

RECENT ADVANCES IN THE SYNTHESIS OF SPIROCYCLIC COMPOUNDS

Abstract

The synthesis of spirocycles has attracted organic chemists over recent years as a result of their striking biological properties and the difficulty in synthesizing them. The aim of this chapter is to summarize potent biological activities exhibited by spirocyclic compounds and the recent diverse chemical approaches used in their synthesis. This may pave the way for superior approaches towards the synthesis of these compounds and thus, help in further drug development.

Keywords: heterocyclic compounds; spirocycles; quaternary carbon

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I. INTRODUCTION

With its origins rooted in organic synthesis and medicinal chemistry, heterocyclic compounds form a class of organic compounds which contains at least one heteroatom like sulphur, nitrogen and oxygen in its structure. Heterocyclic compounds are widespread in nature and occur in various forms. They are the building blocks of a variety of natural products. Moreover heterocyclic compounds are the fundamentals of life such as DNA, RNA, haeme derivatives in blood and chlorophyll for photosynthesis [1]. During the last decades, synthesis and transformations of heterocyclic fused rings, especially that of spirocycle, have received considerable attention owing to their remarkable and expanded applications and poised them as cornerstones in the field of pharmaceutical chemistry. The reason behind the extensive applications of heterocyclic compounds lies in their structural modification i.e., their structure can be formulated as required and these structural changes lead to some fruitful biological activities of the compounds.

Spirocyclic compounds are three dimensional bicyclic molecules that present a twisted structure of two ring systems with just one shared atom between two rings (the spiroatom). The presence of the tetrahedral sp^3 spiro carbon leads to the orthogonal arrangement of the planes of the two spirocyclic rings. Spirocyclic structure was first created by Von Bayer in 1900 as a hydrocarbon compound consisting of two fused rings connected by a quaternary carbon atom and proposed the name of the synthesized compound as spirocyclane [2]. Due to asymmetric characteristic of the molecule, spirocyclic compounds have been found to play an important role in several biological processes. These compounds exhibit diversified biological, pharmacological and therapeutic properties. When a spirocyclic compound is compared to an analogous monocyclic ring system, a spirocyclic ring system tends to have lower lipophilicity which is responsible for the pharmacokinetic properties in drug candidates and less number low energy conformations for the ring [3,4]. Additionally, spirocyclic compounds exhibit improved metabolic stability and solubility in aqueous solutions as compared to their monocyclic structures [5]. These factors have contributed significant advances towards the controlled synthesis of spirocyclic compounds. Spirocyclic compounds are conformationally rigid and at the same time, they are flexible enough, which relieves them from permeability and absorption issues [6,7]. This facilitates their incorporation in molecules which exhibits striking pharmacological properties such as anticancer, anti-Alzheimer's, antioxidant [8-10]. Spirocyclic scaffolds are present in a variety of architecturally complex natural products which display excellent pharmacological activity against various biological targets including receptors and enzymes as well as against acute thrombosis [11], hypertension [12], and tumor growth [13]. A broad overview of the related activities is discussed below:

II. BIOLOGICAL ACTIVITIES OF SPIROCYCLIC COMPOUNDS

1. Antimicrobial activity: Spirocyclic moieties present in both natural and pharmaceutical compounds display wide range of antibacterial activity. Exiguaquinol (**1**) is the first natural product that was isolated from Australian sponge *Neopetrosia exigua* and has the potential to inhibit *Helicobacter pylori* glutamate racemase MurI [14]. Gamma-rubromycin (**2**), isolated from the culture broth of *Streptomyces* sp. Al originating from orange grove soil samples collected from Israel, showed marked inhibitory function against a range of Gram-positive bacteria, particularly *Bacillus subtilis* and *Staphylococcus aureus* as well as Gram-negative bacteria such as *Escherichia coli* Fig 1

[15,16]. Purpuromycin (**3**), containing a spiroketal ring system, was first isolated from *Actinoplanes ianthinogenes* and was found to exhibit antimicrobial activity against various bacterial strains including *Staphylococcus aureus*, fungi and protozoa [17]. In fungi, the activity is due to inhibition of RNA synthesis. The compound displays excellent activity against *Gardnerellavaginalis*, *Candia albicans* and *Trichomonasvaginalis*, which are the pathogens of common vaginal infections [18]. Phomopsichalasin (**4**), isolated from *Phomopsis* sp., is also known for its antimicrobial activities (Figure 1) [19].

