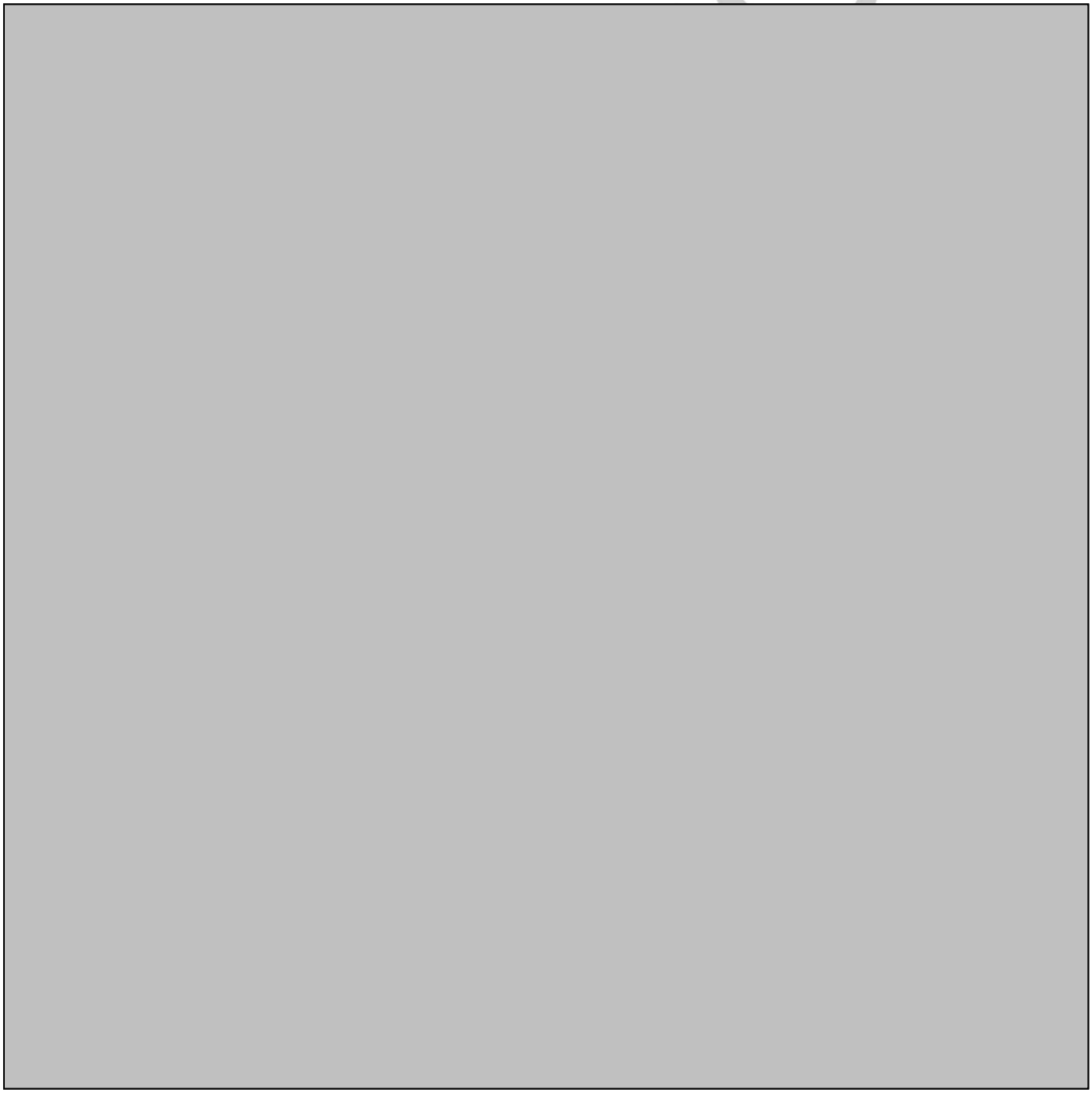
Spiro-2-oxindoles *via* 1,3-dipolar cycloadditions. A decade update.

Giorgio Molteni*[a] and Alessandra Silvani[a]

Dedicated to Prof. Franco Cozzi in occasion of his 70th birthday.



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Abstract: The huge variety of spirooxindole three-dimensional scaffolds encompasses relevant bioactive natural alkaloids as well as useful therapeutic agents. In view of the challenging features of the spirooxindole skeletons and their desirable properties, several synthetic routes have been devoted to their preparation. Because of the variety of both 1,3-dipolar species and 2-oxindoles bearing a C=X double bond (X = C<, N-, O) in the 3-position, a prominent role relies upon a 1,3-dipolar cycloaddition as the key step of the whole synthetic sequence. The present paper aims to discuss the developments in the field of spirooxindole synthesis *via* a 1,3-dipolar cyloaddition occurred in the 2011-2020 decade. The literature data on this subject are reviewed in a systematic way according to the type of the 1,3-dipole and the oxindole dipolarophile.

1. Introduction

Spirooxindoles belong to an astonishingly various array of well-defined three-dimensional skeletons. By a structural standpoint, the presence of the spiranic carbon makes spirooxindoles capable of axial chirality within the $\mathbf{D}_{nd}$ symmetry group.[1] The most intriguing aspects of spirooxindoles are related to their appartenance to -or similarity with- natural alkaloids;[2] this circumstance leads to a broad activity in a number of therapeutic fields as antibacterial, anticancer, antifungal and antiviral drugs.[3-5] In a few recent years, the great synthetic interest towards the spirooxindole scaffolds prompted to hundreds of reports, thus requiring the rationalisation of the recent achievements in the field. Due to the desirable biomedical properties of the spirooxindole skeletons, attention have been payed to both their racemic[6] and asymmetric synthesis[7,8] with emphasis to the organocatalytic[9-11] and formal annulation methods.[12] The main routes to the spirooxindole skeletons rely upon spirocyclisation and cycloaddition protocols.[13-15] By limiting ourselves to the cycloadditive approach, it can be recognised that a number of reports has appeared concerning the recent developments of 1,3-dipolar cycloadditions including their synthetic versatility,[16] the use of non-conventional solvents like ionic liquids,[17] water[18] or aqueous media[19] and the application of inorganic nanocatalysts.[20,21] Furthermore, the 1,3-dipolar cycloadditions to 2-oxindoles bearing a C=X double bond in the 3-position represent a fertile field in the synthesis of a variety of spirooxindoles.[15] This assumption is related to the rich chemistry of 1,3-dipolar cycloadditions towards the indolic dipolarophiles **A**-**C** (Figure 1). The scope of the present review article is to provide the state of the art of such concerted reactions. In order to best define these boundaries, it should be added that: (*i*) formal cycloadditions will be not considered here because their mechanism escapes from the concerted and synchronous nature of 1,3-dipolar cycloadditions as established by Huisgen,[22,23] and (*ii*) dipolar cycloadditions of indoles bearing an 1,3-dipolar functionality will be considered only with the indolic dipolarophiles **A**-**C**, since a comprehensive review on other dipolarophiles appeared in 2020.[24] For the sake of simplicity, the results will be summarised according to the 2-oxindole and 1,3-dipole type, and to the racemic or asymmetric nature of the cycloaddition. Although intended for an audience of organic chemists, it was avoided to produce a mere list of hundreds of cycloadducts that would result rather tedious.

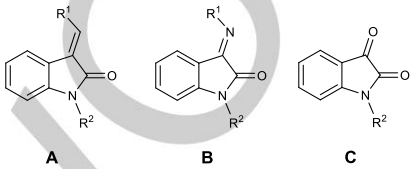


Figure 1. 2-Oxindole dipolarophile types.

Giorgio Molteni, born in 1963, received his MSc and PhD in Chemistry at the University of Milan. Since 2001 he was appointed Assistant Professorat the Chemistry department of the same University. He explored the synthetic, mechanistic and theoretical aspects of 1,3-dipolar cycloadditions. Recently, his research activity relies upon the catalysis of cycloadditions by metal-oxide nanoparticles and the behaviour of 1,3-dipolar species in aqueous medium. He is member of the National centre of Pericyclic Reactions.

Alessandra Silvani, born in 1967, received her MSc and PhD in Chemistry at the University of Milan. Since 2001 she was appointed Assistant Professor and since 2018 Associate Professor in Organic Chemistry at the Chemistry Department of the same University. Her research activity is focused on organic synthesis and medicinal chemistry, including the asymmetric synthesis of natural products-like molecules and of conformationally controlled peptidomimetics. In the recent years, her interest was mainly focused on the generation of chemical diversity by means of multicomponent reactions around the privileged spiro-2-oxindole scaffold.

2. Cycloadditions to 3-alkylidene-2-oxindoles - A-type dipolarophiles

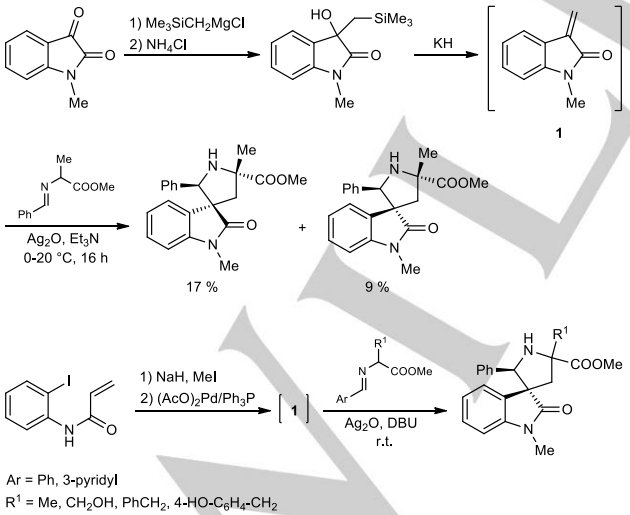
The synthetic methodologies developed for the construction of 3-methylene- and 3-(monosubstituted)- alkylidene 2-oxindoles,[25] as well as their usefulness in organic synthesis,[26,27] have been reviewed recently. Such trisubstituted alkenes constitute the ideal starting reagents for the construction of three- to seven-membered 3-spiro(carbo)- or 3-spiro(hetero)-cyclic indoles.[15] As it will be discussed in the following sections, emphasis will be given to the cycloadditive aspects concerned to the synthesis of 3-spiro(2-oxindolo)five-membered heterocycle.

2.1. Azomethine ylide cycloadditions

Following the seminal papers by Houk,[28,29] azomethine ylide cycloadditions to monosubstituted ethylenes should be fast with both electron-poor and electron-rich dipolarophiles. These predictions rely upon the simple frontier molecular orbital theory (FMO),[30] suggesting that the HOMO or the LUMO of the 1,3-dipole control are involved, respectively. Since the 3-methylene oxindoles are generally representative of trisubstituted ethylenic dipolarophiles, some caution about the predicted regioselectivity output of the cycloaddition should be taken, and a case-by-case approach appear to be desirable. The stereochemical diversity that occurs in the catalytic asymmetric azomethine ylide-alkene cycloadditions[31,32] is also operating in the reactions involving the 3-methylene oxindole dipolarophile. The different relative orientation of the cycloaddends are function of both the organic ligand and the metal, thus accounting for all the observed regio- and stereoselectivity possibilities.

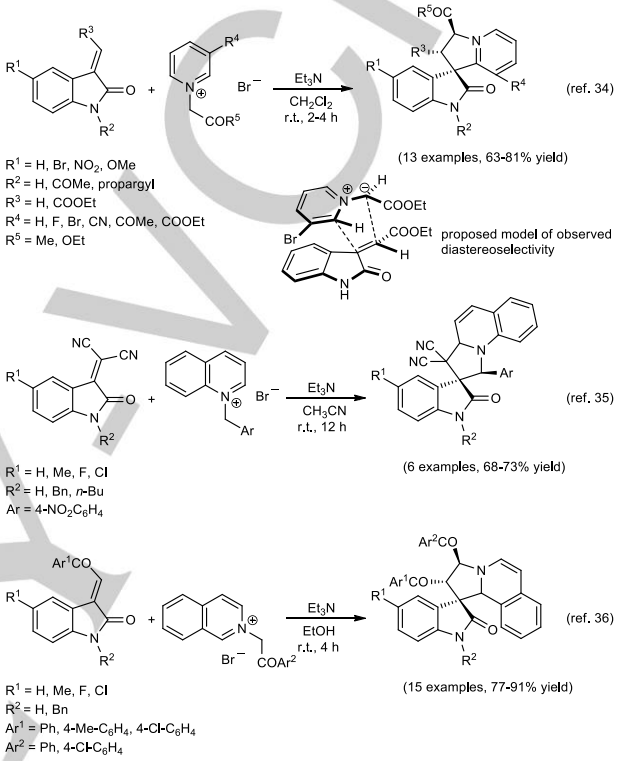
2.1.1 Racemic azomethine ylide cycloadditions

Two cascade approaches to racemic spiro-oxindoles have been exploited, both involving *in situ* formation of the 3-methylene oxindole dipolarophile **1** and its subsequent trapping by azomethine ylide generated *in situ* from the corresponding iminoesters. The first approach is based upon a Peterson olefination sequence, and the azomethine ylide cycloaddition onto the intermadiate **1** gave a mixture of diastereoisomers with low overall yield (Scheme 1). The Heck-based strategy depicted in the Scheme 1 gave better results (7 examples, 59-72% overall yield and d.r. up to 90/10).[33] From these first example it can be inferred that cycloadditions are fully regioselective but their stereochemical outcome can be not very favourable. Furthermore, a model explaining the observed stereoselectivity was not proposed.



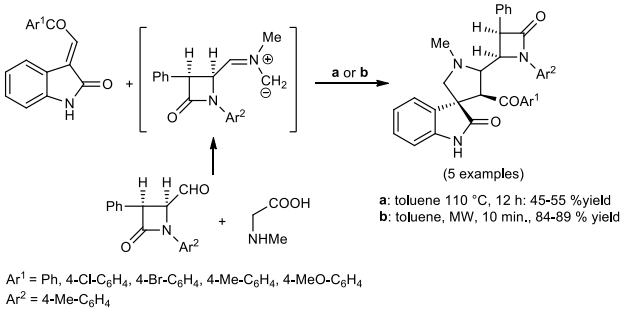
Scheme 1. Peterson olefination- and Heck-based protocols giving spiro(2-oxindolo) pyrrolidines.

This latter point have been fully elucidated in the cycloaddition between 3-alkylidene oxindoles and pyridinium-,[34] quinolinium-[35] or isoquinolinium[36] ylides, demonstrating that such reactions occur with full regio- and diastereoselectivity *via* an *exo* approach of the cycloaddends. To this purpose, it can be inferred from Scheme 2 that cycloadditions of both pyridinium- and isoquinolinium ylides gives the same regio- and stereoselectivity, which is opposite to that observed with quinolinium ylides. No rationalisation of this behaviour has been provided. It needs to be added that in some cases the resulting cycloadducts show the same relative stereochemistry of the bioactive oxindole alkaloid strychnofoline.[37]



Scheme 2. Cycloaddition between 3-alkylidene-2-oxindoles and pyridinium-, quinolinium and isoquinolinium ylides.

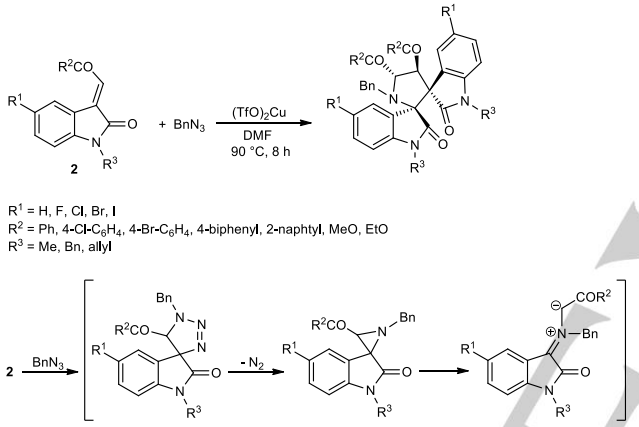
A one-pot synthesis of β-lactam-grafted spiro(2-oxindolo) pyrrolidines has been accomplished through a β-lactam-derived azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles (Scheme 3).[38] This regio- and stereoselective reaction was experienced in different conditions. The cycloaddition's extent was quite satisfactory when carried out under microwave irradiation compared to the usual thermal conditions.



Scheme 3. Cycloaddition between 3-alkylidene-2-oxindoles and a β-lactam-derived azomethine ylide.

