An Update on Catalytic Enantioselective Alkylations of Indoles

Marco Bandini*, Astrid Eichholzer and Achille Umani-Ronchi

Dipartimento di Chimica "G. Ciamician", Via Selmi 2, 40126, Bologna, Italy

Abstract: Indole benzylic stereocenters are molecular frameworks largely present in natural occurring compounds, with their absolute configuration being of key importance in determining the biological activity of the entire molecule. In this context, the development of new catalytic asymmetric strategies for their preparation is a research area of astonishingly rapid growth by means of organic as well as organometallic catalysts. Here, an update of this thriving scenario is presented by focusing in highly stereocontrolled Michael addition approaches, addition to carbonyl units, direct aromatic C-H activation/alkylation, and allylic alkylation.

Keywords: Alkylation, asymmetric catalysis, Friedel-Crafts, indoles.

1. INTRODUCTION

The Friedel-Crafts (FC) alkylation of aromatics ranks as one of the most investigated and utilized basic reactions. Despite its age, pioneering paper dates back to 1877, the employment of the FC alkylation in the synthesis of organic aromatic targets increases along with new achievements regarding *"greenness"*, mildness and selectivity.

Among the plethora of aromatic compounds, indole, informally referred as "*The lord of the rings"*, deserves a special mention. It is present in a countless number of biologically active compounds with particular relevance in pharmaceuticals, fragrances and agrochemicals, moreover, the configuration of the indole benzylic stereocenters of these systems are crucial in determining the activity of the overall molecules.

Enantioselective catalysis has received considerable attention as a remarkable expedient route to the preparation of functionalized indoles *via* alkylation reactions. Old strategies (Lewis acid-based catalysis) and new approaches (organo-catalysis, late-transition metal catalysis) have appeared in the literature over the last decade promoting both intermolecular as well as intramolecular FC reactions [1].

The electron-rich character of this nitrogen-containing benzo-fused aromatic allowed alkylating procedures to be designed starting from widely available, price and environmentally benign unfunctionalized indoles respect to functionalized aromatic systems that are generally required for benzene-like substrates [2]. On the other hand, *hard* (carbonyl compounds) and *soft* electrophiles (Michael acceptors) together with unactivated alkenes have been successfully utilized furnishing high levels of enantioselection.

As a consequence of the consistent number of new examples of stereocontrolled catalytic direct functionalization of indoles from 2005 to date (August 2006), we considered worthy to collect these updates in a Microreview. For reasons of clarity, the examples reported are discussed by reaction type and a particular relevance has been devoted to the chiral catalyst involved.

2.1 Michael Addition

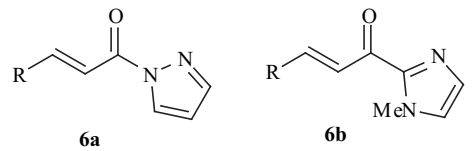
Several types of electron-deficient C-C double bonds proved to be effective alkylating agents for indole functionalisation in the presence of chiral organic as well as organometallic catalysts. However, in order to obtain synthetically useful enantiomeric excesses two-site binding substrates must be employed [3]. Again, only mono-functionalized olefins coupled with strong electron-poor groups (NO_2, CHO, COR) [4] are adequately reactive to be applied in FC indole chemistry whereas synthetically appealing but lowest reactive α,β-unsaturated carboxylic templates fail in furnishing the corresponding indolyl-adducts [5].

2.1.1 α'-Hydroxy Enones with BoxCu(II) Catalysis

α'-Hydro α,β-unsaturated ketones (**1**) represent valuable and readily available Michael acceptors in several enantioselective transformations, as highlighted by Palomo and coworkers [6]. Yet, **1** proved efficiency in FC indole alkylation through metal-assisted activation [7]. The interest on **1** for the synthesis of enantioenriched building blocks stems on the ketol unit that can be peculiarly removed *via* oxidative cleavage ($NaIO_4$-SiO_2) of the corresponding diol (BH_3-THF). The combined use of **1** with catalytic amount (2-10 mol%) of Box-$Cu(OTf)_2$ (**3**) complex allowed variously functionalized β-indolyl ketones **4** to be isolated in high yield and excellent enantiomeric excesses (Scheme **1**). The formation of 5-membered metallo-chelating intermediate, during the enantiodiscriminating step of the reaction, is suggested by the authors.

2.1.2 α,β-Unsaturated 2-Acyl N-Methylimidazoles with pyBoxSc(III) Catalysis

A second class of largely employed enones in asymmetric transformations is unsaturated acyl pyrazoles (**6a**, eq. (**1**)) [8] that guarantee a rigid chelating-mode interaction (5-membered ring) with cationic metal complexes through the nitrogen atom of the heteroaromatic ring. More recently, Evans and coworkers reported on the effectiveness of unprecedented α,β-unsaturated 2-acyl *N*-methylimidazoles (**6b**) as Michael acceptors for FC alkylations with electron-rich heteroaromatics such as indoles, pyrrole and 2-methoxyfurane [9]. Also in this case, the heteroaryl ring can be conveniently removed by the final product using a variety of nucleophiles (RO^-, OH^-, NHR_2, NH_2R) under mild conditions.



6a **6b** (1)

*Address correspondence to this author at the Dipartimento di Chimica "G. Ciamician", *Via* Selmi 2, 40126, Bologna, Italy; E-mail: marco.bandini@unibo.it

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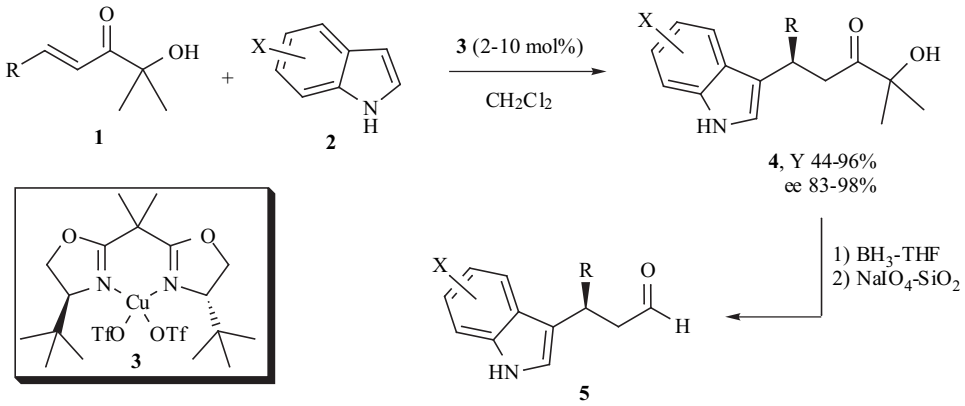


