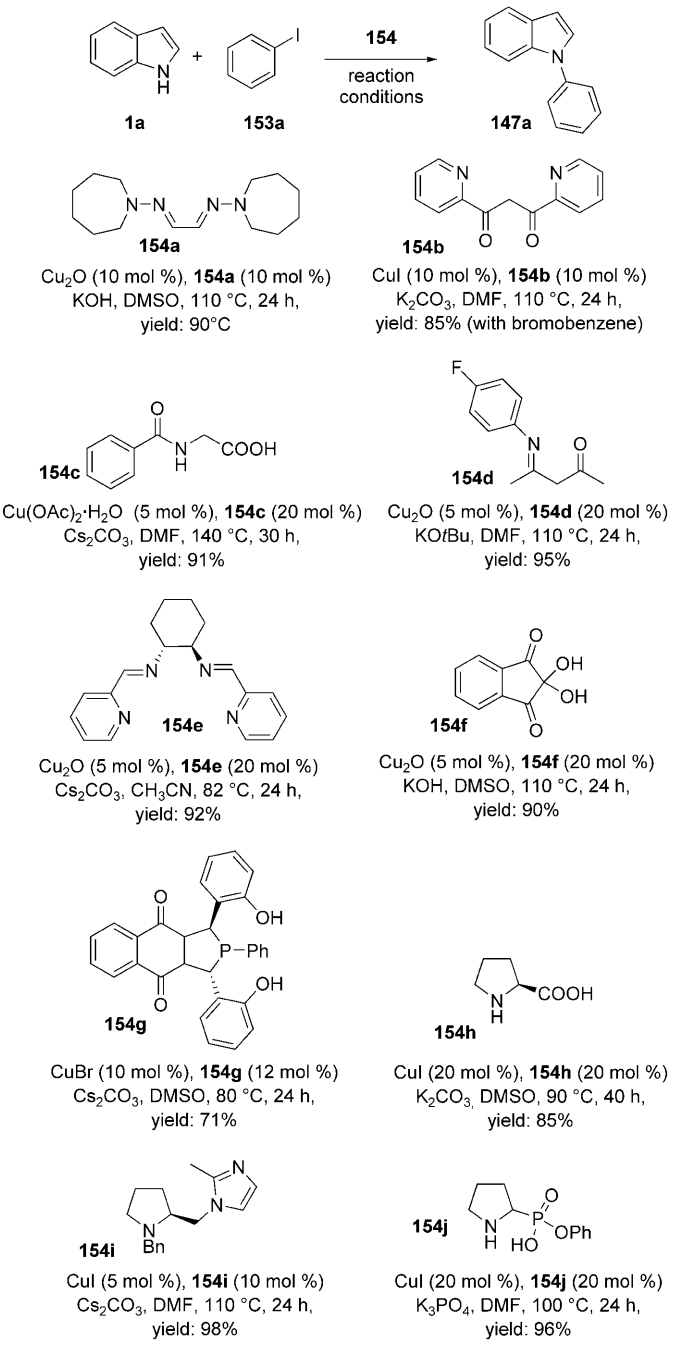
6.2.1. N Arylation

The N-arylated indole scaffold **147** is present in many bioactive molecules,[157] and recently the inhibition of HIV-1 integrase activity by some N-aryl indoles was described.[158] These structural motifs are accessible by nucleophilic aromatic substitution reactions (S_NAr), but limited to strongly electron-deficient arenes, or by Ullmann reactions.[156,159] Here, harsh reaction conditions (prolonged reaction times, high temperatures, stoichiometric amounts of copper additives) are necessary and a narrow range of substrates are tolerated.[160] This lack of efficiency inspired the search for new catalytic C–N coupling reactions of heteroaromatic compounds under mild reaction conditions, high yields and selectivity, as well as wide chemical compatibility.

Over the past two decades, copper-catalyzed reactions became prominent for the N-arylation of indoles, and highly efficient procedures were reported.[15b]

Since the pioneering work by Buchwald and co-workers,[161] who made use of a copper catalyst with chelating diamine ligands, alternative approaches have been investigated that had improvements in terms of mildness, functional-group tolerance, costs, and eventual omission of the base and ligand. For example, moderate to excellent yields were obtained by the implementation of a plethora of ligands such as diamines, *N*-hydroxyimides, diketones, amino acids, and β-ketimines.[162] The ligands **154a–j** and the reaction conditions for the copper-catalyzed arylation of **1a** and iodobenzene (**153**) as a model reaction are depicted in Scheme 51.

