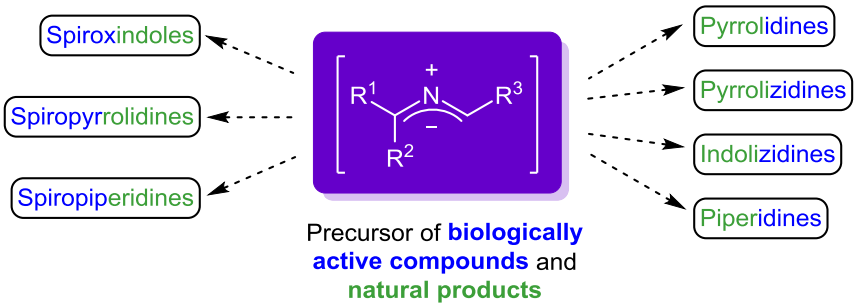
Current trends towards the synthesis of bioactive heterocycles and natural products using 1,3-dipolar cycloadditions (1,3-DC) with azomethine ylides

H. Ali Döndas[a,*]
María de Gracia Retamosa[b]
José M. Sansano[c]
[a] Mersin University, Faculty of Pharmacy. Yenisehir Campus 33169 Yenisehir, Mersin (Turkey).
[b] Instituto de Investigaciones Químicas (CSIC-US) and Centro de Innovación en Química Avanzada (ORFEO-CINQA) Avda. Américo Vespucio, 49,41092 Sevilla (Spain).
[c] Departamento de Química Orgánica, Instituto de Síntesis Orgánica (ISO) and Centro de Innovación en Química Avanzada (ORFEO-CINQA), University of Alicante-03080 Alicante (Spain).

* indicates the main/corresponding author.

yakdas25@mersin.edu.tr



Dedicated to Prof. Ronald E. Grigg

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Abstract In this revision a summary of the trends of the formation of complex or not so complex heterocyclic structures through 1,3-DC of azomethine ylides is described. Diastereo- and enantioselective processes as well as non-asymmetric cycloadditions constitute very important synthetic tools for achieving all these series of compounds. The contents are classified as follows:
1. Introduction
2. Synthesis of spiroxindoles
3. Synthesis of spiropyrrolidines
4. Synthesis of spiropiperidines and piperidines
5. Synthesis of pyrrolidines and fused pyrrolidines
6. Synthesis of pyrrolizidines and indolizidines
7. Synthesis of quinolone and isoquinolines
8. Conclusions

Key words Azomethine ylide · dipolar cycloaddition · natural products · bioactivity · heterocycles

1. Introduction

Biomimetic studies and biosynthetic theories strongly support that general [3+2] cycloadditions[1] take place frequently in nature.[2] In this line, azomethine ylides are useful synthetic intermediates to access complex molecules, and in consequence, their precursors are valuable building blocks in the elaboration of structurally diverse biologically important heterocycles and natural products. The main utility of these dipolar intermediates is as component of 1,3-dipolar cycloaddition (1,3-DC) together with electrophilic alkenes. Inter- and intramolecular versions of these types of 1,3-DCs provide a potentially flexible and versatile entry into the complex molecular framework with a pyrrolidine core. These cycloadditions reach a special dimension when the catalytic enantioselective process is successfully implemented. In this way, up to four contiguous stereogenic centers can be unambiguously generated in just one single step.

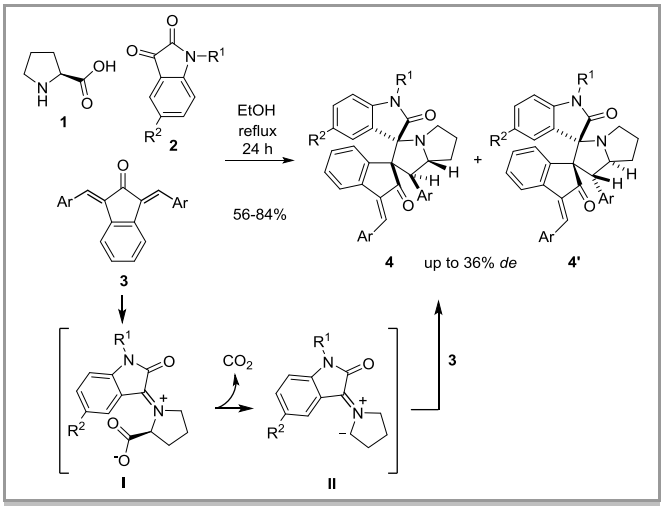
There are many excellent reports and reviews in the literature about the generation, and applications concerning 1,3-DCs with azomethine ylides but this field is in continuous expansion.[3] In this review the literature from 2015 through 2016 was covered organizing the research in terms of biologically important heterocycles and natural product from cascade 1,3-DC of azomethine ylide to the most simple cycloaddition [the application of this strategy to the generation of new materials or polymers is not covered in this review].

2. Synthesis of spirooxindoles

Spirooxindole skeleton has an important biological role in bioorganic and medicinal chemistry as well as in the drug discovery programs.[4] Synthesis of novel potentially bioactive spirooxindoles has been reviewed in a recent paper and the work related to spirooxindolepyrrolidines was also detailed.[5] However, in this review some very recent publications have not been highlighted. Therefore, in this revision the most recent work regarding to spiroxindolepyrrolidines, obtained from a multicomponent 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylides with the appropriate alkene, is reported.

The synthesis of spirooxindolepyrrolizidine derivatives **4** and **4'**, as well as their in vitro bioactivity against *Mycobacterium tuberculosis*, were reported by Askri et *al*. Compounds **4** and **4'** were prepared from non-stabilized azomethine ylides, generated *in situ* from isatin derivatives **2** and L-proline **1**. Subsequent 1,3-DC with (*E*,*E*)-1,3-bis(arylidene)indan-2-ones **3** yielded the

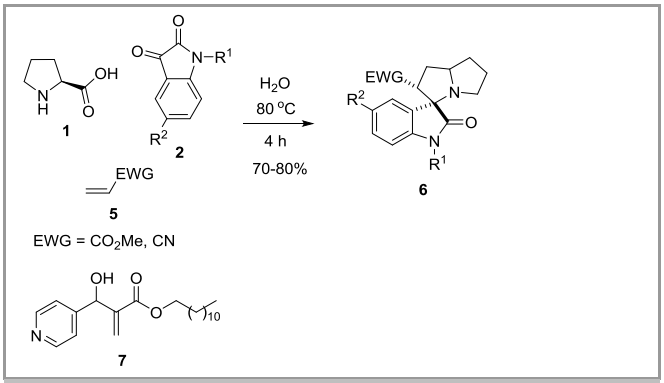
corresponding dispirooxindolepyrrolizidines in a one-pot three component domino reaction with poor diastereoselectivities (Scheme 1).[6, 7] In general, in these type of cycloadditions regarding iminium-decarboxylation route, the iminium salt **I** formed between compounds **1** and **2** undergoes a spontaneous decarboxylation to give the intermediate azomethine ylide **II**, which reacts with the electrophilic alkene with total regioselection.



Scheme 1 Synthesis of diastereomeric mixtures of spirooxindoles **4** and **4'**.

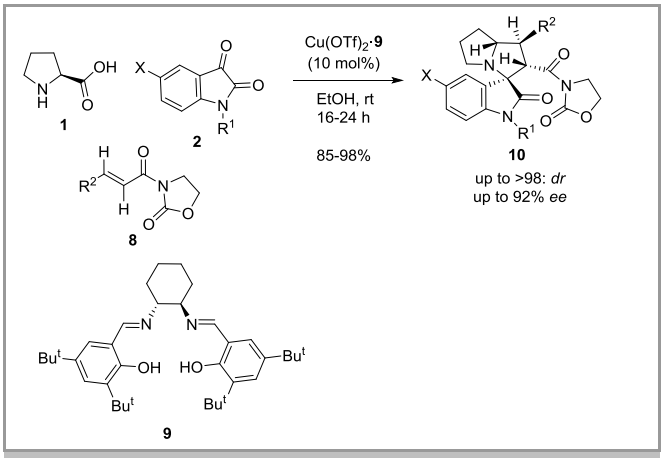
An environmentally friendly synthesis of spirooxindolo-pyrrolizidines **6** was reported by Tiwari *et al*. starting from proline **1**, isatins **2**, and acrylonitrile or methylacrylate in water. The reaction proceeded regioselectively in a three-component manner. Again, the *in situ* generation of fleeting non-stabilized azomethine ylide, and subsequent 1,3-DC reaction with these electron deficient alkenes **5** as dipolarophiles, afforded biologically active spirooxindolopyrrolizidine derivatives **6** (Scheme 2).[8]

A variant of this green process was the 1,3-DC run with a Morita–Baylis–Hillman (MBH) adduct **7** (Scheme 2), derived from pyridine-4-carboxaldehyde and lauryl acrylate, giving similar spirocycloadducts in good yields but employing toluene instead of water.[9]



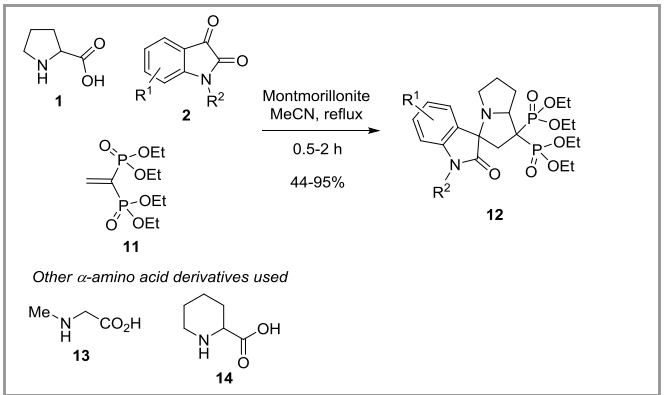
Scheme 2 Green multicomponent synthesis of spirooxindolopyrrolizidines **6**.

Potentially bioactive spiroheterocycles **10**, containing both spirooxindole and pyrrolizidine core structures, were enantioselectively prepared by Taghizadeh and co-workers. The 1,3-DC was carried out in the presence of $Cu(OTf)_2$·bis(arylmethyleneamine) **9** chiral complex, ethanol, proline **1**, isatins **2**, and acrylic dipolarophiles **8** under mild conditions (Scheme 3).[10]



Scheme 3 Enantioselective synthesis of spiranic compounds **10**.

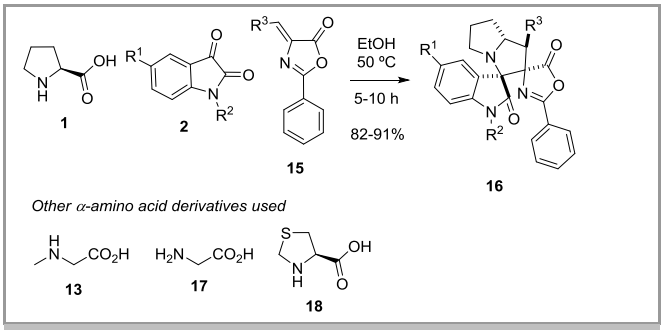
Highly activated tetraethyl vinylidene-1,2-(bis)phosphonate **11** was allowed to react with isatins **2** and various amino acids (proline **1**, sarcosine **13**, or piperidine-2-carboxylic acid **14**) in the presence of montmorillonite as catalyst. The 1,3-DC occurred in refluxing acetonitrile obtaining spirotetracyclic adducts **12** as a mixture of diastereoisomers in moderate to good yields (Scheme 4).[11]



Scheme 4 Preparation of spirooxindoles **12** bearing geminal bisphosphonate unit.

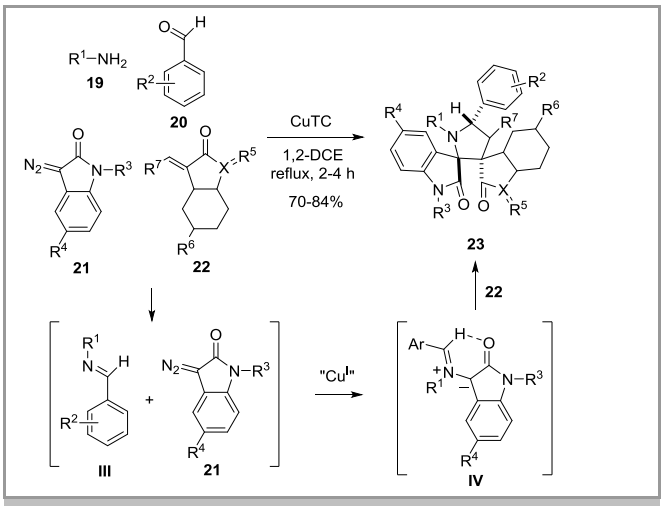
Alkylidene oxazolones **15** were selected as dipolarophiles to synthesize biologically important spirooxindole frameworks **16**. Diverse isatins **2** and a variety of amino acids such as glycine **17**, sarcosine **13**, L-proline **1**, or thiazolidine-4-carboxylic acid **18**, afforded, in a one-pot tricomponent process, regio- and diastereoselective 1,3-DCs (Scheme 5). Biological evaluation of

compounds **16** against several cancer cell-lines revealed that some of them possessed antitumor activity.[12]



Scheme 5 Synthesis of spirooxindoles **16**.

A range of potentially bioactive substituted dispiro-pyrrolidines/-imidazolidines **23** were prepared in the presence of copper(I) thiophene-2-carboxylate (CuTC) catalyst in refluxing 1,2-dichloroethane (1,2-DCE). Here, the *in situ* generated imine **III** reacted with the copper(I)-carbene (obtained by decomposition of diazocompound **21**) giving a fleeting aziridine, which evolved thermally to azomethine ylide **IV** (Scheme 3). The reaction proceeded chemo-, regio-, and diastereoselectively in very good yields. The complexity of the resulting products **23** is obvious because two of the four generated stereogenic centers are quaternary carbons (Scheme 6).[13]



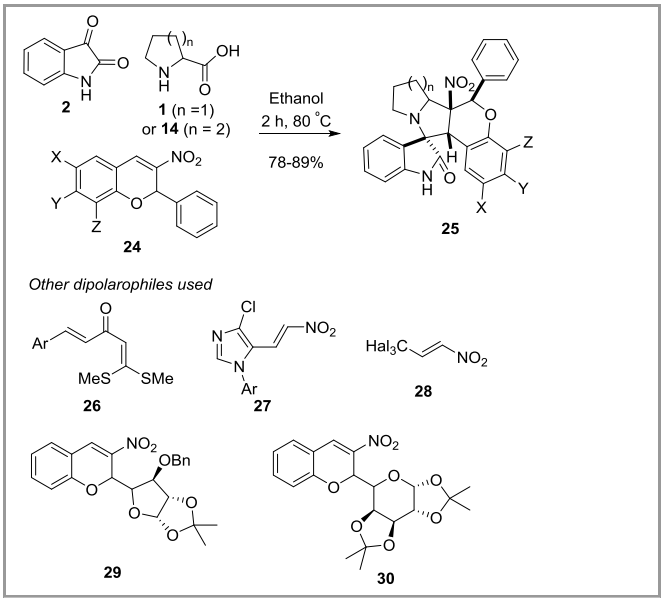
Scheme 6 Synthesis of dispiranic compounds **23**.

Spirooxindolepyrrolidines **25** (n = 1) and an example of spirooxindolepiperidine **25** (n = 2) fused to nitrochromanes were prepared from isatin **2** and proline **1** or pipecolic acid **14** as azomethine ylide sources. The 1,3-DC occurred in refluxing ethanol (Scheme 7), and proceeded with total control of the diastereoselectivity. [14]

A similar cycloaddition with electrophilic alkenes **26**, instead of using nitroalkene **24**, was performed. The cycloaddition proceeded chemo-, stereo- and regioselectively throughout the styrene moiety. [15] In other contribution, (2-nitrovinyl)imidazoles **27** (Scheme 7) were allowed to react under similar reaction conditions producing a 95:5 ratio of the corresponding spirocycloadducts.[16]

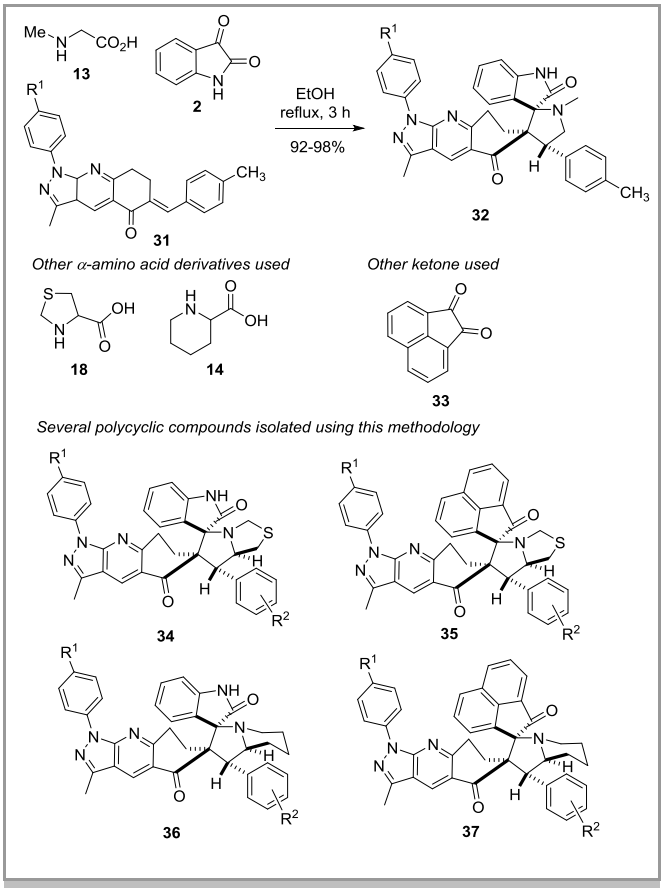
Trihalomethyl-substituted nitroethylenes **28** (Scheme 7) were selected as dipolarophiles to prepare a variety of biologically active spirooxoindolepyrrolidines, which may be of interest for medicinal chemistry.[17]

Analogously, new designed glycol-3-nitrochromenes **29** and **30** (Scherme 7), derived from glyco-β-nitroalkenes and salicylaldehyde, were tested as dipolarophiles in refluxing acetonitrile to give the corresponding biologically active sugar-bearing spirooxindole cycloadducts as single diastereoisomers in good yields.[18]



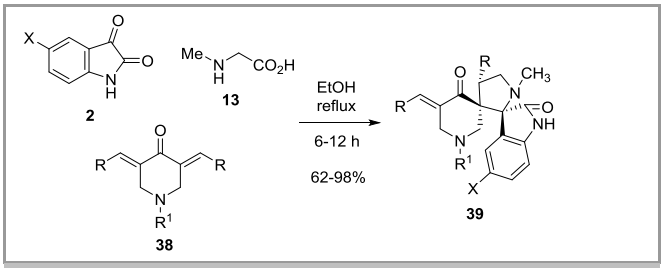
Scheme 7 Synthesis of spirocompounds **25**.

Spirooxindoles **32**, bearing quinoline, pyrrolidine, pyrrolothiazole and indolizine ring system hetereocycles, were prepared by Kumar *et al.* from, sarcosine **13**, isatin **2** and potential bioactive dipolarophiles **31**, derived from pyrazolo[3,4-b]quinolone, such as it is shown in Scheme 8. The ecofriendly reaction was achieved *via* in situ generated azomethine ylide and stereoselective 1,3-DC in a three-component sequential atom economy processes.[19] This protocol was extended to another components such as, thiazolidine-4-carboxylic acid **18** and piperidine-2-carboxylic acid **14**, together with acenaphthenequinone **33**, to access potential bioactive diverse spiro-tethered pyrazolo quinoline heterocycles **34**-**37** (Scheme 8).



