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Decarboxylative 1,3-dipolar cycloadditions of L-proline

Fatemeh Doraghi,[a] Azam Serajian,[b] Somaye Karimian,[c] Mehdi Ghanbarlou,[a] Fatemeh Moradkhani,[a] Bagher Larijani[a] and Mohammad Mahdavi *[a]

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1,3-Dipolar cycloaddition is one of the important chemical reactions between a 1,3-dipole and a dipolarophile to construct a five-membered heterocyclic compound. As an available α-amino acid reactant, L-proline is extensively used in 1,3-dipolar cycloaddition reactions. A diverse spectrum of bioactive spiro and fused N-heterocycles is obtained through this synthetic approach. In this review, we have described the use of L-proline in the synthesis of various spiro- and fused heterocyclic scaffolds.

1. Introduction

1,3-Dipolar cycloaddition (1,3-DC) reaction is a well-known fundamental strategy for the regio- and stereoselective construction of five-membered spiro and fused heterocyclic compounds.[1–5] This synthetic route is considered a powerful tool for the synthesis of many natural products and pharmaceutical molecules containing a pyrrolidine moiety.[6–8] Some of these structures are shown in Scheme 1. 1,3-DC exhibits notable advantages over traditional methods, enabling the construction of complex molecular structures from simple starting materials in a one-pot synthesis without separating intermediates.

Azomethine ylide intermediates generated *in situ* from the decarboxylative condensation of amino acids with isatins/aldehydes act as 1,3-dipoles to react with various dipolarophiles *via* 1,3-DC reaction.[9–12] Azomethine ylides consist of two sp^2 carbon atoms and one nitrogen atom with a HOMO orbital that directly interacts with a LUMO orbital of a dipolarophile. These intermediates are the most efficient synthons in the construction of spiro-heterocycles, such as pyrrolizines, pyrrolizidines, and pyrazolidines. Among these spiro-heterocycles, spiro-oxindoles show a broad spectrum of biological activities, including anticancer,[13,14] antiviral,[15,16] antibacterial,[17,18] anti-malarial,[19] anti-tubercular,[20] and anti-inflammatory.[21]

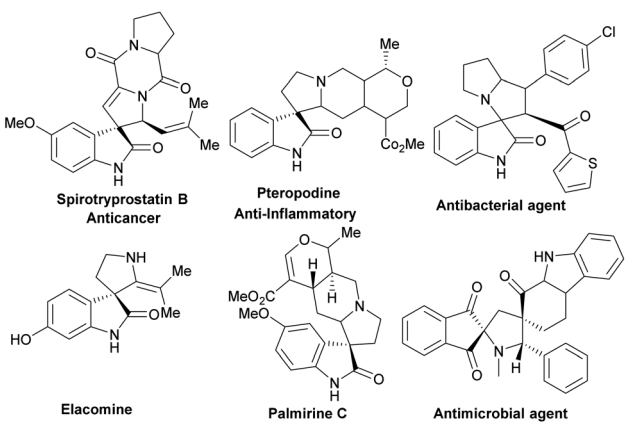
L-Proline is a natural α-amino acid with exceptional conformational rigidity. Due to the presence of a carboxylic acid and an amine, proline is considered a multifunctional amino acid in organic transformations. It can act as a chiral organocatalyst for catalyzing asymmetric catalysis systems, especially aldol condensation, as a chiral bidentate ligand for activating metal complexes, or as a nucleophilic reagent in organic syntheses.[22–24] In addition, the availability, cheapness, stability, and non-toxicity of proline make it an attractive molecule for chemists. This privileged α-amino acid is widely used in the multi-component 1,3-DC reactions towards the synthesis of spiro and fused N-heterocyclic motifs.

There are several review articles on the use of amino acids as reactants in organic transformations.[25–29] In this review, we have described decarboxylative 1,3-DC reactions of L-proline as a versatile α-amino acid over the last decade.

2. 1,3-Dipolar cycloadditions for synthesis of spiro-heterocycles

2.1. 1,3-Dipolar cycloadditions of proline and isatins with dipolarophiles

2.1.1. 1,3-Dipolar cycloadditions with diones as dipolarophiles. In 2013, Ouyang and co-workers introduced a method

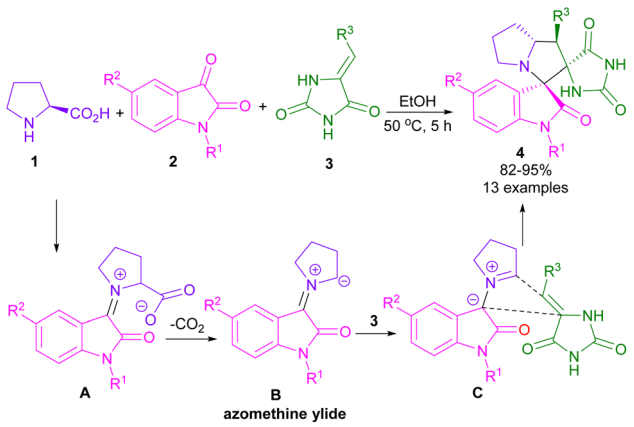


Scheme 1 Some of bioactive spiro-heterocyclic molecules constructing from amino acids.

[a]*Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. E-mail: momahdavi@tums.ac.ir*

[b]*Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, Iran*

[c]*Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*



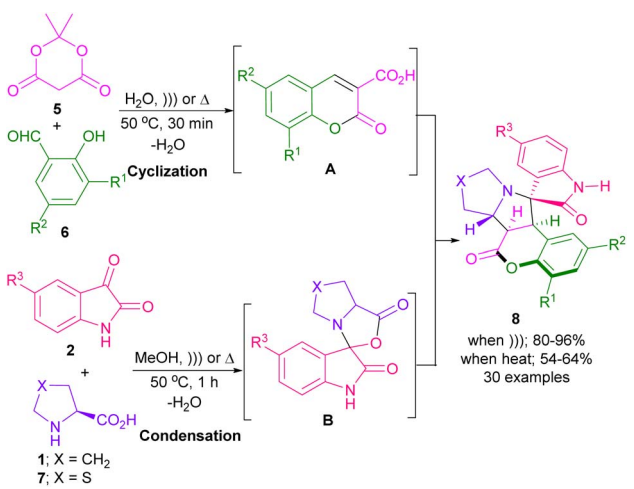
R^1, R^2	R^3	Yield (%)
R^1 = H, R^2 = Br	R^3 = Ph	92
R^1 = $CH_2C_6H_5$, R^2 = H	R^3 = 3,4-ClC_6H_3	83
R^1 = H, R^2 = F	R^3 = 4-BrC_6H_4	90
R^1 = Me, R^2 = H	R^3 = Ph	95
R^1 = $CH_2C_6H_5$, R^2 = H	R^3 = 3,4-ClC_6H_3	83
R^1 = R^2 = H	R^3 = 4-$OMeC_6H_4$	82

Scheme 2 Reaction of isatin and α-amino acid with 5-benzylideneimidazolidine-2,4-dione.

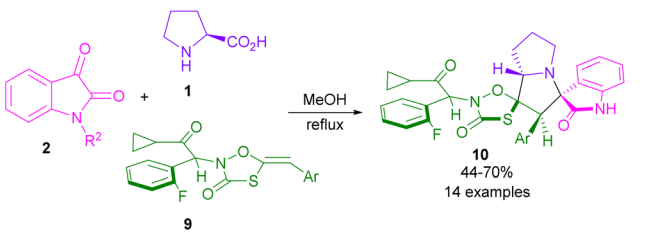
for 1,3-DC of isatin **2**, α-amino acid **1**, and 5-benzylideneimidazolidine-2,4-dione **3** (Scheme 2).[30] The reaction was carried out *via* the formation of azomethine ylide **B** from the decarboxylative condensation of isatin **2** and L-proline **1**, followed by the *endo* cycloaddition with the dipolarophile **3**. A series of regio-, and diastereoselective spiro-pyrrolidines **4** were produced in a multi-component procedure. Moreover, the authors reported the construction of spiro-thiopyrrolidine using L-thioproline as an amino acid reactant.

In 2014, an elegant strategy for the synthesis of spiro-oxindolopyrrolizine, or pyrrolo[1,2-*c*]thiazole fused coumarins **8** was disclosed by Kumar *et al.* (Scheme 3).[31] In this method, the preparation of products was investigated under heating and ultrasound conditions. At first, 2,2-dimethyl-1,3-dioxane-4,6-dione **5**, and salicylaldehydes **6** were treated in H_2O as a green solvent under ultrasonic irradiation to afford coumarin 3-carboxylic acid **A** *via* the aldol condensation and intramolecular cyclization. Afterward, isatins **2**, and cyclic α-amino acids **1**, or **7** were added to the mixture and stirred for another 1 h. The spiro intermediate **B** was formed through the condensation of isatin and amino acid. Decarboxylation of **B**, followed by 1,3-DC with **A** led to the final product **8**. A radical pathway was involved in the decarboxylation step in the presence of ultrasonic irradiation, whereas ionic intermediates were formed under heating conditions. The products were obtained in higher yields in the presence of ultrasound irradiation.

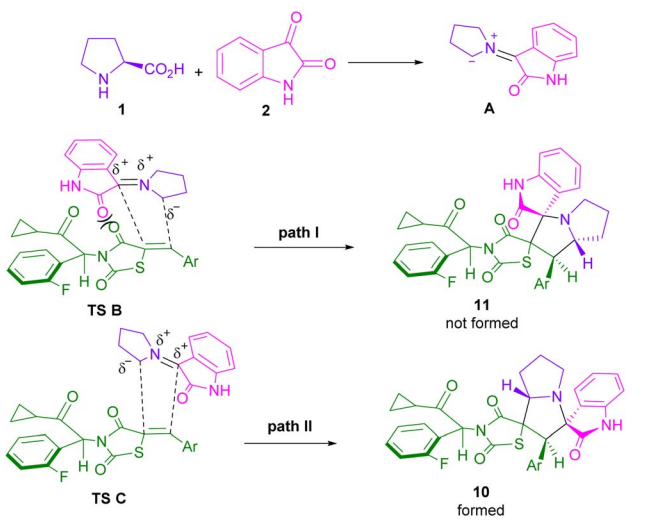
In 2015, the Liu[32] and Shanmugam[33] research teams in two distinct works reported the synthesis of spiro-oxindolopyrrolizines from isatin, L-proline, and different dipolarophiles. Also, Kumar and co-workers were able to make dispiro-oxindolopyrrolizine-thiazolidine-2,4-dione hybrids **10** from the treatment of isatin **2**, L-proline **1** and (*Z*)-5-arylidene-3-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-thiazolidine-2,4-diones **9** (Scheme 4).[34] In this work, an unusual regioisomer was synthesized through a 1,3-DC reaction. It was found that 1,3-dipole **A** passes through uncommon transition state **C**



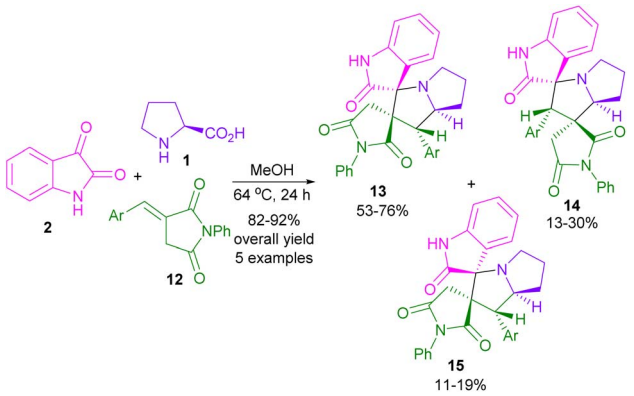
Scheme 3 Synthesis of oxindole-pyrrolizine or pyrrolo[1,2-*c*]thiazole fused coumarin hybrid heterocycles.



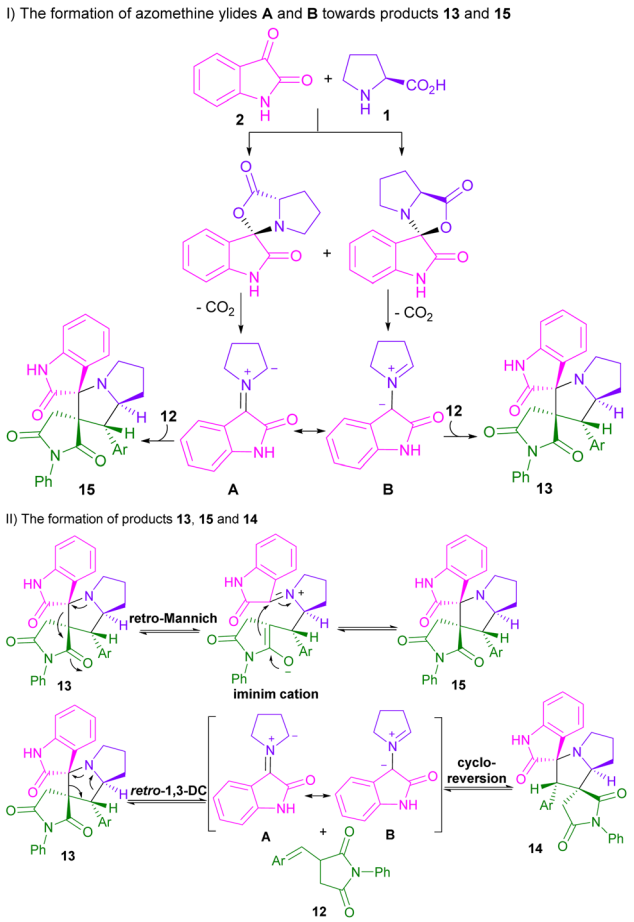
Scheme 4 Reaction of isatin, L-proline and (*Z*)-5-arylidene-3-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-thiazolidine-2,4-diones.



Scheme 5 Two possible pathways for reaction of isatin, L-proline and (*Z*)-5-arylidene-3-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-thiazolidine-2,4-diones.



Scheme 6 Reaction of isatin, L-proline and (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones.

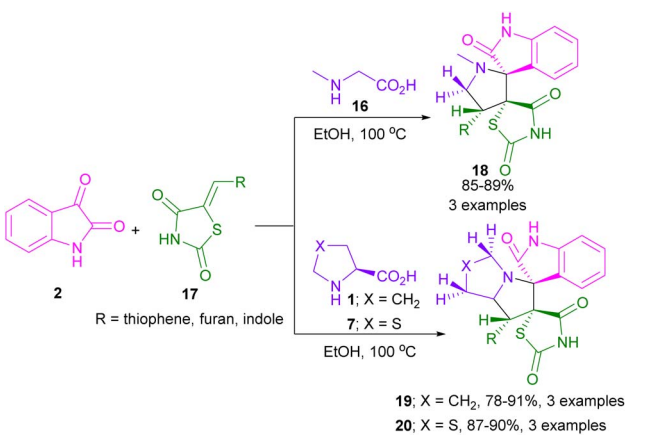


Scheme 7 Plausible mechanism for reaction of isatin, L-proline and (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones.

