2- and 3-Vinylindoles as 4π Components in Cycloaddition Reactions

Elisabetta Rossi,*[a] Giorgio Abbiati,[a] and Valentina Pirovano[a]

[a] Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", 21, Via Venezian, 20133 Milano, Italy

E-mail: elisabetta.rossi@unimi.it

Abstract: The review summarizes the most recent achievements in the chemistry of 2-vinylindoles and 3-vinylindoles. In particular, we focus on the behavior of these compounds as dienes in cycloaddition reactions. The majority of the literature in this field deals with [4+2] cycloaddition, and only one report of [4+1] cycloaddition has appeared in the literature until now. Thus, the main section reviews [4+2] cycloaddition with acti- vated cyclic and acyclic dienophiles under Lewis-acid catalysis or organocatalysis conditions. In addition, cycloadditions performed with simple π-systems as dienophiles, occurring through activation by transition-metal catalysts, are reviewed. This section mainly involves the use of allenes as dienophiles under gold catalysis conditions. In both cases, the authors report excellent levels of diastereoselectivity and enantioselectivity. Two separate subsections deal with the synthesis of natural compounds and with the use of methyleneindolinones as dienophiles.

Elisabetta Rossi obtained her master's degree in Chemistry and Pharmaceutical Technology in 1981 from the University of Milan. In 1984 she obtained a specialization qualification in Analytical and Chemical Methodologies for Fine Chemicals at the Politecnico of Milan. In 1984 she became Assistant Professor, and in 2001, after a four-year period at University of L'Aquila, she was appointed Associate Professor of Organic Chemistry at the University of Milan. Her research activity is focused on the study of new synthetic methodologies for the synthesis and functionalization of heterocyclic compounds through domino and multicomponent approaches, intramolecular cyclization, and cycloaddition reactions by means of metal catalysis by Lewis acids and transition metals (In, B, Sc, Ti, Pd, Au, and Ag).

Giorgio Abbiati obtained his master's degree in Chemistry and Pharmaceutical Technology in 1997 from the University of Milan, and in 2000 he received his Ph.D. in Pharmaceutical Chemistry from the same university. He was appointed Assistant Professor at the Department of Pharmaceutical Sciences of the University of Milan in 2005, becoming Associate Professor of Organic Chemistry in 2015. His more recent scientific interests are focused on the study of new synthetic methodologies for the preparation and the functionalization of heterocyclic compounds, mainly starting from alkynyl scaffolds, by means of homogeneous metal-catalyzed (Ag, Au) domino and multicomponent approaches.

Valentina Pirovano was born in Bergamo (Italy) in 1986. In 2010, after a six-month stay in the research group of Prof. Lutz Ackermann (University of Göttingen), she obtained her master's degree in Chemistry and Pharmaceutical Technology at the University of Milan (Italy). From 2011 to 2014 she pursued a co-tutored Ph.D. under the supervision of Prof. Elisabetta Rossi (University of Milan) and Dr. Rubén Vicente (University of Oviedo, Spain). Since 2014 she has been working as postdoctoral researcher in the group of Prof. Elisabetta Rossi, focusing her studies on transition-metal catal

1. Introduction

On inspection of the structures of 2- and 3-vinylindoles, it is easy to see that they belong to the class of internal-external ring dienes (Figure 1). Therefore, in principle, they should be able to take part as 4π components in [4+*n*] cycloaddition reactions with suitable partners for the synthesis of polycyclic indole derivatives (Figure 1).

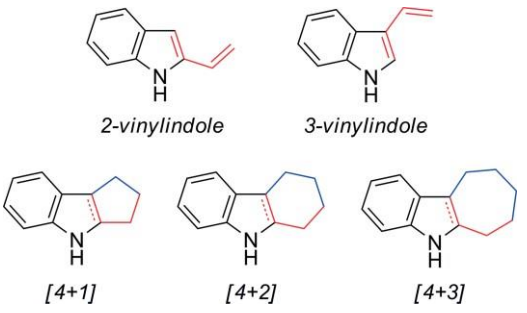
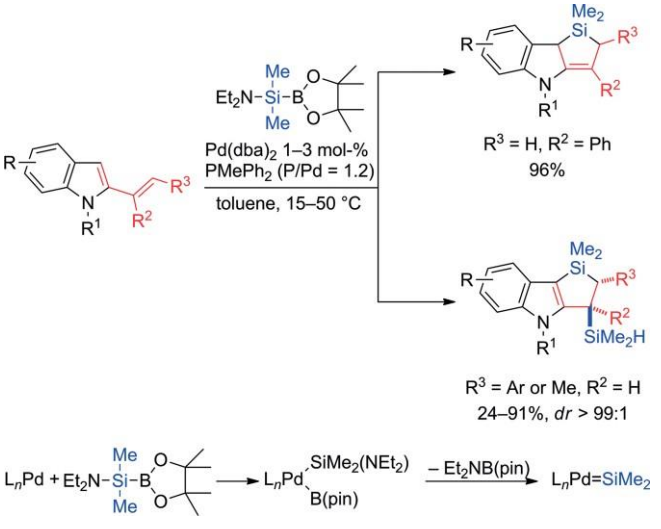


Figure 1. 2-Vinylindole, 3-vinylindole, and some plausible cycloaddition products.

The powerfulness of this principle is well established and, in the case of [4+2] cycloadditions, supported by the huge number of reports published on this topic from the early 1980s onwards.[1] Different orders of cycloaddition reactions are less well, or not at all, explored. In 2011, Suginone, Ohmura and co-workers proposed the first [4+1] cycloadditions involving 2-vinylindoles as dienes.[2] The authors developed a palladium- catalyzed procedure starting from an aminosilylboronic acid and affording a silylene–palladium carbenoid species. This reactant successfully undergoes [4+1] cycloaddition with different *N*-protected 2-[(*E*)-styryl]indoles, giving rise to mono- or disilylated products depending on the indole reagent (Scheme 1).



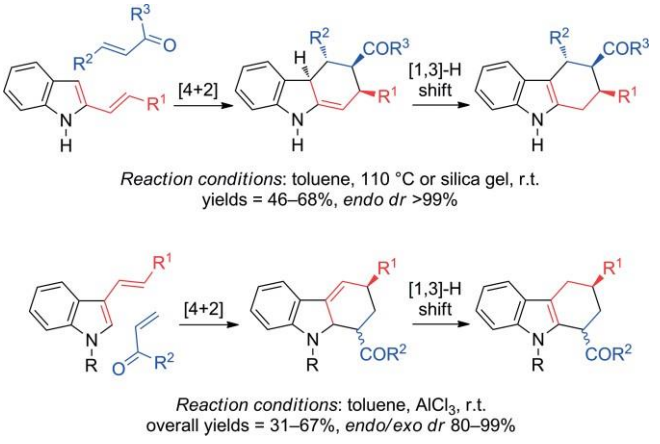
Scheme 1. [4+1] Cycloaddition reactions between 2-vinylindoles and a silylene–palladium species.

To the best of our knowledge, this is the only report of a cycloaddition reaction other than the common [4+2] cycloaddition. Importantly, this work has the merit of having demonstrated that [4+1] cycloadditions between carbenes and vinyl-indoles are possible. Progress in [4+2] cycloaddition for the synthesis of carbazole derivatives and of naturally occurring alkaloids is highlighted by the excellent reviews by Pindur and Kester that cover the literature until 2010.[1] However, over the last years impressive improvements in the form of new proto- cols for the (stereo)selective synthesis of both artificial and naturally occurring carbazoles through [4+2] cycloaddition have been made by several research groups. Thus, in this review we try to analyze carefully the most recent advancements in this field covering the literature published from 2010 onwards. It is worth noting that less recent reports are considered and dis- cussed when necessary. In this paper, [4+2] cycloadditions of vinylindoles are named as Diels–Alder reactions only when a concerted mechanism has been proposed/verified by the authors. The review is organized from the perspective of the nature of the dienophiles (activated vs. inactivated) and of the catalysts (Lewis acids, organocatalysts, and transition-metal catalysts). Two separate subsections summarize the use of methyleneindolinones as dienophiles and the application of [4+2] cycloaddition reactions for the synthesis of indole alkaloids.

2. [4+2] Cycloaddition Reactions of 2- and 3-Vinylindoles

Former systematic studies on this framework started in the 1980s when Pindur and co-workers investigated the participation of 2- and 3-vinylindoles in [4+2] cycloaddition reactions with conventional activated carbodienophiles.[1b,3] Reactions of 2-vinylindoles were thermally promoted or occurred at room temperature in the presence of silica gel. In contrast, reactions of 3-

vinylindoles were catalyzed by aluminum trichloride. In both cases, the reactions provided the corresponding tetrahydrocarbazoles through [4+2] cycloaddition followed by [1,3] hydrogen shift (Scheme 2).

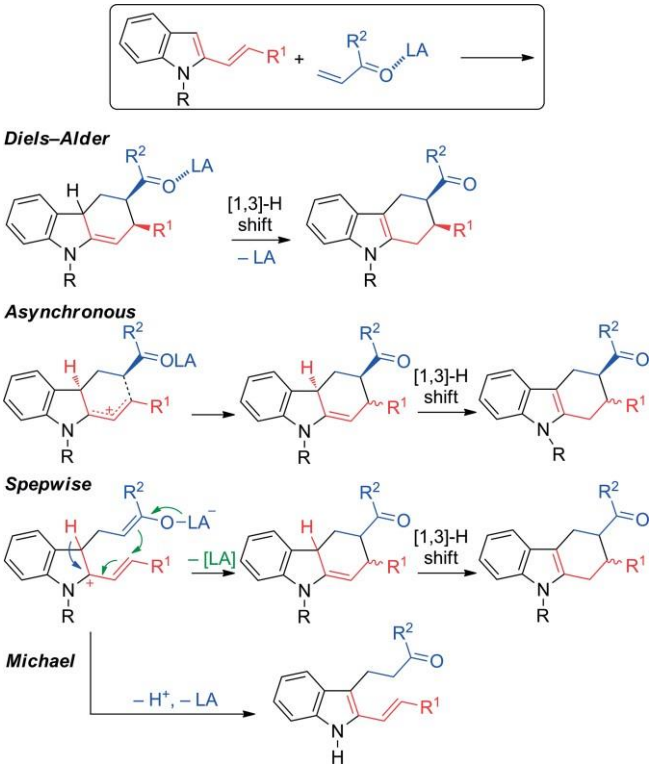


Scheme 2. Pindur's studies on [4+2] cycloaddition reactions of 2- and 3-vinylindoles.

The reactions involving 2-vinylindoles proceeded with total regio- and diastereoisomeric control through a purely $HOMO_{(diene)}/LUMO_{(dienophile)}$-controlled Diels–Alder mechanism. When 3-vinylindoles were employed as dienes, however, more erratic diastereomeric ratios were observed, suggesting contributions of asynchronous or stepwise mechanisms. The major drawbacks for these reactions are the moderate yields and the high reaction temperatures sometimes required, limiting the choice of potential dienophiles. Various modifications to enhance the rates and/or to modulate the (stereo)selectivity of these reactions have been developed, and most of them involve activation of the dienophile by catalytic methodologies: Lewis-acid catalysis or organocatalysis (Brønsted acids and "iminium" methodologies). Moreover, more recently, simple inactivated π-systems have been used as dienophiles in [4+2] cycloaddition reactions with vinylindoles assisted by transition-metal catalysis.

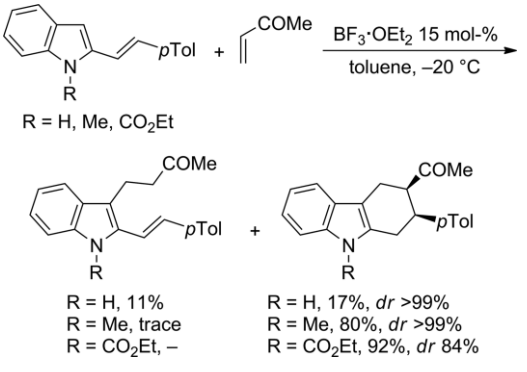
2.1. Activated Dienophiles and Lewis-Acid Catalysis

Complexation between a simple Lewis acid and a functional group of a dienophile lowers the energy of both the HOMO and the LUMO of the dienophile, thus increasing the stabilization of the transition state and enhancing the cycloaddition reaction rate.[4] However, coordination of a Lewis acid to even a simple enone generates a highly polarized complex, increasing the electrophilic nature of the β-carbon atom. The resulting complex can react with the diene through a pure Diels–Alder mechanism or by way of an asynchronous or stepwise mechanism with consequent potential loss, in this latter case, of stereochemical control. Conceivable reaction paths for 2-vinylindoles are shown in Scheme 3. It is worth noting that when working with 2-vinylindoles, if the catalyzed reaction proceeds by a stepwise mechanism a Michael addition product could be formed through a competitive Friedel–Crafts-type reaction.