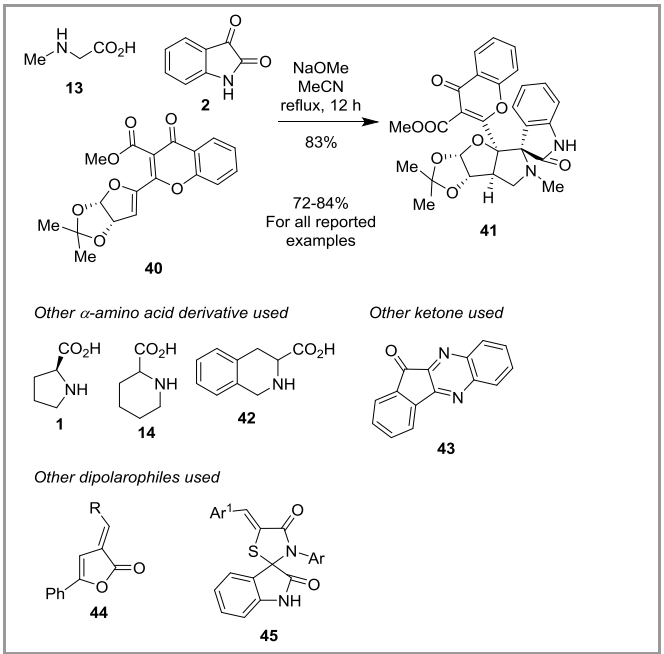
Scheme 8 Synthesis of spiroxindoles **32**, **34**-**37**, from pyrazolo[3,4-b]quinolone **31**.

From symmetric dipolarophiles **38**, sarcosine **13**, and isatin derivatives **2**, a series of dispirooxindoles **39** were obtained in high diastereoselections. They showed higher potency, against the HeLa (cervical) tumor cell line, than reference cisplatin derivatives (Scheme 9).[20,21] In addition, it was discovered that these molecules exhibited antitumor activity against hepatocellular cancer (HEPG2) cell line,[22] breast cancer (MCF7, T-47D) and colon cancer (HCT116).[23]



Scheme 9 Generation of dispiroxindoles **39**.

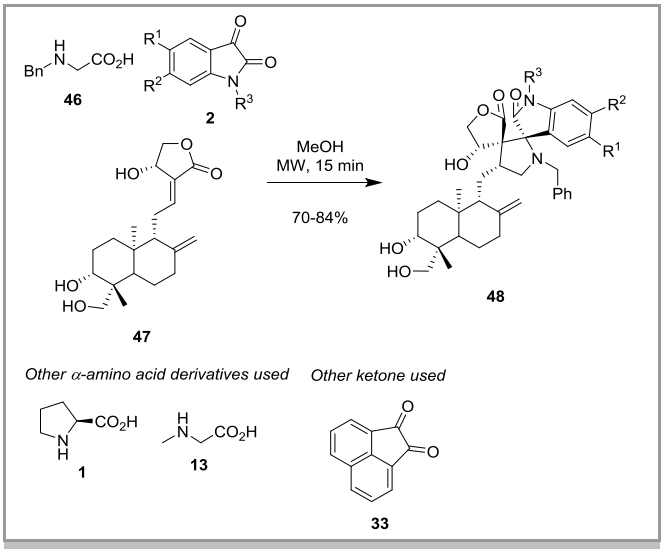
Synthesis of sugar-containing spirocyclic pyrrolidine derivatives **41** were reported by Raghunathan *et al*. Here, α-aminoacids, ketones and electrophilic olefin **40** incorporating a sugar moiety were allowed to react *via* 1,3-DC (Scheme 10). Proline **1**, sarcosine **13**, tetrahydroisoquinolinic acid **42** or pipecolinic acid **14** and acenaphthoquinone **33**, isatin **2**, or indenoquinoxalinone **43** were employed in this cascade protocol to access a variety of biologically important spiroheterocyclic compounds **41** as single diastereoisomers.[24] Regio- and diastereo-selective 1,3-DC also afforded dispirooxindolopyrrolidines in a similar way, but employing 3-arylmethylidene-5-phenyl-3H-furan-2-ones **44**,[25] or 3,5-diarylmethylenespiro[indole-30,2- [1,3]thiazolane]-20(1*H*)-4-diones **45** as dipolarophiles (Scheme 10).[26]



Scheme 10 Synthesis of sugar-containing spirocyclicpyrrolidines **41**.

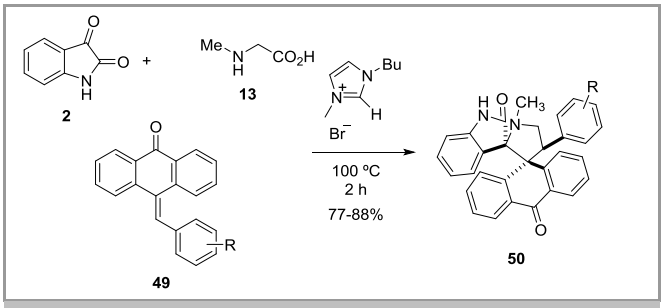
Another potential bioactive dispirooxindolo derivatives **48** were described by Mondal and co-workers from *N*-benzyl glycine **46** and isatins **2** or acenaphthoquinone **33** with andrographolide **47**, isolated from *A. paniculata*, as dipolarophile (Scheme 11). Their cytotoxic potential and antitimural activity of these spiroheterocycles **48** displayed more potency against MCF-7 breast cancer cell line when comparing andrographolide **47** itself.[27]

This promising activity, confirmed by biological tests, moved to the authors to elaborate new semisynthetic antitumor spirooxindole frameworks from acenaphthoquinone **33** (or isatin **2** derivatives) and secondary amino acids such as sarcosine **13**, and proline **1**.[28]



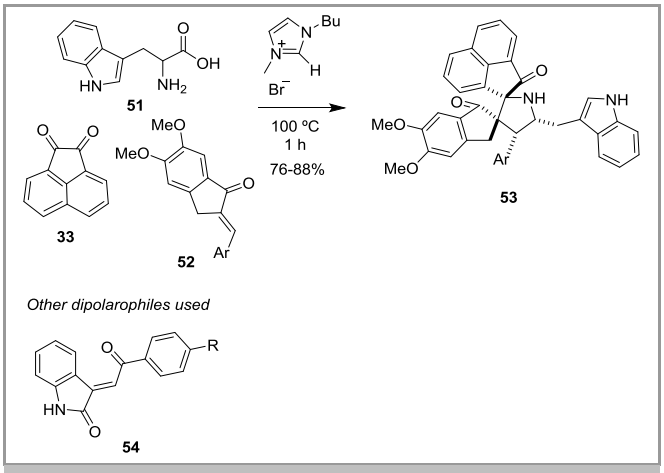
Scheme 11 Synthesis of dispiroandrographolide-type cycloadducts **48** *via* 1,3-DC of azomethine ylides.

Dispiroxindole heterocycles **50**, possessing dihydroanthracene ring system, were diastereoselectively prepared by Arumugam *et al.* in the presence of an ionic liquid (1-butyl-3-methylimidazolium bromide [bmim]Br), isatin **2**, sarcosine **13** and 10-benzylideneanthracen-9(10*H*)-one derivatives **49** (Scheme 12).[29]



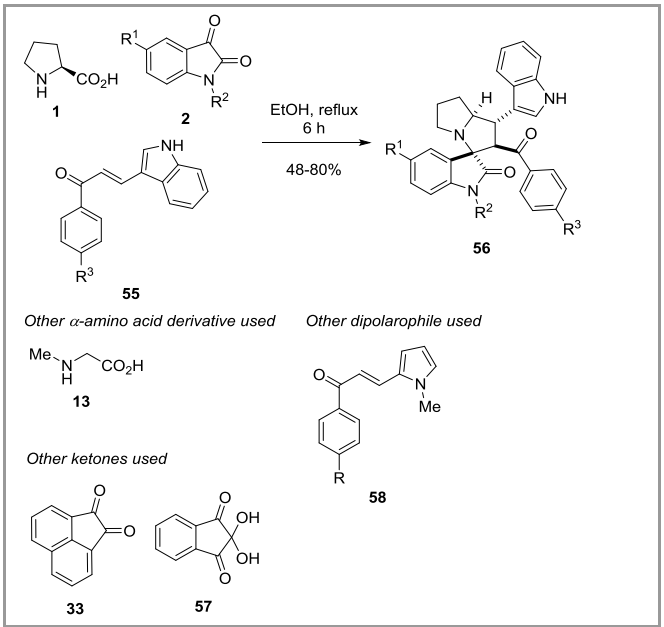
Scheme 12 Preparation of dispirooxindoles **50** using an ionic liquids as solvent.

A series of spiroxindolepyrrolidines **53** showing potential cholinesterase inhibitory activity were prepared by Kumar *et al.* In ionic liquid medium the 1,3-DCs of the azomethine ylide, formed with 1,2-diketones, such as isatins **2** or acenaphthenequinone **33**, and tryptophan **51**, with arylmethylidene inden-1-ones **52**, were successfully achieved. A representative example is shown in Scheme 13.[30] Other dispirooxindolopyrrolidines were prepared using 1-butyl-3-methylimidazolium bromide by mixing the corresponding amino acid, isatin **2**, and (*E*)-2-oxoindolino-3-ylideneacetophenones **54**.[31]



Scheme 13 Potential cholinesterase inhibitors **53** obtained *via* 1,3-DC.

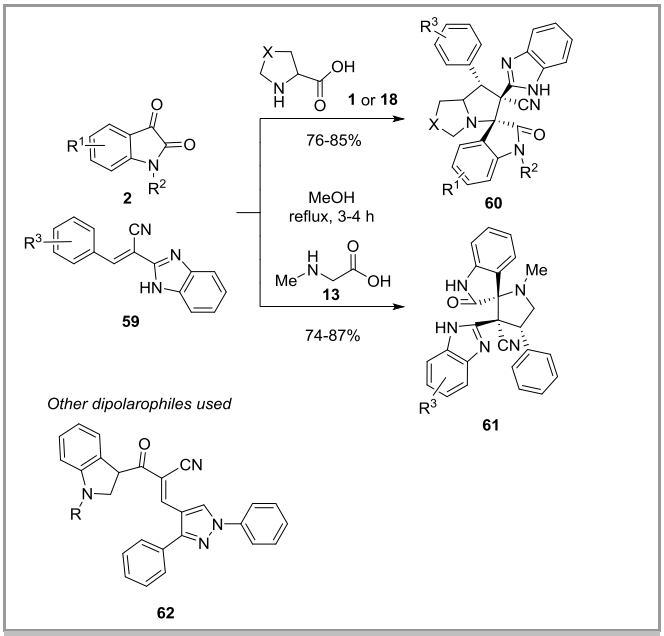
Biologically important aryl-/heteroaryl-substituted functionalized spiroxindole derivatives **56** were obtained employing electrophilic alkenes **55** containing an indole unit. Apart from isatins **2** and proline **1**, other components such as acenaphthoquinone **33** or ninhydrin **57**, sarcosine **13** and alkenes **58** (bonded to a pyrrole ring) were successfully tested. In general, the chemical yields and the diastereoselections were very high (Scheme 14).[32]



Scheme 14 Sythesis of biologically important aryl-/heteroaryl-substituted cycloadducts **56**.

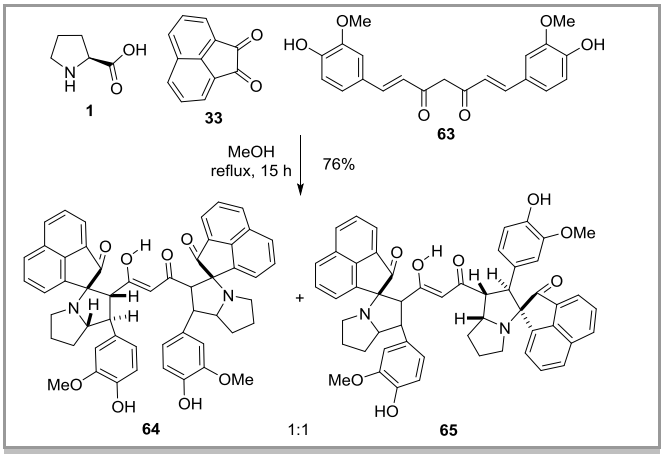
Spiroxindole-fused cycloadducts **60** and **61** were reported by Perumal *et al.* from 1,3-thiazolane-4-carboxylic acid **18** or sarcosine **13** and substituted isatins **2** as source of azomethine ylide intermediates. The 1,3-DC with benzimidazolphenylacrylonitrile **59** as dipolarophile occurred, in refluxing methanol, in very high yields and excellent diastereoselections (Scheme 15). This protocol, operating in a one-pot three-component manner,[33] was employed in the

reactions involving nitrile **62** (Scheme 15). The combination of **62** with isatin derivatives **2** and with the corresponding α-amino acid (**1**, **13**, or **18**) furnished biologically important cycloadducts with very interesting activities against bacteria and fungi.[34]



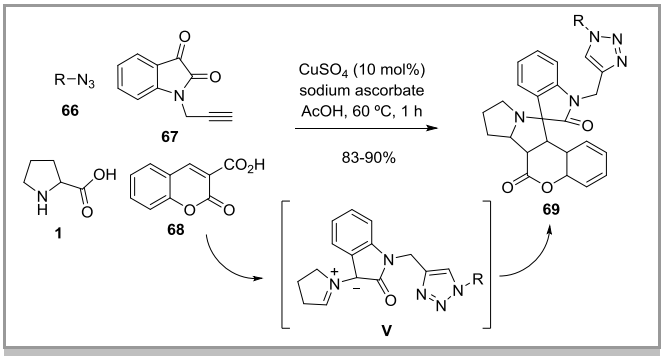
Scheme 15 Synthesis of spiroxindole-fused heterocycles **60** and **61**.

Preparation of dispiro-acenaphthylen-2-one curcuminoids **64** and **65** were described by Mondal *et al*. from acenaphthoquinone **33** and proline **1** as precursors of the corresponding azomethine ylide, together with curcumin **63** as dipolarophile. This attractive natural compound allowed the preparation of spirocycloadducts as 1:1 mixture of **64** and **65** in good yield after a double 1,3-DC (Scheme 16).[35]



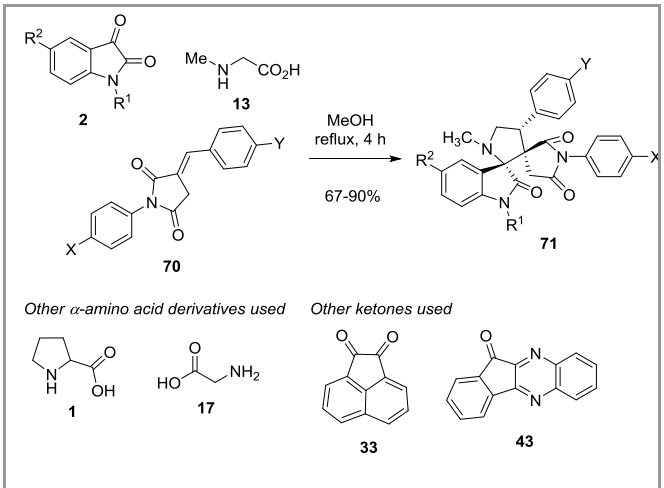
Scheme 16 Synthesis of dispiro-oxindole analogues **64** and **65** from curcumin **63**.

Synthesis of spirooxindolepyrrolizines **69**, bearing a 1,2,3-triazole moiety, was reported by Khurana *et al. via* stereo- and regioselective 1,3-DC. The *in situ* generated azomethine ylide **V** in glacial acetic acid triggered this one-pot four component domino strategy (Scheme 17). This cascade reaction involved the formation of the triazole derived from *N*-propargylated isatin **67** and aryl azides **66** in the presence of copper(II) sulfate. Then, the reaction with L-proline **1** or sarcosine **13** and decarboxylation of the resulting intermediate afforded the corresponding azomethine ylide **V**, which reacted with coumarin-3-carboxylic acid **68** as dipolorophile giving the desired spirooxindoles **69** in very good yields (Scheme 17).[36]



Scheme 17 Synthesis of spirooxindolepyrrolizines fused to coumarin ring heterocycles **69**.

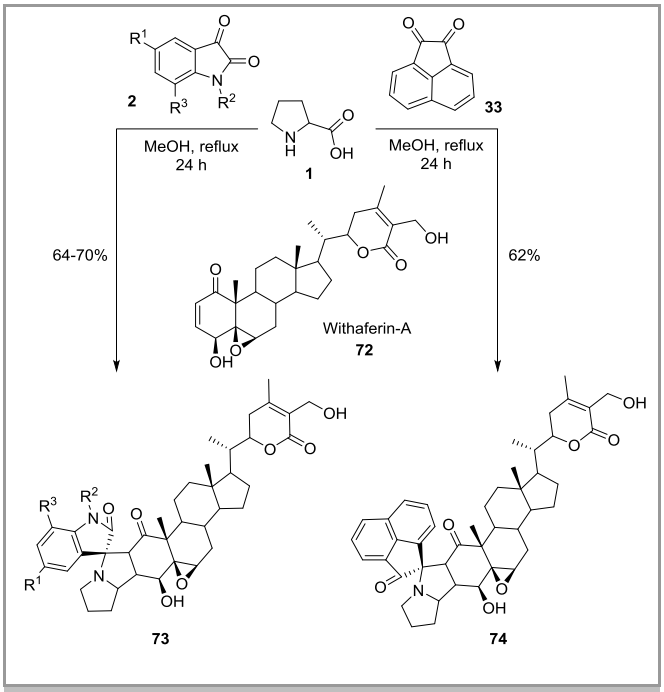
Dispirooxindolepyrrolidines **71** were reported by Singh *et al.* and prepared from sarcosine **13**, isatins **2** with *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones **70** as dipolarophiles. These products were diastereoselectively isolated in high yields (Scheme 18).[37] Glycine **17** or sarcosine **13** with isatins **2**,[38] or even proline **1** plus acenaphthenequinone **33** or indenoquinoxaline-11-one **43** were also essayed in the presence of dipolarophiles **70**.[39]



Scheme 18 Substituted spiroxindoles **71** obtained *via* 1.3-DC of azomethine ylides.

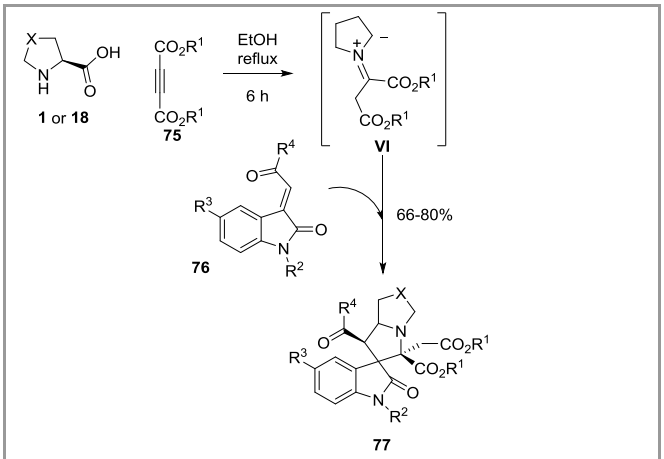
Spiro-pyrrolizidinooxindoles **73** and **74**, derived from isatins **2** or acenaphthoquinone **33**, respectively, bearing a withaferin-A system were isolated by Mondal and co-workers. Proline **1** was selected as precursor of the azomethine ylide, which furnished exclusively *cis*-fused cycloaducts **73** and **74** in a total atom-

economic one-pot three-component manner (Scheme 19). Their bioactivities were evaluated exhibiting a very promising cytotoxicity towards various cancer cell lines.[40]



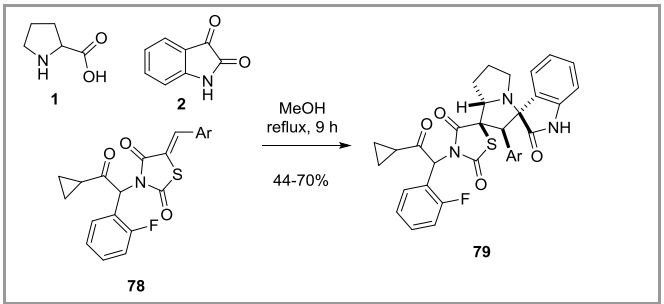
Scheme 19 Spiropyrrolizidino polycycles bearing withaferin-A sterodial ring system **73** and **74**.

