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Review

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Synthesis of oxygen- and sulfur-containing heterocycles from 1,1-disubstituted vinylbromides

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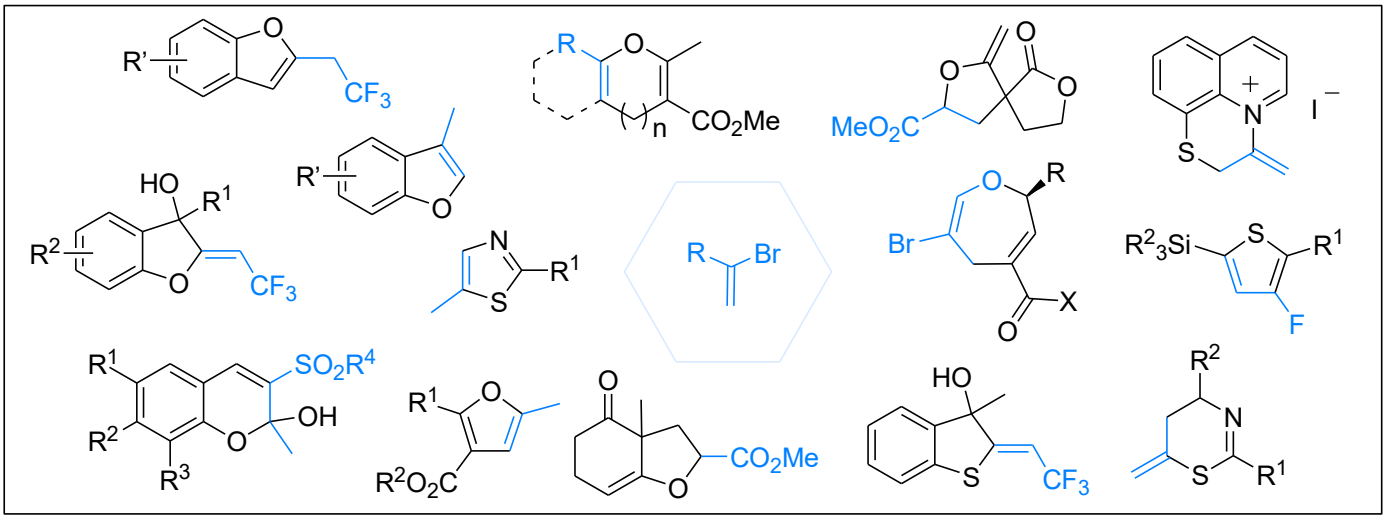
Abstract

The present short review focuses on the application of 1,1-disubstituted vinyl bromides as a useful platform for the construction of oxygen- and sulfur-containing heterocycles over the past decades up to 2025. Because vinyl bromides possess both a reactive C–Br bond and a polarized C=C bond, their dual functionality enables diverse transformations such as transition-metal-catalyzed cross-couplings, intramolecular cyclizations, nucleophilic substitutions, rearrangements, and tandem or cascade reactions that are employed to access furan, benzofuran, chromene, thiophene, or benzothiophene derivatives.



Keywords: Vinyl bromide, furan, benzofuran, chromene, thiophene, benzothiophene

Table of Contents

1. Introduction
2. Discussion
   2.1 Synthesis of *O*-heterocyclic compounds
      2.1.1 Furans, benzofurans and derivatives
      2.1.2 Chromen derivatives
      2.1.3 Other oxygen-containing heterocycles
   2.2 Synthesis of *S*-heterocyclic compounds
3. Conclusions

Acknowledgements

References

1. Introduction

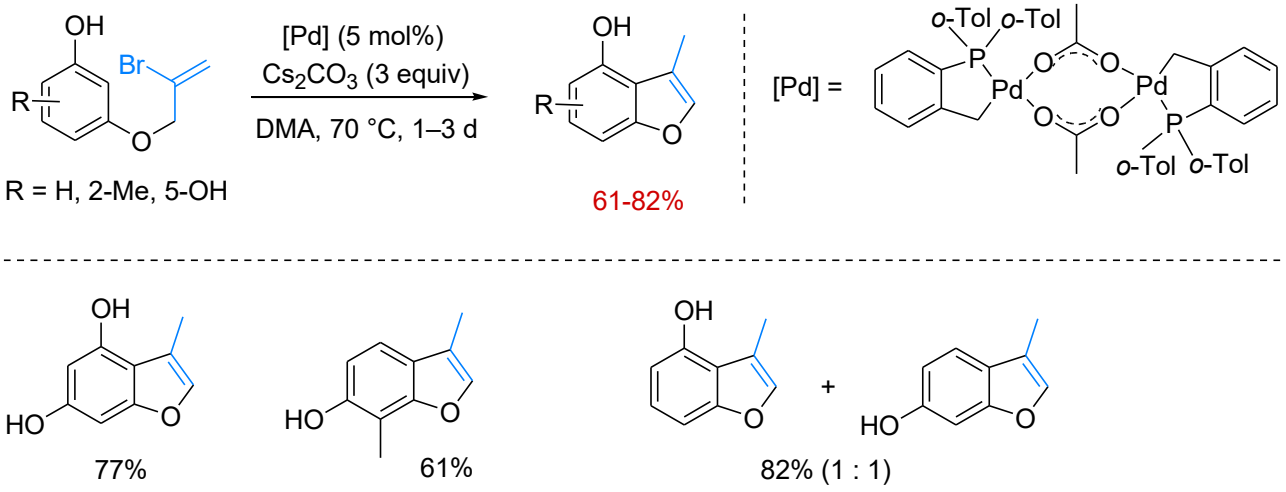
Oxygen- and sulfur-containing heterocycles constitute fundamental structural motifs in a wide range of natural products, pharmaceuticals, agrochemicals, and functional materials. Consequently, the development of efficient and versatile synthetic strategies for their construction remains a central objective in organic synthesis.[1-7] Among the many approaches investigated, the use of halogenated alkenes as multifunctional building blocks has attracted sustained interest, owing to their capacity to engage in diverse bond-forming processes through complementary modes of reactivity.[8] In this regard, 1,1-disubstituted vinyl bromides occupy a distinctive position. These substrates combine a reactive carbon–bromine bond with a polarized carbon–carbon double bond, enabling participation in transition-metal-catalyzed cross-couplings, intramolecular cyclizations, nucleophilic substitutions, rearrangements, and tandem or cascade reactions. The interplay between these reactive elements allows 1,1-disubstituted vinyl bromides to serve as flexible precursors for the rapid assembly of structurally diverse heterocyclic frameworks and we have recently reported their use in the construction of nitrogen-containing heterocycles.[9] Over the past several decades, substantial progress has been made in exploiting 1,1-disubstituted vinyl bromides for heterocycle synthesis. These advances encompass palladium-, copper-, silver-, and base-mediated processes, as well as catalyst-free and enantioselective transformations. Collectively, these methodologies have enabled efficient access to a broad spectrum of oxygen- and sulfur-containing heterocycles, including furans, benzofurans, chromenes, thiophenes, benzothiophenes, and related ring systems, often with high levels of regio- and chemoselectivity. Although reviews have addressed the synthesis of heterocycles[10-14] or the reactivity of vinyl halides more generally, a focused and comprehensive analysis of oxygen- and sulfur-heterocycle formation specifically from 1,1-disubstituted vinyl bromides has not yet been presented. The present review fills this gap by summarizing and evaluating developments reported up to 2025. Emphasis is placed on reaction design, mechanistic understanding, scope and limitations, and synthetic utility, with the aim of providing a coherent framework for current achievements and future opportunities in this area.

2. Discussion

2.1 Synthesis of *O*-heterocyclic compounds

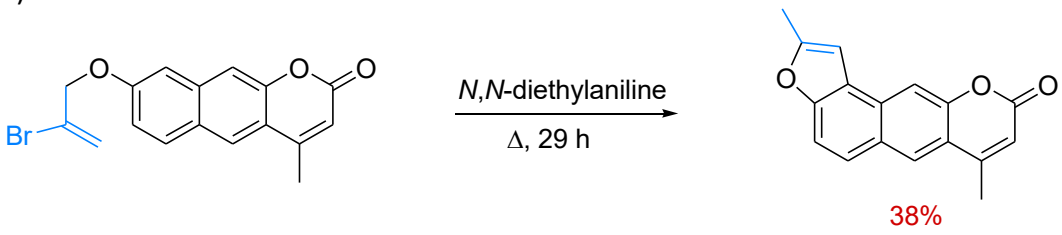
Oxygen-containing heterocycles constitute an important class of compounds accessible from 1,1-disubstituted vinyl bromides, owing to the favorable interaction of the vinyl bromide motif with oxygen-based nucleophiles and its compatibility with metal-catalyzed and base-mediated cyclization processes. This section summarizes representative strategies for the construction of furans, benzofurans, chromenes, and related oxygen heterocycles, with emphasis on reaction scope, regioselectivity, and mechanistic features governing ring formation.

2.2.1.Furans, benzofurans and derivatives. Intramolecular cyclizations of a range of substrates containing various vinyl bromide side chains were investigated for the synthesis of polysubstituted furans. For instance, Rawal *et al*. described in 1997 a palladium-catalyzed intramolecular cyclization of vinyl bromides with phenols to access benzofurans, indoles and a benzopyran.[15] The cyclization reaction of the phenol containing a vinyl bromide chain was performed in the presence of a catalytic amount of the Herrmann-Beller palladacycle catalyst and Cs_2CO_3 as a base in DMA (dimethylacetamide) for 1.5-3 days. Under these conditions, the corresponding benzofurans were obtained with yields ranging from 61% to 82%, with a 1:1 mixture of "ortho" and "para" benzofurans formed in the cyclization of 3-((2-bromoallyl)oxy)phenol (R = H) (Scheme 1).



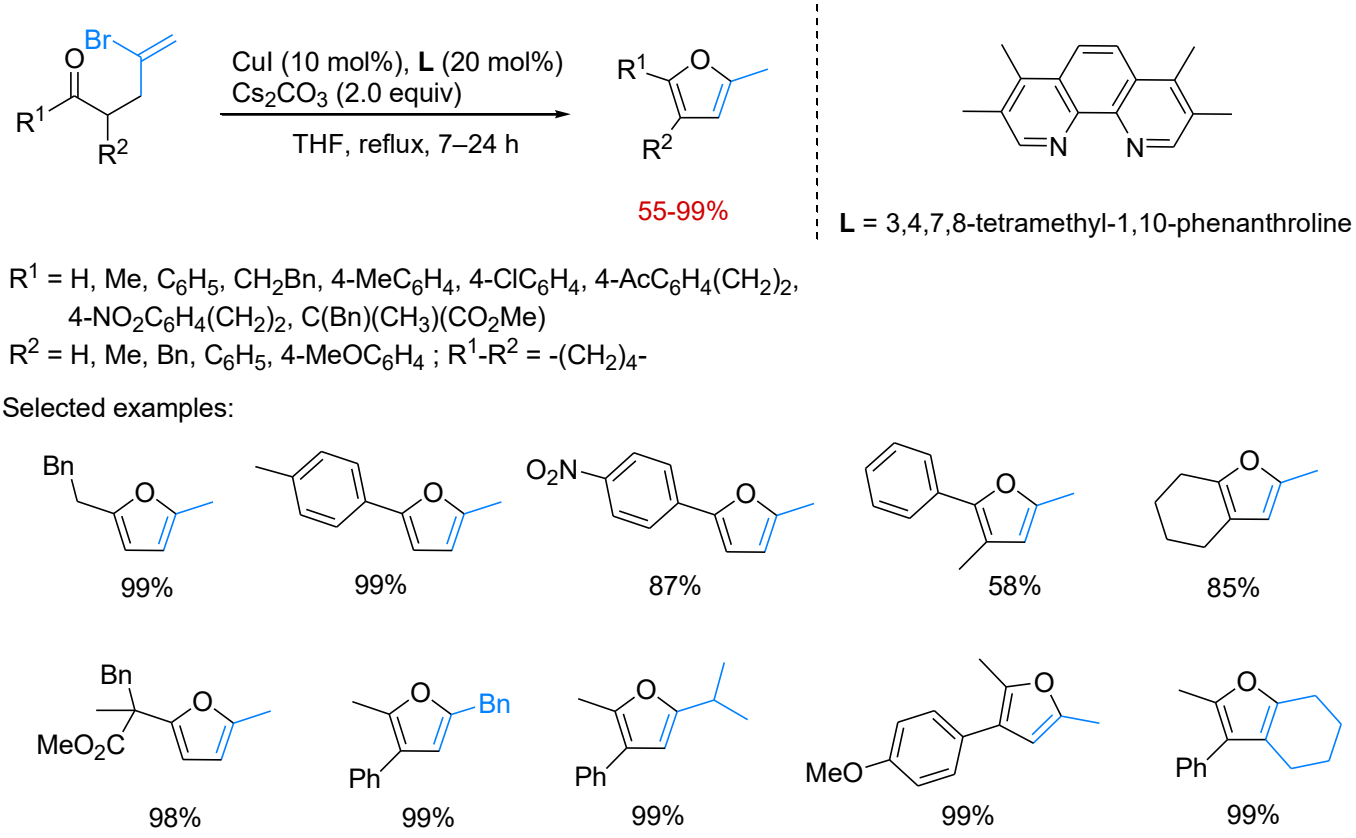
Scheme 1. Synthesis of benzofurans via palladium-mediated cyclization.