Scheme 3. Lewis-acid-catalyzed [4+2] cycloaddition reactions of 2-vinyl- indoles: conceivable reaction paths.

However, over the years, judicious choice of substrates, catalysts, and reaction conditions has allowed these difficulties to be circumvented and the desired diastereo- and enantioselectivity to be achieved. We have extensively studied the reactivity of 2-vinylindoles with open-chain carbon–carbon dienophiles under Lewis-acid catalysis conditions.[5] To underline the influence of the protecting group at the indole nitrogen atom we performed three experiments involving methyl vinyl ketone as dienophile and *N*-unsubstituted, *N*-methyl-, and *N*-ethoxy-carbonyl-2-*p*-methylstyrylindole as dienes. The reactions were conducted in the presence of boron trifluoride–diethyl ether as catalyst, and the obtained results are summarized in Scheme 4.

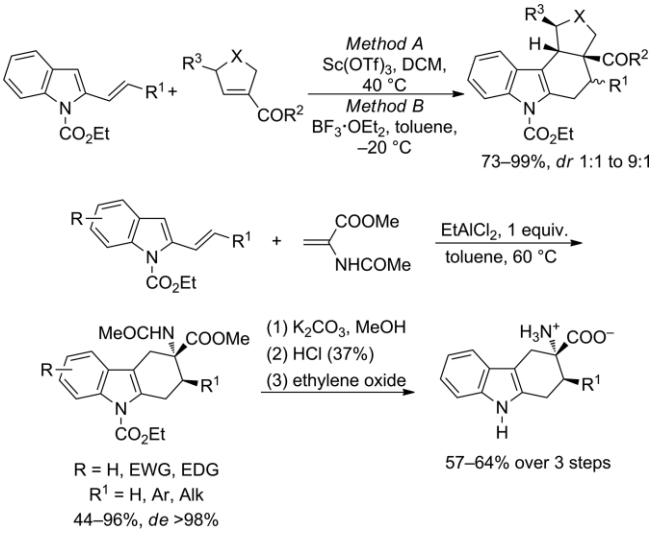


Scheme 4. Influence of the protecting group on the indole nitrogen atom on BF_3·OEt_2-catalyzed cycloadditions with methyl vinyl ketone.

Working with *N*-unsubstituted indole we isolated both the Michael addition product and the [4+2] cycloaddition product in very poor yields. In contrast, when we employed the *N*- methyl and *N*-ethoxycarbonyl-substituted indoles the desired tetrahydrocarbazoles were obtained, in 80/92 % yields and in 99/84 % diastereoisomeric excesses, respectively. Thus, the formation of alkylation by-products can be avoided by working with *N*-alkyl- or *N*-EWG-substituted indoles and, as we will see, this is true for all reported Lewis-acid-catalyzed [4+2] cycloaddition reactions of vinylindoles. Moreover, beside boron trifluoride, we tested a plethora of Lewis acids in the same model reaction. The best results are outlined in Table 1.

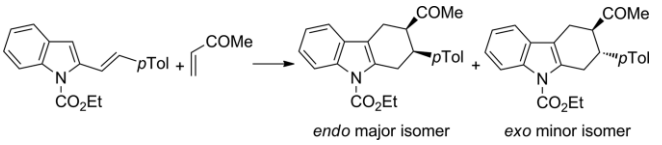
N-Ethoxycarbonyl-2-*p*-methylstyrylindole was selected as substrate, because the corresponding carbazole can easily be deprotected under mild reaction conditions (K_2CO_3 in methanol at room temperature). As well as boron trifluoride–diethyl ether, scandium,

copper(II), and aluminum catalysts also gave rise to a good balance between yield and diastereoselection at room temperature. Additionally, the good results obtained in copper(II)-catalyzed reactions, together with the recent increase in popularity of both silver- and gold-based catalysts, prompted us to test the catalytic activity of the entire series of coinage metals in our intermolecular cycloaddition reactions. Coinage metal salts display σ- and π-philic properties to activate either the carbon–carbon or carbon–heteroatom multiple bonds. Thus, testing their performance in our reactions appeared particularly attractive. Silver triflate gave similarly good results with a catalyst loading of 2 mol-%. A cationic gold(I) complex generated in situ from (triphenylphosphane)gold(I) chloride and silver triflate provided better results: 96 % yields and 86 % *de*. Next, gold(III) chloride was tested at room temperature in toluene, giving rise to similar results; however, there was a tangible reduction in the reaction time. [4+2] Cycloaddition reactions of 2-vinylindoles were also extended to different 2-vinylindoles and/or to more challenging dienophiles. The diastereoselectivity for the *endo* product remained high whatever the 2-vinyl- indole employed. However, the introduction of a substituent at the (3-position of the dienophile resulted in almost complete loss of diastereoselectivity. Further applications of these reac tions include the use of (hetero)cyclic dienophiles[6] and of methyl 2-acetamidoacrylate (dehydroalanine)[7] for the synthesis of [*c*]-carbo- or -furoannulated tetrahydrocarbazoles and of 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acids (constrained analogues of tryptophan; Scheme 5).



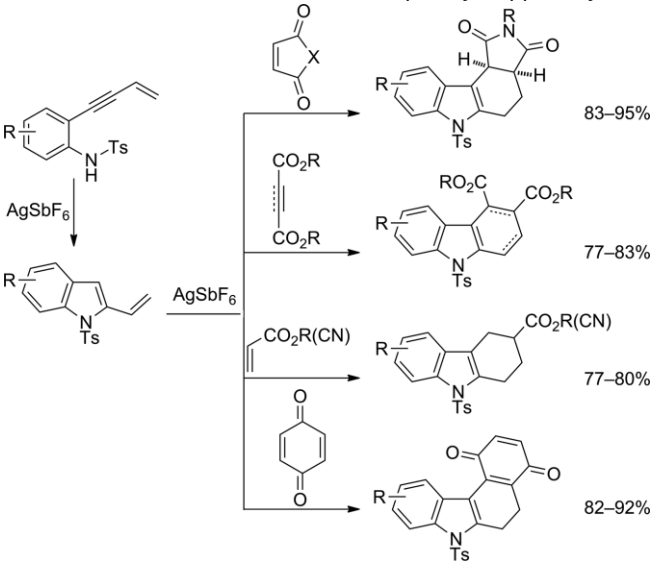
Scheme 5. 2-Vinylindoles: Lewis-acid-catalyzed [4+2] cycloaddition reactions.

Table 1. 2-Vinylindoles: Lewis-acid-catalyzed [4+2] cycloaddition reactions.



Catalyst [mol-%]	Solvent	*T* [°C]	*t* [h]	Yield [%]	*de* [%]
BF_3OEt_2 [15]	toluene	–20	1.5	92	84
$EtAlCl_2$ [15]	toluene	r.t.	5	73	81
$Mg(ClO_4)_2$ [15]	toluene	110	24	77	43
$Sc(OTf)_3$ [15]	CH_2Cl_2	r.t.	24	95	67
$Cu(OTf)_2$ [15]	toluene	r.t.	96	81	71
$Cu(OTf)_2$ [15]	CH_2Cl_2	r.t.	24	94	78
AgOTf [2]	toluene	r.t.	24	88	78
$Au(PPh_3)Cl/AgOTf$ [2]	toluene	r.t.	24	96	86
$AuCl_3$ [2]	toluene	r.t.	1.5	99	85

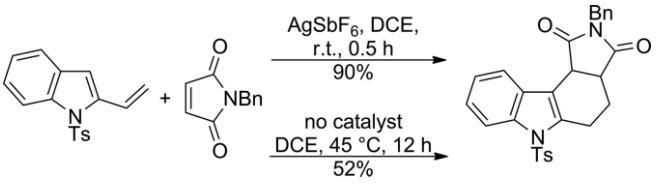
The reactions were catalyzed by scandium triflate or boron trifluoride–diethyl ether and by ethylaluminum dichloride, respectively. When working with dehydroalanine, 1 equiv. of catalyst was necessary, because it coordinates with both amide and ester carbonyl groups. Furthermore, as observed with β-substituted enones, low levels of diastereoselection were also often observed with cyclic dienophiles, whereas on employment of dehydroalanine the diastereoselction was almost complete. In a more recent paper, Kamal and co-workers merged related [4+2] cycloadditions in a cascade process involving *N*-tosyl-2-ene- yne-anilines and both symmetrical and unsymmetrical dienophiles.[8] In particular, with $AgSbF_6$ as Lewis acid, *N*-tosyl-2-ene-yne-anilines generate the corresponding 2-vinylindoles in situ, and these are subsequently trapped by various dienophiles (Scheme 6).



Scheme 6. Silver-catalyzed domino aza-annulation/Diels–Alder cyclization of 2-ene-yne-anilines.

Thus, the whole cascade process encompasses an intramolecular hydroamination process followed by a [4+2] cycloaddition reaction, giving rise to carbazoles, dihydrocarbazoles, and tetrahydrocarbazoles, depending on the employed dienophiles. As reported in the former examples, 2-vinylindole intermediates bear an EW group at the nitrogen atom. Moreover, the catalyst screening revealed that a cationic gold(I) complex, generated in situ by chloride abstraction from (triphenylphosphane)gold(I) chloride and silver hexafluoroantimonate, is also able to catalyze the reaction.

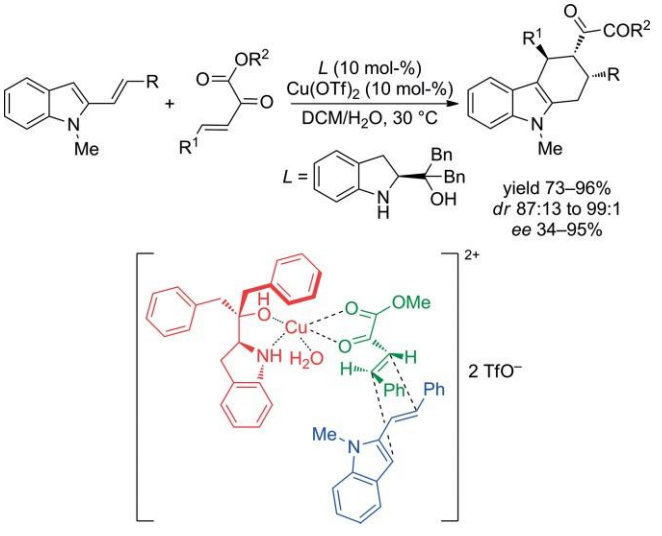
In contrast, under the same reaction conditions, conventional Lewis acids afforded the corresponding 2-vinylindole as the sole reaction product. The reacting indoles are always unsubstituted at the vinyl moiety, and so these cycloadditions each afford only one diastereoisomer. An active role for the silver catalyst in both reaction steps was claimed by the authors based on several control experiments (Scheme 7).



Scheme 7. Control experiments on the role of $AgSbF_6$ in the domino reaction.

Thus, on starting from preformed *N*-tosyl-2-vinylindole and in the absence of catalyst the corresponding carbazole was obtained in a yield lower than that in the silver-catalyzed reaction even after a prolonged reaction time at 45 °C.

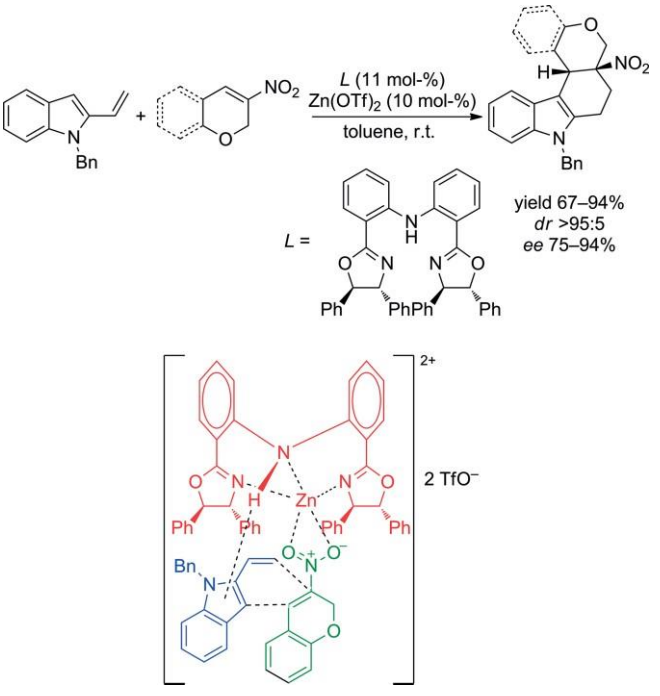
The various protocols described so far allow for the synthesis of carbazole derivatives, frequently with a high degree of diastereoselection, with the aid of Lewis-acid catalysis. Examples of enantioselective reactions are less common, and achieving enantioselectivity in these reactions is still a challenging objective. Two examples of chiral Lewis-acid-catalyzed reactions have recently been reported. Lu and co-workers developed a Lewis acid complex, consisting of copper(II) triflate and an indolinylmethanol chiral ligand, capable of catalyzing reactions between *N*-methyl-2-vinylindoles and (3,γ-unsaturated α-keto esters for the synthesis of highly substituted tetrahydrocarbazoles as new drug candidates (Scheme 8).[9]



Scheme 8. Enantioselective [4+2] cycloaddition catalyzed by a chiral copper complex.

