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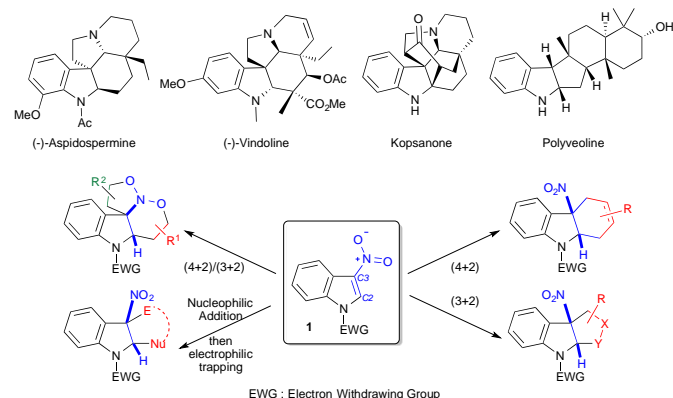
Reactivity of 3-nitroindoles with electron-rich species

Batoul Rkein,^a Antoine Bigot,^a Léo Birbaum,^a Maxime Manneveau,^a Michaël De Paolis,^a Julien Legros^a and Isabelle Chataigner^{a,b*}

The indol(in)e building block is one of the “privileged-structures” for the pharmaceutical industry since this fragment plays a central role in drug discovery. While the electron-rich character of the indole motif has been investigated for decades, exploiting the electrophilic reactivity of 3-nitroindole derivatives has recently been put at the heart of a wide range of new, albeit challenging, chemical reactions. In particular, dearomatization processes have considerably enriched the scope of C2=C3 functionalizations of these scaffolds. This feature article showcases this remarkable electrophilic reactivity of 3-nitroindoles with electron-rich species and highlights their value to generate diversely substituted indol(in)es. This compilation underlines how these heteroaromatic templates have gradually become model substrates for electron-poor aromatic compounds in dearomatization strategies.

1. Introduction

Indoles and their derivatives are important scaffolds in organic chemistry.¹ Notably, the indoline motif has found major applications as biologically relevant compound for instance, in the indole alkaloids family with aspidospermine or vindoline molecules as salient examples (Scheme 1). These patterns are also found in useful ligands and organocatalysts. For many years, indole dearomatization strategies have led to elegant alkaloids syntheses mainly by taking advantage of the well-recognized C3-nucleophilicity of this electron-rich heterocycle.² Complementarily, indoles substituted by electron-withdrawing groups, in particular 3-nitroindole derivatives **1**, have been reported to exhibit an unexpectedly remarkable reactivity toward different electron-rich species, particularly in cycloaddition or annulation reactions.³ This has led to the expedient synthesis of functionalized indolines, which often retain a tetrasubstituted centre at the *cis* 5-membered cycle junction. The C2=C3 double bond of nitroindoles can indeed behave either as a dienophile, a dipolarophile or a Michael acceptor (Scheme 1). Complementarily, the C2=C3-N=O system of 3-nitroindoles has been shown to exhibit a heterodienic character. Herein we present an overview of these reactivities of 3-nitroindoles towards different electron-rich species, mainly in (formal) cycloaddition reactions, including catalytic and stoichiometric methodologies. Reductive transformations of 3-nitroindoles for the generation of 3-aminoindole derivatives, are not discussed here.



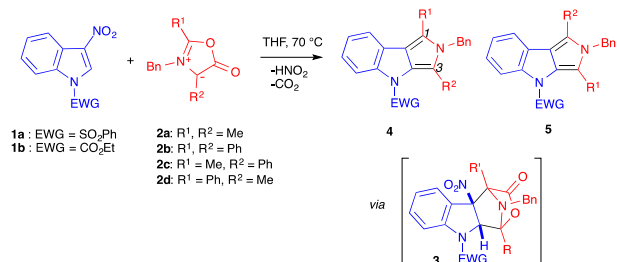
Scheme 1: Selected indoline containing compounds and general reactivity of 3-nitroindoles **1** with electron-rich species

2. (3+2) (Formal) cycloadditions

21. With azomethine ylides and related dipoles

(3+2) Cycloaddition reactions involving electron-poor indoles were first reported by Gribble *et al.*, in 1998, in the presence of mesoionic münchnones (1,3-oxazolium-5-olates) **2a-b**, bearing the same substituents in position 2 and 4. The reactive species were generated *in situ*, using the appropriate *N*-acylamino acid derivative in the presence of *N,N'*-diisopropylcarbodiimide (DIPC) as dehydrating agent. These electron-rich 1,3-dipoles were thus reacted with 3-nitroindoles **1**, protected/activated as *N*-carbamates or -sulfonamides, in refluxing THF. At this temperature, the (3+2) cycloadditions could be achieved and the bridged tetracyclic cycloadduct intermediate **3** instantaneously lost carbon dioxide and nitrous acid to form the re-aromatized pyrrolo[3,4-*b*]indoles **4**, isolated in moderate to good yields (Table 1, entries 1-4).⁴

Table 1. Reactions of 3-nitroindoles with mesoionic münchnones



Entr y	EWG	R ¹	R ²	4/5 ratio	Yield (%) ^a
1	SO ₂ Ph	Me	Me	-	67
2	SO ₂ Ph	Ph	Ph	-	65
3	CO ₂ Et	Me	Me	-	39
4	CO ₂ Et	Ph	Ph	-	60
5	SO ₂ Ph	Me	Ph	≥ 6:94	74
6	SO ₂ Ph	Ph	Me	70:30 to 90:10	76
7	CO ₂ Et	Me	Ph	5:95 to 0:100	65
8	CO ₂ Et	Ph	Me	50:50 to 60:40	89

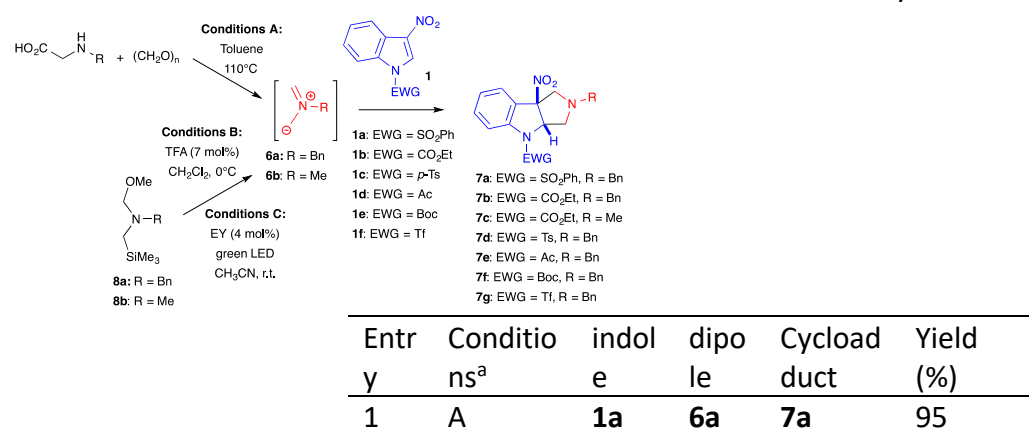
a: overall yield

Two years later, the same group used unsymmetrical münchnones **2c-d** in the same transformation (Table 1, entries 5-8).⁵ Surprisingly, the regioselectivity displayed in the formation of the dihydropyrrolo[3,4-*b*]indoles **4** and/or **5** did not systematically follow the Frontier Molecular Orbital (FMO) theory rules. The major or exclusive product was the one where the phenyl group is in position 1 of the isolated dihydropyrrolo[3,4-*b*]indole. Although the exact reasons for this regioselectivity were not quite clear, the authors proposed that either favourable π -interactions between the indole nitro group and the phenyl ring of the münchnone in the transition state could induce the observed regioselectivity, or that it may be a consequence of a highly asynchronous transition state where bond making between

the methylated carbon atom of the münchnone and the C2 of the nitroindole precedes bond making involving the phenyl substituted carbon atom of the münchnone, for steric reasons. Noteworthy, the indolic nitrogen atom has to bear an electron-withdrawing group for the reaction to proceed, as *N*-methyl-3-nitroindole was completely recovered after 24 h of reflux in the presence of **2d**. This requirement will be found in many other transformations involving 3-nitroindoles as electrophilic species.

In 2007, Gribble and coll. described non-stabilized azomethine ylides as suitable 1,3-dipoles for the (3+2) cycloaddition of 3-nitroindoles.⁶ Azomethine ylides **6** were classically generated *in situ* from the corresponding α -amino acids and paraformaldehyde in refluxing toluene. In this case, treatment of 3-nitroindoles **1a-b** with an excess of dipole precursor cleanly afforded the dearomatized hexahydropyrrolo[3,4-*b*]indoles **7a-c**, in good to excellent yields, without the loss of nitrous acid (Table 2, entries 1-3). 2-Nitroindoles proved also reactive toward the same dipole in these conditions. In contrast however, attempting the cycloaddition with 1,2-bis(phenylsulfonyl)indole failed, underlying the importance of the nitro group for this transformation. In 2011, our group revisited these (3+2) dearomative cycloadditions with the same non-stabilized azomethine ylide **6a**, generated this time from hemiaminal **8a** at 0 °C under TFA catalysis.⁷ These conditions were compatible with different nitroarenes, including nitrobenzenes and were applied to 3-nitroindoles to deliver the corresponding dearomatized cycloadduct in high yields (Table 2, entries 4-7).⁸ The lability of some protecting groups such as *tert*-butoxycarbonyl (Boc) or trifluorosulfonyl (Tf) limited their use in this case but these milder thermal conditions allowed to significantly decrease the dipole precursor quantity from 5 to 1.2 equiv. Noteworthy, this (3+2) cycloaddition with azomethine ylides generated in acidic conditions not only applies to 3-nitroindoles but could be extended to indoles bearing keto, ester, or cyano groups in position 3.^{8,9} More recently, Lequeux and coll. developed a photocatalyzed reaction for the formation of azomethine ylide **6a**, at room temperature, under non-acidic conditions.¹⁰ To this end, they used Eosin Y (EY), an organic dye, to decompose hemiaminal **8a** and generate the dipole under green light irradiation. Although the article focuses mainly on the preparation of fluorinated pyrrolidines, the authors included one example of a (3+2) dearomative cycloaddition with *N*-tosyl-3-nitroindole **1c**, which showed excellent conversion of the heteroaromatic substrate under these photocatalyzed conditions (Table 2, entry 8).

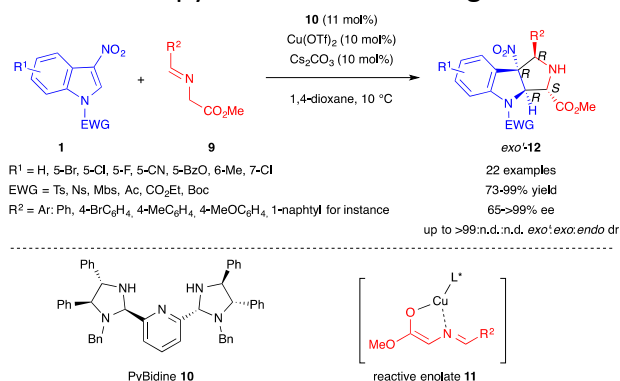
Table 2: Reactions of 3-nitroindoles with non stabilized azomethine ylides **6**



2	A	1b	6a	7b	96
3	A	1b	6b	7c	69
4	B	1c	6a	7d	85
5	B	1d	6a	7e	86
6	B	1e	6a	7f	59
7	B	1f	6a	7g	14
8	C	1c	6a	7d	92

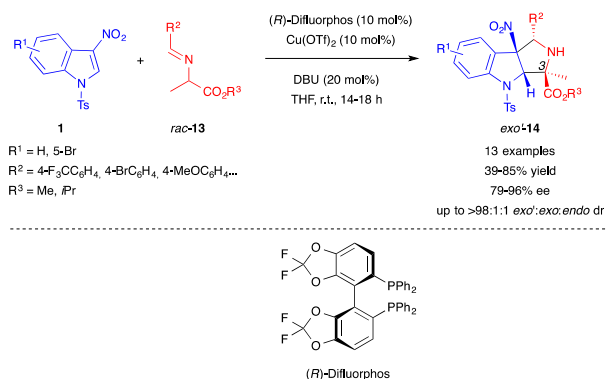
a: Conditions A: 5 equiv aminoacid, 12 equiv paraformaldehyde in toluene at 110°C. Conditions B: 1.2 to 2 equiv **8a**, TFA (7 mol%) in CH₂Cl₂, 0 °C to r.t.. Conditions C: 2 equiv **8a**, eosin Y disodium salt (4 mol %) with a 5 W green LED in CH₃CN at r.t..