Alternatively, a Claisen rearrangement of a (β-bromoallyloxy)naphthopyrone to the corresponding furonaphthopyrone was also reported. Thus, heating 8-((2-bromoallyl)oxy)-4-methyl-2*H*-benzo[*g*]chromen-2-one in *N*,*N*-diethylaniline led to the formation of 2,7-dimethyl-9*H*-benzofuro[5,4-*g*]chromen-9-one in 38% yield (Scheme 2).[16]



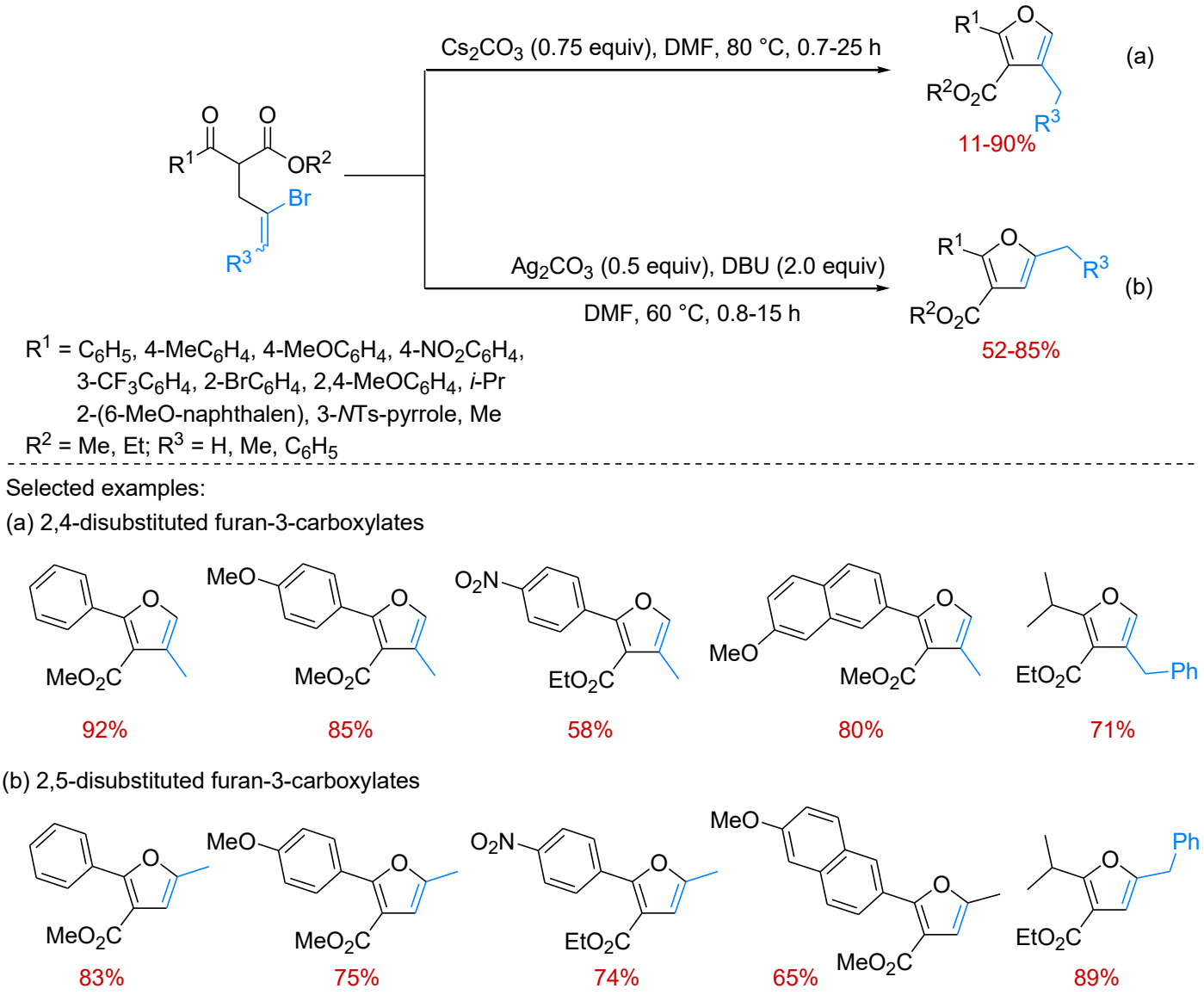
Scheme 2. Synthesis of a furonaphthopyrone via a Claisen rearrangement.

Li and coworkers explored in 2010 the synthesis of variously substituted furans by Cu(I)-catalyzed intramolecular *O*-vinylation of ketones with vinyl bromides. The reaction was performed with a set of various ketones bearing a vinyl bromide moiety in the presence of 10 mol% of CuI, 20 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline, 2 equiv of Cs_2CO_3 in refluxing dioxane affording various furan derivatives with yields ranging from 55% to 99% (Scheme 3).[17]



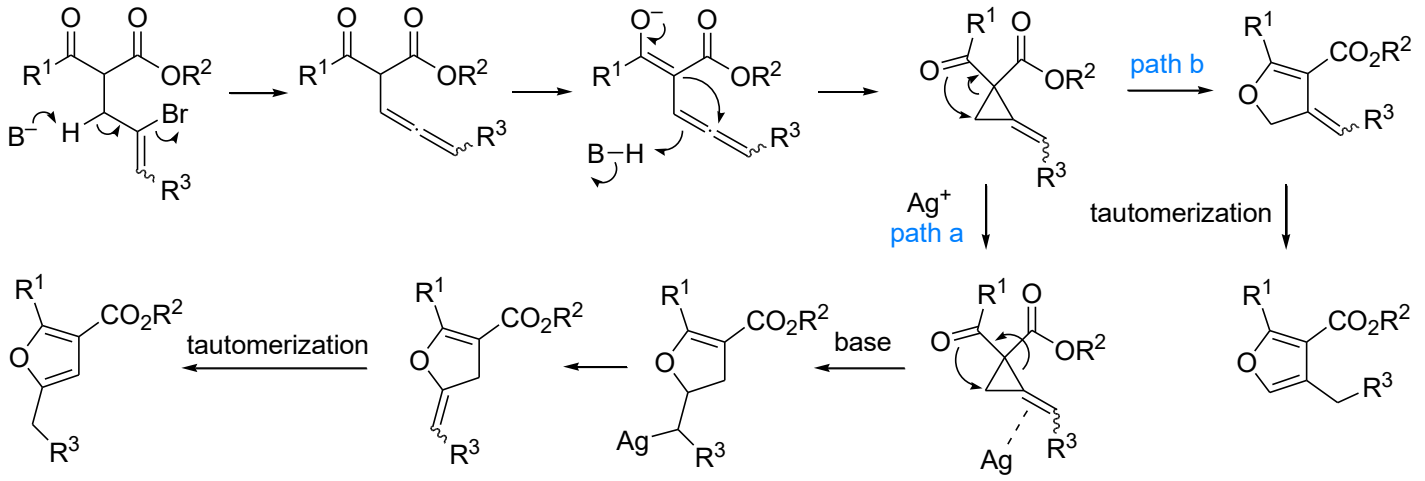
Scheme 3. Synthesis of dihydrofurans and derivatives by copper-catalyzed *O*-vinylation.

In 2015, Wu, Chang and coworkers reported the regioselective synthesis of 2,4- and 2,5-disubstituted furan-3-carboxylates. The former were obtained by treatment of 3-substituted 2-(2-bromoallyl)-3-oxo-1-carboxylates with Cs_2CO_3 in DMF in 58-92% yield (Scheme 4a) whereas the latter were formed in 38-89% yield using Ag_2CO_3 in the presence of DBU (Scheme 4b).[18] The reaction tolerated 3-aryl substituted substrates having either an electron-donating or an electron-withdrawing group, and aliphatic β-keto esters were also suitable for this transformation.



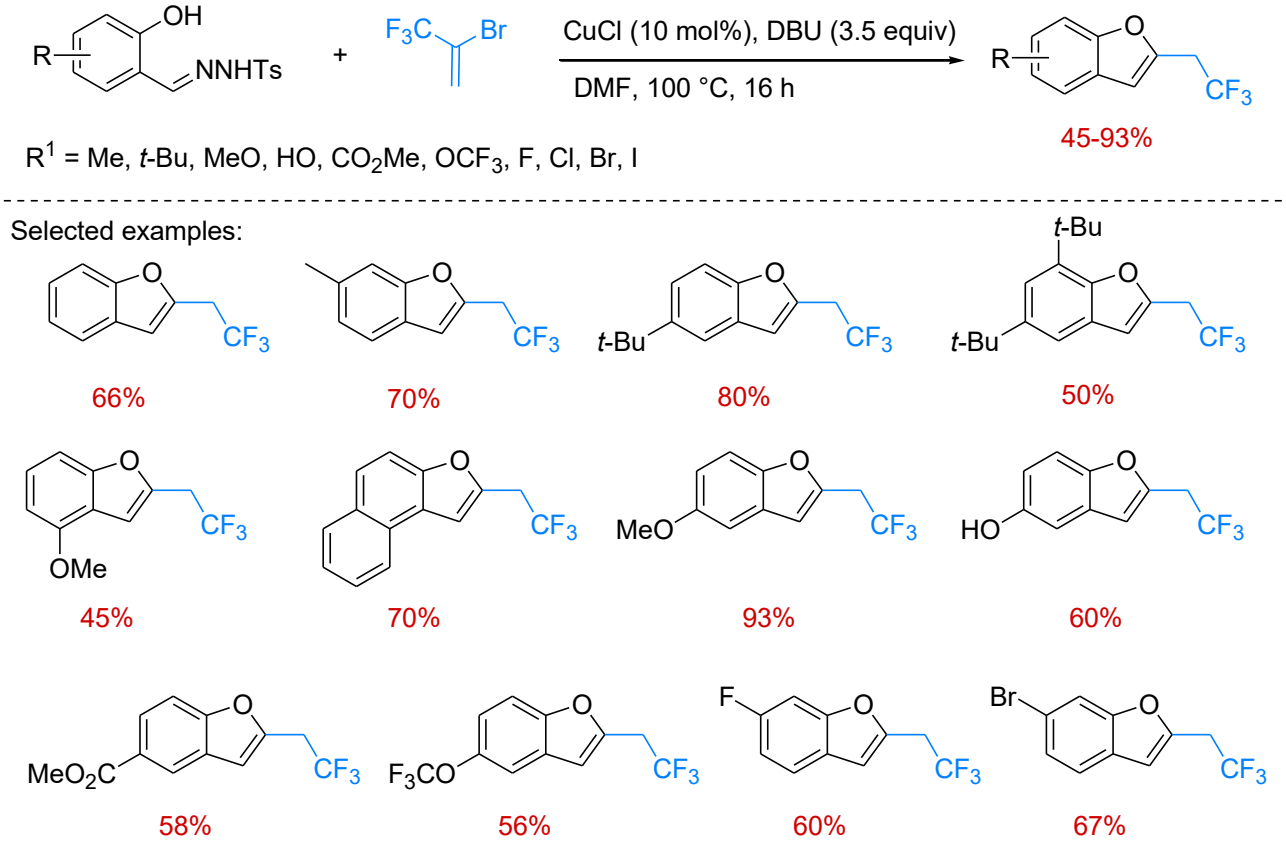
Scheme 4. Regioselective synthesis of 2,4- and 2,5-disubstituted furan-3-carboxylates.

A plausible mechanism for the regioselective formation of the 2,4- and 2,5-disubstituted furan-3-carboxylates was proposed by the authors (Scheme 5). In the presence of a base, an allenic intermediate is formed and the resulting enolate then undergoes an intramolecular addition on the allene function to give a methylenecyclopropane intermediate. Activation of the double bond with Ag_2CO_3 (path a) followed by concomitant cyclopropane ring opening and cyclization leads to a 2,3-dihydofuran which after β-elimination and tautomerization gave the 2,5-disubstituted furan-3-carboxylate. Alternatively, in the absence of silver salt (path b), cyclopropane ring opening and subsequent intramolecular nucleophilic addition would occur on the less sterically hindered carbon atom of the cyclopropane ring, leading after tautomerization to the 2,4-disubstituted furan-3-carboxylate.