Good *endo* selectivity and moderate to good enantiomeric excesses were achieved at 30 °C in a mixture of dichloromethane and water as solvents. The authors suggested that a concerted mechanism was operative in these reactions and described a plausible transition state featuring a distorted octahedral geometry at the copper center (Scheme 8). As can be seen, the 2-vinylindole approaches the double bond of the dienophiles from the bottom, probably because the benzylic chain of the ligand partially shields the opposite face of the keto ester, and an *endo* geometry seems to be favored. As a result, the predominant formation of one of the four conceivable stereoisomers was observed. The authors found also that the water is essential for high *ee* values; its coordination to the copper atom enhances the facial selection.

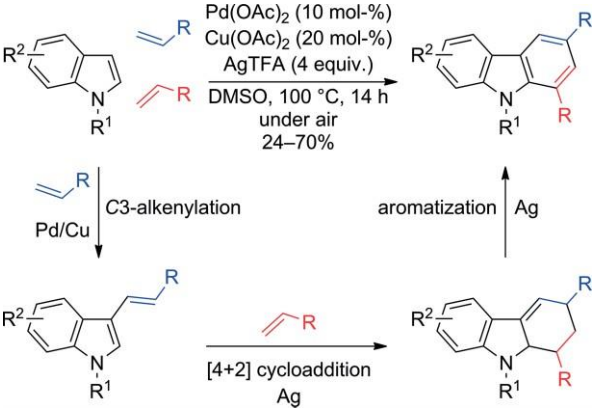
Two years before, Ding and Xiao reported enantioselective cycloadditions between 2-vinylindoles and 3-nitro-2*H*-chromenes in the presence of a zinc triflate/bis(oxazoline) complex (Scheme 9).[10]



Scheme 9. Enantioselective [4+2] cycloaddition catalyzed by a chiral zinc complex.

Almost complete diastereoselection and enantioselectivity ranging from 75 to 94 % were observed. In the proposed transition state, two complementary interactions are responsible for the observed selectivity (Scheme 9). Zinc activates the nitro group of the dienophile in a geometry dictated by the presence of an interaction between the ligand NH group and the π-system of the indole. These two examples demonstrate that chiral Lewis acid complexes are able to catalyze [4+2] cycloaddition reactions of 2-vinylindoles, affording the corresponding tetrahydrocarbazoles with good *ee* values. However, the dienophilic opposite numbers are limited to particular and well-fixed atom arrangements, and application of this synthetic strategy to a wider range of dienophiles needs to be developed in the future.

Lewis-acid-catalyzed [4+2] cycloadditions between 3-vinylindoles and classical dienophiles have been less well investigated than those involving 2-vinylindoles. Apart from the pioneering works[1,3] by Pindur (see Scheme 2), no comprehensive investigations into the catalytic activity of simple Lewis acids in these cycloadditions have been made. Spotty examples reported in the literature refer to specific substrates (dienes and dienophiles) for the synthesis of particular classes of indole derivatives. Two of these involve 3-vinylindoles in sequential onepot processes: a *C*3-alkenylation/Diels–Alder/aromatization sequence and a Diels–Alder/ene reaction. In the first example, the whole sequence is an indole-to-carbazole π-extension reaction performed in the presence of a palladium/copper/silver trimetallic system (Scheme 10).[11]

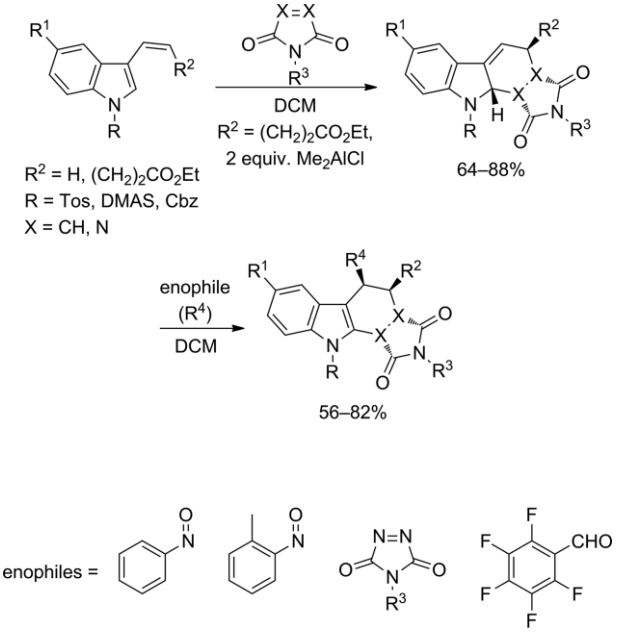


Scheme 10. One-pot indole-to-carbazole π-extension.

The first step involves a palladium(II)-catalyzed intermolecular alkenylation of the starting indoles by *C*3-regioselective C–H functionalization, giving rise to a 3-vinylindole intermediate. This reaction step works with copper(II) acetate as oxidizing agent to convert palladium(0) into palladium(II).[12] Then, a silver-catalyzed [4+2] cycloaddition with a second molecule of alkene affords a tetrahydrocarbazole, which is oxidized to the final carbazole in a silver-promoted process. An excess of silver salt is necessary to

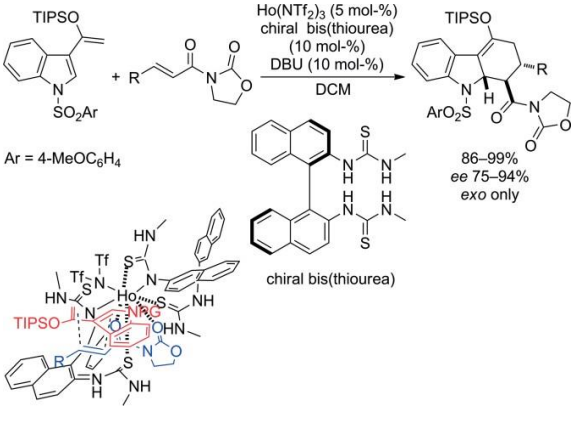
trigger both the cycloaddition and the oxidation steps. An alkyl protecting group seems to be required to ensure the formation of the desired compounds. The authors applied this protocol to the synthesis of a granulatimide derivative pertaining to an interesting class of Chk1 kinase inhibitors.

In the second example,[13] 3-vinylindoles, protected at the nitrogen atom with EW groups, are involved in [4+2] cycloadditions with maleimides or 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (Scheme 11). The peculiarities of these reactions are at least two. A Lewis acid promoter (dimethylaluminum chloride, 2 equiv.) is required only when the 3-vinylindole bears a substituent on the vinyl moiety. Moreover, the reaction products arise from a simple *endo*-selective [4+2] process not followed by an aromatization step ([1,3]-H shift) and favored by the presence of an EW group at the nitrogen atom. The dearomatized indoles can undergo diastereospecific intermolecular ene reactions, giving rise to highly substituted indole derivatives. Tested enophiles range from nitrosoarenes to PTAD and pentafluorobenzaldehyde (Scheme 11).



Scheme 11. [4+2] Cycloaddition/ene reactions of 3-vinylindoles (can be performed in a one-pot fashion).

With unsubstituted 3-vinylindoles the reactions can also be performed in a one-pot fashion, with addition of the dienophile to the reaction mixture first and then of the enophile. Reaction conditions are flexible in both steps depending on the substitution pattern of the reacting species. As in the case of 2-vinylindoles, examples of Lewis-acid-catalyzed enantioselective reactions of 3-vinylindoles are rare. In an original work, Nishida and co-workers, inspired by the structure of the Danishefsky diene, employed 3-[1-(silyloxy)vinyl]indoles in [4+2] cycloaddition with substituted 3-acryloyloxazolidin-2-ones.[14,15] The reactions are catalyzed by a chiral holmium(III) complex generated in situ from holmium trifluoromethanesulfonimide and a chiral bis(thiourea) (Scheme 12).

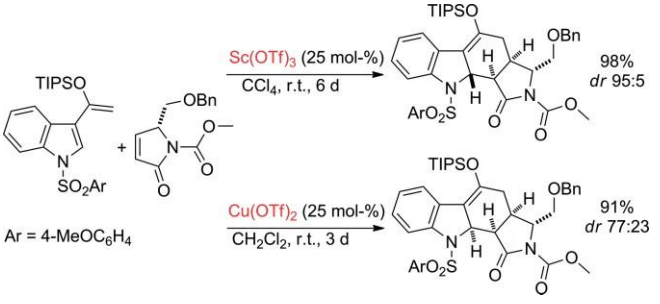


Scheme 12. Enantioselective [4+2] cycloaddition catalyzed by a chiral holmium complex.

The electron-rich diene reacted smoothly with a plethora of differently substituted 3-acryloyloxazolidin-2-ones, and the obtained cycloadducts showed *exo* structures and high *ee* values. MS experiments revealed that a complex formed by two molecules of thiourea and one of holmium is the active catalytic species able to induce the correct approach of diene and dienophile. DBU acts as a base to deprotonate the urea. This straightforward approach leads to compounds possessing three contiguous stereogenic

centers; a fourth center can be added by treating the obtained carbazole derivative with an alkyl halide in the presence of TBAF as a base. Further manipulations of the obtained compounds lead to tetracyclic skeletons.

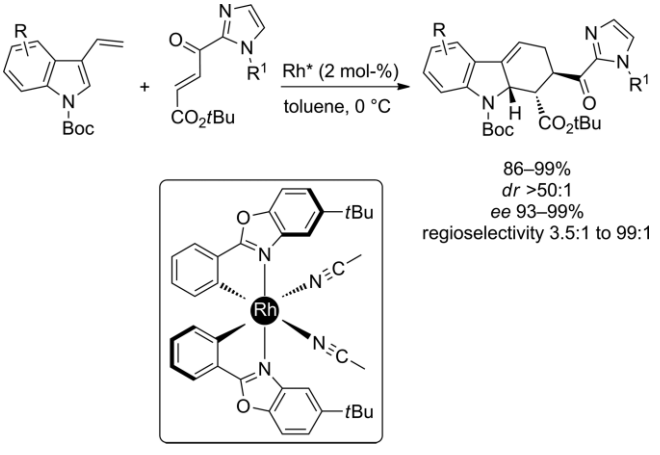
The same research group published a straightforward approach to the same class of carbazole derivatives by treating the same electron-rich indolyl-diene with a chiral cyclic (*Z*)-olefin derived from pyroglutamic acid (Scheme 13).[16]



Scheme 13. Scandium or copper triflate catalyzed enantioselective [4+2] cycloaddition with a chiral dienophile.

Either *exo* or *endo* chiral cycloadducts could be obtained, in the presence of scandium or copper triflate, respectively, with good to moderate diastereomeric ratios. The origin of the stereocontrol might be related to the difference in bulkiness of the intermediate complexes in the presence of the different Lewis acids. In addition, the authors developed the subsequent stereoselective alkylation of the cycloadducts, leading to highly substituted hydrocarbazoles, each with five continuous chiral centers including a quaternary carbon atom.

Finally, an asymmetric synthesis of hydrocarbazoles catalyzed by a chiral rhodium-based Lewis acid was reported (Scheme 14).[17]

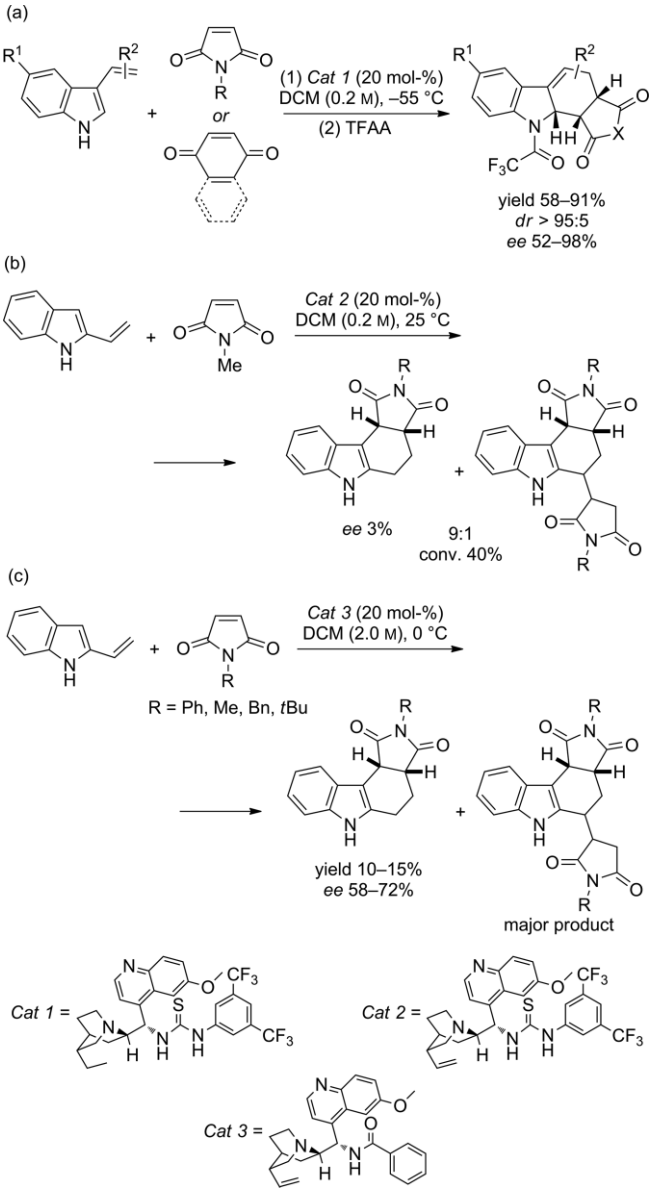


Scheme 14. Enantioselective [4+2] cycloaddition catalyzed by a chiral-atmetal rhodium complex.