In 2014, Arai and coll. reported the first example of an enantioselective (3+2) dearomative formal cycloaddition involving 3-nitroindoles **1** (Scheme 2).¹¹ The authors used glycine-derived imino esters **9** in the presence Cs₂CO₃ as base and Cu(OTf)₂ associated to the chiral PyBidine ligand **10** as catalyst to form the reactive chiral enolate **11** acting as a surrogate of a stabilized azomethine ylide dipole. The proposed mechanism involves a stepwise transformation, *via* two *anti*-selective Michael/Mannich reactions. The PyBidine-Cu(OTf)₂ chiral complex would first drive the *anti*-attack on the 3-nitroindole. After C-N single bond rotation, the least sterically hindered nitronate intermediate would cyclize, leading to the formation of pyrroloindolines **12** in good to excellent yields, with nearly perfect *exo'*-selectivity.



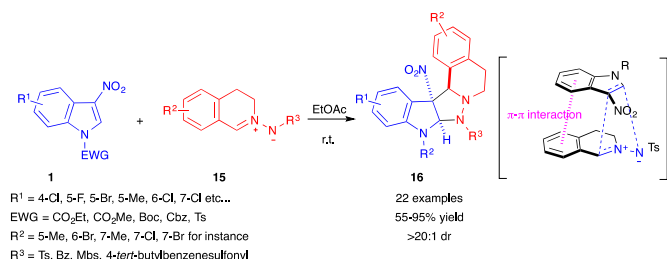
Scheme 2: Enantioselective (3+2) formal cycloaddition of 3-nitroindoles with glycine-derived iminoesters

Two years later, Gerten and Stanley extended this kind of reactivity to enolates derived from alanine imino esters **13**, generating a cycloadduct bearing a quaternary center at position 3 of the pyrrolidinoindoline **14** (Scheme 3).¹² The authors used a catalytic system based on Cu(OTf)₂ and bisphosphine ligand (*R*)-difluorophos to obtain good diastereo- and enantio-selectivity. They also demonstrated the existence of a competitive non-catalyzed *endo*-selective reaction, but showed that the copper complex also catalyzed the epimerization of the *endo*-**14** cycloadduct to the *exo'*-**14** one.



Scheme 3: Enantioselective (3+2) formal cycloaddition of 3-nitroindoles with alanine-derived iminoesters **13**.

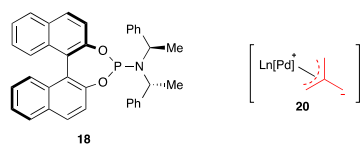
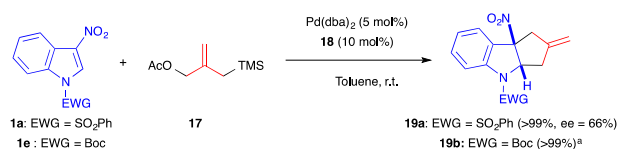
In 2017, Wang and coll. reported the reactivity of 3-nitroindoles **1** as dipolarophiles toward a different kind of nucleophilic 1,3-dipole, cyclic azomethine imines **15**, in a catalyst-free transformation.¹³ The reaction proceeded smoothly in most organic solvents, ethyl acetate giving the best results to afford pyrazolidinic cycloadducts **16** in a diastereoselective fashion, with a diastereomeric ratio above 20:1 in all the reported examples (Scheme 4). According to the authors, this selectivity would come from the favourable π - π interaction between the 6-membered aromatic rings of the indole and the azomethine imine.



Scheme 4: (3+2) Dearomative cycloaddition of 3-nitroindoles **1** with cyclic azomethine imines **15**

22. Dipoles generated under palladium or copper catalysis

Different types of nucleophilic 1,3-dipoles or surrogates can be formed under transition metal catalysis, such as palladium. In 2014, Trost *et al.* first used the palladium-catalyzed trimethylenemethane (TMM) cycloaddition methodology¹⁴ to explore the dearomatization of nitroarenes. By using TMM precursor **17**, Pd(dba)₂ and the bisdiamidophosphite ligand **18**, the authors were able to quantitatively dearomatize diverse nitroarenes, including nitroindoles.¹⁵ This process was the first in which an all-carbon 1,3-dipole generates methylidenecyclopentane containing structures in such dearomatizing (3+2) formal cycloadditions. Applied to phenylsulfonyl- and Boc-protected 3-nitroindoles, in the racemic version of the reaction, performed in the presence of the racemic ligand **18**, the corresponding cycloadducts **19** were obtained in quantitative yields (Scheme 5). With the chiral ligand, a 66% ee was obtained. A stepwise pathway is suggested for this transformation. The TMM dipole **20**, generated *in situ*, would add to the C2 electrophilic position of the nitroindole. Then, in the second step of this formal cycloaddition process, the zwitterionic nitronate intermediate would cyclize *via* an intramolecular attack of the soft carbon nucleophile onto the π -allylpalladium.

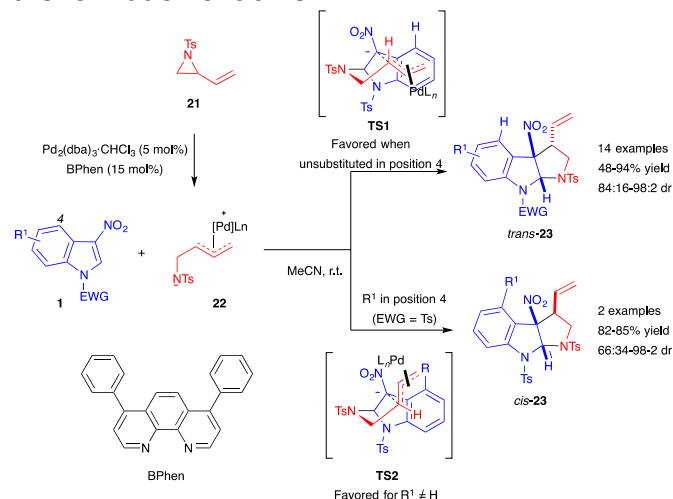


Scheme 5: Pd-catalyzed (3+2) annulation with TMM.

^a performed in the presence of the racemic ligand.

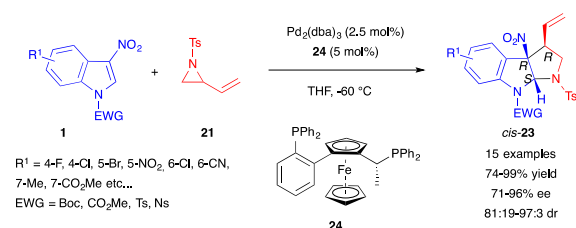
Three-membered rings bearing a vinylic appendage constitute relevant 1,3-dipole precursors in the presence of a transition metal such as palladium.¹⁶ In late 2016, the Hyland group reported the Pd-catalyzed diastereoselective synthesis of pyrrolo[2,3-*b*]indoline using vinylaziridines **21** as dipole precursor.¹⁷ In the presence of phenanthroline (BPhen) ligand and Pd(dba)₃·CHCl₃ as metal source, the authors were able to access pyrroloindolines **23** in high yields with good diastereoselectivity (Scheme 6). They proposed that the stereocontrol of this two-steps formal cycloaddition reaction relied on the substituent of the indole C4-position. With a proton at this position, the nitro-enolate intermediate

would preferentially adopt the **TS1** conformation, which may be stabilized by cation- π interactions between the cationic π -allyl Pd complex and the electron-rich indole. This transition state would then lead to the *trans*-product. Alternatively, if the indole C4-position is substituted, the resulting steric repulsions could disrupt these interactions, leading to the less hindered **TS2**. Additionally, an ester at C4 would be able to interact with the π -allyl Pd complex, stabilizing **TS2** even more, ultimately leading to the formation of *cis*-**23**.



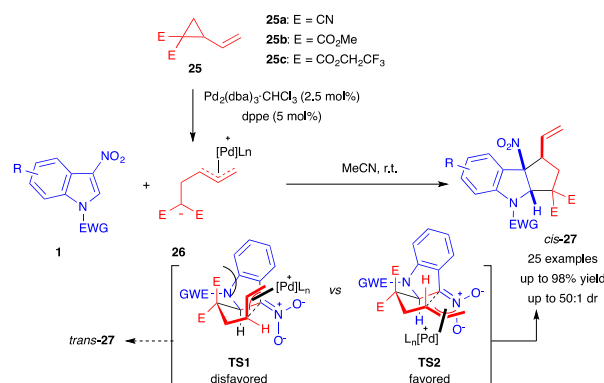
Scheme 6: Pd-catalyzed (3+2) annulation with vinylaziridines **21**.

In 2018, Hou and coll. reported the enantioselective dearomative (3+2) version of this reaction.¹⁸ The authors used cryogenic temperatures and chiral ferrocenyl phosphine ligand **24**, to obtain high enantio- and diastereocontrol over the reaction between substituted 3-nitroindoles **1** and *N*-tosyl vinyl aziridines **21** (Scheme 7). In this case, *cis*-pyrroloindolines **23** were obtained in excellent yields, diastereomeric ratios and enantiomeric excesses. The reaction could be scaled up to a gram scale and the reaction products could be easily converted to amino pyrroloindolines for instance, by reduction of the nitro group using the TMSCl/Zn system.



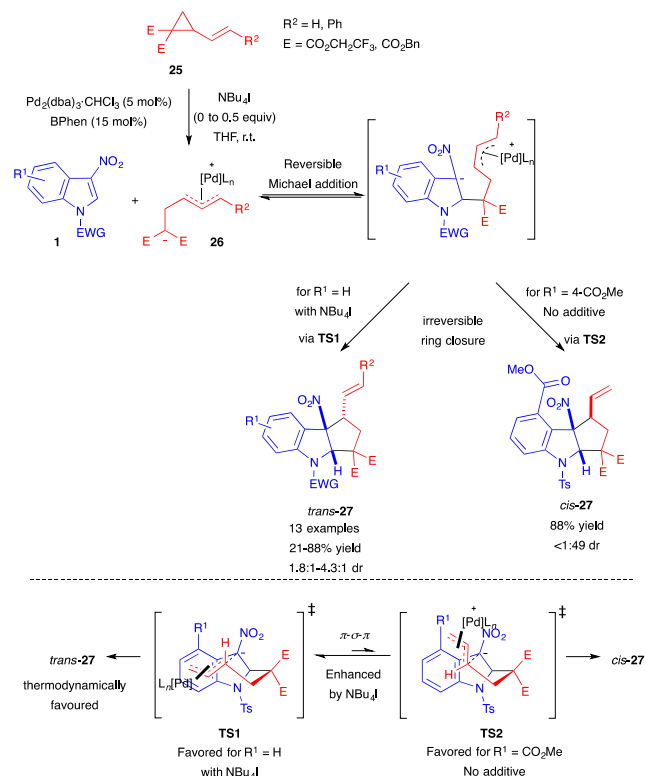
Scheme 7: Enantioselective (3+2) annulation of 3-nitroindoles with vinyl aziridines.

Almost simultaneously to Hyland work, Vitale and coll. reported a Pd-catalyzed (3+2) cyclopentannulation of 3-nitroindoles with various vinylcyclopropanes (VCPs) **25**, bearing cyano or ester electron-withdrawing groups.¹⁹ Their method, involving all-carbon dipoles, allowed the diastereoselective dearomatization of a wide range of nitroindoles, furnishing the corresponding cyclopenta[*b*]indolines **27** in good to excellent yields and moderate to excellent diastereoselectivities (Scheme 8). The method selectively produced the *cis*-isomer of **27**. In order to account for this divergent diastereoselectivity compared to Hyland work, the authors proposed that, after Michael addition of the Pd-VCP 1,3-dipole **26** to the electrophilic 3-nitroindole **1**, subsequent cyclization would occur through either transition state **TS1** or **TS2**, where the forming cycle is not anymore on the indole side. The latter would be favoured as the π -allyl moiety would adopt a *pseudo*-equatorial conformation, minimizing 1,3-diaxial interactions.



