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REVIEW ARTICLE

Sigmatropic rearrangements in the synthesis of heterocyclic compounds and their functionalization

Tubai Ghosh[1], Sougata Santra[2], Grigory Zyryanov[2], Brindaban C. Ranu[1,2,*]

[1] *School of Chemical Sciences, Indian Association for the Cultivation of Sciences, Kolkata 700032, India*

[2] *Department of Organic & Biomolecular Chemistry, Chemical Engineering Institute, Ural Federal University, Yekaterinburg 620002, Russian*

*** Corresponding author:** Brindaban C. Ranu, ocbcr@iacs.res.in

ABSTRACT

Sigmatropic rearrangements are well documented in the carbocyclic as well as heterocyclic chemistry. Various molecules have been obtained from easily accessible starting materials via involvement of sigmatropic rearrangements. This review presented a brief account of the synthesis of some important heterocyclic compounds and their functionalization involving sigmatropic rearrangements, particularly, [3,3]-, [2,3] and [1,5]-ones. The mechanism of some rearrangements has also been discussed.

Keywords: sigmatropic rearrangement; heterocycles; functionalization; green strategy

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1. Introduction

The sigmatropic rearrangement is one of the most important and useful transformations in organic synthesis. It presents a pericyclic reaction involving migration of a σ-bond adjacent to one or more π -bonds to a new position within the same molecule generating a new sigma bond, although total number of σ-bonds and π-bonds remain same[1–4]. Sigmatropic rearrangements thus enable the access to complex molecular systems from readily available starting materials through well-defined predictable transition state[5–9]. The diverse chiral building blocks, natural products, and pharmaceuticals have been synthesized through [3,3], [2,3], [1,5]-sigmatropic rearrangements with high level of diastereo- and enantioselectivity[10–13].

The famous Claisen rearrangement involved the thermal [3,3]-sigmatropic rearrangement of allyl vinyl ether towards the synthesis of γ,δ-unsaturated carbonyl compounds[14]. This rearrangement has become a useful tool for the construction of carbon–carbon bonds and the synthesis of natural products. The substrate scope has been extended to *N*-, *O*- and *S*- containing heterocycles too. Cope rearrangement also utilizes [3,3]-sigmatropic rearrangement, and has been employed to form new carbon–carbon bonds through thermal pseudocyclic reaction of hexa-1,5-dienes, with modifications applied for the heteroanalogue also[15].

Heterocycles occupy the major space in organic chemistry and receive much attention because of their applications. Most of the

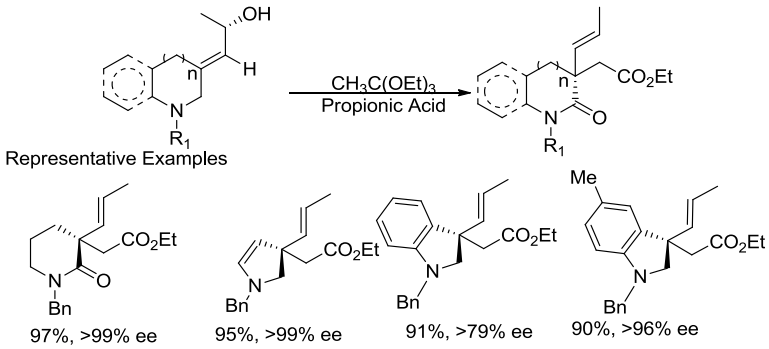
natural products and pharmaceutical agents having biological activities contain heterocycle units in their structures[16–18]. Because of their enormous applications, several methods have been reported so far for the synthesis and functionalization of heterocyclic moieties[19].

2. Review

This review presents an account on the recent developments on the synthesis and functionalization of various biologically active heterocycles via different sigmatropic rearrangements.

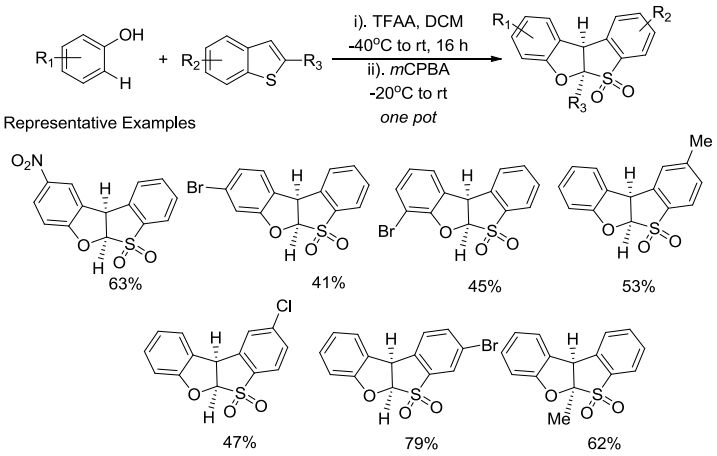
2.1. [3,3]-Sigmatropic rearrangements

Pandey et. al.[20] developed an efficient strategy for the diastereoselective (up to > 99%) access to all quaternary carbon stereo-centers at the C-3 position through [3,3]-Johnson-Claisen rearrangement of γ-hydroxy-α,β-unsaturated lactams (**Scheme 1**). The olefin geometry plays key role in the development of the absolute stereochemistry of the corresponding product. This method was further applied for the total synthesis of (-)-physotigmine with 63% overall yield.

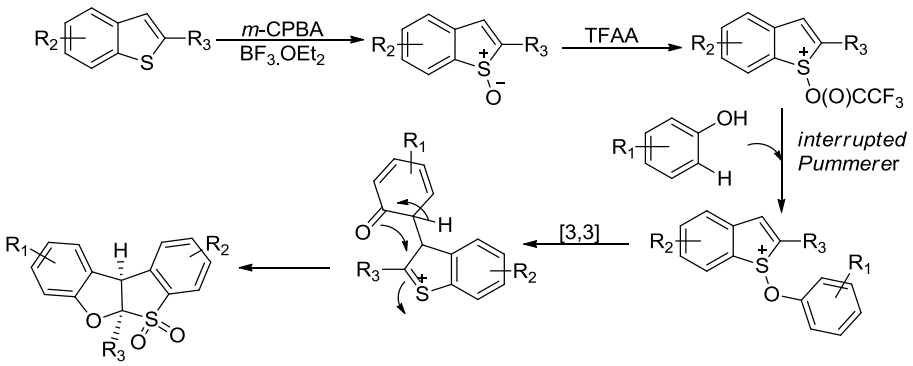


Scheme 1. Generation of all carbon quaternary stereocenters at the C-3 carbon of lactams *via* [3,3]-sigmatropic rearrangement.

Procter et al.[21] demonstrated metal free synthesis of benzofurans from benzothiophenes through a sequential Pummerer reaction and [3,3]-sigmatropic rearrangement **(Scheme 2**). The reaction was performed by the interaction of simple phenol and benzothiophene S-oxides. Initially, the thioacetal was formed by the reaction of activated benzothiophene *S*-oxide 2′ with trifluoroacetic anhydride (TFAA) followed by the addition of phenol. Next, the resultant aryloxysulfonium salt undergoes spontaneous [3,3]-sigmatropic rearrangement and cyclization to furnish another thioacetal intermediate. Oxidation of the thioacetal generates sulfone which in the presence of a base leads to the formation of the corresponding product. The method offers an access to a variety of C3-arylated benzofurans that can undergo further palladium-catalyzed desulfinative coupling with aryl bromides (**Scheme 3**).

