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## Recent developments in thiochromene chemistry

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Thiochromenes are versatile sulfur-containing heterocyclic compounds that have received considerable interest in drug discovery because of their ability to act as crucial building blocks for synthesizing bioactive compounds. In particular, these scaffolds have found utility in the design of anticancer, anti-HIV, antioxidant, and antimicrobial agents, among others. Despite their pharmacological potential, the synthesis of these scaffolds is less explored in contrast to their oxygen-containing counterparts. This review classifies the synthetic processes into Michael addition, cycloaddition, ring-opening, coupling, cyclization and Diels–Alder reactions, and others. Reaction mechanisms, circumstances, and important instances are thoroughly discussed in each area. For instance, chiral catalysts and substrates like mercaptobenzaldehyde and cinnamaldehyde are used in Michael addition processes to achieve excellent enantioselectivity. In cycloaddition reactions, readily available substrates such as thioisatins and alkynes achieve regioselectivity and product production. Thiochromenes are also synthesized by ring-opening reactions with epoxides or aziridines. These reactions demonstrate the importance of catalysts and solvents in reaction control, particularly palladium catalysts for aryl halides and thiol coupling processes. Another major class discussed is cyclization reactions with alkynyl thiols and alkynes under regulated temperature and pressure conditions to efficiently synthesize thiochromenes. With the use of chiral substrates and catalysts, Diels–Alder processes increase yields and selectivity and enhance the variety of thiochromene compounds. This review emphasizes the versatility of thiochromenes in drug discovery and consolidates the existing literature on thiochromenes, scrutinizing the gaps and opportunities for synthesizing novel thiochromene-containing lead molecules.

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## 1. Introduction

Heteroatoms such as oxygen, sulfur, and nitrogen are essential structural elements in several pharmaceutically active ingredients. The widespread use of these atoms as a part of cyclic or



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open chain fragments is due to their abundance in natural products and nucleic acids. Among them, several scientists have primarily explored nitrogen and oxygen over the years due to their ability to modify and improve potency, selectivity and ability to act as bioisosteric replacements to alter the pharmacokinetic properties of drug molecules.<sup>1</sup> In the midst of this is the sulfur atom, which has comparable functional characteristics, including higher volatility and improved reactivity, but has yet to be explored as thoroughly as the other two heteroatoms.

Among the sulfur-based compounds, heterocyclic derivatives like thiazole, thiopyran, benzothiopyran, thiophene, and thioazolidinone are frequently found as a part of several bioactive scaffolds.<sup>2,3</sup> In particular, these mono/bi-cyclic scaffolds with a thio atom serve as building blocks for developing drugs and agricultural products.<sup>4,5</sup> As of 2018, over 285 sulfur-containing compounds were identified in the list of FDA-approved drugs for treating various ailments, and sulfonamides constitute the largest group in this series.<sup>6</sup>

However, despite their success in drug discovery, certain sulfur pharmacophores still need to be explored compared to well-established ones like sulfoxides and thioethers.<sup>7</sup> They include sulfoximine, sulfondiimine, sulfonyl fluoride, and thienopentathiepine, among others. For instance, sulfoximines discovered in the 1970s still represent a class of underrated pharmacophores despite their chemical stability, dual nature as hydrogen bond donors/acceptors, and promising pharmacological activities.<sup>7</sup> Consistent with this, the other sulfur functionalities classified under the less-explored ones, as shown in Fig. 1, demonstrate excellent potential in the development of newer leads in medicinal chemistry. Under this category, thiochromenes or benzothiopyrans have recently

established themselves as distinguished scaffolds owing to the increased attention garnered by these pharmacophores over the years. These scaffolds are the thio-analogs of chromenes and exhibit promising biological activities, ranging from anti-inflammatory to anticancer effects.<sup>8–10</sup>

The pharmaceutical importance of bicyclic ring systems with a thio-atom as the pharmacophore is emphasized by the presence of FDA-approved drugs, namely tazarotene, flupentixol, and metircane (Fig. 2).<sup>11–14</sup> Besides their application in medicinal chemistry, thiochromenes also find use in materials science and optoelectronics due to their characteristic photo-physical behavior, such as slow photodegradation and efficient biomolecular photoreaction in solution. This distinguishing trait facilitates their use in developing laser dyes, organic light-emitting diodes (OLEDs), and fluorescent probes.<sup>15–17</sup>

Despite its structural similarity to chromenes, the synthesis of this sulfur analog is hindered by several challenges due to the inherent nature of sulfur and its structural complexity. This is mainly due to the multiple oxidation states and tendency shown by sulfur atoms to form diverse bonding patterns because of their ability to expand their valence shell to occupy more than eight electrons.<sup>7,18</sup> Additionally, highly reactive sulfur atoms tend to alter the structural integrity of molecules with more than one reactive site.<sup>19</sup> Such changes are often witnessed by the development of undesired by-products or side reactions, which ultimately complicate the purification and isolation of the pure compound. These challenges have emphasized the need for novel synthetic approaches and streamlined reaction sequences to attain thiochromenes with better purity and yield.

The methods used for synthesizing thiochromenes can be transition metal-catalyzed reactions or organocatalytic strat-



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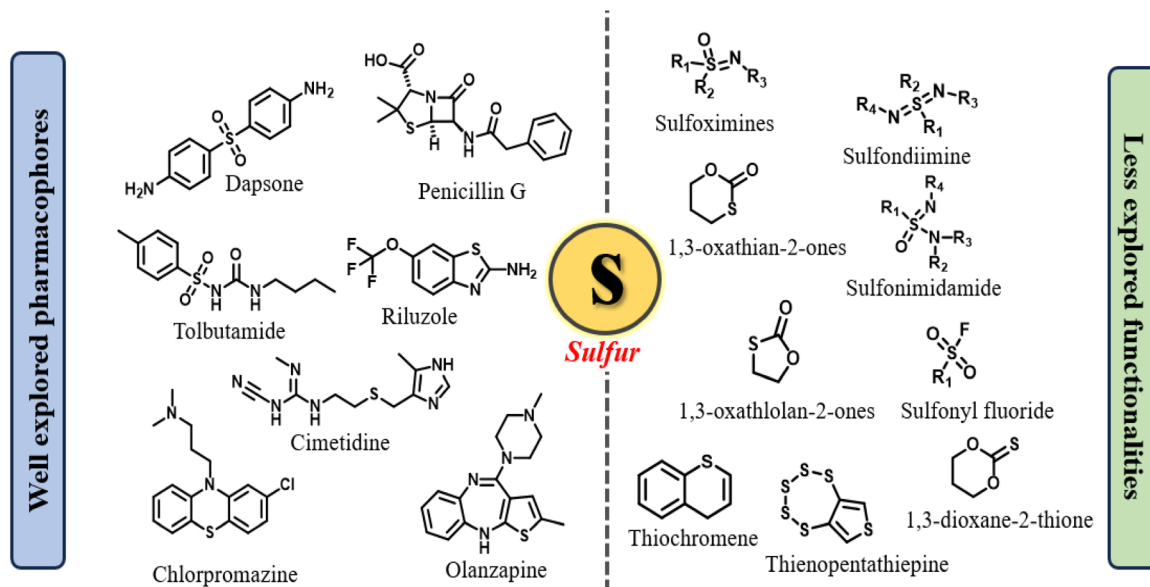


Fig. 1 Representative examples of sulfur-containing scaffolds of biological importance.

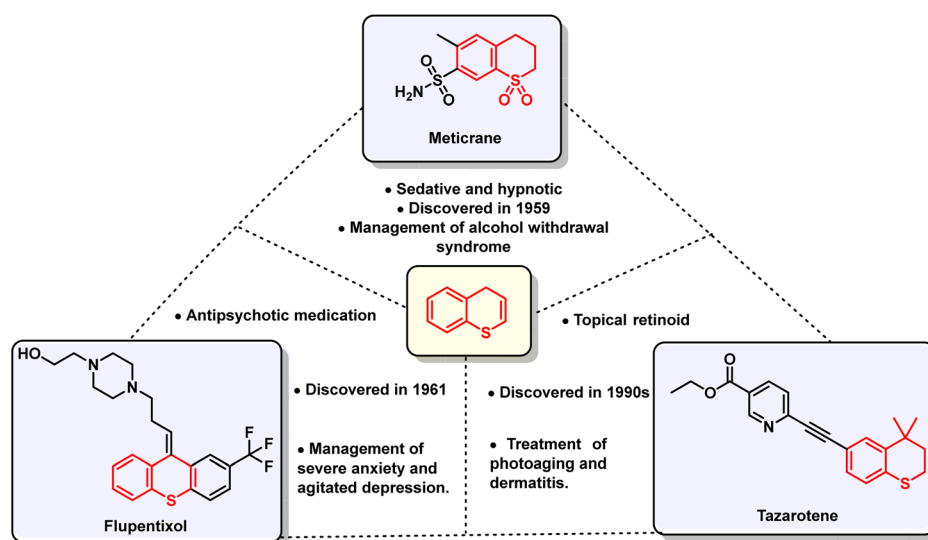


Fig. 2 Structure of FDA-approved drugs containing a thiochromane/thiochromene nucleus.

egies. In the case of the former, transition metal complexes are leveraged to catalyze the critical bond-forming step to aid in synthesizing thiochromenes. One promising protocol emerging under this category is the combination of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) with dimethylformamide (DMF) in the presence of metal catalysts to yield substituted thiochromenes from readily available starting materials.<sup>20</sup> The most significant appeal of these approaches is their high selectivity and faster reaction times, making them admissible thiochromene synthesis options. However, their utility is constrained because of their cost and inability to generate chiral thiochromenes

under more simplified reaction conditions, making it challenging to develop a library of desired compounds.

Organocatalytic approaches act as promising alternatives for thiochromene synthesis. These reactions offer enhanced stereoselectivity and functional group compatibility, countering metal-catalyzed reactions' cons.<sup>21,22</sup> Organocatalysts initiate key transformations by activating specific functional groups, which guide the reaction toward forming the final products. Strategies such as Lewis acid catalysis and intramolecular tandem Michael addition-type reactions work on this principle and assist in generating structurally diverse





thiochromenes.<sup>23,24</sup> In addition to this, such approaches also open avenues for further functionalization at the stereogenic center, broadening these sulfur-containing heterocycles' applicability in medicinal chemistry and materials science.

This comprehensive review endeavors to provide an in-depth analysis of the recent advancements over the decade in synthesizing thiochromenes by categorizing them based on their reaction type. By exploring the reaction compatibility with the substrate and mechanistic insights offered by these methodologies, this work aims to provide an overview of the current landscape in thiochromene-related chemistry.