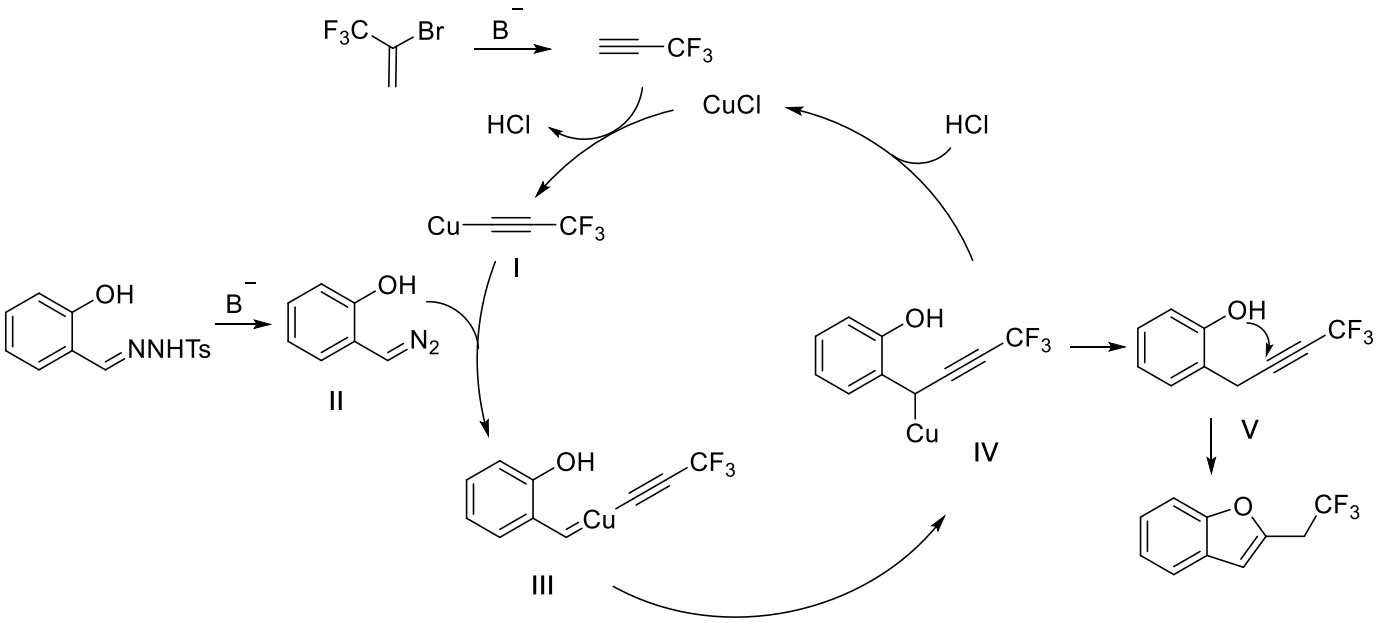
Scheme 5. Proposed mechanism for the regioselective formation of 2,4- and 2,5-disubstituted furan-3-carboxylates.

You, Weng and coworkers developed in 2021 a copper-catalyzed one-pot synthesis of 2-trifluoroethyl-substituted benzofurans using substituted salicylaldehyde *p*-tosylhydrazones and 2-bromo-3,3,3-trifluoropropene (Scheme 6).[19] The reaction was performed with 10 mol% of CuCl as a catalyst and DBU (3.5 equiv) as a base in DMF delivering the 2-(2,2,2-trifluoroethyl)benzofurans with yields ranging from 45% to 93%. The reaction was tolerant of a wide scope of salicylaldehyde *p*-tosylhydrazones and could be performed on gram-scale.



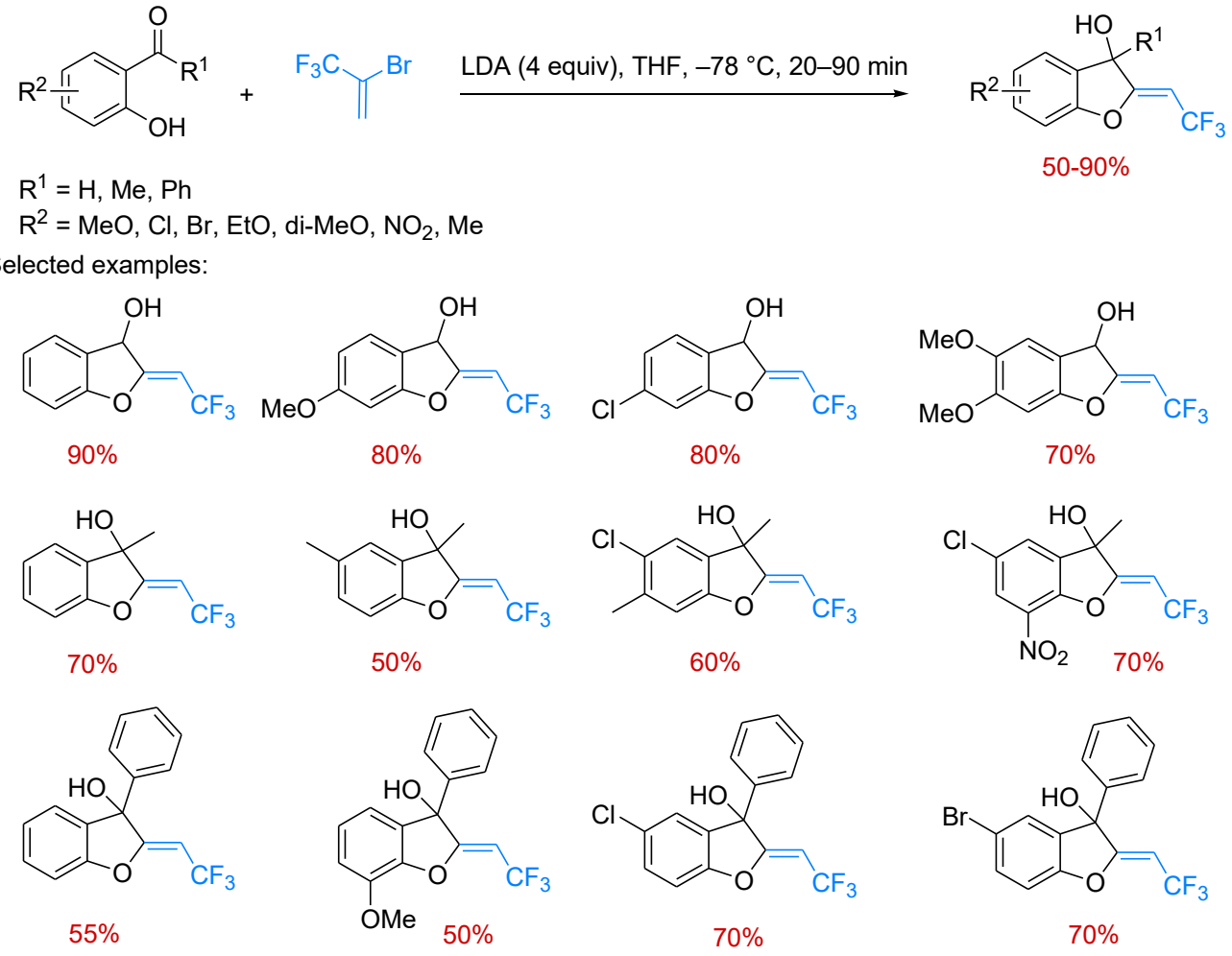
Scheme 6. Copper-catalyzed one-pot synthesis of 2-(2,2,2-trifluoroethyl)benzofurans.

A plausible reaction pathway was proposed for the synthesis of 2-(2,2,2-trifluoroethyl)benzofuran as shown in Scheme 7. A Cu(I) acetylide species **I** is first formed by reaction of CuCl with 3,3,3-trifluoropropyne that was generated *in situ* from 2-bromo-3,3,3-trifluoropropene under basic conditions. The reaction of **I** with 2-(diazomethyl)phenol **II** generated *in situ* from salicylaldehyde *p*-tosylhydrazone would then afford copper-carbene species **III** on which a reductive elimination would provide intermediate **IV**. Acidification of the latter would then regenerate CuCl and deliver 2-propargyl-phenol **V**. An intramolecular addition and subsequent isomerization would then produce the desired 2-(2,2,2-trifluoroethyl)benzofuran.



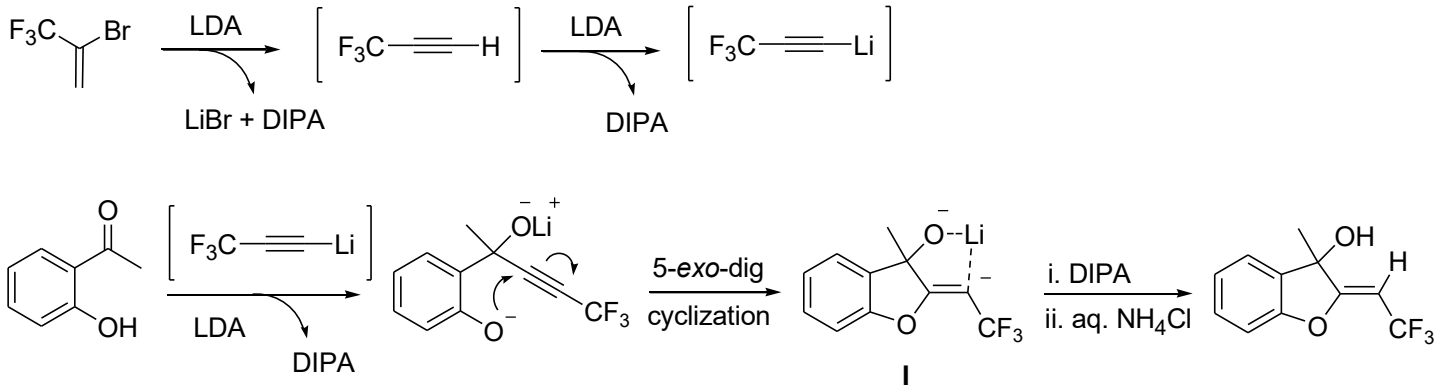
Scheme 7. Plausible reaction pathway for the synthesis of 2-(2,2,2-trifluoroethyl)benzofurans.

Sharma, Singh and coworkers studied in 2024 a catalyst-free one-pot access to CF_3-containing functionalized benzofuran derivatives from readily available aromatic aldehydes or ketones and 2-bromo-3,3,3-trifluoropropene (2-BTP). The reaction was carried out in the presence of 4 equivalents of LDA with variously substituted 2-hydroxyacetophenones and 2-BTP affording the corresponding benzofurans with yields ranging from 50% to 90% (Scheme 8).[20] 2-Bromo-3,3,3-trifluoropropene was employed here as an environmentally benign trifluoromethylacetylene synthon to introduce a CF_3 group.



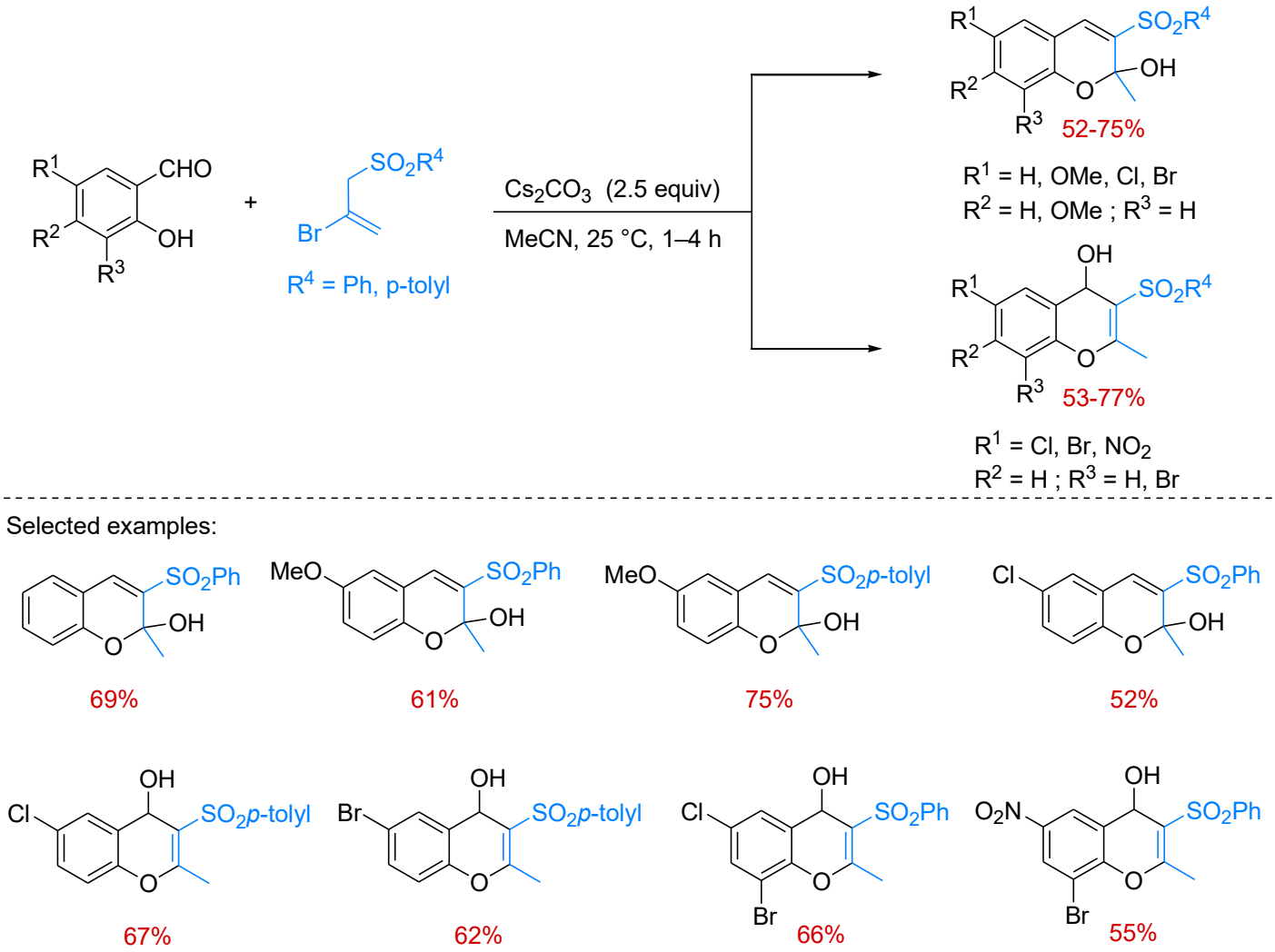
Scheme 8. One-pot access to CF_3-containing benzofurans from aromatic aldehydes or ketones and 2-bromo-3,3,3-trifluoropropene.

