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RECENT PROGRESS ON SYNTHESIS OF SPIROCHROMANONE AND SPIROCHROMANE DERIVATIVES

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Abstract – Nature offers plenty of opportunities to the researchers of different communities to explore heterocyclic compounds. Among the various magic heterocyclic scaffolds, chromane and chromanone are the most privileged heterocycles due to their omnipresence in most value-added chemical entities. On the other hand, spirocyclic heterocyclic moieties offer unique three-dimensional frameworks which can fit into the cavity of the proteins, including enzymes, thereby enhancing the biological properties. Considering the remarkable significance of spirocyclic systems of chromanes and chromanones, various novel strategies such as Kabbe condensation, organocatalyzed reactions,

oxa/sulfa-Michael-aldol cascade reaction, oxa-Michael/addition and 1,3-dipolar cycloaddition, among others, have emerged to access this precious heterocyclic architecture in good to excellent yields. This review summarizes the synthesis of a variety of spirochromane and spirochromanone derivatives covering the literature from 1991-2020.

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1. INTRODUCTION

Heterocycles are the heart of organic and medicinal chemistry research.[1-3] Among various heterocycles, oxygen containing derivatives have always attracted researchers by offering their beautiful architecture and versatile pharmacological properties.[4-6] The eye-catching feature of the spiroheterocycles is their three-dimensional structure and rigid framework, which can easily fit into the active site of the proteins and enzymes.[7,8] Among the different spiroheterocyles, spirochromanones, and spirochromanes are a privileged structure due to their biological properties.[9,10] The molecular hybridization concept was used in drug discovery to combat drug resistance to enrich existing anti-infective agents.[11,12] This approach normally includes the combination of two or more pharmacophores to form a linked novel molecule.[13] The choice of pharmacophoric moieties is depended on their biological profiles, with the optimism that the resulting hybrid structures may show additional attractive pharmacological activities.[14,15] For example,

as illustrated in **Figure 1**, the derivatives[10] of spirochromanones and spirochromanes are antiarrhythmic agents,[16,17] ACC inhibitors,[18] vanilloid receptor antagonists,[19]COM-21-14580
growth hormone secretagogues,[20] histamine receptor antagonists,[21] antiviral agents,[22] estrogen receptor modulators,[23] antineoplastic agents,[24] antifungal agents and DNA polymerase inhibitors.[25]

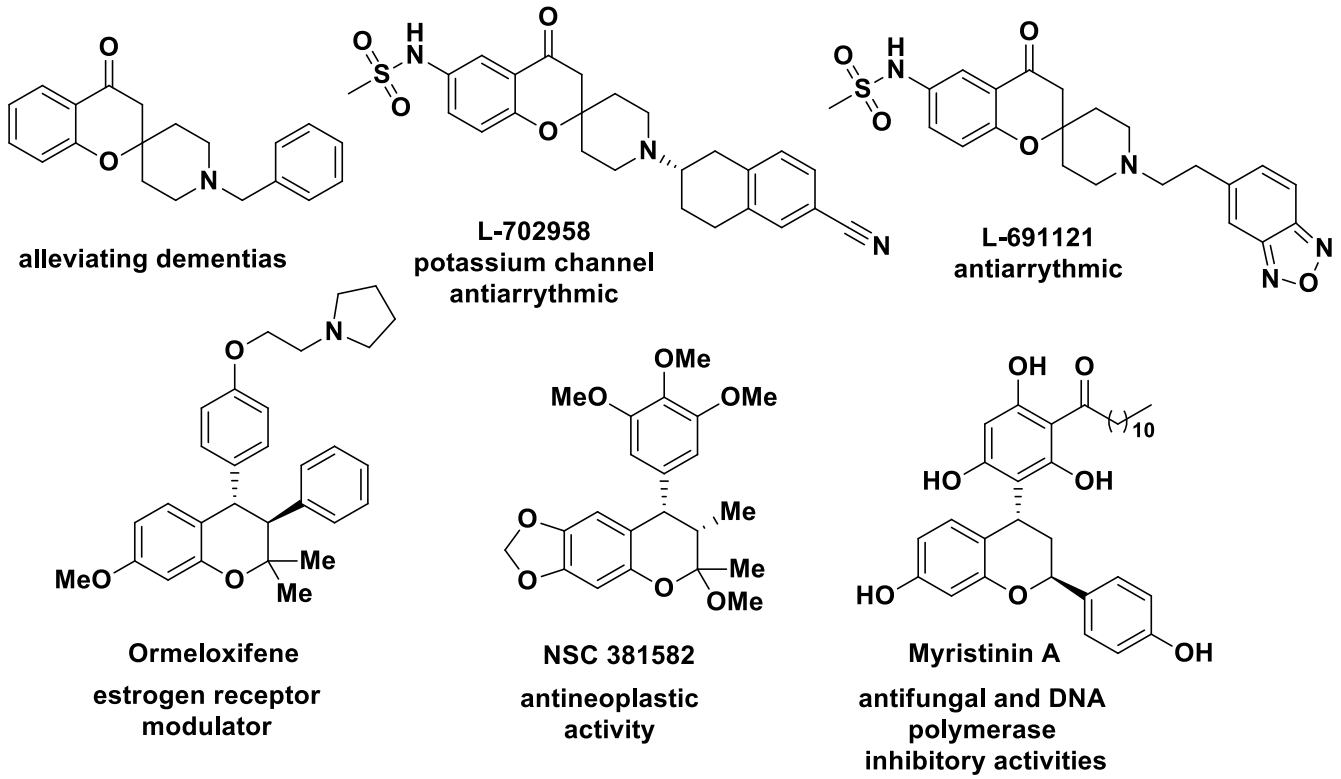


Figure 1. Bio-active spirochromanones and spirochromanes

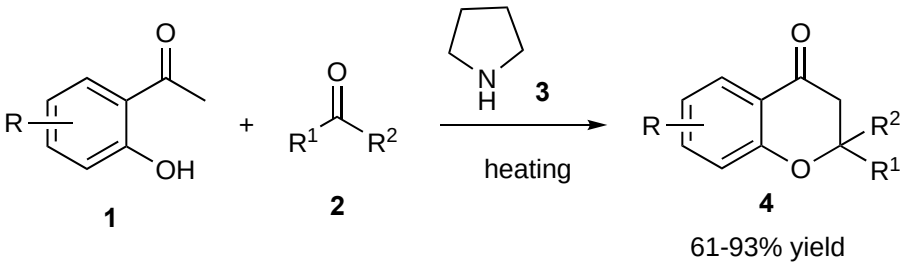
Because of their structural importance, the development of efficient synthetic routes to the spirochromanones and spirochromanes has captured the interest of synthetic organic chemists in the field of heterocyclic and medicinal chemistry.[7,26-28] Herewith, we report a collective work about drug design, synthesis, and discovery of spirochromanone and spirochromane scaffolds during the past decade involving various reaction pathways such as Kabbe condensation, 1,3-dipolar cycloaddition, organocatalyzed Michael addition, and metal-catalyzed reactions, among others.

2.1. SYNTHESIS OF SPIROCHROMANONES

2.1.1. Kabbe condensation

Kabbe reported the condensation of *o*-hydroxyacetophenones **1** with aliphatic ketones or aldehydes **2** to obtain chroman-4-ones **4** in the presence of pyrrolidine **3** in good yields.[28] He also demonstrated the scope and limitation of the methodology with a variety of substituted aldehydes and ketones to generate structural diversity. Most of product **4** can be used for the synthesis of chromenes and chromanes

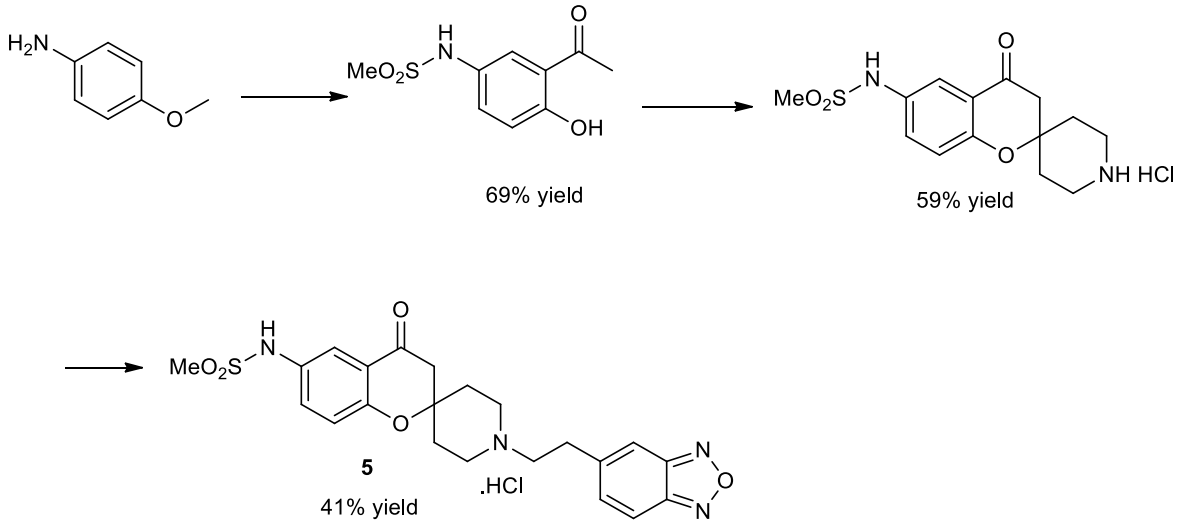
(**Scheme 1**). An alternative Kabbe synthesis of chroman-4-ones **4** involves treatment of *o*-hydroxyacetophenone **1** (R = H) with enolizable aldehydes or ketones **2** in the presence of LDA.[29]



R = H, 6-MeO, 7-OH, 6-OH, 6-Cl, 5,7,8-Me_3, 6-CO_2H; R^1= H, Me; R^2= *i*-Pr, *t*-Bu, *n*-C_9H_{19}, $(CH_2)_2C_6H_5$, Me, *n*-C_6H_{13}, -$(CH_2)_5$-, -$(CH_2)_4$-, $CH(OMe)_2$, $(CH_2)_2CH{=}C(Me)_2$, CO_2H, $(CH_2)_2CO_2H$, $(CH_2)_4CO_2H$, $(CH_2)_3$-NEt_2.

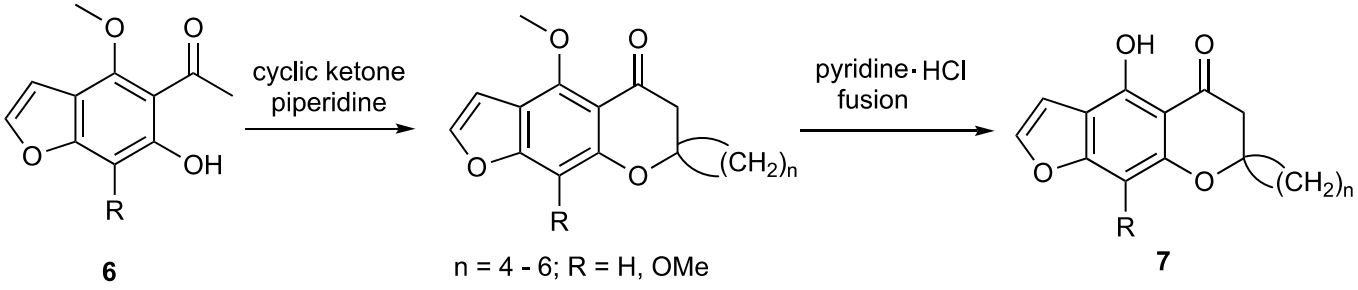
Scheme 1. Synthesis of chroman-4-ones *via* Kabbe condensation

In 1992 a series of 4-oxospiro[benzopyran-2,4'-piperidines] **5** were tested *in vitro* and *in vivo* as class III antiarrhythmic agents. It was shown that conformationally constrained compounds **5** show increased activity. One of the synthesized compounds **5** shows good *in vivo* potency (**Scheme 2**).[16] Similar antiarrhythmic agents are included in **Figure 1**.[17]

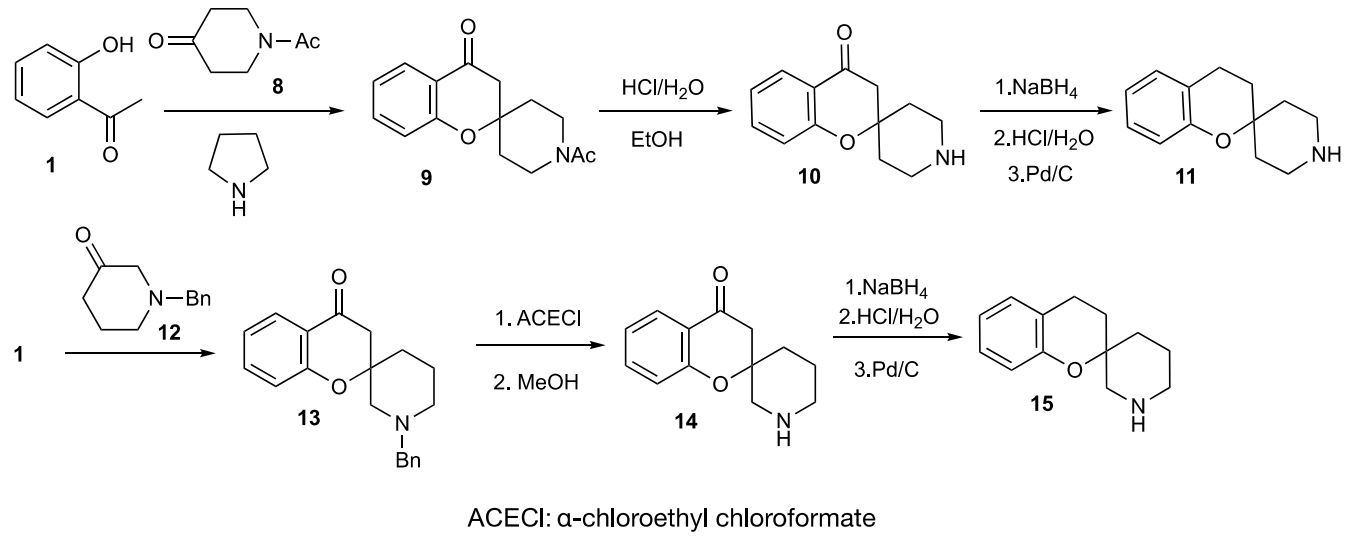


Scheme 2. Synthesis of 4-oxospiro[benzopyran-2,4'-piperidines] **5** as class III antiarrhythmic agents

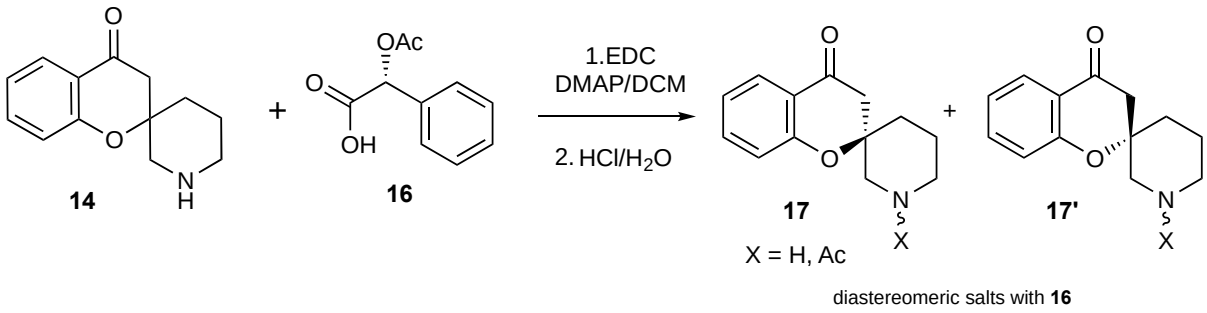
The synthesis of novel substituted spirofurochromanone derivatives **7** *via* Kabbe condensation with *o*-hydroxyacetophenone derivatives visnaginone (R=H) and khellinone (R=OMe) **6** was reported[30] in 1997 (**Scheme 3**). The spiro cyclization of **6** was catalyzed by piperidine, and the intermediate spirofurochromones were demethylated to **7** by treatment with pyridinium chloride. Compounds **7** were reported in quantitative yields.



Scheme 3. Synthesis of spirofurochromanone derivatives **7**



Scheme 4. Synthesis of 2-spirobenzopyrans **11** and **15**

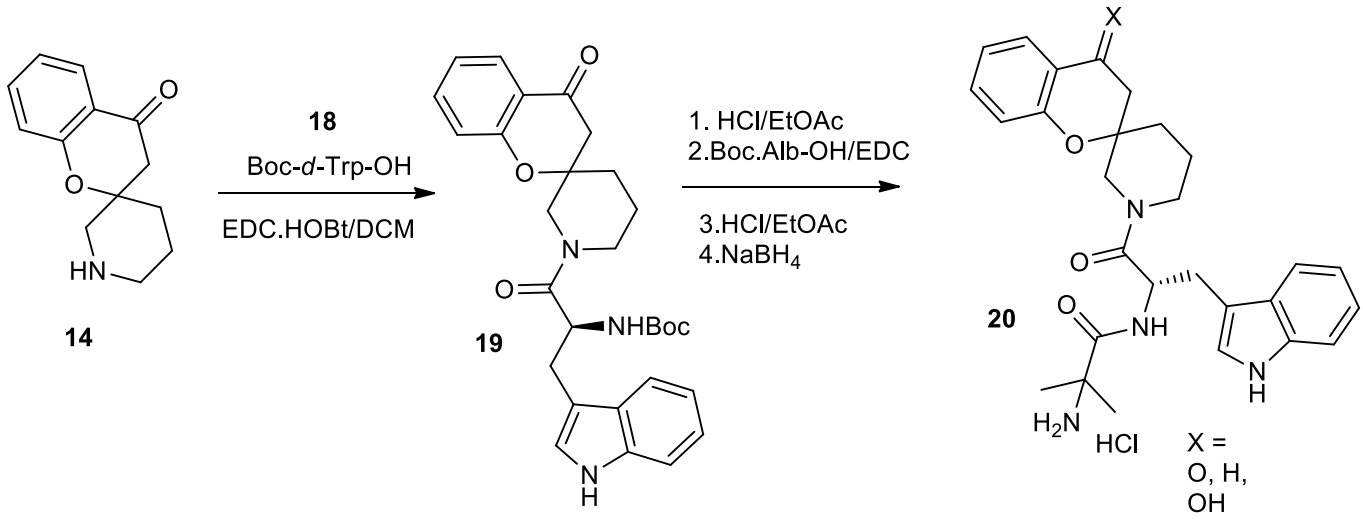


Scheme 5. Chiral resolution of 2-spirobenzopyran-4-one

The synthesis of 2-spirobenzopyran-4-one **9** was conducted by treatment of **1**with commercially available *N*-acetyl-4-piperidinone **8**.[20] Deacetylation of **9** followed by reduction of the resultant intermediate product **10** furnished spiro(2*H*-1-benzopyran-2,4-piperidine) **11** (**Scheme 4**). The positional isomer **15** was obtained by treatment of **1** with **12** followed by hydrolysis of the resultant product **13**, hydrolysis of **13** to **14**, and finally reduction of **14**.