Several features make this reaction quite different from those already reported. Firstly, the asymmetric catalyst exerts both its optical and its catalytic activities through an octahedral rhodium center, and there is no need for chiral ligands for the metal atom (see Schemes 8, 9, and 12 for comparison). Moreover, even though excellent diastereo- and enantioselectivity were usually observed, some difficulties in achieving good levels of regioselectivity were occasionally encountered. As in the case of 2-vinylindoles, development of new and more efficient enantioselective reactions also needs to be established here in the future.

2.2. Activated Dienophiles and Organocatalysis

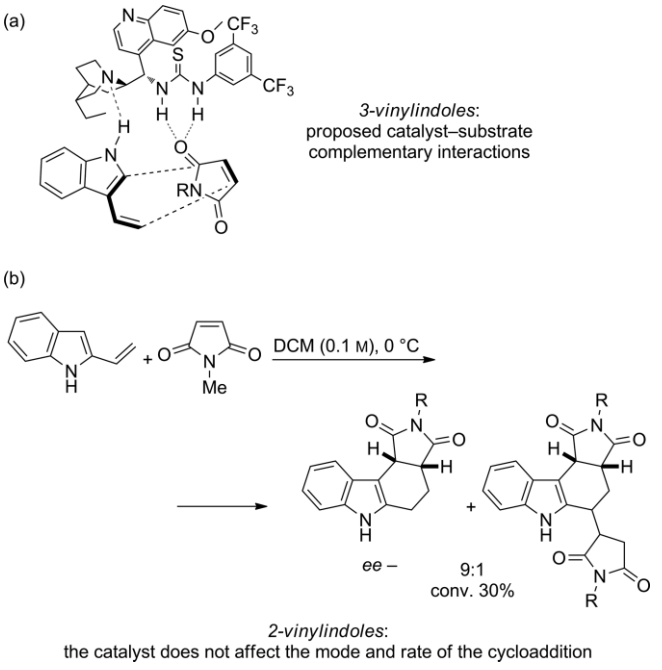
Organocatalytic methodologies applied to the [4+2] cycloaddition reactions of 2- and 3-vinylindoles operate either in the presence of hydrogen-bond-donor or Brønsted-acid catalysts or through the generation of iminium ions from enones and suitably substituted secondary amines. Application of these methodologies has allowed for both diastereo- and enantioselective synthesis of carbazole derivatives. The first examples involving 2- and 3-vinylindoles in hydrogen-bond-donor-organocatalyzed [4+2] cycloaddition reactions were reported by Ricci and co-workers (Scheme 15).[18]



Scheme 15. First examples of hydrogen-bond-donor-organocatalyzed [4+2] cycloaddition reactions of 3- and 2-vinylindoles.

In particular, they account for the different behavior of 2- and 3-vinylindoles in the presence of difunctional hydrogen-bond-donor organocatalysts.

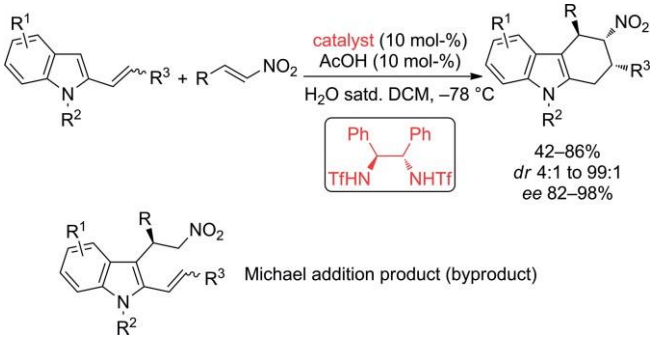
Reactions performed with 3-vinylindoles occurred through a pure Diels–Alder mechanism, furnishing *endo* cycloadducts that could be isolated prior to rearomatization by *N*-derivatization with trifluoroacetic anhydride. Enantioselectivity of up to 98 % could be achieved by using a chiral difunctional acid/base organocatalyst (Scheme 15a). In contrast, only poor results were obtained with 2-vinylindoles under similar reaction conditions (Scheme 15b). However, by working with a different catalyst in more concentrated solutions, tetrahydrocarbazoles could be obtained with *ee* values of up to 72 %, although in poor yields. In addition, products arising from a [4+2]/ene reaction sequence, involving a second molecule of the dienophile, were the main reaction products (Scheme 15c). The authors explained this different behavior with reference to literature and experimental evidence (Scheme 16).



Scheme 16. Behavior of 3- and 2-vinylindoles in hydrogen-bond-donor-catalyzed reactions with maleimides.

In particular, in reactions performed with 3-vinylindoles, the basic moiety of the catalyst can interact with the indole NH group; concurrently, the thiourea moiety activates the cyclic dienophile. This double interaction affects both the mode (*dr* and *ee*) and the rate of the cycloaddition (Scheme 16a). In contrast, the catalyst does not affect the rate of the cycloaddition of 2-vinylindoles. Thus, the model reaction performed with or without the catalyst gives rise to similar results (cf. Schemes 15b and 16b). In a more concentrated solution, the catalyst seems to be able to give rise to a kind of kinetic resolution affording the enantioenriched aromatized carbazole and the ene adduct by increasing the ratio between the rate of formation of ene product and of carbazole.

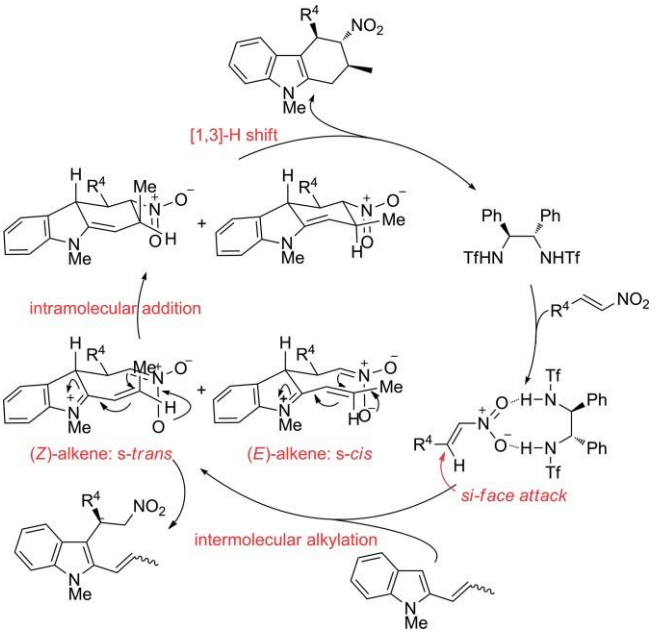
Successful examples of diastereo- and enantioselective reactions between 2-vinylindoles and nitroalkenes, aided by hydrogen-bond catalysis, for the synthesis of carbazoles was reported shortly after by Xiao and co-workers, who achieved reactions between nitroalkenes and (*Z*/*E*)-2-(prop-1-en-1-yl)-1*H*- indoles in the presence of a simple hydrogen-bond donor catalyst, a chiral bis(sulfonamide) (Scheme 17).[19]



Scheme 17. Hydrogen-bond-donor-catalyzed reactions between 2-vinyl- indoles and nitroalkenes.

Accurate screening for the best reaction conditions (catalyst, solvent, temperature, and additive) allowed for the diastereo- and enantioselective synthesis of nitrocarbazoles, avoiding the formation of simple Michael addition products. In this case, consistent with a stepwise process, the (*Z*)-vinylindole was consumed much more rapidly than the (*E*) isomer.

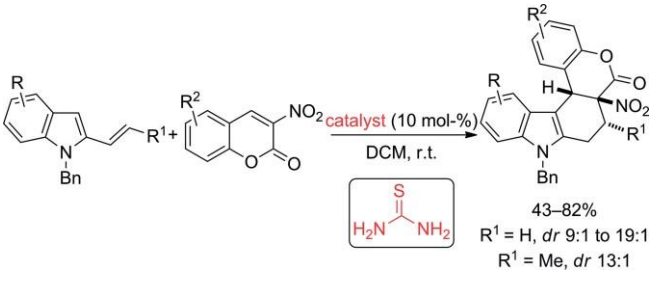
In addition, the competitive formation of the Michael adduct makes the proposed stepwise path more favorable (Scheme 18).



Scheme 18. Mechanism of the hydrogen-bond-donor-catalyzed reactions between 2-vinylindoles and nitroalkenes.

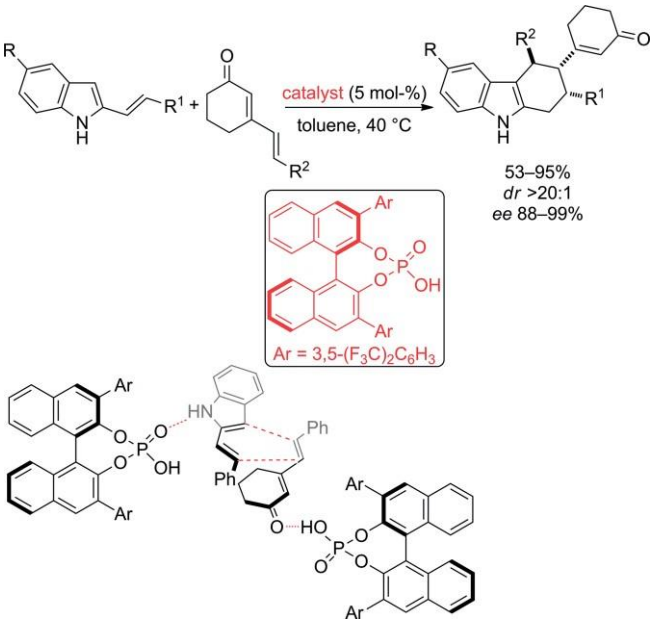
Thus, activation of the alkene nitro group by the chiral bis(sulfonamide) favors the Michael addition of C3 of the *N*- methyl-2-[(*E*/*Z*)-propenyl]indole on the *si*-face of the activated alkene, giving rise to s-*trans* and s-*cis* intermediates. These intermediates contain both iminium and nitronate functions for the subsequent intramolecular cyclization to the indolenine core. A final fast [1,3]-H shift generates the corresponding tetrahydrocarbazole. Rearomatization of the first intermediate gives the Friedel–Crafts alkylation byproduct.

Alongside this, although not claimed by the authors, a similar reaction mechanism could also be operative in the diastereoselective cycloadditions between 2-vinylindoles and 3-nitrocoumarins under thiourea catalysis conditions.[20] The reaction proceeds with *endo* selectivity (*dr* = 13:1) when a 2-(prop-1-en-1-yl)-1*H*-indole [(*E*)/(*Z*) = 2:1] is used as substrate (Scheme 19).



Scheme 19. Thiourea-catalyzed reactions between 2-vinylindoles and 3-nitro-coumarins.

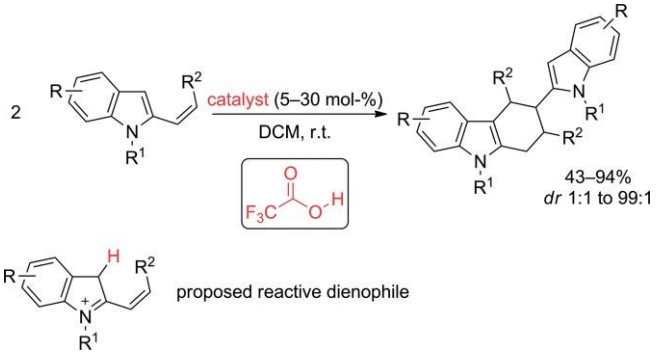
In contrast, the mechanism of the reactions between (*E*)-2- vinylindoles and cyclic 2,4-dienones performed in the presence of chiral phosphoric acids has been investigated in depth (Scheme 20).[21]



Scheme 20. CBA-catalyzed (CBA = chiral Brønsted acid) reactions between 2- vinylindoles and α,β,γ,δ-unsaturated cyclic ketones.