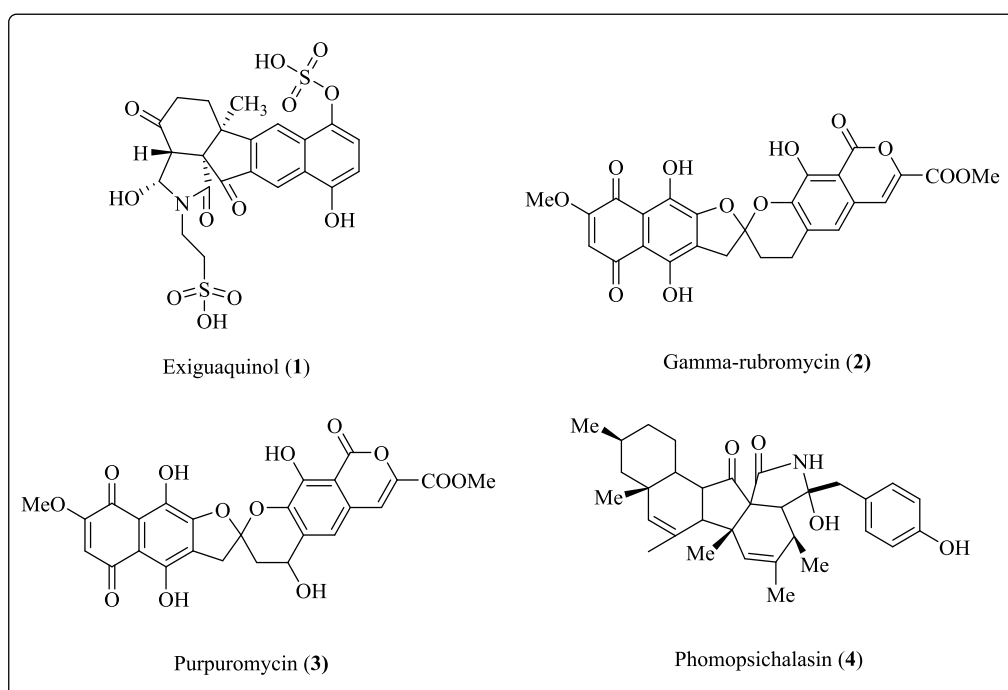


Figure 1: Spirocyclic compounds exhibiting antimicrobial property

2. Chemotherapeutic property: Spiro compounds are also known for their cytotoxicity and play a fundamental role in cancer chemotherapy Cephalostatin I (**5**), which is isolated