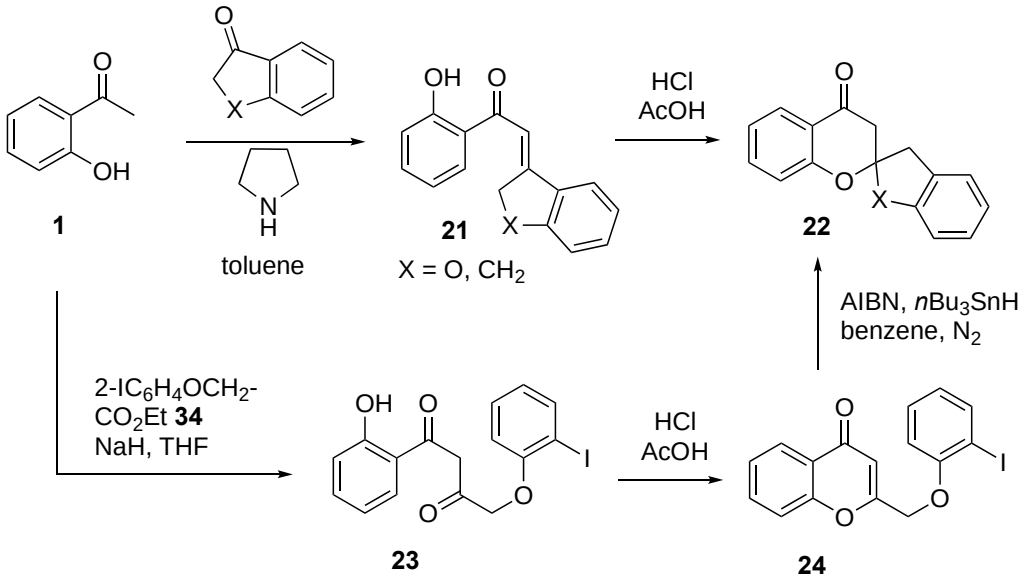
The racemic 2-spirobenzopyran-4-one **14** was subjected to chiral resolution by treatment with (*R*)-(-)-*O*-acetylmandelic acid **16** to form diastereomers **17** and **17'** (**Scheme 5**). For the hormone

secretagogue application, compound **14** and analogues were functionalized with a dipeptide **18** to give derivatives **19** and **20** (**Scheme 6**).



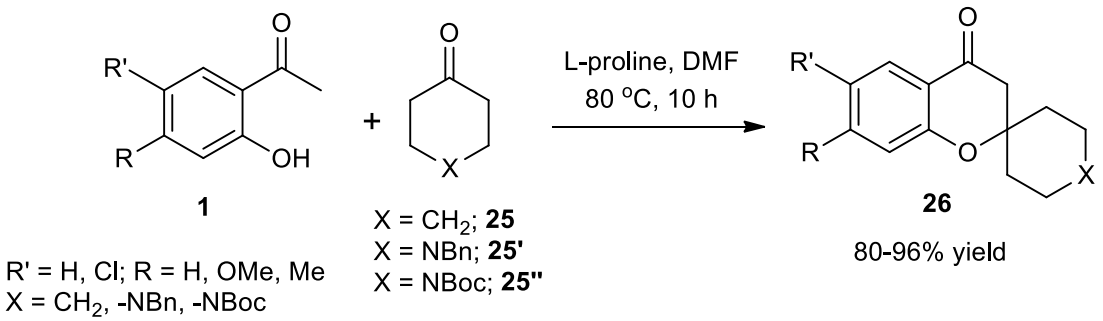
Scheme 6. Incorporation of dipeptide cap **18** into **14** for secretagogue application

Synthesis of 2-spirochroman-4-ones **22**, through the intermediary of **21**, **23** and **24**, is given in **Scheme 7**. These spiroannulated systems were further subjected to oxidative ring expansion by treatment with a hypervalent iodine reagent to obtain rotenoid, benzoxanthones and dehydrorotenoid.[31]



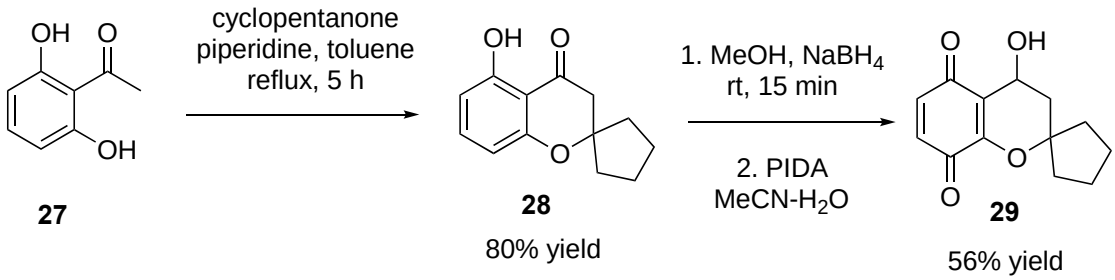
Scheme 7. Synthesis of spiroannulated systems **22**

Chandrasekhar[32] in 2005 reported the synthesis of spirochromanones **26** by the condensation of 2-hydroxyacetophenones **1** with cycloalkanone **25** and its analogues **25'** and **25''** in the presence of L-proline in DMF at 80 °C for 10 h (**Scheme 8**).



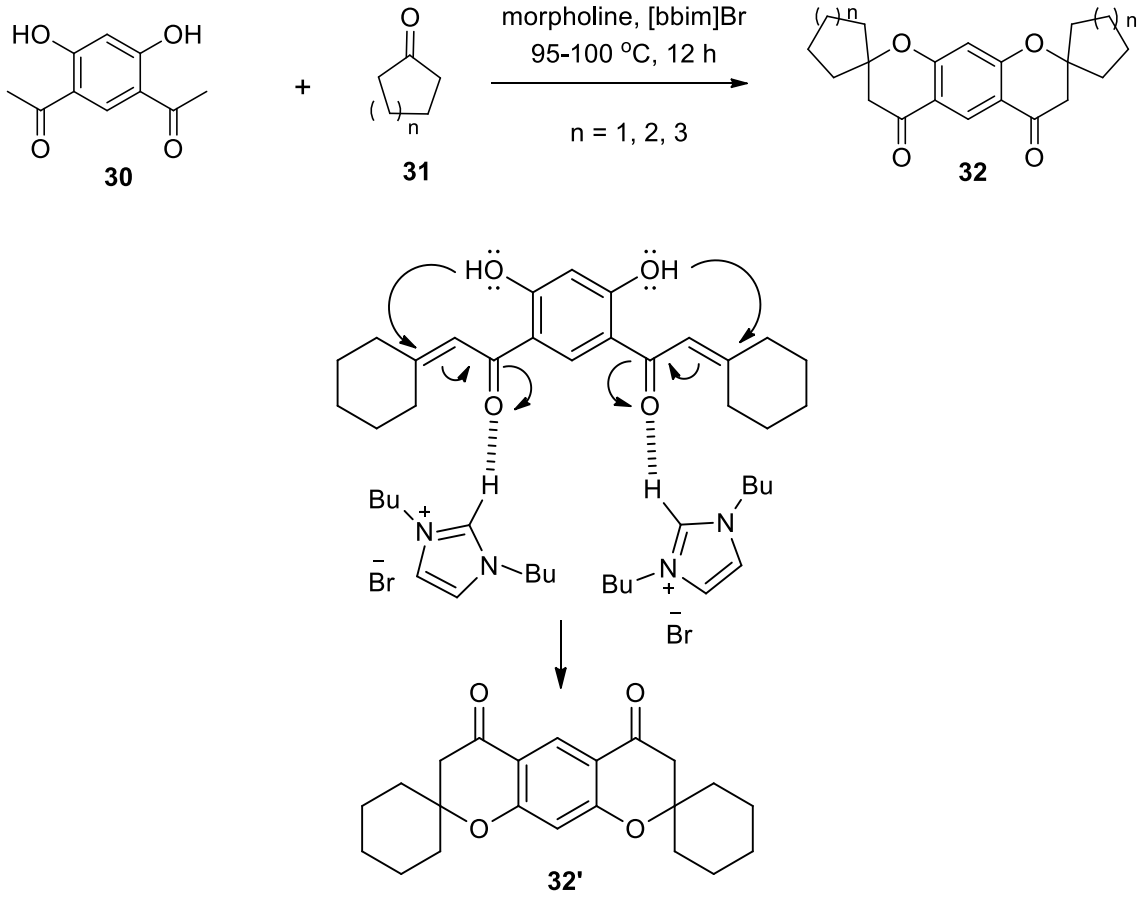
Scheme 8. Synthesis of spirochromanones **26**

Tapia[33] published in 2006 the synthesis of 2-spirobenzopyranoquinone **29** *via* Kabbe condensation of 2,6-dihydroxyacetophenone **27** with cyclopentanone catalyzed by piperidine in toluene under reflux conditions, followed by treatment of the resultant intermediate product **28** with $NaBH_4$ and PIDA (**Scheme 9**).



Scheme 9. Synthesis of 2-spirobenzopyranoquinone

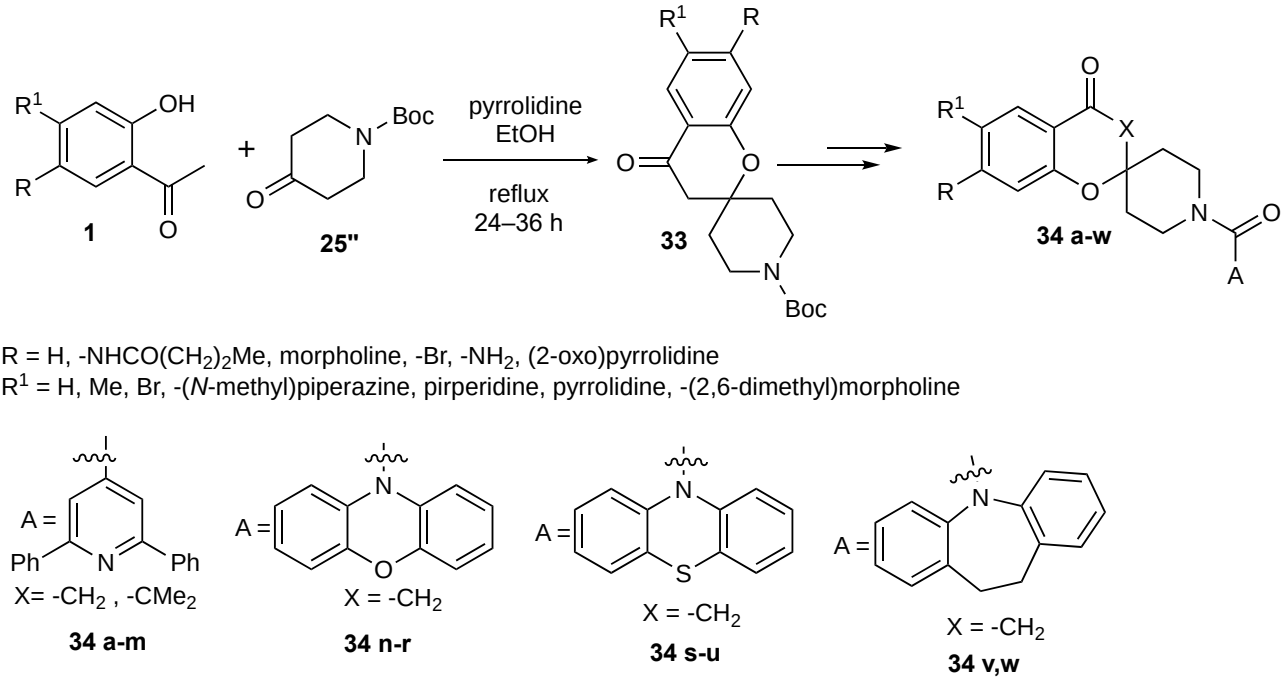
Muthukrishnan[34] in 2009 reported the synthesis of bis-2-spirochromanones **32** (**Scheme 10**) by Kabbe condensation of **30** with cyclic ketones **31**. This reaction was conducted in an ionic liquid in the presence of morpholine.



Scheme 10. Synthesis of bis-spirochromanones **32** with a plausible mechanism

In the proposed mechanism, compound **30** is activated by protonation with [bbim]Br, which leads to the spontaneous formation of an enone followed by cyclization of this unsaturated ketone intermediate to the final product **32** (**Scheme 10**).

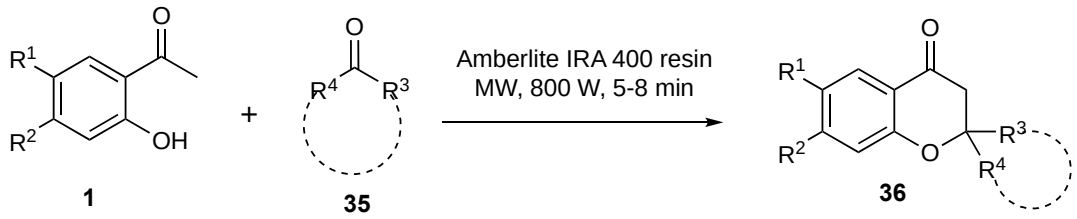
In 2009, Shinde[35] reported the synthesis of various spiro[chromane-2,4'-piperdin]-4-one derivatives **34a-w** by condensation of 2-hydroxyacetophenones **1** with *N*-Boc-4-piperidone **25''**, followed by acidic hydrolysis of the Boc group in the intermediate product **33**. The final step involves coupling with different heterocyclic compounds A (**Scheme 11**). The products were evaluated for the Acetyl-CoA carboxylase (ACC) activity. Various compounds have shown the ACC inhibitory activity at the low nanomolar range. Many compounds **34** reduced the respiratory quotient (RQ) in C57BL/6 mice, indicating the whole body increased by fat oxidation during high carbohydrate diet. The structure-activity relationship of these compounds was discussed. It was concluded that these spirochromanones linked to a hydrophobic core through an amide linkage or attached to the diphenylisonicotinyl hydrophobic core show potential activity towards ACC inhibition. In particular, it was suggested that the position-6 on the aromatic ring of spiro[chromane-2,4-piperidin]-4-one plays an important role in the activity.



R = H, -NHCO$(CH_2)_2$Me, morpholine, -Br, -NH_2, (2-oxo)pyrrolidine
R^1 = H, Me, Br, -(*N*-methyl)piperazine, pirperidine, pyrrolidine, -(2,6-dimethyl)morpholine

Scheme 11. Synthesis and evaluation of 2-spiropiperidinechroman-4-ones **34** as acetyl-CoA carboxylase inhibitors

Tripathi and coworkers[36] in 2010 reported a user-friendly synthesis of 2-spirobenzopyran-4-ones **36** by microwave assisted protocol from the 2-hydroxyacetophenones **1** and cyclic ketones **35** in the presence of amberlite IRA 400 resin (basic resin) under solvent-free conditions (**Scheme 12**).

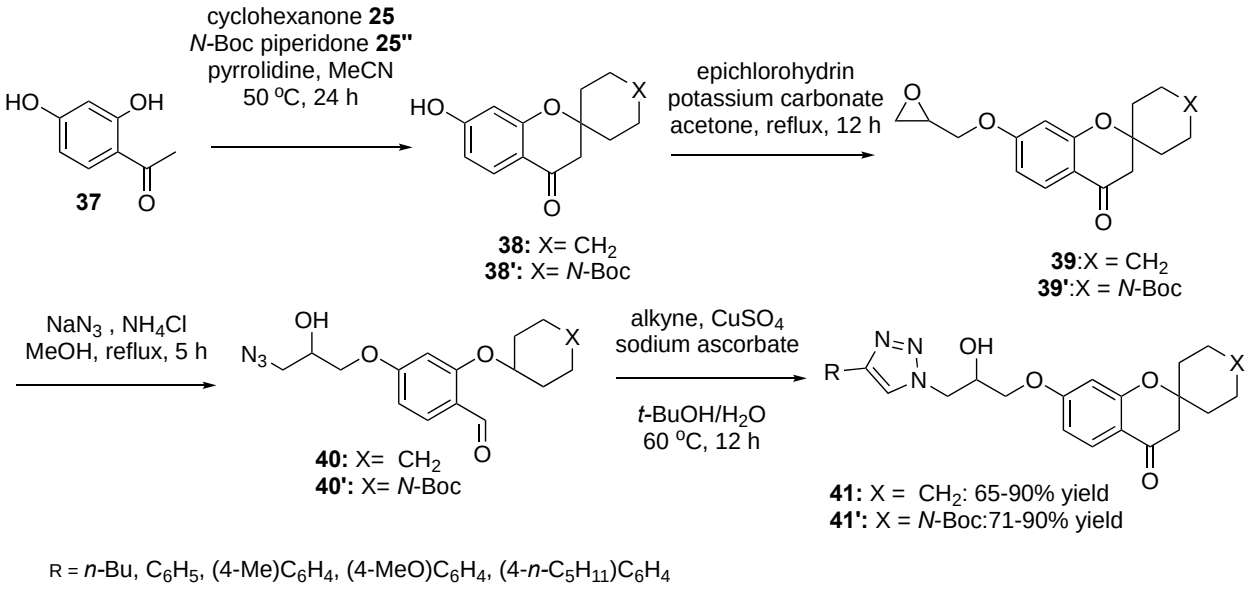


R^1 = H, -OH, -OMe
R^2 = H, -OH, -OMe
R^3 = R^4 = Me, Et, *n*-Bu, *n*-Pr, cyclohexyl, cyclopentyl

Scheme 12. Microwave synthesis of 2-spirobenzopyran-4-ones **36**

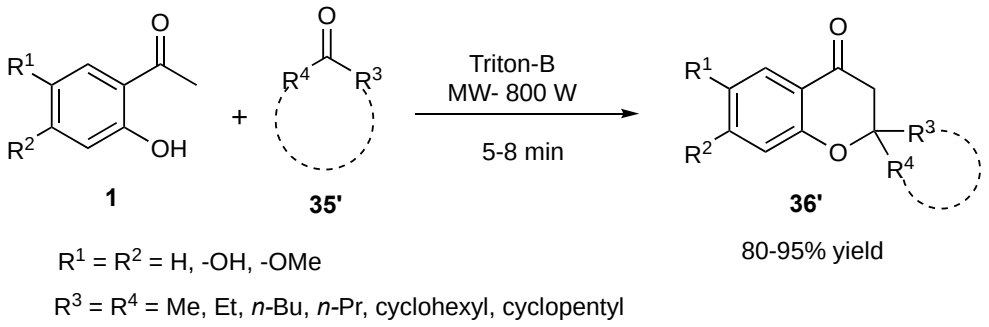
Muthukrishnan and co-workers[37] in 2011 published novel synthesis of 1,2,3-triazole-spirochroman-4-one conjugates **41**/**41'** *via* Kabbe condensation of *o*-hydroxyacetophenone **37** with cyclic ketones **25**/**25''** followed by a series of traditional transformations including azide-alkyne click reaction to incorporate 1,2,3-triazole moiety into the 2-spirochroman-4-one moiety (**Scheme 13**). The intermediate products **38**/**38'** – **40**/**40'** and the final products **41**/**41'** were obtained in good to excellent yields. All these

compounds were subjected to biological evaluation for mycobacterium tuberculosis (virulent strain H37Rv). In particular, compound **41** (X = CH_2, R = 4-*n*-$C_5H_{11}C_6H_4$) showed inhibition with MIC = 0.78 µg/mL.