Of particular interest is the possibility to efficiently combine copper catalysis with amino acids.[163] From a survey of additives, L-proline emerged as the ligand of choice, being successful for primary, secondary, aliphatic, and aromatic amines, even though it was not particularly efficient for the model reaction (**1a**, **153a**). Moreover, the high versatility as well as economical and environmental



Scheme 51. Copper-catalyzed N-arylation of indoles.

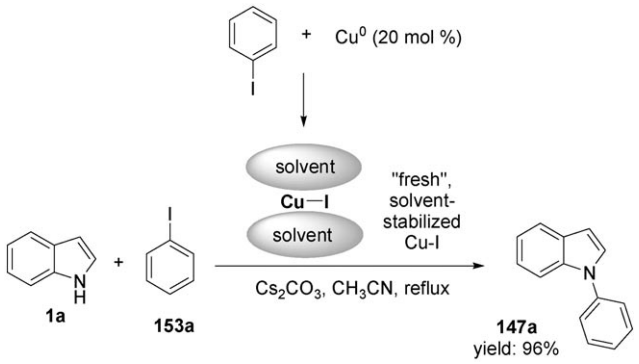
friendliness of L-proline was also successfully demonstrated in the iron-mediated[164] arylation of indoles.[165] Interestingly, an effective $FeCl_3$/dmeda-catalyzed N-arylation of indoles was recently described by Correa and Bolm which provided **147a** in 60% yield.[166]

In this context, a very interesting contribution came from the research group of Taillefer, who reported a novel bimetallic (iron/copper) catalytic system for the arylation of nitrogen nucleophiles. Both the copper and iron centers are actively involved in the formation of the C–N bond.[162d] The coexistence of both catalytic species as well as the complexation of the iron(III) species with acetylacetonate were shown

to be necessary, as no product is formed in the absence of one of the components.

There is notable interest in the development of ligand-free Ullmann reactions, but this field is still relatively unexplored.[163a,167] In this context, Correa and Bolm[168a] reported in 2007 on the development of an efficient and inexpensive ligand-free process catalyzed by CuO (10 mol%). The method allowed the coupling of several nitrogen-containing heterocycles (for example, pyrrole, imidazole, and indole) with aryl iodides and even more challenging bromides. In the same year, Zhu, You et al.[168b] documented an analogous ligandless CuI-catalyzed coupling reaction that was applicable to various nitrogen-containing heterocycles, with aryl bromides and to some extent chlorides used as the coupling partners.

Shortly after, Hu and co-workers published a so called ligand-free approach, in which the coordinating solvent (acetonitrile or propionitrile) took the role of the ligand for the copper catalyst.[169] Under the optimum conditions, the high-yielding arylation of indole (90–95%) in the presence of elemental copper (20 mol%) as the metal source proceeded at 82°C in relatively short reaction times (10–14 h). The authors hypothesized that the copper powder could initially be involved in a slow oxidative addition process with **153a**, thereby creating highly active, "fresh" CuI in situ, which is immediately stabilized by the solvent (Scheme 52).

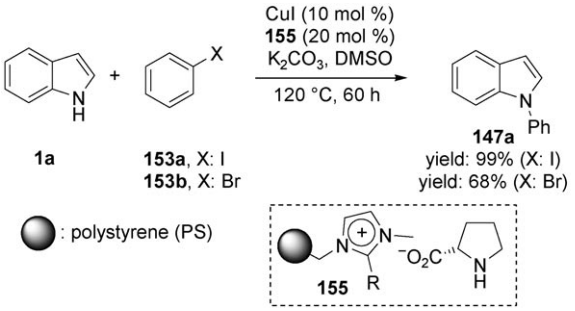


Scheme 52. "Fresh" solvent-stabilized CuI for the N-arylation of indoles.