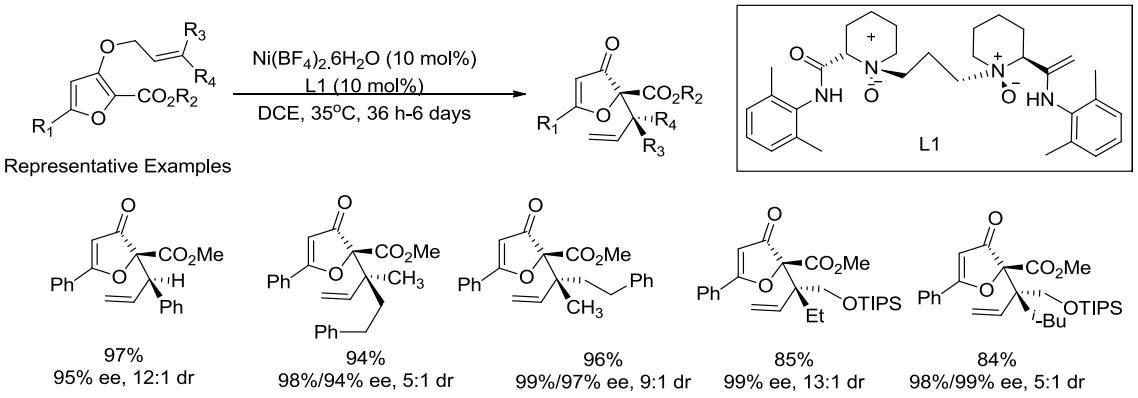


Scheme 2. One-pot synthesis of thioacetal S,S-dioxides by [3,3] sigmatropic rearrangement.



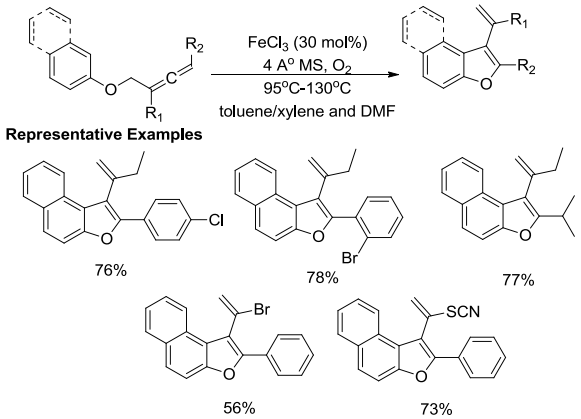
Scheme 3. Proposed reaction pathway for the synthesis of thioacetal S,S-dioxides.

In 2018, Feng et al.[22] reported a catalytic asymmetric dearomatization Claisen rearrangement of allyl furyl ethers for the synthesis of chiral γ,δ-unsaturated carbonyl compounds using chiral *N*,*N*′-dioxide-Ni^{II} as catalyst (**Scheme 4**). All the four stereoisomers of the products were obtained by controlling chirality of the ligand and olefin geometry. This fascinating strategy was further extended for the synthesis of bioactive natural products hyperolactones B, C, and their epimers.



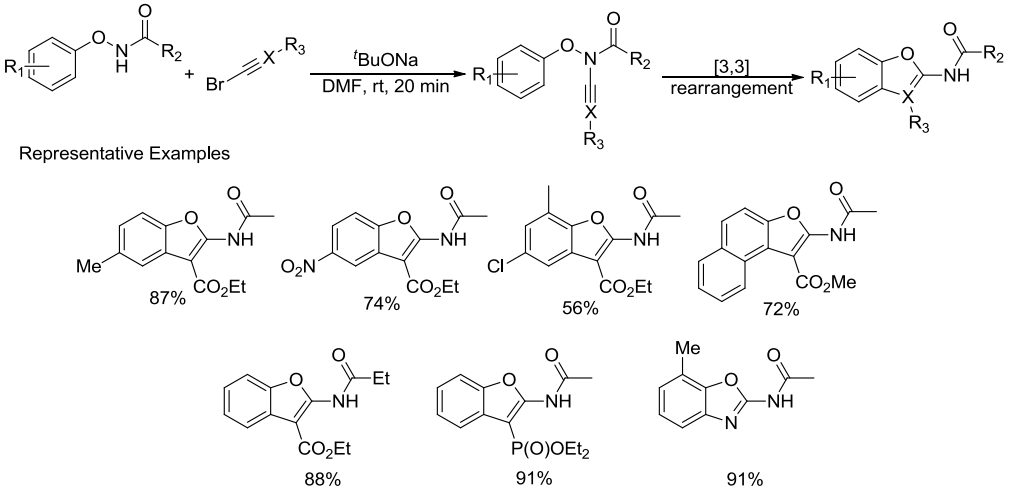
Scheme 4. Ni(II)-catalyzed asymmetric Claisen rearrangement reactions of allyl furyl ethers.

Fe(III)-catalyzed synthesis of naphtha[2,1-*b*]furan derivatives starting from *β*-naphthyl substituted-allenylmethyl ether via a tandem allenic Claisen rearrangement and dehydrogenative cyclization was developed by Zhang et al.[23] (**Scheme 5**). The best result was observed by using 30 mol% $FeCl_3$ in toluene/xylene and DMF solvent at 95–130 °C. The reaction was initiated by the coordination of iron catalyst to the oxygen atom of allene. The reaction occurs *via* chair like transition state and subsequent keto-enol tautomerization and homolytic cleavage. The reduced Fe(II) catalyst was reoxidized to Fe(III) under aerial oxidation.



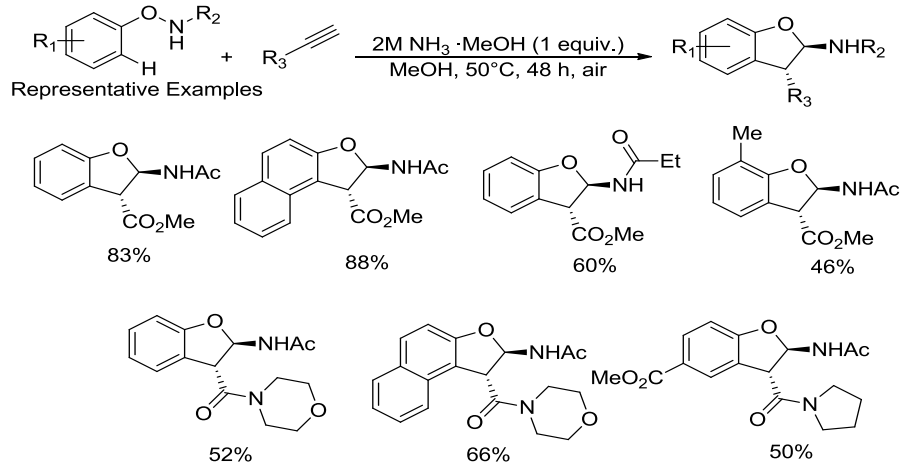
Scheme 5. Iron(III)-catalyzed domino Claisen rearrangement for the synthesis of naphtha[2,1-*b*]furan.

