Recent Advances in the Catalytic Functionalization of “Electrophilic” Indoles

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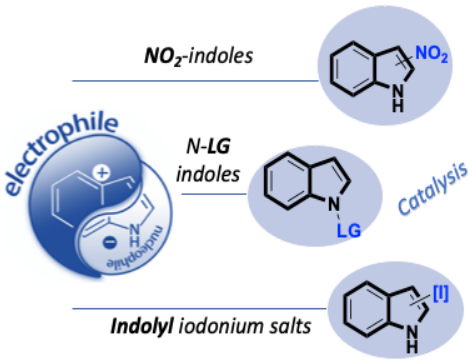
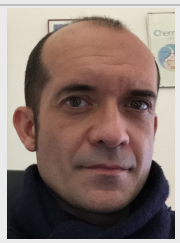
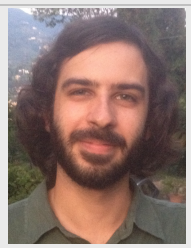


Marco Bandini got the PhD in Chemistry at the University of Bologna in the 2000. After some research periods abroad (University of Chapel Hill, USA and University of York, UK) he got a permanent position at the Alma Mater Studiorum – Università di Bologna where he is currently holding the position of full Professor in organic chemistry. Authors of more than 120 publications, his research interests deal with the development of catalytic systems in synthetic organic chemistry.



Alessandro Cerveri was born in Chiavari (GE), Italy in 1993. He obtained his BS in 2015 from Genova University under supervision of Professor Luca Banfi. Then he moved to Bologna University where he got the Master in Chemistry (2017) and entered the PhD programme under the supervision of Prof. Marco Bandini. His research interests deal with the development of catalytic dearomatization reactions and the use of CO_2 as a C-1 synthon in organic transformations.



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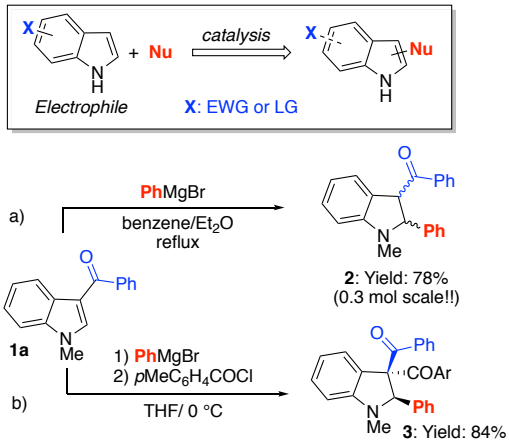
1. Introduction

Over the past few decades, the indole ring has become a common chemical benchmark to text the efficiency of catalytic systems for arene manipulations due to its innate nucleophilicity.[1] This prerogative paralleled the well consolidate role of indolyl cores as platforms to prepare densely functionalized polycyclic fused hetero-scaffolds.[2] Accordingly, a growing interest towards the realization of always more performing and sustainable protocols for the preparation[3] and site-selective manipulation[4] of the indole ring is on-going.

Currently, the field can be considered an established area of research, however the recent interests on the emerging "dark side" of the indole reactivity,[5] namely electrophilicity is expanding the current preparative portfolio of heterocyclic compounds, substatially. In this context, catalysis is opportunely considered the ultimate synthetic tool to boost the impact of the nucleophilic manipulation of indoles in organic synthesis.

The "hidden" electrophilic profile of indole faced a unique historical behavior. Upon the pioneering work by Szmuszkovicz in the early 60s, that involved the regioselective condensation of 3-acylindoles with PhMgBr (Figure 1a)[6a], the approach remained silent for almost 50 years until Liu and coworkers re-discovered the introduction of carboxylic-EWGs (*i.e.* 3-acetylindoles) in the heteroarene perimeter to "reverse" the indole reactivity. Here, the stereochemical profile of a three-component variant was controlled (Figure 1b).[6b]

Figure 1 The pioneering approach on the electrophilic functionalization of indoles (Szmuszkovicz, a) and recent developments (Liu, b).