Substituted spirooxindolepyrrolizines **77** (X = CH_2), and spiro-oxindolethiazoles **77** (X = S) were prepared from a range of secondary α-amino acids (proline **1** or 1,3-thiazolane-4-carboxylic acid **18**) and dialkyl acetylenedicarboxylates **75** as precursors of azomethine ylides **VI**. Interestingly, this way of generating *in situ* azomethine ylides reacted with substituted methyleneoxindoles **76** through a sequential 1,3-DC (Scheme 20). This reaction protocol was also extended to the use of another α-amino acid derivatives to yield the corresponding spiroheterocycles under thermal conditions.[41]



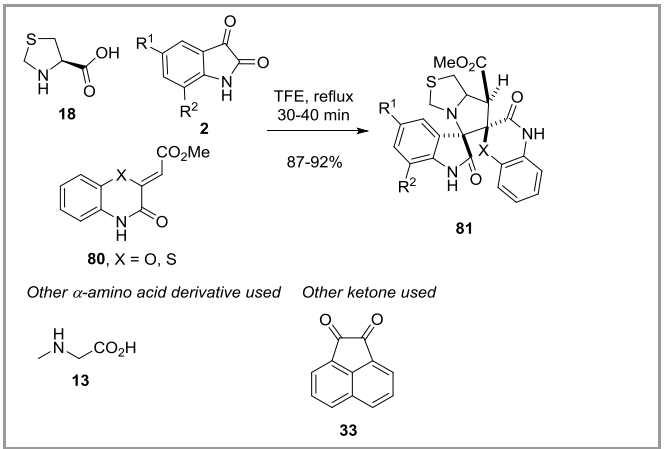
Scheme 20 Synthesis of spirooxindolepyrrolizines **77** (X = CH_2), and spirooxindolethiazoles **77** (X = S) from dialkyl acetylenedicarboxylates.

The unprecedented formation of dispirooxindolepyrrolizine thiazolidine-2,4-diones **79**, contrary to the commonly observed regiochemistry, was described by Kumar *et al. via* one pot three-component 1,3-DC from isatin **2**, proline **1** and (*Z*)-arylidene thiazolidine-2,4-diones **78**. The reaction took place under refluxing methanol with total regio- and diastereoselection (Scheme 21).[42] Many biological studies concerning medical applications of heterocycles **79** are currently in progress.



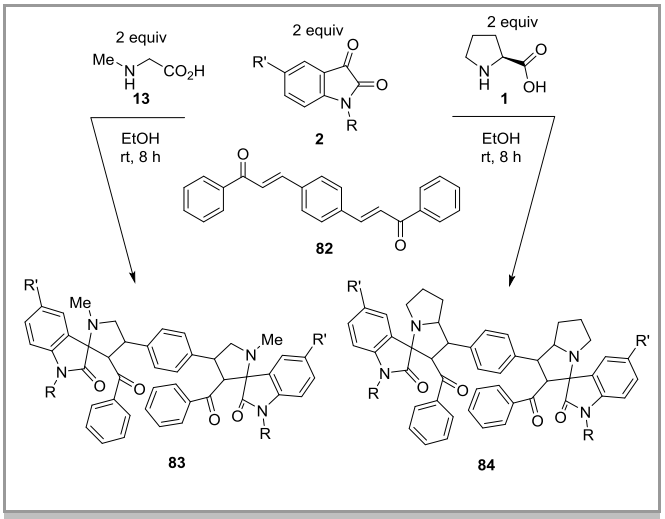
Scheme 21 Synthesis of spirocycles **79** with reverse regiochemistry.

Dandia and co-workers constructed diastereoselectively various biologically important dispiropyrrolidinethiapyrrolizidine frameworks **81**. Trifluoroethanol (TFE) was employed as enviromentally friendly solvent and also as catalyst due to its Bronsted acidity. Isatin derivatives **2** or azanaphthoquinone **80** (X = NH), benzooxazinone **80** (X = O) derived electrophilic alkenes and sarcosine **13** or 1,3-thiazolidine carboxylic acid **18** were the components used in this study (Scheme 22).[43]



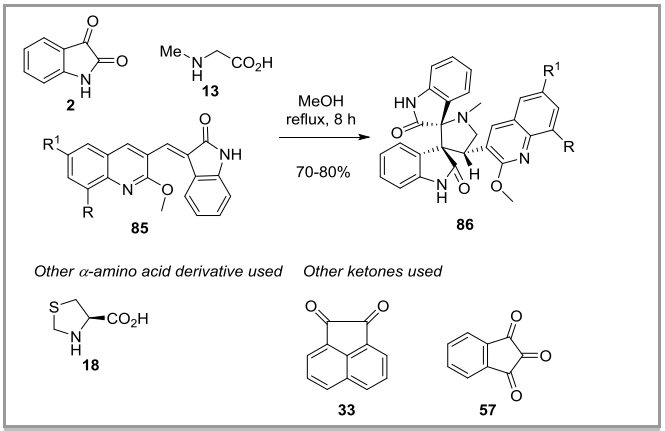
Scheme 22 Preparation of novel dispiroheterocyclic hybrids **81**.

Bisspirooxindolopyrrolidines **83** and bisspirooxindolo-pyrrolizidines **84** were reported by Javidan *et al.* employing bischalcone **82** as bisdipolarophile in the 1,3-DC involving isatins **2** and secondary α-amino acid derivatives such as proline **1** or sarcosine **15**. Final cycloadducts were obtained under mild conditions in very high both chemical yields and diastereoselections (Scheme 23).[44] The biological activity of selected molecules **83** or **84** are under study.



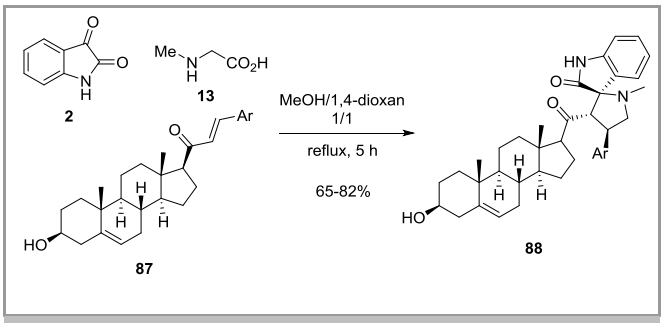
Scheme 23 Bisspirooxindole ring systems **83** and **84** obtained *via* 1,3-DC of azomethine ylides.

Biologically active quinolines containing both indoline and spirooxindole core structures **86** were designed by Mohan and co-workers. The 1,3-DC was carried out from sarcosine **13**/thiazolydine-4-carboxylic acid **18** together with isatins **2**/acenaphthoquinone **33**/ninhydrin **57** and with designed (*E*)-3-[(quinolin-3-yl)methylene]indolin-2-one derivatives **85** as dipolarophiles (Scheme 24). Biological evaluation of this new spiroheterocycles **86** revealed important *in vitro* antioxidant, antidiabetic and acetylcholinesterase (AChE) inhibitory activities.[45]



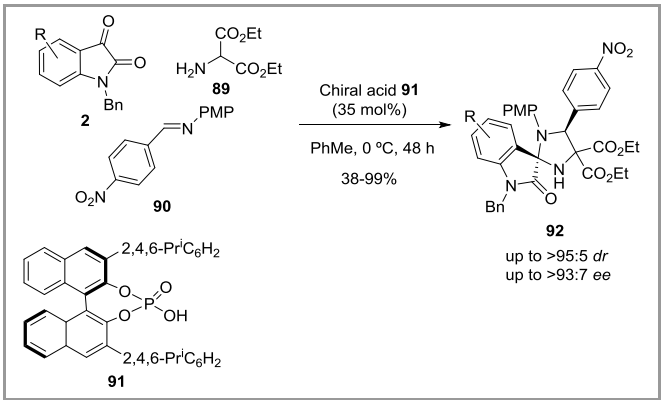
Scheme 24 Synthesis of spirocyclicquinolines **86**.

Bioactive spirooxindoles **88**, incorporating a steroidal framework, were reported. Isatin **2** and sarcosine **13** reacted with a newly designed steroidal dipolarophile **87**, derived from pregnenolone, through a conventional 1,3-DC under mild reaction conditions (Scheme 25). The produced spirooxindolepyrrolidines **88** exhibited antiproliferative activities against four human cancer cell lines including MCF-7.[46]



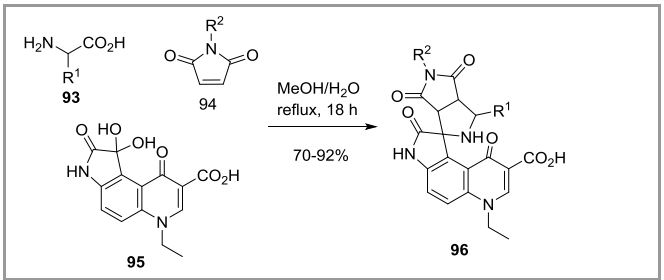
Scheme 25 Synthesis of new steroidal spirooxindole frameworks **88**.

Interesting bioactive chiral enantioenriched spiroxindole derivatives **92** were prepared in the presence of a chiral ligand **91** (35 mol%) from isatins **2**, diethyl 2-aminomalonate **89** and aldimine **90**. This three-component reaction occurred *via* asymmetric 1,3-DC between the imine **90** and the azomethine ylide. The resulting structurally congested imidazolidines **92** were isolated with good chemo-, diastereo- and enantioselections (Scheme 26).[47]



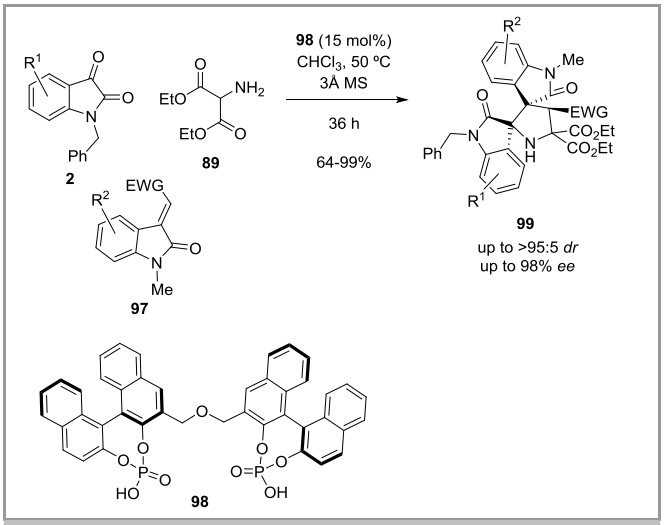
Scheme 26 Synthesis of enantiomerically enriched spiroxindole derivatives **92**.

Synthesis of pentacyclic spirooxindole pyrrolidines **96** were prepared from the *in situ* generated tricyclic azomethine ylide derived from pyridone-annelated isatin **95** and amino acids **93** and maleimides **94** in refluxing aqueous methanol (Scheme 27).[48] It is noteworthy the preference of the attack of amino group of the acids **96** towards the hydrate moiety, rather than the conjugated alkene moiety present in the two components **94** and **95** involving in the cycloaddition.



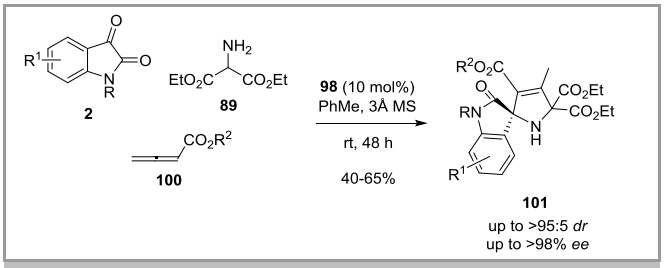
Scheme 27 Synthesis of pentacyclic spirooxindolepyrrolidines **96**.

Dipolarophiles **97** were employed in the enantioselective 1,3-DC catalyzed by chiral bisphosphoric acid **98**. The enantiomerically enriched bis-spirooxindolepyrrolidines **99** were obtained in good yields, very high diastereomeric ratios and excellent enantioselectivities in ethanol at 50 °C. Isatins **2** and diethylaminomalonate **89** were also the precursors of the azomethine ylides (Scheme 28).[49]



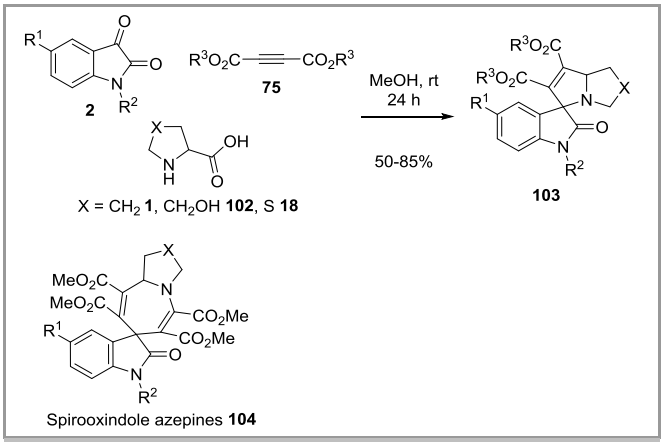
Scheme 28 Enantioselective synthesis of spirocycles **99**.

Biologically important substituted spirooxindole cycloadducts **101** were obtained by Shi and co-workers in the presence of the same chiral bisphosphoric acid **98** as organocatalyst. This enantioselective 1,3-DC with isatins **2**, diethyl aminomalonate **89** and alkyl 2,3-allenoates **100** as dipolarophiles, furnished enantioenriched anticancer and antimicrobial spiro[indoline-3,2′-pyrrole] frameworks **101** in high diastereomeric ratios and good to excellent enantioselections (Scheme 29).[50]



Scheme 29 Synthesis of enantiomerically enriched spirocycles **101**.

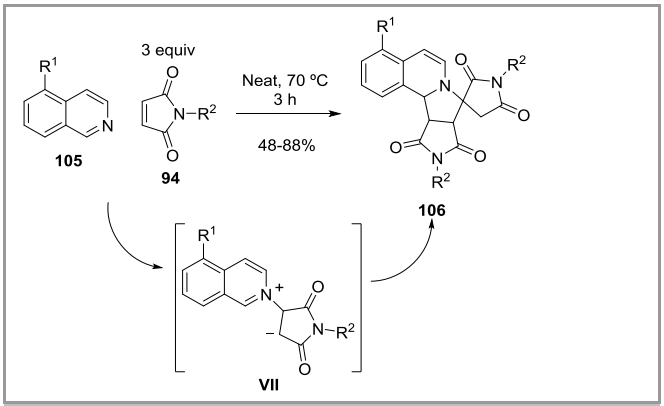
Dialkyl but-2-ynedioates **75** acted as dipolarophiles during the multicomponent 1,3-DC with cyclic α-amino acids such as proline **1**, 4-thiaproline **18**, or (2*S*,4*R*)-4-hydroxyproline **102**, with isatins **2**. The resulting spirooxindolepyrrolizines **103** were isolated in good yields (Scheme 30). In addition, spiroxindoleazepines **104** were isolated as major compounds when two equivalents of electrophilic alkyne **75** were added together with one equiv of the rest of components. In this last example, alkynes behaved such as it was described in Scheme 20.[51]



Scheme 30 Synthesis of spirooxindolepyrrolizines **103** and azepine surrogates **104**.

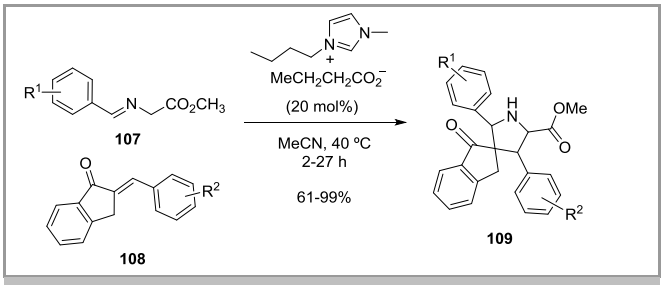
3. Synthesis of spiropyrrolidines

Non-asymmetric synthesis of diazaspiropyrrolidine derivatives **106**, possessing a dihydroisoquinoline moiety, were prepared from isoquinolines **105** with 3 equiv of the corresponding maleimide **94** without solvent at 70 ºC. The intermediate azomethine ylide **VII** was not formed as usual but through a Michael-type addition of the isoquinoline onto malimide followed by a prototropic shift (Scheme 31).[52]



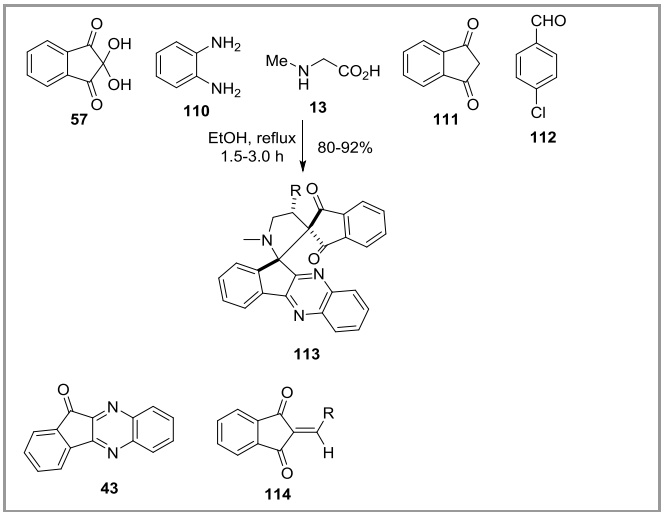
Scheme 31 Synthesis of diazaspiropyrrolidines **106**.

Spiroheterocycles **109**, containing both pyrrolidine and indanone core structures, were synthesized from iminoesters **107** and alkylidene-1-indanone derivatives **108** as dipolarohiles in the presence of a series of imidazolium salts as catalysts. The diastereoselectivities were low but the chemical yields were excellent under mild conditions. The catalyst was efficiently recovered and reused several times without losing efficiency (Scheme 32).[53]



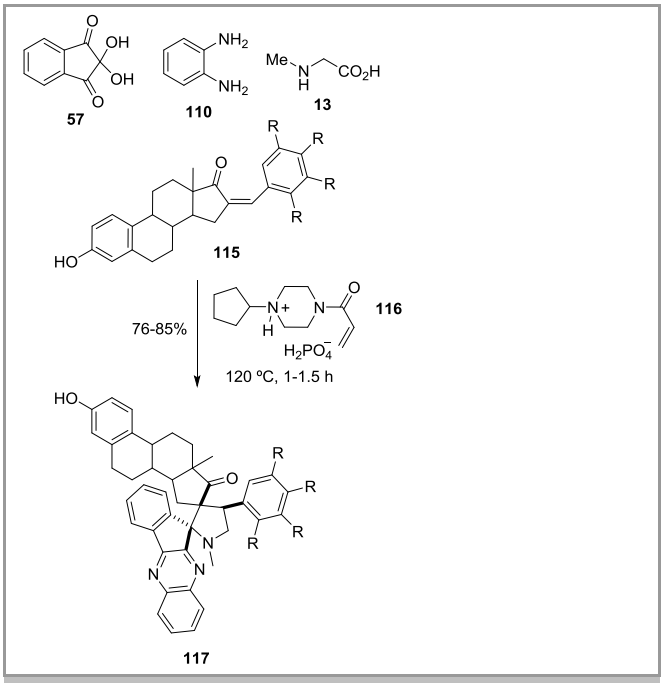
Scheme 32 Synthesis of prolinates **109**.

A pyrrolidine ring bearing two quaternary centers corresponding to spiranic systems **113** was also designed for the construction of natural alkaloids. Liu *et al*. reported a one pot five-component reaction to produce dispiroindenoquinoxalinepyrrolidines **113** from 1,3-indanedione **111**, 1,2-phenylenediamine **110**, ninhydrin **57**, sarcosine **13**, and aromatic aldehydes (for example **112**). A plausible mechanism proposed by the authors suggested that the formation of indenoquinoxaline-11-one **43**, from condensation reaction of 1,2-phenylenediamine **110** and ninhydrin **57**, and subsequent reaction with sarcosine **13** and decarboxylation afforded the corresponding azomethine ylide. Then, stereoselective 1,3-DC with the dipolarophile **114** (derived from the aldehyde **112** and **111**) produced the desired dispiroindenoquinoxalinepyrrolidines **113** (Scheme 33).[54] Some spiropyrrolothiazoles were prepared using a similar strategy but employing different components as (*E*)-β-nitrostyrene,[55] or even 1,3-thiazolane-4-carboxylic acid as dipolarophiles.[56]



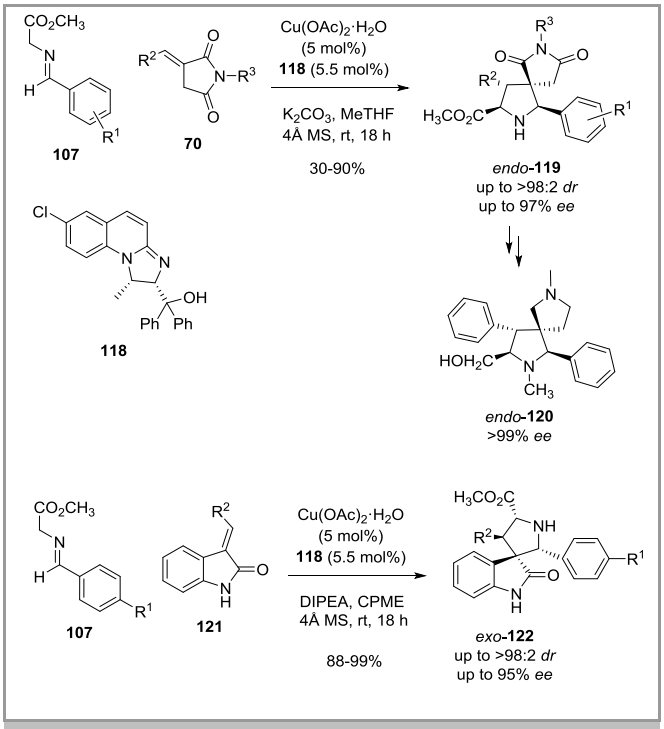
Scheme 33 Synthesis of dispiroindenoquinoxalinepyrrolidines **113** in a one-pot five-component process.