The reaction between *N*-phenoxyacetamides (Ph-ONHAc) and compounds bearing sp-hybridized carbon leads to the synthesis of substituted benzofurans and benzooxazole in the presence of ^{t}BuONa as a base was reported by Yan et al.[24] (**Scheme 6**). *N*-phenoxyacetamides having electron-donating and electron-withdrawing substituents performed equally well providing the corresponding products in moderate to excellent yields. However, in the case of *meta*-substituted *N*-phenoxyacetamides the annulation occurred at the two *ortho* sites, and the yields of the products annulated at the less hindered site were better than the other one. Unfortunately, no reaction was observed in the case of substrates containing electron-deficient groups such as $–CCl_3$, $–CF_3$, and $–C_6F_5$ in acetamide part. Certainly, this is one of the primary limitations. This may be due to the reduced nucleophilicity on the nitrogen atom. When cyanogen bromide (BrCN) was used, benzoxazole was formed. Various experimental and computational studies indicate the involvement of facile Claisen-like [3,3]-sigmatropic rearrangement/annulation process.



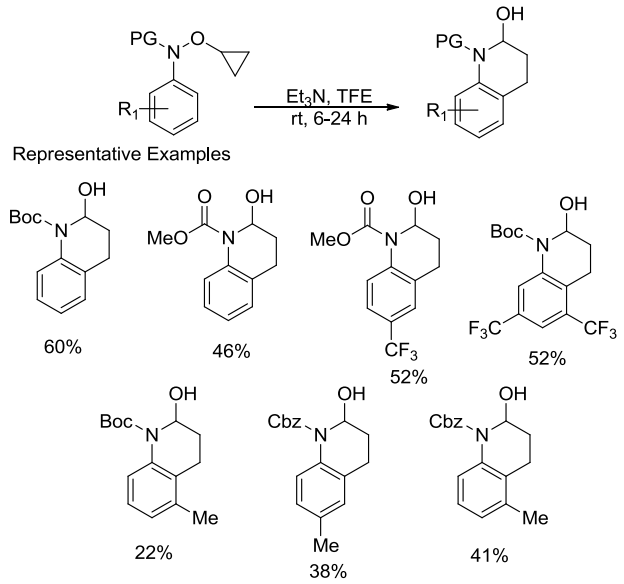
Scheme 6. Synthesis of benzofurans and benzoxazoles through [3,3]-sigmatropic rearrangement.

In 2019, Liu et al.[25] reported the diastereoselective synthesis of *trans*-dihydrobenzofurans by the reaction between *N*-phenoxy amides with terminal alkynes under metal free condition (**Scheme 7**). Different *N*-phenoxy amides having substituents at either *para*-, *meta*- or *ortho*-position reacted with terminal alkynes in the presence of 1 equivalent of NH_3·MeOH in MeOH solvent at 50 ℃ for 48 h under open atmosphere, producing the desired *trans*-dihydrobenzofuran derivatives with moderate to good yields through [3,3]-sigmatropic rearrangement/[3+2]-annulation. In the case of *meta*-substituted *N*-phenoxyacetamides, two inseparable regioisomers were formed. Reactions with electron-withdrawing group-containing *N*-phenoxyacetamides with methyl propiolate produced 2,5-dihydrobenzo[*b*]oxepines as the major product.



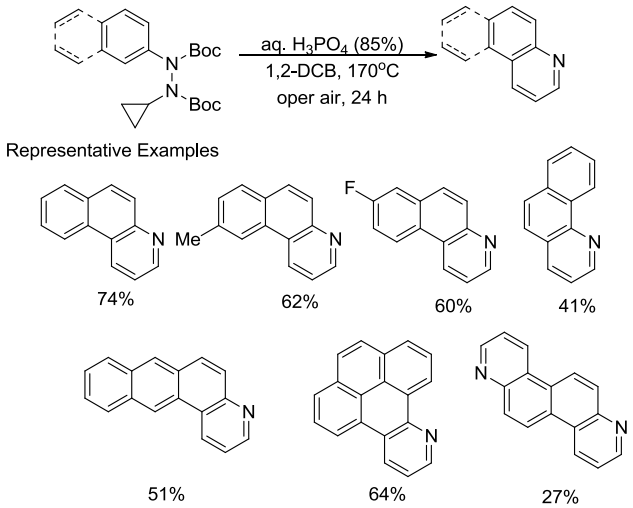
Scheme 7. Metal-free [3,3]-sigmatropic rearrangement/[3+2] for the synthesis of trans-dihydrobenzofurans.

Lovato et al.[26] developed an efficient procedure for the construction of *N*-heterocycles *via* a di-heteroatom [3,3]-sigmatropic rearrangement (**Scheme 8**). In the presence of trimethylamine as a base, various *N*-arylated *O*-cyclopropyl hydroxamates having different *N*-protecting group underwent [3,3]-sigmatropic rearrangement/cyclization/rearomatization to produce tetrahydroisoquinoline derivatives with good to excellent yields. Substrates with electron deficient aromatic ring took longer reaction time compared to the less electron deficient one. Interestingly, *meta*-tolyl Boc-protected reactant rearranged into a mixture of isolable regioisomers whereas, *meta*-tolyl Cbz-protected substrate provided only one regioisomer. This may be due to the π-stacking interactions between the Cbz group and the *N*-aryl group prior to the [3,3]-rearrangement.



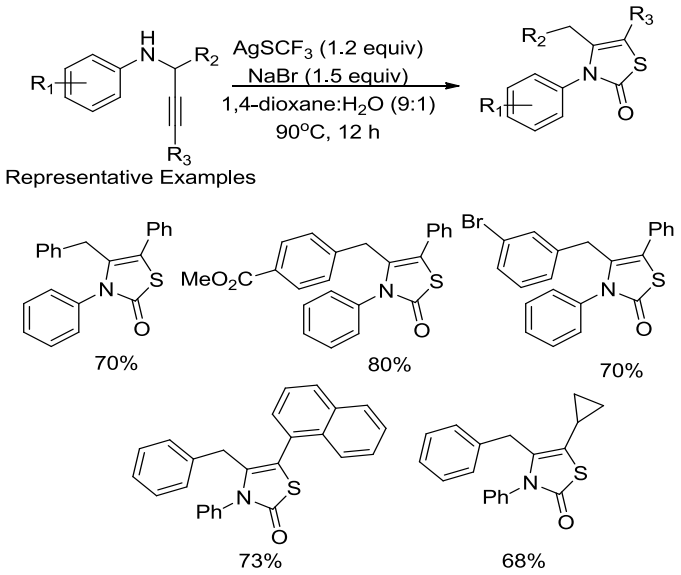
Scheme 8. *O*-Cyclopropyl hydroxylamines as the precursor for the synthesis of *N*-heterocycles *via* [3,3]-sigmatropic rearrangement.

Gerosa et al.[27] developed a Bronsted-acid promoted homo-diaza-Cope rearrangement of *N*-aryl-*N*'-cyclopropyl hydrazines towards the synthesis of substituted quinolone derivatives (**Scheme 9**). This method is considered as homologation of Fischers classical indole synthesis and provides 6-membered *N*-heterocycles, including previously inaccessible pyridine derivatives. This reaction requires 85% of aqueous H_3PO_4 at 170 °C under air for 24 h in 1,2-dichlobenzene solvent. Higher quinolones with four and five rings were obtained when polycyclic hydrazines were reacted under the optimized reaction conditions. Computational analysis has identified a favourable di-protonated pathway.