The subsequent sections will cover the various synthetic strategies employed to generate thiochromenes by categorizing them into seven distinct classes as follows:

- Michael addition
- Cycloaddition reactions
- Ring-opening reactions
- Coupling reactions
- Cyclization reactions
- Diels–Alder reactions
- Miscellaneous reactions

## 1.1. Michael addition

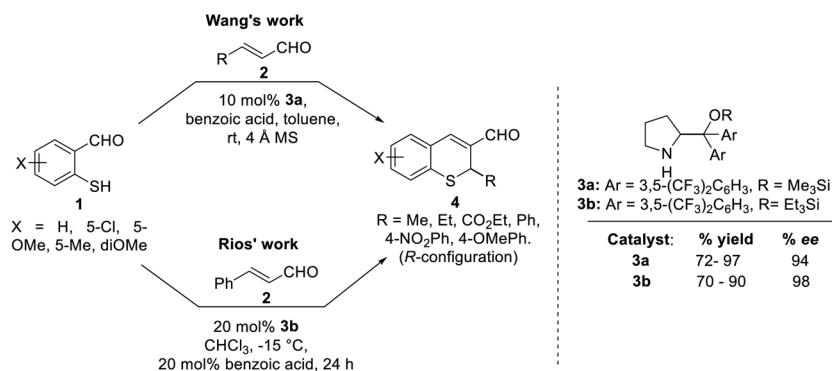
**1.1.1. Enantioselective methods.** In modern chemistry, there is a notable emphasis on thiochromene synthesis, with various research laboratories striving to establish synthetic protocols. However, the exploration of chiral thiochromenes remains somewhat restricted. Prompted by this, Wang's group and Rios' group in 2006 put forth a highly enantioselective pyrrolidine-catalyzed reaction for the synthesis of a library of thiochromenes from mercaptobenzaldehyde (**1**) and cinnamaldehyde (**2**) (Scheme 1).<sup>25,26</sup> Despite its novelty, this protocol suffered from a significant drawback as it offered only *n*-alkyl or phenyl substitutions at the stereogenic center of thiochromenes. Taking this as a challenge, Kinfe *et al.* reported a highly stereoselective approach for the synthesis of *S*-bis(benzyloxy) derivatives of thiochromene-3-carbaldehydes (**7**) with yields of 69–79% *via* a Michael-addition reaction involving an *in situ* generation of  $\alpha,\beta$ -unsaturated aldehydes (**6**) (Scheme 2). Mechanistic insights revealed the formation of only *S*-configuration products

due to the preference of the aldehyde intermediate (**6**) to remain in the OH<sub>5</sub> conformation, which directs the thiolate motif to attach the sugar moiety at the  $\alpha$ -face.<sup>27</sup>

After establishing a sulfa-Michael cascade reaction for the synthesis of 2*H*-thiochromenes from mercaptobenzaldehyde and vinyl phosphonates in their earlier studies,<sup>28</sup> Simlandy's group in the year 2017 tried to control the initial Michael step to facilitate Julia–Kocienski olefination for the enantioselective formation of 3,4-unsubstituted thiochromenes.<sup>29</sup> This attempt proved to be successful by furnishing the desired products in yields of 28–80% with good enantiomeric ratios (*er* = 96 : 3–99 : 1). The reaction proceeded *via* the formation of an iminium intermediate (**8a**), which is bound to the amine catalyst and gets attacked by the vinyl phenyl tetrazole sulfone (vinyl PT sulfone or **9**) in a *Si*-face selective manner. This study further explored the synthetic feasibility of thiochromenes to obtain a thiochromane ring (**11** by reduction) and a thioflavone (**12** by oxidation) (Scheme 3).

Thiols comprise one of the most frequently used substrates for synthesizing thiochromene analogs. Despite their extensive application in this domain, thiols suffer from unpleasant odour and toxicity and potentiate the formation of multiple by-products.<sup>30</sup> To overcome this, Wu *et al.*, in 2023, realized the replacement of thiols with their oxidized products, disulfides, which are more stable and act as thiol surrogates under the reaction conditions.<sup>31</sup> On this note, dithiobenzaldehyde (**14**) was treated with aromatic bromoenal (**13**) in the presence of a reducing agent, PPh<sub>3</sub>, and an N-heterocyclic carbene (NHC) catalyst. Control experiments established the importance of water in this reaction as it took part in the generation of the sulfur anion (**14a**) from dithiobenzaldehyde (**14**) in a manner resembling the Corey–Nicolaou macro-lactonization pathway. Moreover, the addition of this anion to the acyl azolium intermediate (**13a**) is the probable mechanistic pathway that was identified to be the enantio-determining step (sulfa-Michael addition), resulting in the generation of products (**15**) with high enantioselectivities with an enantiomeric ratio as high as 97 : 3 (Scheme 4).

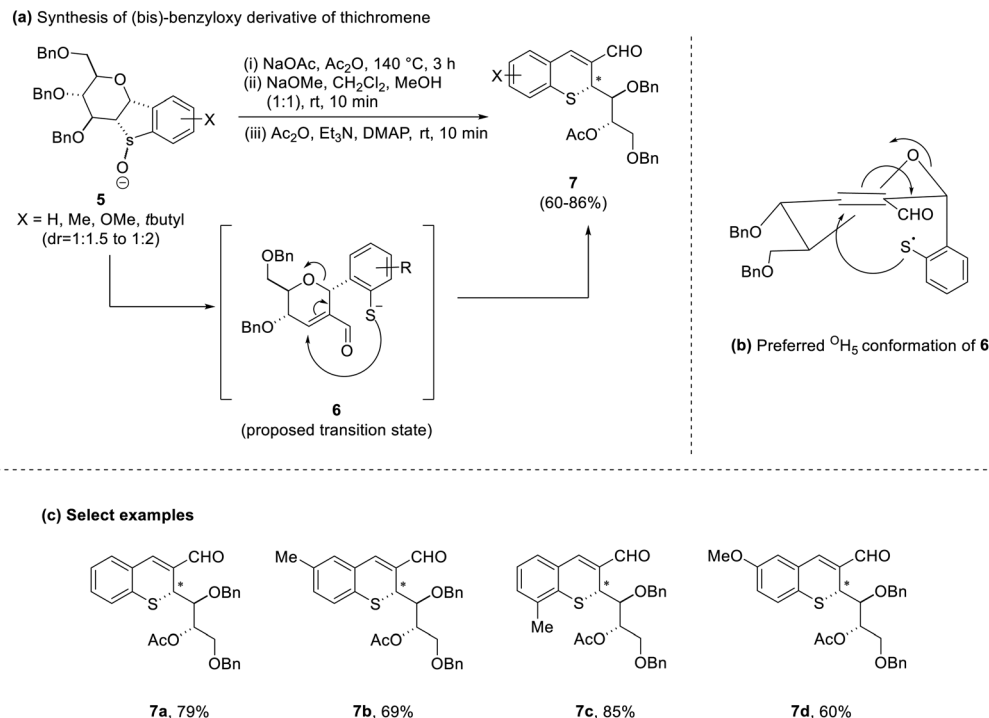
**1.1.2. One-pot synthetic methods.** Taking advantage of the established common strategy, Nguyen *et al.*, in the year 2016,



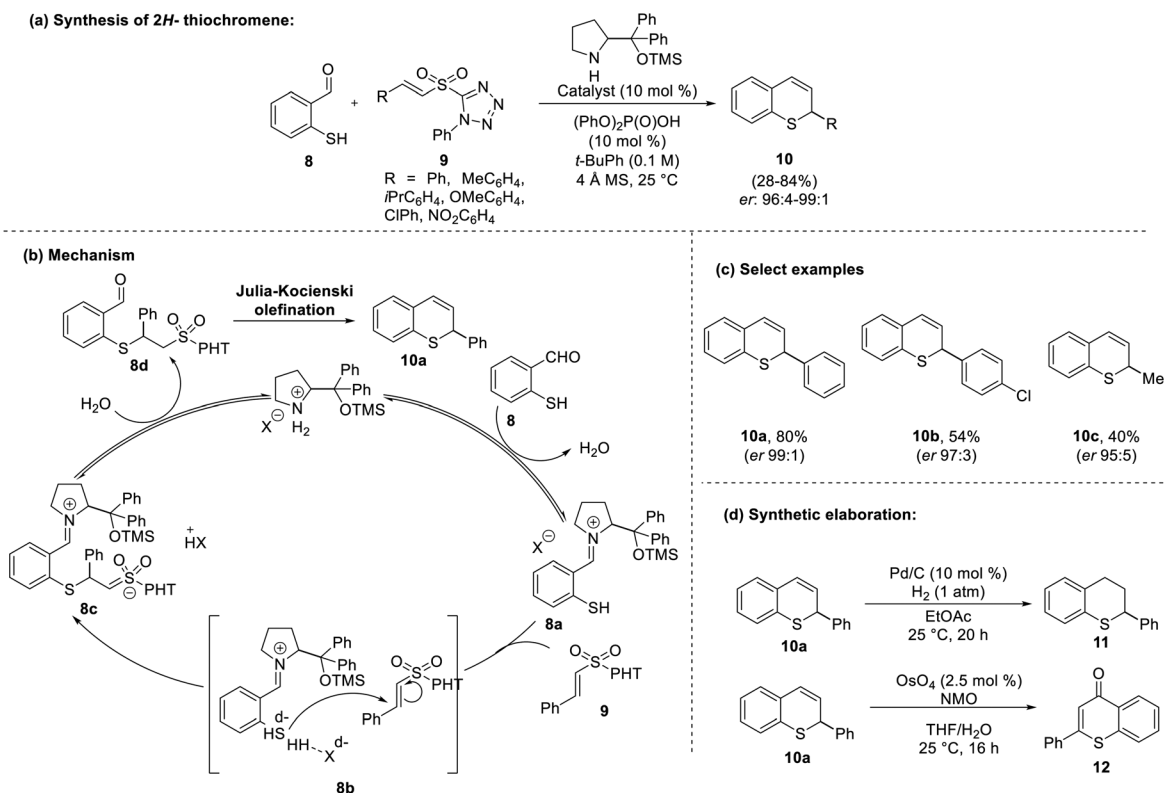
**Scheme 1** Pyrrolidine-catalyzed synthesis of thiochromen-3-carbaldehyde using cinnamaldehyde.