Novel steroid grafted dispiroindenoquinoxalinepyrrolidines **117** were prepared by Raghunathan *et al.* from ninhydrin **57**, sarcosine **13**, 1,2-phenylenediammine **110** and estrone derived dipolarophiles **115** in the presence of an ammonium salt **116** as catalyst. This facile one-pot four-component [3+2]-cycloaddition occurred under mild reaction conditions, easy workup, and in good yields (scheme 34).[57] This method is valuable for the synthesis of steroidal surrogates of biological significance.



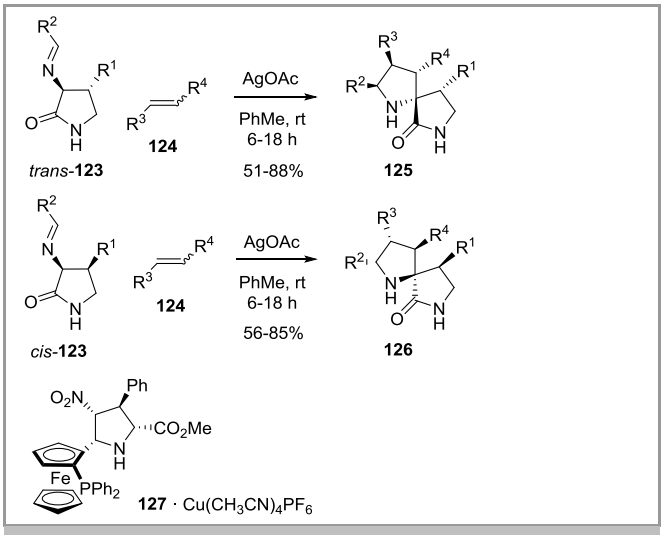
Scheme 34 Preparation of steroidal alkaloids **117**.

Enantioselective 1,3-DC between imino esters **107** and α-alkylidene succinimides **70** were successfully achieved employing $Cu(OAc)_2$ and N,O-chiral ligand **118**. Structurally diverse functionalized *endo*-dispiropyrrolidine cycloadducts **119** were obtained in very high diastereoselection and high to excellent enantioselections (up to 97% ee) (Scheme 35). These cycloadducts were transformed into *N*-methylbispiropyrrolidines and further reduction with $LiAlH_4$ afforded functionalized substituted spiroheterocycles **120** in good yield and up to 99% *ee*. This process was also applied to enantioselective 1,3-DC with 2-oxoindolin-3-ylidenes **121** as dipolarophiles giving biologically active *exo*-dispiropyrrolidine skeletons **122** in good yield and up to 95% *ee* (Scheme 35).[58]



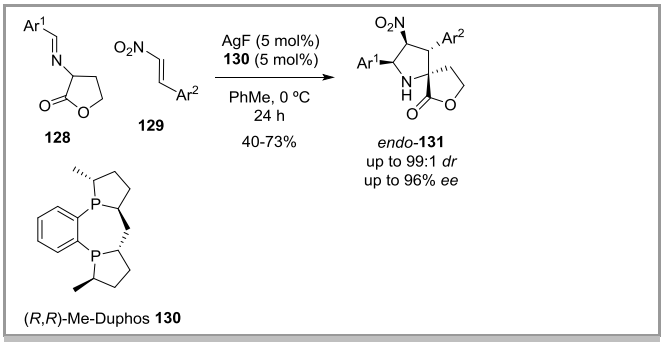
Scheme 35 Enantioselective 1,3-DC of spiranic systems by intermediacy of $Cu(OAc)_2$·**118**.

Synthesis of enantiomerically enriched diaza-bisspiropyrrolidines **125** and **126** was reported by Cossío and co-workers. Initially an interrupted 1,3-DC was performed in the presence of the catalytic complex $Cu(MeCN)_4PF_6$·**127** with the aim of obtaining the *cis*- or the *trans*- γ-lactams **123**, respectively. The diastereoselective 1,3-DC was performed with these imines and nitroalkenes, vinylic sulfones, acrylates, etc., using stoichiometric amounts of AgOAc (Scheme 36).[59] At this moment, this family of spiranic compounds are being evaluating as anticancer agents.



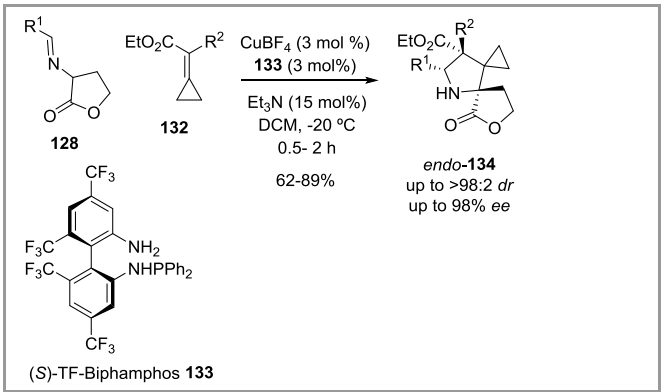
Scheme 36 Synthesis of spirocycles **125** and **126**.

A range of chiral highly substituted spironitroprolinates **131** were reported in the presence of chiral bifunctional catalytic ligand based on [(*R*,*R*)-Me-DuPhos] **130** and AgF as source of chiral induction. The 1,3-DC was run with α-imino-γ-lactones **128** and nitroalkenes **129** as dipolarophiles.[60] The reaction proceeded enantio- and diastereoselectively to form up to four new chiral centers and overwhelmingly *endo*-spiranic cycloadducts **131** (Scheme 37).[61] Biological evaluation of some of these compounds revealed promising antitumor activity.



Scheme 37 Synthesis of enantiomerically enriched spironitrocompounds **131**.

Asymmetric synthesis of biologically important tricyclic spiroheterocycles *endo*-**134** possessing a cyclopropane unit was described. α-Imino-γ-lactones **128** reacted with cyclopropylidene acetates **132** as dipolarophiles using $CuBF_4$·TF-BiphamPhos **133** as catalyst to afford *endo*-spirocycloadducts **134** in good diastereoselectivities and very high enantioselectivities (Scheme 38).[62]

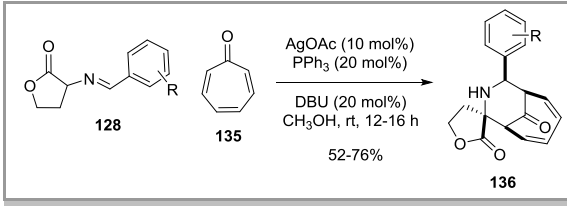


Scheme 38 Synthesis of enantiomerically enriched *endo*-spironitrocompounds **134**.

4. Synthesis of spiropiperidines and piperidines

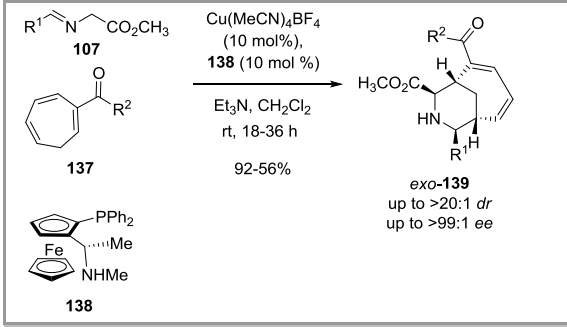
The 2,3-pyrrolidino-3,4-piperidine (4,7-diazabicyclo-[4.3.0]nonane) scaffold is an integral part of the underlying structure of numerous alkaloids possessing diverse bioactivities, including anti-tumor, antibiotic, and insecticidal activity.

Biologically active spiropiperidine derivatives **136** were reported by Guo and co-workers starting from homoserine lactone **128** and tropone **135** as dipolarophile. Here, a [6+3] cascade cycloaddition took place in the presence of AgOAc·PPh_3 as catalyst and DBU as base. The final diastereoselectivity was very high as well as chemical yield under mild reaction condition (Scheme 39).[63]



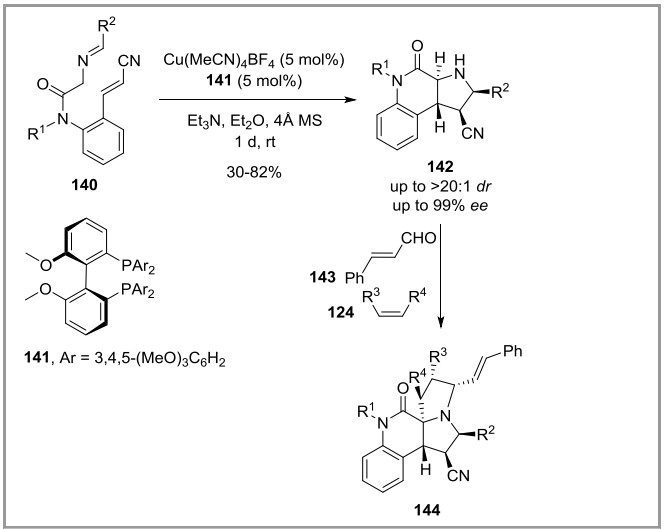
Scheme 39 Preparation of heterocycles **136**

Potentially bioactive functionalized enantioenriched bridged piperidine derivatives **139** were designed by Wang *et al.* in the presence of Cu(MeCN)$_4$BF$_4$·**138** catalytic system. The [3+6] cycloaddition with acyl heptatrienes **137** produced the corresponding *exo*-cycloadducts **139** with multiplication of stereocenters with excellent *exo*-selectivity in good yields and up to 99% *ee* (Scheme 40).[64]



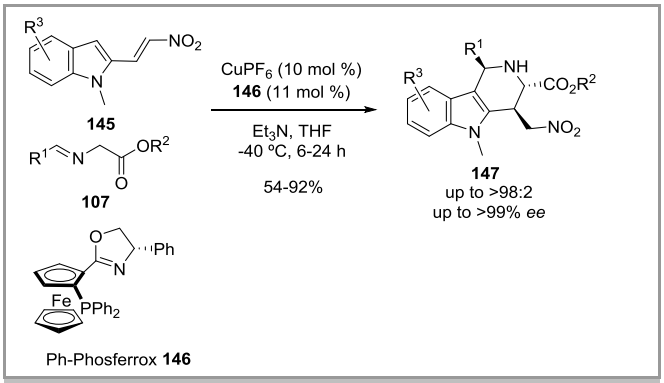
Scheme 40 Enantiomerically enriched *exo*-cycloadducts **139**.

A range of important substituted enantiomerically enriched pyrrolidinopiperidine derivatives **142** were synthesized by Waldmann and co-workers. The intramolecular 1,3-DC reaction of starting iminoamides **140** (generated from the corresponding *N*-Boc protected amine) occurred in the presence of the chiral complex formed by Cu(MeCN)$_4$BF$_4$ and chiral ligand **141**. Final fused bicycle **142** was obtained in good yields, excellent diastereoselections and very high diastereomeric ratio (Scheme 41).[65] Once product **142** was formed, a sequential addition of (*E*)-cinnamaldehyde **143** and alkenes **124** took place yielding fully substituted fussed-pyrrolizidines **144** in good conversions (Scheme 41). The main interest of this work was the definition of the scaffolds of glycosidase inhibitors, which have been the subject of numerous investigations.



Scheme 41 Enantioselective synthesis of cycloadducts **142** and **144**.

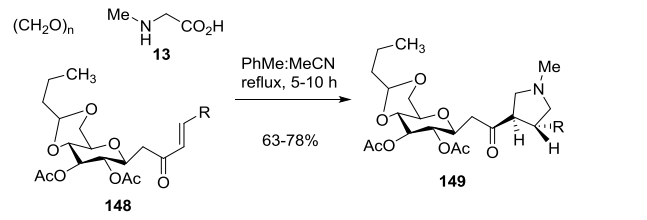
The elaboration of biologically important substituted tetrahydro-γ-carbolines **147** was performed during the enantioselective [3+3] cycloaddition between imino esters **107** and 2-indolylnitroethylenes **145** in the presence of $CuPF_6$·Ph-Phosferrox **146** as catalytic complex. This chemo- and stereoselective [3+3] cycloaddition was produced, rather than expected 1,3-DC, in very high yields, diastereomeric ratios and enantioselectivities (Scheme 42).[66] The proposed stepwise mechanism, caused by the high stability of the resulting enolate of the Michael-type addition, favored the Friedel-Crafts reaction of the nucleophilic 3-position of the indole.



Scheme 42 Synthesis of tetrahydro-γ-carbolines **147** *via* [3+3] cycloaddition.

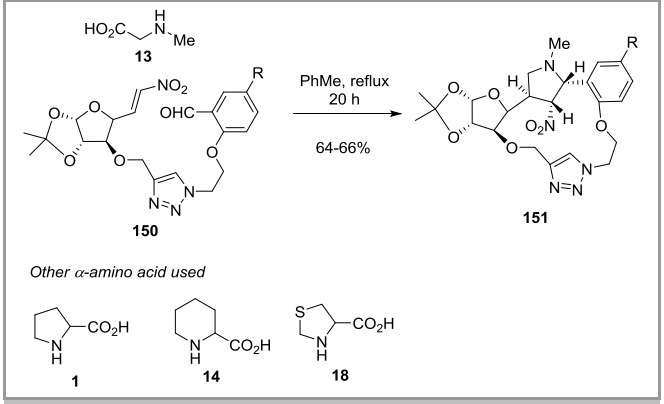
5. Synthesis of pyrrolidines and fused pyrrolidines

Pyrrolidine ring systems possessing a chiral sugar building block **149** were reported by Thangamuthu *et al.* from sarcosine **13**, paraformaldehyde and an electrophilic alkene bonded to a full-protected glucopyranosyl unit **148**. The cycloadduct was isolated in good yield and as only one diastereoisomer (Scheme 43).[67] The biological evaluation of these compounds are currently in progress, demonstrating very promising applications.



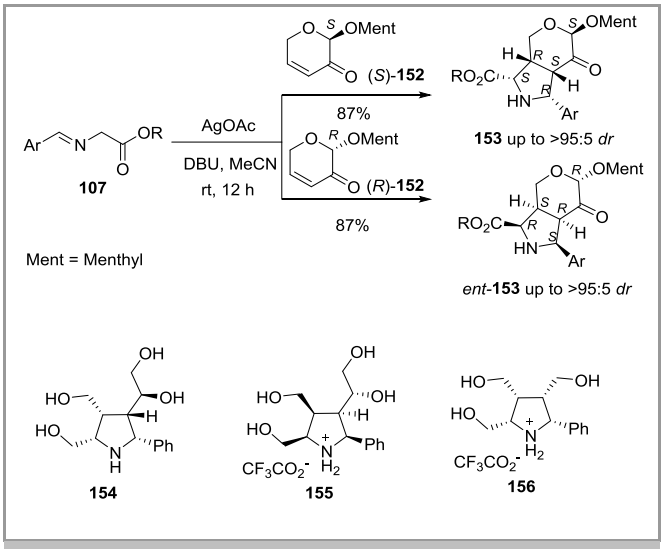
Scheme 43 Diasteroselective synthesis of sugar derivatives **149**.

With the same aim, new pyrrolidine-containing macrocycles **151**, bearing a triazole ring and a sugar (D-glucose) fragment, were prepared *via* intramolecular 1,3-DC of azomethine ylide.[68] The 1,3-DC occurred diastereoselectively in refluxing toluene in good yields independently of the amino acid employed (scheme 44). This strategy provides opportunities for the preparation of libraries of carbohydrate grafted macrocycles with triazole spacer unit for biological screening.



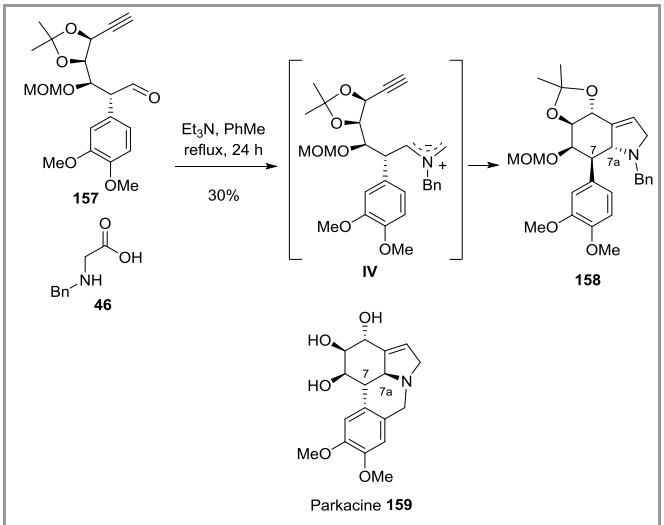
Scheme 44 Synthesis of biologically important macrocycles **151**.

A series of polyhydroxyalkylpyrrolidines **153** and *ent*-**153**, as potential inhibitors of a β-galactofuranosidase, were described by Varela *et al*. employing a silver-catalyzed 1,3-DC from imino esters and (*S*)- or (*R*)-sugar pyranone as dipolarophiles (Scheme 45).[69] After a sequence of reactions comprised by hydrolysis, reductions, *N*-protection, degradative oxidations, etc., allowed the access to polyhydroxyalkylpyrrolidines **154**-**156**, which were evaluated as inhibitors of the β-galactofuranosidase from Penicillium *fellutanum.*



Scheme 45 Synthesis of polyhydroxyalkylpyrrolidines **153** and *ent*-**153** and heterocycles **154**-**156** *via* 1,3-DC of azomethine ylides.

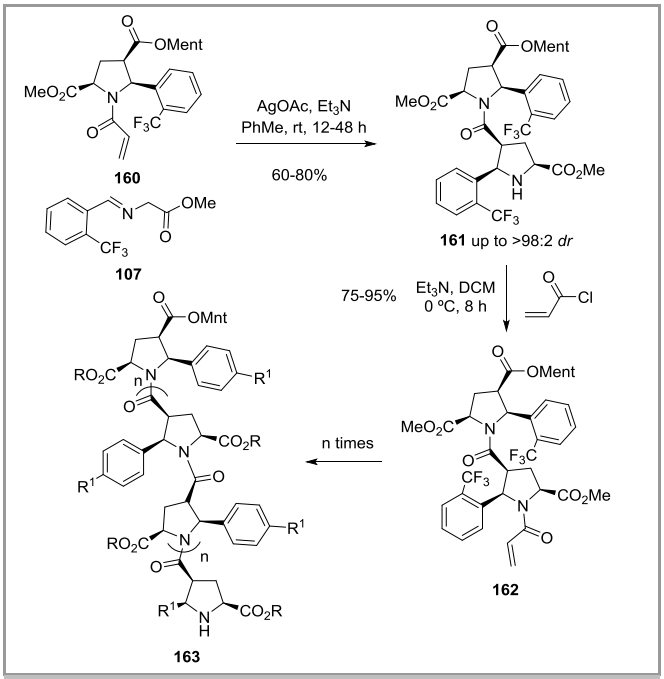
Recently, an approach to the synthesis of parkacine **159** (a lycorine-type alkaloid) was communicated. The key step of the synthesis consisted in an intramolecular 1,3-DC. Chiral hept-6-yne-al derivative **157** was selected to construct the C/D ring system of a lycorine-type alkaloid parkacine. However, the cycloaddition furnished a C/D ring-closure product with opposite configurations at 7- and 7a-carbons, after comparison with the absolute configuration of the natural product (Scheme 46).[70] A possible reason of this epimerization could be caused through imine–enamine tautomerization (previous to the formation of the 1,3-dipole **IV**) involving the stereogenic center bearing the phenyl group.