Prolonged reaction times and the narrow range of substrates tolerated still represent demanding shortcomings in the arylation of heteroaromatic compounds. The research groups of Bellina and Chen addressed these problems, and demonstrated the beneficial effect of microwave irradiation in shortening the reaction times (from hours to only a few minutes). However, these reactions still require stoichiometric amounts of copper.[170]

The terms "green chemistry" and "heterogeneous catalysis" are closely related, since time, material, expensive work-up procedures, and subsequent (often toxic) waste production are minimized in both. In this context, great improvements have recently been made in the heterogeneously catalyzed N-arylation of indoles with insoluble copper sources (for example, Cu_2O/DMSO, Cu-Fe-hydrotalcite, Cu apatites), with generally acceptable recoverability and reusability of the catalytically active species.[171]

Among the methods for the coupling of nitrogen-containing heterocycles with aryl halides, a conceptually new method was provided by You and co-workers, who reported on the efficiency of using supported ionic-liquid catalysis (SILC).[172] The authors also described a protocol for the preparation of multifunctional materials by covalently tethering imidazolium cations to a polystyrene backbone and immobilizing amino acids through ion-pair interactions. The resulting functionalized resin was then treated with a solution of CuI in DMSO to obtain the catalytically active heterogeneous copper species (Scheme 53). Under optimized conditions (10 mol% CuI, 20 mol% **155**) *N*-phenylindole (**147a**) was obtained in 99% yield starting from iodobenzene, and 68% in the case of bromobenzene. A disadvantage of this approach compared to other heterogeneous methods is the long reaction times (60 h) and the laborious recycling of the ionic liquid.

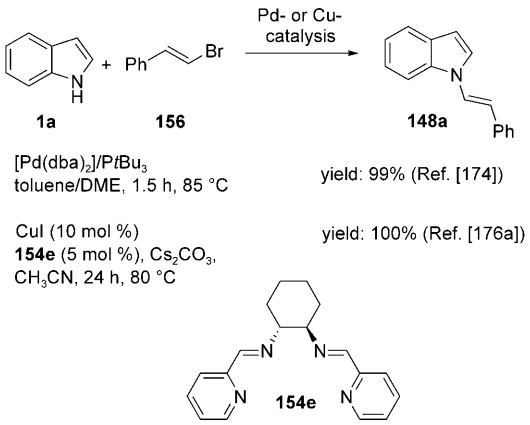


Scheme 53. Solid-phase-bound ionic liquid with proline as the ligand for the copper-catalyzed N-arylation of indole (**1a**).

6.2.2. *N* Vinylation

N-Vinylazoles are important building blocks in pharmacology[173] and material science;[174] however, there is a shortage of mild and atom-economic approaches for their preparation. After publication of a palladium-catalyzed N-vinylation of pyrroles and indoles in 2002,[174] little progress has been made in this area. In 2005, Movassaghi and Ondrus[175] reported the stereospecific synthesis of *N*-vinylindole derivatives by palladium-catalyzed coupling reactions with vinyl triflates. In this study, indole and the less nucleophilic 3-cyanoindole underwent smooth coupling reactions with both cyclic and acyclic vinylating agents. More accessible (*E*)-β-bromostyrenes were also employed effectively in the vinylation of cyclic mono-, di-, and triazoles in the presence of CuI (10 mol%). As an example, the N-vinylation of indole (**1a**) proceeded smoothly to give *N*-vinylindole **148a** in quantitative yield (Scheme 54).[176a]

Finally, an important contribution to the field of copper-catalyzed vinylation of indoles came from Mao et al.[176b] The ligand-free approach resulted in moderate to good yields for several (*E*)-vinyl bromides and demonstrated remarkable tolerance toward functional groups on the indole ring.



Scheme 54. Palladium- or copper-catalyzed direct vinylation of indole under mild conditions.