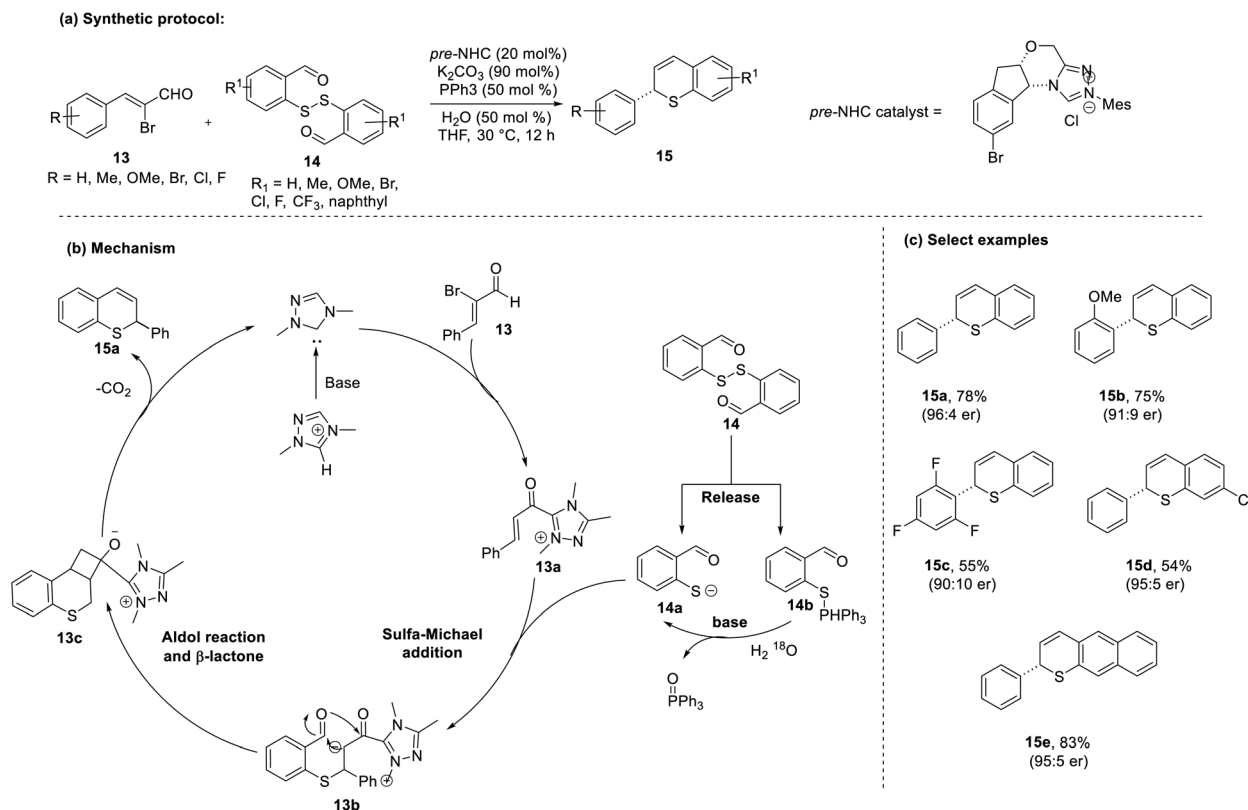
**Scheme 2** (a) Stereoselective synthesis of thichromene-3-carbaldehyde; (b) preferred conformation of the transition state; (c) select examples.



**Scheme 3** (a) Julia–Kocienski olefination for synthesizing thiochromenes; (b) mechanism of the Michael addition reaction; (c) select examples; (d) synthetic application of the protocol.







**Scheme 4** (a) N-Heterocyclic carbene (NHC) catalyzed synthesis of thiochromenes using disulfides as the sulfur source; (b) mechanism of the Michael addition reaction; (c) select examples.

reported a one-pot synthetic method for attaining thiochromene-3-carboxylate derivatives (**18**) in the presence of *p*-toluene sulfonic acid (PTSA).<sup>32</sup> The reaction of mercaptobenzaldehyde (**16**) with methyl ester of cinnamic acid (**17**) was identified to proceed only in the presence of tetramethylguanidine (TMG). Interestingly, the replacement of TMG with other bases such as  $K_2CO_3$ , proline, pipercolinic acid, or triethyl amine hindered the reaction, hinting at the requirement of a strong base with good hydrogen bond formation capacity for the 1,4-thiol Michael reaction to proceed. In the subsequent step, the addition of PTSA resulted in acidic conditions that promote product formation (**18**) in yields of 58–78% by dehydration (Scheme 5).

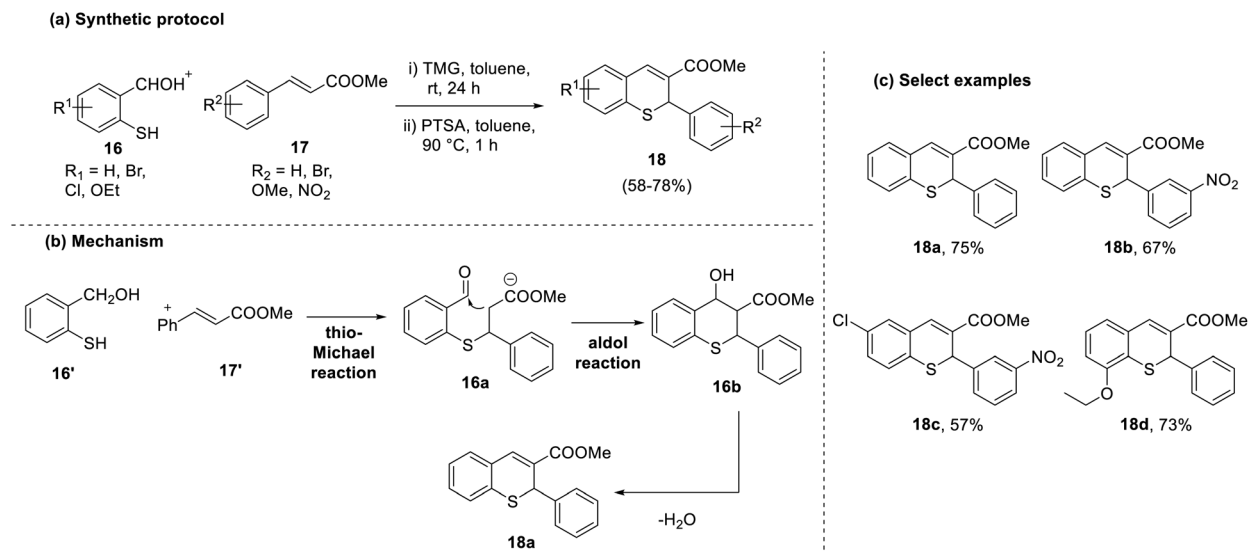
A similar approach was undertaken by Sangeetha *et al.* in 2019 to actualize a one-pot synthetic approach for obtaining thiochromenones by the reaction of halogenated chalcones (**19**) and xanthates.<sup>33</sup> The uniqueness of this reaction lies in its ability to generate iodine *in situ* to yield a halogenated thiochromane intermediate (**20**), which, on reduction, gives the final thiochromenone product. Interestingly, this reaction uses the waste by-product (potassium iodide) to create a facile protocol with minimal waste generation. The same conditions with the addition of iodine during the reduction step result in the formation of bis-thiochromenones (**22**) in considerable yields (52–62%), depicting a simple yet novel route for the generation of such compounds (Scheme 6).

In 2023, Saini and co-workers developed a one-pot Knoevenagel–Michael cascade reaction to synthesize thiochromenes bearing a spirocyclic framework (**26**).<sup>34</sup> In this reaction, the dehydrated derivative of ninhydrin (**23**) reacts with naphthalene thiol (**24**) to generate a Knoevenagel condensation intermediate (**23a**), which then undergoes an addition reaction with 1,3-dicarbonyl compounds (**25**) to release the desired spiroindene-thiochromene derivatives (**26**) *via* removal of a molecule of water (Scheme 7).

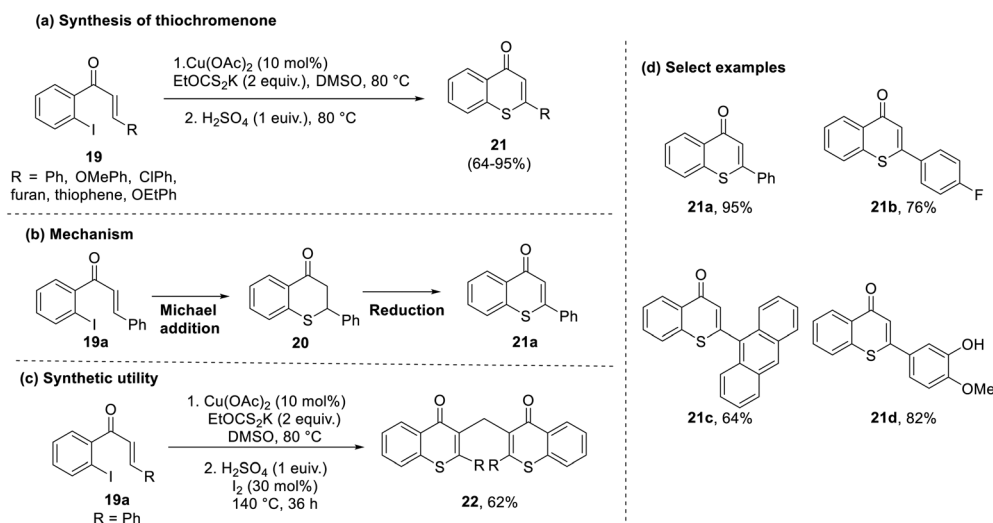
**1.1.3. Sulfa-Michael addition reactions.** Expanding further on this avenue, Agudo *et al.*, in 2017, put forth a unique protocol for facilitating thiochromene synthesis by the sulfa-Michael addition reaction using mercaptobenzoic acid as the sulfur source.<sup>35</sup> This approach employed base-catalyzed reaction conditions for the addition of nitroalkenes (**27**) to mercaptomethyl methanol (**28**) to obtain a mixture of diastereomeric Michael adduct products (**27a** and **27b**) in a ratio of 0.7 : 1.0. The mixture did not undergo diastereomeric salt crystallization using methanol, but proceeded to yield the final thiochromene products (**30a** and **30b**) by sequential oxidation, deprotonation cum Henry intramolecular cyclization by a carbanion and dehydration at the C3–C4 bond of the thiochromene ring (**29b**) (Scheme 8). In the same year, Muthupandi *et al.* attempted a similar reaction by preceding it with aryl C–S bond formation to yield thiochromenes (**34**).<sup>36</sup> This protocol demonstrated good tolerability with a range of substrates to furnish the







**Scheme 5** (a) Thio-Michael addition reaction for the synthesis of thiochromene-3-carboxylate ester; (b) mechanism of the Michael addition reaction; (c) select examples.



**Scheme 6** (a) One-pot reaction to synthesize thiochromenes using xanthate as the sulfur source; (b) mechanism of the Michael addition reaction; (c) synthetic application; (d) select examples of thiochromene derivatives.

corresponding products in 66–98% yields. Furthermore, this work revealed that the copper catalyst was essential for the  $C_{(aryl)}-S$  bond formation and subsequent *in situ* generation of formylbenzenethiolate (**31d**), which then undergoes Michael-aldol elimination (Scheme 9).

Le *et al.*, in the same year, devised a novel and efficient method for attaining thiochromenes by the *in situ* generation of mercaptobenzaldehyde from the reaction of bromobenzaldehyde (**35**) and nitroalkene (**36**).<sup>37</sup> This protocol proceeded by a thiol-Michael addition tandem intramolecular aldol condensation of *o*-formyl thiophenolate to styrene, followed by the dehydration of the ensuing intermediate to achieve the desired thiochromene (**37**). This reaction demonstrated better yields

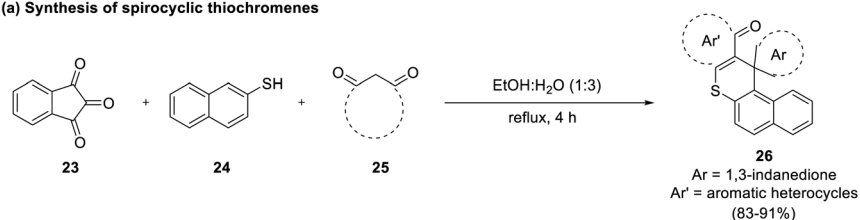
with the use of chalcone (**38a**), cinnamaldehyde (**38b**), and its esters (**38c**) in place of styrene, as the former group furnished the product with one equivalent. At the same time, the latter required 2.5 equivalents (Scheme 10).