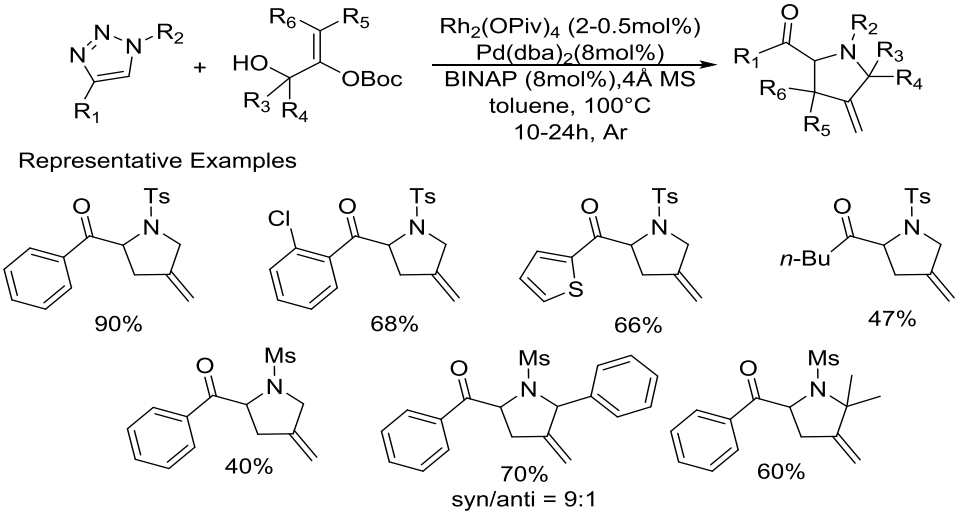
Scheme 9. Quinoline synthesis *via* homo-diaza-Cope rearrangement.

Behera et al.[28] reported an efficient procedure for the preparation of thiazole-2(3*H*)-ones *via* [3,3]-sigmatropic rearrangement/5-exo-dig cyclization of *N*-propargylamines (**Scheme 10**). In this procedure both di- and tri- substituted thiazole-2(3*H*)-ones were obtained starting from *N*-propragyl amines in the presence of 1.2 equivalent silver(I) trifluoromethanethiolate ($AgSCF_3$). A library of thiazole derivatives was synthesized by this method with good to excellent yields. The reaction is also applicable in gram scale giving the same result as in mmol scale. The starting material, *N*-propragyl amines were easily prepared by the A3 -coupling reaction of various amines, aldehydes, and alkynes. The methodology was further applied for the synthesis of thiozole-2(3*H*)-thione derivatives. The photophysical properties of these compounds were also studied.



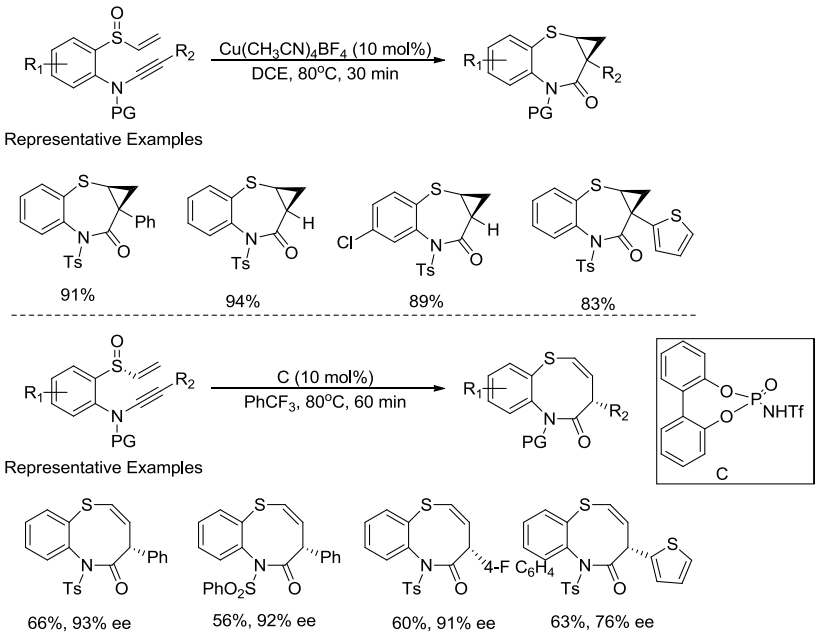
Scheme 10. Synthesis of thiazole -2(3*H*)-ones.

Kim et al.[29] reported the synthesis of *N*-sulfonyl pyrrolidines involving sigmatropic rearrangement of *N*-sulfonyl triazoles and 2-hydroxymethylallyl carbonates by using dual Rh(II)/Pd(0) relay catalysis (**Scheme 11**). Various substituted *N*-sulfonyl pyrrolidine derivatives were obtained using 2 mol% of $Rh_2(OPiv)_4$ in combination with 8 mol% of $Pd(dba)_2$, 8 mol% of BINAP ligand, and 4 Å molecular sieves in toluene at 100 °C for 10 h under argon atmosphere. The reaction proceeds through relay mechanism involving O-H insertion onto the α-imino Rh(II)–carbene, [3,3]-sigmatropic rearrangement, dipole formation through Pd(0)-catalyzed decarboxylation, and finally intramolecular *N*-allylation.



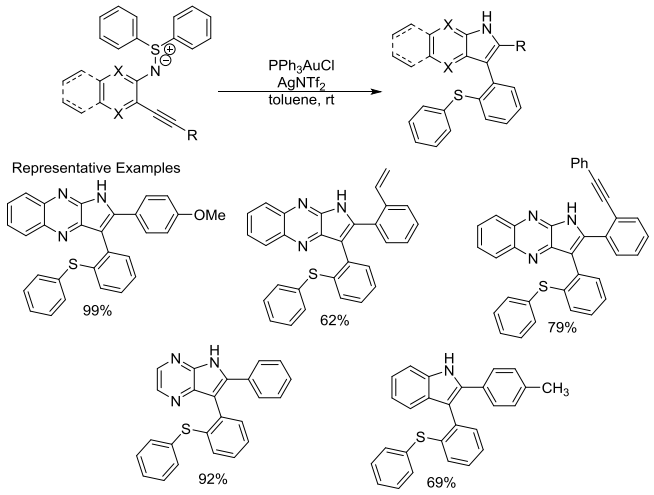
Scheme 11. Dual Rh(II)/Pd(0) relay catalysis for the synthesis of *N*-sulfonyl pyrrolidines.

Catalyst-dependent [3,3]-sigmatropic rearrangement of sulfoxide-ynamides was demonstrated by Zhu et al.[30] (**Scheme 12**). Various important medium-sized *N*,*S*-heterocycles were synthesized with moderate to good yields with wide substrate scope. 1,5-Benzothiazepines were obtained when different sulfonyl-protected sulfoxide-ynamides were reacted in the presence of 10 mol% of $Cu(CH_3CN)_4BF_4$ in DCE solvent at 80 °C for 0.5 hours. However, when 10 mol% of phosphorus-based ligand was used in $PhCF_3$ solvent at 80 °C for one hour, only 1,6-benzothiazocines were formed. The theoretical calculations suggested catalyst-dependent chirality transfer.