Firstly, the authors observed a decrease in selectivity when indoles bearing a substituent at the nitrogen atom were used as dienes. This means that an interaction between the NH group and the Brønsted basic site of the catalyst (P=O) is required along with concomitant Brønsted acid activation of the carbonyl group of the dienophile (P–OH···O=C). Moreover, nonlinear-effect studies, performed to establish whether the optical purity of phosphoric acid was directly associated with the optical purity of the product, revealed that at least two molecules of the chiral acid are involved in the transition state of the enantiodifferentiating step. The proposed mechanistic model is depicted in Scheme 20. However, theoretical demonstration of the occurrence of a pure Diels–Alder reaction was not reported. These reactions are an uncommon example of catalytic asymmetric vinylogous [4+2] cycloaddition involving α,β,γ,δ-unsaturated cyclic ketones as dienophiles. Activation of the more distant double bond is achieved, and the reaction products each possess an α,β-unsaturated system suitable for further manipulations, increasing the molecular and stereochemical complexity.

Furthermore, simple trifluoroacetic acid catalyzed [4+2] cycloadditions of 2-vinylindoles were established for the diastereoselective synthesis of 3-indolyl-substituted tetrahydrocarbazoles from two molecules of (*Z*)-2-vinylindole derivatives reacting both as diene and as dienophile (Scheme 21).[22]



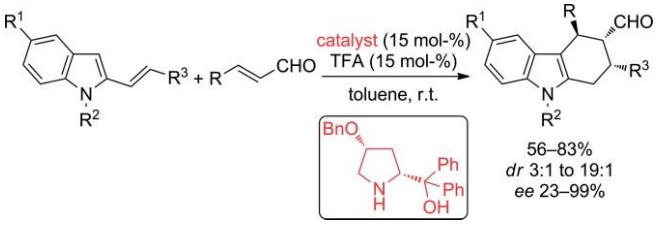
Scheme 21. Brønsted-acid-catalyzed reactions of 2-vinylindoles.

TFAA-catalyzed reactions proceed through protonation of the indole at C3, giving rise to an iminium ion intermediate capable of reacting as an activated dienophile with a second molecule of the 2-vinylindole through a [4+2] cycloaddition/ aromatization pathway. The proposed mechanism was confirmed through deuterium-labeling experiments. For $R^2 \neq H$, even though the diastereoisomeric ratios were determined by ^1H NMR analysis, the mutual positions of substituents in the major diastereoisomer were not disclosed.

Finally, several reports on organocatalytic methodologies applied to the [4+2] cycloaddition reactions of 2- and 3-vinylindoles operating through the generation of iminium ions from enones and suitably substituted secondary amines have appeared in the literature. Along with the work published by MacMillan[23] on the cycloaddition reactions of vinyltryptamines for the synthesis of (–)-minfiensine (see Section 2.5), Zhao developed Diels–Alder reactions between 2-vinylindoles and α,β-unsaturated

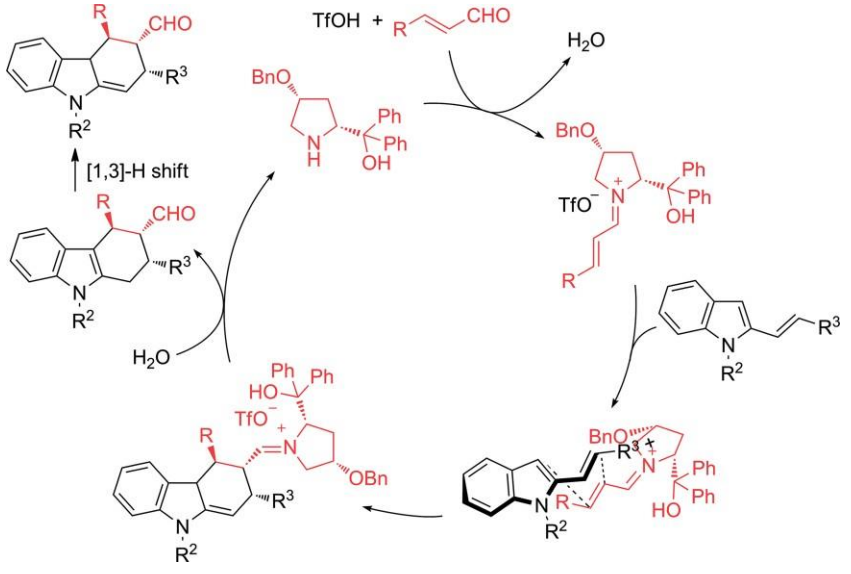
aldehydes assisted by iminium catalysis (Scheme 22).[24]

The authors tested the MacMillan catalyst alongside a series of prolinol derivatives. They found that *cis*-4-benzyloxy-α,α-diphenylprolinol was the best choice for achieving high levels of diastereo- and enantioselection and for avoiding the formation of *C*3-alkylated indole compounds. The scope of the cycloaddition was then studied with different vinylindoles; however, only (3-monosubstituted aldehydes were tested in this study, and the behavior of more challenging dienophiles was not reported.



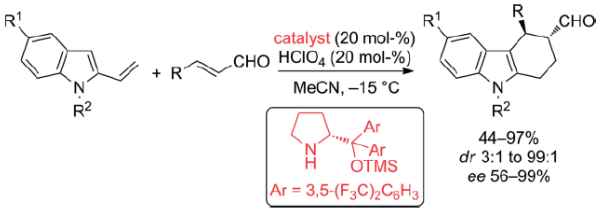
Scheme 22. Prolinol-organocatalyzed [4+2] cycloaddition of 2-vinylindoles.

The authors proposed a catalytic cycle (Scheme 23) involving in the first step the formation of an iminium intermediate, which then reacts in an *endo* concerted way with the 2-vinyl- indole to give another iminium intermediate. Hydrolysis of the iminium species followed by a fast aromatization step releases the catalyst and the reaction product.



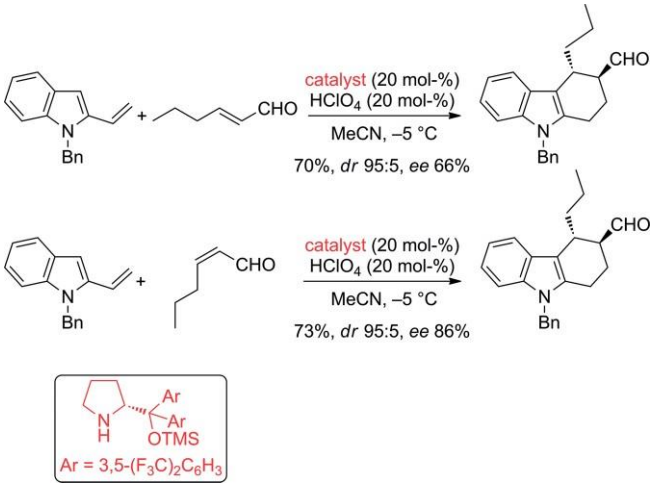
Scheme 23. Proposed mechanism for the enantioselective reactions between 2-vinylindoles and α,β-unsaturated aldehydes under iminium catalysis conditions.

According to the authors' hypothesis, the reaction thus proceeds through a [4+2] concerted synchronous mechanism. Relationships between substituents are governed by a typical suprafacial approach and by a mode of mutual presentation of diene and dienophile counterparts (*endo* vs. *exo* approach). The regiochemistry is determined by a polarity-driven process, whereas the origin of the enantiocontrol is likely to be the extended shielding effect of the pyrrolidine ring substituents in the [4+2] transition state. However, an alternative stepwise pathway cannot be ruled out. Indeed, in a related paper by Chen, Xiao, and co-workers, a stepwise mechanism was proposed for the closely related [4+2] cycloaddition between 2- vinylindoles and α,(3-unsaturated aldehydes catalyzed by a diarylprolinol silyl ether (Scheme 24).[25]



Scheme 24. [4+2] Cycloaddition reactions of 2-vinylindoles organocatalyzed by a prolinol silyl ether.

3,4-Disubstituted tetrahydrocarbazoles were obtained with moderate to excellent yields and diastereo- and enantioselection. In order to discriminate between a concerted or stepwise mechanism and to achieve a better understanding of the reaction mechanism, two experiments were performed with a 2- vinylindole and (*E*)- and (*Z*)-hex-2-enal (Scheme 25).

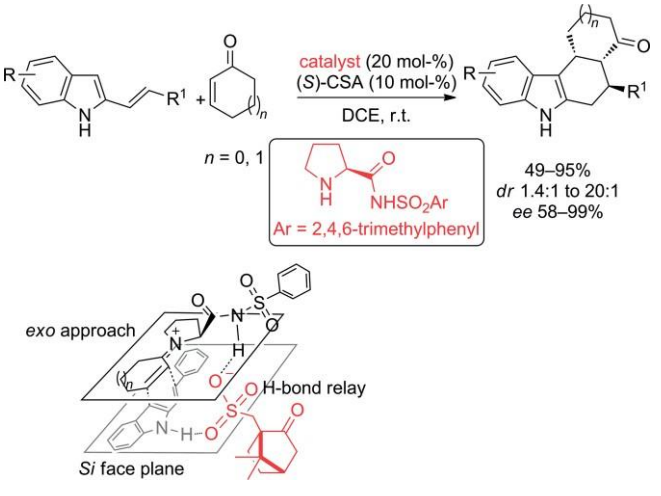


Scheme 25. [4+2] Cycloaddition reactions between a 2-vinylindole and (*E*)- or (*Z*)-hex-2-enal organocatalyzed by a prolinol silyl ether.

Both reactions give the corresponding carbazole with the same configuration, so a stepwise mechanism based on a C3 intermolecular Michael addition followed by an intramolecular cyclization seems to be more likely. The mechanism parallels that shown in Scheme 18 for the hydrogen-bond-donor-catalyzed reactions between 2-vinylindoles and nitroalkenes.

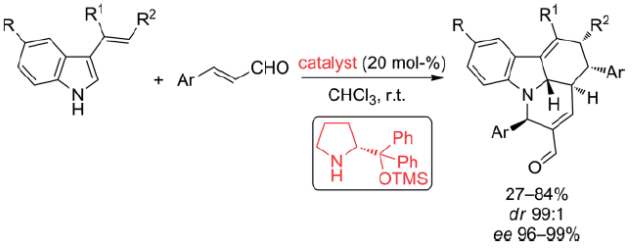
The last two papers reviewed deal with closely related transformations even though the authors proposed different reaction mechanisms. Moreover, as already stated, examples are limited to linear (3-monosubstituted α,(3-unsaturated aldehydes. Moreover, three or two contiguous stereocenters are created depending on the substitution on the vinyl moiety of the reacting indoles.

Extension of organocatalytic methodologies to cyclic enones was recently reported.[26] Also in this case the reactions take advantage of the use of a proline derivative as catalyst, but with the aid of the hydrogen-bond relay of (*S*)-camphorsulfonic acid (Scheme 26). A significant difference between this last report and the previous two lies in the use of *N*-unsubstituted indoles, with the NH group being involved in hydrogen bonding with the (*S*)-camphorsulfonic acid.



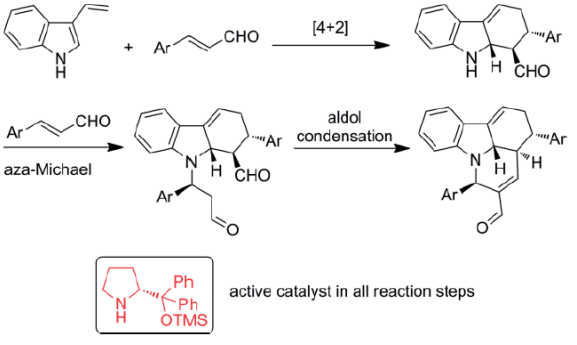
Scheme 26. Prolinosulfonamide-organocatalyzed [4+2] cycloaddition reactions of 2-vinylindoles.

In addition, 3-vinylindoles have also been used as substrates in prolinol-organocatalyzed reactions. In particular, the reaction involves one molecule of a 3-vinylindole component and two molecules of a (3-aryl-substituted α,β-unsaturated aldehyde component for the synthesis of tetracyclic derivatives through a Diels–Alder/aza-Michael/aldol condensation domino sequence (Scheme 27).[27]



Scheme 27. [4+2] Cycloaddition reactions of 3-vinylindoles organocatalyzed by a prolinol silyl ether.

(*S*)-Diphenylprolinol TMS ether was the catalyst of choice for achieving high levels of diastereo- and enantioselectivity. Because of the inherent instability of 3-vinylindoles and despite the fact that the hypothetical reaction stoichiometry requires an indole/aldehyde ratio of 1:2, the reactions were performed with twofold excesses of the indole component (Scheme 28).