In the subsequent year, Sundaravelu and Sekar came out with a double hetero-Michael addition reaction encompassing halo-benzaldehydes (**38**) and substituted chalcones (**39** or **42**) in the presence of a copper catalyst using xanthate (**A**) as the sulfur source and chemoselective reducing agent.<sup>38</sup> This group noted that this reaction resulted in the generation of an amino/bromo-benzoyl-substituted thiochromene ring (**40** or **43**) subjected to intramolecular Michael addition without the formation of by-products. The amine-bearing substrate's sub-

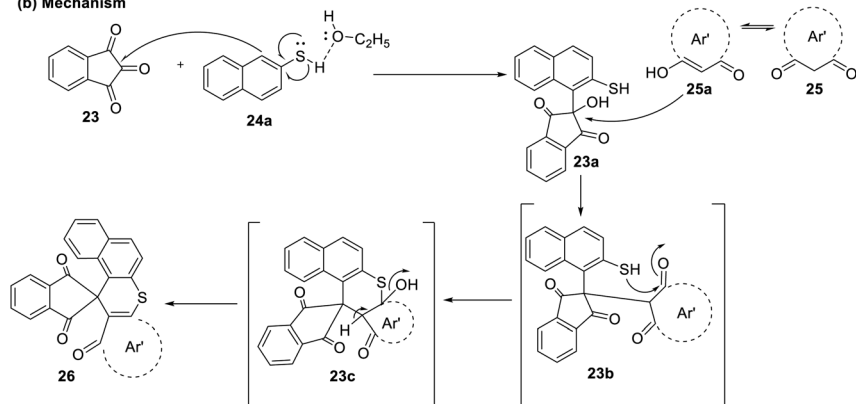




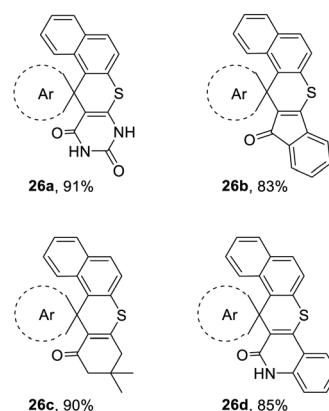
## (a) Synthesis of spirocyclic thiochromenes



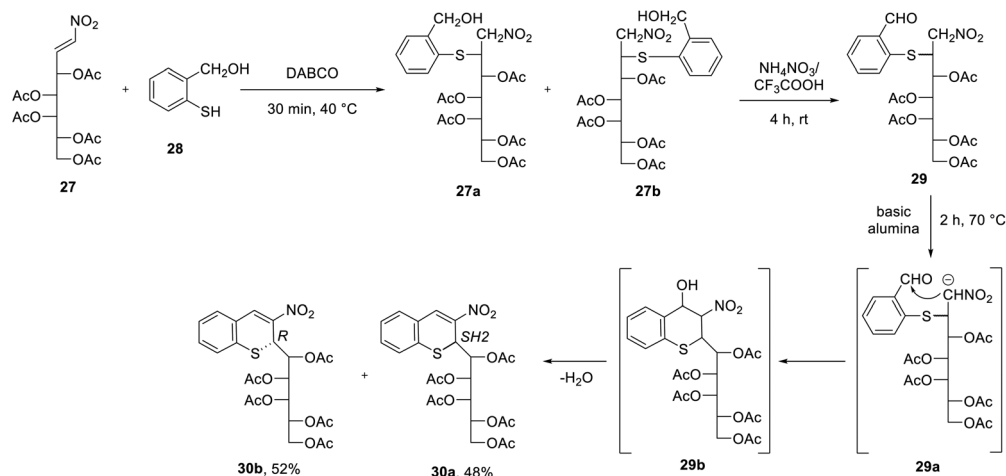
## (b) Mechanism



## (c) Select examples



**Scheme 7** (a) Knoevenagel–Michael cascade reaction to synthesize thiochromenes; (b) mechanism of the Michael addition reaction; (c) select examples.



**Scheme 8** Synthesis of diastereomeric mixtures of thiochromenes from mercaptobenzoic acid.

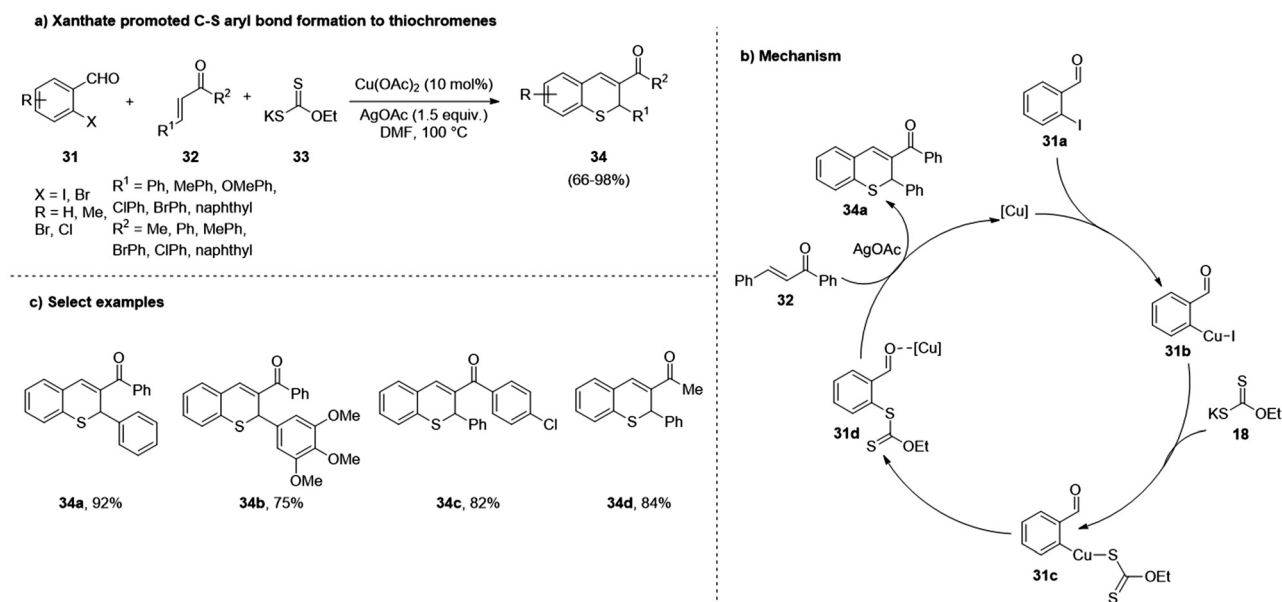
sequent base-catalyzed reaction led to quinolinone ring formation (**41**). In contrast, the progression of the reaction involving the bromo-bearing substrate at increased temperature resulted in the generation of a thioflavone ring (**44**) (Scheme 11).

Control experiments and literature analysis were extensively conducted to further comprehend this reaction's mechanistic intricacies. Through these approaches, the group noted a common pathway that bifurcates into two distinct mechanisms depending on the substrate employed for the cyclization. The

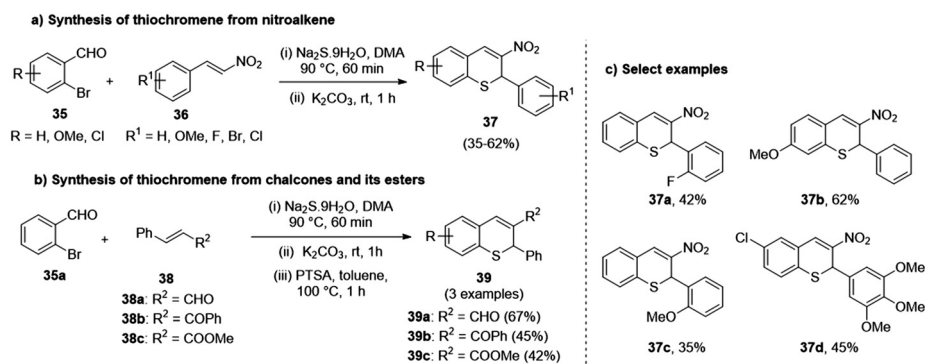
copper complexed halo-benzaldehyde (**38a**) initially exchanges ligands with xanthate (**A**), generating potassium iodide as the by-product. The intermediate (**38c**) formed then undergoes sulfa-Michael addition cum aldol condensation to yield an intermediate (**38e**). In the next stage, two different mechanisms are observed. The bromo-substituted chalcones (**43**) correspond to the formation of chromene-isoflavones (**44**) by intramolecular sulfa-Michael addition, while nitro-bearing chalcones (**40**) undergo the reaction to generate quinolinone rings (**41**) by aza-Michael addition. Intriguingly, both these







**Scheme 9** (a) Xanthate promoted C-S aryl bond formation to synthesize thiochromenes; (b) mechanism of the Michael addition reaction; (c) select examples.



**Scheme 10** (a) Thio-Michael addition reaction using bromobenzaldehyde to synthesize thiochromenes from nitroalkenes; (b) chalcones and their esters; (c) select examples.

parallel pathways proceed *via* an oxidation step catalyzed by the iodine generated *in situ* in the reaction of potassium iodide in the initial steps (Scheme 11).

**1.1.4. Stereoselective methods.** Ortiz *et al.* (2020) exemplified this area of investigation by proposing a series of reactions based on the oxo-Michael aldol reaction of mercaptobenzaldehyde (45) with activated alkenes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and triphenylphosphine (PPh<sub>3</sub>).<sup>39</sup> Intriguingly, the product was formed as a diastereomeric mixture which, on dehydration or oxidation, resulted in thiochromenes (47 or 53) or a tautomeric keto-enol mixture (48 and 49), respectively (Scheme 12).

In the same year, another highly diastereoselective method was reported by Wang and co-workers for the synthesis of annulene fused thiochromenes (56) from bridged biarylenones (54) and mercaptoacetophenones (55) using a chiral

phosphoric acid catalyst.<sup>40</sup> The reaction demonstrated good tolerance towards electron donating and withdrawing functionalities, yielding a single diastereomer (56) with 89–99% enantiomeric excess (ee) and diastereomeric ratio (dr) > 20 : 1. The catalyst employed in this reaction initially reacts with the thiol group to generate a nucleophile that attacks the enone *via* the *Re* face through Michael addition. In the next step, an intramolecular aldol condensation occurs, followed by protonation to produce the desired product (Scheme 13).