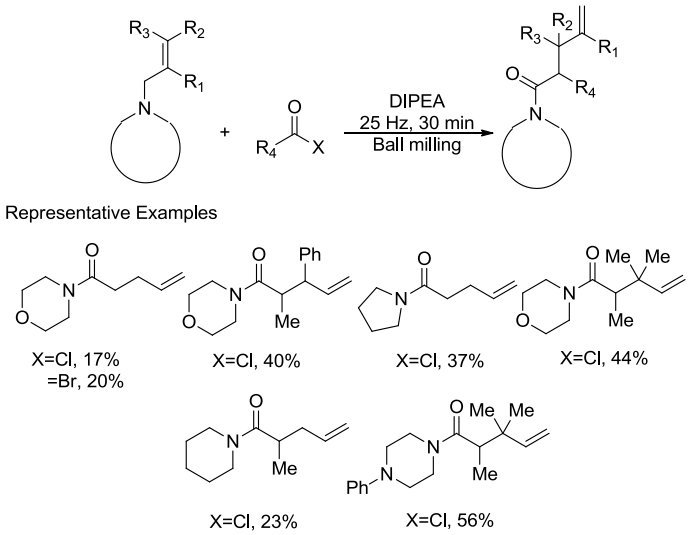
Scheme 12. Cascade cyclization of sulfoxide-ynamide *via* [3,3]-sigmatropic rearrangement.

In 2023, Hashmi et al.[31] reported synthesis of highly functionalized 5*H*-pyrrolo[2,3-*b*]pyrazine derivatives bearing a diaryl sulfide moiety at the C-7 position by the reaction of *ortho*-alkynyl-substituted S,S-diaryl sulfilimines by using gold(I) as the catalyst (**Scheme 13**) at room temperature. The reaction occurs via an unprecedented gold-catalyzed amino sulfonium [3,3]-sigmatropic rearrangement. 2 mol% of each PPh_3AuCl and $AgNTf_2$ and toluene were required for this reaction. Various diaryl sulfilimines having a wide variety of functional groups with diverse electronic and steric properties reacted under the optimized reaction conditions and the corresponding pyrazine derivatives were produced in excellent yields. The reaction proceeds through gold-catalyzed intramolecular sulfonium [3,3]-sigmatropic rearrangement.



Scheme 13. Synthesis of 5*H*-pyrrolo[2,3-*b*]pyrazine gold-catalyzed[3,3]-sigmatropic rearrangement.

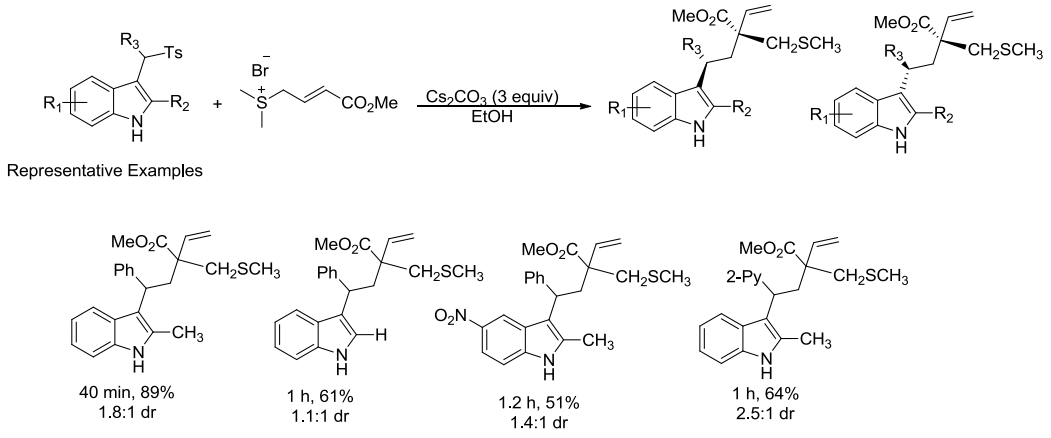
In a recent report Bolm et al.[32] reported synthesis of tertiary amides by the reaction of (heterocyclic) tertiary allylamines and propionyl chlorides through charge-accelerated amide enolate aza-Claisen rearrangement under ball milling condition (**Scheme 14**). The reaction requires a stoichiometric amount of DIPEA as base and uses stainless steel jar and one ball (10 mm in Ø) milled at 25 Hz for 30 min. The product was obtained in 17% yield when propionyl chloride was replaced by acetyl chloride and in 20% yield in case of acetyl bromide. Lower yields of the products were obtained in case of sterically hindered substrates. This method was applied for Belluš–Claisen-type rearrangement for the synthesis of 9-membered lactam under the optimized reaction condition although it has serious limitations in case of acetyl halides.



Scheme 14. Charge-accelerated aza-Claisen rearrangements under ball milling condition.

2.2. [2,3]-Sigmatropic Rearrangements

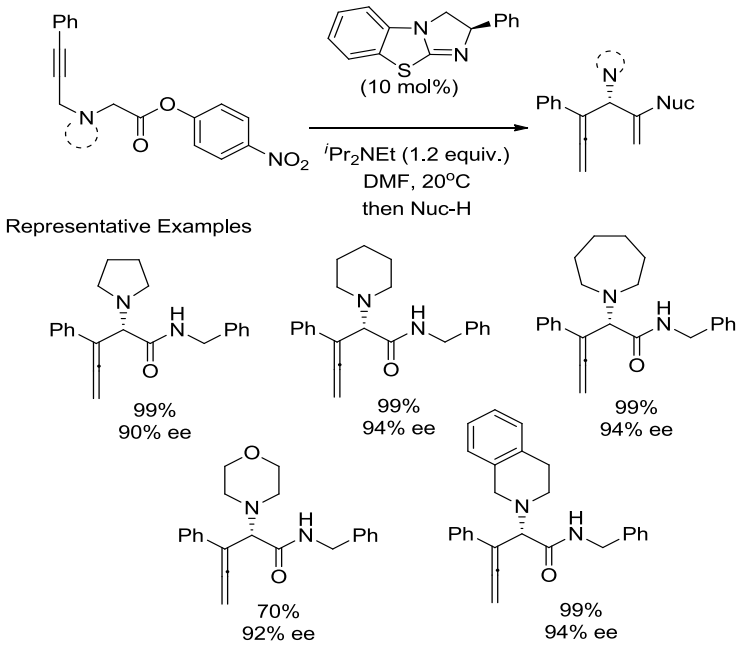
An efficient protocol for the synthesis of 3- substituted indole derivatives bearing homoallyl sulfide moiety *via* domino Michael addition- [2,3]-sigmatropic rearrangement promoted by Cs_2CO_3, was reported by Du et al.[33] (**Scheme 15**). Several 3-alkylated indole derivatives were produced with moderate to good yields and with high diastereoselectivity by using 3 equivalents of Cs_2CO_3 as a base in ethanol at room temperature.



Scheme 15. Cs_2CO_3-promoted Michael addition-[2,3]-sigmatropic rearrangement for synthesis of 3- substituted indole derivatives.