The authors proposed a plausible mechanism for the formation of the CF_3-containing benzofuran derivatives as depicted in Scheme 9. Treatment of 2-bromo-3,3,3-trifluoropropene with an excess of LDA leads to the *in situ* generation of a 3,3,3-trifluoromethyl acetylide species which is then involved in a nucleophilic addition onto the carbonyl functional group of the 2-hydroxyacetophenone. The resulting bis-alkoxide anion then undergoes a 5-*exo*-dig type cyclization that affords the desired benzofuran derivative *via* intermediate **I** that would account for the observed selectivity for the *Z*-configuration.



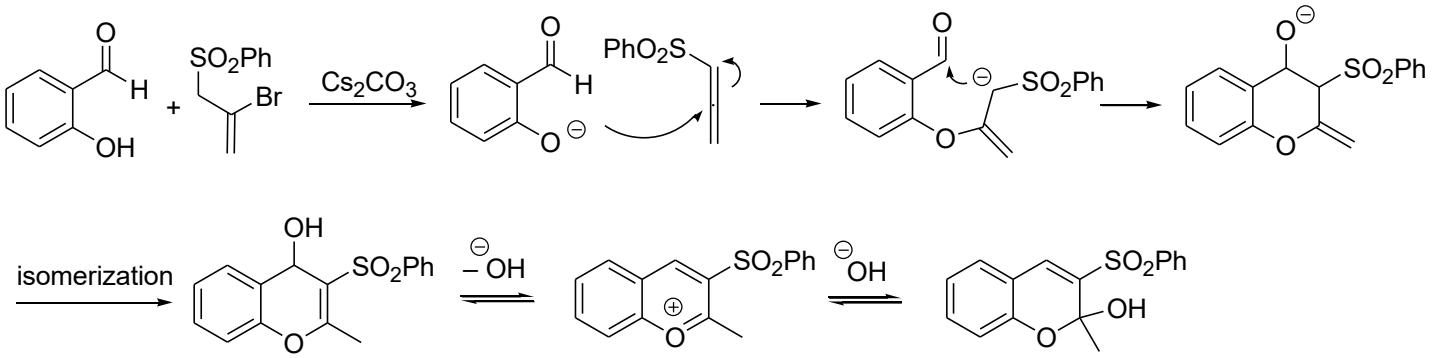
Scheme 9. Plausible reaction mechanism for the synthesis of benzofuran derivatives.

2.1.2 Chromen derivatives. Menon and coworkers published in 2015 the synthesis of 3-sulfonylchromene derivatives by cesium carbonate-mediated cyclo-condensation of 2-bromoallyl sulfones and salicylic aldehydes, where the 2-bromoallyl sulfones functioned as synthetic equivalents of allenylsulfones (Scheme 10).[21] Depending on the substituents carried by the salicylaldehyde, 2*H*- or 4*H*-chromenes were obtained with yields ranging from 52 to 77%. 2*H*-Chromene derivatives were obtained with salicylaldehyde as well as *o*-hydroxybenzaldehydes bearing electron-donating substituents. On the other hand, *o*-hydroxybenzaldehydes having electron-withdrawing substituents afforded the 4*H*-chromenes, whereas halogen-bearing salicylaldehydes deviated from this general trend.



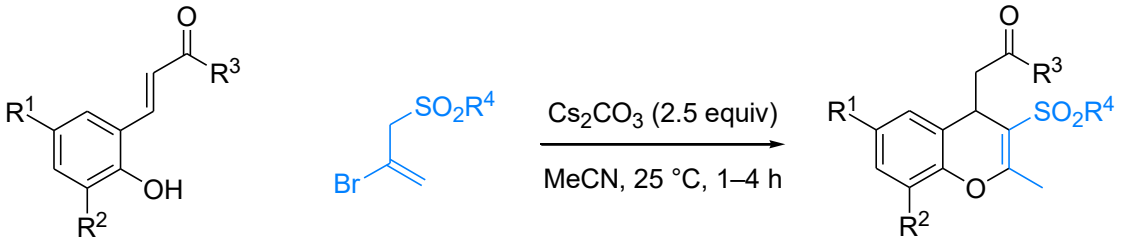
Scheme 10. Synthesis of chromene derivatives by cyclocondensation of salicylic aldehydes and 2-bromoallyl sulfones.

The authors proposed a plausible mechanism for the formation of the chromene derivatives as shown in Scheme 11. Reaction of bromoallyl sulfone with cesium carbonate leads to the formation of an allenyl sulfone that undergoes a conjugate addition with the phenoxide ion. The intramolecular nucleophilic addition of the resulting α-sulfonyl carbanion to the aldehyde is followed by a double-bond isomerization to yield a 4*H*-chromene intermediate. Finally, isomerization of the latter to the 2*H*-chromene derivative proceeds through a benzopyrillium ion.

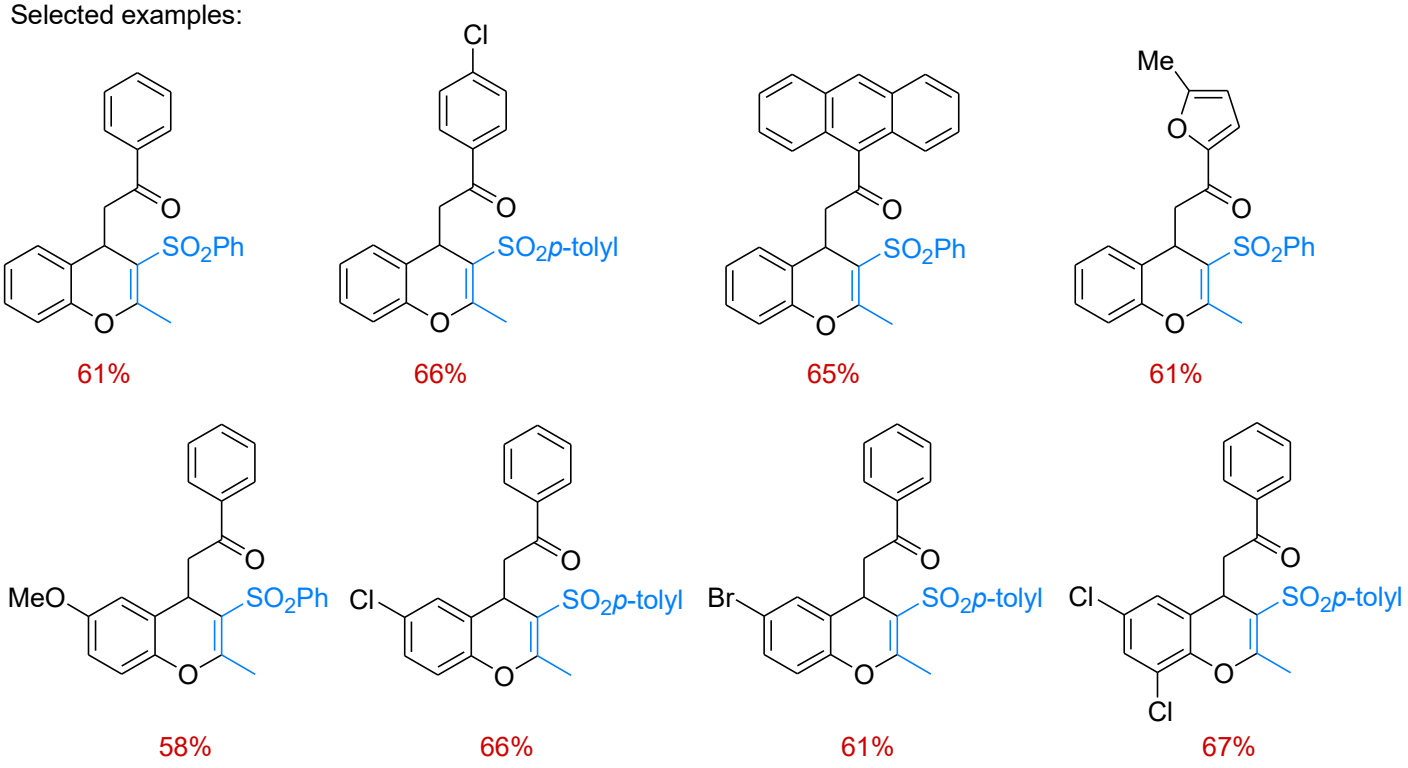


Scheme 11. Plausible mechanistic rationalization for the formation of chromene derivatives

In 2016, the same group described the synthesis of new 4*H*-chromene derivatives *via* a similar base-mediated annulation reaction of *o*-hydroxychalcones and 2-bromoallylsulfones (Scheme 12).[22] The reaction was tolerant to both electron-withdrawing and electron-donating substituents on the *o*-hydroxychalcones and allowed the cyclisation products in yields ranging from 58% to 67%.

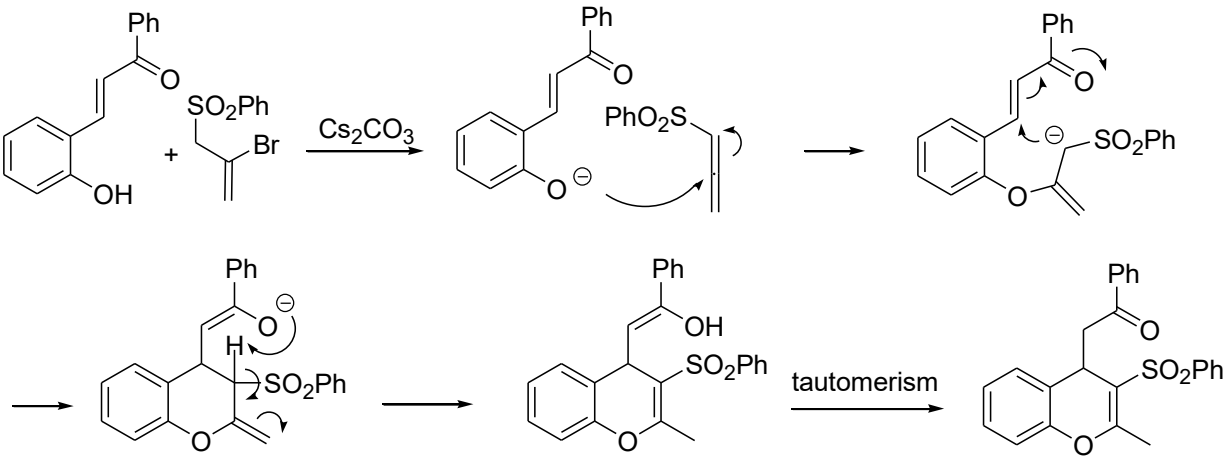


Selected examples:



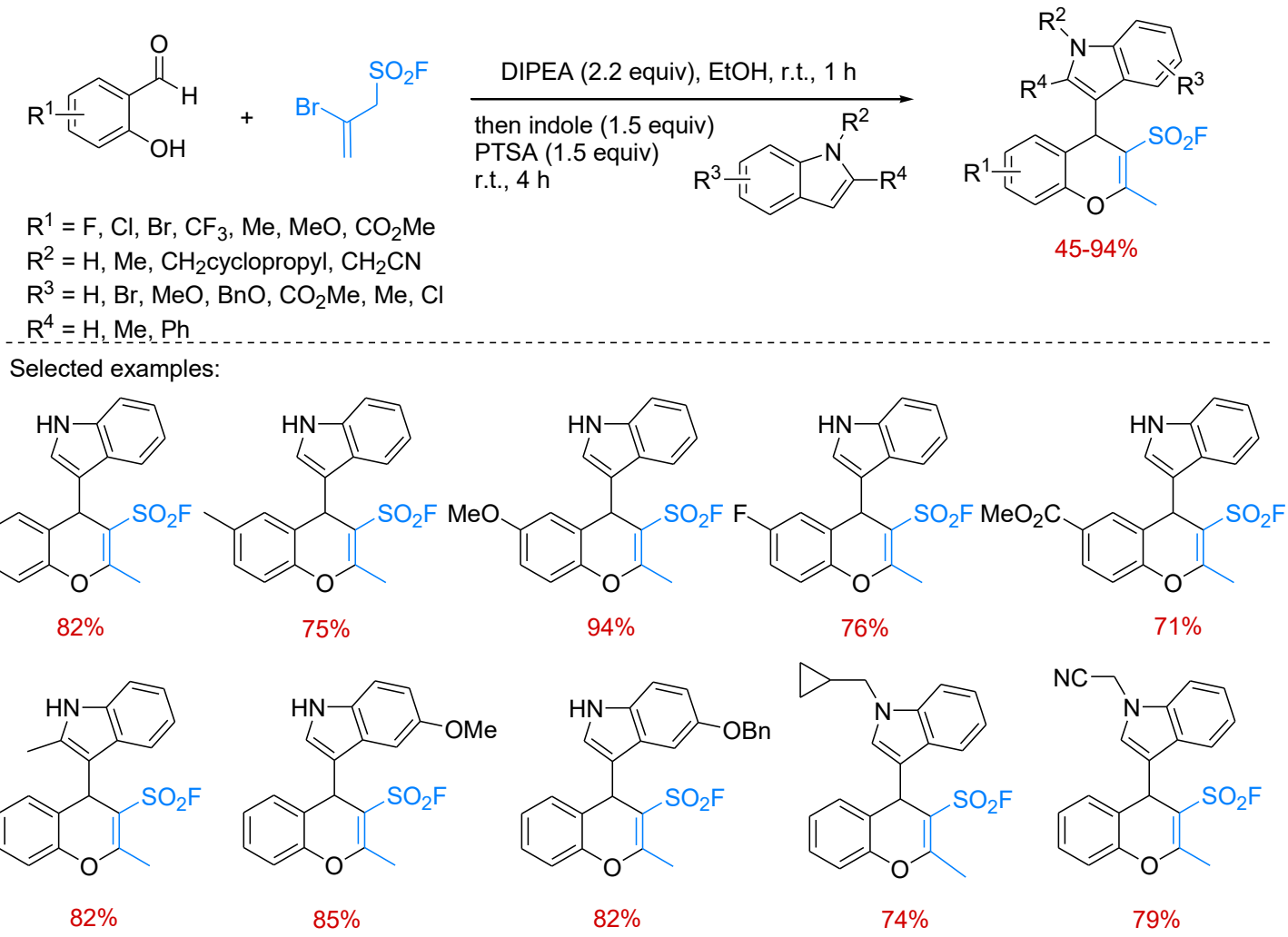
Scheme 12. Synthesis of 4*H*-chromene derivatives via base-mediated annulation *o*-hydroxychalcones and 2-bromoallylsulfones