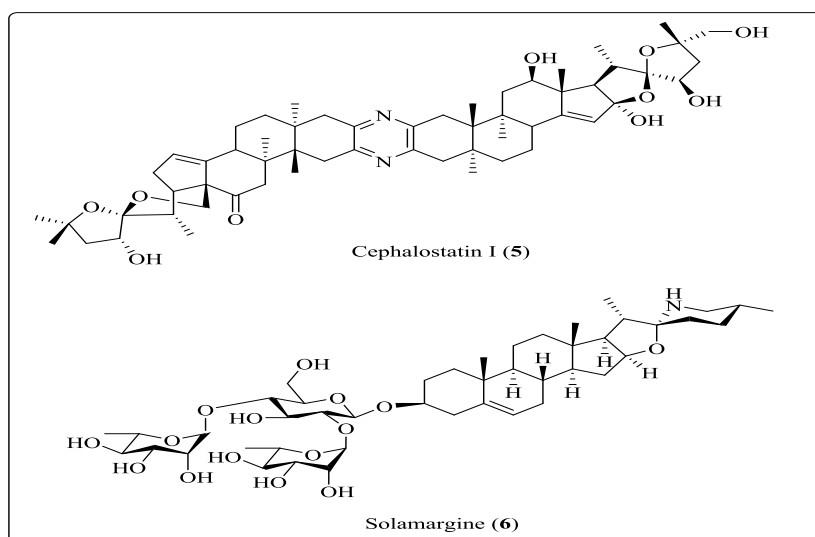


Figure 2: Spirocyclic compounds exhibiting chemotherapeutic property

from the marine worm *Cephalodiscus gilchristi*, contains two highly oxygenated steroidal spiroketal units linked by a central pyrazine ring and display potent cytotoxic activity [20]. Solamargine (6), a steroidal alkaloid glycoside, is highly efficacious against melanomas in preliminary clinical trials without significant side effects or recurrence of cancer 10 years after treatment [21]. The promising anticancer activity of solamargine (6) along with unique mode of action implies its applicability in the treatment of drug-resistant cancers (Figure 2).

- 3. Anti-inflammatory property:** Cynandione B (7), isolated from the rhizome of *Cynanchum taiwanianum*, is a 6,6-monobenzannulated spiroketal exhibiting potent anti-inflammatory property by inhibiting neutrophil activation [22]. A synthetic spirocyclic compound 8 is a potent CCR1 (chemokine receptor) antagonists that participates actively in the treatment of chronic inflammatory diseases (Figure 3) [23].

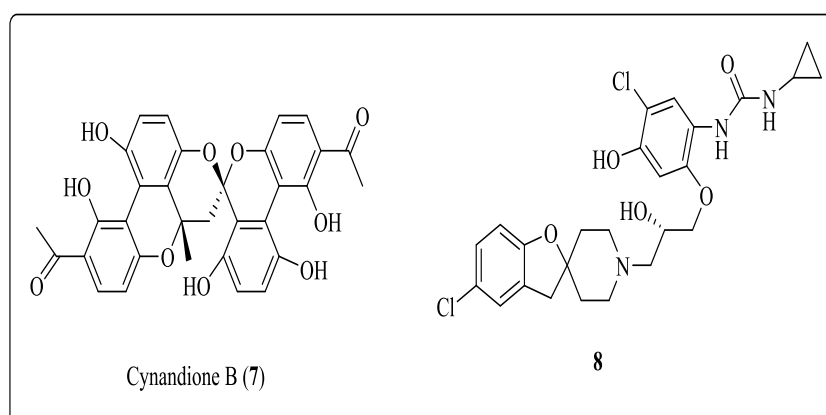


Figure 3: Spirocyclic compounds exhibiting anti-inflammatory property

- 4. Anti-HCV property:** Hepatitis C is a liver infection and is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. MK-8831 (9), possessing a novel

spirocyclic- proline motif, is a potential hepatitis C (HCV) protease inhibitor [24]. Another synthetic spirocycle **10** is a potent HCV NS5A inhibitor and represents a different type of therapy for treatment of hepatitis C viral infection (Figure 4) [25].