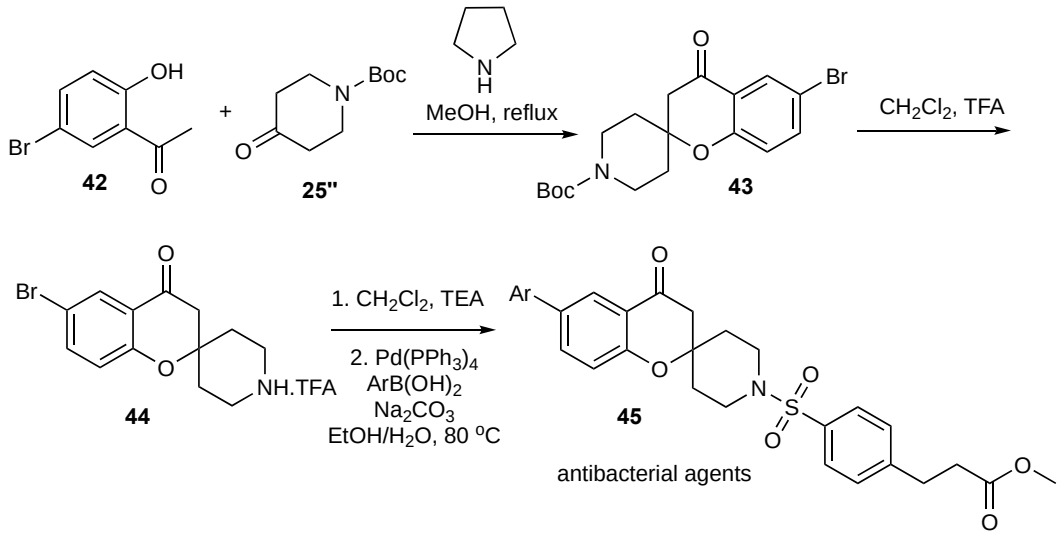
Scheme 13. Synthesis of 1,2,3-triazole-spirochroman-4-one conjugates **41/41'**

Chaturvedi and co-workers[38] reported in 2012 the preparation of diverse substituted benzopyran-4-ones **36'** (**Scheme 14**) *via* microwave-assisted protocol from *o*-hydroxyacetophenone **1**



Scheme 14. Synthesis of 2-spirobenzopyran-4-ones and cyclic ketones **35'** in the presence of benzyltrimethylammonium hydroxide (Triton-B) under solvent-free conditions

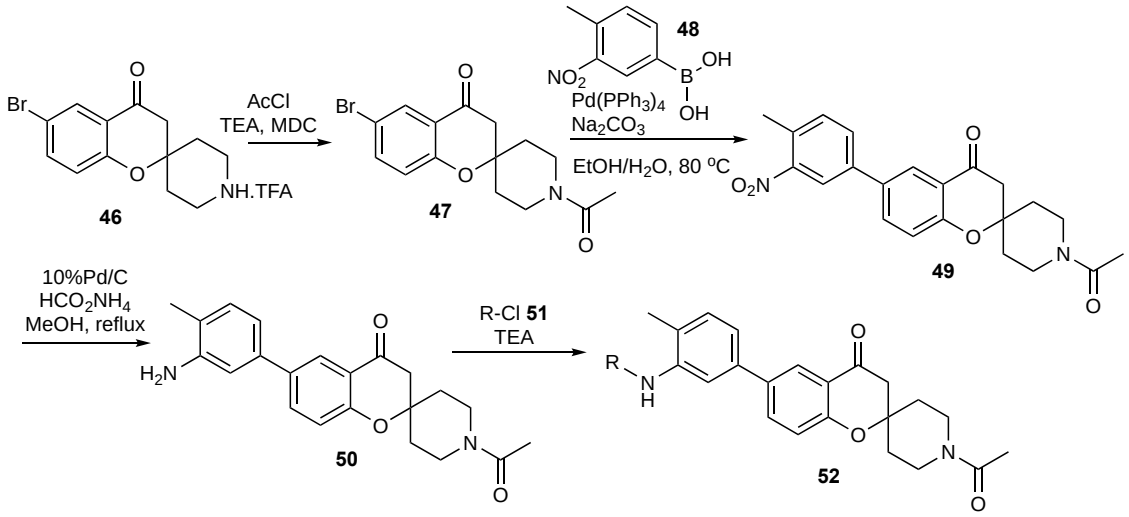
Gajera and co-workers[39] in 2012 reported the synthesis and characterization of aryl-substituted 3-[4-(4-oxo-6-phenyl-spiro[chromane-2,4'-piperidine]-1'-yl)sulfonylphenyl]propanoates **45** starting with the substrates **42** and **25''**. These compounds and the intermediate products **43** and **44** were screened *in vitro* for antibacterial activity against *Escherichia coli*, *Staphllococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis*, antifungal activity against *Candida albicans* (**Scheme 15**).



Ar = 4-C(Me)$_3$-C$_6$H$_5$-, 3,4-(F)$_2$-C$_6$H$_3$-, 4-Me-C$_6$H$_4$-, 4-MeO-C$_6$H$_4$-, 3,5-(Me)$_2$C$_6$H$_3$-, 2,4-(F)$_2$-C$_6$H$_3$-, 3,4-(-OCH$_2$O-)-C$_6$H$_3$-, 4-(N(Me)$_2$-C$_6$H$_4$-, 4-(CF$_3$)-C$_6$H$_4$-, 4-(CF$_3$O)-C$_6$H$_4$-

Scheme 15. Synthesis of 2-spiropiperidinechroman-4-ones **45**

Alkylamides **52** and alkylsulfonamides **52** were prepared from substrates **46,** as shown in **Scheme 16**. Products **52** and the intermediate products **47**, **49,** and **50** were screened for antibacterial and antifungal activities.

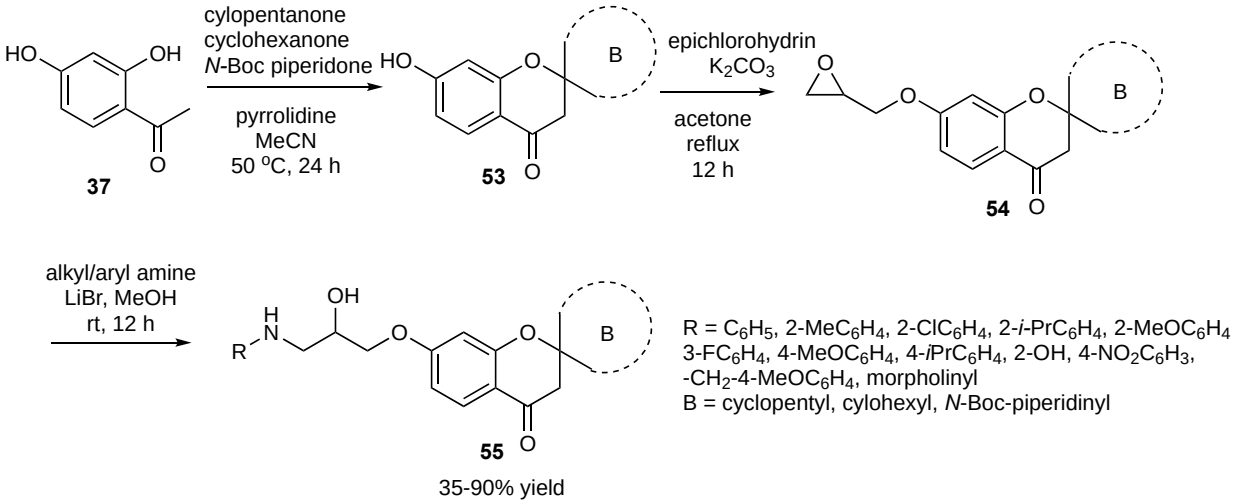


R = -SO$_2$Me, -CO-(cyclopropane), -CO-(isopropane), -CO-CH$_2$-Cl, -SO$_2$-(isobutane), -SO$_2$-(cyclopentane), -SO$_2$-(CH$_2$)-Cl, -SO$_2$-(isopropane), -CO-(morpholine)

Scheme 16. Synthesis of 2-spiropiperidinechroman-4-ones **52**

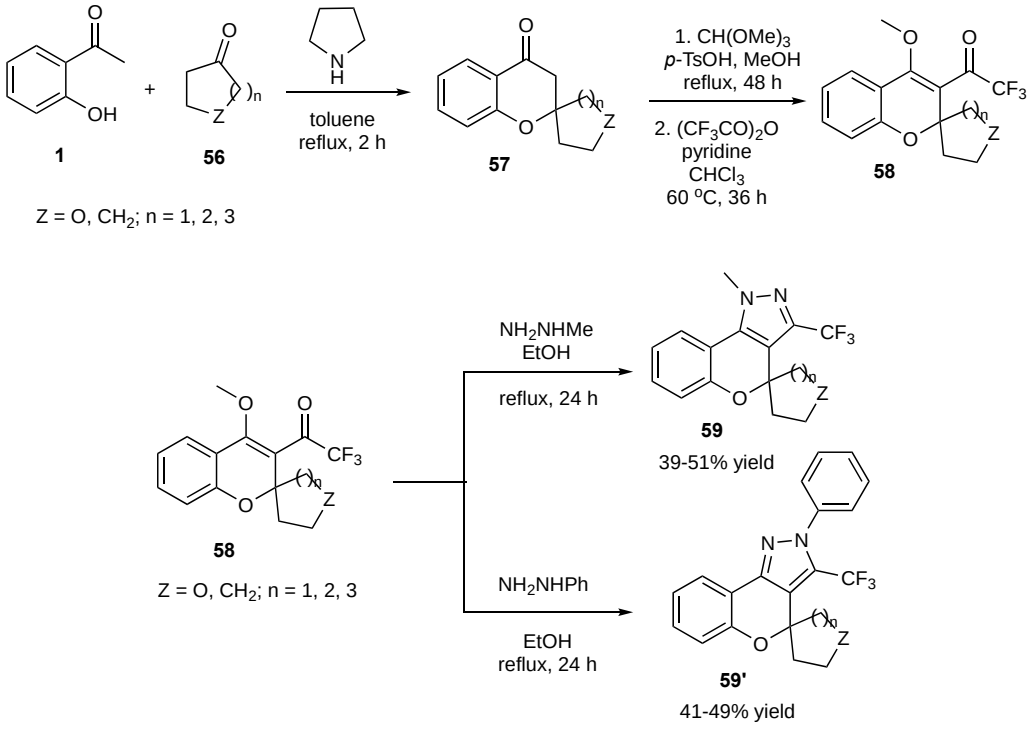
Mujahid and co-workers[40] in 2013 reported the synthesis of a series of amino alcohol functionalized 2-spirochroman-4-one derivatives **55** *via* Kabbe condensation of 2,4-hydroxyacetophenones **37** with cyclic ketones under basic conditions. The intermediate products **53** and **54** and the final products **55** are

shown in **Scheme 17**. These compounds were screened against *Mycobacterium tuberculosis* (virulent H37Rv) *in vitro*. The most active was compound **55** (R = 3-FC_6H_4) with MIC = 3.3µg/mL.



Scheme 17. Synthesis of amino alcohol functionalized 2-spirochroman-4-ones

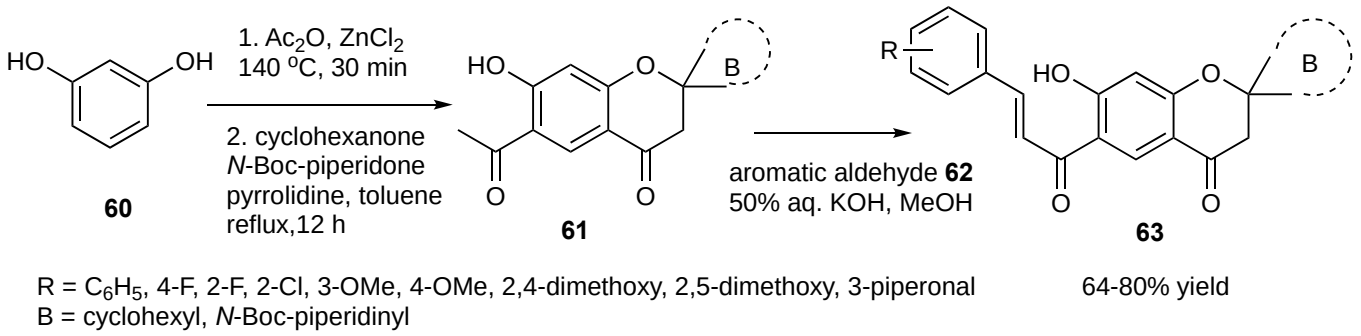
Bonacorso and co-workers[41] in 2014 reported the first regioselective synthesis of novel 2,2,2-triflouro-1-[4-methoxy-spiro(2*H*-chromene-2,1-cycloalkan)-3-yl]ethanones **58** from the spirochroman-4-ones **57**. Compounds **57** were obtained by Kabbe condensation of **1** with carbonyl compounds **56** (**Scheme 18**).



Scheme 18. Synthesis and derivatization of Kabbe adducts **57**

The Kabbe reaction of products **58** with different hydrazine derivatives provided new 3-(trifluoromethyl)-spiro(chromeno[4,3-*c*]pyrazole-4,10-cycloalkanes) **59/59'** (**Scheme 18**). These structures were extensively characterized by spectral methods and single crystal X-ray diffraction.

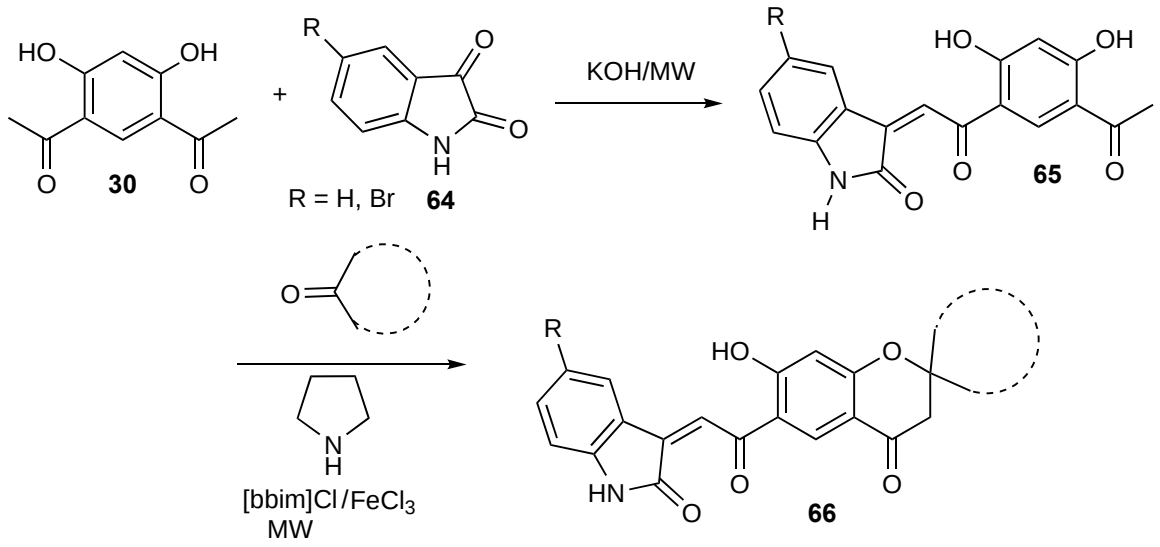
Mujahid and co-workers[42] reported in 2015 the convenient synthesis of 2-spirochroman-4-one chalcone conjugates **63** based on Kabbe condensation of 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(ethan-1-one) **60** with cyclohexanone and *N*-Boc-piperidone (**Scheme 19**).



Scheme 19. Synthesis of spirochromanone chalcone conjugates **63**

The intermediate spiro adducts **61** were allowed to react with various substituted benzaldehydes **62** under basic conditions. These spirochromanone chalcone conjugates **63** were screened against *Mycobacterium tuberculosis* H37Rv strain and subjected to molecular modeling studies using cheminformatics and docking. The docking simulations against known receptors for chalcone derived compounds revealed that MTB phosphotyrosine phosphatase B protein is the most probable target. Five compounds showed significant activity with MIC values ranging from 3.13 to 12.5 µg/mL in the biological assays.

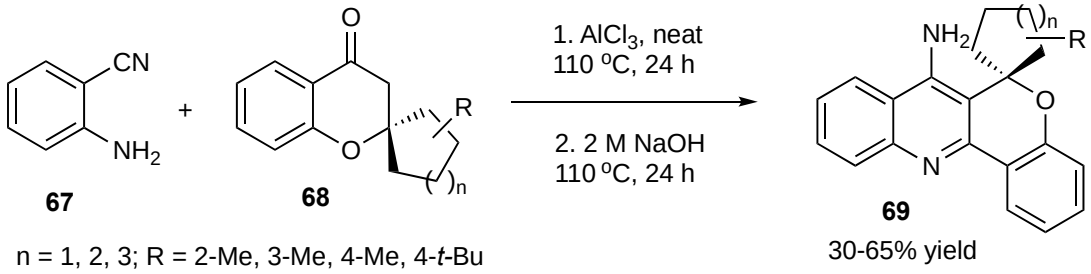
Ashok and coworkers[43] in 2015 reported a two-step synthesis of novel indolin-2-one fused spirochromanone conjugates **66**. The first step involved synthesis of 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2oxoethylidene]indolin-2-ones **65** by treatment of 4,6-diacetylresorcinol **30** with isatin **64** in the presence of a strong base under microwave irradiation. The intermediate product **65** was allowed to react with various cyclic ketones under Kabbe condensation conditions in ionic liquid [bmim]Cl/$FeCl_3$ in the presence of pyrrolidine under microwave irradiation (**Scheme 20**).



Scheme 20. Synthetic route to the indolin-2-one fused spirochroman-4-one conjugates **66**

Products **66** were evaluated for antioxidant activity. Their antioxidant activity IC_{50} range from 1.25 µM to 1.75 µM, when compared with the value of IC_{50} = 8.65 µM for ascorbic acid used as a standard control.

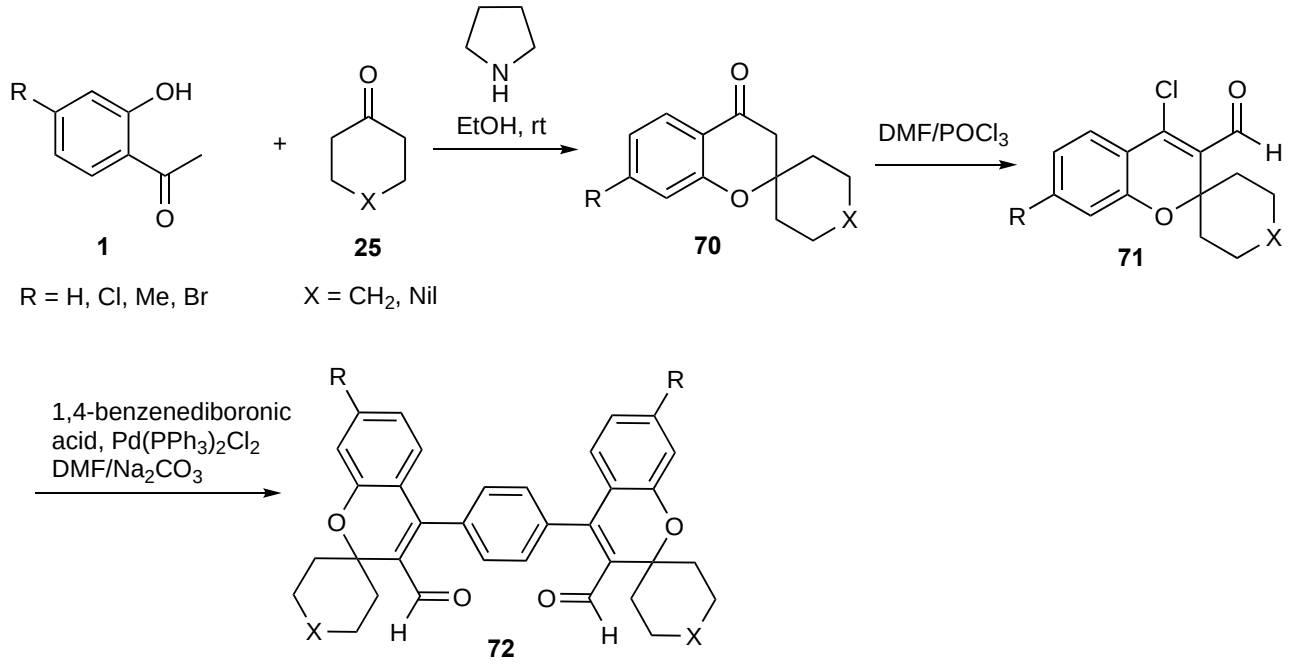
Bonacorso and co-workers in 2015 reported the synthesis of spiro[chromeno[4,3-*b*]quinoline-6,10-cycloalkanes] **69** by treatment of **67** with the spiro[chromane-2,10-cycloalkan]-4-ones **68** as shown in **Scheme 21**. These compounds were screened for cytotoxicity and for inhibition of acetylcholinesterase. Compounds **69** did not show cytotoxicity in human leukocytes at a concentration of 200 µM.