However, across the years, the combination of EWGs (ketones, esters, NO_2) at C(2)- and C(3)-positions and leaving groups (*i.e.* OH, OMs, OTs, SO_2R) at the N(1)-site of the indole core was extensively investigated resulting in the development of several regioselective Michael type- as well as S_N2-type nucleophilic addition processes.[7]

The latter strategies enabled the realization of important synthetic shortcut towards the formation of C-C and C-X bonds via inter- as well as intramolecular processes. Additionally, final re-aromatization or dearomatization of the pyrrolyl core can occur opening unprecedented scenario to access 3D chemical space from the 2D ones.

These early contributions are really worthy to be mentioned since, as the reader will soon realize, most of the recent catalytic strategies for the nucleophilic manipulation of indoles took great advantages by these landmarks. Besides intrinsic differences of the inspiring reaction profiles, the aforementioned procedures are characterized by the use of stoichiometric amounts of additives (commonly basic species). The final "landing" to a desirable catalytic regime was purchased via extensive efforts and required many decades to be finally accomplished.

In the present article a collection of the more representative and recent methodologies for the realization of catalytic nucleophilic functionalization of indoles is proposed with the main purpose to emphasize working plans, scopes, limitations and mechanistic insights. We would like also to emphasize that remarkable progresses have been achieved recently in this field by means of stoichiometric additives[8] or electrochemical tools,[8f] however, these elegant variants of nucleophilic manipulations of indoles can be considered out of the scope of the present selection.

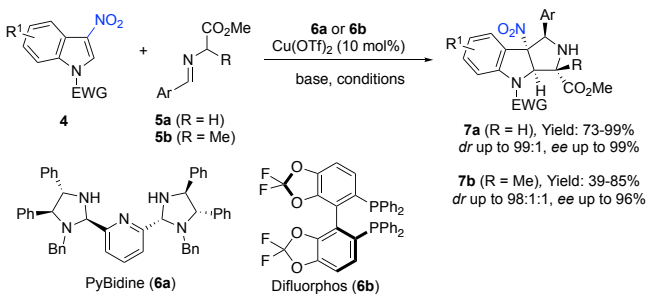
2. 3-Nitroindoles

2.1. Metal-catalyzed dearomatization reactions

The exploitation of the strong electron-withdrawing nitro-group to reverse the natural indole reactivity[9] is probably the most effectively used approach in catalytic and stereoselective methodologies. In particular, C(3)-NO_2-indoles **4** are commonly employed resulting into the construction of cyclic compounds through annulation processes. In many cases, an additional EWG group located at the N(1)-position is needed to guarantee satisfying reactivity of the indolyl core. The process offers several possibilities for the stereoselectivity fine-tuning such as LA or BA-type activation of the "NO_2"-indole group and electrophilic as well as nucleophilic activation of the reaction partner.

The field was pioneered by Arai and Awata in the 2014 that reported the first example of CADA (Catalytic Asymmetric DeAromatization reaction) with umpolung reactivity on the indole unit by means of the nitro-group at the C(3). The [3+2] cycloaddition was performed under Lewis Acid (LA) catalysis, using copper triflate to activate a glycine imino ester **5a**. High stereoselectivity (both diastereo and enantio) was obtained by adopting PyBidine **6** as the chiral ligand (Scheme 1).[10a] The protocol was subsequently extended to alanine analogous **5b** by Stanley and Gerten under similar approach. [10b]

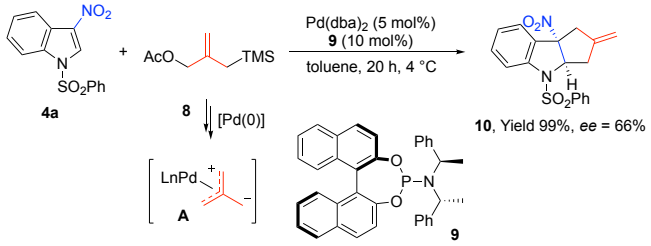
Scheme 1 Copper catalyzed enantioselective [3+2]-cycloadditions of imino-esters and NO_2-indoles.



In this case, the use of difluorphos-Cu(OTf)$_2$ (10 mol%) provided the corresponding [3+2]-cycloadducts **7b** in excellent chemical and stereochemical outcomes.