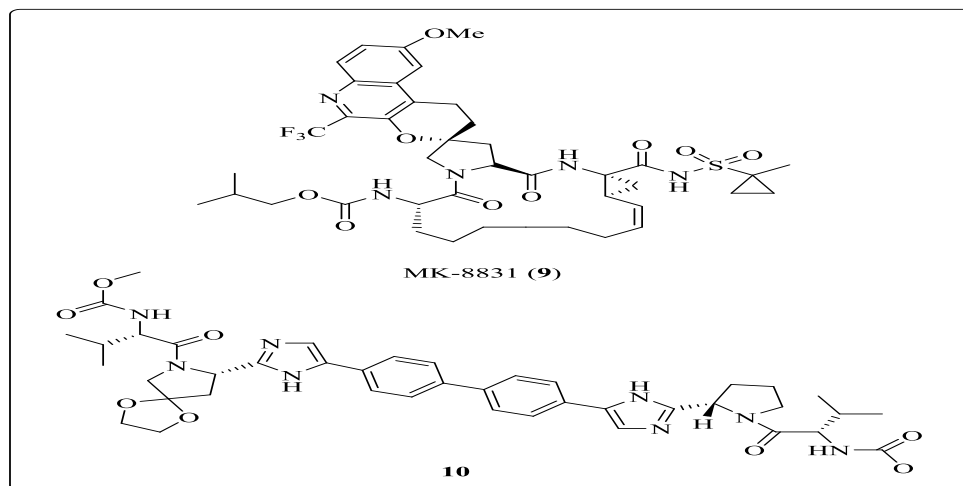


Figure 4: Examples of some spirocyclic compounds exhibiting anti-HCV property

- 5. Photochromic property:** Spiropyrans are one of the most widely studied classes of photochromic materials due to their equilibrating cyclic and acyclic structures and the intense absorption of the colored form in the visible region [26,27]. The unique property of spiroyrans **11** and **12** to exhibit the phenomenon of photochromism upon irradiation by photons has been used for the study of liquid crystals [28]. Photolysis of light-yellow solution of spirobenzothiapyran **13** in polar solvents like methanol and acetone results in color change of the solution to blue-green (Figure 5) [29].

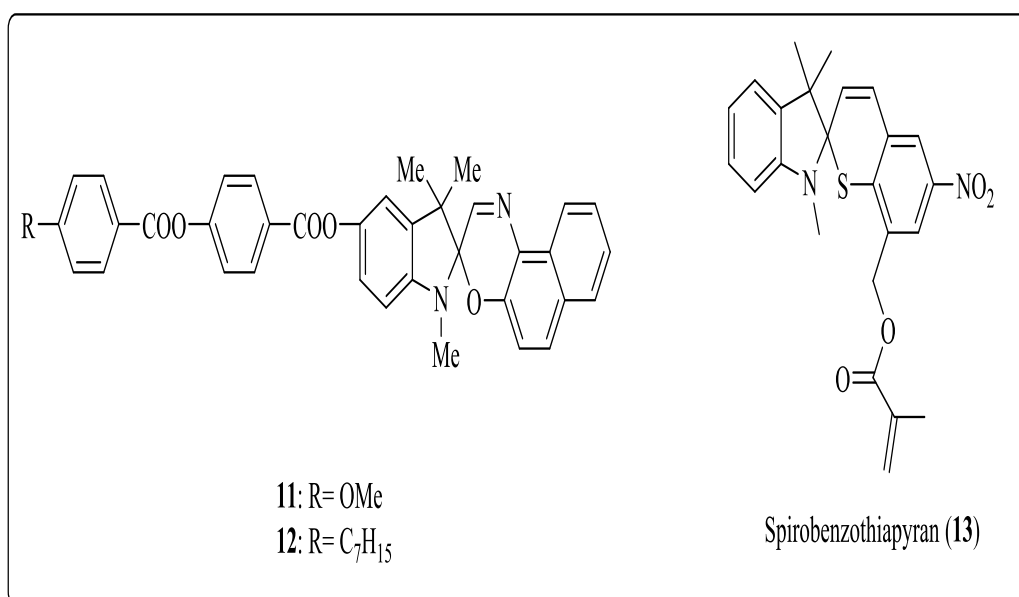
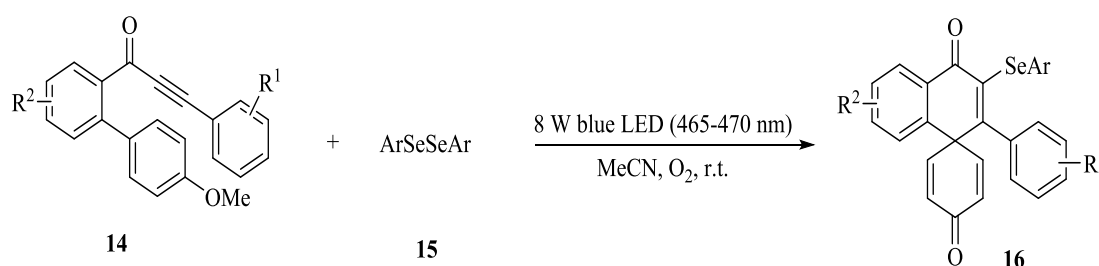