19 Examples of dispiro(pyrrolidine)-2,3′-oxindoles (60-81% yield) were obtained as single diastereoisomers through a Lewis acid [copper(II)triflate]-promoted domino reaction cascade. The initial (uncatalysed) azide-alkene cycloaddition provide a transient spiro(indolo)triazoline intermediate. Subsequent loss of nitrogen affords the spiro(indolo)aziridine, and the aziridine ring opening generated the azomethine ylide intermediate. Cycloaddition of the latter 1,3-dipolar specie with 3-alkylidene-2-oxindoles **2** gave the target dispiro(pyrrolidine)-2,3′-oxindoles containing four contiguous stereocenters (Scheme 4).[39]

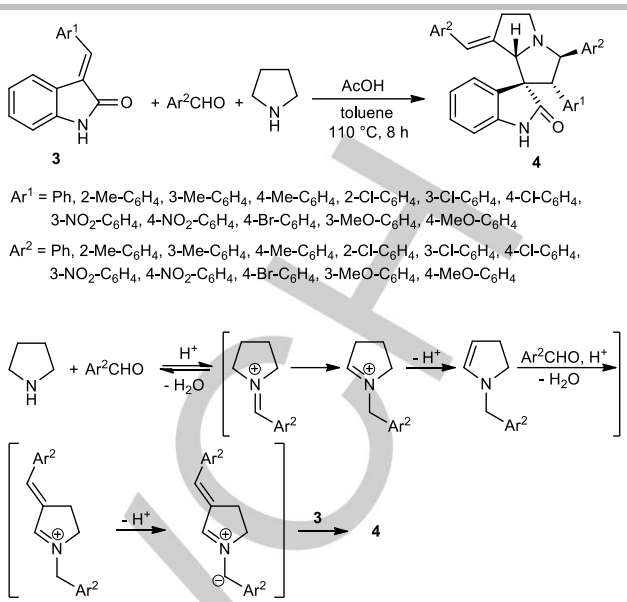
It could be useful to point out that there are no literature evidence that copper(II) is able to catalyse the azide-alkene cycloadditions. Although such reactions are usually carried out at room temperature,[40] the present reaction was performed at 90°C in DMF. In these conditions a thermal cycloaddition is likely to occur, followed by nitrogen extrusion from the triazoline ring, due to the thermal lability of 1*H*-4,5-dihydro-1,2,3-triazoles.[41] The effectiveness of copper(II) triflate could be related to the aziridine ring-opening step.



Scheme 4. Copper(II)-catalysed domino reaction cascade giving dispiro(pyrrolidine)-2,3-oxindoles.

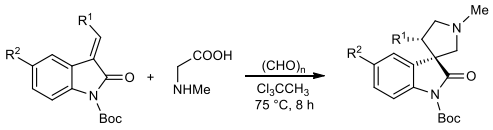
Multicomponent reactions are defined as processes in which three or more starting reagents are converted to a single product, and their usefulness relies upon a number of advantages compared to traditional multistep synthesis.[42] Multicomponent synthetic strategies can lead to various spiro- or fused complex heterocyclic systems that are ideal targets in several fields of medicinal chemistry.[43] This is the case of 1,3-dipolar cycloadditions to 3-alkylidene-2-oxindoles in which both the dipole and the dipolarophile can be generated *in situ*.

A strategy for the synthesis of complex spiro heterocyclic compounds **4** by *in situ* generated azomethine ylide cycloaddition have been pursued in the presence of 3-alkylidene-2-oxindoles **3** as dipolarophiles. This acetic acid-promoted three-component reaction gave the resulting cycloadducts with good yields and good diastereoselectivity (25 examples, 50-80% yields, single diastereoisomer). The reaction mechanism included β-C−H functionalization of pyrrolidine, generation of the azomethine ylide intermediate and subsequent 1,3-dipolar cycloaddition (Scheme 5).[44] The resulting spirooxindole derivatives were investigated by evaluation against mouse colon cancer cells CT26 and human liver cancer cells HepG2 by MTT assay.



Scheme 5. Three-component reaction between pyrrolidine, aromatic aldehydes and 3-alkylidene-2-oxindoles **3**.

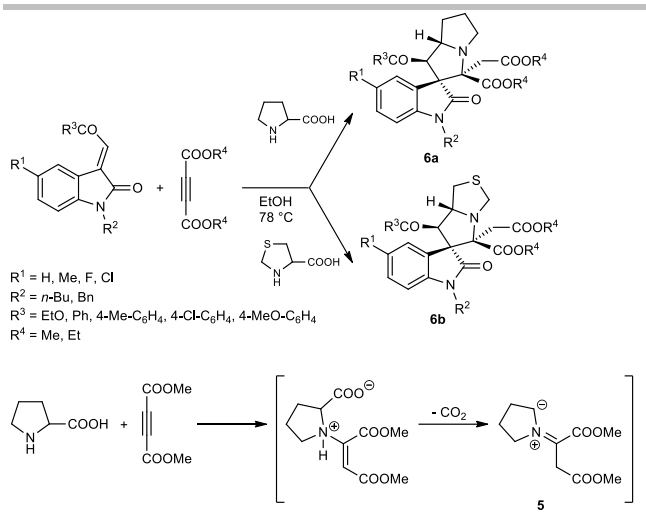
A convenient method for the construction of pyrrolidinyl spirooxindoles relies upon the decarboxylative generation of unstabilised azomethine ylides from the initial condensation between sarcosine and formaldehyde. Subsequent azomethine ylide cycloaddition onto (*E*)-*N*-Boc-3-alkylidene-indolin-2(3*H*)ones has been exploited giving target cycloadducts with good yields and diastereoselectivity, 23 examples, 59-85% yield, d.r. up to > 99/1 (Scheme 6).[45] Some of these compounds exhibit moderate antibacterial activity against Staphylococcus aureus (ATCC-25825). By replacing R^1 with the electron-poor pyrimidine ring, the energy of the dipolarophile LUMO could be lowered favouring the cycloaddition with non-stabilized azomethine ylides.[28,29] This leads to compounds that demonstrated *in vitro* activity against human lung cancer cells A549, human prostate cancer cells PC-3 and human leukemia cells K562.[46]



R1 = (*Z*)-Ph, (*E*)-Ph, 4-NO2-C6H4, 4-CN-C6H4, 3-CF3-C6H4, 2Cl-C6H4, 4-Cl-C6H4, 4-Br-C6H4, 3-Br-C6H4, 2-Br-C6H4, 2-F-C6H4, 3-Me-C6H4, 4-Me-C6H4, 2MeO-C6H4, 3,4-(MeO)2-C6H3, 3-MeO-C6H4, 4-MeO-C6H4, COOEt, 1-naphtyl, 2-tienyl
R2 = Br, F, Me

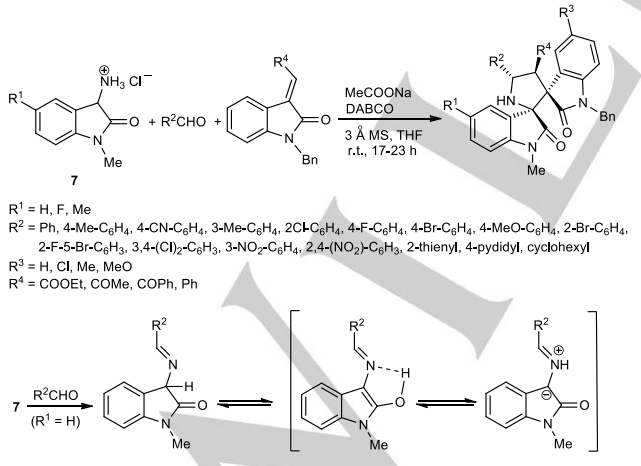
Scheme 6. Three-component reaction between sarcosine, formaldehyde and 3-alkylidene-2-oxindoles.

The uncommon route depicted in Scheme 7 for the generation of azomethine ylides **5** has been applied to the synthesis of densely functionalised spiro(indolo) -pyrrolizines **6a** or -thiazoles **6b** (18 examples, 66-80% yield, only the shown major diastereoisomers were characterised).[47] The main advantage of this three-component reaction relies upon the use of readily available reagents, although the reaction conditions were not properly mild.



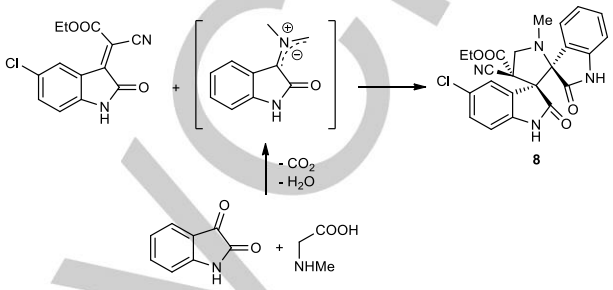
Scheme 7. Three-component reaction between L-proline, alkynes and 3-alkylidene-2-oxindoles.

Starting from 3-aminooxindoles **7**, aldehydes, and 3-alkylidene-2-oxindole dipolarophiles it was established a three-component reaction based upon the intermolecular cycloaddition of an azomethine ylide generated *in situ* to furnish structurally diverse dispiro(pyrrolidine)-2,3′-oxindoles (23 examples, 38-97 % yield, d.r. up to 96 : 4, Scheme 8).[48] A consideration should be formulated regarding this *in situ* generation of the 1,3-dipolar intermediate. It is long known that a thermal method of generating azomethine ylides from α-aminoesters is possible provided that at least one enolizable hydrogen α- to the ester must be present to equilibrate with the corresponding azomethine ylide.[49,50] As is depicted in Scheme 8, the multicomponent reaction occurs at room temperature. This unusual behaviour may be ascribed to the tautomerisation of the imine derived from **7**, facilitated by the intramolecular hydrogen bonding of the resulting intermediate.



Scheme 8. Three-component reaction between 3-aminooxindoles, aldehydes and 3-alkylidene-2-oxindoles.

The three component reaction between isatin, sarcosine and 5-chloro-2-oxo-1,2-dihydroindol-3-ylidene-cyano-acetic acid ethyl ester has been investigated as a model substrate, in order to establish its feasibility and optimize the reaction conditions. The results are depicted in Scheme 9 and Table 1. In this case, the (unstabilised) indolic azomethine ylide was generated *in situ* by decarboxylative condensation between isatin and sarcosine. Subsequent cycloaddition to the above 3-alkylidene oxindole gave the dispiropyrrolidine-bisoxindole **8** in which three novel stereocenters are formed with high stereoselectivity. The ionic liquids [bmim] BF_4 and [bmim] PF_6 were tested as environmentally benign solvents, giving much better results compared to conventional solvents. Further 11 examples were provided with 88-94% yield.[51]

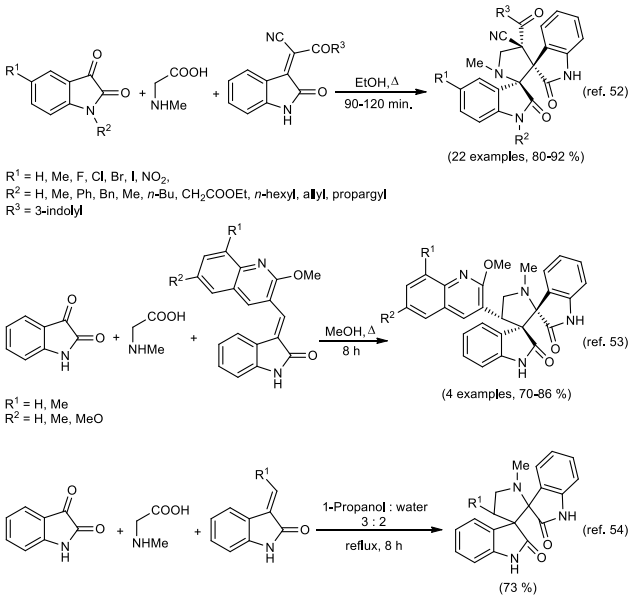


Scheme 9. Three-component reaction between isatin, sarcosine, and 5-chloro-2-oxo-1,2-dihydroindol-3-ylidene-cyano-acetic acid ethyl ester.

Table 1. Three-component reaction between isatin, sarcosine, and 5-chloro-2-oxo-1,2-dihydroindol-3-ylidene-cyano-acetic acid ethyl ester.

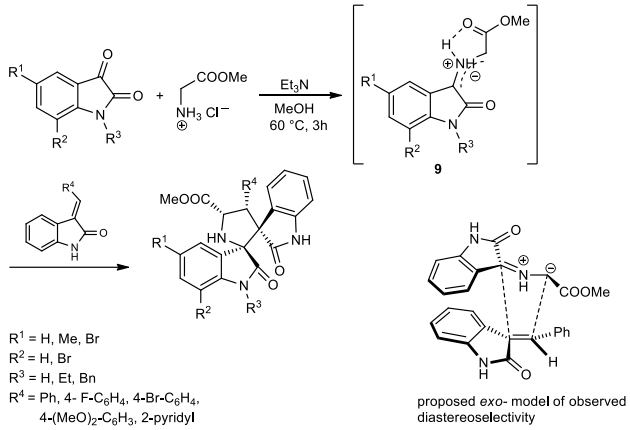
Entry	Solvent	T (°C)	Time (min.)	**8** (%)
1	MeOH	65	120	82
2	EtOH	78	140	80
3	MeCN	82	320	69
4	THF	66	480	42
5	Toluene	110	520	38
6	[bmin] BF_4	80	80	94
7	[bmin] PF_6	80	90	90

Some other examples of three-component reactions based on an unstabilised azomethine ylide cycloaddition as the key step are depicted in Scheme 10.[52-54] The relative cycloadduct stereochemistry was not elucidated in the case of ref. 54.



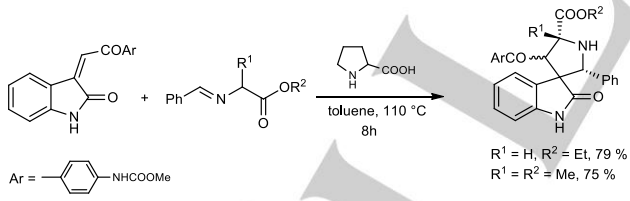
Scheme 10. Three-component reaction between isatin, sarcosine and 3-alkylidene-2-oxindoles.

In a typical three-component reaction, it was possible to generate the stabilised azomethine ylides **9** starting from isatin and methyl glycinate (Scheme 11). Subsequent cycloaddition to 3-alkylidene-2-oxindoles gave spiropyrrolidine bisindoles in good yields (13 examples, 79-99% yield). Although the d.r. was not determined except for cycloadduct with $R^1 = R^2 = R^3 = H$, R^4 = 3,4-$(MeO)_2$-C_6H_3, it was proposed an *exo*-model for the observed stereoselectivity.[55]



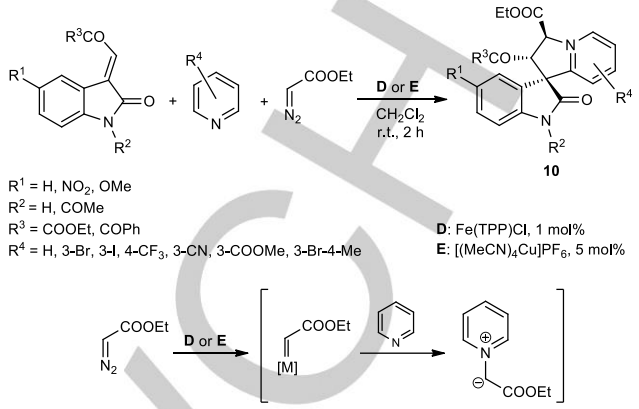
Scheme 11. Three-component reaction between isatin, methyl glycinate and 3-alkylidene-2-oxindoles.