Scheme 46 New approach to the synthesis of parkacine epimer **158** using an intramolecular 1,3-DC as key step.

A series of functionalized β-proline dimers, trimers, etc. (*eg* **162** and **163**), were designed from the corresponding menthyl acrylate **160** and iminoglycinate **107** through a silver-catalyzed

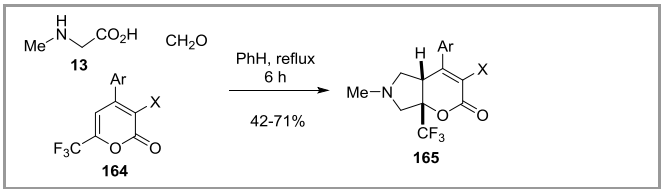
1,3-DC. The repeating acylation with acryloyl chloride, followed by cyclization, allowed the extension of this process towards hexamer chiral β-peptide molecular framework **163** in good yields (Scheme 47).[71] These new poly-β-prolines were generated in the two enantiomeric forms exhibiting an important antitumor activity in HRPC cells.[72]



Scheme 47 Synthesis of functionalized β-proline dimers and oligomers **162** and **163**.

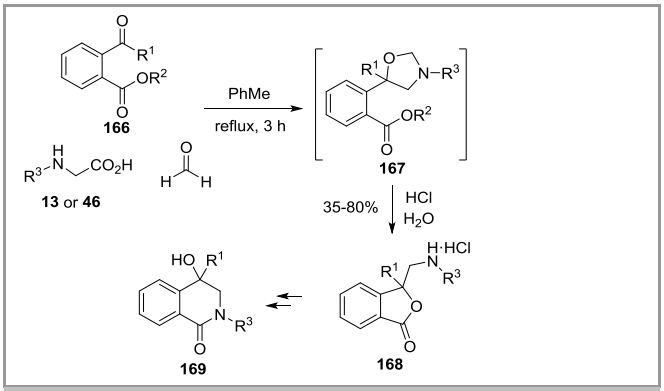
Concerning non-asymmetric approaches, substituted pyrano[2,3-*c*]pyrrolidines were reported by Sosnovskikh and co-workers from sarcosine **13**, formaldehyde and 4-aryl-6-(trifluoromethyl)-2-pyrones **164** as dipolarophiles. The 1,3-DC produced *cis*-fused ring cycloadducts with high diastereoselectivity in refluxing benzene (scheme 48).[73] Several applications of these compounds in medicinal chemistry are being envisaged.

Analogously, the synthesis of benzopyrano[3,4-*c*]pyrrolidines was described in a diastereoselective 1,3-DC between an ∝-iminoester **107** and coumarin in the presence of AgTFA.[74]



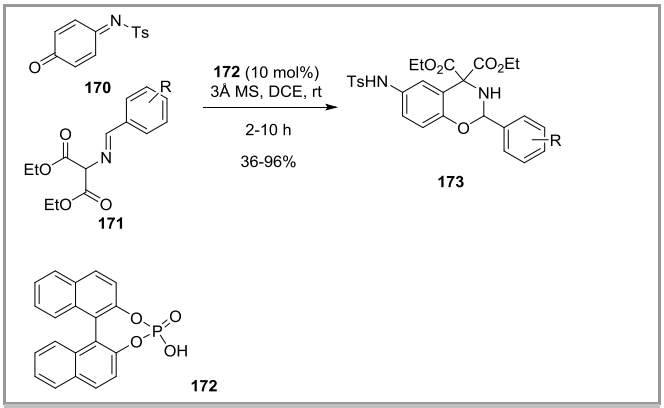
Scheme 48 Synthesis of heterocycles **165**.

Hydroxypiperidones are important structures since the pharmaceutical point of view. They were prepared taking advantage of the use of aldehydes as dipolarophiles such as occurred in the 1,3-DC involving sarcosine **13**, formaldehyde and an aromatic aldehyde or ketone **166**. Ketal hydrolysis and lactonization from **167** afforded isolable compounds **168**, which can be transformed into the corresponding substituted benzo-fused pyperidones **169** (Scheme 49).[75]



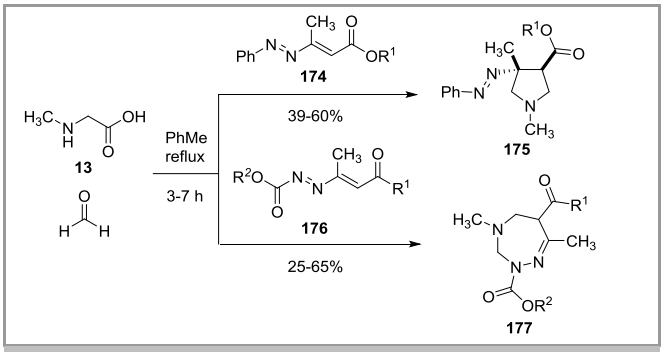
Scheme 49 Synthetic route to access products **169**.

Potential biologically active benzoxazine framework alkaloids **173** were obtained through a [3+3] process rather than the expected 1,3-DC. Racemic binol-derived phosphoric acid **172** acted as Brønsted acid catalyst activating the enone dipolarophile (Scheme 50).[76] A modification of this procedure using $GaBr_3$ instead of the phosphoric acid furnished cycloadducts in better yields and better periselectivities.[77]



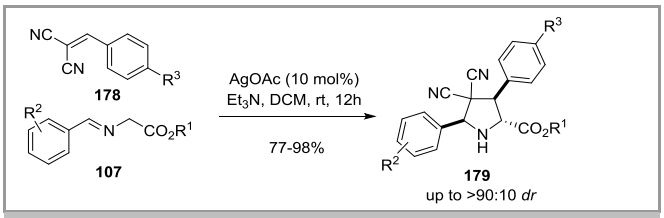
Scheme 50 Synthesis of heterocycles **173**.

A diversity oriented synthesis (DOS) was described during the study of one-pot multicomponent cycloadditions of non-stabilized azomethine ylides (formaldehyde and *N*-alkylamino acids) and 1,2-diaza-1,3-dienes **174** and **176** as dipolarophiles in toluene. It was found that the nature of the substituents in the azadiene was crucial for the cycloaddition in such a way that the presence of an electron-withdrawing group bound to the azo group favored the generation of 1,2,4-triazepines **177** through a [4+3] cycloaddition. However, a phenyl group bonded to this azo moiety furnished pyrrolidines **175** in a typical 1,3-DC in moderate to good yields (Scheme 51).[78]



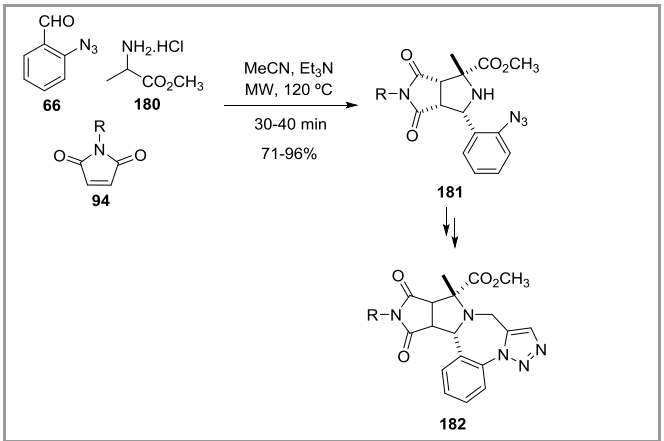
Scheme 51 Synthesis of pyrrolidines **175** or 1,2,4-triazepines **177** *via* 1,3-DC or [3+4] cycloaddition of azomethine ylides, respectively.

AgOAc-catalyzed [3+2] cycloaddition of the azomethine ylides derived from imino esters **107** and alkenes **178** was successfully achieved. Final pyrrolidines **179** were generated in good yields and high diastereomeric ratios under mild conditions (Scheme 52). The biological properties of these compounds are under study.[32]



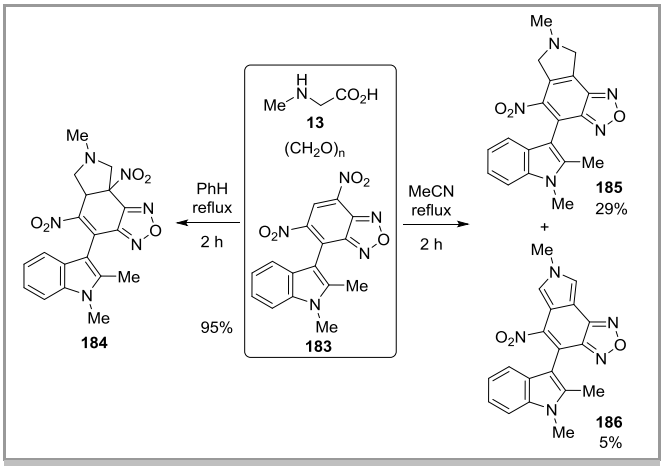
Scheme 52 Synthesis of pyrrolidines **179**.

The 1,3-DC has been considered the key step in the new approach to the synthesis of fused benzodiazepines **182**. This attractive family of compounds are under screening. Firstly, the thermal multicomponent 1,3-DC took place in the presence of alanine derivative **180**, 2-azidebenzaldehyde **66**, and maleimides **94** in short reaction times (Scheme 53). Triazolobenzodiazepine derivatives **182**, obtained as unique diastereoisomers, were prepared from **181** through conventional *N*-propargylation followed by intramolecular copper-free 1,3-DC of the azido group with the alkyne residue.[79]



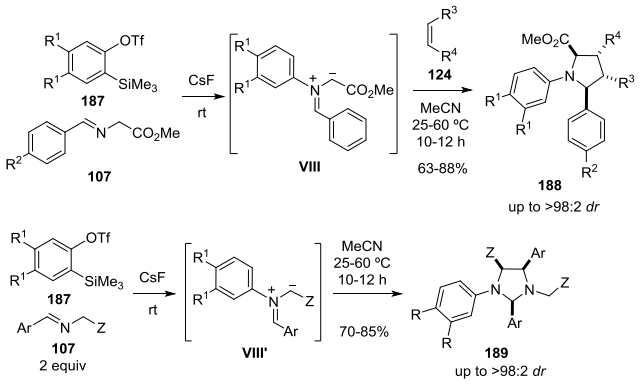
Scheme 53 Stereoselective synthesis of triazolobenzodiazepines **182**.

Unstabilized azomethine ylides, generated from sarcosine **13** and paraformaldehyde, reacted with dihetaryl system **183** to give several cycloaddition adducts depending of the solvent involved. Thus, when benzene was employed product **184** was exclusively formed in quantitative yield. However, in the case of using MeCN, hydropyrrole **185** and pyrrole **186** were obtained as mixture of products in low yields (Scheme 54).[80]



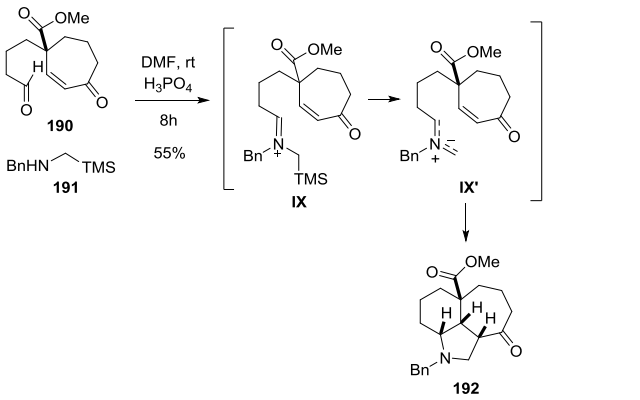
Scheme 54 Sythesis of substituted complex heterocycles **184**-**186**.

A series of substituted *N*-arylpyrrolidines **188**, using various electron-deficient alkenes **124** as dipolarophiles during the reaction of imino esters **107** to aryne precursors **187**, were generated in good chemical yields and very high diastereoselectivities. Here, the direct attack of the imino esters to the aryne and protonation of the resulting anion occurred giving raise azomethine ylides **VIII** and **VIII'**. In addition, imidazolidines **189** were analogously obtained adding 2 equiv of imino ester **107** under mild conditions (Scheme 55).[81] Both types of heterocycles were tested as antiviral agents, specifically to those emerging viral infections.



Scheme 55 Preparation of imidazolidines **189** and substituted pyrrolidines **188** from imines **107** and trimethylsilyl aryl triflates **187**.

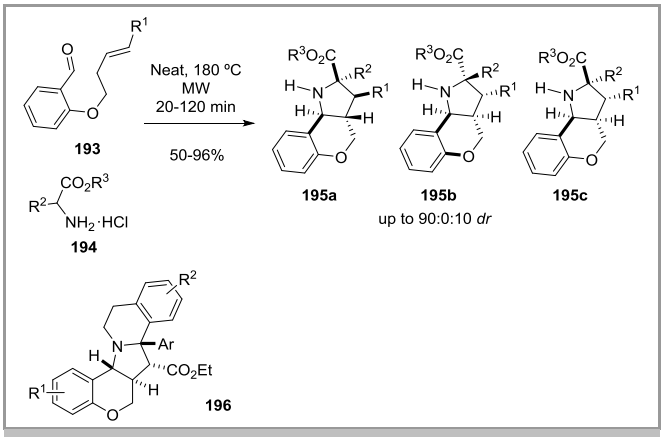
An approach to the synthesis of 6-5-7 ACD azatricyclic ring system of numerous calyciphylline A-type alkaloids was successfully developed combining reagents **190** and **191**. The use of H_3PO_4 as promoter in a highly donating solvent such as DMF produced the expected [3+2] cycloaddition under very mild conditions. The intramolecular 1,3-DC between a nonstabilized azomethine ylide **IX→IX'**, generated by desilylation of *N*-(trimethylsilyl)methyliminium salt, and an electron-poor alkene afforded calyciphylline derivative **192** as unique diastereoisomer (Scheme 56).[82]



Scheme 56 Intramolecular 1,3-DC reaction to yield calyciphylline type alkaloid **192**.

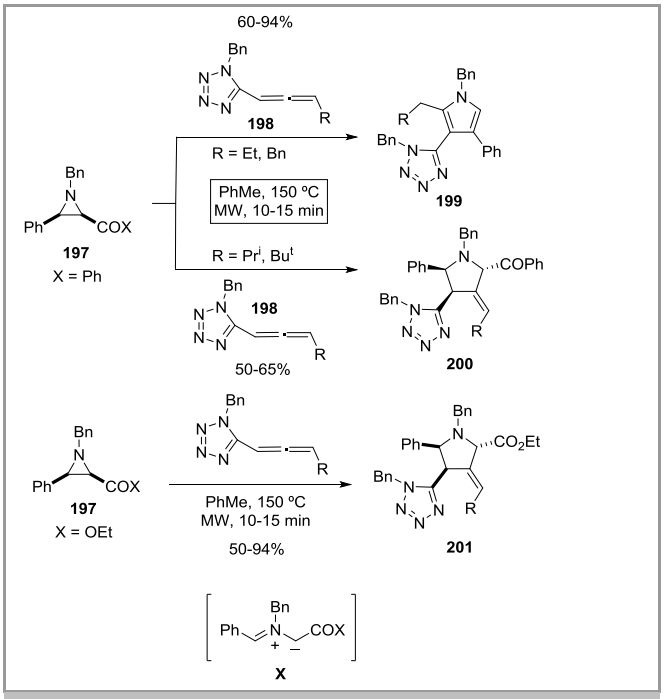
Bioactive compounds bearing the chromene[4,3-*b*]pyrrolidine moiety **195** were constructed by intramolecular 1,3-DC. α-Amino esters **194** and *O*-crotonylsalicylaldehyde **193** under MW or conventional heating afforded alkaloid chromane hetereocycles **195** in good yields *via* imine/[1,2]-prototropic shift route (Scheme 57). The 1,3-DC was diastereoselective in most of cases, obtaining other diastereoisomers in variable proportions.[83]

Similar transformations were reported by Nelson and co-workers in the search of new scaffolds for exploitation in the production of alkaloid-like libraries.[84] In addition, the intramolecular 1,3-DC of allylic aminopyrimidine derivatives was also successful and afforded pyrimidine fused tricyclic systems **196** in very high yields under thermal conditions.[85] As an extension of this work, the synthesis of potential bioactive functionalized fused penta/hexacyclic alkaloids were constructed by the substitution of acyclic amino esters by tetrahydroisoquinolines (Scheme 57).[86]



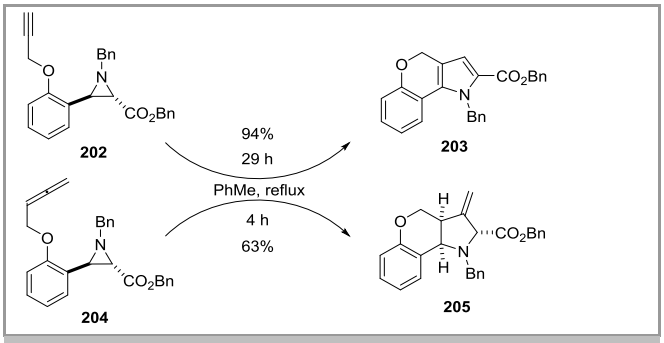
Scheme 57 Synthesis of chromanepyrrolidines **195** and **196**.

Functionalized aziridines **197** were employed as generators of azomethine ylides **X** by thermolysis in the 1,3-DC with allenes **198** bearing a tetrazol moiety. The resulting tetrazolyl-substituted pyrroles **199** or alkylidenepyrrolidines **200** resulted to be very attractive since the pharmaceutic point of view. The nature of the substituent at the terminal position of the allene affected the reaction course when a benzoyl group is bonded to the aziridine ring. However, the presence of an ester group instead (for example in aziridine **197** X = OEt) was not so important producing exclusively pyrrolidines **201** in excellent diasteromeric ratios and high chemical yields (Scheme 58).[87]



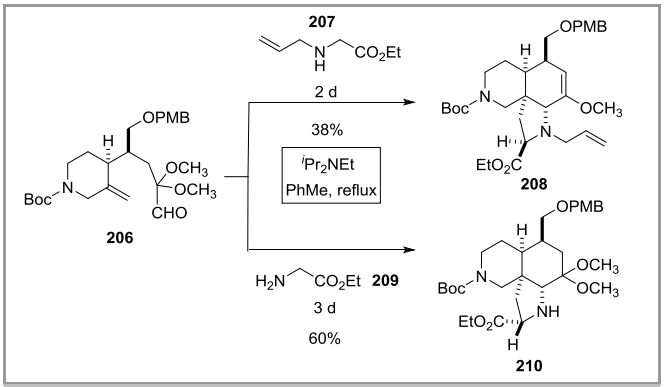
Scheme 58 DOS of pyrroles **198** and pyrrolidines **199** and **201**.

Important chromenopyrrole derivatives **203** and **205**, were prepared by the generation of azomethine ylides from aziridines **202** and **204** bearing terminal alkyne/allene groups, respectively. The stereoselective intramolecular 1,3-DC took place in refluxing toluene giving only one stereoisomer in good chemical yields. The triple carbon–carbon bond led the corresponding 1,4-dihydrochromeno[4,3-*b*]pyrrol **203**, whilst allene allowed the stereoselective synthesis of 3-methylenechromano[4,3-*b*]pyrrole derivative **205** (Scheme 59).[88] An alternative way to obtain the fused pyrrole heterocycle in good yields, consisted in a sequential one-pot 1,3-DC employing synthesis from *N*-substituted-Boc-glycine-O-aryl ester, bearing this arene moiety an alkyne group at its *ortho*-position.[89]



Scheme 59 Synthesis of chromeno[4,3-*b*]pyrrole derivatives **203** and **205**.

