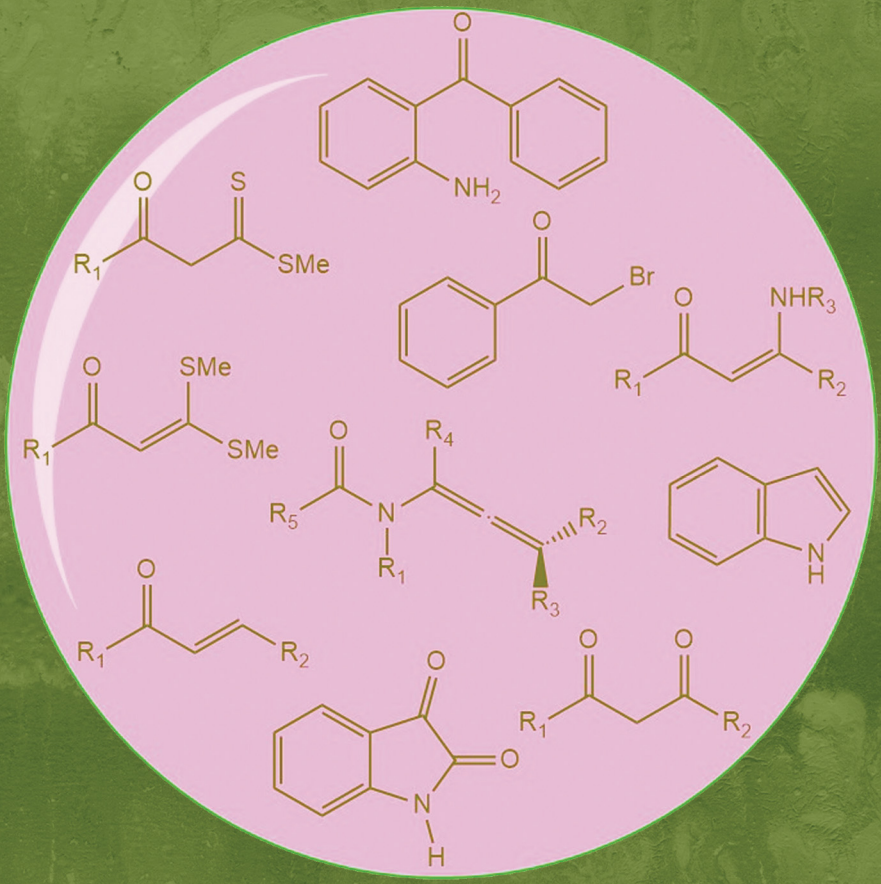

Versatile Precursors in Organic Synthesis

Okram Mukherjee Singh
Thokchom Prasanta Singh

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Cambridge
Scholars
Publishing

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This book first published 2022

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-8866-1
ISBN (13): 978-1-5275-8866-0

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CHAPTER 1

1,3-DIKETONES

1. Introduction

The importance of 1,3-diketones (*β*-diketones) **1** (Figure 1) is difficult to assess in synthetic organic chemistry, but it is one of the most valuable and fundamental intermediates due to the presence of two carbonyl groups in it. Their chemistry is closely associated with well-known name reactions in organic chemistry such as Claisen, Knoevenagel, Michael, etc. The high reactivity of 1,3-diketones helps in broad prospects for constructing C-C bonds, carbo- and heterocycles (Shokova et al., 2015). They are also an excellent versatile intermediate in multicomponent reactions, particularly regio- and stereoselective, which is especially important in synthesizing potentially, biologically active compounds (Bonne et al., 2010; and Colombo and Peretto, 2008). They also act as bidentate ligands in metal catalysis as well as luminescent materials (Vigato et al., 2009).

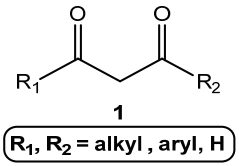
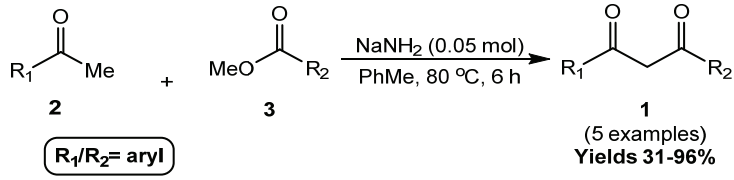


Figure 1. A simple structure of 1,3-diketone compound.

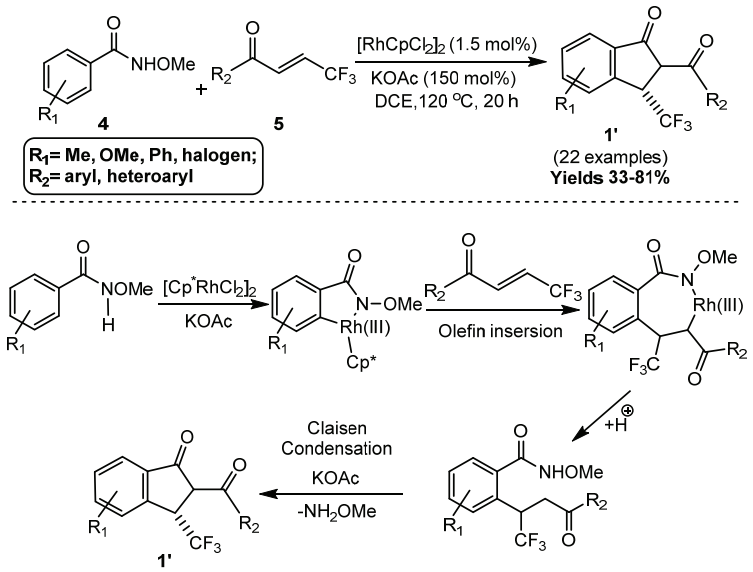
2. Synthesis of 1,3-Diketones

One of the significant methods for the synthesis of *β*-diketones is based on Claisen condensation, which has been known since 1887. It involves acylation of monocarbonyl compounds in the presence of catalysts favoring their enolization (Kel'in, 2003; Kel'in et al., 2003). Acetophenone derivatives **2** were converted into *β*-diketones *via* acylation with aromatic esters **3** under the classical Claisen conditions using $NaNH_2$ as a catalyst, as reported by Wang et al. (2012), (Scheme 1).



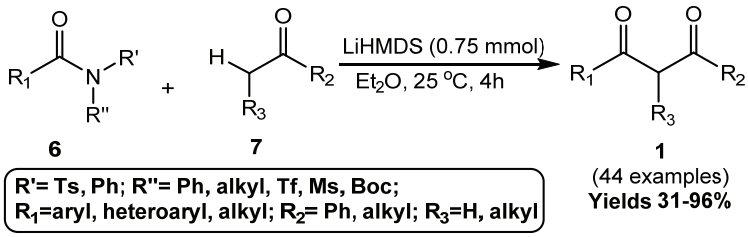
Scheme 1. Synthesis of 1,3-diketones by Claisen Condensation.

The synthesis of 2-acyl-3-trifluromethylindanones **1'** by coupling with *N*-methoxybenzamides **4** and *β*-trifluoromethyl-*α,β*-unsaturated ketone **5** using $[RhCp^*Cl_2]_2$ in the presence of KOAc, DCE at 120 °C was demonstrated by Chaudhary et al. (2020). The reaction mechanism involved sp^2 C-H activation, followed by Claisen condensation involving C-N bond cleavage to form the products (Scheme 2).



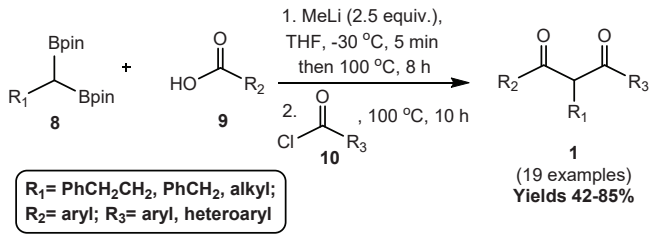
Scheme 2. Synthesis of 1,3-diketone using 2-acyl-3-trifluoromethylindanones.

Chen et al. (2020) reported the synthesis of 1,3-diketones using different tertiary amides **6** with ketones **7** in the presence of lithium bis(trimethylsilyl)amide (LiHMDS). The methodology gave the corresponding 1,3-diketones in good to excellent yields *via* C-N cleavage of amides and deprotonation of ketones. The reactions were performed at room temperature without any catalyst. The advantages of this method are its broad scope, good functional group tolerance of substrates and the potential of this protocol in organic synthesis and industrial manufacture (Scheme 3).



Scheme 3. Synthesis of 1,3-diketones using 3° amides with ketone.

Then, the synthesis of asymmetric 1,3-diketones through diacylation of 1,1-diborylalkanes **8** using two different acyl groups i.e., **9** and **10** were explored (Zou et al., 2019). In this method, an enolate boron species was firstly formed by introducing an acyl group and then it reacted again with another acyl group to form 1,3–diketone (Scheme 4).

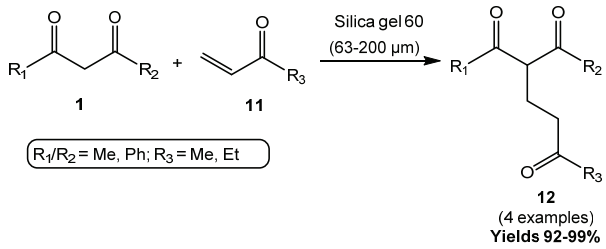


Scheme 4. General synthesis of 1,3-diketones.

3. Functionalization of 1,3-Diketones

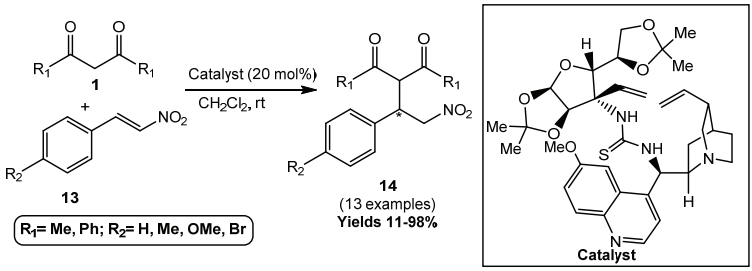
The functionalized 1,3-diketones are clinically significant molecules due to their exhibition of various biological properties such as antibacterial,

antiviral, insecticidal, etc. (Sheikh et al., 2013). The metal-catalyzed C-H and C-O functionalization reactions are also significant because of their potential to streamline organic synthesis by avoiding the prior preparation of activated substrates and reducing the quantity of waste by-products, and thereby making more atom-economic of the reactions (Dooley et al., 2013). In this context, the Michael addition is widely famous as well as recognized as an efficient and vital reaction for the formation of C-C bonds in organic synthesis (Axelsson et al., 2020). The report on a silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compound in the presence of methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) **11**, giving rise to corresponding adducts **12** without volatilization in good yields, was reported in 2020 by Tanemura and Rohand (2020), (Scheme 5).



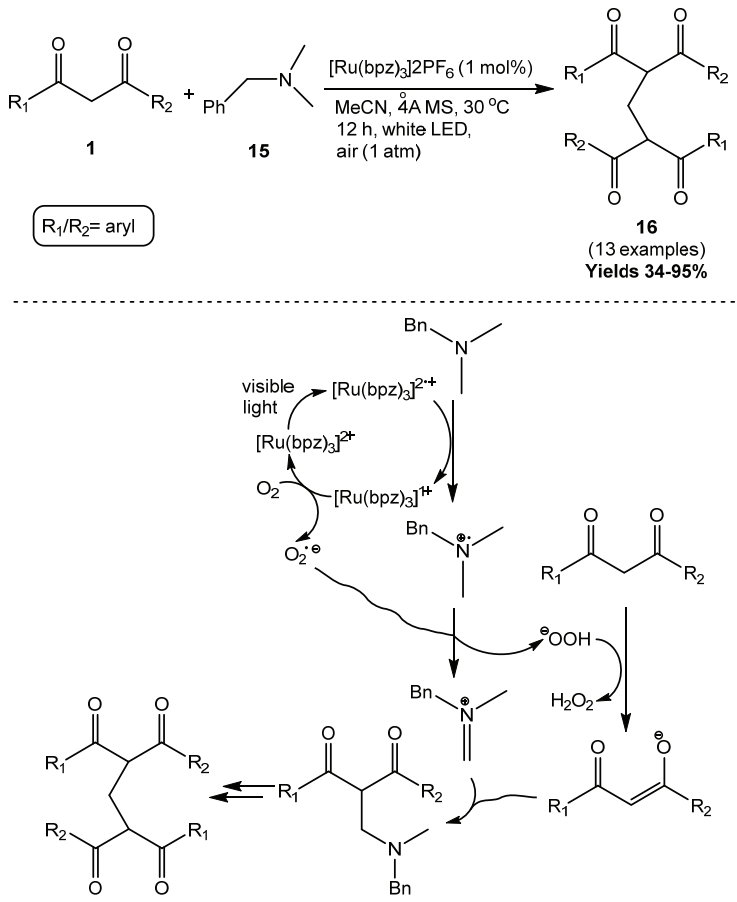
Scheme 5. α-Position functionalization of 1,3-diketone using vinyl ketones.

The Michael addition of 1,3-dicarbonyl compounds to nitrostyrenes **13** to afford the corresponding adducts **14** in excellent yields (up to 98%) was elaborated on (Scheme 6). This protocol used a bifunctional organocatalyst bearing a cinchona-based alkaloid unit, as reported by Roncak et al. (2020).



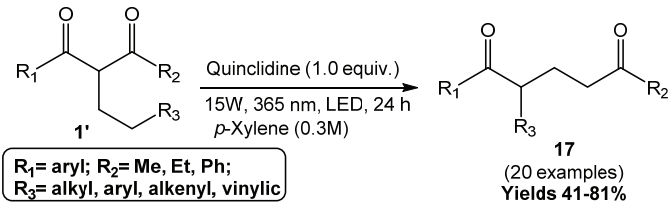
Scheme 6. Asymmetric Michael addition of 1,3-dicarbonyl to *trans*-nitro olefins.

Yoo et al. (2012) developed an efficient protocol for synthesizing methylene-bridged 1,3-diketones **16** through an aerobic photocatalytic oxidative coupling reaction between 1,3-diketones and *N,N*-dimethylbenzyl amine **15**. The mechanism starts with the initial excitation of $[Ru(bpz)_3](PF_6)_2$ by visible light and the subsequent reductive quenching by *N,N*-dimethyl benzylamine generating amine radical cation along with a strongly reducing $[Ru^{I}(bpz)_3]$ complex. The oxygen gas regenerates the photocatalyst and the resulting oxygen radical anion abstracts the proton of the radical cation to furnish another reactive iminium intermediate. This transient species was intercepted by deprotonated nucleophiles derived from 1,3-diketones **1** to give the coupling products **16** (Scheme 7).



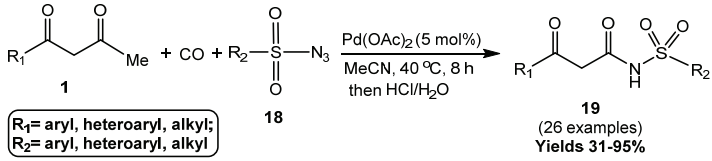
Scheme 7. Photocatalysis of *N,N*-dimethylbenzylamine and 1,3-diketones.

The photolytic [1,3]-benzoyl migration of *β*-benzoyl carbonyl compounds **1'** promoted by organic amine was reported by Zhang et al. (2020). This migration follows a Norrish-Yang cyclization and a retro-Aldol reaction under black light (365 nm) or visible light irradiation. 1,3-diketones bearing two different alkyl (R_2–alkyl) groups that could tolerate giving the benzoyl-shifted products **17** in moderate to good yield (Scheme 8).



Scheme 8. Photolytic formation of 1,5-diketones from 1,3-diketones.

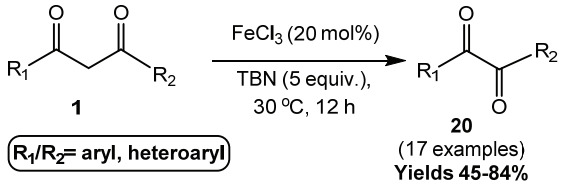
The amidation of 1,3-diketones has been developed (Gu et al., 2020) using carbon monoxide and organic azides **18** in the presence of a Pd-catalyst. This process produces a variety of *β*-ketoamides **19** under mild ligand-, oxidant- and base-free conditions (Scheme 9).



Scheme 9. Synthesis of *β*-ketoamide from 1,3-diketones.

The synthesis of 1,2-diketones **20** through the selective C-C bond cleavage of 1,3-diketones under mild reaction conditions in air by using $FeCl_3$ as the catalyst and tert-butyl nitrite (TBN) as the oxidant, without any solvent, was reported by Huang et al. (2011). This reaction of unsymmetrical 1,3-diketones was highly selective, which could tolerate both electron-donating and electron-withdrawing substituents in the aryl ring of 1,3-diketones to give the corresponding 1,2-diketones **20** in good yields (Scheme 10). Further, the steric hindrance on the aryl ring played a minor role in the reaction. For example, 1- and 2-naphthyl-substituted 1,3-

diketones transformed smoothly to afford the corresponding 1,2-diketones in good yields.

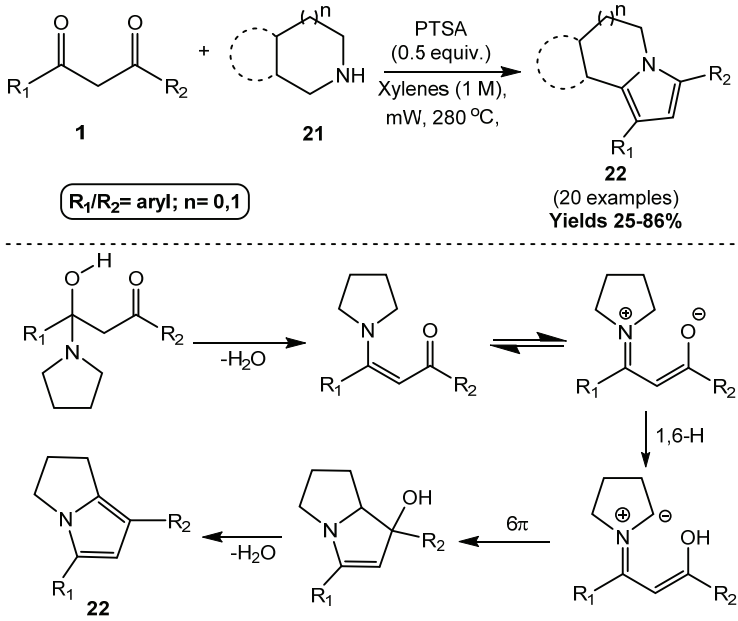


Scheme 10. Synthesis of 1,2-diketones from 1,3-diketones.

4. Application of 1,3-Diketones

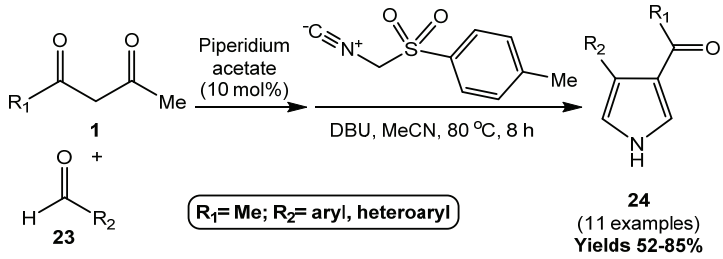
4.1 Synthesis of *N*-containing heterocycles

The 1,3-diketones and cyclic amines **21** readily react under microwave irradiation in the presence of *para*-toluene sulphonic acid (PTSA) to form ring-fused pyrroles in a single operation (Deb and Seidel, 2010). The mechanism involved the formation of *N,O*-acetal, which was simultaneously dehydrated to enaminone. This enaminone undergoes a sequential reaction involving a 1,6-H-shift and 6π-electrocyclization to yield an alcohol bearing intermediate. Finally, the subsequent water loss gives rise to pyrrole **22** (Scheme 11).



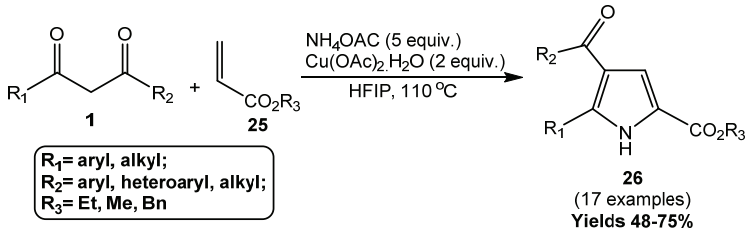
Scheme 11. Formation of ring-fused pyrroles from 1,3-diketones.

The protocol for efficient synthesis of 3,4-disubstituted pyrroles **24** utilizing the three-component reaction of aldehydes **23**, 1,3-diketones and toluene sulfonyl methyl isocyanide (TosMIC) in one-pot conditions was reported by Manasa et al. (2018). This reaction involves a Knoevenagel condensation between an aldehyde and a diketone substrate to give an unsaturated alkene intermediate, which further undergoes a Michael addition with TosMIC in the presence of the 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) leading to 3,4-disubstituted pyrroles (Scheme 12).



Scheme 12. Synthesis of disubstituted pyrroles from 1,3-diketones.

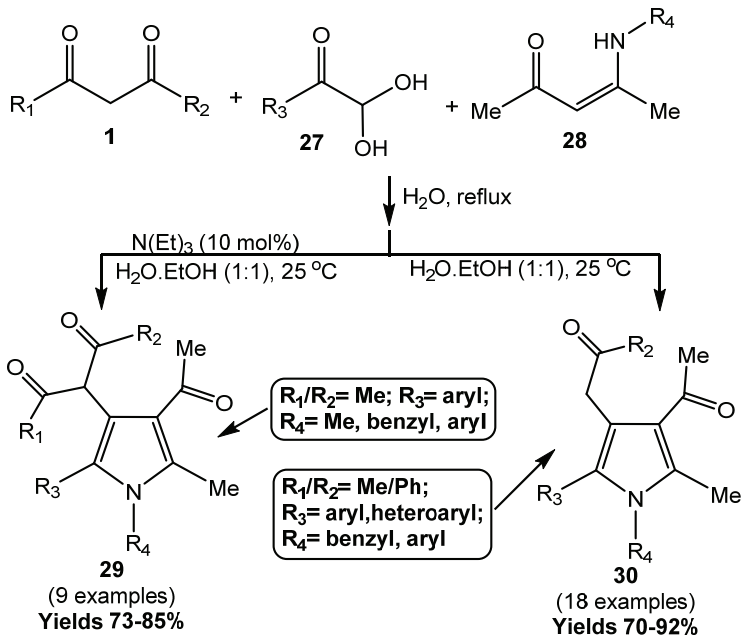
The synthesis of trisubstituted pyrroles **26** from 1,3-diketones was demonstrated by He et al. (2020). They used a copper-mediated one-pot synthesis from 1, 3-diketones and acrylates **25** using ammonium acetate as the nitrogen source and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent (Scheme 13). The reaction achieves C-C and C-N bond formations and provides an efficient approach to access highly functionalized pyrroles without further raw material preparation.



Scheme 13. Synthesis of trisubstituted pyrroles from 1,3-diketones.

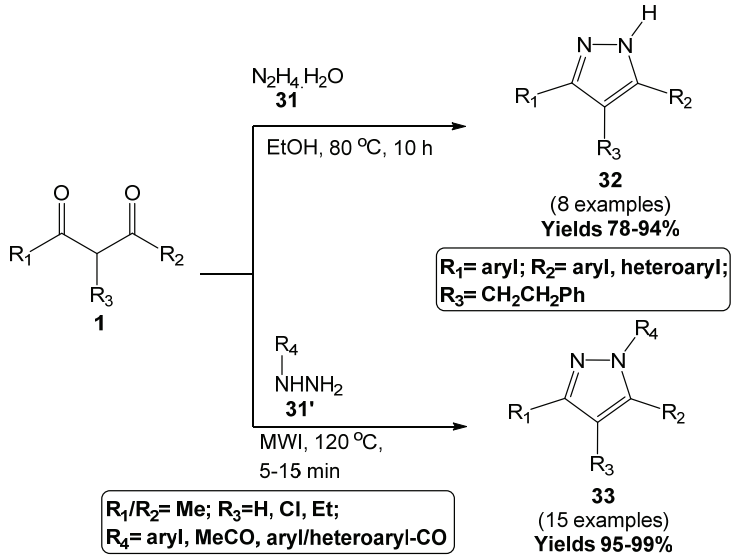
Then, the methodology for synthesizing polyfunctionalized pyrroles **29-30** *via* tetraone derivatives by a three-component reaction between arylglyoxals **27**, 1,3-diketones and enaminoketones **28** was elaborated on by Anary-Abbasinejada et al. (2020). Two types of products were obtained, depending upon the reaction conditions employed. The method's

advantages were the easy workup and using water or an ethanol-water mixture as the environmentally green solvent (Scheme 14).



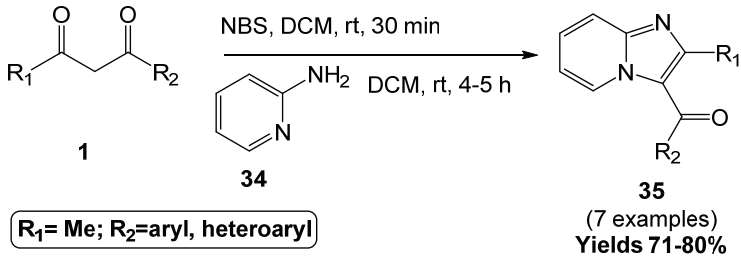
Scheme 14. Synthesis of polyfunctionalized pyrroles from 1,3-diketones.

A series of α-substituted 1,3-diketones were reacted with hydrazine hydrate **31** to produce trisubstituted pyrazoles **32** in excellent yields (Zou et al., 2019). However, a greener procedure for preparing pyrazoles **33** was developed from 1,3-diketones and hydrazines/hydrazides **31'** (Vaddula et al., 2013). The eco-friendly method was accelerated by microwave heating under catalyst- and solvent-free conditions in 5-15 mins, as compared to traditional heating (Scheme 15).



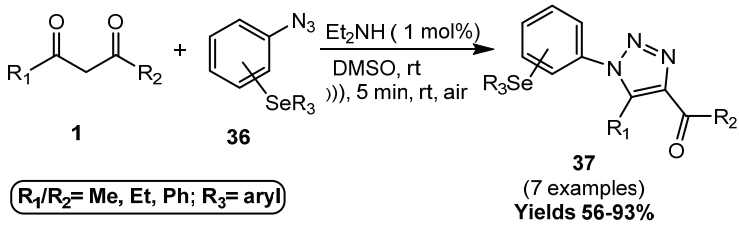
Scheme 15. 1,3-Diketones with hydroxylamines/hydrazines undergo condensation to give pyrazoles.

The simple protocol toward the regioselective synthesis of 1-aryl/heteroaryl-1-(2-methylimidazo [1,2-*α*]pyridin-3-yl)methanones **35** was developed (Aggarwal et al., 2016) by one-pot condensation of 2-aminopyridine **34** with 1,3-diketones. The reaction involves the intermediacy of 2-bromo-1,3-diketones formed *in situ* from 1,3-diketones using *N*-bromosuccinimide (NBS) in dichloromethane (DCM) by stirring at room temperature (Scheme 16).



Scheme 16. Synthesis of imidazo[1,2-*α*]pyridines from 1,3-diketones.

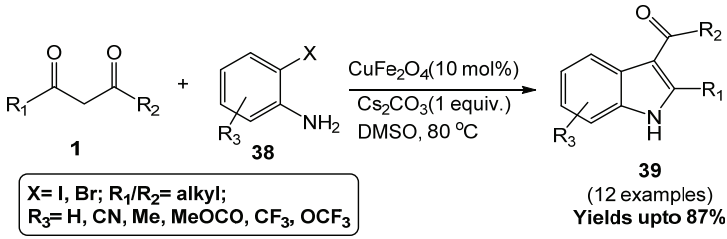
Costa et al. (2017) developed the organocatalytic enamine–azide [3+2] cycloaddition between 1,3-diketones and arylazidophenyl selenides **36** providing an efficient access to new ((arylselanyl)phenyl-1*H*-1,2,3-triazol-4-yl)ketones **37** in the presence of diethylamine (Et_2NH) and dimethyl sulfoxide (DMSO) as solvents. The sonochemically promoted reactions were found to be amenable to a range of 1,3-diketones or aryl azidophenyl selenides giving the desired products in good to excellent yields within short reaction times (Scheme 17).



Scheme 17. Synthesis of triazoles from 1,3-diketones.

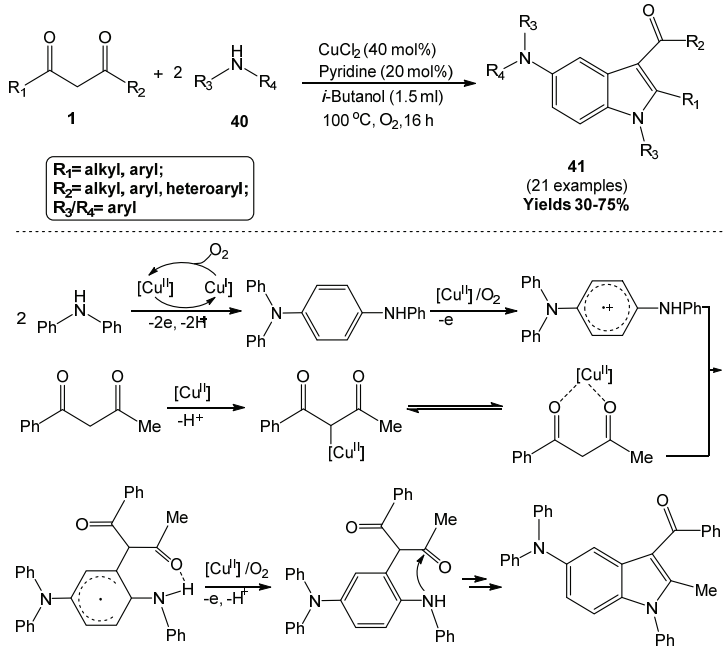
The synthesis of indole derivatives **39** from 1,3-diketones was successfully demonstrated by Vu et al. (2020). Here, 1,3-diketones were coupled with 2-halo substituted anilines **38** in the presence of the heterogeneous catalyst $CuFe_2O_4$ and the base Cs_2CO_3. The solvent used was DMSO and reacted

at 80 °C under argon for 16 h giving good yields of the products (Scheme 18).



Scheme 18. Annulation of 2-haloaniline with 1,3-diketones to give indoles.

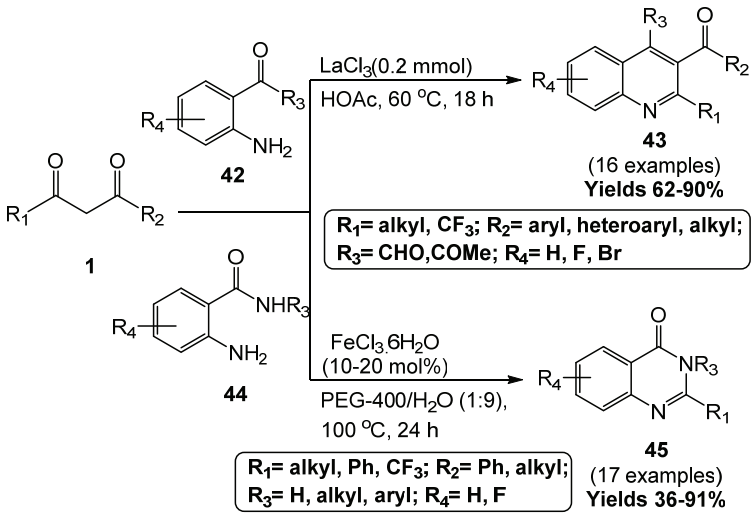
The direct synthesis of functionalized indoles **41** *via* single-electron oxidation (SEO) induced coupling of diarylamines **40** with 1,3-diketones was reported by Liang et al. (2019). It proceeds with good functional group and substrate compatibility, using a readily available and naturally abundant catalyst system, which affords a new class of indoles with the potential for discovery. $CuCl_2$ and pyridine initiated the coupling to afford the desired products **41** in moderate to good isolated yields in iso-butanol as the solvent. Moreover, 1,3-diketones containing an electron-donating group on the aryl ring yielded a much higher product than those with an electron-withdrawing group. The proposed mechanism involved the aerobic copper-catalyzed SEO of the substrate to give the functionalized indoles (Scheme 19).



Scheme 19. Functionalization of indoles *via a* single electron transfer mechanism.

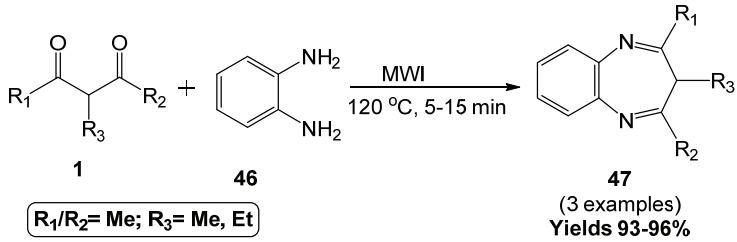
The regioselective and efficient synthesis of substituted quinolines **43** using the lanthanum chloride ($LaCl_3$) mediated Friedländer reaction was demonstrated by Chen et al. (2012). The reaction between an unsymmetrical 1,3-diketone with the corresponding 2-carbonyl aniline **42** gives high regioselective quinoline in moderate to excellent yields. However, the synthesis of 2-substituted quinazolinones **45** from the tandem reaction of 2-aminobenzamides **44** with 1,3-diketones *via* condensation, intramolecular nucleophilic addition, C-C bond cleavage was reported (Shen et al., 2016). The reaction used an iron-catalyzed

solution of poly(ethylene glycol) in an aqueous solution under oxidant-free conditions to get the desired products (Scheme 20).



Scheme 20. Synthesis of quinolines and quinazolines from 1,3-diketones.

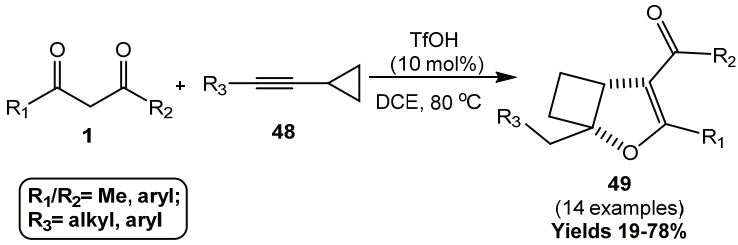
The synthesis of diazepine by reacting 1,3-diketones with *o*-phenylenediamine **46** was reported by Vaddula et al., (2013). The optimized reaction condition for this protocol was subjecting *o*-phenylenediamine **46** (0.5 mmol) and 1,3-diketone (0.55 mmol) to microwave irradiation at 120 °C for 5-20 minutes, getting the diazepines **47** in excellent yields (93–96%) Scheme 21.



Scheme 21. Synthesis of diazepines from 1,3-diketones.

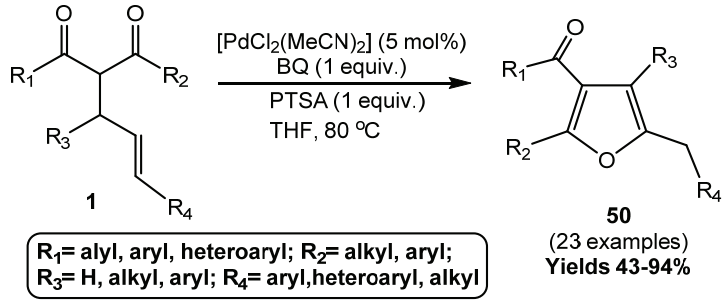
4.2 Synthesis of *O*-containing heterocycles

The trifluoromethanesulfonic acid (TfOH)-catalyzed tandem cyclopropane ring enlargement/C-C formation/etherification reaction between alkynylcyclopropanes **48** and 1,3-diketones giving four-membered carbocycle-fused dihydrofurans **49** that are architecturally interesting was explored by Ye and Yu (2011). A range of aryl and alkyl-substituted 1,3-diketones were compatible in this tandem reaction using dichloroethane (DCE) as the solvent. However, the aryl-substituted 1,3-diketones were better nucleophiles than the alkyl-substituted 1,3-diketones (Scheme 22).



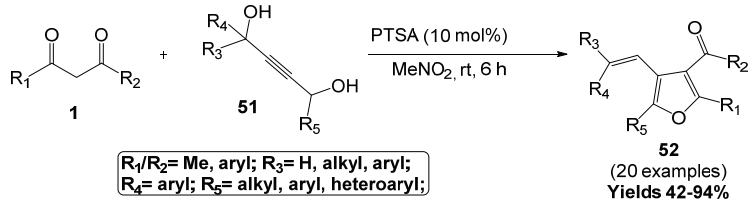
Scheme 22. Synthesis of furan derivatives from 1,3-diketones.

The synthesis of highly functionalized 2-benzyl furans **50** through palladium-catalyzed intramolecular oxidative annulation of 2-cinnamyl-1,3-dicarbonyls **1''** was successfully demonstrated by Nallagonda et al. (2015). The reaction was catalyzed by $[PdCl_2(MeCN)_2]$, in the presence of benzoquinone (BQ) as the oxidant and PTSA as an acid additive in tetrahydrofuran (THF), to give the tetrasubstituted furans in moderate to good yields (Scheme 23).



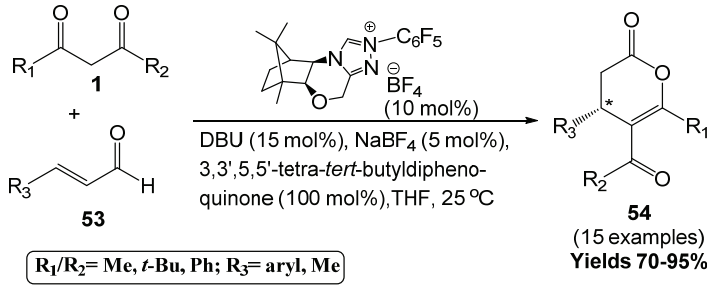
Scheme 23. Synthesis of tetrasubstituted furans from 1,3-diketones.

Mothe et al. (2012) developed a method to prepare tetrasubstituted furans **52** efficiently from cycloisomerization of but-2-yne-1,4-diols **51** with 1,3-diketones catalyzed by PTSA. The orthogonal modes of reactivity of the alcoholic substrates were utilized through slight modification of the reaction conditions resulting in a divergence in product selectivity. The protocol showed that with PTSA as the catalyst and nitromethane ($MeNO_2$) as the solvent, the conditions proved to be broad, resulting in a variety of tetrasubstituted furans that could be furnished in good to excellent yields (Scheme 24).



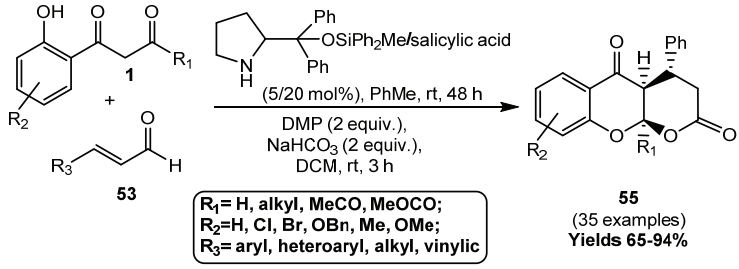
Scheme 24. Synthesis of tetrasubstituted furans from 1,3-diketones.

Rong et al. (2011) developed an enantioselective *N*-heterocyclic carbene (NHC)-catalyzed Michael addition reaction of 1,3-diketones to *α,β*-unsaturated aldehydes **53** using redox oxidation. The reaction was performed in the presence of 10 mol% of camphor-derived triazolium salt, 15 mol% of DBU, 5 mol% of $NaBF_4$ and 100 mol% of 3,3',5,5'-tetra-*tert*-butyldiphenoquinone in THF at 25 °C, giving enantioenriched substituted 3,4-dihydro-α-pyrones **54** in good yields (Scheme 25). However, symmetrical 1,3-diketones with strong electron-withdrawing or bulky groups led to low reactivity and no products were isolated.



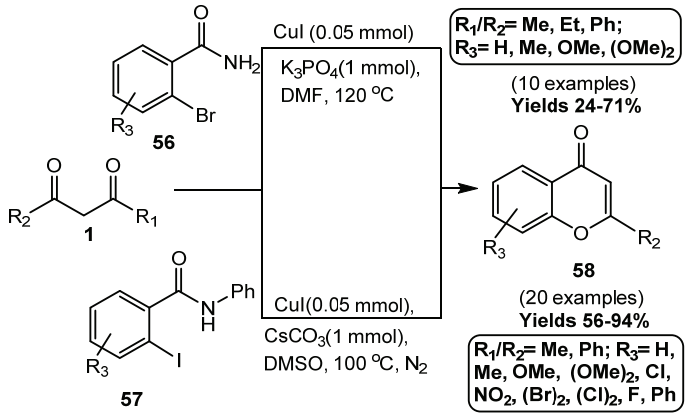
Scheme 25. NHC catalyzed synthesis of 3,4-dihydro-*α*-pyrones using 1,3-diketones.

Lu et al. (2020) developed an enantioselective Michael addition/cycloketalization/hemiacetalization sequence in the presence of a chiral amine catalyst for the facile synthesis of a wide range of lactone-fused tricyclic chromanone derivatives **55** with excellent enantioselectivities and diastereoselectivities from simple 1-(2-hydroxyaryl)-1,3-diketones and *α,β*-unsaturated aldehydes **53** (Scheme 26). It is noteworthy to mention that the R_3 substituents of the *α,β*-unsaturated aldehydes could be in various functional groups, ranging from heteroatom aryl rings to vinyl group and aliphatic substituents. All the cases examined led to good yields of products with 35 examples of up to 94% yield.



Scheme 26. Synthesis of lactone-fused tricyclic chromanones using 1,3-diketones.

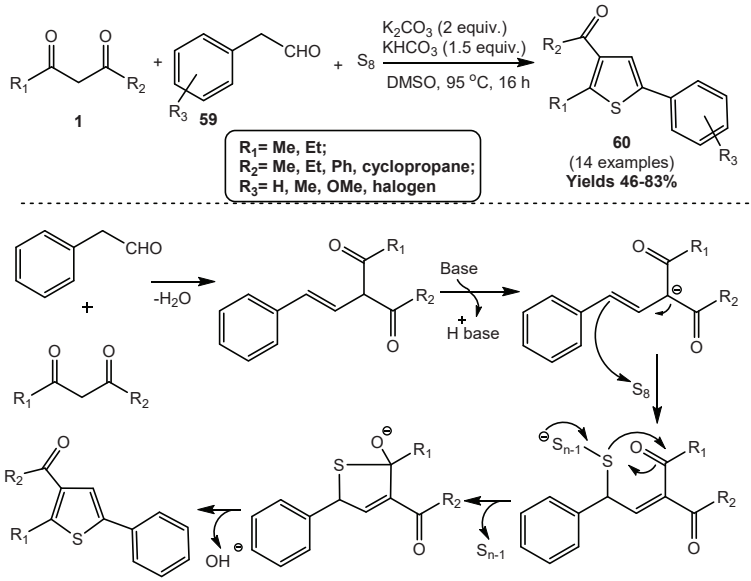
The synthesis of 3-substituted isocoumarins **58** using 1,3-diketones was reported by two groups *viz.* Cai et al. (2012) and Kavala et al., (2012). The former utilized the reaction between *o*-bromobenzamide derivatives **56** and 1,3-diketones *via* CuI-catalyzed in dimethyl formamide (DMF) under the action of K_3PO_4 at 120 °C giving products up to 71% yield. However, the latter used 2-iodo-*N*-phenyl benzamides **57** instead of *o*-bromobenzamides **56** using CuI and $CsCO_3$ in DMSO at 100 °C under N_2. The yields were up to 94% within a short duration (5-60 min) in this method compared to 24 h in the former case (Scheme 27).



Scheme 27. Synthesis of isocoumarins using 1,3-diketones.

4.3 Synthesis of *S*-containing heterocycles

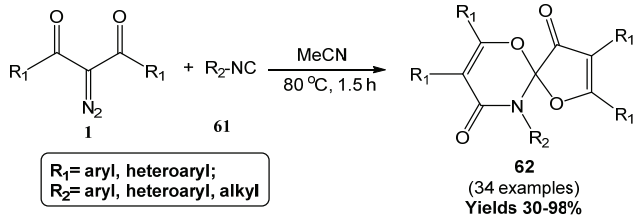
The synthesis of 2-arylthiophenes using the three-component reaction of arylacetaldehydes **59**, 1,3-diketones and elemental sulfur was reported by Huang et al. (2017). This reaction proceeds through the cascade condensation/annulation under the basic buffer system of K_2CO_3 with $KHCO_3$ in DMSO (Scheme 28). It provides a facile entry to 2,3,5-trisubstituted thiophenes **60** with moderate to excellent yields along with good functional group tolerance.



Scheme 28. Synthesis of trisubstituted thiophenes using 1,3-diketones.

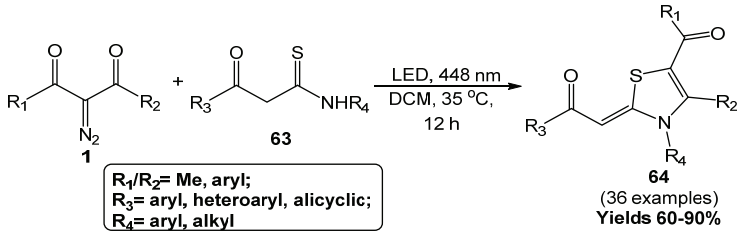
4.4 Synthesis of two-heteroatoms heterocycles

The catalyst-free formal [4+1]/[4+2] cycloaddition of isocyanide **61** with two molecules of acylketene formed *in situ* through the thermal-induced Wolff rearrangement of 2-diazo-1,3-diketones **1** leading to the formation of *O,O,N*-spiro compounds consisting of both 1,3-oxazine and a furan ring **40** was developed (Luo et al., 2020). This protocol displayed good functional group tolerance and was compatible with different isocyanides and 2-diazo-1,3-diketones (Scheme 29).



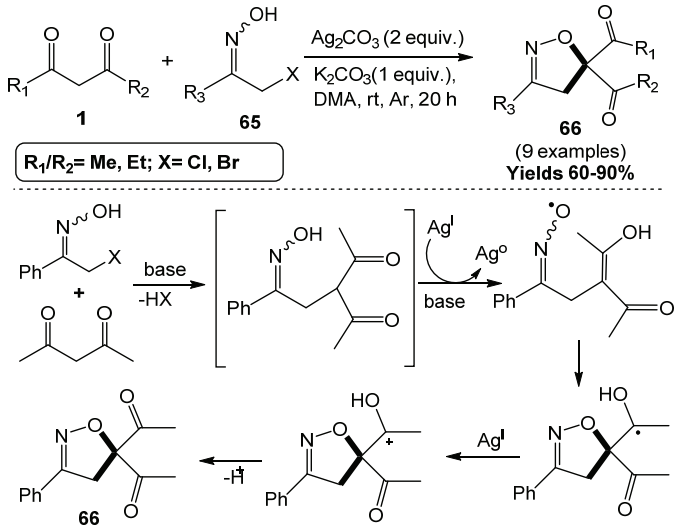
Scheme 29. Constructing of *O,O,N*-spiro compounds.

Ansari et al. (2020) developed a photocatalyst and visible-light mediated chemoselective domino protocol to access fully substituted thiazoline derivatives **64** from *β*-ketothioamides **63** and *α*-diazo 1,3-diketones at moderate temperature in the open air (Scheme 30). The reaction proceeds through *in situ* generation of electrophilic carbenes from α-diazo 1,3-diketones by a low-energy blue LED (448 nm), which undergoes selective coupling with nucleophilic *β*-ketothioamides to give the desired products by the successive formation of C-S and C-N bonds in one stretch.



Scheme 30. Constructing of fully substituted thiazolines.

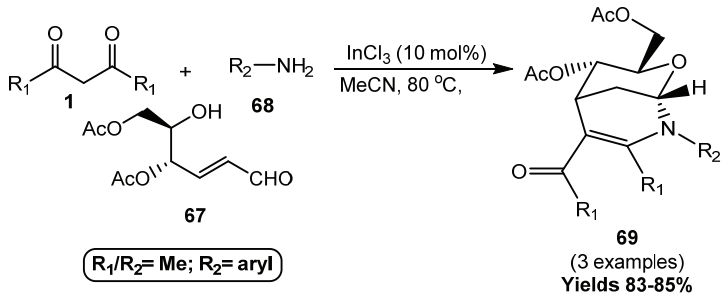
Liu et al. (2014) reported a new radical cyclization of α-halo ketoximes **65** with 1,3-diketones to select Δ^2-isoxazolines *via* silver-mediated radical cyclization. This method was performed using a radical strategy and the addition of an oxygen-centered radical, produced from either unsaturated oximes or hydroxamic acids, giving the desired products **65** up to a 90% yield. The described reaction conditions consist of Ag_2CO_3 (2 equiv.), K_2CO_3 (1 equiv.) and *N,N*-diethylacetamide (DMA) (2 mL) at room temperature under an Ar atmosphere for 20 h (Scheme 31).



Scheme 24. Synthesis of isoxazolines.

Then, the synthesis of oxa-azabicycles **69** through the one-pot three-component reaction from Perlin aldehyde **67**, arylamines **68** and 1,3-diketones using a catalytic amount of indium trichloride was reported by Reddy et al. (2010). In this methodology, *γ*-hydroxy-*α,β*-unsaturated sugar aldehydes (Perlin aldehydes) undergo a smooth coupling with *β*-enamino

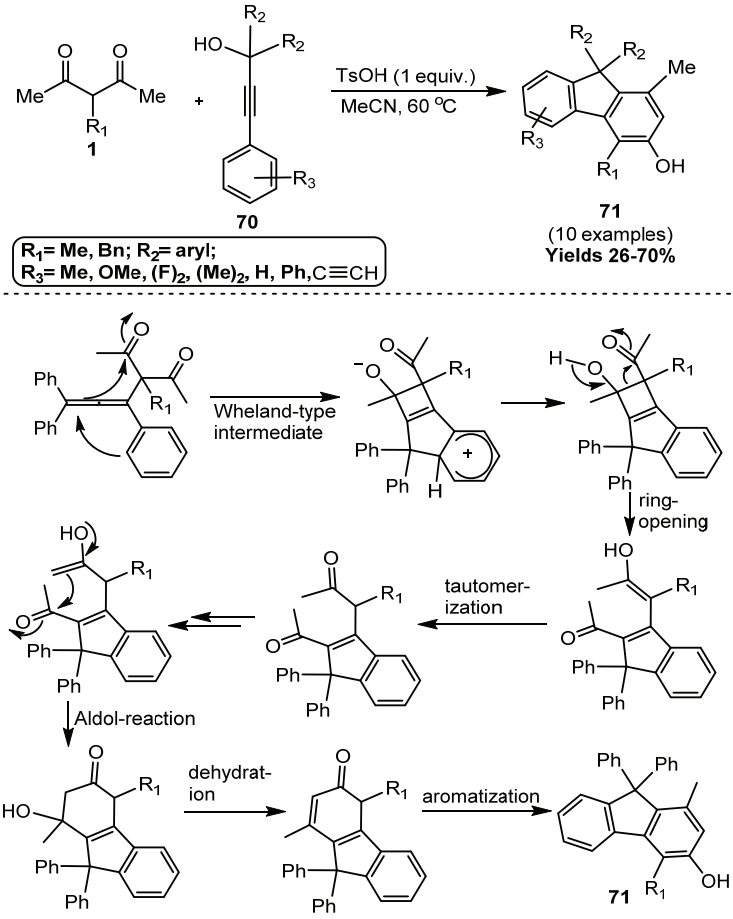
ketones generated *in situ* from arylamines and 1,3-diketones in the presence of 10 mol% $InCl_3$ in acetonitrile at 80 °C, to produce oxa-azabicycles in good yields with high selectivity (Scheme 32).



Scheme 32. Synthesis of oxa-azabicycles using 1,3-diketones.

4.5 Synthesis of carbocycles

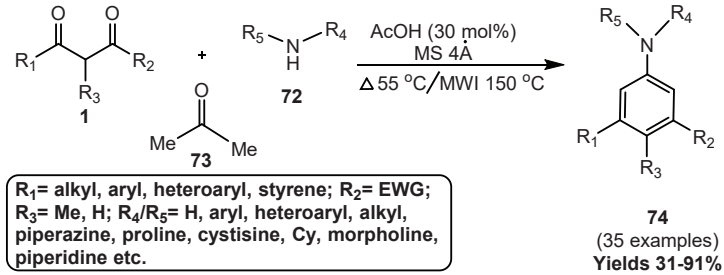
The protocol for synthesizing hydroxylfluorenes **71** by PTSA-mediated tandem alkylation/rearrangements of propargylic alcohols **70** with 1,3-diketones was described by Yao et al. (2012). The reaction was accomplished under mild conditions to offer a straightforward, one-step synthetic route to hydroxylfluorene derivatives. This reaction was proposed *via* dehydration, addition, rearrangement and an aromatization sequence. It generates the desired products from readily available and low-cost starting materials in good yields, with H_2O as the only by-product (Scheme 33).



Scheme 32. Synthesis of hydroxylfluorenes using 1,3-diketones.

Galeev et al. (2019) developed a convenient synthetic method to access *meta*-substituted anilines **74** *via* a metal-free three-component (3+3)-cyclocondensation cascade reaction by employing acetone **73**, amines **72** and 1,3-diketones. This method was based on *in situ* generated imines of acetone with 1,3-diketones either under conventional heating or under

microwave irradiation, allowing the synthesis of a wide range of arylamines containing electron-withdrawing substituents in the *meta*-position, including a trifluoromethyl group or an ester or an amide group (Scheme 33).



Scheme 33. Synthesis of *meta*-substituted anilines using 1,3-diketones.

5. Conclusion

In this chapter, it is being demonstrated that 1,3-diketones are an excellent versatile intermediate used in synthetic organic chemistry with different methodologies. Direct C-C and C-O bond formation *via* facile access to various functionalization could be established and performed one-pot and multicomponent reaction efficiently from this versatile intermediate. Furthermore, the ring-fused heterocycles compound of a five- and six-member ring containing heteroatoms can also be executed from this compound.

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CHAPTER 2

CHALCONES

1. Introduction

Chalcones (Figure 1) are naturally occurring α,β-unsaturated ketones existing as *trans* and *cis* isomers, coined by Kostanecki and Tambor (1899). This versatile molecule contains the reactive keto-ethylenic group (–CO–CH=CH–), a chromophore accountable for the color of the compounds in collaboration with the presence of other auxochromes. The numbering system is different from other flavonoids, being the A-ring numbered from 1 to 6 and the B-ring from 1' to 6'. Chalcones are found in fruits, vegetables, spices, tea and soy-based foodstuff and their 2'-hydroxy derivatives play an essential role in flavonoids' synthesis and biosynthesis as both precursors and products (Rashid et al., 2017). Further, they act as synthons for a range of novel heterocycles having pharmaceutical profiles (Zhuang et al., 2017). Chalcones have attracted much interest due to their broad, interesting biological activities such as antitumor, anti-inflammatory and antimicrobial activity (Singh et al., 2014). Several chalcone-based compounds have been approved for clinical use, such as metochalcone **1A** and sofalcone **1B** (Figure 1) (Sahu et al., 2012).

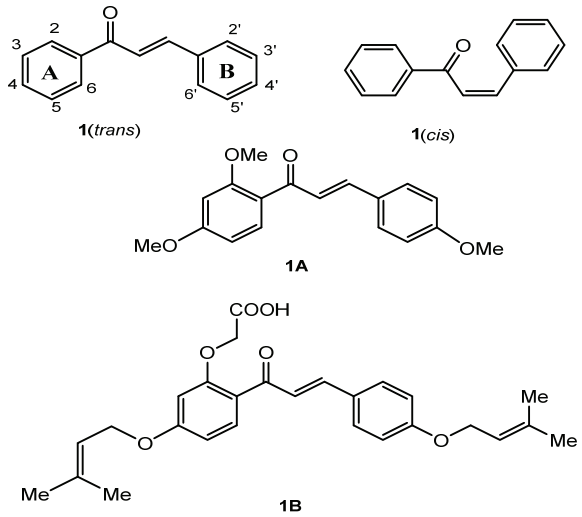
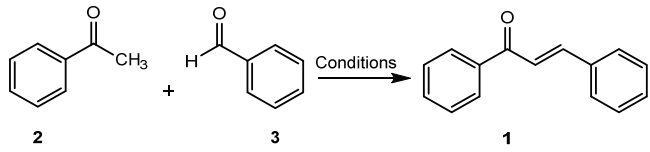


Figure 1. The structures of chalcone **1** and drugs metochalcone **1A** and sofalcone **1B**.

2. Synthesis of Chalcones

There are various well-established methods for preparing chalcones; however, Claisen-Schmidt condensation (Dhar and Barton, 1981) is one of the most popular methodologies among the reported reactions. The condensation involves equimolar quantities of aryl methyl ketone **2** and aryl aldehyde **3** in the presence of alcoholic alkali. The Claisen-Schmidt reaction is usually carried out in aqueous NaOH or KOH or in ethanolic sodium ethoxide at room temperature for several hours (Scheme 1). It can also be performed in basic and acidic conditions such as $Ba(OH)_2$, HCl, $BF_3.OEt_2$ and also using solid-phase catalysts, heterogeneous catalysis, acidic ionic liquids, zeolites, iodine, etc. Nowadays, methods based on eco-friendly mechanisms are also reported using solvent-free conditions, microwave and ultrasound irradiation and grinding for chalcones synthesis

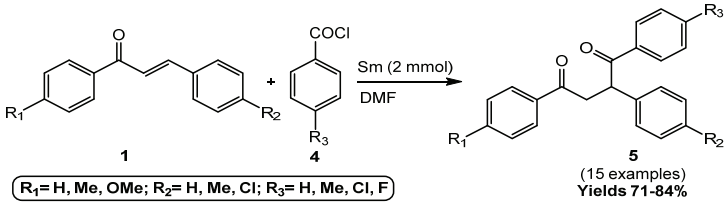
(Calvino et al., 2006). The other known methodologies are the Meyer-Schuster rearrangement, deamination of aziridine, debromination of vicinal dibromides, oxidation of benzylic alcohols, the Wittig reaction, coupling reactions, dehydrogenation and deoxygenation, etc. (Farooq and Ngaini, 2019).



Scheme 1. Synthesis of chalcones by a Claisen-Schmidt condensation.

3. Functionalization of Chalcones

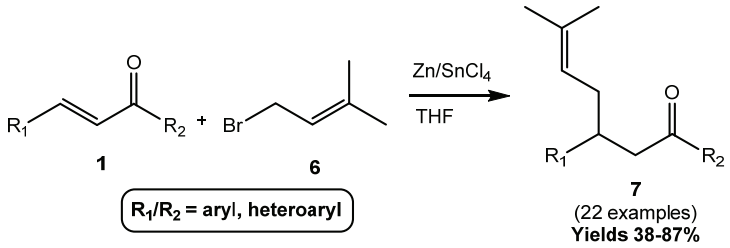
A Michael addition between chalcones and aroyl chlorides **4** forming 1,4-diketones **5** in the presence of Sm metal in dimethylformamide (DMF) was reported (Liu et al., 2010). Here, DMF acts as a stabilizing agent for the intermediates, dissolving samarium salts and promoting the reaction to proceed readily (Scheme 2).



Scheme 2. 1,4-Diketones in the presence of Sm metal.

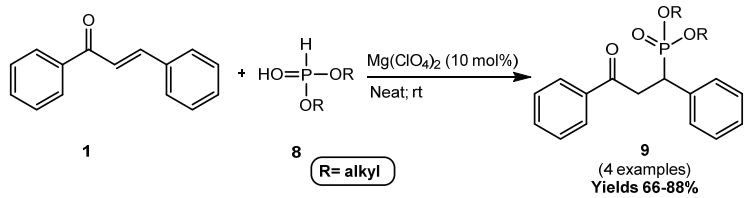
A protocol for introducing a prenyl group into the *β*-position of chalcones **7** by a zinc-mediated conjugate addition of chalcones with 1-bromo-3-methylbut-2-ene **6** in the presence of $SnCl_4$ was demonstrated (Zhao et al.,

2013). The reaction proceeds with a high α-regioselective in a 1,4-Michael addition in tetrahydrofuran (THF) (Scheme 3).



Scheme 3.1,4-Michael addition β-position of chalcones.

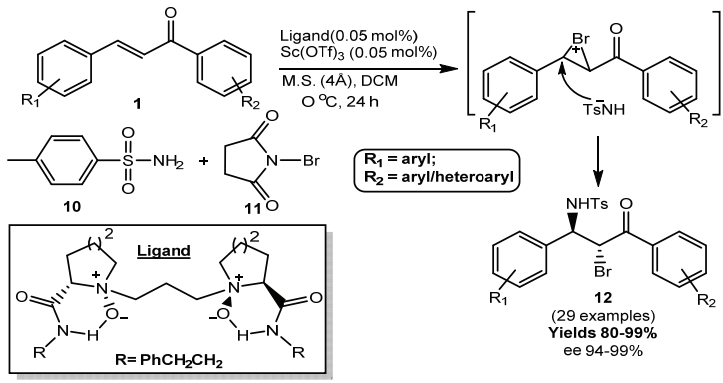
Similarly, a Michael addition of dialkyl phosphite **8** to chalcone in the presence of anhydrous magnesium perchlorate under solvent-free conditions gives phosphonate derivatives **9** of chalcones (Sahu et al., 2018). The results demonstrated that the catalytic (Phospha-Michael addition) PMA of dimethyl phosphite, diethyl phosphite, diisopropyl phosphite, and dibutyl phosphite with chalcone generates the desired products with percentage yields of 66–88% (Scheme 4). The advantages of this protocol lie in its uncomplicated and eco-friendly nature.



Scheme 4. Preparation of phosphonate derivatives of chalcones using $Mg(ClO_4)_2$.

The highly regio- and enantioselective bromoamination of chalcones to afford chiral α-bromo-β-amino ketone derivatives **12** has been reported

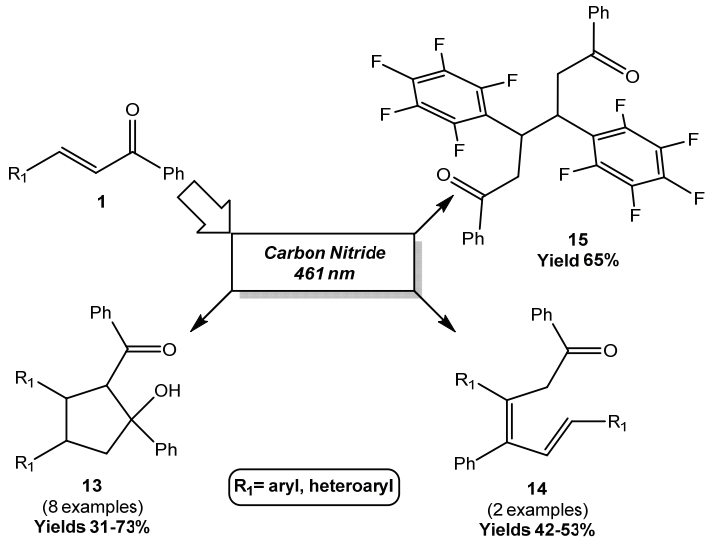
(Cai et al., 2010). The reaction proceeds *via* a unique bromonium-based mechanism and with excellent results (up to 99% ee, and nearly quantitative yields) using 0.05 mol% of the C_2-symmetric *N,N'*-dioxide ligand/scandium(III) complex under mild reaction conditions (Scheme 5). The advantages of this reaction include low catalyst loading and simple procedures for the asymmetric construction of difunctional molecules.



Scheme 5. The asymmetric bromoamination of chalcone.

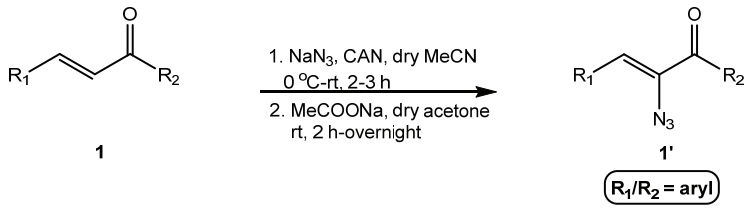
The photocatalytic reduction of chalcones in the presence of triethanolamine as an electron donor and heterogeneous carbon nitride as a visible light photocatalyst was successfully demonstrated by Kurpil et al. (2019). The reaction proceeds to give three different functionalized products depending upon the substitution patterns of the chalcones (Scheme 6). Cyclopentanoles **13** were obtained as major products for most substrates with a 31–73% isolated yield. The two chalcones bearing electron donor groups, 4-$MeOC_6H_4$ and 2-thienyl, selectively gave the *β*-ketodienes **14** with 42% and 53% isolated yields, respectively. The bulky pentafluorophenyl substituent in the starting chalcone leads to the formation of the symmetric linear dimer **15** as the single product, which is

less sterically restrained than the ring structure with an isolated yield of 65%. This reaction could confirm the existence of regioselectivity in heterogeneous photocatalysis versus the homogeneous version with a promising option for dimerization of the double bond and a convenient tool for a modern preparative organic synthesis.



Scheme 6. The photocatalytic reduction of chalcones using carbon nitride.

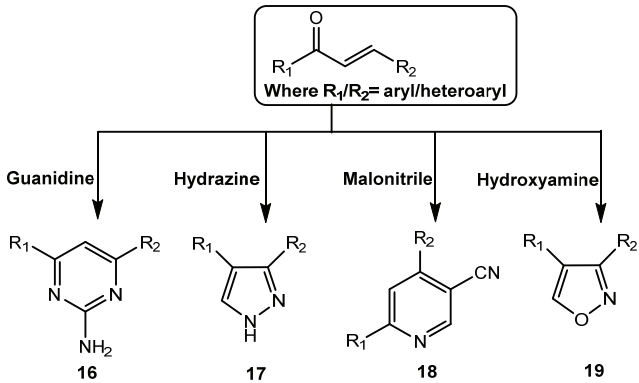
Another important functionalization was the preparation of α-azidochalcones, a versatile precursor for *aza*-heterocycles, as illustrated in the subsequent sections. It was synthesized from the corresponding chalcones in two steps, as reported first by Nair and George (2000) (Scheme 7).



Scheme 7. Preparation of α-azidochalcones.

4. Application of Chalcones in organic synthesis

Chalcones can be used to obtain several heterocycles through ring closure reactions (Scheme 8). It has already been reported that pyrimidines **16**, pyrazolines **17**, cyanopyridines **18** and isoxazoles **19** having different heterocyclic ring systems can be synthesized from chalcones (Taylor and Morrison, 1967; Utale et al., 1998; Vyas et al., 2009; and Crawley and Fanshawe, 1977).

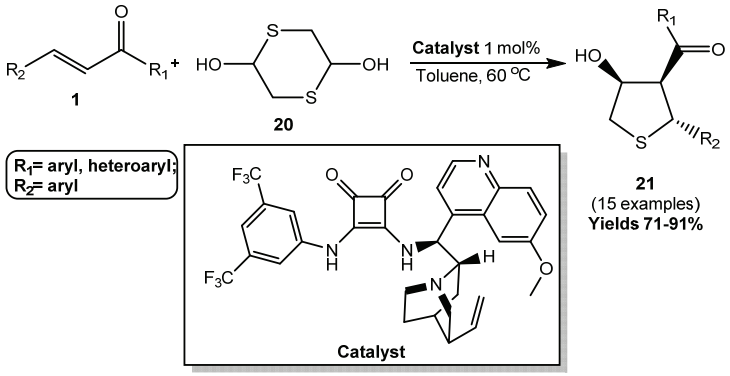


Scheme 8. Synthesis of various heterocycles using chalcones.

Other than these compounds, there are various heterocycles prepared from chalcones which are summarized below.

4.1 Synthesis of *S*-containing heterocycles

Trisubstituted tetrahydrothiophenes **21** with three contiguous stereogenic centers were obtained using a bifunctional squaramide-catalyzed sulfa-Michael/Aldol cascade reaction between 1,4-dithiane-2,5-diol **20** and chalcones (Ling et al., 2012). The reaction afforded trisubstituted tetrahydrothiophenes in generally good yields and high levels of diastereo- and enantioselectivity, with no remarkable effect on the position of the substituents of the phenyl ring of chalcones (Scheme **9)**. Further, the asymmetric synthesis of trisubstituted tetrahydrothiophenes *via* an *in situ* generated chiral fluoride-catalyzed sulfa-Michael/Aldol cascade reaction of 1,4-dithiane-2,5-diol and chalcones was also reported by Duan et al. (2017).

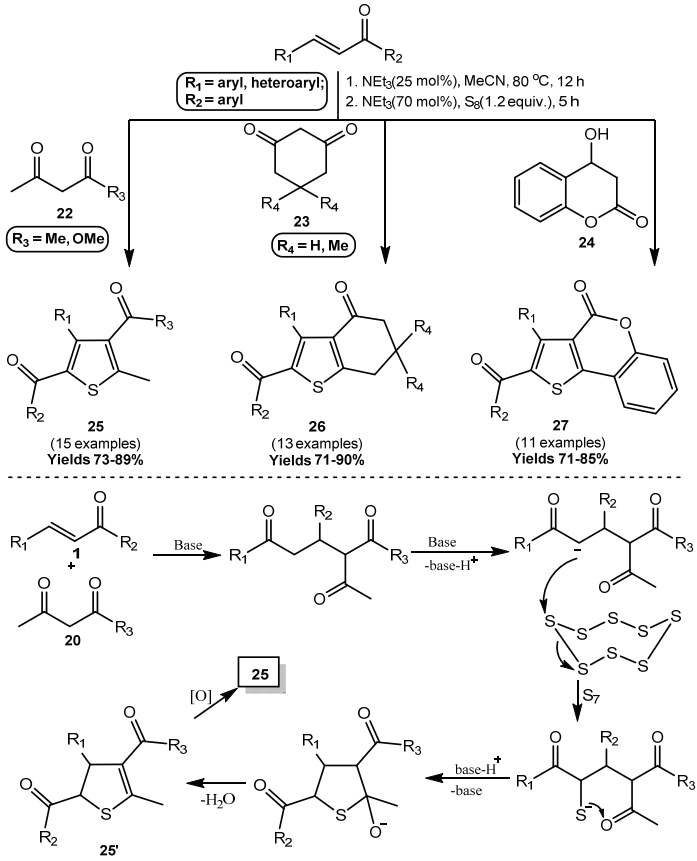


Scheme 9. Organocatalyst synthesis of tetrahydrothiophenes using chalcones.

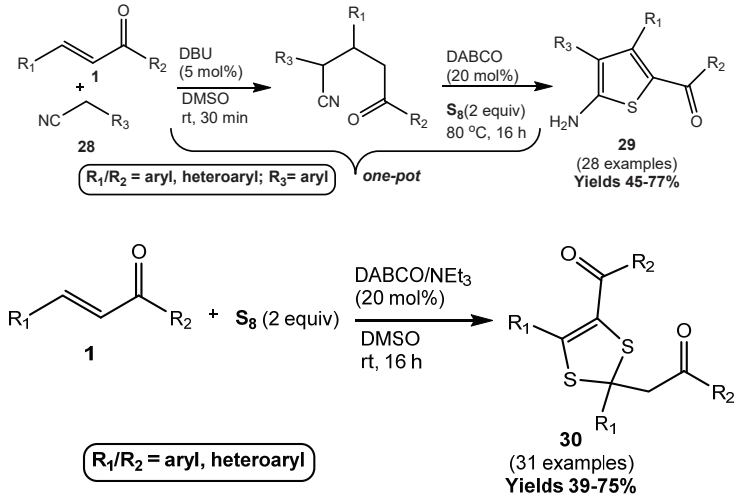
Adib et al. (2018) reported the synthesis of tetrasubstituted thiophenes **25**, **26** and **27** through a one-pot, three-component reaction between chalcones and linear/cyclic 1,3-dicarbonyl compounds **22-24** with elemental sulfur. The reaction was performed in acetonitrile (MeCN) in the presence of triethylamine (NEt_3) at 80 °C and afforded the corresponding substituted

thiophenes in good to excellent yields. However, complicated reaction mixtures were detected with the electron-deficient diketones such as hexafluoroacetylacetone and hexachloroacetylacetone, because the trifluoromethyl and trichloromethyl groups acted as leaving groups. The proposed mechanism involves the Michael addition of chalcone with 1,3-dione. It starts with the deprotonation of 1,5-dione followed by a nucleophilic attack on elemental sulfur giving the sulfide anion. Then, an intramolecular nucleophilic attack of the sulfide anion on the adjacent carbonyl group, and further cyclization and oxidation led to the functionalized thiophene **25** (Scheme 10).