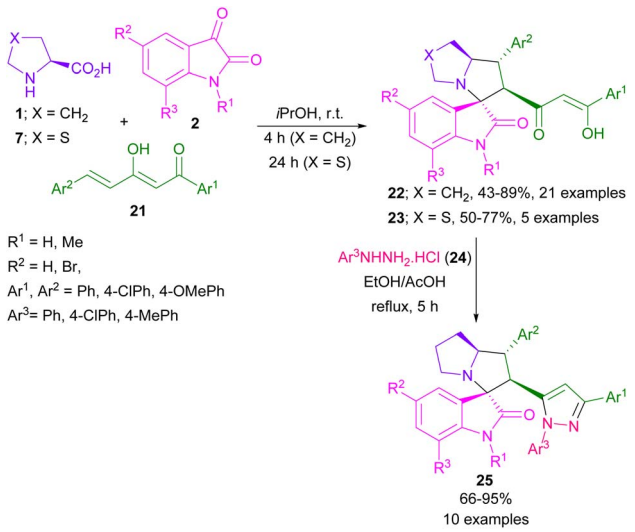
compared to transition state **B**. This may be due to the lower free energy activation in terms of the lack of electrostatic repulsion between the carbonyls of the dipole and the dipolarophile in TS **C**, which favored this pathway (Scheme 5). A variant of the same transformation was developed to make spiro-pyrrolizidines **13**, **14**, **15** from isatin **2**, L-proline **1**, and (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones **12** (Scheme 6).[35] In this 1,3-DC reaction, three stereoisomers were detected in different ratios. Mechanistic studies showed that products **13**, or **15** are formed depending on the formation of ylides **A** or **B**. As shown in section II, Scheme 7, the iminium cation can provide either **13**, or **15** using *retro*-mannich. Also, *retro*-1,3-DC can afford **13** from **A**, or **B** with alkene **12**. Whereas, product **14** was obtained from (3 + 2)-annulation. Also, again (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-diones were used as a dipolarophile for the condensation reaction with azomethine ylide generated form isatin and L-proline to produce spiro-oxindolopyrrolizidines.[36]

In 2021, Bekhradnia and Akhavan described (3 + 2)-cyclization of azomethine ylides with 5-arylidenthiazolidine-2,4-diones **17** as a dipolarophile (Scheme 8).[37] To achieve better results, they used an unexampled $MnCoCuFe_2O_4$@L-proline magnetic nanorod in this cycloaddition reaction. One-pot synthesis of spiro-pyrrolidine/pyrrolizidine/pyrrolothiazolidine scaffolds **18**, **19**, or **20**, tolerance of heteroaryl substituents in dipolarophile, the use of recyclable nanocatalyst, and high regio-, and diastereoselectivities of the products were among the advantages of this methodology. Similar to Bekhradnia's reaction, El-Tahawy and co-workers employed 3-arylidene-1-methyl-pyrrolidine-2,5-diones as a dipolarophile in the reaction with isatins and L-proline to form spiro-oxindolopyrrolizidines.[38] In this method, the cyclization reactions were performed in MeOH as the solvent under reflux conditions. They could also report antimicrobial and anti-coagulant properties of these spiro products in the range of moderate to strong activity.

In 2021, the Barakat[39] and Hügel[40] research groups reported the reactions of isatins, α-amino acids and various dipolarophiles. A series of spiro-oxindolopyrrolizidines were synthesized by Barakat's work, which exhibited potent anticancer activity. In Hügel's report, the resulting spiro products were evaluated as anti-amyloidogenic agents. At the same time, by using azomethine ylides in the reaction with enediones **21**, Korotaev *et al.* could provide spiro-oxindolopyrrolizidine derivatives **22**, **23** (Scheme 9).[41] Afterward, the treatment of the tetracyclic products with arylhydrazine hydrochloride reagents **24**



Scheme 8 Reaction of isatin, amino acids and 5-arylidenthiazolidine-2,4-diones.

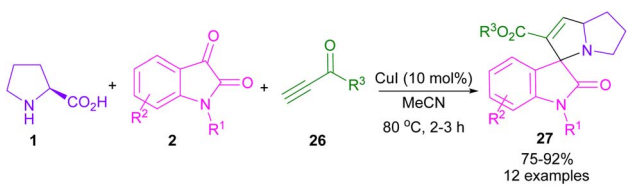


Scheme 9 Reaction of isatins, amino acids and enediones.

led to 5-substituted 1,3-diaryl-1*H*-pyrazole skeletons **25** in moderate to excellent yields.

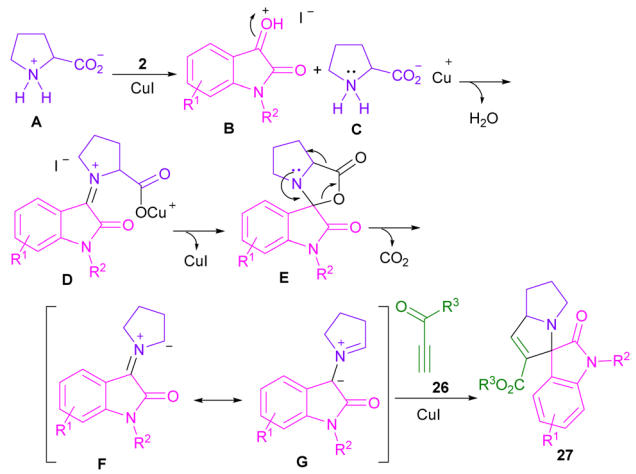
2.1.2. 1,3-Dipolar cycloadditions with alkynes an allenes as dipolarophiles. In 2013, Pal *et al.* found that copper salts can catalyze the 1,3-DC of isatins **2**, L-proline **1**, and terminal alkynes **26** (Scheme 10).[42] In this context, CuI, CuBr, or CuCl served as a catalyst, and products were obtained in 92, 78, and 75% yields. Due to the higher efficiency of CuI, the reaction was carried out in the presence of CuI as an optimal catalyst and bioactive spiro-pyrrolidine oxindoles were isolated in high yields. Considering the mechanism in Scheme 11, the imine intermediate **D** was formed from the reaction of zwitterionic L-proline **A** and isatin **2** under copper catalysis. Next, the dipolar azomethine ylide **F** was obtained by the CO_2 liberation, which was cyclized with the dipolarophile terminal alkyne **26** in the presence of Cu(I) to provide product **27**.

In 2017, the Meshram laboratory synthesized a new family of spiro-oxindole compounds and investigated their cytotoxic activity (Scheme 12).[43] For this purpose, the reaction of isatin **2**, amino acids **1**, **28**, but-2-ynedioates **29**, and phenacyl bromide **30** was conducted with the assistance of MW power. To make

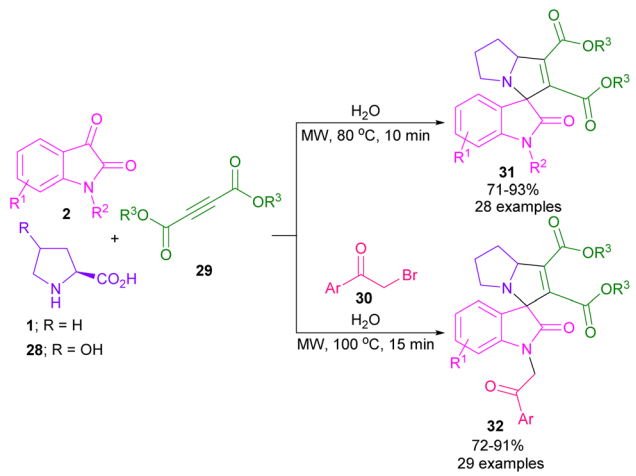


R^1, R^2	R^3	Time (h)	Yield (%)
H	NH_2	2	92
H	NHMe	2	90
H	OEt	2	81
5-Br, H	NHMe	2.5	82
H, -CH_2-*m*ClC_6H_4	NH_2	3	75
5,7-di-NO_2, H	NH_2	2	90

Scheme 10 Reaction of isatin, L-proline and terminal alkynes.

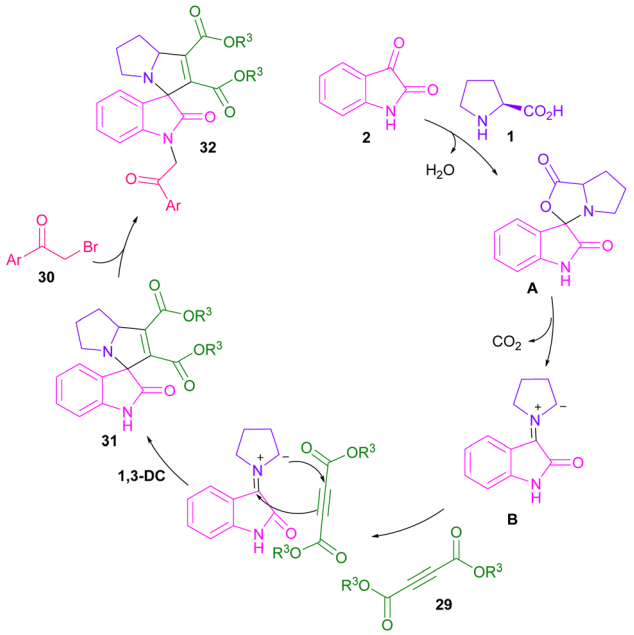


Scheme 11 Possible mechanism for reaction of isatin, L-proline and terminal alkynes.

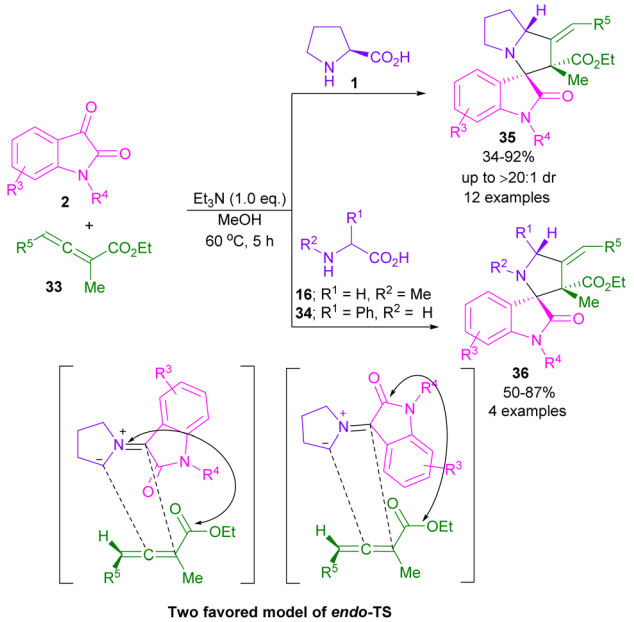


Scheme 12 Reaction of isatin, amino acids, but-2-ynedioates and phenacyl bromide.

oxindoles **31**, isatins **2**, L-proline **1**, or 4-hydroxy proline **28** and but-2-ynedioates **29** were treated in H_2O as a green solvent for 10 min under MW irradiation. Upon the addition of phenacyl bromide **30** in the reaction mixture, including isatin, L-proline and but-2-ynedioate, spiro products **32** were obtained at 100 °C after 15 min. The mechanism involved the initial condensation of α-amino acid **1** with isatin **2** to form azomethine intermediate **B** along with the CO_2 extrusion. Later, 1,3-DC of **B** with but-2-ynedioates **29** afforded product **31**. In another transformation, spiro compound **31** further reacted with phenacyl bromide **29** to render spiro product **32** (Scheme 13). Spiro-oxindolopyrrolizidines **35**, **36** were also achieved in the Chen reaction (Scheme 14).[44] In this work, α, γ-dialkylallenoate esters **33** were reported as dipolarophiles in the reaction with azomethine ylides and led to the *endo*-selective assembly of polycyclic spiro-oxindolopyrrolidines **35**, **36**. Two favorable transition states were proposed for the *endo*-cycloaddition reaction.

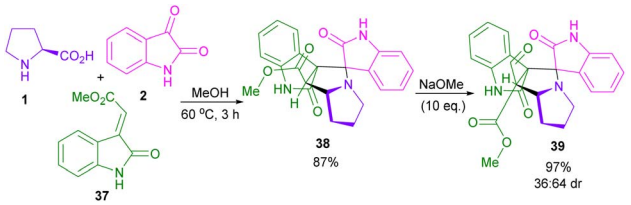


Scheme 13 Possible mechanism for reaction of isatin, amino acids, but-2-ynedioates and phenacyl bromide.

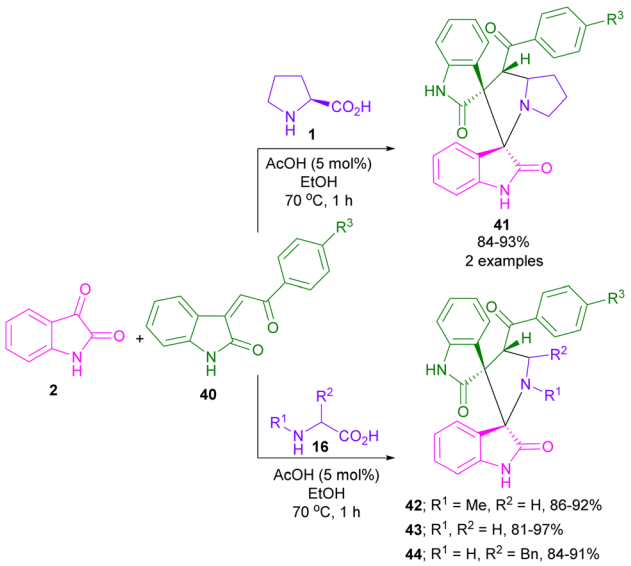


Scheme 14 Reaction of isatin, amino acids, and α,γ-dialkylallenoate.