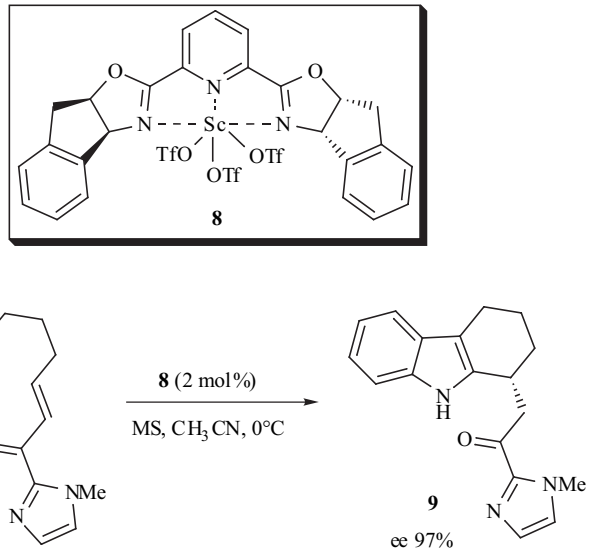
Scheme 1. Use of hydroxy enones as electrophiles in copper catalyzed enantioselective alkylation of indoles.

Excellent levels of stereocontrol (ee up to 99%) were recorded by adopting pyBox-Sc(OTf)$_3$ (**8**, 1-10 mol%) in combination with molecular sieves and CH_3CN in a variable range of temperature (-40°C → 0°C). The synthetic potential of the present procedure is well highlighted by an intramolecular version carried out on the acyclic precursor **7**. Under optimal conditions (**8**, 2 mol%, CH_3CN, 0°C) the cyclization worked smoothly leading to 1-substituted carbazole (**9**) in quantitative yield and 97% ee (Scheme **2**).

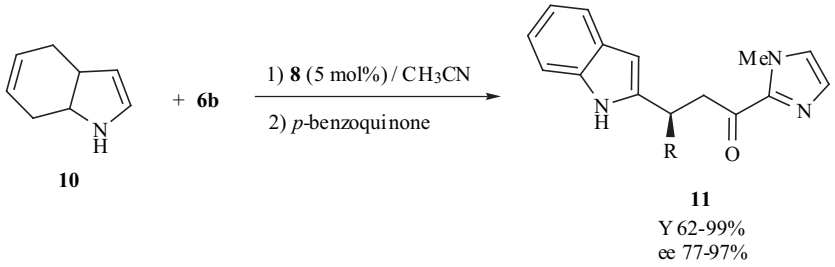
More recently, an extension of this study was presented, by addressing the alkylation of pyrroles. Interestingly, the use of 4,7-dihydroindole **10** as a heteroaromatic nucleophile opened access indirectly to the one-pot synthesis of indole derivatives **11** regioselectively alkylated in position 2 (yield: 62-99%, ee: 77-97%) [10]. In fact, it is known that the aromatization of 4,7-dihydroindoles occurred smoothly in the presence of *p*-benzoquinone (Scheme **3**) [11].

2.1.3 Nitroalkenes with Organic and Organometallic Catalysis

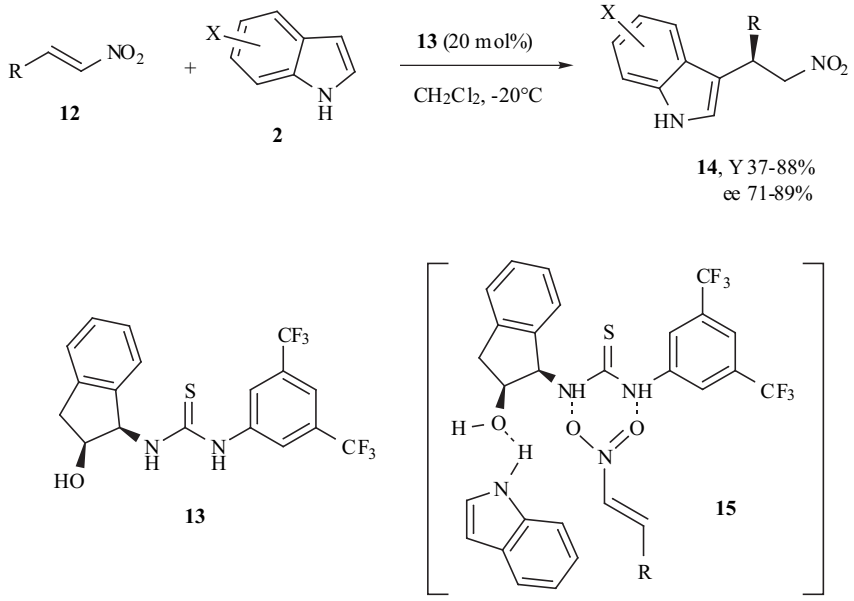
Nitroalkenes are flexible and attractive synthetic building blocks being the nitro moiety conveniently transformed into numerous molecular motifs [12]. The employment of such compounds as Michael acceptors in combination with indoles is highly desirable due to the large number of naturally occurring compounds containing the β-indolyl amine moiety (i.e. tryptamines, carbolines). Despite this interest, until 2006 only moderate levels of both reaction rates and stereoselection have been obtained in the presence of chiral organometallic catalysts probably due to the detrimental coordination of the



Scheme 2. Synthesis of enantiomerically pure carbazole **9** *via* intramolecular pyBox-Sc catalyzed FC.



Scheme 3. Stereocontrolled synthesis of 2-substituted indole **11**, *via* catalytic dihydroindole alkylation followed by one-pot aromatization.