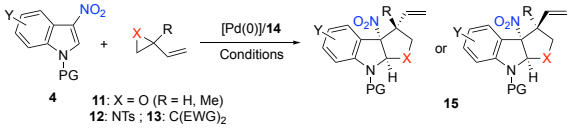
Almost concomitantly, another elegant dearomatization reaction of *N*-phenylsulfonyl-3-NO_2 indoles **4a** was reported by Trost and coworkers.[11] The [3+2]-type cycloaddition performed under phosphoramidite-[Pd(0)] activation of the allyl acetate **8** to give the trimethylenemethane dipolar intermediate **A**. The chiral ligand **9** provided the bicyclic nitro-indoline **10** with a moderate enantiomeric excess (66%, Scheme 2). Interestingly, although only a couple of examples of indole dearomatizations were reported, the strategy could be effectively applied to other electron-poor arenes, like 5-nitroquinolines.

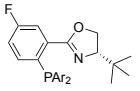
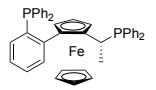
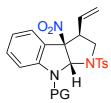
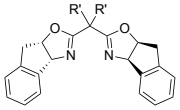
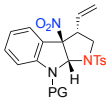
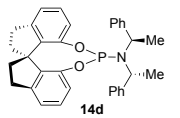
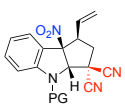
Scheme 2 Pd-catalyzed dearomatization of 3-NO_2-indoles with metallo-dipolar intermediate **A**.



The use of Pd-based ambipolar intermediates was subsequently adopted by using strained functionalized three-member ring precursors with achiral[12] as well as chiral-Pd catalysts. In particular, highly diastereo- as well as enantioselective [3+2]-cycloadditions were documented with vinylepoxides (**11**)[13a] vinylaziridines (**12**)[13b] and vinylcyclopropanes (**13**, Scheme 3).[13d]

Scheme 3 Use of strained-rings **11**-**13** in the enantioselective Pd-catalyzed dearomatization of NO_2-indoles.

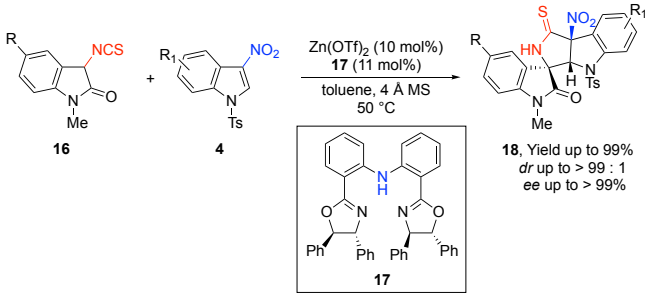


Ligand	Conditions	Product
 **14a** Ar = 3,5-$(CF_3)_2$-C_6H_3	 [Pd(0)] 5 mmol% rt, Toluene	 **15a** Yield up to 99% *dr* up to 95:5 *ee* up to 99%
 **14b**	 [Pd(0)] 2.5 mmol% - 60 °C, THF	 ***syn*-15b** Yield up to 99% *dr* up to 95:5 *ee* up to 96%
 **14c**: R' = *p*-*t*Bu-Bn	 [Pd(0)] 10 mmol% 25 °C, toluene	 ***anti*-15b** Yield up to 92% *dr* up to 99:1 *ee* up to 97%
 **14d**	 [Pd(0)] 2.5 mmol% - 15 °C, CH_3CN	 **15c** Yield up to 80% *dr* up to 88:12 *ee* up to 97%

Interestingly the different methodologies gave access to both the possible diastereoisomers, in accordance with the ligand and the conditions employed. Among them, the case-study proposed by You and Guo faced an interesting solvent-based diastereodivergency. In particular, when toluene was used as the solvent the *syn* adduct was mainly formed, while in acetonitrile, the *anti* isomer was predominant under invariant conditions. Dedicated spectroscopic NMR-based kinetic investigations shed light on the diastereodivergency.