Figure 5: Examples of some spirocyclic compounds exhibiting photochromic property

III. REPORTED PROCEDURES FOR THE SYNTHESIS OF SPIROCYCLIC COMPOUNDS

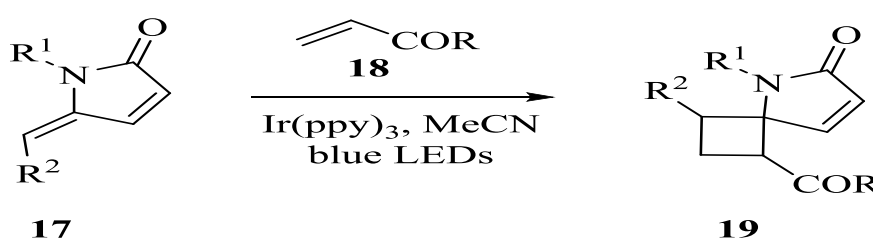
Over the years, organic chemists are in continuous resonance for the synthesis of the myriad of biologically important moieties containing spirocyclic framework. Several strategies have been developed towards the synthesis of these spirocyclic scaffolds, which includes (a) metal-catalyzed spirocyclization, (b) intermolecular double substitutions, (c) intramolecular substitutions, (d) cycloaddition reactions, (e) intramolecular arrangements, and (f) radical cyclizations. In order to provide flavor of these reports, few fruitful recent results on fabrication of various spirocyclic building blocks of valuable molecules by utilizing various reaction strategies have been discussed below.

In a very recent report, Chen and group carried out the synthesis of selenated spiro[5.5]trienones **16** by reacting biaryl ynones **14** with diselenides **15** under green conditions (Scheme 1) [30].



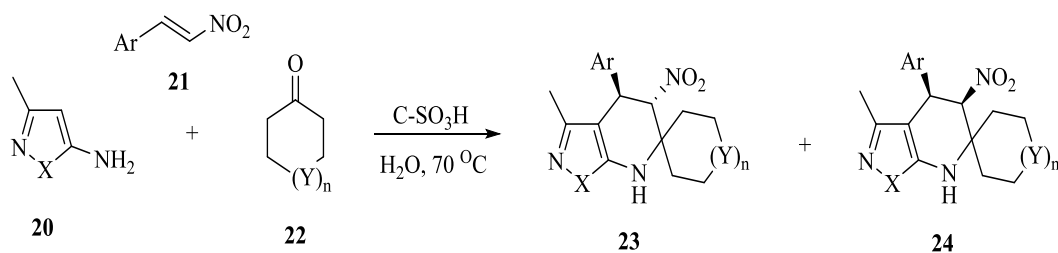
Scheme 1: Synthesis of selenated spiro[5.5]trienones by treating biaryl ynones with diselenides

In a report by Kalaitzakis and team, photocatalyzed [2 + 2]-cycloadditions was carried out between γ -alkylidene- γ -lactams **17** and unsaturated substrates **18** leading to the formation of saturated spirocyclic compounds **19** (Scheme 2) [31].