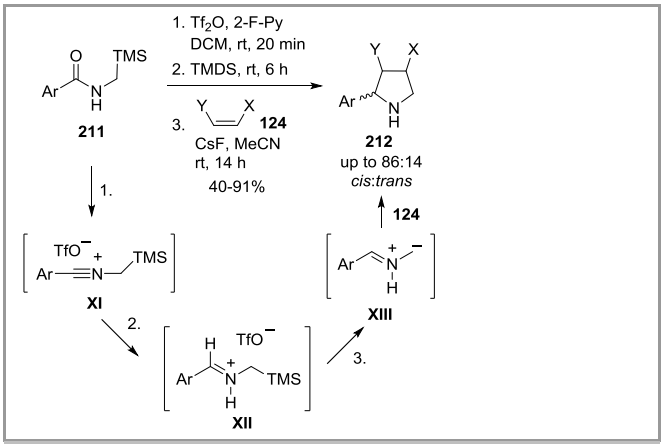
ABC Tricyclic ring system similar to that found in manzamine alkaloid framework was prepared by Coldham *et al.*, 1,3-DC being one of the three key steps of the synthesis. The 1,3-DC was successful with only one diastereomer of **206** demonstrating the high control of the geometry of the transition state. The same aldehyde was able to afford stereodivergent products **208** or **206**, in moderate to good yields, depending on the reagents involved in the generation of the azomethine ylide (Scheme 60).[90]



Scheme 60 Selective synthesis of tricycles **208** and **210**.

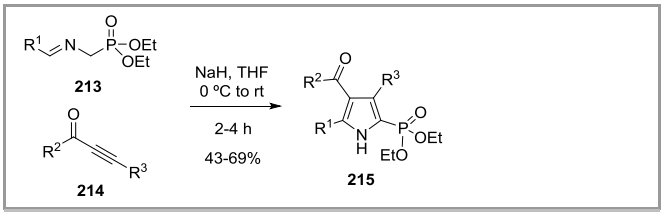
An unprecedented generation of non-stabilized azomethine ylides from *N*-(trimethylsilylmethyl)amides **211** was optimized. The activation of the amide was done with triflic anhydride, then, partial reduction with 1,1,3,3-tetramethyldisiloxane (TMDS), and desilylation with cesium fluoride afforded the final intermediate ylide **XIII**. Operating under mild conditions, the 1,3-DC tolerated several sensitive functional groups and provided cycloadducts **212** in very good yield. The use of various dipolarophiles were successful, *cis*-diastereoselectivity for the substrates bearing an electron-withdrawing group being determined (Scheme 61).[91]

The sequence formed by and nonstabilized azomethine ylide derived from *N*-substituted glycine and formaldehyde → anthraquinone → 1,3-oxazole formation → generation of azomethine ylide → 1,3-DC with electrophilic alkenes was also developed for the preparation of substituted pyrrolidines.[92]



Scheme 61 1,3-DC reaction of nonstabilized azomethine ylides derived from secondary aromatic *N*-(trimethylsilylmethyl)amides **211**.

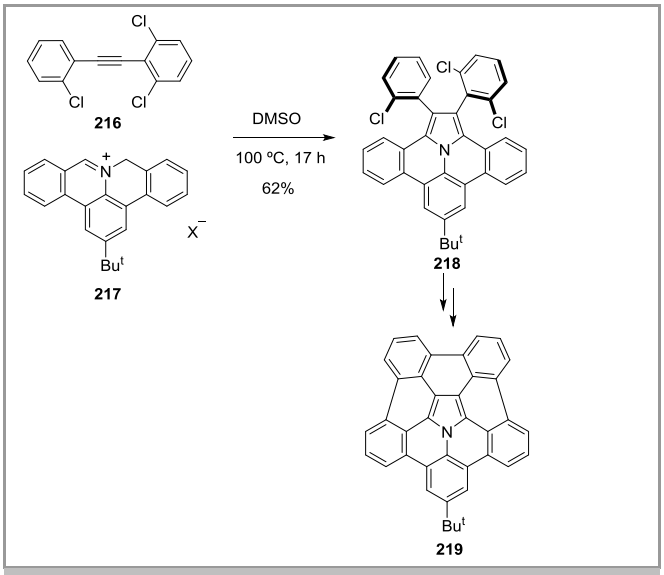
Potentially bioactive pyrroles **215** bearing a phosphonate unit at the 2-position are currently under evaluation. The preparation consisted in a simple 1,3-DC between imino phosphonates **213** and 1,3-DC with ynones **214** giving intermediate cycloadducts, which underwent a subsequent aromatization (Scheme 62). The multicomponent version was essayed but in lower chemical yield.[93]



Scheme 62 Synthesis of pyrroles **215**.

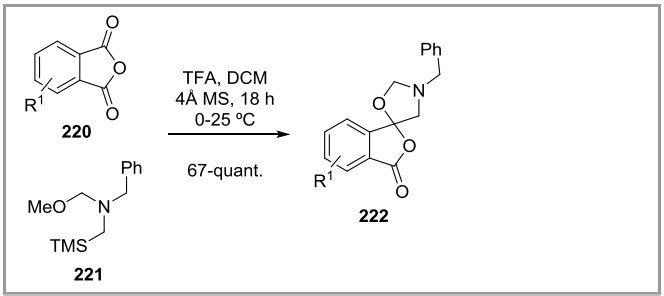
The stability of the pyrrol unit was the driving force to construct a novel nitrogen-doped corannulene derivative **219**. The key 1,3-dipolar cycloaddition of a polycyclic aromatic azomethine ylide precursor **217** with a diarylethyne **216** gave product **218**, which underwent a palladium-catalyzed intramolecular cyclization to complete the synthesis. This molecule represents the first example of a corannulene derivative bearing an internal

heteroatom, having particular and exclusive physical and biological properties (Scheme 63).[94]



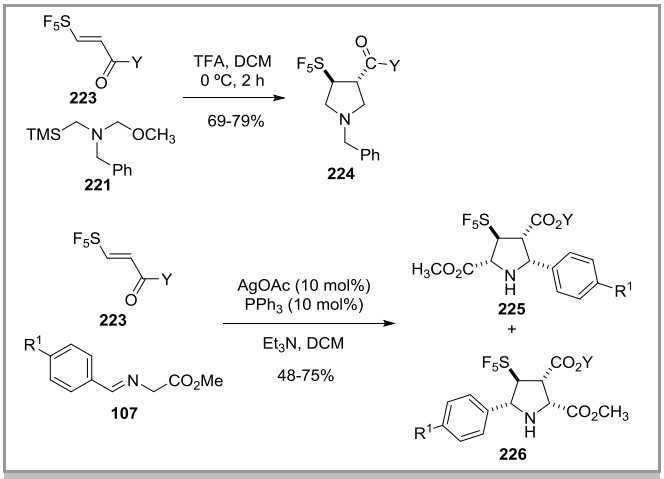
Scheme 63 Synthesis of azacorannulene derivative **219**.

Amine **221** has been widely used for the generation of non-stabilized azomethine ylides under very mild conditions. In other side, the reaction of an azomethine ylide with a carbonyl group of an anhydride is not common. However, isobenzofuranone heterocycles **222** were obtained by the *in situ* generation of a dipole from *N*-silylatedbenzylamine **221** and phthalic anhydrides **220** affording spirooxazolidines **222** in very good yields and elevated regiocontrol (Scheme 64).[95]



Scheme 64 Synthesis of isobenzofuranones **222**.

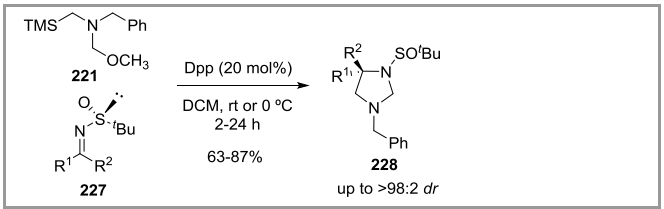
Pentafluorosulfanyl (SF_5) group is not very common in nature, so the biological study of compounds incorporating it is very attractive. Bouillon and co-workers published a 1,3-DC between *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine **221** and SF_5-substituted acrylic ester **223** or its corresponding amide as dipolarophiles afforded trisubstituted pyrrolidines **224** in good yields. In the case of using benzylideneglycine methyl ester **107**, the 1,3-DC was produced in the presence of AgOAc/PPh_3 as catalyst furnishing almost equimolar mixtures of cycloadducts **225** and **226** (Scheme 65). [96]



Scheme 65 Synthesis of heterocycles **224**-**226** from alkenes **223**.

In this context, very interesting imidazolidines **228** were obtained during the employment of *N*-sulfinylketimines **227** as dipolarophiles in 1,3-DC with non-stabilized azomethine ylide precursor **221**. In the presence of substoichiometric amounts of diphenyl phosphate the reaction proceeded in good yields and high diastereoselections (Scheme 66).[97]

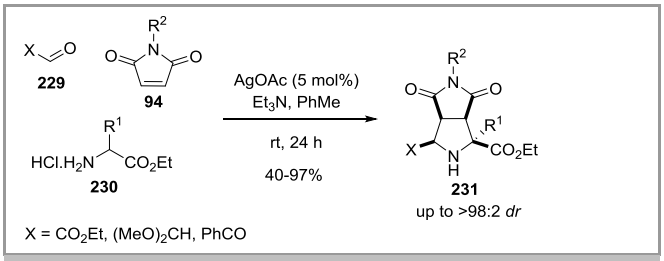
An identical mode of generating the azomethine ylide from the *N*-(trimethylsilylmethyl)benzylamine **221** derivative was employed in the reaction with electrophilic alkenes incorporating a trifluoromethyl group, fluorinated acrylates or 3-fluoromaleimides. The resulting *N*-benzylpyrrolidines were obtained in very high yields.[98,99]



Scheme 66 Synthesis of imidazolidines **228**.

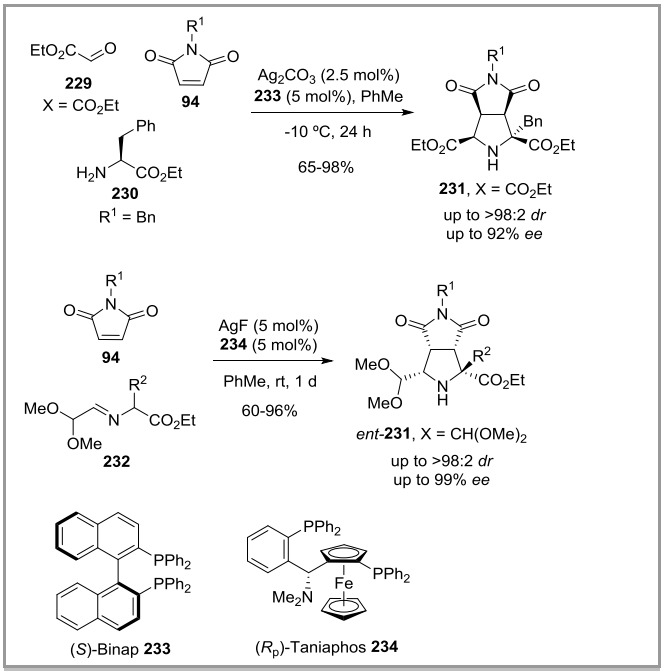
The silver-catalyzed multicomponent reaction between ethyl glyoxylate, 2,2-dimethoxyacetaldehyde, or phenylglyoxal as aldehyde components (in general **229**) with α-amino ester hydrochlorides **230** and a dipolarophile (for example, maleimides **94**) in the presence of trimethylamine, was described. This domino process took place at room temperature by *in situ* liberation of the α-amino ester followed by the formation of the imino ester, which is the precursor of a metalloazomethine ylide. The cycloaddition of this species and the corresponding dipolarophile afforded polysubstituted proline derivatives. Ethyl glyoxylate (**229**, X = CO_2Et) reacted with glycinate, alaninate, phenylalaninate and phenylglycinate at room temperature in the presence of representative dipolarophiles affording *endo*-2,5-cis-cycloadducts **231** in good yields and high diastereoselection. In addition, 2,2-dimethoxyacetaldehyde [**229**, X = $CH(OMe)_2$] was evaluated with the same amino esters and dipolarophiles, under the same mild conditions, generating the corresponding *endo*-2,5-*cis*-

cycloadducts with higher diastereoselections than the obtained in the same reactions using ethyl glyoxylate. In the case of phenylglyoxal (**229**, X = Ph) the corresponding 5-benzoyl-*endo*-2,5-*cis* cycloadducts **231** were obtained in short reaction times and similar diasteroselections (Scheme 67).[100] In these examples, a new functional group, different from alkyl or aryl substituents, was introduced.



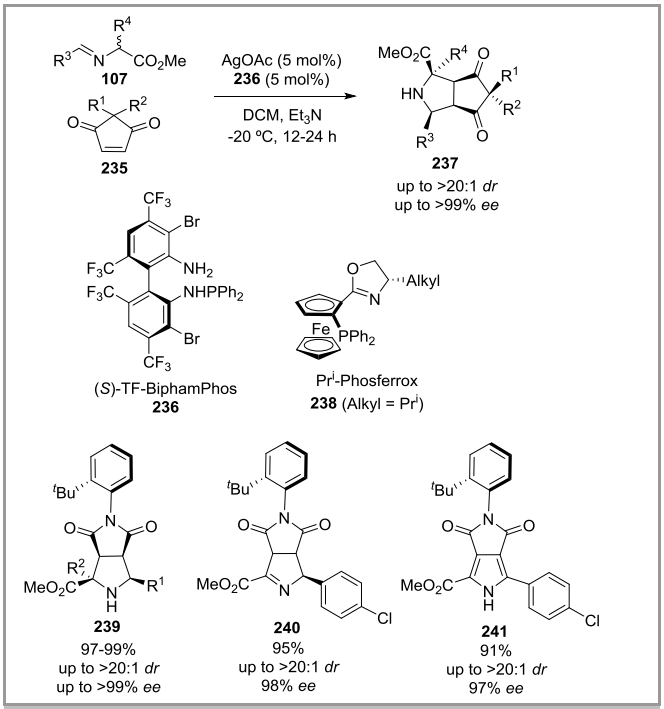
Scheme 67 Synthesis of pyrrolidine cycloadducts **231**.

The enantioselective version of these transformations was also separately reported for reactions run with ethyl glyoxylate and 2,2-dimethoxyacetaldehyde. Enantiomerically enriched substituted fused bicyclic pyrrolidine derivatives (**231**, X = CO_2Et) were obtained in a multicomponent 1,3-DC from ethyl glyoxylate (**229**, X = CO_2Et) and phenylalanine (**230**, R^1 = Bn) in the presence of Ag_2CO_3·(*S*)-Binap **233** catalytic complex. [101] However, Taniaphos **234**·silver fluoride complex was the appropriate catalyst to produce an enantioselective 1,3-dipolar cycloaddition using 2,2-dimethoxyacetaldehyde derived imino esters **232** and maleimides **94** (Scheme 68).[102] The employment of both complexes in their respective transformations allowed the reaction in the absence of an extra base giving high yields and *ee* of the corresponding *endo*-cycloadducts, so they acted as bifunctional catalysts.



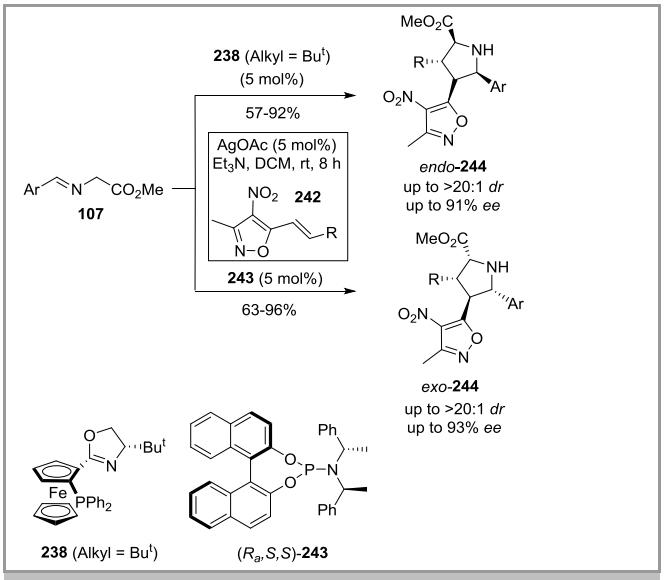
Scheme 68 Enantioselective synthesis of prolinates **231**.

Enantiomerically enriched substituted bicyclic pyrrolidines fused to cyclopentanediones **237** were described by Wang *et al.* in the presence of AgOAc and (*S*)-TF-BiphamPhos **236** as catalytic system. The reaction was performed at -20 ºC affording products **237** in good yield and high optical purity (up to >99 *ee*) (Scheme 69).[103] Bicyclic heterocycles fused by pyrrolidine and cyclopentane moieties play a unique role in numerous bioactive naturally occurring compounds and pharmaceutical ingredients. This chiral catalytic complex was also employed for atroposelective desymmetrization of *N*-(2-t-butylphenyl)maleimides during the enantioselective 1,3-DC affording enantiomerically pure cycloadducts **239**, which could be transformed into pyrrolines (*eg* **240**) and pyrroles (*eg* **241**) in good yields (Scheme 69).[104] A similar approach was reported by Singh *et al.* with excellent enantioselections but employing Pr^i-Phosferrox **238** (R = Pr^i).[105]



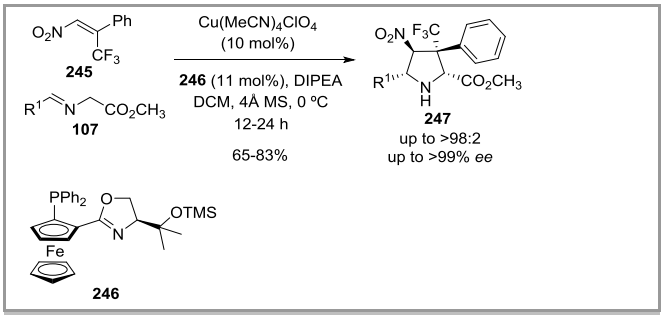
Scheme 69 Asymmetric synthesis of series of heterocycles **237**, and **239**-**241**.

Biologically active isoxazolylpyrrolidines **244** were stereodivergently constructed by Wang and co-workers in the presence of AgOAc and various chiral ligands. The 1,3-DC with imino esters **107**, alkene **242**, using the catalyst system formed with Bu^t-Phosferrox **238** (Alkyl = Bu^t) gave diastereo- and enantioselectively *endo*-cycloadducts **244** in good yields. In contrast, the *exo*-cycloadducts were formed in the presence of chiral phosphoramidite ligand **243** (Scheme 70).[106]



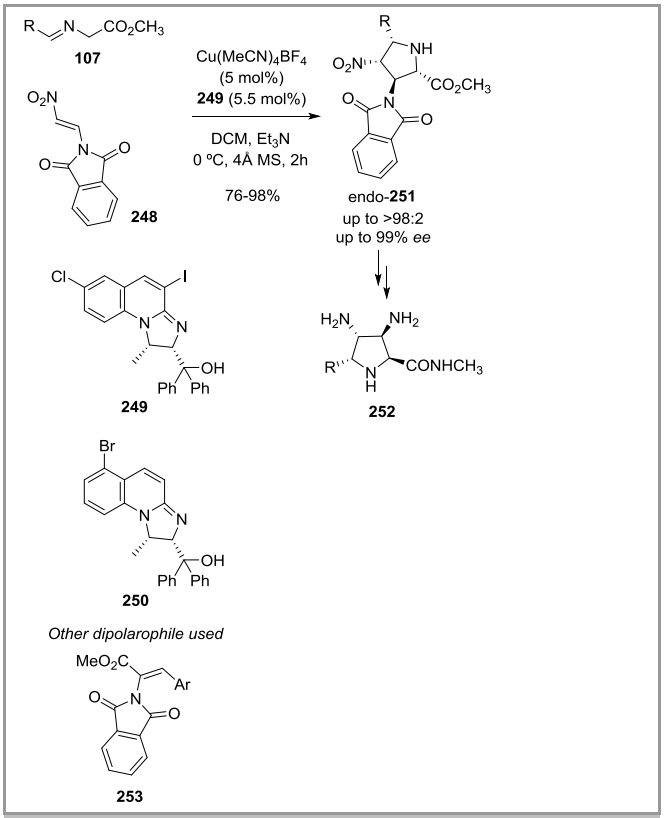
Scheme 70 Modulated synthesis of optically pure *endo*- and *exo*-cycloadducts **244**.