2.1.3. 1,3-Dipolar cycloadditions with indolines and indole as dipolarophiles. In 2020, Siitonen's group was able to present the total synthesis of a 3,3′-spiropyrrolidine oxindole alkaloid called isatin digotindoline C **39** *via* two steps of dehydrogenation and (3 + 2)-annulation (Scheme 15).[45] For this purpose, isatin **2** and L-proline **1** were considered to produce azomethine ylide, and α,β-unsaturated methyleneindoline **37** was used as a dipolarophile for the cyclization with azomethine ylide. In the next step, *anti*-diastereomer of bisoxindole **39** was obtained in



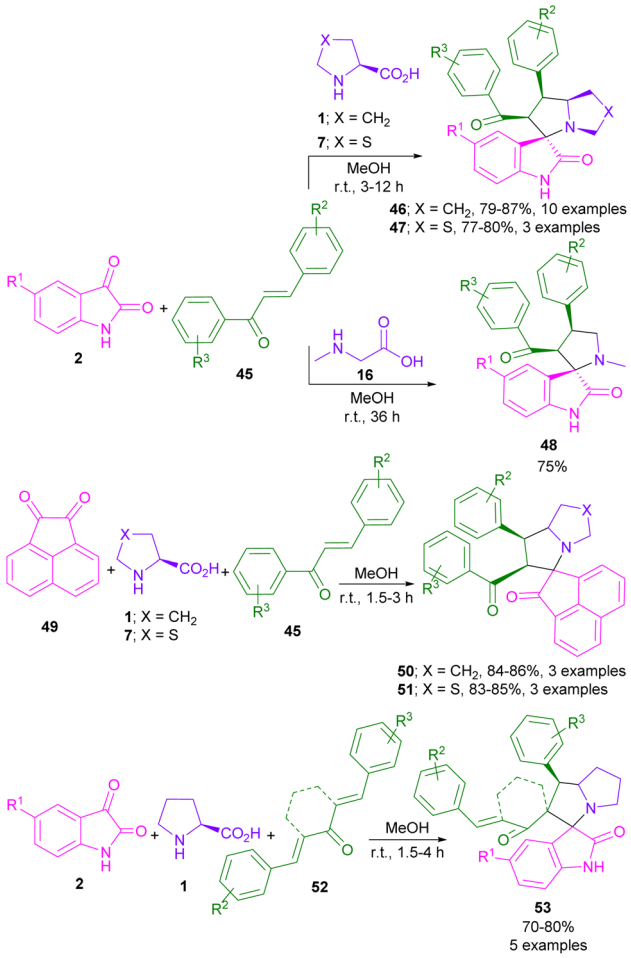
Scheme 15 Reaction of isatin, L-proline and α,β-unsaturated methyleneindoline.



Scheme 16 Reaction of isatins, amino acids and 2-oxoindolino-3-ylidene acetophenones.

a ratio of 64% relative to other *cis*-diastereomer (36%). Also, 2-oxoindolino-3-ylidene acetophenones **40** were reported by Youseftabar-Miri *et al.* as dipolarophiles in the cycloaddition with isatin **2** and L-proline **1** (Scheme 16).[46] Using DFT computations, the researchers demonstrated that the major product is kinetically favored.

2.1.4. 1,3-Dipolar cycloadditions with chalcones as dipolarophiles. In 2014, Lalitha and Revathy reported a three-component transformation, including isatin **2**/acenaphthenequinone **49**, amino acids and chalcones **45** to obtain spiro-oxindolopyrrolizidines **46–48** and spiro-oxindolothiapyrrolizidines **50**, **51** (Scheme 17).[47] L-Proline **1**, L-thiaproline **7**, and sarcosine **16** were used as amino acid precursors. D-Proline, a non-natural isomer of L-proline, did not give the desired product, because of the loss of the stereocentre in proline during the azomethine ylide formation. Acenaphthenequinone **49** resulted in higher yields in shorter reaction times compared to isatins. In a similar method by Jadidi and co-workers, a series of spiro-oxindolopyrrolizidines were synthesized starting from isatin, L-proline, and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones as a dipolarophile.[48] In their reaction performance, they used $Cu(OTf)_2$ as a catalyst in combination with a chiral dinitrogen ligand. The employment of *O*-acryloylacridinediones as dipolarophiles in the reaction with

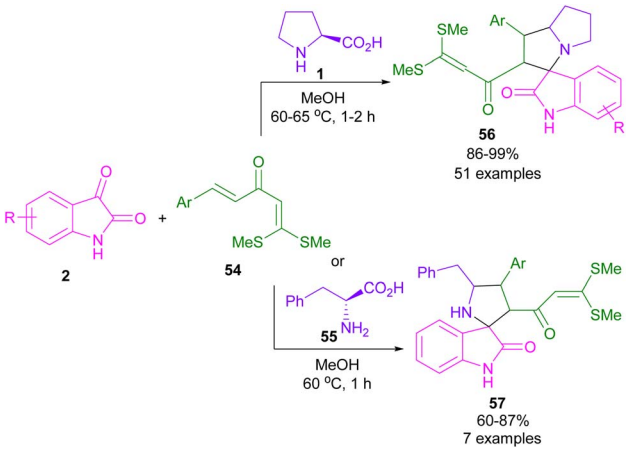


Scheme 17 Reaction of amino acids, isatins, and chalcones.

azomethine ylides generated *in situ* from isatin and L-proline, led to spiro-pyrrolidine/pyrrolizidine scaffolds *via* (3 + 2)-annulation.[49] In another work, Lipson *et al.* could synthesize spiro-oxindolopyrrolidines and pyrrolizidines from isatin, α-amino acids, such as L-proline, and sarcosine with asymmetric dipolarophiles, including acrylamides, and aroyl acrylic acids.[50] Highly reactive aroyl acrylic acids lowered the reaction time (10–15 min).

Regio-, chemo-, and stereoselective synthesis of spiro-oxindolopyrrolizines **56** and spiro-oxindolopyrrolidines **57** was achieved in Shanmugam's work in 2015 (Scheme 18).[51] In this context, amino acids, such as L-proline **1** and phenyl alanine **55** were smoothly reacted with isatin **2** and α-aroylidineketene dithioacetals **54** *via* (3 + 2)-cycloaddition strategy. The utility of this transformation was demonstrated by the gram-scale synthesis of the spiro-oxindole product in excellent yield (3.18 g, 99%) as well as the preparation of spiro-benzimidazole *via* the treatment of spiro-oxindolopyrrolizine with *ortho*-phenylenediamine. In the same year, Zhou *et al.* achieved chiral spiro-oxindolopyrrolizine from the reaction of isatin, L-proline and functionalized oxindole.[52]

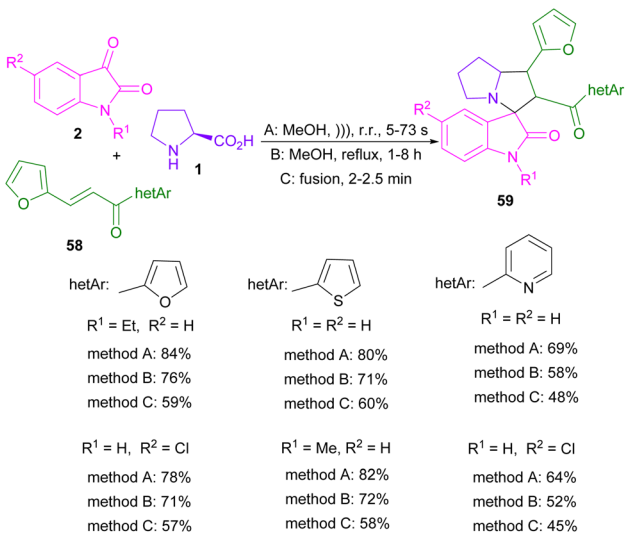
In 2017, a sonication technique was used to synthesize furanyl spiro-oxindolopyrrolizidines and spiro-



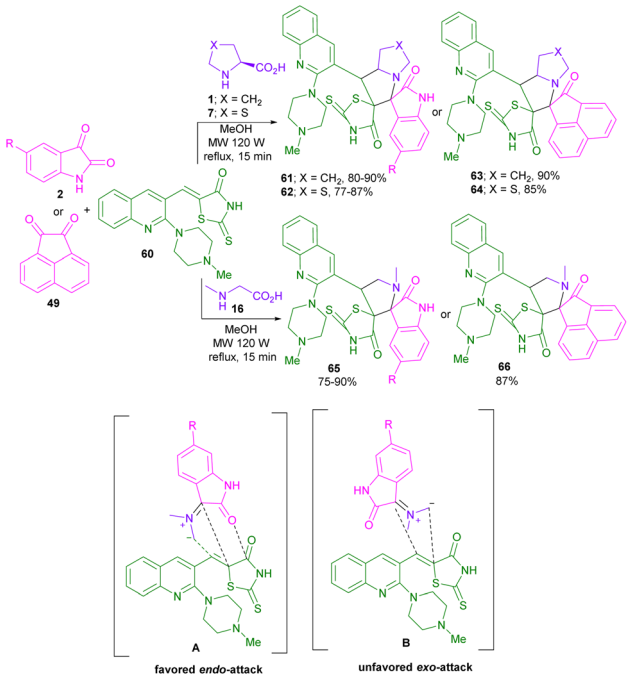
Scheme 18 Reaction of isatin, L-proline/phenyl alanine and α-aroylidineketene dithioacetals.

quinoxalinopyrrolizidines (Scheme 19).[53] Isatin **2**, L-proline **1**, and various chalcones containing heteroaryl moieties **58** were applied as starting materials. Products were made by using three methods including ultrasonic, heating and fusion. A comparison between heating, and fusion conditions with ultrasonic conditions showed that not only the desired products were obtained in a much shorter reaction time, but also in an obviously higher chemical yield.

In 2017, a strategy for the synthesis of piperazinyl-quinolinyl dispiro heterocycles was described by Gengan and co-workers (Scheme 20).[54] In this regard, they performed the reaction of isatin **2** with L-proline **1**/L-thioproline **7**/sarcosine **16**, and chalcone **60** to obtain spiro products **61**, **62**, **65**. Spiro compounds **63**, **64** and **66** were isolated when acenaphthenequinone was used instead of isatin. The reactions were set up in a MW irradiation reflux system. Examining the orbital interaction between the carbonyl group of **60** and azomethine ylide showed the *endo*-selective formation of regioisomer **A**, not *exo*-



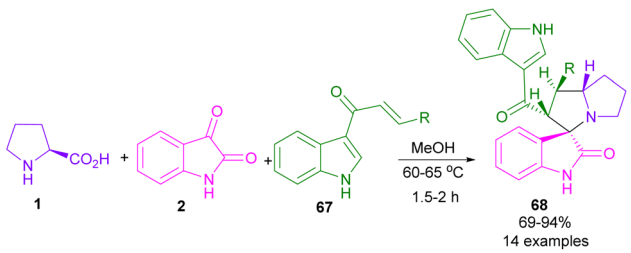
Scheme 19 Reaction of isatin, L-proline, and chalcone.



Scheme 20 Reaction of isatin, amino acids, and α,γ-dialkylallenoate.

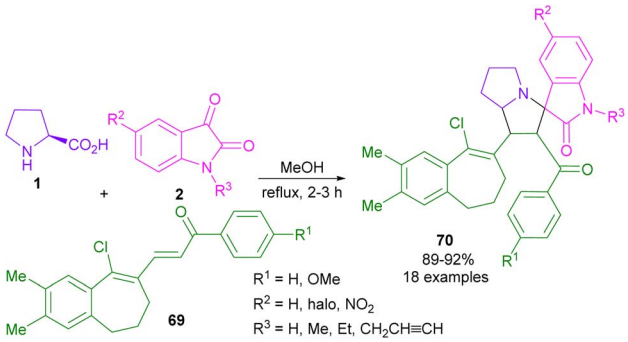
regioisomer **B**. In addition, molecular docking the fluorescence quench titration techniques were performed to investigate the binding ability of the obtained product with human serum albumin (HSA). L-Proline and L-thioproline together with isatin were employed in the synthesis of 3,3′-pyrrolidinyl-dispirooxindoles.[55] In 2021, Zhu,[56] Siva,[57] and Velmathi[58] reported in separate works, the cyclization of azomethine ylides derived from isatin and α-amino acids with (*E*)-3-cinnamoyl-2*H*-chromen-2-ones, chalcones and benzodioxole chalcones as dipolarophiles.

In 2018, the Barakat research group developed a three-component reaction, containing isatin **2**, L-proline **1**, and 3-acyl indoles **67** (Scheme 21).[59] They synthesized a variety of novel spiro-oxindole derivatives **68** and investigated their anti-cancer properties against three cancer cell types (colorectal,



R	Yield (%)	R	Yield (%)
C_6H_5	84	*p*-$CF_3C_6H_4$	76
p-MeC_6H_4	92	*p*-$MeOC_6H_4$	86
2-4-$Cl_2C_6H_3$	74	*m*-FC_6H_4	78
2-Thiophene	94	2-Fuean	89
p-BrC_6H_4	77	3,4,5-Tri-$MeOC_6H_2$	69

Scheme 21 Reaction of isatin, L-proline, and 3-substituted indoles.

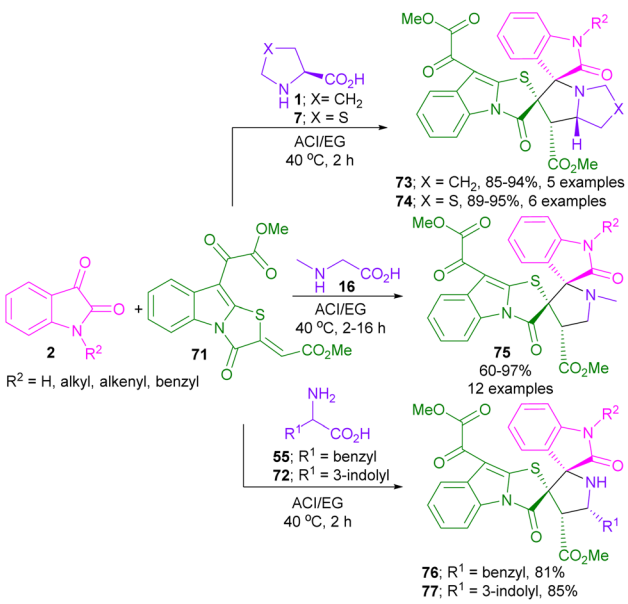


Scheme 22 Reaction of isatin, L-proline, and substituted alkenes.

hepatocellular carcinoma, and prostate). The protocol proceeded through azomethine ylide generation from isatin and L-proline, and 1,3-DC with the activated alkene **67**. The spiro-oxindole compounds showed good cytotoxic activity and selectivity compared to cisplatin. Another synthesis of spiro-oxindoles from isatin, L-proline and 5-arylidene-2-thioxothiazolidin-4-one as a dipolarophile was presented by this group in the same year.[60] DFT calculations, molecular docking and antimicrobial properties of the resulting products were also reported in this work.

In 2019, Nagarapu *et al.* explored a new dipolarophile for the reaction with isatin **2** and L-proline **1** (Scheme 22).[61] They conducted cycloaddition of azomethine ylide with (*E*)-3-(9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulen-8-yl)-1-phenylprop-2-en-1-ones **69** to furnish the corresponding spiro-oxindole derivatives **70**. They also studied anti-proliferative activities of the obtained products against five human cancer cell lines.