A plausible mechanism for the formation of the 4*H*-chromene derivatives is shown in Scheme 13 and involves as previously the formation of an α-sulfonyl carbanion that here undergoes an intramolecular Michael addition to the enone unit delivering the corresponding enolate. The isomerization of the exocyclic olefin moiety into the endocyclic position may be assisted by internal proton transfer and tautomerization of the resultant enol to its keto form gives the final 4*H*-chromene product.



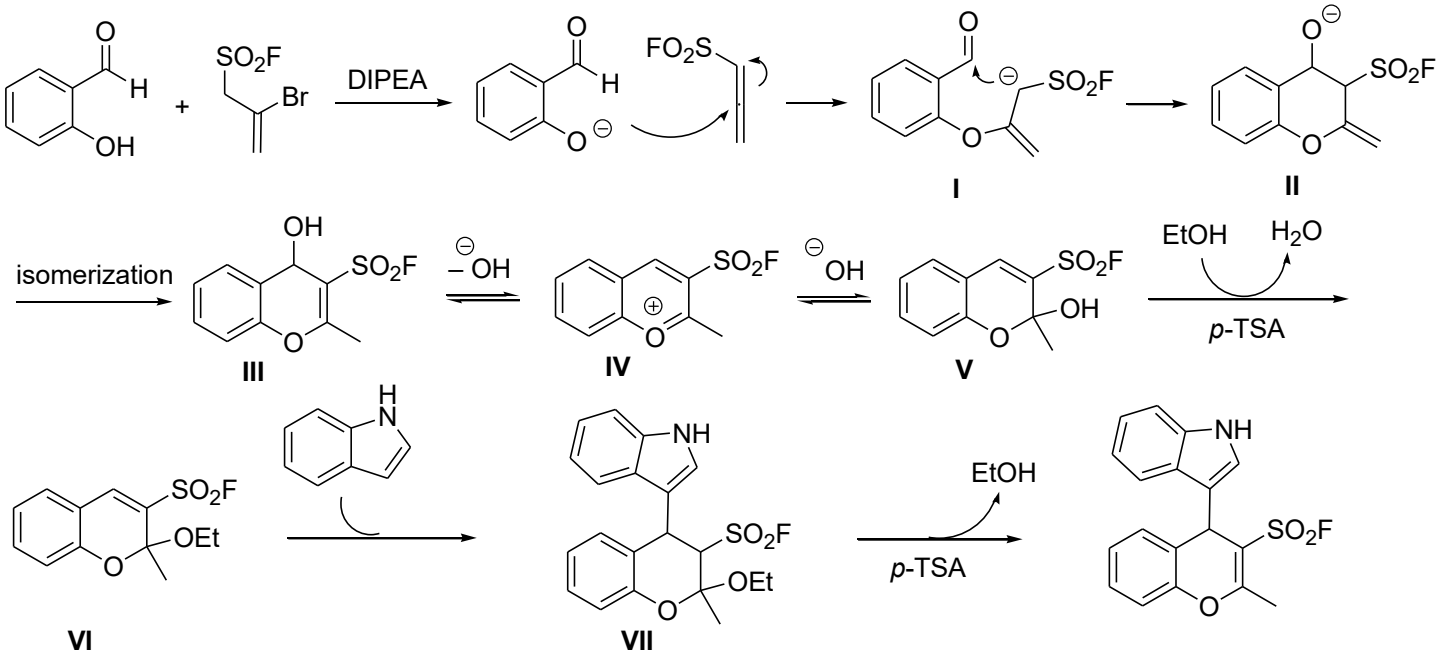
Scheme 13. Plausible mechanistic rationalization for the formation of 4*H*-chromene derivatives

Qin and coworkers reported in 2024 a one-pot three-component synthesis of indolyl-4H-chromene-3-sulfonyl fluoride derivatives *via* a sequential one-pot two-step cyclization reaction of salicylaldehyde, indole, and 2-bromoprop-2-ene-1-sulfonyl fluoride (Scheme 14).[23] The reaction was carried out in the presence of DIPEA (2.2 equiv) and *p*-TSA (1.5 equiv) in EtOH at room temperature and afforded the desired indolyl-4H-chromene-3-sulfonyl fluoride derivatives in yields ranging from 45% to 94%. Both electron-withdrawing and electron-donating substituents on the salicylaldehyde were well tolerated, a wide variety of indoles could be used, and the reaction could be performed on gram-scale.



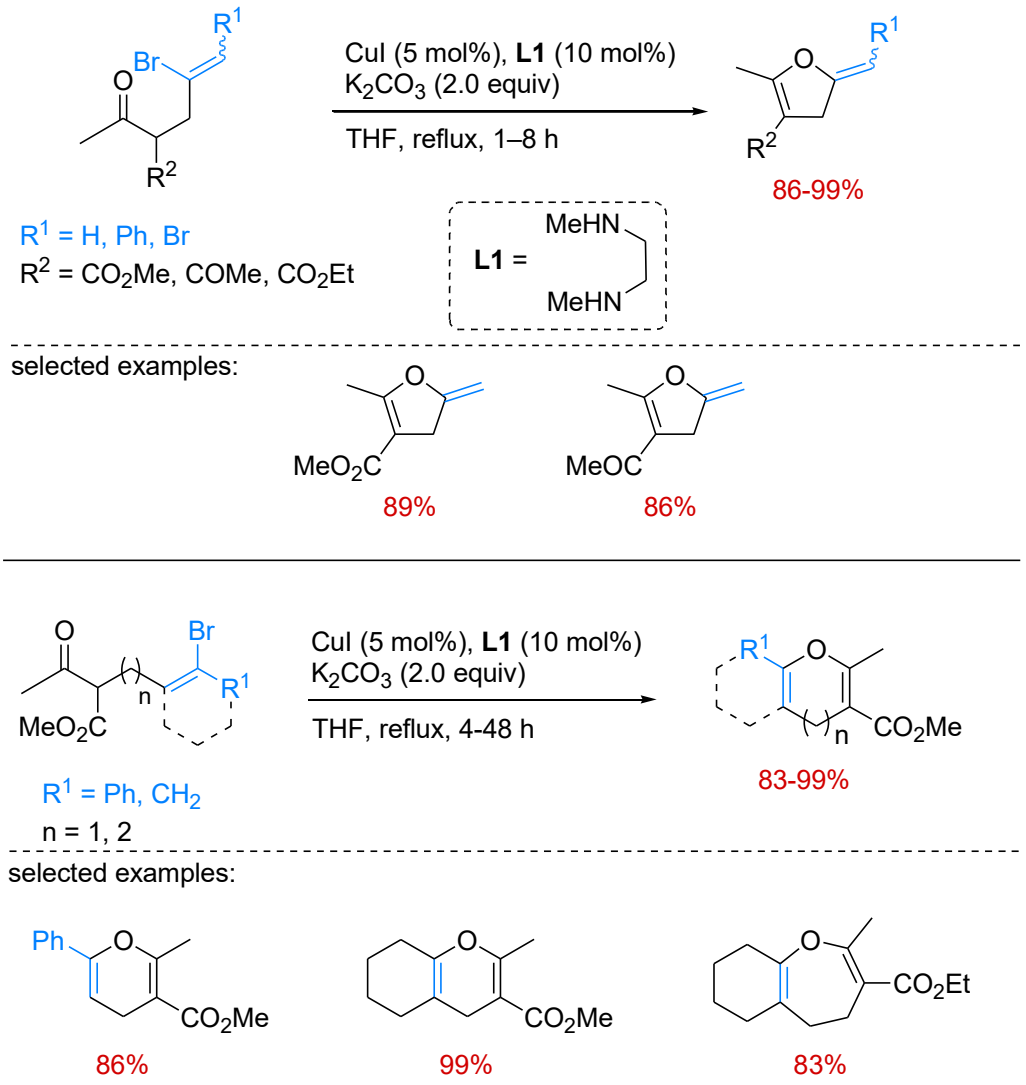
Scheme 14. A one-pot three-component synthesis of indolyl-4*H*-chromene-3-sulfonyl fluoride derivatives.

A plausible mechanism for this reaction was proposed by the authors and is shown in Scheme 15. In the presence of DIPEA, 2-bromoprop-2-ene-1-sulfonyl fluoride would produce the corresponding allenyl sulfone that would undergo a Michael addition with the phenoxide generated from salicylaldehyde under basic conditions. Intramolecular aldol reaction of the resulting intermediate **I** to form **II** and double bond isomerization then furnishes 4*H*-chromene derivative **III**. Dehydration of the latter generates benzopyrillium ion **IV** onto which the addition of a hydroxide ion leads to intermediate **V**. In the presence of EtOH and *p*-TSA, the latter would be converted into intermediate **VI** that would subsequently react with the indole to furnish **VII**. The nucleophilic addition of indole takes place preferentially at the 4-position rather than the 2-position probably because of the steric hindrance of the methyl group and the effect of the sulfonyl fluoride group in 2*H*-chromenes. Elimination of EtOH would finally give the desired indolyl-4*H*-chromene-3-sulfonyl fluoride derivative.



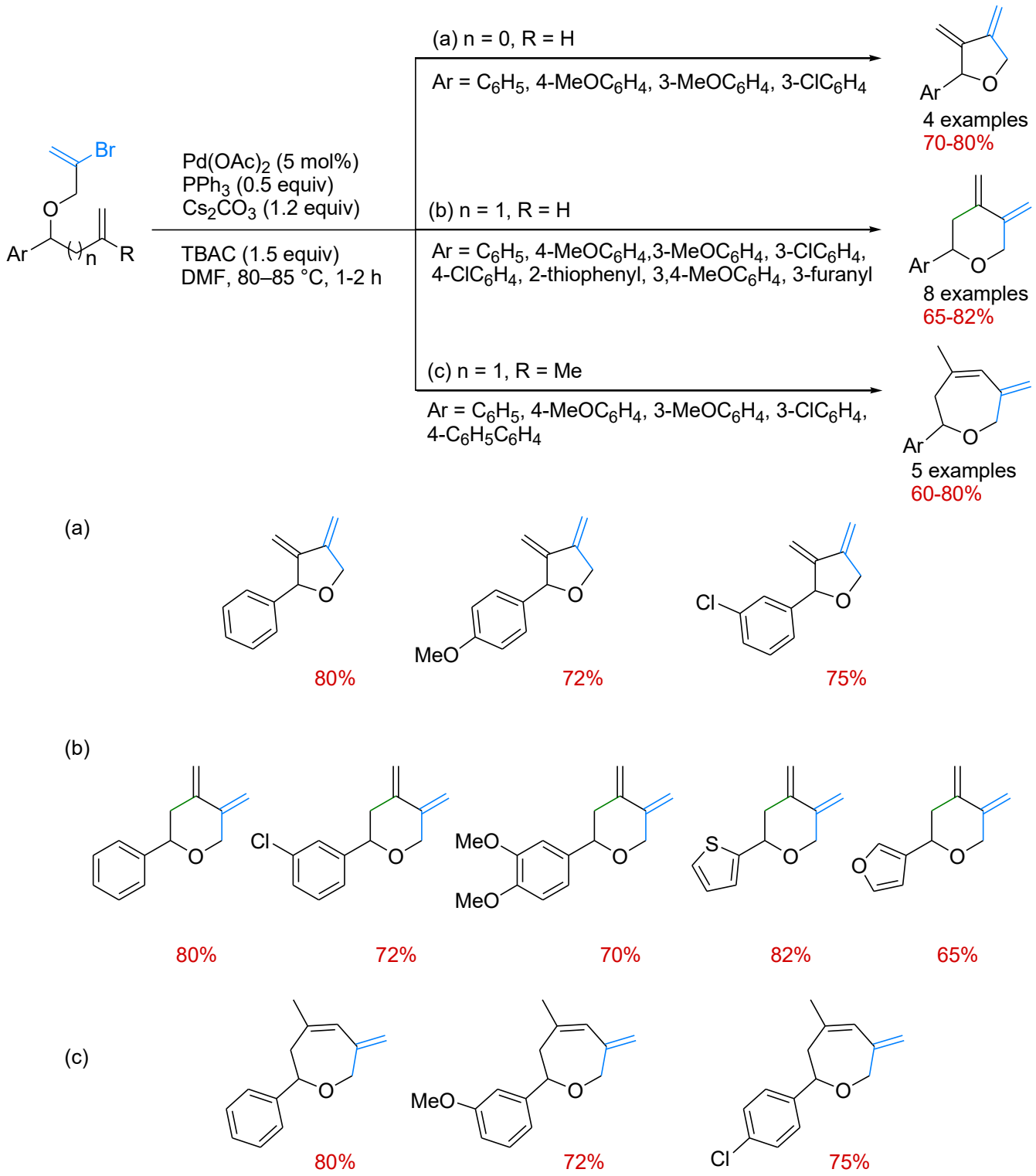
Scheme 15. Proposed mechanism for the synthesis of indolyl-4*H*-chromene-3-sulfonyl fluoride derivatives.