6.3. C–C Bond Formation

6.3.1. Introduction

The central role of aryl indoles in organic chemistry is the driving force behind the intense search for new inter- as well as intramolecular $C(sp^2)$–$C(sp^2)$ coupling reactions to this heteroaromatic scaffold. Metal-catalyzed cross-coupling reactions represent the most reliable strategy for this type of indole functionalization. Based on the type of reaction partners, three different classes of cross-coupling reactions can be recognized: a) reactions with preactivated indoles (for example, Suzuki, Stille, Kumada, Heck reactions);[177] b) direct alkynylation/vinylation/arylation processes, and c) oxidative coupling reactions (Figure 21). Reactions of

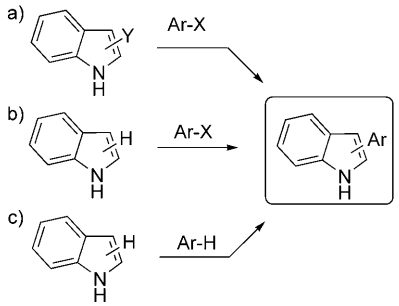
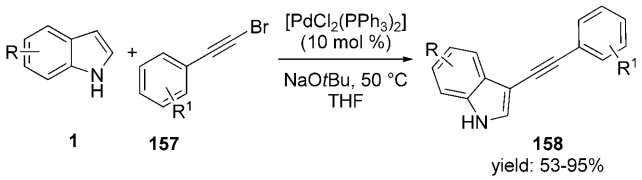


Figure 21. $C(sp^2)$–$C(sp^2)$ linkage of indoles by cross-coupling reactions: a) use of prefunctionalized indoles, b) direct alkynylation/vinylation/arylation, c) oxidative coupling reactions.

type (a), which require two functionalized partners will not be discussed here, as this extensive field goes beyond the scope of this Review.[16] In contrast, over the last decade, efforts have moved to the establishment of catalytic processes that require a minimum functionalization of the reaction partners.[156a]

6.3.2. Direct C-Alkynylation/Vinylation/Arylation

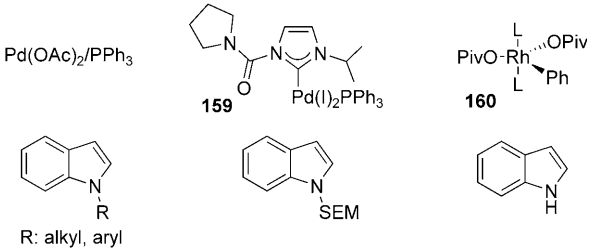
Very recently, the first direct alkynylation of N-fused heterocycles was described by Gevorgyan and co-workers.[178a] Their protocol featured an efficient catalysis with $[PdCl_2(PPh_3)_2]$ in the presence of alkynyl halides. Although the method did not provide direct access to functionalized indoles, it inspired Gu and Wang to develop the first example of C3-selective palladium-catalyzed alkynylation of N(H)-indoles.[178b] Moderate to good yields (53–95%) were achieved, and high regioselectivity (C3-alkynylation) occurred under mild reaction conditions (no air sensitivity, use of unpurified solvents, low reaction temperatures; Scheme 55).



Scheme 55. Direct regioselective palladium-catalyzed alkynylation of indoles.

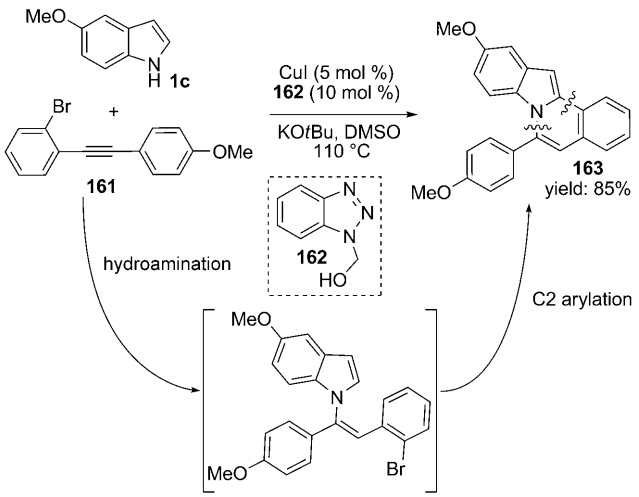
Analogously, the direct arylation and vinylation of unactivated indoles with aryl and vinyl halides, respectively, or pseudohalides have gathered great attention, but there is still a demand for highly regioselective C–H activation procedures that are functional-group tolerant. Whereas the copper-catalyzed procedures can be considered a well-established synthetic route in the case of N-arylations, C–C arylations of indoles are still dominated by palladium catalysis. As the direct arylation of indoles has been comprehensively reviewed recently,[15b] only a few important examples will be presented herein.