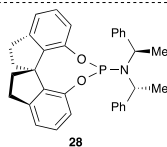
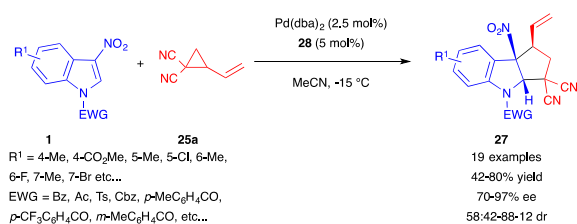
Scheme 8: Pd-catalyzed dearomative (3+2) annulation with VCPs **25** and proposed transition states.

Soon after, Hyland also disclosed the use of 2-vinylcyclopropane-1,1-dicarboxylates as all-carbon dipole precursor for the synthesis of cyclopenta[*b*]indolines **27**.²⁰ The authors used the previous catalytic system, composed of Pd and BPhen, to achieve efficient dearomative (3+2) annulation of 3-nitroindoles **1** (Scheme 9). They were able to control the diastereoselectivity of the annulation process by adding *n*Bu₄NI as a source of halide. The authors proposed that this could enhance the π - σ - π interconversion rate between the different transition states, leading, in most cases, to the probably more thermodynamically stable *trans*-isomers. As in their previous report, an ester substituent at the indole C4-position caused an inversion of the diastereoselectivity, and *cis*-**27** ended up being the major product. Only in this case, the halide additive was not required, as it was detrimental to both the yield and the dr.



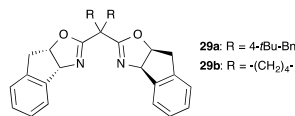
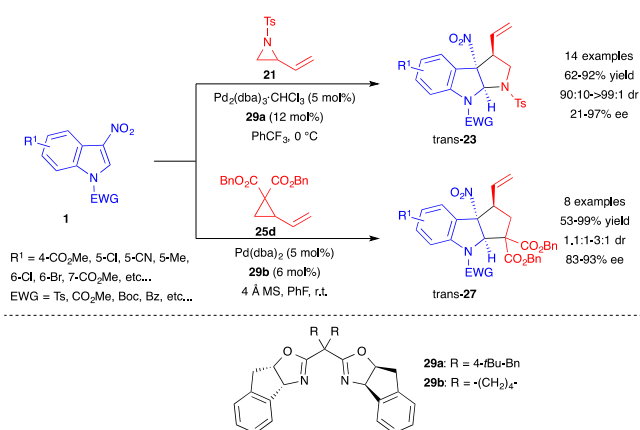
Scheme 9: Pd-catalyzed diastereoselective (3+2) annulation with VCPs

In 2018, Shi and coll. used dicyano VCPs **25a** to develop an enantioselective version of this dearomative (3+2) cyclopentannulation of 3-nitroindoles.²¹ The authors found that their optimal catalytic system, composed of Pd(dba)₂ and chiral phosphoramidite ligand **28**, was able to convert a range of 3-nitroindoles to the corresponding polycyclic adduct **27** in good yields with high enantioselectivity but still with a moderate *cis* diastereoselectivity (Scheme 10).



Scheme 10: Enantioselective (3+2) annulation of 3-nitroindoles with dicyano VCP **25a**.

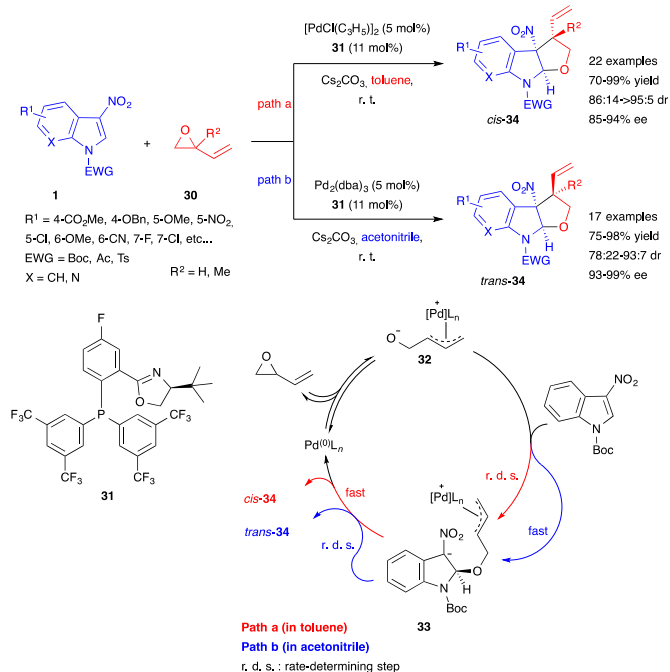
Simultaneously, Wang and coll. developed strategies for the asymmetric (3+2) annulation of 3-nitroindoles with both vinyl aziridines **21** and VCPs **25**.²² The authors used chiral bis(oxazoline) (Box) ligands **29a-b** to convert 3-nitroindoles **1** into the corresponding highly diastereo- and enantioenriched pyrrolo[2,3-*b*]indolines trans-**23** and cyclopenta[*b*]indolines trans-**27**, albeit with lower diastereoselectivity (Scheme 11).



Scheme 11: [PdBox]-promoted stereoselective (3+2) annulation with vinyl aziridines **21** and VCP **25d**.

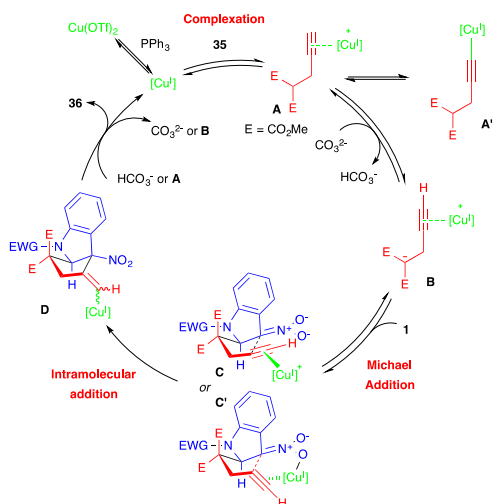
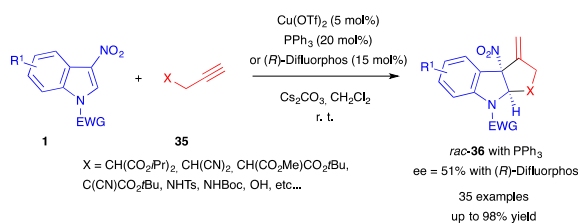
Guo, You and coll. then reported a stereodivergent method for the synthesis of tetrahydrofuroindoles by Pd-catalyzed asymmetric (3+2) annulation of 3-nitroindoles with vinyl oxiranes **30**.²³ By using chiral phosphinooxazoline ligand **31**, a large scope of substituted 3-nitroindoles **1** could be reacted with epoxybutenes **30** in good to excellent yields and stereoselectivities (Scheme 12). Unlike in many dearomatizing annulations of this type, electron-enriched indoles bearing a 5- or 6-methoxy moiety were found to be suitable substrates. Additionally, by choosing either toluene, or a much more polar solvent such as acetonitrile, the authors were able to direct the product diastereoselectivity toward its *cis*- or *trans*-isomer. To explain this stereodivergency, they performed a number of mechanistic experiments, ultimately proposing a mechanism (Scheme 11). Oxidative addition of the Pd⁽⁰⁾ catalyst to the oxirane would lead to the ring-opened 1,3-dipole **32**. In a nonpolar solvent such as toluene (path a), this intermediate would form a tight ion pair, decreasing its nucleophilicity and making the first dearomative Michael addition step rate-determining. Fast cyclization of resulting intermediate **33** would then occur, giving preferentially *cis*-**34**. In contrast, a more polar solvent like acetonitrile (path b) would drive the rapid formation of intermediate, while stabilization of the zwitterion **33** would slow

the cyclization step, thus making it rate limiting. This would give enough time for π - σ - π inversion of the Pd-allyl complex, leading to the formation of diastereoisomer *trans*-**34**.



Scheme 12: Pd-catalyzed enantioselective (3+2) annulation with vinyl oxiranes **30**.

More recently, Vitale and coll. reported a different type of dearomative (3+2) annulation of 3-nitroindoles, involving this time propargylic nucleophiles and copper catalysis.²⁴ Using copper(II) triflate, triphenylphosphine and cesium carbonate, the authors were able to convert a wide range of 3-nitroindoles **1** to the corresponding cyclopenta[*b*]indolines, pyrrolo[2,3-*b*]indolines and furo[2,3-*b*]indolines **35** with propargylic partners **33** (Scheme 13). They also demonstrated the possibility for an asymmetric version of their reaction, using (*R*)-difluorophos (Scheme 3) as chiral ligand, albeit with modest ee (51%). The authors proposed the mechanism shown on Scheme 13. Reduction of $\text{Cu}(\text{OTf})_2$ to the copper(I) catalyst, followed by complexation to the propargylic nucleophile **35** may form the π -alkyne complex **A**, possibly in equilibrium with the alkynylcopper(I) derivative **A'**. **A** would undergo deprotonation to give 1,3-dipole **B**, which would then react with nitroindole **1** to form a nitronate intermediate adduct. It would then cyclize in a *pseudo*-chair-like transition state, either through an *anti*-carbocupration (**C**) or a *syn*-carbocupration (**C'**) pathway, forming intermediate **D**. Subsequent protodecupration with either hydrogenocarbonate, **35** or **A** would then afford cycloadduct **36**, as well as regenerating copper(I).

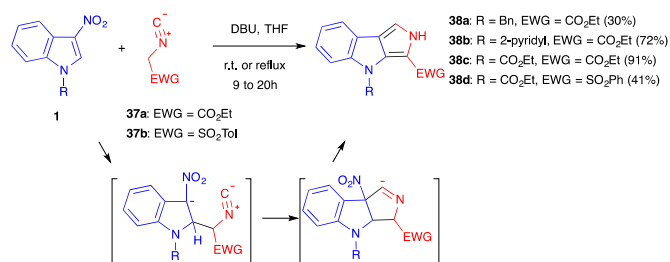


Scheme 13: Cu-catalyzed racemic dearomative annulation with propargylic nucleophiles.

23. 1,3-Dipoles (or surrogates) generated in the presence of organic promoters

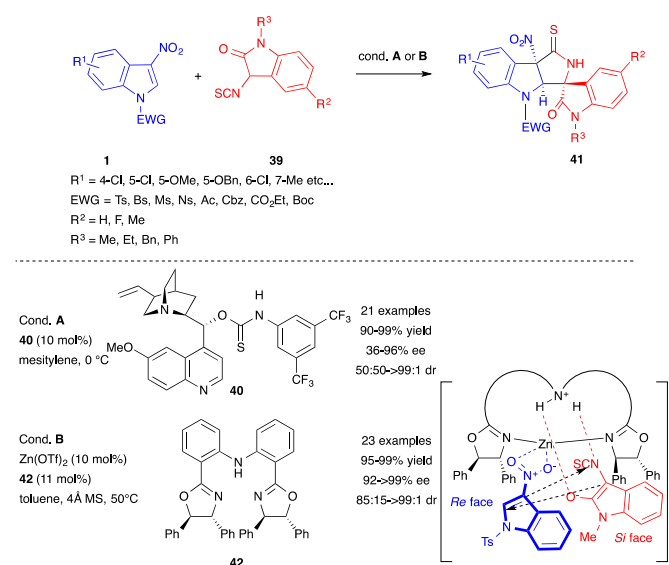
3-Nitroindoles are prone to react with enolates in nucleophilic addition reactions (*vide infra*). If the enolate anion bears an additional reactive site, in position 3 relative to the enolate carbon atom this can lead to an intramolecular cyclization and an overall formal (3+2) cycloaddition process. Different enolates of this kind have been used throughout the years in such annulation reactions.