2.1.3 Other oxygen-containing heterocycles. In 2005, Li and coworker developed a copper-promoted intramolecular *O*-vinylation of carbonyl compounds enabling a general, mild and efficient access to 5-, 6- or 7-membered oxygen-containing heterocycles with 83 to 99% yield (Scheme 16).[24] Diverse bromoenones were treated in the presence of 5 mol% of CuI, 10 mol% of dimethylethylenediamine, 2 equiv of K_2CO_3 in refluxing THF to provide the corresponding cyclic alkenyl ethers. The transformation accommodates di-, tri- and tetra-substituted vinyl bromides to produce in a short reaction time (1-4 h) 5-membered cyclic alkenyl ethers with a complete retention at the double bond. The method was extended to 6- and 7-membered cyclic alkenyl ethers with a lower kinetics of the reaction (4-48h) compared to the 5-membered rings. This method could be useful for natural product synthesis.



Scheme 16. Synthesis of dihydrofurans and derivatives by copper-catalyzed *O*-vinylation.

In 2008, Ray and coworkers described the Pd(0)-catalyzed intramolecular Heck reaction of monosubstituted alkenes to efficiently access 2-aryl substituted tetrahydrofurans (70-80% yield, Scheme 17a) and 2-aryl substituted tetrahydropyrans (65-82% yield, Scheme 17b) *via exo*-trig cyclization with two adjacent exocyclic double bonds that can be useful for further cycloaddition reactions to access diverse substituted fused pyrans and furans.[25] Finally, 1,1-disubstituted alkenes follows *endo-trig* cyclisation to provide the corresponding 2,3,6,7-tetrahydrooxepines (60-80% yield, Scheme 17c). Diverse Heck precursors were cyclized using 5 mol% of $Pd(OAc)_2$, 0.5 equiv of PPh_3 and Cs_2CO_3 (1.2 equiv) in DMF at 80-85°C to yield various oxygen-containing 5-, 6- or 7-membered heterocycles. The reactions tolerated substrates having both electron-donating as well as electron-withdrawing substituents.

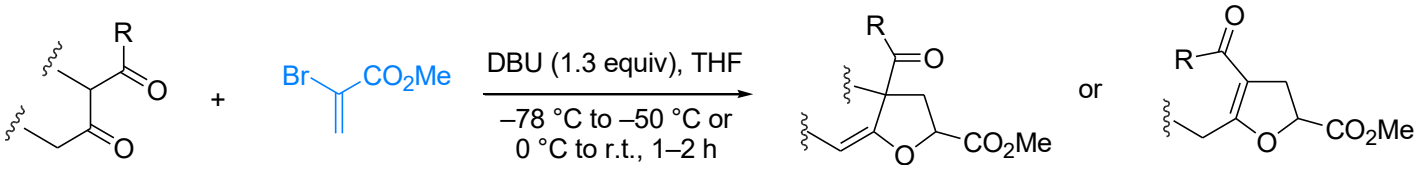


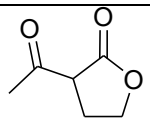
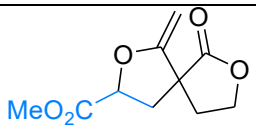
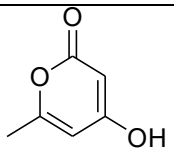
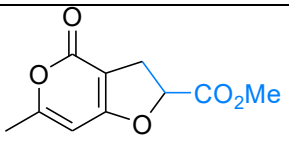
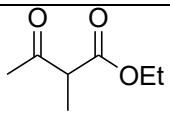
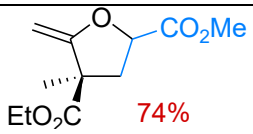
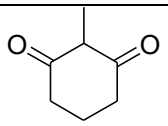
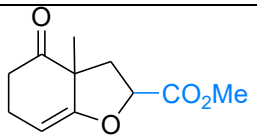
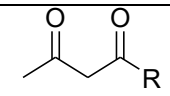
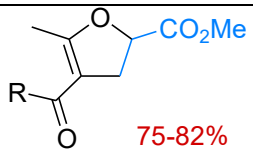
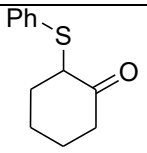
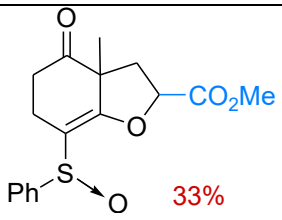
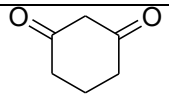
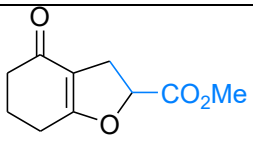
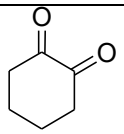
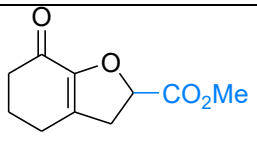
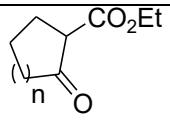
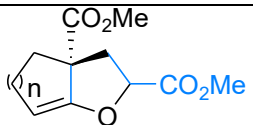
Scheme 17. Synthesis of 5-, 6- or 7-membered oxygenated heterocycles by intramolecular Heck coupling.

The [3+2] heteroannulation of enolates of 1,3-dicarbonyl compounds to methyl *a*-bromoacrylate led to diversely substituted hydrofuran and benzofuran derivatives in 44-92%. yields (Table 1).[26-27] All reactions were conducted with cyclic and acyclic 1,3-dicarbonyl compounds using DBU in THF allowing *in situ* generation of the corresponding enolate from dicarbonyl derivatives to perform Michael addition on the methyl-2-bromoacrylate at room temperature followed by subsequent cyclization by *O*-alkylation reaction. This transformation enabled an easy access to a broad variety of heterocyclic compounds by varying the carbonyl

partner used. A family of hydrofuran derivatives including spirodihydrofurans (Table 1, entry 1), hydrofurans (Table 1, entries 2 and 3) and benzodihydrofurans (Table 1, entries 4–9) were obtained using this tandem intermolecular Michael addition/intramolecular *O*-alkylation reaction sequence. This practical route opens the way to natural product synthesis.

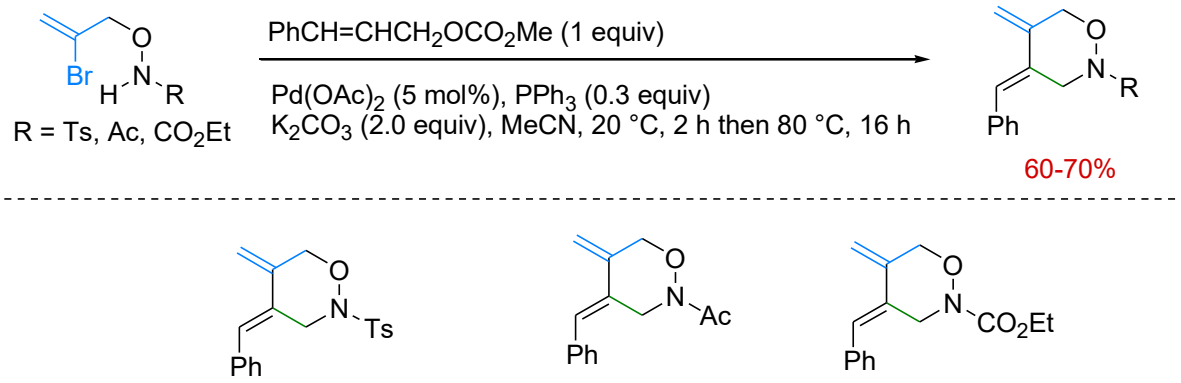
Table 1. Synthesis of various 5-membered *O*-containing heterocycles.



Entry	Starting material	Product	Entry	Starting material	Product
1		 96%	6		 63%
2		 74%	7		 92%
3	 R = Me, OMe	 75-82%	8		 33%
4		 83%	9		 44%
5	 n = 1, 2				

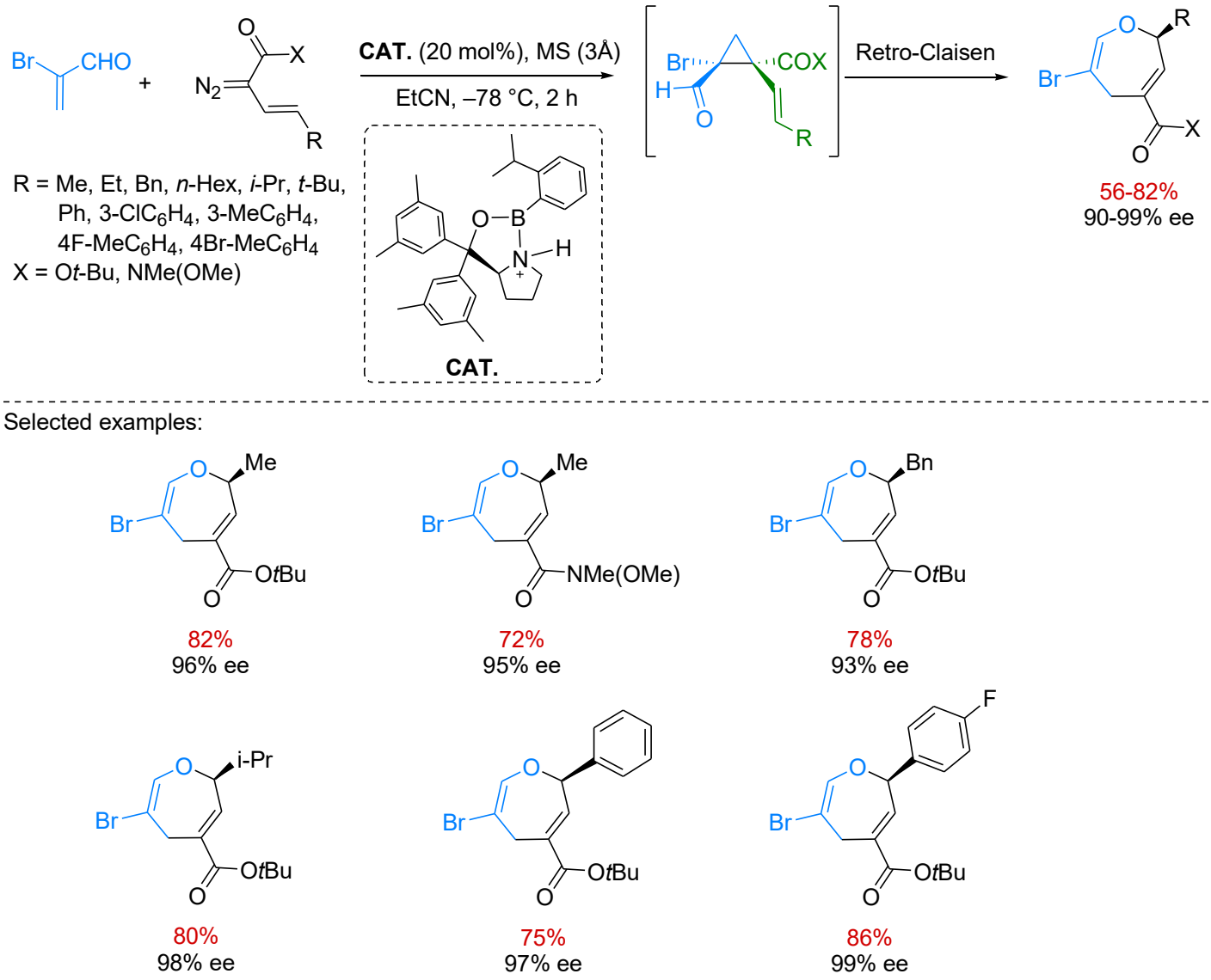
In 1999, Blechert and coworkers achieved an intramolecular tandem reaction initiated by Pd-promoted allylic amination of vinylbromide derivatives and followed by Heck coupling to access three hydroxylamine 1,3-exocyclic dienes containing an N-O bond and bearing a phenyl group attached to the diene moiety (Scheme 18).[28] The reaction was carried out in the presence of 2 equiv of K_2CO_3, 5 mol% of $Pd(OAc)_2$ and 30 mol% of

PPh_3 in MeCN (20°C to 80°C for 2-16 h) to afford the corresponding phenyl-substituted dienes in 60-70% yield. The resulting 1,3-dienes have been used to perform a formal Diels-Alder reaction with diverse indoles.