A different approach for the metal-catalyzed enantioselective dearomatization of electron-poor indoles was proposed in the 2015 by Yuan and coworkers.[14] In this highly selective [3+2]-cyclization reaction a bis(oxazoline)-Zn$(OTf)_2$ complex promoted the activation of 3-isothiocyanato oxindoles **16**, enabling the selective condensation with **4** and delivering the densely functionalized polycyclic spirooxindoles **18**. From mechanistic experiments and nonlinear effect studies a double role of the catalyst was revealed. While the Zn(II) core acts as Lewis Acid for the activation of the nitro moiety, the linking NH group was proven fundamental to trigger the C(3)-attack to the oxindole (Scheme 4).

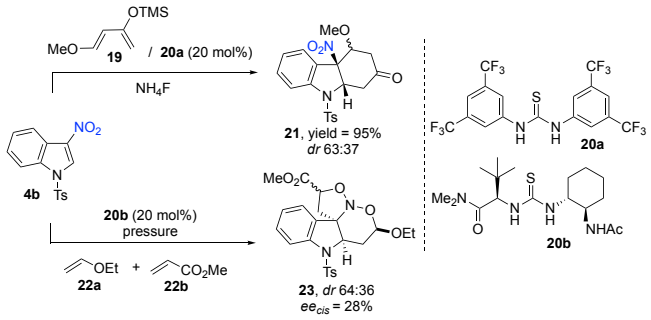
Scheme 4 Stereocontrolled synthesis of spirooxindoles **18** via Zn-catalyzed [3+2]-cycloaddition-type reaction with 3-isothiocyanato oxindoles.



2.2. Organo-catalyzed reactions

The use of 3-NO_2-indoles as hetero-dienes and dienophiles in [4+2]-cycloaddition reactions was initially described by thermal and pressure activations in the combination of π-systems.[15a,b] The addition of achiral Schreiner's thiourea **20a** (20 mol%) inspired Chataigner and coworkers to investigate the condensation of N(1)-sulfonyl-C(3)-NO_2-indole **4b** with Danishefsky diene **19** or vinylether **22a** in a [4+2]-cycloaddition process that yielded the corresponding indolines **21** and **23** in moderate diastereoselection (Scheme 5)[15c] Efforts towards the realization of an enantioselective variant with chiral thiourea **20b** were also highlighted in the paper but modest stereoselections were obtained (*ee* up to 28%).

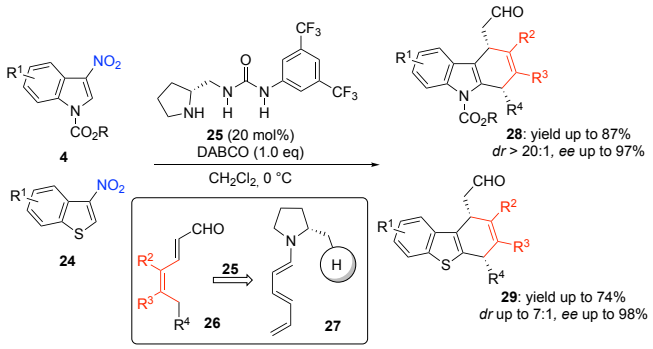
Scheme 5 Early studies on organocatalyzed Diels-Alder reactions with the electron-deficient indole **4b**.



The enantioselective [4+2]-cycloaddition between 3-nitroindoles and *in situ* formed chiral trienamine **27** was elegantly reported by Jørgensen and coworkers in the presence of proline-urea organocatalyst **25**.[16] From a mechanistic view point, the initial formation of the dearomatized polycyclic indoline led to a fast elimination of nitrous acid to deliver the final densely functionalized dihydrocarbazoles **28** (Scheme 6). The overall stereochemical profile of the protocol was attributed to the

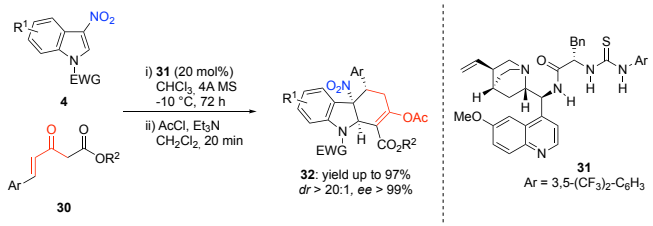
synergic action of the proline moiety (formation of chiral trienamine **27**) and to the thiourea group (hydrogen-bond activation of NO_2 group). The possibility to extend the substrate scope to 3-nitrobenzothiophenes **24** was also documented.