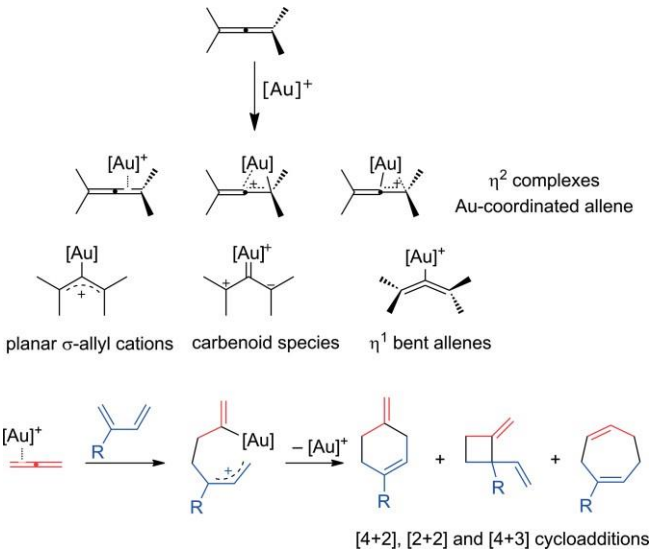
Scheme 28. Proposed mechanism for the enantioselective reaction between 3-vinylindoles and α,β-unsaturated aldehydes under iminium catalysis conditions.

Thus, the initially formed [4+2] cycloadduct reacts with a second molecule of aldehyde in an aza-Michael reaction involving the indole nitrogen atom. Finally, intramolecular aldol condensation allows for the construction of the fourth ring. It is worth mentioning that the first two reaction steps work through iminium activation, whereas the final step occurs through enamine activation. Moreover, the same catalyst is operative along the entire cascade process, leading to tetracyclic derivatives with at least four stereogenic centers. In this case, discussion of the mode of cycloaddition – concerted versus asynchronous – was omitted.

2.3. Unactivated π-Systems and Transition-Metal Catalysis

Recently, several reports on [4+2] cycloaddition reactions between vinylindoles and transition-metal-activated π-systems have appeared in the literature. As stated before, classical [4+2] cycloadditions require the presence of polarized functional groups in the substrates to facilitate the transformation, and – in general – the reactivity of inactivated olefins, allenes, and acetylenes is very poor. However, metal catalysts can promote these cycloaddition reactions efficiently and selectively, because complexation of a metal atom to the π-system temporarily polarizes and activates these otherwise unreactive species, opening the way to improved reactivity and new chemistry. Reported examples have explored the reactivity of allenes as dienophiles in [4+2] cycloaddition reactions with 2- and 3-vinylindoles under gold-catalysis conditions. Because of their soft Lewis-acid and carbophilic characters, gold(I) catalysts can activate allenes selectively, allowing the formation of electrophilic species capable of reacting with different nucleophiles (Scheme 29).

When π-systems – dienes in particular – are involved as nucleophiles the formation of a bond, normally at the external allene carbon atom, may be followed by the creation of a second C–C bond, resulting in formal [4+2], [2+2], or [4+3] cycloaddition products. Thus, allenes can participate as C2 or C3 synthons in cycloaddition reactions, and the achievement of selective transformations is often an exciting objective. In 2013 we reported the first examples of gold-catalyzed intermolecular [4+2] cycloaddition reactions between 2-vinylindoles and *N*- allenamides for the preparation of tetrahydrocarbazoles.[28] -

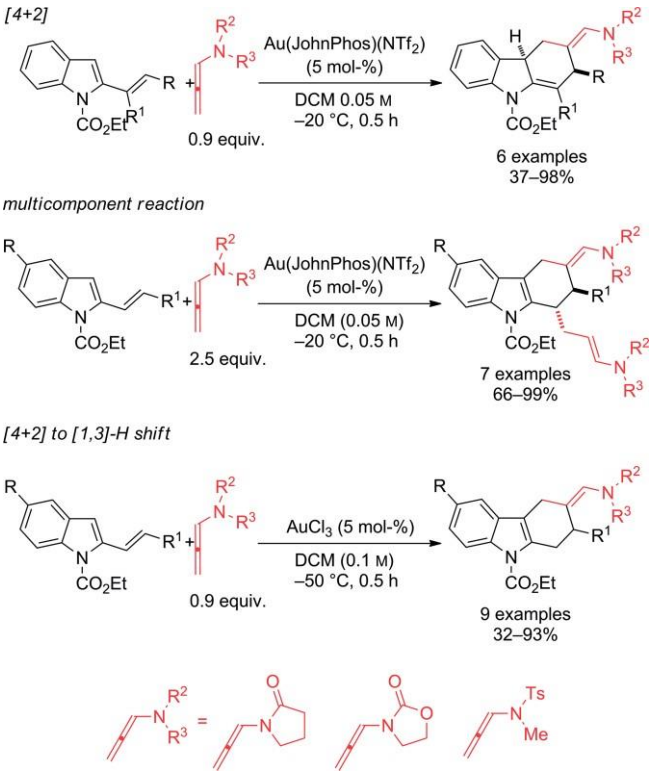


Scheme 29. Allenes and gold catalysis.

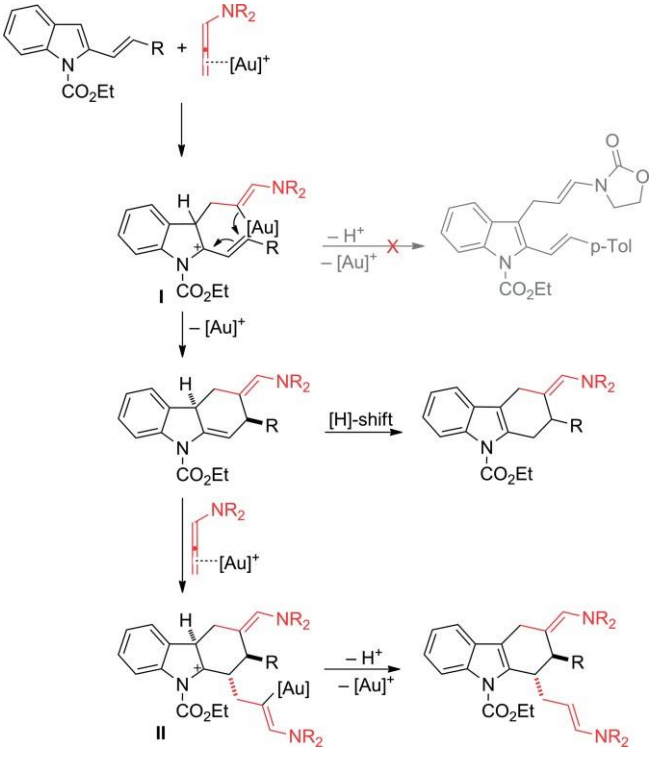
We found that careful modulation of the reaction conditions (gold species, stoichiometry, and temperature) allowed for the selective preparation of non-aromatized and aromatized carbazole derivatives (Scheme 30). In particular, dearomatized carbazoles were obtained through a simple [4+2] process on working in dilute solution with Au(JohnPhos)NTf_2. Moreover, under the same reaction conditions, in the presence of an excess of allene, compounds arising from a multicomponent reaction sequence involving one molecule of vinylindole and two molecules of the allene were prepared through a process that is uncommon in gold catalysis and not previously reported in cycloadditions with allenamides. Finally, simple gold(III) chloride is able to catalyze the formation of tetrahydrocarbazoles through a sequential [4+2] process/[1,3]-H shift.

The reactions were performed with *N*-carbamate-protected indole derivatives in order to avoid the formation of hydroarylation products. It is worth noting that all tetrahydrocarbazoles were obtained as single chemo-, regio-, and diastereoisomers. Moreover, we found that the dearomatized carbazoles arising from the simple [4+2] process are the common precursors of both tetrahydrocarbazole and multicomponent compounds (Scheme 30).

A plausible mechanistic rationale for these transformations involves gold-promoted activation of the allene followed by nucleophilic attack by the indole through C3 to afford an intermediate of type **I**. Then cyclization occurs, in a process that is faster than protodemetalation. This cyclization leads to a carbazole, which is in turn transformed into an aromatized indole or undergoes a hydroarylation reaction with a second molecule of the gold-activated allene to afford the multicomponent compound after aromatization and protodemetalation (Scheme 31).



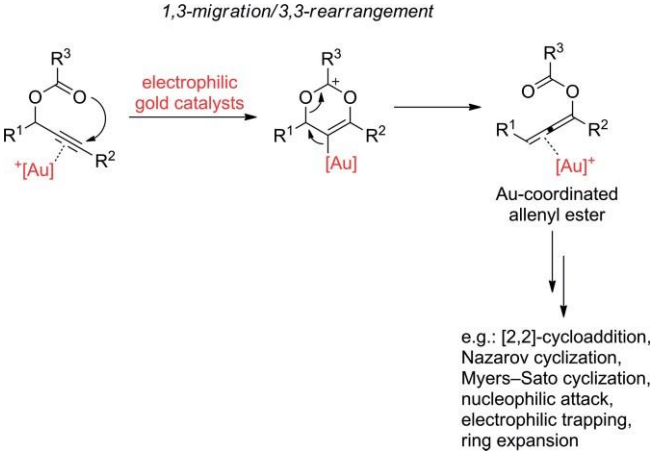
Scheme 30. Gold-catalyzed [4+2] cycloaddition reactions between 2-vinylindoles and allenamides.



Scheme 31. Mechanistic rationale for the gold-catalyzed [4+2] cycloaddition reactions between 2-vinylindoles and allenamides.

It was also demonstrated that 3-vinylindoles can participate in these reactions, affording dearomatized indoles or multicomponent adducts depending on the reaction conditions.

The scope of these transformations was broad with regard to the nature of vinylindoles, but limited to *N*-allenamides as dienophiles. In fact, the use of other allenyl derivatives, such as allenyl ethers, led to unsatisfactory results in terms of (*E*)/(*Z*) selectivity and yield. To address these difficulties, we envisioned the possibility of using allenyl esters as allenyl ether surrogates.[29] Importantly, allenyl esters can be prepared from propargylic esters through 3,3-rearrangement in the presence of cationic gold(I) catalysts. The use of the electrophilic cationic gold catalyst enables not only the generation of the allenyl ester but also its subsequent activation for further transformations through cascade reactions (Scheme 32).

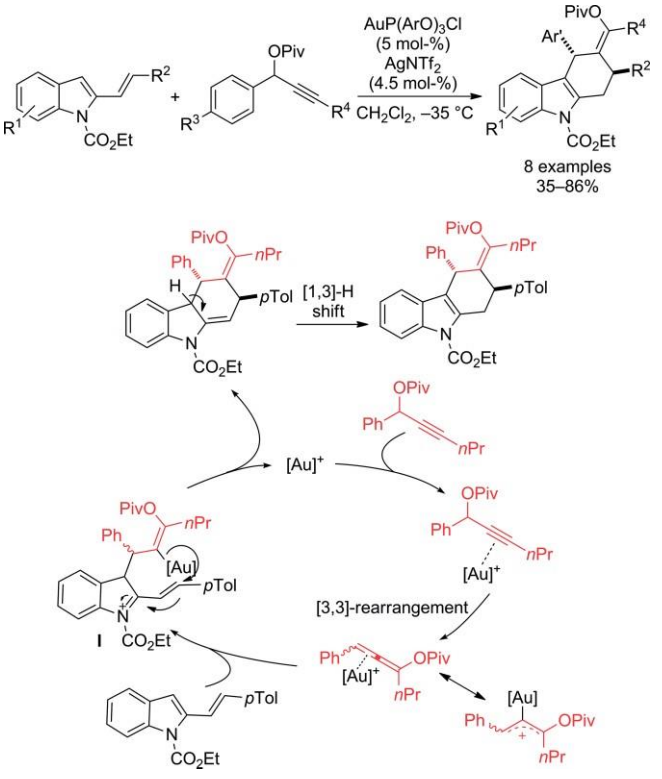


Scheme 32. Gold-catalyzed 3,3-rearrangement of propargylic esters.

On this basis, we developed a new cascade reaction sequence in which both the [3,3]-propargylic rearrangement and the [4+2] cycloaddition can be catalyzed by the same gold species, giving access to highly functionalized products (Scheme 33).

As expected, the catalyst of choice was the electrophilic cationic gold(I) tris(2,4-di-*tert*-butylphenyl) phosphite, and optimization of the reaction conditions led to the isolation of the desired tetrahydrocarbazoles as single regio- and stereoisomers in moderate to good yields. The suggested mechanism for the formation of tetrahydrocarbazoles is shown in Scheme 33 for a model compound. Activation of the propargylic ester by the cationic gold(I) catalyst triggers the [3,3]-sigmatropic rearrangement leading to the corresponding gold-activated allene. This species, in equilibrium with the oxonium resonance form, reacts with the 2-vinylindole to give intermediate **I**. Subsequent cyclization leads to the carbazole with complete *trans* diastereoselectivity, probably owing to a constrained arrangement between *p*-tolyl and phenyl groups during the cyclization step. Final elimination of $[Au]^+$ and [1,3]-H shift afford the product and regenerate the catalytic species.