Scheme 18. Synthesis of hydroxylamine-derived exocyclic 1,3-dienes.

Ryu *et al* developed in 2017 a catalytic enantioselective synthesis of 2,5-dihydrooxepines from α-bromoacrolein and diverse γ-aryl- and γ-alkyl-α-vinyldiazoesters or α-vinyl- α-diazo Weinreb amide (Scheme 19).[29] Optimization of the reaction conditions were examined by varying the structure of a boracycle catalyst **CAT** and the solvents demonstrating that sterically hindered complex **CAT** containing 3,5 dimethylphenyl substituents and a 2-isopropylphenyl substituent was the best for the transformation. The reaction of 1 equiv of α-vinyldiazoester with 1.5 equiv of α-bromoacrolein was performed in propionitrile at –78°C for 2 h in the presence of 20 mol % of **CAT**. This was the first catalytic asymmetric synthetic method to access 2,5-dihydrooxepin derivatives *via* a *cis*-1-formyl-2-vinylcyclopropane intermediate through tandem cyclopropanation/retro-Claisen rearrangement from α-bromoacrolein and vinyldiazo in 56% to 86% yields. The reactivity of γ-aryl α-vinyldiazo esters was lower than that of γ-alkyl α-vinyldiazo esters. A variety of chiral 2,5-dihydrooxepins with aryl substituents were produced in enantioselectivities up to 99%.



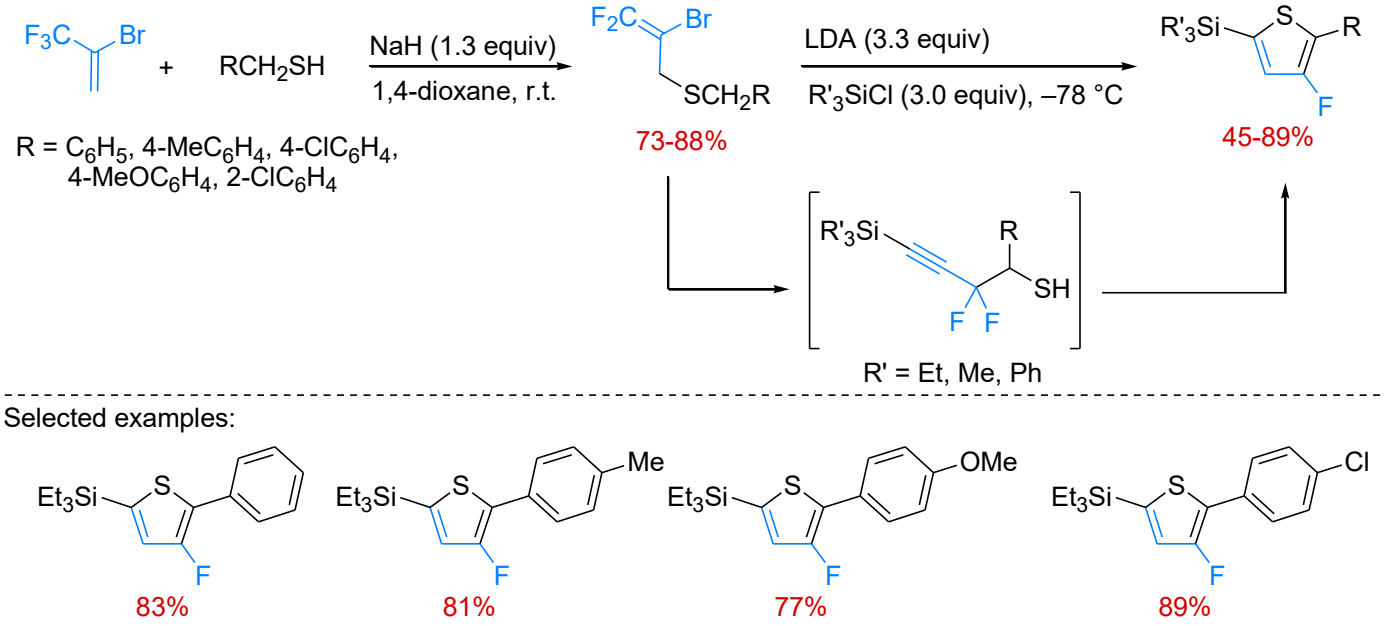
Scheme 19. Enantioselective synthesis of 2,5-dihydrooxepines.

2.2 Synthesis of *S*-heterocyclic compounds

In comparison to oxygen-containing analogues, the synthesis of sulfur heterocycles from 1,1-disubstituted vinyl bromides has been less extensively explored, yet it offers distinctive reactivity patterns arising from the higher nucleophilicity and polarizability of sulfur. Vinyl bromides enable both direct C–S bond formation and rearrangement-based or annulative pathways, allowing access to thiophenes, benzothiophenes, and related sulfur-containing ring systems. This section highlights representative methodologies and mechanistic features that underpin S-heterocycle construction from vinyl bromide precursors.

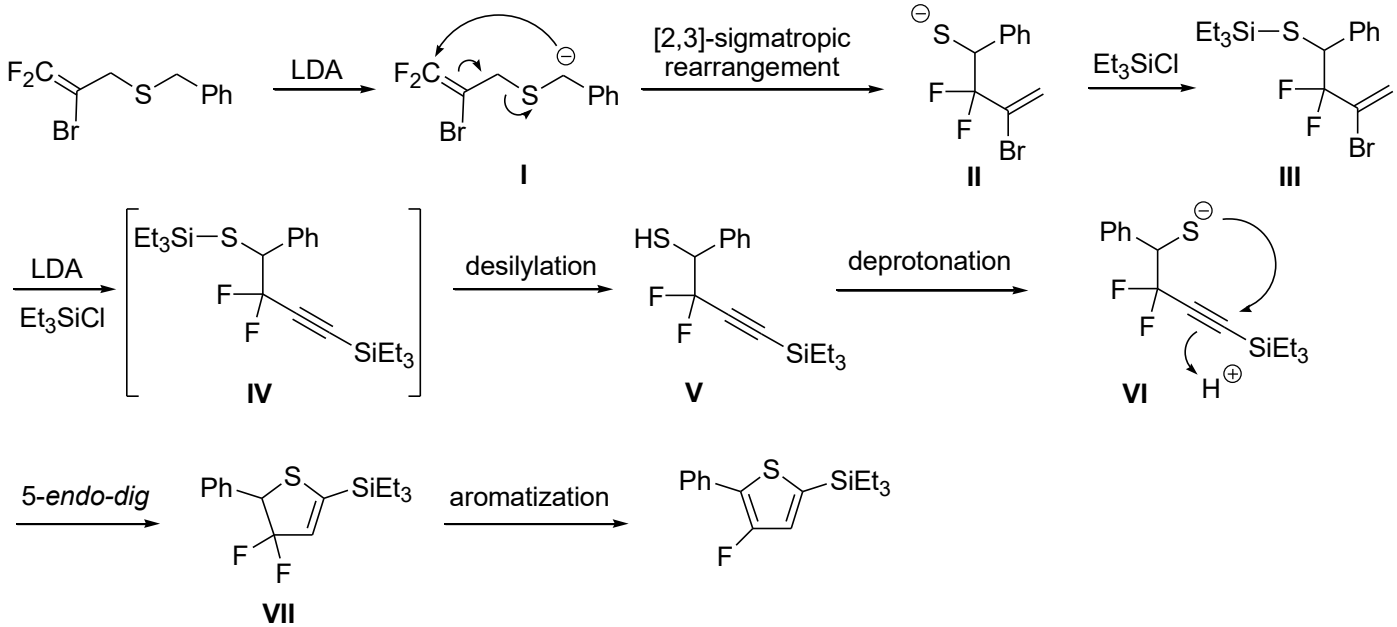
2.2.1 Synthesis of thiophene and benzothiophene derivatives. Hanamoto and coworkers disclosed the first successful S_N2'-type reaction of 2-bromo-3,3,3-trifluoropropene with a series of benzylthiol derivatives which reacted in the presence of 1.3 equiv of NaH in 1,4-dioxane at room temperature to produce 2-bromo-3,3-difluoroallyl sulfides in 73-88% yields (Scheme 20).[30] After extensive screening of the reaction parameters including chlorosilanes (Et_3SiCl, Me_3SiCl, $PhMe_2SiCl$, $Ph_2MeSiCl$), additives (Et_3N) and work up, the 2-bromo-3,3-difluoroallyl sulfides were transformed to the corresponding 2-phenyl 3-fluoro-5-triethylsilylthiophenes in 45-83% yields in a one-pot procedure, in the presence of 3.3 equiv of LDA and 3 equiv of R_3SiCl at –78°C. A

variety of 2-aryl-3- fluoro-5-silylthiophenes were thus efficiently prepared through this cascade reactive sequence.



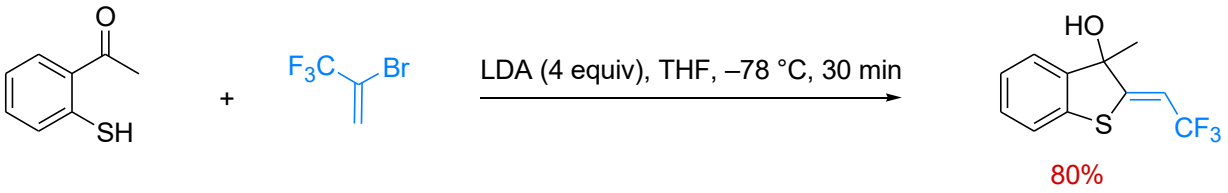
Scheme 20. Synthesis of thiophene derivative from vinyl bromides.

The authors suggested a plausible reaction mechanism shown in Scheme 21. After deprotonation of 2-bromo-3,3-difluoroallyl benzyl sulfide at the benzylic position, the resulting carbanion **I** undergoes a [2,3]sigmatropic rearrangement to give a *gem*-difluorohomopropargyl thiolate **II**. The latter is trapped by Et_3SiCl to form intermediate **III** that is subsequently converted into the silylated acetylene **IV**. Desilylation of **IV** and deprotonation under basic aqueous conditions leads to the free *gem*-difluorohomopropargyl thiolate **VI** that undergoes an intramolecular 5-*endo-dig* cyclization to afford 4,4-difluoro-3,4-dihydrothiophene **VII**. This compound then easily undergoes aromatization on silica gel column chromatography to yield the desired 3-fluorothiophene.



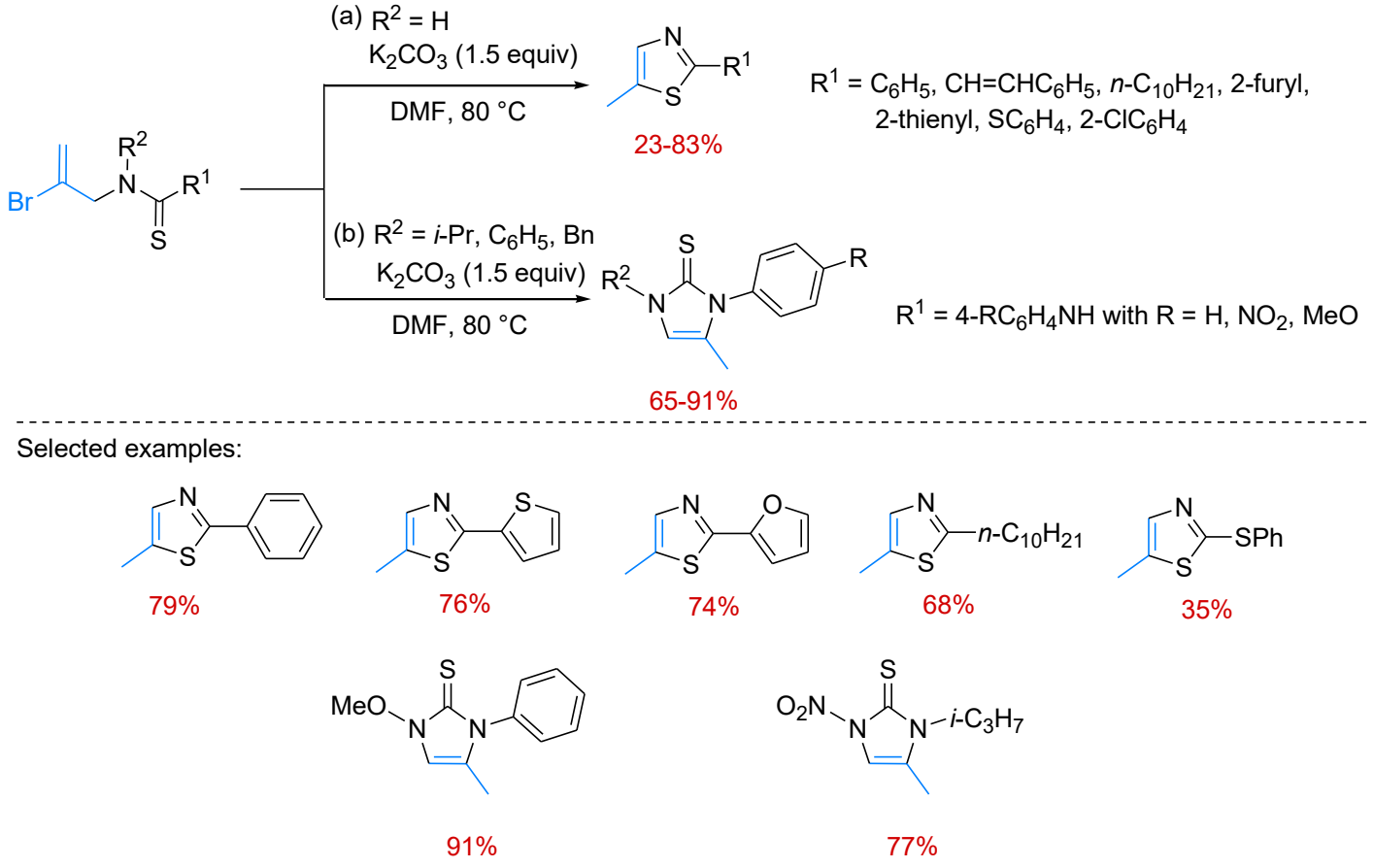
Scheme 21. Plausible mechanism for 3-fluorothiophene formation.