Switching the attention to the catalysed azomethine ylide cycloaddition, a method for the construction of pyrrolidinyl spirooxindoles has been established by using 3-methylene-2-indolinone carbamates in the presence of catalytic amounts (20 mol%) of L-proline (Scheme 12). The ambivalent nature of L-proline is believed to provide the protonation of the imino nitrogen atom and the symultaneous deprotonation of the α-carbon atom generating the azomethine ylide 1,3-dipolar intermediate. The reaction was carried out at high temperature giving two examples of regio- but not stereoselective cycloaddition.[56]



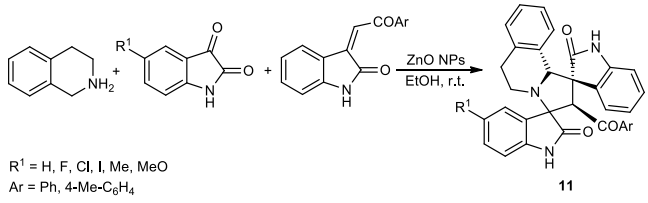
Scheme 12. Proline-catalysed azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

The blue microcrystals of iron(III) (tetraphenylporphyrinato) chloride [Fe(TPP)Cl] and the colourless tetrakis (acetonitrile) copper(I) hexafluorophosphate (both complexes belongs to the C_{4v} point group) were able to catalyse the *in situ* formation of pyridinium ylides from α-diazoacetates *via* a metal carbene intermediate. Subsequent cycloaddition to 3-alkylidene-2-oxindoles afforded tetrahydroindolizidines **10** with 53-93% yields (18 examples) according to a genuine three-component reaction protocol.[57] Tetrahydroindolizine cycloadducts were obtained with d.r. between 80 : 20 and 100 : 0 in favour of the diastereoisomer depicted in Scheme 13. The model proposed for the observed stereoselectivity was quite similar to that showed in Scheme 2. Unfortunately, no indications about catalyst's recovery and the recycling were given.



Scheme 13. Fe(TPP)Cl- and $[(MeCN)_4Cu]PF_6$-catalysed three-component azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

Three-component reactions based onto the intermolecular azomethine ylide cycloaddition have been also exploited in the presence of unsupported, partially aggregated zinc(II) oxide nanoparticles as catalysts. As can be seen in Scheme 14, the dispiro-2',4'-(2-oxindolo) indolizidine **11** skeleton[58] was obtained at room temperature in ethanol or water (10 examples, 83-97% yield). The initial condensation between tetrahydroisoquinoline and isatin provide the precursor of the azomethine ylide intermediate whose subsequent cycloaddition onto the appropriate dipolarophile gives the target molecules **11** as single diastereoisomers. Curiously, these reactions occurred in the absence of a basic agent. Inexpensive ZnO nanoparticles were tested in order to determine their recyclability. Unfortunately, the efficiency of the nanocatalyst declined at every cycle, and after the third one the nanoparticles resulted as aggregates.

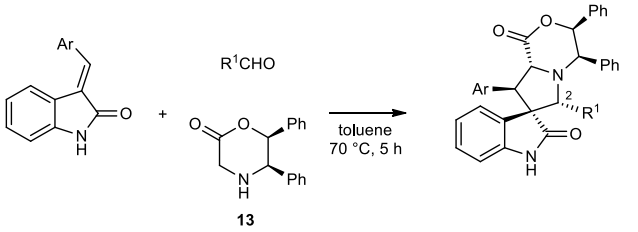


Scheme 14. Three-component azomethine ylide cycloadditions catalysed by unsupported partially aggregated ZnO nanoparticles.

2.1.2 Asymmetric azomethine ylide cycloadditions

Seminal studies towards the asymmetric synthesis of enantiopure spirooxindoles system have been pursued in the early 2000.[59] Within a three-component reaction, the key azomethine ylide intermediate was generated by reacting the enantiopure morpholine derivative **13** with an aldehyde in the presence of 3 Å molecular sieves. Subsequent cycloadditions to the appropriate 3-alkylidene-2-oxindoles constituted the key step in the asymmetric total synthesis of (+)- and (-)-spirotryprostatin B, a class of antimicotic arrest agents firstly

isolated by the fermentation broth of *Aspergillus fumigatus*. A similar example of uncatalysed cycloadditions is proposed in Scheme 15 (11 examples, 60-80 % yields, e.e. not available).[60] In the cycloadducts **13**, the absolute configuration of the pyrrolydine ring C2 is not consistent to that found in the previous paper,[60] and the rationale of this unusual selectivity is not clear.

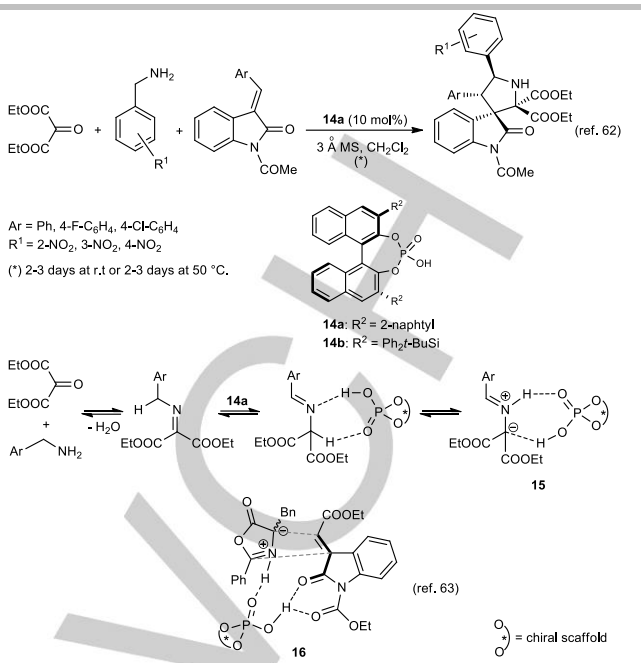


Ar = Ph, 3-MeO-C_6H_4, 2-pyridyl, 2-thiophenyl
R^1 = *i*-Bu, *n*-Pr, 2,2-dimethyl-propyl, 2,2-dimethyl-butyl

Scheme 15. Uncatalysed asymmetric three-component azomethine ylide cycloaddition.

For the sake of clarity, the most recent examples of catalysed asymmetric azomethine ylide cycloadditions to 3-alkylidene oxindoles are grouped as non metal- and metal-catalysed processes. As far as non metal-catalysed cycloadditions are concerned, the organocatalysts belong to BINOL-type phosphoric acid, thiourea and squaramide derivatives. All of these enantiopure scaffolds are usually capable of directional hydrogen bonding with the cycloaddends leading to the asymmetric complexation of the 3-alkylidene-2-oxindole dipolarophile and/or the azomethine ylide intermediate. In some cases, the complexed cycloaddends can be looked as they take part to an intramolecular-like cycloaddition, giving a better regio- and stereocontrol compared to the corresponding "fully intermolecular" reactions. The same considerations also applies in the case of metal-catalysed asymmetric azomethine ylide cycloadditions, bearing in mind that the metal-ligand complex is always the actual catalyst.

A Brønsted acid-catalyzed three-component asymmetric 1,3-dipolar cycloaddition[61] reaction between α-ketoesters, benzylamines and 3-alkenyl-2-oxindoles dipolarophiles was exploited in the presence of catalytic amounts of the BINOL derivative **14a**. As can be inferred from Scheme 16, 9 examples of enantiopure spiro(indolo) pyrrolidines were obtained with 86-98 % yield and 91-94 % e.e. The chiral phosphoric acid **14a** was an excellent catalysts for the transamination of the α-keto ester imines and the subsequent generation of the complexed azomethine ylide-type intermediate **15**, this latter specie allow the enantioselective dipolar cycloaddition to the 3-alkenyl-2-oxindoles.[62] The Brønsted acid catalysis provided by the chiral phosphoric acid **14b** was also effective to promote a similar enantioselective cycloaddition of azlactones providing 22 examples of enantiopure spiro(indolo) pyrrolidines with 70-93 % yield, d.r. >20:1 and 87-97 % e.e. through the intermediate **16** (Scheme 16).[63]



Scheme 16. BINOL-type phosphoric acid-catalysed asymmetric azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles: three-component reaction (ref. 62) and azlactone-indolic dipolarophile reactive intermediate **16** (ref. 63).

The enantiopure thiourea derivatives **17**-**20** were used successfully as organocatalysts in the asymmetric azomethine ylide cycloaddition involving 3-alkenyl-2-oxindoles (Figure 2).

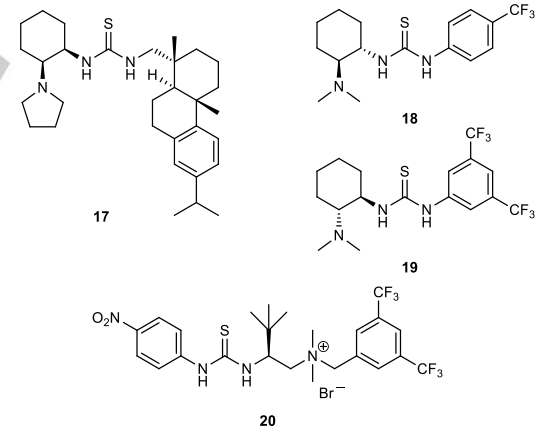
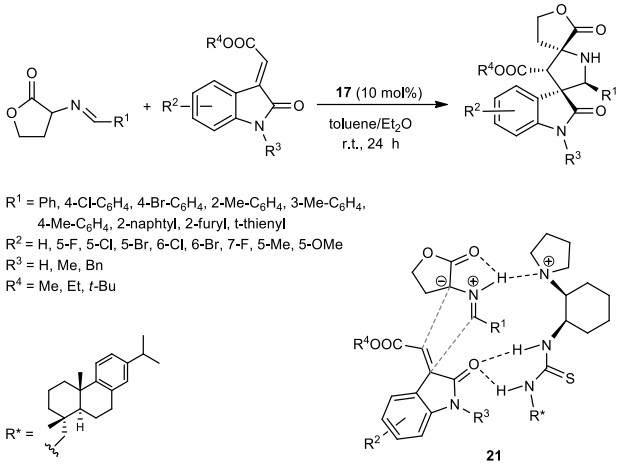


Figure 2. Enantiopure thiourea organocatalysts.

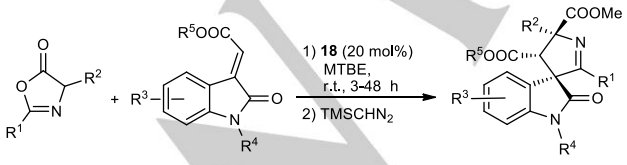
Rosin-derived tertiary amine thiourea bifunctional catalysts **17** has been applied to the asymmetric synthesis of the spiro(indolo)pyrrolidine skeleton by means of the azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.[64] In this reaction, a serie of homoserine lactones derived from various aromatic or aliphatic aldehydes provided the precursors of the azomethine ylide intermediates affording 23 examples of the corresponding spiro cycloadducts in good to excellent yields and stereoselectivities (86-97 % yield, 90-97 % e.e., 14 : 1 to 20 : 1 d.r., Scheme 17). The reactive intermediate **21** was proposed in order to rationalise the stereochemical outcome of the cycloaddition.



Scheme 17. Thiourea-catalysed asymmetric homoserine-lactone-derived azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

The scope of the asymmetric azlactone-derived azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles organocatalysed by the thiourea derivative **18** was examinated. In general, the reaction proceeded with good to excellent diastereoselectivity and excellent enantioselectivity to afford the desired spirocyclic-2-oxindoles in high yields (Scheme 18).[65] Most of the reactions gave good cycloadduct yield with good diastereoselectivity and moderate to excellent enantioselectivity (21 examples, 70-95% yield, 75:25 to 93:7 d.r. and 47-98% e.e.). Notably, the presence of an ester substituent at the alkylidene terminus of the 3-methylene-2-oxindole had a minor impact on the efficiency, enantio- and diastereo- selectivity of the reaction, regardless of the electronic nature, bulkiness, or position of substituents on the 3-alkylidene-2-oxindole. No model was proposed to rationalise the stereoselectivity behaviour of the cycloaddition.

Good results were also obtained in the presence of the enantiopure thiourea derivatives **19** and **20**, which were able to catalyse the asymmetric azomethine ylide cycloaddition of aldehyde imines to 3-alkylidene-2-oxindoles. In the presence of the former catalyst, enantiopure bis(trifluoromethyl)-substituted spiro(indolo)pyrrolidines were obtained starting from *N*-trifluoromethylimines (12 examples, 92-99 % yield, > 95:5 d.r. and 90-96 % e.e.) through an intermediate quite similar to **21**.[66] The latter catalyst provided 35 examples of enantiopure spiro(indolo)pyrrolidines with 80-99 % yield, 82:18-99:1 d.r. and 90-99 % e.e.).[67]



Scheme 18. Thiourea-catalysed asymmetric azlactone-derived azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

Generally, the introduction of a trifluoromethyl pendant in a molecule is able to modify its physico-chemical properties enhancing the bioavailability of the parent molecule.[68] The azomethine ylide cycloaddition carried out in the presence of Cinchona-derived squaramide catalysts **22** and **23** depicted in Figure 3 gave the CF_3-containing spiro(indolo)pyrrolidine or dispirooxindole cycloadducts in good yields and excellent d.r. and e.e.

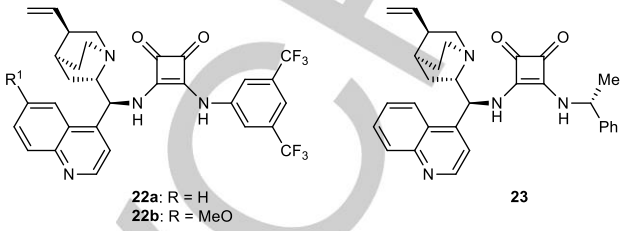
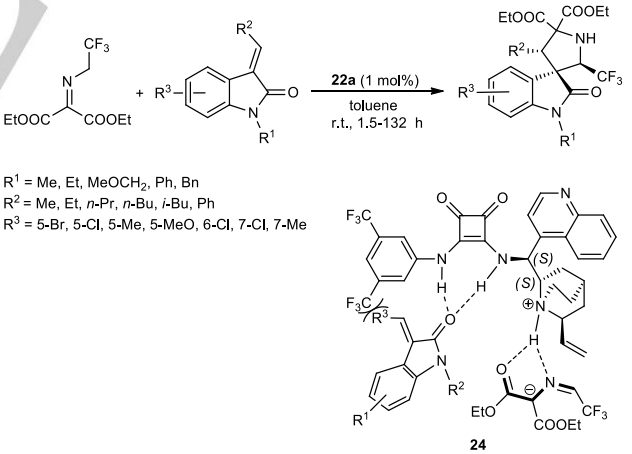


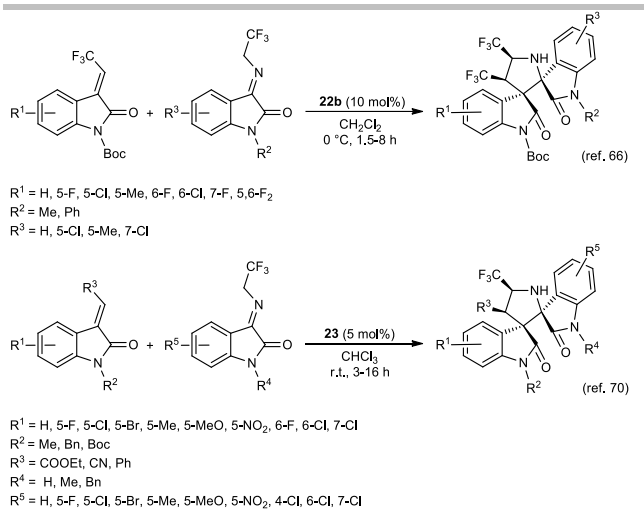
Figure 3. Enantiopure squaramide organocatalysts.

In Scheme 19 the results obtained in the presence of organocatalyst **22a** are outlined. Cycloaddition of 2-ketomalonic ester-derived azomethine ylides to 3-alkylidene-2-oxindoles gave rise to 19 spiro(indolo)pyrrolidine cycloadducts with 57-96 % yield, 86:14 to 95:5 d.r. and 53-99 % e.e.[69] The substituent of the alkenyl moiety played a key role in the reaction, the replacement of methyl- with more sterically-demanding alkyl groups slowed the cycloaddition rate. The reactive intermediate **24** was proposed to rationalise both the stereochemical outcome of the cycloaddition and its rate dependance by R^2. To reinforce the synthetic utility of this cycloaddition, gram-scale reactions were also carried out.