In 1997, Gribble and coll. first showed that 3-nitroindoles **1** protected/activated as *N*-benzyl, *N*-pyridyl or *N*-ethoxycarbonyl compounds could react with ethyl isocyanoacetate **37a** or tosylmethyl isocyanide **37b** in the presence of an organic base such as DBU (Scheme 14).²⁵ Compounds **35** were formed, according to a Barton-Zard reaction, by conjugate nucleophilic addition of the enolate anion on the nitroindole substrate, followed by intramolecular 5-*endo*-dig cyclisation of the intermediate nitronate on the isocyanide. After, reprotonation of the formal cycloadduct, base-catalysed elimination of the nitro group and tautomerization leading to the formation of a pyrrole ring, the compounds **38** were obtained in moderate to high yields, depending mainly on the electron-withdrawing character of the nitrogen substituent of **1** ($\text{CO}_2\text{Et} > \text{pyridyl} > \text{benzyl}$). The more attracting groups probably facilitated the key initial nucleophilic addition. When even more electron-withdrawing groups such as phenylsulfonyl were used, however, an abnormal regioselectivity was observed for this reaction, leading to a ring opening/rearrangement and a regioisomeric cycloadduct (*vide infra*, §51).²⁶



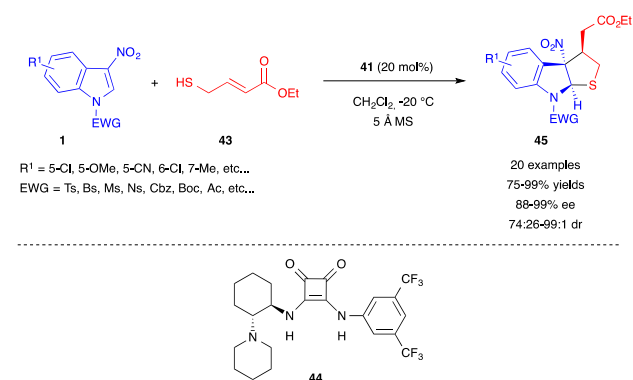
Scheme 14: Barton-Zard reactions involving 3-nitroindoles

In 2015, Yuan and coll. reported the organocatalyzed asymmetric Michael/cyclization cascade reaction between 3-nitroindoles **1** and 3-isothiocyanato oxindoles **39**.²⁷ Using the chiral bifunctional catalyst **40**, based on the quinine structure, the authors were able to access a wide range of spirocyclic oxindoles **41** in excellent yields with great stereoselectivity (Scheme 15). The first step of the process was the Michael addition of the enolate derived from **39** to the electrophilic C2 position of the activated 3-nitroindole and was followed by an intramolecular cyclization on the electrophilic central carbon atom of the isothiocyanide. The same year, this group updated the transformation by switching the organocatalyst to a Zn(OTf)₂/diphenylamine-linked bis(oxazoline) complex (Scheme 15).²⁸ The use of the Lewis acid catalyst with ligand **42** improved the results. The proposed mechanism of this latter process suggested a transition state where the catalytic complex plays a dual role. Indeed, the Zn(II) core would activate the 3-nitroindole while the NH link would serve as Lewis base, directing the 3-isothiocyanato oxindole for the key Michael addition step.



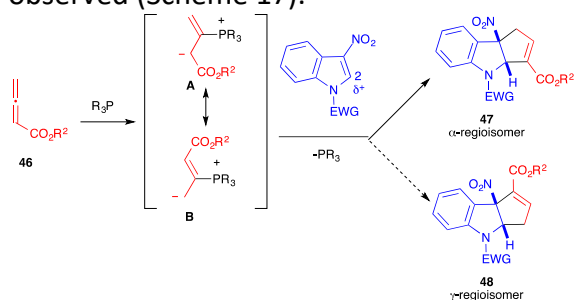
Scheme 15: Organocatalyzed vs metal-catalyzed asymmetric spirocyclic oxindoles synthesis.

In 2019, Yuan and coll. reported a different type of asymmetric dearomative (3+2) annulation of 3-nitroindoles, triggered by a thiol **43** bearing a Michael acceptor moiety.²⁹ They used a chiral tertiary amine-squaramide bifunctional organocatalyst **44** to control the enantioselective, stepwise double Michael addition between ethyl 4-mercapto-2-butenoate **43** and 3-nitroindoles **1** (Scheme 16). This reaction tolerated a wide range of substitution on the electrophilic 3-nitroindoles and furnished tetrahydrothiophendolines **45** in good to excellent yields with great enantio- and diastereoselectivity.



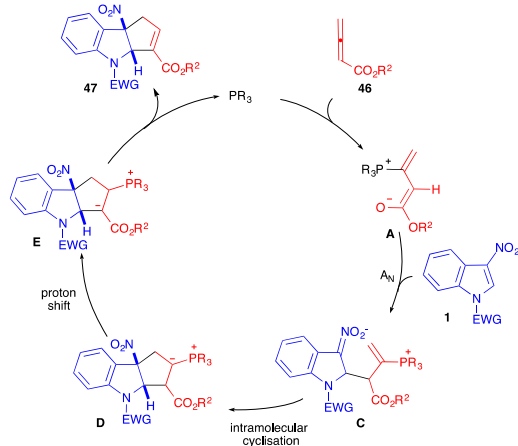
Scheme 16: Organocatalyzed thiol-triggered (3+2) annulation of 3-nitroindoles.

In 2019, almost simultaneously, different publications reported the reactivity of allenates **46** toward 3-nitro-indole derivatives **1** in the presence of phosphine organocatalysts, in the so-called Lu annulation, to generate fused cyclopentannulated indolines.^{30,31,32,33,34,35} In the literature, Lu annulation processes have been shown to lead to two possible *alpha* and *gamma* regioisomers, the result of the two possible additions of the mesomeric 1,3-dipole **A** or **B**. Thus, the nucleophilic addition of the dipole to the position 2 of the electrophilic nitroindole can potentially lead to the formation of two regioisomers **47** and **48**. In all these publications, the unique formation of the β -cycloadduct **47** was observed (Scheme 17).



Scheme 17: Regioselectivity of the dearomative (3+2) Lu annulation with 3-nitroindoles.

The mechanism proposed for this reaction and supported by DFT calculations,^{30,31} involves, first, the addition of the phosphine catalyst to the allenate leading to the reactive 1,3-dipole **A**, stabilized by the positive $P^+ \cdots O^-$ interaction.³¹ The electron-rich dipole would then add regioselectively to the nitroindole dipolarophile to furnish nitronate **C**, that would cyclize intramolecularly generating the formal β -cycloadduct **D**. A proton shift is then required to produce **E**. The presence of water molecules (or other proton relay) in the reaction medium would facilitate this otherwise highly energetic reaction. The formal cycloadduct **47** would then be formed by expulsion of the catalyst (scheme 18). Lu and coll. showed, through intermolecular competition experiments, that the nucleophilic addition of the dipole **A** onto **1** was the rate determining step in his case, involving β -unsubstituted allenates.²⁷

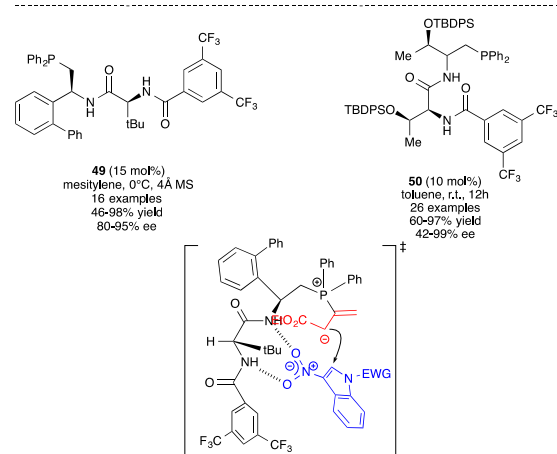
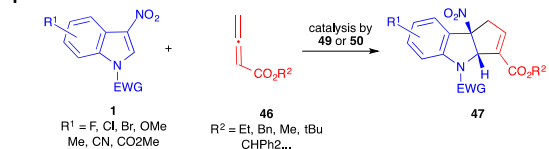


Scheme 18: Catalytic cycle proposed for this (3+2) annulation reaction

These (3+2) dearomative cycloadditions were first reported by the Zhang and Lu groups, with unsubstituted allenates **46** in the presence of dipeptidic phosphine catalysts **46** and **47**. Different indoles **1** were dearomatized in a highly enantioselective fashion with these chiral bifunctional organocatalysts (Scheme 19).^{30,31} These catalysts would play a dual role, here, allowing the formation of the reactive dipole while activating the electrophilic nitroindole by hydrogen bonds in the meantime, thus bringing the reactive parts in a close environment. The presence of the amido protons probably

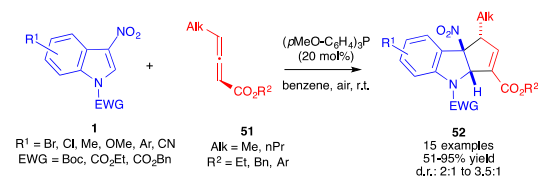
also helped the proton shift required within the catalytic cycle.^{34,35} SPINOL-derived phosphine and amido-phosphine derived from cyclohexyl-1,2-diamine could also be used as chiral organocatalysts in these reactions albeit with lower enantioselectivity.^{32,33}

Zhang and coll. showed that indoles **1** protected as carbamates were more reactive than their sulfonamidic analogues.³⁰ This was correlated by the authors to the unexpected lower aromaticity of the former, a feature already observed on different electrophilic indole derivatives in (4+2) cycloadditions processes.³⁶



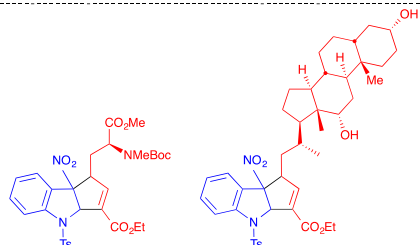
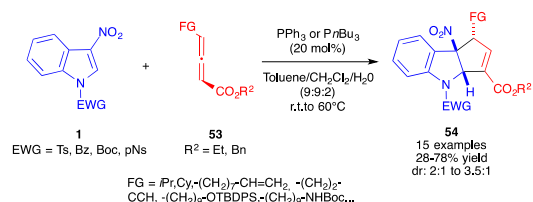
Scheme 19: Enantioselective Lu (3+2) annulations with 3-nitroindoles in the presence of bifunctional dipeptidic phosphine organocatalysts.

Bandini and coll. reported the formal (3+2) cycloaddition in the presence of β -alkyl allenates **51** bearing methyl or *n*-propyl substituents.³⁴ In the presence of the commercially available tri(*p*-methoxyphenyl)phosphine, the corresponding β -cycloadducts **52** were formed in good to high yields and diastereoselective ratios ranging from 2:1 to 3.5:1, with a preferentially *trans* relative stereochemistry (Scheme 20).



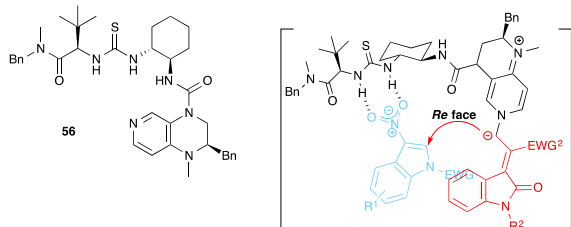
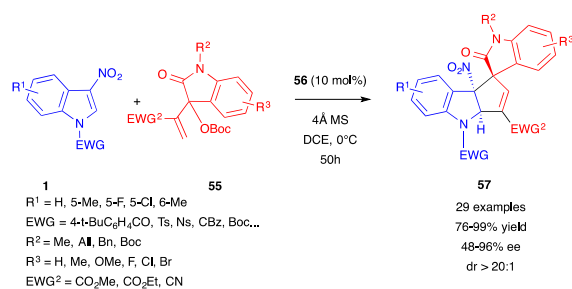
Scheme 20: Dearomative (3+2) annulations with 3-nitroindoles **1** in the presence of β -alkyl allenates.