Scheme 21. Synthesis of spiro[chromeno[4,3-*b*]quinoline-6,10-cycloalkanes] **69**

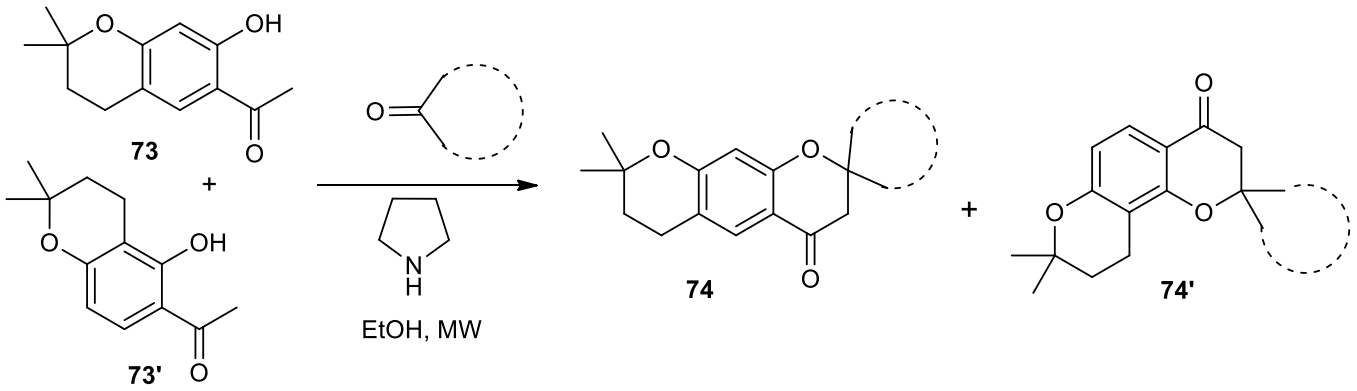
Ashok and co-workers[44] in 2015 reported the synthesis of novel Kabbe adducts **70** by condensation of 2-hydroxyacetophenones **1** and cyclohexanone **25** catalyzed by pyrrolidine in ethanol at room temperature. The Vilsmeier reaction of **70** yielded 4-chloro-3-formylspirochromanones **71**, the reaction of which with 1,4-diboronic acid under Suzuki coupling conditions furnished 1,4-spirochromanonebenzenes

72 (**Scheme 22**). These compounds were screened *in vitro* for antimicrobial activity against Gram-positive bacteria *Bacillus subtilis* (MTCC 121) and Gram-negative bacteria *Escherichia coli* (MTCC 7390) using streptomycin as standard. They were also studied for antifungal activity against *Aspergillus terreus* and *Aspergillus niger*.



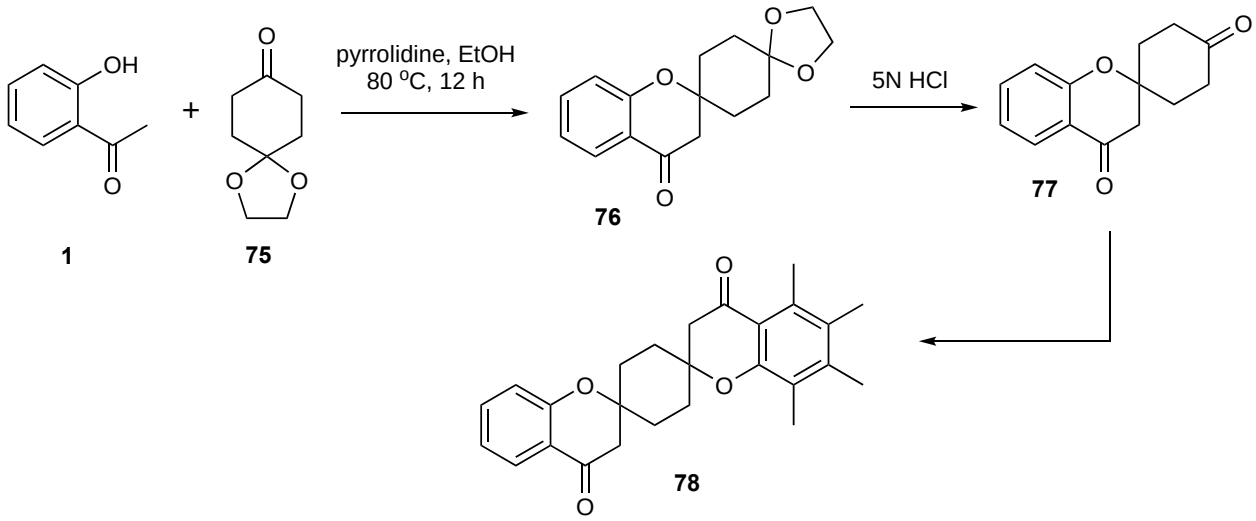
Scheme 22. Synthesis of 1,4-spirochromanonebenzenes **72**

In 2016 Ashok and co-workers[45] synthesized novel spirochroman-4-ones **74** and **74'** by the reaction of hydroxyacetophenones **73** or **73'** and cyclic alkanones (**Scheme 23**). The pyrrolidine catalyzed reaction was conducted under microwave irradiation. The products were tested for antioxidant and anti-inflammatory activity.



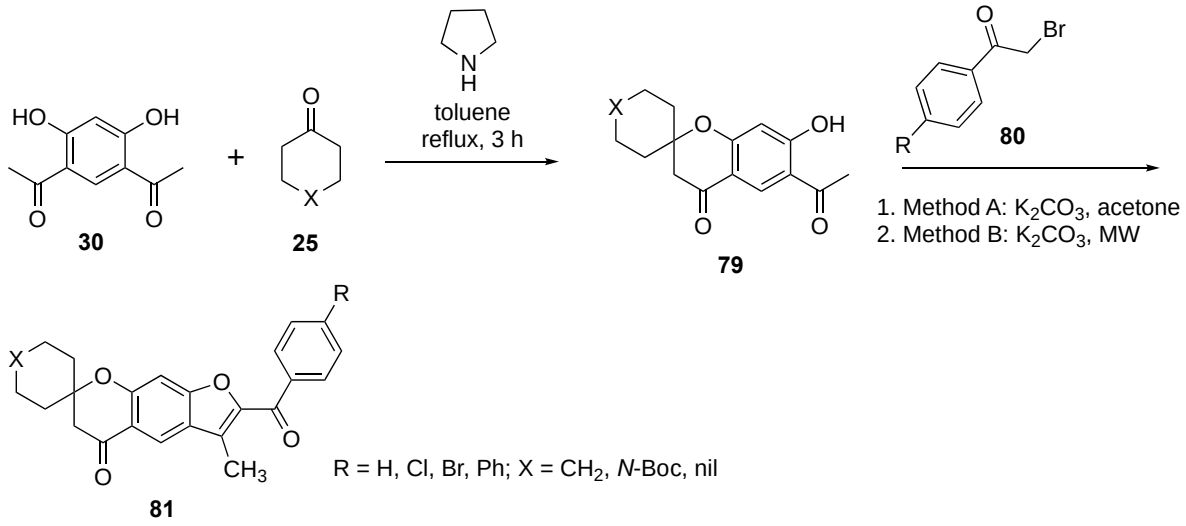
Scheme 23. Synthesis of novel chroman based spirochromanones **74** and **74'**

Ashok and co-workers[46] in 2017 reported the synthesis of novel bis-spirochromanones **78** employing a double Kabbe condensation approach (**Scheme 24**). The first step involved the reaction of *o*-hydroxacetophenone **1** with 1,4-dioxaspiro[4.5]decan-8-one **75** catalyzed by pyrrolidine, in ethanol at 80 ºC for 12 h to yield dispiro[chromane-2,1'-cyclohexane-4',2"-[1,3]dioxolan]-4-one **76**. This Kabbe adduct contained a protected ketone group in an acetal form deprotected under strongly acidic conditions by treatment with 5N HCl to furnish the spiro[chromane-2,1'-cyclohexane]-4,4'-dione **77**. This product was used for the second Kabbe condensation under similar conditions to obtain bis-spirochromanone **78**. The final compound **78** was screened against *Mycobacterium tuberculosis* (H37Rv) strain and exhibited good antimycobacterial activity with minimum inhibitory concentration as low as 3.125 µg/mL.



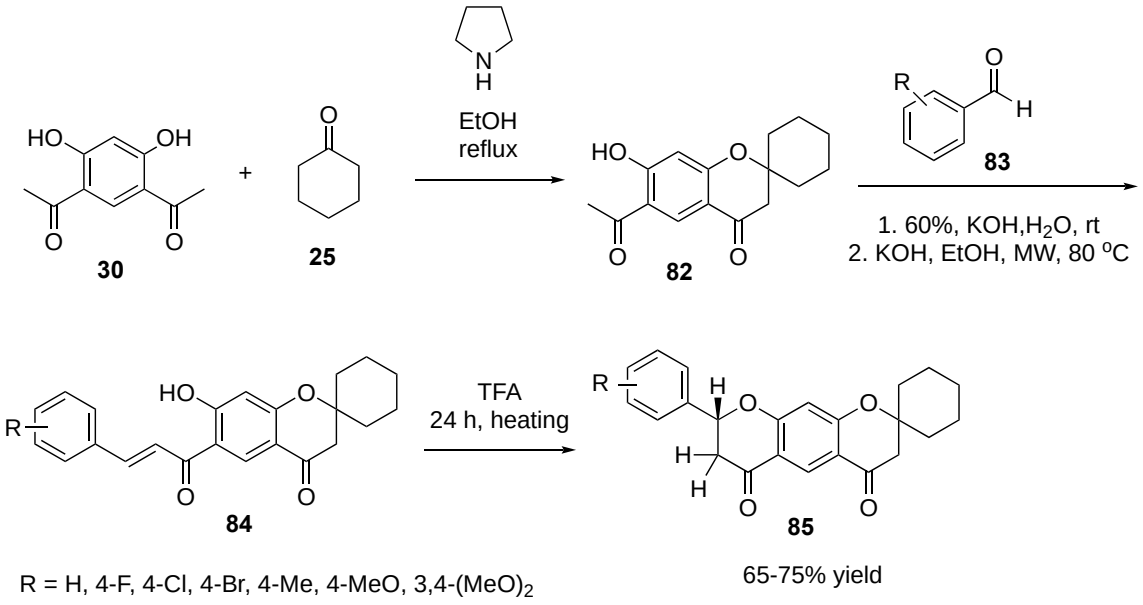
Scheme 24. Synthesis of bis-spirochromanones **78**

In 2017 the same group reported the synthesis of spirofurochromanones[47] **81** based on the Kabbe condensation of 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(ethan-1-one) **30** with cyclic carbonyl compounds **25**, **25'** and **25''** in toluene catalyzed by pyrrolidine under reflux conditions for 3 hours. The resulting products **79** were allowed to react with phenacyl bromide **80** in the presence of potassium carbonate to obtain spirofurochromanone **81** with good yields using a conventional approach and under microwave irradiation (**Scheme 25**). All these compounds were evaluated for anti-inflammatory and antioxidant activity using DPPH radical scavenging assay. Most of these compounds are active in the hydrogen peroxide assay.



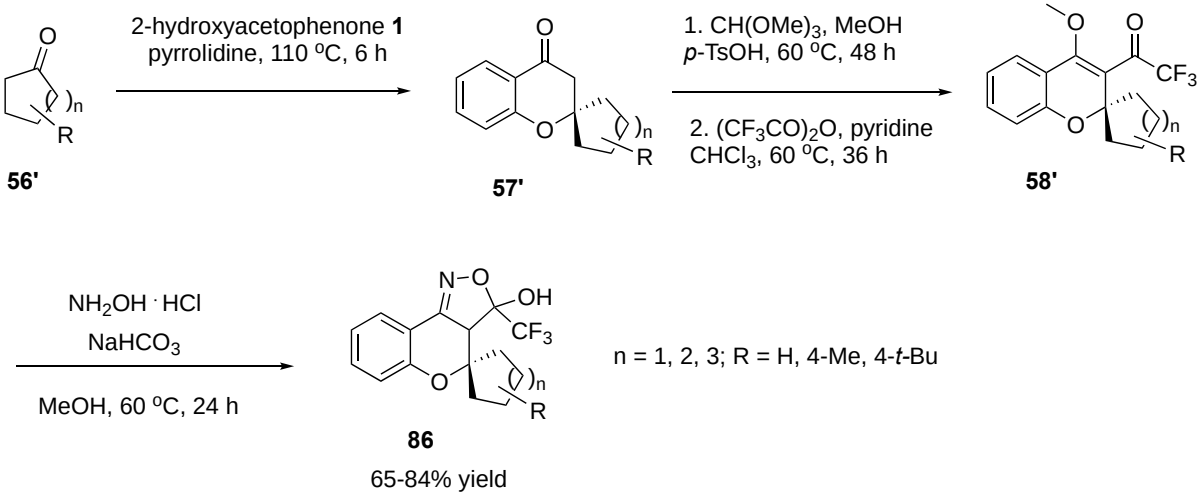
Scheme 25. Synthesis of spirofurochromanones **81**

Ramakishore and co-workers[48] in 2017 reported the synthesis of spiro[chromene-2,1'-cyclohexan]-4(3*H*)-one derivatives **82** by Kabbe condensation 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(ethan-1-one) **30** with cyclohexanone **25** in ethanol in the presence of pyrrolidine as a base at reflux temperature. The resultant product **82** was allowed to react with various benzaldehydes **83** under the strong basic conditions in water to give the chalcone containing sprichroman-4-ones **84**. These chalcone hybrids were subjected to intramolecular cyclization to flavanone containing spirochromanones **85** in trifluoroacetic acid (**Scheme 26**) in good to excellent yields. All these hybrid molecules were screened against the antibacterial and antifungal activity.



Scheme 26. Synthesis of spirochromanone hybrids **85**

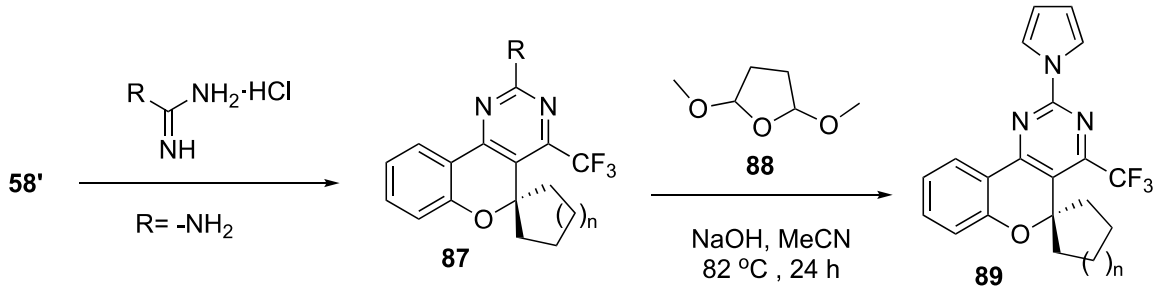
Bonacorso and co-workers[49] in 2017 published the first synthesis of trifluoromethyl substituted spirotetracyclic isoxazoline derivatives **58'** and isoxazoles **86** *via* Kabbe condensation. Initially, the intermediate spiro[chromane-2,10-cycloalkan]-4-ones **57'** (Kabbe adducts) were synthesized by the reaction between 2-hydroxyacetophenones **1** with cycloalkanones **56'** catalyzed by pyrrolidine (**Scheme 27**).



Scheme 27. Synthesis of novel trifluoromethyl substituted spirotetracyclic isooxazoline derivatives **86**

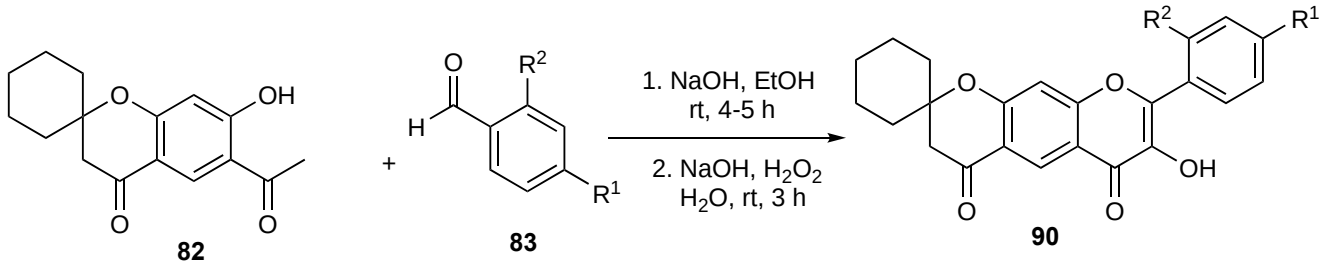
2,2,2-Trifluoro-1-[4-methoxy-spiro(2*H*-chromene-2,10cycloalkane)-3-yl]ethanones **58'** were allowed to react with hydroxylamine hydrochloride in methanol in presence of sodium carbonate for 24 h at 60 °C to obtain the final targets isooxazoles **86**. These products were characterized *via* ^{1}H, ^{13}C and ^{19}F NMR.

Treatment of compounds **58'** with amidine salts in which R = Me, Ph, NH_2 furnished products **87**. The reaction of **87** (R = NH_2) with 2,5-dimethoxytetrahydrofuran **88** under acidic conditions gave 2-(pyrrol-1-yl)-4-(trifluoromethyl)-chromeno[4,3-*d*]pyrimidines **89** (**Scheme 28**) in good yield. Following biological evaluation, it was concluded that compound **89** (n = 2) is a promising analgesic drug in the treatment of pathological pain, such as arthritis.