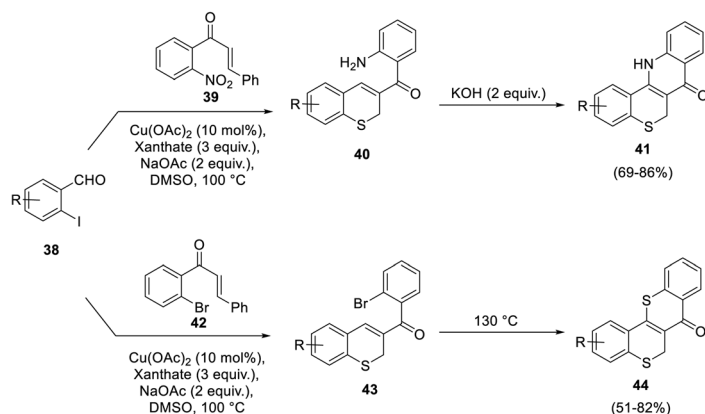
## 1.2. Cycloaddition reactions

Inami *et al.* in 2014 put forth a facile approach for synthesizing thiochromones by reacting thioisatins (57) with alkynes (58).<sup>41</sup> While the reaction involved a decarbonylative cycloaddition to furnish the final product (59) as a single regioisomer, specific substrates resulted in a mixture of regioisomers. Using octyne,

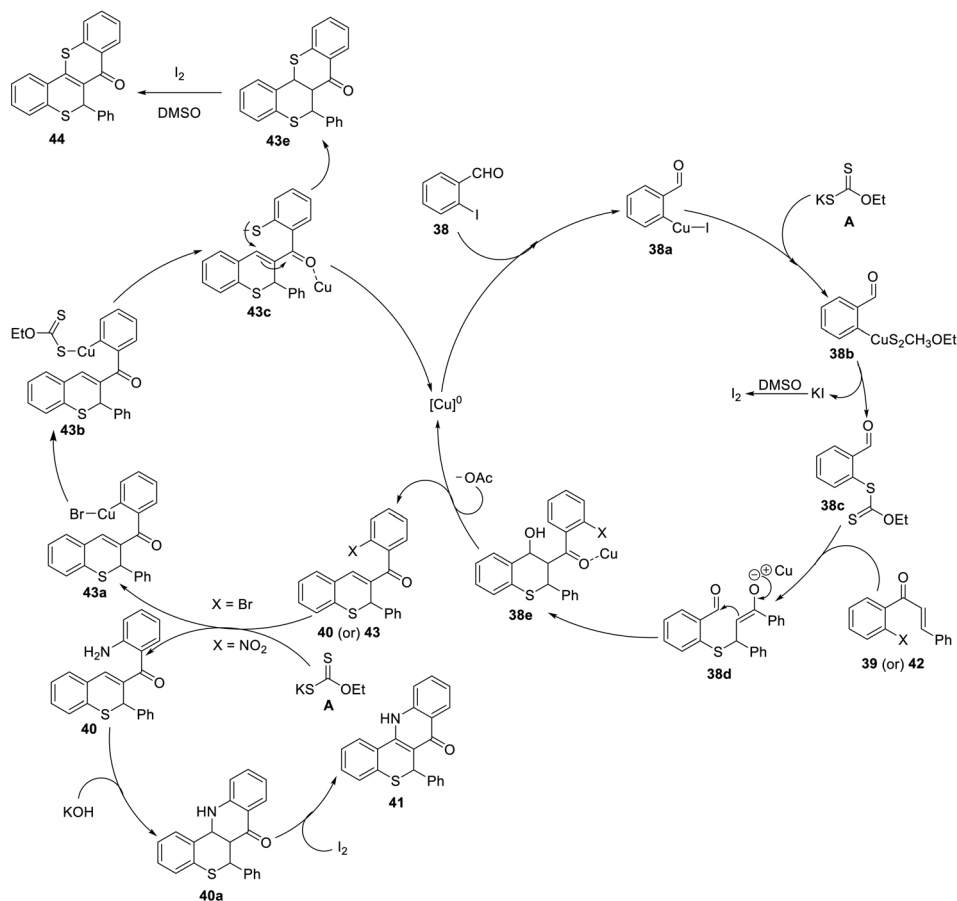




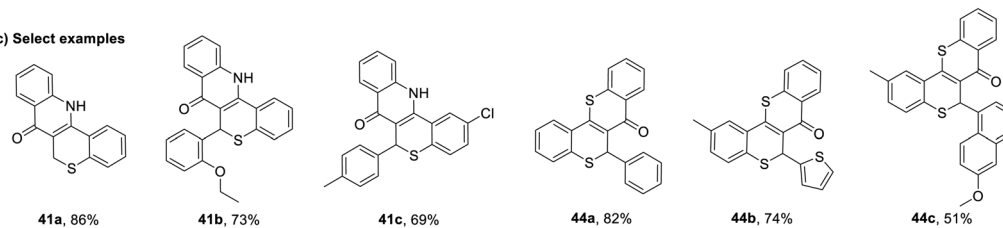
## (a) Synthesis of heterocyclic ring bearing thiochromenes



## (b) Mechanism



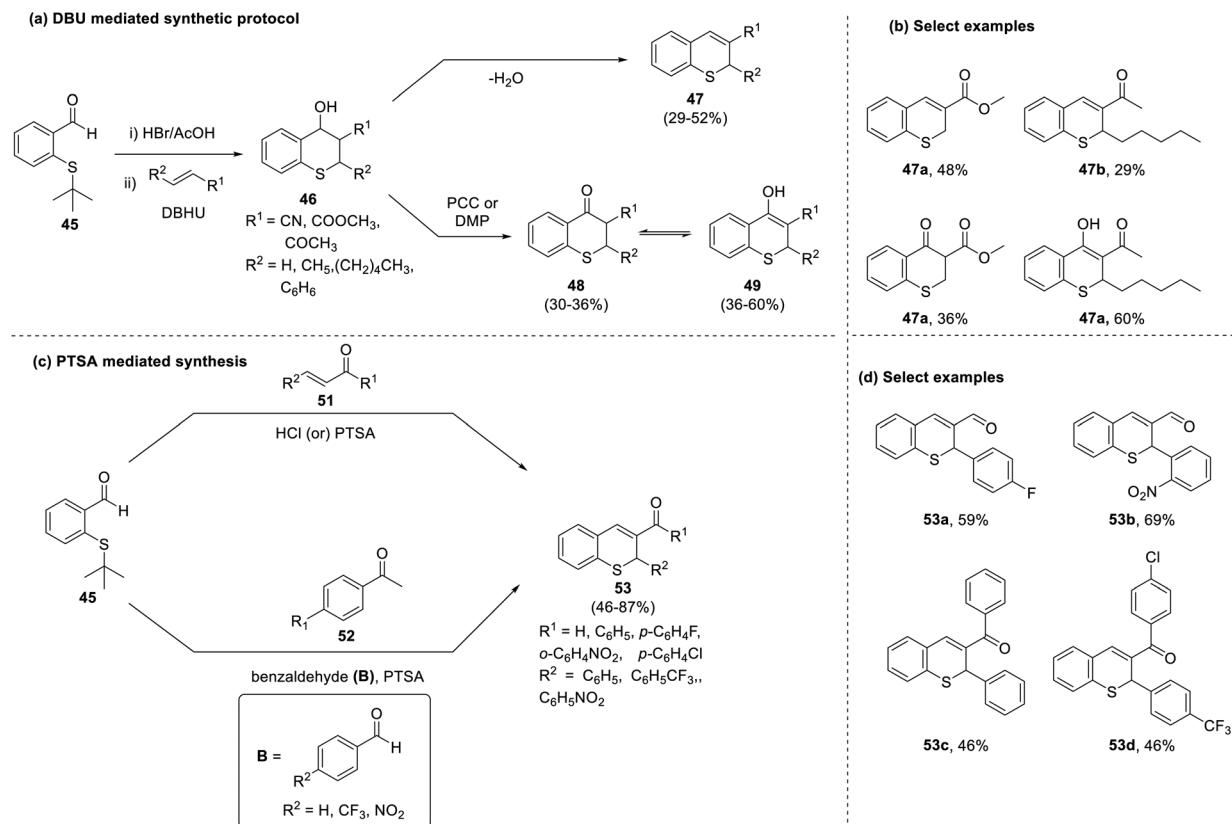
## (c) Select examples



**Scheme 11** (a) Chemoselective synthesis of thiochromenes by the sulfa-Michael addition reaction; (b) mechanism of the Michael addition reaction; (c) select examples.







**Scheme 12** (a) 1,8-Diazabicyclo-[5.4.0]-undec-7-ene (DBU) mediated cyclization to synthesize thiochromenes; (b) select examples; (c) PTSA mediated synthesis of thiochromenes; (d) select examples.

methyl or phenyl cyclopropyl acetylene, and terminal alkynes gave rise to a mixture of isomers (Scheme 14).

Continuing with this approach, Zhu *et al.*, in 2018, revamped the previous work by establishing a [3 + 2 + 1] cyclization protocol for achieving thiochromenones (63) by the use of aromatic sulfides (60) and alkynes (62) by a rhodium-catalyzed reaction.<sup>42</sup> This reaction tolerated electron donating and withdrawing functionalities but failed to generate the products with internal alkynes. The other recalcitrant alkynes for this reaction were cyclohexyl acetylene and octyne (Scheme 15).

In 2023, Pan *et al.* further exploited this area by developing a [3 + 2 + 1] transannulation protocol whereby thiadiazoles (64) reacted with alkynes (65) using a de-nitrogenative carbonylation approach.<sup>43</sup> In this method, carbon monoxide (CO) acted as the C1 synthon, and PPh<sub>3</sub> was used to convert the rhodium catalyst into a highly reactive species. With the help of mechanistic investigations, the reaction was noted to proceed by forming a cyclorhodium intermediate that undergoes CO insertion and furnishes the thiochromenone product (66) *via* reductive elimination (Scheme 16).