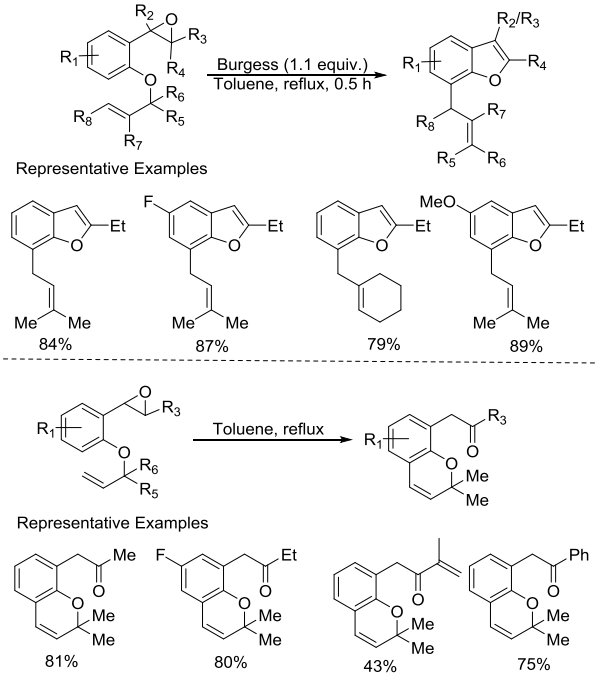
Highly efficient asymmetric synthesis of allenyl α-amino amides by an isothiourea catalyzed enantioselective [2,3]-sigmatropic rearrangement of propargyl ammonium salts was reported by Song et al.[34] (**Scheme 16**). After careful optimization, the best condition was achieved by using 20 mol% of chiral isothiourea as catalyst, 1.2 equivalents of $^{i}Pr_2NEt$ in DMF at 20 °C under stirring for 12 h, followed by the addition of $BnNH_2$. Various propargyl ammonium salts containing both electron donating and withdrawing

substituents were well accepted in the [2,3]-rearrangement reaction to afford the corresponding allenyl α-amino amides with good yields (up to 99%) and with excellent enantioselectivities (with 90–94% ee).



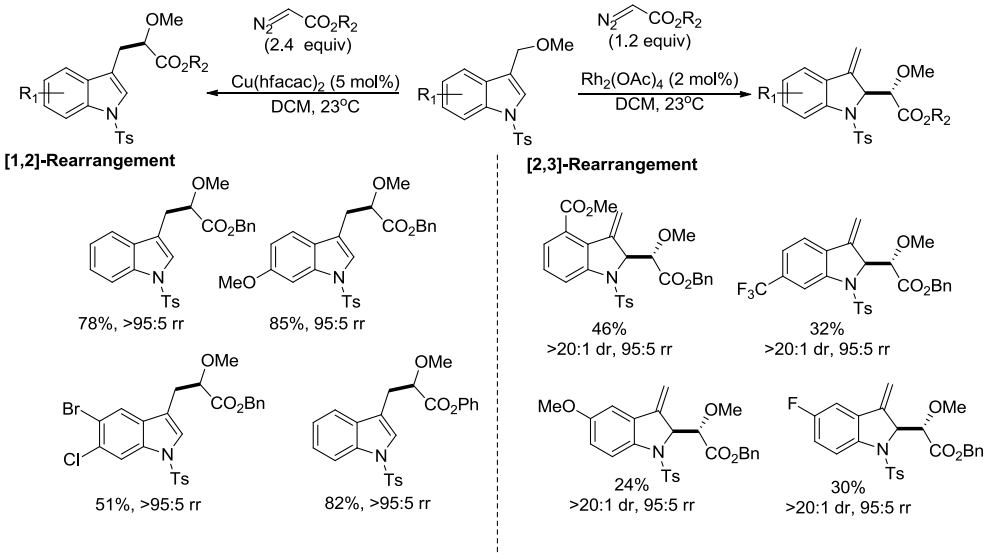
Scheme 16. Asymmetric synthesis of allenyl α-amino amides.

One-pot four-step divergent synthesis of polysubstituted benzofurans and 2*H*-chromenes *via* cascade approach starting from 1,2-*trans*-disubstituted epoxide substrates was reported by Song et al.[35] (**Scheme 17**). This reaction requires 1.1 equivalents of Burgess reagent as dehydrating agent in 0.05 M toluene as solvent under refluxing condition. The starting material bearing alkenyl or benzoyl substituents would lead to slightly lower yields. Besides, the synthesis of benzofurans, 2*H*-chromenes was also achieved under oxidative oxa-6π electrocyclization in the presence of an oxidant. The mechanism of the reaction involves aromatic [2,3]-Claisen rearrangement/Meinwald rearrangement/dehydrative or oxidative cyclization. This methodology was further applied for the total synthesis of natural product liparacid A in seven steps.



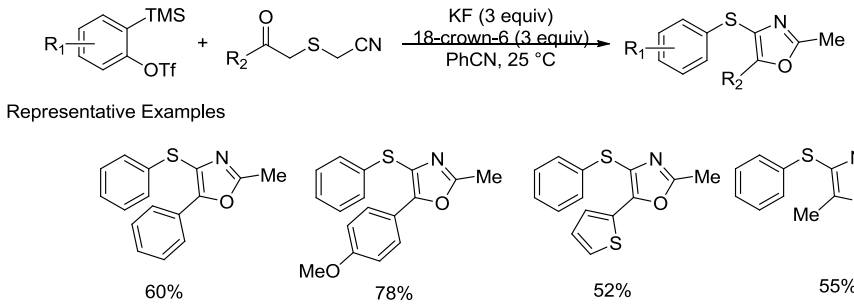
Scheme 17. One-pot divergent synthesis of benzofurans and 2*H*- chromenes.

In 2021, a catalyst controlled regio-divergent rearrangement of oxonium ylides derived from substituted indoles and diazoesters was reported by Tambar et al.[36] (**Scheme 18**). Interestingly, copper catalyst promotes a regioselective [1,2]-rearrangement whereas, rhodium catalyst favours regioselective and diastereoselective [2,3]-rearrangement. Both control experiments and DFT calculations revealed that metal-free ylide in the rhodium catalyzed reaction favoring [2,3]-sigmatropic rearrangement, and a metal-coordinated ion-pair in case of copper catalyzed [1,2]-rearrangement were involved. This protocol was further applied for the total synthesis of indole-based alkaloid (±)-sorazolon B.



Scheme 18. Catalyst controlled [1,2]/[2,3]-rearrangements for the synthesis of indole derivatives.