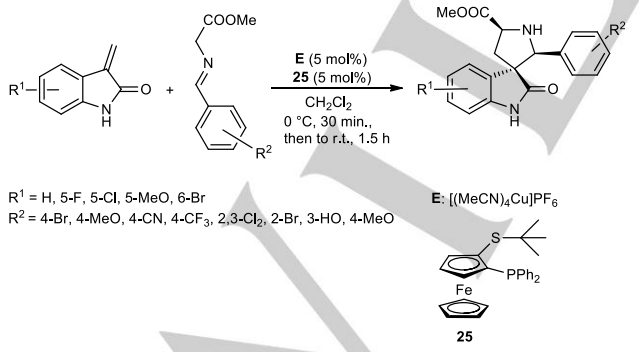
Scheme 19. Cinchona-derived squaramide **22a**-catalysed asymmetric 2-ketomalonic ester-derived azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

Cycloadditions between trifluoromethyl-containing indolic azomethine ylide and 2-oxindole dipolarophiles (fluorinated of not) in the presence of catalysts **22b** and **23** were also carried out affording trifluoromethylated 3,3'-pyrrolidinyl-dispirooxindoles. In the case of the former organocatalyst, 12 examples were obtained (85-99 % yield, >95:5 d.r., 80->99 % e.e.),[66] while the latter gave further 25 examples with quite similar high cycloaddition outcome (Scheme 20).[70]



Scheme 20. Cinchona-derived squaramide **22b**- and **23**-catalysed asymmetric (indolic) azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles.

Enantiopure spiro(indolo)pyrrolidines as precursors of the pentacyclic alkaloid spirotryprostatin A were synthesised by the asymmetric copper(I)-catalysed azomethine ylide cycloaddition to 3-alkylidene-2-oxindoles in the presence of the enantiopure ferrocenyl ligand **25** (Scheme 21).[71] In this protocol, the stabilised azomethine ylide intermediate was generated from the corresponding *N*-(benzylidene)glycine methyl ester by using triethylamine as non-complexating basic agent and (acetonitrile)copper(I) hexafluorophosphate (see also Scheme 13). A variety of mono- and polysubstituted (benzylidene)glycine azomethine ylides bearing electron-withdrawing and electron-donating substituents reacted with moderate yield but good enantioselectivity and, except for ortho-substituted azomethine ylides, the diastereoselectivity was high (11 examples, 40-69 % yield, 67:33 to 95:5 d.r., 84-97 % e.e.). The final products were isolated as single diastereomers after two steps. Further functionalisation gave six examples of the pentacyclic scaffold of spirotryprostatin A.



Scheme 21. Copper(I)-catalysed asymmetric cycloaddition of *N*-(benzylidene) glycine methyl ester-derived azomethine ylides to 3-methylene-2-oxindoles.

Other approaches to spirotryprostatin A were provided by asymmetric azomethine ylide cycloadditions catalysed by silver(I) acetate[72,73] in the presence of triethylamine and the organic ligand (*S*)-TF-BiphamPhos **26** (5 mol%). The reactions occurred at r.t. in 3-5 h. Cycloadduct structures and the proposed reactive complexes are depicted in Figure 4. It is worth noting that cycloadduct **27a** was active only against Gram-positive bacteria, and selective antibacterial activity was exhibited by spiro(indolo)pyrrolidines **27a**,**b** against *Streptococcus lactis*.

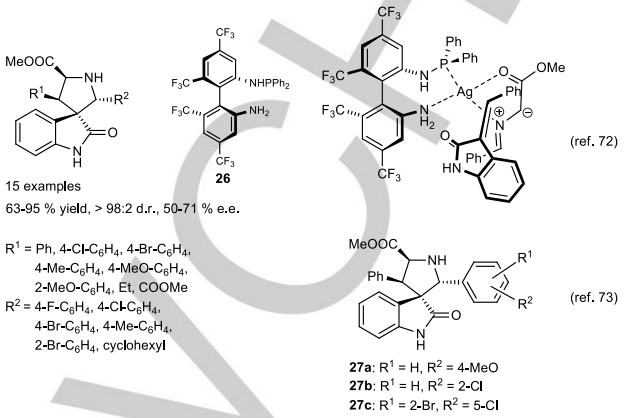
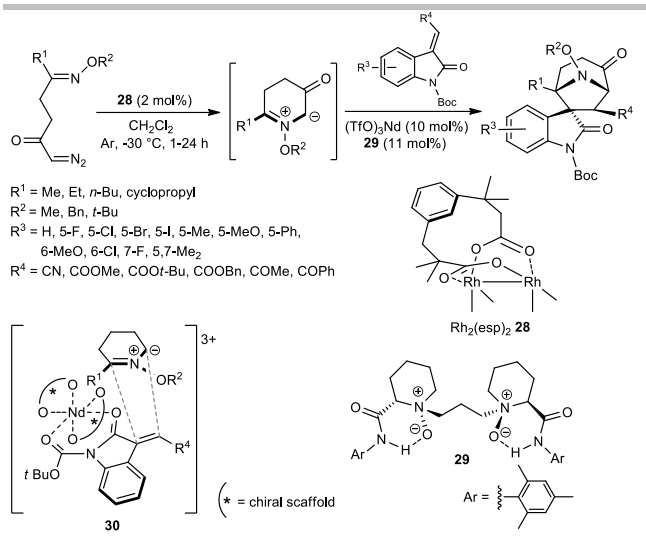


Figure 4. Asymmetric azomethine ylide cycloadditions catalysed by silver(I) acetate and (S)-TF-BiphamPhos **26**.

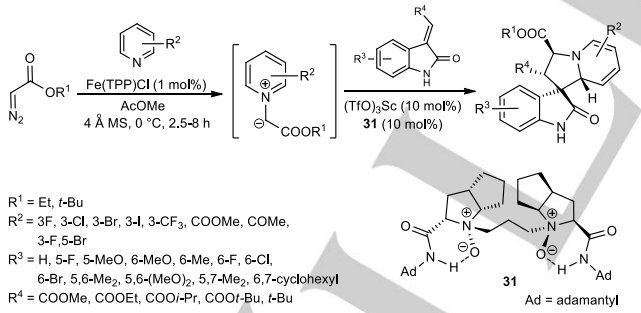
Tropane alkaloids containing the 8-azabicyclo[3.2.1]octane scaffold as alstonisine and chitosenine exhibit antispasmodial[74] and ganglionic-transmission-inhibiting[75] activity. The asymmetric synthesis of this spirotropanyl-2-oxindole scaffold was pursued by means of a bimetallic relay catalysis strategy (Scheme 22).[76]

According to Padwa's seminal paper,[77] *E*-oximino α-diazo ketones were submitted to treatment with achiral rhodium(II) complex **28** to generate transient (cyclic) azomethine ylides. The subsequent asymmetric cycloaddition to 3-alkylidene-2-oxindoles was achieved by using neodinium(III) triflate as the Lewis acid in the presence of the enantiopure *bis*-piperidine *N*,*N*'-dioxide **29** as the chiral organic ligand. This lanthanide-catalysed asymmetric cycloaddition covered a broad scope affording 24 examples of the spirotropanyl oxindole cycloadduct in high yields as well as diastereo- and enantio-selectivity (52-96 % yield, 75:25 to >95:5 d.r., 70->99 % e.e., see Scheme 22). Coordination of the indolic C=C dipolarophile by the complex $(TfO)_3Nd$-**29** lead to a decrease of the energy difference between the dipolarophile LUMO and the dipole HOMO, thus enhancing the cycloaddition rate. The stereochemical behaviour of this asymmetric azomethine ylide cycloaddition was rationalised through the reactive intermediate **30**. The distorted octahedral arrangement formed by the interaction between the 1,3-dicarbonyl moiety of the 3-alkenyl-2-oxindole with the $(TfO)_3Nd$-**29** complex is responsible for the observed *exo* stereoselectivity.



Scheme 22. Spirotropanyl-2-oxindoles by bimetallic relay catalysis strategy.

In a similar way, the asymmetric cycloaddition of pyridinium ylides to 3-alkylidene-2-oxindoles was successfully developed by the achiral Fe(TPP)Cl/chiral cyclopenta[*b*]pyrrolo-*N*,*N*'-dioxide **31**-scandium(III) bimetallic relay catalytic system (Scheme 23).[78] The generation of the pyridinium ylide intermediate occurred *in situ* by reaction between pyridines and alkyldiazoacetates *via* a iron-carbenoid intermediate. In fact, small amounts (2-5%) of several by-products were isolated, due to the direct carbenoid insertion or diazo cycloaddition to the indolic dipolarophile. Anyway, 25 examples of novel tetrahydroindolizidines were obtained in 55-99 % yield, 88:12 to 95:5 d.r. and 71-99 % e.e. The stereochemical outcome of this asymmetric pyridinium ylide cycloaddition was rationalised through a distorted octahedral reactive intermediate similar to **30**.

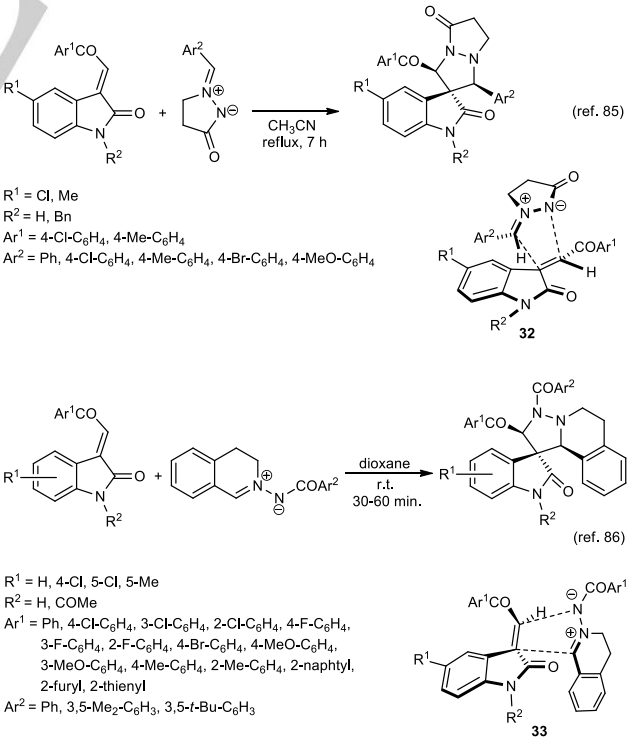


Scheme 23. Tetrahydroindolizine-2-oxindoles by bimetallic relay catalysis strategy.

2.2. Azomethine imine and nitrone (azomethine oxide) cycloadditions

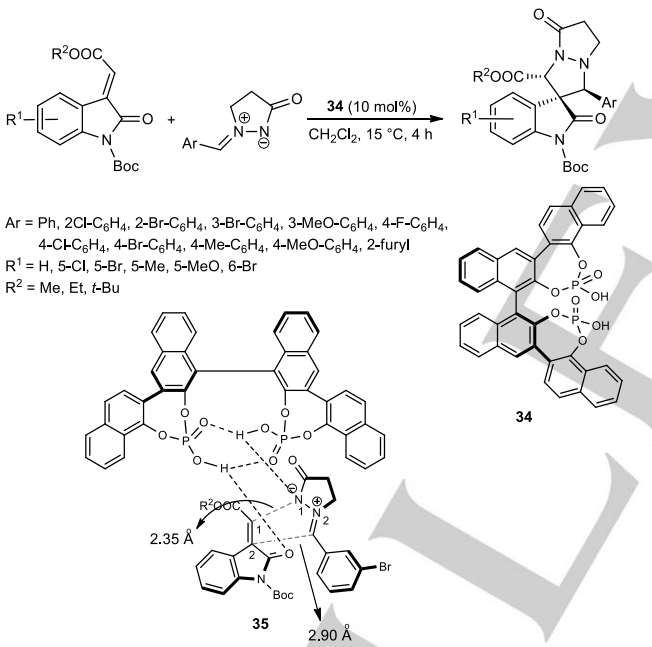
Since their first appearance at the end of XIX century, the development and the applications of nitrone (azomethine oxides) and azomethine imine chemistry followed a different fate. As the former were soon recognised as species "capable to undergo addition 1,3",[79] the systematic study of azomethine imines did not begin until 1960. Huisgen's monumental work on 1,3-dipolar cycloadditions allowed the classification of nitrones and azomethine imines as belonging to the family of azomethinium betaines.[23] Then, the behaviour of such 1,3-dipoles was studied deeply[80-84] and the issue of cycloaddition regio- and stereoselectivity was rationalised in the light of the FMO theory.[28,29] To this purpose, the frontier orbitals of the parent azomethine imine predict rapid reactions with both electron-deficient and electron-rich monosubstituted ethylenic dipolarophiles. However, in the case of the widely studied isoquinolinium imines, a large destabilization of the HOMO and a smaller stabilization of the LUMO arise. In this case, the cycloaddition should be controlled by the 1,3-dipole HOMO with electron-poor dipolarophiles giving selectively 3-substituted-pyrazolo[5,1-*a*]isoquinolines. For one of the most studied nitrones, namely *C*-phenyl-*N*-methylnitrone, the frontier orbital energies show that LUMO-dipole control should work in the case of electron-rich dipolarophiles, while the HOMO-dipole control should be effective with electron-poor dipolarophiles. As a consequence, mixtures of adducts can be expected in reactions of monosubstituted ethylenes with methylene nitrones, while 4-substituted isoxazolidines should be formed with *C*-aryl-*N*-alkylnitrones.

Stable, cyclic azomethine imines were reacted with 3-alkylidene-2-oxindoles to give spiro(2-oxindolo)pyrazolo[1,2-*a*]pyrazole and spiro(2-oxindolo)pyrazolo[5,1-*a*]isoquinoline skeletons (Scheme 24). In the former case, the intermolecular cycloaddition of 5-oxopyrazolidinium imides provided 10 examples with 55-70% yield, and the products were obtained as single diastereoisomer.[85] In the latter case, isoquinolinium imide cycloaddition furnished 24 examples with 76-97 % yield, and single diastereoisomers were found.[86] The relative stereochemistry outcome of these racemic azomethine imine cycloadditions were rationalised on the basis of the intermediates **32** and **33**, respectively.



Scheme 24. 5-Oxopyrazolidinium- and isoquinolinium imides cycloadditions to 3-alkylidene-2-oxindoles.

Several well-investigated BINOL-derived mono-phosphoric acid catalysts as **14a** gave high product yield and selectivity in the cycloaddition between azomethine ylides and 3-alkykidene-2-oxindoles (see Scheme 16). Unfortunately, these catalysts were not effective in the cycloaddition involving azomethine imines. It is likely that in this latter reaction both cycloaddends are hydrogen-bond receptors which cannot be efficiently activated by a single traditional mono-phosphoric acid. To circumvent this difficulty, the chiral BINOL-derived tetranaphtol catalyst **34** was evaluated in the asymmetric cycloaddition between azomethine imines and 3-alkylidene-2-oxindoles providing 18 examples with good yields, diastereo- and enantioselectivities (81-94 % yield, d.r. 86:14 to 95:5, e.e. 91->99 %), Scheme 25.[87] To gain some insight on the mechanism of this asymmetric cycloaddition, DFT calculations showed that in the best transition structure **35** the cycloaddends are hydrogen-bonded with the OH groups of both phosphoric acid moieties. In particular, the electron-poor 3-alkylidene-2-oxindole is activated by H-bonds while the azomethine imine 1,3-dipole may locate on backward by the other OH group of the phosphoric acid moiety. The calculated distances of the incipient C_1-N_1 (2.35 Å) and C_2-N_2 (2.90 Å) bonds speak in favour of a concerted but not synchronous process.



Scheme 25. Asymmetric azomethine imine cycloaddition to 3-alkylidene-2-oxindoles catalysed by BINOL-derived tetranaphtol **34**.

The racemic nitrone cycloaddition between *C*-aryl-*N*-phenylnitrones and 3-alkylidene-2-oxindoles was performed under microwave irradiation.[88] As expected by previous FMO predictions, complex mixtures of regio- and stereoisomeric cycloadducts were sometimes obtained. However, the fluorinated (2-oxindolo)isoxazolidine **36** (Figure 5) displayed antiinflammatory activity through inhibition of TNF-a-induced ICAM-1 expression on human endothelial cells. It needs to be recalled that neutrophil adhesion to the endothelial monolayer requires a series of interactions that are primarily mediated by ICAM-1. Interestingly, compound **36** significantly inhibited the adhesion of neutrophils to the endothelium in a concentration dependent way with an IC_{50} value of 12.5 mM.