### 1.3. Ring-opening reactions

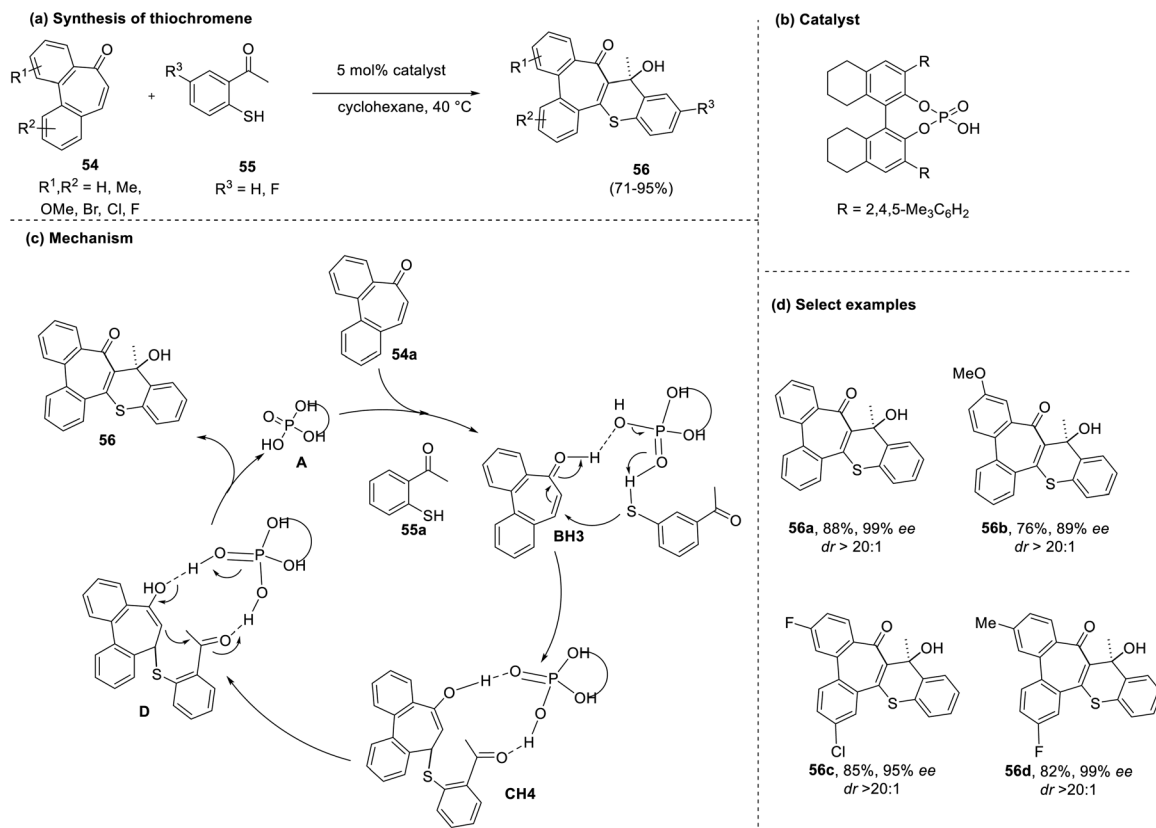
The chemical versatility of chromenes and thiochromenes has established them as significant building blocks for synthesizing promising therapeutic agents. In this context, synthetic

protocols, mainly catalyst-aided reactions, have been primarily explored for these motifs of interest. While these methods offer thiochromenes in good yields, their economic feasibility hinders their widespread utility. In a bid to tackle this, Roy *et al.*, in 2014, devised a simple methodology utilizing a mild chlorinating agent, 2,4,6-trichloro-1,3,5-triazine (TCT) (68), to furnish thiochromenes (69) *via* ring opening of hydroxyl thiochromane possessing a cyclopropane moiety (67).<sup>20</sup> This protocol, carried out under anhydrous conditions, resulted in excellent yields of *E*-configuration thiochromenes (69) (84–88%). Mechanistic studies revealed the concurrence of cyclopropane ring opening to release the angle strain and subsequent dehydrogenation at the C3–C4 position to form a diene by the release of the leaving group. The synthetic applicability of this reaction was tested for the generation of cannabinoid derivatives (71) by the Diels–Alder reaction wherein a benzodioxole-containing substrate (69c) was reacted with *N*-phenyl maleimide (70) (Scheme 17).

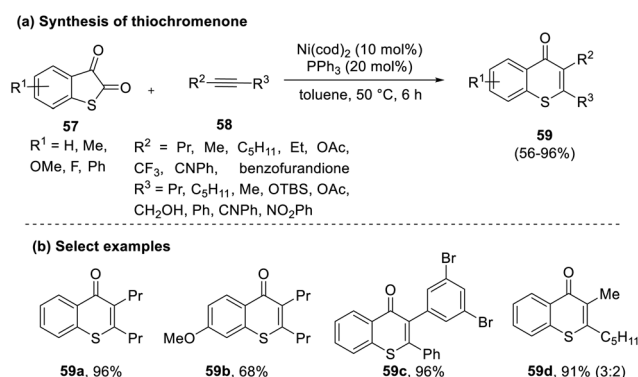
In 2020, Ponra and co-workers explored the ring opening of cyclopropyl thioethers (72) using palladium as the metal catalyst.<sup>44</sup> In continuation of their interest in the ring opening of cyclopropanes, this group tested the reactivity of the thioether analog (72) in the presence of various palladium catalysts. However, it was observed that the use of palladium (0) catalysts, particularly palladium acetate, was the best choice. An







**Scheme 13** (a) Chiral phosphoric acid-catalyzed synthesis of thiochromenes; (b) chiral phosphoric acid catalyst; (c) mechanism for the synthesis of thiochromenes; (d) select examples.



**Scheme 14** (a) Nickel-catalyzed decarbonylative cycloaddition to synthesize thiochromenones; (b) select examples.

investigation of the substrate scope revealed that the reaction tolerated electron-donating functionalities but generated poor yields using chloro-substituted thioethers. Furthermore, isomerization of the double bond of the thiochromene (73), resulting in regioisomers with an isomeric ratio of 2.5 : 1, was noticed in the presence of substrates bearing acyl groups. In the mechanistic inspection, the principal intermediate formed is a seven-membered palladacycle (72c), which undergoes subsequent elimination to generate the final product (73). The oxi-

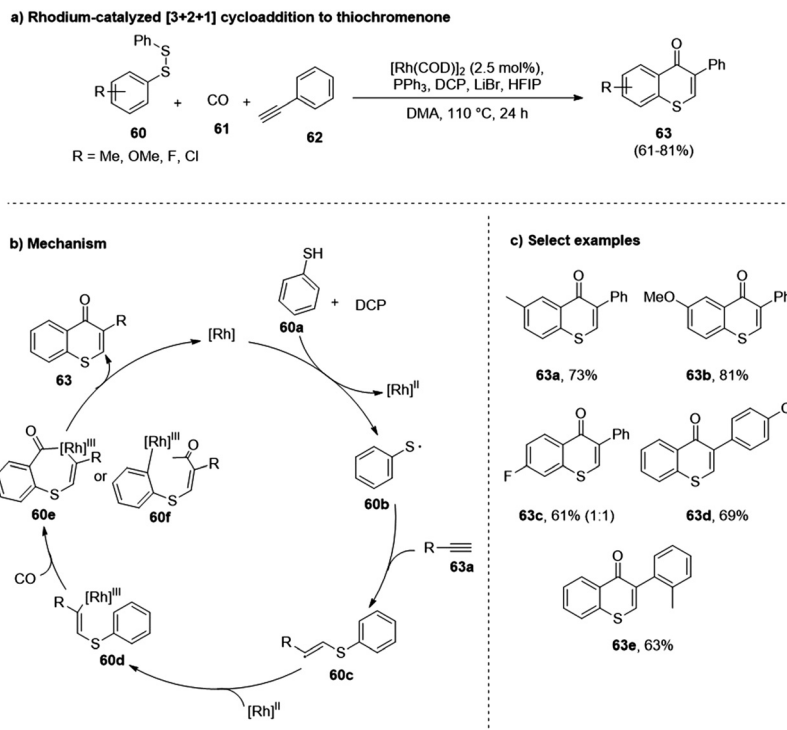
dative addition of the Pd(0) catalyst to the thioether is the only sluggish step in this reaction, and this is attributed to the presence of the sulfur atom *ortho* to the halogen, which results in a rise in the electron density of the aromatic ring, thereby hampering the oxidative addition (Scheme 18).

#### 1.4. Coupling reactions

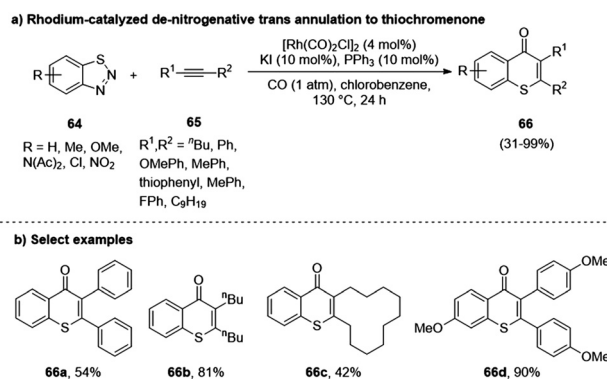
Coupling reactions have been of paramount importance in generating C–S bonds. However, such reactions often face limitations due to catalyst poisoning and using thiol as the precursor. Considering this, Shen and co-workers in 2016 envisaged a one-pot technique utilizing a reagent capsule to generate a thiochromenone (76) by circumventing the catalyst poisoning and undesired side products usually encountered in these cases.<sup>45</sup> To facilitate this, the reaction was carried out between halogenated benzenes (74), aromatic acetylenes (75), and sodium sulfide nonahydrate in the presence of a palladium catalyst. While sodium sulfide served as a conducive sulfur source, it was also identified to contribute towards catalytic poisoning and side-product formation. Shen and his group tackled this by encapsulating anhydrous sodium sulfide in paraffin wax capsules and controlling their release with time to obtain the final product (76) in good yields (Scheme 19).







**Scheme 15** (a) Rhodium-catalyzed [3 + 2 + 1] cycloaddition to synthesize thiochromenones; (b) mechanism of cycloaddition; (c) select examples.



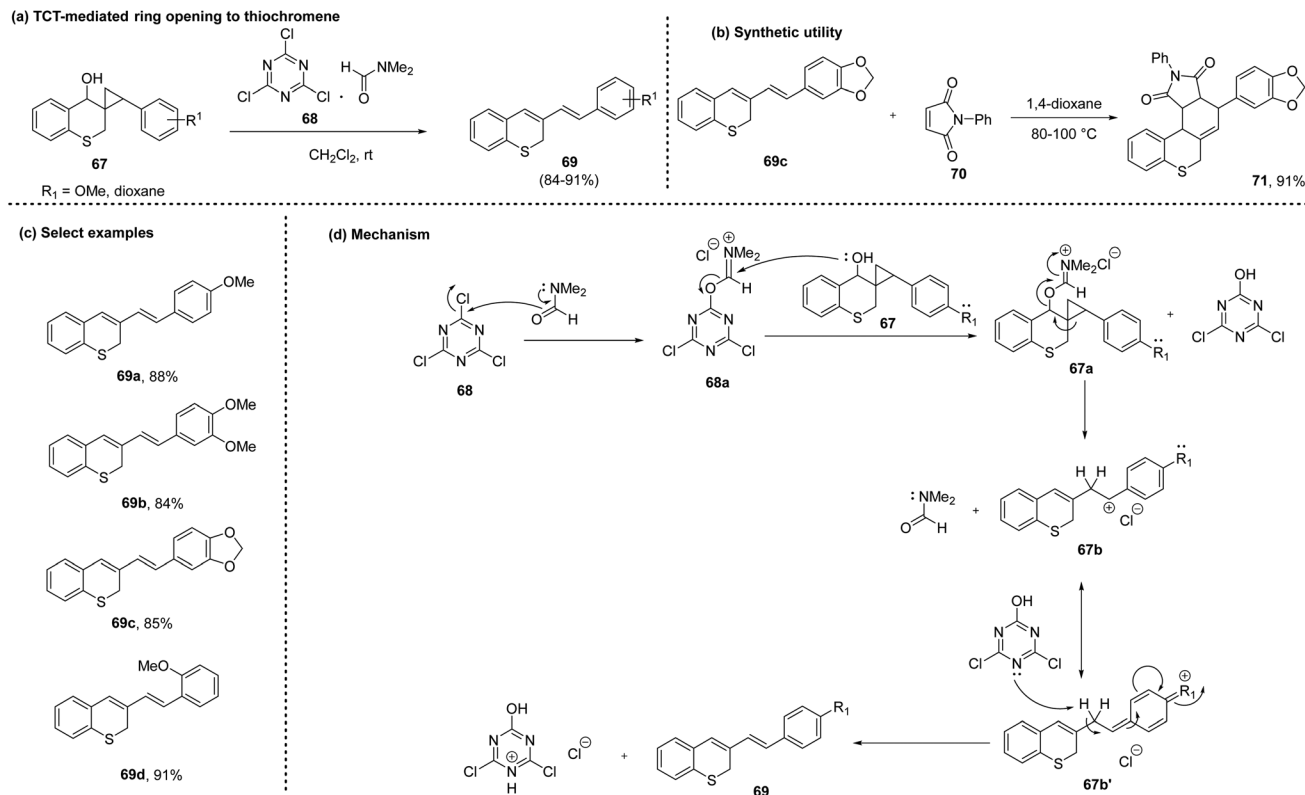
**Scheme 16** (a) Rhodium-catalyzed de-nitrogenative transannulation to synthesize thiochromenones; (b) select examples.