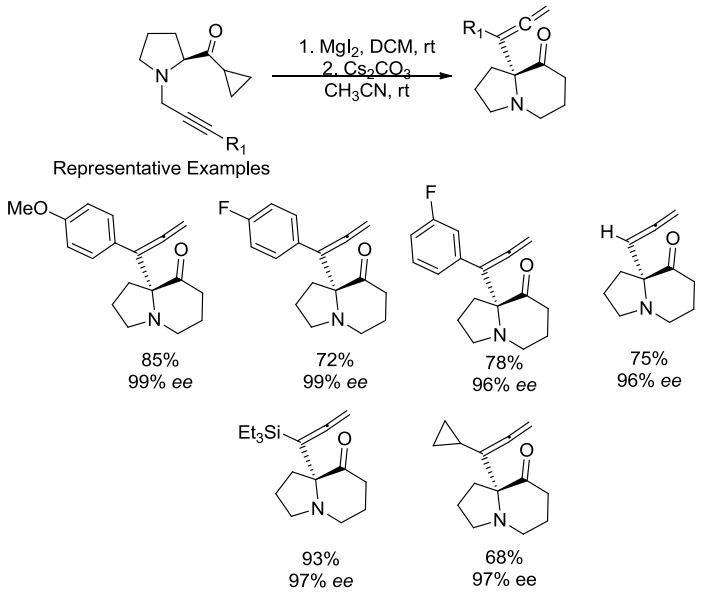
Biju et al.[37] reported metal free efficient synthesis of 2,4,5-trisubstituted oxazoles under mild conditions by the reaction of 2-substituted thio/amino acetonitriles with in-situ generated arynes via [2,3] sigmatropic rearrangement-annulation cascade process (**Scheme 19**). Thioethers having electron-releasing, -neutral and electron-withdrawing substituents at the *para* position of the β-aryl group underwent efficient [2,3] sigmatropic rearrangement-annulation cascade in the presence of 3 equivalents of KF as a fluoride source, 3 equivalents of 18-crown-6 as an additive in CH_3CN at 25 °C for 12 h. The reaction initially generates sulfur/ nitrogen ylides by the initial *S/N* arylation followed by proton transfer, which then undergoes selective [2,3]-sigmatropic rearrangement involving the –CN moiety and a subsequent annulation to furnish the respective products in moderate to good yields.



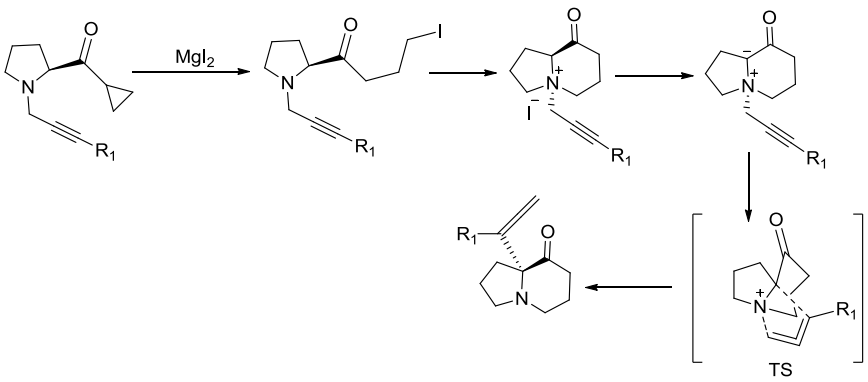
Scheme 19. Aryne induced [2,3] sigmatropic rearrangement for the synthesis of trisubstituted oxazoles.

Sequential nucleophilic ring opening of cyclopropyl ketones, *N*-quaternization, deprotonation, and finally [2,3]-sigmatropic rearrangement of ammonium ylides towards the synthesis of chiral indolizidines with bridgehead aza quaternary stereocenters starting from easily accessible chiral cyclopropyl ketones was developed by Xi et al.[38] (**Scheme 20**). Initially, cyclopropyl ketone reacts with 2 equivalents of MgI_2 and generates γ-haloketones which then undergoes *N*-quaternization, deprotonation, followed by [2,3]-sigmatropic

rearrangement in the presence of Cs_2CO_3 and leads to indolizidines with good yields and excellent enantiopurities. Interestingly, the presence of a triethylsilyl group at the alkyne moiety did not affect the reaction efficiency. A possible reaction pathway has been depicted in **Scheme 21**.



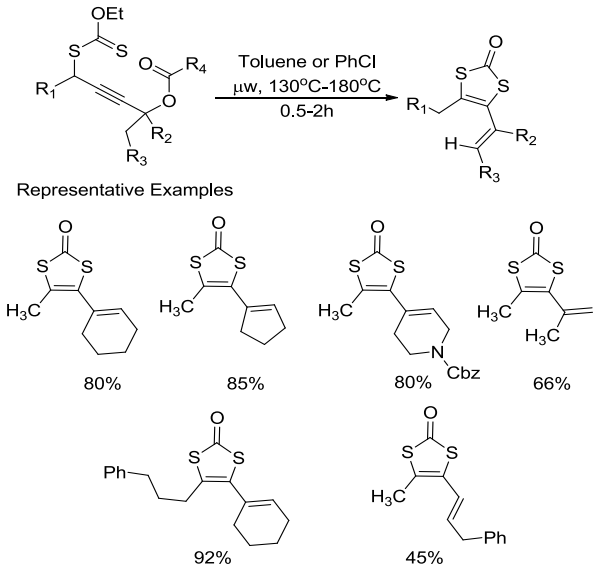
Scheme 20. [2,3]-Sigmatropic rearrangement of ammonium ylides generated from cyclopropyl ketones.



Scheme 21. Possible reaction pathway.

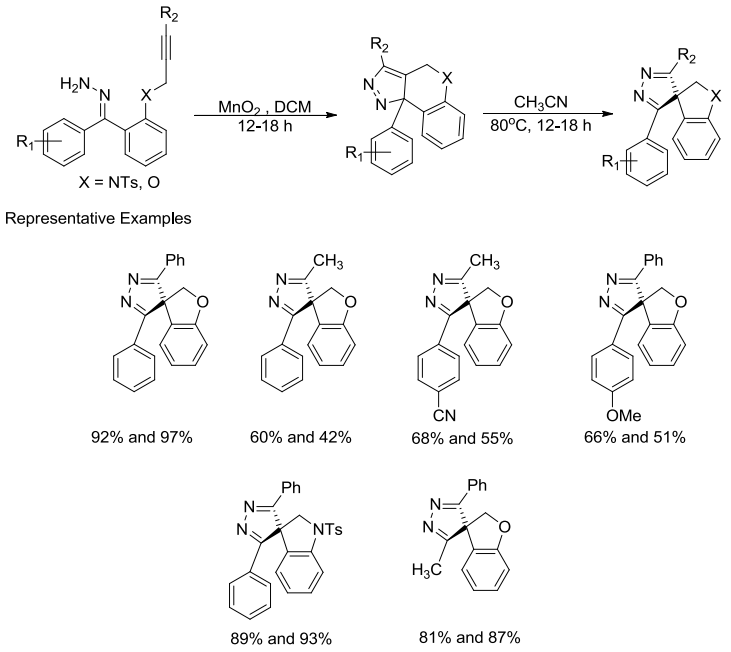
2.3. [1,5]-Sigmatropic Rearrangements

1,3-Dithiol-2-ones are 5-membered sulfur containing heterocycles which show notable aromatic character. They are primarily recognized as universal precursors for the synthesis of tetrathiafulvalenes upon phosphite mediated reductive coupling[39]. Zard et al.[40] reported the synthesis of a series of conjugated 4-alkenyl-1,3-dithiol-2- ones under microwave irradiation of *S*-(4-acyloxy-2-alkynyl)-*O*-ethyl xanthates (**Scheme 22**). Cyclohexanone derived propargyl xanthate, *N*-Cbz-protected piperidine propargyl xanthate provided the corresponding dithiolone with good to excellent yields. The propargyl xanthates derived from unsymmetrical ketones led to the formation of equimolar mixture of two products. In case of propargyl xanthates derived from aldehydes the corresponding product was obtained under the same reaction condition without any difficulty. The reaction occurred through a combination of [3,3] and [1,5] sigmatropic rearrangements as well as via the intermediacy of a reactive betaine which induces the ionic elimination of the acyloxy moiety. Deuterium-labelling experiment confirms the involvement of [1,5]-sigmatropic rearrangement.