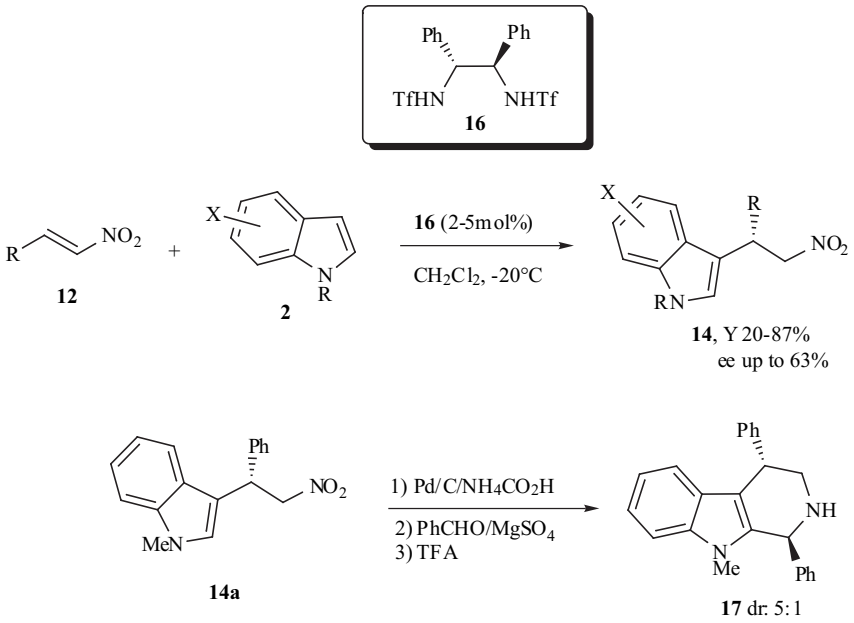
Scheme 4. Stereocontrolled addition of indoles to nitroalkenes mediated by thiourea **13** as the chiral catalyst.

metallo-center by the product and by the difficulties of catalaphoric centers to discriminate between the highly coordinating oxygen atoms of the nitro group [13].

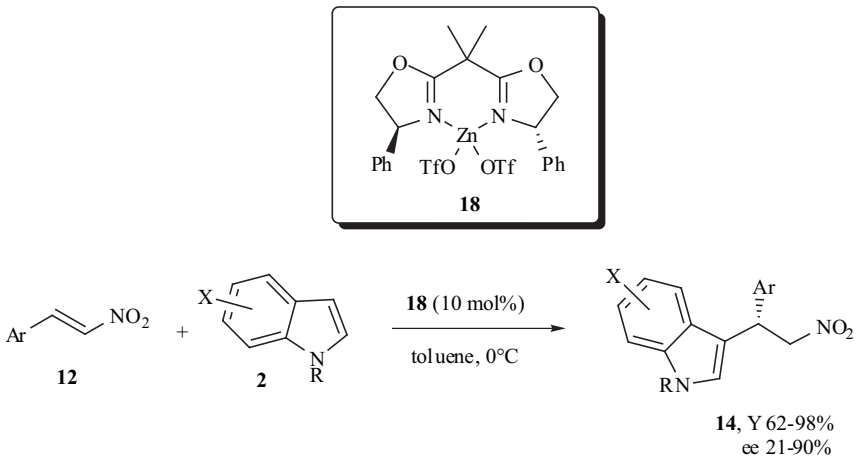
These drawbacks have been faced and partially have been overcome by Ricci and coworkers that elegantly described the use of the chiral thiourea **13** embedding DACH (1,2-diaminecyclohexane) as the chiral backbone. A double-hydrogen bonding-based catalysis is invoked to be operating in the present FC alkylation of indoles with nitroolefins [14]. The use of 20 mol% of catalyst smoothly promoted the 1,4-addition of variously functionalized indoles (hetero-aromatics bearing electron-poor substituents caused a significant drop in chemical as well as optical yield) to both aromatic and aliphatic *trans*-nitroalkanes (**12**) to give β-indolyl nitroalkenes **14** in good yield and ee up to 89% (Scheme **4**).

Insight into the stereodiscriminating substrate-catalyst interactions were obtained by comparative experiments carried out with tailored synthesized catalysts. Such a study prompted the authors to suggest a bi-functional acid/base action [15] of **13** with the advantage to simultaneously active both reaction partners (**15**).

Simultaneously, Jørgensen and coworkers proposed an alternative hydrogen-bonding based stereoselective process for the FC alkylation of indoles to nitroolefins [16]. In this case, *C*2-symmetry *bis*-sulfonamide **16**, derived by 1,2-diphenyl-ethylenediamine, promoted the Michael addition with moderate stereochemical outcomes (ee up to 63%) in the presence of *N*-alkylated indoles. Then, the potential of this catalytic approach was demonstrated by adopting **14a** for the synthesis of the corresponding polycyclic compound **17** (Pictet-Spengler



Scheme 5. Use of chiral bis-sulfonamide **16** as a hydrogen-bonding catalyst for FC alkylation of indoles.



Scheme 6. Box-Zn catalyzed addition of indoles to nitrostyrenes.

condensation [17]) in good diastereoisomeric ratio (5:1, Scheme **5**).

If copper-based catalysts represent the LAs of choice for Michael-type FC alkylations with α,β-unsaturated carbonylic compounds, chiral $Zn(OTf)_2$ complexes show to be prominent organometallic catalysts in conjugate additions of indoles to nitroalkenes [18]. In fact, Box-$Zn(OTf)_2$ complex **18** (10 mol%) positively promoted the addition of indoles to substituted nitro-styrenes [19] giving rise to **14** with moderate to high enantiomeric excesses (Scheme **6**).