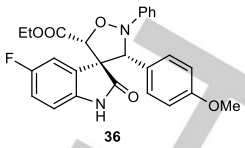
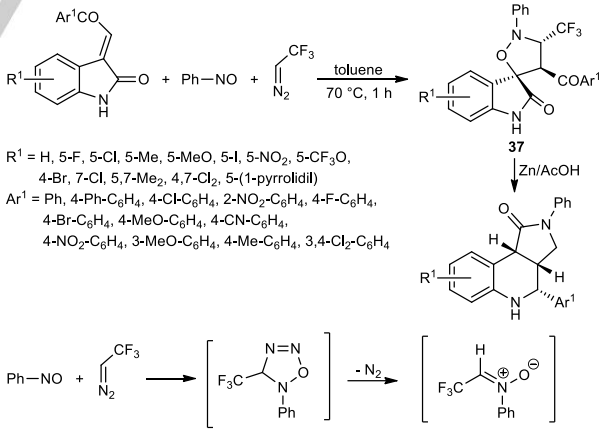


Figure 5. Fluorinated (2-oxindolo)isoxazolidine **36** as antiinflammatory through inhibition of TNF-a-induced ICAM-1 expression on human endothelial cells.

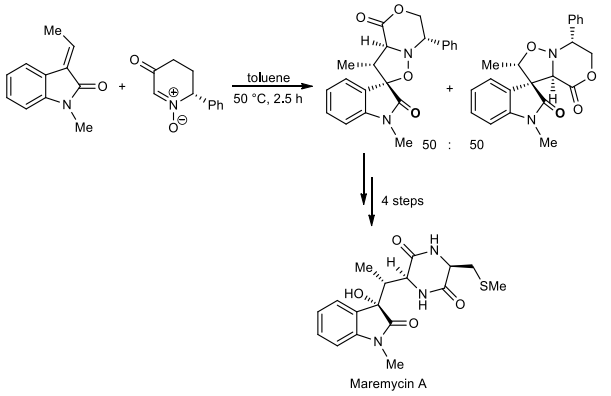
A three-component racemic reaction between trifluorodiazoethane, nitrosobenzene and 3-alkylidene-2-oxindoles was proved to be an efficient entry for the synthesis of trifluoromethylated spiro(2-oxindolo)isoxazolidines (25 examples, 56-83% yield, single diastereoisomer), see Scheme 26.[89] From the mechanistic point of view, the initial dipolar cycloaddition of trifluorodiazoethane to nitrosobenzene provides a labile oxatriazoline intermediate which is capable to undergo easy nitrogen extrusion generating the corresponding trifluoroethyl nitrone. Subsequent regioselective cycloaddition of the latter with the indolic dipolarophile afforded the target trifluoromethylated spiro(2-oxindolo)isoxazolidines **37**. It should be added that some amount of the corresponding trifluoromethylated spiro(2-oxindolo) cyclopropane (< 5 %) was formed due to the direct cycloaddition of trifluorodiazoethane to the indolic dipolarophile. As a further synthetic step, the isoxazolidine cycloadducts were submitted to acidic cleavage of the N-O bond with zinc powder in AcOH. To this purpose, a series of unusual rearrangements occurred giving pyrroloquinolines as single diastereoisomer.



Scheme 26. Diastereoselective three-component reaction between trifluorodiazoethane, nitrosobenzene and 3-alkylidene-2-oxindoles.

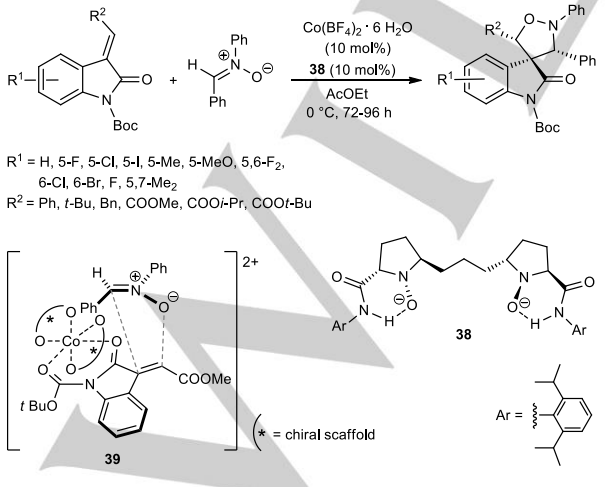
Maremycins are a group of structurally diverse 2,5-diketopiperazine natural products featuring *S*-methyl-L-cysteine as rare amino acid building block.[90] Following a previous report by the same Authors,[91] the total syntheses of maremycin A and maremycin D1 were reported in which the key step is the asymmetric cycloaddition of an enantiopure morpholinonitrone with (*E*)-3-ethylidene-1-methylindolin-2-one.[92] This thermal cycloaddition afforded quantitatively an

equimolecular mixture of enantiopure regioisomeric cycloadducts. The left cycloadduct in Scheme 27 was submitted to further transformations obtaining maremycin A.



Scheme 27. Asymmetric cycloaddition between a morpholinonitrone to (*E*)-3-ethylidene-1-methylindolin-2-one in the synthesis of maremycin A.

The asymmetric nitrone cycloaddition to 3-alkylidene-2-oxindoles has been performed successfully in the presence of the enantiopure *N*,*N*'-dioxide ligand **38** complexed with cobalt(II) tetrafluoroborate.[93] Spiro(2-oxindolo)isoxazolidines with three contiguous stereocenters were obtained (29 examples, 85-99 % yield, > 95:5. d.r., 90-98 % e.e.), see Scheme 28. The electronic features of R^2 influenced the cycloaddition outcome. In the presence of an electron-donating phenyl- or *t*-butyl group the reaction did not occur, conversely the best results were obtained with R^2 = COO*t*-Bu. The protecting group on the nitrogen atom of the indole moiety was also crucial for both the activation and stereocontrol. As illustrated by the intermediate complex **39**, the two oxygen atoms of the indolic C=O and the *N*-Boc pendant are coordinated with Co(II) to form a distorted octahedral complex. Since the *Si* face of the methyleneindolinone is shielded by the 2,6-diisopropylphenyl group of the ligand, the nitrone would attack from the *Re* face to afford the cycloadducts depicted in Scheme 28.

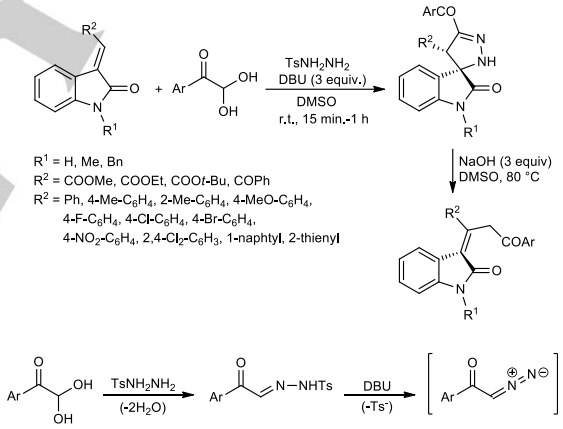


Scheme 28. Asymmetric nitrone cycloaddition to 3-alkylidene-2-oxindoles catalysed by *N*,*N*'-dioxide ligand **38** complexed with $Co(BF_4)_2$.

2.3. Diazocompound cycloadditions

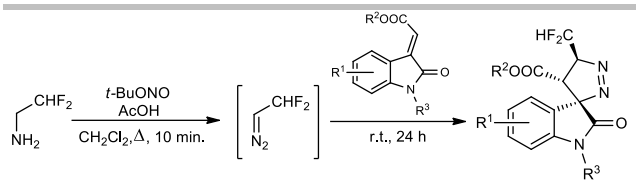
As stated by Huisgen in 1987,[94] the diazoalkane cycloadditions to electron-poor carbon-carbon multiple bond compounds is probably the 1,3-dipolar cycloaddition most intensively studied for synthetic purposes.[95] Diazocompounds belong to the class of diazonium betaines and are linear 1,3-dipoles in their ground state. Their cycloadditions with monosubstituted ethylenes are usually HOMO-dipole controlled processes leading to 3-substituted pyrazolines. Thus, the presence of a conjugate or an electron-withdrawal substituent on the dipolarophile enhances the cycloaddition rate, as confirmed by the the Hammett ρ = + 0.90 in the reactions of substituted styrenes with diazomethane. Conversely, electron release substituent(s) on the diazoalkane also accelerates the cycloaddition as shown by the order of reactivity $MeCHN_2$> CH_2N_2>> Ph_2CN_2> $EtOOCCHN_2$.[29]

In a three-component reaction, α-diazoacetophenones were generated *in situ* from phenylglyoxal and tosylhydrazine in the presence of DBU as shown in Scheme 29. Subsequent regio- and diastereoselective cycloaddition to 3-alkylidene-2-oxindoles afforded 17 examples of racemic spiro(2-oxindolo)pyrazolines (58-91 % yields, > 95:5 d.r.). Mild conditions and simple reaction workup were achieved without the use of any transition metal catalyst (Scheme 29).[96] Further transformation of the pyrazoline cycloadducts were performed to give open-chain (indolic)-1,5-dicarbonyls.



Scheme 29. Three-component regio- and diastereoselective reaction between phenylglyoxal, tosylhydrazine and 3-alkylidene-2-oxindoles.

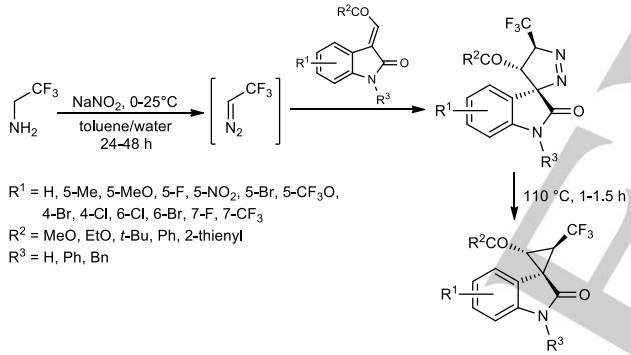
The difluoromethyl moiety ($-CF_2H$) can act as a bioisostere for alcohols, thiols and the hydroxymethyl group.[97] Furthermore, it can also act as a lipophilic hydrogen bond donor due to the presence of a slightly acidic C-H bond.[98] These properties make interesting the incorporation of the difluoromethyl group into the spiro(2-oxindolo)pyrazoline skeleton. To pursue this target, 2,2-difluoroethylamine was reacted with *t*-butyl nitrite, and the so-formed 2,2-difluorodiazoethane underwent a diastereoselective cycloaddition to 3-alkenyl-2-oxindoles. The resulting racemic spiro-adducts containing three contiguous stereocenters were obtained with 31-84 % yield and 72:28 to 99:1 d.r. (21 examples, see Scheme 30).[99] Although no rationale was found to explain the substituent influence on the cycloaddition yield, the process was amenable to the gram scale without loss of diastereoselectivity.



R^1 = H, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 5-I, 5-CF_3O, 6-Cl, 6-Br, 7-MeO, 7-F, 7-Cl, 7-Br
R^2 = Me, *n*-Pr, *t*-Bu
R^3 = Et, Bn, Ph, Boc

Scheme 30. Regio- and diastereoselective cycloaddition between 2,2-difluorodiazoethane and 3-alkylidene-2-oxindoles.

2,2,2-Trifluorodiazoethane has been the subject of a very recent review.[100] The intervention of such 1,3-dipole allowed the synthesis of racemic spiro(cyclopropyl)-2-oxindoles by nitrogen extrusion from the primary spiro(2-oxindolo)pyrazoline cycloadduct, the thermal ring contraction of Δ^1-pyrazolines to cyclopropanes being a well-known matter.[95] 21 Examples of the mentioned primary cycloadducts were obtained with 74-99 % yield and > 95:5 d.r. (Scheme 31).[101] Similar good results were also obtained by the cycloaddition-ring contraction sequence of non-fluorinated aryldiazomethanes $ArCHN_2$ to 3-alkylidene-2-oxindoles (31 examples, 72-93 % yield).[102]

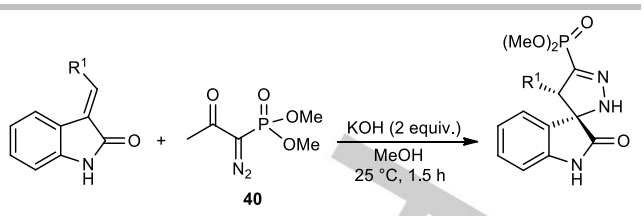


R^1 = H, 5-Me, 5-MeO, 5-F, 5-NO_2, 5-Br, 5-CF_3O, 4-Br, 4-Cl, 6-Cl, 6-Br, 7-F, 7-CF_3
R^2 = MeO, EtO, *t*-Bu, Ph, 2-thienyl
R^3 = H, Ph, Bn

Scheme 31. Regio- and diastereoselective cycloaddition-ring contraction sequence between 2,2,2-trifluorodiazoethane and 3-alkylidene-2-oxindoles.

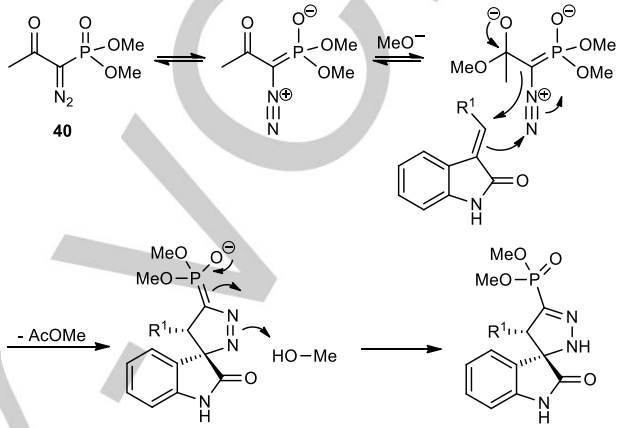
The synthesis of 3-phosphonyl-5-substituted pyrazoles have been developed by employing the Bestmann-Ohira reagent **40**.[103] In order to synthesise the spiro(2-oxindolo)pyrazole skeleton functionalised with the phosphonyl group, the base-promoted regio- and diastereoselective cycloaddition of **40** has been performed to 3-alkylidene-2-oxindoles obtaining 18 examples of racemic spiro(2-oxindolo)-Δ^2-pyrazolines (61-95 % yield, 80:20 to > 95:5 d.r.), Scheme 32.[104] Some insights about the cycloaddition mechanism are also outlined in Scheme 32.

Further 1,3-hydrogen shift followed by air-promoted oxidation of the latter spirocyclic scaffold afforded the fully unsaturated pyrazole derivatives **41**, Scheme 33, 14 examples with 78-85% yield, d.r. not determined.[105]

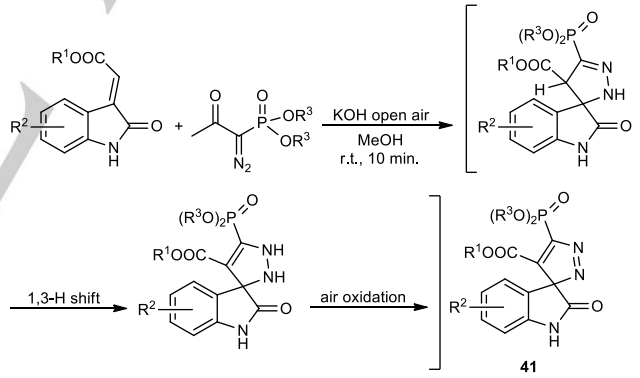


40

R^1 = Ph, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-CN-C_6H_4, 4-$(HO)_2B$-C_6H_4, 2-Cl-C_6H_4, 3MeO-C_6H_4, 1-naphtyl, 2-thienyl, 2-furo, *i*-Pr



Scheme 32. Regio- and diastereoselective cycloaddition between the Bestmann-Ohira reagent **40** and 3-alkylidene-2-oxindoles.