Deepthi and his team in 2020, developed a (3 + 2)-annulation approach for the synthesis of spiro-oxindolopyrrolidines in



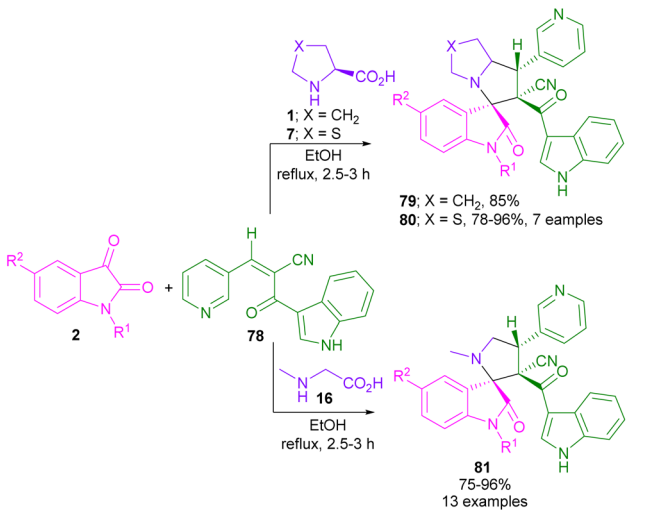
Scheme 23 Reaction of isatin, amino acids and thiazolo[3,2-*b*]indole.

a deep eutectic solvent called acetylcholine iodide-ethylene glycol (ACI/EG) (Scheme 23).[62] In this regard, isatin, amino acids, together with thiazolo[3,2-*b*]indole **71** were utilized in ACI/EG solvent to provide spiro-pyrrolidine oxindoles containing four stereocenters in high to excellent yields. Various amino acids, such as L-proline **1**, L-thioproline **7**, sarcosine **16**, L-phenyl alanine **55**, and L-tryptophan **72** were feasible in this method. All products were observed in the form of *cis* diastereoisomer.

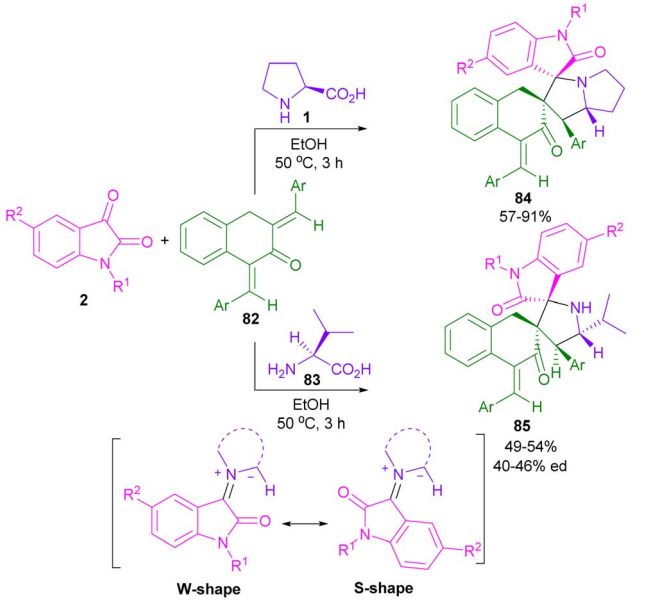
In 2022, the synthesis of spiro-oxindolopyrrolidines containing indole and pyridine rings **79–81** was presented by the Maheswarai library (Scheme 24).[63] The reaction proceeded through the formation of azomethine ylides from α-amino acids and isatins, followed by (3 + 2)-cycloaddition with (*E*)-2-(1*H*-indole-3-carbonyl)-3-(pyridin-3-yl)acrylonitrile **78**. Additionally, anticancer activity, and cytotoxic activity, as well as molecular docking of the obtained products were studied in this work.

The Lamsabhi research team introduced the synthesis of a new class of spiro-oxindolopyrrolizidines and pyrrolidines through a four-component (3 + 2)-cyclization reaction (Scheme 25).[64] In this regard, they treated isatins **2**, and L-proline **1**/L-valine **83** with *p*-substituted 1,3-bis(arylidene)tetral-2-ones **82** in EtOH as a solvent. According to the results of DFT calculations, the authors realized that due to the higher reactivity of the double bond at the 3-position relative to the double bond at the 1-position in enone **82**, the reaction proceeded with high chemoselectivity and two products **84** and **85** were detected with high diastereomeric excess. It was said that the unsymmetrical reaction was carried out through the formation of two W-shaped and S-shaped azomethine ylide intermediates.

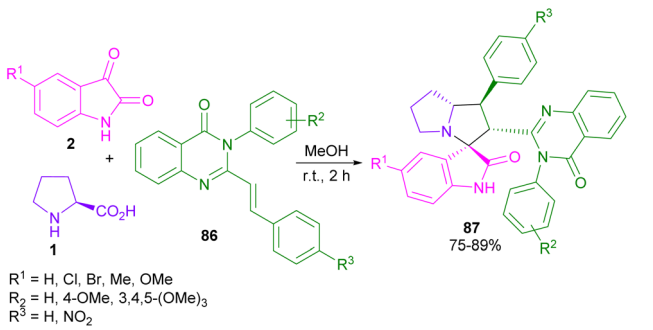
2.1.5. 1,3-Dipolar cycloadditions with quinolines, and quinazolines as dipolarophiles. In 2014, Maurya and Kamal *et al.* performed a multi-component reaction of isatins **2**, L-proline **1** and 2-styrylquinazolin-4(3*H*)-ones **86** to make spiropyrrolidine-quinazolinones **87** (Scheme 26).[65] The reaction was carried out through the initial interaction between isatin and amino acid towards azomethine ylides, which then underwent stereoselective 1,3-DC with alkene **86**. The protocol takes advantage of high atom-economic, good product yield, and broad substrate tolerance. A variant of the same method



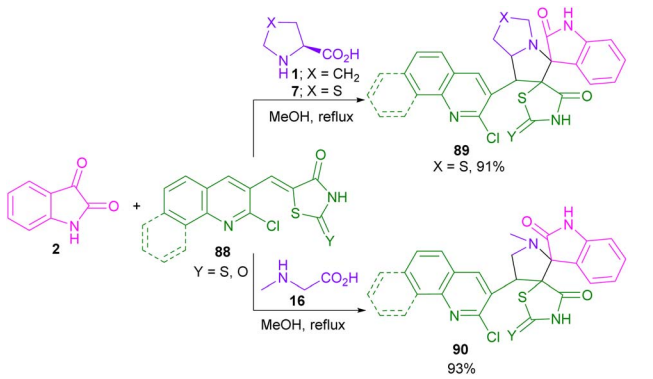
Scheme 24 Reaction of isatins, amino acids and (*E*)-2-(1*H*-indole-3-carbonyl)-3-(pyridin-3-yl)acrylonitrile.



Scheme 25 Reaction of isatins, amino acids and *p*-substituted 1,3-bis(arylidene)tetral-2-ones.



Scheme 26 1,3-DC reactions of azomethine ylides and 2-styrylquinazolin-4(3*H*)-ones.

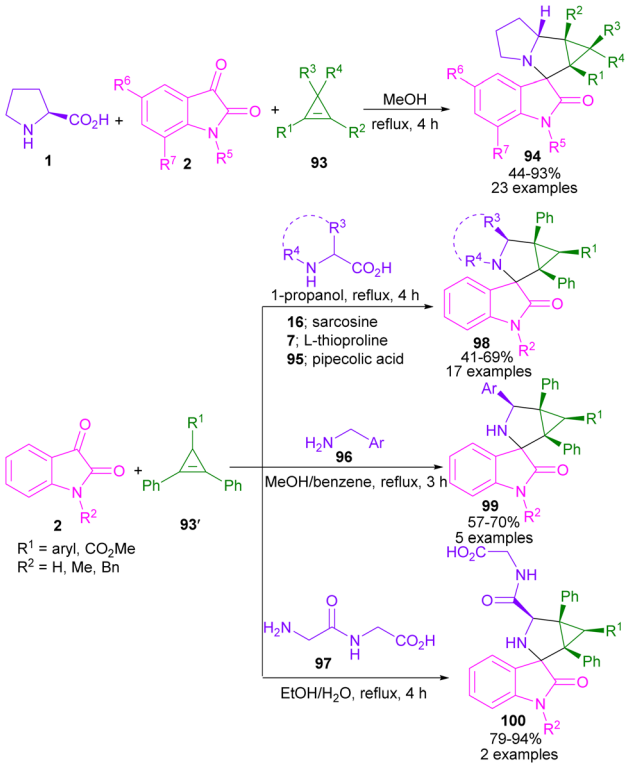


Scheme 27 Cycloaddition of isatin, amino acids and quinolinyl dipolarophiles.

was reported by Perumal *et al.*, involving 1,3-DC of azomethine ylides with alkyl indeno[2,1-*b*]quinoxalin-11-ylidene acetate **88** access to dispiropyrrolidine and dispiro-pyrrolizidine oxindoles.[66] Sarcosine **16**, L-proline **1**, and L-thioproline **7** can be included in this transformation. 1,3-DC of isatin, amino acids, and quinolinyl dipolarophiles led to novel quinolinyl dispiro heterocyclic compounds **89**, **90** (Scheme 27).[67] Amino acids participated in the formation of azomethine ylide intermediates with isatins, which then underwent cycloaddition with alkene **88**.

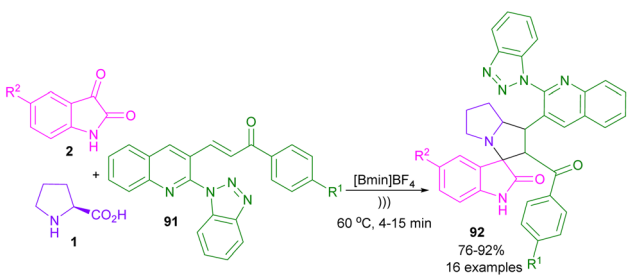
In 2019, for the synthesis of benzotriazoloquinolinyl spirooxindolopyrrolizidines **92**, Basavoju and co-workers used the ultrasound method in the reaction of isatins **2**, and L-proline **1** with 3-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)quinolin-3-yl)-1-phenylprop-2-en-1-one **91** (Scheme 28).[68] Screening of organic solvents, such as MeOH, EtOH, 1,4-dioxxane, and MeCN led to products in moderate yields under conventional conditions. While, the use of ionic liquids, like [Bmim]BF_4 and [Bmim]HSO_4 as green solvents could increase the reaction rate and product yield. Consequently, the best result was obtained in the presence of [Bmim]BF_4 and ultrasonic. Lastly, they evaluated the antimycobacterial and anti-proliferative activities of some of the obtained products.

2.1.6. 1,3-Dipolar cycloadditions with cyclopropenes and azirines as dipolarophiles. In 2017, the synthesis of unprecedented 3-spiro[cyclopropa[*a*]pyrrolizine]oxindoles and 3-spiro[3-azabicyclo[3.1.0]hexane]oxindoles from (3 + 2)-cycloaddition of substituted isatins, α-amino acids and cyclopropenes **93** was presented in the Boitsov work (Scheme 29).[69] Various amino acids, including L-proline **1**, sarcosine **16**, L-4-thiazolidine carboxylic acid 7, DL-pipecolinic acid **95**, and dipeptide Gly-Gly **97**, as well as benzylamine **96** as an amine precursor were participated in this transformation. Higher yields were observed when L-proline, or dipeptide Gly-Gly **97** were used to generate azomethine ylides. However, in all cases, high diasteroeselectivity were evident in products. Additionally, the anticancer activities of the resulting products were evaluated in this study. Sosnovskikh *et al.* utilized 3,3,3-trihalogen-1-nitropropenes as the activated alkene to react with azomethine ylides derived from isatin and L-proline.[70] The cycloaddition led to a series of spiro-oxindoles comprising trihalomethyl and nitro functional groups.



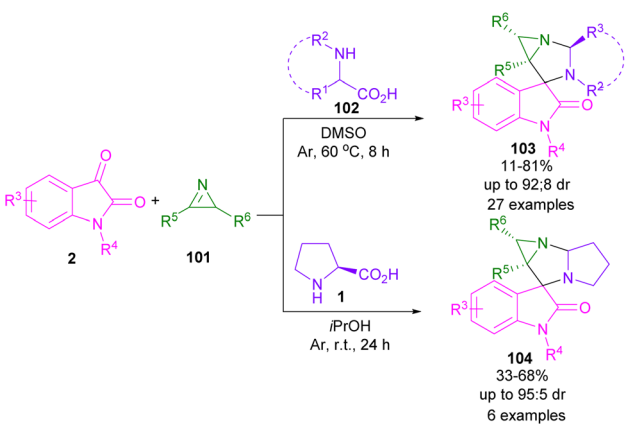
Scheme 29 Reaction of isatins, α-amino acids and cyclopropenes.

In 2019, Han,[71] Pavlovska,[72] Srinivasan,[73] and Deepthi[74] research teams reported the synthesis of spiro-oxindolopyrrolizines staring from isatin, L-proline and different dipolarophiles. For example, Kanizsai and co-workers used 2*H*-azirines **101** with isatin **1** and α-amino acids **1**, **102** to make 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindoles **103**, **104** (Scheme 30).[75] Various amino acids, such as D-2-phenylglycines bearing electron-donating, or electron-withdrawing groups, S-

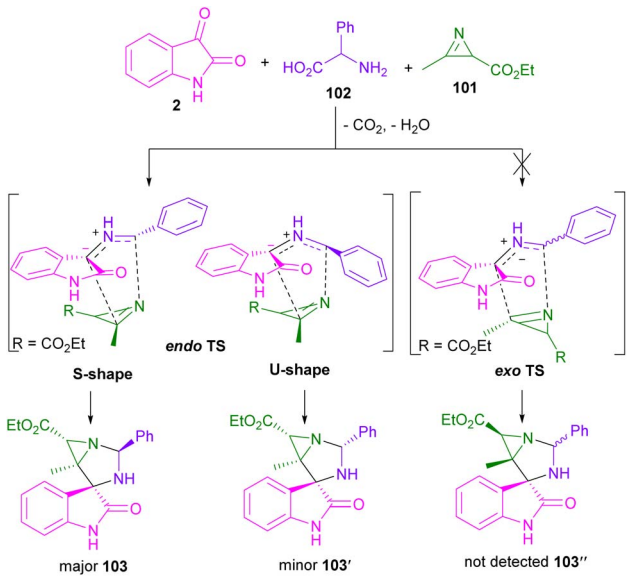


R^1	R^2	Time (min)	Yield (%)
H	H	4	90
Me	H	9	84
H	Cl	7	88
OMe	H	12	76
OMe	Br	15	78
Cl	Cl	5	91
Br	Cl	8	89

Scheme 28 Reaction of isatin, L-proline and quinoline dipolarophile.



Scheme 30 Reaction isatins, amino acids, and 2*H*-azirines.