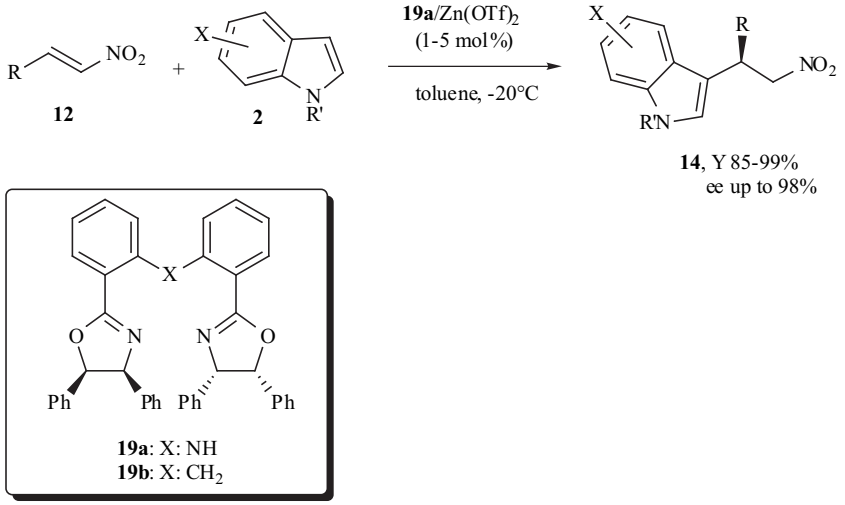
An improvement in terms of both chemical and optical outcomes was presented recently by Du and coworkers that replaced the $Box(Ph)_2$ ligand used in **18** with new bi-functional tridentate bis-oxazoline **19a** [20]. Here, synthetically useful enantiomeric excesses (up to 98%) were obtained with a variety of nitroalkenes bearing both aromatic and aliphatic substituents at the β-position. In the context of the present investigation, it should be emphasized that the catalyst loading was lowered to 1 mol% with less effects on the stereochemical course (Scheme **7**).

The bifunctional character of **19a** is proposed on the basis of comparative experiments with ligand **19b**, in which the bridging amino group is replaced by a methylene. The dramatically lower ee obtained with **19b** prompted the authors to suggest a simultaneous activation of indole and nitroalkene by NH and Zn centre, respectively.

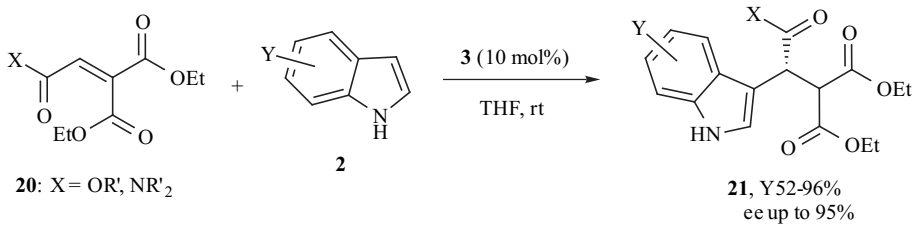
2.1.4 Ethenetricarboxylate with BoxCu(II) Catalysis

Among the *soft* electrophiles used in Michael addition, alkylidene and arylidene malonates are of pivotal importance and numerous stereocontrolled copper-promoted protocols have appeared over the last decade [21]. However, they generally suffer from significant restrictions mainly regarding the scope of substrate (only aryl or methyl substituted substrates were addressed). Yamazaki and coworker [22] recently updated these seminal papers by using a range of highly functionalized ethenetricarboxylates (**20**) that still offers the possibility of a two-site binding interaction to the metal with the vicinal ester moieties.

Again, the (*S,S*)-2,2'-isopropylidenebis-(4-*tert*-butyl-2-oxazoline)-$Cu(OTf)_2$ complex **3** showed highest catalytic activity in affording the desired indole-adducts **21** in moderate to good yields and ee up to 95% (Scheme **8**). Finally, computational studies carried out on a model **3**-**20** adduct allowed to rationalize the absolute stereochemistry obtained and to discuss the enantiodiscriminating event operating during the reaction course.



Scheme 7. Bifunctional tridentate Box ligand in zinc catalyzed addition of indoles to nitrostyrenes.



Scheme 8. Ethenetricarboxylate compounds (**20**) in asymmetric copper catalyzed alkylation of indoles.

2.1.5 Stereoselective Al and Al/In Catalyzed Intramolecular Indole Alkylation

In the field of catalytic alkylation of indoles, intramolecular processes play a central role opening direct access to a large number of polycyclic compounds. However, despite this interest, intramolecular processes remained very little explored than that intermolecular analogous with only few cases facing stereochemistry issues [23]. In fact, tedious and time-demanding synthetic pathways for the preparation of acyclic precursors are generally required.

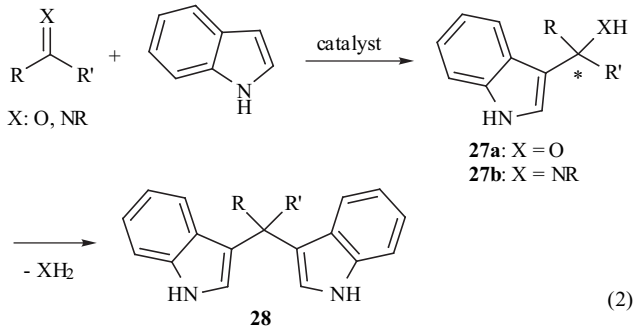
Therefore, key requisite in order to develop a powerful intramolecular enantioselective strategy is the design of flexible and rapid means to obtain the cyclization precursors that should be available in high and stereocontrolled manner (C-C double bond configuration) and on relatively large scales.

In this context, we recently revised the synthesis of a new class of configurationally pure 4-substituted tetrahydropyranyl indole precursors (**24**) by employing a cross-metathesis (CM) step [24] between indole-allyl species **22** and enones (i.e. MVK **23**) as the key step (Scheme **9**) [25]. Concerning the cyclization step, a survey of reaction parameters was performed by showing a [SalenAlCl]:$InBr_3$ 2:1 mixture, as the best catalytic system for the intramolecular regioselective FC reaction. In particular, the bimetallic regime furnished **26** in high yield and promising ee (up to 60%).

2.2 Addition of Indoles to C=X (X: O, N) Groups

3-Indolyl methanalcohols (**27a**) and 3-indolyl methanamines (**27b**) are pivotal molecular motifs embedded in numerous pharmacologically active compounds. A direct route to their preparation would involve the *C*-3 regioselective addition of indoles to carbonyl compounds (aldehydes/ketones/imines). To keep the reaction conditions as mild as possible (prevention of polymerizations) the use of additive in catalytic quantities showed effectiveness. This approach would open access to the highly desirable control of the reaction stereochemistry through the employment of chiral additives.