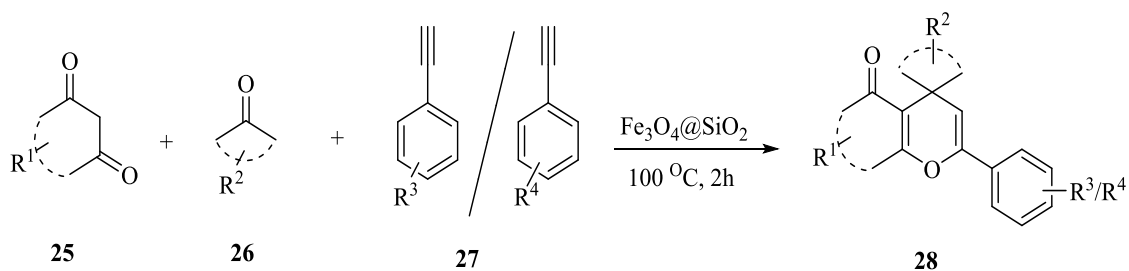
Scheme 2: Synthesis of saturated spirocyclic compounds by photocatalyzed [2 + 2]-cycloadditions reaction

Zhang and team members developed an efficient method for the one-pot three component reaction between an amine **20**, unsaturated nitro compound **21** and cyclic ketone **22** leading to the formation of spirocycloalkane fused pyrazolo[3,4-*b*]pyridine derivatives **23** and **24** (Scheme 3) [32].



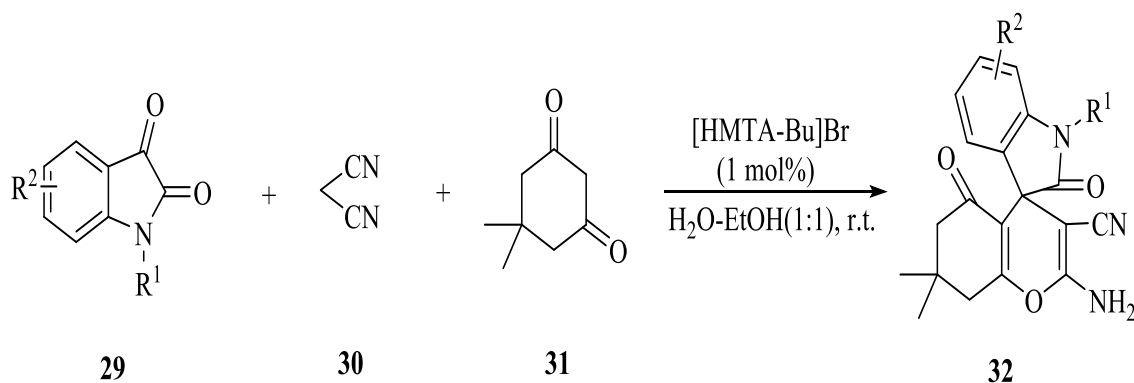
Scheme 3: Synthesis of spirocycloalkane fused pyrazolo[3,4-*b*]pyridine by reacting an amine and an unsaturated nitro compound with a cyclic ketone

In a report by Suri and team members, a one-pot domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction was carried out by treating 1,3-dicarbonyl **25**, ketones **26** and alkenes/alkynes **27** in the presence of magnetically separable silica (Fe₃O₄@SiO₂) catalyst under solvent-free condition leading to the spirocyclic chromenones **28** (Scheme 4) [33].