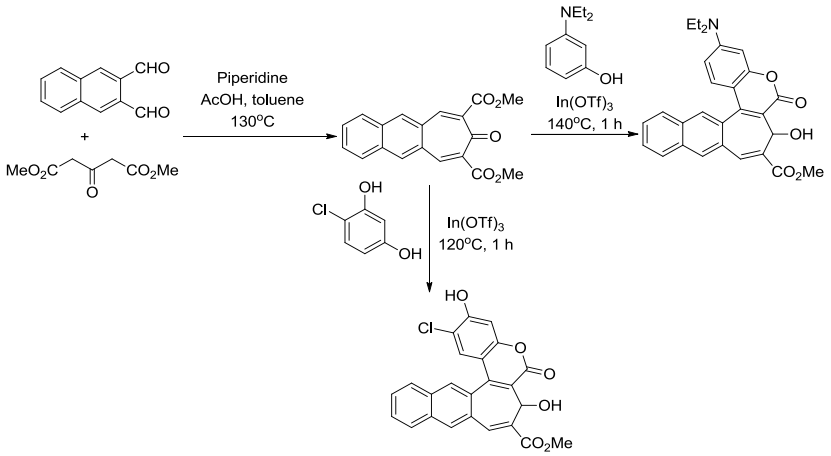
Scheme 22. Synthesis of 4-alkenyl-1,3- dithiol-2-ones *via* [1,5]-sigmatropic rearrangement.

Dimirjian et al.[41] developed an excellent protocol for the synthesis of spirobicyclic pyrazoles *via* intramolecular dipolar cycloadditions/[1s,5s]-sigmatropic rearrangements (**Scheme 23**). Various propargylic hydrazones underwent oxidation in the presence of MnO_2 followed by dipolar cycloaddition (DPC) of a diazo-alkane with alkyne and finally [1s,5s] sigmatropic rearrangement. A library of spirobicyclic pyrazoles were obtained in good yields.



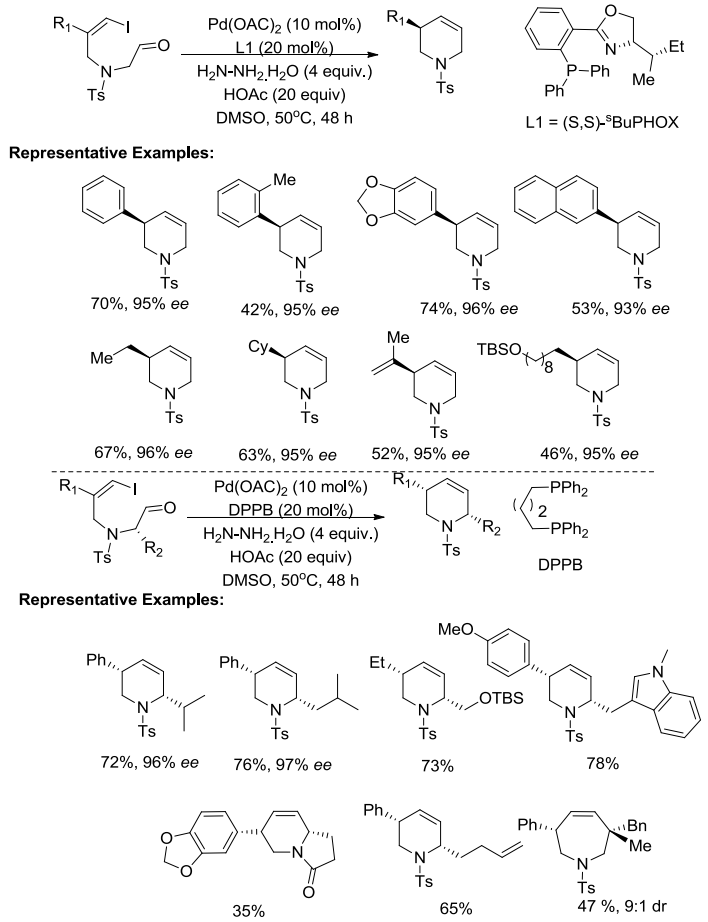
Scheme 23. Synthesis of spirobicyclic pyrazoles through intramolecular dipolar cycloadditions/[1s, 5s]-sigmatropic rearrangements.

A series of helical coumarins were synthesized by addition of phenol to a cyclic *α,β*-unsaturated ester followed by intramolecular transesterification and [1,5] sigmatropic rearrangement (**Scheme 24**)[42]. Initially, naphthalene-2,3-dicarbaldehyde underwent double Knoevenagel condensation with acetone-1,3-dicarboxylate, leading to the formation of dimethyl 7-oxo-7H-benzo[7]-annulene-6,8-dicarboxylate, which finally reacted with 3-diethylaminophenol and 4-chlororesorcinol in the presence of indium triflate as Lewis acid and the corresponding helical coumarins were obtained in 47% and 44% yields. These molecules were further used for the synthesis of more rigid and helical coumarin-pyrazolones which showed green fluorescence.



Scheme 24. Synthesis of helical coumarins through [1,5]-sigmatropic rearrangement.

Recently, Tong et al.[43] developed stereoselective hydrazone-type Heck reaction and denitrogenative [1,5]-sigmatropic rearrangement for the synthesis of tetrahydropyridine using a combination of palladium/ligand (**Scheme 25**). *N*-[(*Z*)-3-Iodoallyl]-aminoacetaldehyde reacts with 80 % aqueous hydrazine to provide the corresponding hydrazone in the presence of 20 equivalents of acetic acid as an additive and the combination of 10 mol% of $Pd(OAc)_2$ and 20 mol% of (S,S)-s BuPHOX as the catalyst (**Scheme 24**). The substrate-induced diastereoselective version was also explored, giving exclusively *cis*-2,5-disubstituted THPs in the presence of [1,4-bis(diphenylphosphaneyl)butane] (DPPB) as ligand (**Scheme 25**). This catalytic protocol was further extended successfully for the synthesis of various useful bioactive targets, including 3-ethylindoloquinolizine, preclamol, and niraparib.



Scheme 25. Stereoselective hydrazone-type Heck reaction and denitrogenative [1,5]-sigmatropic rearrangement for the synthesis of tetrahydropyridine.

In general, the traditional sigmatropic rearrangements require stoichiometric amount of catalyst and base, and in several cases harsh reaction conditions such as high temperature are used. The enantioselectivities are not always satisfactory. These limitations were overcome to some extent with the use of well-tailored substrates and carefully selected chiral metal-complexes as active catalysts.

3. Conclusion

We have presented here a brief account of the applications of sigmatropic rearrangements, particularly [3,3]-, [2,3] and [1,5]- for the synthesis of various important heterocyclic compounds and their functionalization. The sigmatropic rearrangements are of much importance as these are basically green avoiding loss of atoms and generation of waste. A variety of heterocyles including indoles, benzofurans, pyrazoles, oxazoles, coumarins, and tetrahydropyridines have been obtained successfully involving one or more of these rearrangements. The reaction pathways of several rearrangements have also been discussed. We believe, this review will attract the attention of a wide section of synthetic chemists in academia as well as pharmaceutical industry and will serve as a useful reference for further research.

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Conflict of interest

The authors declare no conflict of interest.

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