Again, the three-component reaction of arylacetonitriles **28**, chalcones and elemental sulfur in two steps was exposed by Nguyen et al. (2020). The first step consists of a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed formation of a Michael adduct between arylacetonitriles and chalcones in dimethyl sulfoxide (DMSO). The second step is a cascade of a 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed sulfuration of the Michael adduct with elemental sulfur followed by an oxidative cyclization to afford thiophenes (Scheme 11). This method was applied to a wide range of arylacetonitriles and prepared a library of tetrasubstituted thiophenes **29** with yields ranging from average to good. Further, chalcones and elemental sulfur were used to prepare the tetrasubstituted 1,3-dithioles **30** (Nguyen et al., 2020). The reaction was found to proceed at room temperature in the presence of a nitrogen-based (DABCO/NEt_3) catalyst in DMSO as the solvent.



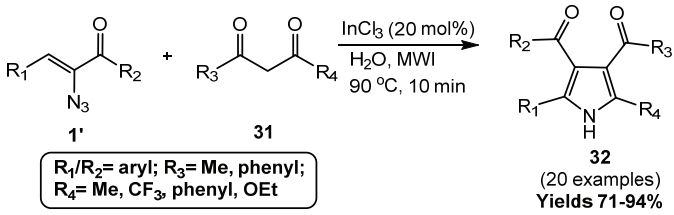
Scheme 10. Synthesis of tetrasubstituted thiophenes and proposed mechanism.



Scheme 11. Synthesis of tetrasubstituted thiophenes and 1,3-dithioles using chalcones.

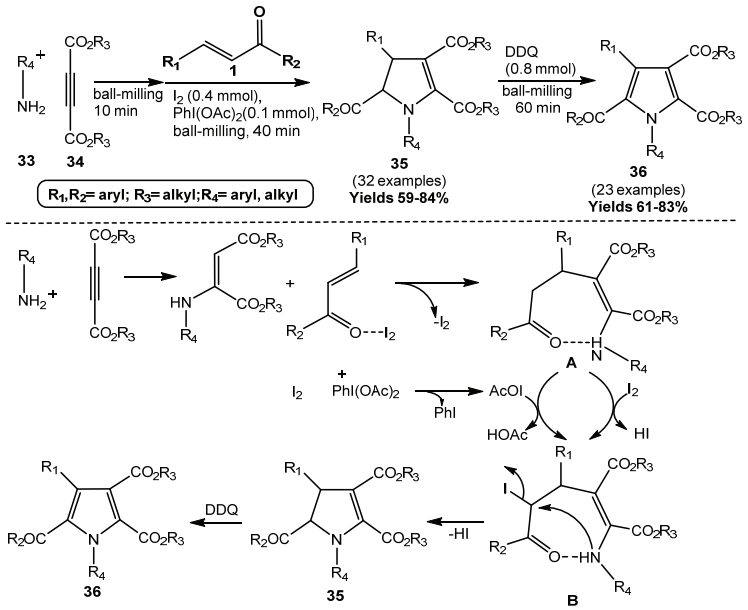
4.2 Synthesis of *N*-containing heterocycles

The regioselective synthesis of polysubstituted pyrroles **32** from α-azido chalcones **1'** and 1,3-dicarbonyl compounds **31** was described by Suresh et al. (2013). The reaction in water was influential in the presence of $InCl_3$; however, the reaction duration was much shorter (10 minutes) when the transformation was assisted by microwave irradiation (MWI) compared to 30 mins without MWI. The substituted pyrroles were isolated, with good to excellent yields of 71–94% (Scheme 12).



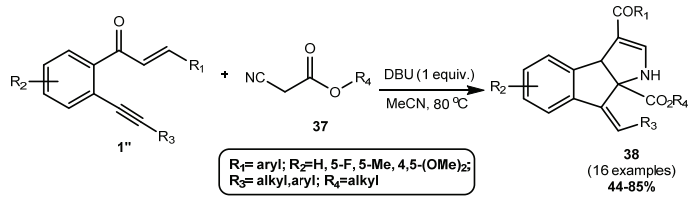
Scheme 12. Synthesis of tetrasubstituted pyrroles using chalcones.

The synthesis of polysubstituted pyrroles **36** using one-pot multicomponent *via* I_2/PhI(OAc)$_2$-promoted cyclization of amines **33** with alkyne esters **34** and chalcones **1** under solvent-free ball-milling conditions, and further oxidation with DDQ, was successfully demonstrated (Xu et al., 2018). This methodology has various advantages, such as high efficiency, mild reaction conditions, broad substrate scope and feasibility for large-scale synthesis. The mechanism proceeds with the amine reacting with the alkyne ester to give *β*-enamino ester, which reacts with chalcone through a Michael addition to generate an intermediate **A**. Then, hydrogen bonding between the NH moiety and the C=O connected to the R_4 group reacts with I_2 or the *in situ* generated AcOI from I_2 and PhI(OAc)$_2$ to give iodide-intermediate **B**. Finally, an intramolecular S_N2-type reaction of **B** occurs with the elimination of HI, affording the polysubstituted *trans*-2,3-dihydropyrrole **35**, which undergoes dehydrogenation aromatization in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the corresponding pyrrole **36** (Scheme 13).



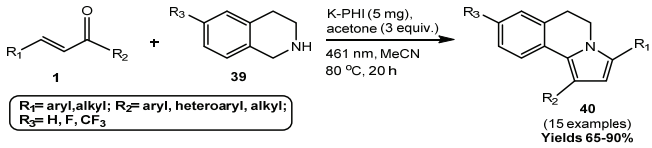
Scheme 13. Synthesis of polysubstituted pyrroles using chalcones.

The 1,8-diazabicyclo(5.4. 0)undec-7-ene (DBU)-promoted cascade reaction of (*E*)-2-alkynylchalcones **1''** and 2-isocyanoacetates **37** affording tetrahydroindeno[2,1-*b*]pyrroles **38** was reported (Zheng et al., 2011). The reaction occurs in an air atmosphere, under mild conditions and without loss of efficiency for a wide range of substituents in acetonitrile (MeCN) (Scheme 14).



Scheme 14. DBU-mediated cascade reaction of chalcones with 2-isocyanoacetates.

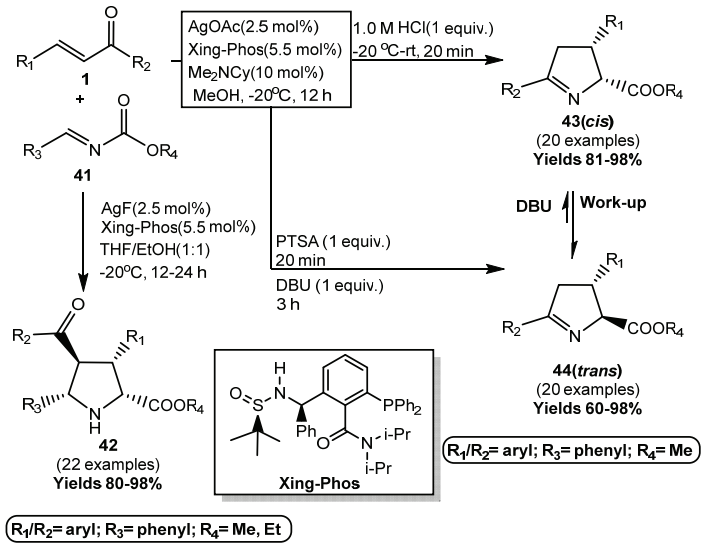
The use of *N*-centered radicals addition to the C=C bonds pathway was also applied for the pyrrole synthesis. Recently, a photocatalytic reaction between tetrahydroisoquinoline **39** and chalcones that gives *N*-fused pyrroles **40** was reported using potassium poly(heptazine imide) (K-PHI) as a visible light active heterogeneous and recyclable photocatalyst (Kurpil et al., 2019). With this protocol, fifteen *N*-fused pyrroles with 65–90% yields were successfully synthesized. The newly synthesized compounds were characterized by UV–Vis and fluorescence spectroscopy, while the fluorescence quantum efficiency of the fluorinated compound was 24% (Scheme 15).



Scheme 15. Photocatalytic synthesis of pyrroles using chalcones.

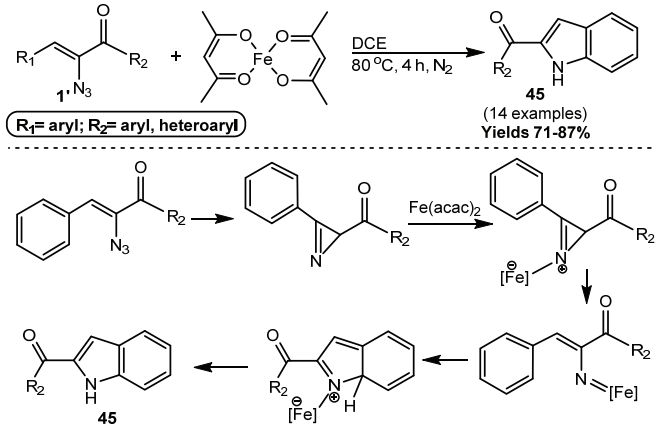
The first example of highly enantioselective and *exo*-selective silver-catalyzed [3+2] cycloaddition of chalcones with glycine aldimino esters **41** was reported (Bai et al., 2015). The reaction proceeds using silver-xing-phos as a catalyst system giving the corresponding chalcone-derived pyrrolidines **42** (Scheme 16) with multiple stereogenic centers in good yields and high diastereoselectivity (up to >98:2 dr) as well as excellent enantioselectivity (up to 99:1 er). Similarly, they exposed again the asymmetric Michael addition of the same substrates as in (Bai et al., 2016) catalyzed by silver/xing-phos for the divergent synthesis of chiral Δ(1)-pyrrolines, i.e., **43** and **44** (Scheme 16). The difference in acidic or basic workups was revealed in this protocol, giving the stereo-divergent

synthesis of *trans*-isomers of Δ(1)-pyrroline derivatives with excellent enantioselectivities.



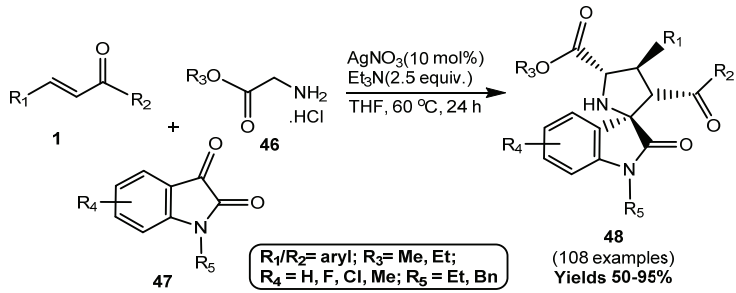
Scheme 16. Divergent synthesis of pyrrolidines and pyrrolines from chalcones.

The synthesis of substituted indoles using *α*-azidochalcones and metal *β*-diketonates was described by Rajaguru et al., 2017). In this protocol, metal *β*-diketonates as bifunctional reactive partners by varying reaction conditions have been demonstrated. With a copper complex, the synthesis of substituted pyrroles in micellar media *via* 2*H*-azirine intermediates has been achieved under mild conditions. At the same time, with $Fe(acac)_2$ as a catalyst, the reaction proceeds smoothly to yield indoles **45** regioselectively in dichloroethane (DCE) (Scheme 17).



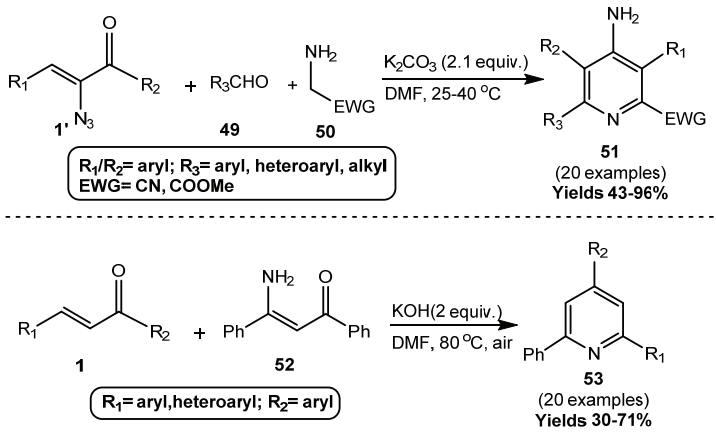
Scheme 17. Synthesis of indoles from α-azidochalcones.

The synthesis of spiropyrrolidine oxindoles **48** *via* Ag-catalyzed protocol was successfully reported by Yue et al. (2018) using triethylamine (Et_3N) in tetrahydrofuran (THF). Here, a [3+2] cycloaddition of azomethine ylides was generated *in situ* from the condensation of substituted isatins **47** and primary α-amino acid esters **46** with chalcones (Scheme 18). The products, having four consecutive stereocenters, including spiroquaternary stereocenters fused in one ring structure, were obtained in moderate to high yields (50–95%).



Scheme 18. Synthesis of spiropyrrolidine oxindole derivatives using chalcones.

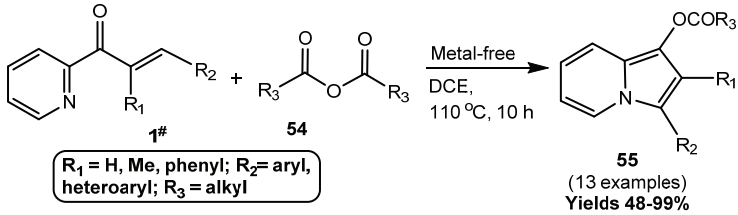
A one-pot, three-component domino reaction to prepare polysubstituted 4-aminopyridines **51** using α-azidovinylketones, aldehydes **49** and methylamine derivatives **50** was established by Shao et al. (2012). The attractive feature of this protocol was the atom economy count since only nitrogen and water molecules were lost in this reaction. Then, another protocol was also established to construct substituted pyridines **53** from *N*-unsubstituted enaminones **52** and chalcones using KOH/DMF (Zhang et al., 2018). The system works without any transition metal and shows good functional group tolerance. It provides a rapid synthesis of 2,4,6-triarylpyridines **53** through Michael/cyclization reaction patterns (Scheme 19).



Scheme 19. Synthesis of pyridines from chalcones.

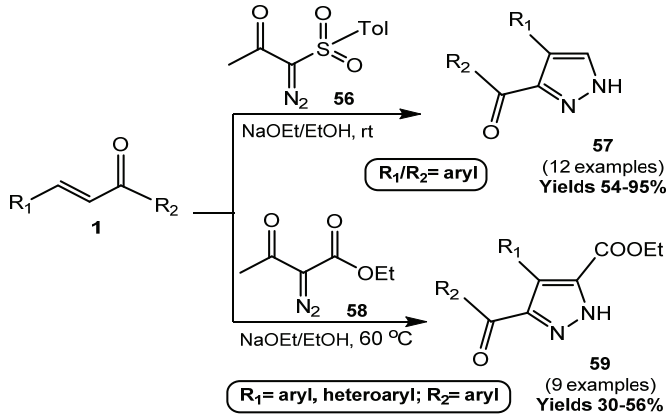
The intramolecular C-N bond formation *via* C-H bond activation to afford indolizine derivatives 55 using pyridyl chalcones **1**[#] and anhydrides **54** was exposed without any catalyst (Wu et al., 2015) in DCE as the solvent (Scheme 20). It provides a new method of constructing synthetically and

medicinally important indolizine derivatives and offers an opportunity to achieve C-H functionalization under metal-free conditions.



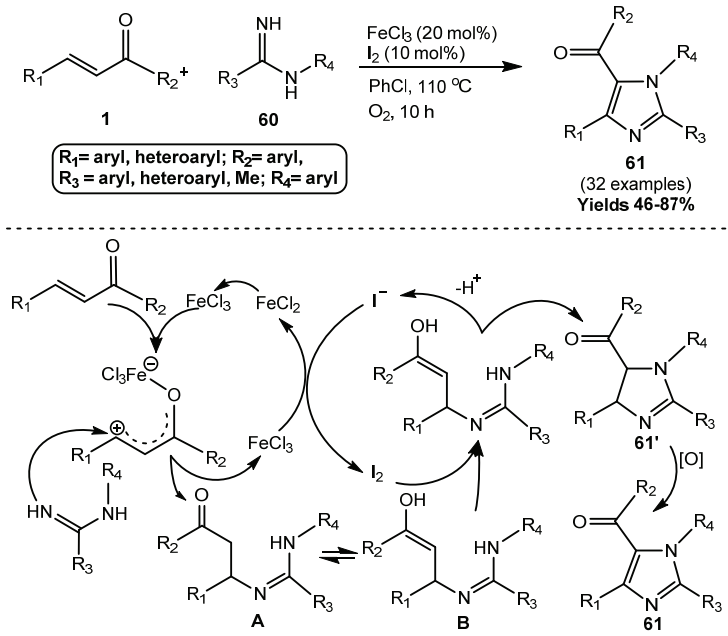
Scheme 20. Synthesis of indolizines from pyridyl chalcones.

A convenient way of preparing 3-acylpyrazoles **57** from diazosulfone **55** and chalcones was reported using a base (NaOEt in EtOH) (Nair et al., 2018). The pyrazoline derivatives which are the initial cycloadducts, could also be isolated and characterized in few cases. The pyrazoline derivatives undergo an alkoxide mediated 1,4-elimination *viz.* decarboxylation-detosylation to afford the pyrazole derivatives (Scheme 21). The same group (Nair et al., 2016) also reported the synthesis of the base mediated deacylation of *α*-diazo-*β*-ketoester **58** generating a diazoester anion, a reactive 1,3-dipole, which undergoes [3+2] annulation with chalcones to afford pyrazole ketoesters **59** in moderate yields.



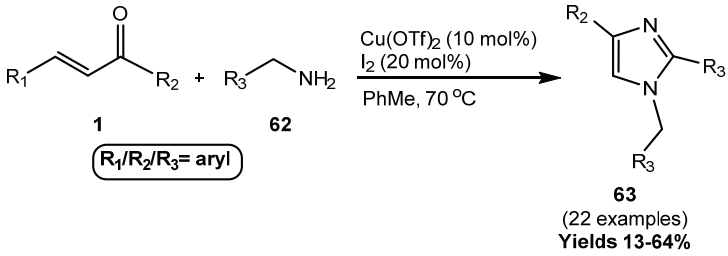
Scheme 21. 1,3-Dipolar cycloaddition for pyrazoles synthesis.

An efficient method for synthesizing tetrasubstituted imidazoles **61** from amidines **60** and chalcones *via* $FeCl_3/I_2$-catalyzed aerobic oxidative coupling had been developed by Zhu et al. (2015) in chlorobenzene (PhCl). They used readily available amidines **60** and chalcones as the starting materials and this method could tolerate a wide range of functional groups present in the substrates. The probable mechanism started with the activation of chalcone by $FeCl_3$ and the addition of *N*-arylbenzamidines to form the Michael adduct **A**, which tautomerize to the enol form **B**. On the other hand, **B** reacts with I_2 to produce the intermediate **C**, followed by a subsequently intramolecular cyclization to afford **61'**, which was oxidated to the desired product **61** under aerobic conditions (Scheme 22).



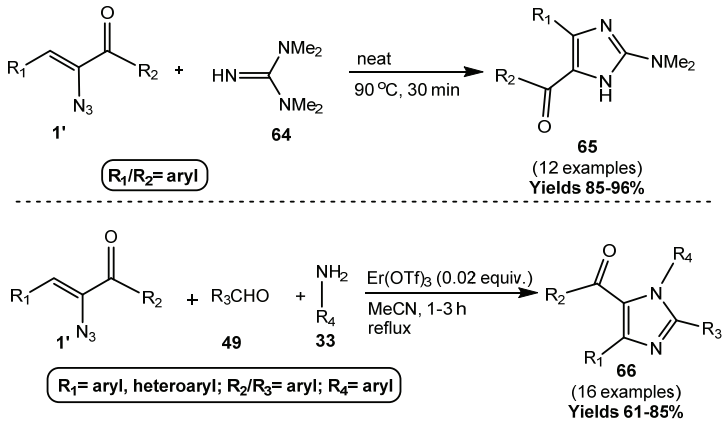
Scheme 22. Synthesis of tetrasubstituted imidazoles from amidines and chalcones.

The C−C bond cleavage of chalcones and benzylamines **62** leading to the synthesis of 1,2,4-trisubstituted-(1*H*)-imidazoles **63** catalyzed by $Cu(OTf)_2$-/I_2 was demonstrated by Salfeena et al. (2018). In this reaction, *α,β*-unsaturated C-C bond cleavage took place, and the *β*-portion was eliminated from the reaction (Scheme 23). The different types of aryl- and heteroaryl substituted chalcones and benzylamines were well tolerated in this remarkable transformation.



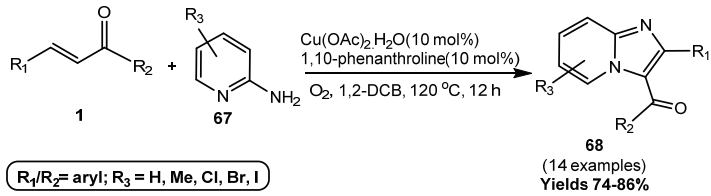
Scheme 23. Synthesis of imidazoles from benzylamines and chalcones.

However, a much more efficient method for the preparation of highly functionalized 1*H*-imidazoles compared to the above two methods (Schemes 22-23) was the one reported by Adib et al. (2017). Just heating a mixture of an *α*-azidochalcone and *N,N,N',N'*-tetramethylguanidine **64** at 90 °C for 30 minutes under neat conditions gave the corresponding 2,4,5-trisubstituted 1*H*-imidazole **65** *via* the Michael addition-cyclization in excellent yields. Another method for synthesizing tetrasubstituted imidazoles **66** using a one-pot three-component reaction using α-azido chalcones, arylaldehydes **45** and anilines **33** was reported by Rajaguru et al. (2014). This protocol employs erbium triflate as a catalyst resulting in an excellent yield of the products (Scheme 24).



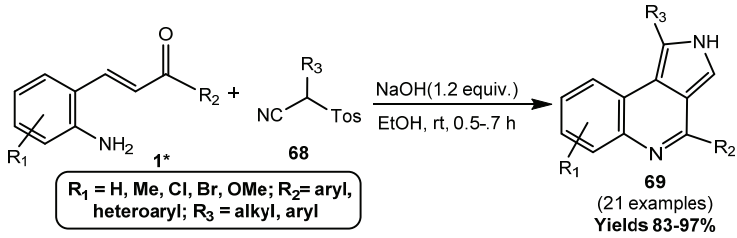
Scheme 24. Synthesis of imidazoles from α-azidochalcones.

The copper (II) acetate-catalyzed aerobic oxidative amination to synthesize 3-aroylimidazopyridines **68** from readily accessible chalcones and 2-aminopyridines **67** with high yields and regioselectivity was reported (Monir et al., 2014.). The reaction proceeds through the tandem Michael addition followed by intramolecular oxidative amination in 1,2-dichlorobenzene as a solvent with ligand 1,10-phenanthroline (Scheme 25). A similar reaction was also performed using a $CuFe_2O_4$ superparamagnetic nanoparticle catalyst, iodine, an oxygen oxidant and 1,2-dichlorobenzene (1,2-DCB) as the solvent (Nguyen et al., 2019).



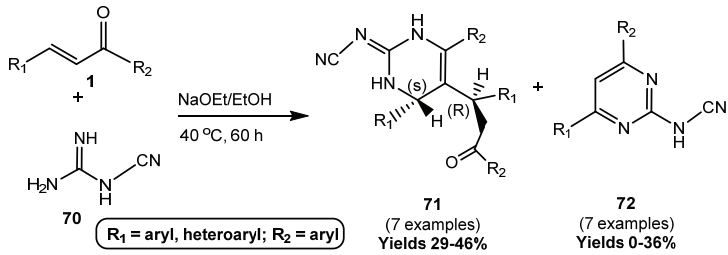
Scheme 25. Synthesis of imidazopyridines from chalcones.

Hu et al. (2014) developed a tandem formal [3+2] cycloaddition/cyclization reaction of aminochalcones **1*** with tosylmethyl isocyanide derivatives **68** for the synthesis of various tricyclic pyrrolo[3,4-*c*]quinolines **69**. In this protocol, three new bonds and two rings are generated successively using NaOH in EtOH as the solvent (Scheme 26). Its rapidity, high efficiency, mild reaction conditions, high to excellent product yields and readily available substrates are salient features of this protocol.



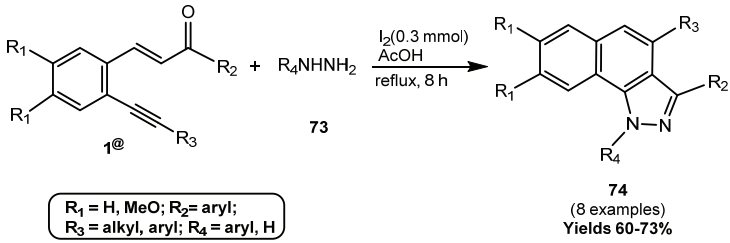
Scheme 26. Synthesis of pyrrolo[3,4-*c*]quinolines from 2-aminochalcones.

A series of dihydrochalcones **71**-**72** containing cyanoiminopyrimidine moiety was synthesized from cyanoguanidine **70** and chalcones in the presence of EtONa under an air atmosphere (Scheme 27). The nucleophilicity of the guanidine fragment in cyanoguanidine was slightly increased under basic conditions, making its reaction with α,β-unsaturated carbonyl compounds feasible *via* the Michael addition to progress the reaction as reported by Moustafa and Amer. (2018).



Scheme 27. Synthesis of pyrimidines from chalcones.

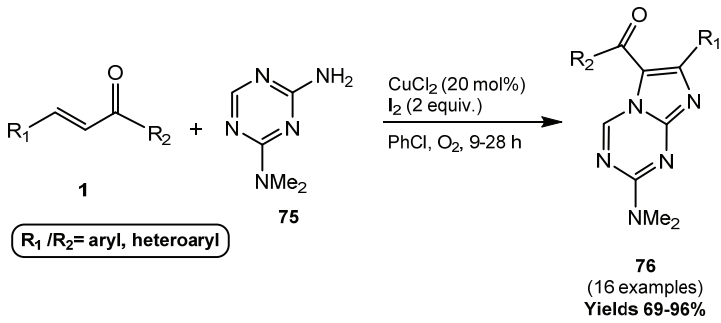
The iodine-mediated synthesis of 1*H*-benzo[*g*]indazoles from *o*-alkynylarene chalcones **1**[@] was reported by Akbar and Srinivasan (2013). In this tandem reaction, arylhydrazine/hydrazine **73** on treatment with chalcones underwent oxidative cyclocondensation to yield *o*-alkynylarylpyrazoles as intermediates, which underwent electrophilic hydroarylation to afford benzindazoles in good yields (Scheme 28).



Scheme 28. Synthesis of benzindazoles from *o*-alkynylarene chalcones.

An efficient method for the synthesis of aroylimidazo[1,2-*a*][1,3,5]triazines **76** through copper-catalyzed iodine-promoted oxidative cyclization of 2-amino-1,3,5-triazines **75** and chalcones was reported (Li et al., 2017). The reaction proceeds *via* a tandem pathway of an initial 1,4-Michael addition followed by copper-catalyzed oxidative C–N bond

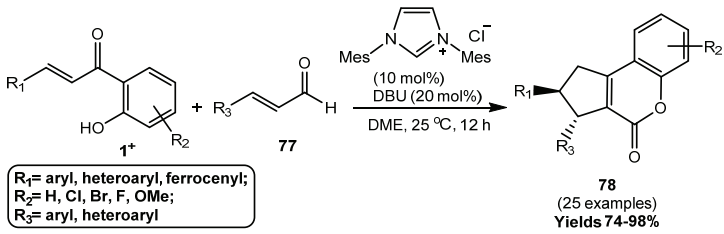
formation to provide imidazo[1,2-*a*][1,3,5] triazines with high regioselectivity (Scheme 29).



Scheme 29. Synthesis of aroylimidazo[1,2-*a*][1,3,5]triazines from chalcones.

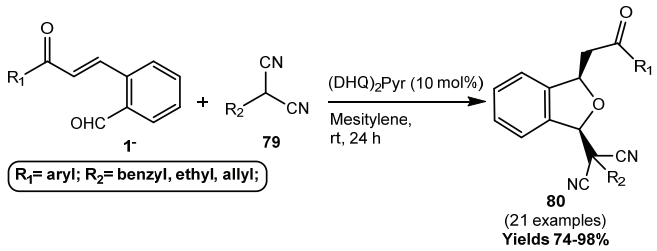
4.3 Synthesis of *O*-containing heterocycles

The diastereoselective synthesis of functionalized coumarins **78** catalyzed by *N*-heterocyclic carbene (NHC)-through homoenolate annulation with 2-hydroxy chalcones $\mathbf{1}^{+}$ in *N,N*-dimethylacetamide (DME) was reported (Bhunia et al., 2013). The feasibility of the reaction was the ease of *δ*-lactonization over the *β*-lactonization giving good to excellent yields of the products. Moreover, the broad substrate scope, high yield of products and mild reaction conditions are the notable features of the present reaction (Scheme 30).



Scheme 30. Synthesis of coumarins from 2-hydroxy chalcones.

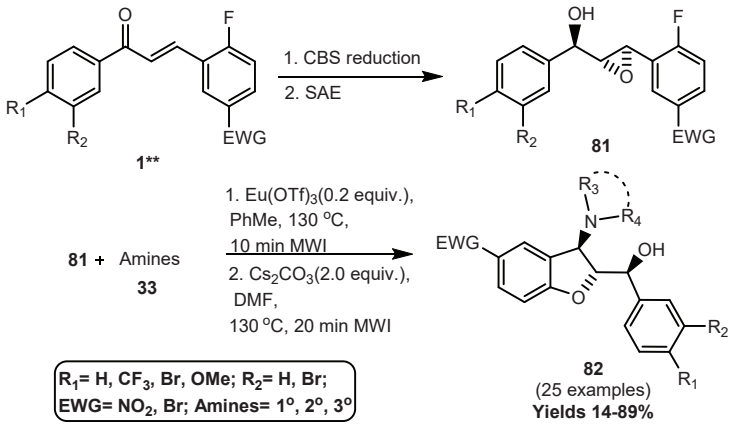
The chemoselective 1,2-addition of malononitriles **79** to *ortho*-formyl chalcones **1**$^{-}$ forming functionalized furans **80** using hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether-$(DHQ)_2Pyr$ has been reported by Maity et al. (2017). In this protocol, alkyl (hard) malononitriles undergo an asymmetric 1,2-addition followed by an *oxa*-Michael reaction cascade to afford 1,3-disubstituted isobenzofurans with high enantio- and diastereoselectivity (Scheme 31). However, for aryl malononitriles, a 1,4-asymmetric addition followed by Aldol reaction give indanol moiety in the presence of another cinchona alkaloid-based bifunctional chiral organo-catalyst.



Scheme 31. Synthesis of isobenzofurans from 2-formyl chalcones.

Another method for the synthesis of functionalized benzofurans, involving four steps, has been developed by Helgren et al. (2018). The reaction

begins with the Aldol condensation to generate chalcone intermediates **1**** and followed by a Corey-Bakshi-Shibata (CBS) reduction and subsequent Sharpless asymmetric epoxidation (SAE) to access stereoisomeric epoxyalcohols. The final step was a one-pot acid-catalyzed epoxide opening with various amines assisted by microwave irradiation. This was followed by an intramolecular nucleophilic aromatic substitution reaction to generate the 3-amino-2,3-dihydrobenzofurans. The yields for this protocol were typically lower with primary amines (32–62%) than secondary amines or anilines (49–89%).

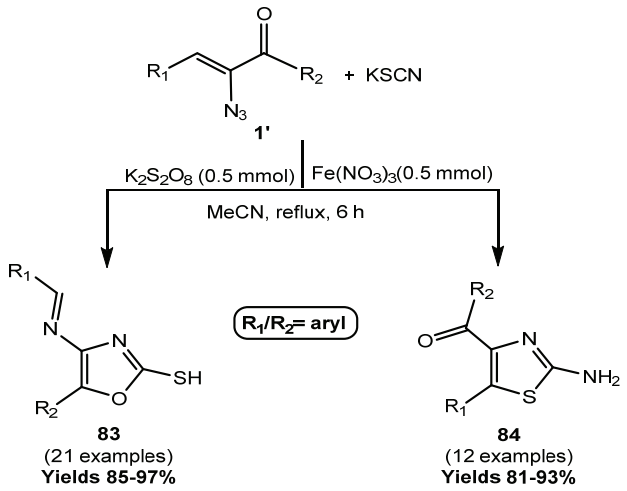


Scheme 31. Synthesis of dihydrobenzofurans from chalcones.

4.4 Synthesis of *N,O*/*N,S*-containing heterocycles

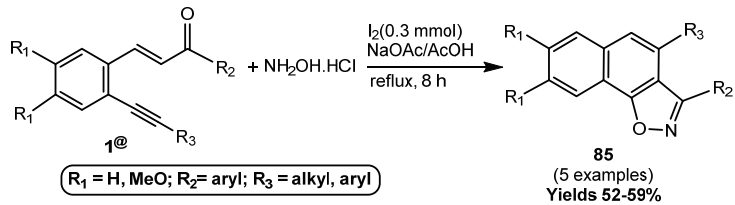
The synthetic utility of *α*-azidochalcones was further demonstrated by Harisha et al. (2020) for synthesizing highly substituted oxazoles **83** and 2-aminothiazoles **84** using potassium thiocyanate and employing potassium persulfate and ferric nitrate, respectively. This protocol gains a streamlined

workup and eliminates air-sensitive techniques to afford the product in excellent yields in a greener medium (Scheme 32).



Scheme 32. Synthesis of oxazoles and 2-aminothiazoles from *α*-azidochalcones.

The synthesis of naphtho[2,1-*d*]isoxazoles from **85** from *o*-alkynylarene chalcones **1**[@] using hydroxylamine was reported by Akbar and Srinivasan (2013). The hydroxylamine reaction with *o*-alkynylarene chalcones yields oxazoles as intermediates, which underwent electrophilic hydroarylation to afford the naphthisoxazoles in moderate yields (Scheme 33).



Scheme 33. Synthesis of isoxazoles from *o*-alkynylarene chalcones.

5. Conclusion

The chemistry of chalcones has been an exciting field for both organic and medicinal chemists for designing aza-heterocycles. The advances in the last decade for the synthesis of pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, pyridines, pyrimidines, thiophenes, and dithioles from chalcone-type compounds are presented in this chapter. In the 21st century, chalcones continue to be a privileged building block in the synthetic field, being expected to further progress in these fields.

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CHAPTER 3

β-ENAMINO CARBONYL COMPOUNDS

1. Introduction

Enaminones **1** are versatile intermediates containing the system N–C=C–C=O and their chemistry has received considerable attention in recent years (Elassar and El Khair, 2003). They are known for constructing heterocycles as well as pharmaceutical compounds (Spivey et al., 2003) and also as the ligands for transition metal-catalyzed synthetic methods (Yoshii et al., 2015). The versatility of enaminones is due to their promptness to both electrophilic attack at the electron-rich C-2 and nucleophilic attack at electron-deficient C-1and C-3 with various organic reagents (Ferraz and Goncalo, 2007). Further, they are essential subunits present in some biologically important natural products and therapeutic agents (Comer and Murphy, 2003). They are also intermediates for synthesizing several amino acids, aminols, peptides and alkaloids (Palmieri and Cimarelli, 1996). In addition, open-chain enaminones (the characteristic group is part of a chain) may be potential prodrugs since they could release biologically active primary amines (Fraser, 1996). Thus, due to the importance of enaminones as bioactive leads and versatile building blocks, chemists constantly hunt for their novel synthesis and application in organic chemistry.

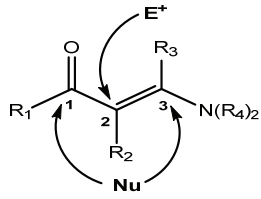
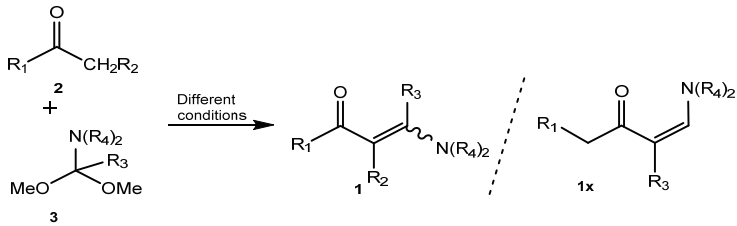


Figure 1. The structure of enaminone.

2. Synthesis of Enaminones

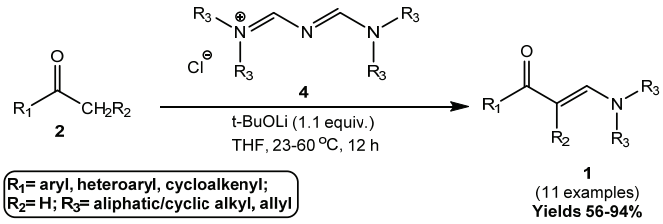
The development of an efficient protocol for synthesizing enaminones from readily available starting materials has attracted considerable attention in organic chemistry (Martin et al., 1994). Generally, active methylene ketones **2** condense readily with dialkylamino dimethyl acetals **3** to yield the enaminones **1,** in different conditions, as shown in Scheme 1. The disadvantages of this protocol include moderate yields, non-selective enolization and, thus, isomeric constitutional products wherein the two different ketone *α*-positions have been functionalized.



Scheme 1. Synthesis of enaminones using dialkylamino dimethyl acetals and ketones.

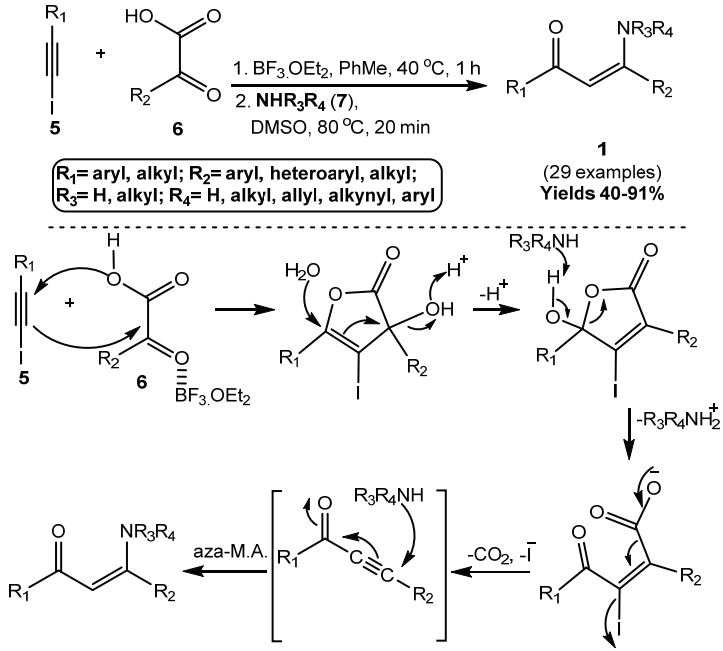
However, the scalable synthesis of enaminones using Gold's reagents prepared from cyanuric chloride **2** and *N,N*-dialkylformamides **4** was

reported by Schuppe et al. (2017). The synthetic equivalents of *N,N*-dimethylformamide dimethyl acetal were used in an optimized and scalable procedure for the regioselective synthesis of a variety of enaminones from ketones (Scheme 2).



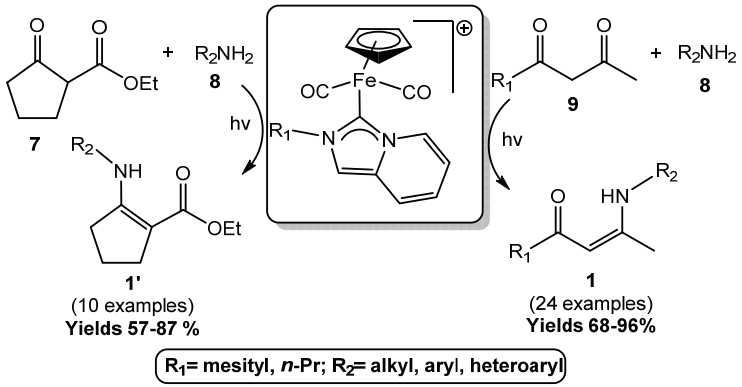
Scheme 2. Selective enaminone formation using Gold's catalyst.

There are several reports on the synthesis of enaminone using *α*-keto acids. Zeng et al. (2019) reported enaminone synthesis using *α*-keto acid **6** and 1-iodoalkyne **5** in the presence of Lewis acid ($BF_3 \cdot OEt_2$) in toluene (PhMe) followed by amine-mediated ring-opening. This protocol allowed the synthesis of those products bearing the transition metal-sensitive groups and also its three-component process achieved a wide range of functionalized products. The proposed mechanism started with $BF_3 \cdot OEt_2$-catalyzed cyclization of the substrates giving an intermediate and converting into furanone. Then, ynone was formed *via* an amine-mediated ring-opening and followed by a decarboxylation/deiodination step. Finally, enaminone was produced by an aza-Michael addition between ynone and amine (Scheme 3).



Scheme 3. Synthesis of enaminone using *α*-keto acid.

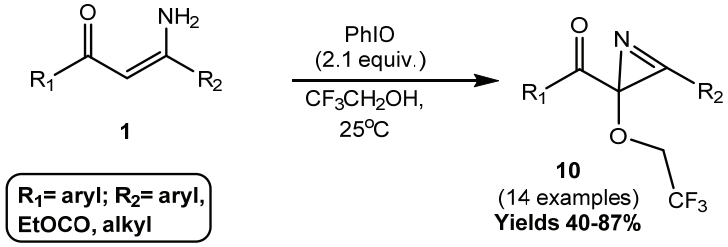
Then, one of the conventional approaches for the synthesis of the *β*-enaminone involves the condensation of 1,3-dicarbonyl compounds **7**/**9** with amines **8** as described by Prakasham et al. (2019). They elaborated on the condensation reaction between the cyclic **7** and acylic 1,3-dicarbonyl compounds **9** with various aliphatic amines **8** like ethyl amine, *n*-propyl amine, isopropyl amine, *n*-butyl amine and morpholine yielding aliphatic *β*-enamino esters **1/1'**. The Fe-NHC complex catalyzed the reaction to give the products **1/1'** in moderate to high yields (57–96%) under an ambient condition in the presence of UV light irradiation (λ = 294 nm) at 27 °C, as shown in Scheme 4.



Scheme 4. *β*-Enaminone synthesis from 1,3-dicarbonyl compounds.

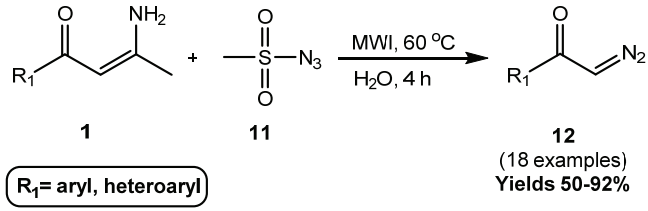
3. Functionalization of *β*-Enaminones

The synthesis of the trifluoroethoxylated 2*H*-azirines **10** using *α*-unsubstituted enamines and PhIO in trifluoroethanol (TFE) was reported by Sun et al. (2013). The process involves a cascade reaction of metal-free intermolecular oxidation of C=O bond formation and a subsequent intramolecular oxidative azirination (Scheme 5).

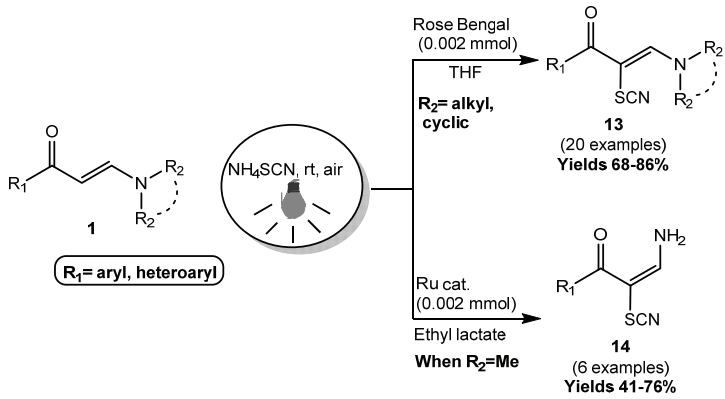


Scheme 5. Synthesis of 2*H*-azirines using α-unsubstituted enamines.

When enaminones were allowed to react with methyl sulfonyl azide **11** in pure water through microwave irradiation (MWI), *α*-diazoketones **12** were synthesized as reported by Gan et al. (2020). Besides the green medium and energy source, the reaction provides additional sustainability advantages from the total catalyst- and additive-free conditions as shown in Scheme 6. The same group also reported the visible-light-induced C-H bond thiocyanation on the *α*-site of tertiary enaminones (Gao et al., 2019) under metal-free, photocatalytic conditions in the presence of Rose Bengal. It enables the synthesis of thiocyanated alkene **13** derivatives using NH_4SCN as the thiocyano source under an aerobic atmosphere and, further, on employing $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as the photocatalyst switches the reaction pathway to provide NH_2-functionalized thiocyanated enamines **14** *via* the difunctionalization process consisting of C−H bond thiocyanation and vinyl C-N bond transamination (Scheme 7).

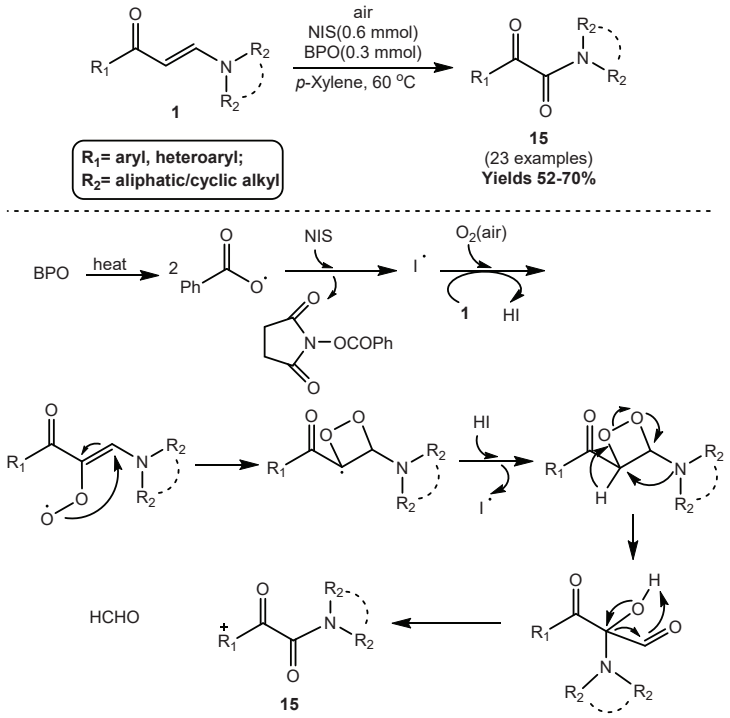


Scheme 6. Synthesis of *α*-diazoketones.



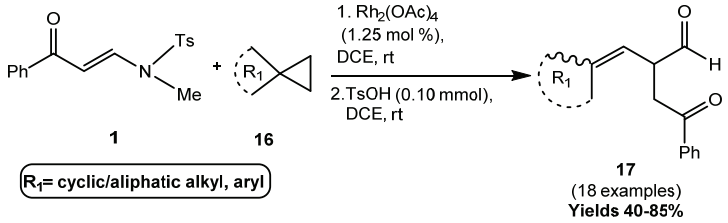
Scheme 7. The thiocyanation of tertiary enaminones.

In the same year, Yang et al. (2019) also reported the synthesis of *α*-ketoamide **15** using enaminone in the presence of benzoyl peroxide (BPO) and *N*-iodosuccinimide (NIS), under an aerobic atmosphere. This tandem oxidation of the enaminone C=C double bond and subsequent C-N bond formation was realized by thermo-induced free-radical transformation giving products with moderate yields, as shown in Scheme 8 along with the probable mechanism.



Scheme 7. NIS-mediated α-ketoamide synthesis from enaminone.

Enaminones were also used to prepare functionalized α-vinyl aldehydes **17** with high *E/Z* stereoselectivity using $Rh_2(OAc)_4$-catalyzed and subsequent reaction using *p*-toluenesulfonic acid (PTSA) as reported by Chen et al. (2019) in dichloroethane (DCE). The reaction leads to enaminones' cyclopropanation with vinyl carbenoids generated from cyclopropenes **16** *in situ,* giving the aminocyclopropane intermediates. Then, selective C-C bond cleavage of the intermediates gives α-vinyl aldehyde derivatives in moderate to good yields (Scheme 8).

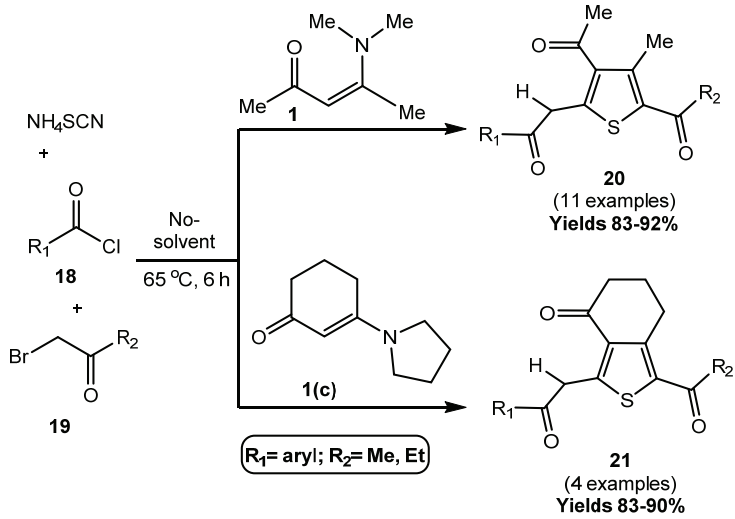


Scheme 8. Preparation of α-vinyl aldehydes from enaminones.

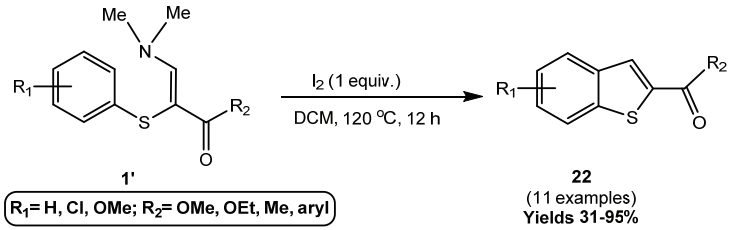
4. Application in Organic Synthesis

4.1 Synthesis of *S*-containing heterocycles

The synthesis of tetrasubstituted thiophenes **20-21** *via* one-pot reaction between ammonium thiocyanate, acyl chlorides **18**, α-halocarbonyls **19** and enaminones was described by Hossaini et al., 2011. The reactions were performed under solvent-free conditions at 65 °C giving high yields of the products, as shown in Scheme 9. The synthesis of the benzo[*b*]thiophenes **22** through the intramolecular cyclization of the enaminones mediated by iodine in dichloromethane (DCM) as the solvent was also explored giving the products **22** up to 90% yield (Labarrios et al., 2014) in Scheme 10.



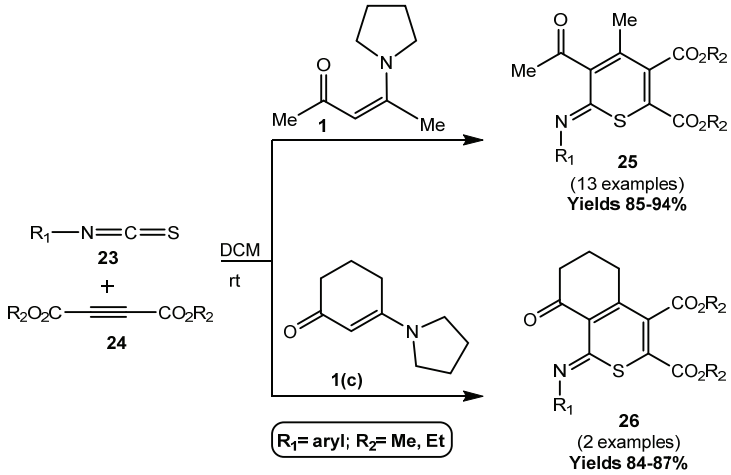
Scheme 9. Synthesis of tetrasubstituted thiophenes using enaminones.



Scheme 10. Synthesis of benzo[*b*]thiophenes using enaminones.

Then, Hamadi et al. (2011) described the synthesis of iminothiopyran-2,3-dicarboxylates **25** and isothiochromene-3,4-dicarboxylates **26** *via* one-pot reactions between acetylenic esters **24**, aryl isothiocyanates **23** and enaminones at room temperature with DCM as a solvent (Scheme 11). The advantages of this protocol include (a) the reaction was performed under neutral and mild conditions, (b) no catalyst was involved and (c) the

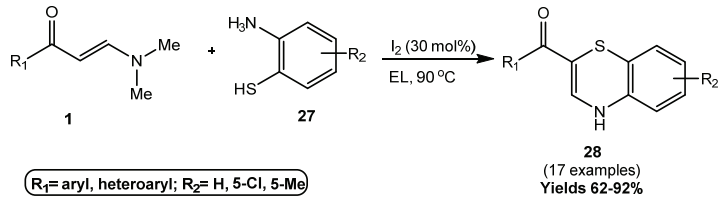
simple reaction environment makes it an attractive alternative to the complex multistep approaches.



Scheme 11. Synthesis of thiopyran derivatives using enaminones.

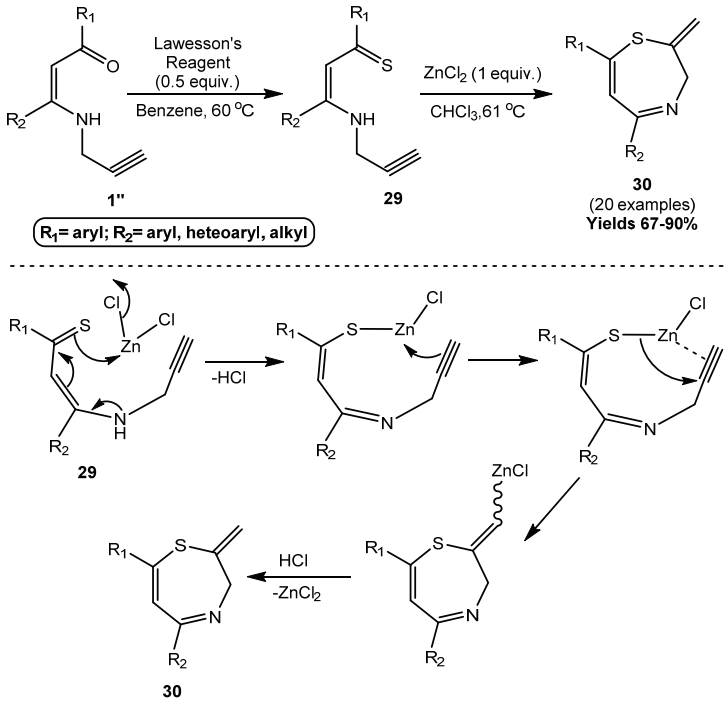
4.2 Synthesis of *N, S*-containing heterocycles

The green protocol for synthesizing 1,4-benzothiazines **28** was reported by Wan et al. (2018) using a catalytic amount of I_2. The reaction between *N,N*-dimethyl enaminones and *ortho*-aminothiophenols **27** give 1,4-benzothiazines in good yields *via* cascade C-N bond transamination and C(sp^2)-H sulfenylation. The advantage of this method was employing ethyl lactate (EL) as a green medium with molecular iodine as the sole catalyst. Further, the simple operation, acceptable substrate tolerance and sustainability make it a handy complementary tool in synthesizing important *N, S*-containing heterocyclic products (Scheme 12).



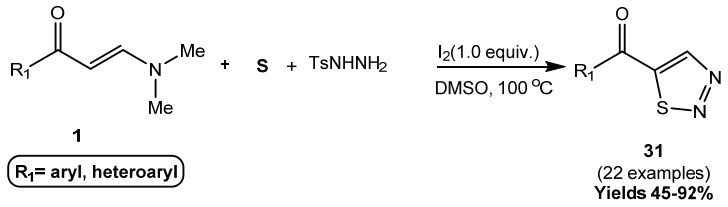
Scheme 12. Synthesis of 1,4-benzothiazines from enaminones.

The construction of functionalized 1,4-thiazepine rings from *N*-propargylic *β*-enaminothiones was reported by Kelgokmen and Zora (2018). Enaminothiones **29** were prepared from the corresponding *β*-enaminones in good to high yields by thionation with Lawesson's reagent. Treatment of *N*-propargylic *β*-enaminothiones with zinc chloride in refluxing chloroform afforded 2-methylene-2,3-dihydro-1,4-thiazepines **30** in good to high yields *via* electrophilic cyclization. The mechanism proceeds as the reaction of *N*-propargylic *β*-enaminothione **29** with zinc chloride through vinylogous amido−imido tautomerization affords an intermediate. The subsequent coordination of the alkyne unit to zinc generates another intermediate and then intramolecular cyclization occurs to give a vinyl zinc intermediate. It leads to further hydrolysis with HCl produced *in situ* yielding 1,4-thiazepines **30** (Scheme 13).



Scheme 13. Synthesis of 1,4-benzothiazines from enaminones.

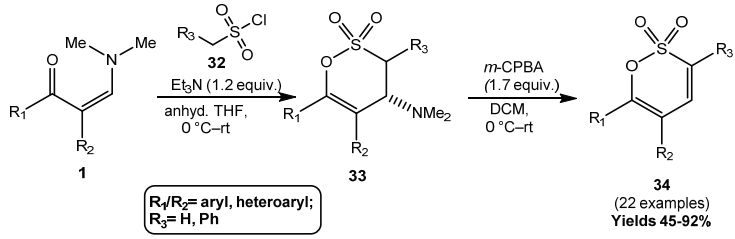
The I_2/dimethyl sulfoxide (DMSO)-mediated three-component protocol for synthesizing 1,2,3-thiadiazoles **31** from enaminones, tosyl hydrazine and elemental sulfur was reported by Yang et al. (2019). Three new C-S, S-N and C-N bonds were constructed in this method (Scheme 14).



Scheme 14. Synthesis of 1,2,3-thiadiazole from enaminones.

4.3 Synthesis of *O, S*-containing heterocycles

The efficient synthesis of 1,2-oxathiine 2,2-dioxides **34** having aryl and heteroaryl substituents has been reported (Aiken et al., 2019) using triethylamine (Et_3N) and *m*-chloroperoxybenzoic acid (*m*-CPBA). The products were obtained through a Cope elimination protocol from their respective 4-dimethylamino-3,4-dihydro **33** precursors, which were derived from sulfene **32** additions to enaminoketones, as shown in Scheme 15.

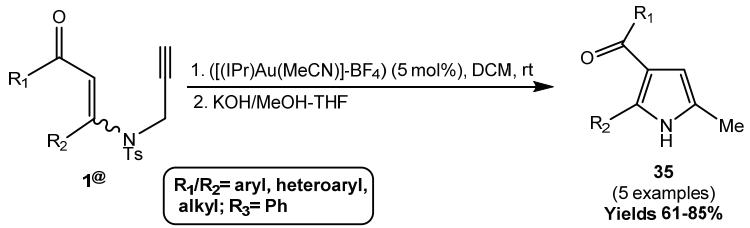


Scheme 15. Synthesis of 1,2-oxathiine 2,2-dioxides from enaminones.

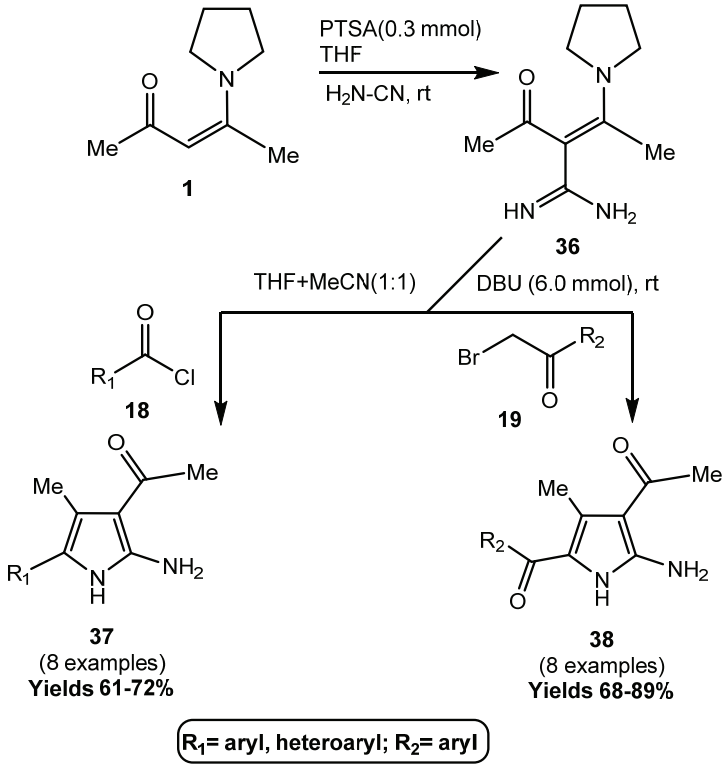
4.4 Synthesis of *N*-containing heterocycles

The synthesis of trisubstituted pyrrole derivatives **35** from *N*-propargyl *β*-enaminones using the cationic *N*-heterocyclic carbene-gold(I) complex ([(IPr)Au(MeCN)]-BF_4) catalyst was successfully demonstrated by Saito et al. (2010) (Scheme 16). Then, an efficient and facile synthesis of tera-substituted-2-aminopyrroles starting from enaminone was reported by Jalani et al. (2011). They started the reaction from enaminone–amidine adduct **36** and various phenacyl **19** or benzyl **18** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), giving the products in good to excellent yields. The reaction proceeds through an intramolecular 5-*exo*

trig cyclization resulting in diversely tetrasubstituted 2-aminopyrroles (Scheme 17).

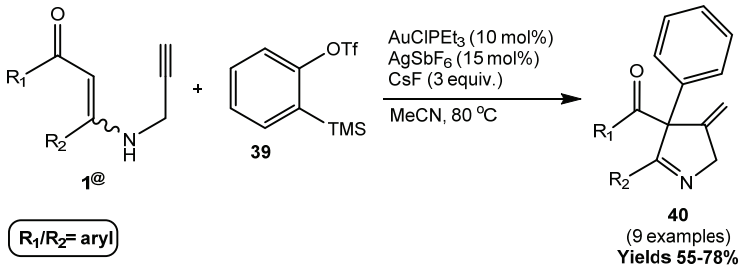


Scheme 16. Synthesis of trisubstituted pyrroles from enaminones.



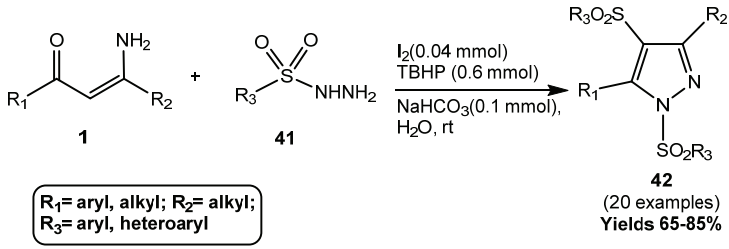
Scheme 17. Synthesis of tetrasubstituted pyrroles from enaminones.

The reaction between *N*-propargylic *β*-enaminones and arynes **39** was developed (Goutham et al., 2014) to synthesize 3-methylene-1-pyrrolines bearing quaternary stereocenters and exocyclic double bonds **40**. The products were obtained by utilizing the combination of $AuClPEt_3$ (10 mol%), $AgSbF_6$ (15 mol%) and CsF (3 equiv.) in MeCN at 80 °C giving the products in moderate yields of 57–78%, as shown in Scheme 18.



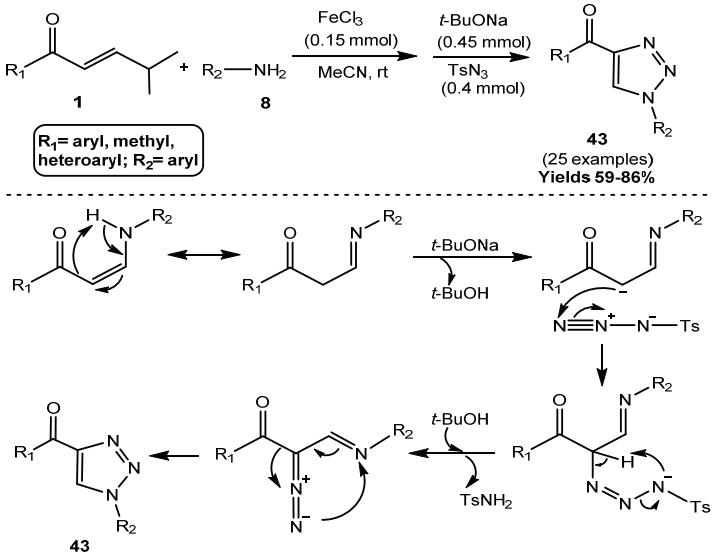
Scheme 18. Synthesis of pyrrolines from enaminones.

Then, the synthesis of fully substituted pyrazoles **42** through cascade reactions between NH_2-functionalized enaminones and sulfonyl hydrazines **41** was developed by Guo et al. (2019). The hydrophilic primary part of the amino group in the enaminones was utilized for the smooth proceeding of the reaction in pure water in the presence of molecular iodine, (*tert*-butyl hydroperoxide) TBHP and $NaHCO_3$ *via* cascade C-H sulfonylation and pyrazole annulation (Scheme 19).



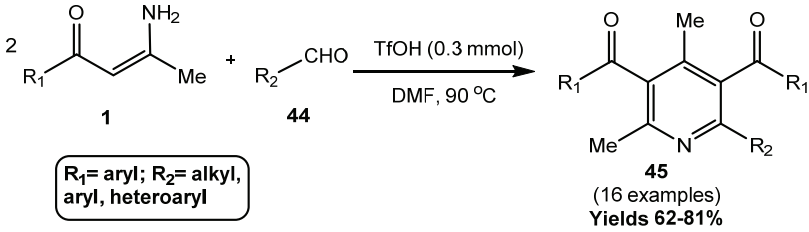
Scheme 18. Synthesis of pyrazoles from enaminones.

The reactivity of secondary enaminones was also demonstrated (Wan et al., 2016) for the domino reaction between NH-enaminones and tosyl azide **TsN_3** to synthesize various *N*-substituted 1,2,3-triazoles **43**. They employed *t*-BuONa as the base promoter; the reactions proceed efficiently at room temperature with good substrate tolerance (Scheme 19). The generation of various *N*-substitutions in the products *via* *N*-substituted enaminones rather than organoazides demonstrates its advantages for synthesizing 1,2,3-triazoles. The mechanism proceeds with NH-enaminones affording the anion in the presence of a base *via* the tautomer. Then, the nucleophilic addition of anion to the N-N triple bond in tosyl azide yields an intermediate. The generation of a diazo intermediate *via* a typical Regitzdiazo transfer and the intramolecular cyclization then yields the 1,2,3-triazoles **43.**

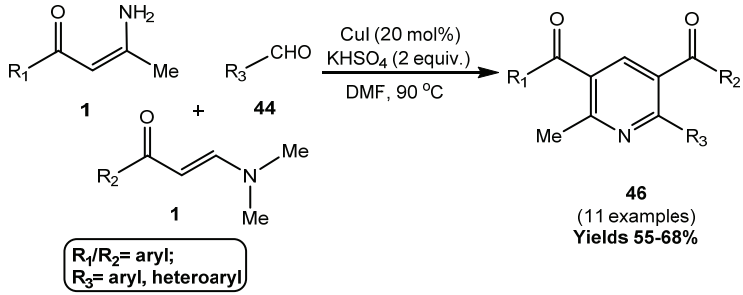


Scheme 19. Synthesis of 1,2,3-triazoles from enaminones.

Wan et al. (2016) reported the synthesis of fully substituted pyridines **45** using two moles of primary enaminones and aldehydes **44**. Dimerizing primary enaminones have accomplished the products with a distinctive pattern *via* the cascade generation of two C−C and one C−N bond by simply using triflic acid (TfOH) as a promoter (Scheme 20). Whereas, the synthesis of structurally unsymmetrical 2,3,5,6-tetrasubstituted pyridines *via* the three-component reactions of two different enaminones and an aldehyde was demonstrated by Li, Wang, et al. (2019) (Scheme 21).

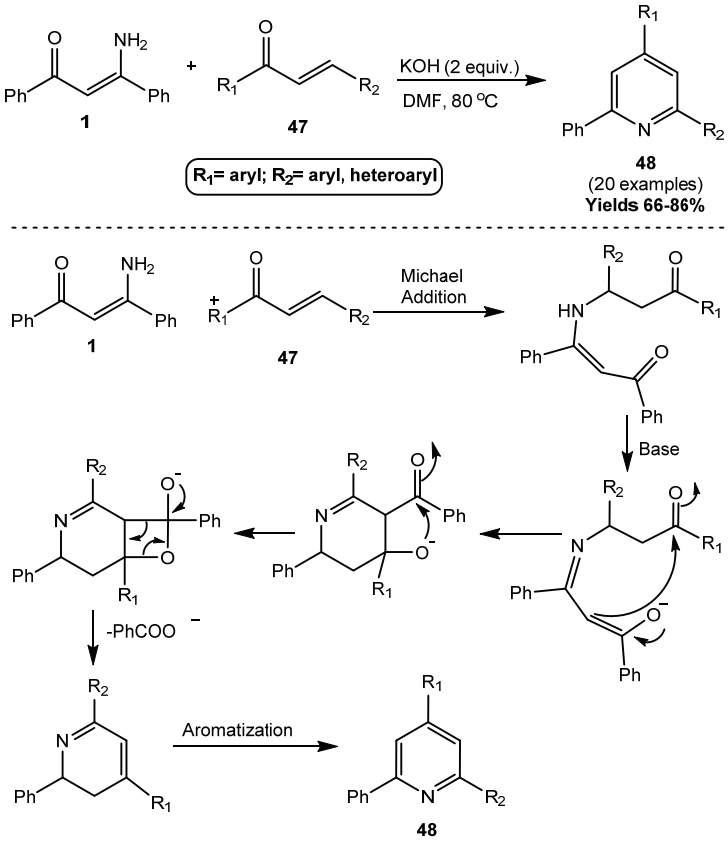


Scheme 20. Synthesis of fully substitute pyridines from enaminones.



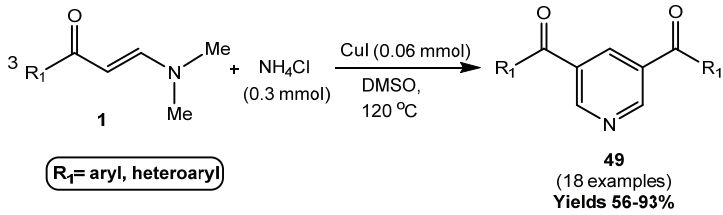
Scheme 21. Synthesis of tetrasubstituted pyridines from enaminones.

The construction of 2,4,6-trisubstituted pyridines **48** from *N*-unsubstituted enaminones and chalcones **47** promoted by the KOH/DMF system in the absence of transition metal was reported by Zhang et al. (2018). The proposed mechanism proceeds *via* a Michael addition reaction between enaminone and chalcone to form an intermediate. Then, base-promoted 1,5-H shift leads to iminoenolate intermediate and then subsequent intramolecular nucleophilic additions and elimination of arylformate leads to the final product **50** through aromatization (Scheme 22).



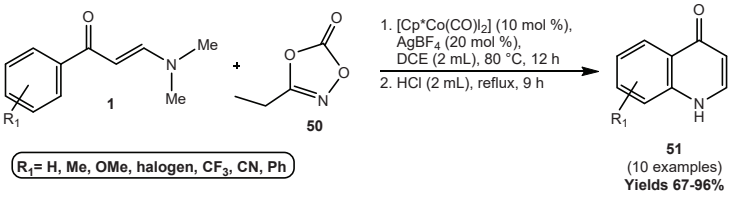
Scheme 22. Synthesis of tetrasubstituted pyridines from enaminones and chalcones.

The synthesis of 4-unsubstituted pyridines of both symmetrical **49** and unsymmetrical structures from enaminones and ammonium chloride using copper-catalyzed was demonstrated by Wan et al. (2014). In this protocol, the transformations of enaminones with C-N and C-C bond cleavages provide the C2-C3/C5-C6 and C4 building blocks to construct the pyridine ring in moderate to good yields, respectively (Scheme 23).



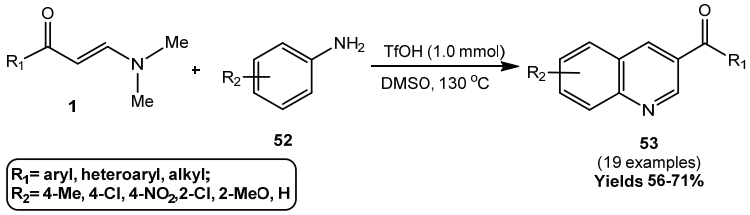
Scheme 23. Synthesis of symmetrical disubstituted pyridines from enaminones.