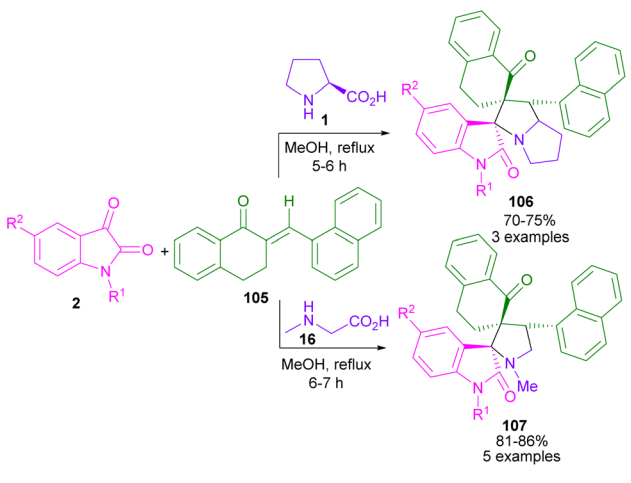
Scheme 31 Possible mechanism for reaction isatins, amino acids, and 2*H*-azirines.

benzylcysteine, tryptophan, serine, glutamine, and aliphatic norleucine were compatible in this methodology. However, L-proline worked well in *i*PrOH as the optimal solvent at ambient temperature. The authors proposed a possible mechanism, involving the generation of azomethine ylide **A** from **1** and **2**. Regioselective 1,3-DC of **A** with 2*H*-azirine **101** can occur through *endo*-TS, or *exo*-TS. However, no exocyclic product was detected, possibly due to the steric repulsion between the methyl group in azirine and the phenyl ring in oxindole. In the case of *endo*-cyclic compounds, the S-shaped conformation of **A** was sterically more favorable than the U-shaped conformation, so this conformer underwent *endo*-selective 1,3-DC to yield diastereomer **103** (Scheme 31).

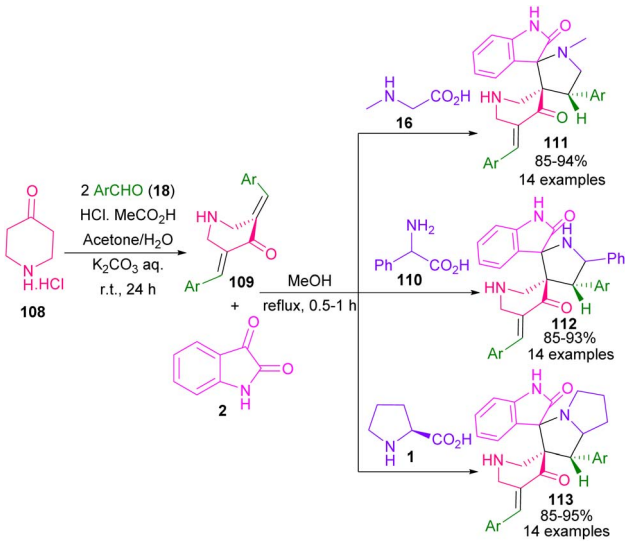
2.1.7. 1,3-Dipolar cycloadditions with ketones as dipolarophiles. In 2013, Raghunathan and co-workers reported a protocol for the construction of naphthyl dispiro-pyrrolidine/pyrrolizidine **106, 107** through 1,3-DC of isatin, or N-substituted isatin **2**, sarcosine **16**/L-proline **1**, and naphthylidene tetralone **105** (Scheme 32).[76] The reaction proceeded through the formation of azomethine ylides, which reacted with naphthylidene tetralone **105** as dipolarophiles. It was reported that anthrylidene tetralone was not feasible in this three-component reaction. Using the same method, Raghunathan *et al.* could prepare spiro-pyrrolidine/spiro-pyrrolizidine/spiro-thiazolidine-grafted macrocycles starting from isatin, or acenaphthenequinone and amino acids. They also achieved spiropyrrolidine-oxindole grafted 3-nitrochromanes by using 3-nitrochromenes instead of acenaphthenequinone.[77,78] Several amino acids, such as L-proline, sarcosine, and thiazolidine-4-carboxylic acid could be incorporated in this synthetic method.

Spiropyrrolidine and pyrrolizine derivatives were obtained from a multi-component reaction between 4-piperidone hydrochloride monohydrate **108**, aryl aldehyde **18**, isatin **2** and amino acids (Scheme 33).[79] Sarcosine **16**, L-proline **1**, and phenylglycine **110** were used as the α-amino acid reactants. At the first step, 3,5-bis[(*E*)-arylmethyl idene]tetrahydro-4(1*H*)-pyridinones **109** were constructed from the reaction of 4-piperidone hydrochloride monohydrate **108** with 2.0 equivalent of aryl aldehyde **18**. Then, the treatment of isatin **2** with α-amino acids **16**, **110**, or **1** led to *N*-methyl spiro-pyrrolidines **111**, *N*-α-phenyl spiropyrrolidines **112**, or spiro-pyrrolizines **113**, respectively. In addition, the evaluation of anti-proliferative activities of the resulting products was also studied in this work.

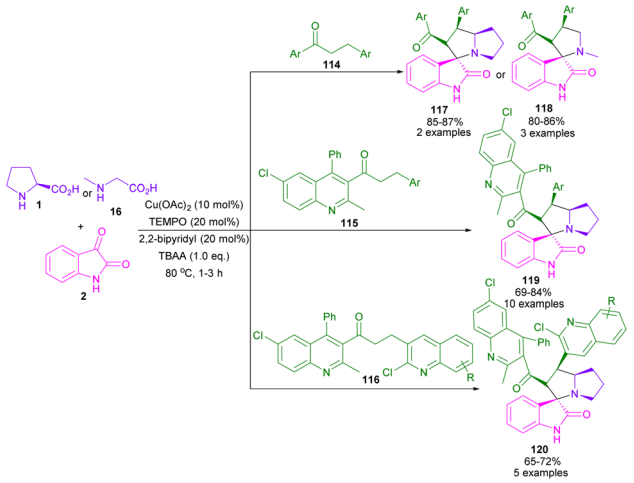
In 2020, Khan *et al.* used $Cu(OAc)_2$ and TEMPO to catalyze the dehydrogenation of alkylated ketones to act as an activated alkene in 1,3-DC with azomethine ylides (Scheme 34).[80] In this method, L-proline and sarcosine were used as the α-amino acid components. Various alkylated ketones **114**, quinolinyl-alkylated ketones **115** and **116** were well tolerated in this cycloaddition transformation. The reaction proceeded through a radical pathway in the dehydrogenation of alkylated ketone,



Scheme 32 Reaction of isatins, and sarcosine/L-proline with naphthylidene tetralone.



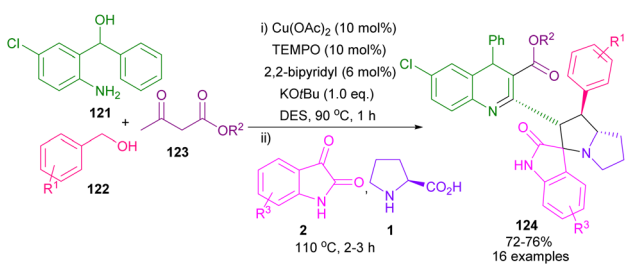
Scheme 33 Synthesis of spiropyrrolidine and pyrrolizine derivatives.



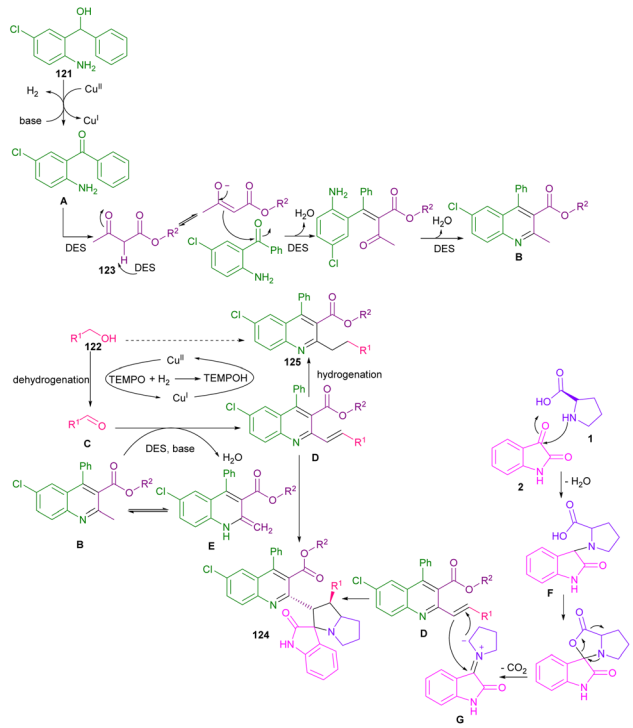
Scheme 34 Cu-catalyzed reaction of isatin, amino acids and alkylated ketones.

followed by an ionic pathway in (3 + 2)-annulation with azomethine ylide. Finally, antioxidant, and anti-diabetic activities of the spiro products were investigated in this work. In another report by the Khan team, they again employed $Cu(OAc)_2$/TEMPO as an efficient catalytic system for the dehydrogenative Friedlander annulation of secondary alcohols, followed by $C(sp^3)$-H functionalization by primary alcohols, and subsequent regioselective 1,3-DC with azomethine ylids (Scheme 35).[81] Considering the mechanism in Scheme 36, from the interaction of active TEMPO with Cu(II) ions, TEMPOH and Cu(I) species were generated, which transferred an electron to **121**. Ketone **A** which formed through this process, reacted with alkyl acetoacetate **123** to produce methyl quinoline **B** after the dehydration in a deep eutectic solvent (DES). In this procedure, DMU-tartaric acid was used as a green DES solvent. Next, **C** was reacted with aldehyde to obtain 2-strylqunolines **D**. At this time, the hydrogenation of **D** by Cu(I) ions could provide product **125**. On the other hand, azomethine ylide **G** was formed from the condensation of isatin **2** with L-proline **1**. Finally, product **6** was obtained by cycloaddition of **G** with **D**.

2.1.8. 1,3-Dipolar cycloadditions with azolidines and oxazoles as dipolarophiles. In 2016, the Menéndez research group made 2-pyrrolin-5-ones **125** from primary amines, 1,3-dicarbonyl compounds, and 2-bromoesters and successfully applied them in (3 + 2)-cyclization reaction with isatin **2** and α-amino

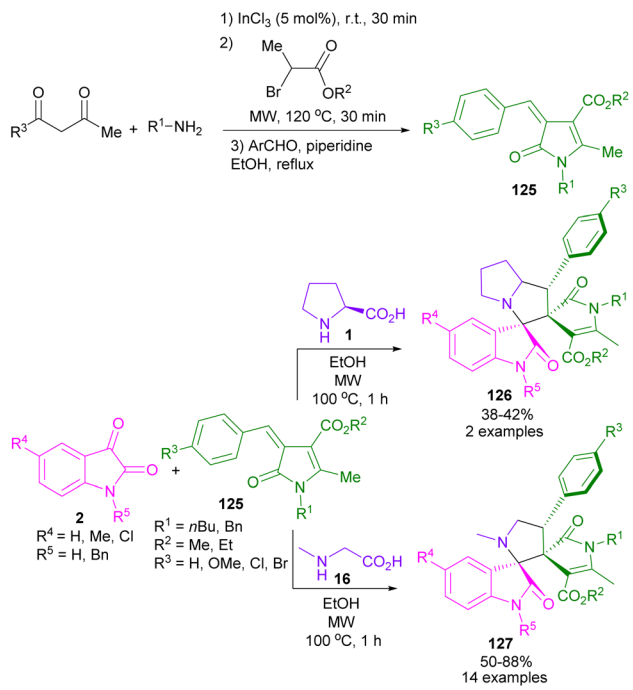


Scheme 35 Reaction of secondary, and primary alcohols with isatin, and L-proline.



Scheme 36 Tentative mechanism for reaction of secondary, and primary alcohols with isatin, and L-proline.

acids, such as L-proline **1**, and sarcosine **16** (Scheme 37).[82] A series of spiro-pyrrolidines **126**, **127** were synthesized in acceptable yields under MW irradiation at 100 °C for 1 h. It should be noted that sarcosine as an amino acid component is a better reactant due to the less steric hindrance in comparison

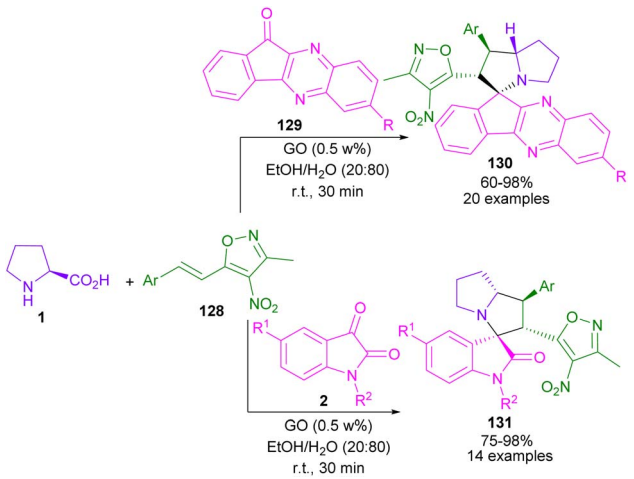


Scheme 37 Reaction of isatins, amino acids and 2-pyrrolin-5-ones.

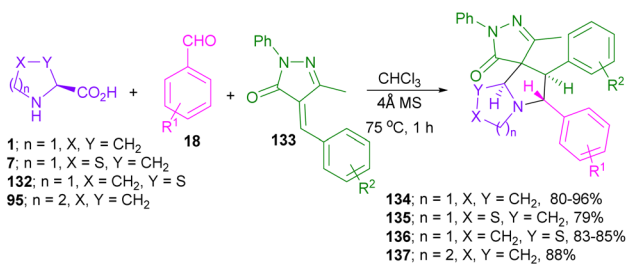
with L-proline. However, in both resulting products, only the *endo* structure was constructed during the regioselective mechanism.

In 2018, Chowhan and co-workers found that Graphene oxide (GO) can catalyze the cycloaddition between azomethine ylides generated from indeno quinoxalinone (11*H*-indeno[1,2-*b*] quinoxalin-2-one) **129** and L-proline **1**, with 3-methyl-4-nitro-5-alkenylisoxazole **128** as a dipolarophile (Scheme 38).[83] Spiro-oxindoles **131** were also obtained from isatin **2**, L-proline **1**, and substrate **128** in the presence of the GO catalyst. The protocol has the advantages of low catalyst loading with recyclability, high product yields, broad functional group tolerance, the performance of the reaction at room temperature in a short time, and the gram-scale synthesis of the spiro products.