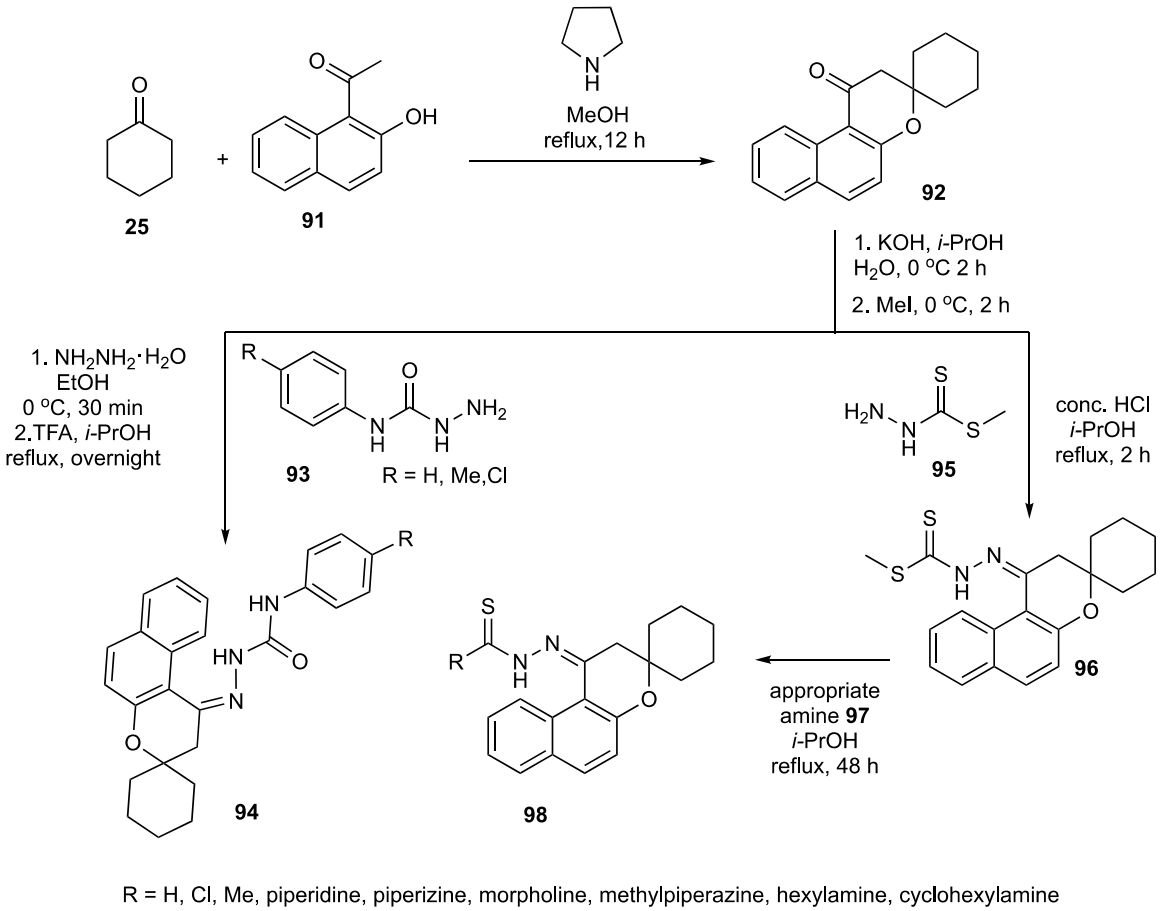
Scheme 28. Synthesis of 2-(pyrrol-1-yl)-4-(trifluoromethyl)-chromeno[4,3-*d*]pyrimidines **89**

In 2017 Ashok and co-workers[50] reported the synthesis of novel spirochromanone-flavonol derivatives **90** by Kabbe condensation of acetophenone derivative **82** with benzaldehydes **83** in the presence of pyrrolidine under microwave irradiation. The final spirochromanone-flavanol derivatives **90** were obtained in good to excellent yields (**Scheme 29)**. All these compounds were subjected to *in vitro* evaluation of antimicrobial activity and demonstrated moderate to good antimicrobial activity.



Scheme 29. Synthesis of novel spirochromanone derivatives **90**

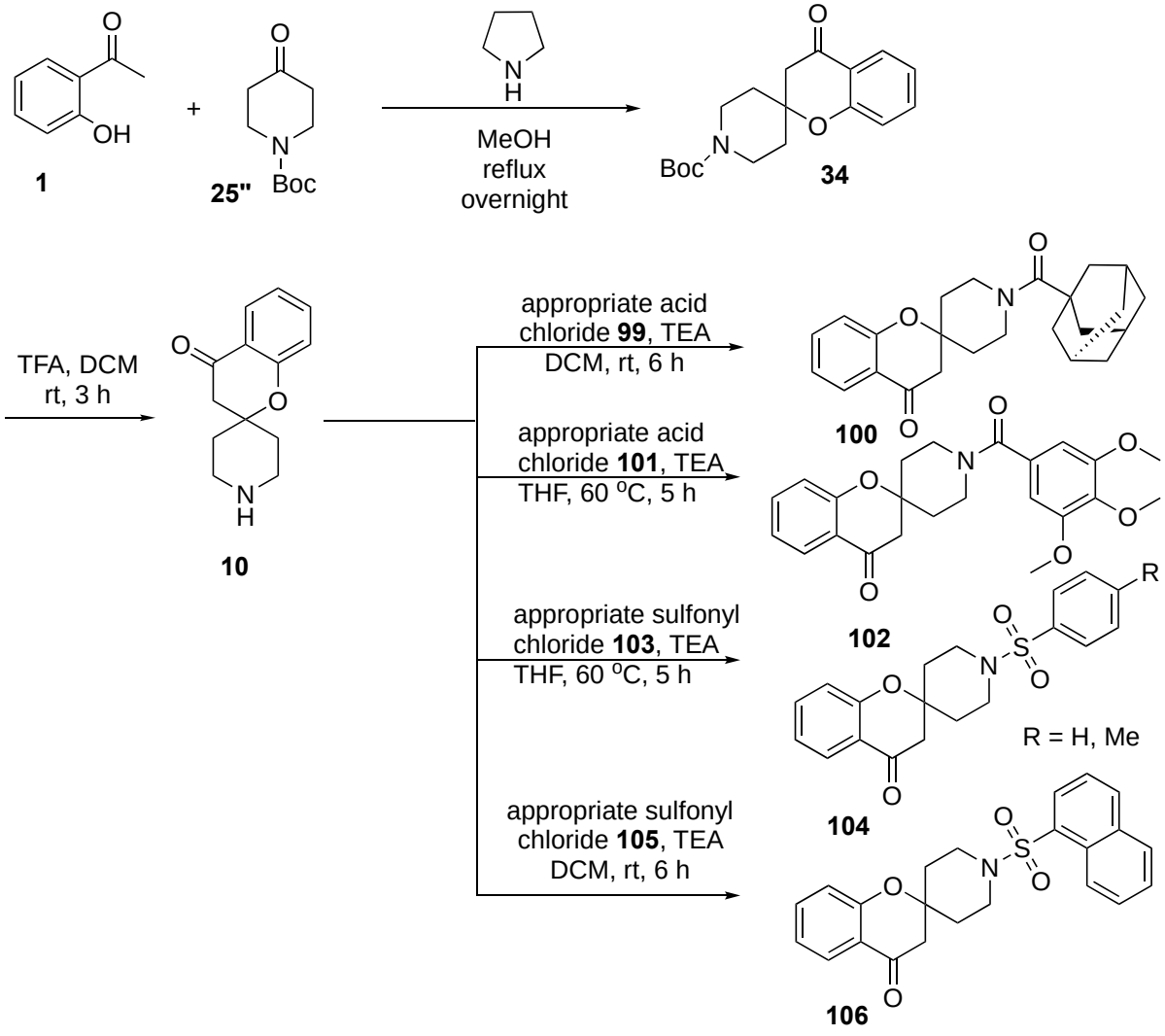
Abelatef and co-workers[51] in 2018 reported the synthesis of novel spirochromanone **92** (**Scheme 30**).



Scheme 30. Synthesis of novel spirobenzo[*h*]chromene derivatives **94**, **96** and **98**

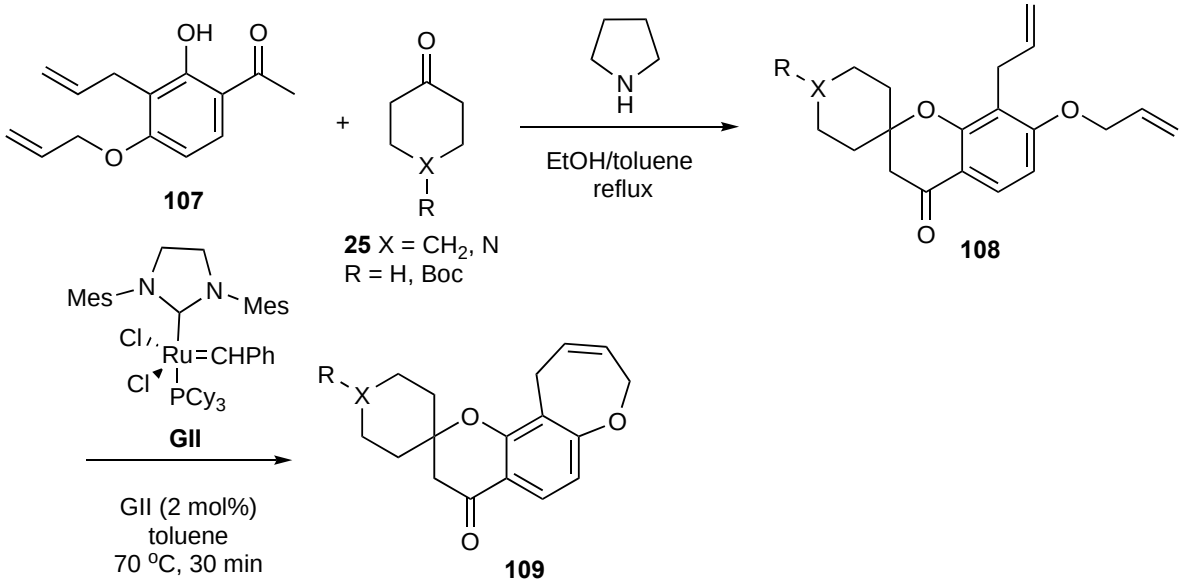
Product **92** was functionalized at the carbonyl group by the reaction with hydrazine-carbodithioate **95**. The intermediate compound **96** was subsequently allowed to react with amines **97** to replace *S*-methyl group to obtain thiosemicarbazide compounds **98**. On the other hand, treatment of **92** with phenyl semicarbazides **93** furnished semicarbazides **94**. These compounds were assessed as anti-cancer agents against MCF-7 (human breast carcinoma), A549 (human lung carcinoma), and HT-29 (human colorectal) adenocarcinoma) cell using MTT assay.

In 2018, Abelatef and co-workers[52] synthesized spiro[chromane-2,4'-piperidin]-4-one derivatives **100**, **102**, **104**, **106** with the intermediaries of **34** and **10**, as shown in **Scheme 31**. These molecules were evaluated as cytotoxic agents against three human cancer cell lines, namely MCF-7 (human breast carcinoma), A2780 (human ovarian cancer), and HT-29 (human colorectal adenocarcinoma) using the MTT assay. Compound **106** with a sulfonyl spacer exhibits a potent activity with values of IC_{50} ranging between 0.31 and 5.62 µM.



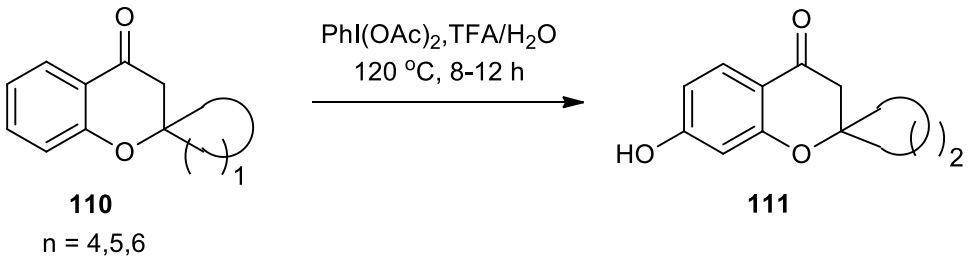
Scheme 31. Synthesis of spiro[chromane-2,4´-piperidin]-4-one derivatives **100**, **102**, **104** and **106**

Ashok and co-workers[53] in 2018 published the synthesized novel 8',11´-dihydrospiro[cyclohexane-1,2´-oxepino[2,3-*h*]chromen]-4´(3'*H*)-ones **109** using the intramolecular ring closure metathesis as a key step. Initially, 2,4-dihydroxyacetophenone was allylated with allyl bromide under basic conditions (K_2CO_3/acetone), and the resultant 4-*O*-allylated product **107** was subjected to Kabbe condensation with cyclic ketones **25** to yield spirochromanone substrates **108**. Ring closure metathesis of **108** in the presence of Grubbs second-generation catalyst yielded the spirochromanone fused oxepines **109** (**Scheme 32**).



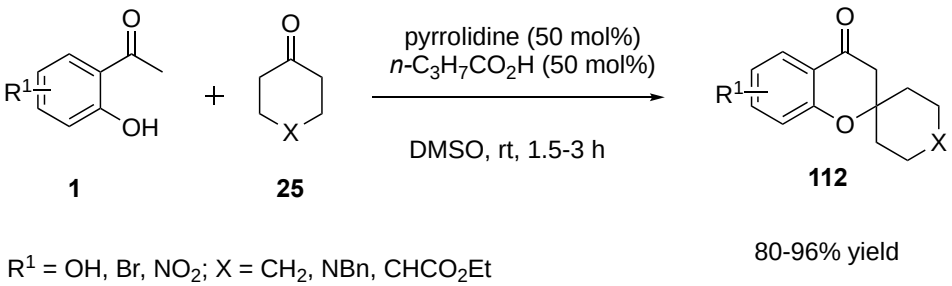
Scheme 32. Synthesis of 8´,11´-dihydrospiro[cyclohexane-1,2´-oxepino[2,3-*h*]chromen]-4´(3´*H*)-ones **109**

Muthukrishnan and co-workwers[54] in 2018 reported the functionalization of spirochroman-4-one **110** to **111** *via* transition metal-free efficient C-H hydroxylation at C6 position selectively using hypervalent iodine reagent $PhI(OAc)_2$ (**Scheme 33**).



Scheme 33. Synthesis of C-6 hydroxylated spirochromanones **111**

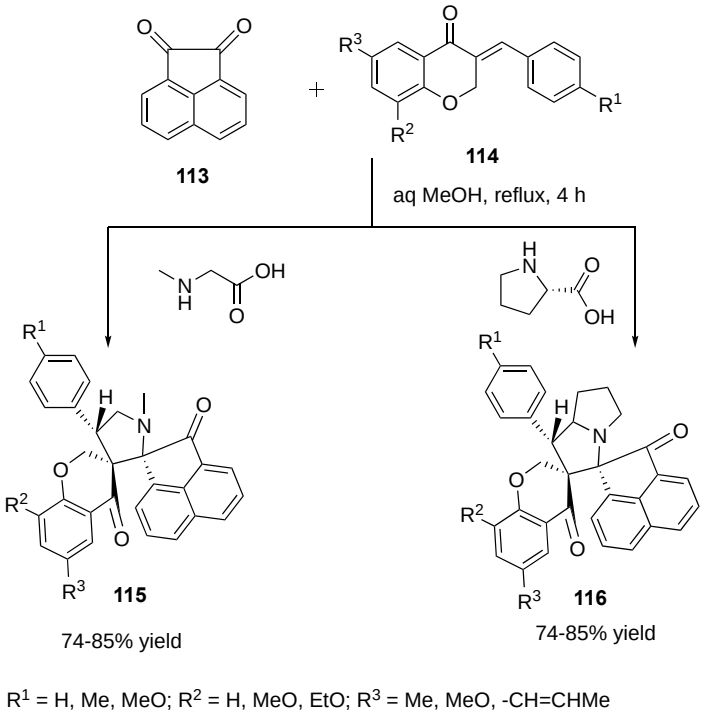
The Kapuriya group[55] in 2020 reported the synthesis of 2-spirochroman-4(*H*)-ones **112** using pyrrolidine/butanoic acid in DMSO as bifunctional organocatalyst in the Kabbe condensation reaction. A vast range of privileged spirochroman derivatives were obtained in excellent yield by the reaction of substituted 2-hydroxyacetophenone **1** with cyclic ketones **25**. Reaction provided poor yield when TFA, $HClO_4$, or *p*-TsOH was used as Lewis acid. Trace yields were obtained when $AlCl_3$, $MgBr_2(OEt)_2$ and $Bi(OTf)_3$ were used as acid precursors (**Scheme 34**).



Scheme 34. Synthesis of 2-spirochroman-4(*H*)-ones **112**

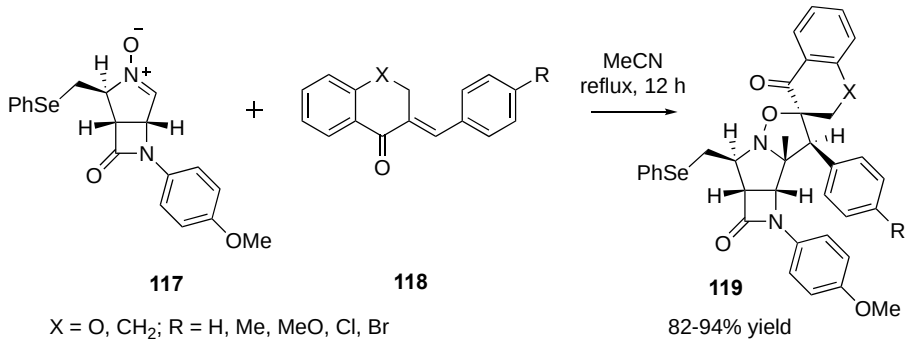
2.1.2. 1,3-Dipolar cycloaddition

The Ramkumar group[56] in 2009 reported the regioselective synthesis of dispiroheterocyclic chromanones **115** and **116** by the 1,3-dipolar cycloaddition reaction of azomethine ylides (generated *in situ*) to the condensation products of acenaphthenequinone **113** with **114**. The regio and stereoselective formation of *syn-endo* cycloadducts was confirmed by X-ray crystallographic study (**Scheme 35**).



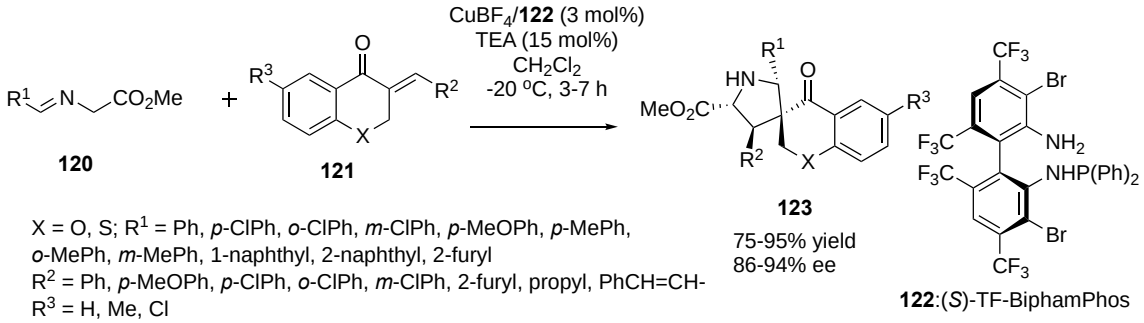
Scheme 35. Regioselective synthesis of dispiro heterocyclic adducts **115** and **116**

The Raghunathan group[57] in 2010 reported the regioselective synthesis of novel *β*-lactam fused spiroisoxazolidine chromanones **119** in good yields under conventional and microwave radiation following 1,3-dipolar cycloaddition of **117** and **118**. Reaction carried out under MW irradiation provided higher yield (82-94%) over conventional heating (45-55%) (**Scheme 36**).



Scheme 36. Synthesis of *β*-lactam fused spiroisoxazolidine chromanones **119**

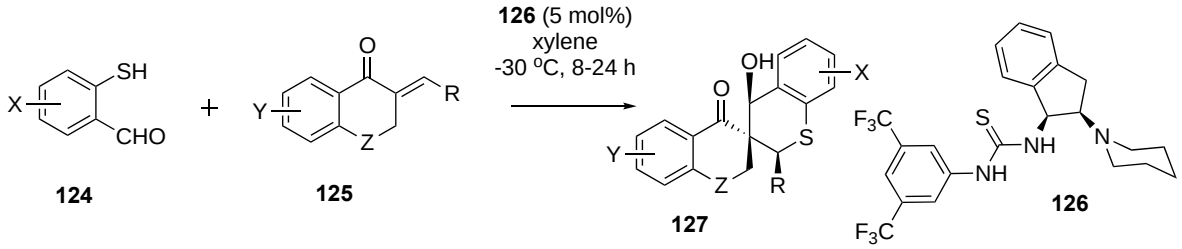
The Wang group[58] in 2011 reported the facile synthesis of highly functionalized spiro-[4-chromanone-3,3'-pyrrolidine] derivatives **123** bearing one spiro quaternary and three tertiary stereogenic centers in good yield with excellent enantioselectivity by the reaction of *N*-(4-chlorobenzylidene)glycine methyl ester **120** with (*E*)-3-benzylidenechroman-4-one **121** using 3 mol% of Cu(I)/TF-BiphamPhos **122** as catalyst and 15 mol% Et_3N as base in the 1,3-dipolar cycloaddition reaction. Solvent screening data indicated that dichloromethane is best solvent in comparison to MeCN, THF, EtOAc and toluene. Decreasing the reaction temperature from room temperature to -20 ^oC surprisingly enhanced the yield and enatioselectivity of the reaction. In the substrate scope, an array of imino ester derivatives **120** bearing electron-donating, electron withdrawing, heteroaryl as well as sterically hindered substituents were found to be well tolerated under the optimized reaction conditions. The reaction failed with alkyl substituted imino ester. Alkyl, alkenyl, aryl as well as heteroaryl chromanone derivatives **121** were used in this reaction. Additionally, the use of *thio*-chromanone provided the desired products in excellent yield and enantioselectivity (**Scheme 37**).