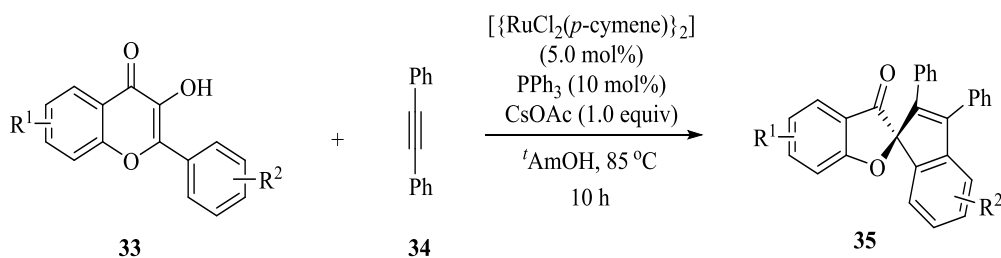
Scheme 4: Synthesis of spirocyclic chromenones by domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction

In a recent report, Li and team members carried out the reaction of isatin **29** with malononitrile **30** and enol derivatives **31** for the synthesis of spiro[4*H*-pyran-3,3'-oxindoles] **32** catalyzed by [HMTA-Bu]Br in aqueous ethanol solution (Scheme 5) [34].



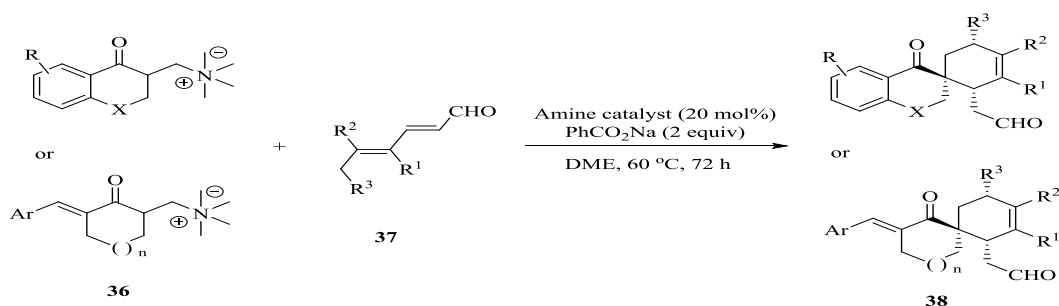
Scheme 5: Synthesis of spiro [4*H*-pyran-3, 3'-oxindoles] by reacting isatin with malononitrile and enol derivatives in the presence of [HMTA-Bu]Br catalyst

Very recently, Gogoi and his team developed a highly efficient decarbonylative cycloaddition reaction of 3-hydroxy-2-phenylchromones **33** with alkynes **34** accelerated by Ru-catalyst to yield spiro benzofuranones **35** (Scheme 6) [35].



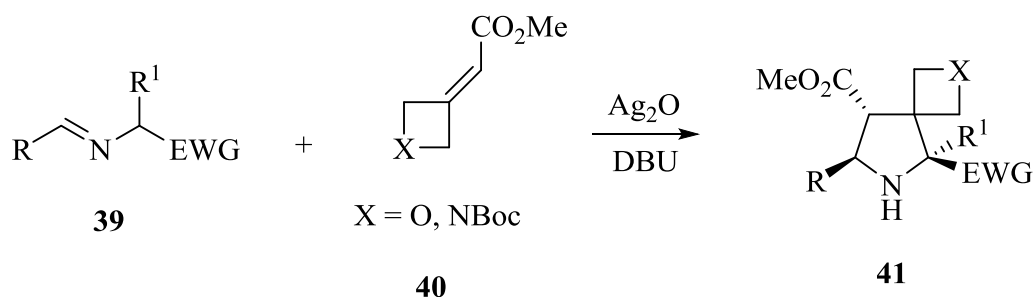
Scheme 6: Synthesis of spiro benzofuranones by decarbonylative cycloaddition reaction

A novel method was developed by Zhang and group members for the construction of a spectrum of spirocyclanes **38** through exo-Diels-Alder reaction of α -methylene carbonyl compounds, generated *in situ* from stable methiodide salts of Mannich bases **36**, with 2, 4-dienals **37** via trienamine activation of a chiral secondary amine (Scheme 7) [36].