Attractive nitroprolinates **247** incorporating a trifluoromethyl group were employed in several biological tests. They were enantioselectively prepared from imino esters **107** and β-(trifluoromethyl)nitroalkenes **245** by intermediacy of a chiral copper(I)·**246** complex under mild conditions. In general enantio- and diastereoselections were excellent and chemical yields were good (Scheme 71).[107]



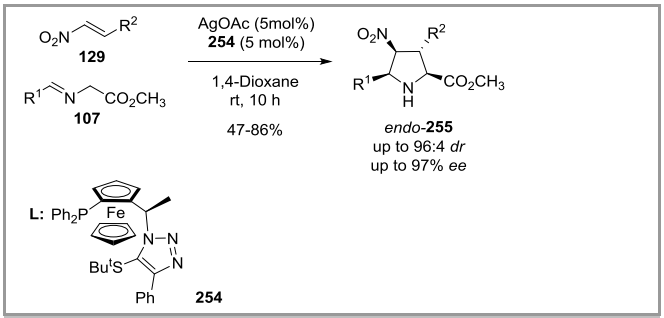
Scheme 71 Enantioselective preparation of nitroprolinates **247**.

Diamino substituted pyrrolidine derivatives **252** are very attractive compounds in many scientific areas. Their synthesis was accomplished in a Cu(MeCN)$_4$BF$_4$·chiral bidentate ligand **249** catalyst system from iminoesters **107** and β-phthalimidonitroethylene **248**. The *endo*-cycloadducts **251** were obtained as unique diastereoisomers and immediately underwent reduction with Ni-Raney followed by generation of the second free amino group (Scheme 72).[108] An analogous process, in which a modulation of the ligand was attempted, was reported during the enantioselective 1,3-DC of imino esters **107** and 2-phthalimidoylacrylates **253**, mediated by chiral ligand **250**, in very good yields and both excellent diastereo- and enantioselectivities.[109] In general, prolinates and nitroprolinates exhibit many useful properties in sciece.



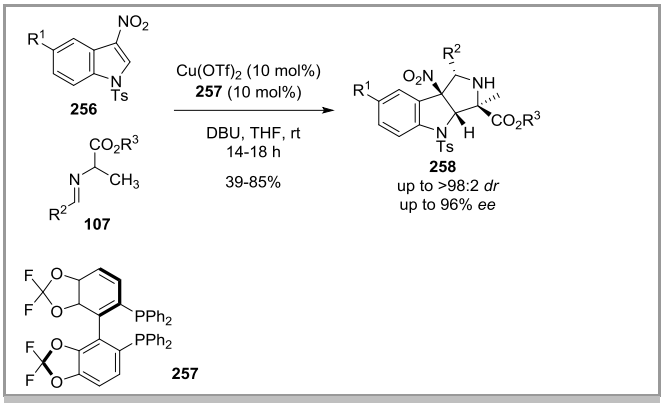
Scheme 72 Synthesis of enantiomerically enriched diamino substituted pyrrolidines **253**.

These imino esters also were allowed to react with nitrostyrene derivatives **129** through an enantioselective 1,3-DC reported by Fukuzawa *et al.*. AgOAc·ThioClickFerrophos (TCF) **254** complex, acting in a bifunctional mode, was the best catalyst to yield the corresponding *endo*-cycloadducts **255** (Scheme 73).[110,111]



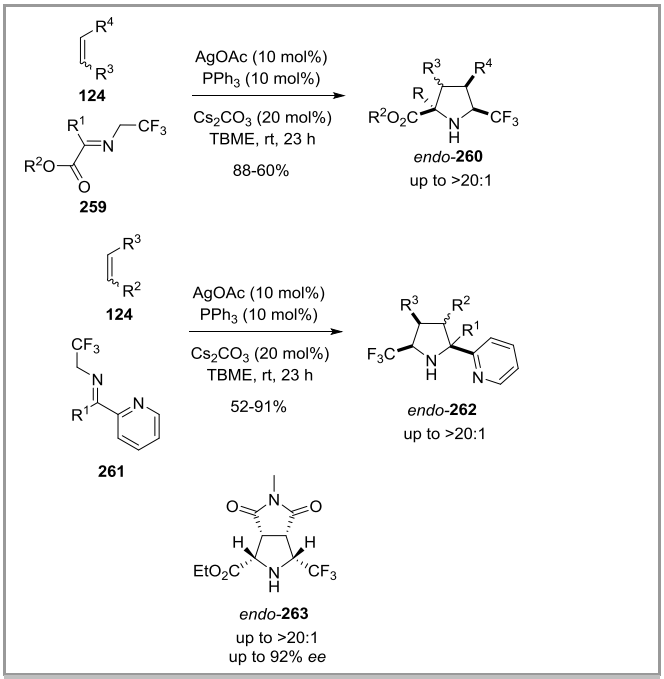
Scheme 73 Enantioselective synthesis of nitroprolinates **255**.

Enantioenriched *exo*'-pyrroloindolines **258** possesing four stereogenic centers were reported in the presence of an in situ generated catalyst system obtained from Cu(OTf)$_2$ and (*R*)-Difluorphos **257**, from alanine imino esters **107** and 3-nitroindole surrogates **258**. The dearomative 1,3-DC occurred in high diastereoselections and with notable enantioselectivities (Scheme 74).[112] These tricyclic entities are present in many natural products and is a straightforward and simple manner to access them.



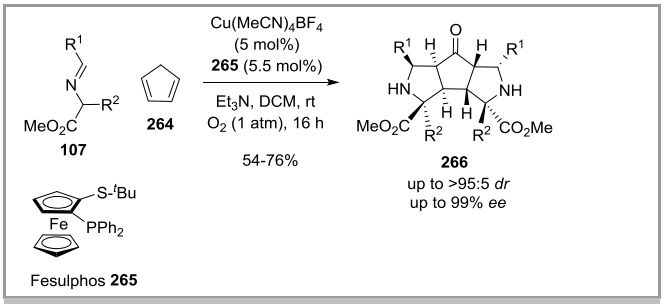
Scheme 74 Asymmetric synthesis of polycyclic compounds **258**.

The synthesis of trifluoromethylated pyrrolidine derivatives **260** and **262** was reported by Carretero and co-workers. The hetereocycles were obtained from a series of trifluoromethyl-substituted iminoesters **259** or trifluoroethyl imines possessing a 2-pyridyl unit **261**. The 1,3-DC proceeded in *tert*-butyl methyl ether (TBME) in very good yields and excellent *endo*-diastereoselections with a variety of dipolarophiles **124** in the presence of AgOAc/PPh_3 and Cs_2CO_3 as base (Scheme 75).[113] The enantioselective transformation using the chiral complex formed by AgOAc/Taniaphos **234** afforded *endo*-diastereoselection with high enantioselectivities of **262** (up to 92% *ee*) under the same conditions.



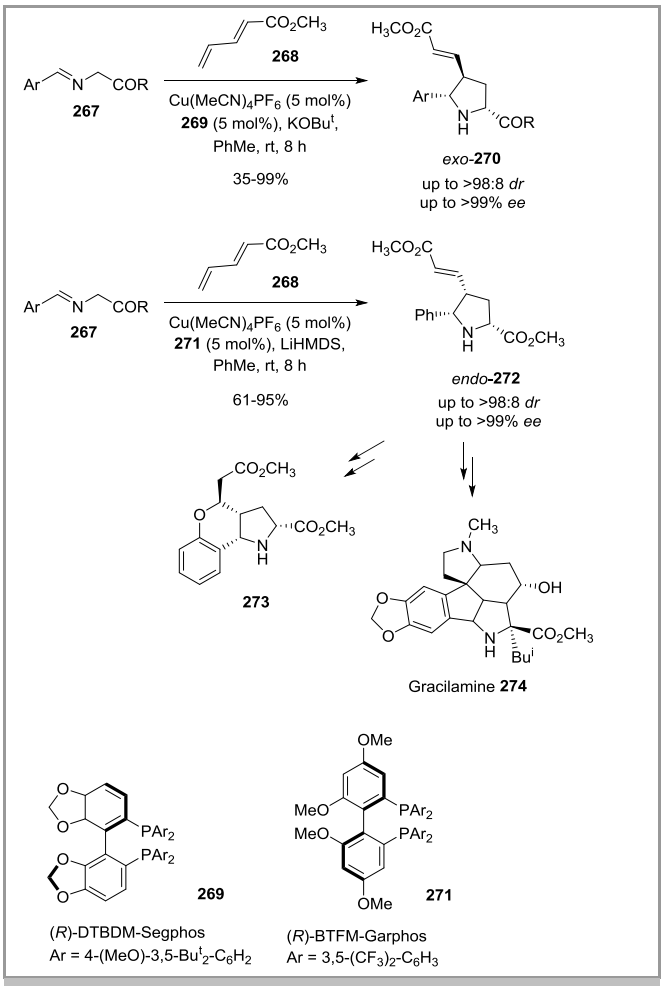
Scheme 75 Synthesis of trifluoromethylated pyrrolidine derivatives **260**, **262** and **263**.

Some fused tricyclic heterocycles **266** were enantioselectively constructed by Waldmann and co-workers in the presence of $Cu(MeCN)_4BF_4$·Fesulphos ligand **265** catalyst. Iminoesters **107** (2 equiv), cyclopentadiene **264** and the catalyst, under the optimized conditions, developed a multicomponent cascade reaction which allows the highly diastereo- and enantioselective synthesis of complex natural product cores **266** with eight stereocenters in moderate to good yields (Scheme 76).[114] A notable feature of the process was the aerobic copper-catalyzed oxidation of cyclopentadiene to cyclopentadienone previous to the 1,3-DC.



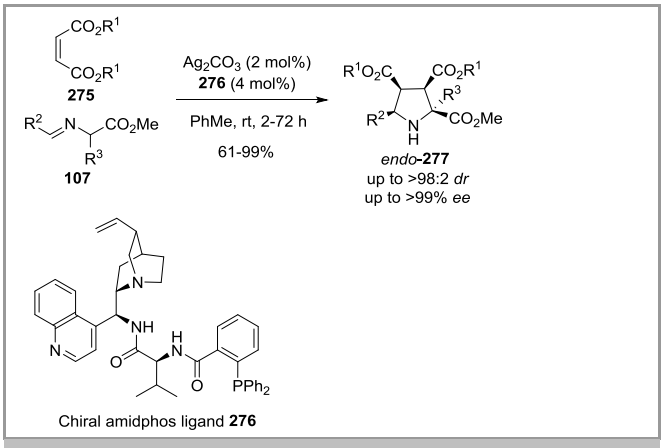
Scheme 76 Natural product frameworks **266** obtained *via* double 1,3-DC of azomethine ylides.

Carretero and co-workers have designed a very interesting stereodivergent methodology based in a 1,3-DC of azomethine ylides and an activated 1,3-diene **268**. The cycloaddition occurred selectively at the terminal C=C bond of the diene and, in basis of the chiral ligand employed, the diastereoselection can be controlled. Thus, DTBM-Segphos **269** and BTFM-Garphos **271** favored the formation of the *exo*- and *endo*-cycloadducts **272**, respectively, in good yields, high diastereocontrol and excellent enantioselectivities (Scheme 77).[115] This process had potential versatility to access to chromeno[4,3-*b*]pyrrole structures **273** and the tetracyclic skeleton core of the alkaloid gracilamine **274**. The same research group reported a diastereoselective one-pot synthesis of hexahydrocyclopenta[*b*]pyrrole derivatives using a similar catalytic system with (*E*)-tert-butyl 6-bromo-2-hexenoate and α-imino esters. This enantioselective 1,3-DC was followed by an intramolecular alkylation.[116]



Scheme 77 Biologically important substituted pyrrolidines **270** ans **272** and alkaloid framework of natural product **274** *via* enantioselective 1,3-DC of azomethine ylides.

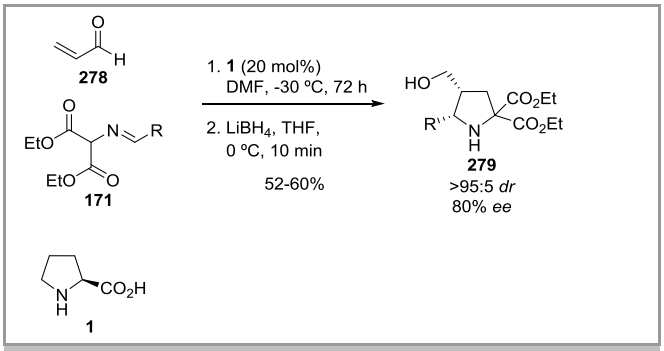
Tetrasubstituted *endo*-pyrrolidines **277** were prepared in the presence of a metal catalyzed system (Ag_2CO_3/chiral amidphos ligand **276**). Imino esters **107** and dialkyl maleates **275** reacted at room temperature in good yields. This multifunctional catalyst was able to act in particular reactions with a Brönsted acid domain (Scheme 78).[117,118]



Scheme 78 Enantioselective generation of *endo*-cycloadducts **277**.

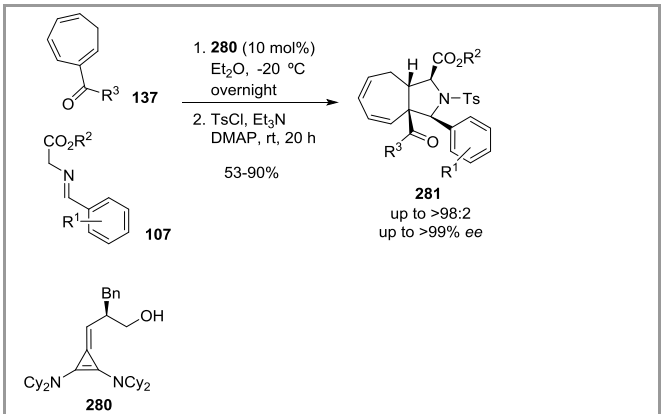
Chiral C-3 unsubstituted pyrrolidine cycloadducts **279** were reported by Vicario and co-workers in the presence of L-proline **1** as catalyst with the idea of preparing deoxyazasugar surrogates. The 1,3-DC was set up from diethyl arylideneaminomalonates **171** and with acrolein **278** as dipolarophile affording chiral cycloadducts, which were reduced to the corresponding primary alcohols **279** in good yields and high diastereo- and enantioselections (Scheme 79).[119]

These imino esters **171**, derived from aminomalonates, and ethynyl ketones were also employed by Deng and co-workers in the enantioselective synthesis of chiral functionalised 2,5-dihydropyrrole framework. In this example, the complex formed by $Cu(OAc)_2$·Ph-PhosFerrox **146** was the selected catalyst affording cycloadducts in both high diastereoselectivities (98:2–>99:1) and enantioselectivities (89–92% *ee*).[120]



Scheme 79 Organocatalyzed 1,3-DC affording adducts **279**.

Chiral organocatalysts were also very effective in enantioselective 1,3-DC of azomethine ylides generated from imino esters **107** and alkenes **137**. Bioactive substituted pyrrolidines **281** fused to a cycloheptatriene unit were reported by Jørgensen *et al.* in the presence of chiral cyclopropenediamines **280** as chiral base catalyst. The reaction proceeded stereoselectively and produced one diastereoisomer in high enantioselections (Scheme 80).[121] The transformations done in the diene part of cycloadduct gave access to new potentially bioactive heterocycles.

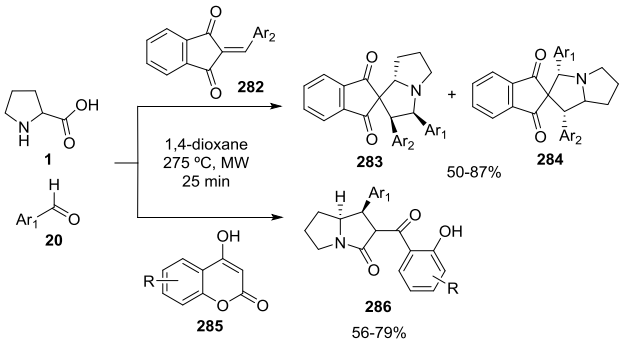


Scheme 80 Synthesis of substituted pyrrolidines **281** fused to a

cycloheptatriene unit.

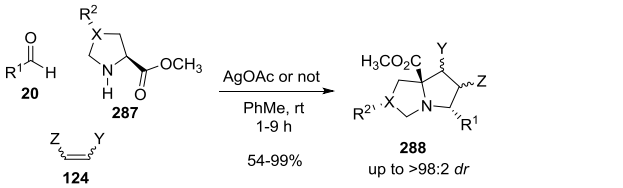
6. Synthesis of pyrrolizidines and indolizidines

Pyrrolizidine nucleus is a very attractive skeleton due to the biological importance of molecules containing it. In this line, a range of biologically important spiropyrrolizidines **283** and **284** and pyrrolizinones **286** were reported by Yang *et al*. The three-component 1,3-DC of the corresponding 1,3-diketones **282** or hydoxycoumarins **285**, aromatic aldehyde **20** and proline **1** took place in short reaction times assisted by microwave irradiation (Scheme 81).[122]



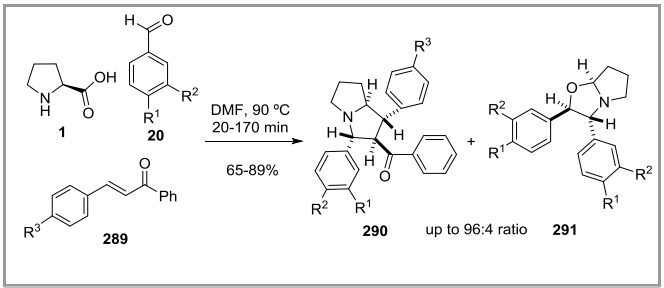
Scheme 81 Synthesis of functionalized pyrrolizidines **283** and **284** and pyrrolizinones **286**.

Highly substituted pyrrolizidines **288**, bearing multiple functionality moieties, were prepared in a multicomponent 1,3-dipolar cycloaddition. This simple process involved prolinate hydrochlorides **287**, aldehydes **20** and the corresponding dipolarophiles **124**. The reaction proceeded with both high regio- and diastereoselectively to yield heterocycles in the presence or in the absence of AgOAc as catalyst depending on the aldehyde employed (Scheme 82).[123] This cascade allowed the access to diverse molecular complexity, multiplication of stereocenters and access to potential bioactive pyrrolizidine alkaloids.



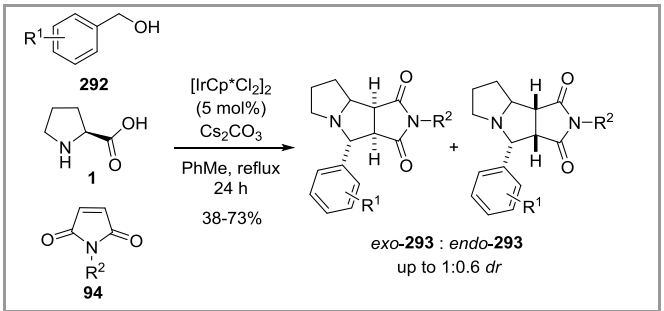
Scheme 82 Synthesis of highly substituted pyrrolizidines **288** *via* multicomponent 1,3-DC.

Another example of the synthesis of trisubstituted pyrrolizidines was recently reported *via* 1,3-DC of nonstabilized azomethine ylides and chalcones **289** as electron-deficient dipolarophiles in DMF. The reaction proceed regio- and diastereoselectively in a one-pot three-component reaction manner obtaining the desired compounds **290** together with an oxapyrrolizidine derivative in variable proportions. These substituted oxazolidines **291** arose when an excess of arylaldehyde **20** was employed, which acted as dipolarophile as well (Scheme 83). [124]



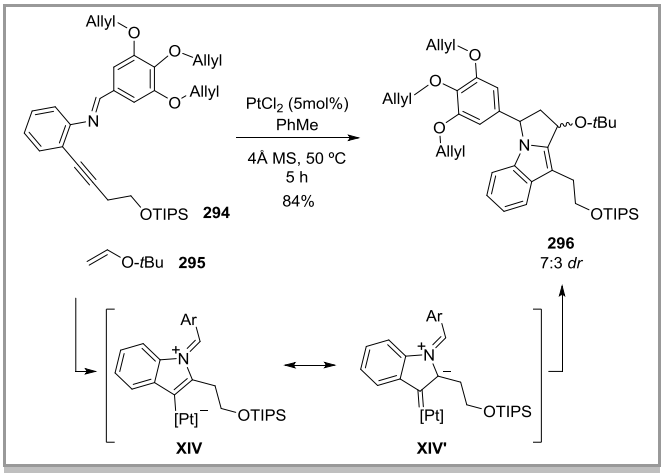
Scheme 83 Preparation of trisubstituted pyrrolizidines **290** and disubstituted oxazolidines **291**.