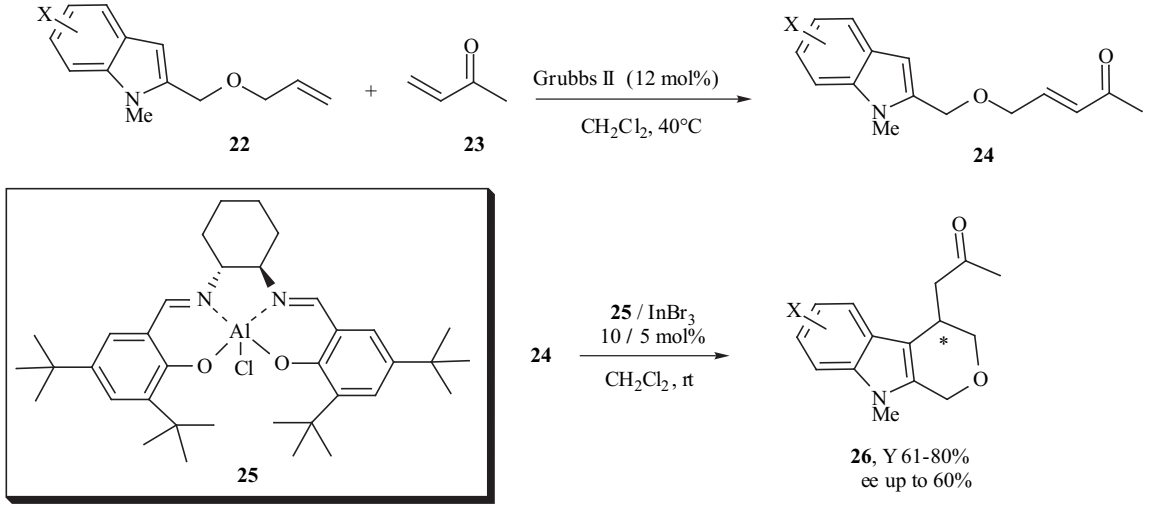
Main drawbacks in this synthetic route to **27** arose from the concomitant formation of *bis*(indolyl)-methane derivatives (**28**) that derive from a frequently spontaneous decomposition of the reaction products (Eq. **2**) [26].



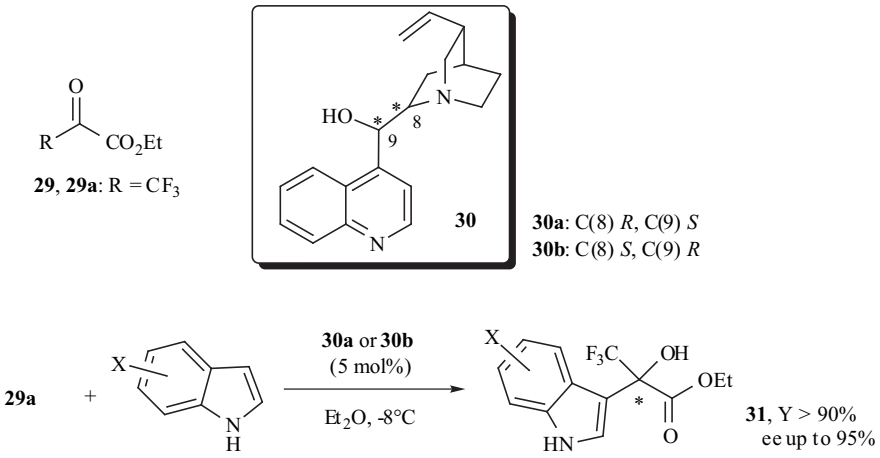
2.2.1 Stereoselective Organocatalyzed Addition of Indoles to Pyruvates

Among the plethora of carbonyl compounds, pyruvate **29** showed to be highly promising for indole-alkylation chemistry. Remarkable reactivity and suitability for chelating metallo-substrate interactions concur for its success in asymmetric transformations.

After pioneering papers, involving chiral organometallic complexes as catalysts [27], Török and Prakash reported on the



Scheme 9. Bimetallic stereoselective synthesis of tetrahydropyranyl indoles **26**.



Scheme 10. Alkaloid catalysis in the addition of indoles to trifluoropyruvate **29**.

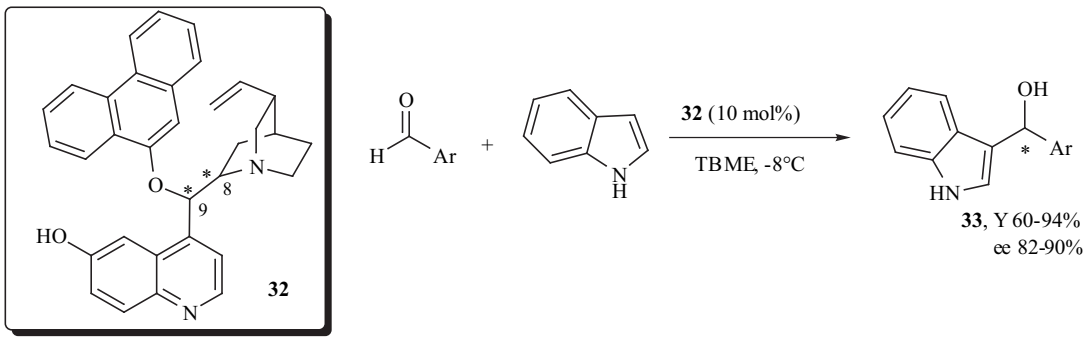
use of cinchona alkaloid derivatives (cinchonidine and cinchonine **30a**,**b**) for the enantioselective addition of indoles to trifluoropyruvate **29a** (Scheme **10**) [28]. The products of hydroalkylation **31** were obtained in excellent yield and high ee and, due to the presence of the trifluoromethane group, they represent useful building blocks for the synthesis of fluorinated drugs. Both experimental and analytic evidences prompted the authors to discuss the acid-base bifunctional role of the organocatalyst, with the possibility to bring both pyruvate and indole proximal in space.