Sundaravelu *et al.* devised a greener approach for C–S coupling to achieve thiochromene derivatives. This protocol employed xanthate (78) as the sulfur surrogate and proceeded under visible light conditions, which is crucial for the initial C–S bond formation between the xanthate (78) and halogenated benzaldehydes (77). This step facilitated intermolecular charge transfer, followed by inter/intramolecular Michael addition to attain the final product (79).<sup>46</sup> Interestingly, the use of crotonaldehyde resulted in the formation of the thiochromene ring (81) under the same reaction conditions, while chalcones led to the corresponding thiochromanol (dr: 77 : 23 to 83 : 17) (83) (Scheme 20).

The existing literature for synthesizing thiochromene-4-imines (86) showed that an improvement is required regarding the regioselectivity and higher loading of catalysts and ligands. Singh and co-workers proposed a greener approach using D-glucosamine as the ligand under Cu(I)-catalyzed conditions to address these challenges.<sup>47</sup> This reaction proceeded through the formation of a copper complex (84b), which transitions to form a thiolate anion (84c) that ultimately generates a thietane ring (84e) by C–S bond formation. This four-membered cycle then undergoes cyclative rearrangement induced by the attack of the alkynyl group to yield the desired product (72–86%) (86) (Scheme 21).

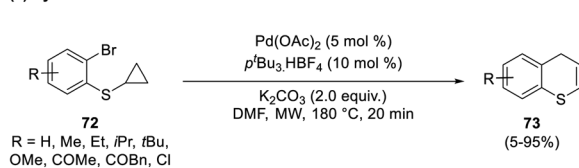




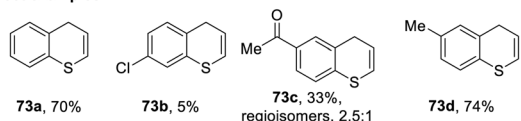


**Scheme 17** (a) 2,4,6-Trichloro-1,3,5-triazine (TCT)-mediated ring opening to synthesize thiochromenes; (b) synthetic application; (c) select examples; (d) mechanism of ring opening.

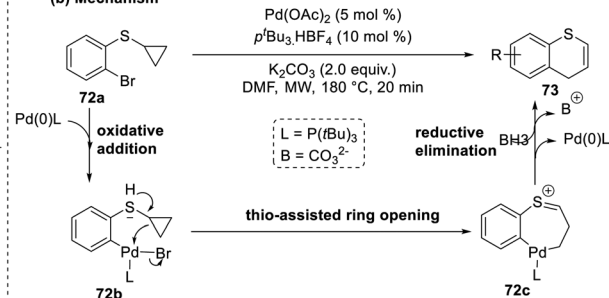
**(a) Synthesis of 4H-thiochromene**



**(c) Select examples**



**(b) Mechanism**



**Scheme 18** (a) Palladium-catalyzed ring opening of cyclopropyl thioether to synthesize thiochromenes; (b) mechanism of ring opening; (c) select examples.

In 2023, Deepika *et al.* reported a novel de-nitrative C-S coupling methodology for synthesizing pyrazole-tethered thiochromenes (**89**) using elemental sulfur (**88**) as the sulfur source.<sup>48</sup> This environmentally benign protocol leveraged 1,4-diazabicyclo-[2.2.2]-octane (DABCO) for activating the sulfur source and aided in regioselective C-H bond formation, simultaneously removing the nitro motif from the arene ring. Following control experiments, two possible mechanistic pathways were identified for this reaction. In path A, the reaction proceeds through the Michael addition of a trisulfur anion to the double bond of the chalcone, which subsequently under-

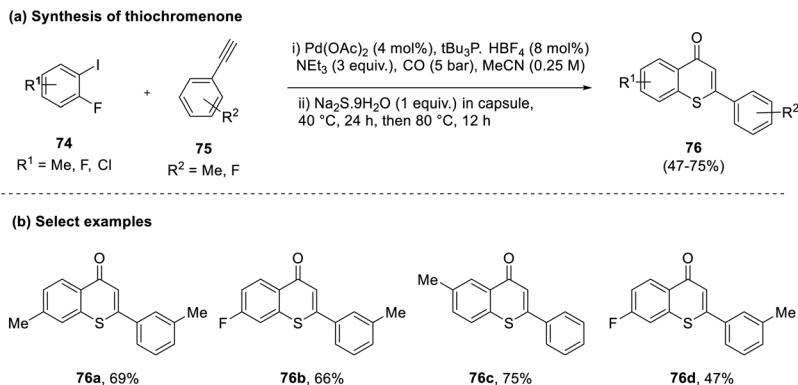
goes S-S bond cleavage and an intramolecular nucleophilic substitution reaction to generate the final product (**89**). Contrarily, the other pathway proceeds by generating a polysulfide zwitterion. In both pathways, DMSO was crucial as it stabilized the intermediates and radicals generated during the reaction mechanism (Scheme 22).

### 1.5. Cyclization reactions

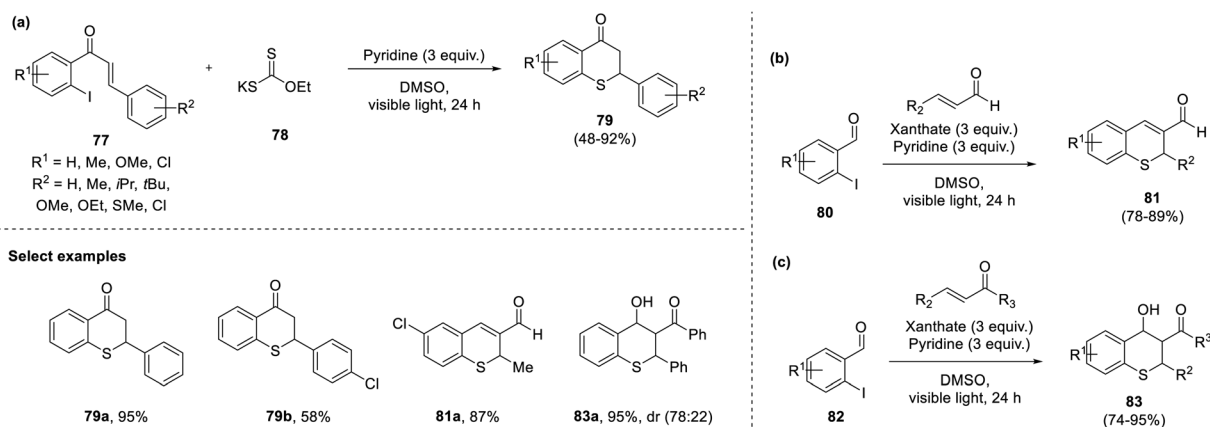
In furtherance of the work exploring cyclization reactions for thiochromene synthesis, Yugandar and co-workers in the year 2017 reported a one-pot palladium-catalyzed intramolecular







**Scheme 19** (a) Reagent capsule-based approach to selectively synthesize thiochromenes; (b) select examples.



**Scheme 20** (a) Visible light-mediated synthesis of thiochromenes; (b) synthetic application; (c) select examples.

cyclization of haloarenes (**90**) with a thieno-fused thiodiketone (**91**).<sup>49</sup> This reaction proceeded *via* two steps, forming an open chain thiovinyl ketone (**A**) in the first step, which is then cyclized to afford a thiochromene derivative (**92**) using 10 mol% palladium acetate. While thienyl- and furanyl-substitutions at the thiocarbonyl portion of diketones were well tolerated in this reaction, the introduction of a pyrrole ring or thienyl ring with a dimethylamino substituent at this end caused a deviation from the desired product, leading to the formation of the corresponding benzothiophene product (Scheme 23).

The reactions of sulfur-containing allenes (**93**) under acidic conditions with halogens have been studied by several groups like Zhou *et al.* and Ma *et al.*<sup>50,51</sup> However, despite the promising results obtained from these studies, the electrophilic activation reactions entailing these molecules have been uncharted. To bridge this gap, Lozovskiy's group, in 2018, investigated the transformation of sulfur-containing allenes (**93**) under the influence of different Brønsted acids and observed the formation of a thiochromene system (**94**) with the use of trifluoroacetic acid at high temperature.<sup>52</sup> Using NMR and DFT calculations, the *ortho*-carbon of the phenyl ring was dis-