In 1985 the first direct C2 coupling between N-protected indoles and chloropyrazines was reported;[179] it took almost 20 years until attention returned with the regioselective approach by Sames and co-workers (C2-arylation of N-substituted indoles).[180] In two consecutive reports, a range of variously functionalized indoles was selectively arylated in the presence of $Pd(OAc)_2/PPh_3$[180a] or **159**[180b] as the catalytic systems. It is noteworthy that the replacement of one molecule of PPh_3 with a permanent N-heterocyclic carbene (NHC) ligand improved the stability of the entire complex remarkably and resulted in higher selectivity (minimization of competitive biphenyl formation). Finally the goal to target "… C–H bonds exclusively in the presence of … acidic N–H bonds …"[180c] was accomplished successfully by the same research group through the use of a competent in situ assembled rhodium(III)–aryl complex **160** (Scheme 56).



Scheme 56. Palladium- and rhodium-catalyzed regioselective C2-arylation of indoles.

The activity of copper(I) salts in promoting the hydroamination of nitrogen-based heteroaromatic compounds, prompted Verma, Larock et al. to design an elegant tandem approach to indolo[2,1-*a*]isoquinolines **163** starting from 2-haloarylakynes **161** and variously functionalized indoles (Scheme 57).[181] Mechanistically, consecutive N1–C and C2–C bond-forming events are invoked during the course of the reaction, and the use of inexpensive hydroxymethylbenzotriazole (**162**) as the copper ligand led to excellent yields.

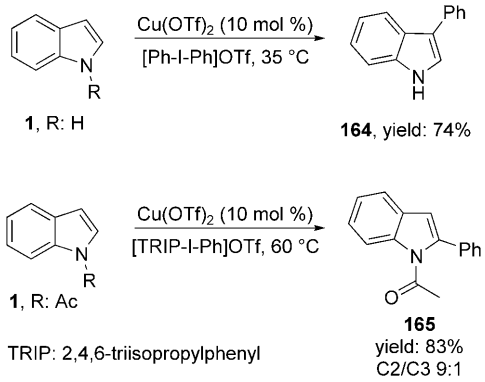


Scheme 57. Copper-catalyzed tandem synthesis of indoloisoquinolines.

Much effort has been directed to the development of base-free,[182a] ligand-free,[182b,c] and low-temperature[182d] catalytic C-arylations of indoles. Valuable approaches to lower the working temperature were proposed independently by the research groups of Sanford[183a] and Larrosa.[183b] In the first case, a catalytic redox couple (Pd^{II}/Pd^{IV}) efficiently promoted the C2-arylation of indoles with aryl iodonium salts at room temperature. In the second case, the addition of Ag_2O (0.75 equiv) as a halide scavenger improved the activity (electrophilicity) of the Pd catalyst drastically, thereby leading to a broadened substrate scope and allowing the reaction to be carried out at room temperature over 15 h.

In 2007, He and co-workers developed a direct C3-arylation of indoles.[184a] Here, the use of air-stable palladium complexes with phosphinous acid (POPd) allowed the selective cross-coupling of unprotected indoles with inexpensive and readily available aryl bromides. Heterogeneous palladium-catalyzed C3-arylation of C2-substituted indoles was also recently reported.[184b] Under optimized conditions, bromobenzene coupled with indoles in the presence of $[Pd(NH_3)_4]^{2+}$/NaY-zeolite (1 mol% Pd) and K_2CO_3. The authors believe that two concurrent mechanisms—the electrophilic substitution and the nucleophilic aromatic substitution—could occur.

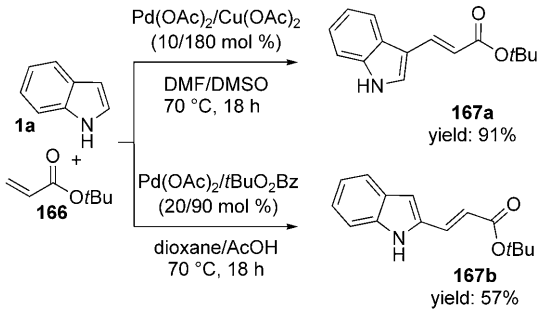
Can C2- and C3-arylations conveniently be accomplished by the same catalytic system simply by fine-tuning the experimental conditions? Gaunt and co-workers responded to this intriguing challenge by developing a regioselective approach based on $Cu(OTf)_2$ catalysis.[185] The high yielding protocol is based on the assumption that a d^8-configured Cu^{III} species, like other d^8 metal ($[Pd^{II}]$) species, could favor C–H activation. These highly reactive Cu^{III} species were created by treating $Cu(OTf)_2$ with diaryl iodine(III) reagents (for example, symmetric [Ph-I-Ph]OTf and asymmetric [TRIP-I-Ph]OTf biaryl iodonium salts). The switch in selectivity in favor of C2 substitution was accomplished with the same catalytic system used for *N*-acetylindole (Scheme 58).