2.2.2 Simple Aldehydes as Electrophiles in Organocatalyzed Enantioselective Alkylation of Indoles

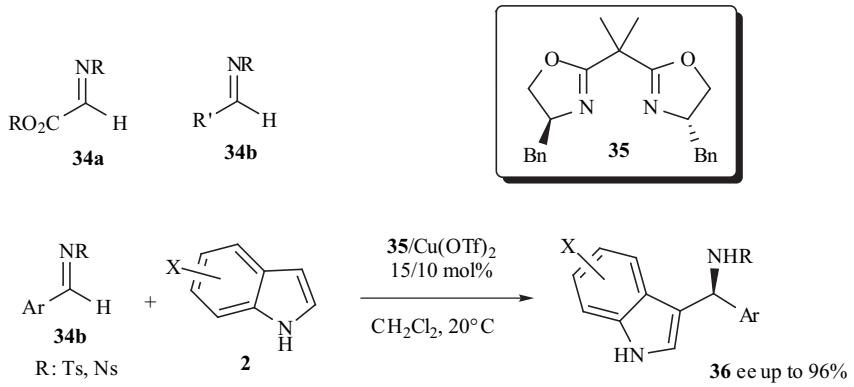
Despite the considerable substrate scope with respect to indole, the previous method lacks in generality for electrophile, being limited only to trifluoropyruvate. In this context, Deng and coworkers described new bi-functional cinchona alkaloids **32** able to promote the addition of indoles to a variety of α-ketoesters, and aldehydes [29]. Worthy to note are the results obtained with simple aromatic aldehydes that furnished the corresponding hydroalkylated compounds **33** in good yield (the amount of bisindolyl alkane ranged from 5 to 33%) and reasonable ee (82-90%, Scheme **11**).

2.2.3 Enantioselective Addition of Indoles to Imines

Also aza-carbonyls were deeply investigated as powerful electrophiles in the FC-alkylation of indoles and numerous attempts were carried out with highly reactive α-imino esters (**34a**) [30]. The use of simple aldimines **34b** was faced only recently, however, activated substrates (i.e. *N*Ts, *N*-Ns



Scheme 11. Bifunctional cinchona alkaloid catalyzed hydroalkylation of indoles with simple aldehydes.



Scheme 12. Box-copper catalyzed addition of indoles to *N*-sulfonyl arylimines.

derivatives) are necessary in order to obtain reasonable reaction rates.

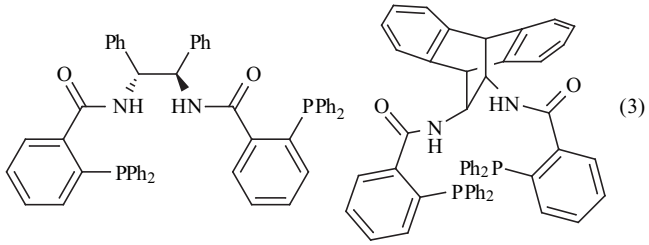
Here, Zhou and coworkers highlighted the role of cationic Box ligand **35**, in combination with $Cu(OTf)_2$ (10 mol%), in promoting the enantiocontrolled addition of indoles to *N*-sulfonyl arylaldimines [31]. Interestingly, under optimal conditions (CH_2Cl_2, 20°C) only traces of the corresponding *bis*(indolyl) methanamine (**28**) were formed (Scheme **12**). The sulfonyl group proved to be essential in chemical as well as stereochemical terms, in fact, by running the FC alkylation in the presence of *N*Ph imine the corresponding indolyl-methanamine was obtained in considerable lower yield and racemic form.

A general study concerning scope in electrophilic substrate was discussed by Deng and coworkers that highlighted the effectiveness of chiral organic catalysts (modified cinchona alkaloids, **37a**,**b**) in the enantioselective addition of indoles to *N*-tosyl aryl and alkylaldimines. The role of the residue at the C-9 position of the alkaloid scaffold showed to be remarkably crucial for the reaction course. In particular, the replacement of the hydroxyl group with a thiourea increased dramatically the turnover of the reaction with ee up to 97% (Scheme **13**) [32].

2.3 Allylic Alkylation

Nucleophilic allylic alkylation is a well established route to the preparation of poly-functionalized compounds [33]. The reaction usually involves late-transition metal complexes as catalysts (Pd, Ni, W, Mo) that originate reactive η^3-bound π-allylmetallo species through the oxidative addition to symmetric as well as asymmetric allyl unit. Here, the use of chiral ligands allows ato-complex intermediates with enantiotopic carbon atoms to be formed. Both *hard* and *soft* nucleophiles have been successfully employed in combination with numerous chiral organometallic species, making this process a benchmark transformation to test catalytic performances of new chiral transition metal complexes [34].

Very recently, our group and others described variants of the allylic alkylations in which indoles were employed as nucleophiles and adequate optimizations of the reaction conditions led powerful routes to the synthesis of highly functionalized indoles in regioselectively manner [35]. Enantioselective versions of these Pd-mediated alkylations were subsequently detailed by us and Trost in the presence of chiral palladium complexes based on Trost's ligands (diphenylphosphino benzoic acid: DPPBA, **38a** and **38b**, Eq. **3**) [36].

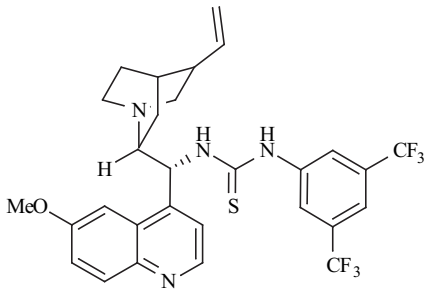


(3)

38a **38b**

2.3.1 Stereocontrolled Synthesis of THBC and THGC via Intramolecular Catalytic Alkylation of Indoles

Our approach consisted in the intramolecular alkylation of indoles *via* an allylic carbonate/acetate tethered to the heteroaromatic ring through an aminic side-chain (**39a**,**b**) [37]. The methodology proved efficiency for the synthesis of both