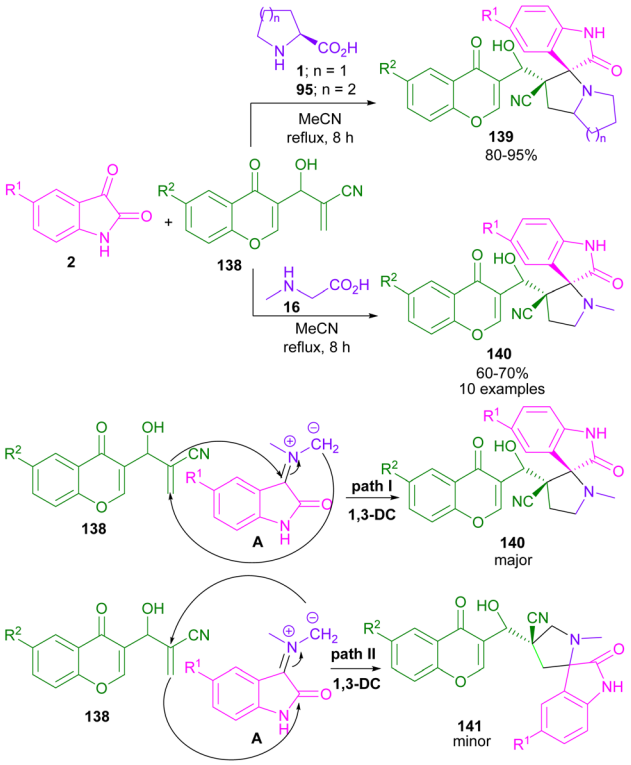
In 2021, a one-pot three-component synthesis of aza-spirocyclic pyrazolones was performed by Tiwari and his team (Scheme 39).[84] In this method, several amino acids, including L-proline **1**, thiazolidine-4-carboxylic acid **7**, thiazolidine-2-carboxylic acid **132**, and pipecolic acid **95** were smoothly reacted with aryl aldehydes **18** to form azomethine ylide intermediates for further annulation with alkylidenes pyrazolones **133**. The evaluation of azetidine-2-carboxylic acid and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid as an amino acid precursor was not effective. In the case of aldehydes, electron-rich and electron-poor aldehydes, heteroaromatic aldehydes



Scheme 38 GO-catalyzed reaction of azomethine ylide with dipolarophiles.



Scheme 39 Reaction of aryl aldehydes, amino acids and unsaturated alkylidenes.

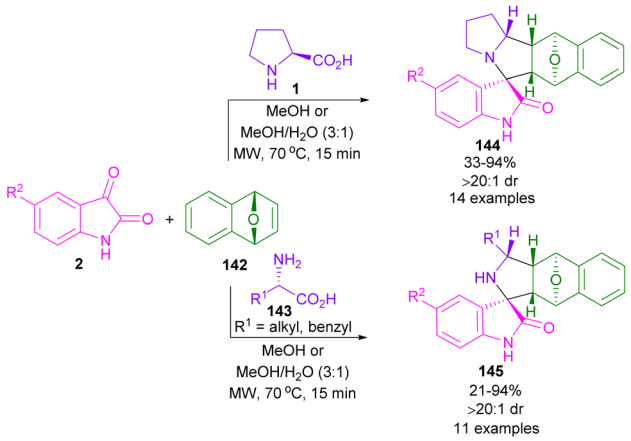


Scheme 40 Reaction of isatin, amino acids and with Baylis–Hillman adduct.

as well as polycyclic aldehydes were well tolerated in this transformation. A good result was also obtained in the gram-scale synthesis of the spiro product (4.25 g, 86% yield).

2.1.9. 1,3-Dipolar cycloadditions with chromenes and naphthalenes as dipolarophiles. In 2013, Reddy and Yuvaraj demonstrated that 1,3-DC of isatin, and amino acids (sarcosine, L-proline, and DL-pipecolinic acid) with Baylis–Hillman adducts **138** can lead to spiro-pyrrolidine oxindoles **139**, **140** (Scheme 40).[85] Two regioisomers were made from 1,3-DC of dipolarophile **138** with azomethine ylide **A** with the isomer preference in path **I**. This phenomenon was due to the energetically favored interaction between the HOMO orbital of a dipole with the LUMO orbital of a dipolarophile compared to the HOMO orbital of a dipolarophile and the LUMO orbital of a dipole. The use of dimethyl 2-(alkyl-, or arylthio)fumarates as a dipolarophile in the reaction with L-proline, and isatin led to the stereo-, and regioselective synthesis of spiro-oxindolopyrrolizidine, or pyrrolidine derivatives.[86] Whereas, dimethyl 2-(aryloxy)fumarates as a dipolarophile resulted in a mixture of regioisomers. The reaction was carried out in EtOH, or MeCN as a solvent in a short reaction time (<5 min).

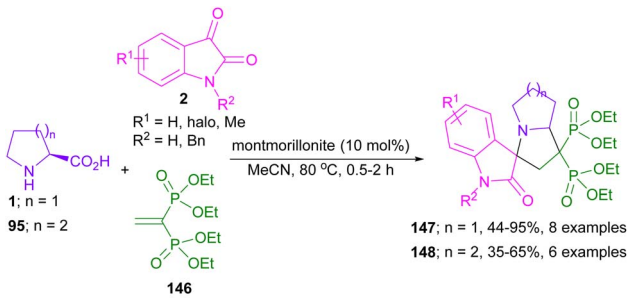
In 2023, a microwave-promoted (3 + 2)cycloaddition of azomethine ylide with 1,4-dihydro-1,4-epoxynaphthalene **142** was reported by Zhao *et al.* (Scheme 41).[87] Novel oxygen-bridged spiro-oxindole compounds were constructed in a very short time under MW irradiation. In addition to L-proline, a large spectrum of amino acids, including L-alanine, L-phenylalanine, 4-iodo-L-phenylalanine, L-homophenylalanine, L-tyrosine, L-



Scheme 41 Reaction of isatin, amino acids and 1,4-dihydro-1,4-epoxynaphthalene.

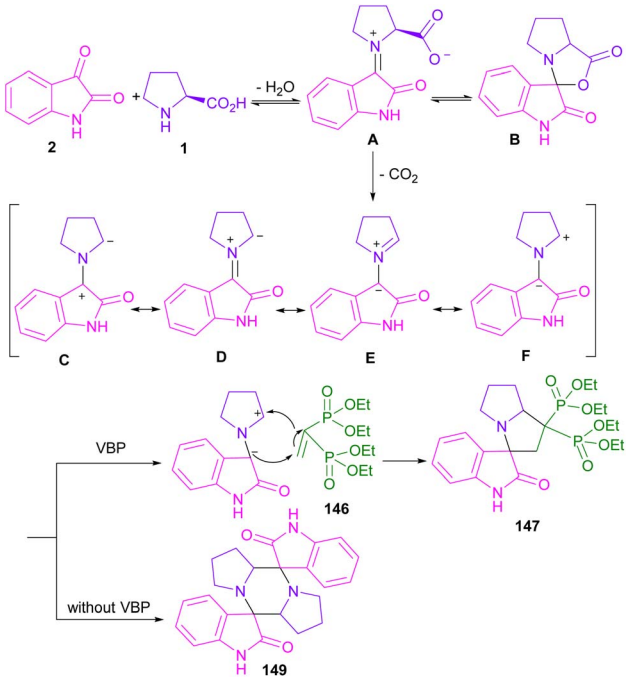
methionine, L-lysine, L-leucine, and L-thiproline were well tolerated in this green synthetic methodology. L-Isoleucine, and *trans*-4-cyclohexyl-L-proline resulted in two diastereomers. While L-serine, L-piperidine-2-carboxylic acid, and peptide L-Ala-L-Ala-OH were not workable.

2.1.10. 1,3-Dipolar cycloadditions with S/Se/P/EWG-substituted alkenes as dipolarophiles. In 2015, the Wu team explained a procedure for the assembly of a new library of spiro-indolopyrrolizine, spiro-indoloindolizine, and spiro-indolopyrrolidine gem-bisphosphonates (Scheme 42).[88] In this regard, they treated isatin with amino acids, such as L-proline **1**, or pipecolic acid **95** to generate azomethine ylides in the presence of montmorllonite catalyst for further reaction with tetraethyl vinylidenebis(phosphonate) **146**. According to the mechanism in Scheme 43, azomethine ylide **E** was formed through the release of H_2O and CO_2. Due to the stability of the negative and positive charges by the carbonyl unit and the electron lone pair of the nitrogen atom, **E** is the most stable



Ar^1	Ar^2	n	dr	Yield (%)
H	H	1	100:14	80
3-Cl	H	1	100:0	57
4-Me	Bn	1	100:17	47
H	H	2	100:46	65
Br	H	2	100:4	45
H	Bn	2	100:5	35

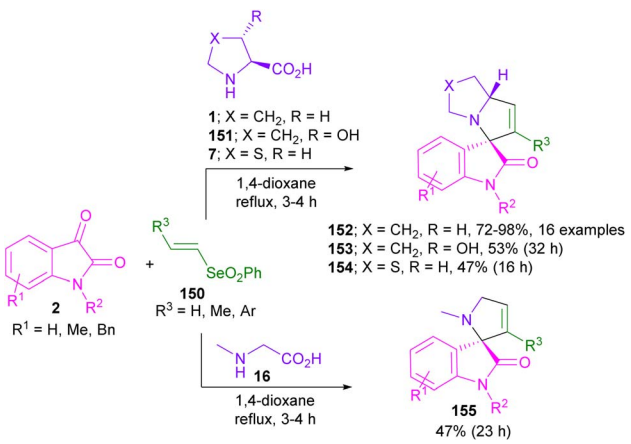
Scheme 42 Reaction of isatins, tetraethyl vinylidenebis(phosphonate), and amino acids.



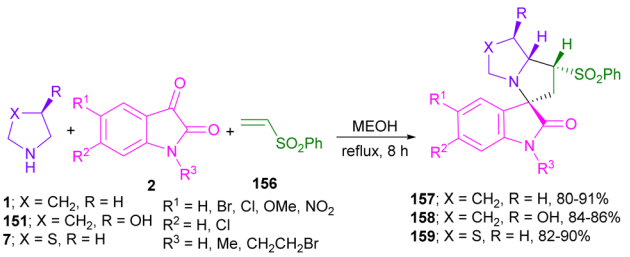
Scheme 43 Plausible mechanism for reaction of isatins, tetraethyl vinylidenebis(phosphonate), and amino acids.

resonance form that can participate in 1,3-DC with alkene **146** to yield product **147**.

Vinyl selenones **150** served as an efficient dipolarophile in (3 + 2)-cycloaddition with azomethine ylide to synthesize a wide variety of spiro-oxindolopyrrolizine derivatives **152–155** (Scheme 44).[89] The selenonyl group was able to activate the alkene and released as a leaving group in the form of benzeneseleninic acid. Several amino acids, such as L-proline **1**, L-thioproline **7**, *trans*-4-hydroxy-L-proline **151** and sarcosine **16** worked well in the condensation with isatins. In a variant of the same method, phenyl vinyl sulfones **156** were applied in 1,3-DC with isatins and amino acids to give spiro-oxindole-based phenylsulfones **157–159** (Scheme 45).[90] L-Proline **1**, *syn*-4-hydroxy-L-proline **151**, and L-thioproline **7** as amino acids were



Scheme 44 Reaction of isatin, amino acids and vinyl selenones.



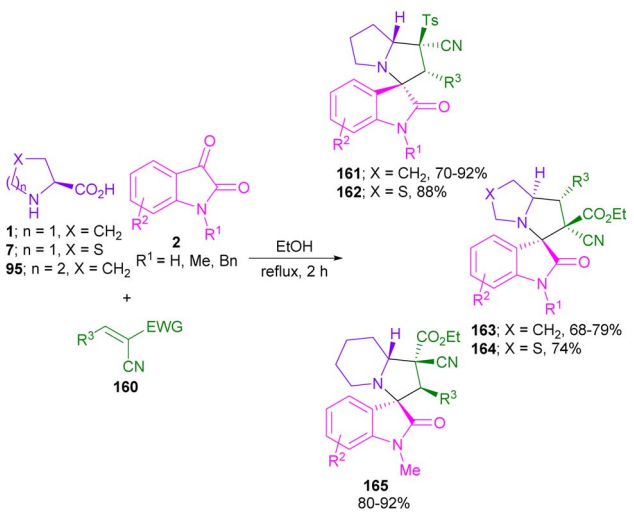
Scheme 45 Reaction of isatin, amino acids and phenyl vinyl sulfones.

participated in the reaction with substituted isatins to produce azomethine ylides. The final spiro products exhibited antiviral activity against SARS-CoV-2.

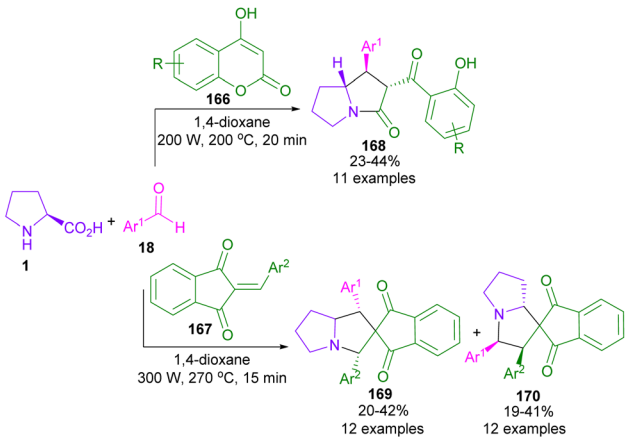
In 2022, conjugated arylcyanosulfones **160** were applied by Chen and Wang *et al.* for a 1,3-DC reaction with isatin and L-proline (Scheme 46).[91] Various 3,3′-pyrrolidinyl-spiro-oxindole structures were obtained depending on the steric effect between electron-withdrawing groups (EWG) and substituents (R^3) of the electrophilic substrates **160** in the formation of the final product. Therefore, the presence of *p*-toluenesulfonyl (Ts) as the EWG led to the formation of diastereomer **161** and **162** in the presence of L-proline, or L-thioproline. The replacement of Ts with CO_2Et gave diastereomer **163**, or **164**. The spiro products **165** were isolated when pipecolic acid was reacted with *N*-methyl isatins **2** and alkenes **160** bearing CO_2Et as the EWG. In contrast, the reaction was not significantly affected by the electronic effects of the functional groups on the substrates.