Soon after, we reported the dearomative (3+2) annulation of 3-nitroindoles **1** with other β -substituted allenyl ester **53** (Scheme 21).³⁵ β -Allenates bearing more hindered alkyl groups such as *i*Pr or Cy, with diverse functionalities such as alkenes, alkynes, protected alcohols or amines, or substituents derived from biomolecules such as amino and deoxycholic acids proved to react smoothly with 3-nitro-*N*-Ts indoles **1c** in the presence of a commercially available phosphine catalyst (PPh₃ or PBU₃). The reaction also led to the exclusive formation of the functionalized β -regioisomer **54**, in moderate to good yields and with diastereoselectivities up to 3:1, in favour of the *trans* diastereomer. The reaction was best performed in the presence of water to facilitate the [1,2]-*H* shift.



Scheme 21: (3+2) Formal cycloadditions in the presence of β -functionalized allenates **53**.

Starting from a different substrate that is an isatin-derived Morita-Baylis-Hillman (MBH) carbonate **55**, Gao, Ge, Tian and coll. recently showed that a related enantioselective (3+2) annulation reaction could be performed on electrophilic 3-nitroindoles **1**, in the presence of a bifunctional DMAP-thiourea organocatalyst **56**.³⁷ Spirooxindoles **57**, bearing a cyclopentannulated indoline and three consecutive stereocenters, were thus obtained in high yields and enantioselectivities (Scheme 22).



Scheme 22: (3+2) annulation between 3-nitroindoles **1** and isatin-derived MBH carbonate **55** in the presence of the bifunctional organocatalyst **56**.

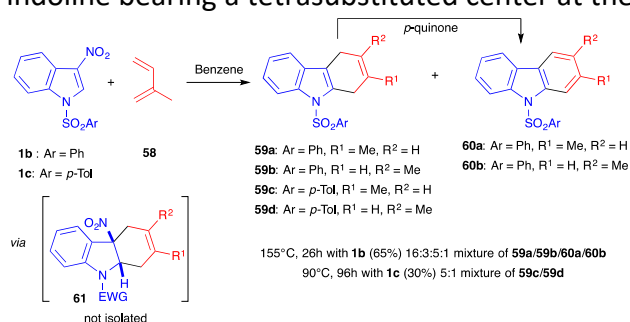
3. (4+2) (Formal) cycloadditions

Complementary to (3+2) cycloaddition/annulation reactions, the (4+2) reactions involving 3-nitroindoles **1** allow to generate tricyclic indolines combining 6-5-6 rings, encountered in (polyhydro)carbazole derived structures. In this case the C2=C3 double bond is involved as an electron-poor dienophile with electron-rich 1,3-dienes or 1,4-dipoles.

31. (4+2) Cycloadditions

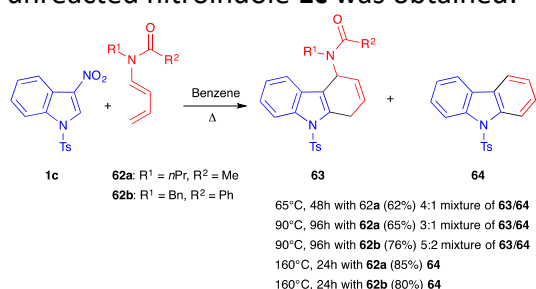
Before the (3+2) reactions mentioned above were described, Wenkert *et al.* first reported in 1988 the normal electron demand (NED) Diels-Alder reaction involving different electron-poor indole derivatives.³⁸ 3-Nitroindoles were the most reactive ones and 1-benzenesulfonyl-3-nitroindole **1b** reacted with a 12-fold excess of isoprene (**58**) to generate a 16:3:5:1 mixture of dihydrocarbazoles (**59a** and **59b**) and carbazoles (**60a** and **60b**) in an overall 65% yield (Scheme 23). With this neutral apolar

electron-rich diene, more drastic conditions were needed compared to the (3+2) cycloadditions/annulations described previously and the reaction was performed at high temperature (155 °C), for 26 h. This led to the rearomatization of the primary cycloadducts by extrusion of nitrous acid and aromatization, by oxidation, into the corresponding carbazoles. The authors showed that the cycloaddition required the presence of an electron-withdrawing group on the nitrogen atom of the indole dienophile, a feature shared with the (3+2) reactions described above. Later, Mancini and coll. showed that the similar *N*-tosylated nitroindole **1c** would lead to a 3:1 mixture of regioisomeric dihydrocarbazoles **59c** and **59d**, along with unreacted nitroindole, and that no carbazole formation was observed when decreasing the temperature to 90 °C for 96 h,³⁹ revealing that the complete aromatization is a process favoured by high temperature. The primary nitroindoline cycloadduct **61** could not be observed in these thermal conditions. This characteristic contrasts with the reactivity observed with other electrophilic indoles (substituted in position 3 by an acetyl, ketoester or ketoamide group for example), for which the cycloaddition reaction led to the formation of a dearomatized of indoline bearing a tetrasubstituted center at the ring junction.^{39,40}



Scheme 23: (4+2) Diels-Alder reaction between 3-nitroindoles **1** and isoprene under thermal activation.

In 1999, Mancini and coll. described the reactivity of 3-nitroindole **1c** toward dienamides **62**.⁴¹ Heating the mixture at 90 °C for 4 days afforded a mixture of the dihydrocarbazole **63** and carbazole **64** in an overall 65% and 76% yield, respectively (Scheme 24). The presence of a unique regioisomer **63** suggested a total control of the regiochemistry in the presence of this more polarized diene. Increasing the temperature to 160 °C led, here again, to the aromatization and carbazole **64** was the only product isolated in this case. In 2001, the same team reported that lowering the temperature to 65 °C did not allow to isolate the primary nitroindoline cycloadduct, and a similar 4:1 mixture of **63/64**, along with unreacted nitroindole **1c** was obtained.

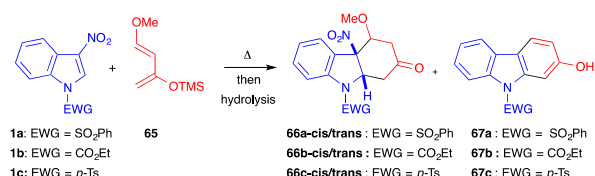


Scheme 24: (4+2) Diels-Alder reaction between 3-nitroindoles **1c** and dienamides **62** under thermal activation.

When the diene bears a trimethylsilyloxy substituent in position 1, the thermal reaction was shown later to lead to the hydroxycarbazole after 48 h at 90 °C in benzene.⁴²

In the presence of the 1,3-dioxygenated Danishefsky diene **65**, Gribble and coll. showed in 2001 that differently protected 3-nitroindole derivatives could react under thermal conditions (Scheme 25).⁴³ Reacting the *N*-

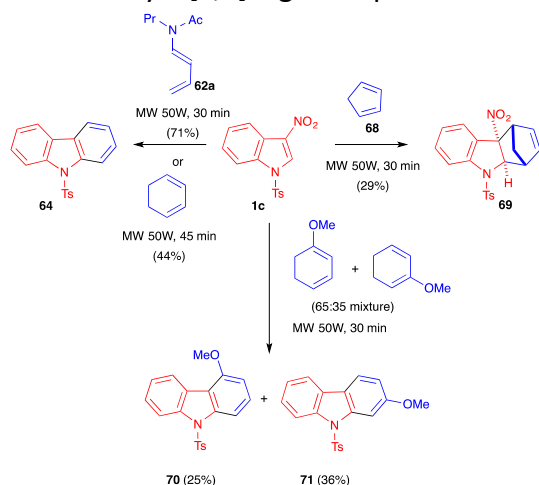
phenylsulfonylindole **1a** with **65** in refluxing toluene afforded a mixture of the nitroindoline **66a-trans** (56%) along with the re-aromatized carbazol-2-ol **67a** (35%). Thus, with this more reactive diene, this showed that the (4+2) dearomatized cycloadduct was stable and could be isolated, even with a leaving group such as nitro. With the carbamate protected indole **1b**, the cycloaddition led to the isolation of carbazolol **67b** in a good yield of 85%. The same year, Mancini and coll. showed that, in the presence of sulfonylindole **1c**, decreasing the temperature to 65 °C allowed to isolate both the *cis* and *trans* diastereomer in an overall 64% yield (39% *cis*-diastereomer, 25% *trans*).³⁹ A smaller amount of the re-aromatized carbazol-2-ol **67** was also isolated in this case (17%). This suggested that the *cis* isomer, which was not isolated in the reaction with **1a**, was more sensitive to heating.



With **1a**: Toluene, 110°C, then HCl hydrolysis: **66a-trans** (56%), **67a** (35%)
 With **1b**: Toluene, 110°C, then HCl hydrolysis: **67b** (85%)
 With **1c**: Benzene, 65°C: **66c-cis** (39%), **66c-trans** (25%), **66c** (17%)

Scheme 25: (4+2) Diels-Alder reaction between 3-nitroindoles **1c** and Danishefsky diene **65** under thermal activation.

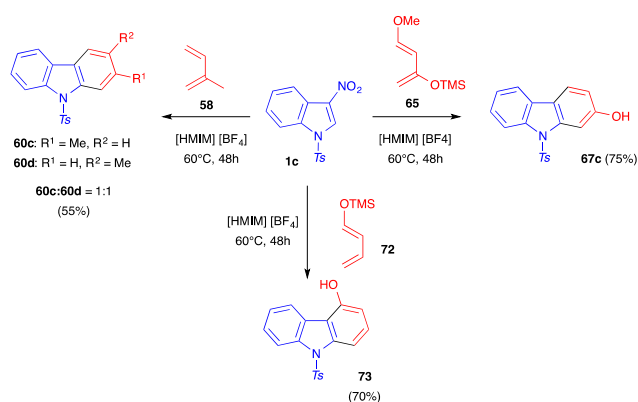
These reactions were also performed under microwave irradiation as an alternative to conventional heating.⁴⁴ Gómez and coll. showed, in 2009, that 3-nitroindole **1c** reacted with a variety of dienes under MW irradiation (50 W, 100 °C), in solvent free conditions. As shown on Scheme 26, this activation mode allowed to significantly decrease the reaction time to 30-45 minutes and furnished the aromatized cycloadducts. They were obtained via (4+2) cycloaddition/elimination/retro-Diels-Alder or (4+2) cycloaddition/elimination(s) sequences except in the case of cyclopentadiene (**68**). With this latter reactive diene, the dearomatized nitroindoline **69** was isolated as a single diastereomer, without loss of nitrous acid, in a modest 29% yield. Computational studies suggest that this stereochemical outcome would arise from an unexpected hetero-Diels-Alder cycloaddition involving the C=C-N=O electron-poor dienic moiety of the indole and one of the electron-rich C=C bond of the cyclopentadiene and would be followed by a [3,3]-sigmatropic shift.



Scheme 26: Reactivity of 3-nitroindole **1c** toward different dienes under microwave irradiation.

In 2012, Mancini and co-workers showed that these Diels-Alder reactions could also be performed in protic ionic liquids such as [HMIM][BF₄].⁴¹ Thus, nitroindole **1c** reacted with dienes such as

isoprene **58**, 1-trimethylsilyloxybutadiene **72** or Danishefsky diene **65**, for 24-48 h at 60 °C in this neoteric solvent (Scheme 27). After the polar cycloaddition, the carbazole adducts were isolated in good yields. These conditions seemed to favour the elimination reactions occurring after cycloaddition leading to the completely aromatized adducts as sole or highly favoured compounds in all cases.



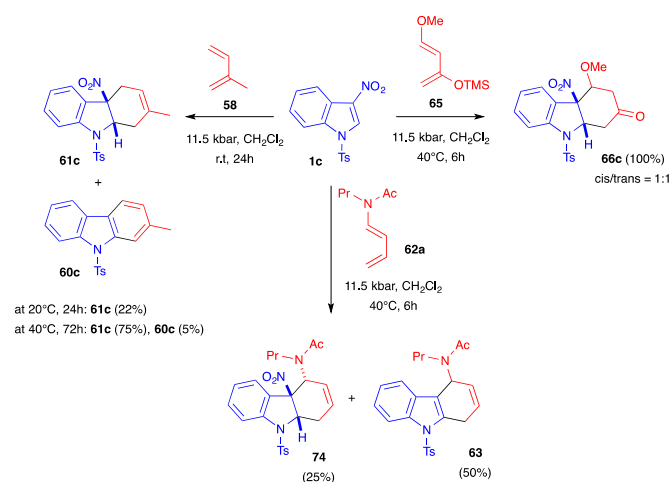
Scheme 27: Reactivity of 3-nitroindole **1c** toward different dienes in protic ionic liquid [HMIM][BF₄].