Scheme 37. Synthesis of spirochromanone pyrrolidine derivatives **123**

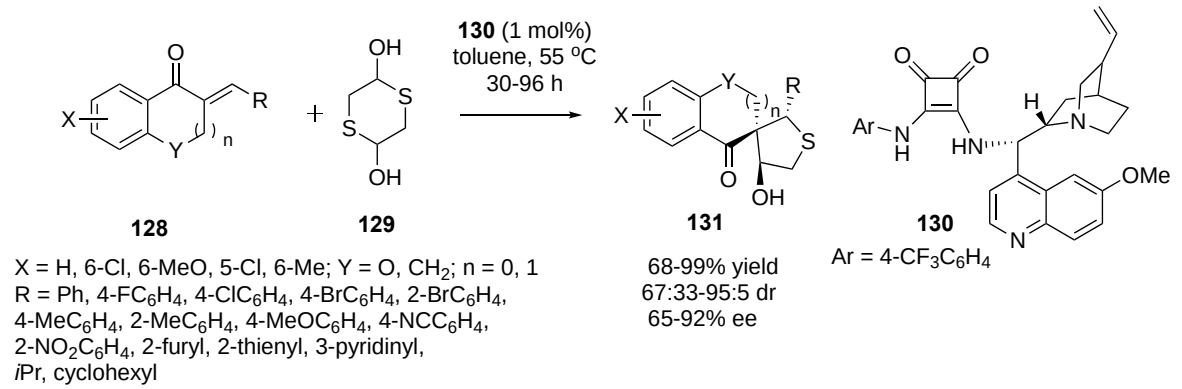
2.1.3. Organocatalyzed reactions

The Wang group[59] in 2010 reported the enantioselective synthesis of spirochromanone-thiochromane derivatives **127** in high yield with excellent stereoselectivities by the reaction of 2-mercaptobenzaldehyde **124** with benzylidenechroman-4-one **125** in the presence of a chiral bifunctional indane **126** as the organocatalyst. In the substrate scope, the electronic and steric effect of the substituents was found to have a minimal effect on the progress of the reaction. However, the diasteroselectivity of the reaction was reduced with thiochromanone as the substrate (**Scheme 38**).



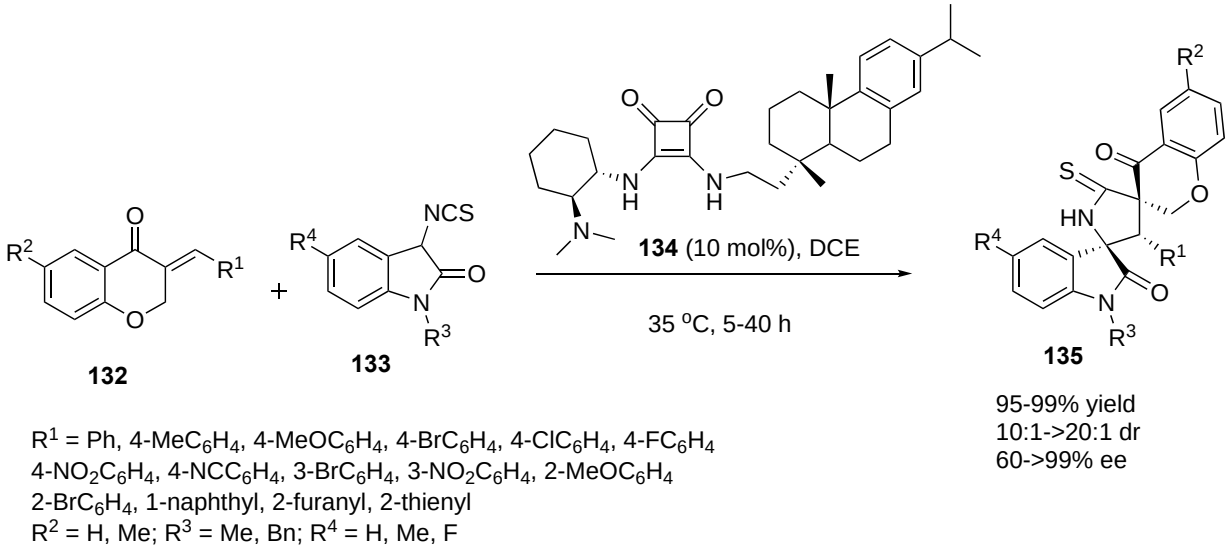
Scheme 38. Synthesis of spirochromanone-thiochromane derivatives

The Du group[60] in 2014 reported the asymmetric construction of chiral spirocyclic tetrahydrothiophene chromanone derivatives **131** with three contiguous stereocenters by the sulfa-Michael/aldol cascade reaction of benzylidenechroman-4-ones **128** with 1,4-dithiane-2,5-diols **129** using chiral bifunctional squaramide **130** as the organocatalyst. The desired products were obtained in high to excellent yield with excellent stereoselectivities. In the substrate scope, substituents at *ortho* position of the Michael acceptor slightly lowered the yield and enantioselectivity of the product. The desired product was not obtained with (*E*)-3-alkylidenechroman-4-one as the Michael acceptor (**Scheme 39**).



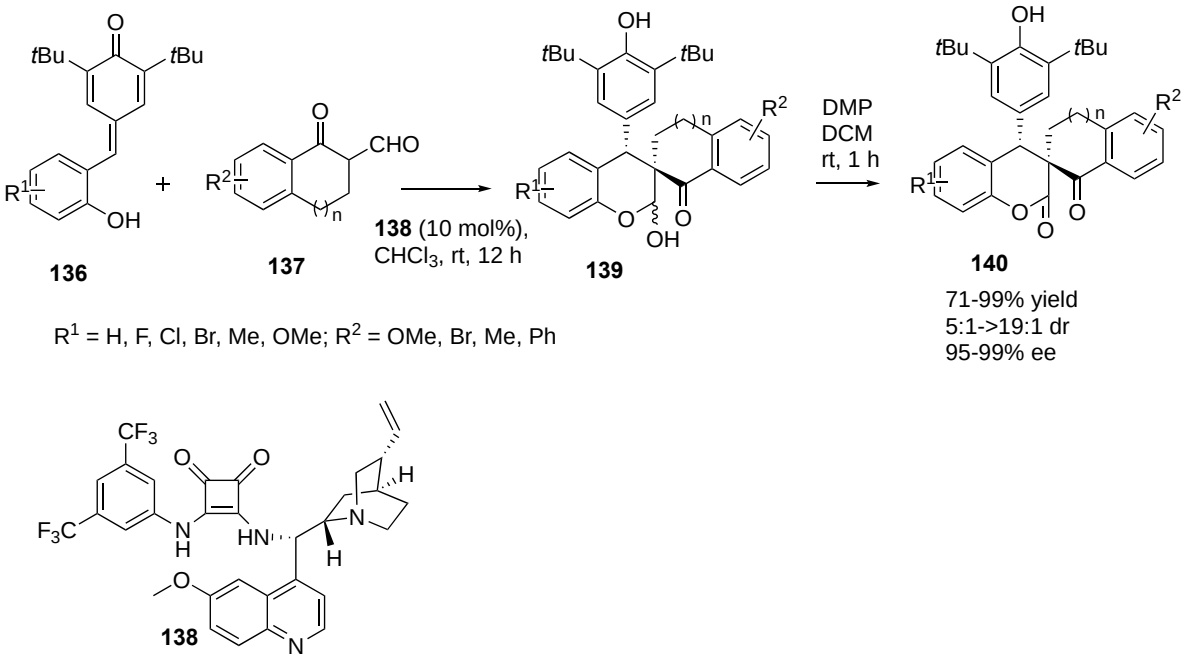
Scheme 39. Synthesis of spirocyclic tetrahydrothiophene chromanone derivatives **131**

Lin, Weng, and Lu[61] in 2018 reported the stereoselective synthesis of dispirochromanone oxindoles **135** with three continuous stereogenic centers by the asymmetric Michael/cyclization cascade reaction of 4-chromanones **132** as Michael acceptors with isothiocyanato oxindoles **133** as Michael donors using chiral bifunctional squaramide **134** as the organocatalyst. In the substrate scope it appeared that the position and electronic nature of substituents on the arylidenechroman-4-ones **132** had a minimal effect on the enantioselectivity of the reaction. It was also noticed that the reactions of benzylidenechroman-4-ones **132** with electron-poor groups on the phenyl ring exhibited slightly lower enantioselectivities over electron-rich groups. Also, substrates **133** bearing *ortho* substituents provided lower enantioselectivity than *para* and *meta* isomers. The enantioselectivity of the reaction decreased to 60% when *N*-benzyl-3-isothiocyanato was used as the substrate but the yield and diastereoselectivity was not affected (**Scheme 40**).



Scheme 40. Organocatalyzed synthesis of dispirochromanone oxindole derivatives **135**

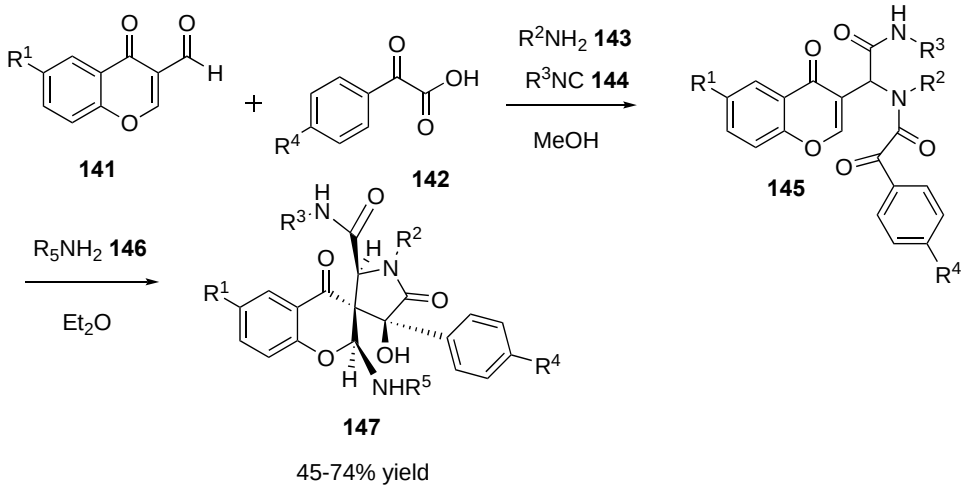
The Li group[62] in 2018 reported the synthesis of spirochromanone derivatives **139** by the reaction of *o*-hydroxyphenyl substituted *p*-quinone methides **136** with 1-oxotetraline-2-carbaldehydes **137** using chiral bifunctional squaramide **138** as the organocatalyst in the enantioselective 1,6-addition/acetalization reaction. The products **139** were oxidized to **140**. A vast range of *p*-quinine methides **136** and 1-oxotetraline-carbaldehydes **137** were used in this reaction. The reaction provided the target molecules in excellent yield (up to 99%) and stereoselectivities (>19:1 dr and up to 99% ee). Solvents play a major role in the outcome of the reaction. The use of toluene, benzotrifluoride, diethyl ether and tetrahydrofuran diminish the yield and stereoselectivity. The addition of molecular sieves (4A) had no influence on the reaction. Decreasing the mol% of the catalyst decreased the yield of the reaction (**Scheme 41**).



Scheme 41. Synthesis of spirochromanone derivatives **140**

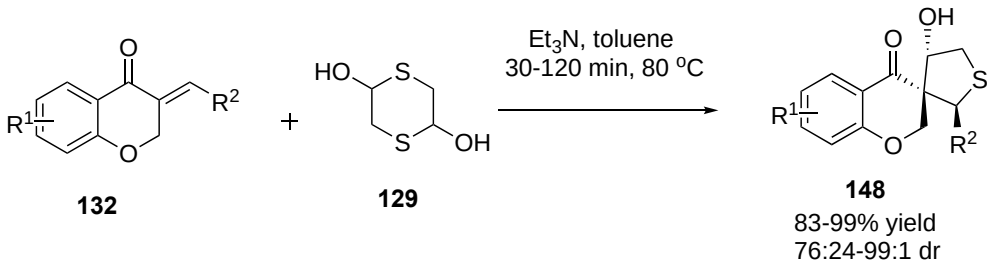
2.1.4. Miscellaneous

The groups of Marcaccini and Marcos[63] in 2009 reported the synthesis of a series of highly functionalized natural products spiropyrrolidinochromanones **147** following one-pot, two-step, diastereoselective four-component Ugi reaction. Nucleophilic conjugate addition and intramolecular cyclization reaction of 3-formylchromones **141**, amines **143**, isocyanides **144,** and glyoxylic acid **142** followed by cyclization of the intermediate product **145** reactions with amines **146**, provided the spiroadducts **147** in 45-74% yield (**Scheme 42**).

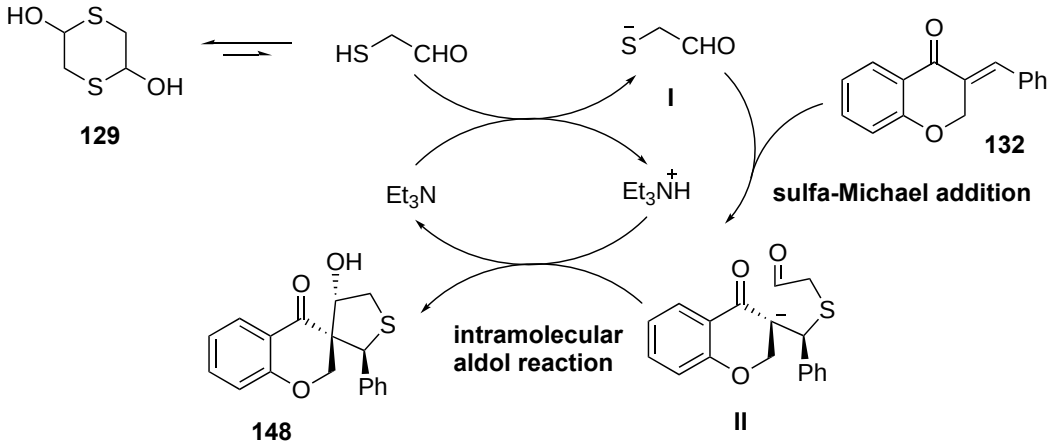


Scheme 42. Synthesis of spiropyrrolidinochromanones **147**

The groups of Wang and Kong[64] in 2015 reported the synthesis of 4'-hydroxy-2'-aryl-4',5'-dihydro-2'*H*-spiro[chromane-3,3'-thiophen]-4-ones **148** with three continuous stereocenters in high yields (83-99%) with good to excellent diastereoselectivities (76:24-99:1) by the sulfa-Michael/aldol cascade reaction of (*E*)-3-arylidenechroman-4-ones **132** with 1,4-dithiane-2,5-diol **129**. Under optimized conditions, the reaction was conducted in toluene at 80 ^{o}C in the presence of 20 mol% of Et_3N as catalyst. In the substrate scope, the electronic and steric effects of the substituents were found to have a negligible effect on the yield of the reaction. With the exception of R^1 = 6-Cl, the reaction with other substituents provided excellent stereoselectivities. The tentative mechanism for the formation of the product is shown in **Scheme 43**. Initially, the 2-mercaptoacetaldehyde **I**, generated *in situ* from 1,4-dithiane-2,5-diol **129**, undergoes intramolecular sulfa-Michael addition reaction with 3-benzylidenechroman-4-one **132** to provide the enolate intermediate **II** which subsequently undergoes intramolecular aldol reaction to deliver the final spiro chromanone-tetrahydrothiophene adduct **148** (**Scheme 43**).

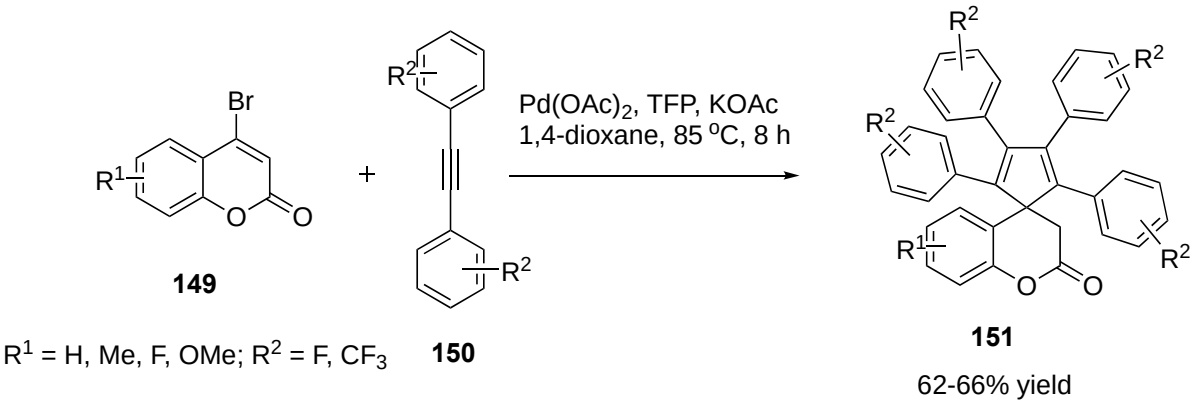


R^1 = H, 6-Me, 6-Cl; R^2 = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-*i*PrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 2-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-HO-3-$MeOC_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 4-$Me_2NC_6H_4$, 2-furyl, 2-thienyl, 2-pyridyl, 2-naphthyl, PhCH=CH-



Scheme 43. Synthesis of spiro chromanone-tetrahydrothiophene adduct **148**

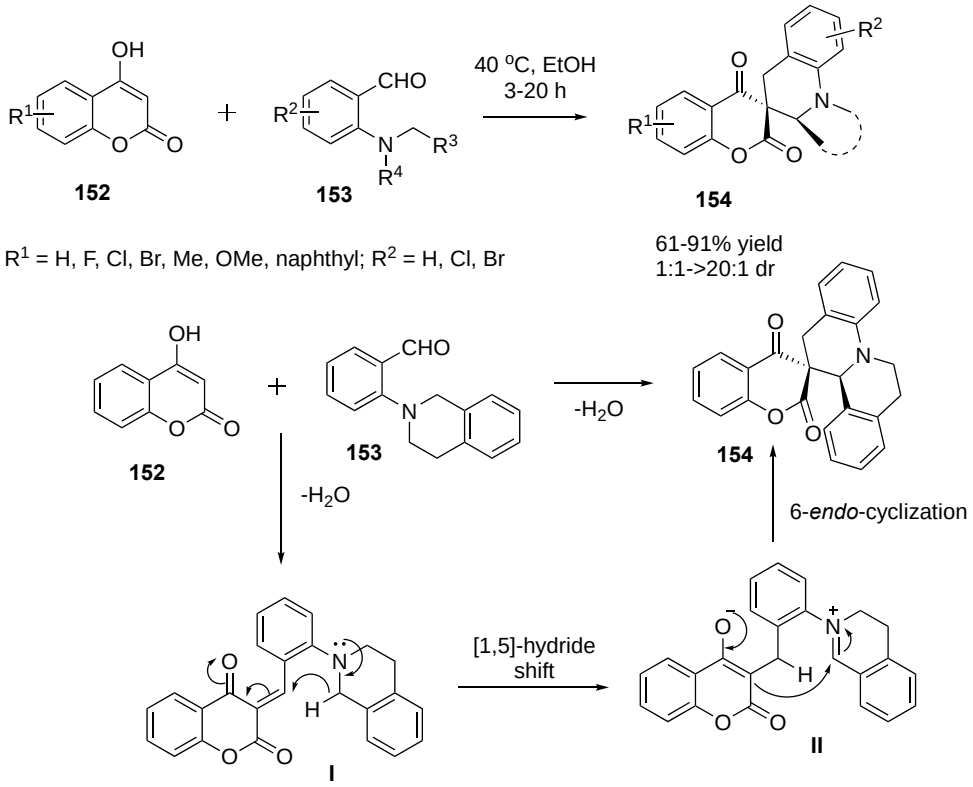
The Gogoi group[65] in 2020 reported the synthesis of a broad range of pentadiene fused spirochromanone derivatives **151** in good yield by palladium catalyzed spiroannulation of 4-bromocoumarins **149** with alkynes **150**. The reaction failed when $R^2 = CF_3$ (**Scheme 44**).