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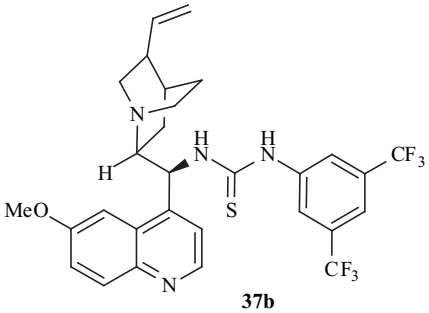

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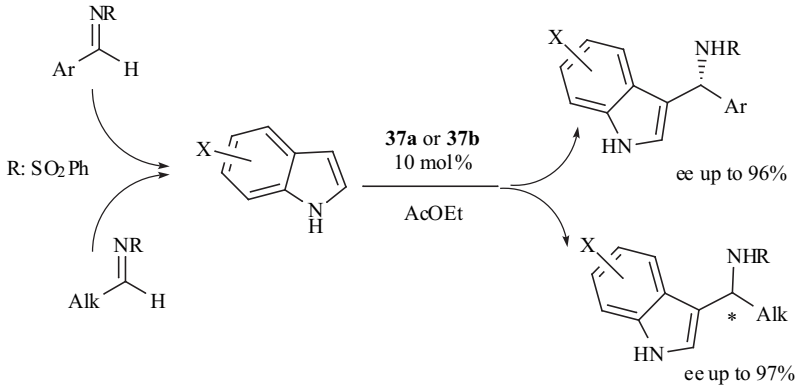
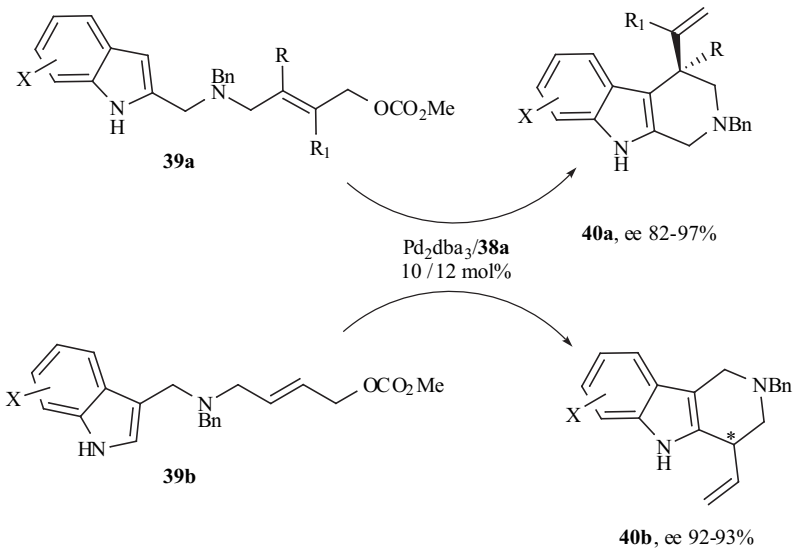
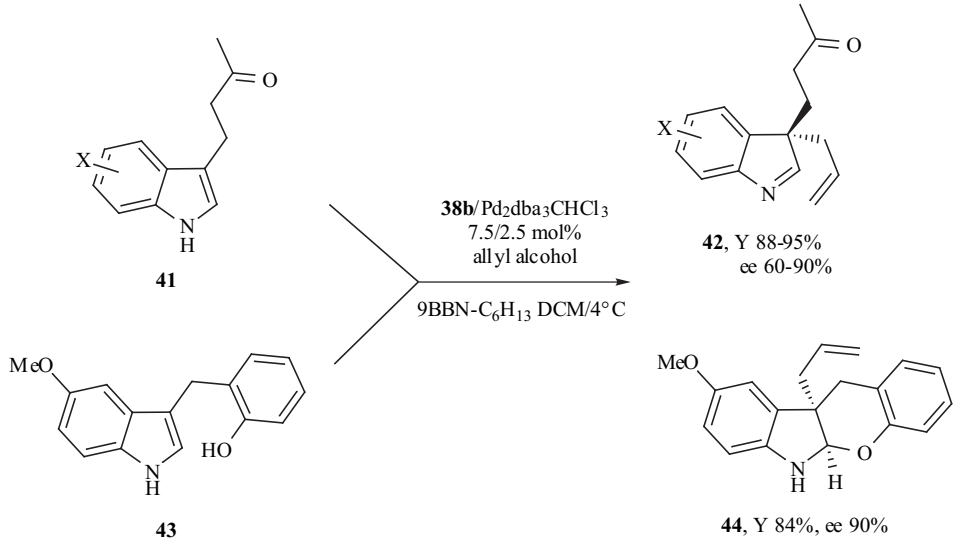


Scheme 13. Use of thiourea-cinchona alkaloids in the FC addition of indoles to aryl and alkyl imines.



Scheme 14. Intramolecular allylic alkylation of indoles as a means of chiral Pd(0) complexes.



Scheme 15. Regioselective allylic alkylation of 3-substituted indoles with trialkylboranes and allyl alcohol.

tetrahydro-β- (**40a**) and tetrahydro-γ–carbolines (**40b**). The absolute regiochemistry (only *C*-alkylation was recorded) was accompanied by high yields (up to 95%) and excellent ee (up to 97%). Worthy to note is the possibility to obtain also quarternary stereocenter starting from challenging trisubstituted C-C double bonds (Scheme **14**).