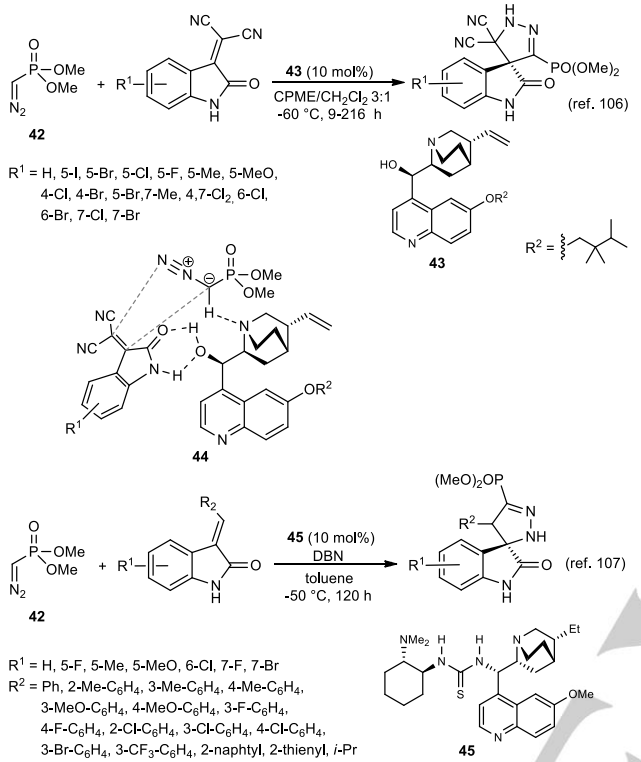
41

R^1 = Et, Me
R^2 = 5-Cl, 5-F, 5-MeO, 5-F_3CO, 5-NO_2, 4-Cl, 6-Br
R^3 = Et, Me

Scheme 33. Regioselective cycloaddition-air oxidation sequence between Bestmann-Ohira reagents and 3-alkylidene-2-oxindoles.

The regioselective asymmetric cycloaddition between the Seyferth-Gilbert reagent **42** and isatylidene malononitriles was performed successfully in the presence of the cinchona alkaloid derivative **43** as the catalyst. This protocol leads to 15 examples of enantiopure spiro(2-oxindolo)phosphonyl pyrazolines in 75-99 % yield, 73-99 % e.e., d.r. not determined. To rationalise the cycloaddition stereochemical outcome it was proposed the model **44** as the reactive intermediate, see Scheme 34. To reinforce the synthetic utility of this procedure, the asymmetric three-component reaction between isatin, malononitrile, and the reagent **42** based on sequential Knoevenagel condensation-dipolar cycloaddition sequence

was also exploited.[106] Curiously enough, the opposite cycloaddition regioselectivity was observed in a similar reaction carried out in the presence of the enantiopure thiourea-base organocatalyst **45** (22 examples, 45-99 % yield, 80: 20 to > 95:5 d.r., 86-95 % e.e.), Scheme 34.[107] In this latter case, no models were proposed to account for the observed stereoselectivity.

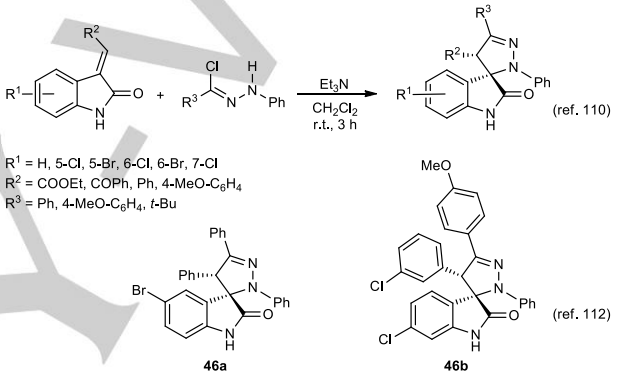


Scheme 34. Asymmetric cycloadditions between the Seyferth-Gilbert reagent **42** and 3-alkylidene-2-oxindoles.

2.4. Nitrilimine and nitrile oxide cycloadditions

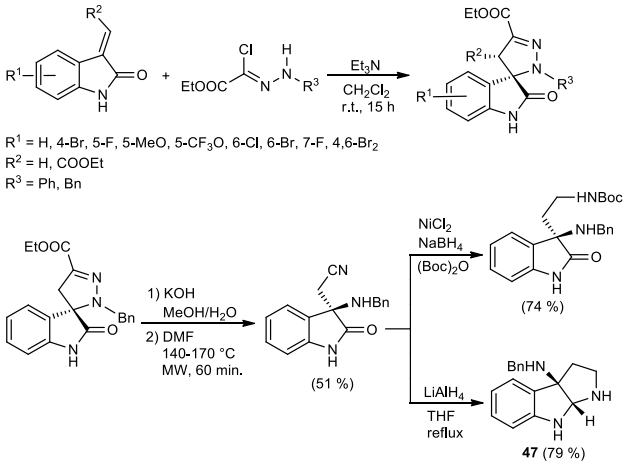
The nitrilimine structure was first perceived by Huisgen in 1959,[108] while the illustrious chemistry of nitrile oxides dates back to the beginning of the XX century.[109] Both nitrilimines and nitrile oxides belongs to the class of nitrilium betaines, so they are linear 1,3-dipoles in their ground-state. The rationalisation of nitrilimine reactivity and regioselectivity with electron-rich dipolarophiles relies upon the 1,3-dipole LUMO, affording 5-substituted Δ^2-pyrazolines. With electron-poor ethylenes, both HOMO and LUMO interactions are important, and the 5-substituted pyrazoline product is favoured again. Nitrile oxide cycloadditions with electron-rich and conjugated monosubstituted ethylenes are usually fast and controlled by the dipole LUMO, giving 5-substituted isoxazolines. Electron-poor ethylenes also react rapidly due to the influence with both dipole HOMO and LUMO orbitals. In this case, the formation of small amounts of the 4-substituted isoxazolines can be expected.[29]

Since nitrilimines are labile 1,3-dipoles, their generation generally occurs *in situ* by dehydrohalogenation of the corresponding hydrazonoyl chlorides.[108] The racemic synthesis of spiro(2-oxindolo)pyrazolines was accomplished by treating the appropriate hydrazonoyl chloride with 3-alkenyl-2-oxindoles in the presence of triethylamine as the organic basic agent. The regioselective cycloaddition of the dipolar intermediate gave 19 examples of the above spiro cycloadducts with 80-90 % yield, d.r. not determined, Scheme 35.[110] Other 24 examples were provided by a quite similar approach with similar results.[111,112] Biological evaluation of the so-obtained spiro(2-oxindolo)pyrazoline library showed antiproliferative activity in HCT-116 $p53^{(+/+)}$ human colorectal cancer cell line with two derivatives displaying good activities (**46a**: IC = 13.1 ± 1.0 μM, **46b**: IC = 10.9 ± 0.8 μM), see Scheme 35. Both spiro(indolo)pyrazolines **46** were able to induce apoptosis and cell cycle arrest. Cytotoxic effects induced by **46** occurred in cancer cells without eliciting cell death in non-malignant human colon fibroblasts. Furthermore, it was demonstrated that the combination of **46a** with sub-toxic concentrations of the chemotherapeutic agent 5-fluorouracil exerted a synergistic inhibitory effect on HCT-116 colon cancer cell proliferation.



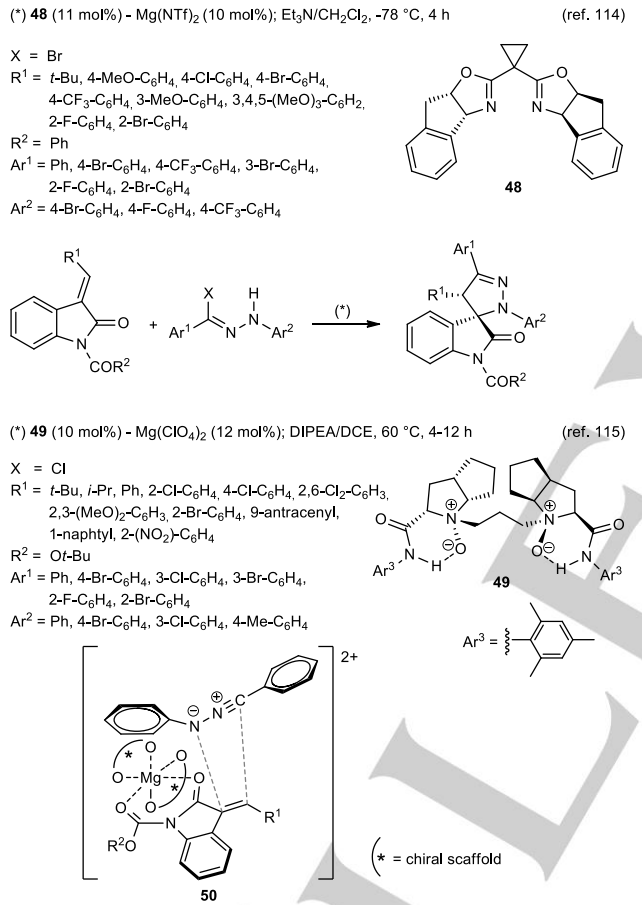
Scheme 35. Nitrilimine cycloaddition to 3-alkylidene-2-oxindoles.

Spiroadducts similar to **46** were obtained in high yields and with excellent regio- and diastereoselectivities (18 examples, 81-93 % yield, > 95:5 d.r.), Scheme 36.[113] Further elaboration of these primary cycloadducts constituted a versatile tool in the construction of indolo β-amino nitriles, indolo 1,3-diamines, and pyrrolo[2,3-*b*]indolines **47**.



Scheme 36. Nitrilimine cycloaddition to 3-alkylidene-2-oxindoles and subsequent synthetic transformations.

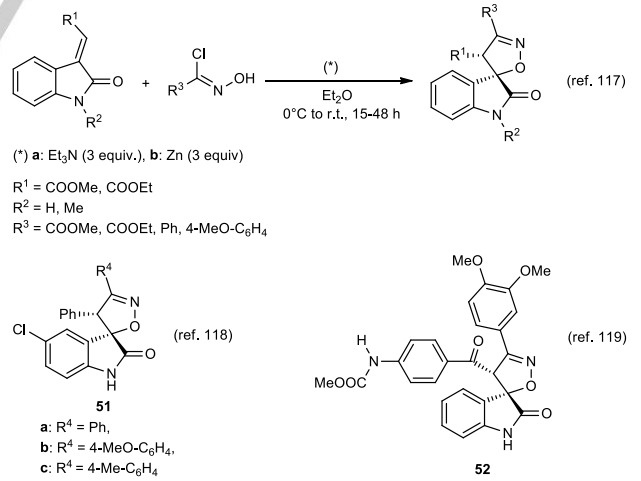
Two reports concerned to the asymmetric nitrilimine cycloadditions on 3-alkylidene-2-oxindoles deserve attention. In the first case, the reaction was catalysed by the complex that arises from magnesium triflate and the ligand **48** (Scheme 37).[114] The resulting 16 enantiopure spiro(2-oxindolo) pyrazolines were obtained with 43-90 % yields, > 95:5 d.r. and 61-99 % e.e. In the second case, the catalyst was the chiral magnesium perchlorate complex of the *N*,*N*'-dioxide ligand **49** (see also Scheme 37).[115] Further 31 examples of enantiopure pyrazole derivatives were provided with 56-98 % yield, 80:20 to 90:10 d.r. and 75-99 % e.e. As can be inferred from Scheme 37, a curious reactivity behaviour arises by comparing the experimental conditions. In fact, according to ref. 114 the nitrilimine cycloaddition proceeds sluggishly in 3 h at -78 °C, while by following the indications given in ref. 115, 60 °C and 4-12 h are required to obtain good conversion of the reactants.



Scheme 37. Asymmetric nitrilimine cycloaddition to 3-alkylidene-2-oxindoles.

A plausible rationalisation of this heterogeneous behaviour can be ascribed to the nature of the hydrazonoyl halide, since it is known that hydrazonoyl bromides reacts more easily compared to the corresponding chlorides.[116] Other experimental differences between the two approaches, namely the magnesium salt and the R^2 substituent to the 3-alkylidene-2-oxindole, are much more difficult to take in account for. To explain the observed stereoselectivity, the complex **50** has been proposed as a plausible reaction intermediate. This appeared reasonable on the basis of HRMS analysis of a mixture of 3-alkenyl-2-oxindole and the catalyst, suggesting that the indolic dipolarophile could interact with the Mg(II) center in a bidentate way. This coordination would lower the energy of the dipolarophile LUMO leading to a better HOMO-nitrilimine control of the cycloaddition. Due to the peculiar arrangement of the complex formed by the catalyst and the cycloaddends, the nitrilimine moiety should attack the *Si* face of the double carbon-carbon bond belonging to the 3-alkenyl-2-oxindole.

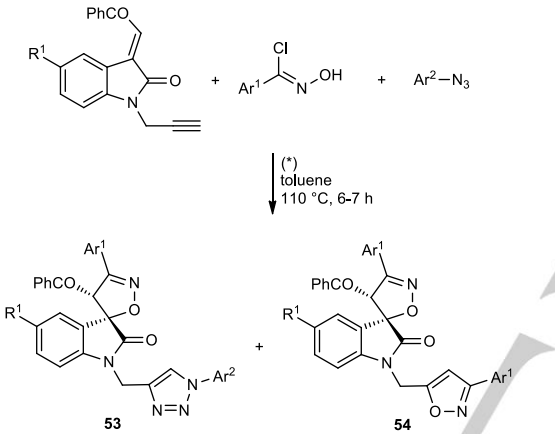
Few reports are concerned to the synthesis of spiro(2-oxindolo) isoxazolines from the direct cycloaddition of nitrile oxides to the 3-alkylidene-2-oxindole dipolarophile. The nitrile oxide intermediate is usually generated *in situ* by: (*i*) dehydrohalogenation of the corresponding cloroxime in the presence of stoichiometric amounts of an organic base, or (*ii*) by dehydration of primary nitroalkanes (Mukaiyama reaction).[109] The presence of the dipolarophile is always needed to avoid the fast dimerisation of the 1,3-dipole. Racemic nitrile oxide cycloadditions to the carbon-carbon double bond of 3-alkyidene-2-oxindoles were achieved with very variable yields as a function of both cloroxime and organic base (triethylamine) concentrations (5 examples, 16-94 % yields, d.e. not indicated). More reliable results were obtained by treating one equivalent of indolic dipolarophile with three equivalents of cloroxime and zinc powder (8 examples, 71-92 % yield, d.e. not indicated), see Scheme 38.[117] It can be noted that, notwithstanding the heterogeneous reaction medium, the effectiveness of Zn(0) as dehydrohalogenating agent may be due to the formation of zinc(II) chloride. No intermediate was proposed to rationalise the cycloaddition stereoselectivity outcome. Among the spiro(2-oxindolo) isoxazolines obtained by quite similar reactions, compounds **51** exhibits *in vitro* antiproliferative activity in a human hepatocellular carcinoma HepG2 cell line,[118] while compound **52** showed *in vitro* antifungal activity against *Candida albicans, Microsporum canis, and Trichophyton rubrum* (Scheme 38).[119]



Scheme 38. Nitrile oxide cycloaddition to 3-alkylidene-2-oxindoles and some bioactive cycloadducts.

An efficient three-component reaction between chloroximes, arylazides and 1-alkynyl-3-alkylidene-2-oxindoles was carried out leading to the site-selective formation of double-cycloadducts **53**, the reaction is actually a double dipolar cycloaddition. The first one occurs between the nitrile oxide, generated *in situ* from the corresponding chloroxime, and the

carbon-carbon double bond of the 3-alkylidene-indole moiety. The second cycloaddition is a typical copper(I)-catalysed azide-alkyne "click" reaction[120] that occurs simultaneously to the terminal alkyne pendant in the 1-position of the indole ring. Both cycloadditions are regioselective, and in the case of the nitrile oxide reaction a good degree of diastereoselectivity was observed. Of course, notwithstanding the known, lesser reactivity of nitrile oxides toward triple carbon-carbon bonds compared to that of arylazides in the "click" conditions, the unavoidable formation of some amount of cycloadducts **54** as minor products was also observed. 15 Examples of double cycloaddition products **53** were obtained with 70-85 % yield, d.r. not indicated (Scheme 39), and their structure was proved by X-ray diffraction methods.[121] The antibacterial activity of major double cycloadducts **53** was screened against four bacteria, namely *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus pyogenes*, showing that they exhibit remarkable activity against most of the tested bacteria.

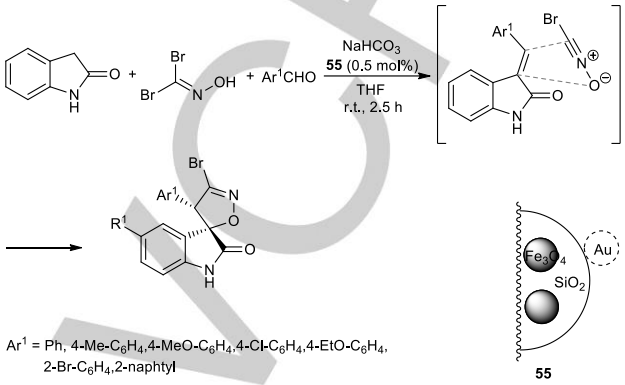


(*) $CuSO_4 \cdot 5H_2O$ (10 mol%), sodium ascorbate (20 mol%), Et_3N (2 equiv.)