Scheme 44. Synthesis of pentadiene fused spirochromanone derivatives **151**

The Wang group[66] in 2020 reported the catalyst-free synthesis of spiro[benzoquinolizidinechromanones] **154** in high yield with excellent diastereoselectivities by the reaction of 4-hydroxycoumarins **152** and *o*-amino substituted benzaldehydes **153** by tandem condensation/1,5-hydride transfer/cyclization process. The developed protocol offers a high atom economy and step economy, high levels of stereocontrol, mild conditions, and a simple work-up. The presence of Lewis acid as a presumed catalyst did not significantly enhance the yield of the reaction. Compared to aprotic solvents, the reaction was faster in protic solvents, which might be due to the hydrogen bonding effect. In the substrate scope, 4-hydroxycoumarins **152** bearing electron-donating or electron-withdrawing substituents undergo the reaction smoothly irrespective of the position and nature of the substituents.

Similarly, the use of *o*-amino substituted benzaldehydes **153** bearing halo substituents provide good yield of the products. However, the diasteroselectivity of the reaction decreases greatly with indolizine and azepine as model substrates, but the yield is not affected. The tentative mechanistic pathway for the formation of the product is shown below. Condensation of 4-hydroxycoumarin **152** with *o*-amino substituted benzaldehyde **153** provides intermediate **I**, which subsequently undergoes a 1,5-hydride shift and 6-*endo*-cyclization to afford the final product **154** (**Scheme 45**).

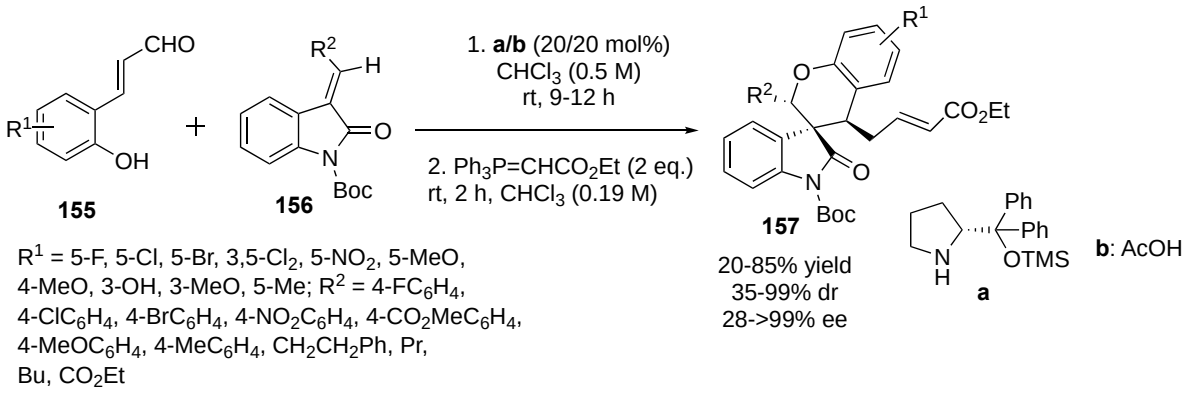


Scheme 45. Synthesis of spirobenzoquinolizidinechromanones **154**

2.2. SYNTHESIS OF SPIROCHROMANES

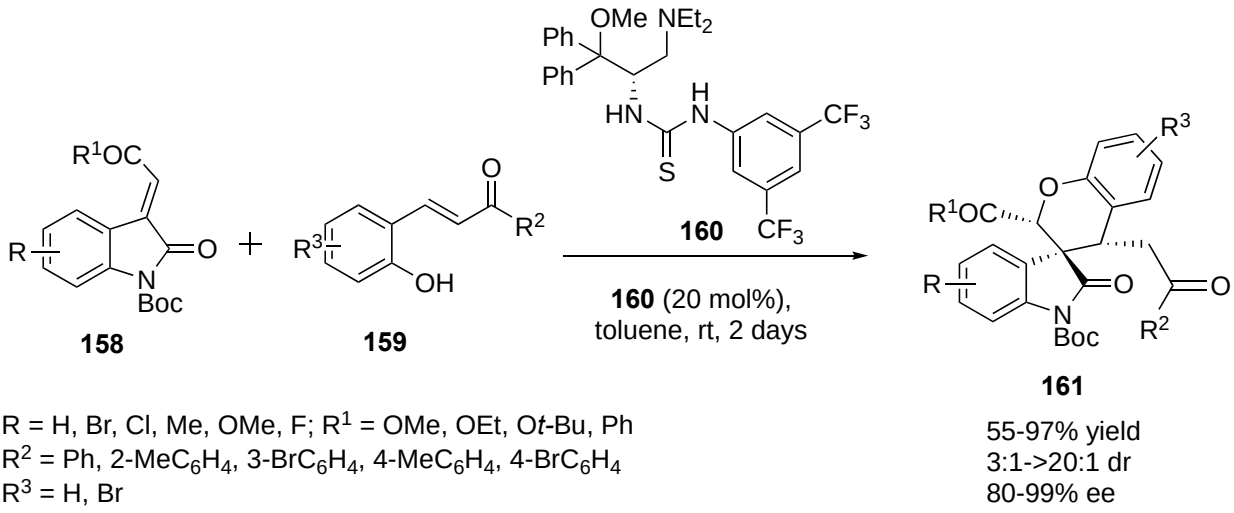
2.2.1. Organocatalyzed Michael addition

Ramachary and co-workers[67] in 2014 reported the asymmetric synthesis of functionalized spirochromane-[3,3'-indolin]-2'-ones **157** with three continuous stereocenters with high stereoselectivities by the reflexive-Michael reaction of hydroxyenals **155** with (*E*)-3-alkylideneindolin-2-ones **156** in the presence of proline/AcOH as catalyst at room temperature. Diminished stereoselectivity was observed when *N*-Boc was replaced by *N*-Ac. Reaction failed when indole without any protecting group was considered as the substrate (**Scheme 46**).



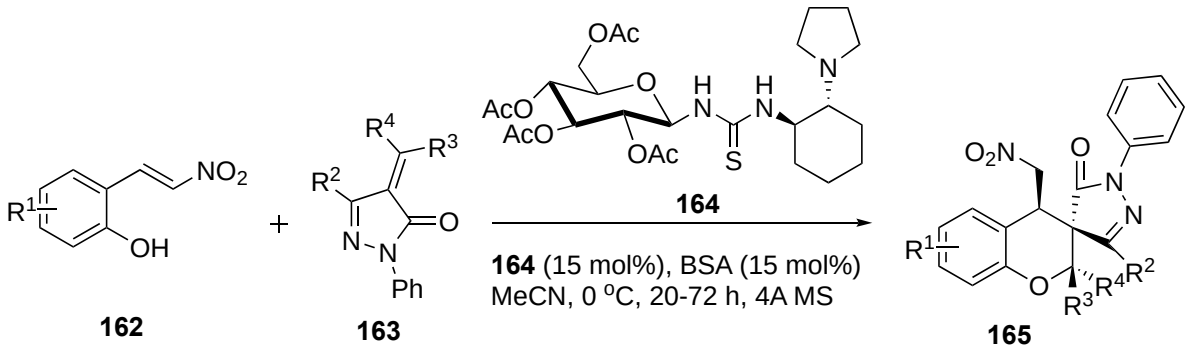
Scheme 46. Synthesis of functionalized spiro[chromane]-3,3'-indolin]-2'-ones **157**

The Zhao group[68] in 2014 synthesized chiral spirooxindole-chromane scaffolds with three continuous stereocenters **161** in moderate to excellent yield with excellent enantioselectivity by the reaction of methyleneindolinone **158** and *o*-hydroxychalcone **159** at room temperature following asymmetric *oxa*-Michael-Michael cascade sequence in the presence of chiral tertiary amine-thiourea **160** as the organocatalyst. Low yield was observed when the reaction was carried out at 0 °C. The reaction did not proceed when the Boc protection of methyleneindolinone **158** was replaced by Ac or Bn. Electron-donating and electron-withdrawing substituents in the aromatic ring of the substrate have a negligible influence on the yield (**Scheme 47**).



Scheme 47. Synthesis of spirooxindole-chromane scaffolds **161**

The Miao group[69] in 2015 elegantly explored the synthesis of spiro[chromane-3,3'-pyrazole] scaffolds **165** by the reaction of 4-alkenylpyrazolin-3-one **163** with (*E*)-2-(nitrovinyl)phenol **162** *via* *oxa*-Michael-Michael addition reaction in the presence of a chiral bifunctional amine thiourea **164** as the catalyst. The domino cascade reaction offered the desired molecules in excellent yields and stereoselectivities, leading to the formation of three contiguous stereocenters under low catalyst loading (15 mol%). Unsatisfactory yields were obtained when a chiral bifunctional indane-thiourea derivative was used as the organocatalyst. In comparison to the use of polar protic solvents, the use of polar aprotic solvents increased the rate of the reaction and promoted the formation of products in good steroselectivities and a shorter reaction time. Decreasing the catalyst loading diminished the yield of the reaction. The presence of an acidic additive had found to have a pronounced effect in increasing the yield of the reaction offering high catalytic performance. In the substrate scope, all reactants were found to be well tolerated under the optimized conditions regardless of the position and nature of the substituents (**Scheme 48**).

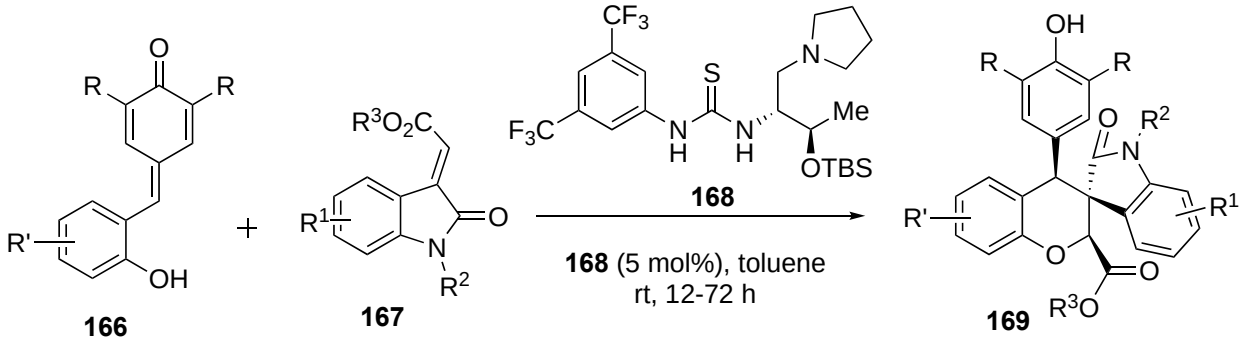


R^1 = H, 6-Br, 6-NO_2, 5,6-C_4H_4, 6,8-$C(Me)_3$, 7-MeO; R^2 = Me, Ph
R^3= Ph, *o*-FC_6H_4, *p*-FC_6H_4, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *m*-BrC_6H_4, *p*-BrC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, *m*-$NO_2C_6H_4$, furyl, Me; R^4 = H, Me

73-99% yield
>20:1-93:7 dr
64->99% ee

Scheme 48. Synthesis of spiro[chroman-3,3'-pyrazol] scaffolds **165**

The Enders group[70] in 2016 elegantly discussed the synthesis of 4-phenyl substituted 3-spiro-oxindole-chromane derivatives **169** in good to excellent yields with very high stereoselectivities by the *oxa*-Michael/1,6-addition reaction of *o*-hydroxyphenyl-substituted *p*-quinone methides **166** and isatin-derived enolates **167** in the presence of 5 mol% of bifunctional thiourea derivative **168** as the organocatalyst. It is noteworthy that electronic and steric effects of the substituents on the substrate have a negligible effect on the rate of the reaction irrespective of their position and nature (**Scheme 49**).

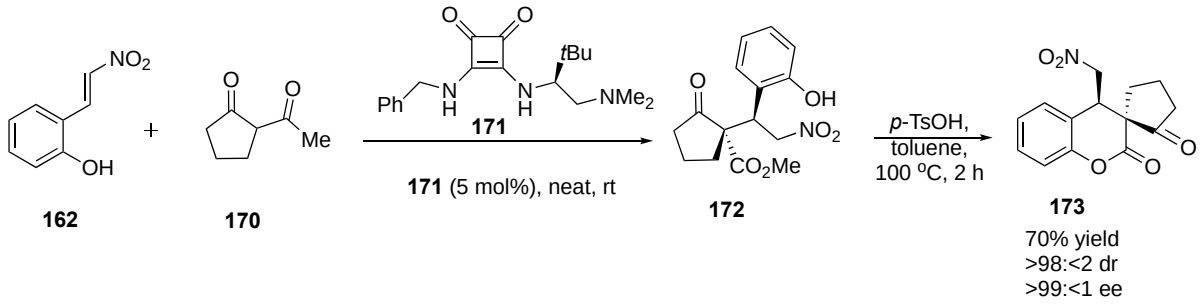


R' = H, 4-Cl, 4-Br, 4-Me, 4-MeO, 5-MeO, 6-MeO; R = *t*-Bu, *i*-Pr
R^1 = 5-H, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 5-I, 5-NO_2, 5-CF_3O, 6-Cl
R^2 = Boc,Cbz, CO_2Me, CO_2Ph; R^3 = MeO, EtO, BnO

51-98% yield
10:1->20:1 dr
92->99% ee

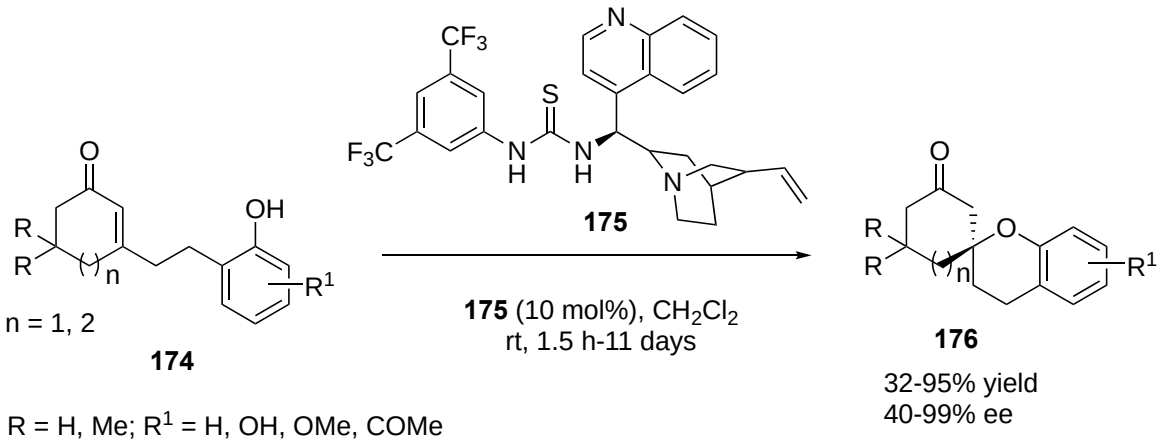
Scheme 49. Synthesis of 4-phenyl substituted 3-spiro-oxindole-chromane derivatives **169**

The groups of Andrés and Pedrosa[71] in 2018 reported the enantioselective synthesis of spirochromanone derivative **173** in high yield with excellent stereoselectivity by the Michael addition reaction of 2-(2-nitrovinyl)phenol **162** and 2-acetylpentanone **170** in the presence of squaramide **171** as a catalyst followed by cyclization of the intermediate product **172** (**Scheme 50**).



Scheme 50. Enantioselective synthesis of spirochromanone **173**

The groups Yoshida and Takao[72] in 2020 reported the organocatalytic enantioselective construction of spirochromane derivatives **176** with a tetrasubstituted stereocenter by the intramolecular *oxy*-Michael addition reaction of **174**. The target spirochromane derivatives **176** were obtained in high yields with excellent enantiomeric excess (up to 99%) using bifunctional cinchona alkaloid thiourea **175** as the novel catalyst. The developed protocol could be applied to the asymmetric formal synthesis of (-)-(*R*)-cordiachromene. Dichloromethane is the optimized solvent, and the use of THF as the solvent resulted in low yield and enantioslectivity. Similarly, decreasing the reaction temperature provided diminished yield and enantioselectivities. The use of substrate **174** bearing two hydroxyl groups provided lower yield (32%) and enantioselectivity (40% ee) (**Scheme 51**).

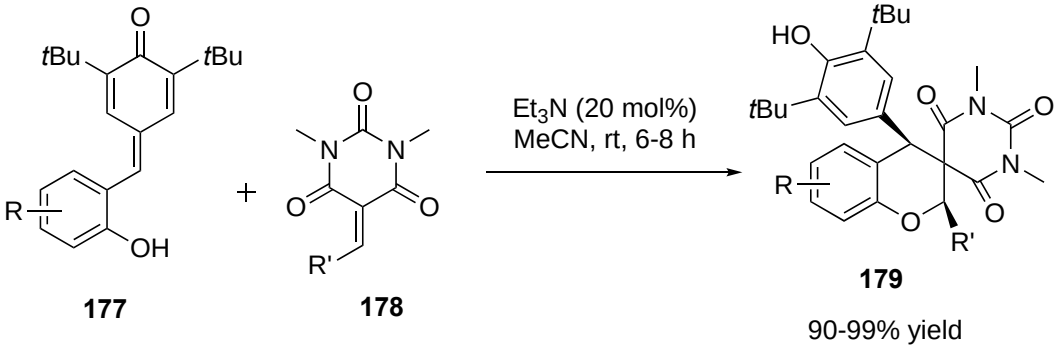


Scheme 51. Enantioselective construction of spirochromane derivatives **176**

2.2.2. *Oxa*-Michael/1,6-addition reactions

The Liang group[73] in 2019 reported the synthesis of a library of spiro-barbituratechromanes **179** in excellent yields (90-99%) and high diastereoselectivities by the reaction of the substrates **177** with barbiturate-based olefins **178** at room temperature following domino *oxa*-Michael/1,6-addition reaction in the presence of Et_3N as the catalyst. In the absence of base, the yield of the reaction was sharply decreased. A trace amount of product was observed with DBU/CH_2Cl_2 and Et_3N/toluene. Both increasing

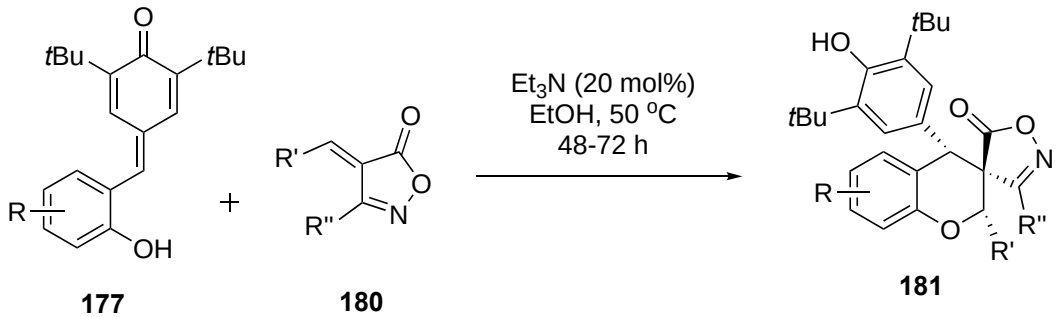
or decreasing the temperature from 25 °C diminished the yield of the reaction leading to the formation of side products. It is noteworthy that many substrates could be used under standard conditions irrespective of the position and nature of the substituents (**Scheme 52**).