The synthesis of quinolones **51** through Co(III)-catalyzed enaminone-directed C-H amidation was reported by Shi et al., (2017). The C-H coupling between enaminones and dioxazolones **50** with subsequent deacylation of an installed amide group allows consecutive C-N coupling to final quinolones with wide ranges of compatible substituent patterns (Scheme 24).



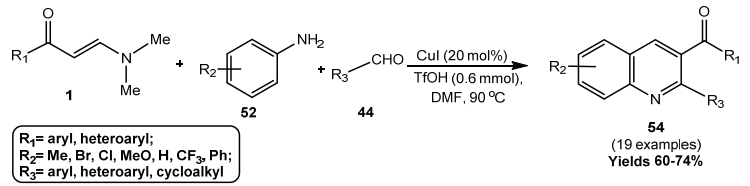
Scheme 24. Synthesis of quinolone from enaminones.

The domino reactions between *N,N*-dimethyl enaminones and anilines **52** affording quinolines **53** have been accomplished *via* the promotion of triflic acid (Wan et al., 2017). The construction of the quinolines was feasible through cleavage of the C=C double bond and C-N bond in the enaminones, which provides C2-C3 and C4 fragments, respectively. Here, the products have been formed with the construction of two new C-C and a new C-N bonds (Scheme 25).



Scheme 25. Synthesis of mono-substituted quinolines from enaminones.

Then, the regioselective synthesis of 2,3-disubstituted quinolines **54** *via* three-components reaction of enaminones, aldehydes **52** and anilines **44** was successfully demonstrated by Li et al. (2017). Unlike conventional Povarov reactions giving 2,4-disubstituted quinolines, the present method allows the fast and regioselective formation of 2,3-disubstituted quinolines as a modified new version of the Povarov reaction with moderate yields (Scheme 26).

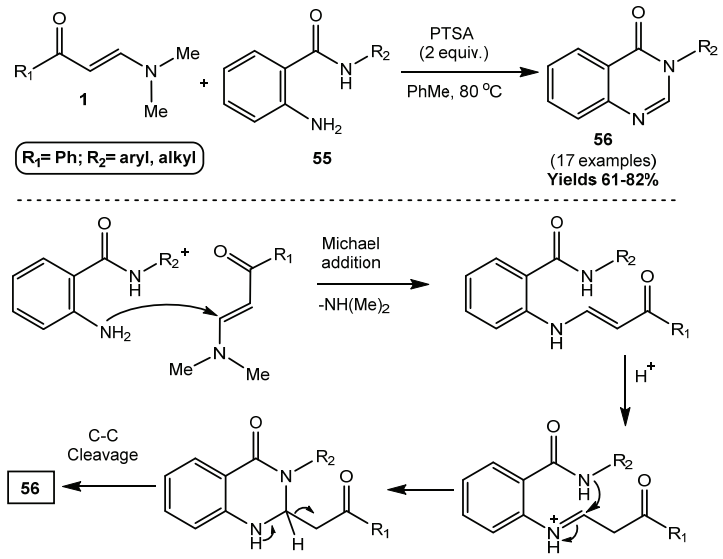


Scheme 26. Synthesis of disubstituted quinolines from enaminones.

4.5 Synthesis of two & three *N*-containing heterocycles

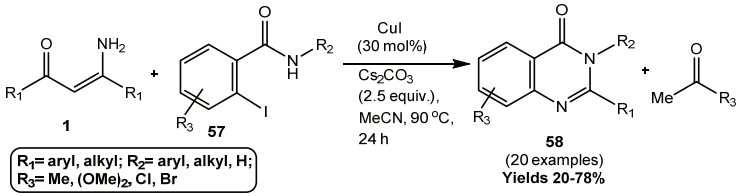
The reaction of *o*-aminobenzamides **55** with enaminone *via* C-N and C-C bond cleavage leading to quinazolinones **56** promoted by PTSA was developed by Ambethkar, Kalaiselvi, et al. (2017). The reaction proceeds with an initial Michael addition between the reactants and elimination of Me_2NH as a by-product. Then enamine-imine tautomerization occurred in

the presence of acid and subsequent intermolecular nucleophilic addition leading to final products **56** *via* C-C bond cleavage reaction (Scheme 27).



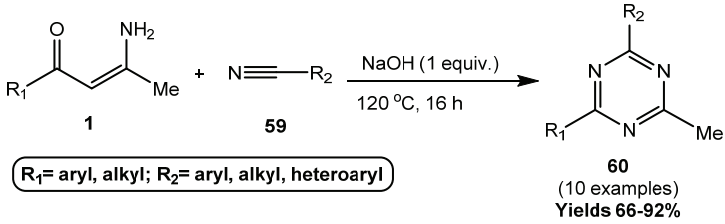
Scheme 27. Synthesis of mono-substituted quinazolinones from enaminones.

Then, *o*-iodobenzamides **57** was used to synthesize disubstituted quinazolinones, as reported by Songsichan et al. (2014). Here, *o*-iodobenzamides and enaminones undergo cascade transformations giving quinazolinones **58** *via* a copper-catalyzed Ullmann-type coupling, a Michael addition and a retro-Mannich reaction. The unique feature of this protocol was that *Z*-enaminones reacted without external ligands, however, *E*-enaminones required the assistance of ligands (Scheme 28).



Scheme 28. Synthesis of disubstituted quinazolinones from enaminones.

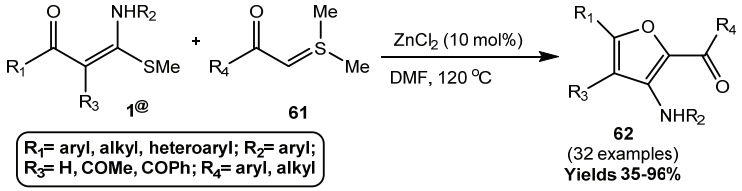
The synthesis of diversely functionalized pyrimidines **60** using enaminones and nitriles **59** without any catalyst was demonstrated by Su et al. (2018). In this reaction, various nitriles worked well with enaminones, yielding the corresponding pyrimidines in good to excellent yields. However, aromatic nitriles (78−84%) were more reactive than alkyl nitriles (66−73%), which was attributed due to the stronger electrophilicity of the C-N triple bonds of aromatic nitriles (Scheme 29).



Scheme 29. Synthesis of trisubstituted pyrimidines from enaminones.

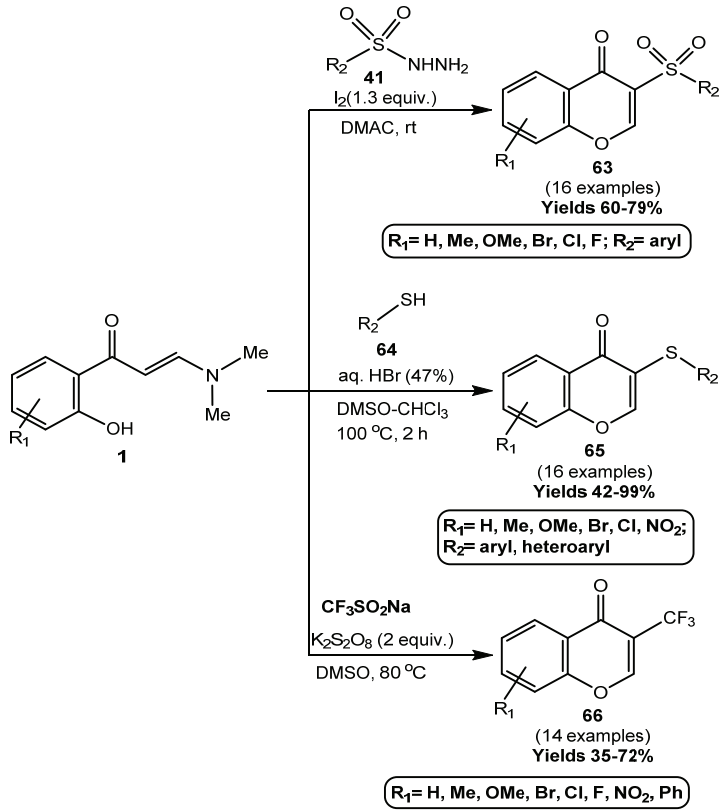
4.6 Synthesis of *O*-containing heterocycles

The synthesis of 2-acyl-3-aminofuran derivatives **62** *via* [4+1] annulation of alkylthio-substituted enaminones **1@** (i.e., *α*-oxo ketene *N,S*-acetals) with sulfur ylides **61** catalyzed by $ZnCl_2$ was successfully performed by He et al. (2020). This [4+1] annulation featured allows for broad substrate scopes, high efficiency and good functional-group tolerance (Scheme 30).



Scheme 30. Synthesis of 2-acyl-3-aminofurans from alkylthio-substituted enaminones.

The chemo-selective synthesis of 3-sulfonyl chromones **63** from enaminones and sulfonyl hydrazines **41** through radical C(sp^2)–H sulfonylation and C(sp^2)–N bond oxygenation was reported by Wan et al. (2017). This domino reaction proceeded according to a free-radical mechanism initiated by molecular iodine without any catalyst in *N,N*-dimethylacetamide (DMAC) as solvent. Again, Sorabad and Maddani. (2019) developed a regioselective approach for synthesizing sulfenylated chromones **65** from enaminones and aryl thiol **64** promoted by a combination of aqueous HBr-DMSO. The use of the catalytic amount of inexpensive aq. HBr in combination with DMSO as an oxidizing agent yields the product in excellent yields. Then, the synthesis of 3-trifluoromethyl chromones **66** through C-H bond trifluoromethylation and chromone annulation reactions of enaminones have been reported (Yu et al. 2020). The reactions were carried out efficiently with the promotion of $K_2S_2O_8$ without using any transition metal catalyst or additive, (Scheme 31).

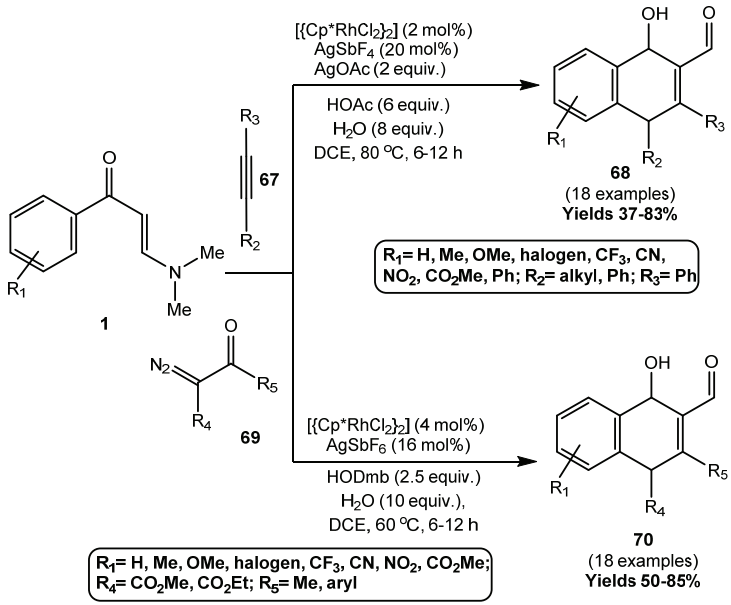


Scheme 30. Synthesis of 3-sulfonyl, -sulfenyl and -trifluoromethylchromones from enaminones.

4.6 Miscellaneous

The method for enaminone-directed C-H functionalization and its utility in the Rh^{III}-catalyzed synthesis of naphthalenes **68** and **70** *via* coupling with alkynes or *α*-diazo-*β*-ketoesters was reported by Zhou et al. (2016). This method integrated two fundamentally reactive functionalities (hydroxy and aldehyde groups) into the newly formed products. Thus, a broad range of

substituents was tolerated, rendering target products readily accessible for further extension (Scheme 31).



Scheme 31. Synthesis of naphthalenes from enaminones.

5. Conclusion

Enaminones are powerful synthons in organic chemistry as well as an integral part of several bioactive products found in nature, as demonstrated in this chapter. The presence of multifunctional groups and heteroatoms facilitates multiple nucleophilic and electrophilic additions at different positions to produce complex molecular structures. They are well utilized in the preparation of electron-rich dienes for Diels–Alder reaction and also for the synthesis of various heterocyclic and carbocyclic compounds.

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CHAPTER 4

ALLENAMIDES

1. Introduction

Allenamides **1** are functionally derived from allenamines, such as allenol ethers, allenyl sulfides as well as being classified as heteroatom-substituted allenes. Allenamides (Figure 1) exhibit higher stability than their parent allenamines and have received significant consideration from the synthetic organic community during the past decade (Lu et al., 2013). Since the first citation of the synthesis of allenamides and their characterization (Hubert and Viehe, 1968), they have been widely explored and applied as one of the most potent and versatile building blocks in the field of organic synthesis.

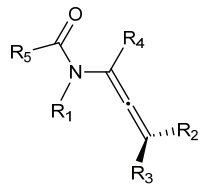
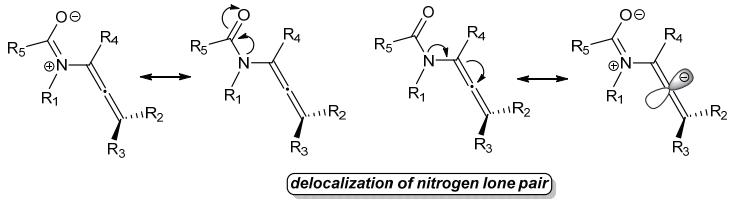
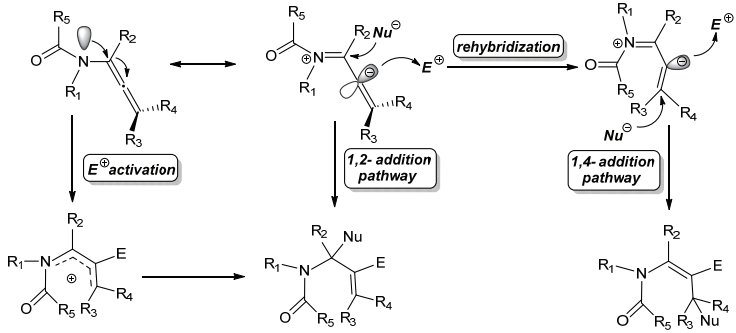


Figure 1. Structure of allenamide.

The π-donating ability of a nitrogen atom in allenamides rendered them more electron-rich than simple allenes, making them susceptible to electrophilic activation. The resonance form of allenamides exerted an electronic partiality by the delocalization of the nitrogen lone pair to the allenic moiety (Scheme 1). Therefore, electrophiles and nucleophiles' consecutive addition can achieve a highly regioselective transformation of allenamides (Li et al., 2020) (Scheme 2).



Scheme 1. Resonance form of allenamides.

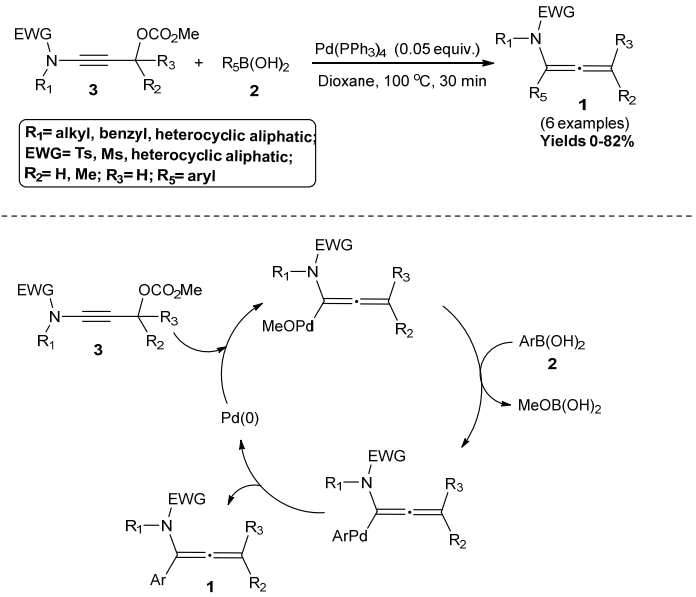


Scheme 2. Reaction types of allenamides.

2. Synthesis of Allenamides

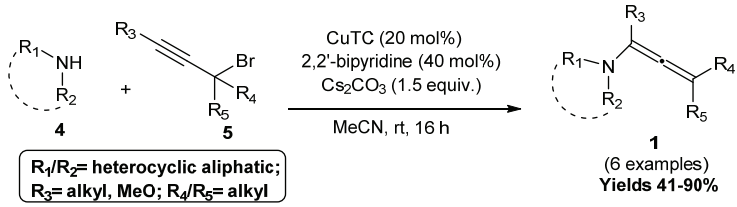
Cao et al. (2012) reported an efficient methodology for the synthesis of multi-substituted allenamides **1** *via* the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of 3-alkoxycarbonyloxy ynamides **3** and arylboronic acids **2**. In this protocol, 3-alkoxycarbonyloxy ynamides **3** were easily prepared from amides and alkynyl bromides in moderate to good yields by Hsung's method (Zhang et al., 2006). But, amides such as *N*-benzylbenzamide and *N*-phenylacetamide did not give 3-alkoxycarbonyloxy ynamides. Mechanistically, the reaction of 3-alkoxycarbonyloxy ynamide 3 with Pd(0) afforded an intermediate on a

trans-metalation reaction with aryl boronic acid **2** followed by a reductive elimination generating the desired allenamide products **1** (Scheme 3).



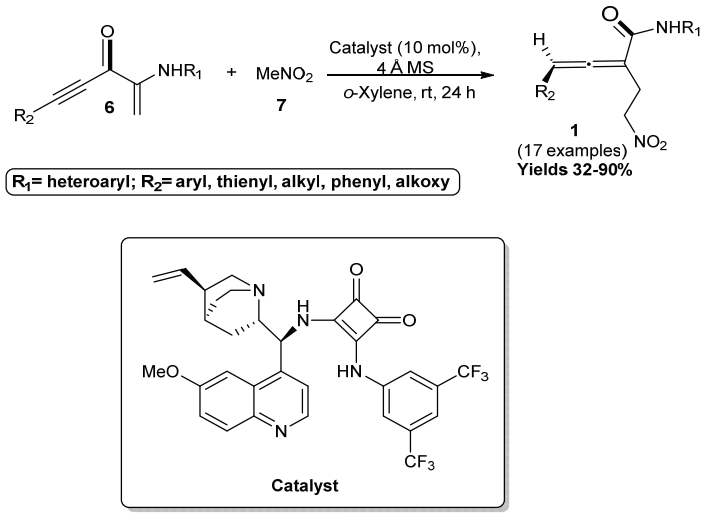
Scheme 3. Synthesis of multi-substituted allenamides and its mechanism.

Demmer et al. (2016) reported an efficient method for synthesizing allenamides **1** from oxazolidinones **4** and propargylic bromides **5** on activation with a combination of a copper catalyst and 2,2′-bipyridine derivatives *via* an S_N2 reaction. This methodology is performed under mild reaction conditions and is applicable to the preparation of mono-, di- and trisubstituted allenamides (Scheme 4).



Scheme 4. Synthesis of allenamides from oxazolidinones and propargylic bromides.

More recently, an asymmetric catalytic synthesis of 2,3-allenamides **1** from hydrogen-bond-stabilized enynamides **6** was described. The reaction was performed in the presence of quinine-based bifunctional squaramide organo-catalysts in high yields and excellent stereoselectivities by Ma et al. (2019) (Scheme 5).



Scheme 5. Asymmetric catalytic synthesis of 2,3-allenamides.

3. Functionalization of Allenamides

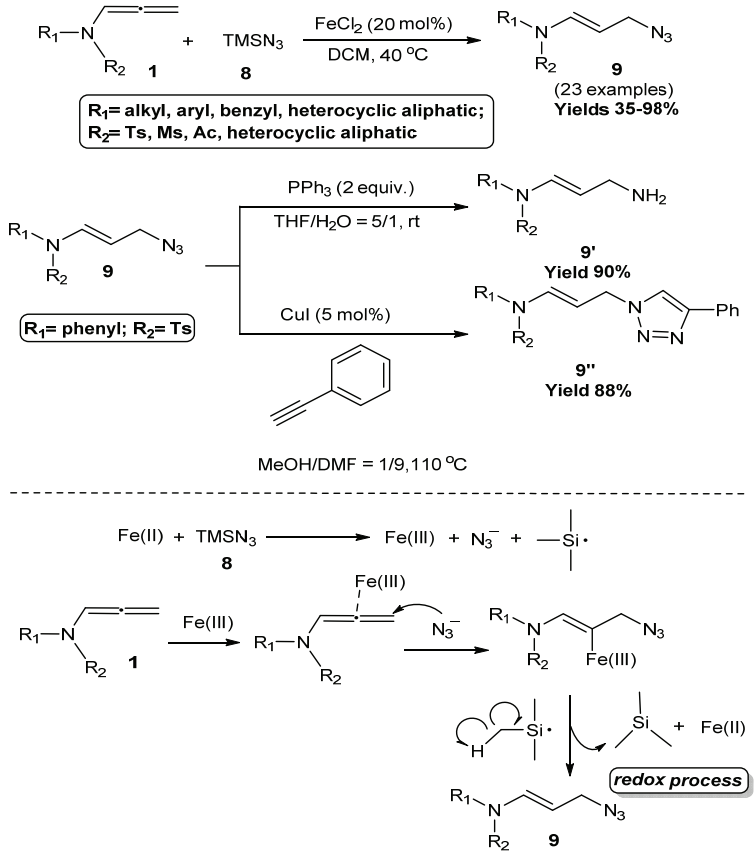
3.1 Metal catalyzed functionalization of Allenamides

Liu et al. (2020) developed a cost-effective and efficient methodology for the synthesis of (*E*)-allyl azides **9** *via* iron(II)-chloride catalyzed regioselective azidation of allenamides **1** with trimethylsilyl azide ($TMSN_3$) **8** in good to excellent yields (Scheme 6). Moreover, the versatility of azide group has led to *in situ* transformations of allylic azides **9** to allyl triazoles **9″** and allyl amines **9′**. This new strategy has shown huge functional group compatibility, which allows for the preparation of substrates with expanding molecular complexity. According to the proposed mechanism, a single electron transfer (SET) from Fe(II) to $TMSN_3$ **8** led to the formation of Fe(III), N_3^- and intermediates affording the desired products **9**.

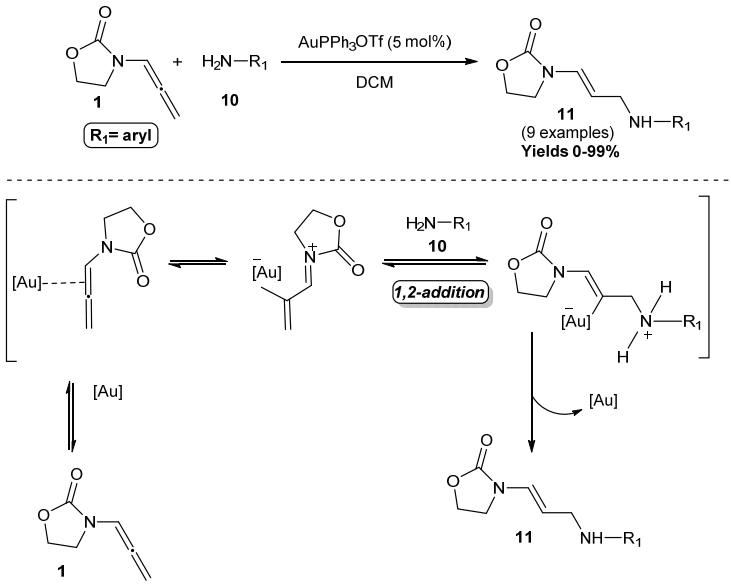
A facile and stereoselective Au(I) catalyzed intermolecular hydroamination of allenamides **1** with aryl-amines **10** was reported (Hill et al., 2010) for the synthesis of allylamino *E*-enamides **11** in high yields (Scheme 7). The allylamino enamides **11** formed in this protocol can be a valuable building block in organic synthesis due to the presence of two vital functionalities, i.e., allyl amines and enamides, within one framework. The allenamide **1** was activated by the cationic Au(I) salt to give a conjugated *N*-acyliminium intermediate species. Then, the *N*-acyliminium intermediate underwent 1,2-addition followed by proto-demethylation affording the desired *E*-enamides **11**.

An alcohol-allenamide C-C coupling under transfer hydrogenation conditions was reported by Zbieg et al. (2010) for the synthesis of *anti*-1,2-amino alcohols **13** as a single diastereomers. In this methodology, the

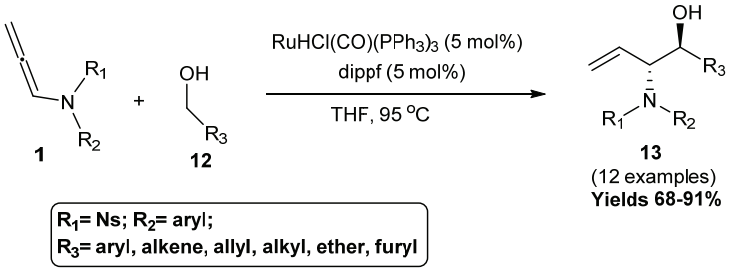
coupling of allenamide **1** and alcohol **12** was promoted by the ruthenium complex obtained by the combination of $RuHCl(CO)(PPh_3)_3$ and bis(diisopropylphosphino)ferrocene (dippf) to afford the products **13** up to a 91% isolated yield (Scheme 8).



Scheme 6. Synthesis of (*E*)-allyl azides and its possible mechanism.



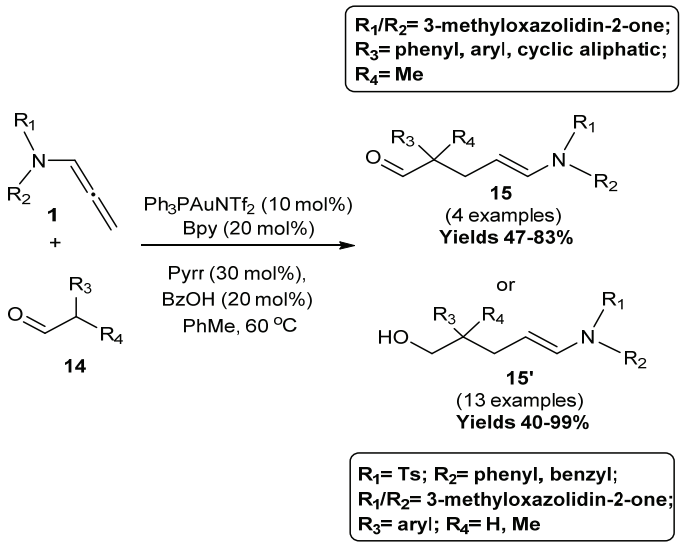
Scheme 7. Au(I) catalyzed intermolecular hydroamination of allenamides.



Scheme 8. An alcohol-allenamide C-C coupling for the synthesis of *anti*-1,2-amino alcohols.

Fernandez-Casado et al. (2016) developed a synergistic gold and enamine catalyzed intermolecular alkylation reaction for the synthesis of aldehydes **15** or alcohols **15′** (in some cases isolated after reduction to the alcohols) *via* simultaneous generation of an enamine **15** and gold activated

allenamide (Scheme 9). This protocol involved the alkylation of aldehydes **14** with allenamides **1**, which afforded functionalized aldehydes **15** incorporating tertiary and even quaternary α-stereocenters with moderate to good yield and enantioselectivity.

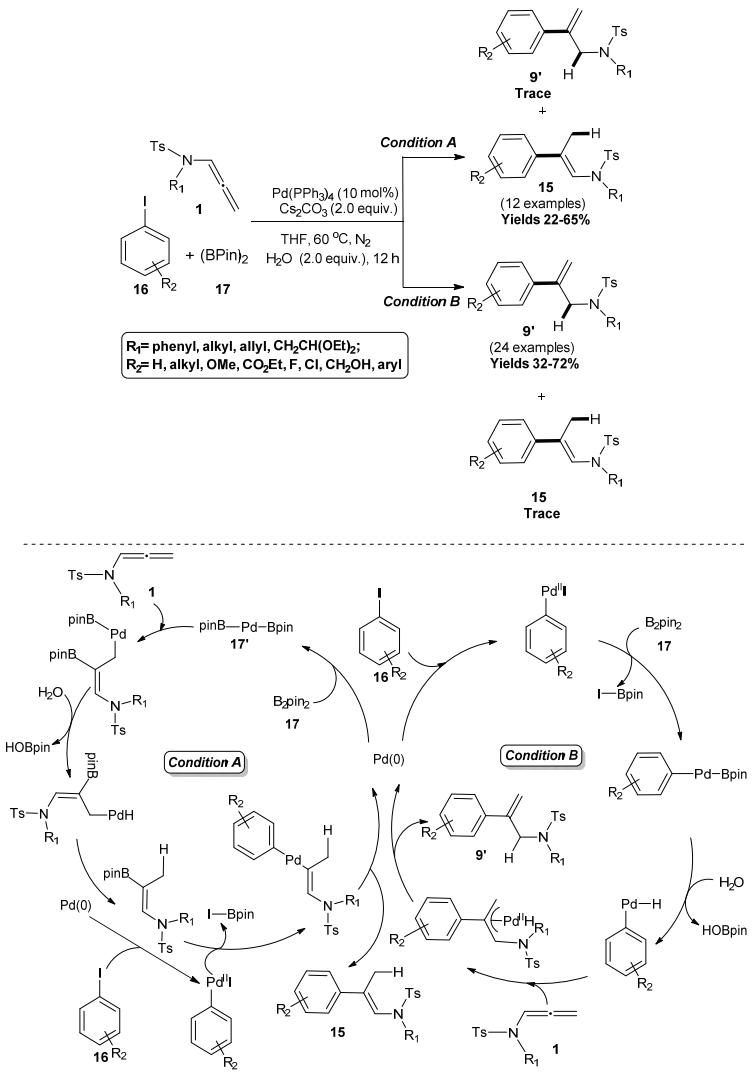


Scheme 9. Synergistic gold and enamine catalyzed intermolecular alkylation reactions.

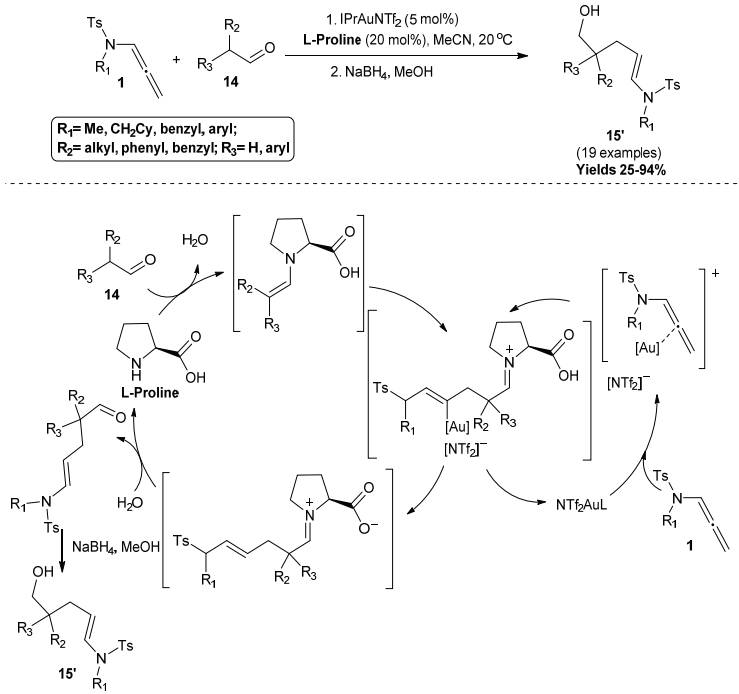
A novel palladium-catalyzed regiocontrollable hydroarylation of allenamides **1** through the reaction of allenamides **1**, and iodobenzene derivatives **16** with B_2pin_2 **17**/H_2O was demonstrated by Cui et al. (2019). Deuterium-labeled experiments indicated that the hydrogen source in this reaction was from H_2O. The adjustment catalyst loading and iodobenzene derivatives **16** have successfully achieved the regioselectivity of this reaction. The reaction performed well, affording allylamines **9′** or enamines **15** efficiently with an extensive functional group tolerance in moderate to excellent yields. The catalytic cycle was carried out in two

different conditions (**A** and **B**); Condition **A**: Insertion of allenamide **1** to boryl palladium (B-Pd) species **17′** (generated by the oxidative addition of B_2pin_2 **17** to the palladium) through the formation of an intermediate affording the desired products **15** with simultaneous regeneration of the Pd(0) catalyst. Condition **B**: Palladium complex, generated by the oxidative addition of $Pd(PPh_3)_4$ to iodobenzene derivatives **16**, underwent trans-metalation with B_2pin_2 **17** *in situ* to offer a Pd^{II} intermediate. Coordination of the Pd^{II} intermediate with water, which might facilitate the H atom transfer from H_2O to palladium has afforded the [Pd-H] species with the release of HOBpin. Then, the insertion of allenamide **1** to the [Pd-H] species formed an π-allylpalladium intermediate, which gave the desired products **9′** through reductive elimination and regenerated the Pd(0) catalyst (Scheme 10).

Ballesteros et al. (2016) reported an enantioselective, gold-organocatalyzed synergistic C-C bond formation by the intermolecular α-addition reaction of allenamides **1** and aldehydes **14** (Scheme 11). According to the proposed mechanism, the electrophile generated from the activation of allenamide **1** by gold(I) was trapped by an *in situ* formed enamine **15′**, formed by the reaction of the aldehyde **14** with the organocatalyst. The enamine **15′** formation and the regeneration of both types of active catalysts were facilitated by a Brønsted acid.

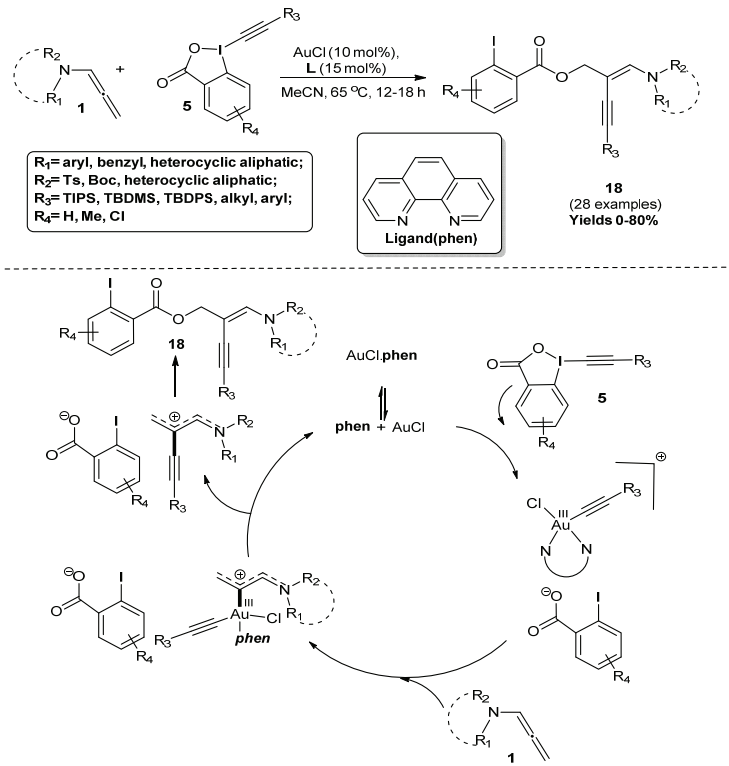


Scheme 10. Palladium-catalyzed hydroarylation of allenamides.



Scheme 11. *α*-Addition reaction of allenamides and aldehydes.

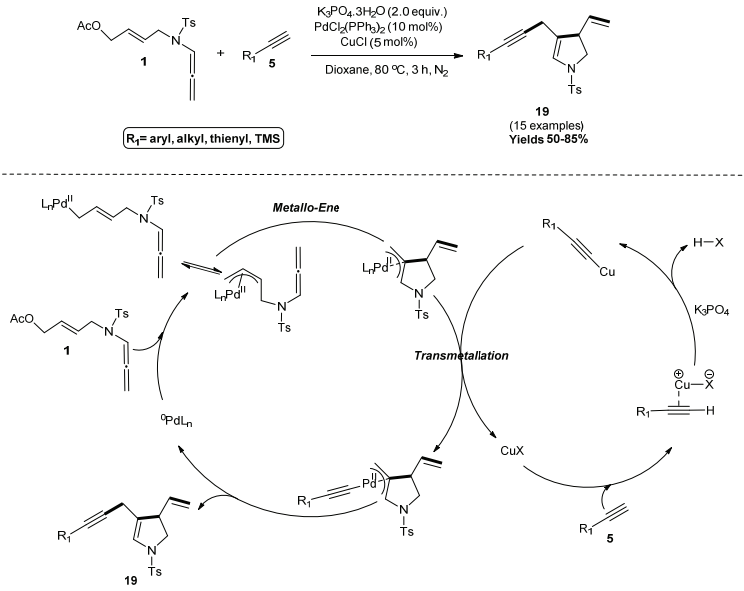
Banerjee et al. (2019) designed an atom-economical methodology for the synthesis of 1,3-enynes **18** *via* a redox-neutral Au(I)/Au(III) catalyzed 1,2-oxyalkynylation of *N*-allenamides **1** with ethylnylbenziodoxolones **5** in the presence of phenanthrene (phen) as a ligand in acetonitrile. The proposed mechanism of this reaction is shown in (Scheme 12).



Scheme 12. Au catalyzed 1,2-oxyalkynylation of *N*-allenamides.

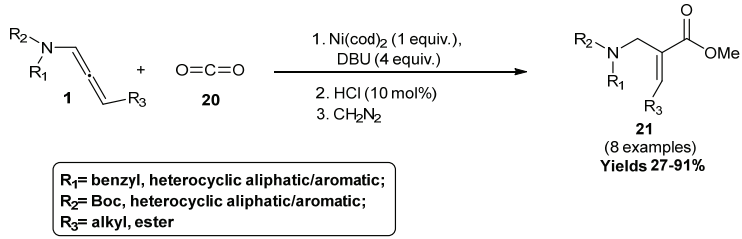
A mild palladium/copper co-catalyzed cascade metallo-ene/Sonogashira coupling of allenamides *via* allenamide allyl acetate **1** reaction with terminal alkynes **5** for the synthesis of polyfunctionalized 2,3-dihydropyrrole derivatives **19** with a 1,6-enyne skeleton in moderate to good yields was reported by Liang et al. (2018). In this protocol, Csp^3-Csp^2 and Csp^3-Csp bonds were built in one pot. The reductive elimination from the π-allyl palladium complex showed excellent regioselectivity, providing the terminal C1 position coupling product without the internal C3 coupling product detected. Initially, an intermediate was formed by the

oxidative addition of allyl acetate to Pd(0). Then, the intermediate, on transformation to an π-allyl palladium intermediate, followed by insertion into the allenamide, **1** generated the Csp^3-Csp^2 bond and π-allyl palladium intermediate. In the meantime, an π-alkyne complex was produced in the presence of the base and copper, making the terminal proton more acidic, leading to the generation of a copper acetylide compound. Finally, trans-metalation formed the palladium complex, which on reductive elimination afforded the final products **19** with the Csp^3-Csp bond formation (Scheme 13).



Scheme 13. Palladium/copper co-catalyzed cascade metallo-ene/Sonogashira coupling reaction.

Nickel(0)-promoted carboxylation of allenamides **1** with an atmospheric pressure of carbon dioxide **20** was reported by Saito et al. (2014) in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). The reaction has proceeded through a nickelalactone intermediate from the reaction of the allenamides **1** and carbon dioxide **20**, affording *β*-amino acid derivatives **21**. The substituents firmly influenced the regioselectivity at the oxidative addition stage on the allene part (Scheme 14).

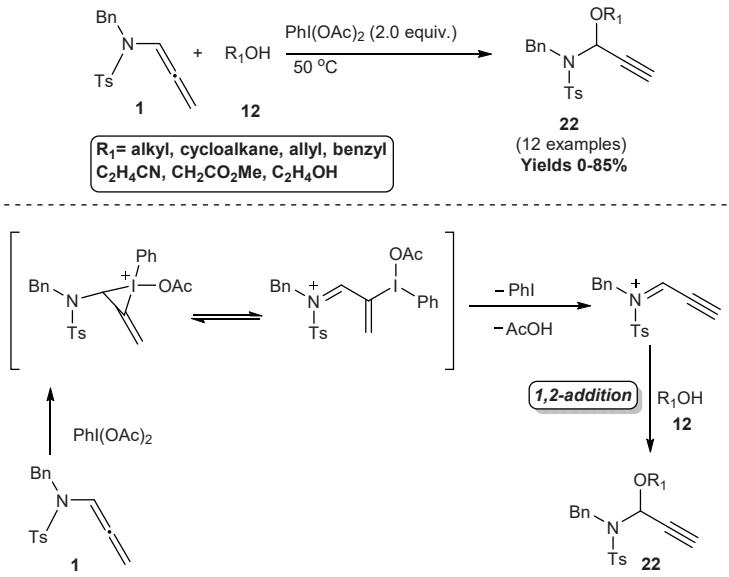


Scheme 14. The nickel(0)-promoted carboxylation of allenamides.

3.2 Metal-free functionalization of allenamides

Huang et al. (2020) demonstrated the synthesis of propargylic *N,O*-acetals **22** in high yields with excellent regioselectivity by hypervalent iodine mediated electrophilic activation of allenamides **1** in alcohol **12**, which act as both nucleophile and solvent *via* 1, 2-addition of alcohol **12** to the sulfimide ion intermediate. This methodology proceeds rapidly under mild conditions and was able to tolerate the alcohols and substrates to a vast extent. Initially, an iodo(III) cyclopropane intermediate was generated by the electrophilic addition of $PhI(OAc)_2$ to the allenamides **1**. Through a decyclization process, the intermediate was transformed to a conjugated sulfimide ion. Then, reductive elimination of HOAc and iodobenzene

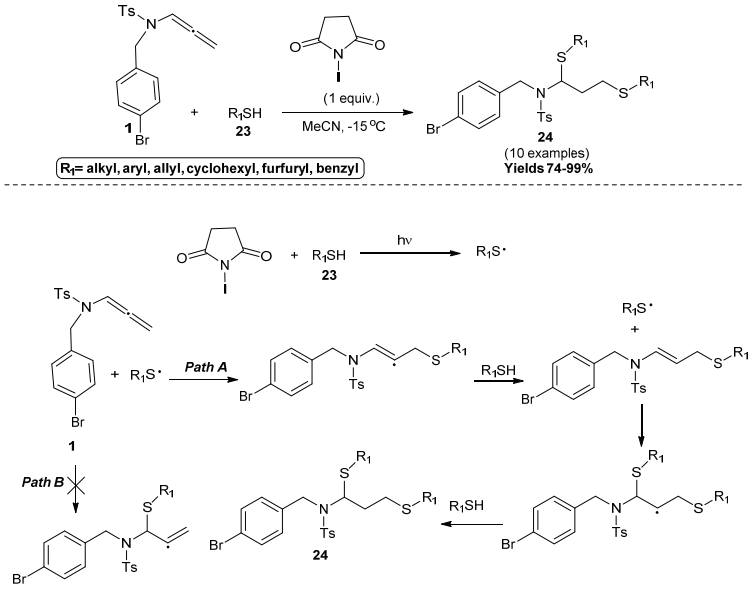
followed by 1,2-nucleophilic addition with alcohol **12** generated the desired products **22** (Scheme 15).



Scheme 15. Synthesis of propargylic *N,O*-acetals and its plausible mechanism.

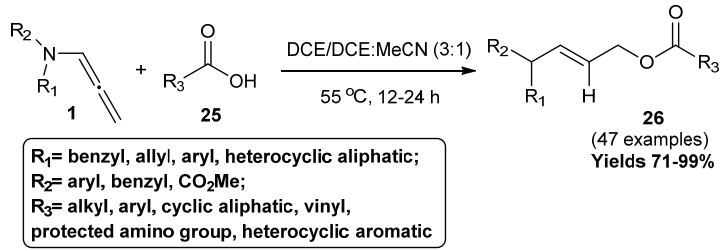
An efficient N-iodosuccinimide (NIS)-promoted bis-sulfenylation of allenamides **1** for synthesizing 1,3-dithioethers **24** was developed by Yuan et al. (2020). The reaction proceeded through a two-step radical addition of thiols **23** to the allenamides **1**, affording the desired products **24** with good functional group tolerance and high efficiency. Mechanistically, PhS· radicals were liberated by the reaction of PhSH with Iodine radicals formed through the light decomposition of NIS. The vinyl radical intermediate was formed by the PhS· radicals on selective addition to the terminal C=C double bond of the allenamides **1**. The addition at proximal C=C double bond is more uncertain because of the relative stability of the

radical vinyl intermediate compared with the product formed through path B. Then, the radical vinyl intermediate on hydrogen atom abstraction generated the linear allylic thioether and PhS· radicals. Subsequently, the addition of PhS· radicals to the proximal C=C double bond of the allylic thioether formed a carbon radical intermediate, which finally afforded the 1,3-dithioether product **24** by the abstraction of a hydrogen atom from PhSH (Scheme 16).



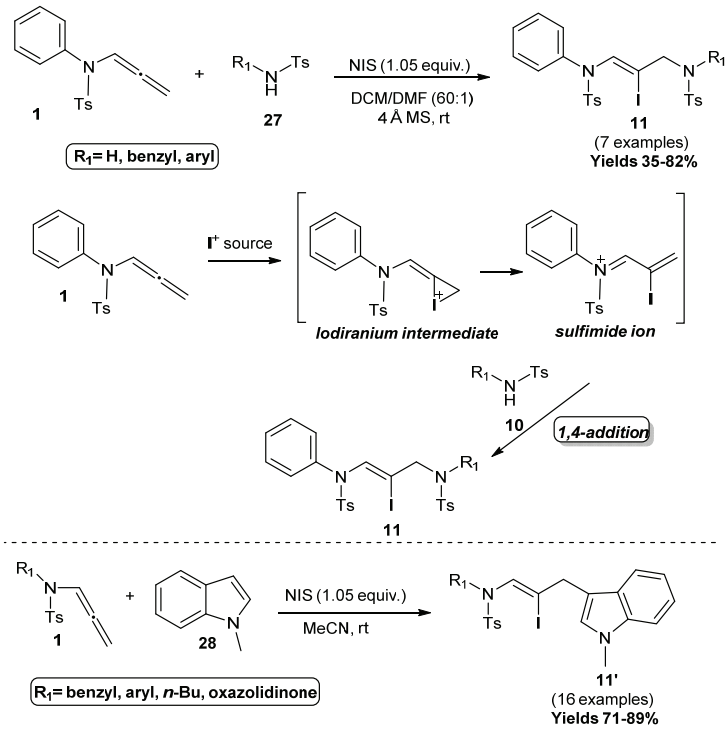
Scheme 16. NIS-promoted bis-sulfenylation of allenamides.

A complete chemo-, regio- and stereocontrol, metal-free hydrocarboxylation of allenamides **1** with various functionalized carboxylic acids **25** for the synthesis of *γ*-acyloxyenamides **26** with exclusive *E*-selectivity was reported by Pradhan et al. (2020) in either dichloroethane (DCE) or dichloroethane:acetonitrile (DCE:MeCN) as the solvent (Scheme 17).



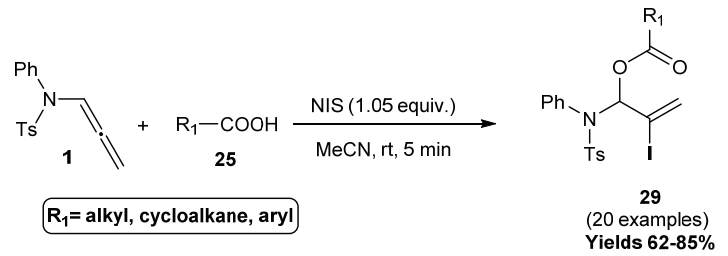
Scheme 17. Hydrocarboxylation of allenamides using carboxylic acids.

i et al. (2016) developed NIS-mediated intermolecular iodoamination of allenamides **1** with sulfonamides **27** to synthesize iodine-substituted allylamino *Z*-enamides **11** in high regio- and stereoselectivity in dichloromethane (DCM) and dimethylformamide (DMF) as the solvent. An iodiranium intermediate was produced by the allenamides **1** in the presence of iodine as a weak Lewis acid, which afforded a conjugated sulfimide ion species. The sulfimide ion species underwent a decyclization reaction by delocalizing the nitrogen lone pair towards the alkene. Finally, the iodine-substituted allylamino *Z*-enamide **11** was afforded by 1, 4-addition of sulfimide ion species with a nucleophile **27** (Scheme 18). In another study (Li et al., 2016), iodine-substituted *Z*-enamides **11′** were obtained in good yields under mild conditions in MeCN *via* NIS-mediated intermolecular iodo functionalization of allenamides **1** with indoles **28** (Scheme 18).



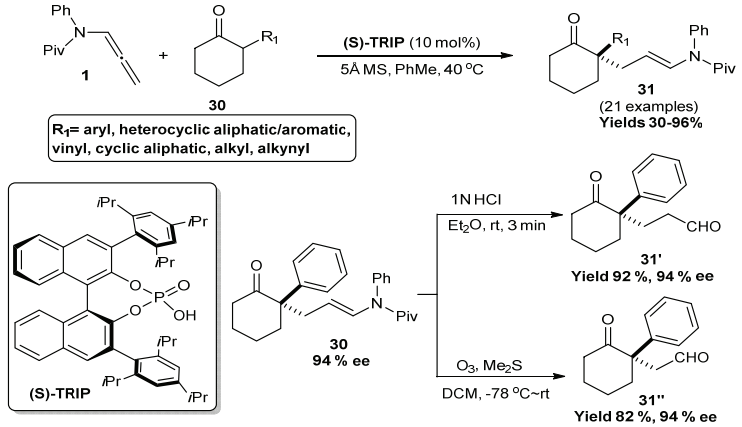
Scheme 18. *N*-iodosuccinimide-mediated intermolecular iodoamination of allenamides.

Luo et al. (2019) reported a NIS-mediated C-H functionalization of allenamides **1** to synthesize branched allylic esters **29** *via* regioselective acyloxylation with carboxylic acids **25** at the proximal carbon of allenamides **1**. The reaction proceeded rapidly and tolerated a broad scope of substrates (Scheme 19).



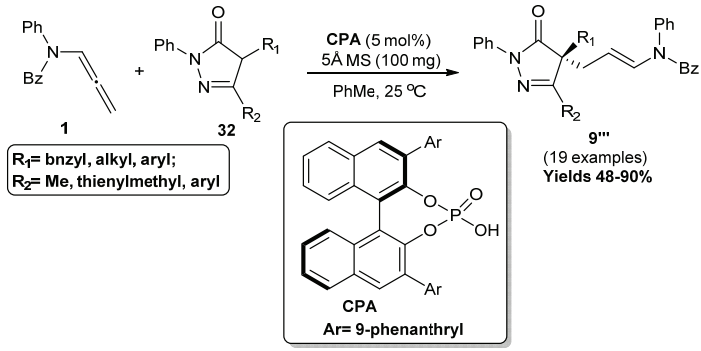
Scheme 19. *N*-iodosuccinimide-mediated C-H functionalization of allenamides.

Yang and Toste, (2016) described a chiral phosphoric acid (3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-binaphtholate, (S)-TRIP) catalyzed asymmetric addition of unactivated α-branched cyclic ketones **30** to allenamides **1** generating an all-carbon quaternary stereocenter with extensive substrate scope and high enantioselectivity. The reaction produced a chiral quaternary stereocenter with broad substrate scope. The products **31** were effortlessly transformed into their corresponding 1,4- and 1,5- ketoaldehydes **31′** and **31″**, both being significant building blocks in organic synthesis (Scheme 20).



Scheme 20. Chiral phosphoric acid-catalyzed asymmetric addition of α-branched cyclic ketones to allenamides.

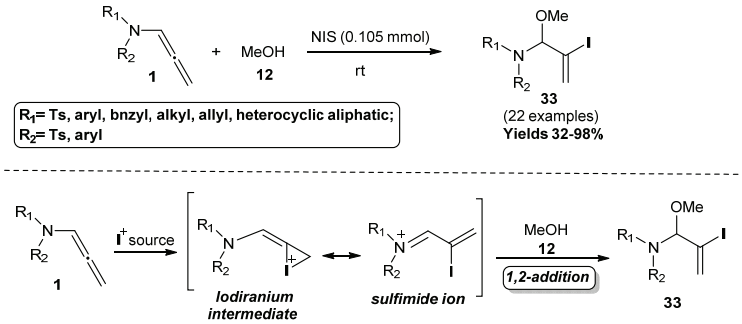
Yang et al. (2018) described a chiral phosphoric acid (CPA)-catalyzed asymmetric allylic alkylation of pyrazolones **32** to allenamides **1** generating an all-carbon quaternary stereocenter with broad substrate scope and good enantioselectivity (Scheme 21). The reaction was explored under mild conditions giving excellent product **9”’** yields with a relatively low catalyst loading.



Scheme 21. CPA-catalyzed asymmetric allylic alkylation of pyrazolones to allenamides.

Another NIS-mediated regioselective 1,2-addition of alcohols **12** to allenamides **1** for the synthesis of *N,O*-aminals **33** was developed by Yuan et al. (2018). This novel reaction proceeded rapidly and exhibited broad substrate scope for various allenamides. It also demonstrated that NIS effectively activated the terminal C=C bond of allenamides generating a conjugated sulfamide ion species. Initially, electrophilic halogenation facilitated by the interaction between the iodine-based electrophile and the π- system of the allenamide **1** generated the iodiranium intermediate. Further, the resonance stabilization of the intermediate through the delocalization of the nitrogen lone pair toward the alkene and the

subsequent 1,2- addition by the nucleophile **12** afforded *N,O*-aminal **33** (Scheme 22).

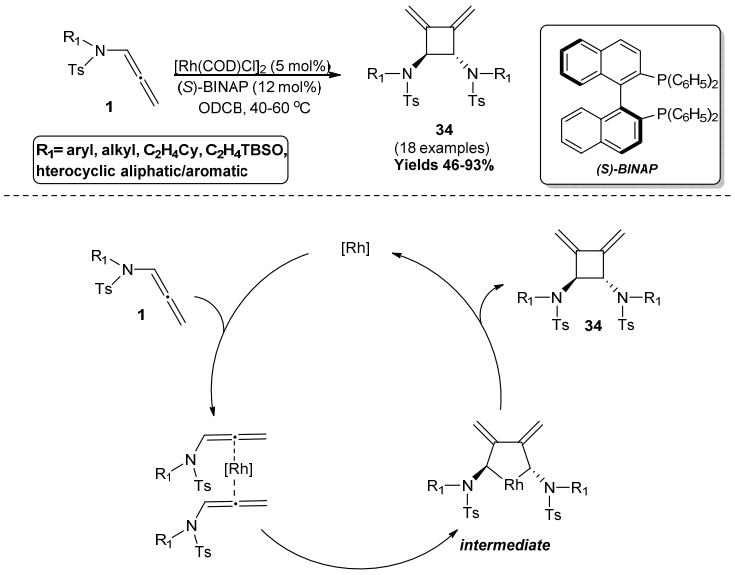


Scheme 22. NIS-mediated regioselective 1,2-addition of alcohols to allenamides.

4. Application of Allenamides in organic synthesis

4.1 Cycloaddition reactions of Allenamides

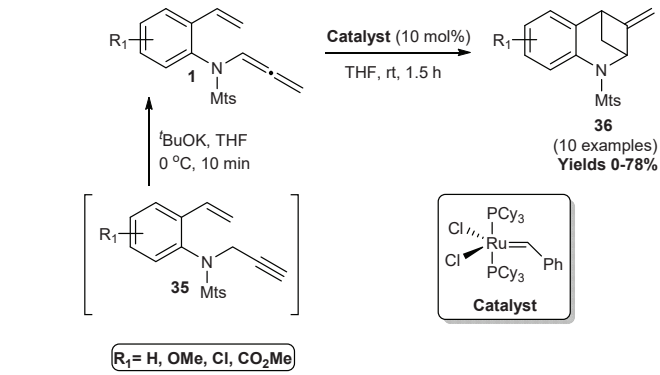
An efficient and enantioselective protocol for synthesizing cyclobutane-1,2-diamine **34** was developed by Zheng et al. (2018). The reaction proceeded through the Rh-catalyzed intermolecular head-to-head [2+2] cycloaddition of allenamides **1**. The desired cyclobutane-1,2-diamine derivatives **34** were obtained in moderate to good yields with excellent enantioselectivity in the presence of $[Rh(COD)Cl]_2$ and (S)-(−)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) ((S)-BINAP) in 1,2-dichlorobenzene (ODCB) at 60 ºC. The mechanism of this reaction based on the Hammett-plot was established, in which the rhodium-acyclopentane intermediate was regioselectively produced by the allenamides **1** with a Rh catalyst. Then, cyclobutane-1,2-diamine **34** was afforded by the enantioselectivity controlled reductive elimination of the intermediate (Scheme 23).



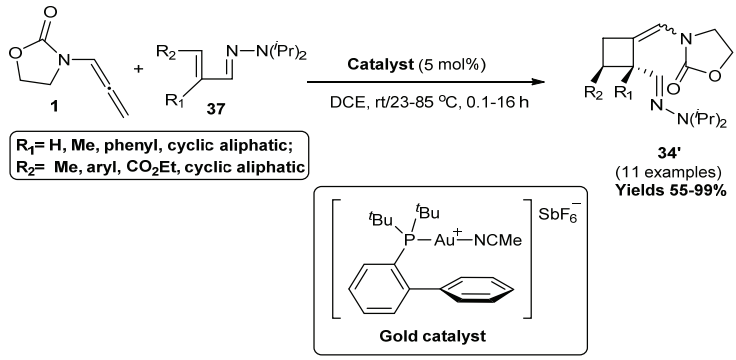
Scheme 23. [2+2] Cycloaddition of allenamides and its possible mechanism.

A novel non-metathesis reaction for the synthesis of azabicyclo[3.1.1]heptanes **36** was reported (Nada et al., 2016) *via* the ruthenium-catalyzed intramolecular [2+2] cycloaddition of allenamide-enes **1** at room temperature in tetrahydrofuran (THF) as the solvent (Scheme 24).

Bernal-Albert et al. (2014) successfully reported the regio- and diastereoselective methodology for the synthesis of substituted cyclobutanes **34′** in good to excellent yields *via* a gold(I)-catalyzed [2+2] cycloaddition of *α,β*-unsaturated *N,N*-dialkyl hydrazones **37** with allenamides **1** (Scheme 25).



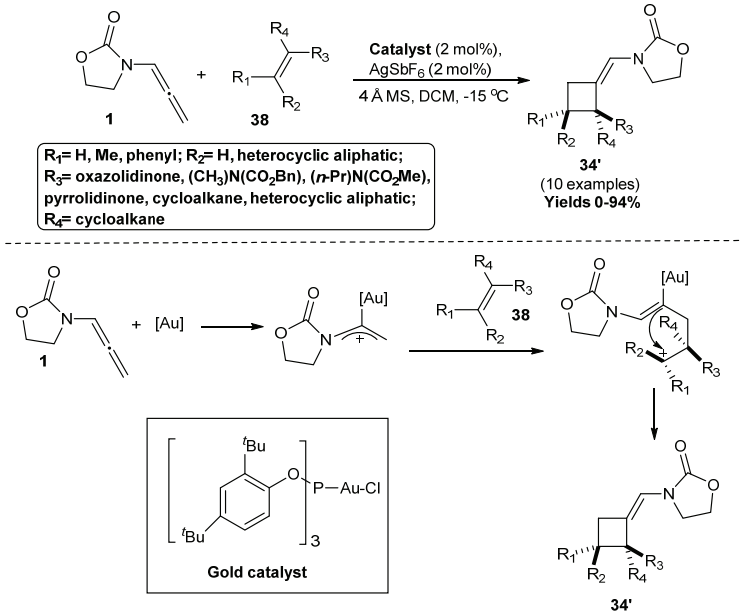
Scheme 24. Synthesis of azabicyclo[3.1.1]heptanes.



Scheme 25. [2 + 2] Cycloaddition of *α,β*-unsaturated *N,N*-dialkyl hydrazones with allenamides.

Another efficient, regio- and stereocontrol protocol affording substituted cyclobutene **34′** was reported (Faustino et al., 2012) through the intermolecular gold-catalyzed [2+2] cycloaddition of allenamides **1** with alkenes **38**. Mechanistically, Au-allyl cation species were afforded through allene activation by the Au catalyst. Then, a nucleophilic intermolecular interception of the cation species by the alkenes **38** generated a cationic

intermediate, providing the regioselectivity-determining step, with the formation of the more stabilized bencylic or imonium cation being favored. Later, rotation around the sigma C-C bond resulted in losing the stereochemical information approaching from the alkenes **38**. Finally, the final [2+2] adducts **34′** were afforded by a ring-closing process *via* the attack of the vinyl gold species on the stabilized cation with the elimination of the Au complex (Scheme 26).

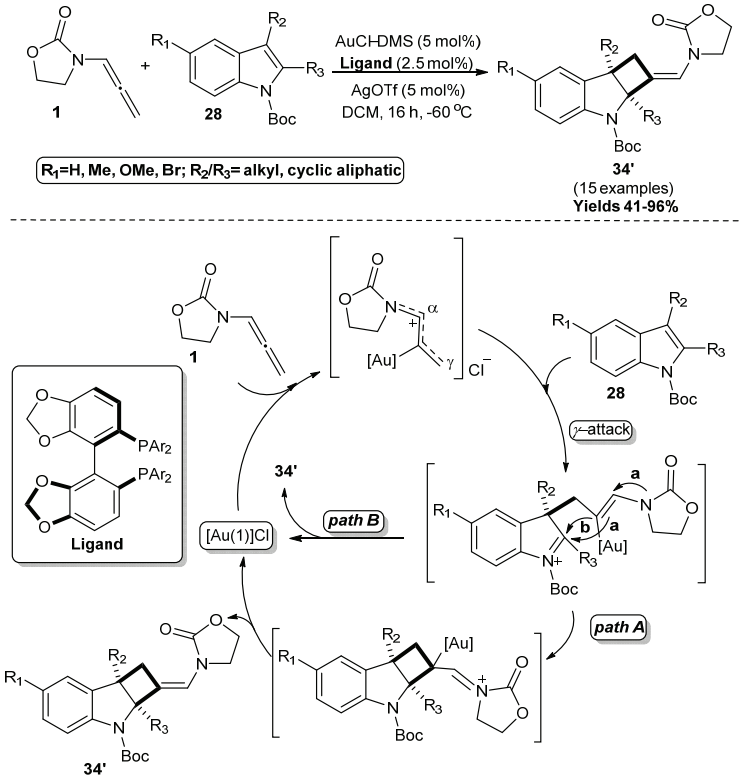


Scheme 26. [2+2] Cycloaddition of allenamides with alkenes.

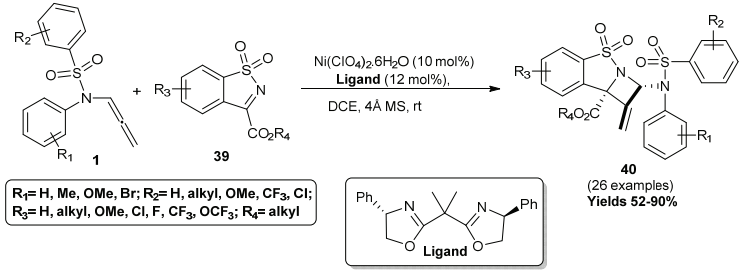
Jia et al. (2015) developed an enantioselective synthesis of functionalized 2,3-indoline-cyclobutanes **34′** with high yield and excellent stereochemical control through the chiral gold-catalyzed intermolecular dearomative [2+2]-cycloaddition reactions of the substituted indoles **28** and allenamides **1**. Initially, the allenamide **1** by the chiral cationic gold

complex generated the electrophilic intermediate. The gold-alkenyl intermediate was formed by the regioselective attack of the substituted indole derivatives **28** at the *γ*-position of the electrophilic intermediate. In path A: based on the nucleophilicity of the enamine moiety, a second ring-closing generated an alkyl-gold intermediate. Finally, a rearrangement of the alkyl-gold intermediate afforded the final products **34′** and restored the catalytic species. Path **B**: In this pathway, the final products **34′** were directly obtained by the gold-alkenyl intermediate in a concerted-like pathway. The high stereoselectivity observed in the second ring-closing event (i.e., the arrangement of the *exo*-C=C double bond with configuration *Z*) prompted the proposal that the concerted-like reaction of path **B** was the most probable way (Scheme 27).

The $Ni(ClO_4)_2$-catalyzed enantioselective [2+2] cycloaddition of *N*-allenamides **1** with cyclic *N*-sulfonylketimines **39** was developed (Liu et al., 2017), affording polysubstituted chiral azetidines **40** bearing quaternary stereocenters in good yields and excellent enantioselectivity (up to 99%). In this reaction, the cycloaddition occurred regioselectively at the proximal C=C bonds of the *N*-allenamides (Scheme 28).

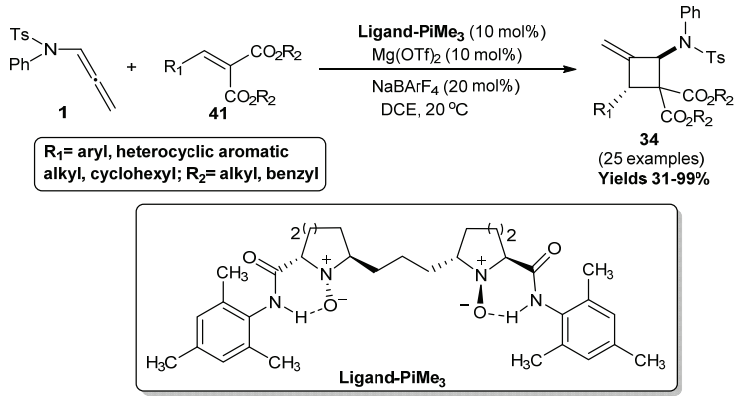


Scheme 27. Enantioselective synthesis of functionalized 2,3-indoline-cyclobutanes.



Scheme 28. [2+2] Cycloaddition of *N*-allenamides with cyclic *N*-sulfonylketimines.

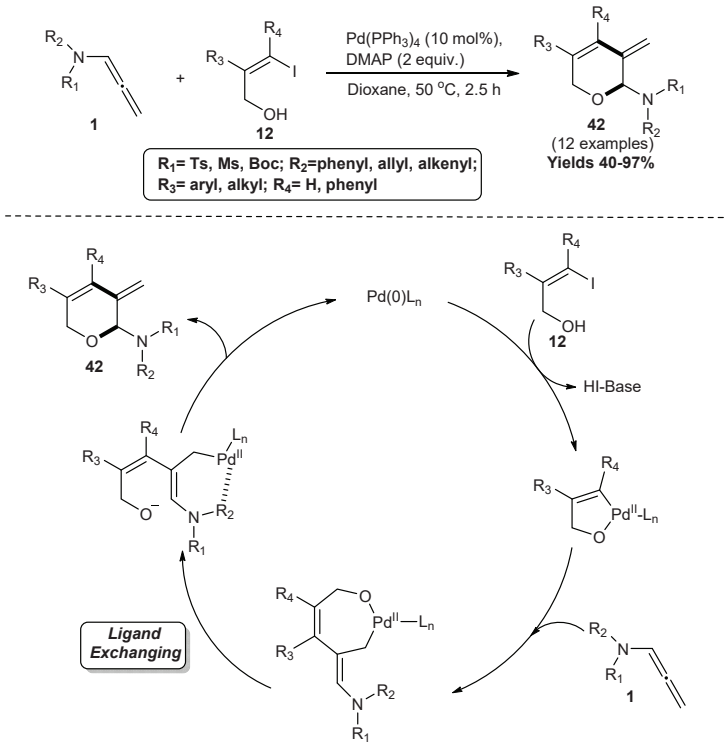
A chiral Mg^{II}/*N,N'*-dioxide catalyzed enantioselective [2+2] cycloaddition reaction of alkylidene malonates **41** with *N*-allenamides **1** was developed by Zhong et al. (2018). This reaction protocol afforded various polysubstituted methylenecyclobutanes **34** under mild conditions with good yields (up to 99%) and excellent enantioselectivity (up to 96% ee) (Scheme 29).



Scheme 29. Enantioselective [2+2] cycloaddition reaction of *N*-allenamides.

A palladium-catalyzed chemo- and regioselective [4 + 2] formal cycloaddition reaction of 3-iodo-2-phenyl allylic alcohol **12** and allenamides **1** affording the 2-aminodihydropyran derivatives **42** in moderate to good yields in the presence of 4-dimethylaminopyridine (DMAP) was reported by Yan et al. (2019). A five-membered vinyl palladium complex was generated by the oxidative addition of $Pd(PPh_3)_4$ to **12** in the presence of a base. Then, insertion of allenamide **1** to the complex formed a seven-membered ring intermediate. A subsequent intramolecular ligand exchange of the intermediate with a double bond

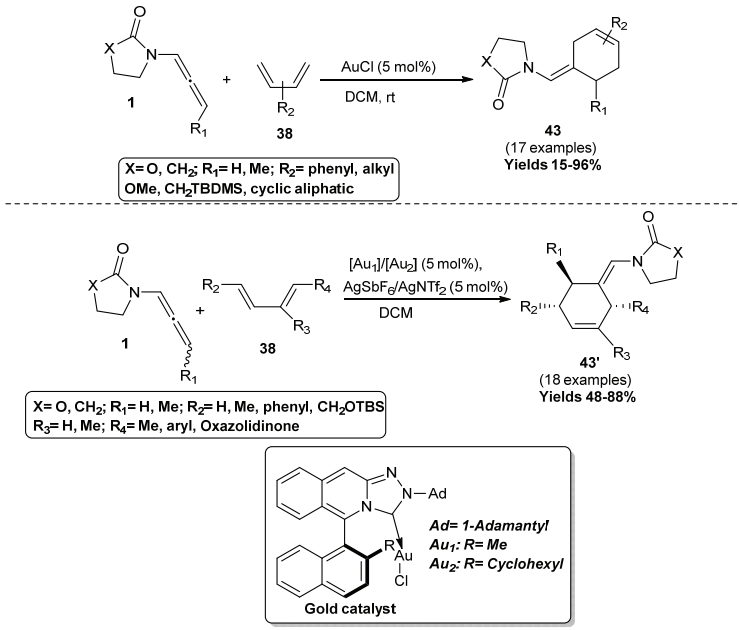
followed by a high selectivity proximal S_N2 substitution generated the desired products **42** (Scheme 30).



Scheme 30. Chemo- and regioselective [4+2] formal cycloaddition reaction.

An intermolecular [4 + 2] cycloaddition reaction was reported (Faustino et al., 2011) to synthesize substituted cyclohexenes **43** with excellent regio- and diastereoselectivity. The reaction proceeded through a gold-catalyzed annulation of allenamides **1** and acyclic conjugated dienes **38** (Scheme 31). Further, they developed the synthesis of optically active cyclohexenes **43′** in the presence of an axially chiral triazoloisoquinolin-3-ylidene ligand in good yields under similar reaction conditions as mentioned above. This

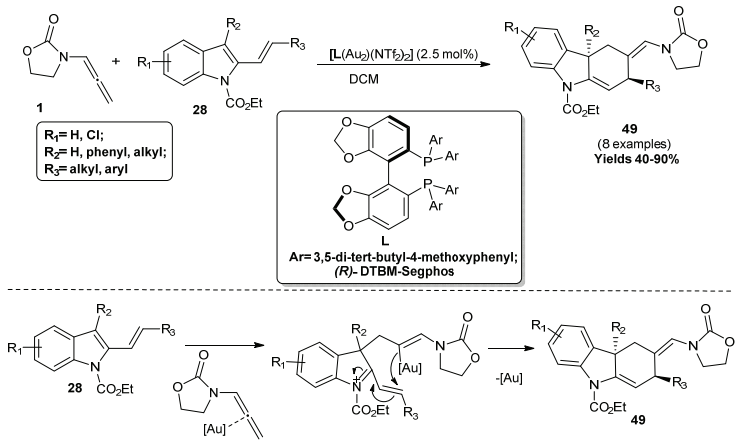
led to the introduction of diverse substitution patterns up to three stereocenters and providing a practical approach to a diversity of optically active cyclohexene products **43′** which are not easily accessible using other methodologies (Francos et al., 2012).



Scheme 31. Intermolecular [4 + 2] cycloaddition reaction for the synthesis of substituted cyclohexenes.