2.2. 1,3-Dipolar cycloadditions of proline and aldehydes with dipolarophiles

2.2.1. 1,3-Dipolar cycloadditions with diones as dipolarophiles. In 2016, Yang and co-workers found that the microwave can accelerate the multi-component reaction of L-proline, aryl/heteroaryl aldehydes, and 1,3-diketones (Scheme 47).[92] Two different dipolarophiles, such as 4-hydroxycoumarins **166** and



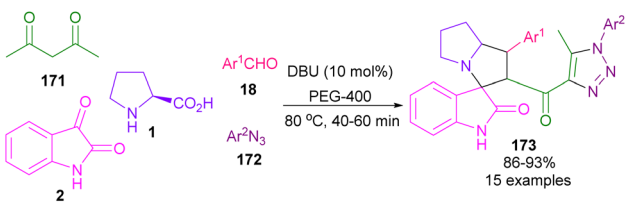
Scheme 46 Reaction of isatins, amino acids and conjugated arylcyanosulfones.



Scheme 47 Reaction of L-proline, aryl aldehydes, and 1,3-diketones.

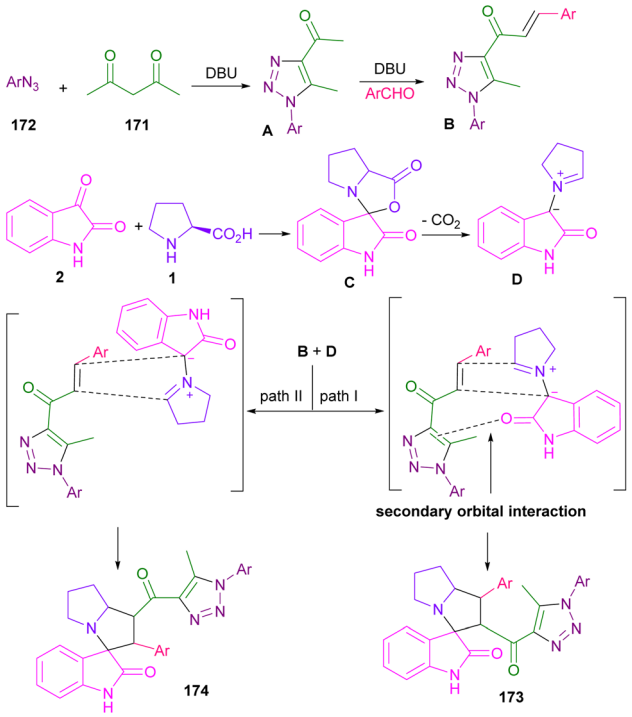
2-arylmethylene-indene-1,3-diones **167** were employed to make pyrrolizidines and pyrrolizinones. It should be noted that the performance of the multi-component reaction in the presence of 1,3-indanedione **166** using thermal conditions resulted in lower yields of products at longer reaction times (15% of **169**, 15% of **170** after 1 h). This transformation was accomplished *via in situ* generation of azomethine ylide from L-proline and aryl aldehyde, followed by (3 + 2)-cycloaddition in the presence of **167**, or Michael addition using **166** as a dipolarophile.

In 2016, the Askri and Kumar research groups used isatin and L-proline to synthesize spiro-oxindolopyrrolizidine derivatives through the reactions of azomethine ylides with (*E*,*E*)-1,3-bis(arylidene)indan-2-one,[93] or acrylonitrile/methyl acrylate[94] as a dipolarophile. Meantime, Khurana *et al.* presented a one-pot five-component reaction for the assembly of triazolyl spirocyclic oxindole frameworks (Scheme 48).[95] In their protocol, isatin **2**, L-proline **1**, aryl azides **172**, aryl aldehydes **18**, and acetylacetone **171** were used as starting reactants and the reaction was carried out in the presence of DBU as a catalyst. The authors suggested a tentative mechanism for this five-component reaction, involving the formation of triazole **A** *via* the interaction of acetylacetone and azide in the presence of



Ar^1	Ar^2	Time (min)	Yield (%)
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	40	93
4-MeC_6H_4	4-$NO_2C_6H_4$	55	87
4-MeC_6H_4	4-MeC_6H_4	60	86
4-$NO_2C_6H_4$	3-Cl-4-FC_6H_3	40	90
4-BrC_6H_4	4-BrC_6H_4	50	89
4-$NO_2C_6H_4$	7-Chloroquinoline	40	91
4-MeC_6H_4	7-Chloroquinoline	55	87

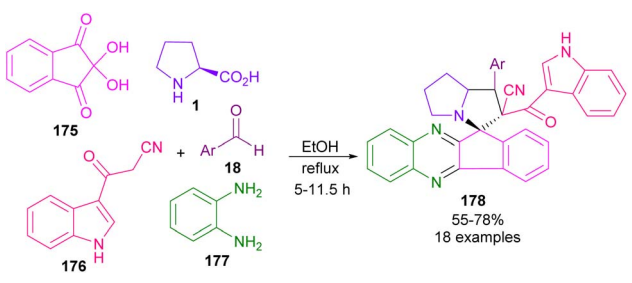
Scheme 48 Multi-component reaction of isatin, L-proline, aryl azides, aryl aldehydes, and acetylacetone.



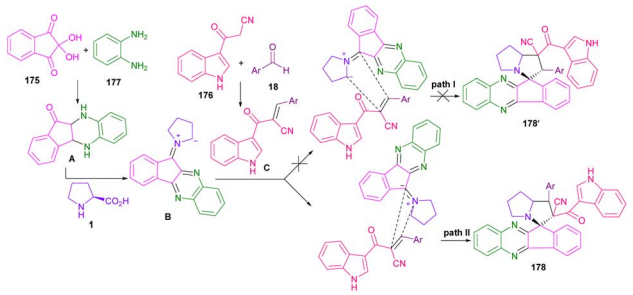
Scheme 49 Tentative mechanism for reaction of isatin, L-proline, aryl azides, aryl aldehydes, and acetylacetone.

a base. Then, **A** was subjected to the aldol condensation in the presence of aryl aldehyde to form chalcone **B**. At the same time, the condensation of isatin with L-proline, followed by the decarboxylation yielded **D**, which then underwent (3 + 2)-cycloaddition with **B** through two possible pathways. In path I, the intermediate was stabilized by a secondary orbital interaction between the double bond of the triazole ring and the carbonyl group of isatin in TS, which afforded product **173**. While, in path II, there was no such stabilization and product **174** was not observed in the reaction (Scheme 49).

An elegant multi-component strategy, including dione-ninhydrin **175**, *ortho*-phenylenediamine **177**, L-proline **1**/sarcosine **16**, aryl aldehyde **18** and 3-cyanoacetyl indole **176** for the synthesis of spiro-pyrrolidines and spiro-pyrrolizidines **178** was disclosed by Zhu and co-workers in 2018 (Scheme 50).[96] They treated these five reactants in EtOH as a benign solvent under reflux conditions to achieve polycyclic spiro compounds in a one-pot fashion. The reaction started with the condensation of



Scheme 50 Reaction of ninhydrin, 1,2-phenylenediamine, amino acids, 3-cyanoacetyl indoles and aryl aldehydes.

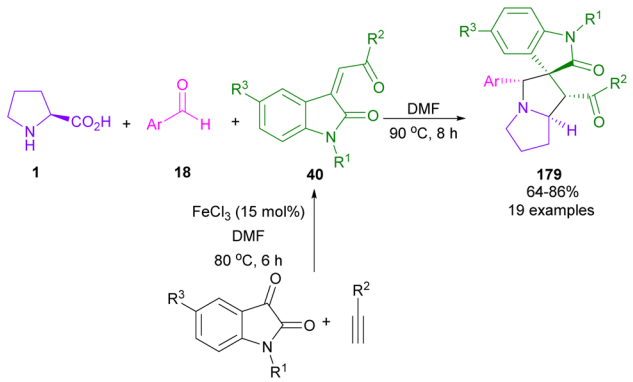


Scheme 51 Proposed mechanism for reaction of ninhydrin, 1,2-phenylenediamine, amino acids, 3-cyanoacetyl indoles and aryl aldehydes.

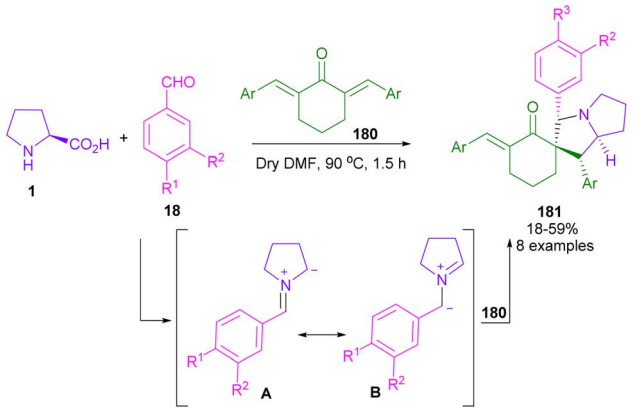
ninhydrin **175** with diamine **177** to give indenoquinoxaline-11-one **A**, which could react with amino acid **1** to obtain azomethine ylide **B**. Meantime, Knoevenagel reaction between indole **176** and aldehyde **18** gave adduct **C**, which underwent 1,3-DC with **B** to deliver product **178** (Scheme 51). Another use of dione-ninhydrin and isatin in the generation of azomethine ylides from amino acids was observed in the Koodlur report.[97] In this work, 1,3-DC was carried out in the presence of isatin/dione-ninhydrin, amino acids (L-proline, L-thioproline, or sarcosine), and ethynyl azaindole as a dipolarophile.

2.2.2. 1,3-Dipolar cycloadditions with indolines as dipolarophiles. In 2018, Mukhopadhyay and Basu found that spiro-oxindolopyrrolizidines **179** could be prepared from the 1,3-DC of azomethine ylides with (*E*)-3-(2-oxo-2-arylethylidene)indolin-2-ones **40** as dipolarophiles (Scheme 52).[98] For the synthesis of dipoarophiles, they first treated isatin and internal alkynes in the presence of $FeCl_3$ as a catalyst. In the next stage, the cycloaddition reaction was conducted in the presence of L-proline, aryl aldehydes, and activated alkene **40** in DMF as the optimal solvent. The reaction efficiency was moderate in the EtOH, MeCN, and $MeNO_2$ and very low in toluene and THF as solvents.

2.2.3. 1,3-Dipolar cycloadditions with chalcones as dipolarophiles. In 2015, Banerji and Gayen were able to synthesize a new class of spiro-pyrrolizidine compound **181** by the azomethine ylide formation from aryl aldehydes **18** and L-proline **1** (Scheme 53).[99] This intermediate then reacted with diaryl



Scheme 52 Reaction of isatin, L-proline, and (*E*)-3-(2-oxo-2-arylethylidene)indolin-2-ones.



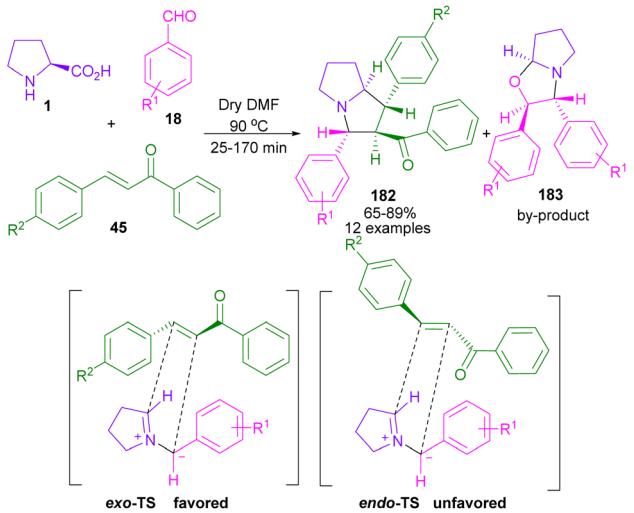
Scheme 53 Cycloaddition of isatin, amino acids and dibenzylidene cyclohexanone.

cyclohexanone under regio-, and stereoselective cyclization. It was seen that one of the double bonds in the dipolarophile remain unaffected. A year later, Banerji *et al.* used aryl aldehydes **18** to form azomethine ylides from L-proline **1** (Scheme 54).[100] In the next phase, they treated chalcone **45** with these imine intermediates to make tri-substituted pyrrolizidines and di-substituted oxazolidines. Pyrrolizidines **182** were obtained as the main products from (3 + 2)-cycloaddition of azomethine ylide with chalcone, while oxazolidines **183** were identified as by-products because of cycloaddition of azomethine ylides with the second molecule of aryl aldehyde. DFT calculations revealed an *exo*-TS as the favored TS in 1,3-DC of azomethine ylide to chalcone.

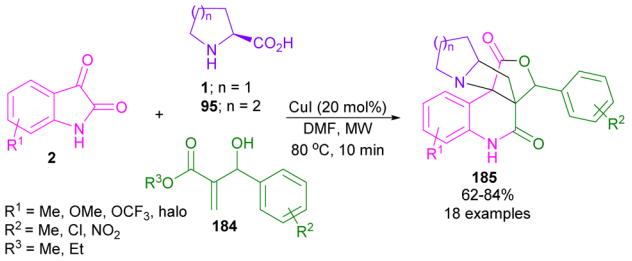
3. 1,3-Dipolar cycloadditions for synthesis of fused-oxindoles

3.1. 1,3-Dipolar cycloadditions of proline and isatins with dipolarophiles

In 2020, Reddy and co-workers described a microwave-assisted 1,3-DC of azomethine ylide with Baylis–Hillman adducts **184**



Scheme 54 Reaction of arylaldehydes, L-proline and chalcones.



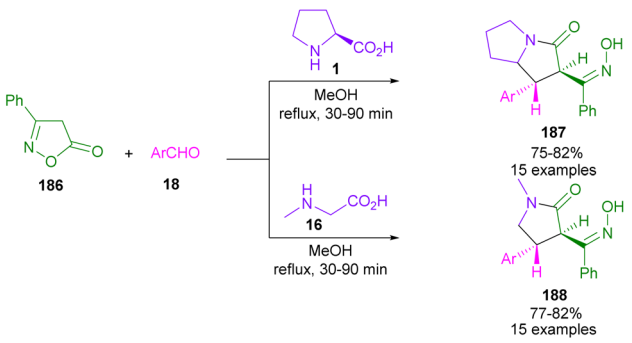
Scheme 55 Reaction of isatin, amino acids and Baylis–Hillman adducts.

(Scheme 55).[101] In this strategy, a new class of fused 2-quinolinones **185** were constructed from isatins **2**, α-amino acids **1**, or **95**, and the activated alkenes **184** under MW irradiation. CuI could catalyze the condensation of isatin and amino acid to azomethine ylide. Comparison of conventional and MW methods showed that the reaction in an oil bath takes 12 h, while 10 min in the presence of MW is sufficient to complete the reaction.