Compared to thermal conditions, the reactions are favoured in this solvent due to the activation of the dienophilic nitroindole by hydrogen bonding between the oxygen atoms of the nitro group and the acidic hydrogen atom of [HMIM][BF₄]. Evaluation of the electrophilicity of the nitroindole by DFT computations indeed showed that if nitroindole **1c** is a “strong electrophile” in the electrophilicity scale developed by Domingo and co-workers (global electrophilicity, $\omega = 2.25$ eV),⁴⁵ the activated dienophile **1c**-[HMIM][BF₄] is even more electrophilic ($\omega = 3.48$ eV in the gas phase, $\omega = 2.98$ eV when an implicit solvent is considered in the calculations). The regioselectivity observed for these processes is also in line with the calculated local electrophilicities that showed that the C2 carbon atom of the nitroindole was much more electrophilic than the C3 carbon atom (0.48 vs 0.07 eV for **1c** and 0.75 vs 0.04 eV for **1c**-[HMIM][BF₄]).

Diels-Alder reactions are generally characterized by largely negative volume of activation (-25 to -45 cm³.mol⁻¹). Thus, these transformations are often highly accelerated under high pressure. In 2001, taking advantage of this phenomenon, electron-poor indoles bearing electron-withdrawing groups in position 3 were reported to react at room temperature under 12-16 kbar pressures with different electron-rich dienes to yield the corresponding dearomatized primary indolines.⁴⁶ In these conditions, the cycloaddition reaction was promoted while, in contrast, the rearomatization process which involves elimination reaction(s), generally characterized by positive activation volumes, were disfavoured.

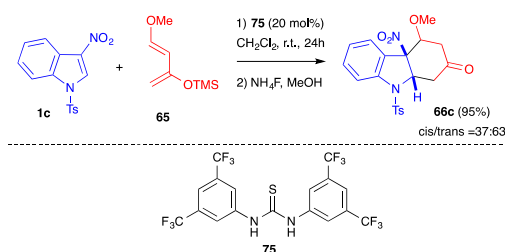
Soon after, Mancini and coll. elegantly demonstrated the reactivity of *N*-sulfonyl-3-nitroindoles **1c** toward various 1,3-dienes under hyperbaric conditions. Interaction of **1c** and isoprene **58** under a 11.5 kbar pressure, at room temperature, for 24h led to the formation of the expected dearomatized cycloadduct **61a**, obtained as a single regioisomer, showing the positive effect of high pressure on the transformation (Scheme 28).³⁹ The isolated yield however remained low (22%). Increasing both the temperature to 40 °C and the reaction time to 3 days enhanced the yield to 75%. In these conditions, traces of the corresponding rearomatized carbazole were observed (5%), together with some unreacted indole (20%). **1c** could also react with the dienamide **62a** under the same pressure. The cycloaddition led, this time, to a mixture of the desired dearomatized cycloadduct **74**, and the corresponding denitrated compound **63**, obtained in a 1:2 ratio, along with unreacted indole (24%). Satisfyingly, the cycloaddition was also performed with Danishefsky diene **65**. With this more reactive diene, a total

conversion of the indole **1c** was observed, leading to the nitrocycloadduct **66c** (1:1 d.r.) with no traces of the rearomatized cycloadducts.



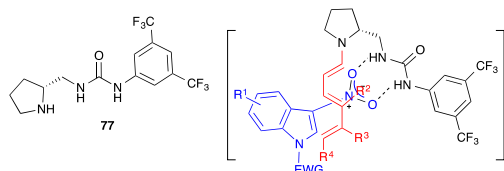
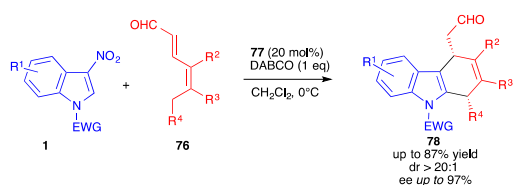
Scheme 28: Dearomative (4+2) cycloadditions of 3-nitroindole **1c** with different dienes under high pressure activation.

In 2015, our group reported the dearomative (4+2) cycloaddition of 3-nitroindole **1c** in the presence of Danishefsky diene **65** at room temperature in the presence of a thiourea organocatalyst.⁴⁷ The achiral Schreiner thiourea catalyst **75** indeed promoted the Diels-Alder reaction at room temperature. In these mild thermal conditions, no elimination reaction occurred after cycloaddition and the corresponding adducts **66c** (63:37 of *trans/cis* diastereomer) were isolated in 95% yield (Scheme 29). Attempts to perform this reaction in an enantioselective manner in the presence of chiral thiourea or squaramide catalysts however led to low enantioselectivities.



Scheme 29: Dearomative (4+2) cycloadditions of 3-nitroindole **1c** with Danishefsky diene **65** under thiourea organocatalysis.

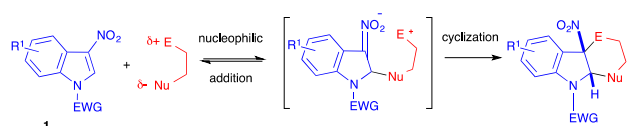
An achievement in the field of enantioselective (4+2) cycloadditions with 3-nitroindoles was the organocatalytic approach reported by Jørgensen and co-workers in 2016 (Scheme 30).⁴⁸ The cycloaddition of 3-nitroindole derivatives **1** with 2,4-dienals **76** was performed in a highly enantioselective fashion in the presence of proline-urea organocatalyst **77**. This trienammine pathway showed to be efficient at low temperature and furnished, in the basic conditions of the reaction, chiral dihydrocarbazole **78** in good yields (up to 87%) and enantioselectivities (up to 97% *ee*) after nitrous acid elimination. The bifunctional organocatalyst brings closer the diene/dienophile substrates, by allowing the formation of the electron-rich trienammine while activating the nitroindole by hydrogen bondings, thus inducing an efficient facial discrimination.



Scheme 30: Organocatalyzed enantioselective (4+2) cycloadditions of 3-nitroindoles with 2,4-dienals **72**.

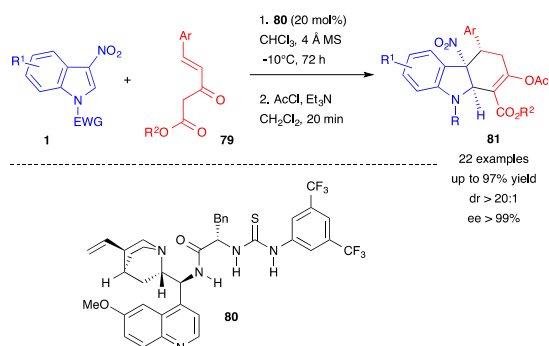
3.2. (4+2) Annulations

(4+2) Dearomative annulations involving 3-nitroindoles as electrophiles emerged more recently, taking advantage of the possible addition of nucleophiles at the C2 position of 3-nitroindoles (Scheme 31). If the nucleophile is a 1,4-zwitterionic dipole, the nitronate intermediate can subsequently cyclize intramolecularly in a (4+2) formal cycloaddition process. The first addition step is the dearomatizing one, often reversible, and the second cyclization step thus shifts the equilibrium toward the formation of the dearomatized cycloadduct. This strategy is compatible with the use of relatively mild nucleophiles for the first determining step.



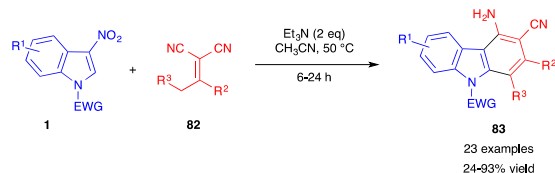
Scheme 31: General dearomative (4+2) annulations of 3-nitroindoles

In 2017, Xu, Yuan and coll. reported the first organocatalyzed reaction of 3-nitroindoles **1** with Nazarov reagents **79**, which possess a nucleophilic α -carbon and an electronically deficient C=C double bond, in presence of the thiourea organocatalyst **80** (Scheme 32).⁴⁹ Its bifunctional nature allowed, here again, the activation of the 3-nitroindole **1** by the formation of multiple hydrogen bonds with the amide/thiourea moiety and the simultaneous activation of **79** through the tertiary amine function of the catalyst. This dual activation was crucial for the reactivity and the stereocontrol. After acylation, the chiral hydrocarbazole skeletons **81** were obtained in good to high yields with excellent diastereo- and enantio-selectivities.



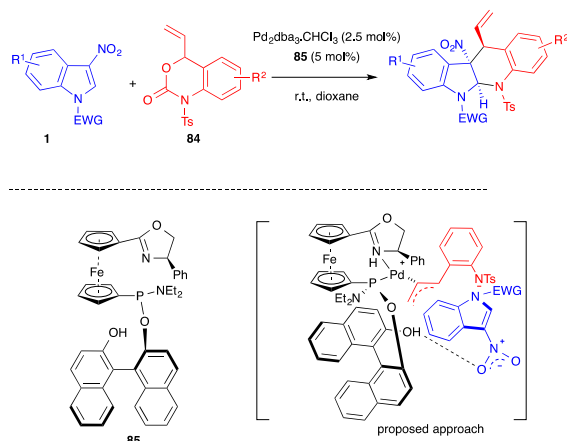
Scheme 32: Enantioselective dearomative (4+2) annulations of 3-nitroindoles with Nazarov reagents **79**.

In 2018, Yang and coll. reported the (4+2) annulation of 3-nitroindoles **1** with alkylidene malononitriles **82** (Scheme 33).⁵⁰ In the presence of triethylamine, carbazol-4-amine derivatives **83** were obtained via a four-steps sequence involving (i) vinylogous Michael addition, (ii) cyclization, (iii) isomerization, (iv) nitrous acid elimination. This reaction was recently extended to different α,β -dicyanoalkenes **82**.⁵¹



Scheme 33: (4+2) annulations of 3-nitroindoles with alkylidene malononitriles **82**.

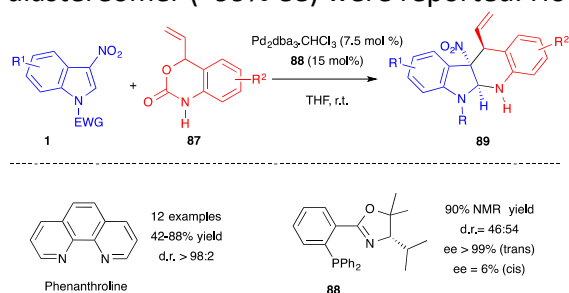
In 2019, Ding, Hou and coll. developed a palladium-catalyzed asymmetric decarboxylative (4+2) annulation of 3-nitroindoles **1** with benzoxazinanones **84a** (Scheme 34).⁵² In the presence of $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (2.5 mol%) and a chiral SIOCPbox ligand **85** (5 mol%), a series of chiral dearomatized tetrahydro-5*H*-indolo[2,3-*b*]quinolines **86a** were obtained in high yields, up to 97%, and good to excellent stereoselectivities ($\text{dr} > 95:5$, $\text{ee} = 79-95\%$). *N*-tosyl protected vinyl benzoxazinanones **84** were required and no reaction took place when replacing the tosyl group with a proton, a nosyl or an acetyl group. The authors proposed a transition state involving a dual role of the catalyst, allowing the formation of the π -allylic 1,4-dipole and activating the nitro group of the indole with the phenol hydroxyl group of the ligand to account for the observed stereoselectivities.



Scheme 34: Enantioselective palladium catalyzed decarboxylative (4+2) annulations of 3-nitroindoles with *N*-tosyl vinyl benzoxazinones **84**.