Scheme 6 Chiral trienamines as key intermediates in the cycloaddition process involving nitroindoles.



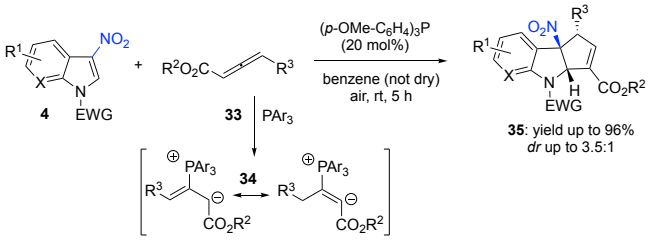
Subsequently a different enantioselective organocatalyzed [4+2]-dearomative cyclization was proposed by Yuan and coworkers by combining the Nazarov reagent **30** and 3-nitroindole **4** to form fully dearomatized hydrocarbazole skeletons **32**.[17] The use of a chincona-thiourea **31** proved to be decisive for the activation stereocontrol of the protocol exerting the classic dual-activation mode: H-bond acceptor (quinuclidine ring), H-donor (thiourea unit). The resulting product **32** was isolated by final acylation of the enol moiety with acetyl chloride (Scheme 7).

Scheme 7 Enantioselective organocatalyzed [4+2]-cycloaddition of C(3)-nitroindoles and Nazarov reagent **30**.



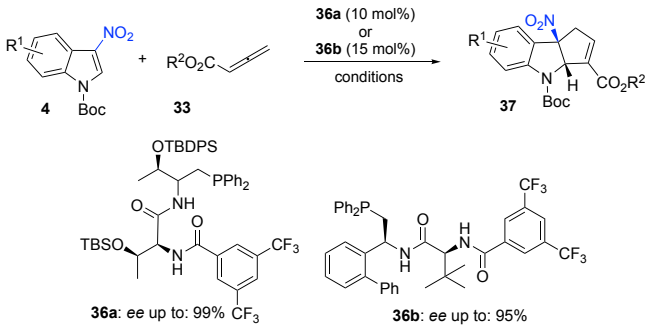
The organo-catalytic approach was also employed in the [3+2]-cycloaddition mode involving C(3)-nitroindole and α-allenylesters **33**.[18a] The employment of a nucleophilic catalyst (pMeOC$_6$H$_5$)$_3$P (10-20 mol%) enables the formation of dipolar intermediates **34** that matched the Michael acceptor reactivity of **4** (Scheme 8). The resulting dihydrocyclopenta[b]indoles **35** were isolated regiospecifically in high yields (up to 96%) and moderate diastereoselection. Full mapping of the reaction machinery via DFT calculations revealed a step-wise mechanism and provides insight for the diastereoselection recorded. Similar approach was also documented by De Paolis, Chataigner and coworkers with densely functionalized γ-substituted allenotes.[18b] The "rush" towards the phosphine catalyzed dearomatization of 3-NO_2-indoles with simple mono-substituted allenoates counts also the recent reports by Ye[18c] and Shi describing very similar chemical outcomes.[18d]

Scheme 8 Diastereoselective phosphine catalyzed [3+2]-cycloaddition of allenoates **33** and 3-NO_2-indoles.



Interestingly, almost simultaneously, the enantioselective variant of the afore described dearomatization process was documented by two teams with similar approaches. In particular, Zhang[19a] and Lu[19b] employed chiral phosphines carrying hydrogen-bond donor groups **36a** (10 mol%) and **36b** (15 mol%) capable of engaging both substrates in dual activation mode. The corresponding cycloadducts **37** were isolated in high yields and excellent enantioselectivity by using monosubstituted allenoates (Scheme 9).