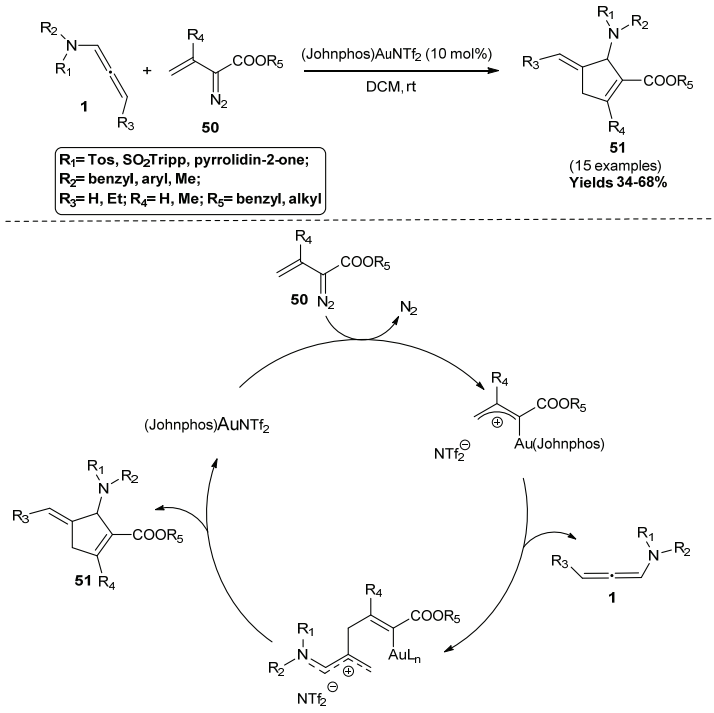
An enantioselective gold-catalyzed dearomative [4+2] cycloaddition reaction of 3-substituted 2-vinylindoles **28** with allenamides **1** for the synthesis of tetrahydrocarbazoles **49** with high chemo-, regio- and enantioselectivity in DCM was reported by Pirovano et al. (2017). The reaction was initiated with a new bond between the C2 of the indole **28** and the external allene carbon atom, affording the dearomatized cationic

intermediates. Then, the formation of second carbon-carbon generated the [4+2] cycloaddition products **49** with the simultaneous release of the catalyst (Scheme 32).



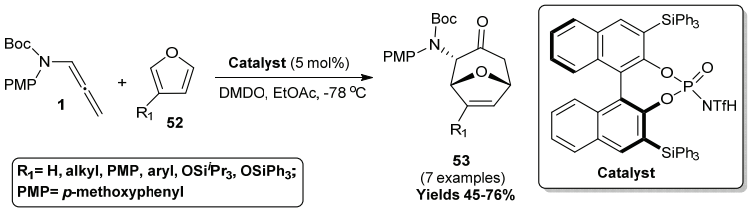
Scheme 32. Gold-catalyzed dearomative [4+2] cycloaddition reactions affording tetrahydrocarbazoles.

Lopez et al. (2016) designed a johnphosAuNTf$_2$-catalyzed [3+2] carbocycloaddition reaction of *N*-allenamides **1** with alkenyl diazo compounds **50** leading to methylidenecyclopentene derivatives **51**. Mechanistically, a gold-vinyl carbene intermediate was generated by the reaction of alkenyl diazo compounds **50** with a gold complex. Subsequently, the nucleophilic attack of the central carbon atom of the allenamide **1** followed by cyclization through the attack of the vinyl gold to the electrophilic iminium carbon atom afforded the desired products **51** (Scheme 33).



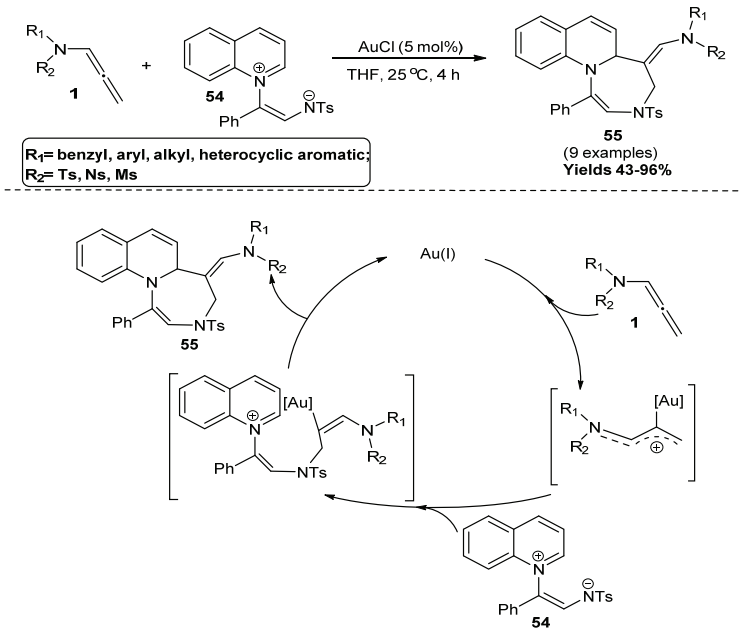
Scheme 33. Gold(I)-catalyzed [3+2] carbocycloaddition reaction of *N*-allenamides.

The regio-, diastereo-, and enantioselective 1,1′-bi-2-naphthol (BINOL)-based *N*-trifluoromethanesulfonyl phosphoramides catalyzed [4+3] cycloaddition between furans **52** and oxyallyl cations generated *in situ* by the oxidation of the allenamides **1** for the synthesis of seven-membered rings **53**, with dimethyldioxirane (DMDO) as the oxidant, was reported (Villar et al., 2017). In this methodology, the catalyst system displayed a broad substrate scope, including a variety of substituted allenamides and furans and the excellent performance of *γ*-substituted allenamides as oxyallyl cation precursors (Scheme 34).



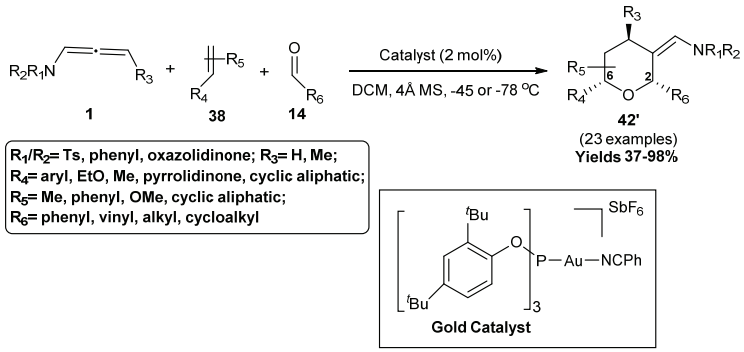
Scheme 34. [4+3] Cycloaddition between furans and allenamides.

De et al. (2018) demonstrated an efficient and ligand-free, gold-catalyzed [5+2] cycloaddition of allenamides **1** with quinolinium zwitterions **54** through a gold-bound allylic cation intermediate. The reaction protocol afforded a variety of fused 1,4-diazepine derivatives **55** in a stereospecific manner with good to excellent yields. The reaction initiated with the allenamides **1** by the gold catalyst afforded an Au-bound allylic cation. Quinolinium zwitterions **54** on nucleophilic attacked by the nitrogen of the allenamides generated an Au-linked intermediate, which on subsequent intramolecular cyclization formed the seven-membered 1,4-diazepines **55** with the generation of the Au catalyst (Scheme 35).



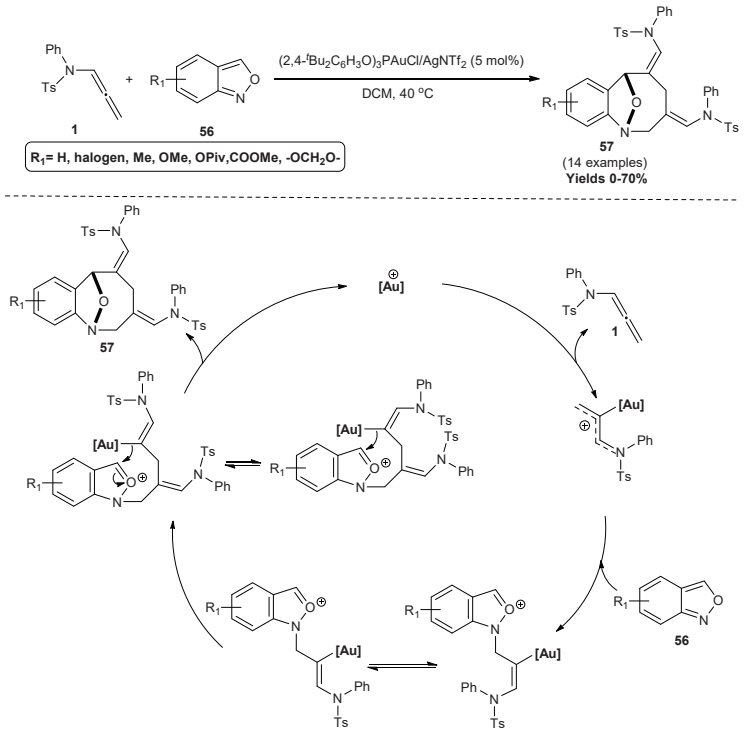
Scheme 35. [5+2] Cycloaddition of allenamides with quinolinium zwitterions.

Different types of 2,6-disubstituted tetrahydropyrans (THPs) **42′** were prepared (Faustino et al., 2015) through a highly regio- and chemoselective intermolecular [2+2+2] cycloaddition of allenamides **1** with alkenes **38** and aldehydes **14** in the presence of catalytic amounts of a phosphite gold complex. This protocol has offered efficient, atom-economical and stereoselective access to a variety of 2,6-disubstituted THPs **42′** from easily accessible or even commercially available materials (Scheme 36).



Scheme 36. Synthesis of 2,6-disubstituted tetrahydropyrans.

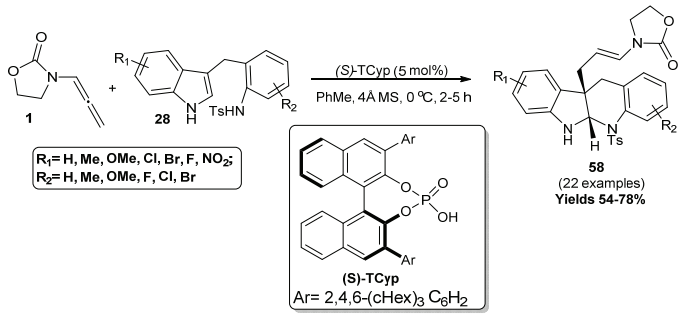
An efficient method for synthesizing oxabridged eight-membered heterocycles **57** with a unique *E*/*Z* configuration *via* a gold-catalyzed formal [4+2+2] cycloaddition reaction of anthranils **56** with allenamides **1** was reported by Wang et al. (2020). According to the proposed mechanism, a highly reactive alkenyl-gold species has been generated through the electrophilic activation of allenamides **1** by an Au(I) catalyst. The nucleophilic addition of anthranils **56** to the distal double bond of the alkenyl-gold species with the formation of intermediates, followed by an internal nucleophilic addition to the oxocarbenium ion, afforded the annulated products **57** (Scheme 37).



Scheme 37. Gold-catalyzed formal [4+2+2] cycloaddition reaction.

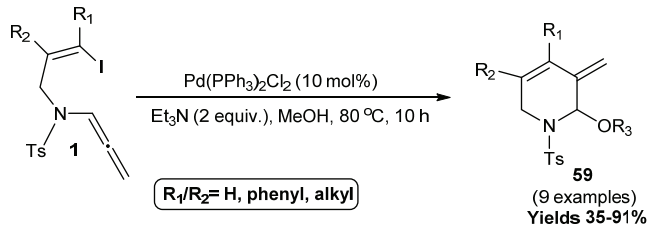
4.2 Cyclization reactions of Allenamides

A catalytic, asymmetric and dearomative cyclization of homotryptamine derivatives **28** with allenamides **1** was developed (Biswas et al. 2020) to synthesize enantio-enriched indolo[2,3-*b*]quinoline **58** frameworks. In this protocol, an allenamide **1** was used as a suitable electrophilic precursor and the activation of the allenamide **1** in the presence of chiral phosphoric acids generated the dearomative cyclization up to 99% *ee* (Scheme 38).



Scheme 38. Cyclization of homotryptamine derivatives with allenamides.

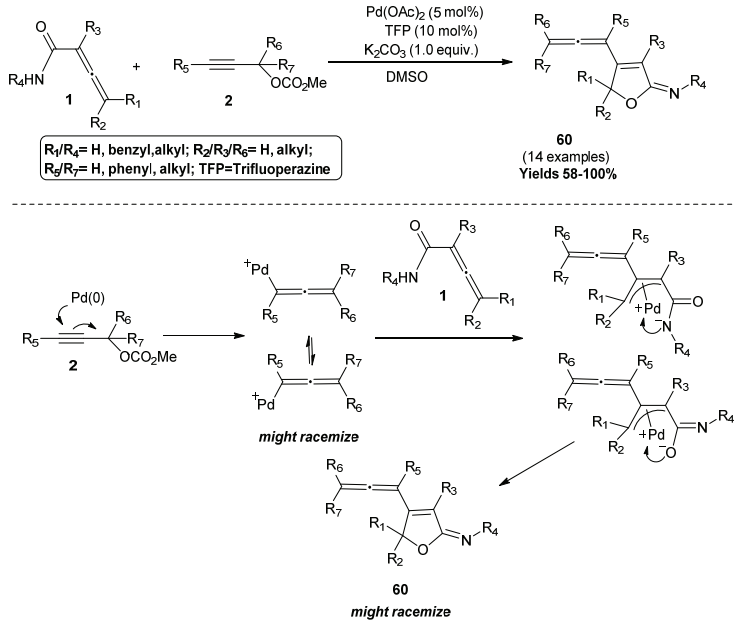
The cyclic *N,O*-acetals **59** were successfully synthesized (Xie et al., 2014) from the palladium(0)-catalyzed cyclization of vinyl iodide-tethered allensulfonamide **1** in the presence of triethylamine (Et_3N) in moderate to good yields (Scheme 39).



Scheme 39. Pd(0)-catalyzed cyclization of allensulfonamide for the synthesis of cyclic *N,O*-acetals.

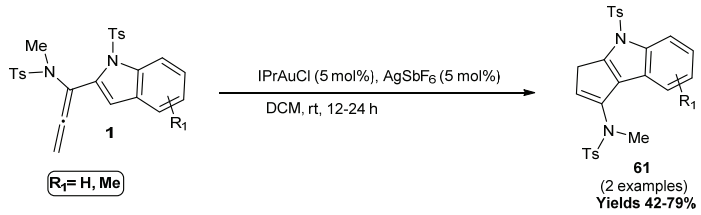
An efficient route for the synthesis of *β*-allenyl furanimine derivatives **60** *via* a $Pd(OAc)_2$/TFP-catalyzed cyclization reaction of 2,3-allenamides **1** in the presence of propargylic carbonates **2** was reported by Chen et al. (2011). The proposed mechanism starts with the propargylic carbonate framed in an allenylic palladium in the presence of the *in situ* formed Pd(0). The allenylic palladium on intermolecular carbopalladation with the

allenamides **1** generated a π-allylic palladium intermediate through either *N*-attack or *O*-attack. Then, the *O*-attack-type product furanimine **60** was afforded due to the tremendous steric hindrance at the 4-position (Scheme 40).



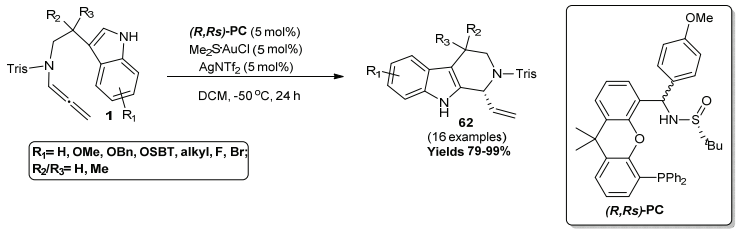
Scheme 40. Synthesis of *β*-allenyl furanimine derivatives from 2,3-allenamides.

An efficient and regioselective strategy for synthesizing aromatic-ring fused cyclopentenamides **61** *via* a gold(I)-catalyzed imino-Nazarov cyclization using *α*-aryl-substituted allenamides **1** was described by Ma et al. (2012) in DCM as shown in (Scheme 41).



Scheme 41. Synthesis of aromatic-ring fused cyclopentenamides.

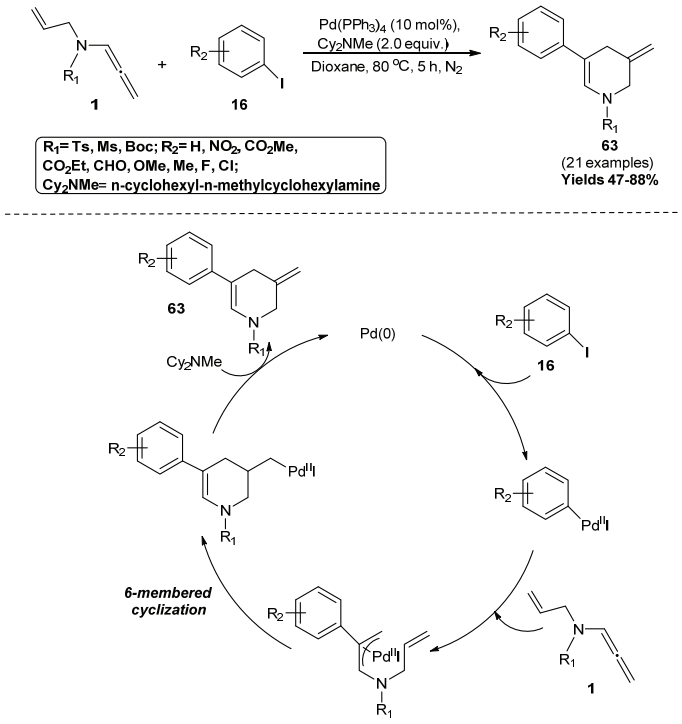
Highly enantioselective, asymmetric gold-catalyzed intramolecular cyclization of *N*-allenamides **1** utilizing a designed chiral sulfinamide phosphine ligand (PC-Phos) was reported (Wang et al., 2017) for the synthesis of chiral tetrahydrocarbolines **62** in good yields with high *ee*'s and moderate to excellent diastereoselectivities (Scheme 42).



Scheme 42. Gold-catalyzed intramolecular cyclization of *N*-allenamides.

An approach to the 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivative **63** was described (Yan et al., 2017) *via* an efficient one-pot palladium-catalyzed cyclization-Heck reaction of allenamides **1**. This product **63** with characteristic non-conjugated diene having one endo-enamine and one exocyclic double bond can be used to prepare industrially and pharmaceutically important piperidine-containing compounds further. Mechanistically, a palladium complex was afforded by the oxidative addition of $Pd(PPh_3)_4$ to **16**. Then, the insertion of

allenamides **1** to the complex formed the π-allylpalladium intermediate. Finally, a subsequent 6-*exo*-trig cyclization and β-hydrogen elimination generated the 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives **63** (Scheme 43).



Scheme 43. Synthesis of 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives.

5. Conclusion

The present chapter shows the versatility of allenamides in various transformations, including cycloadditions/annulations and cyclization with

suitable catalysts and ligands. Various transition-metal-catalyzed functionalization and transition-metal-free functionalization of allenamides have been performed successfully using well-established methodologies. Therefore, it is evident that allenamides have received progressively increasing attention in the past ten years.

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CHAPTER 5

ISATIN

1. Introduction

Isatin **1** (1*H*-indole-2,3-dione) (Figure 1) is an organic compound derived from indole with a molecular formula of $C_8H_5NO_2$. It was first obtained by Otto Linné Erdman (Erdmann, 1840) as a product from the oxidation of indigo dye by nitric acid and chromic acid. In nature, isatin is found in plants of the genus *Isatis*, in *Calanthe discolor* LINDL (Yoshikawa et al., 1998) and in *Couroupita guianensis* Aubl (Bergman et al., 1985). It has been found as a component of the secretion from the Bufo frog's parotid Melochia tomentosa gland. In mammalian tissue, isatin functions as a modulator of biochemical processes which have been the subject of several discussions. In humans, it is a metabolic derivative of adrenaline (Ischia et al., 1988). Substituted isatins are also found in plants, such as the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the *Caribbean tumorigenic* plant as well as from fungi, 6-(3′-methylbuten-2′-yl)isatin was isolated from *Streptomyces albus* (Grafe and Radics, 1986) and 5-(3′-methylbuten-2′-yl)isatin from *Chaetomium globosum*. Isatin is a synthetically versatile substrate and can be used to synthesize various heterocyclic compounds and can also be used as raw material for drug synthesis. Furthermore, isatin derivatives exhibit specific chemical reactions such as oxidation, Friedel-Crafts reaction, ring expansion and aldol condensation.

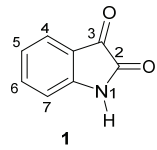

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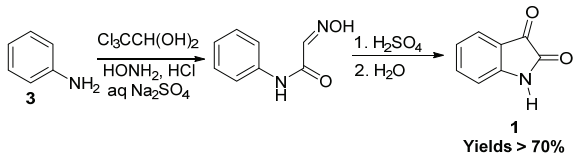
Figure 1. Isatin (1*H*-indole-2,3-dione)

2. Synthesis of Isatin

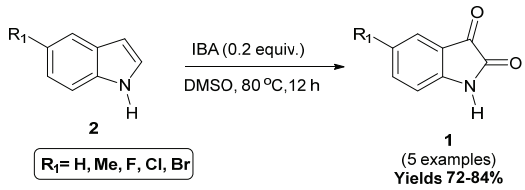
The conventional protocol used to prepare various isatin derivatives are the Sandmeyer, Stolle, Gassman and Martinet methods. The Sandmeyer methodology (Sandmeyer, 1919) is one of the oldest ways to synthesize isatin. This method involves the condensation of chloral hydrate **2** with a primary arylamine **3** in the presence of hydroxylamine hydrochloride, in aqueous sodium sulfate forming an α-isonitrosoacetanilide. Isolation of this intermediate and subsequent electrophilic cyclization, promoted by strong acids such as sulfuric acid, furnishes **1** in >75% yield (Scheme 1).



Scheme 1. Synthesis of isatin by Sandmeyer methodology.

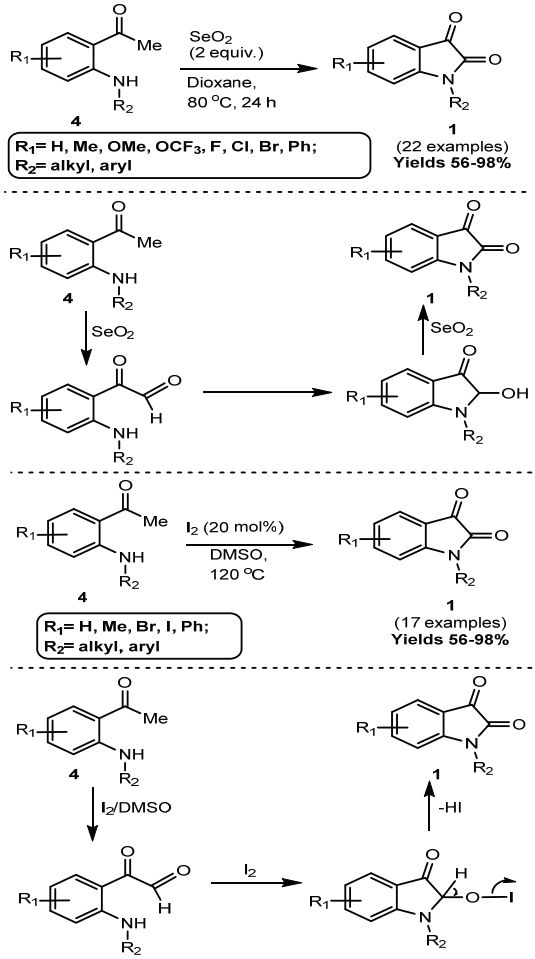
These approaches with substrates containing *meta*-substituted or electron-withdrawing substituents lead to the formation of the target compounds with low yields or as, mostly, inseparable mixtures of regioisomeric products (Bogdanov and Mironov, 2018). These circumstances have prompted investigators to find new, mild, convenient and functional group-tolerant strategies for synthesizing isatins. The oxidation of indoles

is one of the convenient ways of preparing isatins. Thus, a simple way of oxidizing indoles with oxygen in the presence of cheaper iodosobenzoic acid (IBA) was reported (Bindu et al., 2017). They could prepare 5-substituted (bromo, chloro, fluoro, methyl) isatins with high yields in dimethyl sulfoxide (DMSO). However, the oxidation reaction failed in the case of 5-nitroindole (Scheme 2).



Scheme 2. Synthesis of isatin by oxidation of indoles.

Then, another method involves cyclizing *o*-aminoacetophenones using SeO_2 in dioxane (Liu et al., 2013) or Kornblum oxidation of 2-aminoacetophenones using an I_2/DMSO (dimethyl sulfoxide) system (Rajeshkumar et al., 2014). Both methods could prepare various substituted *N*-arylisatins that were selectively obtained in good to excellent yields. The reaction tolerates a wide range of functionalities as shown in Scheme 3.

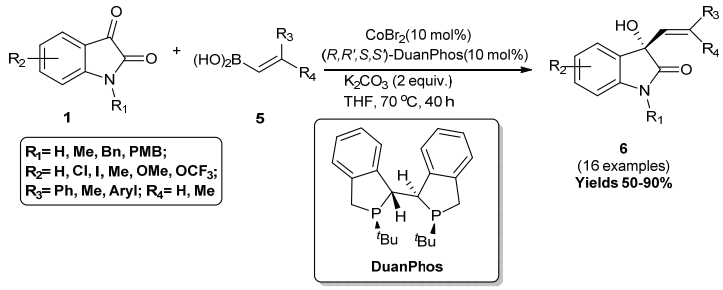


Scheme 3. Synthesis of isatin from *o*-aminoacetophenones.

3. Functionalization of Isatins

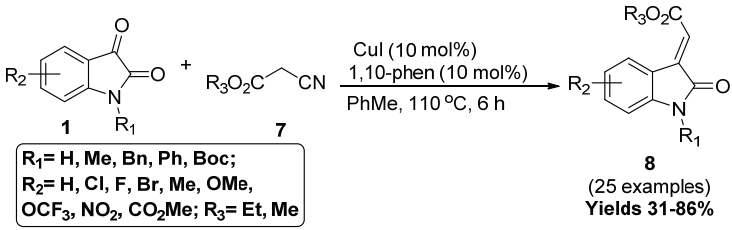
The $CoBr_2$-catalyzed enantioselective vinylation of isatins **1** by vinyl boronic acids **5** in the presence of DuanPhos was reported by Huang et al.

(2016) for the synthesis of the tertiary allylic alcohols **6** in moderate to good yields in tetrahydrofuran (THF) as the solvent (Scheme 4).



Scheme 4. Synthesis of the tertiary allylic alcohols from isatins.

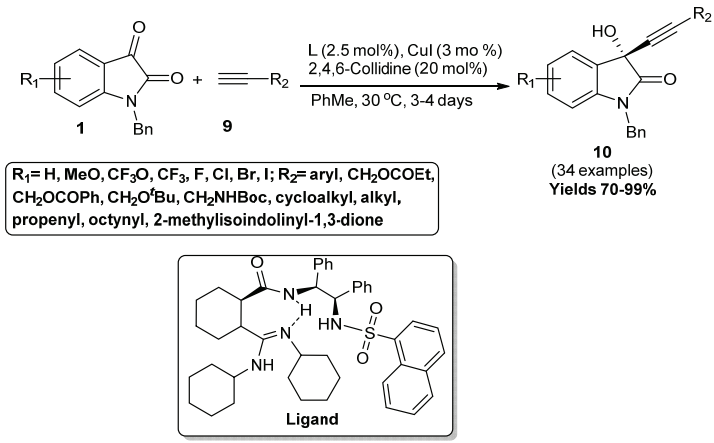
The synthesis of 3-ylideneoxindoles **8** from isatins and ethyl isocyanoacetate **7** was reported using the CuI/1,10-phenanthrene catalytic system in toluene (PhMe) (Yuan et al., 2018). Here, ethyl isocyanoacetate acts as a latent two-carbon donor like the Wittig reagent, with a tandem procedure including 1,3-dipolar cycloaddition/inverse 1,3-dipolar ring-opening/olefination allowing the preparation of 3-ylideneoxindoles **8** with broad functional group tolerance (Scheme 5).



Scheme 5. Synthesis of the 3-ylideneoxindoles from isatins.

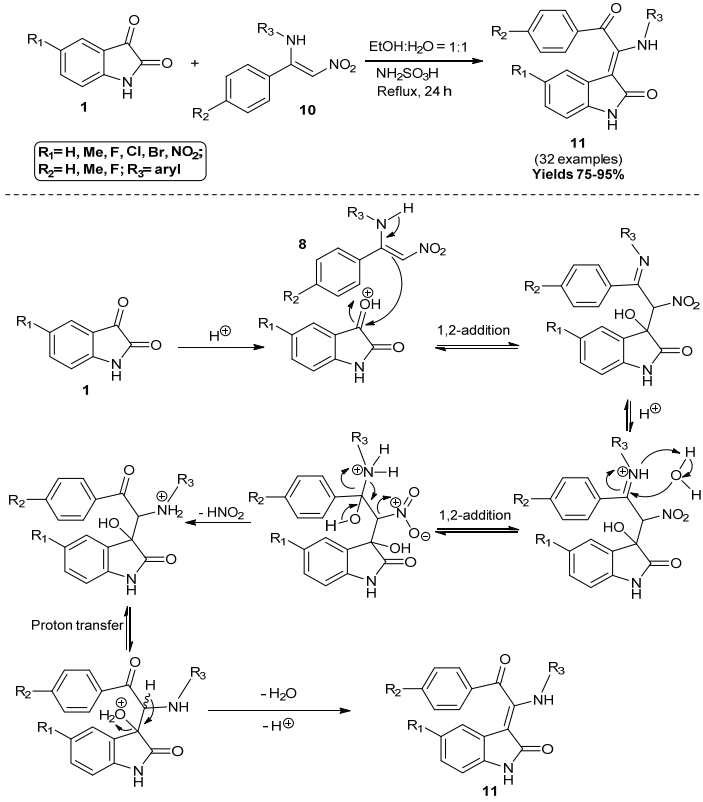
The enantioselective alkynylation of isatins **1** using aryl-substituted alkynes **9** for the synthesis of 3-substituted 3-hydroxyoxindoles **10** in the

presence of bifunctional guanidine/CuI as a catalyst, under mild reaction conditions, was accomplished (Chen et al., 2016) (Scheme 6). In another study, zinc dust was also used as a catalyst in the same reaction (Singh et al., 2017).



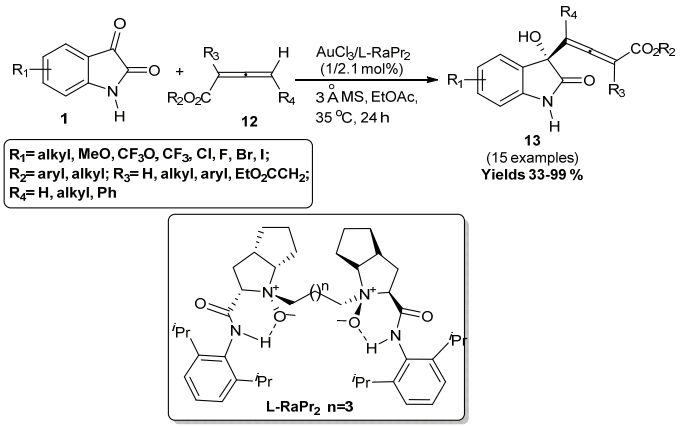
Scheme 6. CuI/guanidine catalyzed alkynylation of isatins.

An environmentally-friendly method for the synthesis of functionalized (*Z*)-3-(1(-arylamino)-2-oxoarylidene)indolin-2-ones (AOIDOs) **11** *via* sulfamic acid (NH_2SO_3H)-catalyzed unprecedented cascade reaction of isatins **1** with nitro-substituted enamines **10** was recently reported **(**Zhang et al., 2020). The reaction proceeds through a novel mechanism with the loss of HNO_2 and an intramolecular 1,2-migration rearrangement, as shown in Scheme 7.



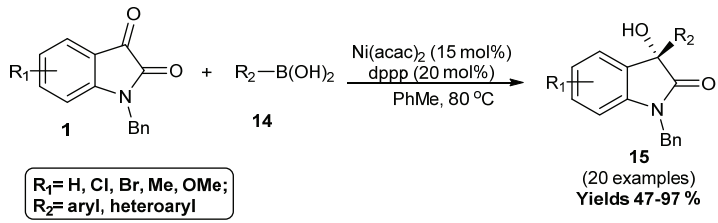
Scheme 7. Synthesis of functionalized (*Z*)-3-(1(-arylamino)-2-oxoarylidene)indolin-2-ones.

Then, the diastereo- and enantioselective alleno aldol addition of allenic esters **12** to isatins **1** in the presence of $AuCl_3$ and chiral *N,N'*-dioxide L-$RaPr_2$ for the synthesis of the carbinol allenoates **13** has been reported (Wang et al., 2016). The steric hindrance of vicinal 4-substituted bulky halogen atoms such as 4-Cl and 4-Br decrease the yields and enantioselectivity. The best enantioselectivity was provided by 5,7-dimethyl-substituted isatin (Scheme 8).



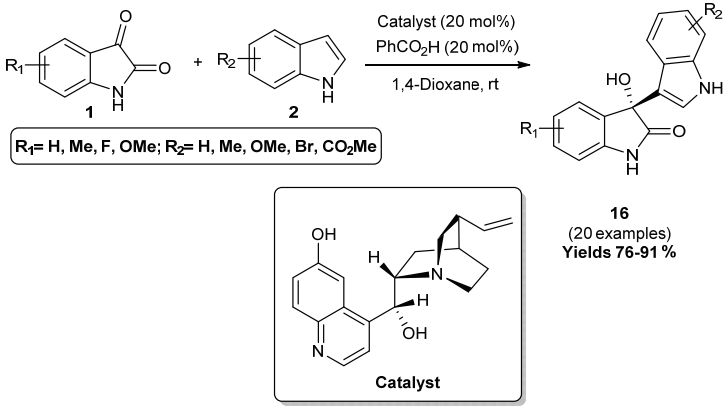
Scheme 8. The synthesis of carbinol allenoates by alleno aldol addition.

The addition of arylboronic acids **14** to isatins in the presence of Ni-catalyst was first developed by Zhang et al. (2018). In this reaction, $Ni(acac)_2$ and 1,3-bis(diphenylphosphino)propane (dppp) as the phosphine ligand promoted and gave 3-aryl-3-hydroxy-2-oxindoles up to 97% yields, (Scheme 9). Substituted phenylboronic acids, fused-ring and heterocyclic boronic acids reacted smoothly with isatins in this protocol. The functional groups in *para*-substituents with different electronic effects reasonably influenced the reaction yields. Whereas, *ortho*-substituents of arylboronic acids showed significant steric hindrance and, hence, lower the product yields.



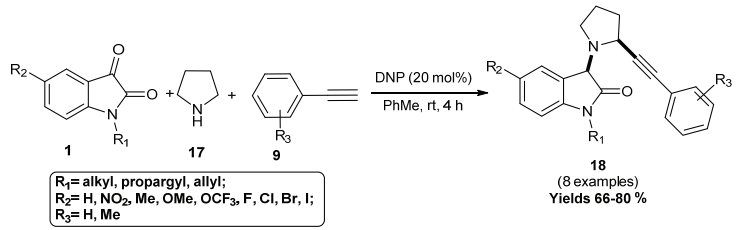
Scheme 9. The synthesis of oxindoles from isatins.

Also, the cupreine-catalyzed direct enantioselective Friedel-Crafts reaction of indoles **2** with isatins **1** affording chiral 3-indolyl-3-hydroxy-2-oxindoles **16** in good yields and with high enantioselectivities was reported (Deng et al., 2010), (Scheme 10).



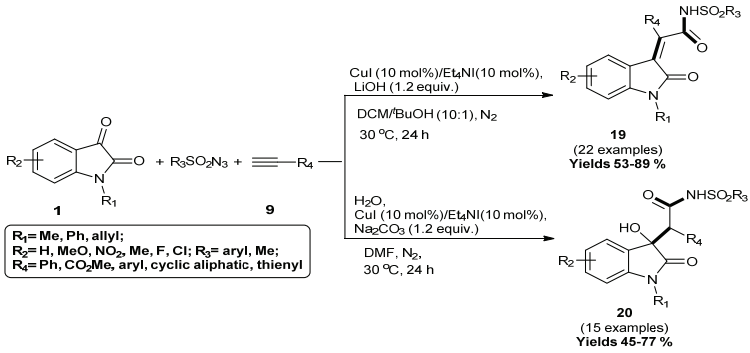
Scheme 10. Cupreine-catalyzed Friedel-Crafts reaction of indoles with isatins.

The 2,4-dinitrophenol (DNP) facilitated, three-component, reaction of isatins **1**, cyclic-amines **17** and alkynes **9** to synthesize mono-functionalized α-alkynyl-3-amino-2-oxindole derivatives **18** was developed by Kumar et al. (2016). This methodology could completely suppress the homocoupling of alkynes leading to the desired products in moderate to good yields (Scheme 11).



Scheme 11. Substrate scope for the formation of α-alkynyl-3-amino-2-oxindole.

A tunable copper-catalyzed azide-alkyne cycloaddition (CuAAC)-initiated multicomponent reaction strategy for the synthesis of 3-functionalized indolin-2-ones has been reported (Cheng et al., 2016). Here, the reaction of isatins **1**, tosyl azides and terminal alkynes **9** in the presence of CuI and Et_4NI was developed. This tandem process can be manipulated to proceed in a three-component and four-component fashion, respectively. Thus, a range of (*Z*)-3-alkenyloxindoles **19** in dichloromethane (DCM) and tert-butanol (^{t}BuOH) or 3-substituted 3-hydroxyoxindoles **20** in *N,N*-dimethylformamide (DMF) were obtained from the same starting materials by changing the reaction conditions and reagents used (Scheme 12).

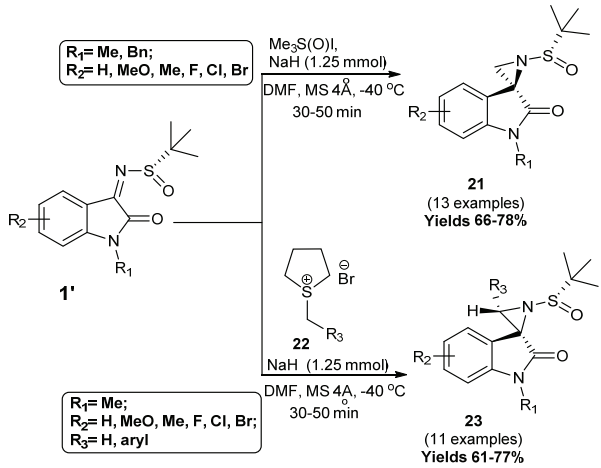


Scheme 12. Synthesis of 3-functionalized indolin-2-ones.

4. Applications of Isatin in organic synthesis

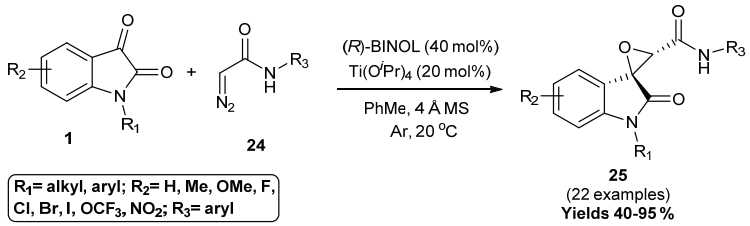
4.1 Two-component reactions of Isatin

The asymmetric synthesis of chiral spiro-aziridine oxindoles **21** and **23** *via* the aza-Corey-Chaykovsky reaction of isatin-derived *tert*-butanesulfinyl ketimines **1'** was explored (Hajra et al., 2016). In this protocol, *in situ* generated sulfur ylide from trimethylsulfonium iodide or the reaction of benzyl sulfur ylides generated from *S*-benzyl tetrahydrothiophenium bromide **22** react with chiral *tert*-butanesulfinyl ketimines **1'** in the presence of NaH and DMF as the solvent (Scheme 13).



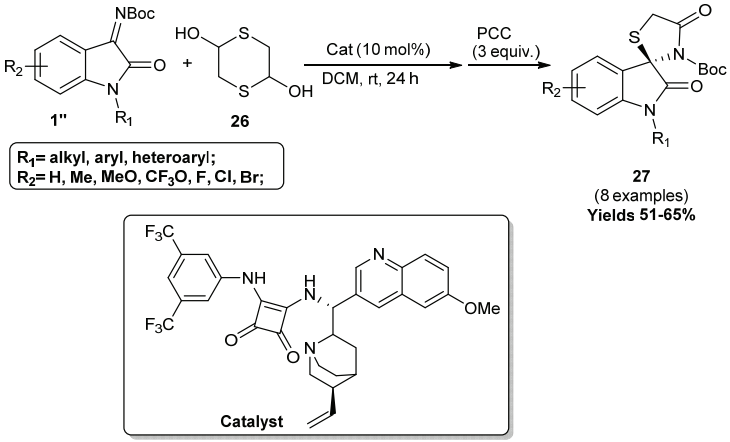
Scheme 13. Asymmetric synthesis of 3-substituted spiro-aziridine oxindoles.

Chai et al. (2017) developed an efficient chiral 1,1′-bi-2-naphthol (BINOL)/$Ti(OiPr)_4$ complex catalyzed asymmetric Darzens reaction of *N*-protected isatins **1** with diazoacetamides **24** for the synthesis of *spiro*-epoxyoxindoles **25** in good yields (Scheme 14).



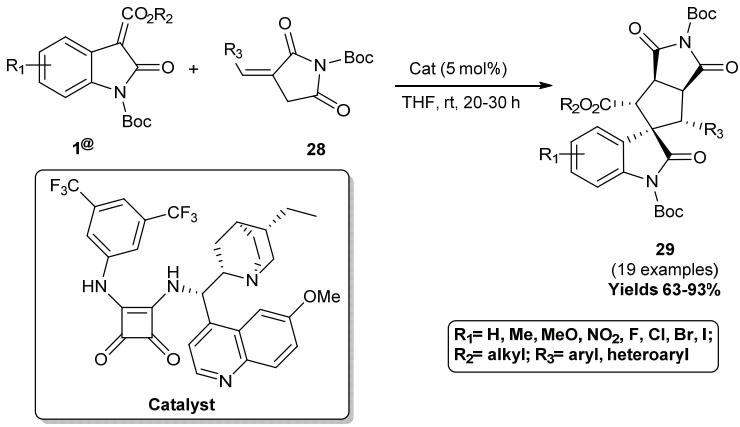
Scheme 14. Synthesis of *spiro*-epoxyoxindoles.

Cheng et al. (2016) developed an enantioenriched spirooxindole-based 4-thiazolidinones **27** *via* the catalytic asymmetric [3+2] annulation of isatin ketimines **1"** with the 1,4-dithiane-2,5-diol **26** (Scheme 15). This protocol uses a bifunctional catalyst in DCM as the solvent followed by simple oxidation using pyridinium chlorochromate (PCC) with high enantioselectivity (up to 98% *ee*).



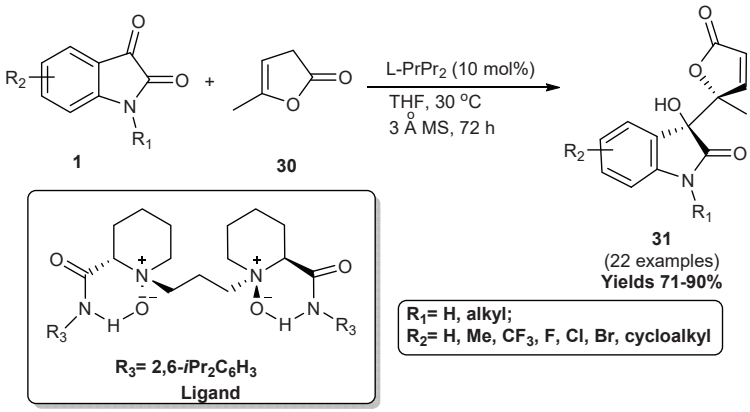
Scheme 15. Synthesis of 4-thiazolidinones from isatin ketimines.

Zhao and Du (2016) developed an efficient asymmetric synthesis of spirooxindoles **29** through a cascade Michael/Michael reaction containing five contiguous stereocenters from the reaction of isatin-derived enoates **1**[@] and α-alkylidene succinimides **28**. The reaction was catalyzed by a bifunctional tertiary amine-squaramide catalyst in THF at room temperature for 20-30 hours (Scheme 16).



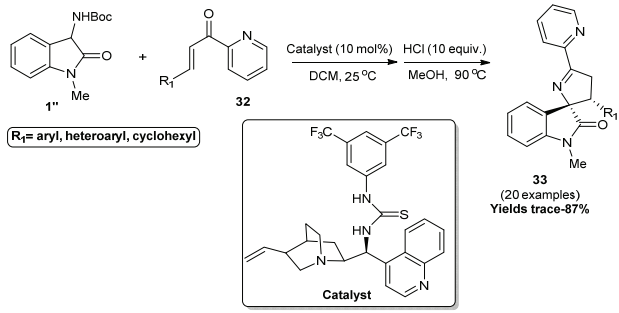
Scheme 16. Michael/Michael reaction for the asymmetric synthesis of spirooxindoles.

An asymmetric vinylogous aldol reaction of nonactivated natural α-angelica lactone **30** to isatins was developed using *N,N'*-dioxide-$Sc(OTf)_3$ complex as the catalyst (Tang et al., 2017). In this reaction, different γ-hydroxy butenolides **31** bearing congested adjacent tetrasubstituted stereocenters were obtained in good yields with high diastereoselectivities and excellent enantioselectivities (Scheme 17).



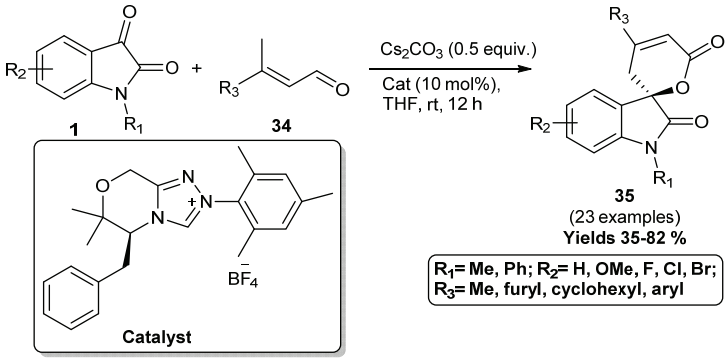
Scheme 17. Asymmetric vinylogous additions of γ-butenolides to electrophiles.

Cui et al. (2017) reported a new strategy for highly diastereo- and enantioselective synthesis of spiro[pyrrolidin-3,2-oxindole] derivatives **33** *via* the asymmetric Michael/cyclization reaction sequence of isatin derivatives **1′** with 2-enoylpyridines **32** through dehydration and deprotection with conc. HCl (Scheme 18).



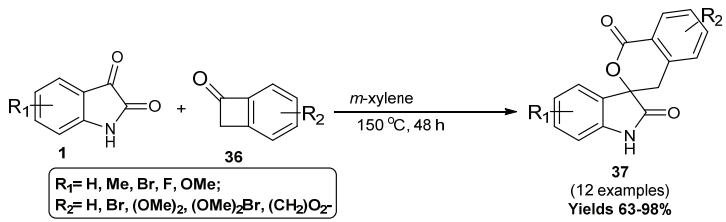
Scheme 18. Synthesis of spiro[pyrrolidin- 3,2-oxindole] derivatives.

An enantioselective [4+2] assemble leading to spirolactones **35** *via* chiral *N*-heterocyclic carbene (NHC)-catalyzed remote *γ*-carbon addition of enals **34** with isatins **1** was reported (Rong et al., 2016), (Scheme 19).



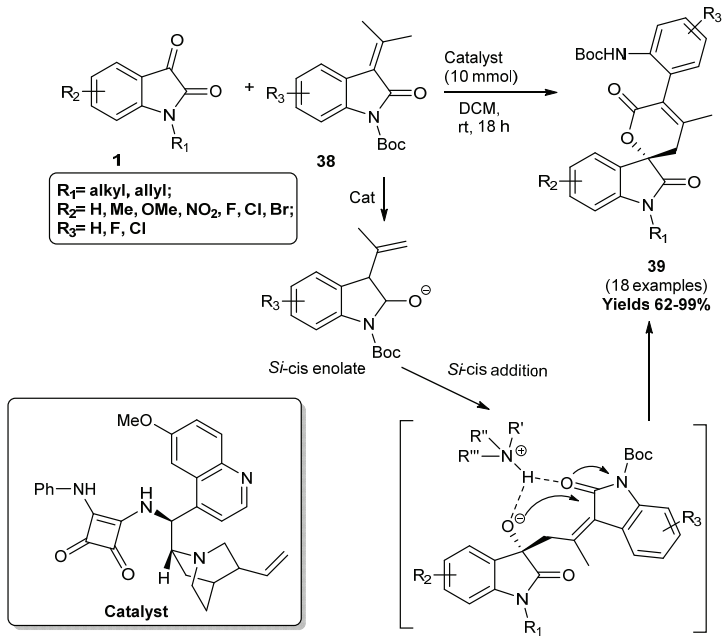
Scheme 19. Enantioselective synthesis of spirolactones.

The synthesis of 2-oxindole spirolactones **37** from benzocyclobutenones **36** engaging in intermolecular [4+2] cycloadditions with isatins was developed (Wurm et al., 2017). During the reaction, benzocyclobutenones undergo cyclo-reversion to form transient *α*-oxo-orthoquinodimethanes or "ortho-quinoid ketene methides" at 150 °C in *meta*-xylene as the solvent. This process could tolerate various functional groups and substitution patterns and be applied to unprotected isatins bearing free NH-functionalities (Scheme 20).



Scheme 20. Synthesis of 2-oxindole spirolactones.

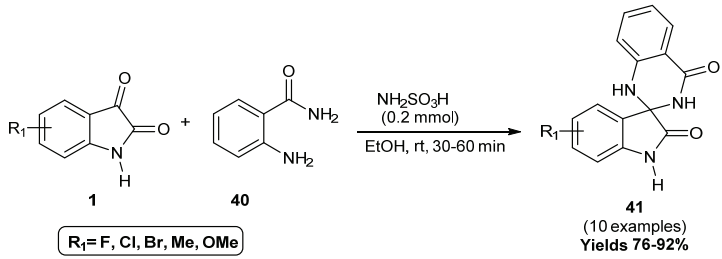
Han and Chang (2016) reported a vinylogous Aldol-cyclization cascade reaction of 3-alkylidene oxindoles **38** to isatins **1** by using bifunctional organocatalysts in DCM at room temperature. According to the proposed mechanism, first oxindole **38** was deprotonated by the catalyst and generated *s-cis* enolate, which was then added through the *Si* face to isatin **1** to give an alkoxide intermediate. After cyclization and protonation of the alkoxide intermediate, the desired product **39** was delivered in good yields and the catalyst was regenerated (Scheme 21).



Scheme 21. Aldol-cyclization cascade reaction of 3-alkylidene oxindoles to isatin.

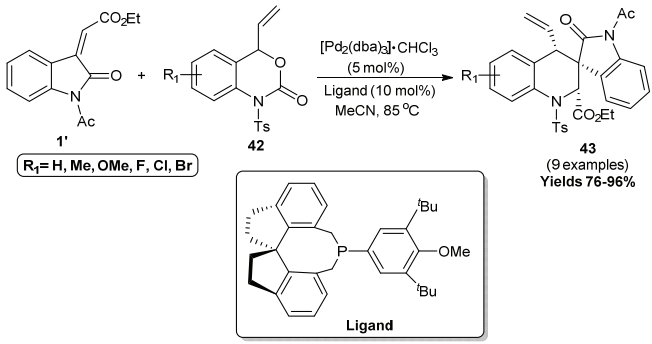
The synthesis of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones **41** through the reaction of isatins **1** and anthranilamide **40** catalyzed by sulfamic acid was developed in ethanol (Mane and Pore, 2016). The newly

synthesized products were fluorescent active with absorption in the UV region (302, 362 nm) and emission in the visible region (413-436 nm) with Stokes shift of 44-72 nm (Scheme 22).



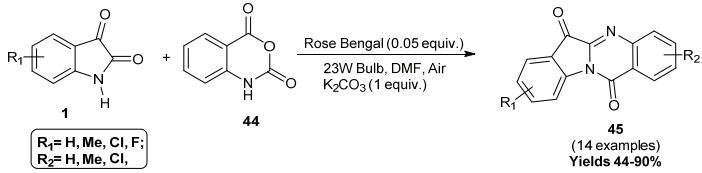
Scheme 22. Synthesis of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones.

Mei et al. (2017) reported Pd/chiral ligand-catalyzed asymmetric decarboxylative [4+2] cycloaddition of isatin derivatives **1'** with methyleneindolinones **42** for the synthesis of chiral tetrahydroquinoline-based 3,3′ spirooxindoles **43** in high yields (up to 96%) and with excellent diastereo- and enantioselectivities. This protocol demonstrates the efficiency of the catalytic system for the synthesis of enantio-enriched polycyclic compounds (Scheme 23).



Scheme 23. Synthesis of chiral tetrahydroquinoline-based 3,3′ spirooxindoles.

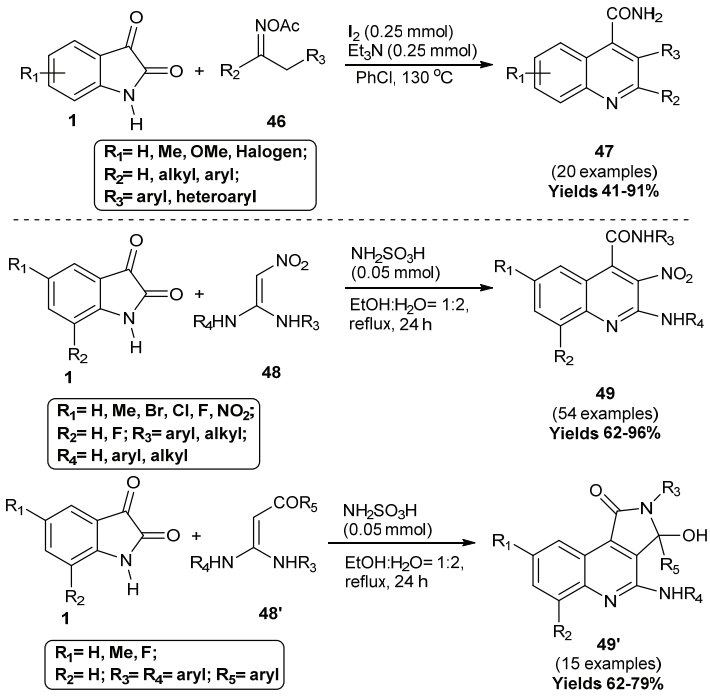
The synthesis of diverse tryptanthrin derivatives **45** mediated by visible light and catalyzed by an organic dye using isatin and isatoic anhydride **44** has been achieved (Hou et al., 2018). The reaction mixture was irradiated with a 23W fluorescent bulb in the presence of Rose Bengal; the self-condensation of isatin, as well as the cross-condensation of isatin and isatoic anhydride **44** through an energy transfer reaction process leads to products **45** in moderate to good yields (Scheme 24).



Scheme 24. Synthesis of tryptanthrin derivatives.

A method for preparing quinoline **47** using molecular iodine in the N-O reduction of ketoxime acetates **46** with isatin was explored (Gao et al., 2018). In this protocol, N-O/C-N bond cleavages and C-C/C-N bond formation to furnish pharmacologically significant quinoline-4-carboxamide derivatives were demonstrated using triethylamine (Et_3N) in chlorobenzene (PhCl) as the solvent (Scheme 25). Then, another method for synthesizing poly-substituted quinoline-4-carboxamides **49** was developed by refluxing a mixture of isatins **1** and various kinds of 1,1-enediamines **48** in a reaction catalyzed by NH_2SO_3H (Wang et al., 2018). If the electron-withdrawing group in 1,1-enediamines **48** was changed to Ar-CO i.e., 1,1-enediamines **48'** with a similar reaction condition**,** a new pyrrol-2-one ring was established, leading to 2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-ones **49'** with moderate yields, wherein the amide group

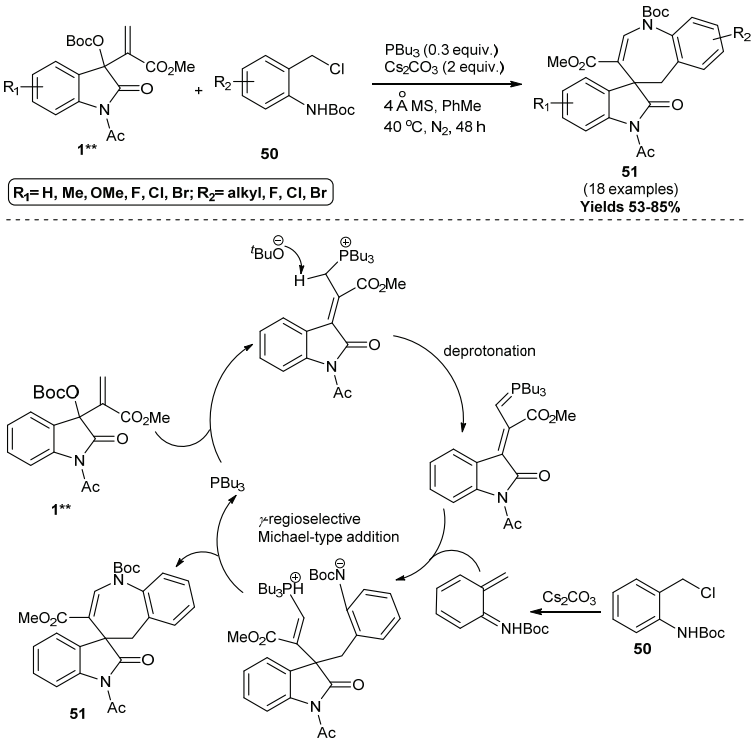
attacked the carbonyl of the target compounds to form the new ring (Scheme 25).



Scheme 25. Synthesis of quinoline-4-carboxamides.

The synthesis of quaternary aza-spirocycloheptane oxindoles **51** *via* the [4+3] cycloaddition reaction of Morita-Baylis-Hillman (MBH) carbonates derived from isatin **1**** and (*N*-chloromethyl)aryl amides **50** catalyzed by a Lewis base and a Brønsted base was explored (Liu et al., 2016). The proposed mechanism starts with the nucleophilic reaction of tributylphosphine (Bu_3P) with MBH carbonates affording an intermediate with the simultaneous release of CO_2. The *in situ* generated *tert*-butoxide anion then deprotonated the intermediate formed to yield the allylic

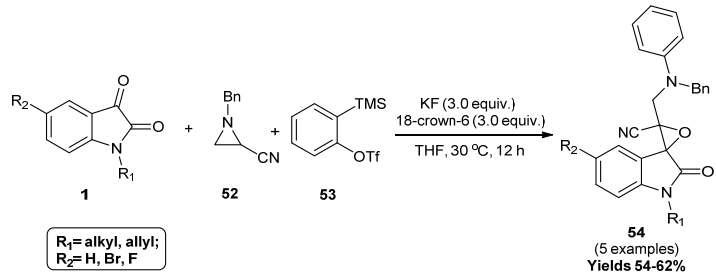
phosphonium ylids. The γ-regioselective Michael addition between allylic phosphonium ylide and aza-o-quinone methide generated the elimination of **50** in the presence of Cs_2CO_3. It was followed by intramolecular cyclization, affording the desired products **51** with the regeneration of Bu_3P. The corresponding quaternary aza-spirocycloheptane oxindole was efficiently synthesized in good yields (Scheme 26).



Scheme 26. Synthesis of aza-spirocycloheptane oxindole and its mechanism.

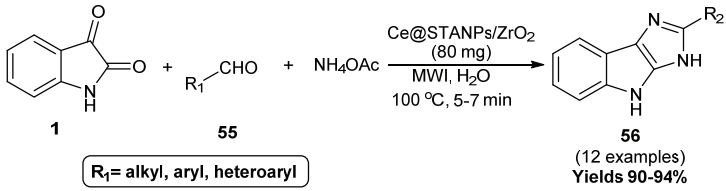
4.2 Three-component reactions of Isatin

The synthesis of trisubstituted *N*-aryl-*α*-amino epoxides **54** was reported (Roy et al., 2016) using the three-component reaction of isatins **1**, *N*-substituted aziridine **52** and 2-(trimethylsilyl)aryl triflate **53** using potassium fluoride (KF) and 18-crown-6 in THF (Scheme 27). The substitution on the carbocyclic ring of isatin with halogens and the variation of N-substitution on isatin was tolerated well without affecting the outcome of the reaction.



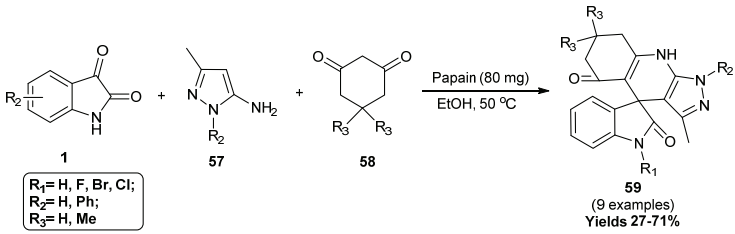
Scheme 27. Synthesis of trisubstituted *N*-aryl-*α*-amino epoxides.

An efficient protocol for the synthesis of isatin-based imidazoles **56** (Khan and Siddiqui, 2018) using recyclable cerium-immobilized silicotungstic acid nanoparticle-impregnated zirconia (Ce@STANPs/ZrO_2) under microwave irradiation in water from isatin, aldehydes **55** and ammonium acetate NH_4OAc was reported. In this reaction, Ce@STANPs/ZrO_2 was used for C=O bond activation in the overall reaction to synthesize the products. The protocol's advantages were the recyclability of the catalyst, green reaction conditions, excellent yields (up to 94%) and a shorter reaction time (within 5–7 minutes) (Scheme 28).



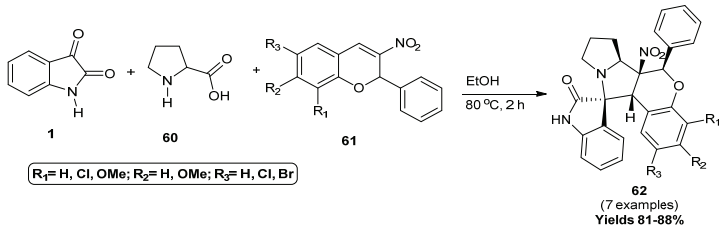
Scheme 28. Synthesis of isoxazole-fused spiropyrrolidine oxindoles.

An environmentally-friendly method for synthesizing spiropyrazolo[3,4-*b*]pyridine derivatives **59** using isatin, cyclic-1,3-diketone **58**, and 3-methyl-5-aminopyrazole **57** was developed (Liang et al., 2017). This one-pot reaction was catalyzed by enzyme-papain in ethanol, also the newly synthesized compounds possessed fluorescent properties (Scheme 29).



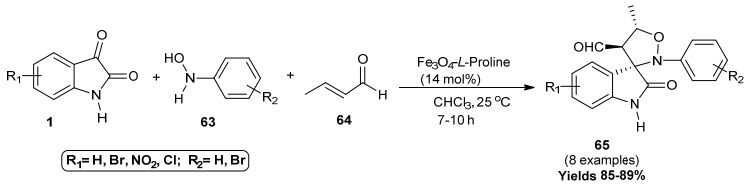
Scheme 29. Synthesis of spiropyrazolo[3,4-*b*]pyridines.

Nayak et al. (2016) reported an environmentally-friendly synthesis of spirooxindole-pyrrolidine/piperidine-fused nitrochromanes **62** through cycloaddition reaction of isatin **1**, proline **60** and nitrochromene **61** (Scheme 30). The reaction was performed in refluxing ethanol without any catalyst for 2 h, giving good yields.



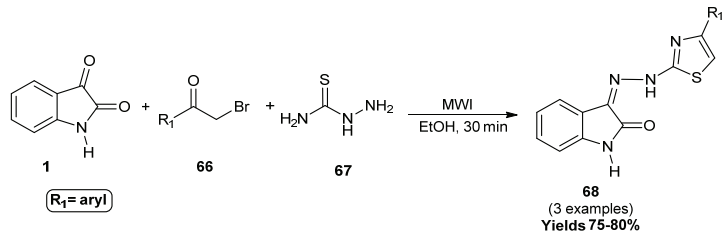
Scheme 30. Synthesis of spirooxindole-pyrrolidine/piperidine-fused nitrochromanes.

Safaei-Ghomi and Zahedi (2016) reported the application of Fe_3O_4-*L*-proline nanoparticles (NPs) as a chiral catalyst to achieve high diastereoselectivities in the asymmetric 1,3-dipolar cycloaddition reaction of isatins **1**, *N*-arylhydroxylamines **63** and enones **64** for the synthesis of spiroisoxazolidines **65** (Scheme 31). In this reaction, *L*-proline functionalized Fe_3O_4 nanoparticles as a magnetic organocatalyst gave isoxazolidine products in high yields with an *endo*-configuration in chloroform.



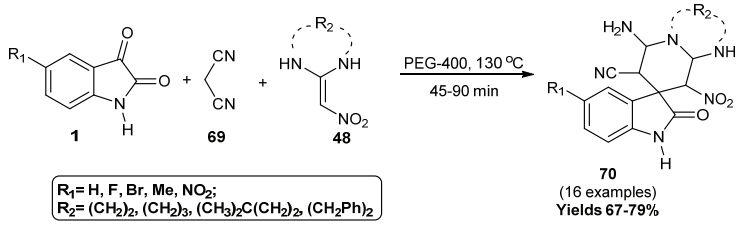
Scheme 31. Synthesis of spiroisoxazolidines using Fe_3O_4-*L*-proline NPs.

The microwave-assisted one-pot synthesis of 4-phenyl-1,3-thiazole derivatives **68** *via* the Hantzsch thiazole reaction of isatin **1**, 2-bromoethanones **66** and thiosemicarbazide **67** was developed (Yogi et al., 2016) in ethanol in 30 minutes (Scheme 32).



Scheme 32. Hantzsch thiazole reaction of isatin, 2-bromoethanones and thiosemicarbazide.

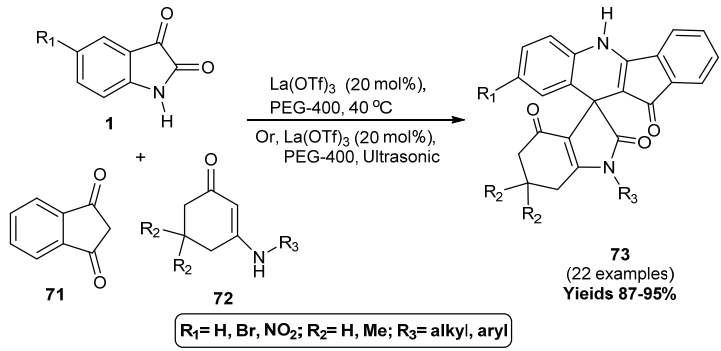
An efficient and green approach for the synthesis of spiro-dihydropyridine derivatives **70** was developed (Maryamabadi et al., 2016) through a one-pot multicomponent condensation of isatin derivatives **1** and malononitrile **69** with ketene aminals **48** under catalyst-free conditions in poly-ethylene glycol-400 (PEG-400) as a highly efficient and green biodegradable polymeric medium (Scheme 33).



Scheme 33. Catalyst-free synthesis of spiro-dihydropyridines from isatin.

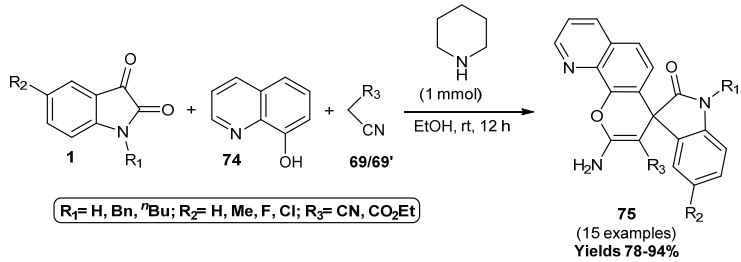
Kumari et al., (2016) reported an efficient methodology for the synthesis of substituted spiro[indolo-3,10′-indeno[1,2-*b*]quinoline]-2,4,11′-triones **73** by the three-component reaction of isatins **1**, 1,3-indanedione **71** and enaminones **72** using $La(OTf)_3$ as a catalyst in PEG-400 under conventional heating (25-30 min) or ultrasonic irradiation (7–10 minutes) (Scheme 34). The advantages of this method include atom economy, green

reaction media, high yields, less reaction time and recyclability of the catalyst.



Scheme 34. Synthesis spiro[indolo-3,10′-indeno[1,2-*b*]quinoline]-2,4,11′-triones.

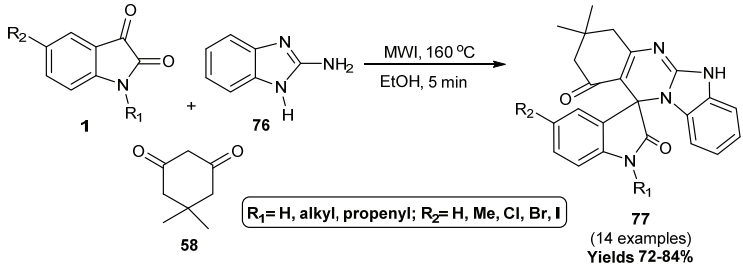
Shi and Yan. (2016) reported a method of three-component condensation of isatins **1**, 8-hydroxyquinoline **74**, and malononitrile **69** or ethyl cyanoacetate **69'** for the preparation of functionalized spiro[indoline-3,4′-pyrano[3,2-*h*]quinolines] **75** in high yields using piperidine in ethanol at room temperature (Scheme 35).



Scheme 35. Synthesis of spiro[indoline-3,4′-pyrano[3,2-*h*]quinolines.

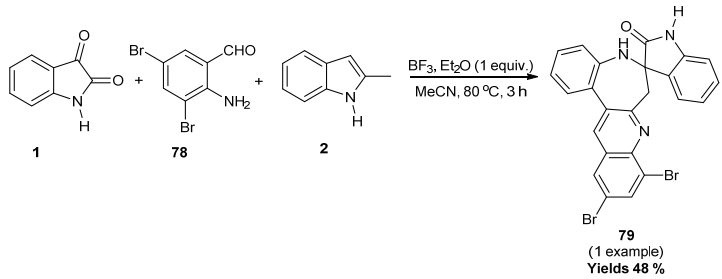
A novel three-component reaction for synthesizing spiro-benzimidazoquinazolinones **77** *via* the reaction of isatins **1**, dimedone **58**

and 2-aminobenzimidazole **76** under microwave irradiation was reported by Maloo et al. (2016). This one-pot process involves the formation of one C-C and two C-N bonds during the synthesis of the spiro-compounds (Scheme 36).



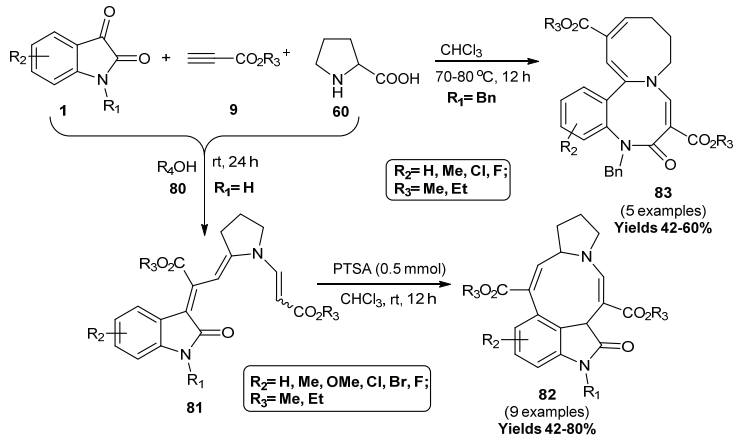
Scheme **36**. Synthesis of novel spiro-benzimidazoquinazolinones.

The synthesis of a quinoline-fused-1-benzazepine **79** was established (Min et al., 2016) by condensing isatin **1** with a *C,N*-1,6-binucleophile generated from *o*-aminobenzaldehyde **78** and 2-methylindole **2** through a Mannich-type reaction using boron trifluoride etherate **(**$BF_3.Et_2O$) in acetonitrile as the solvent within 3 hours (Scheme 37).



Scheme 37. Synthesis of a quinoline-fused-1-benzazepine.

The synthesis of unique nine-membered pyrrolo[1′,2′:1,9]azonino[6,5,4-*cd*]indoles **82** in the presence of *para*-toulenesulphonic acid (PTSA) through the multicomponent reaction of *L*-proline **60**, isatins and excess of methyl propiolates **9** was explored (Cao et al., 2019). The products were converted from 2-(oxoindolin-3-ylidene)propylidene)pyrrolidin-1-*yl*)acrylates **81** in good yields. On the other hand, refluxing the reaction in chloroform unprecedently resulted in eight-membered azocino[1,2-*a*]benzo[*c*][1,5]diazocines **83** as the main products (Scheme 38).

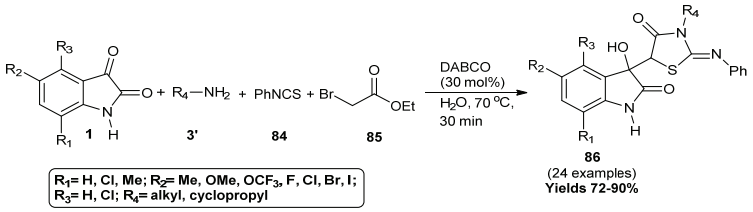


Scheme 38. Synthesis of eight- and nine-membered heterocycles.