Scheme 58. Site-selective copper-catalyzed arylation of indoles.

6.3.3. ***Oxidative Coupling Reactions***

The Fujiwara–Moritani oxidative Heck coupling[186] is a well-known protocol that enables alkenylation of functionalized aromatic compounds without the need for preactivation of the arene unit. Surprisingly, despite the enormous synthetic potential of this method, the catalytic oxidative coupling of indoles with unactivated olefins received only minor attention until 2003, when the research groups of Stoltz[187a] and Beccalli[187b,c] described independently the palladium-catalyzed oxidative annulation of indoles by means of molecular O_2 and benzoquinone, respectively, as stoichiometric oxidants.[188] Intermolecular variants of the catalytic Fujiwara–Moritani oxidative Heck coupling of indoles generally suffer from a lack of regioselectivity at C2 and C3. Capito, Brown, and Ricci have recently overcome this drawback simply by inserting a pyridyl directing group at the N1-position (cat: $[PdCl_2(CH_3CN)_2]/Cu(OAc)_2$).[189a] However, the method was limited to electron-deficient C–C double bonds. Another example of vinylation assisted by a directing group was described by Miura and co-workers, who used indolecarboxylic acids.[189b] The authors showed that the directing carboxylic acid group leads to C2- and C3-vinylindoles by C–H vinylation and subsequent decarboxylation. The role of the solvent in controlling the regiochemistry of the process was also investigated:[189c] while strongly coordinating solvents (for example, DMF/DMSO) led to the expected C3-alkenylation product **167a**, less-coordinating 1,4-dioxane under acidic conditions completely reversed the regioselection in favor of the C2 site, with formation of **167b** (Scheme 59). A hypothetical C3→C2 migration of the substituents was a possible explanation for the finding.



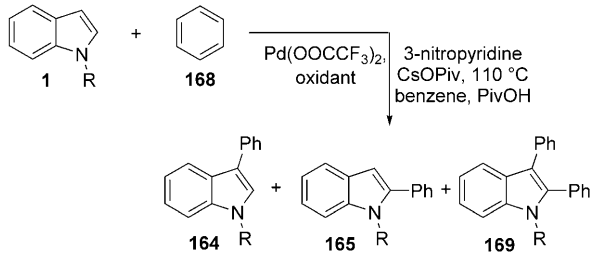
Scheme 59. Tuning the regiochemistry in the palladium-catalyzed oxidative alkenylation of indoles by the reaction conditions.

Catalytic enantioselective Fujiwara–Moritani coupling reactions are still almost unexplored. A promising level of enantiocontrol (up to 54% *ee*) was obtained by using chiral pyridine-oxazolines (PyOXs) in palladium-catalyzed processes.[190]

The oxidative palladium-catalyzed coupling of unactivated indoles with unfunctionalized arenes has been extensively investigated by Campeau and Fagnou.[191] The challenging task in this type of reactions is to find a suitable catalytic system that is able to activate one aryl species exclusively in the first step, and to switch selectivity toward the other arene species in the second stage of the catalytic cycle. Homocoupling reactions would become competitive side processes in catalytic systems that did not operate by this route. Palladium(II) species have been shown to display dual reactivity with arenes: electrophilic aromatic metalation (S_EAr) and concerted proton-transfer palladation. A combination of these two reactivities in one catalytic cycle would meet the crucial challenges of reactivity and selectivity. By exploiting the influence of N-protecting groups on indole reactivity, Fagnou and co-workers were able to successfully couple *N*-acetylindoles with benzene in good yields.[192] Whereas the use of $Cu(OAc)_2$ as the oxidant favored C3-arylation, the selectivity could be switched to the C2-position simply by using AgOAc as an external oxidant (Scheme 60).