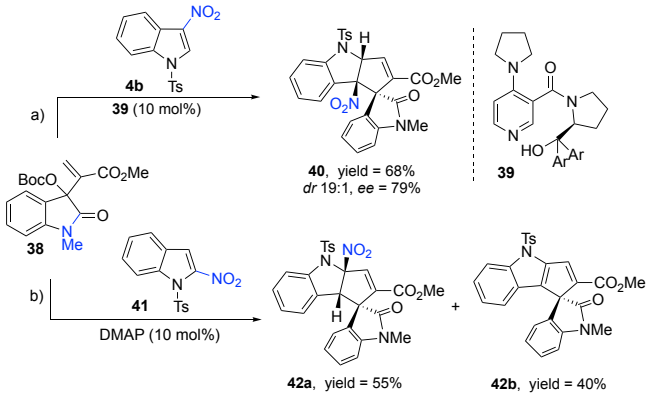
Scheme 9 Enantioselective phosphine catalyzed [3+2]-cycloaddition of allenoates and 3-NO_2-indoles.



In this context, a [3+2]-cycloaddition-type enantioselective dearomatization of 3-NO_2-indoles with thio-Michael acceptor was elegantly described very recently by Yuan and colleagues in the presence of chiral thiourea catalyst.[20]

Finally, the organocatalyzed asymmetric Morita-Baylis-Hillman (MBH) type condensation of *N*Ts-3-NO_2-indole and readily available MBH carbonate **38** was realized by Chen and coworkers.[21] The employment of chiral DMAP-type organocatalyst **39** yielded the spiro-compound **40** in 68% yield and 79% *ee* (Scheme 10a). Switched regioselectivity and partial re-aromatization (*i.e.* loss of HNO_2) were observed when the *N*Ts-2NO_2-indole **41** was subjected to analogous condensation with **38** in the presence of DMAP (10 mol%, Scheme 10b).

Scheme 10 Organocatalyzed condensation of C(3)- and C(2)-NO_2-indoles with MBH acceptor **38**.



3. Indolyl iodonium salts

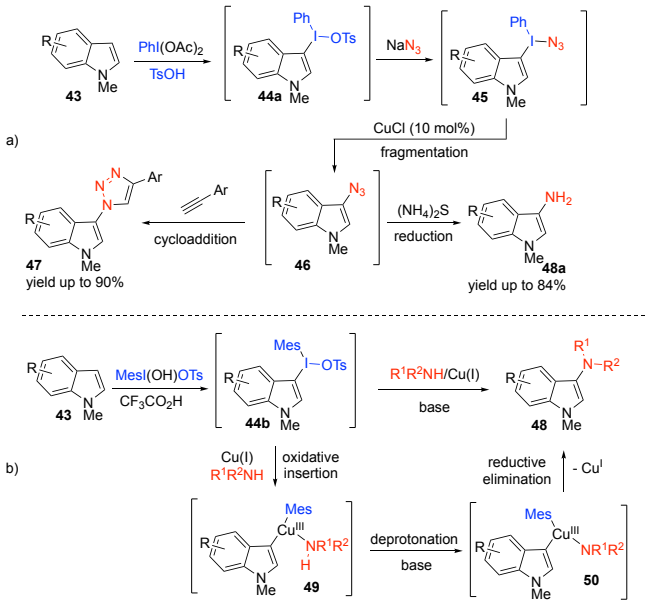
The introduction of hypervalent iodine groups into organic compounds is known to generate *umpolung* of the natural reactivity of the parent organic species.[22] However, despite the undoubted synthetic valence, it took quite a while before readily accessible and substantially stable indolyl-iodonium salts were achieved via the introduction of EWGs at the N(1)- or C(2)-position.[23]

Concomitantly, the electrophilic profile of the heterocyclic core was investigated in different organic transformations mostly carried out under metal catalysis.

In this direction, Suna and coworkers documented on the undirect copper (CuCl) catalyzed C-H azidation of *N*Me-indoles **43** via regioselective fragmentation of the iodonium azide intermediates **45**.[24a] The resulting azido-indoles **46** were successfully employed in the one-pot preparation of C(3)-triazoles **47** in moderate to good yields (up to 90%, Scheme 11a). Additionally, the synthetic utility of azides **46** was also proved in the synthesis of C(3)-NH_2-indoles **48** via reductive azidation-reduction sequence (yield up to 84%).