R = H, MeO, Me, F, Cl, Br
R' = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 2-furyl, 2-thiophene, cyclohexyl,

Scheme 52. Synthesis of spiro-barbituratechromans **179**

The groups of Yu and Zhou[74] in 2019 reported the synthesis of a series of spiroisoxazolonechromanes **181** in high yield and diastereoselectivity by the *oxa*-Michael/1,6-addition reaction of *o*-hydroxyphenyl substituted *p*-quinone methides **177** and unsaturated isoxazolones **180** in EtOH using Et_3N as base. Solvents such as CH_2Cl_2, $CHCl_3$, THF, and toluene had a substantial influence on the diastereoselectivity of the reaction though the yield was not affected. Any deviation from the optimized temperature of 50 °C decreased the rate of the reaction leading to the formation of byproducts. Diastereoselectivities were lower when alkyl-substituted oxazolones **180** were used as the substrates (**Scheme 53**).

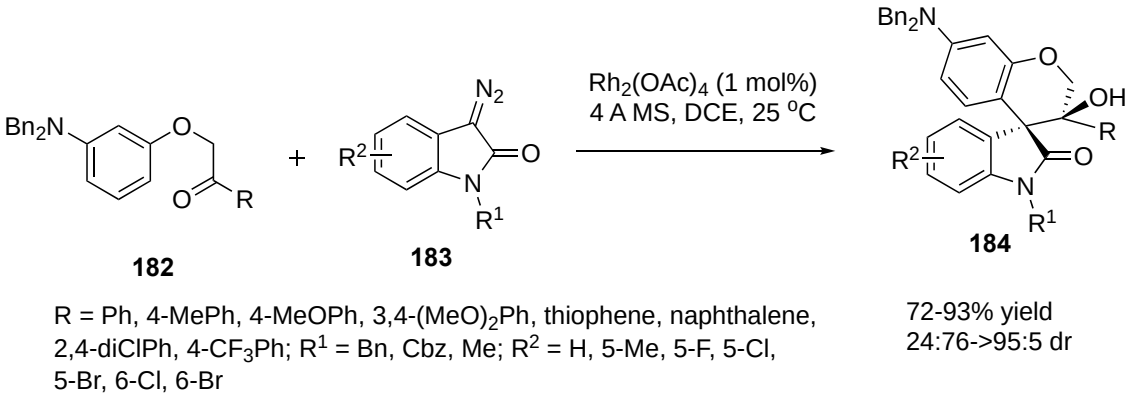


R = H, Me, F, Cl
R' = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 2-thiophene, cyclohexyl, naphthyl; R'' = Me, Et

Scheme 53. Synthesis of spiroisoxazolone-chromans **181**

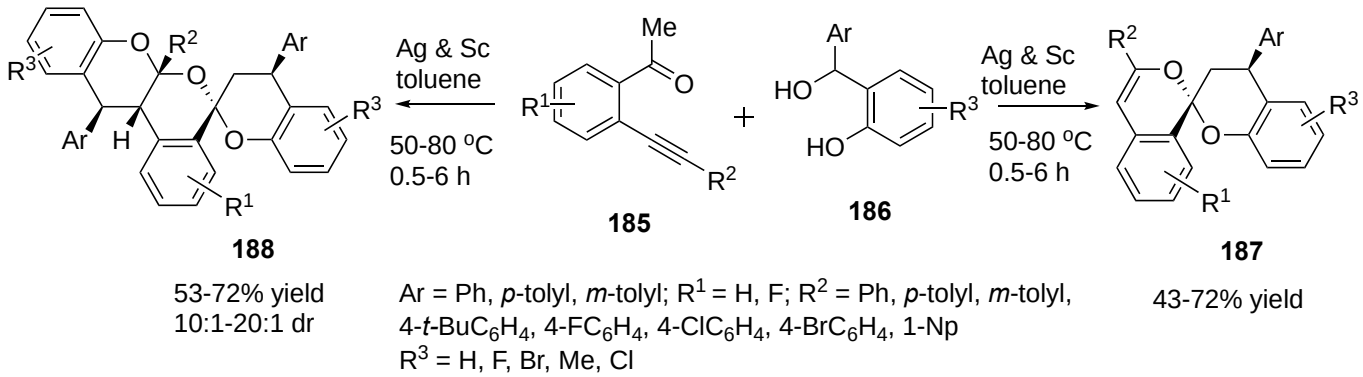
2.2.4. Metal catalyzed cyclization reactions

The Hu group[75] in 2017 discussed the $Rh_2(OAc)_4$ catalyzed synthesis of a series of functionalized spirochromane-oxindole derivatives **184** with two adjacent quaternary carbon centers in excellent yield and high diastereoselectivity by the aromatic C-H functionalization of α-phenoxyketones **182** with 3-diazooxindoles **183**. Solvents play a significant role in the reaction. The deleterious yield was observed for the reaction conducted in xylene, toluene, or chloroform. In the substrate scope, electron-rich and electron-poor substrates were found to be well tolerated under the optimized conditions, irrespective of the nature and position of the substituent. However, replacing R^1 = Bn by Cbz or Me in 3-diazooxindoles **183** slightly reduced the yield of the product (**Scheme 54**).



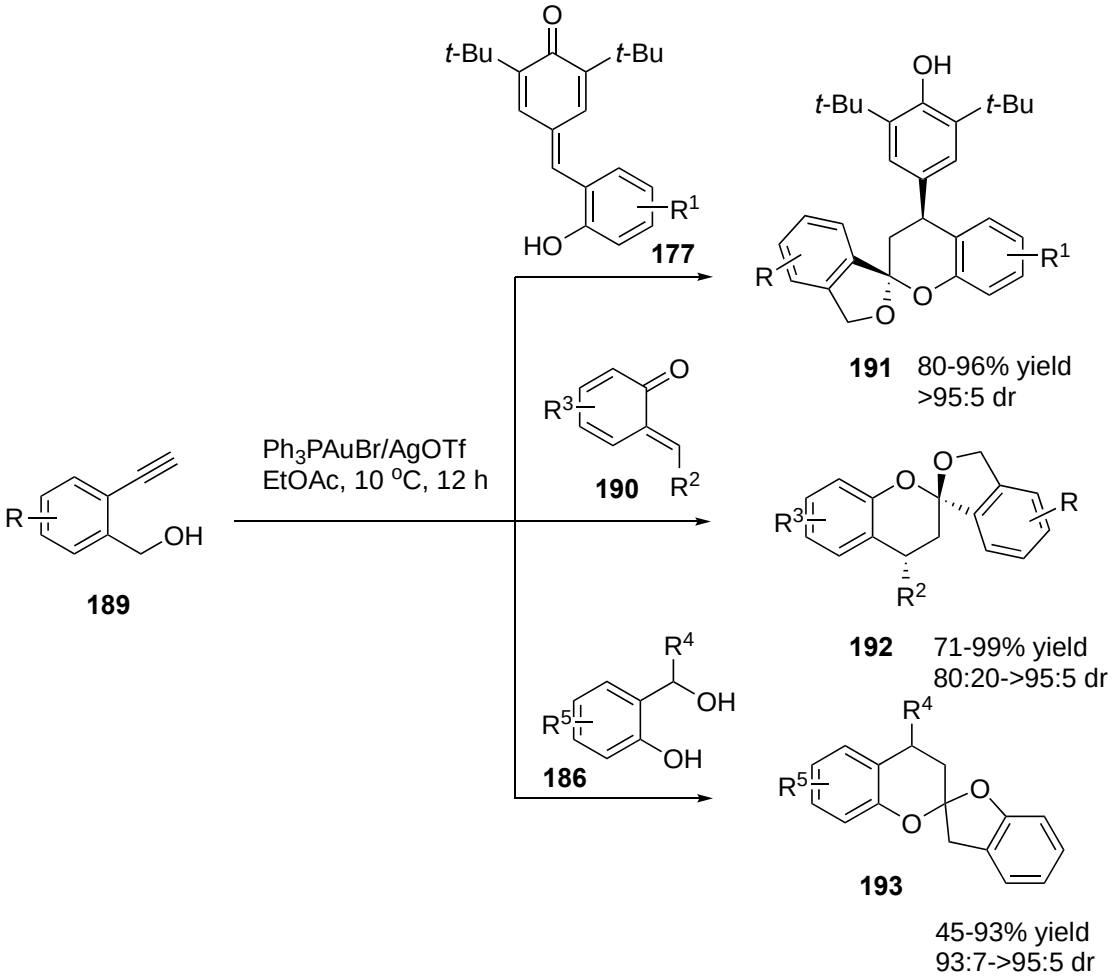
Scheme 54. Synthesis of spirochromane-oxindole derivatives

The groups of Hao, Tu, and Jiang[76] in 2017 reported the silver and scandium mediated synthesis of various structurally diverse spirochromane derivatives **187** and **188** in moderate to good yields by the reaction of α-alkynyl ketones **185** and *o*-hydroxybenzyl alcohols **186** by dehydroxylative cyclizations followed by Diels-Alder reaction. The reactions failed in the absence of $Sc(OTf)_3$. Trace amounts of the products were obtained when *o*-hydroxybenzyl alcohols **186** with Ar = 1-naphthyl was used as the model substrate (**Scheme 55**).



Scheme 55. Synthesis of spirochromane derivatives **187** and **188**

The group of Wang and Shi[77] in 2018 reported the synthesis of spirochromane derivatives **191-193** in high yield (up to 99%) with excellent distereoselectivities (up to >95:5 dr) following gold catalyzed *oxa*-[4+2] cyclization of *o*/*p*-quinone methides **189** with alkynyl benzyl alcohols **177**, **190**, **186**. Increasing the reaction temperature from 10 °C lowered the yields of the products. Reaction failed with an alkynyl amide analogue instead of **189** as the substrate. The reaction resulted in a low yield in the absence of PPh_3AuBr and failed in the absence of AgOTf (**Scheme 56**).

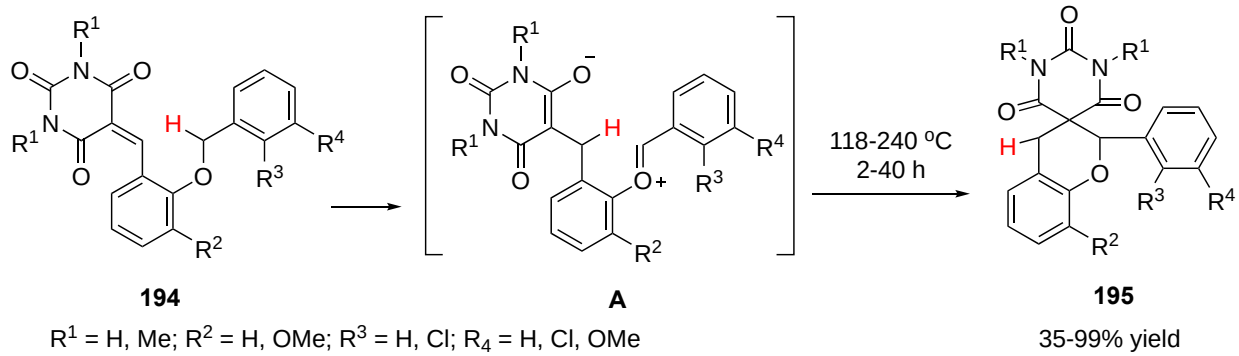


R = H, 3-F, 4-Me, 4-Cl, 5-F, 5-MeO; R^1 = H, 3-MeO, 4-MeO, 5-*t*-Bu, 5-MeO, 5-Me, Ph, 2-MeC_6H_4 3-MeC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 2-thiophenyl
R^2 = Ph, 2-$MeOC_6H_4$, 2-MeC_6H_4, 2-FC_6H_4, 2-thiophenyl, R^3 = H, MeO; R^4 = Ph, *t*BuC_6H_4, 4-MeC_6H_4 $(Me)_2CH$-; R^5 = H, MeO, F

Scheme 56. Metal catalyzed synthesis of spirochromane derivatives **191-193**

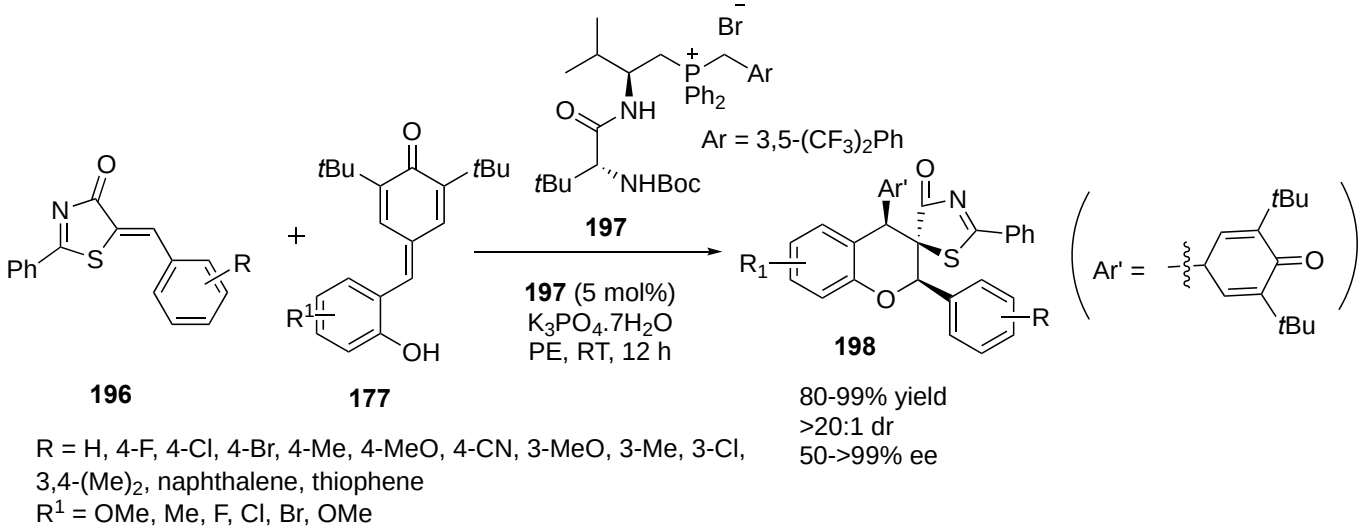
2.2.5. Miscellaneous

The group of Krasnov and Khrustalev[78] in 2017 reported the synthesis of 2,4,6-trioxoperhydropyrimidine-5-spiro-3'chromanes **195** by thermally induced 1,5-hydride transfer in **194**, followed by cyclization reaction of the resultant intermediate product **A** (**Scheme 57**).



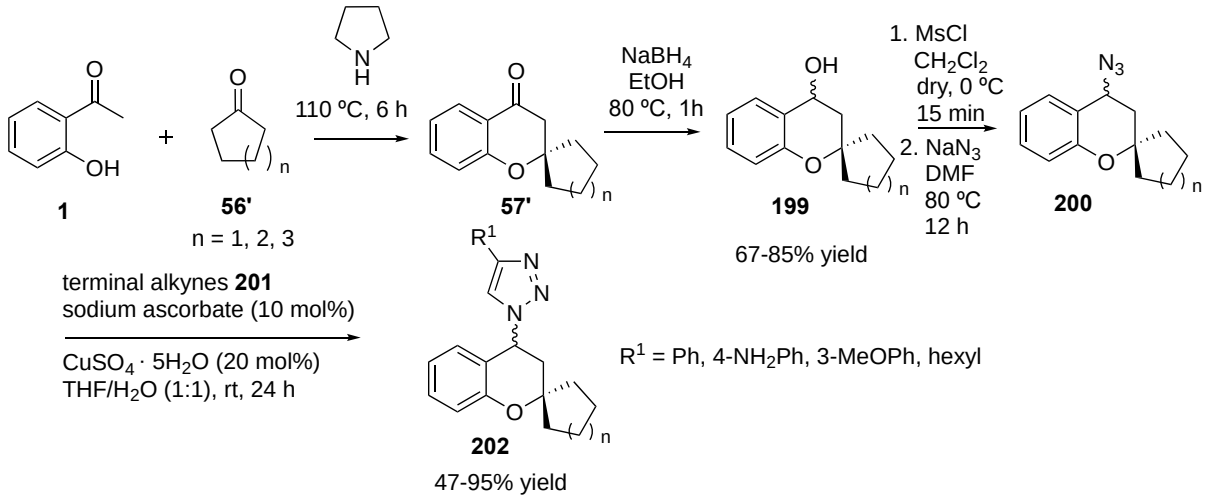
Scheme 57. Synthesis of 2,4,6-trioxoperhydropyrimidine-5-spiro-3'-chromanes **195**

Wang and co-workers[79] in 2020 reported the enantioselective formal [4+2] annulations reaction of 5-alkenylthiazolones **196** with hydroxyl substituted *p*-quinone methides **177** using dipeptide based phosphonium salt **197** as a catalyst. A wide range of functionalized spiro-chromane-thiazolone derivatives **198** with three contiguous stereocenters was obtained in high yields and excellent stereoselectivities (>20:1 dr and up to >99% ee) under low catalyst loading and mild reaction conditions. The position and electronic nature of the substituents do not significantly affect the yield of the reaction. Steric hindrances of the bulky groups are also tolerated under optimized conditions. However, only moderate enantioselectivity was observed when R = 2-thienyl (**Scheme 58**).



Scheme 58. Synthesis of spiro-chromane-thiazolone derivatives

Iglesias, Bonacorso, and co-workers[80] in 2020 reported the regioselective synthesis of a wide range of 4-(alkyl/aryl)-1-spiro[chromane-2,1'-cycloalkan]-4-yl-1*H*-1,2,3-triazoles **202** as shown in **Scheme 62**. The intermediate products **57'**, **199,** and **200** are shown. Significantly lower yields of the final product **202** were obtained when the $CuSO_4$ catalyst was replaced by CuI (**Scheme 59**).



Scheme 59. Synthesis of 1-spiro[chromane-2,1'-cycloalkan]-4-yl-1*H*-1,2,3-triazoles **202**

CONCLUSIONS

In this review we summarized various reaction pathways leading to the synthesis of spirochromanones and spirochromanes, which have attracted attention in the past years. The past ten years have witnessed great development of diverse spirochromanone and spirochromane compounds. In this review, many biologically active and synthetically important structures were obtained by the simple Kabbe condensation, organocatalyzed Michael addition reaction, 1,3-dipolar cycloaddition reaction, and metal-catalyzed reaction, among other approaches, and by further post-transformation of the synthesized heterocycles. Most of the described spirochromanones and spirochromanes show biological activities, including anti-cancer, antiarrhythmic, antimycobacterial, antioxidant, and antifungal properties. These structures are of great importance in future drug design.

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Chemistry, Molecular Sciences and Chemical Engineering, Elsevier: 2020, DOI: 10.1016/B978-0-12-409547-2.14957-1

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