4.3 Four-component reactions of Isatin

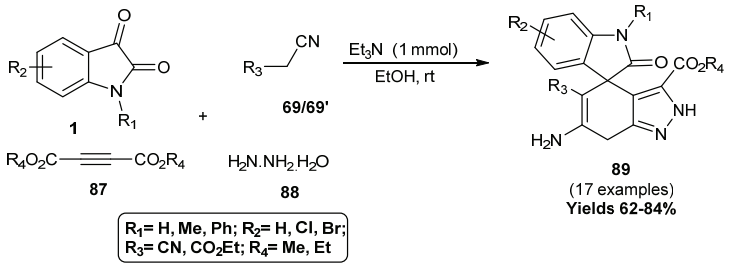
A one-pot four-component protocol for the synthesis of a novel class of functionalized (*Z*)-5-(3-hydroxy-2-oxoindolin-3-yl)-2-iminothiazolidin-4-ones **86** by the reaction of substituted isatins **1**, amines **3'**, phenylisothiocyanate **84** and ethyl bromoacetate **85** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst in aqueous medium had been reported by Bejjam et al. (2016). The 5-halo isatins reacted under

standard conditions resulting in moderate yields of products, while other 5-substituted isatins reacted smoothly to furnish the desired products in high yields. Disubstituted isatins reacted similarly to monosubstituted isatins and afforded comparatively less yields of the desired products under standard reaction conditions (Scheme 39).



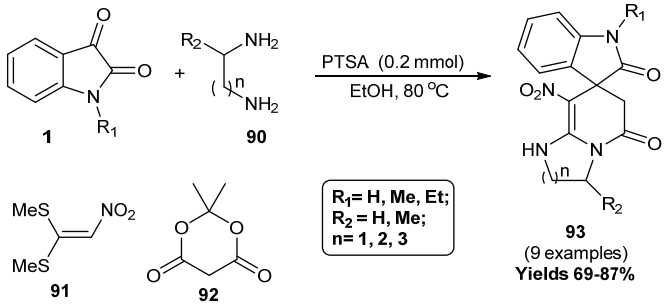
Scheme 39. Synthesis of thiazolidin-4-one derivatives.

The synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylate derivatives **89** from the one-pot four-component reaction of isatin, malononitrile **69/69'**, hydrazine derivatives **88** and dialkyl acetylenedicarboxylates **87** was established (Pal et al., 2013). In this protocol, two C-C bonds, two C-N bonds and one C-O bond have formed using Et_3N as the base catalyst in ethanol at room temperature (Scheme 40).



Scheme 39. Synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylates.

The synthesis of novel spiropyridineoxindole derivatives **93** containing a pyridone ring *via* a four-component reaction between various diamines **90**, 1,1-bis(methylthio)-2-nitroethylene **91**, isatin derivatives and Meldrum's acid **92** was demonstrated using PTSA in ethanol (Rahimi et al., 2019).



Scheme 40. Synthesis of spiropyridineoxindole derivatives.

5. Conclusion

This chapter demonstrates that isatin is a very versatile substrate with special significance for synthesizing various organic compounds. Many spiro-fused heterocyclic frameworks have been prepared from isatins using various well-established methodologies. Multicomponent reactions of isatin with many critical substrates have synthesized a wide variety of higher membered heterocycles with seven, eight and nine-membered rings.

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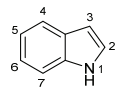
CHAPTER 6

INDOLE

1. Introduction

Indole (also known as 1*H*-benzo[*b*]pyrrole) (Figure 1) is one of the essential aromatic *N*-heterocycles among the "*privileged scaffold*" widely distributed in nature (Wan et al., 2019). The indole ring systems are found in a broad range of natural sciences and industries (Kinoshita et al., 2020). It is also an intercellular signal molecule that controls various aspects of bacterial physiology, including spore formation, resistance to drugs, plasmid stability, biofilm formation and virulence (Lee and Lee, 2010). Its derivative amino acid, tryptophan, is also a precursor of the neurotransmitter serotonin (Nelson and Cox, 2005). They are promising agents against tuberculosis, malaria, cancer, diabetes, migraines, hypertension, convulsions, bacterial infections of methicillin-resistant *Staphylococcus aureus* (MRSA) and viruses (Singh and Singh, 2018, and Jia et al., 2020). This scaffold undoubtedly represents one of the most well-known structural subunits for discovering new drug candidates.



1

Figure 1. Structure of indole.

It is a planar bicyclic molecule possessing aromatic characteristics according to Huckel's rule (10 π-electrons) (Sravanthi and Manju, 2016). It has a unique chemical structure with four different reactive centers: carbon atom 3, nitrogen atom 1, the C2-C3 π-bond and the C2-N sigma bond (Figure 2). It can also be protonated with strong acids in which protonation at the C3 position is more accessible than at the N-atom. The cycloaddition reactions of the C2-C3 π-bond and C2-N sigma bond of indole are also observed (Ziarani et al., 2018)

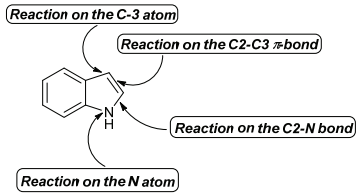


Figure 2. Reactive sites of indole.

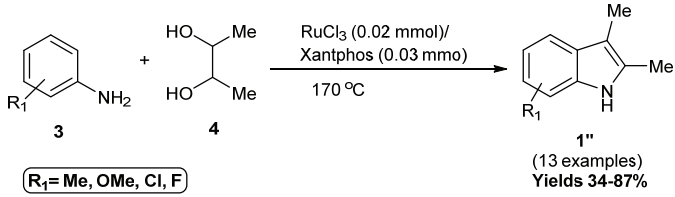
2. Synthesis of Indole

Fischer indole synthesis, discovered in 1883 by Emil Fischer, is the oldest and most widely used method for the synthesis of indole in which substituted phenyl hydrazine reacts with an aldehyde or ketone under acidic conditions (Fischer and Jourdan, 1883; Fischer and Hess, 1884).

A "greener" $AgNO_3$-catalyzed approach to indole derivatives **1**' through intramolecular cyclization of acetylenic free amines **2** in water has been reported by Sun et al. (2017). In this protocol, no strong base/acid catalysts or *N*-substituted substrates were required to achieve this cycloisomerization (Scheme 1). According to the authors, hydrogen bonding between the water medium and the substrate plays a vital role in improving chemical reactivity and regioselectivity.

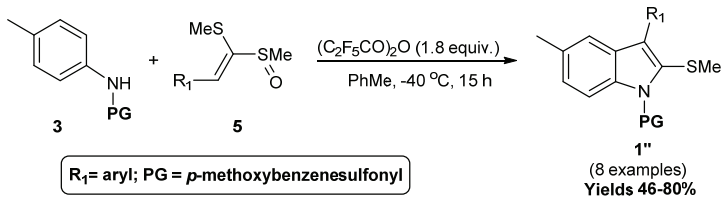
Scheme 1. The synthesis of 2-monosubstituted indoles in water.

A straightforward and atom-economical method for synthesizing 2,3-disubstituted indoles **1"** by condensation of anilines **3** and 1,2-diols **4** under neat conditions with a catalytic amount of $RuCl_3$/xantphos was developed by Tursky et al. (2010) (Scheme 2).



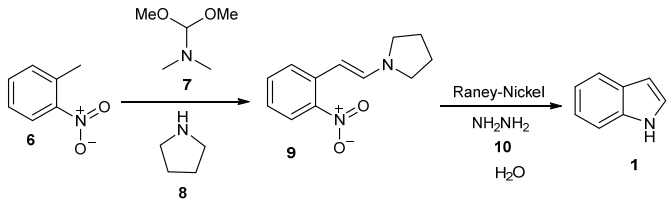
Scheme 2. Synthesis of 2,3-disubstituted indoles by condensation of anilines and 1,2-diols.

Meanwhile, Kinoshita et al. (2020) designed an *S–N* variant of the *N–N*-based Fischer indole synthesis by treating sulfonanilides **3'** and ketene dithioacetal monoxides **5** using an acid anhydride which provides *N*-sulfonyl-2-methylsulfanylindoles **1"**. The protective group could be removed easily using cesium carbonate in hot methanol/THF (Scheme 3).



Scheme 3. Synthesis of indole from protected aniline and ketene dithioacetal monoxide.

The Leimgruber-Batcho indole synthesis is also an efficient method of synthesizing indole and substituted indoles from *o*-nitrotoluenes **6** (Batcho and Leimgruber, 1985). The reaction involved the formation of an enamine **9** using *N,N*-dimethylformamide dimethyl acetal **7** and pyrrolidine **8** (Maehr and Smallheer, 1981). This intermediate **9** on reductive cyclization by Raney nickel and hydrazine **10** formed the desired indole **1** (Scheme 4).

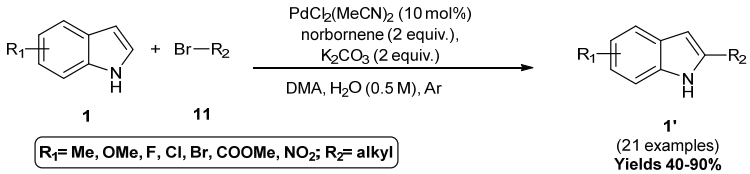


Scheme 4. Leimgruber-Batcho indole synthesis.

3. Functionalization of Indoles

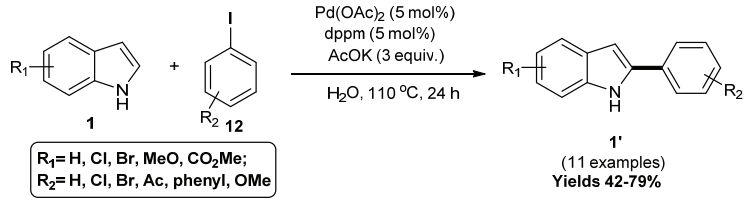
The direct functionalization of indole derivatives has received massive consideration since this scaffold is ubiquitous in biologically active compounds and natural products (Cacchi et al., 2011). Thus, enormous efforts have been dedicated to developing various efficient methods of

functionalization (Leitch et al., 2017). Jiao and Bach (2011) reported a palladium-catalyzed direct 2-alkylation reaction of free NH-indoles through the reaction of indoles **1** and alkyl bromide **11** yielding 2-alkylated indoles **1'** in *N,N*-dimethylacetamide (DMA) and water as solvent. This methodology utilized the norbornene-mediated cascade C-H activation process at the indole ring leading to high regioselectivity and excellent functional group tolerance (Scheme 5).



Scheme 5. Pd-catalyzed C-H alkylation of NH-indoles.

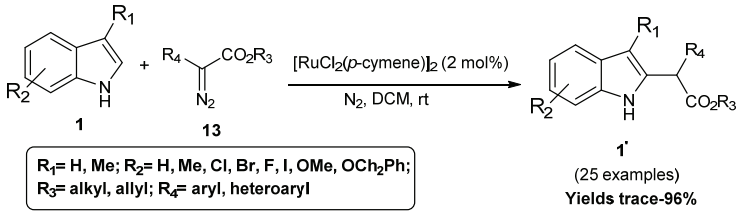
Then, the development of site-selective Pd-catalyzed C-H arylation of NH-indoles through the reaction of indole derivatives **1** and aryl iodides **12** providing the desired C2-arylindoles **1'** was also developed (Joucla et al., 2010). This methodology displayed high chemo/regioselectivities and structural versatility concerning either indole or aryl moieties (Scheme 6).



Scheme 6. Pd-catalyzed C-H arylation of NH-indoles.

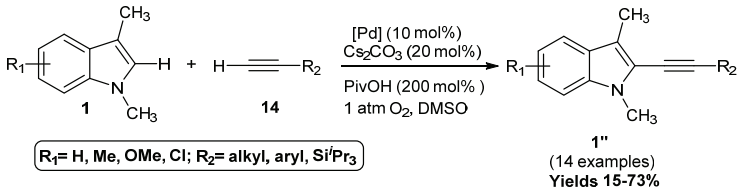
Further, $[RuCl_2(p\text{-cymene})]_2$ catalyzed C2-selective carbenoid functionalization of NH-indoles **1** by employing α-aryldiazoesters **13** as a

carbenoid source was explored by Chan et al. (2010). The reaction gives the corresponding 2-alkylated indoles **1'** up to 96% yields, the *ortho*-substituted aryl i.e., R_4 was ineffective and was also sensitive to the steric properties of the diazo esters. For instance, a reaction with the 1-naphthyl derivative of **13** gave merely a 22% yield of the product (Scheme 7).



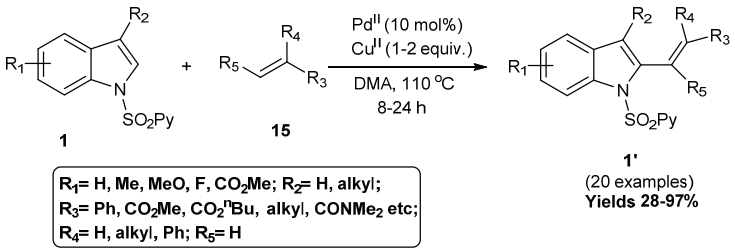
Scheme 7. Ru-catalyzed C2-selective functionalization of NH-indoles.

Yang et al. (2010) developed a direct oxidative Heck-Cassar-Sonogashira (HCS) type alkenylation of indoles giving 1,2,3-trisubstituted indoles **1"** *via* the reaction of 1,3-dimethylindole **1** with terminal alkynes **14** under an atmosphere of O_2 in the presence of a Pd^{II} catalyst and a buffer system composed of 20 mol% Cs_2CO_3 and 200 mol% pivalic acid (PivOH) in dimethyl sulfoxide (DMSO) (Scheme 8). This HCS-type reaction did not require indolyl halide or alkynyl halide pre-generation and only a catalytic amount of base is required. Furthermore, oxygen was used as the ultimate green terminal oxidant and the only benign side-product was water.



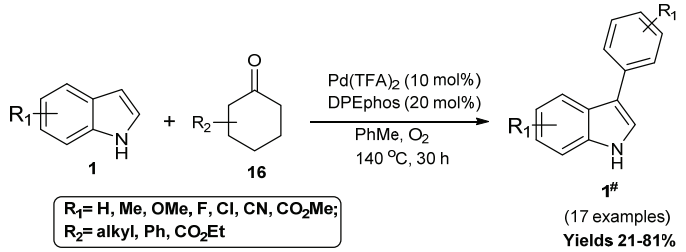
Scheme 8. Pd-catalyzed oxidative alkynylation of indoles with terminal alkynes.

Then, the C-H alkenylation of indoles using substituted alkenes **15** through Pd^{II}-catalyzed with complete C2 regiocontrol affording the corresponding products was reported by Rubia et al. (2010) (Scheme 9). The catalyst system in this reaction endures a wide variety of substituted alkenes **15**, which on reductive desulfonylation of the indoles **1** afforded the free NH indoles **1'** in good yields in DMA.



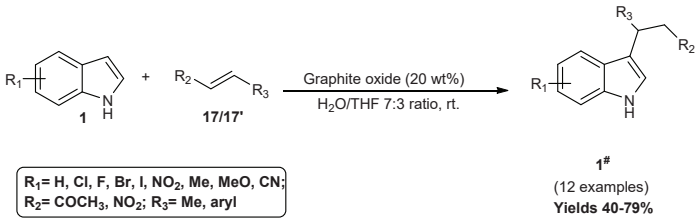
Scheme 9. Pd^{II}-catalyzed C-H functionalization of indoles.

A Pd-catalyzed regioselective direct arylation of indoles **1** with cyclohexanones **16** was developed (Chen et al., 2014) to synthesize 3-arylindoles **1**$^{\#}$ *via* an alkylation and dehydrogenation sequence using molecular oxygen as the hydrogen acceptor (Scheme 10). Here, (bis{2-diphenylphosphino}phenyl)ether was used as an effective phosphine ligand in toluene (PhMe).



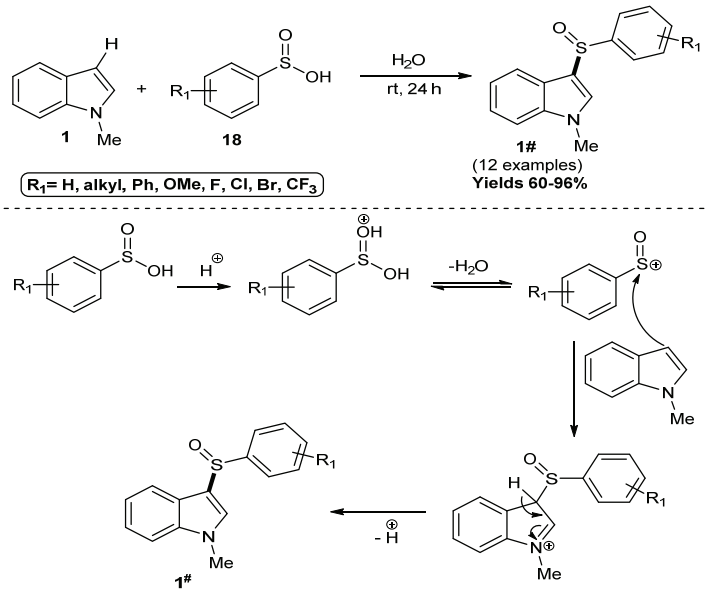
Scheme 10. Palladium-catalyzed direct arylation of indoles with cyclohexanones.

The Friedel-Crafts addition of indoles **1** to *α,β*-unsaturated ketones **17** and nitro styrenes **17'** affording various indole derivatives **1#** using graphite oxide as a catalyst in good to excellent yields was reported by Kumar and Rao. (2011). In this methodology, the heterogeneous graphite oxide could be quickly recovered and recycled up to five cycles without losing its activity (Scheme 11).



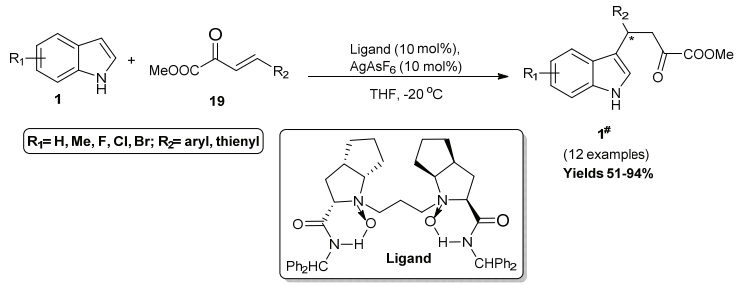
Scheme 11. Friedel-Crafts addition of indoles to *α,β*-unsaturated ketones and nitro styrenes.

A novel and highly efficient strategy for synthesizing 3-arylsulfinylindoles **1#** *via* electrophilic sulfenylation of indoles **1** with arylsulfinic acids **18** under metal- and additive-free conditions at room temperature in water was reported (Miao et al., 2015). According to the proposed mechanism, the reaction was proceeded by the protonation of arylsulfinic acid **18**, forming an intermediate under acidic conditions, which on dehydration released sulfinyl cation. Subsequently, the direct electrophilic substitution of an indole **1** at the C-3 position, with the loss of a proton, afforded the desired products **1#** (Scheme 12).



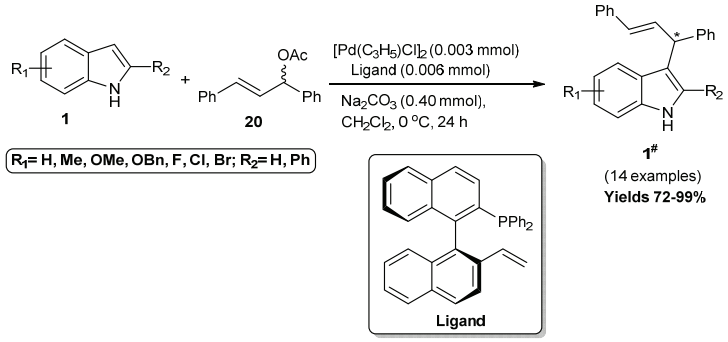
Scheme 12. Synthesis of 3-arylsulfinylindoles from indoles and arylsulfinic acids.

Liu et al. (2010) reported the enantioselective, asymmetric Friedel-Crafts alkylation of indoles **1** and *β,γ*-unsaturated *α*-ketoesters **19** for the synthesis of various indole esters **1**# in good to excellent yields in tetrahydrofuran (THF). This methodology employed an $AgAsF_6$-Ligand catalytic system applicable to heteroaromatic and fused ring substrates, giving the desired indole esters **1**# with the same enantioselectivity of 84% *ee* (Scheme 13).



Scheme 13. Asymmetric Friedel-Crafts alkylation of indoles and β,γ-unsaturated α-ketoesters.

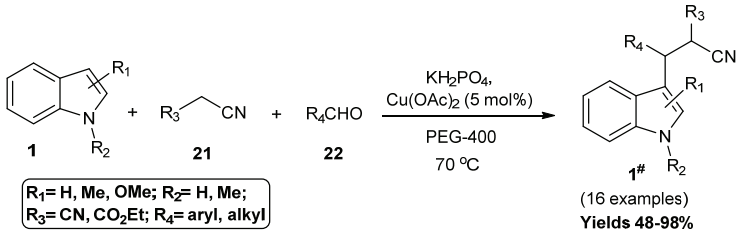
Pd-catalyzed enantioselective allylic alkylations of indoles through a reaction of indoles **1** with 1,3-diphenyl-2-propenyl acetate **20** was developed (Cao et al., 2011) in the presence of chiral binaphthyl-based terminal alkene-phosphine ligand affording the desired products **1**$^{\#}$ in high yields with good to excellent *ee*'s (Scheme 14).



Scheme 14. Pd-catalyzed enantioselective allylic alkylations of indoles.

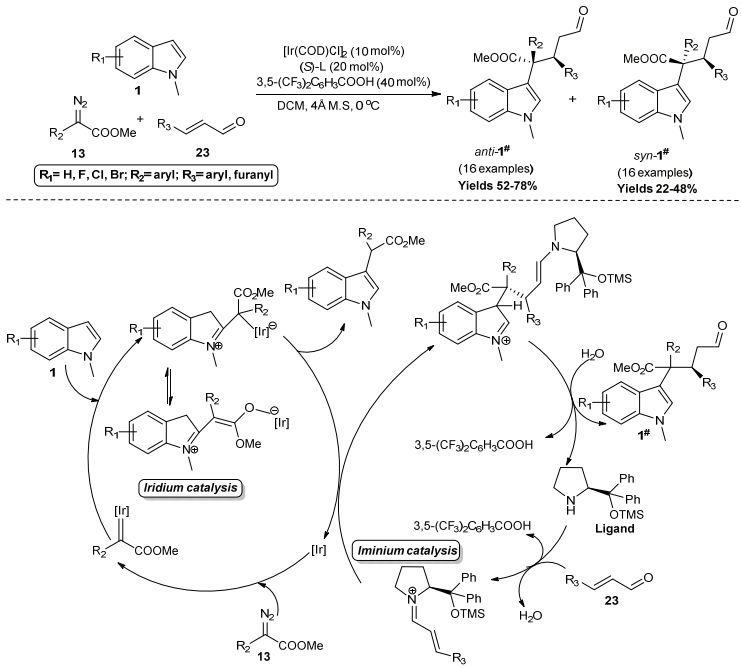
An efficient condensation reaction of indole **1**, aldehydes **22** and malononitrile **21** with polyethylene glycol (PEG) in the presence of KH_2PO_4 and $Cu(OAc)_2$ as the catalyst for the synthesis of 3-indole

derivatives **1**# was reported (Chandrasekhar et al., 2012). This multicomponent reaction (MCR) under ligand-free conditions occurred first through Knoevenagel condensation followed by a Michael addition of indole (Scheme 15).



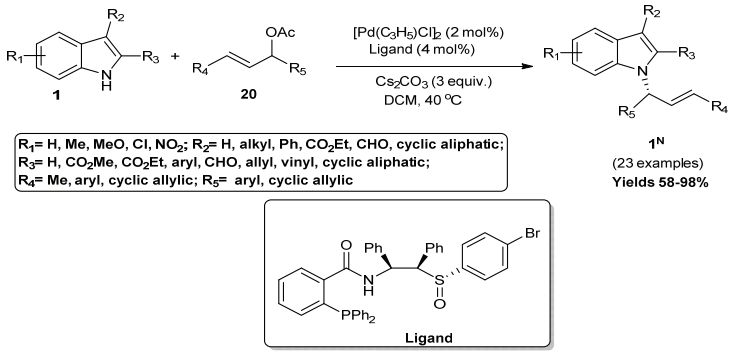
Scheme 15. Copper (II)-catalyzed synthesis of 3-indole derivatives.

Li et al. (2016) designed 3-substituted indole derivatives **1**# in good yields with moderate diastereoselectivity as well as excellent enantioselectivity (up to 98% *ee*) through the three-component reaction of aryldiazoacetates **13**, indoles **1** and enals **23** in the presence of an iridium complex/chiral amine co-catalyst (Scheme 16). According to the proposed mechanism, iridium catalyzed the diazo decomposition of **1** and **13**, generating a zwitterionic intermediate or enolate**.** In the case of iminium catalysis, the formation of an iminium ion was accelerated by the additive acid, which successfully trapped the zwitterionic intermediate to afford an enamine. Finally, the desired products **1**# were obtained by the acid-promoted hydrolysis of the enamine and by regenerating the chiral amine.



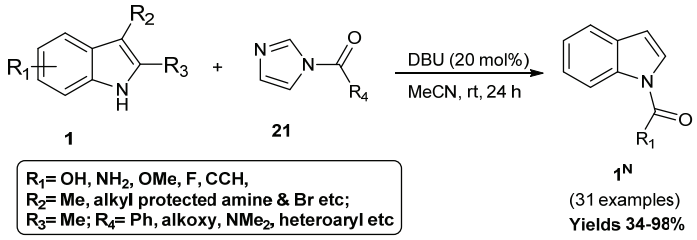
Scheme 16. Iridium/iminium co-catalyst synthesis of 3-substituted indole derivatives.

An efficient Pd/sulfoxide-phosphine complex-catalyzed direct asymmetric *N*-allylic alkylation of indoles has been developed (Chen et al., 2015) to synthesize various *N*-allylated indoles $\mathbf{1}^{\mathbf{N}}$ *via* reaction of indoles **1** and 1,3-disubstituted allyl acetate **20** in good yields with excellent enantioselectivities (Scheme 17).



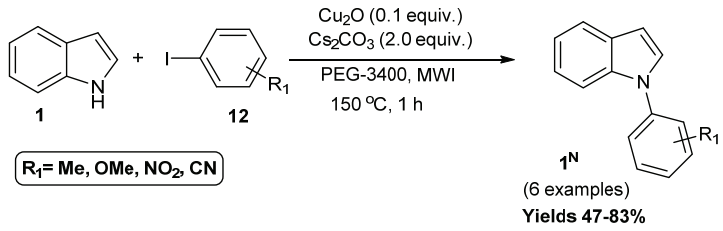
Scheme 17. Asymmetric *N*-allylic alkylation of indoles.

Heller et al., (2012) had reported the chemoselective *N*-functionalization of indoles *via* 1,8-diazabicyclo-[5.4.0] undec-7-ene (DBU) catalyzed reaction of indoles **1** with imidazole carbamates **21** as an acyl donor which afforded the desired products, i.e., *N*-acylated indoles $\mathbf{1^N}$ in excellent yields (Scheme 18).



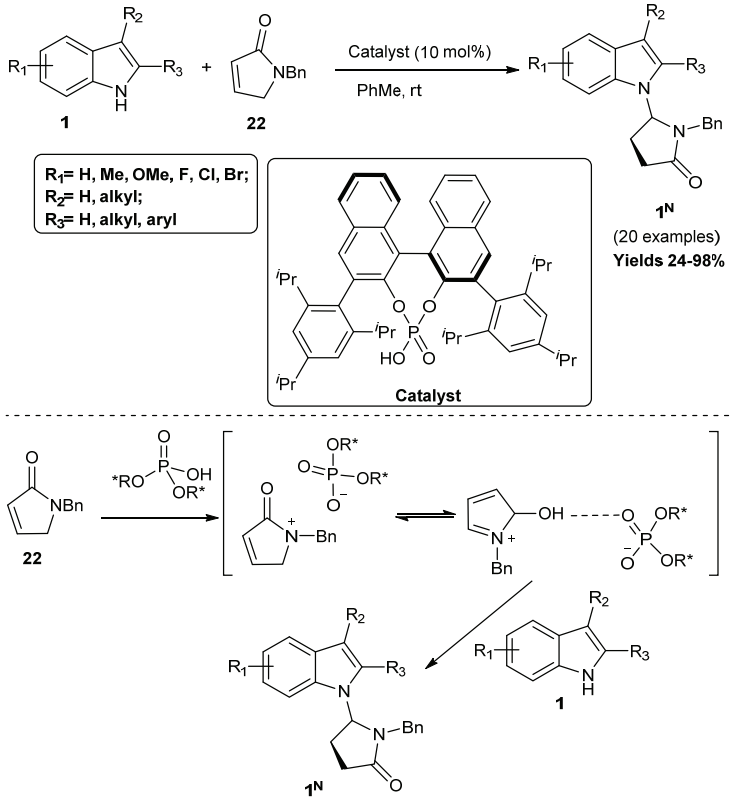
Scheme 18. Chemoselective *N*-functionalization of indoles.

Copper-catalyzed microwave-enhanced protocol for *N*-arylation of indoles *via* the reaction of indoles **1** with aryl halides **12** in the presence of high molecular weight poly(ethylene glycol) (PEG-3400) as a solvent which afforded *N*-arylindoles $\mathbf{1^N}$ was reported by Colacino et al. (2010) (Scheme 19).



Scheme 19. Copper-catalyzed microwave-enhanced synthesis of *N*-arylindoles.

Xie et al. (2011) reported a chiral Brønsted acid catalyzed enantioselective N-H functionalization of indoles with *α,β*-unsaturated *γ*-lactams **22 (**Scheme 18). In this methodology, deprotonation of chiral phosphoric acid by *α,β*-unsaturated *γ*-lactam **22** gives rise to a chiral conjugate base/*N*-acyliminium ion pair**.** The N-atom of indole **1** was activated to react with the cyclic *N*-acyliminium ion via the interaction the acidic N-H atom of the indole **1** with the conjugate base of the chiral Brønsted acid through hydrogen bonding, affording the desired *N*-functionalized indoles $\mathbf{1^N}$ in good yields (Scheme 20).



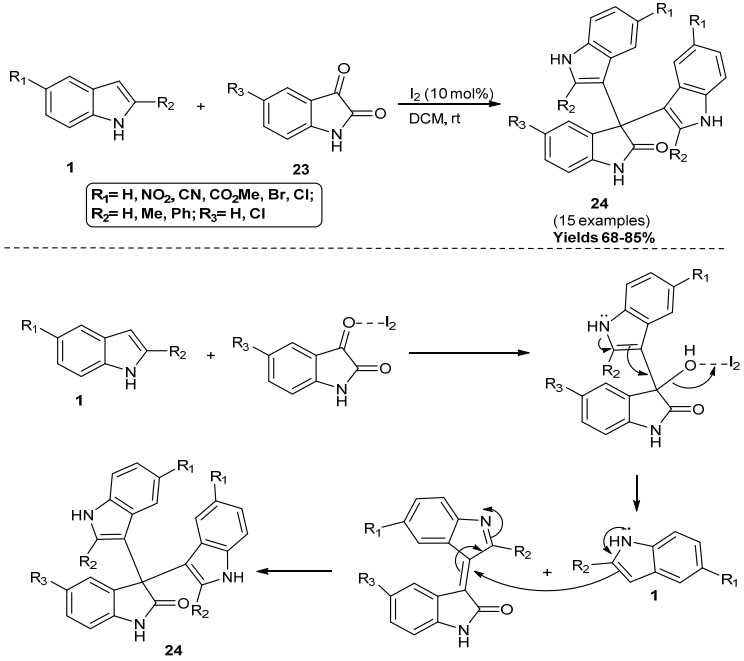
Scheme 20. Chiral Brønsted acid catalyzed enantioselective N-H functionalization of indoles.

4. Application of Indole in heterocyclic frameworks

4.1 Synthesis involving two-component reactions of Indole

Reddy et al. (2012) reported a facile synthesis of di(indolyl)indolin-2-ones **24** *via* condensation of isatin **23** with indoles **1** in the presence of the catalytic amount of molecular iodine under mild conditions. Mechanistically, the reaction proceeded by activating isatin **23** by molecular iodine. The

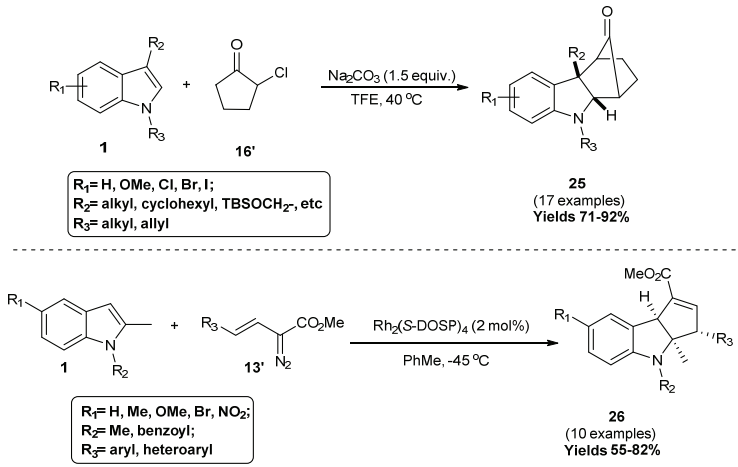
nucleophilic attack of indole **1** on the activated isatin led to the formation of an intermediate which on successive dehydration and the addition of another equivalent of indole **1** on a conjugated 3*H*-indol-3-ylidene afforded the desired di(indolyl)indolin-2-ones **24** (Scheme 21).



Scheme 21. Iodine-catalyzed condensation of isatin with indoles.

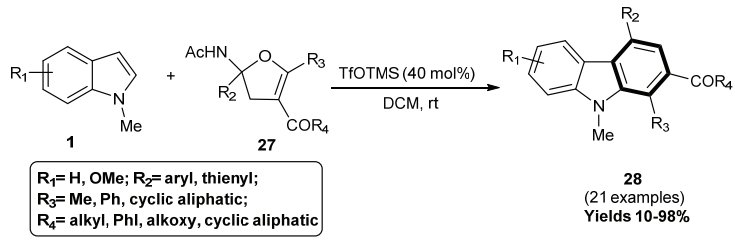
Li et al. (2014) developed a highly efficient and diastereoselective [3+2] dearomative annulation of 3-substituted indoles **1** with 2-chlorocyclopentanone **16'** affording the cyclohexa-fused indolines **25** in good to excellent yields in 2,2,2-trifluoroethanol (TFE) (Scheme 22). The reaction accelerated well in electron-rich indoles, whereas it appeared unreactive in indoles with the relatively strong electron-withdrawing group. This protocol provides easy access to highly functionalized

cyclohexa-fused indoline compounds, one of the common structures of many natural products. Lian and Davies (2010) also reported an efficient and enantioselective Rhodium-catalyzed [3+2] annulation of *N*-substituted indoles **1** with substituted methyl-vinyldiazoacetate **13'** leading to cyclopenta-fused indolines **26** which was proceeded by zwitterionic intermediates (Scheme 22).



Scheme 22. Annulation of 3-substituted indoles with *α*-haloketones and methyl-vinyldiazoacetate.

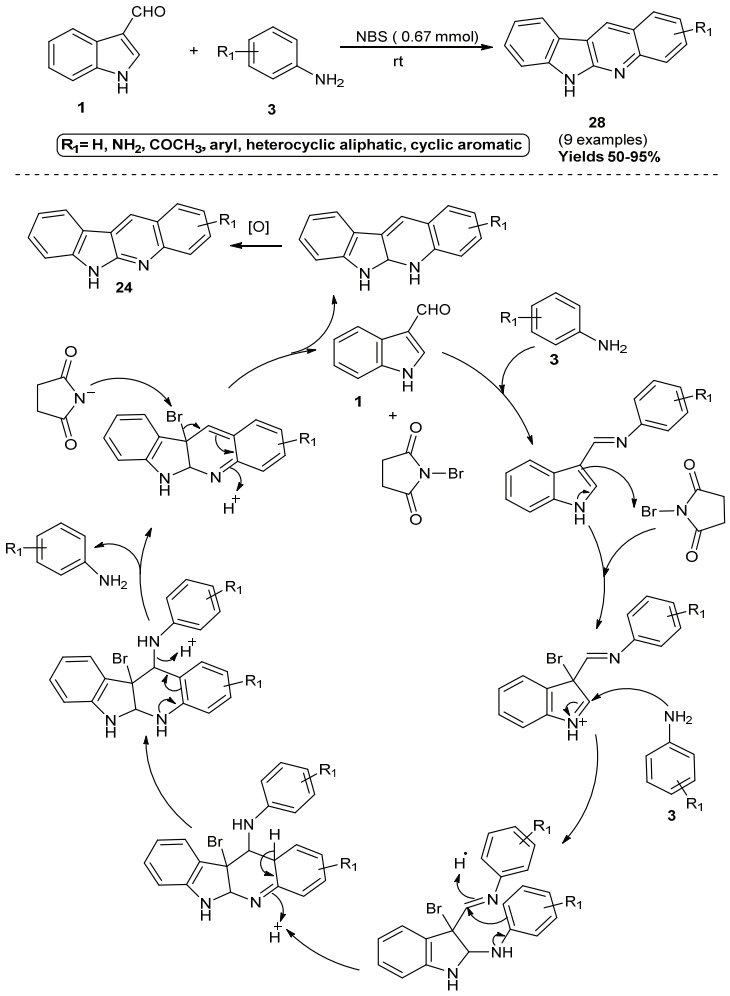
A convenient strategy for synthesizing carbazoles **28** *via* ring-opening annulation of indoles **1** with 2-amidodihydrofurans **27** in the presence of trimethylsilyl trifluoromethanesulfonate (TfOTMS) as a catalyst with a high degree of chemoselectivity and regioselectivity was developed (Zhao et al., 2015) (Scheme 37).



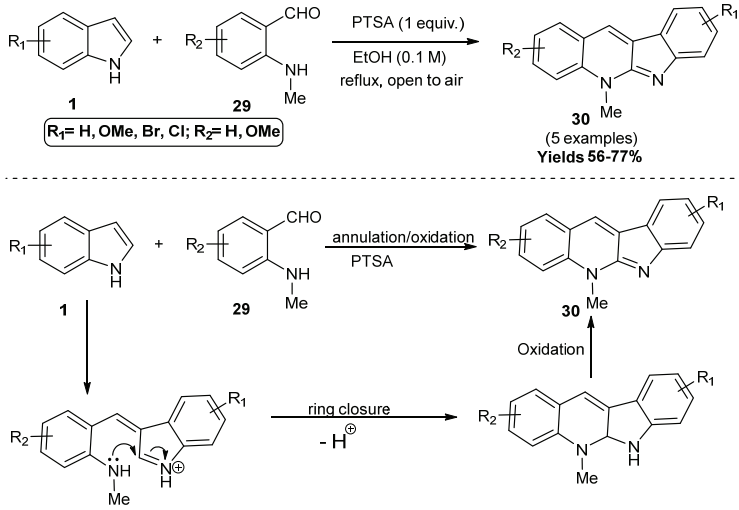
Scheme 23. Ring-opening annulation of indoles with 2-amidodihydrofurans.

Ghorbani-Vaghei and Malaekehpoor (2012) developed *N*-bromosuccinimide (NBS)-catalyzed synthesis of polycyclic indolo[2,3-*b*]quinoline derivatives **28** in good to high yields through the reaction of various aryl amines **3** with indole-3-carbaldehyde **1** at room temperature under mild conditions (Scheme 24). According to the proposed mechanism, *N*-bromosuccinimide released Br^+ *in situ*, an electrophilic species. Initially, NBS-catalyzed the formation of an imine and 3-bromo-indolinium cation as intermediates. The nucleophilic attack by a second mole of aniline **3** followed by intramolecular cyclization and oxidation afforded the desired indoloquinoline derivatives **28**.

The *p*-toluenesulfonic acid (PTSA)-promoted annulation/oxidation cascade reaction of indole **1** with *N*-methyl aminobenzaldehyde **29** was developed by Vecchione et al. (2011) to synthesize neocryptolepine **30**, a bioactive material with promising leads for new antimalarial agents (Scheme 25). Mechanistically, azafulvenium ion was formed by condensing *N*-methyl aminobenzaldehyde **29** with indole, followed by ring-closure, to form an intermediate. Finally, the desired neocryptolepine **30** was afforded by the oxidation of the intermediate.

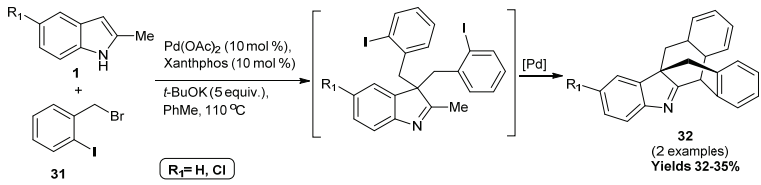


Scheme 24. NBS-catalyzed synthesis of polycyclic indolo[2,3-*b*]quinoline derivatives.



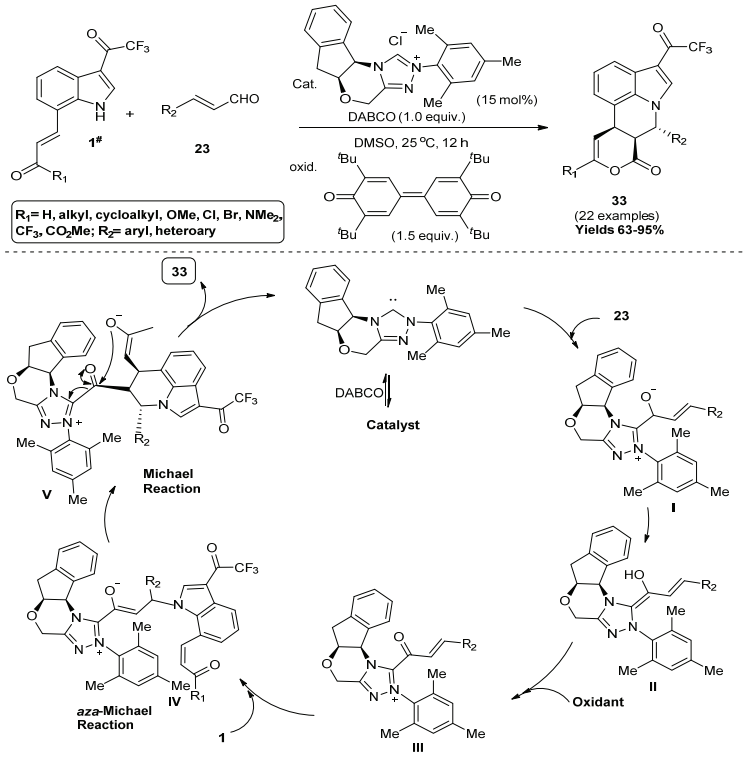
Scheme 25. Annulation/oxidation cascade reaction of Indole with *N*-methyl aminobenzaldehyde.

Abele et al. (2016) developed a novel palladium-catalyzed domino reaction of 2-methylindoles **1** with 2-iodobenzyl bromide **25** using the system of $Pd(OAc)_2$/Xantphos/*t*-BuOK/PhMe leading to an indole-fused tricyclo[7,3,1,0]trideca-2(7),3,5-triene ring (Scheme 26). The products **26a,b** were isolated using column chromatography in 35 and 32% yields. The low yields were attributable to polymerization during the reaction, according to the authors.



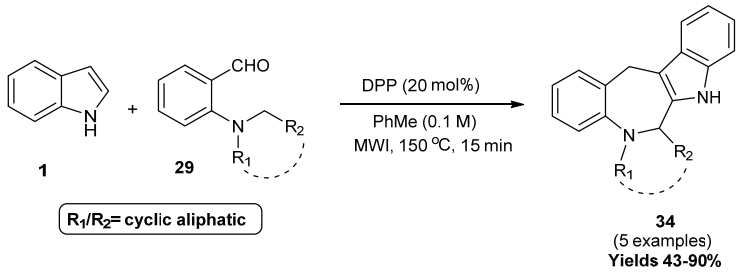
Scheme 26. Synthesis of an indole-fused tricyclo[7,3,1,0]trideca-2(7),3,5-triene ring.

Mukherjee et al. (2018) reported the enantioselective synthesis of pyrroloquinoline derivatives **33** under oxidative *N*-heterocyclic carbene (NHC) catalysis conditions. The catalytically generated chiral *α,β*-unsaturated acylazoliums with the indole derivatives **1** proceeded in an *aza*-Michael/Michael/lactonization sequence affording pyrroloquinoline derivatives **33** in good yields (Scheme 27). The studies were initiated in the carbene generated from the chiral aminoindanol-derived triazolium salt (catalyst) using 1,4-diazabicyclo[2.2.2]octane (DABCO) and the bisquinone as the oxidant. The proposed mechanism starts with the nucleophilic attack of NHC generated from the catalyst to the enal **23**, forming the tetrahedral intermediate (I), which generates the nucleophilic Breslow intermediate (II) on proton transfer. The intermediate II was further oxidized to the key *α,β*-unsaturated acyl azolium intermediate (III) in the presence of the bisquinone oxidant. Then, the nucleophilic attack of **1** to intermediate III *via* the N−H indole moiety provides the NHC-bound enolate intermediate **IV** through intramolecular Michael addition to the vinyl ketone moiety to give the enolate intermediate **V** bearing an NHC-azolium moiety. This intermediate **V** undergoes intramolecular acylation affording the pyrroloquinoline product **33** with the regeneration of the NHC catalyst.



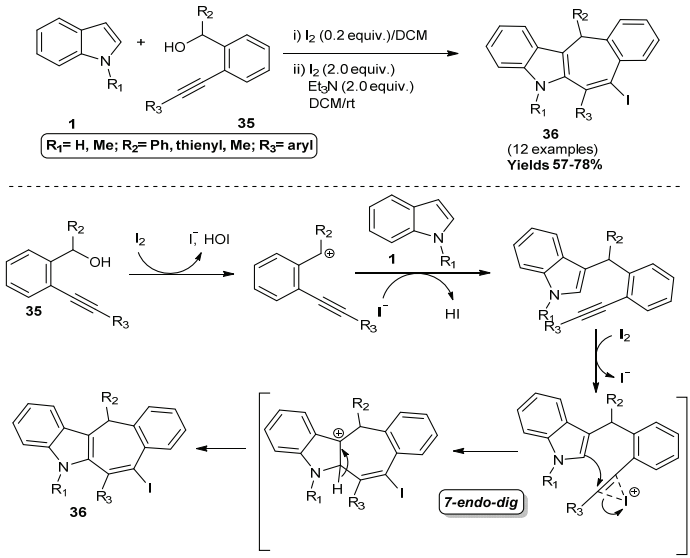
Scheme 27. Enantioselective synthesis of pyrroloquinoline derivatives.

An acid catalyzed, redox-neutral indole annulation reaction was developed (Haibach et al., 2011) to synthesize polycyclic azepinoindoles **34** by the reaction of aminobenzaldehydes **29** and indoles **1** with 20 mol% of diphenyl phosphate (DPP) in toluene under microwave irradiation (MWI) (Scheme 28). The reaction proceeded through a condensation/1,5-hydride shift/ring-closure sequence which afforded the desired products **34** in a single step with good to excellent yields.



Scheme 28 Acid catalyzed redox-neutral indole annulation cascade.

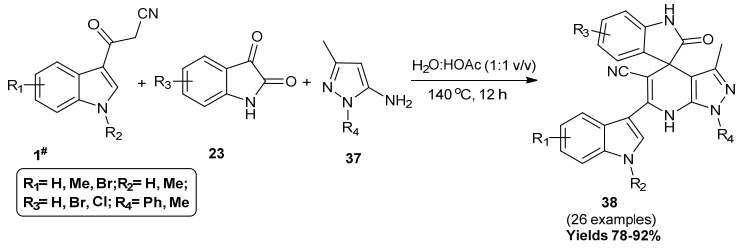
An environmentally-friendly and flexible approach for synthesizing tetracyclic heteroazulene derivatives **36**, a biologically and pharmaceutically important compound in the presence of molecular iodine, was reported by Sarkar et al. (2014). A sequential alkylation and alkenylation of indole **1** with *o*-alkynyl benzyl alcohol derivatives **35** was involved in this reaction, which afforded the desired product**s 36** in moderate to good yields (Scheme 29). The mechanism proceeds with iodine coordinating with the -OH group of **35** to generate carbocation, which reacts with indole **1** at the more nucleophilic C-3 center. An electrophilic iodonium species was formed by coordinating the alkyne unit through the iodine molecule, thus, activating the triple bond toward nucleophilic ring-closure of the indole **1** at the C-2 carbon through electrophilic 7-*endo-dig* iodocyclization, forming an intermediate. Subsequently, the desired heteroazulene ring **36** was afforded by the aromatization of the intermediate *via* the elimination of H^+.



Scheme 29. Synthesis of tetracyclic heteroazulene derivatives.

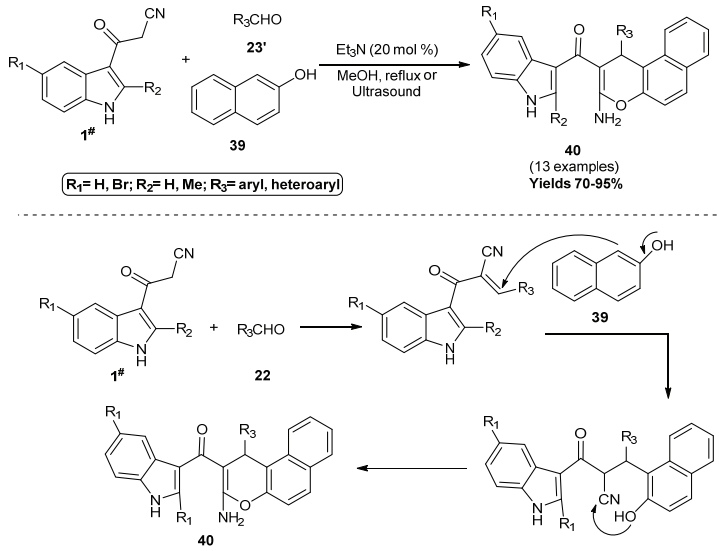
4.2 Synthesis involving three-component reactions of indole

An atom-economical and efficient approach for the synthesis of a series of polysubstituted 6′-(1*H*-indol-3-yl)-1′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-2-one derivatives **38** *via* a one-pot three-component reaction of 3-cyanoacetyl indoles **1**[#], isatins **23** and 1*H*-pyrazol-5-amines **37** in high yields was developed by Chen et al. (2010) (Scheme 30).



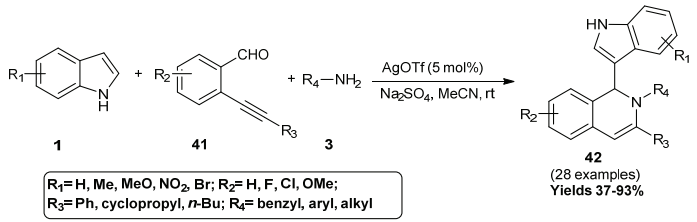
Scheme 30. Synthesis of polysubstituted dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-2-one.

A regioselective triethyl amine (Et_3N) catalyzed condensation of 3-cyanoacetylindoles **1**, *β*-naphthol **39** and aryl aldehydes **23'** in methanol under ultrasonic irradiation was reported (Roghayeh et al., 2012) for the synthesis of novel-fused 1*H*-benzo[*f*]chromen-indole derivatives **40** in good to high yields. The antibacterial activity of the products was examined, in which most of the compounds exhibited excellent antibacterial activity against *Micrococcus luteus*. Mechanistically, Knoevenagel condensation of 3-cyanoacetylindoles **1** and aryl aldehydes **23'** generated an enone intermediate. Then, a Michael-type nucleophilic addition of a *β*-naphthol ring to the enone intermediate with subsequent cyclodehydration afforded the desired compounds **40** (Scheme 31).



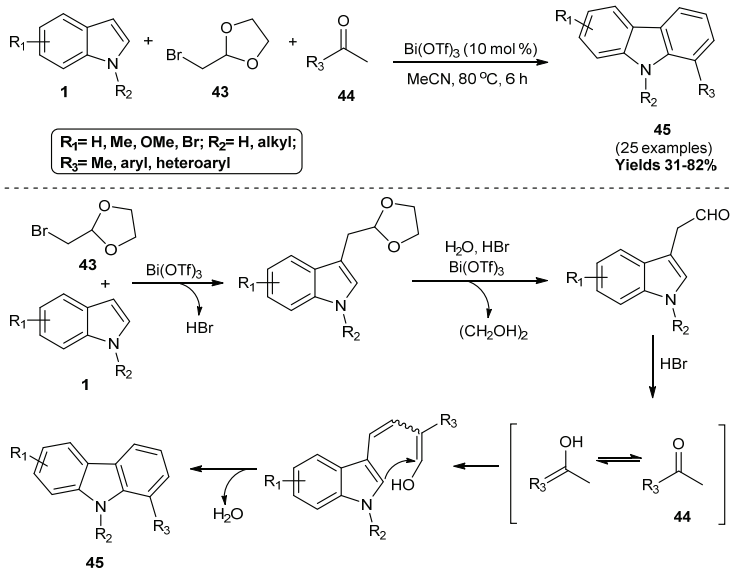
Scheme 31. Triethylamine catalyzed synthesis of novel-fused 1*H*-benzo[*f*]chromen-indole.

A silver-catalyzed three-component tandem reaction of indoles **1**, 2-alkynylbenzaldehydes **41** and amines **3** for the synthesis of 1-(1*H*-indol-3-yl)-1,2-dihydroisoquinolines **42** in good yields was reported by Yu and Wu. (2010). This methodology was effective in different indoles bearing electron-rich and electron-poor groups attached to the aromatic ring (Scheme 32).



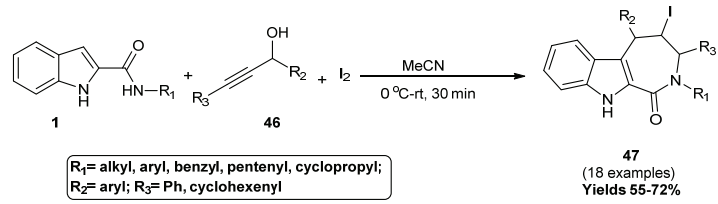
Scheme 32. Silver-catalyzed synthesis of 1,2-dihydroisoquinolines.

Gu et al. (2018) reported a straightforward approach for synthesizing carbazole derivatives **45** by three-component reaction of indoles **1**, α-bromoacetaldehyde acetals **43** and ketones **44** in the presence of bismuth (III) triflate as the catalyst (Scheme 33). Tryptaldehyde-type acetal was generated by an acid catalyzed Friedel-Crafts alkylation of **1** with **43** and this acetal underwent deacetalization to give a tryptaldehyde derivative. Then, the enol form of **44** trapped the tryptaldehyde derivative to give a C3-vinylndole derivative which finally formed **45** through an intramolecular condensation reaction.



Scheme 33. Three-component reaction for the synthesis of carbazole derivatives.

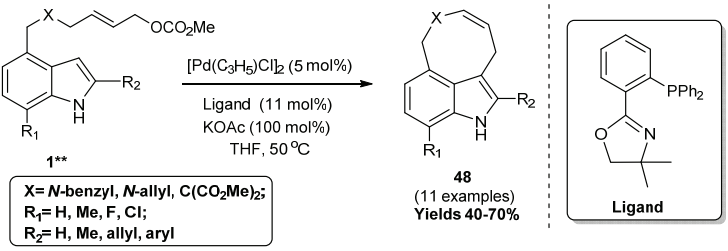
Sharma et al. (2011) described an efficient approach for synthesizing indoloazepinones **47** through a three-component reaction of indole-2-carboxamides **1***1,3-disubstituted propargyl alcohols **46** and I_2 (5 equiv.) **(**Scheme 34). This methodology involved a C-H functionalization/alkyne activation/intramolecular hydroamidation/deprotonation domino sequence. The regioselective electrophilic 7-*endo*-dig iodo-cyclization during the intramolecular hydroamidation which afforded the desired seven-membered azepinone **47** ring annulated to the indole was the prominent feature of this sequence.



Scheme 34. Synthesis of indoloazepinone from indole-2-carboxamides, propargyl alcohols, and I_2.

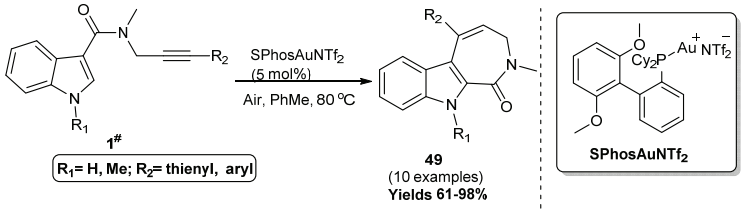
4.3. Miscellaneous reaction of Indoles

An indole-based peri-annulated compound developed (Xu et al., 2013) through a palladium-catalyzed Friedel-Crafts type allylic alkylation reaction of indole **1**** fused through C4-C3 was explored in THF as the solvent. This protocol afforded the indole-based nine-membered ring products **48** in 40–70% yields (Scheme 35).



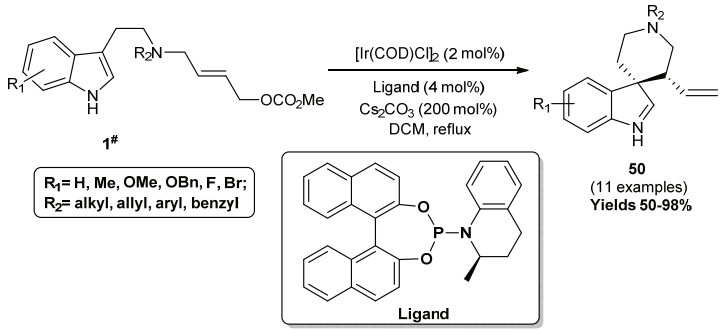
Scheme 35. Palladium-catalyzed synthesis of indole-based peri-annulated compounds.

The conversion of alkyne-substituted indole-3-carboxamides **1** to azepino-[3,4-*b*]indol-1-ones **49** through 3,2-shift of an acylamino substituent on indole was reported using $SPhosAuNTf_2$ (SPhos=2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl) as a catalyst by Hashmi et al. (2012) (Scheme 36).



Scheme 36. Gold catalyzed synthesis of azepino- [3,4-*b*]indol-1-ones.

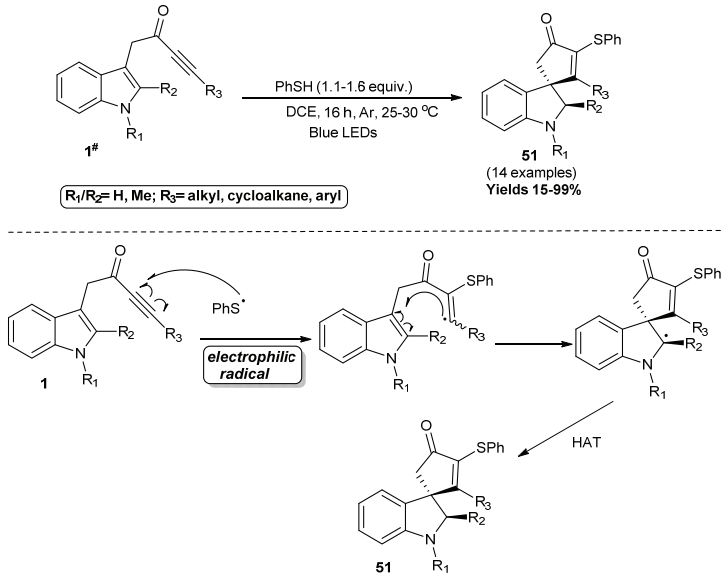
Wu, He, et al. (2010) reported the synthesis of enantioenriched spiroindolenine derivatives **50** *via* Ir-catalyzed intramolecular C-3 allylic alkylation of indoles **1**# in the presence of 2-methyl-1,2,3,4-tetrahydroquinoline-derived phosphoramidite ligand (*R,Ra*)-L with 92–98% yields (Scheme 37).



Scheme 37. Ir-catalyzed intramolecular C-3 allylic alkylation of indoles.

Eong et al. (2020) reported a mild and straightforward synthetic protocol of visible-light-induced intramolecular charge transfer in the radical spirocyclization of indole-tethered ynone **1**# in dichloroethane (DCE) (Scheme 38). This protocol afforded sulfur-containing spirocycles **51** in high yields, in which neither transition metal catalysts nor photocatalysts are required. Indole-tethered ynones **1** react with a thiyl radical from

thiophenol (PhSH) through regioselective addition to the alkyne group followed by cyclization at the 3-position of indole to generate a spirocyclic radical intermediate. The radical intermediate, through hydrogen atom transfer (HAT), afforded the spirocyclic indoline **51**.



Scheme 38. Synthetic of spirocyclic indoline from indole-tethered ynone.

5. Conclusion

The versatility of indole as a substrate for the synthesis of various *N*-heterocyclics are summarized. Multicomponent reactions of indoles with many critical substrates have synthesized a wide variety of natural and synthetic indole derivatives. Many indoles annulation cascade reactions have also successfully synthesized heterocycles of different sizes and ring systems using various ligands and catalysts.

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CHAPTER 7

2-AMINOBENZOPHENONES

1. Introduction

2-Aminobenzophenones (Figure 1) have become a fundamental class of compounds in organic chemistry. These compounds have shown a desirable pharmacological use as antimitotic, antitumor and antiproliferative agents as well as skeletal muscle relaxants (Liou et al., 2002; Singh et al., 2015). They are an interesting precursor for the synthesis of many heterocycles, such as acridones, quinolines, quinazolines, quinolinones, quinoxalinones, fluorenones, benzisoxazoles, indazoles, indoles, 2-quinazolinones, benzothiophenes, diaryldibenzodiazocines and benzodiazepines (Dabiri et al., 2010; Reddy et al., 2017). 2-Aminobenzophenones have drawn much attention due to their application in various pharmaceutical activities in medical chemistry (Liou et al., 2006), and in materials chemistry (Castellano et al., 2014). Consequently, vast demands for diverse 2-aminobenzophenones in many fields have promoted the development of practical and diversified synthetic methods (Xie et al., 2012; and Mizuno and Yamano, 2005).

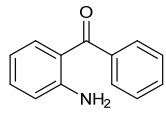

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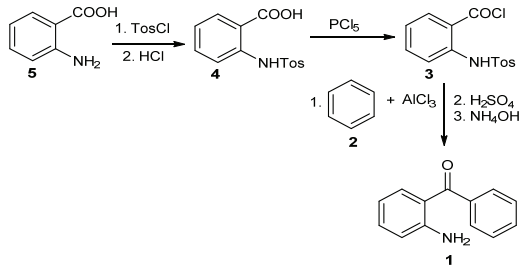
Figure 1. Structure of 2-aminobenzophenone.

2. Synthesis of 2-Aminobenzophenone

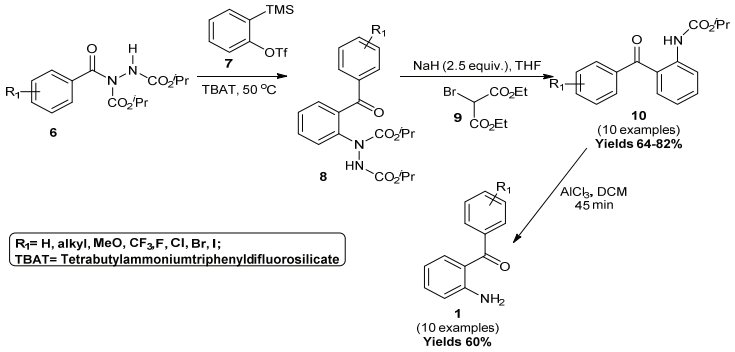
Graebe and Ullmann (1894) reported the synthesis of 2-aminobenzophenone by Hofmann rearrangement of *o*-benzoylbenzoic acid amide with sodium hypobromite formed from bromine in an alkaline medium. A standard process for the synthesis of 2-aminobenzophenone **1** was developed (Scheifele et al., 1952) with an overall yield of 54% from anthranilic acid **5**, which, after protecting the amino group with tosyl chloride reacted with phosphorus pentachloride to form the acid chloride **3**. The acid chloride reacts with benzene **2** in a Friedel-Crafts acylation to form the protected benzophenone (Scheme 1). The tosyl group was treated with strong acids such as concentrated sulfuric acid or hydrochloric acid and the amino function was released with ammonium hydroxide. However, this process suffered from poor substrate scope when utilizing electron-poor arenes.



Scheme 1. Synthesis of 2-aminobenzophenone.

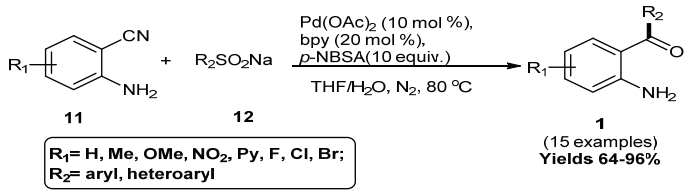
Ahmed et al. (2019) reported the conversion of acyl hydrazides **6** into 2-aminobenzophenones **1** *via* a two-step process, involving a molecular rearrangement of acyl hydrazides **6** with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **7** followed by a one-pot addition-elimination procedure using diethyl bromomalonate **9** as an alkylating agent. The

assembly of the scaffold was tolerant of a wide variety of functional groups with good to excellent yields (Scheme 2). The carbamate group on the product may be removed by treating the protected 2-aminobenzophenones **10** with a Lewis acid, $AlCl_3$ in dichloromethane, which afforded highly valuable 2-aminobenzophenones **1**. This reaction proved to be tolerant of different electronic environments, having no significant effect on the yield.



Scheme 2. Synthesis of 2-aminobenzophenone from acyl hydrazides.

An efficient protocol for synthesizing 2-aminobenzophenone **1** *via* a palladium-catalyzed direct addition of sodium arylsulfinates **12** to unprotected 2-aminobenzonitriles using 2,2'-bipyridine (bpy) and *p*-nitrobenzene-sulfonic acid (*p*-NBSA) as an additive was reported by Chen et al. (2014). This method represents a convenient and practical strategy for synthesizing 2-aminobenzophenones (Scheme 3).

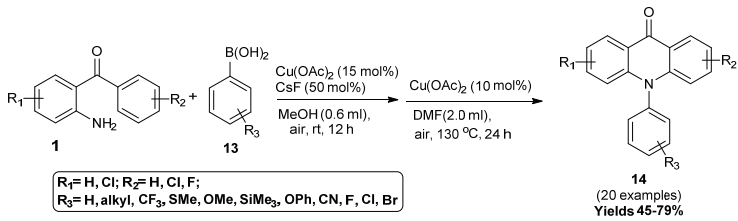


Scheme 3. Synthesis of 2-aminobenzophenones from 2-aminobenzonitriles.

3. Application of 2-Aminobenzophenone in heterocyclic chemistry

3.1 Synthesis of Acridone derivatives

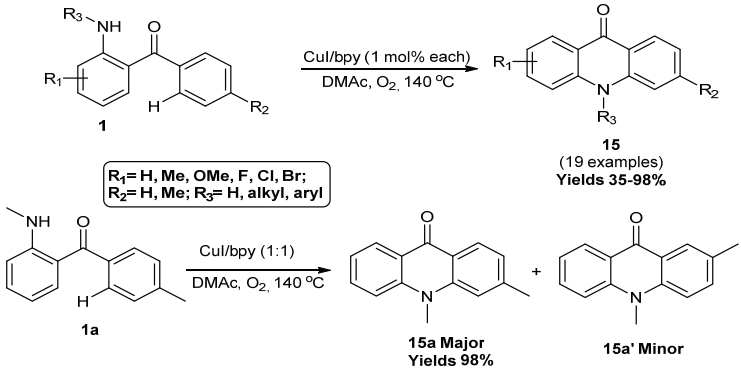
He et al. (2019) reported a one-pot method for the synthesis of *N*-aryl acridone **14** from 2-aminobenzophenones **1** and aryl boronic acids **13** under the catalysis of copper/air *via* sequential oxidative Chan-Evans-Lam (CEL) C-N cross-couplings and the following oxidative cross-dehydrogenative coupling (CDC) of C-N bonds (Scheme 4).



Scheme 4. Synthesis of *N*-aryl acridone.

A one-pot CuI/bpy-catalyzed intramolecular oxidative C-H bond functionalization and C-N coupling of 2-aminobenzophenones **1** in dimethylacetamide (DMAc) was developed (Huang et al., 2013) for the synthesis of 6-membered acridone **15** derivatives in good to excellent yields. 2-Aminobenzophenone **1** having a methyl substitution at the *para*

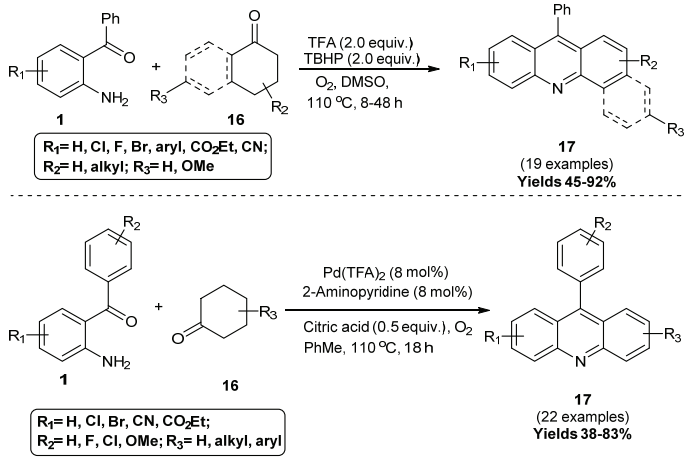
position of the phenyl ring gives two regio-isomers in a 5:2 ratio in a combined yield of 98% (Scheme 5). The primary product has exhibited the expected acridone structure **15a** with the methyl substituent *para* to the keto group, whereas the minor acridone product **15a'** has the methyl substituent *meta* to the keto and *para* to the amino group. The minor isomer in the reaction appeared to have a structure with the substituents on the phenyl ring undergoing a 1,2-shift toward the keto group compared to the structure of the major product.



Scheme 5. CuI/bpy-catalyzed synthesis of acridone from 2-aminobenzophenones.

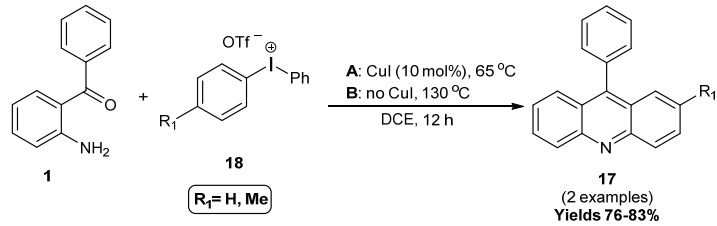
A metal-free method for synthesizing acridine derivatives **17** from cyclohexanones **16** and 2-aminobenzophenone **1** using the combination of triflouroacetic acid (TFA), *tert*-butyl hydroperoxide (TBHP), DMSO and O_2 *via* annulation/aerobic dehydrogenation was explored by Senadi et al. (2016) (Scheme 6). Further, another protocol was described to synthesize acridines **17** from cyclohexanones **16** and 2-aminobenzophenone **1** *via* oxidative annulation (Mu et al., 2017). The reaction was performed in the presence of $Pd(TFA)_2$ (8 mol%), 2-aminopyridine (8 mol%) and citric acid (0.5 equiv.) in toluene at 110 °C in an oxygen atmosphere affording a 43-

83% product yield within 18 hours (Scheme 6). However, cyclohexanones **16** with the 4-position bearing a sterically hindered group such as a *tert*-butyl and phenyl group reacted with **1** to give acridines with decreased yields, indicating the steric factor. The use of molecular oxygen as the sole oxidant which produces water as the only byproduct makes this protocol attractive for industrial prospects from the point of view of green and sustainable chemistry.



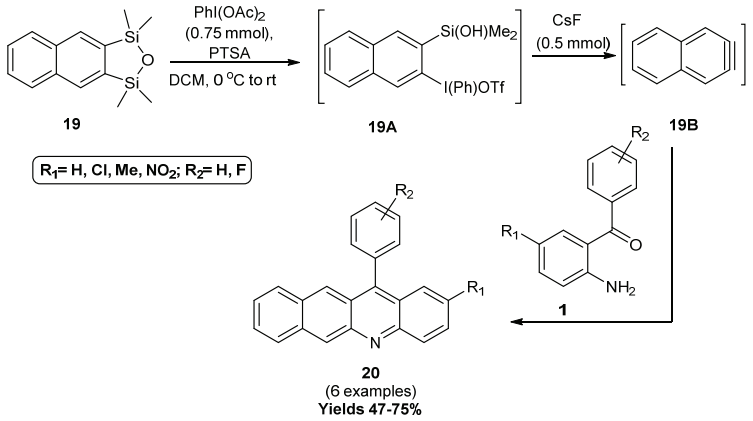
Scheme 6. Synthesis of acridines from cyclohexanones and 2-aminobenzophenones.