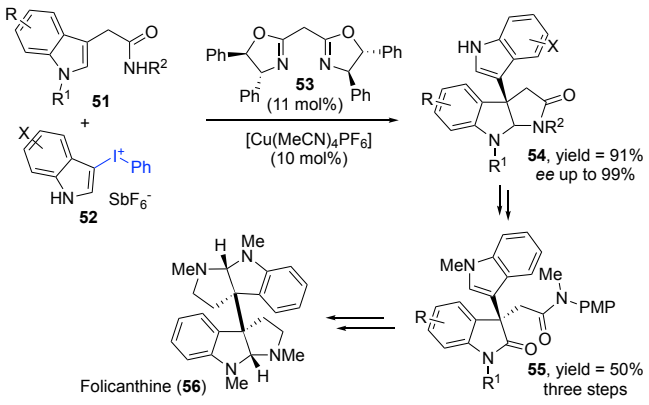
Shortly after, the same team reported on the C(3)-nucleophilic amination of electron-rich heteroarenes (*i.e.* indoles and pyrroles) via similar methodology, the initial formation of unsymmetrical iodanes (**44b**) carrying a mesitylene ring and subsequent cross-coupling reaction with aliphatic as well as aromatic amines was realized under Cu(I)- or Cu(II)-catalysis.[23b] Mild reaction conditions, wide functional group tolerance and high regioselectivity characterized the methodology that was proposed to proceed via classic oxidative insertion of the copper into the C(3)-I bond (**49**), N-H deprotonation (**50**) and final reductive elimination (Scheme 11b).

Scheme 11 Copper-catalyzed nucleophilic manipulation (*i.e.* amination, azidation) of *in situ* prepared C(3)-indolyl iodonium derivatives.



A significant advancement in the field was brought by You and coworkers with the synthesis of 3-indolylphenyliodonium salts **52** and their consequent employment as electrophilic arylating agents in the enantioselective synthesis of pyrroloindolines **54**.[25] The combination of chiral bis-oxazoline ligand **53** (11 mol%) and $[Cu(CH_3CN)_4]PF_6$ (10 mol%) trigger the cascade dearomative protocol of C(3)-indole acetamides **51** in high yield and *ee* up to 99% (Scheme 12). The synthetic utility of the methodology was unambiguously proved by preparing the advanced intermediate **55** for the synthesis of folicanthine **56**.

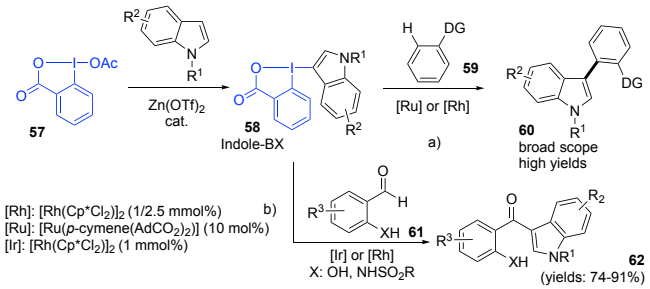
Scheme 12 Enantioselective Cu(I)-catalyzed dearomatization of indole acetamides with electrophilic trapping 3-indolylphenyliodonium salts **52**.



Finally, efforts towards the realization of bench-stable hypervalent iodine-indole reagents **58**, featuring *umpolung* reactivity, were finally carried out by Waser and colleagues.[26] In particular, the authors proposed a straightforward synthesis of C(3)-indole carrying benziodoxole (BX) unit that proved to be stable up to 150 °C and find remarkable applications in the Rh or Ru-catalyzed arylation of variously substituted arenes (**59**). Excellent regioselectivity was achieved by means of directing group strategy (Scheme 13a). The same team extended this methodology also to the selective Rh or Ir-catalyzed C-H activation of formyl group of *ortho*-substituted benzaldehydes and consequent heteroarylation with indole-BX reagents **58**.[26d] The methodology enabled the

direct preparation of acylated indoles **62** in high yields that are not trivially achievable via classic Friedel-Crafts acylation reactions (Scheme 13b).