A novel one-pot three component iridium catalyzed dehydrogenation/1,3-dipolar cycloaddition cascade utilizing benzylic alcohols **292** was published. Benzylic alcohols **292**, L-proline **1**, and maleimides **94** as dipolarophiles reacted in refluxing toluene for 24 h furnishing antimicrobial surrogates **293** as mixtures of *endo*/*exo*-diastereoisomers in good yield (Scheme 84).[125]

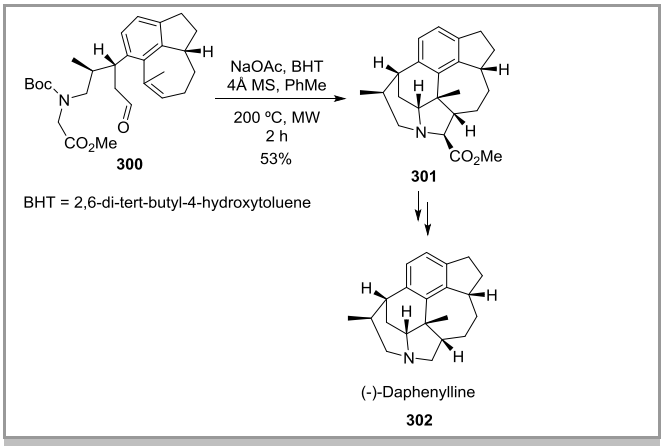


Scheme 84 Construction of tricyclic fused ring pyrrolidines **293**.

The total synthesis of the proposed structure of yuremamine **296** was achieved from a [3+2]-cycloaddition of the platinum-containing azomethine ylide (**XIV→XIV'**). The spectral data of the synthetic sample along with its diastereomers were different from the reported one. Lavonoidal skeleton, based on a funcionalized pyrrolo[1,2-*a*]indole core, was achieved with $PtCl_2$ (5 mol%) and 4A MS from the corresponding imine **294** derived from *ortho*-alkynylanilines. The intermediate platinum-containing azomethine ylide **XIV'** underwent and intermolecular 1,3-DC with vinyl ether **295**. The intermediate platinum carbine suffered a 1,2-migration of the substituent $(CH_2)_2OTIPS$ with regeneration of the platinum catalyst to afford the already mentioned pyrroloindole skeleton **296** (Scheme 85).[126]

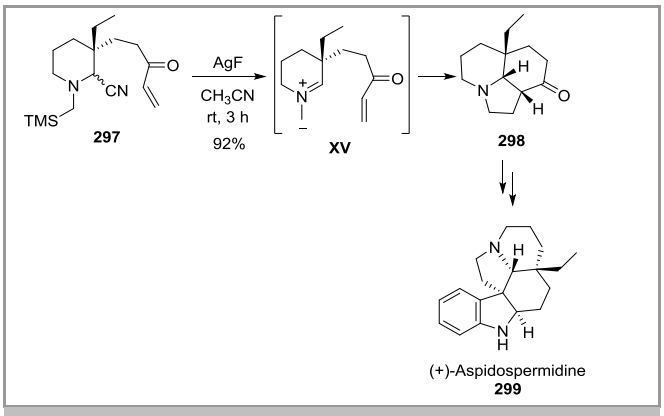


Scheme 85 Synthesis of lavonoidal skeleton of yuremamine **296**.



Scheme 87 Intramolecular 1,3-DC of cyclic azomethine ylide employed in the synthesis of (+)-daphenylline **302**.

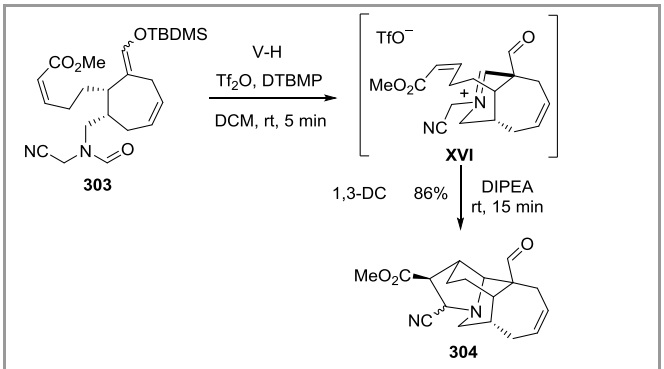
Pandey *et al.* have recently developed a route to total synthesis of both enantiomers of the biologically active (+)-aspidospermidine **299**, whose key step was the preparation of a fused indolizidine core through 1,3-DC using a non-stabilized azomethine ylide **XV** from precursor **297**. The enantiomerically pure starting material afforded only one diastereoisomer possessing the precise absolute configuration in all stereogenic centers (Scheme 86).[127]



Scheme 86 Diastereoselective approach to total synthesis of (+)-aspidospermidine **299**.

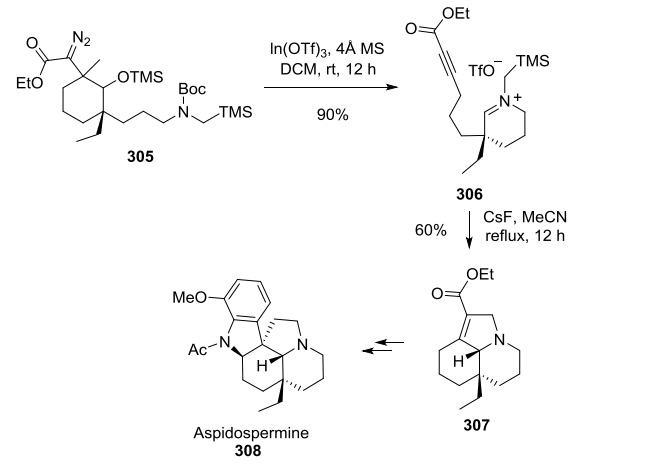
Following an intramolecular key 1,3-DC pattern, Fukuyama and co-workers accomplished the total synthesis of (-)-daphenylline **302**. The completion of the synthesis of core ABC tricyclic ring **301** occurred stereospecifically in moderate yield under very harsh reaction conditions due to the low activation of the dipolarophile present in structure **300**. In this example, a stabilized azomethine ylide was generated *in situ* by the iminium route (Scheme 87).[128]

Biologically important core intermediates **304** permitted the access to extremely complex (±)-caldaphnidine C type alkaloids. Bélanger *et al.* designed a sequential Vilsmeier–Haack (V-H) cyclization and intramolecular 1,3-DC of an azomethine ylide with an electrophilic alkene as one of the key step of the total synthesis. The V-H cyclization occurred rapidly generating an iminium salt **XVI**, which was deprotonated and allowed to react with the activated olefin at room temperature in high yields (Scheme 88).[129]



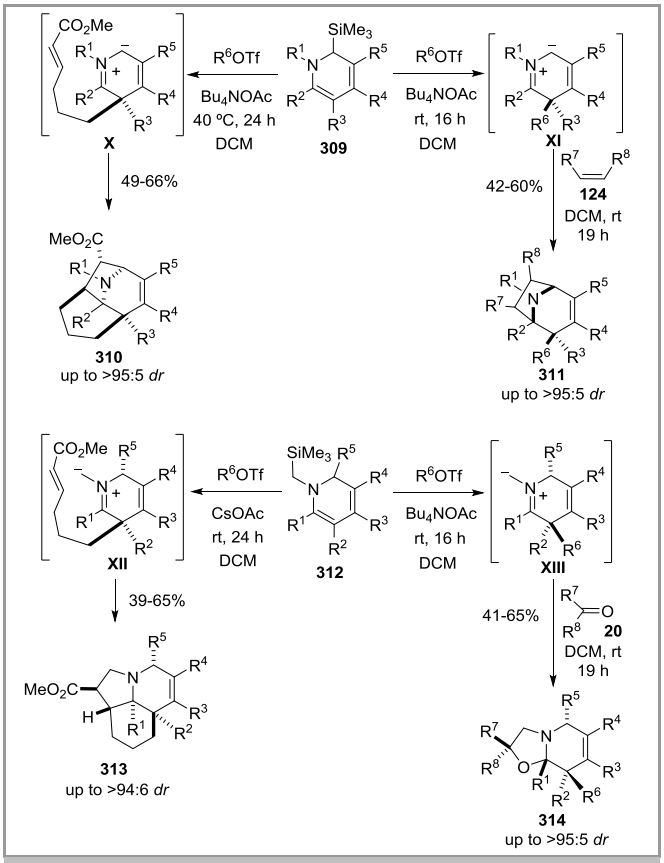
Scheme 88 Synthesis of core intermediate to access (±)-caldaphnidine C type alkaloid **304**.

Recently Brewer *et al.* have reported an approach to the synthesis of the biologically active tricycle, which is the core CDE-ring system of the aspidosperma alkaloid family **308**. Initially, the fragmentation of diazo ester **305** took place using $In(OTf)_3$ under mild conditions affording an intermediate stable iminium salt. After treatment of **306** with CsF in acetonitrile the tricyclic cycloadduct **307** was isolated in good yields as a single diastereomer (Scheme 89).[130]



Scheme 89 Ring Fragmentation/Intramolecular Azomethine Ylide 1,3-DC for the synthesis of the aspidosperma tricyclic core **308**.

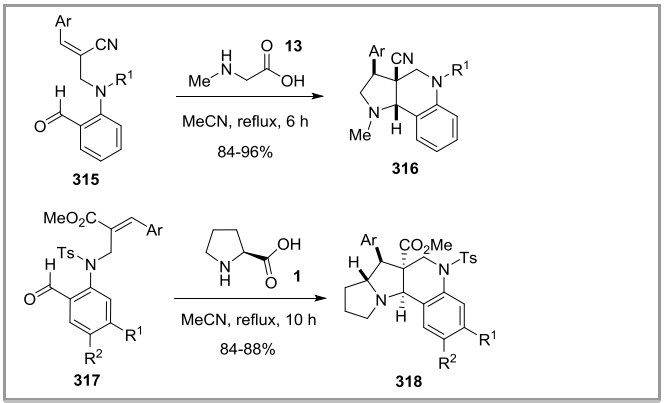
Ellman and co-workers described the synthesis of potentially bioactive tropanes **310** and **311**, and indolizidines **313** and **314** skeletons through intramolecular 1,3-DC. Non-stabilized azomethine ylides, generated from readily prepared 2-trimethylsilyl-substituted 1,2-dihydropyridines **309** or from *N*-(trimethylsilylmethyl)-1,2-dihydropyridines **312** *via* protonation or alkylation followed by desilylation, were selected to react with alkenes or alkynes. In the first example, densely substituted tropanes **310** and **311**, incorporating quaternary carbons, were obtained in good yields and with high regio- and stereoselectivities. However, *N*-trimethylsilylmethyl derivatives **312** furnished regio- and diastereoselectively indolizidines **313** or fused oxazolidine heterocycles **314** depending on the dipolarophile employed (Scheme 90).[131] These cascades represented a powerful approach for the rapid assembly of biologically and pharmaceutically relevant nitrogen heterocycle scaffolds. Additionally, all these heterocycles reported in this work are difficult to synthesize by other methods. The implementation of this sequence into the synthesis of natural products are underway.



Scheme 90 Synthesis of tropanes **310** and **311** and skeletons **313** and **314**.

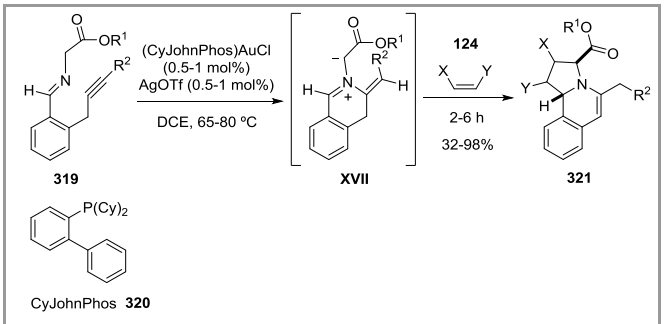
7. Synthesis of quinolines and isoquinolines

Tri- and tetra-cyclic pyrrolo/pyrrolizinoquinoline **316** and **318** were prepared. *N*-allylated aldehyde **315** and sarcosine **13** produced tricyclic pyrrolo[3,2-*c*]quinolines **316** in good yields. The analogous reactions were surveyed with proline **1** instead of sarcosine **13** and aldehyde **317** giving attractive fused tetracyclic pyrrolizinoquinolines **318** with a promising biological potential. The reaction afforded the best yields in refluxing acetonitrile with a total diastereoselection (Scheme 91).[132]



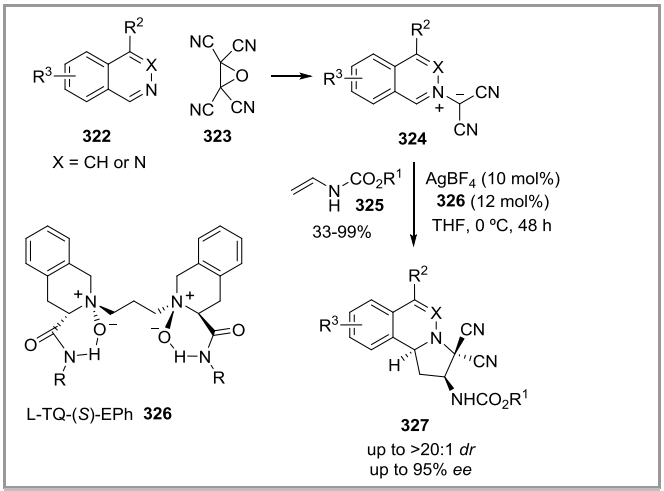
Scheme 91 Synthesis of tri- and tetracyclic pyrroloquinolines **316** and **318**.

Biologically important substituted pyrrolo[2,1-a]isoquinolines **321** were described by Matsuya and co-workers in the presence of a [(CyJohnPhos)AuCl/AgOTf] catalytic system in 1,2-dichloroethane (DCE). In this stereoselective process, a previous 6-*exo*-dig-cyclization occurred generating the azomethine ylide **XVII**, which reacted with several dipolaraophiles **124** affording pyrroloisoquinoline heterocycles **321** (scheme 92).[133]



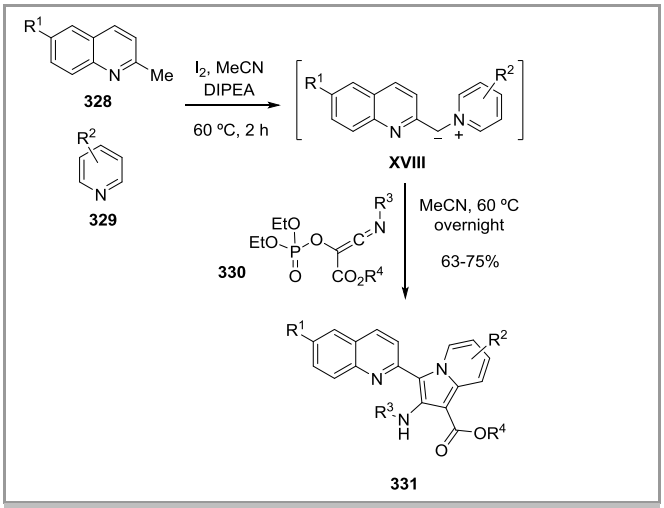
Scheme 92 Stereoselective synthesis of pyrrolo[2,1-*a*]isoquinolines **321**.

Chiral pyrroloisoquinolines **327** (X = CH) and pyrrolophthalazine **327** (X = N) were reported employing an asymmetric inverse-electron demand 1,3-dipolar cycloaddition of isoquinolinium methylides **324** with enecarbamates **325**. The catalytic system was formed by $AgBF_4$ and a chiral *N*,*N*′-dioxide **326**. Azomethine ylides **324** (isoquinolinium dicyanomethanide or phthalazinium dicyanomethanide) were generated from isoquinolines or phthalazines **322** and tetracyanoethylene oxide (TCNEO) **323**. Final fused tricyclic heterocycles **327** were obtained in good to excellent chemical yields, high diastereoselections and very good enantioselectivities (Scheme 93).[134,135]



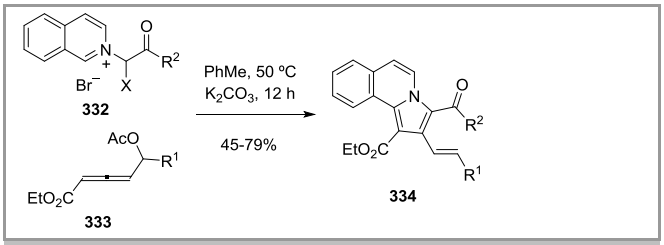
Scheme 93 Enantioselective synthesis tricyclic entities **327**.

Biologically active heterocycles **331**, containing both indolizines and quinoline core structures, were designed by Yavari and co-workers. Pyridinium ylides **XVIII**, generated by an iodine-mediated reaction of 2-methylquinolines **328** and pyridines **329**, underwent 1,3-DC with phosphorylated hydroxyketenimines **330**. This one pot multicomponent cascade process afforded the desired heterocycles **331** in good yields (Scheme 94).[136]



Scheme 94 Synthesis of heterocycles **331**.

Pyrroloisoquinolines **334** were generated in moderated to high yields *via* 1,3-DC of azomethine ylide, obtained from isoquinolinium salts **332** with substituted ethyl allenoates **333**. The pyrrole structure was achieved after elimination and isomerization occurring during the cycloaddition under basic media (Scheme 95).[137] The synthetic utility of the cycloaddition products **334** can be demonstrated by simple chemical manipulations permitting the construction of more sophisticated biologically active compounds.



Scheme 95 Synthesis of pyrroloisoquinolines **334**.

8. Conclusions

According to all these sections it is reasonable to conclude that 1,3-DC involving azomethine ylides is a powerful tool in both asymmetric or not asymmetric modalities able to give access to a wide family of skeletons. The exploration and exploitation of their biological activity is preferential for the discovery of new applications of the resulting cycloadducts in many scientific areas. The scope of theses cycloadditions seems to be unlimited and one of main interests of these 1,3-DC is the building of central subunits of complex alkaloids in a reduced number of reaction steps.

Acknowledgment

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Biosketches

	H.Ali Döndaş received his BSc. in 1990 from İnönü University, He received his MSc. in 1993 from Çukurova University and received his PhD degree in 1997 under the supervision of Professor Ronald Grigg (University of Leeds, UK) and received Best Ph.D Thesis award. In 1997 he was appointed Assistant Professor and become Associate Professor in 2001 at Mersin University. Since March 2007, he has been promoted to full Professor at Mersin University Faculty of Pharmacy, were he is currently the head of department at Basic Pharmaceutical Science. He has been working as Post-Doctoral Research Fellows (2000-2001) at University of Leeds (UK) with Professor Ronald Grigg and Post-Doctoral Research Fellows (2004) at University of Gent, Faculty of Bioscience Engineering Gent-Belgium with Professor Norbert De Kimpe. He has also been working as Visiting Researcher in 1998, Visiting Scholar in 2003 and 2005 at the University of Leeds, He was invited Visiting Research Scientist at the University of Leeds in 2008, 2015 and 2016.
	Maria de Gracia Retamosa received her Ph.D. in 2008 at University of Alicante (Spain) under the guidance of Prof. Carmen Nájera and José Miguel Sansano. After that, she did several postdoctoral stays [Prof. Michael Greaneyat at the University of Edimburgh (UK, 2009), Prof. Jesús M. Sanz at the University Miguel Hernández (Elche, Spain, 2009–2011) and Prof. Fernando P. Cossío at the University of the Basque Country and Donostia International Physics Center (Spain, 2012–2016)]. Recently, she has joined to the group of Prof. Rosario Fernández and José M. Lassaletta as a postdoctoral researcher [CSIC (Sevilla, Spain)]. Her current research interests include asymmetric metal and organocatalysis and synthesis of compounds with pharmacological interest.
	José Miguel Sansano was born in Rojales (Alicante), studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. His Thesis was supervised by Prof. C. Nájera and dealt about sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. In 2010 he was promoted to Full Professor in the same University. He was invited visiting Professor at Chuo University in 2014. He is coauthor of more than 100 articles and he has supervised 10 PhD students.

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