A modular method for synthesizing acridines **17** from 2-aminobenzophenone **1** and diaryliodonium salts **18** was demonstrated by Pang et al. (2015). The reactions in DCE proceeded smoothly under Cu-catalyzed (condition A) or metal-free reaction conditions at an elevated temperature (condition B) through a tandem arylation/Friedel-Crafts reaction (Scheme 7).



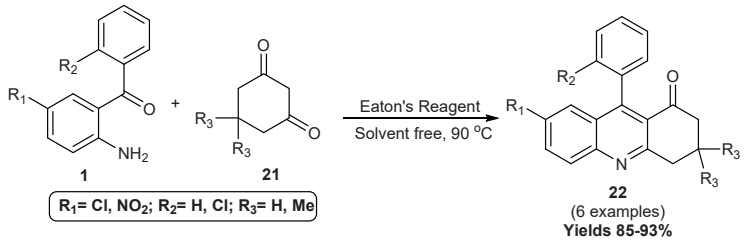
Scheme 7. Synthesis of acridine from 2-aminobenzophenone and diaryliodonium salts.

Zhang et al. (2014) reported the synthesis of benzo[*b*]acridine derivatives **20** through nucleophilic additions and aromatization reactions of naphthyne **19B** generated *in situ* from the 2,3-naphthoxadisilole arynes **19** with 2-aminobenzophenone **1** in good yields at room temperature using $PhI(OAc)_2$ and PTSA. These compounds have shown their potential application as strong deep-blue or green emitters for OLED because of their high fluorescence quantum yields along with good thermal stability (Scheme 8).



Scheme 8. Synthesis of benzo[*b*]acridines from 2-aminobenzophenones.

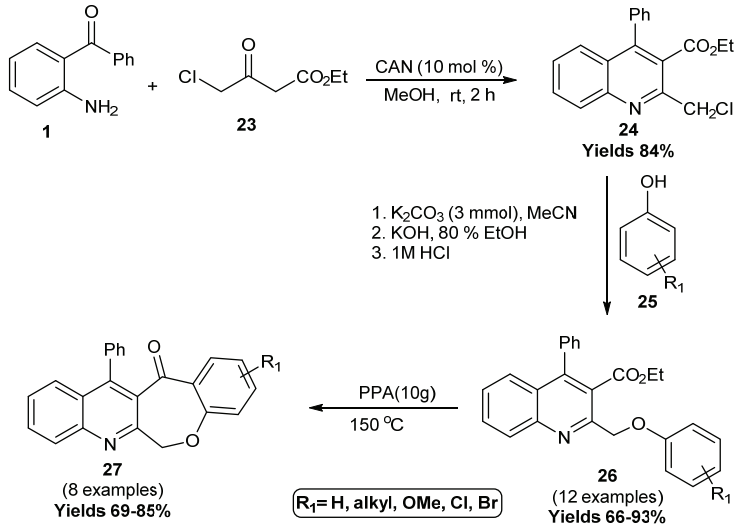
Satheeshkumar et al. (2015) developed a method for the synthesis of 3,4-dihydroacridin-1(2*H*)-one **22** *via* a one-pot Friedländer reaction of 2-aminobenzophenones **1** with 1,3-cyclic diketones **21** in the presence of freshly prepared Eaton's reagent (phosphorus pentoxide–methanesulfonic acid) without solvent (Scheme 7).



Scheme 9. Synthesis of 3,4-dihydroacridin-1(2*H*)-one.

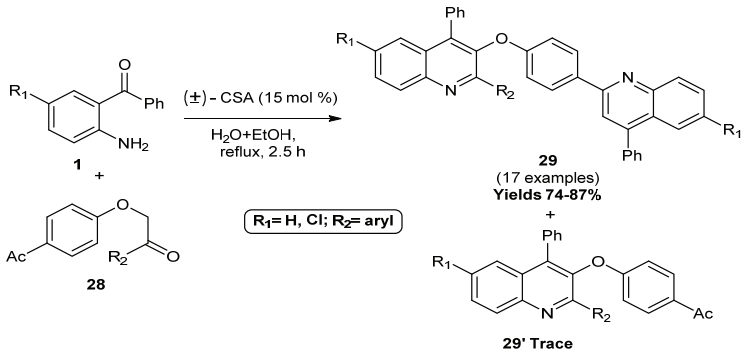
3.2 Synthesis of Quinoline derivatives

Gao et al. (2012) developed a strategy involving a three-step route for the synthesis of tetracyclic-fused quinoline systems, 12-phenylbenzo[6,7]oxepino[3,4-*b*]quinolin-13(6*H*)-one **27** *via* the intramolecular Friedel-Crafts acylation reaction of 2-(phenoxymethyl)-4-phenylquinoline-3-carboxylic acids **26** by the treatment with polyphosphoric acid (PPA). The required starting compound **24** was first obtained by a Friedländer reaction of 2-aminobenzophenone **1** with 4-chloroethylacetoacetate **23** using CAN (cerium ammonium nitrate) as a catalyst. The substrates, 2-(phenoxymethyl)-4-phenylquinoline-3-carboxylic acid **26** were then prepared through a one-pot reaction of ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate **24** and substituted phenols **25** (Scheme 10).



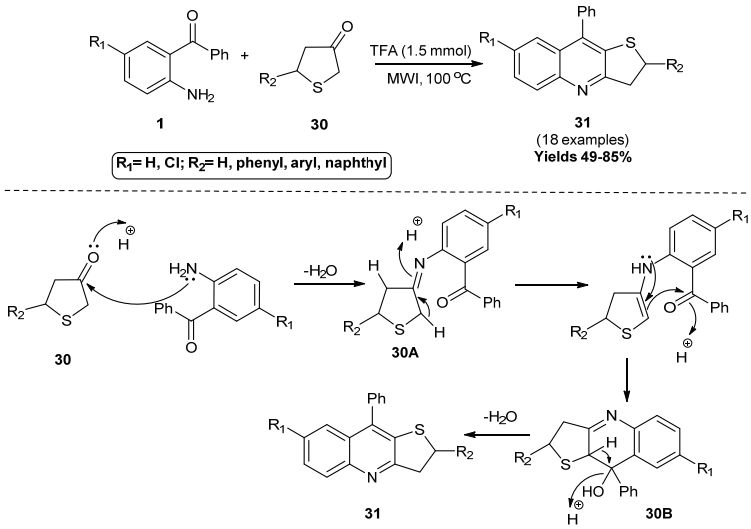
Scheme 10. Synthesis of oxepino[3,4-*b*]quinolin-(6*H*)-one.

The synthesis of a series of phenoxy-linked bisquinoline derivatives **29** from the Friedländer annulation of 2-(4-acetylphenoxy)-1-aryl-1-ethanones **28** with 2-aminobenzophenone **1** was reported by Paul et al. (2012). The reaction was catalyzed by (±)-camphor-10-sulfonic acid (CSA) giving good yields of the products and the monoquinolines **29'** were also obtained in trace amounts (Scheme 11). The advantages of this protocol include the simple experimental procedure and good yields, starting from an inexpensive and water-soluble catalyst.



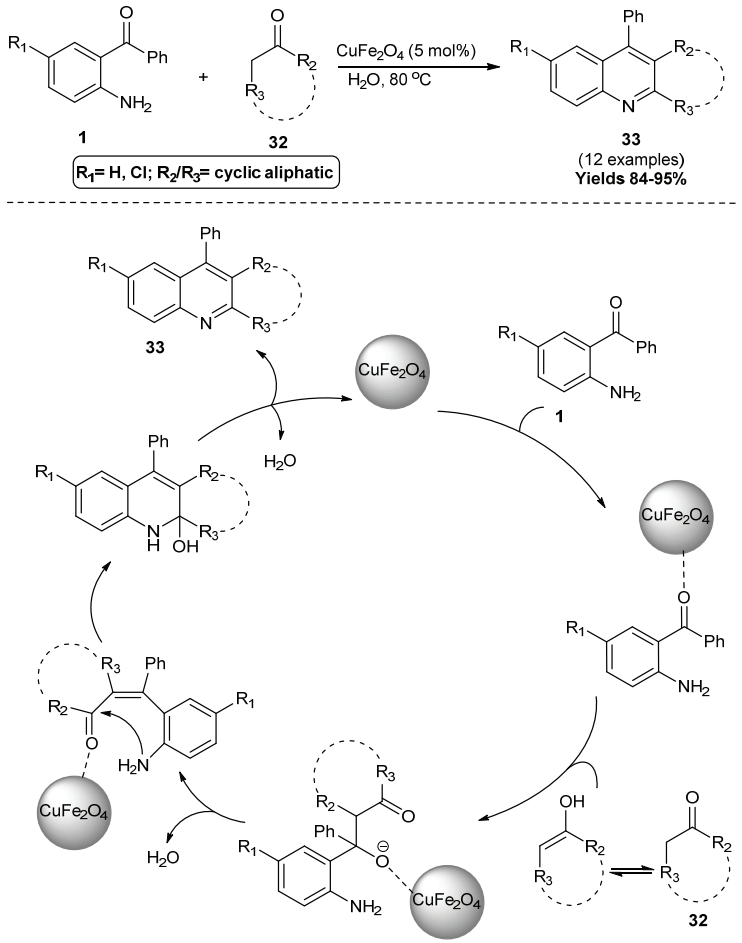
Scheme 11. Synthesis of phenoxy-linked bisquinoline derivatives.

A series of 2,9-diaryl-2,3-dihydrothieno[3,2-*b*]quinolines **31** have been synthesized regio-selectively by Balamurugan et al. (2010) *via* a Friedländer annulation of 5-aryldihydro-3(2*H*)-thiophenones **30** and 2-aminobenzophenones **1** in the presence of trifluoroacetic acid under microwave irradiation giving good yields at 100 °C (Scheme 12). The products were screened for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). According to the proposed mechanism, the condensation of 5-aryldihydro-3(2*H*)-thiophenones **30** and 2-aminobenzophenones **1** formed an imine **30A** which tautomerizes to furnish the enamine **30B**, and the subsequent annulation afforded the desired product **31**.



Scheme 12. Synthesis of 2,9-diaryl-2,3-dihydrothieno[3,2-*b*]quinolines.

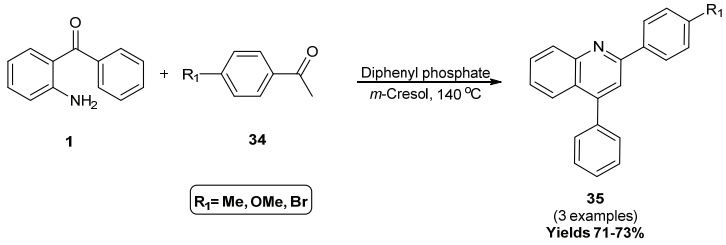
The greener approach for synthesizing quinolines **33** *via* the reaction of 2-aminobenzophenone **1** with *α*-methylene ketones **32** using magnetically separable, green and reusable $CuFe_2O_4$ nanoparticles (NPs) was developed (Baghbanian and Farhang, 2014). The catalyst was prepared by the thermal decomposition of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in water along with sodium hydroxide. The corresponding substituted quinolines **33** were obtained in excellent yields within short reaction times. A possible mechanism of this reaction was proposed, as shown in (Scheme 13). The carbonyl groups of 2-aminobenzophenone **1** and *α*-methylene ketones **32** were activated by $CuFe_2O_4$ NPs followed by Aldol condensation with the formation of an intermediate giving the desired quinoline derivatives **33**.



Scheme 13. The reaction of 2-aminobenzophenone with α-methylene ketones.

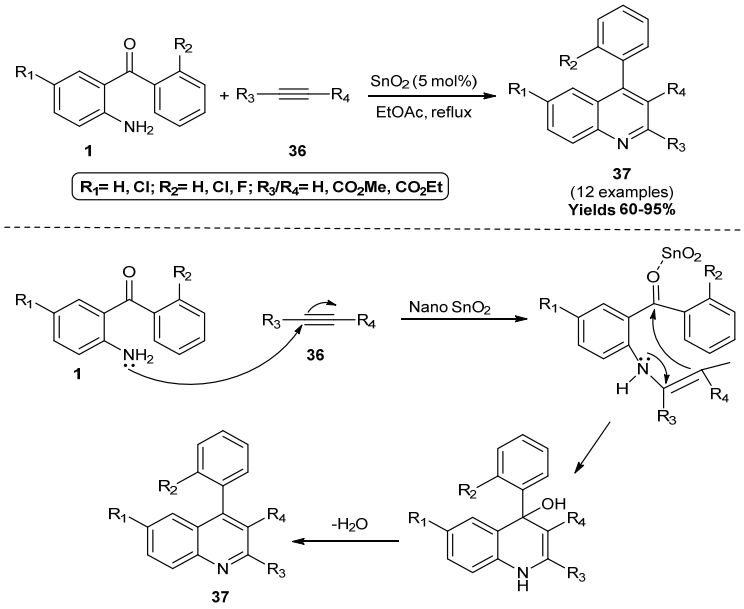
Dahule et al. (2015) synthesized a series of blue light-emitting 2,4-diphenylquinoline **35** through the Friedländer condensation of 2-aminobenzophenone **1** and corresponding acetophenone **34** (Scheme 14). The three synthesized polymeric compounds demonstrate a bright emission in the blue region in the solid-state's 405–450 nm wavelength

range. The attachment of methyl, methoxy and bromine substituents to the diphenyl quinoline ring in these phosphors resulted in the tuning of the color of the phosphorescence.



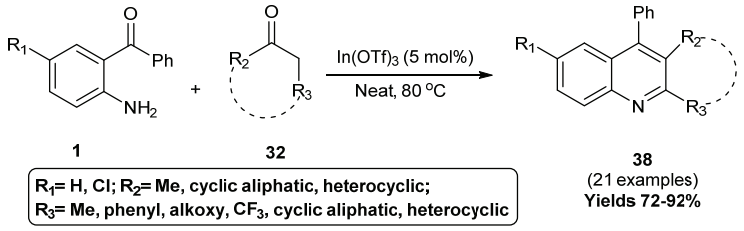
Scheme 14. Synthesis of organic phosphors (2,4-diphenylquinoline).

A methodology for synthesizing quinoline derivatives **37** was developed (Qandalee et al., 2013), giving high yields *via* the two-component reaction of 2-aminobenzophenones **1** with acetylenic mono or diesters **36** under mild conditions in the presence of the nanoparticle SnO_2 as the catalyst in ethyl acetate (EtOAc). Mechanistically, the acetylenic ester attack by nucleophilic amine leads to forming an intermediate on the surface of nano SnO_2, which can act as a Lewis acid to increase the electrophilicity of the carbonyl group of 2-aminobenzophenone **1**. A product **37** was formed by losing one molecule of water under reflux conditions (Scheme 15).



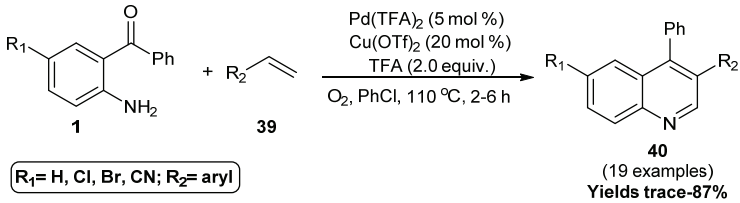
Scheme 15. Synthesis of 4-arylquinoline derivatives.

Tanwar et al. (2015) reported the synthesis of functionalized quinolines **38** *via* In(OTf) $_3$-catalyzed Friedländer reaction of substituted 2-aminobenzophenone **1** with ketones **32** containing an active methylene group under solvent-free conditions (Scheme 16).



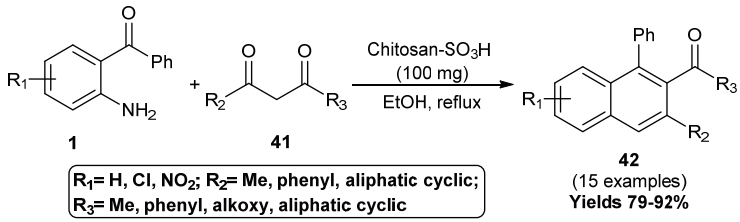
Scheme 16. In(OTf) $_3$-catalyzed synthesis of functionalized quinolines.

Senadi et al. (2015) reported a regioselective synthesis of 3,4-disubstituted quinolines **40** from 2-aminobenzophenone **1** and simple alkenes **39** *via* anti-Markovnikov selectivity under $Pd(OAc)_2/Cu(OAc)_2$ catalytic system and molecular oxygen as a terminal oxidant (Scheme 17).



Scheme 17. Regioselective synthesis of 3,4-disubstituted quinolines.

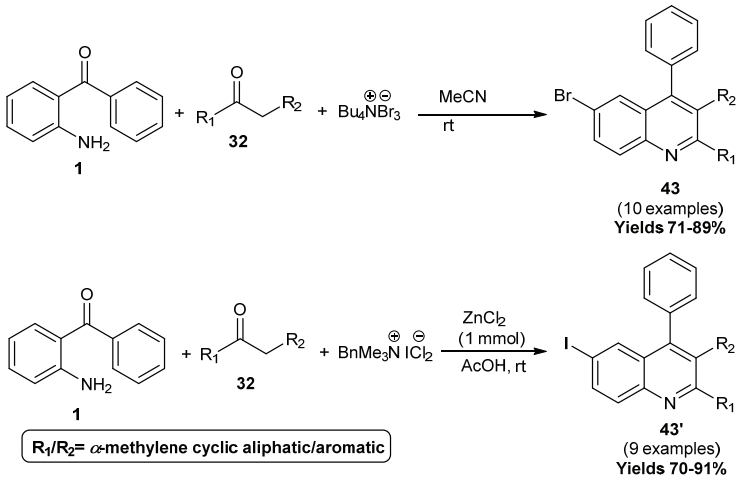
A chitosan-SO_3H catalyzed Friedländer condensation/annulation reaction of 2-aminobenzophenone **1** with α-methyleneketones **41** was reported (Reddy et al., 2013) for the synthesis of quinolines **42** with high yields in short reaction times. In this methodology, the use of recyclable and biodegradable chitosan-SO_3H makes it quite simple, more convenient and economically viable (Scheme 18).



Scheme 18. Quinolines synthesis in the presence of chitosan-SO_3H.

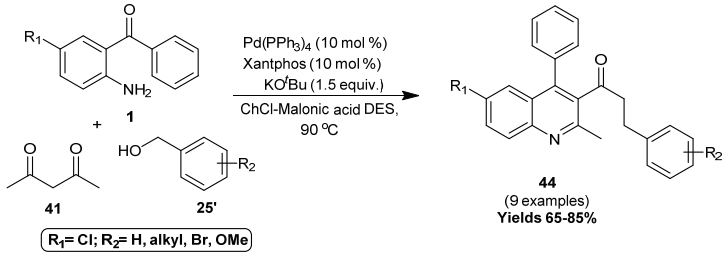
The synthesis of novel 6-bromoquinolines **43** through a one-pot three-component protocol by treating 2-aminobenzophenone **1**, α-methylene carbonyl compounds **32** and tetrabutyl-ammonium tribromide was

developed by Wu et al. (2010). They also extended this reaction to the preparation of 6-iodoquinolines **43'** using benzyltrimethylammonium dichloroiodate in the presence of $ZnCl_2$ (Scheme 19).



Scheme 19. Synthesis of 6-bromoquinolines and 6-iodoquinolines.

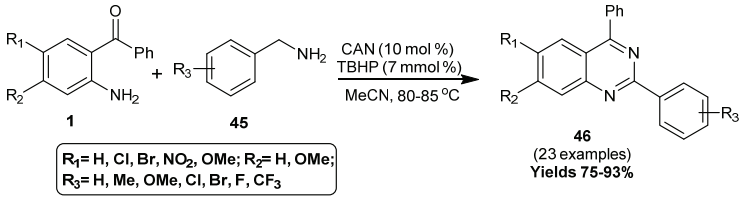
Then, a sequential Friedländer reaction of 2-aminobenzophenone **1**, 1,3-dicarbonyl compounds **41** and benzyl alcohols **25'** in ChCl-based deep eutectic solvent (DES) using $Pd(PPh_3)_4$, xantphos, KO^{t}Bu as the catalyst was successfully investigated for the synthesis of quinoline derivatives **44** (Teja and Khan, 2019). The C-C bond formation through sp^3-C-H functionalization involved a broad scope of the substrates, chemoselectivity and environmentally friendly strategy (Scheme 20).



Scheme 20. Synthesis of quinolines from 2-aminobenzophenone, acetylacetone and benzyl alcohols.

3.3 Synthesis of Quinazoline derivatives

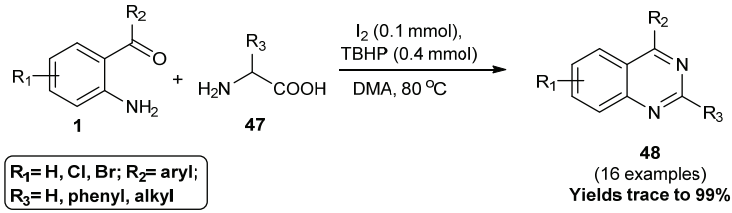
Karnakar et al. (2011) designed an efficient methodology for the synthesis of 2-phenylquinazolines **46** *via* a ceric ammonium nitrate (CAN)-*t*-butyl hydroperoxide (TBHP) catalyzed reaction of 2-aminobenzophenones **1** and benzylamines **45** in acetonitrile. The corresponding products **46** were obtained in good to excellent yields (Scheme 19).



Scheme 21. Synthesis of 2-phenylquinazolines using 2-aminobenzophenones and benzylamines.

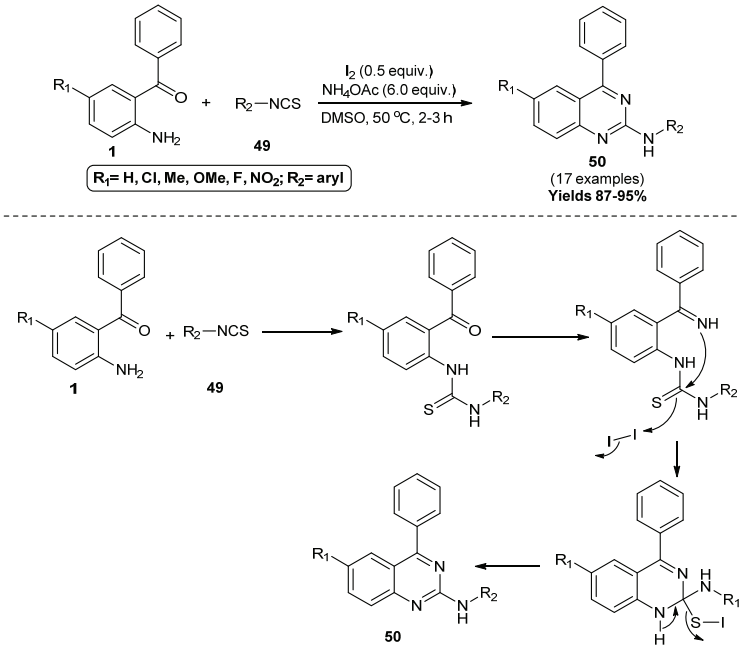
Again, intramolecular oxidative decarboxylative coupling of primary α-amino acids **47** with 2-aminobenzophenone **1** under mild and neutral conditions for the synthesis of quinazolines **48** was developed (Yan and Wang, 2011). The protocol employed a molecular I_2 and *t*-butyl

hydroperoxide (TBHP) catalytic system in dimethylacetamide (DMA), displaying many advantages such as being metal-free, water and air-tolerant, having low toxicity, and being environmentally benign (Scheme 22).



Scheme 22. Synthesis of quinazolines from *α*-amino acids and 2-aminobenzophenone.

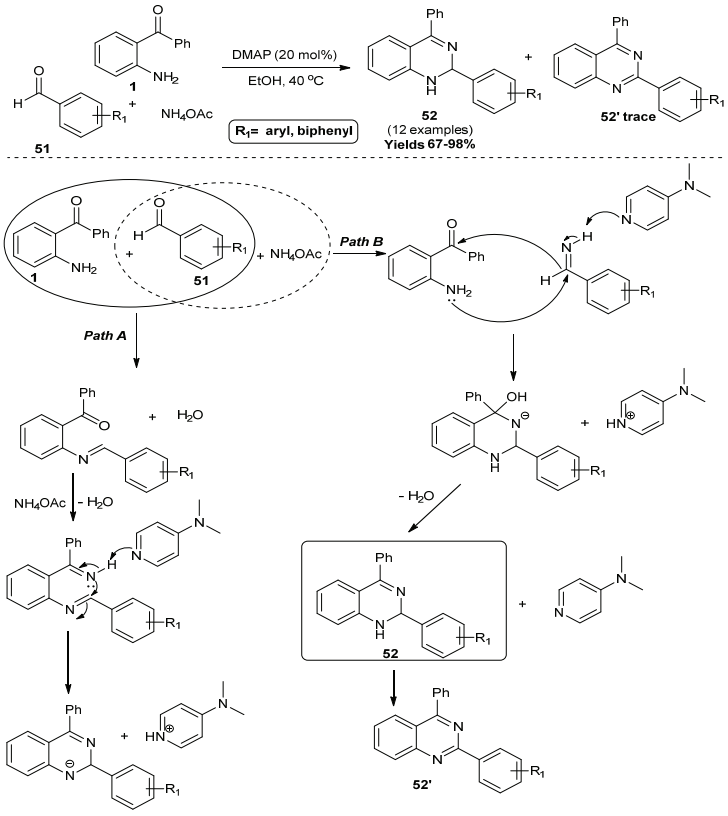
Nagesh and Krishna, (2013) have developed an efficient method for synthesizing *N*,4- disubstituted quinazoline-2-amines **50** from 2-aminobenzophenone **1** and isothiocyanates **49**. This methodology used ammonium acetate as a nitrogen source in the presence of I_2 in DMSO (Scheme 23). In this reaction, 2-aminobenzophenone **1** condensed with isothiocyanates **49** to afford a thiourea intermediate, which further reacts with NH_4OAc to give an imine intermediate. Then, an intramolecular attack of the imine NH group on the thiocarbonyl carbon with concomitant trapping of the S anion affords the cyclized product. The cyclized product on aromatization leads to the formation of the desired products **50** in good to excellent yields.



Scheme 23. Synthesis of disubstituted quinazoline-2-amine.

The one-pot three-component methodology for the synthesis of 1,2-dihydroquinazolines **52** *via* a 4-(*N*,*N*-dimethylamino)pyridine (DMAP) catalyzed reaction of aromatic or heteroaromatic aldehydes **51**, 2-aminobenzophenone **1** and ammonium acetate under mild conditions was developed (Derabli et al., 2014). The proposed mechanism starts with DMAP acting as a base on two pathways. The first reaction mechanism (path **A**) proceeded through the condensation of the aldehyde **52** with 2-aminobenzophenone **1** and further with ammonium acetate giving a diimine intermediate. Then, the carbanion intermediate produced by the deprotonation of the diimine intermediate undergoes intramolecular cyclization to give the desired product 1,2-dihydroquinazoline **52**. Product

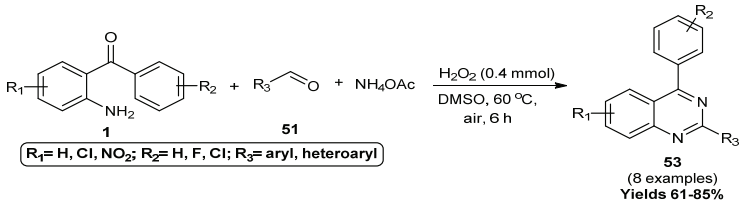
52 could be aromatized by air to give the corresponding quinazoline **52'** in a trace amount. In another mechanism (path **B**), the aldehyde **51** condensed with NH_4OAc to give an aldimine intermediate. This reaction with 2-aminobenzophenone **1** followed by dehydration leads to the desired product 1,2-dihydroquinazoline **52** (Scheme 24).



Scheme 24. Synthesis of 1,2-dihydroquinazoline and its proposed mechanisms.

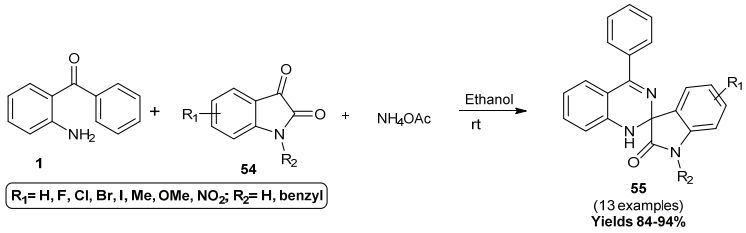
A hydrogen peroxide-mediated one-pot three-component synthesis of 2,4-substituted quinazoline **53** through the reaction of 2-aminobenzophenone

1, aldehydes **51** and ammonium acetate was also developed by Trinh et al. (2020) (Scheme 25).



Scheme 25. An efficient metal-free synthesis of 2,4-substituted quinazoline.

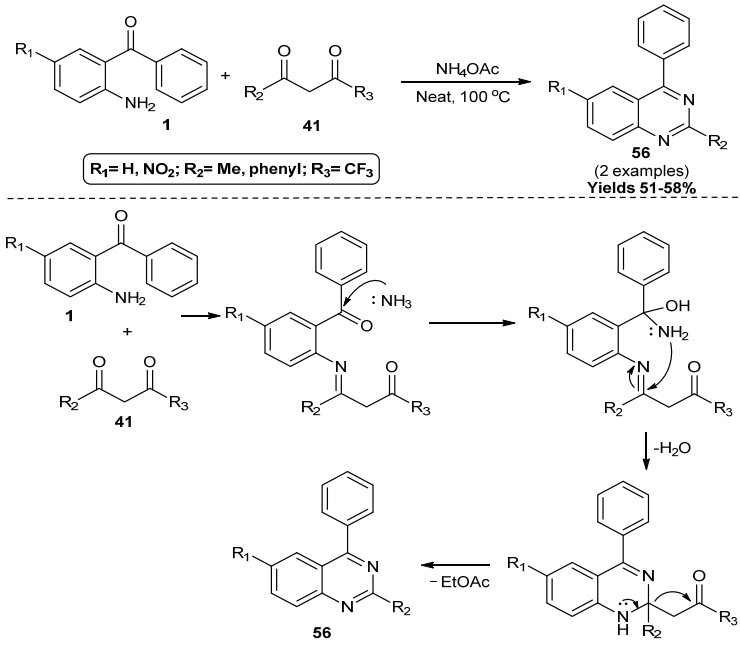
A catalyst-free three-component protocol for the synthesis of 4′-phenyl-1′*H*-spiro[indoline-3,2′-quinazolin]-2-one **55** was reported (Kamal et al., 2015) *via* the reaction of 2-aminobenzophenones **1**, isatins **54** and ammonium acetate in excellent yields using ethanol as a solvent. The products showed antibacterial activity with MIC values 7.8 lg/ml selectively against Gram-positive bacteria, *Micrococcus luteus* MTCC 2470 and MIC values ranging between 3.9 and 7.8 lg/ml against Gram-negative bacteria, *Klebsiella planticola* MTCC 530 (Scheme 26).



Scheme 26. Synthesis of 4′-phenyl-1′*H*-spiro[indoline-3,2′-quinazolin]-2-one.

Dayakar and Raju, (2018) developed a facile and selective one-pot three-component approach for synthesizing quinazolines **56** using 2-aminobenzophenones **1**, 1,3-diketones **41** and ammonium acetate. The

condensation of 2-aminobenzophenones **1** and 1,3-diketones **41** provides Schiff's base, followed by the nucleophilic addition of NH_3 to keto carbonyl (C=O), affording an intermediate. The subsequent intramolecular nucleophilic addition of imine with EtOAc elimination leads to the formation of the desired products (Scheme 27).

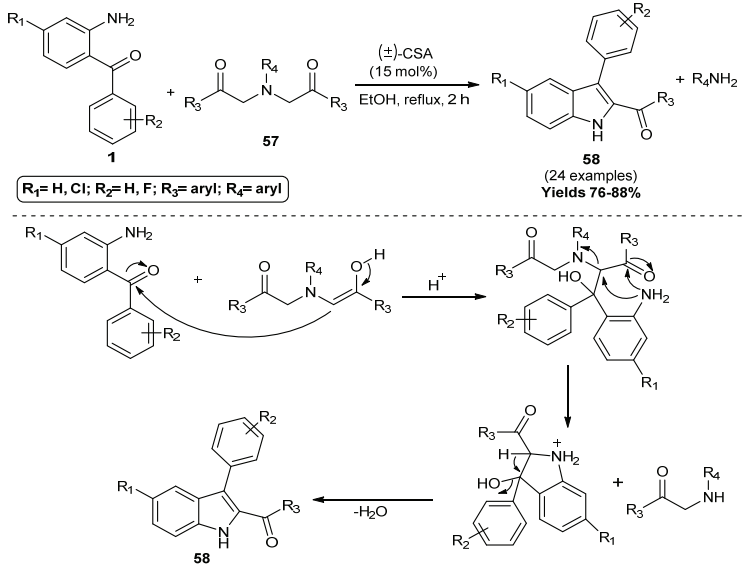


Scheme 27. One-pot approach for the synthesis of quinazolines.

3.4 Synthesis of Indole derivatives

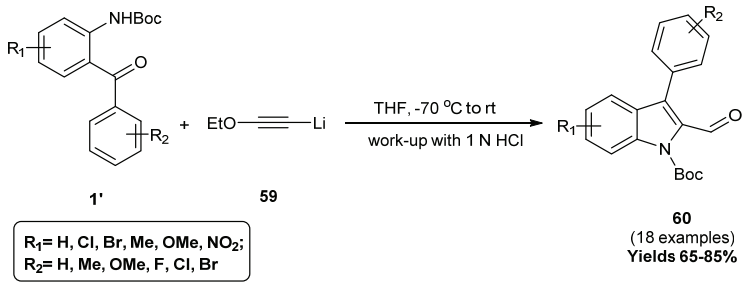
Paul and Muthusubramanian, (2013) explored the synthesis of 2-aroyl-3-arylindoles **58** by an abnormal Friedländer reaction between diphenacylaniline **59** and 2-aminobenzophenone **1** in the presence of (±)-camphorsulfonic acid as a catalyst (Scheme 28). The mechanism starts

with the cleavage of diphenacylaniline **59** under acidic conditions, providing the reactive $PhCOCH_2^+$ species and aniline. The phenacyl cation reacts with 2-aminobenzophenone **1** to give the indole products to eliminate water molecules.



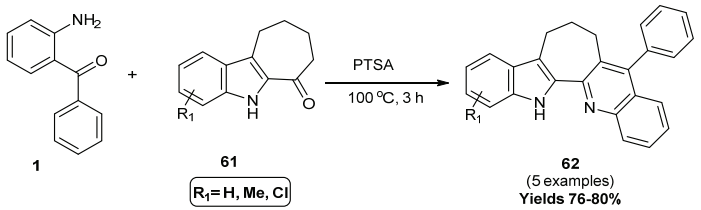
Scheme 28. Synthesis of 2-aroyl-3-arylindole and its proposed mechanism.

Then, the synthesis of indole-2-carboxaldehydes **60** was explored (Thirupathi et al., 2014) *via* a one-pot addition/cyclization reaction of *N*-Boc-2-aminobenzophenone **1'** and ethoxyacetylide **59**, which included a nucleophile-triggered 5-*exo*-dig cyclization (Scheme 29).



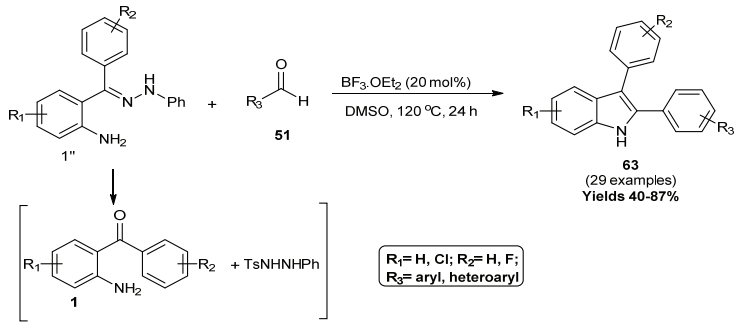
Scheme 29. Synthesis of indole-2-carboxaldehydes from *N*-Boc-2-aminobenzophenone.

Yamuna et al. (2011) developed an efficient method for the preparation of quinolino[2′,3′:7,6]cyclohept[1,2-*b*]indoles **62** *via* the Friedländer and Pfitzinger condensations of 1-oxo-cyclohept[*b*]indole **61** with 2-aminobenzophenone **1** in the presence of a catalytic amount of PTSA (Scheme 30).



Scheme 30. The preparation of quinolino[2′,3′:7,6]cyclohept[1,2-*b*]indoles.

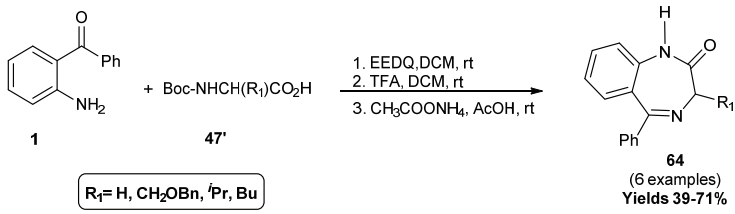
The synthesis of 2,3-diarylindoles **63** through the intramolecular addition of hydrazones **1"** (bearing no α-H, derived from 2-aminobenzophenones **1** and phenylhydrazines**)** to the *in situ* generated imine intermediates has been developed (Maurya et al., 2018) (Scheme 31). In this protocol, aryl aldehydes **51** bearing electron-withdrawing groups provided the corresponding products in good to excellent yields.



Scheme 31. Transition-metal-free synthesis of 2,3-diarylindoles.

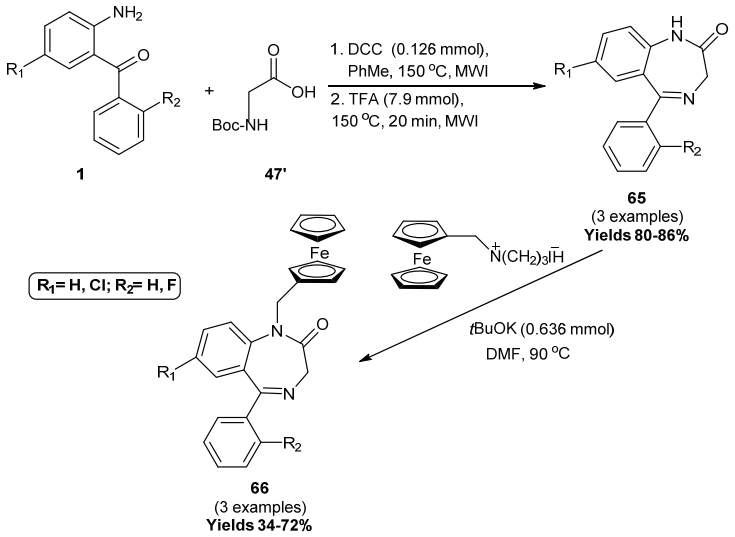
3.5 Synthesis of Azepine derivatives

Spencer et al. (2011) developed a method to synthesize 1,4-benzodiazepines **64** from 2-aminobenzophenone **1** and Boc-protected amino acids **47'** in a three-step process (Scheme 32). The reaction procedure involves stirring 2-aminobenzophenone **1** and *Boc*-protected amino acids **47'** overnight with 25.0 mmol of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in DCM at room temperature. It was followed by dissolving in TFA/DCM and further stirred for 2.5 h at room temperature. Then, the resulting oil was treated with ammonium acetate (125.0 mmol) and acetic acid (AcOH) (30 mL) to get the products.



Scheme 32. Synthesis of 1,4-benzodiazepines from 2-aminobenzophenone.

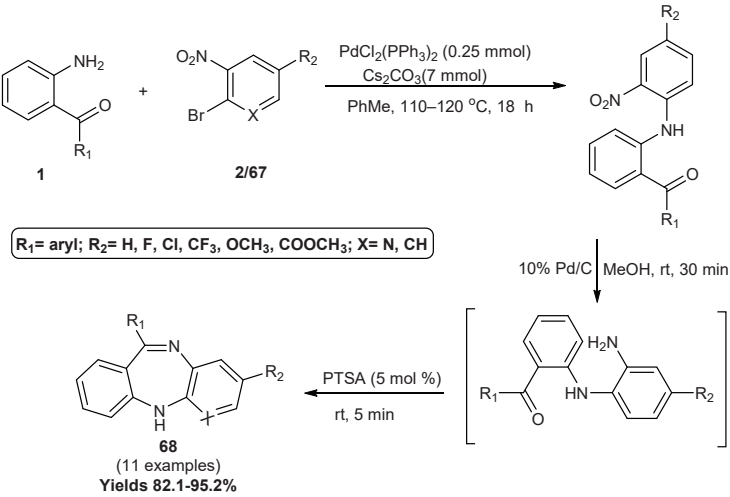
An efficient one-pot microwave-assisted synthesis of 1,4-benzodiazepin-2-one **65** through condensation of 2-aminobenzophenone **1** and Boc-protected amino acid **47'** was explored (Maguene et al., 2011) using dicyclohexylcarbodiimide (DCC). The products **65** on further alkylation with ferrocenyl-methyltrimethyl ammonium iodide in the presence of potassium *tert*-butoxide afforded ferrocenylmethyl benzodiazepines **66** in moderate yields (Scheme 33).



Scheme 33. Synthesis of benzodiazepines and ferrocenylmethyl benzodiazepines.

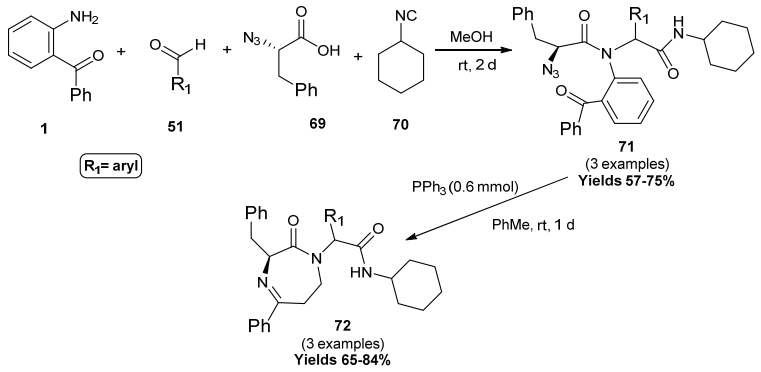
The synthesis of substituted 1,4-diazepines **68** *via* a Pd catalyzed amination and sequential hydrogenation condensation reaction of 2-aminobenzophenone **1** with 2-bromonitrobenzene **2** or 2-bromo-3-nitropyridine **67** was developed by Wang et al. (2013) (Scheme 34). This method provides an extension on the substrate scope of Buchward's

strategy and also an alternative route for the synthesis of 1,4-diazepine derivatives.



Scheme 34. Pd catalyzed synthesis of substituted 1,4-diazepines.

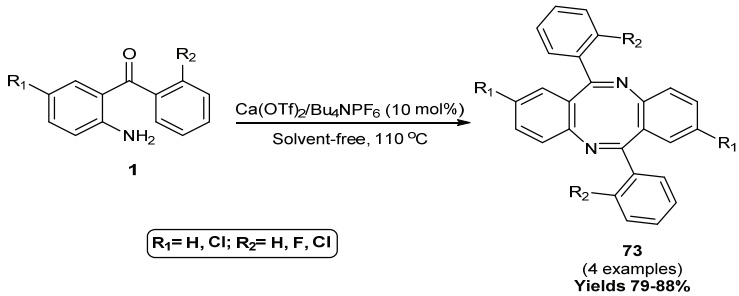
The sequential Ugi reaction between *p*-substituted benzaldehydes **51**, 2-aminobenzophenone **1**, cyclohexyl isocyanide **70** and (*S*)-3-phenyl-2-azidopropionic acid **69** followed by a Staudinger/aza-Wittig cyclization in the presence of triphenylphosphine leading to 5-oxo-1,4-diazepine-3-carboxamides **60** was developed by Lecinska et al. (2010) (Scheme 35).



Scheme 35. Synthesis of 5-oxo-1,4-diazepine-3-carboxamides using the Ugi reaction.

3.6 Synthesis of Azacine derivatives

Calcium catalyzed homodimerization of 2-aminobenzophenone **1** to dibenzo[1,5]diazacines **73** was reported by Yaragorla and Pareekin, (2018). In this reaction, 2-aminobenzophenone **1** underwent intermolecular condensation to yield the product using an environmentally benign catalyst $Ca(OTf)_2$ under solvent-free conditions in good yields (Scheme 36).



Scheme 36. Calcium catalyzed homodimerization of 2-aminoaryl ketones to dibenzodiazocines.

4. Conclusion

The present chapter focuses on the versatility of 2-aminobenzophenone as a substrate and its significance for synthesizing some heterocyclic compounds *viz* acridones, quinoline, quinazolinones, indoles, diazepine, etc. The functionalization of this compound will be of great interest for broadening the synthesis of the wide range of heterocycles in the near future.

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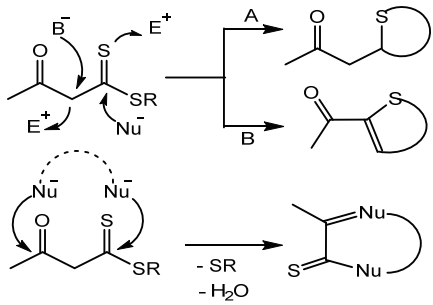
CHAPTER 8

β–KETODITHIOESTERS

1. Introduction

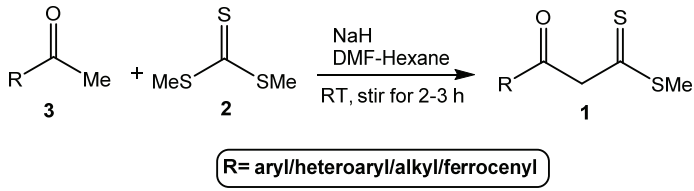
β–Ketodithioesters (KDEs), also referred to as β–oxodithioesters (ODEs) were envisioned by Beer and co-workers in 1934 (Gibson, 1934). KDEs (Ramadas et al. 1983) exhibit intriguing nucleophilic reactivity, as shown in Scheme 1. The ambident electrophilicity flanks these at the 1,3-carbon centers because of carbonyl and thiocarbonyl functionalities. Many tunable functionalities in the synthon provide tremendous synthetic scope to be utilized as versatile building blocks in synthesizing various heterocycles (Junjappa and Ila, 2004).



Scheme 1. Reactive sites of KDEs.

2. Synthesis of *β*-Ketodithioesters

β-KDEs with a general formula **1** (Scheme 2) has been generally prepared from active methylene ketones **3** by stirring with (*S,S*)-dimethyltrithiocarbonate **2** in the presence of NaH in DMF–hexane (1:4) mixture in room temperature (Singh et al., 1982). However, different types of **1** have also been prepared using carbon disulfide (CS_2) in the presence of potassium *tert*-butoxide followed by alkylation to substituted acetophenone (Dalgaard et al., 1973). The transformation of ketene-*S,S*-dithioacetals **4** to **1** was also reported through a sulfo-hydrolysis with H_2S in the presence of BF_3–Et_2O in dioxane (Nair and Asokan, 1999).



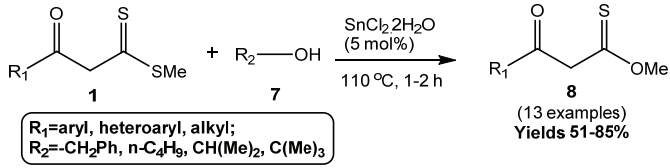
Scheme 2. Synthesis of KDEs using *S,S*-dimethyltrithiocarbonate.

The past two decades have witnessed rapid progress in the KDEs's chemistry, especially in synthesizing functionalized heterocyclic compounds *via* tandem two-component and multicomponent reactions. This chapter mainly summarizes the progress of KDEs in the last decade, and it is divided into different sections according to the types of compounds formed.

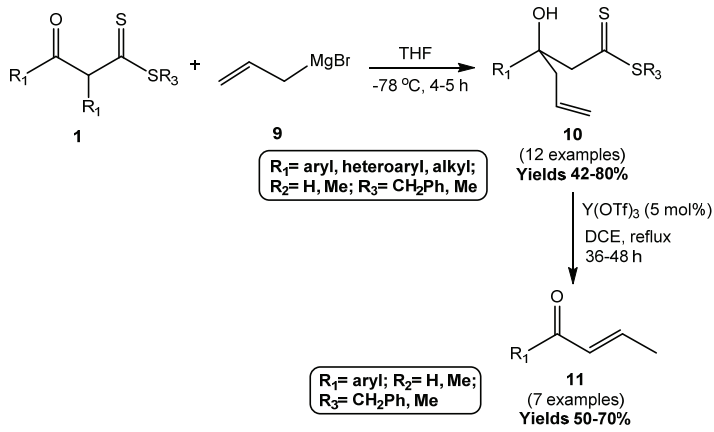
3. Functionalization of KDEs

Various types of functionalization have been performed successfully from KDEs to other well-known building blocks such as ketene-*S,S*-acetals **4**, β-

oxothioamides **5** or ketene-*N,S*-acetals **6**, further the thiocarbonyl group could be converted into a carbonyl group (Singh et al., 2013). The successful demonstration of the *trans*-esterification of **1** using different alcohols in the presence of 5 mol % of $SnCl_2$, giving the products **8**, under solvent-free conditions for the first time with good yields was reported by Devi et al. (2013[a]) (Scheme 3). The reaction was also tried with different catalysts such as $CuCl_2$, $ZnCl_2$, $AlCl_3$, and $FeCl_3$. However, these catalysts could not improve the reaction yield compared to $SnCl_2$ as the catalyst. On the other hand, when KDEs were treated with allyl magnesium bromide **9**, it led to a selective addition of carbonyl carbon providing the *tert*-homoallylic alcohol adducts **10** exclusively in tetrahydrofuran (THF). Then, a selective C-C cleavage was performed in which **1'** was treated with $Y(OTf)_3$ in dry dichloroethane (DCE) at refluxing condition. Here, $Y(OTf)_3$ selectively activates and cleaves the $C_{(sp3)}$-$C_{(sp3)}$ bond eliminating the dithioacetate moiety. Then, subsequent conversion of the terminal double bond to the non-terminal one resulted in forming α,β-unsaturated ketones **11** in 50-70% yields (Chowdhury et al. 2013[a]). Thus, two compounds were formed from the same starting materials in this work (Scheme 4).

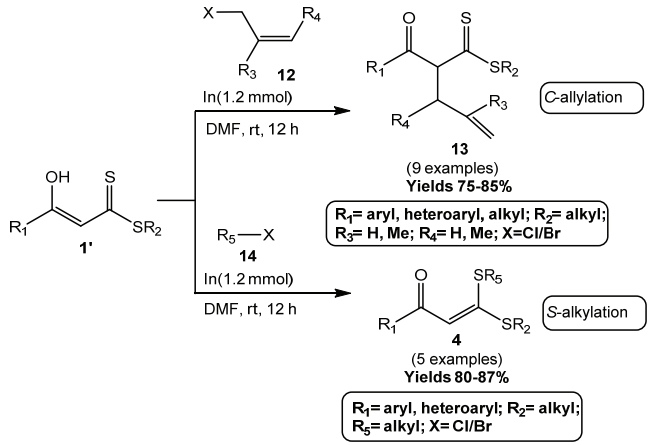


Scheme 3. Trans-esterification of KDEs using alcohols in the presence of $SnCl_2$.



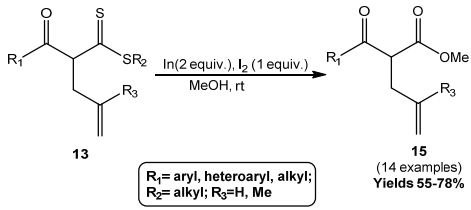
Scheme 4. Transformation of KDEs into *α,β*-unsaturated ketones.

Chowdhury et al. (2014[a]) developed facile indium (0)-mediated regioselective alkylation for the α-enolic ester/dithioester **1'** systems that proceed through a C_{sp3}–S/O cross-coupling reaction between an alkylindium reagent and α-enolic esters/dithioesters. Here, the treatment of *α*-enolic dithioester **1'** with indium(0)powder and allyl halide **12** in *N,N*-dimethylformamide (DMF) at room temperature provided the *α-C*-allylated product **13** in moderate yields; however, *S*-alkylated product **4**, i.e., ketene-*S,S*-acetals was formed when alkyl halides are used instead of allyl halides, as shown in Scheme 5.



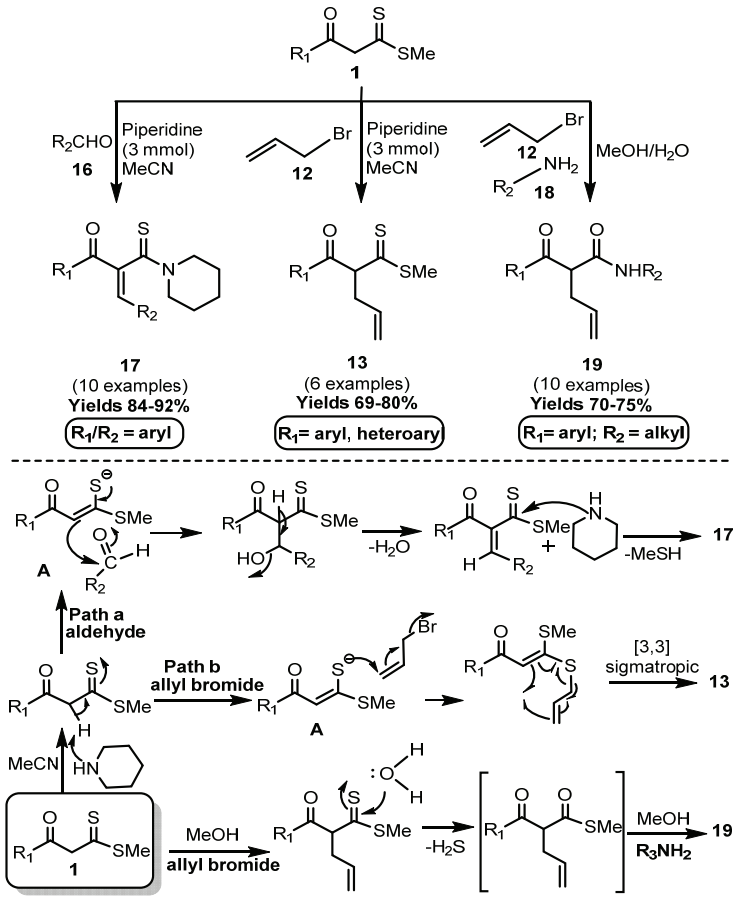
Scheme 5. Synthesis of *S*-alkylated and *C*-allylated products from α-enolic dithioesters.

Further, the selective conversion of the dithioester to an ester was successfully performed using In/I_2 in methanol (MeOH) at room temperature (Chowdhury et al., 2015) (Scheme 6). Initially, they were expecting a cyclized product from the treatment of methyl 2-benzoylpent-4-edithioate **13a** (1 mmol) in MeOH with indium powder (2 equiv.), in the presence of iodine (1 equiv.) at room temperature. However, after stirring for 24 hours instead of getting their desired product, it resulted in the replacement of the dithioester group of the precursor with the methyl ester group leading to the formation of the methyl 2-benzoylpent-4-enoate (**15a**) in 75% yield. Thus, a series of α-allyl-β'-oxodithioesters **13** has been converted to the corresponding α-allyl-β'-oxoesters **15**. Here, the dithioester groups of the starting **13** was selectively transformed to the corresponding methyl esters while the other functionalities within the moiety remained unaffected.



Scheme 6. The conversion of dithioester to an ester using In powder.

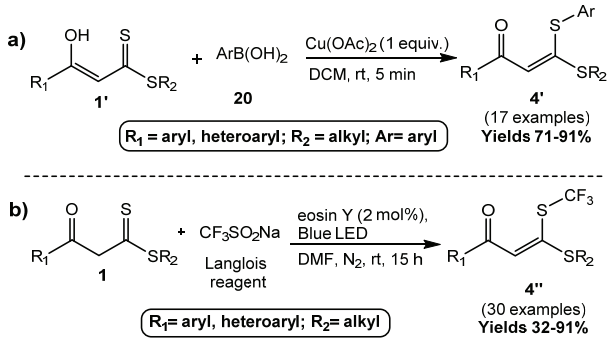
The diversity-oriented synthesis (DOS) of thioamides, *α*-allylated thioesters and *β*-ketoamides using KDEs in good yields was reported by Chanu et al. (2020). This protocol showed the dual role of piperidine as a base and a nucleophile in the Knoevenagel condensation reaction of aromatic aldehydes and *β*-KDEs, resulting in the formation of trisubstituted (*Z*)-prop-2-en-1-ones **17** stereoselectively in acetonitrile (MeCN). *β*-KDEs were further utilized in allylation reactions with allyl bromide and alkylamines, leading to allylated *β*-ketodithioesters **13** and allylated *β*-ketoamides **19** in good yields. Here, the formation of the ketoamide **19** instead of the thioamide was probably due to simultaneous hydrolysis and *trans*-esterification in the presence of alcohol followed by a successive replacement of the alkoxy groups by stronger amino nucleophiles **18**. Finally, three diversification reactions were carried out on **1**, yielding products with three new molecular scaffolds **17**, **13**, and **19** (Scheme 7). These reactions were based on the reactivity centers present in **1**, having both electrophilic and nucleophilic moieties.



Scheme 7. DOS of *β*-benzoylthioamide, *α*-allyl-thioester and *α*-allyl-ketoamide from KDEs.

Koley et al. (2015) developed an efficient one-pot regioselective protocol for *S*-arylation leading to the unsymmetrical ketene *S*-aryl, *S*-alkyl acetals **4'** through the cross-coupling of arylboronic acids **20** with α-enolic dithioesters **1'** at room temperature under ligand-free and base-free mild

conditions. In this reaction, $Cu(OAc)_2$ acts as an effective promoter for this transformation (Scheme 8a). Further, the trifluoro-methylation of KDEs *via* a visible-light photocatalysis giving thioxo *S*-triflinated ketene-*S,S*-acetals was reported recently by Soni et al. (2020). The reaction was performed with the Langlois' reagent (CF_3SO_2Na, sodium triflinate) as a source of CF_3 radicals in eosin Y, which acts as a hydrogen atom transfer (HAT) catalyst. They could establish a library of triflinated ketene-*S,S*-acetals in good to excellent yields bearing a diverse synthetically useful functional groups of different electronic and steric nature (Scheme 8b).



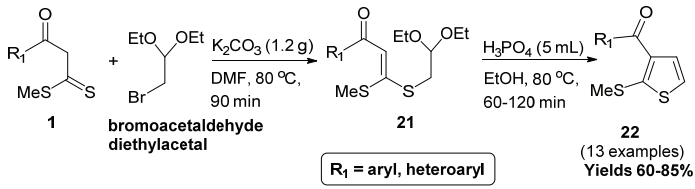
Scheme 8. The *S*-arylation and triflouromethylation of KDEs using $ArB(OH)_2$ and Langlois's reagent.

4. Application of KDEs in organic chemistry

4.1 Synthesis of *S*-containing heterocycles

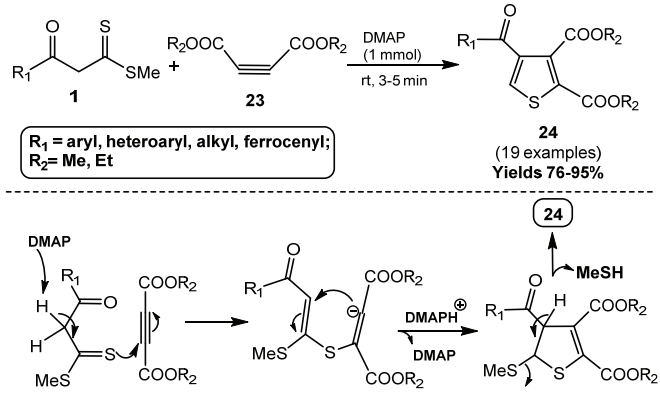
The reactions of the nucleophilic sites (S and *α*-C atoms) of KDEs with different dielectrophilic reagents could form multisubstituted thiophene derivatives regioselectively. Kumara et al. (2016) developed the synthesis of 2,3-disubstituted thiophenes **22** from KDEs **1**, by reacting with bromoacetaldehyde diethylacetal in the presence of anhydrous K_2CO_3 in DMF

at 80 °C to generate the corresponding mixed acetals **21**. The newly formed acetals **21** undergo cyclization in the presence of ethanolic orthophosphoric acid (H_3PO_4) to afford the desired products **22** in good yields (Scheme 9).



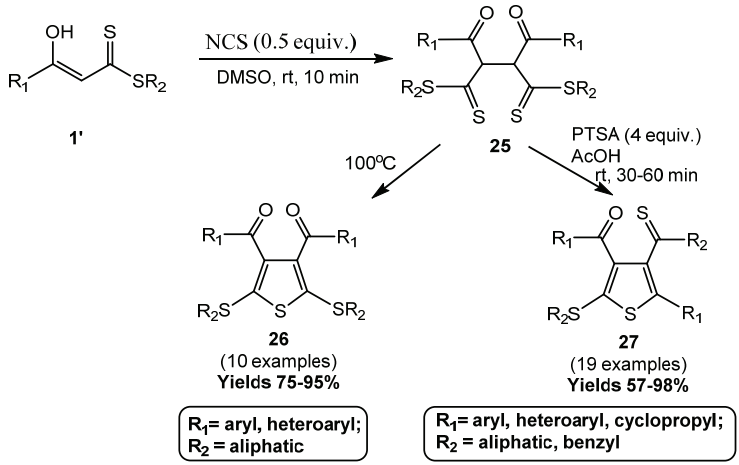
Scheme 9. Synthesis of di-substituted thiophenes.

Nandi et al. (2011) developed a general method for synthesizing 2,3-dicarboalkoxy-4-aroyl/heteroaroyl/alkanoyl thiophenes **24** promoted by 4-dimethylaminopyridine (DMAP). It involves reacting KDEs and dialkyl acetylene dicarboxylate **23** for 3-5 minutes of stirring in dichloromethane (DCM) at room temperature in the presence of DMAP. The reaction pathway follows [3+2] heteroannulation of **1** and **23** *via* 1-2(C-S) and 3-4(C-C) bond connections (Scheme 10).

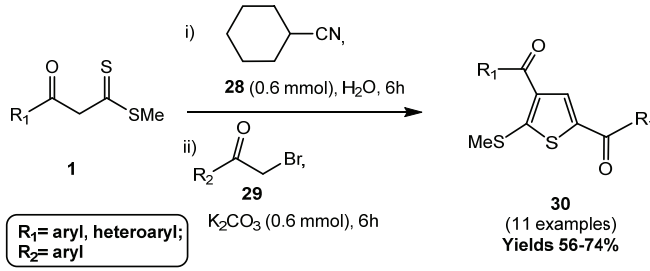


Scheme 10. Synthesis of thiophenes from KDEs and dialkyl acetylene dicarboxylates.

The C-C homocoupling of α-enolic dithioesters **1'** leading to fully substituted symmetrical thiophene **26**/**27** *via* a chemoselective Paal-Knorr pathway was also reported by Ramulu et al. (2015). The *N*-chlorosuccinimide (NCS) facilitates C-C coupling to give α,α'-bis(*β*-ketodithioesters) **25**, which on further heating at 100 ºC gives the fully substituted thiophenes **26** with a unique symmetrical substitution pattern in a one-pot, two-step reaction sequence (Scheme 11). However, *para*-toluenesulfonic acid (PTSA) mediated synthesis of a tetrasubstituted thiophenes has been achieved in quantitative yields by chemo- and regioselective dehydrative cyclization of **25** at room temperature as reported by Ramulu et al. (2016). The reaction proceeds through C_{α}–$C_{\alpha'}$ single bond rotation with the dithioester group at the 4-position of the thiophene ring, transforming into a thiazoline group (Scheme 11). While an efficient methodology for the preparation of a trisubstituted thiophenes **30** *via* the one-pot, three-component reaction of KDEs with an isocyanide **28** and *α*-haloketones **29** was reported (Moghaddam et al., 2014). The reaction proceeds in water without using any catalyst, in which the abstraction of the acidic proton of the KDE by **28** was the initial step of the protocol (Scheme 12).



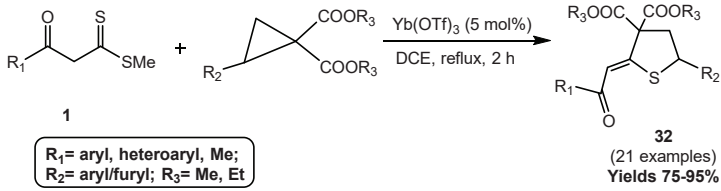
Scheme 11. Synthesis of sym- and unsymmetrical tetrasubstituted thiophenes.



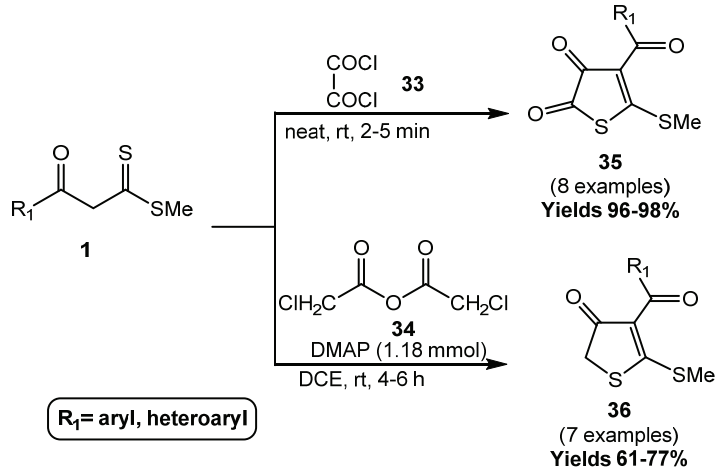
Scheme 12. Synthesis of trisubstituted thiophenes from KDEs.

The synthesis of tetrahydrothiophene derivatives **32** from cyclopropanes **31** and KDEs catalyzed by $Yb(OTf)_3$ was reported by Wang et al. (2015). It was the first example of using KDEs as dipolarophiles to react with cyclopropanes behaving as donor-acceptor (Scheme 13). Then, the efficient methods for preparing polyfunctionalized thiophene-2,3-diones **35** and thiophen-3(2*H*)-ones **36** using KDEs were also described (Madabhushi et al. 2015). Here, KDEs react directly with oxalyl chloride

33, producing the product **35** in 96-98% yields and with chloroacetic anhydride **34,** giving the desired compounds **36** in 61-77% yields in the presence of DMAP (Scheme 14).



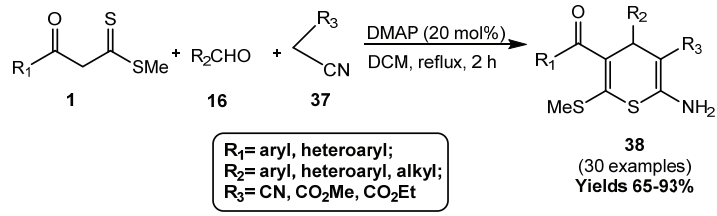
Scheme 13. Synthesis of tetrahydrothiophenes from various KDEs.



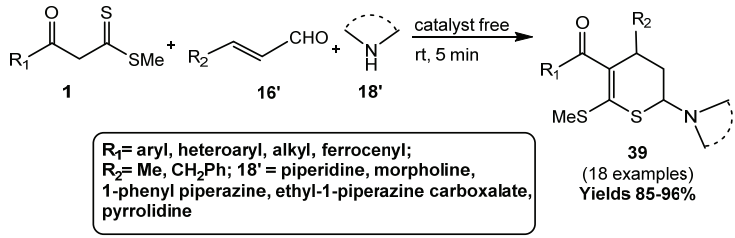
Scheme 14. Synthesis of polyfunctionalizedthiophene-2,3-diones and thiophen-3(2*H*)-ones.

Verma et al. (2012) reported the synthesis of pentasubstituted thiopyran derivatives **38** *via* one-pot three-component coupling of **1**, aldehydes **16** and active methylene compound **37** promoted by DMAP in DCM as the solvent (Scheme 15). According to them, the reaction pathway follows 1-

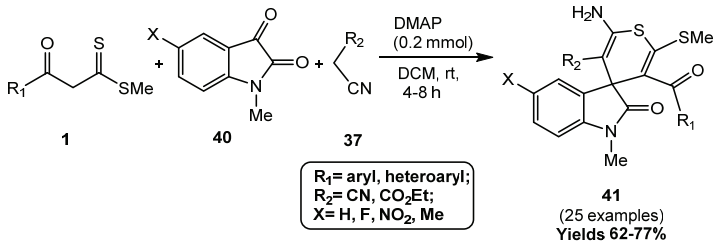
2(C-S) and 3-4, 4-5(C-C) bond formation through the domino Knoevenagel/Michael/cyclization sequence. Further, Koley et al. (2013) developed an efficient approach to 5,6-dihydro-4*H*-thiopyrans **39** *via* one-pot three-component domino coupling of **1**, *α,β*-unsaturated aldehydes **16'** and cyclic aliphatic secondary amines **18'** at room temperature under the catalyst- and solvent-free conditions giving an excellent yield of the products (Scheme 16). Then another one-pot multicomponent synthesis of the spiro[indoline-3,4′-thiopyran]-2-ones **41** using **1**, *N*-methyl isatin **40** and **37** with DMAP as the catalyst in Scheme 17, was reported by Kurva et al. (2017[a]).



Scheme 15. Synthesis of pentasubstituted thiopyrans *via* heteroannulation of KDEs.

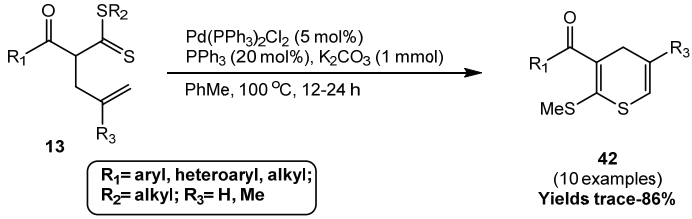


Scheme 16. Synthesis of tetrasubstituted thiopyrans.



Scheme 17. Synthesis of spiro[indoline-3,4′-thiopyran]-2-ones.

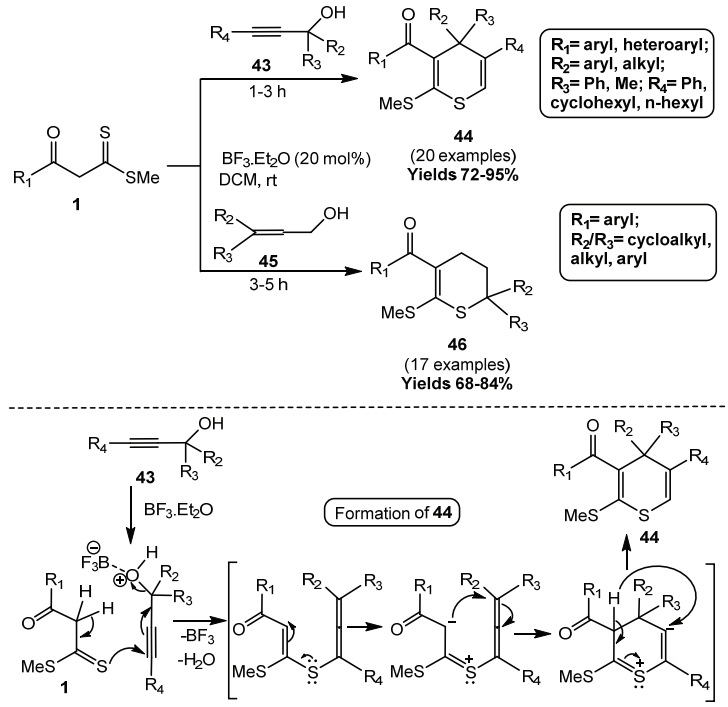
The synthesis of 4*H*-thiopyran derivatives **42** through an intramolecular C−S fusion of *α*-allyl-*β*′-ketodithioesters **13** was reported (Chowdhury et al., 2014[b]). In this method, Pd activates the C_{δ}−H of the allyl termini and facilitates the intramolecular C_{δ}−S coupling to furnish the six-membered thiopyran skeletons exclusively (Scheme 18).



Scheme 18. Synthesis of trisubstituted thiopyrans using Pd catalyst.