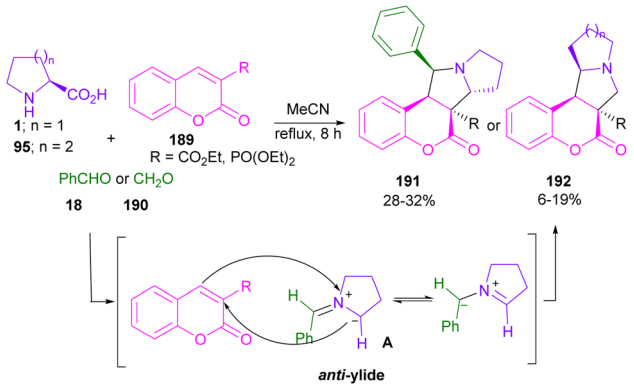
3.2. 1,3-Dipolar cycloadditions of proline and aldehydes with dipolarophiles

In 2013, Perumal *et al.* developed a three-segment approach, including aryl aldehydes, 3-phenyl-5-isoxazolone, and secondary amino acids (Scheme 56).[102] When L-proline **1** reacted with aryl aldehyde **18** and 3-phenyl-5-isoxazolone **186**, pyrrolizidinones **187** were obtained, while pyrrolidinone scaffolds **188** were isolated using sarcosine **16** as an amino acid reactant. In another work, the reaction of amino acids **1**, or **95**, aldehydes **18**, or **190** and 2-substituted coumarins **189** resulted in the formation of 1-benzopyrano[3,4-*c*]pyrrolidine frameworks **191**, **192** through the 1,3-DC process (Scheme 57).[103] Various benzopyranopyrrolidines were prepared from the addition of anti-ylide of **A** to coumarin.

In 2014, Yang and co-workers developed a microwave-promoted reaction of L-proline with aryl aldehydes, and 1,3-diketones, such as 4-hydroxycoumarin and pyran (Scheme 58).[104] Interestingly, when 2.0 equivalents of aryl aldehyde **18** were used, a series of highly functionalized pyrano[2,3-*b*] pyrroles **194**, **195** were constructed, while the stereoselective



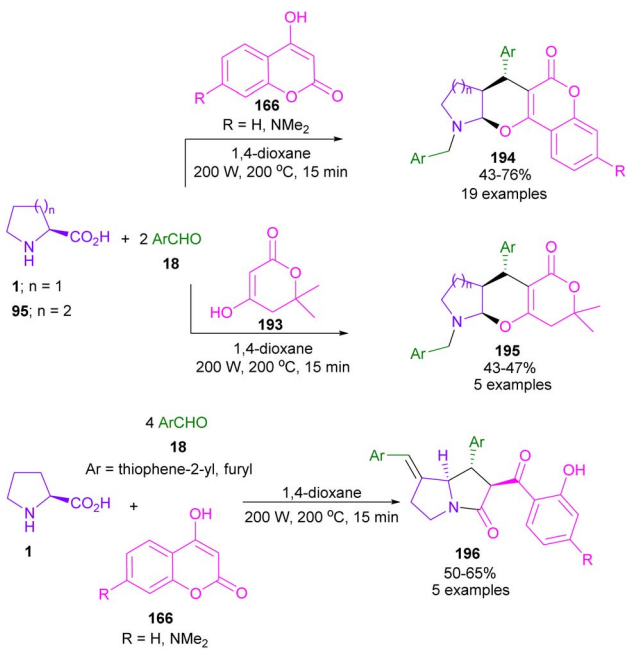
Scheme 56 Reaction of aryl aldehydes, 3-phenyl-5-isoxazolone and secondary amino acids.



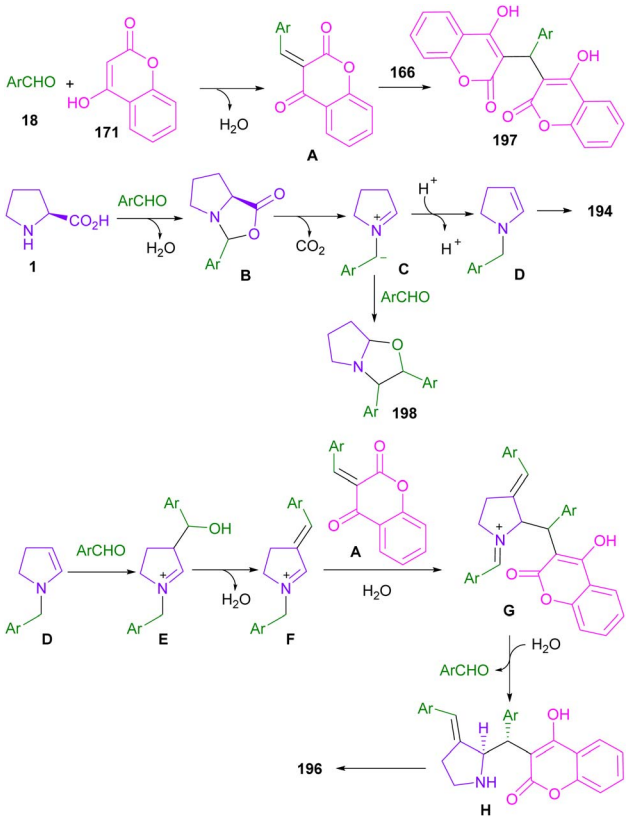
Scheme 57 Reaction of amino acids, aldehydes and coumarins.

formation of pyrrolizinones **196** was achieved in the presence of 4.0 equivalents of thiophene, or furan carbaldehyde **18** under MW conditions. Not only proline **1**, but also pipecolic acid **95** was included in this α,β-difunctionlization reaction. The researchers showed that azomethine ylide can be produced by MW-promoted decarboxylative coupling of L-proline and aryl aldehyde. This intermediate then underwent proton-mediated isomerization to enamine **C**, or **D**. Depending on the concentration of aryl aldehyde, enamine can give two different products. Enamine **D** was subjected to the attack of **A**, followed by the cyclization to afford pyrano[2,3-*b*]pyrrole **194**. While the condensation of enamine **D** with aryl aldehyde and subsequent conjugate addition with **A** delivered pyrrolizinone **196** (Scheme 59).

In 2016, Higashi and Arimitsu *et al.* reported the synthesis of trifluoromethylated pyrrolizidines **200** from L-proline **1**, aryl



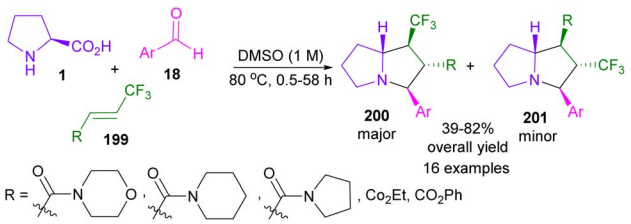
Scheme 58 Microwave-promoted reaction of amino acids, aldehydes, and 1,3-diketones.



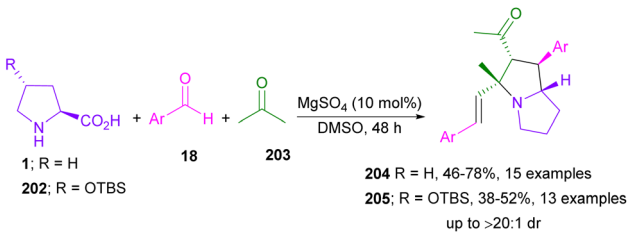
Scheme 59 Proposed mechanism for MW-promoted reaction of amino acids, aldehydes, and 1,3-diketones.

aldehydes **18**, and β-trifluoromethyl acrylamide **199** (Scheme 60).[105] With the assistance of DFT calculations, the researchers were able to identify the reason for excellent diastereoselectivity (>20 : 1) and moderate regioselectivity (up to 5.9 : 1) observed in products. The use of L-proline and aldehydes in the synthesis of bicyclic hexahydropyrrolo[1,2-*c*]oxazol-1-ylphosphonates starting from acylphosphonates was also reported in Subasi's report.[106]

In 2018, the Wei laboratory succeeded in synthesizing multifunctionalized pyrrolizidines **204** through the 1,3-DC between aryl aldehydes **18**, L-proline **1**, and acetone **203** (Scheme 61).[107] In addition to L-proline **1**, (2*S*,4*R*)-4-OTBS-proline **202** was amenable to this transformation. The reaction involved the formation of enamine **A** from oxazolidinone. The aldol addition and the aldol condensation can both occur to render **B** and **D**,



Scheme 60 Reaction of L-proline, aldehydes, and β-trifluoromethyl acrylamide.

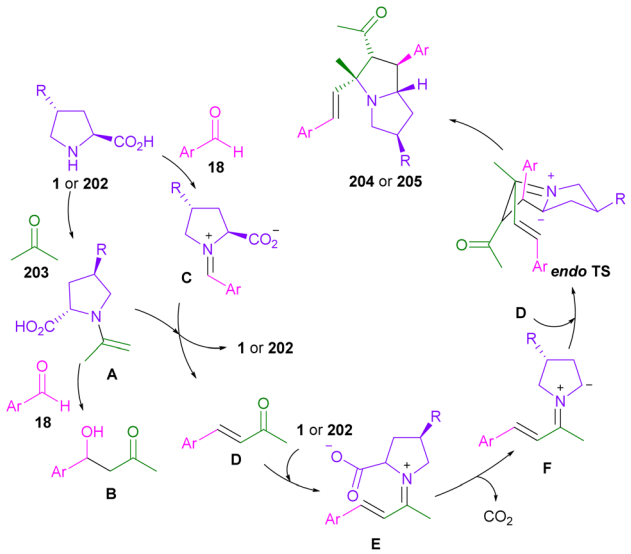


Scheme 61 Reaction of amino acids, aryl aldehydes and ketone.

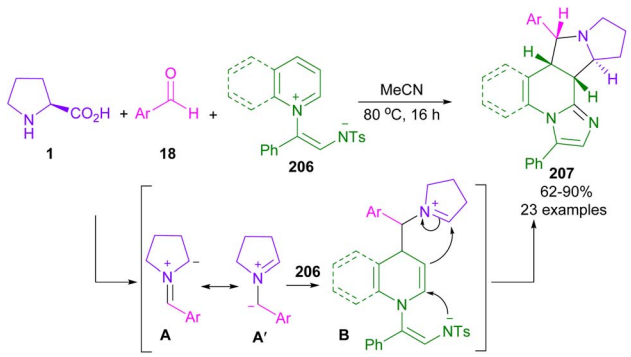
respectively. The aldol condensation pathway was promoted by $MgSO_4$. In the next step, the iminium salt **E** was produced from the condensation of L-proline and α,β-unsaturated ketone **D**. The decarboxylation of **E** resulted in azomethine ylide **F**, followed by 1,3-DC with **D** to yield the *endo*-product **204**, or **205** (Scheme 62).

A year later, in another work, Yoo *et al.* used L-proline **1** and aryl aldehydes **18** for the generation of azomethine ylides **A**, or **A′** for further reaction with a series of N-aromatic zwitterions **206** *via* (3 + 2)-annulation reaction (Scheme 63).[108] Polycyclic fused pyrrolizidines **207** were constructed through the formation of azomethine ylide **A′** against **A**, followed by intramolecular cyclization with **206** to obtain intermediate **B**. It was obvious that the electron deficiency of aryl aldehyde (Ar = 4-$NO_2C_6H_4$) causes stability in intermediate **A′**.

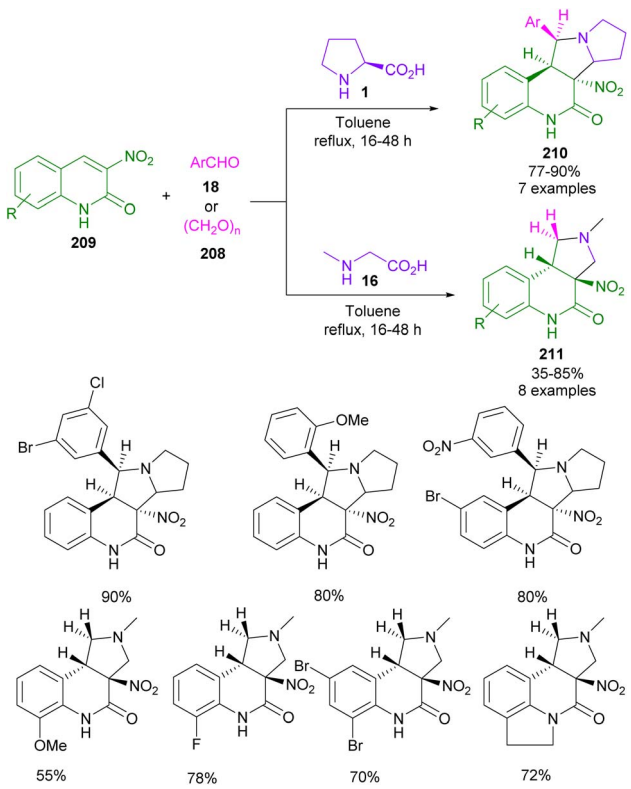
In 2023, Nyerges and co-workers developed an approach for the preparation of unprecedented pyrrolo[3,4-*c*]quinolinone derivatives from azomethine ylides (Scheme 64).[109] In this procedure, L-proline **1**, or sarcosine **16** were treated with aryl aldehyde **18**, or formaldehyde **190** to produce azomethine ylide. Then, this dipole intermediate was added to 3-nitro-2(1*H*)-quinolinone **209** to give an *anti-endo* isomer of 3*a*-nitro-4-oxo-1,2,3,3*a*,5,9*b*-hexahydropyrrolo[3,4-*c*]quinoline-4-ones **210**, and **211** in a regio-, and stereoselective manner as the only



Scheme 62 Possible mechanism for reaction of amino acids, aryl aldehydes and ketone.



Scheme 63 Reaction of N-aromatic zwitterions, aldehydes, and amino acids.



Scheme 64 Reaction of isatin, amino acids and 3-nitro-2(1*H*)-quinolinone.

cycloadduct. However, aryl aldehyde with a large *ortho*-substituent near the reaction centre showed a direct effect on the stereochemistry of the cycloaddition, where a *syn-endo* isomer was also observed as the other diastereomer.

4. Conclusions

The remarkable features of L-proline have made this α-amino acid an appropriate candidate for 1,3-dipolar cycloaddition reactions. Due to the presence of carboxylic acid and amine functional groups, L-proline can easily react with 1,2-dicarbonyl compounds to produce azomethine ylide for further reaction

with various organic dipolarophiles. In this context, we have covered important L-proline incorporations in 1,3-DC reactions. Most of these reactions are carried out under mild conditions without the need for catalysts, oxidants, or additives. Methanol and ethanol are commonly used organic solvents in these 1,3-DC reactions. In most reports, products are obtained in high yields with good regio-, and diastereoselectivity. Despite great advances in the azomethine ylide cycloadditions, various functionalized dipolarophiles for the preparation of enantioenriched bioactive spiro-oxindole scaffolds remain unexplored. Moreover, the combination of radical approaches, such as visible-light and electrochemistry with azomethine ylide reactions may lead to better results in the reaction rate and efficiency.

Conflicts of interest

There are no conflicts to declare.

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