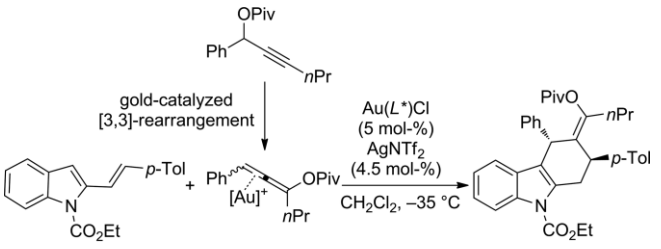
In some preliminary tests on an enantioselective version of this cascade reaction sequence, chiral phosphoramidites belonging to the class of BINOL and spirobiindane derivatives were used as ligands, because the corresponding highly electrophilic gold(I) catalysts should be able to both trigger the [3,3]-rearrangement and form the gold-activated species (Scheme 34). A spirobiindane ligand gives the best results in terms of yield and enantioselection when the reaction is performed in the presence of 4 Å molecular sieves. Tetrahydro-carbazole was thus obtained in 62 % yield and in an 85:15 enantiomeric ratio.



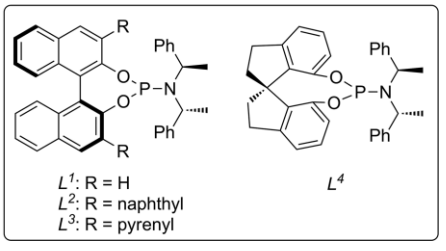
Scheme 33. Gold-catalyzed [4+2] cycloaddition reactions between 2-vinylindoles and allenyl esters.

Related enantioselective reactions performed with 3-vinylindoles and allenamides were reported by Xia and Zhang.[30] In particular, they studied the reactions between 3-vinylindoles and *N*-allenamides catalyzed by a chiral H_8-BINOL-derived phosphoramidite gold(I) complex (Scheme 35).

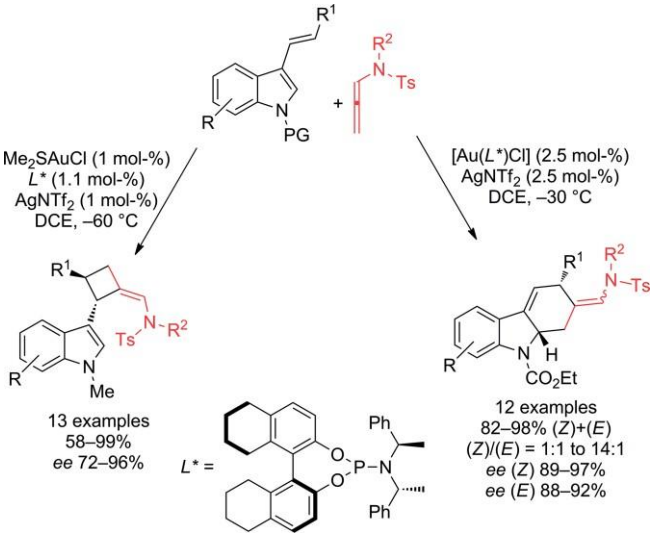
As we observed, the presence of a carbamate moiety on the indole core favors a [4+2] process, giving rise to dearomatized indoles. However, both (*E*) and (*Z*) isomers at the exocyclic double bond were isolated in variable ratios, and each of them in good to excellent enantiomeric excesses. Moreover, on switching to *N*-allyl-, *N*-benzyl-, or free (NH) indoles the favored reaction path is [2+2] cycloaddition involving the exocyclic double bond of the vinylindole. The corresponding cycloadducts were isolated as single (*Z*) stereoisomers with 72–96 % *ee* values. Thus, the cycloaddition mode exclusively depends on the nature of the *N*-substituent at the indole nitrogen atom, and this was explained by DFT calculations. In particular, the calculated electrostatic potentials of the *N*-Me derivatives display a positive electrostatic potential in the vicinity of the electrondonating methyl group and a negative potential at the vinyl moiety. Consequently, addition of the electrophilic gold-activated allene is favored at the exocyclic vinyl double bond, giving rise, through a stepwise process, to [2+2] cycloaddition compounds. On the contrary, the *N*-CO_2Et derivatives show a negative electrostatic potential in the vicinity of the carbonyl group, favoring the interaction of the electrophilic species at the indole C2 atom and the subsequent formation of [4+2] cycloaddition compounds.



Entry	L*	Additive	Yield [%]	e.r.
1	L^1	–	90	40:60
2	L^2	–	42	80:20
3	L^3	–	47	81:19
4	L^4	–	42	84:16
5	L^4	4 Å MS	62	85:15



Scheme 34. Reactions between 2-vinylindoles and allenyl esters in the presence of chiral gold(I) catalysts.



Scheme 35. Gold-catalyzed [4+2] cycloaddition reactions between 3-vinylindoles and allenamides.

2.4. Methyleneindolinones

A huge number of cycloaddition reactions between 2- and 3-vinylindoles and methyleneindolinones for the synthesis of carbazolespirooxindoles have recently been developed, especially in their enantioselective versions (Figure 2).

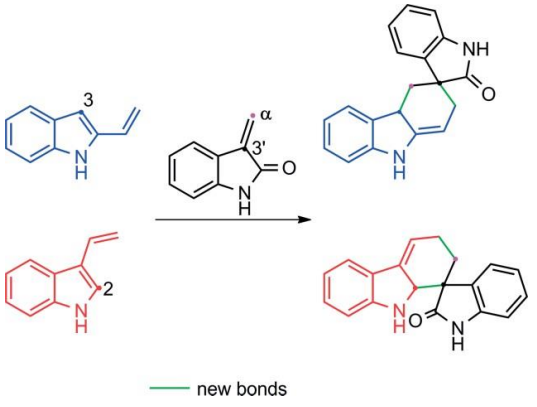
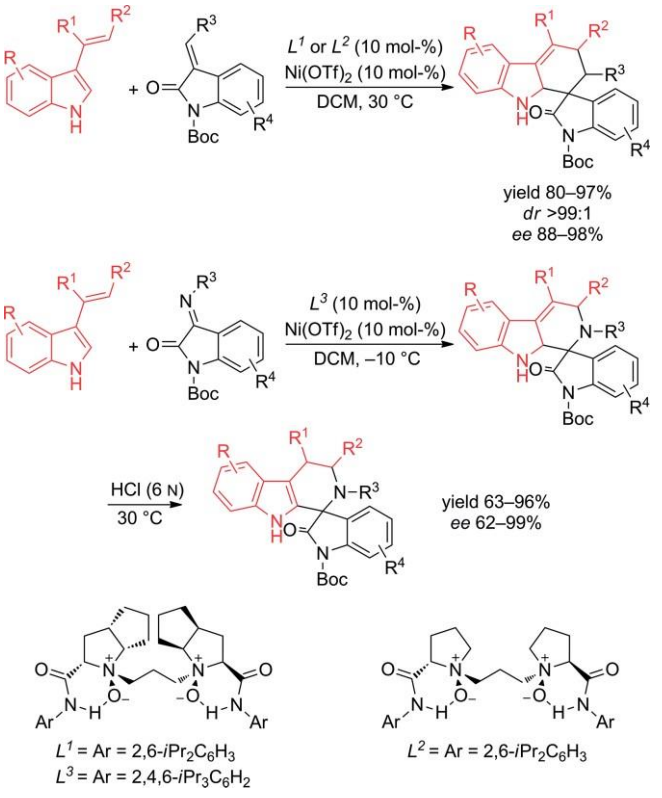


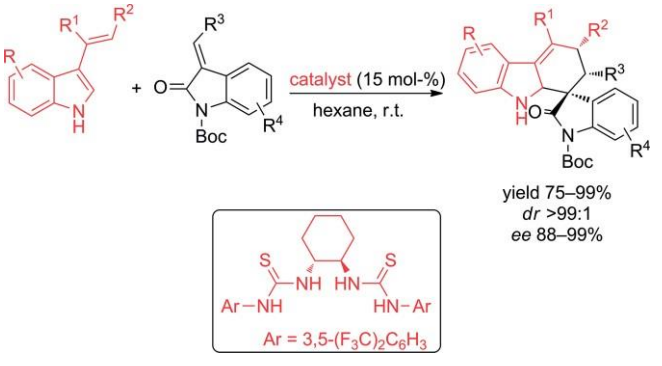
Figure 2. Carbazolespirooxindoles from 2-vinylindoles (blue) and 3-vinylindoles (red).

It is worth noting that the reactions allowed for the regioselective construction of carbazolespirooxindoles in which a new quaternary carbon atom at C3′ is formed after the formation of new bonds between the external carbon atom of the diene and positions 3 and α and 2 and 3′ of vinylindoles and oxindoles, respectively. Carbazolespirooxindoles can be regarded as merged forms of two privileged structures: spirooxindoles and tetrahydrocarbazoles, both possessing noteworthy biological properties. Carbazolespirooxindoles have attracted great attention over recent years as potential new bioactive compounds (antitumoral, anti-HIV, antimalarial, and antidiabetic). Their syntheses are mainly based on the methodologies reported in the previous sections. For example, Feng and coworkers established very efficient catalytic asymmetric [4+2] cycloaddition reactions between 3-vinylindoles and methyleneindolinones[31] or isatin-derived ketimines[32] with the aid of chiral Ni^{II} complexes as catalysts (Scheme 36).



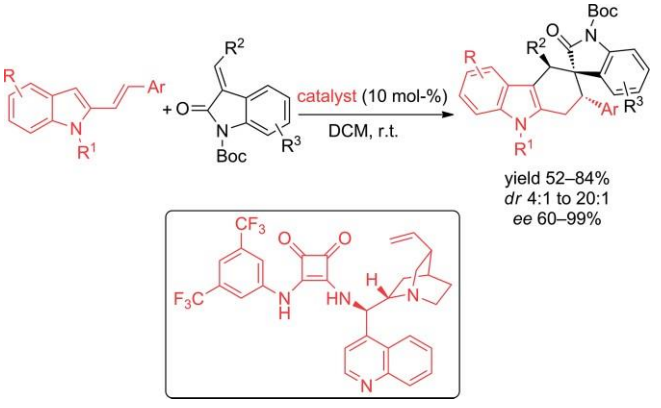
Scheme 36. Cycloaddition reactions between 3-vinylindoles and methyleneindolinones or isatin-derived ketimines in the presence of chiral Ni^{II} complex catalysts.

It is worth noting that, when working with methyleneindolinones, exo cycloadducts are always obtained as single diastereoisomers whatever the substituents on the reacting dienes and dienophiles. Diastereoselectivity is maintained regardless of the N-protecting groups of the two substrates. However, a severe drop in the enantioselectivity is observed when N-substituted dienes or N-H and N-Me dienophiles are employed, indicating that both the hydrogen atom at the indole nitrogen atom and the carbonyl-based protecting group on the oxindole are necessary to maintain the enantiocontrol and are probably involved in coordination with the chiral catalyst. The authors ascribed the observed regio- and exo selectivity to π–π interactions between the two indole systems in the transition state. The behavior of isatin-derived ketimines parallels that of methyleneindolinones. However, the first example of [4+2] enantioselective cycloadditions between vinylindoles and methyleneindolinones was reported in 2011 by Barbas,[33] who made use of a bis(thiourea) catalyst as an H-bonding organocatalyst to perform the desired enantioselective transformation (Scheme 37).Similarly, enantioselective cycloadditions between 2-vinylindoles and methyleneindolinones occur through a hydrogenbonding activation mode. In particular, a cinchonidine-squaramide catalyst[34] and a chiral phosphoric acid[35] were recently employed for the stereoselective construction of a spirotetrahydrocarbazole-oxindole framework. In the first work, a plethora of hydrogen-bond-donor chiral catalysts ranging from cinchonine-derived thiourea to cinchonidine-thiourea and cinchonidine-based squaramides were tested in a model reaction, and the best reaction conditions were applied to the synthesis of a series of functionalized carbazole-spirooxindoles (Scheme 38). It is worth noting that the urea-based catalyst employed by Barbas was ineffective, giving the corresponding carbazole-oxindole only in moderate yields and with poor stereoselectivities.



Scheme 37. Cycloaddition reactions between 3-vinylindoles and methyleneindolinones under organocatalysis conditions.