The observations by DeBoef and co-workers, which also emphasize the fundamental role of the solvent and the oxidant in controlling the site selectivity of inter- as well as intramolecular oxidative arylations of *N*-acetylindoles, are in accord with these findings.[193]

The high synthetic value of oxidative coupling reactions and the demand for mechanistic elucidation will ensure further developments in this field in the future.

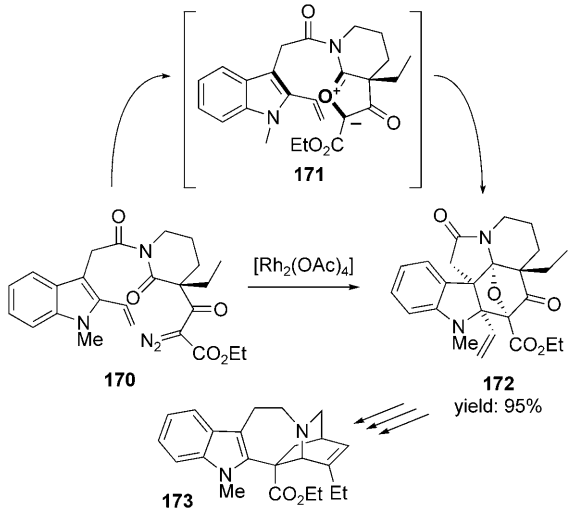


R: Ac	$Cu(OAc)_2$	8.9	1	0.25
R: Ac	AgOAc	1	4	0
R: Piv	AgOAc	1	8.7	0.3

Scheme 60. Palladium-catalyzed oxidative coupling of unfunctionalized indoles with benzene by using $Cu(OAc)_2$ or AgOAc as the oxidant.

7. Diels–Alder Reactions

The participation of indoles in cycloaddition reactions as the dienophile (A) or diene (D) is frequently exploited in the synthesis of complex polyfunctionalized indole-based compounds.[2a] The potential of Diels–Alder reactions for the construction of naturally occurring indole alkaloids was emphasized by Padwa et al., who reported an intramolecular rhodium(II)-catalyzed cycloaddition of indole diazoamides.[194] The [4+2] cycloaddition between the 1,3-dipole (**171**) and the C2–C3 π bond of the indole system in **170**,[195] led to the pentacyclic polyfunctionalized compound **172** in 95% yield as a single isomer, which is a valuable building block for the preparation of catharanthine **173** (Scheme 61).

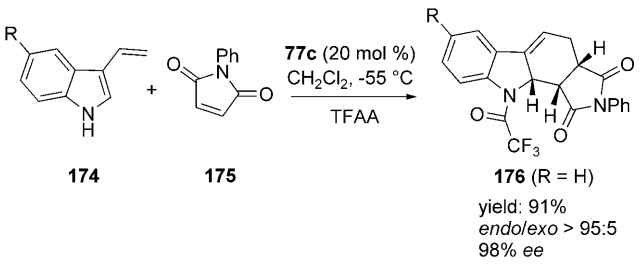


Scheme 61. Stereoselective rhodium-catalyzed [4+2] cycloaddition with indole as the dienophile.

2- or 3-Vinylindoles are known to participate in Diels–Alder cycloadditions with a variety of cyclic and open-chain carbon dienophiles.[196] In general, anellation reactions under conventional heating are slow (days);[197] thus, acid catalysis is routinely adopted to speed up the reaction. Rossi and co-workers recently used this approach in the synthesis of functionalized tetrahydrocarbazoles.[198] Catalytic amounts of $Mg(ClO_4)_2$, $Sc(OTf)_3$, or $Cu(OTf)_2$ efficiently assisted the [4+2] cycloadditions between a number of 2-vinylindoles and electron-poor alkenes.[199]

Finally, the still unexplored field of asymmetric catalytic Diels–Alder processes involving indoles was addressed by Bernardi, Ricci, and co-workers, who documented the efficiency of chiral thioureas in promoting highly stereocontrolled Diels–Alder reactions of 3-vinylindoles **174**. A library

of highly functionalized partially hydrogenated carbazoles (**176**) was isolated with enantiomeric excesses constantly higher than 90% *ee* by using chiral bifunctional thioureas **77c** (20 mol%, Scheme 62).[200]



Scheme 62. Enantioselective organocatalyzed Diels–Alder reaction with 3-vinylindoles.