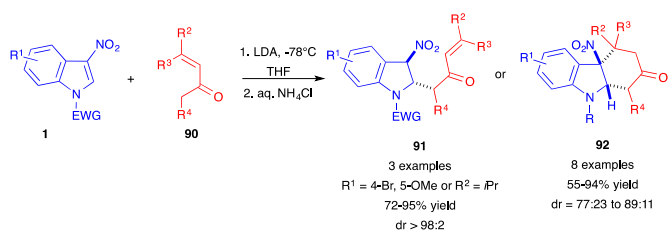
Hyland and co-workers demonstrated recently that the same reaction was also possible in the presence of unprotected vinyl benzoxazinones **87**, using higher catalyst loading $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (7.5 mol%) and ligand (15 mol%) (Scheme 35).⁵³ In a diastereoselective version of the process, the reaction could be promoted by the simple and air-stable phenanthroline ligand. Excellent yields and *trans* diastereoselectivities were reported with this catalytic system, even in the absence of any electrophilic activation of the nitro group. To account for this *trans* preference, the authors proposed a reversible nucleophilic attack at the C2 position of the indole to generate a nitronate, which would undergo a ring-closure *via* a favoured boat-like transition state. Noteworthy, *N*-sulfonylated nitroindoles **1** were required for this process as *N*-carbonylated substrates proved inert or led to decomposition. In addition, C3-substituted acetyl, cyano, and methyl ester indoles failed in the reaction, showing, here again, the

importance of the nitro group in position 3 for enhancing the electrophilicity of the indole ring. When performed in the presence of a chiral phosphinooxazoline ligand **88**, high yield and ee for the *trans* diastereomer (>99% ee) were reported. However, the dr was significantly impacted (Scheme 35).



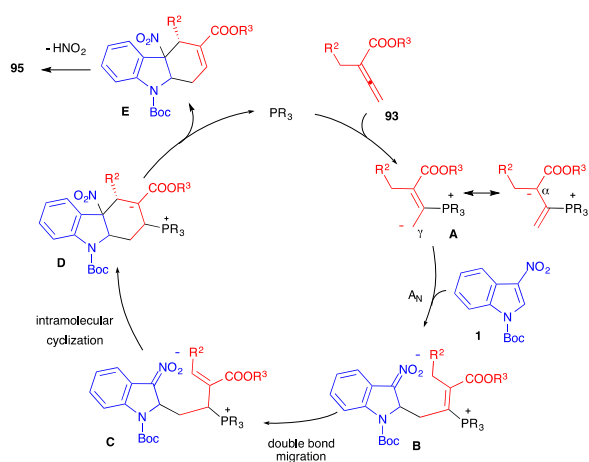
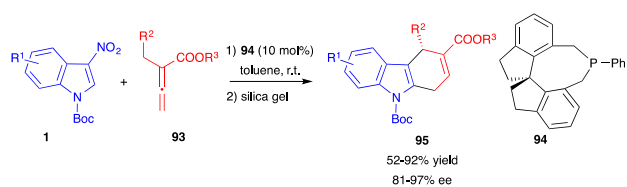
Scheme 35: Palladium catalyzed decarboxylative (4+2) annulations of 3-nitroindoles with unprotected vinyl benzoxazinones **87**.

In 2019, the dearomative (4+2) annulation of 3-nitroindoles **1** in the presence of enolizable vinylketones **90** was reported in basic conditions, at low temperatures (Scheme 36).⁵⁴ The *in situ* generated lithium enolates add to the C2-position of the nitroindoles **1**. Then, depending on the substrates, *trans* 1,4-adducts **91** or, most of the time, *in situ* cyclized adducts **92** were isolated in good yields. This method constitutes an alternative to the classical Diels-Alder cycloaddition performed in the presence of 2-silyloxy-1,3-dienes, such as Danishefsky diene, for which the re-aromatized carbazolols **64** are often isolated (*vide supra*).



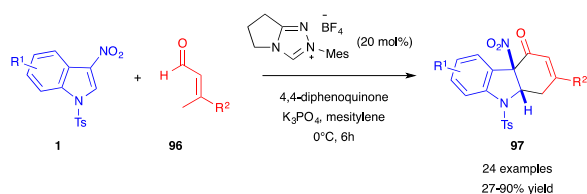
Scheme 36: Dearomative (4+2) annulations of 3-nitroindoles with enolizable vinyl ketones **90**.

Guo and coll. recently reported the phosphine-catalyzed enantioselective (4+2) annulation of 3-nitroindoles **1** with allenates **93** at room temperature, in the presence of a chiral phosphine catalyst **94** (Scheme 37).⁵⁵ Such a process generally leads to the generation of tetrahydrocyclopenta[*b*]indoline **47**, according to a (3+2) Lu annulation (*vide supra*, Scheme 17). With allenates **93**, bearing an alpha substituent, most of the time benzylic, a different and complementary pathway was observed. The dipole **A** generated after nucleophilic addition of the phosphine on the allenate reacted with the electrophilic indole through its less sterically hindered β -position, this time, leading to a nitronate zwitterion **B**. Migration of the double bond, followed by intramolecular cyclization would lead to **D**, which would release the catalyst and furnish the formal (4+2) cycloadduct **E**. In the reported reaction conditions, rearomatization of the 5-membered ring by loss of nitrous acid would then afford the isolated dihydrocarbazole **95** in good yields and enantioselectivities.



Scheme 37: Enantioselective phosphine-catalyzed (4+2) annulations of 3-nitroindoles with allenates **93**.

In 2020, Huang, Li and coll. reported a novel type of dearomative (4+2)-annulation of 3-nitroindoles **1** with β -substituted crotonaldehydes **96** (Scheme 38).⁵⁶ Under an oxidative N-heterocyclic carbene (NHC) catalyzed process, dearomatized hydrocarbazolones **97** were obtained in good yields. The use of a chiral NHC catalyst allowed to perform an enantioselective version of this reaction, with ee up to 74%. This was however detrimental to the isolated yield (18%).

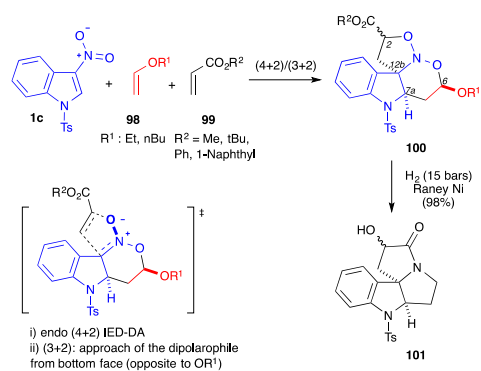


Scheme 38: Oxidative NHC-catalyzed (4+2) annulation of 3-nitroindoles **1** with β -substituted crotonaldehydes **96**.

4. (4+2)/(3+2) cycloaddition reactions

The cycloadditions/annulations described so far rely on the electrophilic character of the $\text{C}2=\text{C}3$ double bond of the 3-nitroindole derivatives. Based on the reactivity of the $\text{C}2=\text{C}3-\text{N}=\text{O}$ system as an electron-poor heterodiene,⁵⁷ in 2007, the first multicomponent domino (4+2)/(3+2) cycloaddition process was reported in the presence of *N*-tosyl-3-nitroindoles **1c**. Performed in the presence of an electron-rich vinyl ether dienophile **98** and an electron-poor acrylate dipolarophile **99**, the reaction led to the formation of a nitrosoketal **100** in one operation (Scheme 39).⁵⁸ Under reductive conditions, **100** could be converted into **101** in high yields, through (i) N-O hydrogenolyses, (ii) formation of an imine and its reduction into pyrrolidine, (iii) lactamization.

In an attempt to develop an enantioselective version of this reaction, it was performed in the presence of different chiral thioureas or sulfonamides, but the enantioselectivities remained low (up to 30% ee).⁴⁷



Scheme 39: Domino (4+2)/(3+2) cycloaddition 3-nitroindole **1c** with vinyl ethers **98** and acrylates **99**.

In this reaction, 4 stereocenters were created and 8 couples of diastereomers potentially obtained. High pressure conditions proved to lead to the best distereoselectivity (Table 3, compare entries 1-4). The two diastereomers obtained in these conditions were shown to differ in the relative positions of the centre alpha to the ester group, the result of an *endo* (4+2) inverse electron demand hetero-Diels-Alder reaction (relative stereochemistry of C_{7a} and C₆), a face selective (3+2) cycloaddition (dipolarophile from the face opposite to OR¹, relative stereochemistry of C_{12b}), while the *endo vs exo* approach of the dipolarophile is poorly controlled (two diastereomers differing in the relative stereochemistry of C₂). Switching to an acrylate bearing a more hindered aromatic moiety led to a higher diastereoselectivity (Table 3, entry 7).

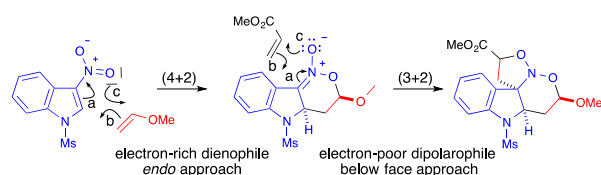
Table 3: Reactions of 3-nitroindoles with ethyl vinyl ether **98a** (R¹ = Et) and acrylates **99**

Entry	Conditions	R ²	Yield (100) (%)	dr
1	CH ₂ Cl ₂ , r.t., 168h	Me	20	50/50/0 /0
2	Tol., 110°C, 60h	Me	83	45/45/5 /5
3	MW (120W), 130°C, 1h	Me	75	35/35/1 5/15
4	HP (12kbar), r.t., 24h	Me	83	55/45/0 /0
5	HP (12kbar), r.t., 24h	tBu	83	60/40/0 /0
6	HP (12kbar), r.t., 24h	Ph	92	66/34/0 /0
7	HP (12kbar), r.t., 24h	1-naphthyl	99	78/22/0 /0

DFT calculations, reported on these multicomponent domino (4+2)/(3+2) cycloadditions of 3-nitroindoles confirmed that, the *endo* approach with the regiochemistry observed experimentally was indeed the most favourable pathway for the primary (4+2) cycloaddition reaction.⁵⁹ The 3-nitroindole reacted through its LUMO as an electron-poor heterodiene in a concerted though asynchronous inverse demand hetero-Diels-Alder. The electronic rearrangements observed during this step were in line with

the expected pathway and, for this first cycloaddition process, the FMO model provided perfectly reliable predictions (Scheme 40).

The results computed for the subsequent (3+2) cycloaddition reaction were also in line with the experimental results, with a more favoured approach of the dipolarophile from the face opposite to the alkoxy group of the intermediate. A small *endo* and *exo* difference also accounted for the poor diastereoselectivity experimentally observed. During the second (3+2) cycloaddition step, however, unexpected electronic rearrangements were observed. Even if electron-deficient acrylate appeared to react in preference to electron-rich vinyl ether with the intermediate nitronate, the calculations demonstrated that the electron-poor dipolarophile provided the electrons to the electron-rich dipole (Scheme 40, arrow b for the (3+2) step).

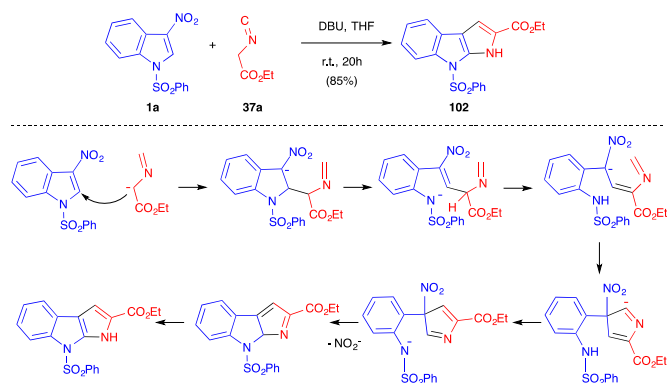


Scheme 40: Electronic rearrangements computed for the most favoured pathway in the two steps (4+2)/(3+2) sequence.