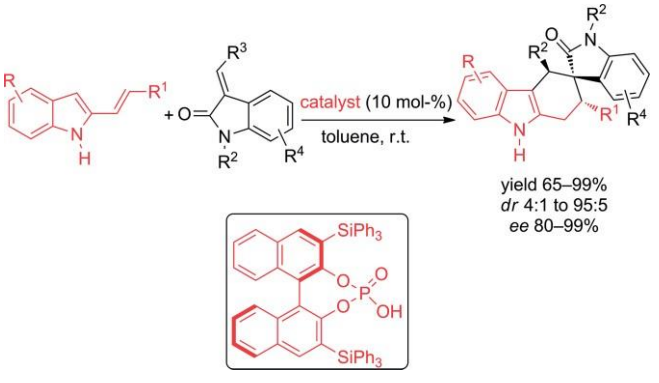
Also in this case, three or four stereogenic centers were formed simultaneously, one of them being the quaternary spirocarbon atom, and *exo* cycloadducts were exclusively formed with excellent enantiomeric ratios. Interestingly, as observed in the Ni^{II}-catalyzed reactions, the *N*-H group of the vinylindole and the bulky electron-withdrawing group on the oxindole are essential to provide the desired stereocontrol. On the basis of several ^{1}H and ^{13}C NMR experiments, the authors propose activation of the oxindole through H-bonding with the thiourea, even if the mechanism of this reaction has not been completely elucidated. The authors suggest that π–π and H- bond interactions are responsible for the observed selectivity.



Scheme 38. Cycloaddition reactions between 2-vinylindoles and methyleneindolinones under organocatalysis conditions.

The obtained compounds each contain three contiguous stereogenic centers with the quaternary one situated away from the indole core nucleus. Thus, in this example and in the following one, the reactions afford mismatched structures with respect to the products obtained with 3-vinylindoles.

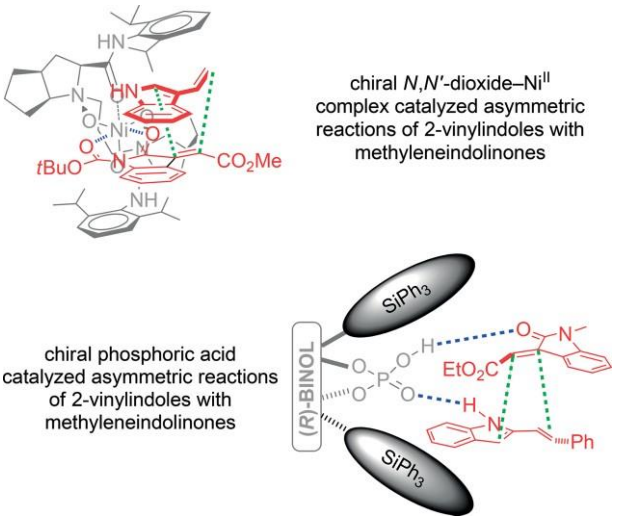
In the second example, Shi and co-workers employed a chiral BINOL-derived phosphoric acid as catalyst in closely related reactions (Scheme 39).[35]



Scheme 39. Cycloaddition reactions between 2-vinylindoles and methyleneindolinones under organocatalysis conditions.

The differences between the two proposed methodologies lie in the substitution patterns around the indole and methyleneindolinone reagents. Thus, in the first case the reacting indoles were N-alkyl- or N-Boc-substituted, whereas in the second example N-H and N-H or N-alkyl pairs were used. In both cases, an EW group at the exocyclic double bond of the methyleneindoline component is mandatory to achieve the desired transformations.

All papers discussed in this section deal with the diastereoand enantioselective synthesis of carbazole-oxindole derivatives. However, only in few cases have the authors accounted for the origin of the observed selectivities (Scheme 40).



Scheme 40. Proposed transition states for catalyzed cycloaddition. Coordination with the catalysts in red and cycloaddition mode in green.

In particular, in the nickel-catalyzed reactions the proposed transition state involves coordination of the metal atom with both oxindole carbonyl groups, whereas with the chiral phosphoric acid, hydrogen bonds with the hydrogen atom at N1 of the indole and with the oxygen atom of the oxindole carbonyl group explain the stereochemical course of the reactions. All these particular interactions furthermore outline the importance of the correct substitution pattern around the reactant species.

2.5. Application of [4+2] Cycloaddition to the Synthesis of Indole Alkaloids

Several sections of the review by Kester, Berthel, and Firooznia[1c] describe the synthesis of indole alkaloids through [4+2] cycloadditions of 2- and 3-vinylindoles.[1c] In particular, the synthesis of linear tri- and tetracyclic indole alkaloids, as well as of *Vinca* and *Aspidosperma* alkaloids, from 2-vinylindoles and of α- and γ-carboline alkaloids from 3-vinylindoles are discussed. In addition, one of the most impressive reports in this field appeared in 2009. The MacMillan group reported the enantioselective total synthesis of (+)-minfiensine, an indole alkaloid from *Strychnos minfiensis* structurally related to the akuammiline alkaloids vincorine and echitamine (Figure 3).[23]

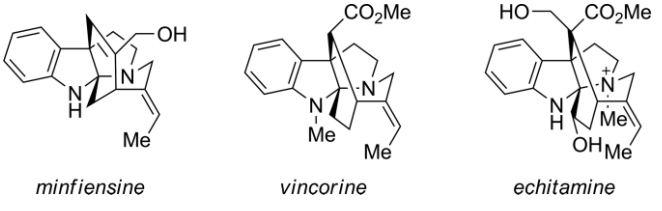
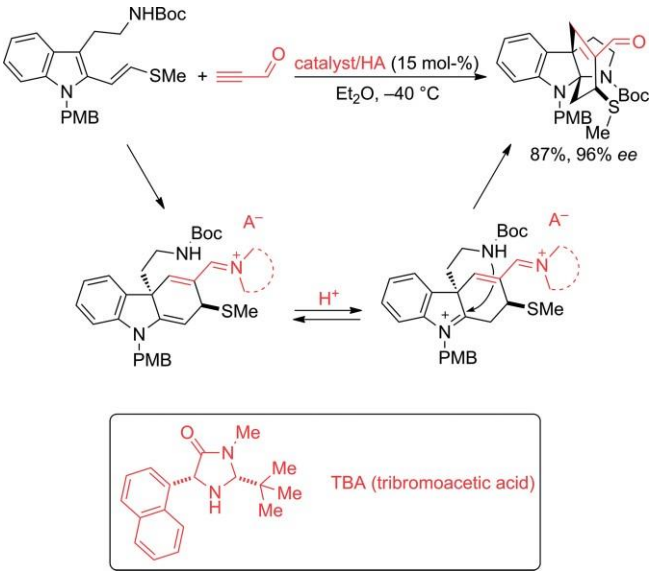


Figure 3. Minfiensine and related akuammiline alkaloids.

The key of the nine-step synthesis is a cascade reaction involving an organocatalyzed [4+2] cycloaddition reaction between a doubly protected [2-(2-methylthio)vinyl]tryptamine derivative and propynal, followed by an intramolecular 5-*exo* amine heterocyclization giving rise to the tetracyclic pyrrolo-indoline core (Scheme 41).



Scheme 41. Enantioselective cascade process to the pyrroloindoline core.

The origin of the enantiocontrol is the formation of a conformationally constrained iminium intermediate capable of forcing the cycloaddition mode towards the regioselective formation of the *endo* cycloadduct in a stereocontrolled manner (Figure 4).

Figure 4. Mutual approach between diene and dienophile in [4+2] cycloaddition for the synthesis of the tetracyclic pyrroloindoline core.

Similar straightforward approaches were next used for the enantioselective syntheses of *Strychnos*, *Aspidosperma*, and *Kopsia* alkaloids from a common tetrahydro-1*H*-pyrrolo[2,3-*d*]- carbazole-4-carbaldehyde intermediate (Figure 5).[36]

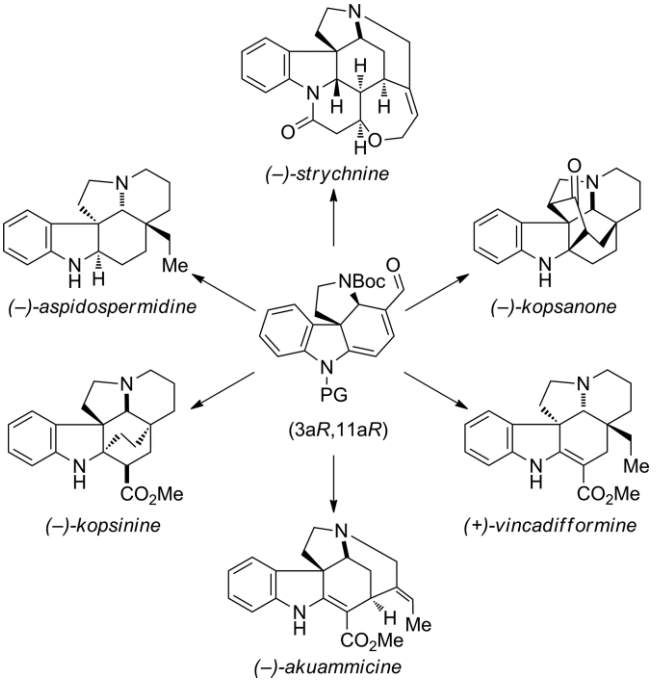
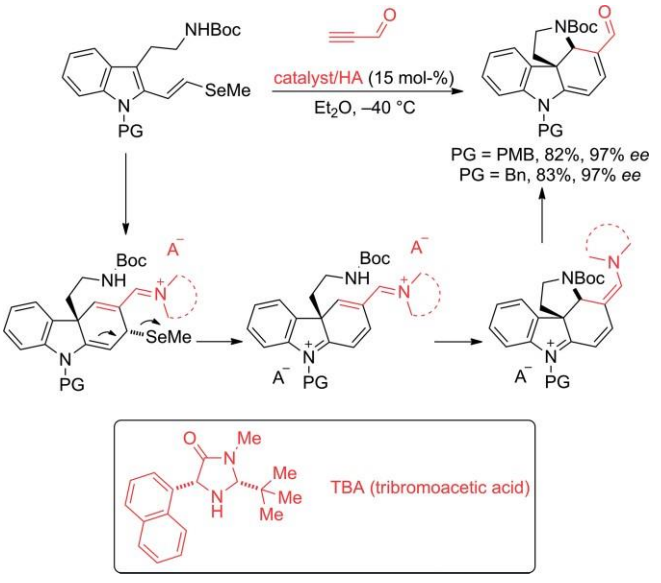


Figure 5. Indole alkaloids synthesized from a tetrahydro-1*H*-pyrrolo[2,3-*d*]- carbazole-4-carbaldehyde intermediate (number of steps ≤ 8).



Scheme 42. Enantioselective cascade process affording the tetrahydro-1*H*- pyrrolo[2,3-*d*]carbazole-4-carbaldehyde intermediate.

This compound is structurally related to the pyrrolocarbazole used in the minfiensine synthesis and was prepared by way of a parallel cascade process involving in the first step a [4+2] cycloaddition between a [2-(2-methylseleno)vinyl]tryptamine derivative and propynal (Scheme 42). The reaction is promoted by the same imidazolinone/Brønsted acid catalytic system as used in the minfiensine synthesis.

After the first cycloaddition step, the presence of the selenomethyl group favors a β-elimination process, affording an unsaturated iminium ion bearing a reactive carbamate side chain at the angular position. A final intramolecular cyclization process affords, after hydrolysis, the desired compound in 82 % yield and 97 % *ee*. The same strategy was extended to the total enantioselective synthesis of (–)-vincorine[37] and (–)-minovincine[38] alkaloids by use of suitably substituted 2-vinyltryptamine derivatives and enals or alkynones, respectively, as substrates for the cycloaddition step.

3. Final Remarks

Although we have made some comments in each section and subsection, we would like to add several final remarks we think could be useful for readers and for those interested in developing the chemistry of vinylindoles. In the future, the development of cycloaddition reactions other than classical [4+2] cycloadditions is likely to be a challenging objective. For example, the achievement of [4+1] cycloadditions could give rise to new carbocyclic and heterocyclic systems. A recently published review represents a good starting point and an excellent source of inspiration.[39] Higher-order cycloadditions such as [4+3] are, in our opinion, more difficult to achieve. Three-carbon units such as oxy- and aminoallyl cations are good partners in these transformations. However, their use is somewhat limited to highly reactive 4π components such as furan or cyclopentadiene, and the reactions require the presence of stoichiometric amounts of suitable promoters.[40] In this field, more recently several authors have reported on the use of allenyl derivatives as C_3 synthons in the presence of gold or platinum catalysts.[41] We would like to remind readers that this review deals exclusively with the chemistry of vinylindoles as 4π components in cycloaddition reactions. However, a closely related field of investigation involves the development of cycloaddition involving the indole exocyclic double bond as dienophile in [4+2], [3+2], and [5+2] reactions, and several interesting papers have appeared recently.[42]

Finally, even though the field of classical [4+2] cycloadditions is well explored we are pretty sure that there is enough space for further investigations. For example, enantioselective Lewis acid-catalyzed reactions have been explored only in the presence of particular dienophiles, and extension of this methodology to classical open-chain and cyclic dienophiles needs to be studied.

In addition, activation of π-systems through transition-metal-catalyzed reactions is almost unexplored if we rule out the gold-catalyzed cycloaddition between allenes and vinylindoles.

Keywords: Vinylindoles - Cycloaddition - [4+2] – Cycloadditions - Lewis acids - Organocatalysis - Transition-metal catalysis

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