An efficient method for preparing tetrasubstituted 4*H*-thiopyran derivatives **44** using 1,1,3-trisubstituted prop-2-yn-1-ol **43** and **1** was reported (Madabhushi et al., 2014). The optimized reaction condition was established in the presence of $BF_3.Et_2O$ as a catalyst and DCM as the solvent at room temperature. Initially, **1** and propargyl alcohol **43** undergo Lewis's acid assisted dehydration reaction followed by intramolecular cyclization of the resulting allenyl vinyl thioether and 3,5-H transfer to give the 4*H*-thiopyran **44** as shown in Scheme 19. Further, the synthesis of

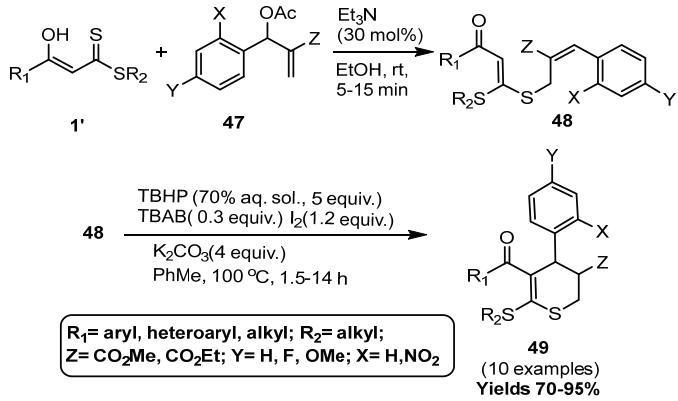
3,4-dihydro-2*H*-thiopyrans **46** using another type of alcohol, i.e., 3,3-disubstituted allylic alcohols **45** with **1** under a similar reaction condition, was explored by Kurva et al. (2017[b]).



Scheme 19. Synthesis of multisubstituted thiopyrans catalyzed by $BF_3.Et_2O$.

An efficient one-pot allylic alkylation of *α*-enolic dithioesters **1'** with methyl 3-acetoxy-3-phenyl-2-methylenepropanoate **47** has been successfully demonstrated in ethanol at room temperature by Soni et al. (2019). The beauty of this protocol was the isolation of *S*-allylated *β*-oxoketene dithioacetals **48**. They further exploited the newly synthesized trisubstituted olefin **48** to construct polysubstituted dihydro-2*H*-thiopyran-carboxylates **49**. In this protocol, **48** was treated with *tert*-butyl

hydroperoxide (TBHP), tetrabutylammonium bromide (TBAB), K_2CO_3 and I_2 in toluene at 100 °C. To their delight, the reaction proceeded smoothly to give the dihydro-2*H*-thiopyran derivatives **49** in excellent yields (up to 95%) and with high diastereoselectivity *via* $C_{sp}2$-$C_{sp}2$ coupling (Scheme 20).

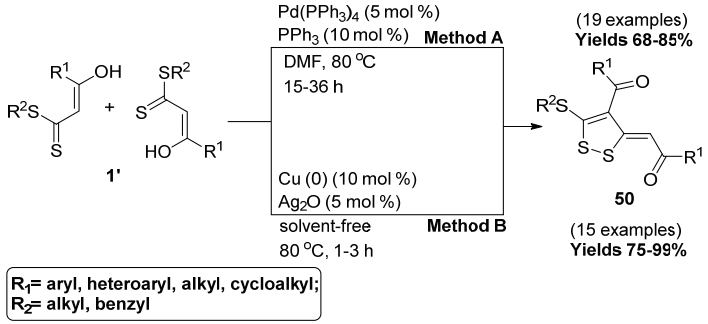


Scheme 20. Synthesis of polysubstituted dihydro-2*H*-thiopyran-carboxylates.

4.2 Synthesis of two *S*-containing heterocycles

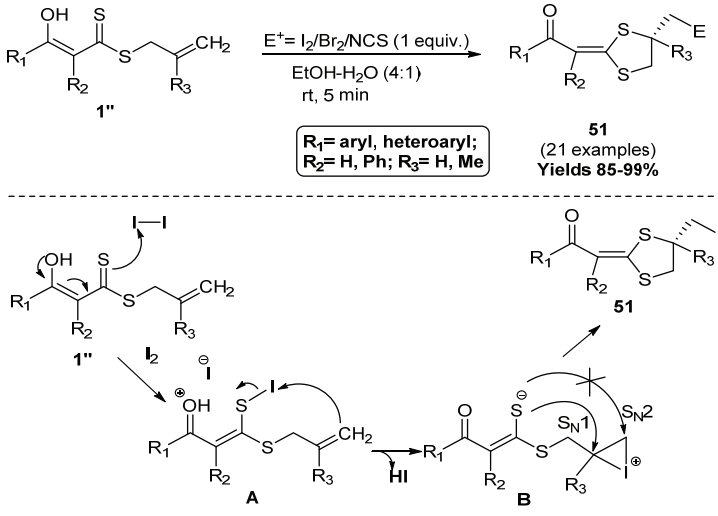
An efficient method for synthesizing 3,4,5-trisubstituted 1,2-dithioles **50** *via* a palladium-catalyzed homocoupling of *α*-enolic dithioesters was reported by Chowdhury et al. (2013[b]). Here, Pd (0) efficiently catalyzes the activation and cleavage of S-H and C-S bonds to achieve a cascade coupling, which results in the concomitant formation of new S-S and C-C bonds (Scheme 21). Similarly, an operationally more straightforward protocol for the synthesis of **50** using **1'** catalyzed by the Cu (0) under solvent-free conditions was reported by Ramulu et al. (2015). Here, Cu (0) with Ag_2O as an oxidant and promoter could be recycled at least four times with no activity loss, making this protocol an ideal alternative to

existing methods. The present protocol exhibits remarkable features such as readily available, reusable catalyst, inexpensive reaction system, no extra ligand and base, limited reaction time, excellent functional group tolerance, and good to excellent yields.



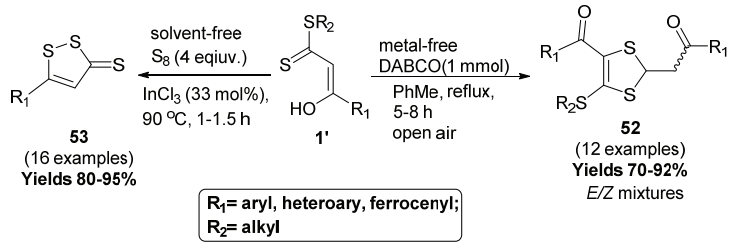
Scheme 21. Synthesis of trisubstituted 1,2-dithioles.

An effective iodocyclization of *S*-allylated α-enolic dithioesters **1"** for synthesizing 2-alkylidene-1,3-dithiolanes **51** mediated by the molecular iodine has been reported for the first time and established a library of diverse 1,3-dithiolanes (Ramulu et al., 2015). The eye-catching features of this protocol include the mild reaction conditions with short reaction time, high atom economy/selectivity and broad substrate scope (Scheme 22). As suggested, the probable mechanism starts with a selective nucleophilic attack of thiocarbonyl sulfur to iodine, giving an intermediate **A**. Which undergoes heterocyclization through an allylic double bond to generate the intermediate **B** by eliminating HI. Then, the nucleophilic attack of the enethiolate anion selectively at tertiary carbocation *via* an S_N1 afforded the products **51,** since the departure of iodine gives more stable carbocation at the tertiary end than the primary end through the S_N2 pathway.



Scheme 22. Synthesis of 2-alkylidene-1, 3-dithiolanes.

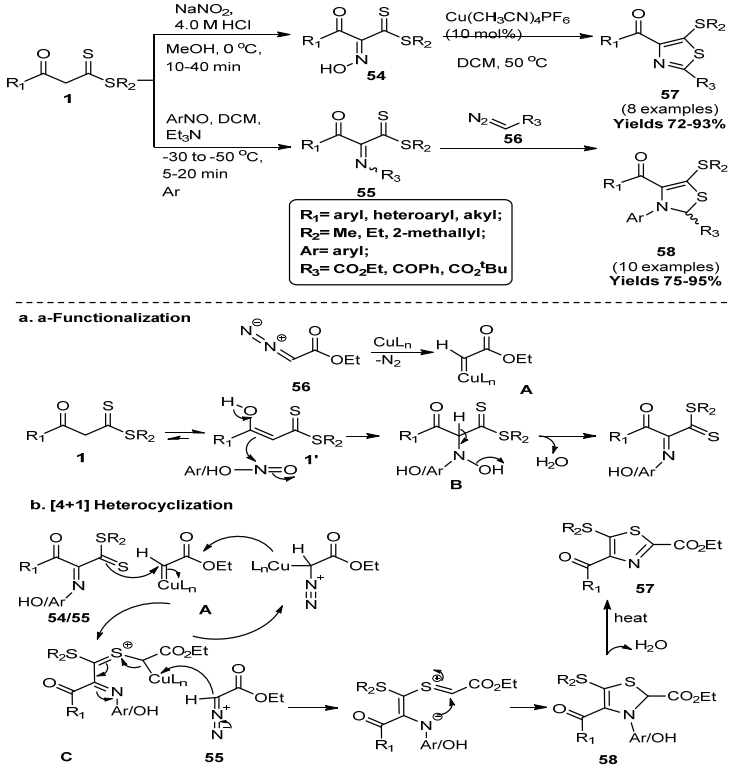
Koley et al. (2016[a]) developed a simple cascade methodology to synthesize 1,2- and 1,3-dithiole derivatives **52**/**53** from a common acyclic *α*-enolic dithioester **1'**. The 1,2-dithioles **53** were constructed by the reaction of dithioesters with elemental sulfur in the presence of $InCl_3$ under solvent-free conditions where two bonds of S−S and C−S were formed *via in-situ* generated open-chain intermediates followed by an intramolecular heterocyclization. Whereas 1,3-dithioles **52** have been achieved *via* 1,4-diazabicyclo[2.2.2]octane (DABCO) mediated self-coupling of dithioesters in open-air, enabling the formation of two new C-S bonds and one ring in a single operation in a contiguous fashion (Scheme 23). Thus, two types of dithioles were obtained from the same starting material, i.e., **1'**.



Scheme 23. Synthesis of 1,2- and1,3-dithioles.

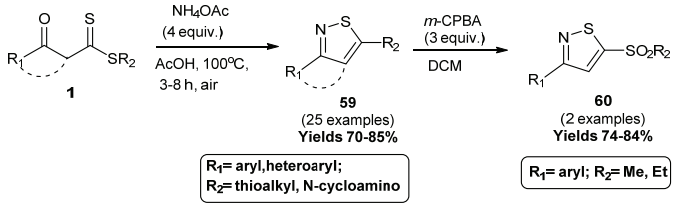
4.3 Synthesis of *S,N*-containing heterocycles

Thiazole is a versatile privileged scaffolds in many natural products and biologically active compounds. Srivastava et al. (2017) explored the utility of an underdeveloped class of precursor-α-(*N*-hydroxy/aryl)imino-*β*-oxodithioesters **54/55**, which were obtained by the reaction of *β*-oxodithioesters **1** with nitrous acid and nitrosoarenes, respectively. Then, these were further utilized as a 4 atoms synthon towards a Cu-catalyzed [4+1] heterocyclization with diazocarbonyl as one carbon synthon to develop a straightforward approach for the DOS of 2,4,5-trisubstituted thiazoles **57** and 2,3,4,5-tetrasubstituted 2,3-dihydrothiazoles **58** (Scheme 24). The chemo-selective concise one-pot strategy reported herein allows a novel entry to the fully substituted thiazoles **57** and 2,3-dihydrothia-zoles **58** with complete control over substitution at the various rings position, which would otherwise be more difficult to prepare by alternative routes.



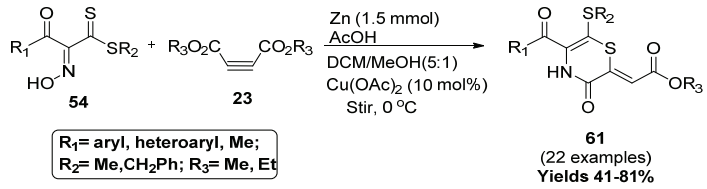
Scheme 24. Synthesis of thiazoles and 2,3-dihydrothiazoles.

Shukla et al. (2016) utilized *β*-oxodithioesters **1** and ammonium acetate to synthesize the isothiazoles **59** for the first time. Ammonium salts such as $(NH_4)_2CO_3$ and HCO_2NH_4 were also utilized, but no improvement was observed. The reaction proceeds through an imine formation/cyclization/ aerial oxidation sequence, leading to a library of substituted isothiazoles in good yields. The protocol was extended towards the functionalization of the isothiazoles **59** to an alkylsulfonyl derivatives **60** by treating the isothiazoles with *meta*-chloroperoxybenzoic acid (mCPBA) in DCM at room temperature (Scheme 25).



Scheme 25. Synthesis of isothiazoles.

The synthesis of 1,4-thiazine-3-ones **61** *via* domino reduction/annulation of an *α*-hydroxyimino-*β*-oxodithioesters **54** with internal alkynes **23** has been reported. Here, *α*-hydroxyimino-*β*-oxodithioesters **54** were prepared from *α*-enolicdithioesters **1'** *via* nitrosation (Nagaraju et al. 2014). This protocol allows the formation of azaheterocycles *via* C-S/C-N bonds, displaying a broad scope concerning the substituents (Scheme 26).

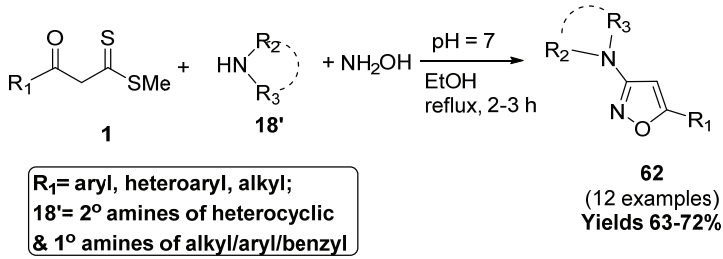


Scheme 26. Synthesis of 1,4-thiazine-3-ones.

4.4 Synthesis of *O,N*-containing heterocycles

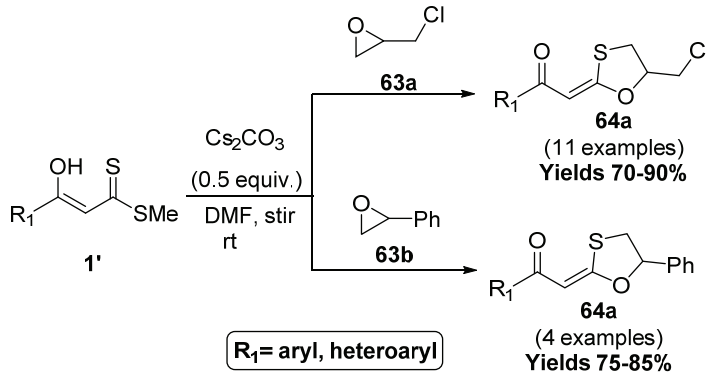
Samai et al. (2013) reported the synthesis of isoxazoles **62** from *β*-oxodithioesters **1**. The reaction process involves the cyclocondensation of *β*-oxodithioesters **1**, amines **18'** and hydroxylamine in refluxing ethanol, giving the product a single regioisomer in good yields. The reaction tolerated a broad range of *β*-oxodithioesters **1**, primary aliphatic amines and cyclic secondary amines. The cyclocondensation protocol was equally

facile with aromatic amines. However, aliphatic amines react faster than aromatic amines (Scheme 27).



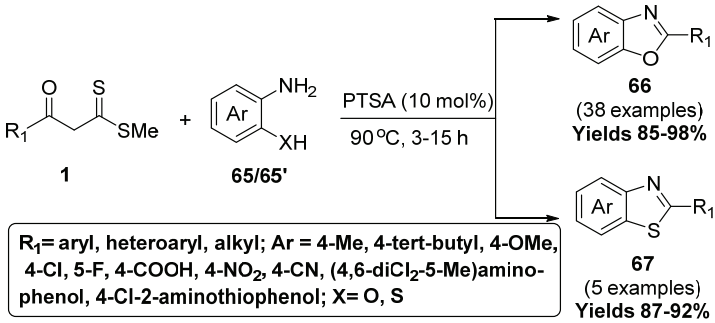
Scheme 27. Synthesis of isoxazoles.

Shukla et al. (2014) have developed a regioselective protocol for synthesizing functionalized 1,3-oxathiolan-2-ylidenes **64a/b** through [2+3] heteroannulation of α-enolic dithioesters **1'** with epoxides **63a/b** in the presence of Cs_2CO_3 at room temperature. This transformation involves the construction of two new bonds (C–S and C–O) and one ring with both reactants being utilized efficiently. A broad spectrum of α-enolic dithioesters **1'**, regardless of the substituents' steric and electronic nature, gave the products good yields (Scheme 28).



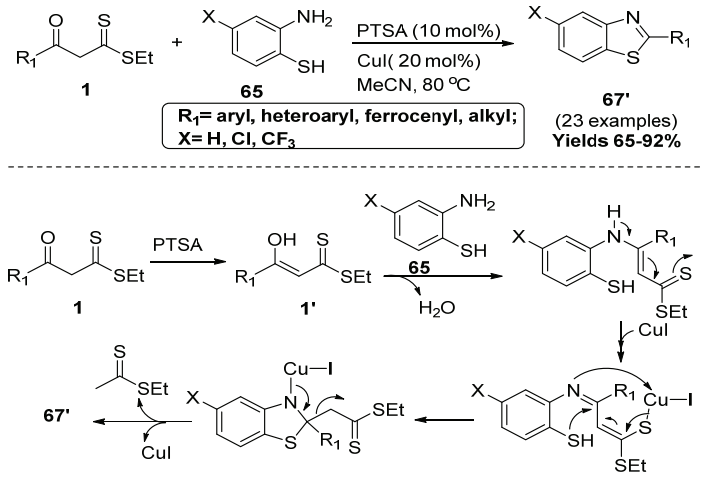
Scheme 28. Synthesis of 1,3-oxathiolan-2-ylidenes.

Srivastava et al. (2017) have developed an efficient one-pot cascade method to construct a diverse 2-aryl/hetaryl/alkyl benzazoles such as benzoxazoles **66** and benzothiazoles **67** using 2-amino(thio)phenols **65/65'** and *β*-oxodithioesters **1** catalyzed by *para*-toulenesulfonic acid. Two new bonds are formed during the reaction *via* N-H/O-H and N-H/S-H functionalization (Scheme 29).



Scheme 29. Synthesis of benzazoles from amino(thio)phenols and *β*-oxodithioesters.

An efficient synthesis of 2-substituted benzo[*d*]thiazole derivatives **67'** has been accomplished using a catalyst combination of PTSA and CuI through a one-pot condensation reaction of 2-aminothiophenols **65** and *β*-oxodithioesters in acetonitrile at 80 °C (Ghosh et al. 2018). Initially, **1** undergoes enolization in the presence of PTSA to give an intermediate **1'**, reacting with 2-aminothiophenol **65** to generate the mono enamino dithioester intermediate A, which further coordinates with CuI to form an iminium intermediate B. The intermediate B undergoes an intramolecular nucleophilic addition to furnish the adduct C. And the product **67'** was obtained after eliminating CuI and ethyl ethanedithioate through C-C bond cleavage, as shown in Scheme 30.

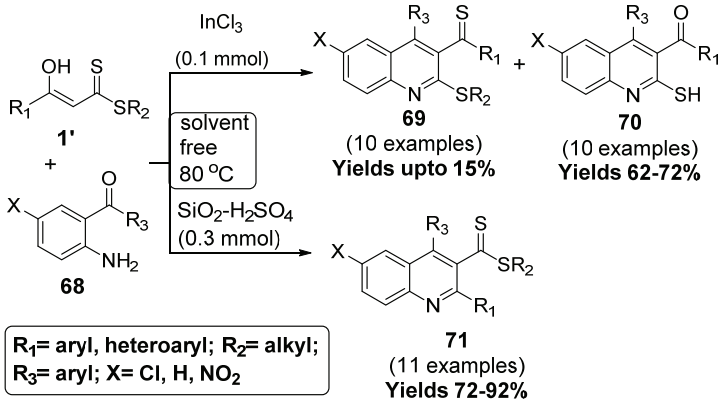


Scheme 30. Synthesis of various 2-substituted benzo[*d*]thiazoles.

4.5 Synthesis of *N*-containing heterocycles

An efficient one-pot, solvent-free methodology for synthesizing highly functionalized quinolones **69**, **70** and **71** through the site-selective

coupling of *ortho*-aminoaryl ketones **68** with *α*-enolic dithioesters **1'** has been reported (Scheme 31). The carbonyl and the thiocarbonyl moiety in *α*-enolic dithioesters **1'** were employed to construct the three differently substituted quinolines in a chemoselective manner by variation of acid catalysts (Koley et al. 2016[b]). The formation of two new bonds (one C-C and one C-N) and one ring in a single operation is a salient feature of this protocol.

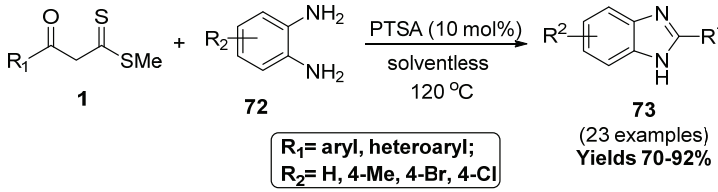


Scheme 31. Synthesis of quinolines from *ortho*-aminoaryl ketones and α-enolic dithioesters.

4.6 Synthesis of two *N*-containing heterocycles

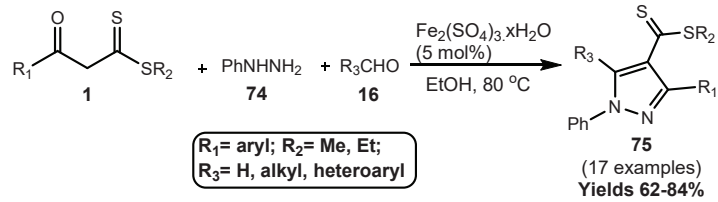
For the first time, Srivastava et al. (2018) devised a simple one-pot domino heteroannulation of *β*-oxodithioesters **1** with 1,2-phenylenediamines **72** under metal-free and solventless conditions to benzimidazoles **73** using a catalytic amount of PTSA. Under the optimal conditions, the reaction proceeded smoothly to give diverse C-2 substituted benzimidazoles in good to high yields. Notably, the reaction

tolerates a broad range of functional groups such as electron-rich, electron-neutral and electron-poor present in **72**. Significantly, the presence of various groups makes these compounds an excellent entrant as precursors for further synthetic renovations (Scheme 32).



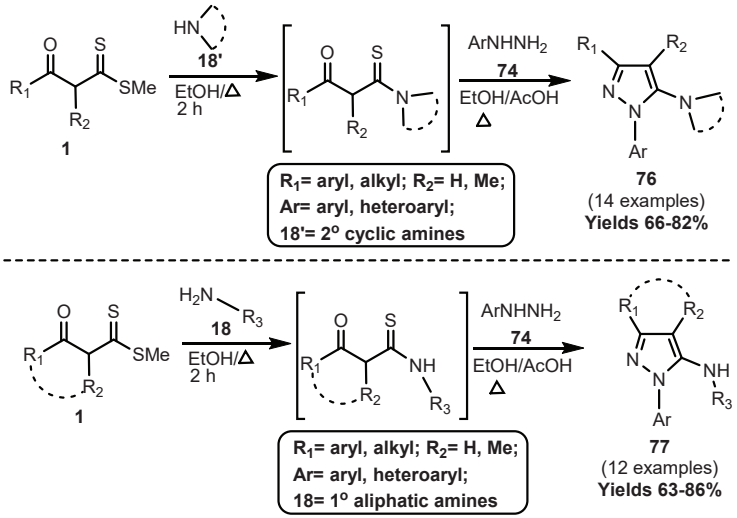
Scheme 32. Synthesis of benzimidazoles.

Khan et al. (2013) have developed a synthetic protocol for synthesizing trisubstituted 1*H*-pyrazole-4-carbodithioates **75** by a sequential multicomponent one-pot condensation of aldehydes **16**, phenylhydrazine **74** and **1** using ferric sulfate as a catalyst. Ferric sulfate (5 mol %) in ethanol at 80 °C gave the best yields (Scheme 33). It was mentioned that catalysts in ethanol, such as $Co(OTf)_2$, $In(OTf)_3$, $ZnCl_2$, l-proline and $FeCl_3$, provided lower yields and required longer reaction times. Various solvents were also examined with 5 mol% of ferric sulfate under identical reaction conditions. However, ethanol was the best solvent compared to the others tested in their report.



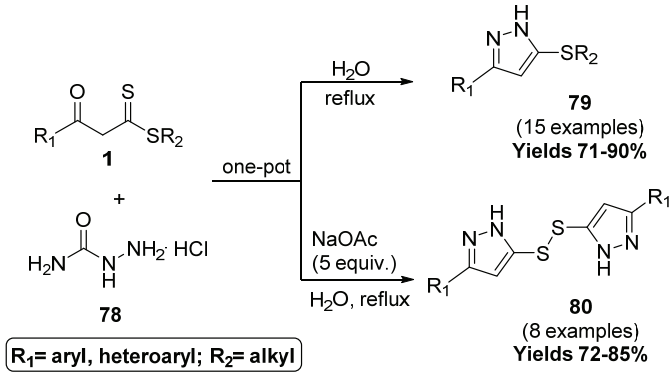
Scheme 33. Synthesis of pyrazoles using sequential one-pot MCR.

Nandi et al. (2012) have developed an efficient synthesis of 1-aryl-3,4-substituted-5-(cycloamino) **76** and (alkylamino)pyrazoles **77** (Scheme 34). The reaction of *β*-oxodithioesters with primary aliphatic or cyclic secondary amines **18**/**18'** and arylhydrazines **74** in refluxing ethanol in the presence of a catalytic amount of acetic acid gives the products moderate to good yields. *β*-Oxothioamide compounds were shown to be the actual reactive species in these reactions.



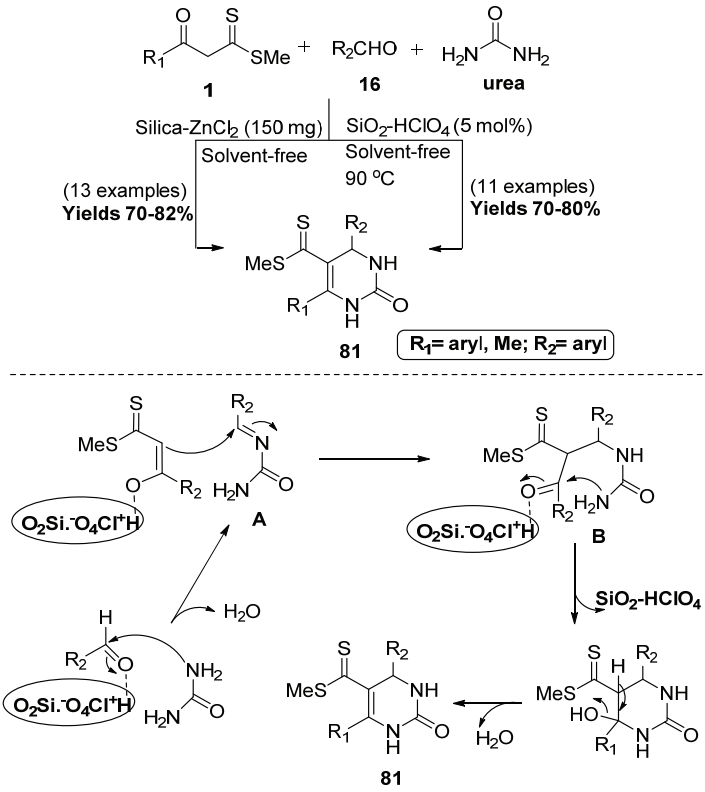
Scheme 34. Synthesis of pyrazoles using sequential one-pot MCR.

Koley et al. (2018) reported coupling semicarbazide hydrochloride **78** with *β*-oxodithioesters **1** in water to construct pyrazoles **79** in good to excellent yields and disulfide-tetheredpyrazoles **80** in good yields. The pH of the medium played a vital role in forming the two different products. Adding NaOAc (5 equiv.) affords the disulfide-tethered pyrazoles, while a neutral medium leads to the formation of pyrazoles (Scheme 35).



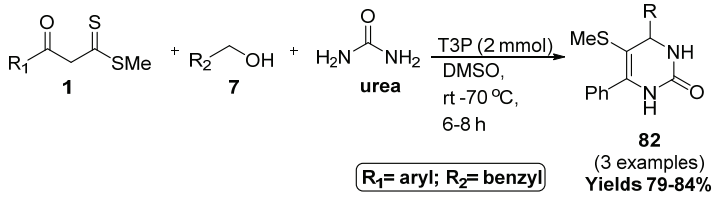
Scheme 35. Synthesis of pyrazoles and disulfide-tethered pyrazoles.

The utilization of *β*-oxodithioester is an alternative to the 1,3-dicarbonyl compounds in the Biginelli reaction in the presence of catalyst Silica–$ZnCl_2$ (Devi et al. 2015) and SiO_2-$HClO_4$ (Chanu et al. 2018) respectively, under the solvent-free conditions (Scheme 36). Thus, in good yields, a series of dihydropyrimidinones **81** were synthesized using *β*-oxodithioester **1**, aromatic aldehydes **16** and the urea at 80 ºC. A plausible mechanism for synthesizing 5-methylmercaptothiocarbonyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones **81** involved the acid-catalyzed formation of an acyl imine intermediate **A** formed by the reaction of the aldehyde with urea, this is the critical rate-limiting step. Interception of the iminium ion by *β*-oxodithioester **1** produces an open-chain ureide **B** that subsequently cyclized to the dihydropyrimidinone **81**.



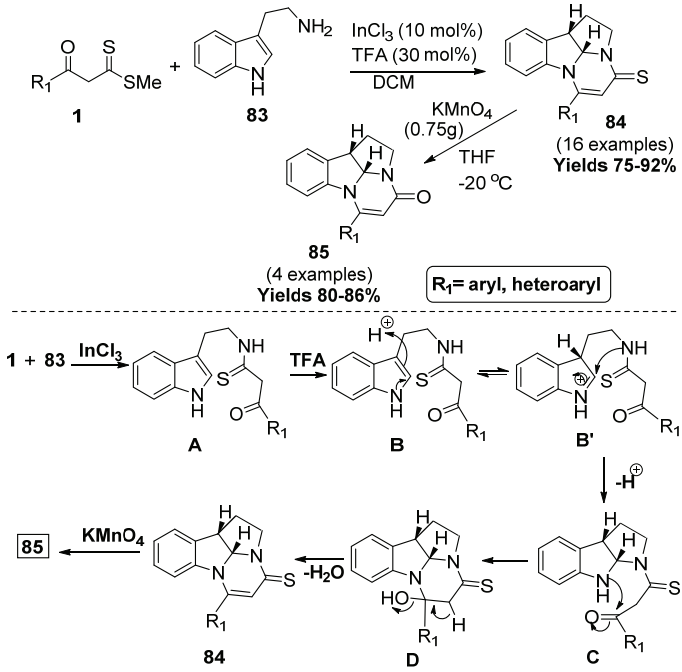
Scheme 36. Synthesis of dihydropyrimidinones in a one-pot MCR.

Another route to dihydropyrimidinones **82** with good yields has been reported by Revanna et al. (2014), in a one-pot three-component oxidative cyclocondensation of a variety of alcohols **7**, *β*-KDEs and urea using propanephosphonic acid anhydride (T3P) in dimethylsulfoxide (DMSO) as the solvent (Scheme 37).



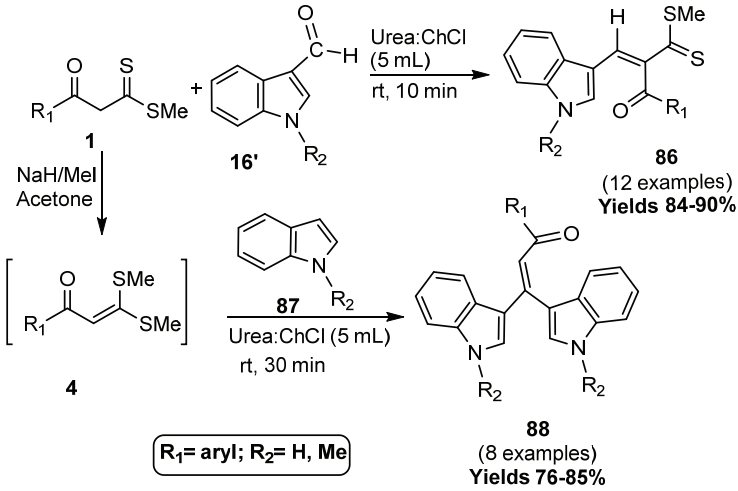
Scheme 37. Synthesis of dihydropyrimidinones using alcohols.

The application of *β*-oxodithioesters **1** to synthesize a tetracyclic [6,5,5,6] indole ring **84** in a tandem cycloannulation reaction with tryptamine **83** was described for the first time by Singh et al. (2013). In this protocol, three C-N bonds and two new rings were constructed with all reactants efficiently utilized in the chemical transformation (Scheme 38). Further experiments of oxidative dehydrogenation using $KMnO_4$ led to the isolation of an unexpected oxidative desulphurization products **85** instead of the expected dehydrogenated products in tetrahydrofuran (THF). The reaction of **1** and tryptamine **83** was presumably initiated by forming a thioamide **A** in an acidic solution, which underwent protonation to generate intermediates **B** and **B'**. The intermediate **B'** was transformed to tetrahydro pyrrolo[2,3-*b*]indole system **C** by an intramolecular nucleophilic attack at the C2 of the indole. Participation of the indolyl NH in the intramolecular cyclization with a nucleophilic attack at the carbonyl group followed by an elimination of H_2O leads to the formation of tetracyclic [6,5,5,6] indole ring **84** in good yields.



Scheme 38. The mechanism for synthesizing of tetracyclic [6,5,5,6] indole ring.

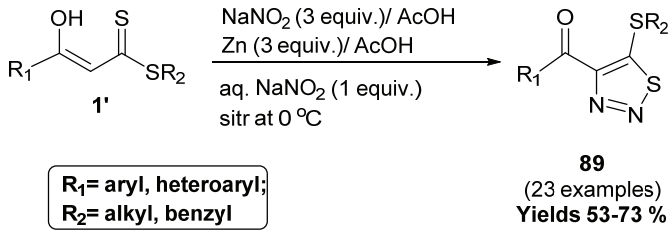
Further, Devi et al. (2020) explored the inherent ambident reactive sites (electrophilic and nucleophilic) of *β*-KDEs **1**. It was realized by treating them with indoles and indole-3-carbaldehydes **16'**, resulting in the two different types of densely functionalized alkenes. Knoevenagel condensation of *β*-KDEs with indole aldehydes has been conducted smoothly using the eco-friendly deep eutectic solvent (DES) to yield monoindole substituted alkenes **86**. On the other hand, C-3 alkylation of indoles with ketene-*S,S*-acetal by a conjugate-addition-substitution pathway resulted in the regioselective synthesis of bisindolyl alkenes **88** using DES as the medium (Scheme 39).



Scheme 39. Mono and bis-indolyl alkenes from β-ketodithioesters.

4.7 Synthesis of two *N*- and one *S*-containing heterocycles

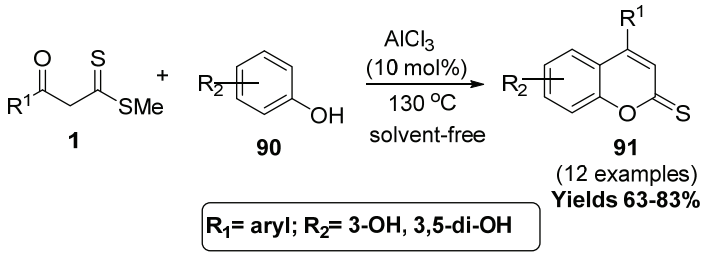
Nagaraju et al. (2014) developed a straightforward synthesis of 1,2,3-thiadiazoles **89** from α-enolic dithioesters **1'** *via* nitrosation/reduction/diazotization/cyclization sequence in one-pot through the formation of cascade 1–2 (N–S) and 3–4 (C–N) bonds (Scheme 40).



Scheme 40. Synthesis of 1,2,3-thiadiazoles.

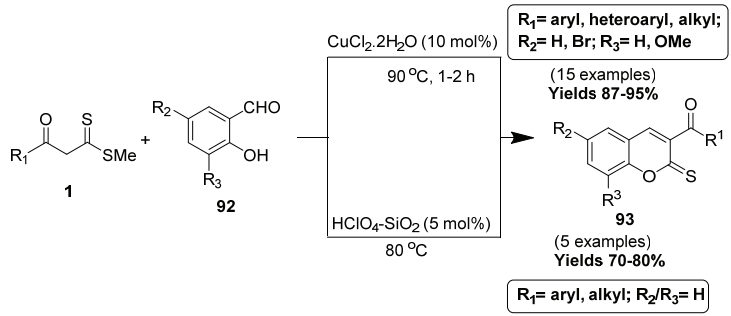
4.8 Synthesis of *O*-containing heterocycles

The utilization of *β*-oxodithioester **1** to synthesize 2*H*-chromene-2-thiones **91** *via* the Pechmann reaction was demonstrated by Devi et al. (2013[b]). The reaction proceeds *via* a ring annulation of **1** with phenols **90** catalyzed by $AlCl_3$ under solvent-free conditions (Scheme 41). Notably, this method tolerates various substituents in both components, giving the product good yields.



Scheme 41. Synthesis of 2*H*-chromene-2-thiones.

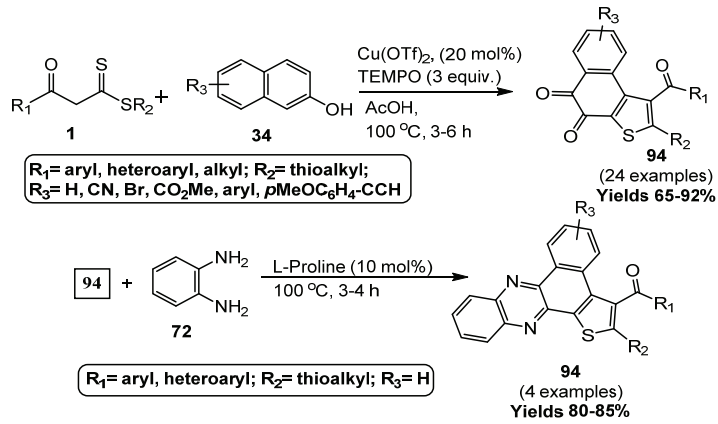
Devi et al. (2013[c]) demonstrated cupric chloride catalyzed synthesis of coumarins **93** by condensing *β*-oxodithioesters **1** with salicylaldehyde **92** under solvent-free conditions (Scheme 42). This method was also reported by the same authors using $SiO_2.HClO_4$ as a recyclable heterogeneous catalyst (Chanu et al. 2018). However, cupric chloride shortened the reaction time and enhanced the yields (87-95%) compared to 70-80% yields for the reaction using $SiO_2.HClO_4$.



Scheme 42. Synthesis of coumarins under solvent-free conditions.

4.9 Synthesis of fused heterocycles

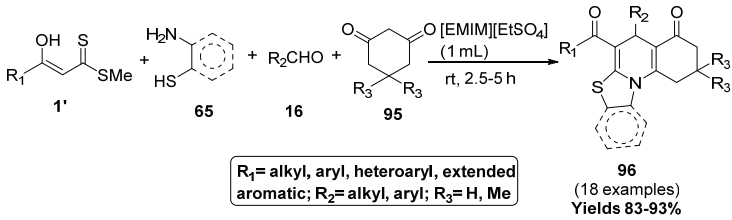
Then, an efficient copper-catalyzed and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated synthesis of 2,3-disubstituted naphtho[2,1-*b*]thiophene-4,5-diones **35** *via* a cross-dehydrogenative thienannulation was achieved by Shukla et al. (2018). The reaction progressed *via in situ* generated naphthalene-1,2-diones by dearomatization of *β*-naphthols **34** with an oxidative hetero annulation of **1'** chemoselectively in a reaction pot. Then, **35** undergo L-proline-catalyzed cross-dehydrative coupling with *ortho*-phenylenediamine **36** enabling the pentacyclic benzo[*a*]thieno[3,2-*c*]phenazines **37** in good yields under solvent-free conditions (Scheme 43).



Scheme 43. Synthesis of naphtho[2,1-*b*]thiophene-4,5-diones and benzo[*a*]thieno[3,2-*c*]phenazines.

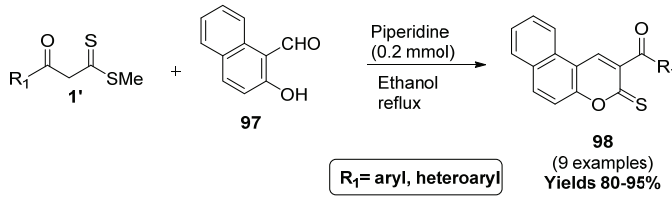
Singh et al. (2018) developed a one-pot four-component annulation coupling to thiazoloquinolinone derivatives **96** from *α*-enolic dithioesters **1'**, cysteamine/2-aminothiophenols **65**, aldehydes **16** and cyclic 1,3-diketones **95** in an ionic liquid (IL) at room temperature. They started with nonaromatic protic ionic liquids such as [Pyr]-[HCOO], [Pyr][NO_3], [HMPy]-[HCOO], [EtPip][$EtSO_4$], and [EtMPy][$EtSO_4$]. All the above ILs promoted the reaction well, producing the desired product **96** in an excellent yield. To check the generality of the protocol, they further investigated protic aromatic ILs such as [EMIM][$EtSO_4$], [BMIM][Br], [EtP][$EtSO_4$], and [MeP][$MeSO_4$]. It was observed that $EtSO_4$ anion-based ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate [EMIM][$EtSO_4$] afforded maximum conversion in minimum time, providing the desired product **96** in 93% of yields within 2.5 hours, thus showing better efficacy than other ILs. This method leads to forming five consecutive new bonds (2 C−C, 2 C−N and 1 C−S) and two rings with all reactants efficiently

utilized in a single operation, making the protocol very effective and green (Scheme 44).



Scheme 44. Synthesis of thiazoloquinolinones in one-pot four components fashion.

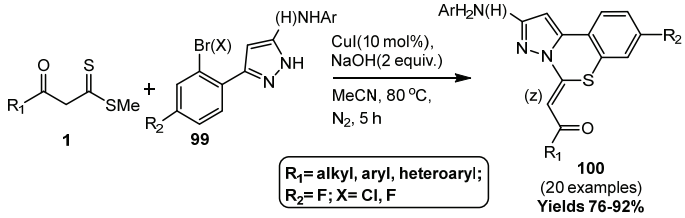
Chanu et al. (2017) described a Knoevenagel cyclocondensations of *α*-hydroxy naphthaldehyde **97** with *β*-oxodithioesters **1** furnishing 2*H*-benzo[*f*]chromene-2-thiones **98** in the presence of piperidine in ethanol (Scheme 45). Some of the synthesized compounds exhibited excellent antifungal and antibacterial activities.



Scheme 45. Synthesis of 2*H*-benzo[*f*]chromene-2-thiones and 2*H*-benzo[*f*]chromen-2-ones.

The chemoselective synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives **100** has been developed by tandem Ullmann coupling reactions of *β*-oxodithioesters (ODEs) with 3-(2-bromoaryl)-1*H*-pyrazoles **99** in C-S bond formation manner, in which ODEs play dual roles as both a substrate

and a ligand as reported by Wen et al. (2015). Thus, a library of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives was established with good to excellent yields using CuI as the copper source in the presence of NaOH in MeCN at 80 °C under the N_2 atmosphere (Scheme 46).



Scheme 46. Synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives.

4. Conclusion

The present chapter focuses on the versatility of *β*-oxodithioesters as the building blocks of numerous heterocyclic compounds and building up various critical substrates for organic synthesis. Thus, by applying many well-established methodologies, various heterocycles of different sizes and ring systems can be readily synthesized utilizing *β*-oxodithioesters.

5. References

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CHAPTER 9

α-OXOKETENE DITHIOACETALS

1. Introduction

α-Oxoketene dithioacetals (ketene-*S,S*-acetals) **1** (Figure 1), bearing a carbonyl group at the *α*-C atom, are well-known versatile intermediates and have diverse applications in organic synthesis (Dieter, 1986; Junjappa et al., 1990; and Pan et al., 2013). They are excellent three-carbon synthons having the 1,3-electrophilic centers exhibiting different electrophilicity. The *β*-carbon having bis-alkylthio group behaved as a soft electrophilic center while the carbonyl carbon is a hard electrophilic center. They can be visualized as masked *β*-ketoesters as the ketene dithioacetal moiety can be readily converted to an ester group. Further, they may be regarded as *α,β*-unsaturated ketones with a highly functionalized *β*-carbon. The electrons on alkylated S-atoms are efficiently pulled by aroyl or acyl group in the α-position of dithioacetal through a double bond, rendering the whole system highly polarized donor-acceptor ethylene. Hence, different types of nucleophiles can attack the system leading to the construction of various heterocycles and aromatic carbocycles.

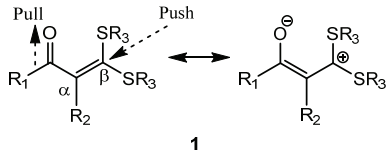
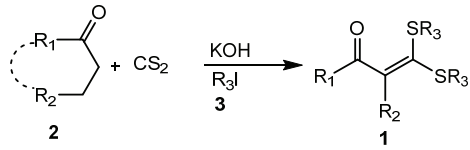


Figure 1. Reactive profile of ketene-*S,S*-acetal.

2. Synthesis of ketene-*S,S*-acetals

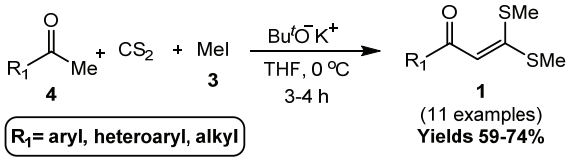
The synthesis of ketene-*S,S*-acetals **1** was reported for the first time by Kelber (1910) using the reaction of the carbon disulfide (CS_2) with an active methyl ketone **2** in the presence of potassium hydroxide followed by alkylation in a one-pot reaction (Scheme 1). Enormous advancement has been made in ketene-*S,S*-acetals since their discovery in 1910.



Scheme 1. The synthesis of the ketene-*S,S*-acetals *via* Kelber's method.

Choi et al. (1988) successfully prepared ketene-*S,S*-acetals directly from ketones in good yields using potassium carbonate in *N,N*-dimethylformamide as the solvent. Then, Ouyang et al. (2006) also reported the synthesis of ketene-*S,S*-acetals in good yields using water as the medium and tetrabutylammonium bromide (TBAB) as the phase transfer catalyst in a solid-liquid system. Several simple synthetic procedures are available for transforming active methylene compounds into α-functionalized ketene-*S,S*-acetals and other novel molecules using ketene dithiolate. For example, Verma et al. (2012) modified and improved the yields of ketene *S,S*-acetals **1** by treating the corresponding aryl/heteroaryl/aliphatic ketones **4** with the

carbon disulfide in the presence of potassium *tert*-butoxide followed by alkylation with the methyl iodide **3** in tetrahydrofuran (THF) as shown in Scheme 2. Nowadays, the chemistry of ketene-*S,S*-acetals has extensively been explored as a*n* S-containing synthon leading to the synthesis of various vital carbocycles and heterocycles.

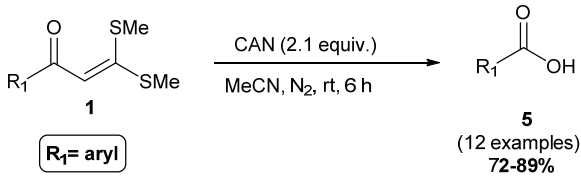


Scheme 2. Synthesis of ketene-*S,S*-acetals from ketones.

3. Functionalization of Ketene-*S,S*-acetals

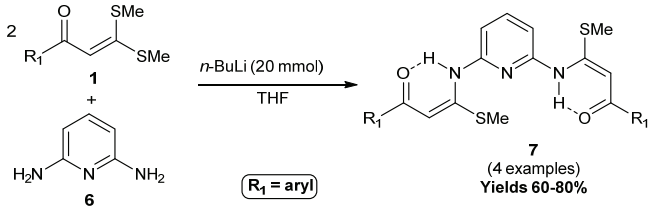
The α-C of ketene-*S,S*-acetals is reactive towards electrophiles and this electrophilic susceptibility makes the α-functionalization of ketene-*S,S*-acetals a convenient tool for the construction of diverse scaffolds and other valuable building blocks.

Chemoselective oxidative conversion of α-aroylketene-*S,S*-acetals to the aryl carboxylic acid **5** in the presence of ceric ammonium nitrate (CAN) in acetonitrile (MeCN) has been achieved under mild reaction conditions (Babu and Shanmugam, 2017). The internal nitrate ligand in the CAN acted as an oxidant and favored selective conversion of α-aroylketene-*S,S*-acetals to an aryl acid (Scheme 3). This synthetic strategy was compatible with various aromatic groups under mild conditions, having electron-rich and deficient α,β-unsaturated systems.



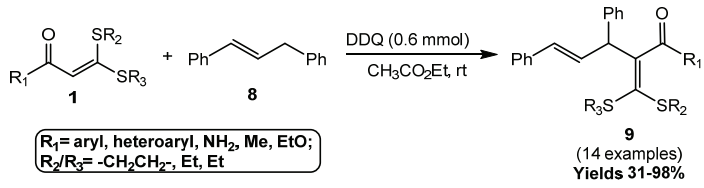
Scheme 3. Synthesis of carboxylic acids from α-aroylketene-*S,S*-acetals.

Then, Singh et al. (2013) developed a synthetic methodology for the preparation of pyridine substituted ketene-*S,N*-acetals with an *E*-configuration from ketene-*S,S*-acetals (Scheme 4). The presence of several electrophilic and nucleophilic reactive sites in *S,N*-acetals makes it an essential synthon in regioselective ring-closure strategies to yield exciting and novel molecules containing pyridine and other heterocycles.



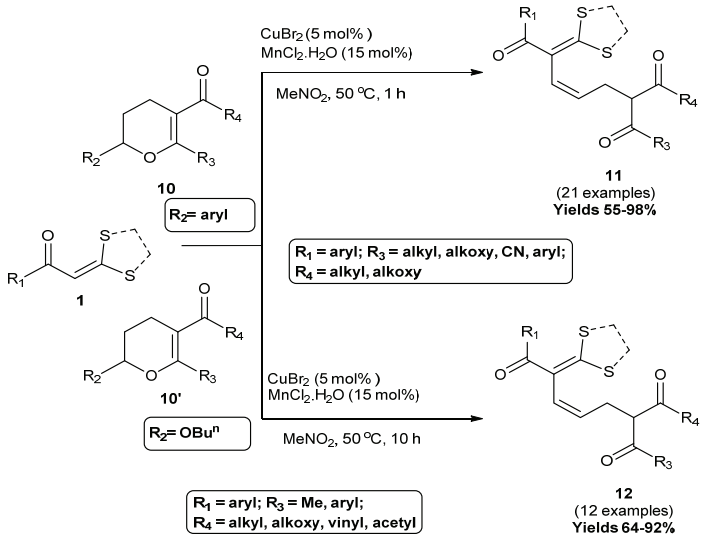
Scheme 4. Synthesis of ketene-*S,N*-acetals from ketene-*S,S*-acetals.

Cheng et al. (2017) reported a novel 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated metal-free cross-dehydrogenative coupling reaction of push-pull α-oxo ketene dithioacetals with 1,3-diarylpropenes **8** giving the C(sp^2)-H and C(sp^3)-H coupling products **9** in moderate to good yields. In this protocol, 2-furoyl-, 2-thienoylketene dithioacetals and ketene-*S,S*-acetals with functional groups at the α-position, such as acetyl, carbamoyl and ethoxycarbonyl were feasible for the coupling giving the products in good yields (Scheme 5).



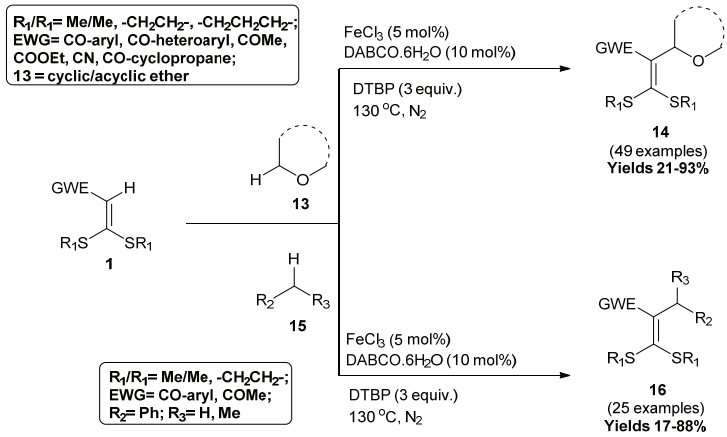
Scheme 5. Synthesis of α-alkylation products from ketene-*S,S*-acetals.

Liu et al. (2015) had accomplished an electrophilic ring-opening reaction of 2-substituted 3,4-dihydropyrans **10**/**10'** with ketene-*S,S*-acetals with a unique synergistic effect of the $CuBr_2$ and $MnCl_2.4H_2O$ catalyst in nitromethane ($MeNO_2$) as the solvent. This experiment demonstrates the concept of synergistic catalysis in overcoming the difficulties of organic synthesis and enables them to access a specific class of molecules that are valuable for organic synthesis. In the first case, when 2-aryl-3,4-dihydropyrans **10** were used, Friedel-Crafts ring-opening products **11** was generated with the help of the catalytic system employed. However, with 2-alkoxy-3,4-dihydropyrans **10'** an intramolecular Michael addition of the ring-opening products was developed, leading to an efficient protocol to access some densely substituted buta-1,3-dienes **12** (Scheme 6).



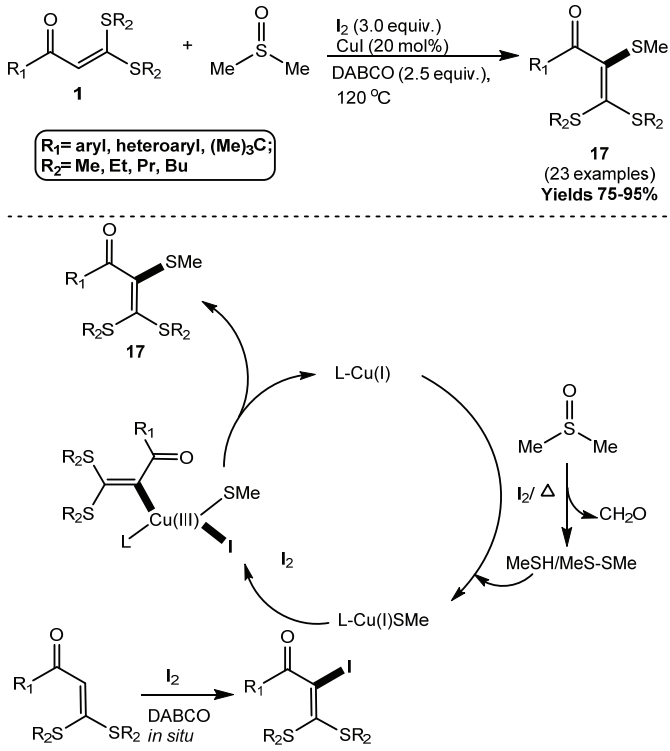
Scheme 6. Ring-opening reactions of 2-substituted 3,4-dihydropyrans with ketene-*S,S*-acetals.

Wang et al. (2017) described an oxidative C–H alkylation of *S*,*S*-functionalized internal olefins employing simple ethers **13** and toluene derivatives **15** as the cross-coupling partners. FeCl3 mediated the reaction with di-*tert*-butyl peroxide (DTBP) as the oxidant and 1,4-diazabicyclo[2.2.2]octane (DABCO·$6H_2O$) as the additive giving rise to two different products **14** and **16**. The alkylthio functionality was essential for the internal olefinic C-H bond to undergo alkylation with the O-adjacent C(sp^3)-H bonds of ethers and benzylic C-H bonds of toluene derivatives, respectively (Scheme 7).



Scheme 7. C-H alkylation of ketene-*S,S*-acetals.

The selective thiomethylation of an α-Csp^2 atom of ketene-*S,S*-acetals **17** using the dimethyl sulfoxide (DMSO)-iodine-Cu(I) system was successfully demonstrated by Shukla et al. (2015). In this protocol, interestingly DABCO plays a dual role of a ligand as well as a base, and DMSO acts both as a source of the thiomethyl group and as a solvent. The plausible mechanism starts with the iodination of ketene-*S,S*-acetals **1** to give an α-aroyl-α-iodoketene dithioacetal. On the other hand, DMSO in the presence of iodine generates precursor MeSH or MeS-SMe, which undergoes nucleophilic coordination with the Cu(I) species in the presence of DABCO to form a complex L-Cu(I)-SMe. This complex subsequently undergoes oxidative addition with *in situ* formed α-aroyl- ketene-*S,S*-acetals to give the Cu(III) complex. Then, upon reductive elimination gave the thiomethylation of ketene-*S,S*-acetals **17** with an elimination of the Cu(I) species to complete the catalytic cycle (Scheme 8).



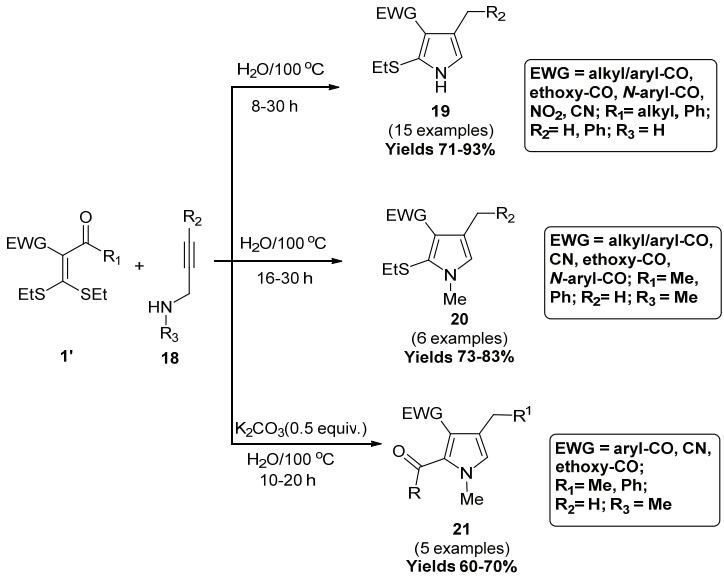
Scheme 8. *α*-Thiomethylation of ketene-*S,S*-acetals with dimethyl sulfoxide.

4. Application of Ketene-*S,S*-acetals in organic synthesis

4.1 Synthesis of *N*-containing heterocycles

Ren et al. (2013) synthesized a series of tri- and tetrasubstituted pyrroles **19-21** from α-acyl ketene-*S,S*-acetals **1'** through the [3+2] cycloaddition with 1° and 2° propargyl amines **18** as 1,3-dipoles by using water as the solvent. The reaction of **1'** with 1° amines affords the 2,3,4-trisubstituted pyrroles **19** in good yields. However, the reaction with 2° amines gives two different products depending upon using an external base i.e., K_2CO_3. In the absence

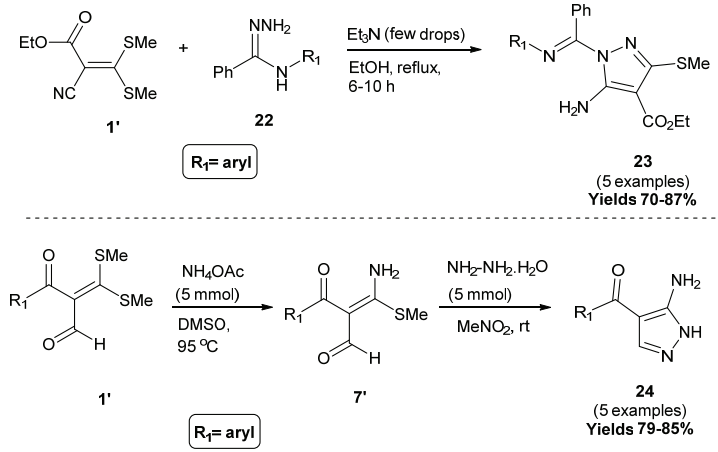
of K_2CO_3, 1,2,3,4-tetrasubstituted pyrroles **20** bearing an ethylthio group at the C-2 position were obtained. In contrast, 1,2,3,4-tetra-substituted pyrroles **21** bearing an acetyl group at the C-2 position were isolated when K_2CO_3 was added (Scheme 9).



Scheme 9. Synthesis of tri- and tetrasubstituted pyrroles from α-acyl ketene-*S,S*-acetals.

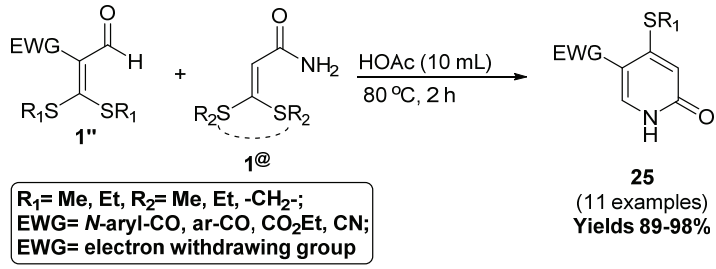
Aly et al. (2015) synthesized 1,3,4,5-tetrasubstituted pyrazoles **23** by reacting 2-cyano-3,3-bis(methylthio)acrylate **1'** with *N*-arylbenzamidrazones **22** in absolute dry EtOH in the presence of few drops of triethylamine (Et_3N) giving the products in good yields of 70-87%. On the other hand, Sreedevi et al. (2014) reported the synthesis of 3,4-disubstituted pyrazoles from aroyl formyl ketene-*S,S*-acetals **1**' (Scheme 10). The reaction procedure involves treating aroyl formyl ketene-*S,S*-acetals with ammonium acetate in DMSO

to form valuable intermediates 3-amino-2-aroyl-3-(methylsulfanyl)-2-propenals **7'**, which then react with hydrazine hydrate in acetonitrile medium at room temperature affording the products **24** in good yields of 79-85%.



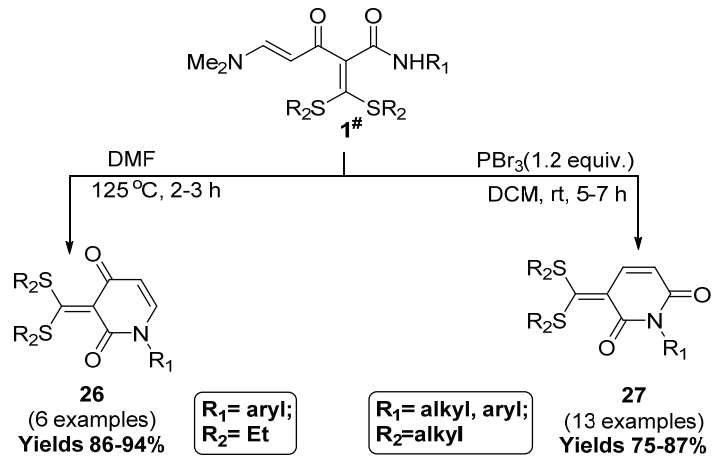
Scheme 10. Synthesis of tetra- and disubstituted pyrazoles from ketene-*S,S*-acetals.

Han et al. (2015) developed an efficient protocol for synthesizing substituted 2-pyridones **25** using acetic acid (HOAc)-catalyzed [3+3] annulation reaction of α-EWG-α-formyl ketene-*S,S*-acetals **1''** with α-carbamoyl ketene-*S,S*-acetals **1**[@]. This protocol involves a sequential Baylis–Hillman reaction and intramolecular cycloaddition, followed by the Michael addition and alkyl thiol elimination steps (Scheme 11).



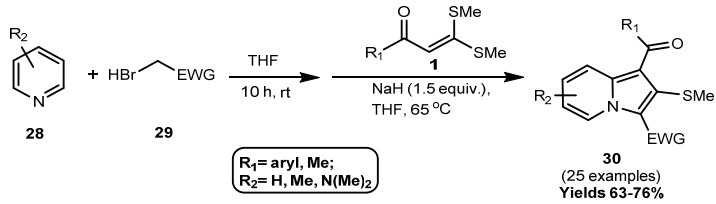
Scheme 11. Synthesis of substituted 2-pyridones from ketene-*S,S*-acetals.

A synthetic methodology to prepare substituted pyridine-2,4(1*H*,3*H*)-diones **26** from α-alkenoyl-α-carbamoyl ketene-*S*,*S*-acetals **1**[#] was explored by Liu et al. (2010). The substrate **1**[#] on treatment with *N*,*N*-dimethylformamide at 125 °C underwent an intramolecular *aza*-nucleophilic vinyl substitution reaction (a formal [5C+1N] annulation) to give the corresponding substituted pyridine-2,4(1*H*,3*H*)-diones in high yields. This method was extended by Shi et al. (2015); however, substituted pyridine-2,6(1*H*,3*H*)-diones **27** were obtained instead of **26** *via* an intramolecular [5+1] annulations of **1**[#] mediated by phosphorus bromide in dichloromethane (DCM) as the solvent at room temperature with longer duration of reaction time (Scheme 12).



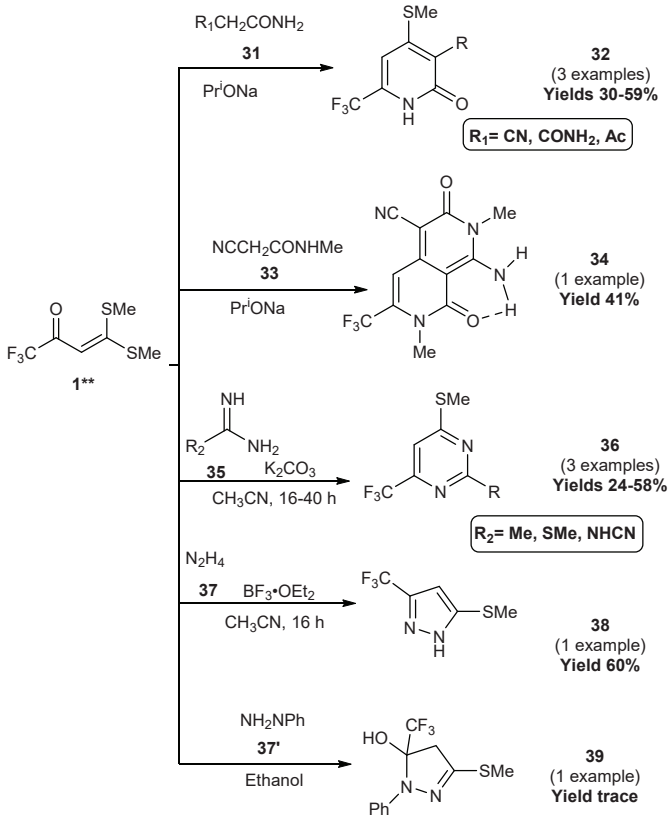
Scheme 12. Synthesis of substituted 2-pyridines from ketene-*S,S*-acetals.

Then, Ramesh et al. (2019) reported a one-pot three-component domino reaction of pyridines **28**, 2-bromoacetonitrile/ethyl 2-bromoacetate **29** and ketene-*S,S*-acetals promoted by the NaH, leading to the synthesis of the indolizines **30**. Here, *in situ* generated pyridinium ylides react with ketene-*S,S*-acetals giving the desired products in good yields. In this reaction, three new bonds and one new ring were efficiently formed in one sequence without using any catalyst (Scheme 13).



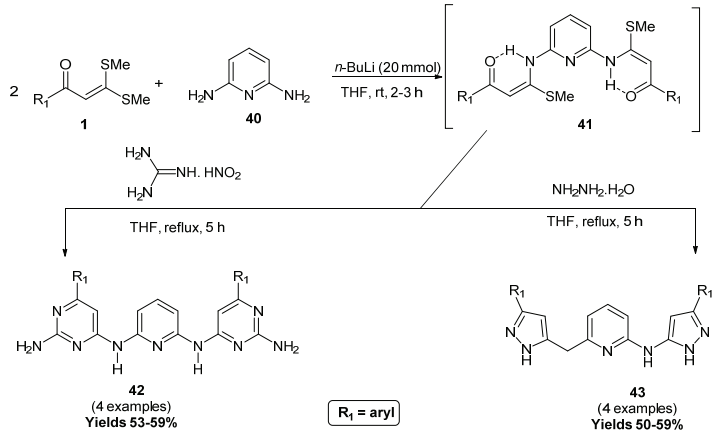
Scheme 13. Synthesis of indolizines from ketene-*S,S*-acetals.

Barabanov et al. (2012) developed a protocol for synthesizing a novel trifluoro-methylated 2-pyridines **32**, 2,7-naphthyridine **34**, pyrimidines **36**, pyrazole **38** and pyrazol **39** from trifluoroacetyl ketene-*S,S*-acetal **1****. The protocol involves the reaction of **1**** with aliphatic-amides **31**, amidines **33**, hydrazines **35/37** and phenylhydrazine **37'** to give the corresponding heterocycles in different reaction conditions, though the yields were low in most cases, as shown in Scheme 14.



Scheme 14. Synthesis of trifluoro-methylated *N*-containing heterocycles.

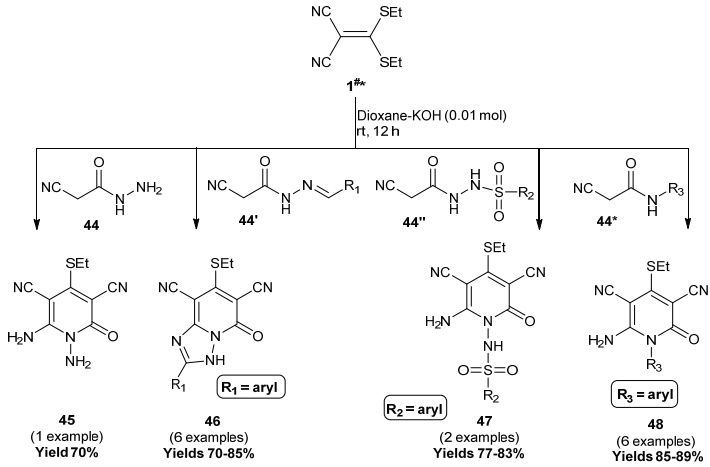
Singh et al. (2013) developed a facile method to prepare polyaza pyrimidines **42** and polyaza pyrazoles **43** from ketene-*S,S*-acetals **1**. This protocol was based on one-pot, three-component cyclocondensation of ketene-*S,S*-acetals **1**, 2,6-diaminopyridine **40** and guanidine or hydrazine in THF as the medium. The polyaza-*S,N*-acetals **41** has been generated *in situ* by treating ketene-*S,S*-acetals with 2,6-diaminopyridine in the presence of *n*-butyl lithium, which was subsequently treated with guanidine nitrate and hydrazine hydrate to afford the **42** and **43**, respectively, with moderate yields (Scheme 15).



Scheme 15. Synthesis of polyaza pyrimidines and polyaza pyrazoles.

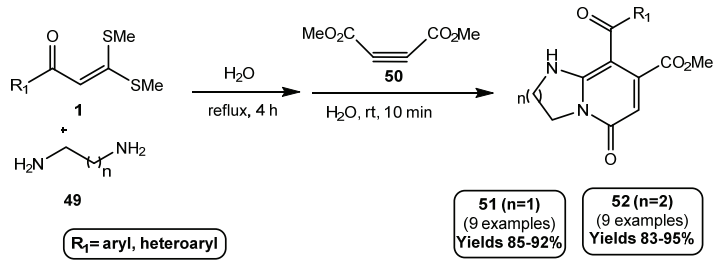
The synthesis of *N*-substituted derivatives of 4-ethylsulfanyl-2-pyridones **45**, **47-48** and triazolopyridines **46** was carried out by Azzam and Elgemeie. (2019). This method involves reaction of 2,2 dicyanoethene-1,1-bis(ethylthiolate) **1#*** with *N*-cyanoacetohydrazide **44**, *N*'-[(aryl)-methylene]-2-cyanoacetohydrazides **44'**, cyanoaceto-*N*-phenylsulfonyl-hydrazide **44''** and cyanoacetanilides **44*** to form the corresponding

pyridines. The starting material **1#*** was prepared by treating malononitrile with the carbon disulfide and the ethyl iodide in the presence of sodium ethoxide at room temperature (Scheme 16).



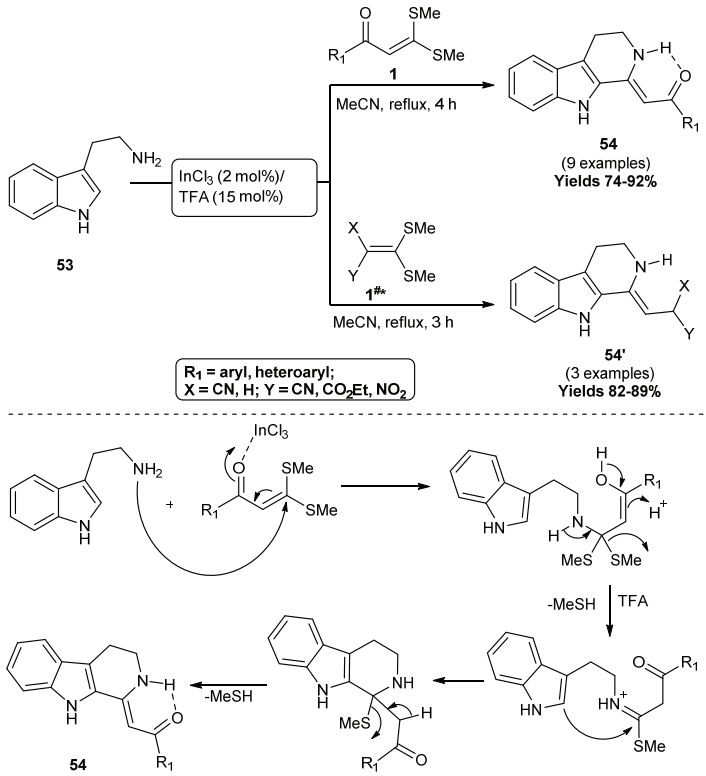
Scheme 16. Synthesis of *N*-substituted 4-ethylsulfanyl-2-pyridones and triazolopyridines.