R^1 = H, Br
Ar^1 = Ph, 4-Me-C_6H_4
Ar^2 = Ph, 4-Me-C_6H_4,4-MeO-C_6H_4,4-Cl-C_6H_4,4-NO_2-C_6H_4

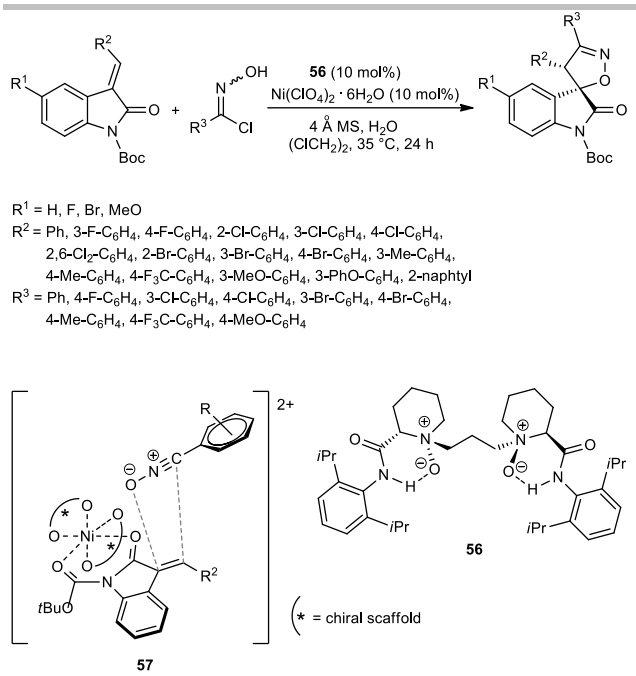
Scheme 39. Double cycloadditive, three-component reaction between nitrile oxides, arylazides and 1-alkynyl-3-alkylidene-2-oxindoles.

A regio- and diastereo-selective three component reaction between aldehydes, dibromoformaldoxime and 2-oxindole has been pursued in the presence of ferrite-silica nanoparticles decorated with Au(0) nanoparticles **55** (Fe_3O_4@SiO_2@Au) as the nanocatalyst, Scheme 40. From the synthetic standpoint, a sequential Knoevenagel condensation-nitrile oxide cycloaddition led to the formation spiro(2-oxindolo) isoxazolines under mild reaction conditions (7 examples, 78-85 % yield, d.r. and relative stereochemistry were not indicated).[122] Both cycloaddends, namely bromonitrile oxide and 3-alkylidene-2-oxindole, were generated *in situ*, the former by action of sodium hydrogencarbonate to dibromoformaldoxime, the latter by Knoevenagel condensation between 2-oxindole and aromatic aldehydes. The spiro(2-oxindolo) isoxazoline cycloadducts apparently result from the regioselective attack of bromonitrile oxide to the carbon-carbon double bond of the 3-alkylidene-2-oxindole. From the mechanistic standpoint, Au(0) nanoparticles can act as efficient catalyst by activating bromonitrile oxide through the lanthanide contraction effect.[123] The nanocatalyst preparation involved: (*i*) co-precipitation method in basic solution for the synthesis of Fe_3O_4@SiO_2 nanoparticles, and (*ii*) deposition of gold(0) nanoparticles onto Fe_3O_4@SiO_2 through chemical reduction of $HAuCl_4$ by sodium citrate. The nanocatalyst was recovered with the aid of an external magnet and was used after five runs without significant loss of activity.



Scheme 40. Fe_3O_4@SiO_2@Au-Catalysed three-component reaction between 2-oxindole, aromatic aldehydes and dibromoformaldoxime.

An asymmetric nitrile oxide cycloaddition to 3-alkylidene-2-oxindoles was pursued in the presence of the chiral nickel(II)-*N*,*N*′-dioxide ligand **56** complex as the catalyst. Mild reaction conditions were experienced leading to regioisomeric mixtures of spiro(2-oxindolo) isoxazoline cycloadducts in 68:32 to >99:1 ratio in favour of the major one depicted in Scheme 41. It should be added that high regioselectivities were achieved in most cases, *e.g.* 2-halo-substituted dipolarophiles gave regioisomeric ratio up to 99:1. It was found that the addition of water had a positive effect on both the product(s) yield and stereoselectivity, possibly because small amounts of water absorb the hydrochloric acid that arises in the formation of the nitrile oxide from the corresponding chloroxime. In the presence of 4 Å molecular sieves, the adverse effect of hydrochloric acid to the chiral metal complex catalyst was minimized to a certain degree, but the cycloaddition yields remained moderate. Although higher yields could be obtained by the addition of a base (K_2CO_3), the stereoselectivity dropped sharply (11 % e.e. for R^1 = H, R^2 = R^3 = Ph), in this case the precipitation of mixed Ni(II) oxide-hydroxide and carbonates can be envisaged as a very deleterious reaction towards the *in situ* formation of the *N*,*N*′-dioxide **56**-Ni(II) complex. Except for the cycloaddition yields, the data concerned to d.r. and e.e. are referred to the major regioisomer (27 examples, 30-65 % combined yield of the two regioisomers, >99:1 d.r., 96 - > 99 % e.e.).[124] To demonstrate the syntheric utility of the above approach, the reaction was scaled up to a gram scale. The complex **57** has been proposed as a plausible reaction intermediate on the basis of the X-ray structural analysis of the *N*,*N*′-dioxide-Ni(II) complex.



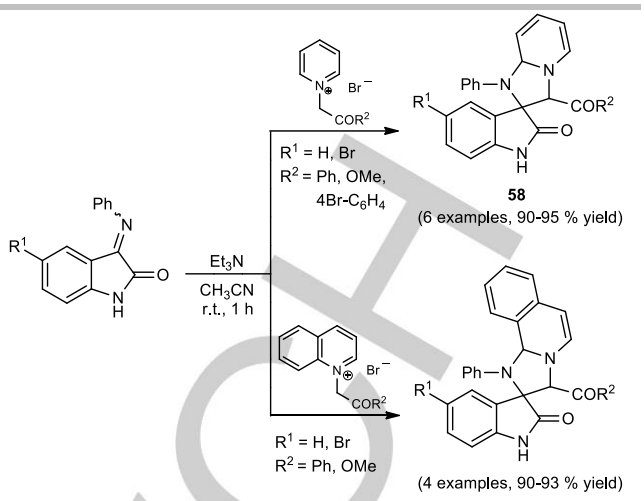
Scheme 41. Asymmetric nitrile oxide cycloaddition to 3-alkylidene-2-oxindoles.

3. Cycloadditions to 3-imino-2-oxindoles - B-type dipolarophiles

Although 3-imino-2-oxindoles exhibit a wide spectrum of interesting biologic activities,[125] they have seldom been employed as heterodipolarophile couterparts in 1,3-dipolar cycloadditions. As can be stated in the above paragraph, this situation is in sharp contrast with the 3-alkenyl-2-oxindole dipolarophile. In fact, it is perceived that alkenes usually behaves as effective dipolarophiles, while the imines derived from isatins exhibit relatively low reactivity toward dipolar cycloaddition. As will be shown in the following sections, some efforts should be taken to remove the intrinsic hurdle for this kind of reaction.

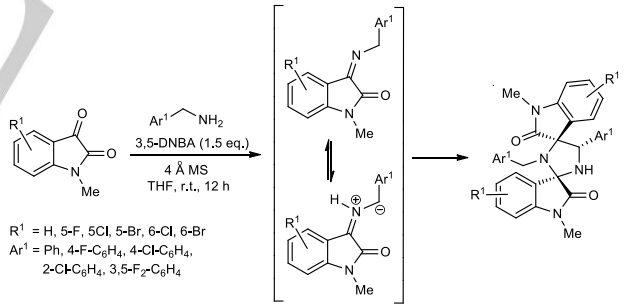
3.1. Azomethine ylide and azomethine imine cycloadditions

The racemic cycloaddition between isatin-3-imines and pyridinium or isoquinolinium ylides gave spiro(2-oxindolo)imidazolines (10 examples, 90-95 % yield, d.r. not indicated, relative stereochemistry not shown). Mild conditions, operational simplicity and easily accessible starting materials were the peculiar features of these cycloadditions (Scheme 42).[126] To gain some insight about their concerted nature, DFT calculations were performed at the M06-2X/6-31G* level, locating a TS with the very low barrier height of 5.2 kJ mol^{-1} for compound **58a** (R^1 = H, R^2 = Ph).



Scheme 42. Cycloaddition between isatin-3-imines, and pyridinium- or isoquinolinium ylides.

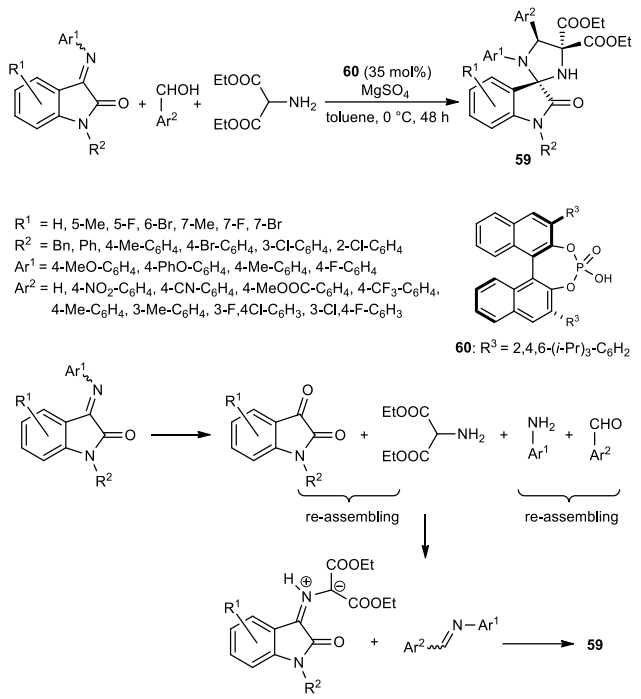
An acid-promoted self-1,3-dipolar cycloaddition of isatin-3-imines derived from isatins and benzylamines was developed in the construction of the dispiro(2-oxindole)imidazolidine skeleton (12 examples, 59-94 % yield, single diastereoisomer), Scheme 43. Both cycloaddends were generated *in situ*. The formation of the indole heterodipolarophile, namely the isatin-3-imine, occurred by condensation of benzylamines with isatins, while the azomethine ylide intermediate was provided by 1,2-prototropy of the so-formed isatin-3-imine. The self-cycloaddition was efficiently promoted by dinitrobenzoic acid (3,5-DNBA, pKa = 2.77) as the additive,[127] and a base-catalysed strategy has also been developed.[128]



Scheme 43. Self-cycloaddition between isatin-3-imines and azomethine ylides.

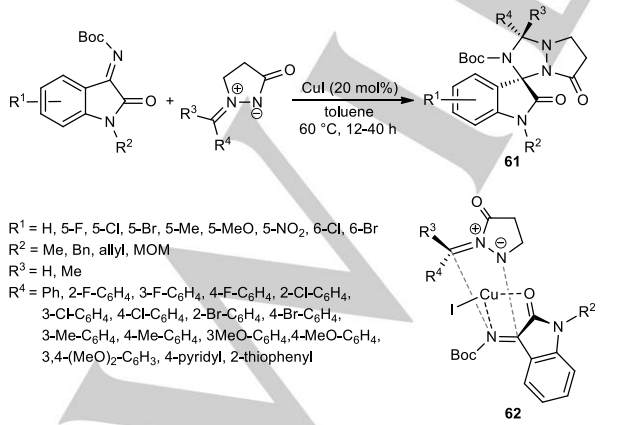
The asymmetric, three-component reaction between isatin-3-imines, aromatic aldehydes and diethyl 2-aminomalonate was carried out in the presence of the BINOL-type catalyst **60** affording the spiro(2-oxindolo) imidazolidines **59** (26 examples, 43-76 % yield, > 95:5 d.r., 72-96 % e.e.), Scheme 44. It is likely that the observed cycloadducts originate by the decomposition of the initial isatin-3-imines to isatins and subsequent re-assembling with the initial aromatic aldehyde. The so-formed indolic azomethine ylide should then be responsible for the attack onto the heterodipolarophilic C=N moiety of the newly-formed aldimmine. To verify this chemo-selective reaction pathway, four control experiments were carried out.[129] It was also inferred that the Brønsted acid catalysis provided by the chiral phosphoric acid **60** should

work by complexating both cycloaddends in a similar way as shown in Scheme 16.



Scheme 44. BINOL-type acid-catalysed asymmetric three-component reaction between isatin-3-imines, aromatic aldehydes and diethyl 2-aminomalonate.

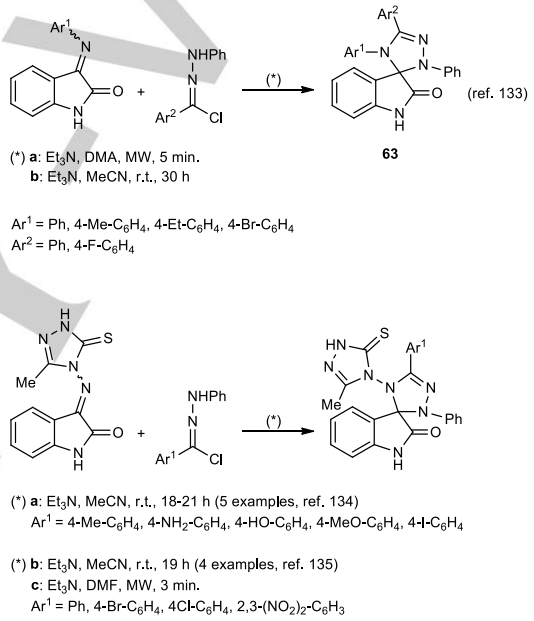
As far as the azomethine imine 1,3-dipole is concerned, the diastereoselective cycloaddition between 5-oxopyrazolidinium imine and isatin-3-imines were successfully performed in the presence of copper(I) iodide as the catalyst. Spiro(2-oxindolo)-3,1'-pyrazolo[1,2-*a*][1,2,4]triazoles **61** were obtained (26 examples, 77-94 % yield, > 99:1 d.r.), Scheme 45.[130] The model proposed to account for the observed relative stereochemistry relies upon the complexation between CuI and the isatin-3-imine. To avoid the strong steric repulsion between R^4 and Boc, substituents arrangement should result as depicted in the case of intermediate **62**, Scheme 45.



Scheme 45. 5-Oxopyrazolidinium imine cycloaddition to isatin-3-imines.

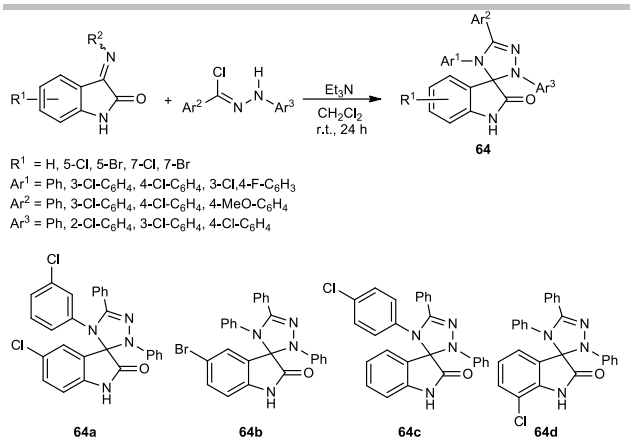
3.2.Nitrilimine and nitrile oxide cycloadditions

Both nitrilimine and nitrile oxide cycloadditions to the carbon-nitrogen double bond are long-known as they were fully investigated by Huisgen, although in the light of the present understanding of these reactions the first example of nitrilimine cycloaddition to the C=N moiety dates back to 1938.[131] More recently, some insights about the stereoselectivity outcome of these cycloadditions and the computational description of the *E-Z* isomerisation of the C=N bond were given.[132] The racemic spiro(2-oxindolo)-1,2,4-triazole skeleton **63** was first reported in 2001 by nitrilimine cycloaddition to isatin-3-imines. Both microwave-induced and conventional thermal reactions were exploited, obtaining good cycloaddition yields (88-95 %, 7 examples), see Scheme 46.[133] Similar reaction conditions were exploited in the nitrilimine cycloadditions with an isatin-3-imine bearing the 1*H*-1,2,4-triazol-5-thione ring (see also Scheme 46).[134,135]



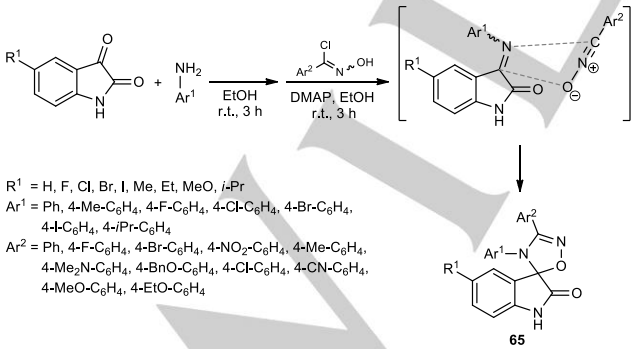
Scheme 46. Nitrilimine cycloaddition to isatin-3-imines.