As part of their work on the formation of benzofuranyl and indolyl heterocycles under catalyst-free conditions from 2-hydroxyacetophenones or 2-aminoacetophenones and 2-bromo-3,3,3-trifluoropropene in 2024, Sharma, Singh and coworkers also reported the reaction with a thiol. Thus the use of 2-mercapto acetophenone with 2-BTP in the presence of 4 equiv of LDA afforded the benzothiophene derivative in 80% yield (Scheme 22).[20]



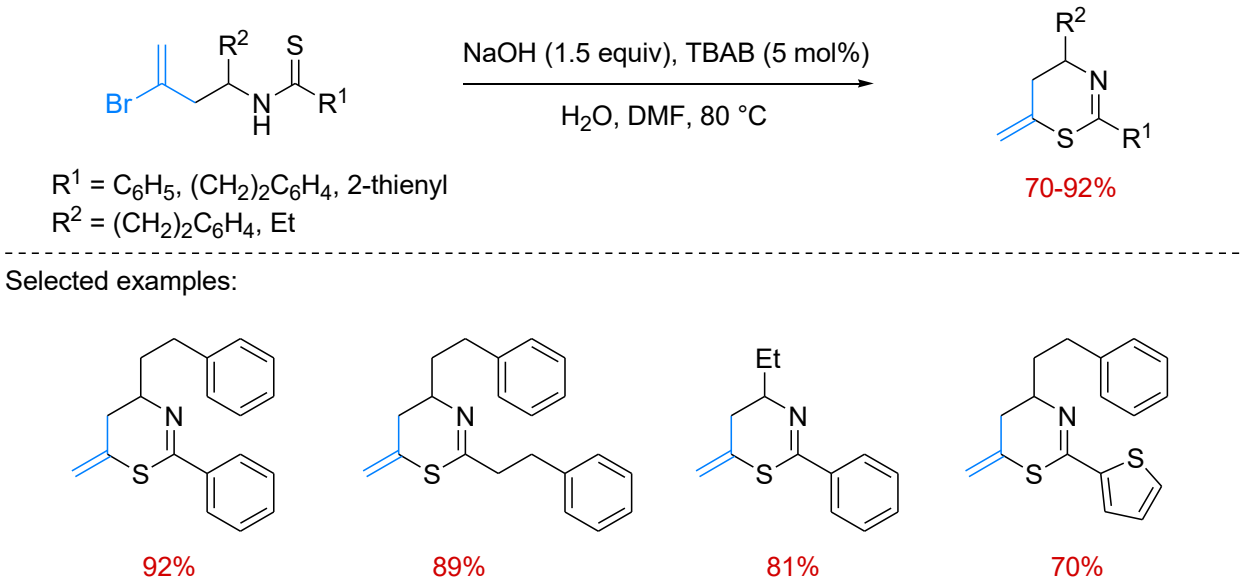
Scheme 22. Synthesis of benzothiophene derivative using 2-mercapto acetophenone.

2.2.2 Synthesis of thiazole and imidazole-2-thione derivatives. The formation of substituted thiazoles and imidazole-2-thiones was described by Narasaka *et al*. by intramolecular nucleophilic substitution reaction of vinyl bromides with thioamide or thiourea moieties.[31] The cyclizations of various *N*-(2-bromoprop-2-enyl)thioamides proceeded smoothly in the presence of 1.5 equiv of K_2CO_3 in DMF at 80 °C to give 2,5-disubstituted thiazoles in 23-83% yields (Scheme 23a). Similarly, a series of 1-(2-bromoprop-2-enyl)thioureas were transformed into 1,3,4-trisubstituted imidazole-2-thiones using the same reaction conditions in 65-91% yields (Scheme 23b).



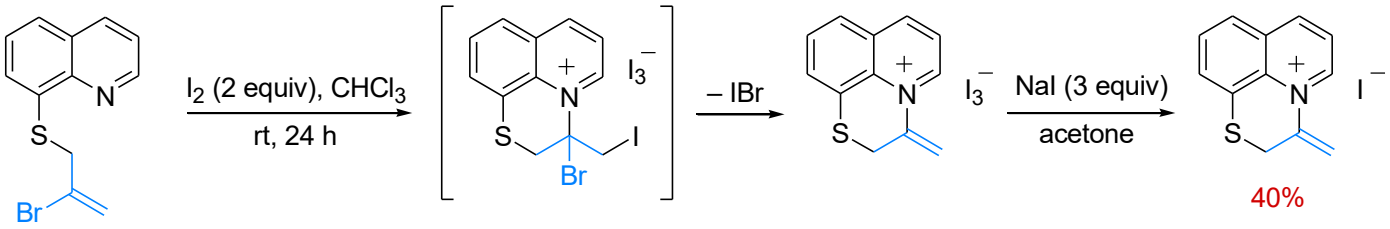
Scheme 23. Synthesis of 2,5-disubstituted thiazoles and imidazole-2-thiones.

Liu *et al.* synthesized variously substituted 6-alkylidene-5,6-dihydro-4H-1,3-thiazine derivatives via the cyclization of *N*-3-bromo-3-alkenylthioamides with yields ranging from 70% to 92% (Scheme 24).[32] An intramolecular vinylic nucleophilic substitution reaction allowed to achieve the 6-membered heterocycles.



Scheme 24. Synthesis of benzothiophenes.

Vershinina and coworkers described in 2020 the conversion of 8-(2-bromoprop-2-enylsulfanyl)quinoline into 3-methylene-2,3-dihydro[1,4]thiazino[2,3,4-*ij*]quinolinium iodide through iodocyclization and elimination of iodine bromide (Scheme 25).[33] The iodocyclization was carried out in the presence of 2 equiv of iodine leading, after elimination of IBr, to the corresponding 3-methylene-2,3-dihydro[1,4]thiazino[2,3,4-*ij*]quinolinium triiodide. Reaction of the latter with sodium iodide then delivered the monoiodide product in 40% yield.



Scheme 25. Formation of 3-methylene-2,3-dihydro[1,4]thiazino[2,3,4-*ij*]quinolinium iodide.

3. Conclusions

The studies surveyed in this review demonstrate that metal-catalyzed approaches, mainly using Pd and Cu catalysts, efficiently produce diverse O- and S-heterocycles with high regio- and stereocontrol and broad substrate scope. However, they often require expensive catalysts, ligands, and harsh conditions. In contrast, base-mediated or catalyst-free methods are simpler, cheaper, and more sustainable, enabling efficient annulation and cascade reactions. Their main limitations are the use of strong bases and lower stereochemical

control compared with metal-catalyzed systems. The mechanistic proposals discussed in these studies highlight the versatility of 1,1-disubstituted vinyl bromides. Proposed pathways commonly involve allenic, acetylide, cyclopropane, or carbene intermediates, especially in base-mediated and copper-catalyzed reactions, but detailed mechanistic studies are rare. Despite the diversity of products formed, common mechanistic patterns emerge: vinyl bromides frequently behave as latent allene or alkyne equivalents through dehydrohalogenation, followed by intramolecular nucleophilic attack and cyclization. Both oxygen- and sulfur-containing heterocycles are often generated through tandem addition–cyclization sequences, while metal-catalyzed reactions typically involve oxidative addition, intramolecular vinylation, and reductive elimination. Overall, the utility of vinyl bromides arises from both the reactivity of the C–Br bond and their ability to generate reactive intermediates that converge toward diverse heterocyclic frameworks. Recent studies on 1,1-disubstituted vinyl bromides increasingly emphasize more sustainable synthetic approaches. Several methods employ catalyst-free or low catalyst-loading conditions, one-pot or cascade processes, and efficient annulation strategies that reduce purification steps and improve atom economy. Vinyl bromides also serve as practical surrogates for less stable allenes or alkynes. However, many protocols still rely on polar aprotic solvents, elevated temperatures, or metal catalysts, highlighting the need for milder, greener, and more sustainable methodologies in future developments.

As shown in this review, 1,1-disubstituted vinyl bromides represent a highly versatile and strategically valuable class of intermediates for the synthesis of oxygen- and sulfur-containing heterocycles. Their intrinsic dual reactivity enables access to a wide range of heterocyclic frameworks through diverse mechanistic pathways, including transition-metal-catalyzed cyclizations, intramolecular O- and S-vinylations, base-mediated annulations, rearrangements, and multistep cascade processes. Significant methodological advances have been achieved, including regioselective and chemoselective transformations, catalyst-free protocols, and asymmetric variants. In many cases, vinyl bromides function as practical surrogates for less accessible or less stable intermediates, such as allenes or acetylenes, thereby expanding the synthetic toolbox available for heterocycle construction. The broad substrate scope and functional group tolerance observed in numerous examples further underscore the utility of these approaches for complex molecule synthesis. Despite this progress, important challenges and opportunities remain. Sulfur-containing heterocycles and enantioselective variants remain comparatively underexplored. The frequent use of strong bases, polar aprotic solvents, elevated temperatures, and transition-metal catalysts also raises sustainability and functional-group compatibility issues. Future progress will therefore require milder, more selective, and greener methodologies together. Given their demonstrated adaptability, 1,1-disubstituted vinyl bromides are expected to remain central intermediates in the synthesis of heterocycles of relevance to medicinal chemistry, materials science, and related fields.

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Authors' Biographies

Anne Westermeyer was born in 1993 in Paris, France. She obtained her PhD in 2020 at Chimie ParisTech under the supervision of Dr. Virginie Vidal and Dr. Phannarath Phansavath with the financial support of SEQENS under the scientific supervision of Dr. Gérard Guillamot. Her PhD research focused on the valorisation of three 1,1-disubstituted vinyl bromides. Following this, she joined Weylchem Lamotte as a fine chemical researcher and R&D project leader.

Gérard Guillamot started his career in Industry in 1984 after a PhD in organic chemistry. He worked first for Merrell Dow Pharmaceuticals for 10 years, as a research engineer in Chemical Development, then for Schwarz Pharma for 5 years as an R&D manager, after that he moved to PCAS (a French CDMO) as an R&D Director for 17 years. Since 2017, he acts as a Scientific Director within SEQENS (a French CRDMO). As a senior fellow, he is collaborating with Academy and CNRS (French National Agency for Research) in France, monitoring the PhD thesis financed both by SEQENS and a government agency (ANRT). Recently, he participated to develop a common technical platform between Academy & SEQENS. His main interests in the last decade are focused towards 'Flow Chemistry' and 'H.T.E.' in Chemical development. He is also part of the Scientific Council of SEQENS and a member of the French Chemical Society and the American Chemical Society.

Virginie Vidal was born in Paris (France). She completed her PhD at Paris-Sud University under the supervision of Prof. H.P. Husson and Dr. J. Royer (Gif, France) and was a FRM post-doctoral fellow at the University of Montreal with Prof. S. Hanessian (Canada, 1989-1990), and in 1991 with Prof. P. Potier and Dr. R. H. Dodd (Gif). She was appointed as a CNRS Associate Researcher with Prof. J. P. Genêt at Ecole Nationale Supérieure de Chimie de Paris. She is currently CNRS Research Director at Chimie ParisTech-PSL (Paris, France). Her research interests focus on the development of transition-metal catalysis and the design of atropisomeric ligands (Synphos and Difluorphos). The synthesis of biorelevant targets is also a focus in her research group. She was Chair of the Division of Organic Chemistry of the French Chemical Society (2009−2012).

Phannarath Phansavath was born in Vientiane (Laos). She received her PhD from Pierre & Marie Curie University in 1997 under the supervision of Prof. M. Malacria and Dr C. Aubert. After postdoctoral studies in the group of Prof. C. Bolm at the Institut für Organische Chemie, RWTH Aachen (Germany), she was appointed assistant professor in 1999 in the group of Prof. J.-P. Genêt at Ecole Nationale Supérieure de Chimie de Paris (Chimie ParisTech-PSL). Her current research interests include total synthesis of biologically relevant natural products and transition metal-catalyzed asymmetric reactions.