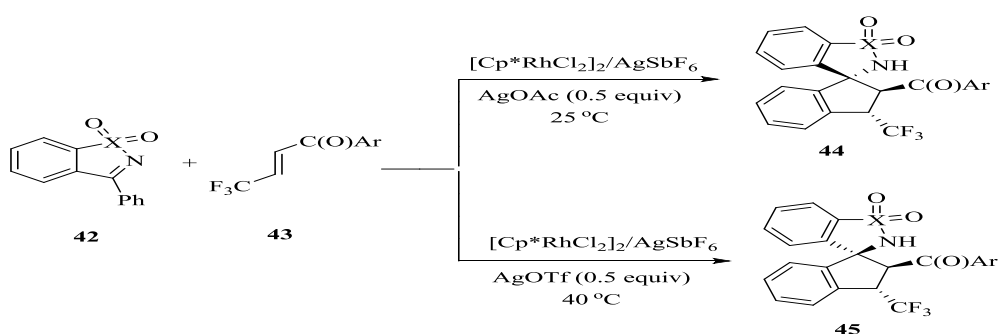
Scheme 7: Synthesis of spirocyclanes through exo-Diels-Alder reaction

A facile 1,3-dipolar cycloaddition reaction between imine **39** and methyl-(oxetane/azetidine-3-ylidene)acetate **40** as dipolarophile catalyzed by silver was developed by Jones and co-workers which afforded oxetane/azetidine containing spirocycles **41** in moderate to good yield (Scheme 8) [37].



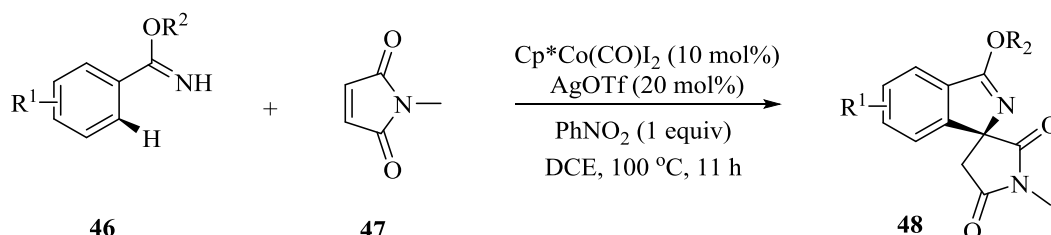
Scheme 8: Synthesis of oxetane/azetidine containing spirocycles through 1,3-dipolar cycloaddition reaction catalyzed by silver

Li's group developed an efficient strategy of Rh (III)-catalyzed [3+2] annulation of cyclic N-sulfonyl or N-acyl ketimines **42** with activated alkenes **43** via C-H activation pathway to construct a library of spirocycle molecules **44** and **45** (Scheme 9) [38]. Interestingly, the stereochemistry of the product could be controlled by maintaining the temperature of the reaction.



Scheme 9: Synthesis of spirocyclic compounds via C-H activation pathway

Lv and group members reported an oxidant-free synthesis of spirocyclic compounds **48** by cobalt-catalyzed reaction between benzimidates **46** and maleimides **47** using nitrobenzene as promoter (Scheme 10) [39].



Scheme 10: Cobalt catalyzed synthesis of spirocyclic compounds

Jagadeesh and co-workers recently employed a novel $\text{BF}_3\cdot\text{OEt}_2$ catalyzed Prins cascade strategy for the stereoselective synthesis of spiro-oxindole derivatives **51** and **52**, by coupling 4-hydroxy-N-methyl-2-methylene-N-phenylbutanamide (**49**) with aldehydes **50** (Scheme 11) [40].



Scheme 11: Synthesis of spiro-oxindoles via $\text{BF}_3\cdot\text{OEt}_2$ catalyzed Prins cascade reaction

Due to the structural simplicity and wide range of biological activity with diverse properties, spirocyclic compounds constitute an ideal lead class of compounds for structural diversification to enhance their promising pharmacological activities and further study.

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