The synthesis of a small library of twenty-six spirotriazoline oxindoles **64** was accomplished by racemic nitrilimine cycloaddition to isatin-3-imines (60-95 % yield), Scheme 47.[111] The *in vitro* antiproliferative activity of compounds **64** was assessed against four different cancer cell lines, and the four spirotriazoline oxindoles **64a**-**d** depicted in Scheme 47 showed selectivity against these cancer cell lines over a non-cancer derived cell line. In particular, these compounds were active against the specific tumor subtype known as triple-negative breast cancer (TNBC), a more aggressive type of cancer with poor prognostic (IC_{50} = 3.5-6.7 μM). Furthermore, cycloadducts **64a**,**b** were able to induce apoptosis and cell cycle arrest and, importantly, cytotoxic effects induced by spirotriazoline oxindoles occurred in cancer cells without eliciting cell death in nonmalignant human colon fibroblasts.



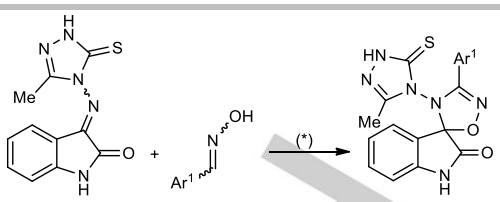
Scheme 47. Nitrilimine cycloaddition to isatin-3-imines giving spiro(2-oxindolo)-1,2,4-triazolines active against TNBC.

The nitrile oxide cycloadditive route to the spiro(2-oxindolo)-1,2,4-oxadiazole skeleton **65** was disclosed in 2000.[136] More recently, a three-component reaction between isatins, arylamines and choroximes was able to provide cycloadducts **65** through the nitrile oxide cycloaddition to the C=N bond of isatin-3-imines. Both cycloaddends were generated *in situ*, the former by dehydrohalogenation of the corresponding chloroxime, the latter by condensation between isatin(s) and aromatic amine(s). Mild reaction conditions were experienced, and no extra additives such as metal ions of catalyst were needed. Wide substrate scope and good functional group tolerance allowed to obtain 22 examples of spiro(2-oxindolo)-1,2,4-oxadiazole cycloadducts with 78-95 % yield, Scheme 48.[137] The antibacterial activities of these compounds were screened *in vitro* against two gram negative and two gram positive bacterial strains (*Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae*). Compound **65a** (R^1 = I, Ar^1 = Ph, Ar^2 = 4-Me-C_6H_4) displayed significant antibacterial activity against *S. aureus* since its effectiveness *in vitro* was comparable to standard drugs as chloramphenicol and ciprofloxacin and better then ampicillin.



Scheme 48. Nitrile oxide cycloaddition to isatin-3-imines giving spiro(2-oxindolo)-1,2,4-oxadiazoles **65**.

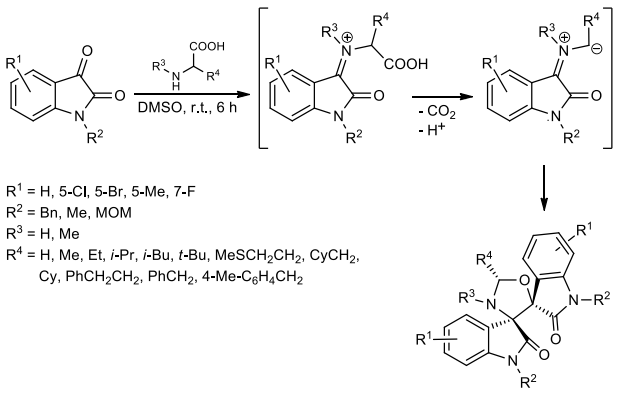
As shown in Scheme 49, nitrile oxide cycloaddition to an isatin-3-imine bearing the 1*H*-1,2,4-triazol-5-thione ring was feasible by both thermal and microwave irradiation (4 + 4 examples).[138]



Scheme 49. Nitrile oxide cycloaddition to *N*-(5-thioxo-1,2,4-triazol-4-yl)-3-iminoisatin.

4. Cycloadditions to isatins - C-type dipolarophiles

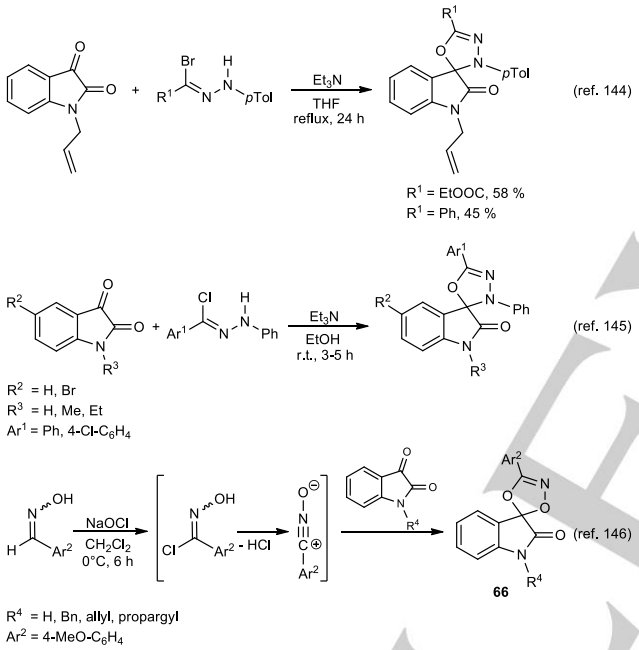
The orange-red monoclinic prism crystals of isatin (1*H*-indole-2,3-dione) were isolated by Erdmann and Laurent in 1840. Since then, an astonishing array of bioactive natural products were found containing the isatin core, and a number of isatin derivatives display an array of chemical reactions such as oxidation, ring expansion, Friedel-Crafts reaction, and aldol condensation.[139-142] The activated carbonyl moiety in the 3-position of the isatin ring can also behaves as the heterodipolarophilic counterpart in 1,3-dipolar cycloadditions, although the number of available examples is quite low compared to the ethylenic dipolarophile. Generally speaking, this paucity of data may be ascribed: (*i*) to the low reactivity usually displayed by the carbonyl group as dipolarophile, and (*ii*) to the lability of the primary adducts obtained by attack of a 1,3-dipolar specie to the carbonyl group.[23] As a matter of fact, the direct azomethine ylide cycloaddition involving the isatin C=O was first performed in 2015.[143] This diastereoselective approach rely upon the decarboxylative generation of the indolic azomethine ylide intermediate by initial condensation between isatin and α-aminoacids. Subsequent cycloaddition to the isatin carbonyl lead to the formation of the novel dispiro(2-oxindolo)oxazolidine skeleton (18 examples, 76-99 % yield, 83:17- >95:5 d.r.), Scheme 50. The operational simplicity of this protocol should be pointed out, since tiny solvent amounts (1 ml/10 mmol) were used and chromatography-free purification of cycloadducts was achieved.



Scheme 50. Azomethine ylide cycloaddition to the isatin 3-carbonyl group.

Switching the attention to the nitrilium betaine-type 1,3-dipoles, the first example of nitrilimine cycloaddition to the isatin carbonyl dates to 2005, obtaining the spiro(2-oxindolo)-1,3,4-oxadiazole skeleton.[144] Curiously, the reaction appeared site-selective towards isatin 3-carbonyl, while the *N*-allyl group remained unchanged. Other five examples were provided with 83-88 % cycloadduct yield by a quite similar approach (Scheme 51).[145]

Nitrile oxides were also able to attack the isatin 3-carbonyl in the presence of a carbon-carbon double- or triple-bond pendant, the reaction was regio- but not site-selective affording mixtures of mono- and bis-adducts with 63:37 (R^4 = propargyl) and 67:33 (R^4 = allyl) ratio (4 examples, 47-76 %). Only the spiro(1,4,2-dioxazolo)-2-oxindole monocycloadducts **66** are shown in Scheme 51. In this case the nitrile oxide intermediate arises from the corresponding oxime by treatment with sodium hypochlorite, and the presence of a basic agent were not needed to achieve the dehydrohalogenation of the chloroxime intermediate (4 examples, 47-76 %).[146]

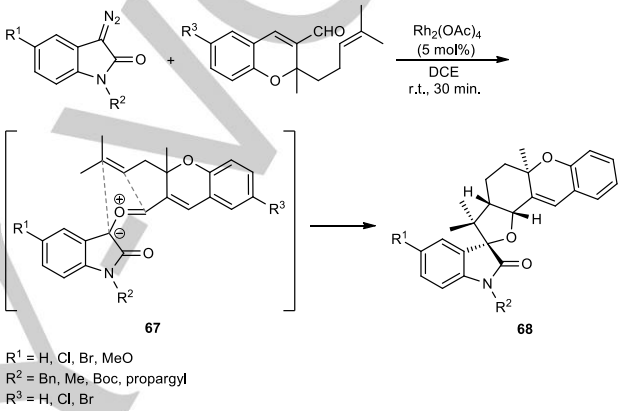


Scheme 51. Nitrilimine and nitrile oxide cycloadditions to the isatin 3-carbonyl group.

5. Intramolecular cycloadditions

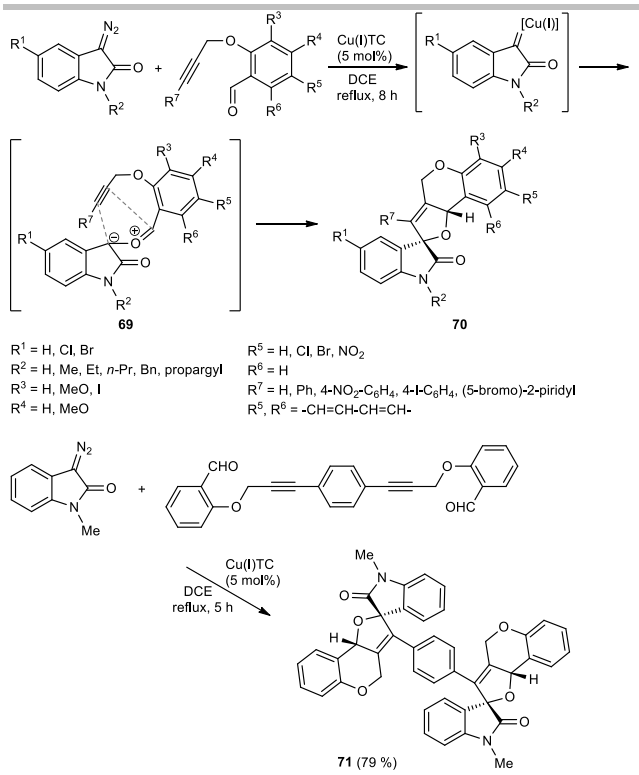
The field of intramolecular 1,3-dipolar cycloaddition have been explored from long time, and a large body of literature is now available on this subject.[147,148] Among the desirable features of intramolecular cycloadditions, it can be recalled that: (*i*) due to the geometrical constraints of bringing the 1,3-dipole into correct internal alignment for reaction, different regioselectivity can be observed compared to the corresponding intermolecular process, (*ii*) the greater steric constraint of intramolecular cycloaddition often gives higher stereoselectivity, and (*iii*) products are usually complex polycyclic, annulated, and fused-ring heterocycles that are difficult to prepare by any other method. Notwithstanding these favourable points, only two recent examples of intramolecular cycloadditions are available involving the formation of spiro(2-oxoindole) cycloadducts.

An approach for the synthesis of biologically active polycyclic spiro(furo)-2-oxindoles was realised through the intramolecular cycloaddition of carbonyl ylides **67**. These labile intermediates were generated by reaction between 3-diazoisatins and chromene-3-carboxaldehyde *via* rhodium-carbene complexes[77] (see also Scheme 22 for intermolecular carbonyl ylide cycloadditions). The intramolecular process was completely chemoselective since no cyclopropanation products due to the insertion of the α-diazoketone to the ethylenic moiety were found. Furthermore, spiro(furo)-2-oxindole cycloadducts **68** were obtained with full regio- and stereo-selectivity (17 examples, 60-88 % yield, single diastereoisomer), Scheme 52.[149]



Scheme 52. Intramolecular cycloaddition of the indolic carbonyl ylide **67**.

The slow addition of 3-diazoisatins to *O*-propargyl salicylaldehydes in the presence of copper(I) thiophenecarboxylate [(Cu(I)TC] gave the spiro(furo[3,2-c]chromene)-2-oxindoles **70**. In fact, the reaction between 3-copper(I)carbene-diazoisatins and salicylaldehydes involved the generation of the carbonyl ylide intermediates **69**, whose subsequent stereoselective intramolecular cycloaddition gave 17 examples of products **70** in 61-84 % yield as single diastereoisomers (Scheme 53).[150] In the same reaction conditions, a bis-propargylated salicylaldehyde reacted with diazoisatin giving the complex bis-cycloadduct **71** as single diastereoisomer.



Scheme 53. Intramolecular cycloaddition of the indolic carbonyl ylide **69**.

6. Conclusions

1,3-Dipolar cycloadditions represent a privileged route in the synthesis of a variety of pentatomic heterocyclic rings sharing a spiranic carbon in the 3-position of the 2-oxindole nucleus. The configurational rigidity of the resulting scaffolds imparts well-defined three-dimensional geometries that are fascinating from the structural standpoint and displays unique biomedical features as anti-cancer or antimicrobial agents. For these reasons, the construction of spiro-2-oxindoles attracts a number of efforts both from academia and industry. Among the spiro-2-oxindole scaffolds synthesised in the decade 2011-2020, some of them have been obtained through racemic cycloadditions. But the most challenging targets have been pursued by asymmetric cycloadditions; such a fertile topic encompasses the use of a variety of inorganic or organic catalytic systems including examples of chiral nanocatalysts. It is hopefully that our own 1,3-dipolar cycloaddition-based organisation of the subject will serve to stimulate and further attract the Chemists focused on the synthesis of spiro-2-oxindoles. Despite the latter sentence may be perceived as somewhat punctilious, the mentioned relevance of the subject makes us certain that in the near future an even wider variety of asymmetric 1,3-dipolar cycloadditions will be successfully applied to the synthesis of spiro-2-oxindoles.

Keywords: spiro-2-oxindoles • 1,3-dipolar cycloaddition • 3-alkylidene-2-oxindoles • 3-imino-2-oxindoles • isatins

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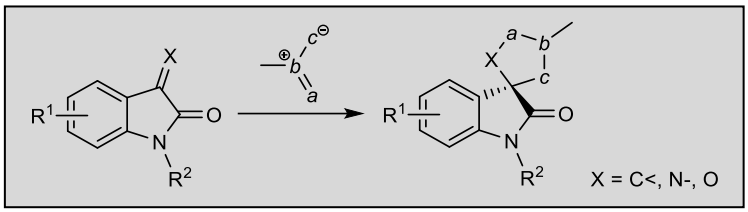

The reactivity of 2-oxindoles bearing a C=X double bond (X = C<, N-, O) in the 3-position towards a variety of 1,3-dipolar species has been reviewed in a systematic way according to the type of the 1,3-dipole, the 2-oxindole dipolarophile and the racemic or asymmetric nature of the cycloaddition. Because of the huge variety of the resulting spiro-2-oxindole skeletons, the developments occurred in the 2010-2020 decade were taken onto account.