2.3.2 Catalytic Enantioselective Alkylation of 2-Substituted Indoles

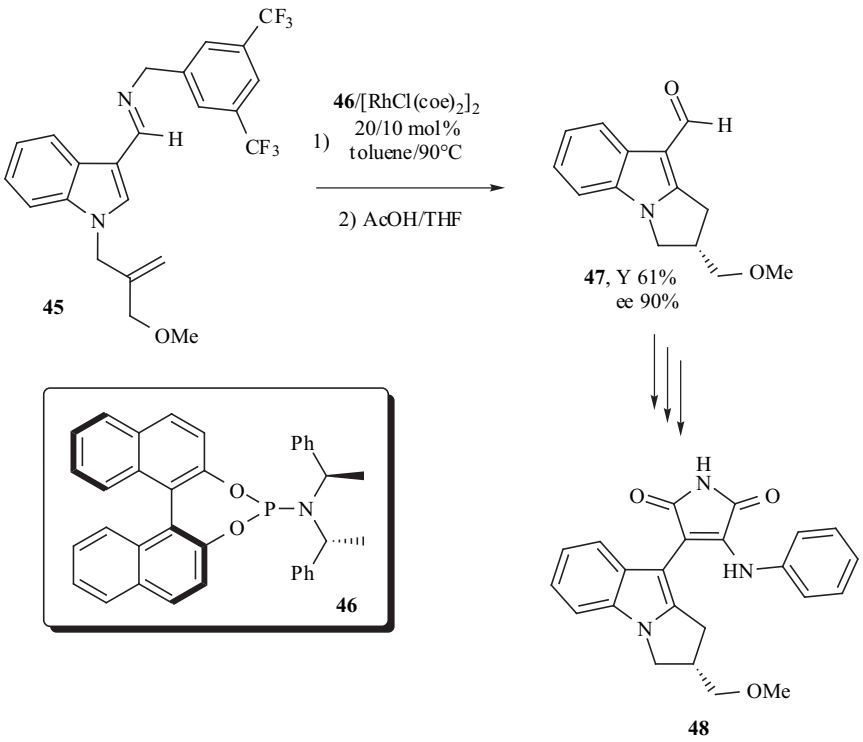
High chemoselectivity was guaranteed also by the intermolecular approach described by Trost and coworkers that uses allylic alcohol and sterically demanding trialkylboranes (best: 9-BBN-C_6H_{13}) for the stereoselective $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%) catalyzed allylation of 3-substituted indoles (**41**) [38]. This elegant investigation gave rise to polyfunctionalized indolenines **42** bearing enantiomerically enriched quarternary stereocenters in the C-3 position. When the starting indoles were substituted with nucleophilic pendants (i.e. **43**), the reaction product further evolved through an intramolecular condensation to give polycyclic compounds (i.e. **44**) in high ee (72-90%, Scheme **15**).

2.4 Indole Alkylation *via* Unactivated Alkenes

The selection of examples reported so far is characterized by a wide scope of substrates and generally requires mild reaction parameters. However, in these protocols, the electrophilic partner of the FC alkylation must be significantly reactive and frequently cost and time-consuming synthetic pathways are necessary for its preparation.

In this context, the use of unactivated C-C double bonds as alkylation agents would represent a powerful answer to this issues, due to their readily availability in large scale and low cost. Here, Csp-H, Csp2-H and Csp3-H bonds activations, through the use of late-transition metal complexes, have been longstanding goals for numerous research teams over the past few years, and highly performing catalytic systems have been reported working under reasonably mild conditions [39].

The stereoselective alkylation of indoles through catalytic C-H bond activations and involving unsubstituted alkenes [23] has been very recently discussed by Bergman and Ellman (Rh catalysis) and Widenhoefer (Pt catalysis) for the synthesis of important indole-containing polyfunctionalized compounds.



Scheme 16. Stereoselective Rh-mediated C-H activation for the synthesis of dihydropyrroloindole.

2.4.1 Stereocontrolled Imine-Directed Alkylation of Indoles via Rh-Catalyzed C-H Aromatic Activation

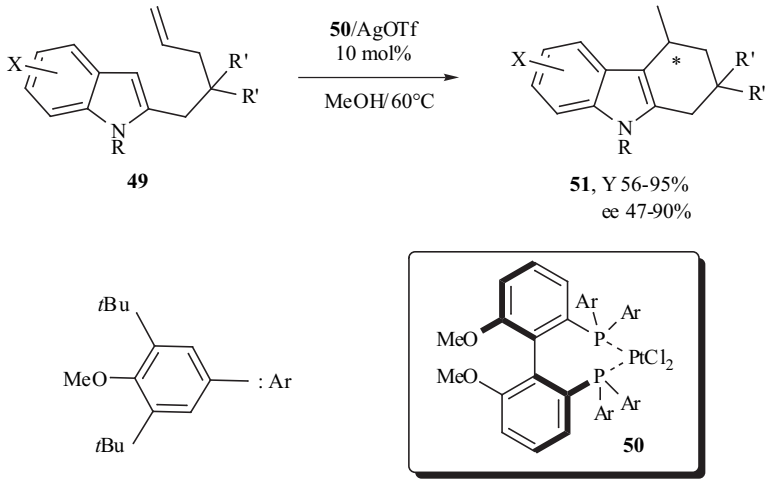
Aim of the Bergman, Ellman's paper is the synthesis of the biologically active dihydropyrroloindole **48** [40]. Pivotal step of the entire process was the enantioselective rhodium-catalyzed cyclization driven by effective DoM (directed orthometalation) groups such as aldoimines containing electronwithdrawing groups in the benzyl amine counterpart **45** [41]. Here, the use of chiral phosphoamidite **46** (20 mol%) and $[RhCl(coe)_2]_2$ (10 mol%) furnished the cyclized product **47** in 61% yield and 90% ee after hydrolysis (Scheme **16**).

2.4.2 Synthesis of Carbazoles via Hydroarylation of Indoles

Target oriented approach is also the investigation by Widenhoefer and coworkers that describe a hydroarylation of unactivated alkenes by means of chiral monocationic phosphine-Pt complex **50** (10 mol%) obtained *in situ via* exchanging reaction with AgOTf (1:1 ratio) [42]. A range of variously functionalized 1-methyl-2-(4-pentenyl)indoles **49** were cyclized to the corresponding tetrahydrocarbazoles **51** in stereocontrolled manner (ee up to 90%) and with a complete control over the regiochemistry of the process (*C*-alkylation product only, Scheme **17**).

CONCLUSIONS

The selection of papers presented in this Microreview clearly underlines the potentiality of stereoselective FC alkylations for the synthesis of enantiomerically enriched indole-based polyfunctionalized compounds that otherwise would be cumbersome to be prepared. High levels of regio- and stereoselection are generally accompanied by mild reaction



Scheme 17. Chiral cationic Pt catalysts for intramolecular alkylation of indoles *via* unactivated alkenes.

conditions. However, there are still several changes ahead and room for further development. For instance, universal catalysts working for ranges of different electrophiles in low loadings have not been forthcoming.

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