Scheme 13 a) Synthesis of thermally stable indole-BX adducts **58** and their use on metal (Ru or Rh) catalyzed arylation reaction via C-H activation; b) C-H activation of aromatic aldehydes with indole-BX **58** to give site-selective acylated indoles **62**.

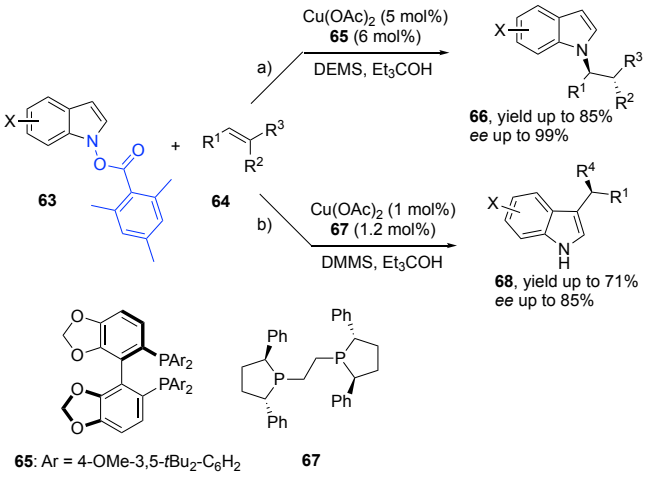


4. *N*-Leaving group indoles

Indoles carrying *N*-OX (X: H, Me, Bz, Ts) units were synthetized by Somei and coworkers nearly two decades ago.[27] Later on, their efficiency on the N(1)-, C(2)- and C(3)-nucleophilic trappings was also investigated extensively by means of several reagents.[28] However, catalytic and stereoselective methodologies were lacking up to recently.

In particular, Buchwald and coworkers have recently documented on the copper catalyzed activation of *N*-benzoyloxy-indoles **63** and subsequent trapping with *in-situ* generated chiral alkyl-copper reagents (L-Cu(OAc)$_2$/Silane/alkene).[29] Regiodivergence towards N(1)- or C(3)-functionalization was effectively recorded via selection of chiral organo ligands. In particular, while (*R*)-DTBM-SEGPHOS **65** (6 mol%) and Cu(OAc)$_2$ (5 mol%) provided the *N*-alkylated compound **66** in excellent yield, *r.r.* (regioselective ratio) and enantiomeric excess (Scheme 14a), the employment of (*S,S*)-Ph-BPE **67** (1.2 mol%) and Cu(OAC)$_2$ (1 mol%) delivered the C(3)-alkylated analogous **68** in moderate to high *r.r.* and good enantiomeric excess (ee up to 85%, Scheme 14b). Both reaction profiles were computed (DFT analysis) via initial stereoselective Cu-H addition the olefin **64** delivering an enantioenriched alkylcopper reagent that could insert oxidatively at the N(1)- or C(3)-position of **63**. Final stereoselective reductive elimination would provide the desired N- or C-alkylated products. Site-specific steric contacts induced by chiral ligands **65** and **67** have been accounted to determine the final regio-outcome.

Scheme 14 Enantioselective copper catalyzed alkylation of *N*-benzoyloxy-indoles **63** (DEMS: diethoxymethylsilane, DMMS: dimethoxymethylsilane).



5. Conclusions and Perspectives

The combination of catalytic tools for the nucleophilic manipulation of privileged indole cores is gaining growing credit within the synthetic organic chemistry scenario. In this direction, pioneering works based on stoichiometric protocols have been elegantly revisited resulting in the creation of chemical diversity in heterocyclic chemistry. The state-of-the-art involves mainly covalently and properly functionalized indole cores (*i.e.* electron-withdrawing groups, leaving groups) to be subjected to organic manipulations and this aspect, time-by-time could also represent a limitation of the approach. Therefore, due to the undoubted importance in terms of chemical perspective related to the present synthetic methodology, important developments are foreseen in the near future, addressing always key aspects such as effectiveness and selectivity.

In conclusion, the realization of *umploung* reactivity of *unfunctionalized* indolyl cores will continue to inspire synthetic chemists as a desirable synthetic challenge not fully realized yet.

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