5. Reactions with other nucleophiles

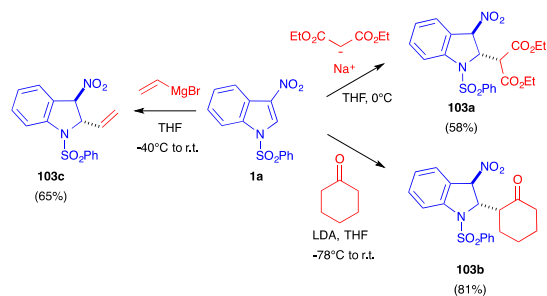
5.1. Nucleophilic addition reactions

The electrophilicity of 3-nitroindole derivatives allows the addition of different types of nucleophiles to the C2 position of the heterocycle, leading to a nitronate intermediate. The addition can be reversible and leads to different types of adducts, depending on the quenching of the intermediate. When reacted with ethyl isocyanoacetate **37a** in the presence of an organic base such as DBU, it has been shown above that 3-nitroindoles **1** protected as N-benzyl, N-pyridyl or N-ethoxycarbonyl compounds underwent a Barton-Zard reaction, by conjugate nucleophilic addition of the enolate anion on the nitroindole substrate, followed by intramolecular 5-*endo*-dig cyclization of the intermediate nitronate on the isocyanide (*vide supra*, Scheme 14).²⁵ When more electron-withdrawing groups such as phenylsulfonyl were activating the indole ring, an abnormal regioselectivity was observed for this reaction, leading to a ring opening/rearrangement and a regioisomeric cycloadduct **102** (Scheme 41).²⁶ The mechanism proposed by Gribble and coll. to account for this unexpected regioselectivity involved first the expected Michael addition of the enolate anion resulting from the deprotonation of the isocyanide on the C2 position of the nitroindole. Then, an expected ring opening would occur. After prototropy, the nitronate anion would add on the isocyanide to form the 5 membered ring. After prototropy, ring closure of the central ring and concomitant elimination of nitrite, a final isomerisation would lead to the isolated compound **102**.



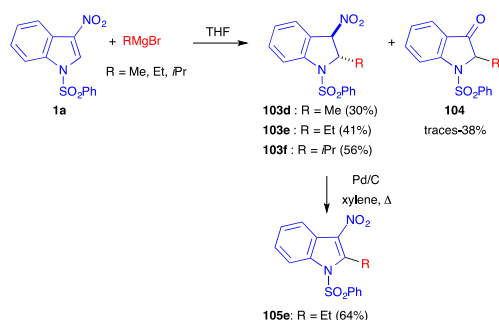
Scheme 41: Abnormal Barton-Zard reaction between indole **1a** and isocyanide **37a**.

Later in 2003, Gribble disclosed several nucleophilic additions of enolates to 3-nitroindole **1a**. Thus, the “simple” addition of the anion on the C2 position of the indole results, after hydrolysis, to the dearomatized indolines **103** (Scheme 42).⁶⁰ Thus, the use of deprotonated diethyl malonate or cyclohexanone led to the formation of the Michael-type nitronate adduct, which furnished selectively the *trans* indoline after hydrolysis. Similarly, addition of a vinyl Grignard reagent led to the *trans* adduct **103c**.



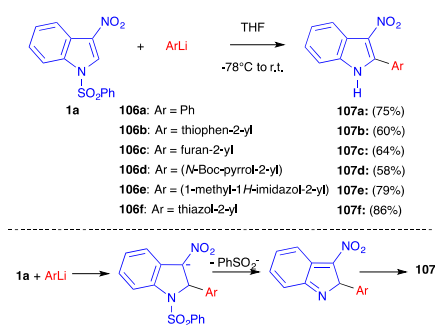
Scheme 42: Michael addition of enolates and vinyl Grignard reagents on nitroindole **1a**.

The use of alkyl Grignard reagents led to the same Michael adducts **103**, however with a small amount of the ketones **104**, resulting from the Nef reaction (Scheme 43). Re-aromatization of **103** into **105** could easily be performed in the presence of Pd/C.



Scheme 43: Nucleophilic addition of alkyl Grignard reagents on nitroindole **1a**.

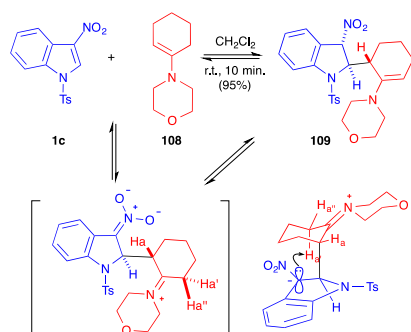
In 2010, the same group reported the nucleophilic addition of (hetero)aryllithiated compounds to 3-nitroindole **1a**. In most cases, the reaction led to the *N*-deprotected adduct **107** in good yields (Scheme 44).⁶¹ The authors proposed a mechanism involving the nucleophilic addition of the lithium compound on the C2 position of the indole, followed by an elimination of the sulfinate anion and prototropy. In one case only, involving a 2-lithioindolic nucleophile, the corresponding *trans* indoline **103** was isolated.



Scheme 44: Nucleophilic addition of organolithium nucleophiles **106** on nitroindole **1a**.

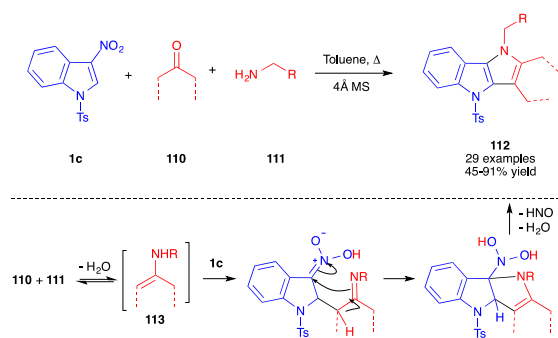
5.2. Nucleophilic additions: the special case of enamines

More recently, the addition of enamines on nitroindoles **1** has been studied. In 2016, the stoichiometric addition of 4-(cyclohex-1-en-1-yl)morpholine **108** on **1c**, in mild anhydrous conditions, was reported to lead to the formation of the unexpected dearomatized indoline **109**, as a single regioisomer and diastereomer (Scheme 45).⁶² It was isolated in an excellent 95% isolated yield, even on a 10 g scale. This formal ene adduct **109** would be formed by nucleophilic addition of the enamine on the C2 position of the nitroindole followed by selective proton abstraction in the conditions of the reaction. The reaction proved to be reversible in solution and the ene adduct **109** was sensitive to water. It was efficiently isolated in this case thanks to its highly crystalline character. When compared to the addition of vinyl ethers that required high temperatures or high pressure conditions, the addition of enamines is much easier, and reflects the much higher nucleophilicity of enamines. DFT computations in this field suggested that the greatest difference between these oxygenated and nitrogenated nucleophiles would come from the much higher stability of the zwitterionic nitronate intermediate resulting from the addition (iminium vs oxonium).⁶³



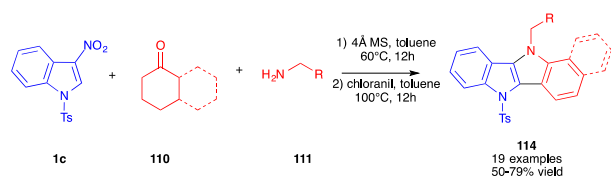
Scheme 45: Dearomatizing formal ene reaction on nitroindole **1c**.

In 2017, John and coll. studied the addition of *in situ* generated enamines toward nitroindoles.⁶⁴ They showed that reacting the nitroindole **1c** with an enolizable ketone **110** and a primary amine **111**, in toluene at 60-110 °C in the presence of 4Å MS led to the formation of aromatized pyrrolo[3,2b]indoles **112** in good yields (Scheme 46). In this case, the involvement of a primary amine would lead to the formation of an imine, in equilibrium with the enamine **113**. The authors proposed a mechanism involving first the nucleophilic addition of the enamine to the C2 position of the indole derivative, as previously observed. In this case, however, the iminium proton could be trapped by one of the nitronate oxygen atom. A second enamine addition would then allow for the five-membered ring closure. This latter would then aromatize by elimination of hyponitrous acid and water, generating **112**.



Scheme 46: Multicomponent reaction involving nitroindole **1c** to generate pyrrolo-indoles **112**.

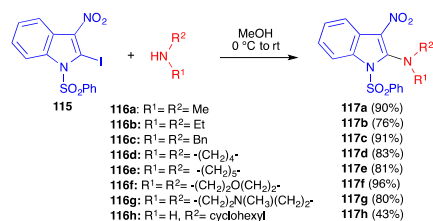
Soon after, the same authors reported an extended version of the methodology toward the synthesis of indolo[3,2b]indoles **114** (Scheme 47).⁶⁵ In this case, in the presence of cyclic ketones, the intermediate pyrrolo[3,2b]indoles, formed after 12 h in toluene at 60 °C, were oxidized *in situ* by addition of chloranil as oxidant. The corresponding fully aromatized compounds **114** were isolated in good overall yields.



Scheme 47: One-pot generation of indolo-indoles **114** from nitroindole **1c**.

5.3. Nucleophilic aromatic substitution reactions

In 2006, Gribble and Roy described an efficient S_NAr reaction involving secondary amines and an activated 2-iodo-3-nitroindole **115** (Scheme 48).⁶⁶ The reaction was performed in mild conditions, with a range of secondary amines **116**, affording the corresponding 2-amino-3-nitroindole **117** in very good yields (76-96%). With the less nucleophilic primary cyclohexylamine, the yield dropped.



Scheme 48: Nucleophilic aromatic substitution between 2-iodo-3-nitroindole **99** and amines **100**.

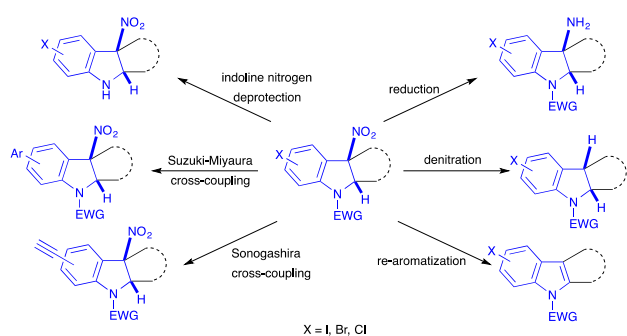
6. Conclusions

3-Nitroindoles **1** exhibit an unexpected, albeit remarkable, electrophilic reactivity toward different electron-rich species, notably in dearomative cycloaddition and annulation reactions. This peculiarity is directly related to the C2=C3 double bond of nitroindoles that can behave either as a dipolarophile, a dienophile or a Michael acceptor in dearomatizing (3+2), (4+2) cycloadditions or nucleophilic addition reactions. Complementarily, the heterodienic character of the C2=C3-N=O system of 3-nitroindoles explains their reactivity in multicomponent tandem (4+2)/(3+2) cycloadditions.

The reported cycloadditions can be concerted; the corresponding transformations generally involve a highly asynchronous transition state with a smaller forming bond at the C2 position. The limit of this concerted asynchronous mechanism is encountered in many other cases with stepwise processes, in

which the first step involves a reversible dearomatizing nucleophilic addition, and the nitronate intermediate is then trapped intramolecularly in a formal cycloaddition process. Recent developments of these reactions include efficient enantioselective strategies, often taking advantage of bifunctional catalysis, activating the electrophilicity of the indole moiety by hydrogen bonding with the nitro group, for instance with thiourea containing catalysts, and the reacting nucleophilic species formed/activated meanwhile, both linked by a chiral tether. All these transformations recently reported on the electrophilic 3-nitroindoles underline how this heteroaromatic motif has become a model substrate for electron-poor aromatic compounds in dearomatization strategies.

The reported transformations have led to the expedient synthesis of differently functionalized indolines, which often retain a tetrasubstituted centre at the *cis* junction of the heterocycle, a feature often retained in natural products of interest. These new structures themselves are potentially relevant compounds for biological or catalytic applications. In addition, after dearomatization, even if the nitro group is still on a benzylic position, it can be simply reduced into the corresponding amino group, using for instance the TMSCl/Zn system, in most cases. Denitration reactions can also be easily performed, notably through radical denitration strategies. Rearomatization of the 5-membered cycle, by elimination of nitrous acid, is also an easy process. All these transformations and post-functionalizations of the 3-nitroindole motif thus make this compound a good scaffold for diversity oriented synthesis (Scheme 49).



Scheme 49: Representative post-functionalizations of the nitroindolines obtained through dearomatizations of 3-nitroindoles.

Acknowledgements

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