Then, Chanu et al. (2014) reported the synthesis of tetrahydroimidazo[1,2-*a*]pyridines **51** and tetrahydropyrido[1,2-*a*] pyrimidines **52** by a one-pot and three-component reaction of ketene-*S,S*-acetals, diamines **49** and dimethyl acetylenedicarboxylate (DMAD) **50** in water. In this method, three new C-N bonds and one C-C bond were formed, leading to the formation of two different heterocyclic systems with excellent yields (Scheme 17).



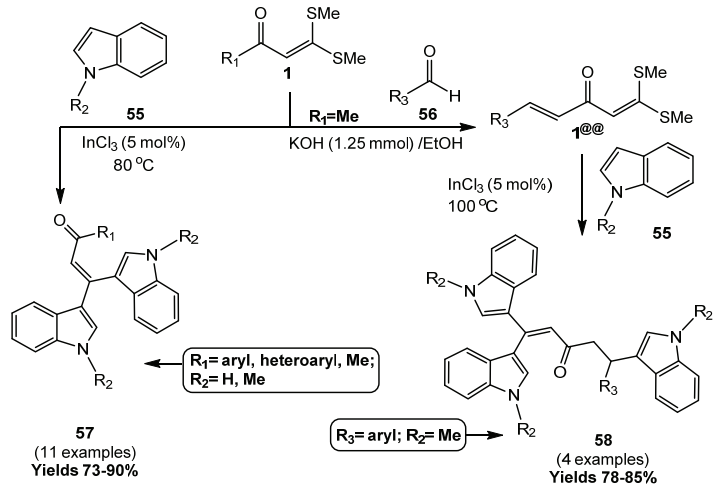
Scheme 17. Synthesis of imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines.

The synthesis of 1-substituted tetrahydro-*β*-carbolines **54** from ketene-*S,S*-acetals and tryptamine **53** in the presence of $InCl_3$/TFA was reported by Singh and Singh. (2016). This method was also extended to ketene-*S,S*–acetals **1#*** derived from electron-withdrawing substituents to give product **54** in good yields. The mechanism was proposed based on the Bischler-Napieralaski reaction. Initially, the nitrogen atom of tryptamine **53** attacks the electrophilic carbon of ketene-*S,S*-acetal **1**, forming a new C-N bond in the presence of $InCl_3$. Then, eliminating one molecule of MeSH generates an iminium intermediate, which undergoes an intramolecular attack of the C-2 of the indole ring to the electrophilic center to form a newly annulated six-membered ring. Finally, the subsequent elimination of one more MeSH gives the final product **54** (Scheme 18).



Scheme 18. Synthesis of 1-substituted tetrahydro-*β*-carbolines from ketene-*S,S*-acetals.

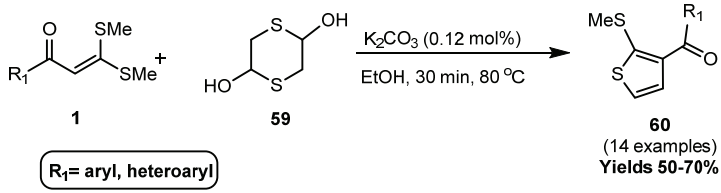
Further, Singh et al. (2014) also demonstrated the synthesis of bis- and trisindolylketones **57**-**58** through the Michael addition of indoles **55** with ketene-*S,S*-acetals using a catalytic amount of the $InCl_3$ under the solvent-free conditions. This reaction avoids the use of toxic solvents and the overall yields of the product was good (Scheme 19).



Scheme 19. Synthesis of bis- and tris-indolylketones from ketene *S,S*–acetals.

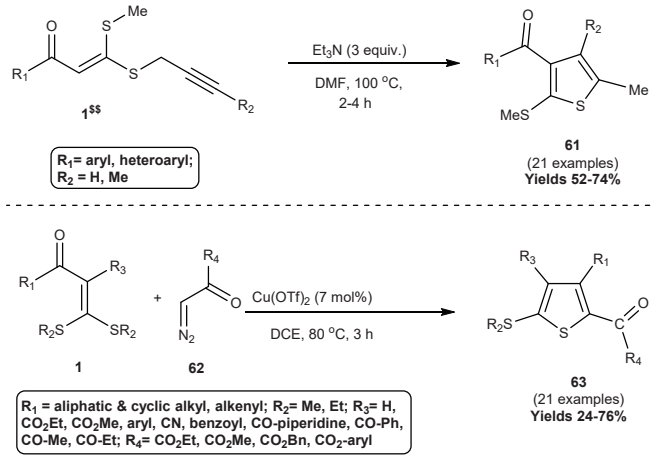
4.2 Synthesis of *S*-containing heterocycles

Kumara et al. (2016) have successfully demonstrated the synthesis of disubstituted thiophenes **60** in 55-70% overall yields. Here, 1,4-dithiane-2,5-diol **59**, a dimer of mercapto acetaldehyde reacts with ketene-*S,S*-acetals in the presence of anhydrous potassium carbonate in boiling ethanol to yield the corresponding 2-(methylthio)-3-aroyl/heteroaroyl thiophenes in average yields(Scheme 20).



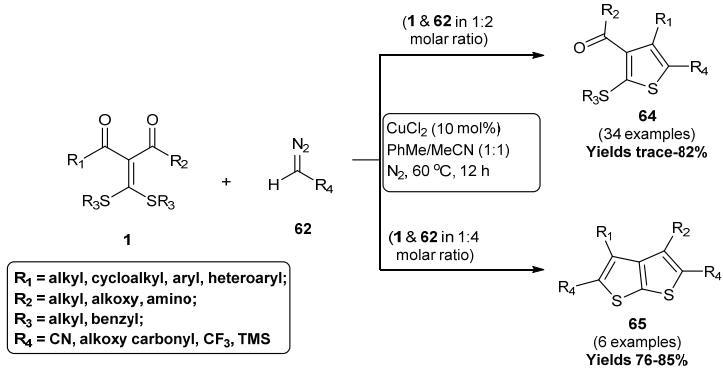
Scheme 20. Synthesis of disubstituted thiophenes from ketene-*S,S*-acetals.

The regioselective synthesis of polysubstituted thiophenes **61** *via* Et_3N mediated Claisen rearrangement reaction of α-oxo-*S*-methyl-*S*-propargyl ketenes **1**[$$] was reported by Kan et al. (2015). The tri- and tetrasubstituted thiophenes were obtained in moderate to good yields in *N,N*-dimethylformamide (DMF) as the solvent within 2-4 hours (Scheme 21). The electronic effects of *para*-substituents with different electron-withdrawing/donating substituents (such as *chloro, iodo, hydrogen, methyl, methoxy* and *phenoxy*) on the aromatic ring were analyzed and it was found that the electron-withdrawing groups usually gave relatively lower yields compared with the electron-donating groups. Sun et al. (2019) developed a copper (II) triflate catalyzed domino reaction between ketene-*S*,*S*-acetals and diazo compounds **62** to synthesize a range of polysubstituted thiophenes **63** in dichloroethane (DCE) as the solvent. This process involved the generation of sulfur ylides with the formation of a C-S bond and cleaving sequence, which could tolerate a diverse range of the acyclic ketene-*S*,*S*-acetals (Scheme 21).



Scheme 21. Synthesis of poly-substituted thiophenes.

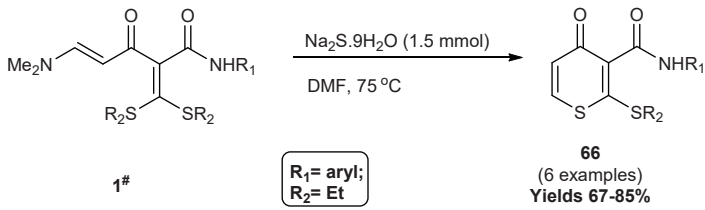
He et al. (2020) developed an efficient protocol for the synthesis of fully substituted thiophenes **64** and thieno[2,3-*b*]thiophenes **65** through the $CuCl_2$-catalyzed annulation of *S,S*-disubstituted enones **1** with diazo compounds **62** under mild conditions. In this process, tetrasubstituted thiophenes **64** and thieno[2,3-*b*]thiophenes **65** were well accessed by variating the feeding ratio of the reactants in good to excellent yields in toluene (PhMe) and acetonitrile (MeCN) as the solvents. When the starting materials **1** and **62** were taken in a 1:2 molar ratio, **64** was obtained without a trace of **65**. However, when the molar ratio of **1** and **62** was changed to a 1:4 molar ratio, **65** was obtained exclusively in good yields (Scheme 22).



Scheme 22. Synthesis of tetra-substituted thiophenes and thieno[2,3-*b*]thiophenes.

A facile and divergent synthesis of substituted 4*H*-thiopyran-4-ones **66** from α-alkenoyl-α-carbamoyl ketene-*S,S*-acetals was developed by Liu et al. (2010). The starting material **1**[#], when subjected to DMF in the presence of $Na_2S{\cdot}9H_2O$ at 75 °C, it underwent a tandem intermolecular and subsequent intramolecular thia-nucleophilic vinyl substitution reactions ([5C+1S]

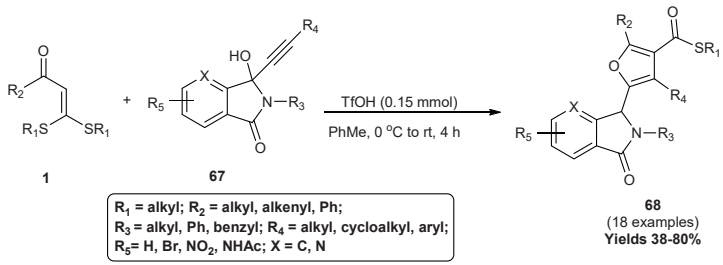
annulation) to give the corresponding products **66** in good yields (Scheme 23).



Scheme 23. Synthesis of 4*H*-thiopyran-4-ones from α-alkenoyl-α-carbamoyl ketene-*S,S*-acetals.

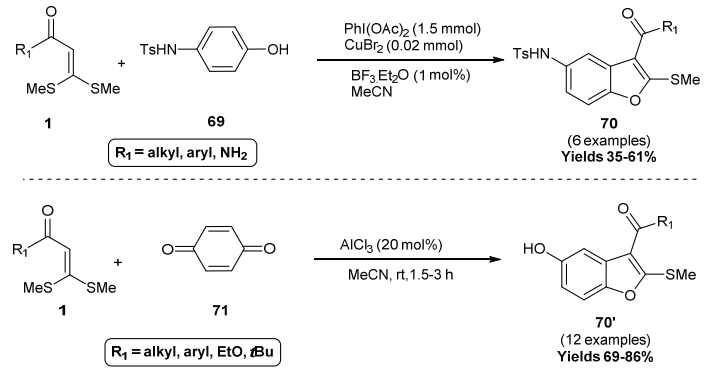
4.3 Synthesis of *O*-containing heterocycles

Bai et al. (2018) reported that the triflic acid (TfOH) promoted [3+2] annulation of ketene-*S,S*-acetals **1** and isoindoline-1,3-dione-derived propargyl alcohols **67** for the synthesis of multisubstituted furan-3-carbothioates **68**. The ketene-*S,S*-acetals and the C-C triple bond of propargylic alcohols **67** behave as a 1,3-bis-nucleophilic two-carbon synthon and 1,2-bis-electrophile, respectively, in this reaction. It also represents the first regioselective annulation of ketene-*S,S*-acetals as 1,3-bisnucleophiles in a cascade manner. The choice of isoindoline-1,3-dione-derived propargyl alcohols was crucial to the uncommon annulation mode between an alkyne-type bis-electrophile and a 1,3-bis-nucleophile under metal-free conditions (Scheme 24).



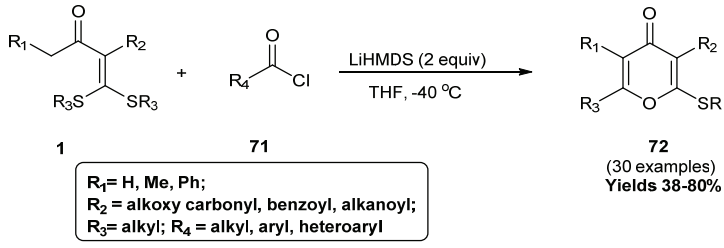
Scheme 24. Synthesis of substituted furan-3-carbothioates.

The synthesis of 2,3-disubstituted benzofuran **70** through a one-pot, two-step sequence involving the reaction between *p*-aminophenols **69** and various ketene-*S,S*-acetals **1** in a multi-catalysis strategy was developed (Yang et al., 2012). The reaction was initiated from the oxidation of aminophenol by hypervalent iodine to form a quinone monoamine. It was then activated *in situ* by BF_3 at the benzenesulfonyl nitrogen atom to induce a regioselective Michael addition with ketene-*S,S*-acetals, which CuBr2 activated to give the 5-aminobenzofurans **70**. Then, a high-yielding and straightforward protocol for synthesizing the 2,3-disubstituted benzofuran **70'** *via* domino coupling of ketene-*S,S*-acetals and 1,4-benzoquinones **71** mediated by $AlCl_3$ at room temperature was reported by Verma et al. (2013) (Scheme 25).



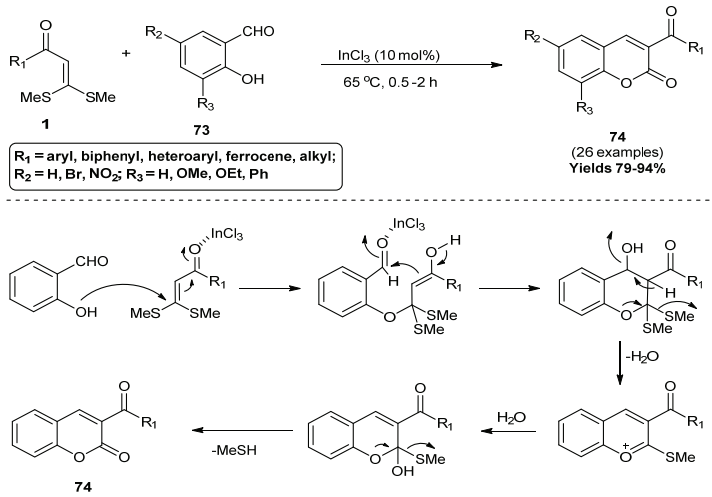
Scheme 25. Synthesis of disubstituted benzofurans from ketene-*S,S*-acetals.

In the meantime, a method for highly functionalized *γ*-pyrones **72** through [4+2] heterocyclization of ketene-*S,S*-acetals **1** with acyl chlorides **71** promoted by lithium bis(trimethylsilyl)amide (LiHMDS) was developed by Wang et al. (2019). This method showed good tolerance to various aromatic acyl chlorides having different substituents. Moreover, the alkyl acyl chlorides with different natures could also proceed toward forming γ-pyrones (Scheme 26).



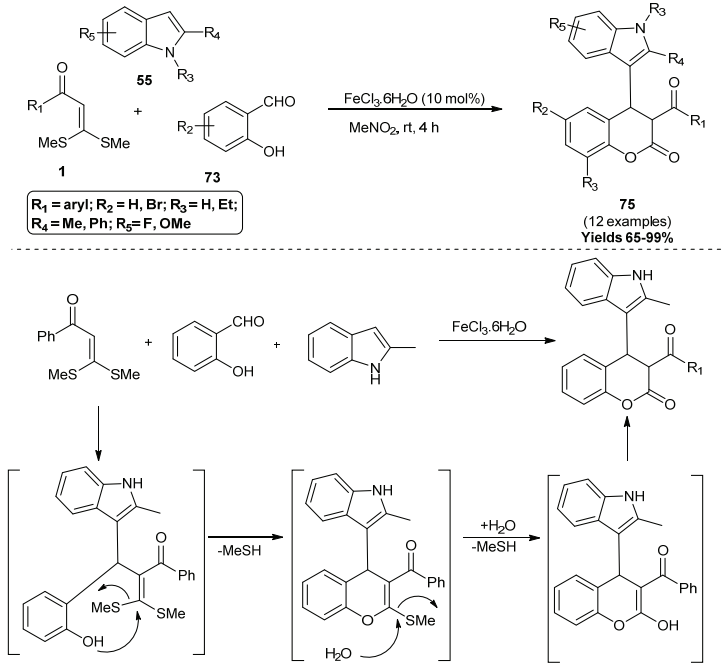
Scheme 26. Synthesis of highly functionalized *γ*-pyrones.

The synthesis of 3-aroyl/heteroaroyl/ferrocenoyl/alkanoyl-2*H*-chromen-2-ones **74** catalyzed by $InCl_3$ *via* the cyclocondensation of ketene-*S,S*-acetals **1** and 2-hydroxyarylaldehydes **70** under solvent-free conditions was also explored (Verma et al. 2012). The protocol involves ring annulation of 2-hydroxyarylaldehydes with a variety of **1**, offering rapid formation into differentially substituted chromen-2-ones **70**. Further, the condensation of ferrocene-derived **1** and 2-hydroxyarylaldehyde **73** furnished coumarin installed on a ferrocene platform (Scheme 27). The proposed mechanism starts with an oxa-Michael type reaction of 2-hydroxyarylaldehyde on the C-1 of the $InCl_3$-linked **1** generating enolate, which undergoes an intramolecular cyclization to another intermediate *via* the Aldol type condensation. This intermediate immediately undergoes dehydration and subsequent hydrolysis of methylthio groups (dehydration) with the extrusion of MeSH, leading to the 3-substituted coumarins **74**.



Scheme 27. Synthesis of 2*H*-chromen-2-ones catalyzed from ketene-*S,S*-acetals.

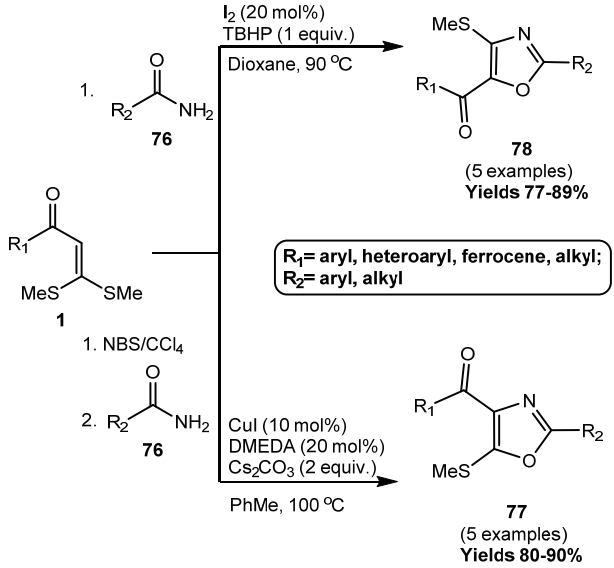
The synthesis of densely substituted dihydrocoumarins **75** using $FeCl_3 \cdot 6H_2O$ as a catalyst *via* the three-component reaction of salicylaldehydes **73**, indoles **55** and ketene-*S,S*-acetals **1** in nitromethane was also explored by Liu et al. (2016). The mechanism starts with the initial electrophilic reaction of **1** with two nucleophiles **55** and **73**, providing an intermediate. This intermediate was then converted into a chromene-type intermediate through an intramolecular substitution and finally undergoing hydrolysis to form the desired product (Scheme 28).



Scheme 28. Synthesis of densely substituted dihydrocoumarins using ketene-*S,S*-acetals.

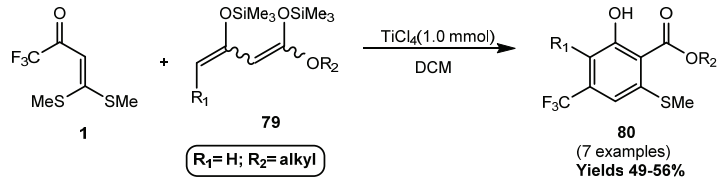
4.4 Miscellaneous

The synthesis of 2,5-substituted 4-acyloxazoles **77** and 2,4-substituted 5-acyloxazoles **78** with complementary regioselectivity from the corresponding ketene-*S,S*-acetals was developed by Kumar et al. (2018). In the first reaction, the ketene-*S,S*-acetals was converted to the corresponding *α*-bromo-*β*-(methylthio)enones followed by the copper-catalyzed inter/intramolecular annulation of this intermediate with various primary amides **76** affording 2,5-substituted 4-acyloxazoles **77** in the presence of 1,2-dimethylethylenediamine (DMEDA) *via* concomitant formation of the C_4-N and C_5-O bond through an enamide intermediate. In the second protocol, the starting ketene-*S,S*-acetals was allowed to furnish *β*-aroylenamides by reacting with various primary amides on subsequent iodine catalyzed intramolecular oxidative C−H functionalization/C−O bond formation and affording the corresponding regioisomeric 2,4-substituted 5-acyloxazoles **78** in excellent yields in the presence of *tert*-butyl hydroperoxide (TBHP) (Scheme 29).



Scheme 29. Synthesis of disubstituted oxazoles using ketene-*S,S*-acetals.

A convenient synthesis of functionalized 6-methylthio-4-(trifluoromethyl)salicylates **80** with average yields *via* formal [3+3]cyclocondensation of 1,3-bis(silyl enol ethers) **79** with the 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (ketene-*S,S*-acetal) **1** in the presence of $TiCl_4$ was demonstrated by Iaroshenko et al. (2011) (Scheme 30).



Scheme 30. Synthesis of salicylates using 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one.

5. Conclusion

This chapter dealing with the applications of ketene-*S,S*-acetals in the synthesis of diverse heterocycles has revealed that it is a versatile intermediate in many cyclization processes. It is a building block for many heterocycles, such as medium-sized, condensed and fused heterocyclic systems. The reactions in heterocyclic syntheses include cycloadditions, addition-eliminations, intramolecular ring cyclizations, cyclocondensation with various nucleophiles and multicomponent reactions (MCR) generating libraries of bioactive heterocycles.

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CHAPTER 10

PHENACYL BROMIDES

1. Introduction

Phenacyl bromide (Figure 1) is an organic compound with the molecular formula of $C_6H_5C(O)CH_2Br$ reported by Emmerling and Engler (1871). It is a colorless solid with a powerful lachrymator that serves as a critical intermediate for developing various bioactive compounds and natural products (Achson, 2009). Moreover, it is commonly used to synthesize five- and six-membered heterocycles and fused heterocyclic compounds through one-pot multicomponent synthesis (Vekariya et al., 2018). Generally, phenacyl bromides were mainly obtained from acetophenones with liquid bromine in the presence of protic and Lewis's acids. Although bromine is hazardous with associated risks in handling and transport, it is still being used by industry and academia due to its low cost, easy availability, and the lack of a better alternative. This chapter intends to briefly review recent research progress concerning the synthesis of various bioactive heterocyclic compounds utilizing phenacyl bromides.

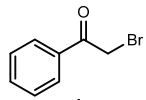

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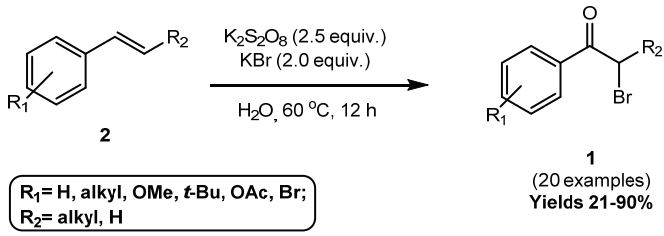
Figure 1. The structure of phenacyl bromide.

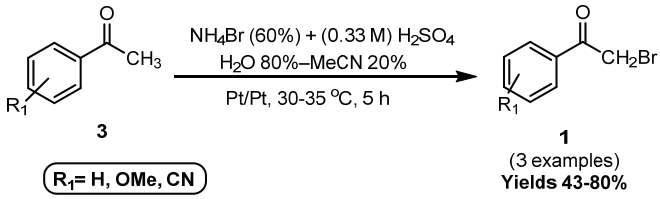
2. Synthesis of Phenacyl bromide

Jiang et al. (2013) developed a protocol for the synthesis of phenacyl bromides **1** from styrene derivatives **2** followed by treatment with KBr in the presence of $K_2S_2O_8$ in H_2O. The styrene derivatives were found to undergo hydroxybromination producing bromohydrins *in situ*, which subsequently underwent oxidation to give a variety of phenacyl bromides in yields ranging from 21 to 90% (Scheme 1). This method uses inexpensive styrenes, non-toxic KBr as the bromine source, $K_2S_2O_8$ as an oxidant and H_2O as the solvent.



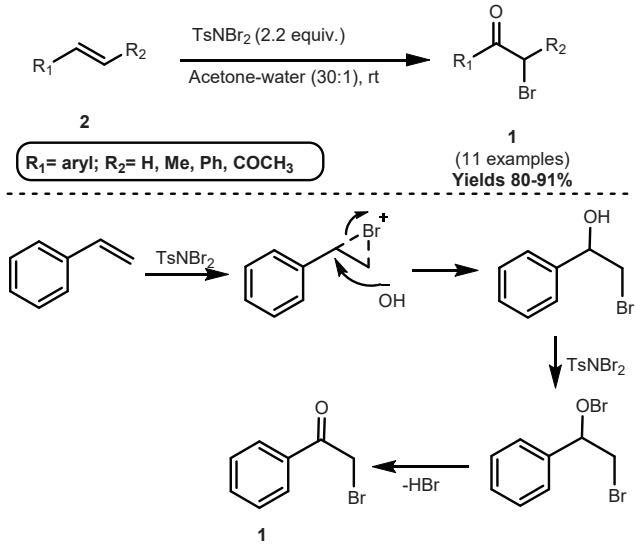
Scheme 1. Synthesis of phenacyl bromides from styrenes in the presence of $K_2S_2O_8$.

The side chain bromination of acetophenone **3** in greener ways by using NH_4Br through *in situ* generated bromonium ions was explored. The reaction was performed using a catalytic amount of H_2SO_4 as a supporting electrolyte in a H_2O:MeCN medium at ambient temperature in an undivided cell equipped with a Pt/Pt electrode (Jagatheesan et al., 2016). This method afforded the product in good yields of 51-80% of α-bromo acetophenone **1** with high selectivity when only 2 Faraday of electricity was passed (Scheme 2).



Scheme 2. Bromination of acetophenone gives phenacyl bromide.

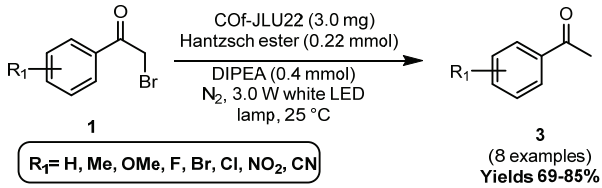
Rajbongshi et al. (2015) developed a metal-free protocol for the synthesis of α-bromo ketones using *N,N*-dibromo-*p*-toluene sulfonamide ($TsNBr_2$), and olefins **2** at room temperature. The reaction was carried out by treating an olefin with $TsNBr_2$ in acetone–water mixture in 30:1 ratio and gave an excellent yield of corresponding *α*-bromo ketone **1** within a short period. The mechanism proceeded with forming a three-membered cyclic bromonium ion intermediate due to the electrophilic addition of the Br^+ ion (generated from $TsNBr_2$) onto the olefin. This intermediate undergoes ring-opening by water *via* an S_N2 pathway to produce bromohydrin. Finally, the resulting bromohydrin undergoes further oxidation *via* an intermediate to produce the final product, *α*-bromo ketone as the product, as shown in (Scheme 3).



Scheme 3. Synthesis of α-bromo ketones from olefin using $TsNBr_2$.

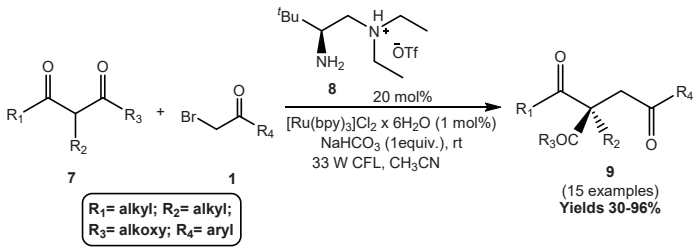
3. Functionalization of Phenacyl bromides

Li et al. (2019) reported a novel pyrene-based two-dimensional covalent organic frameworks (2D-COF) with a high surface area and large pore volume, strong crystallinity and robust stability for organic synthesis of acetophenone derivatives **3** in the presence of *N,N*-diisopropylethylamine (DIPEA). The reaction proceeds through reductive dehalogenation of phenacyl bromide derivatives with moderate to good yields under visible light irradiation. The pyrene-based 2D-COF was named COF-JLU22 (Scheme 4).



Scheme 4. Photoreduction dehalogenation reaction of phenacyl bromide by COF-JLU22.

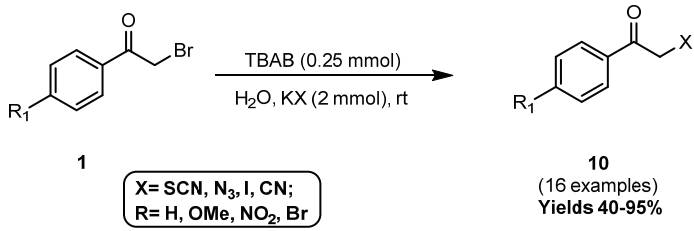
Zhang et al. (2018) explored the *α*-alkylation of *β*-ketocarbonyls using phenacyl bromide *via* direct photolysis by chiral primary amine with high enantioselectivity. In their model reaction, alkylation between acetoacetate **7a** and phenacyl bromide **1** in the presence of the combined catalysis of **8** and $Ru(bpy)_3Cl_2$ gave the desired alkylation adduct **9a** in 88% yield under the optimized condition (Scheme 5). However, the reaction did not occur in the absence of light irradiation.



Scheme 5. Asymmetric α-alkylation of *β*-dicarbonyls *via* asymmetric photoredox catalysis.

An efficient method for synthesizing phenacyl derivatives using tetrabutylammonium bromide (TBAB) as homogenous catalysis in aqueous media was described by Sayyahi and Saghanezhad. (2011). The nucleophilic substitution reactions were performed under ecofriendly

conditions and gave the corresponding α-keto derivatives **10** in high yields up to 95 %. Thus, the best results were obtained when 2-bromo-1-phenylethanone **1** was reacted with sodium thiocyanate in water at room temperature using 0.25 mol of TBAB (Scheme 6).



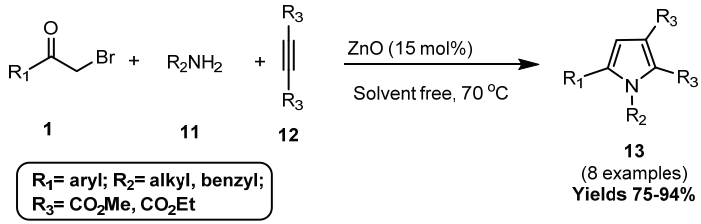
Scheme 6. *α*-Bromo acetophenone reacts with nucleophiles.

4. Synthetic application of Phenacyl bromide

4.1 Synthesis of *N*-containing heterocycles

Phenacyl bromide serves as a critical model for developing various important five- and six-membered heterocyclic compounds. Among them**,** pyrroles are the most important heterocyclic compounds and structural elements of various bioactive natural products possessing broad pharmaceutical activities. They are also valuable intermediates in organic synthesis. Das et al. (2010) developed a three-component reaction using phenacyl bromides in the presence of iron (III) chloride as a catalyst at room temperature affording polysubstituted pyrroles in high yields. Similarly, the synthesis of polysubstituted pyrroles was further extended using *β*-cyclodextrin as a catalyst (Ramesh et al., 2012). Then, the three-component reactions of amines **11**, dialkyl acetylene dicarboxylates **12** and phenacyl bromide **1** catalyzed by ZnO nanoparticle under solvent-free condition for synthesizing polysubstituted pyrroles **13** was demonstrated by Sabbaghan

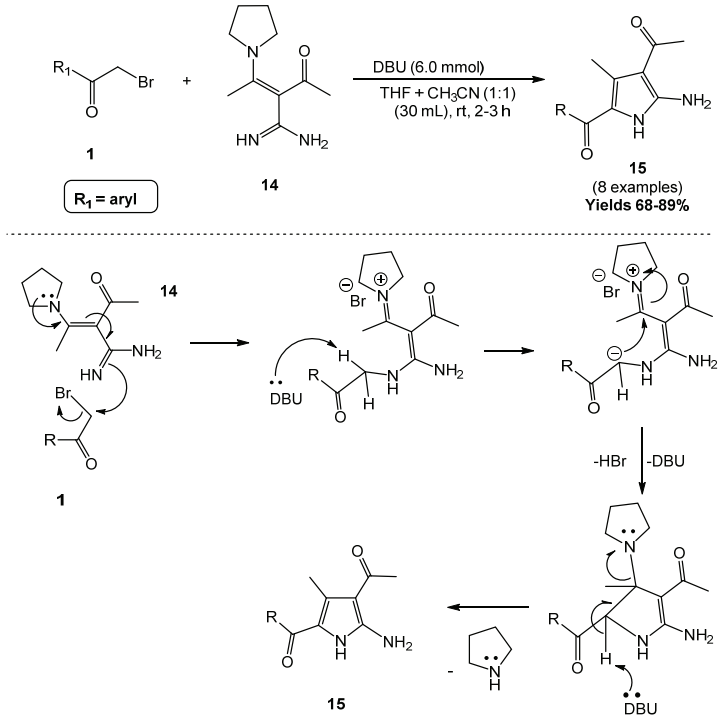
and Ghalaei (2014). Here, nanorod ZnO catalyst exhibited a significant enhancement in the yield of desired products **13** (Scheme 7).



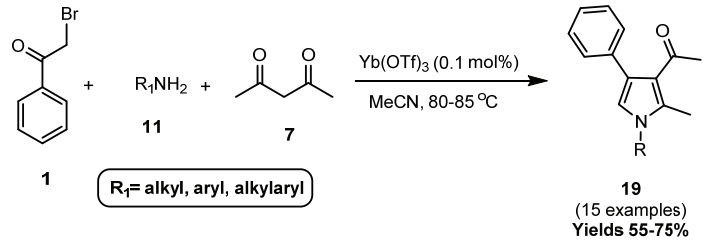
Scheme 7. Nanorod-ZnO catalyzed synthesis of pyrroles under solvent-free conditions.

An efficient synthesis of tetrasubstituted 2-aminopyrroles **15** using the substrates of enaminone–amidine adduct **14** with phenacyl bromides **1** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was reported with good to excellent yields (Jalani et al., 2011). The reaction proceeds through an intramolecular 5-*exo* trig cyclization resulting in diversely substituted 2-aminopyrroles **15** (Scheme 8).

Reddy et al. (2012) also developed a regioselective synthesis of 1,2,3,4-tetrasubstituted pyrroles **19**, using $Yb(OTf)_3$ - mediated three-component reaction of amines **11**, 1,3-diketone **7** and phenacyl bromide **1** in a single pot fashion. The catalyst could be recovered and reused without significant activity loss in this reaction. Different types of amines such as aryl, alkylaryl and alkyl amines and substituents like Cl, Br, OMe, OH and NO_2 present in the amines were well tolerated in this multicomponent reaction (Scheme 9).

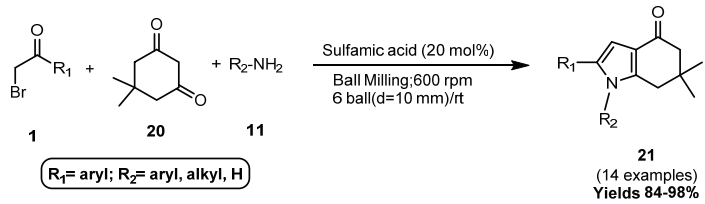


Scheme 8. Synthesis of substituted 2-aminopyrroles catalyzed by DBU**.**



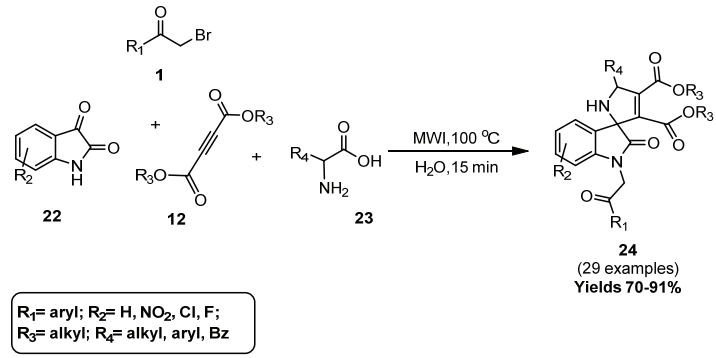
Scheme 9. Synthesis of 1,2,3,4-tetrasubstituted pyrroles by $Yb(OTf)_3$-mediated catalyst.

Lambat et al. (2019) reported an efficient one-pot multicomponent reaction to synthesize 4-oxo-tetrahydroindoles **21** from dimedone compounds **20**, phenacyl bromides and aniline **11** using sulfamic acid (H_2NSO_3H) as a catalyst under ball milling conditions. This reaction with mild reaction conditions could improve selectivity and afforded excellent yields **21** (Scheme 10).



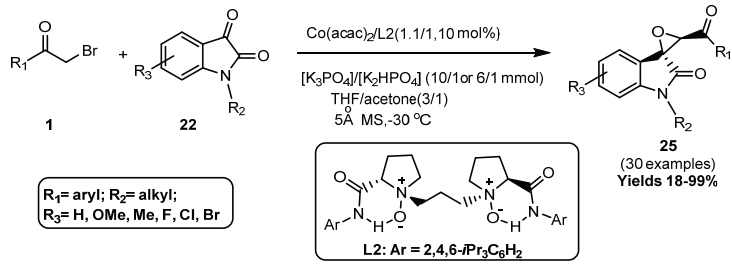
Scheme 10. Synthesis of 4-oxo-tetrahydroindoles derivatives.

Synthesis of novel oxindole derivatives **24** by Mali et al. (2017) *via* multicomponent reaction between isatin **22**, amino acid **23**, but-2-ynedioates **12** and phenacyl bromide was developed. This protocol used microwave irradiation under catalyst and base-free conditions in an aqueous medium and afforded excellent yields of the desired products in a shorter reaction time (Scheme 11).



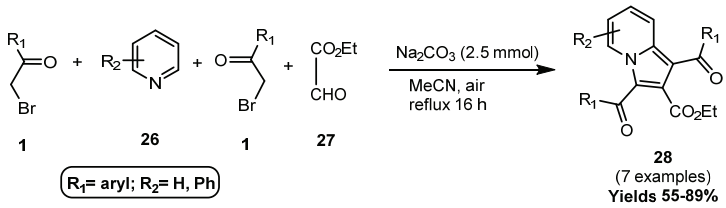
Scheme 11. Synthesis of substituted oxindole derivatives.

Kuang et al. (2014) described an asymmetric synthesis of spiro-epoxyoxindoles **25** using a Darzen reaction between *N*-protected isatins **22** and phenacyl bromides. The optically active products were obtained in moderate to good yields catalyzed by chiral *N,N′*-dioxide-Co(acac)$_2$ complexes in tetrahydrofuran (THF) and acetone as solvents. In this protocol, a retro-Aldol process accompanying the ring closure step was observed, and a chiral control step was the initial Aldol addition (Scheme 12).



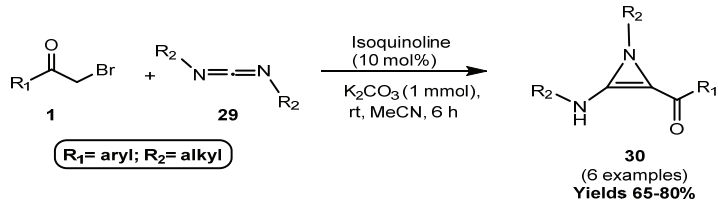
Scheme 12. Synthesis of substituted spiro-epoxyoxindoles.

An efficient one-pot multicomponent reaction for synthesizing polysubstituted indolizine derivatives **28** by treating pyridine **26** and phenacyl bromide with ethyl glyoxalate **27** (Mao et al. 2012) was explored. The reaction was carried out in the presence of Na_2CO_3 under metal-free and mild aerobic conditions in refluxing acetonitrile for 16 hours and obtained a good yield of **28**. The synthesis proceeds with the formation of pyridinium ylides and *α-β* unsaturated ketones with subsequent 1,3-dipolar cycloaddition and an aromatization reaction (Scheme 13).



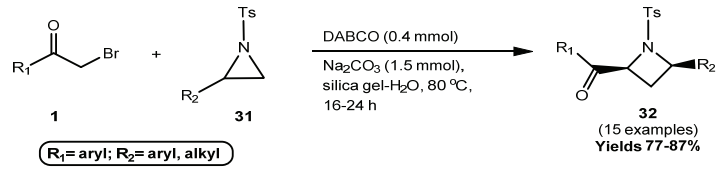
Scheme 13. Synthesis of indolizines catalyzed by Na_2CO_3.

Alizadeh and Rezvanian (2012) developed the synthesis of polysubstituted azirines **30** by reacting phenacyl bromides and *N,N*-dialkylcarbodiimides **29** in the presence of the catalytic amount of isoquinoline in dry acetonitrile. The reactions were performed under mild conditions at ambient temperature and produced azirines **30** in good yields. This protocol effectively synthesized the functionalized azirines and established a new way of employing the isoquinolinium ylide intermediate to initiate a new multicomponent reaction (Scheme 14).



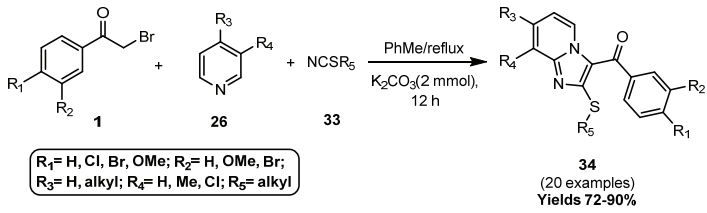
Scheme 14. Synthesis of polysubstituted azirines using isoquinoline-catalyst.

The tertiary amine (DABCO) catalyzed ring expansion reaction of *N*-tosylaziridines **31** to 2-aroyl-*N*-tosylazetidines **32** with nitrogen ylides formed *in situ* from phenacyl bromides in a silica gel-water system was demonstrated by Garima et al. (2010). The reaction could afford chemically and pharmaceutically relevant azetidines in high yields and stereoselectivity in a one-pot process with greener approaches (Scheme 15).



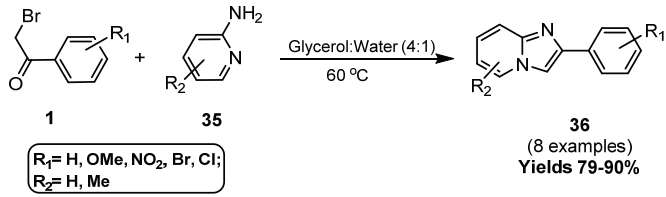
Scheme 15. Synthesis of functionalized azetidines.

Kianmehr et al. (2010) demonstrated an efficient and straightforward method for synthesizing imidazo[1,2-*a*]pyridine **34** derivatives *via a* one-pot three-component reaction between pyridine **26**, phenacyl bromides and thiocyanate **33** in toluene (PhMe). These fully substituted imidazo[1,2-*a*]pyridine derivatives were obtained without using any catalyst or activator in good yields (Scheme 16).



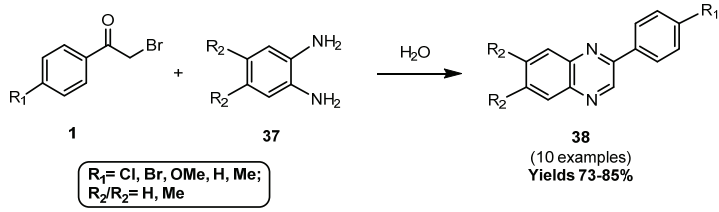
Scheme 16. Synthesis of imidazo[1,2-*a*]pyridine derivatives.

Tufail et al. (2017) developed an environmentally benign glycerol-assisted synthesis of imidazole-fused nitrogen-bridgehead heterocycle compounds **36** in excellent yields by reacting phenacyl bromides with 2-aminopyridines **35** (Scheme 17). Further, Rodríguez et al. (2020) also reported the synthesis of substituted imidazo[1,2-*a*]pyridines **36** from 2-aminopyridines **35** with phenacyl bromides with microwave-assisted and studied the luminescent activity.



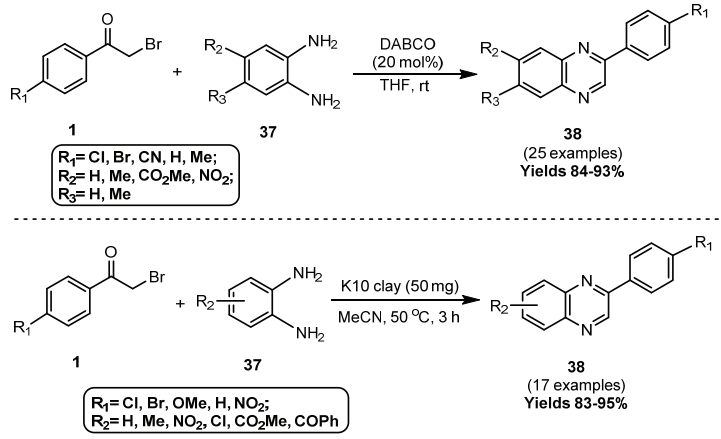
Scheme 17. Synthesis of imidazo[1,2-*a*]pyridines.

The development of a catalyst-free and greener approach for synthesizing quinoxalines **38** from 1,2-diamines **37** and phenacyl bromides *via* a one-pot oxidative cyclization reaction in water was reported by Kumar et al. (2015). This reaction proceeds smoothly in all the cases demonstrating that the presence of withdrawing/donating substituents on the aromatic ring of phenacyl bromide was well tolerated (Scheme 18). However, the reaction employing unsymmetrical diamines afforded the regioisomeric products.



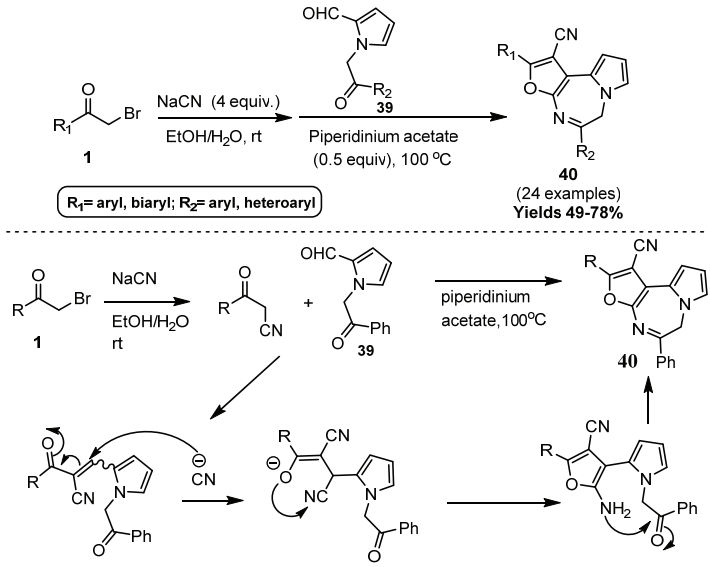
Scheme 18. Synthesis of quinoxaline through oxidative cyclization.

Meshram et al. (2010) also reported a convenient synthesis of quinoxalines **38** by reacting 1,2-diamines **37** with phenacyl bromides in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) through cyclization-oxidation. Similarly, one-pot synthesis of 2-substituted quinoxalines **38** using K10-montmorillonite (K10 Clay) as a heterogeneous catalyst in acetonitrile medium with 1,2-diamines **37** and phenacyl bromides was also explored by Jeganathan et al. **(**2014) resulting in excellent yields of the products (Scheme 19).



Scheme 19. Synthesis of quinoxaline using DABCO and K10 clay as catalysts.

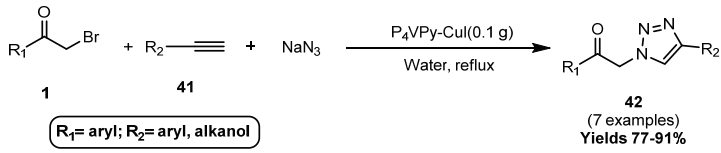
The synthesis of diazepine derivatives (6*H*-furo[3,2-*f*]pyrrolo[1,2-*d*][1,4]diazepines) **40** from a one-pot four-component coupling reaction where multiple bonds (three C−C, one C−O and one C−N) were formed through a domino sequence was reported by Yoon et al. (2020). In this reaction, two heterocyclic rings (furan and diazepine) were sequentially constructed from the monocyclic pyrrole derivative **39** under the environment-friendly reaction conditions to furnish the tricyclic fused scaffold with moderate to good yields (Scheme 20).



Scheme 20. Synthesis of diazepine derivatives.

The synthesis of 1,4-disubstituted-1,2,3-triazoles **42** using polymer-supported nanoparticles of copper (I) iodide [poly(4-vinylpyridine)-CuI (P_4VPy-CuI)] as a catalyst was reported (Albadi et al. 2012). The reaction proceeded *via* Huisgen 1,3-dipolar cycloaddition reaction between α-halo ketones **1**, sodium azide and terminal alkynes **41** in water and obtained a

high yield of substituted triazoles **42**. This highly efficient catalytic system could be recycled for over eight repeated runs (Scheme 21).

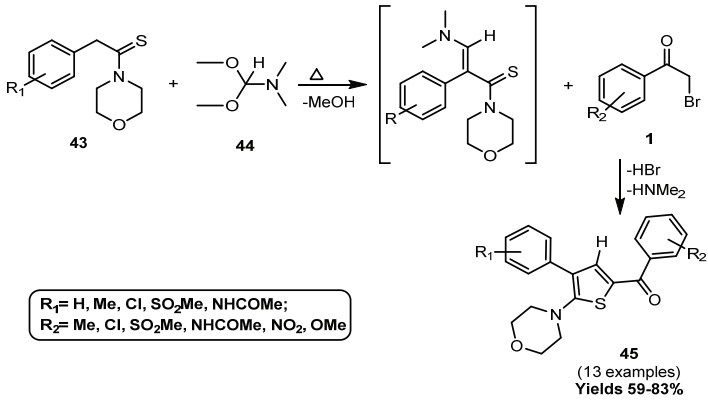


Scheme 21. Synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles.

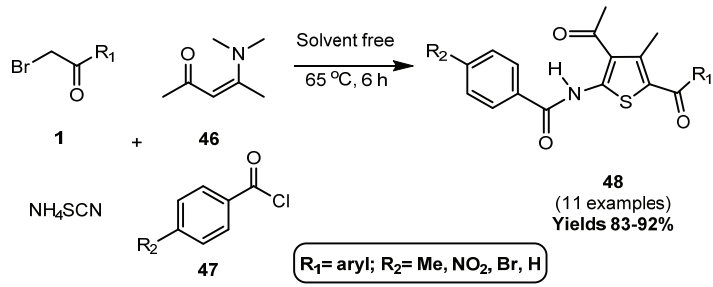
4.2 Synthesis of *S*-containing heterocycles

Jalani et al. (2012) reported the greener and environmentally benign one-pot method for synthesizing tri-substituted thiophenes (2-morpholino-3-aryl-5-aroyl thiophenes) **45** using 1-morpholino-2-arylethanethione **43**, *N,N*'-dimethyl formamide dimethyl acetal **44** and various phenacyl bromides **1** under solvent-free conditions. In this reaction, the driving force was the removal of $HNMe_2$ from 3-(dimethylamino)-1-morpholino-2-arylprop-2-ene-1-thione, resulting in various trisubstituted thiophenes **45** in high yields (Scheme 22).

Also, the one-pot synthesis of tetrasubstituted thiophenes **48** through the four-component reaction between ammonium thiocyanate, acyl chlorides **47**, phenacyl bromides **1** and enaminones **46** was developed by Hossaini et al. (2011) under solvent-free conditions at 65 °C. The advantages of this protocol include mild reaction conditions and high yields of the products **48** (Scheme 23).



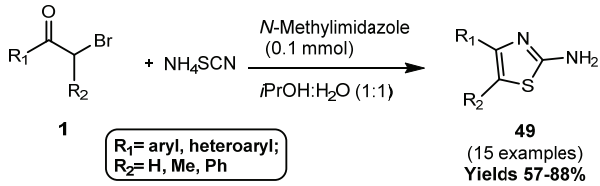
Scheme 22. One-pot synthesis of trisubstituted thiophenes.



Scheme 23. Synthesis of tetrasubstituted thiophenes under solvent-free conditions.

4.3 Synthesis of *S,N*-containing heterocycles

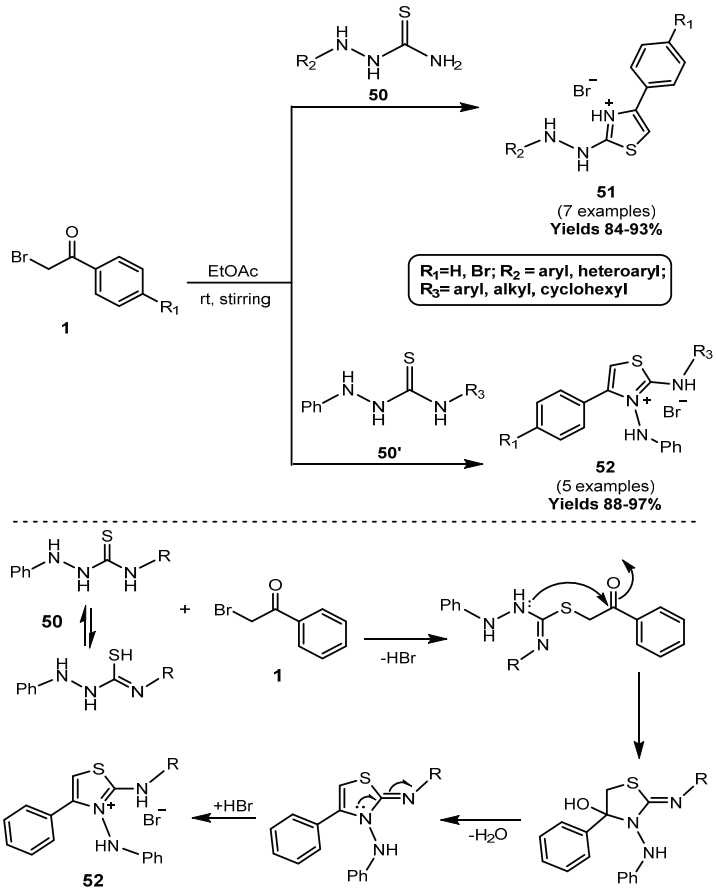
A convenient synthesis of substituted 2-aminothiazoles **49** was explored using *N*-methylimidazole catalyzed cyclization of phenacyl bromides **1** with ammonium thiocyanate in water–alcoholic media (Meshram et al. 2012). This mild protocol could prepare diversely functionalized 2-aminothiazoles **27** in good to moderate yields from readily available starting materials (Scheme 24).



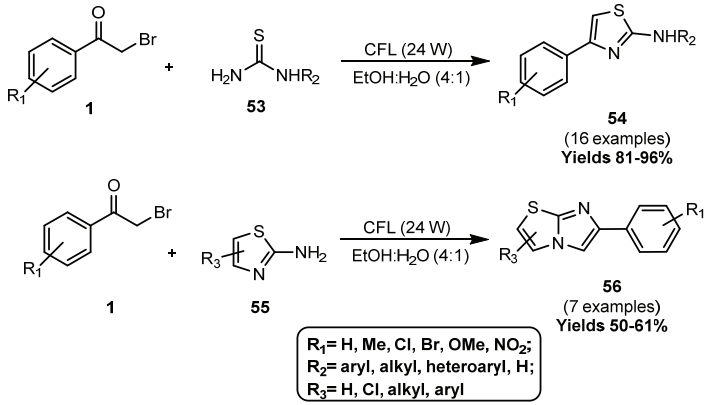
Scheme 24. General synthesis of 4-phenyl-2-aminothiazole.

The green synthesis of two groups substituted thiazolium salts 2,4-disubstituted **51** and 2,3,4-trisubstituted thiazolium bromides **52** from the interaction of mono- and disubstituted thiosemicarbazides **50/50'** with phenacyl bromide in ethyl acetate (EtOAc) was reported recently by Hassan et al. (2020), (Scheme 25). Due to their high nucleophilicity, the proposed mechanism involves the heterocyclization *via* sulfur atom and N^2.

The visible light promoted a catalyst-free approach for synthesizing highly significant thiazoles **54** and imidazo[2,1-*b*]thiazoles **56** under photochemical activation in EtOH:H_2O was developed (Mishra et al. 2016), affording a high yield of the products up to 96% (Scheme 26). This protocol used oxidative coupling of phenacyl bromide **1** with *N*-phenyl thiourea **53** and 2-amino thiazole **55** without heat, base, ligands, or an additional oxidant leading to the formation of C-S and C-N bonds in a greener medium.

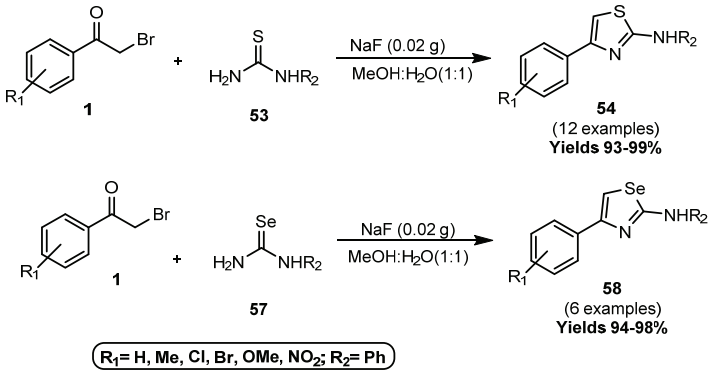


Scheme 25. Synthesis of 2,4-disubstituted thiazole and 2,3,4-trisubstituted thiazole.



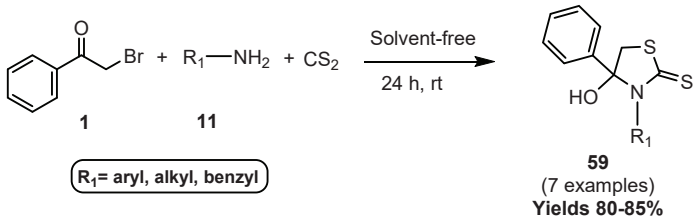
Scheme 26. Synthesis of thiazole derivatives using visible light.

Similarly, the synthesis of 2,4-disubstituted-1,3-thiazoles **54** and selenazoles **58** utilizing phenacyl bromides and thiourea/phenylthiourea **53** or selenourea **57** in aqueous methanol at ambient temperature was explored (Banothu et al., 2014). Sodium fluoride was found to be a mild and efficient catalyst for the synthesis within 1-3 minute in excellent yields (Scheme 27).



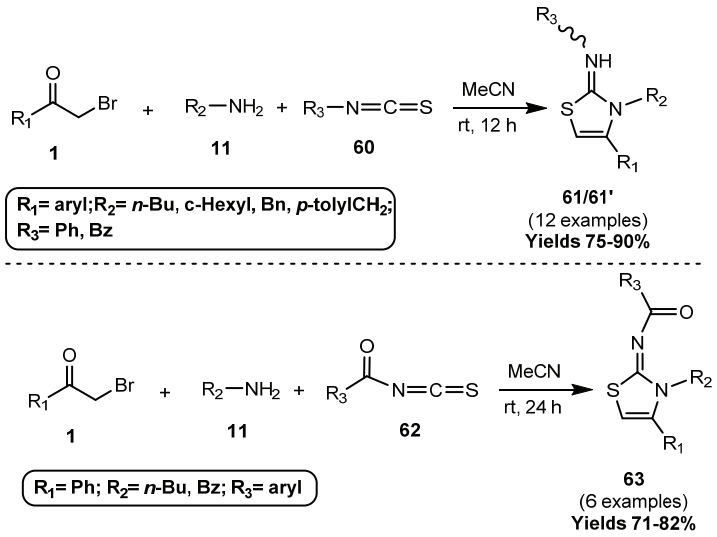
Scheme 27. Synthesis of thiazoles and selenazoles catalyzed by NaF.

Hassanabadi and Barani (2013) had also demonstrated the greener approach with a one-pot three-component reaction between phenacyl bromide and primary amines **11** in the presence of carbon disulfide under solvent-free conditions. They produced a high yield of substituted thiazolidine-2-thiones **59** at room temperature (Scheme 28).



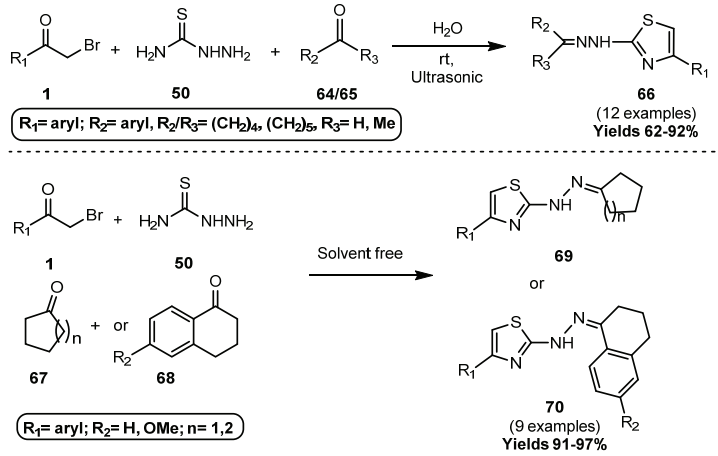
Scheme 28. Synthesis of substituted 4-hydroxy-4-phenylthiazolidine-2-thiones.

An efficient one-pot synthesis of *N*-(4-aryl-3-alkylthiazol-2(3*H*)-ylidene)anilines **61** and *N*-(4-aryl-3-alkylthiazol-2(3*H*)-ylidene)benzamides **61'** by reacting primary alkylamines **11**, isothiocyanates **60** and phenacyl bromide at room temperature without any catalyst was demonstrated by Yavari et al. (2010). This catalyst-free and one-pot synthetic method was facile and could afford a good yield of up to 90% (Scheme 29). Further, Hassanabadi (2013) also successfully demonstrated a three-component and one-pot reaction between phenacyl bromide and aroyl isothiocyanates **62** in the presence of primary amines **11**, giving *N*-(3-alkyl-4-phenyl-3*H*-thiazol-2-ylidene)benzamides **63** with good yields (Scheme 29).



Scheme 29. Synthesis of 2,3-dihydrothiazoles *via* MCR.

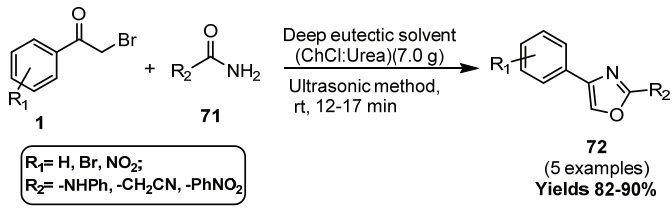
Zhang et al. (2012) developed an efficient one-pot procedure for synthesizing *N*-(4-arylthiazol-2-yl) hydrazones **66** in water under ultrasound irradiation using aromatic aldehydes **64** or ketones **65**, thiosemicarbazide **50** and substituted phenacyl bromide. On the other hand, a novel one-pot reaction for the synthesis of 2,4-disubstituted thiazoles **69/70** was reported by Sujatha and Vedula (2018) through a multicomponent approach under solvent-free conditions. They proceeded with the reaction by reacting cyclic ketones **67/68**, thiosemicarbazide **50** and phenacyl bromides **1** to get substituted thiazoles with high yields (up to 97%) in a short reaction time (Scheme 30).



Scheme 30. Synthesis of 2,4-disubstituted thiazoles *via* multicomponent approach.

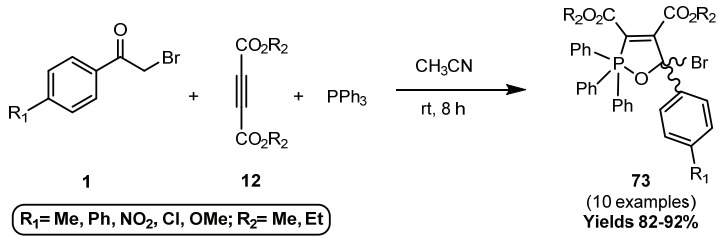
4.4 Synthesis of *N/P,O*-containing heterocycles

A unique combination of deep eutectic solvent (DES) and ultrasonic (US) radiation for clean and efficient synthesis of substituted oxazoles **72** by reacting phenacyl bromides with amide derivatives **71** was demonstrated by Singh et al. (2013). They also compared the reaction with the thermal method and observed that applying ultrasound improved yields and reduced reaction times (in DES that took 3–5 hours in conventional heating) with less energy consumption (Scheme 31).



Scheme 31. Synthesis of oxazole derivatives using DES through ultrasound method.

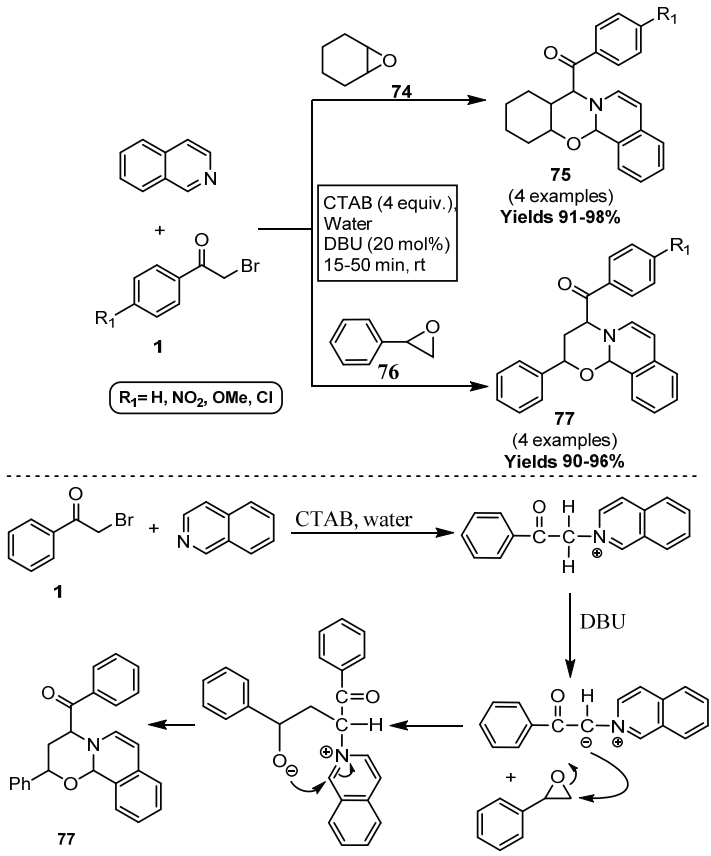
Charat et al. (2011) had developed the synthesis of 1,2-oxaphosphole derivatives **73** using the reaction between electron-deficient acetylenic compounds **12** and phenacyl bromides in the presence of triphenylphosphine with acetonitrile as a solvent and afforded an excellent yield. These oxaphospholes **73** are a starting material for synthesizing various natural products (Scheme 32).



Scheme 32. Synthesis of oxaphospole derivatives.

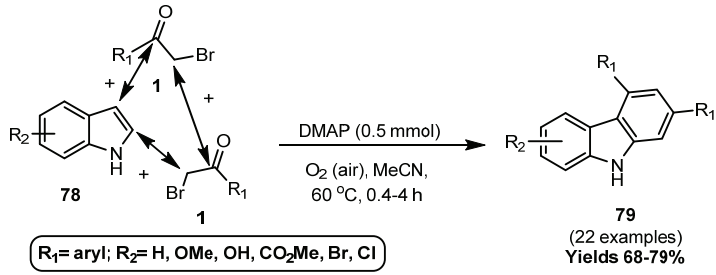
4.5 Miscellaneous formation of cyclic systems

The one-pot synthesis of novel fused heterocycle-oxa-aza-phenanthrene **75** and anthracene derivatives **77** in an aqueous micellar system using DBU in water with surfactant cetyltrimethylammonium bromide (CTAB) was explored (Srivastava et al. 2012). This green synthesis was an efficient and easy synthetic route for constructing the desired products (Scheme 33). Initially, a nucleophilic substitution reaction between isoquinoline and phenacyl bromide led to quaternary ammonium salt, which was then converted into nitrogen ylide in the presence of the base DBU. Then, this intermediate behaving as a carbon nucleophile gives a substitution reaction with epoxide **74** and **76** followed by cyclization, giving the desired products **75** and **77**.



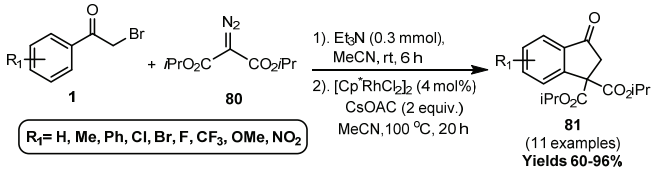
Scheme 33. Synthesis of oxa-aza-phenanthrene and anthracene derivatives.

Recently, Debnath et al. (2020) developed a regioselective synthesis of 3,5-diarylcarbazoles **79** using phenacyl bromides and indoles **78**. In this metal-free reaction, a triple C-C coupling cyclization reaction between the substrates was promoted by 4-dimethylamino pyridine (DMAP) and obtained the products in high yields (68-79%) (Scheme 34).



Scheme 34. Synthesis of diverse 3,5-diarylcarbazoles.

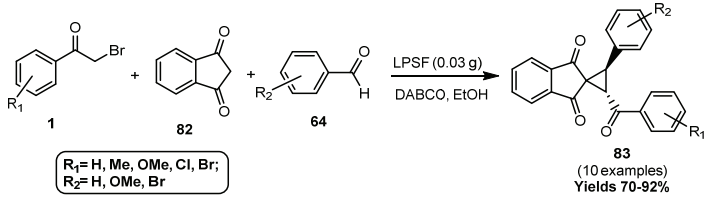
An efficient one-pot synthesis of benzocyclopentanones **81** *via* coupling of diazo esters **80** with α-bromoacetophenones **1** in the presence of triethylamine and Rh(III)-catalyst was reported by Yu et al. (2015). In this protocol, coupling of 1-Br of **1** with di-isopropyl diazomalonate **80** with different solvents catalyzed by $[Cp^*RhCl_2]_2$ (4 mol %) in the presence of CsOAc (2.0 equiv.) gave a high yield of **81** up to 96% (Scheme 35).



Scheme 35. Synthesis of benzocyclopentanone derivatives.

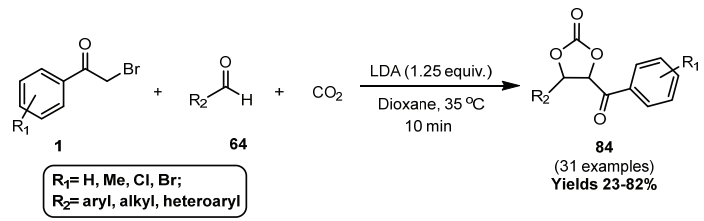
Haji and Maleki (2019) reported a one-pot, two-step tandem synthesis of highly stereoselective polysubstituted cyclopropane derivatives (*trans*-2,3-dihydro-spiro[2-aroyl-3-arylcyclopropane]1,2-indene-1,3-diones) **83**, starting from phenacyl bromide derivatives, 1,3-indanedione **82** and aromatic aldehydes **64** in ethanol using DABCO as a cocatalyst and Fe_3O_4\SiO_2\propyltriethoxysilane\L-proline (LPSF) as a nanomagnetic organocatalyst affording a good yield of products **83** (Scheme 36).

According to the authors, this catalytic system could be recovered by magnetic decantation, and its catalytic activity remains unchanged after ten consecutive cycles.



Scheme 36. Synthesis of polysubstituted cyclopropane derivatives.

One approach for the synthesis of cyclic carbonates **84** *via* a three-component cyclization reaction was developed by Yan et al. (2011). It involves phenacyl bromides, CO_2 and aldehyde **64** in the presence of lithium diisopropylamide (LDA) under mild conditions to generate the products in moderate to good yields within a short reaction time (Scheme 37).



Scheme 37. Synthesis of cyclic carbonate compounds.

5. Conclusion

In this chapter, it is being elaborated that phenacyl bromide is a versatile synthetic intermediate for a variety of biologically active compounds and are precursors for various organic transformations. Moreover, some of the

essential highlights are efficiently used to synthesize five- and six-membered heterocyclic compounds and fused heterocyclic compounds through one-pot multicomponent synthesis.

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