8. Summary and Outlook

Sustainability and efficiency are mandatory requirements in modern organic chemistry. Many of the recent discoveries in the functionalization of indoles critically reported in this Review primarily address these topics. The chemical functionalization of the indole nucleus is a fascinating area that has had a tremendous impact on organic synthesis. The actual range of synthetic methods available constitutes a valuable know-how for scientists that are asked daily to synthesize complex molecular structures containing indoles. The introduction of innovative and highly efficient metal-based and metal-free catalytic systems have enabled direct indole derivatizations that seemed unlikely to be realized a few years before. Functional-group manipulation, preactivation of aromatic systems, and protecting-group chemistry are conveniently kept to a minimum in these new methods.[201]

So, what next? From a glance at the content of this Review, it would appear that many of the goals in indole chemiistry have been reached. The combination of unusual Lewis acid catalysts (for example, late-transition-metal species) or organocatalysts with new techniques has brought indole chemistry to a new dimension.

However, as frequently happens in organic chemistry, providing new solutions inevitably generate new intriguing challenges. Chemical processes involving multiple C–H bond activations, stereoselection in alternative reaction media, and selective domino reactions are only a few of the future targets in indole chemistry. The scope of the actual catalytic protocols is generally evaluated by screening a simple indole nucleus with nearly innocent ancillary substituents. However, tolerance toward a broad range of functional groups will become an essential requisite for their employment as practical catalytic methods in the total synthesis of complex indole-containing structures. All these considerations lead us to conclude that much more is still to come in this fascinating area.

List of Abbreviations

9-BBN	9-borabicyclononane
AAA	asymmetric allylic alkylation
acac	acetylacetonate
Alk	alkyl
Ar	aryl
BHT	butylhydroxytoluene
bmim	1-butyl-3-methylimidazolium
Bn	benzyl
boc	*tert*-butoxycarbonyl
box	bisoxazoline
Bs	benzensulfonyl
CD	circular dichroism
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CTH	carbohydrate-based tolylsulfonyl hydrazines
Cyp	cyclopentyl
DBIm	1-butyl-3-decylimidazolium
DBSA	dodecylbenzene sulfonic acid
DCE	dichloroethane
de	diastereomeric excess
DME	dimethoxyethane
dmeda	*N*,*N*′-dimethylenediamine
DNBS	2,4-dinitrobenzene sulfonic acid
dppba	diphenylphosphanylbenzoic acid
ds	dodecyl sulfate
EDG	electron-donating group
ee	enantiomeric excess
EWG	electron withdrawing group
FAP	fluorapatite
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
hmim	*n*-hexylmethylimidazolium
HPA	hydroxyapatite
IL	ionic liquid
ILIS	ionic liquid immobilized on silica
ind	indole
IPA	isopropyl alcohol
lut	lutidine
MVK	methyl vinyl ketone
MW	microwave
NHC	N-heterocyclic carbene
PFO	perfluorooctanoate
phebim	1,3-bis(2′-imidazolinyl)phenyl
Phg	phenylglycine
Piv	pivaloyl
*p*TSA	*para*-toluenesulfonic acid
py	pyridine
PyOX	pyridine-oxazoline
SA	sulfamic acid
SEM	2-(trimethylsilyl)ethoxymethyl
SILC	supported ionic liquid catalysis
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butyl methyl ether
TBS	tributylsilyl
TFA	trifluoroacetic acid

TfOH	trifluoromethanesulfonic acid
THBC	tetrahydro-β-carboline
THGC	tetrahydro-γ-carboline
THIQ	tetrahydroquinoline
TIPS	triisopropylsilyl
THPI	tetrahydropyrano[3,4-*b*]indole
TOF	turnover frequency
tox	trisoxazoline
Tr	triphenylmethyl
TRIM	triindolylmethane
TRIP	2,4,6-triisopropylphenyl
Trp	tryptophan
Trp-OMe	tryptophan methyl ester
Ts	toluene-4-sulfonyl

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