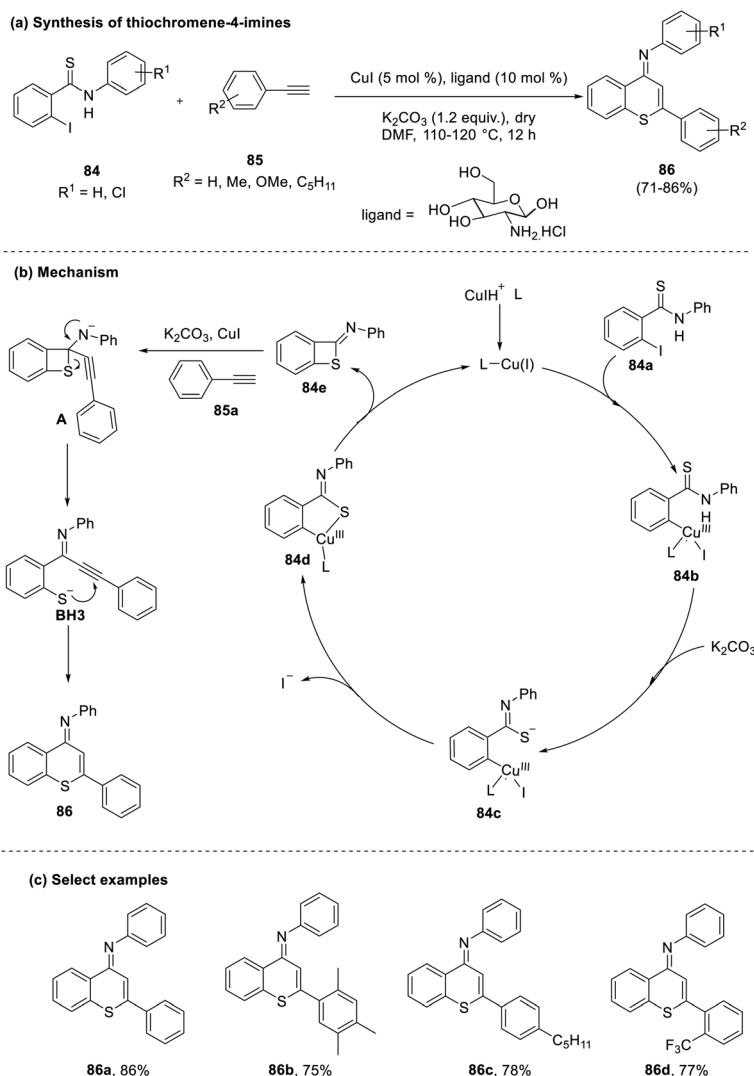
cerned to be a highly reactive electrophilic center, which aided in intramolecular cyclization towards heterocycle formation. Furthermore, allenes with a *p*-methyl phenyl ring resulted in the formation of a 7-methyl substituted product as opposed to the 6-methyl substitution due to a [6,7]-methyl shift, which occurs due to the action of the superacid at high temperatures (Scheme 24).

In the same year, Wang's group unveiled a novel protocol for the synthesis of halogenated thiochromenes conjugated with aliphatic amines (**101**) like piperidine, *N*-methyl piperazine, diethyl amine, and pyrrolidine.<sup>53</sup> Friedel–Crafts reaction conditions were employed to facilitate the intramolecular cyclization of thiophenols (**95**) with simple chiral carboxylic acids to furnish thiochromanones (**97**), which were then subjected to the Vilsmeier–Haack protocol to achieve the thiochromene scaffold (**98**). These compounds were then substituted with aliphatic amines under alkaline conditions to obtain the final thiochromene rings substituted with heterocyclic rings (**101**) in yields of 46–82% (Scheme 25).

Ma *et al.* envisaged a Ullmann-type coupling of aryl thioamides (**102**) with phenylacetylene (**103**) for the synthesis of thiochromene-4-imines (**104**) using *L*-proline as the ligand.







**Scheme 21** (a) Glucosamine-mediated cyclization to synthesize thiochromenes; (b) mechanism of coupling; (c) select examples.

This actualized reaction preferentially generated (*E*)-configuration products.<sup>54</sup> A plausible mechanism was identified through X-ray analysis and literature findings, as shown in Scheme 26. The reaction proceeds through coupling with a copper catalyst to form a complex (A), which, under redox conditions, furnishes a 2-imino-benzothietane intermediate (E). In the subsequent step, the thietane ring opens, and a nucleophilic attack occurs, generating the desired product.

Shigeno and co-workers in 2018 proposed a two-step *peri*-selective methodology for the synthesis of benzo thiochromenes (**108**) from the reaction of a methyl thioether derivative of naphthalene (**105**) with aromatic aldehydes (**106**) in the presence of a rhodium catalyst.<sup>55</sup> The first step of the reaction was not compatible with aliphatic alkynes. In contrast, the use of diphenyl or unsymmetrical alkynes gave a mixture of products with an *E/Z* ratio of up to 11 : 89. In the final step, a 6-*endo-trig* pattern of annulation was observed to yield the final product in good yields (40–69%) (Scheme 27).

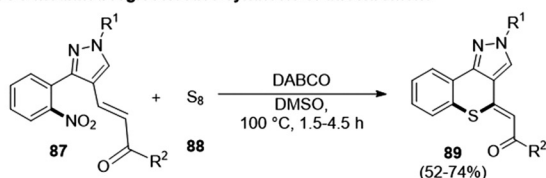
Intrigued by the importance of sulfur derivatives, Ali's group in 2019 sought to explore the chemical reactivity of enaminones (**109**) against phosphorus sulfides. This approach resulted in the formation of trichrome-4-thione (**112**) *via* intramolecular annulation of the thio-analog of an enaminone.<sup>56</sup> Interestingly, when the same reaction was carried out using Lawesson's reagent as the thionation reagent, a [4 + 2] cycloaddition reaction took place, resulting in the formation of an oxathiaphosphine ring in place of the anticipated thiochromene ring (Scheme 28).

In the same year, Zhou *et al.* devised a novel strategy employing carbene chemistry to generate a thiochromenone (**117**) from the hydroacylation cum cyclization of a thiadiazole (**113**) and propionaldehyde (**114**) in the presence of a rhodium catalyst.<sup>57</sup> While the reaction was well tolerated with most of the substrates, propionaldehydes with iodophenyl, dimethyl pentanyl, and cyclopropyl substitutions were identified to be un-reactive substrates, possibly due to the steric effects of



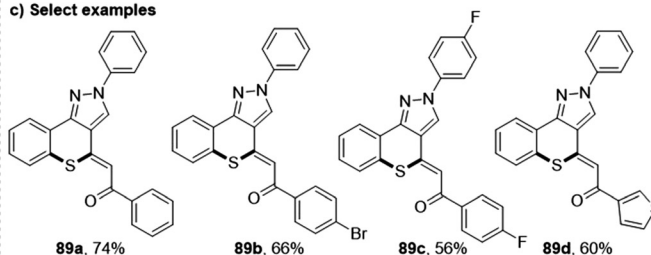


## a) DABCO mediated regioselective synthesis of thiochromene

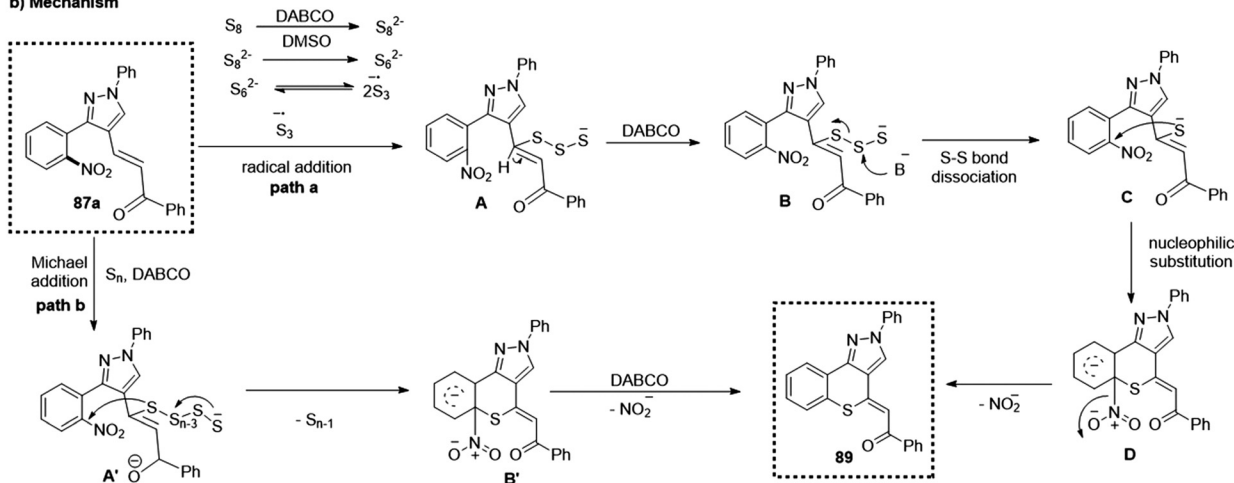


$R^1 = \text{Ph, MePh, ClPh, FPh, BrPh, diClPh}$   
 $R^2 = \text{Ph, MePh, ClPh, FPh, BrPh, thiophenyl}$

## c) Select examples

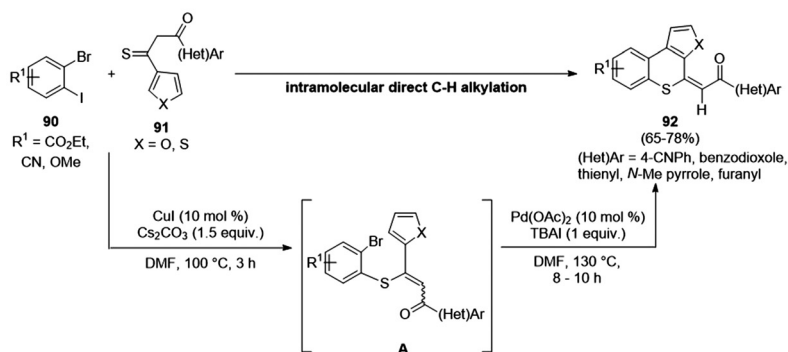


## b) Mechanism

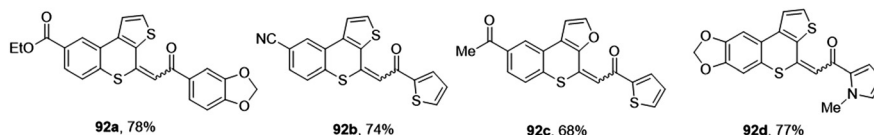


**Scheme 22** (a) 1,4-Diazabicyclo-[2.2.2]-octane (DABCO) mediated regioselective synthesis of thiochromenes; (b) mechanism involved in the formation of thiochromene-4-imines; (c) select examples.

## a) Palladium-catalyzed direct C-H alkylation to thiochromene



## b) Select examples



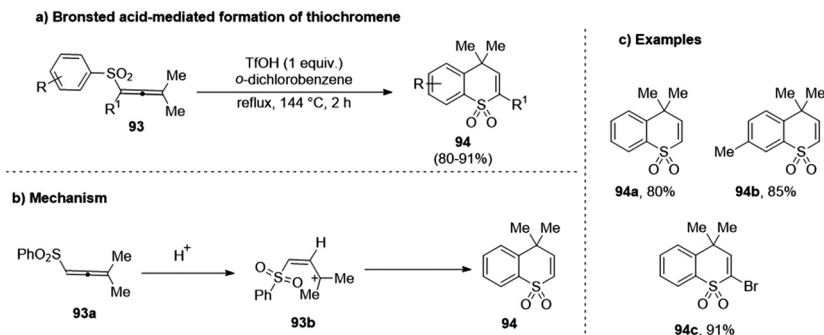
**Scheme 23** (a) Palladium-catalyzed direct C-H alkylation to synthesize thiochromenes; (b) select examples.

these groups. Expansion of the substrate scope demonstrated that alkenyl aldehydes are suitable substrates that are annulated in the presence of low catalyst levels. Further investigations revealed that the reactions proceeded only when the

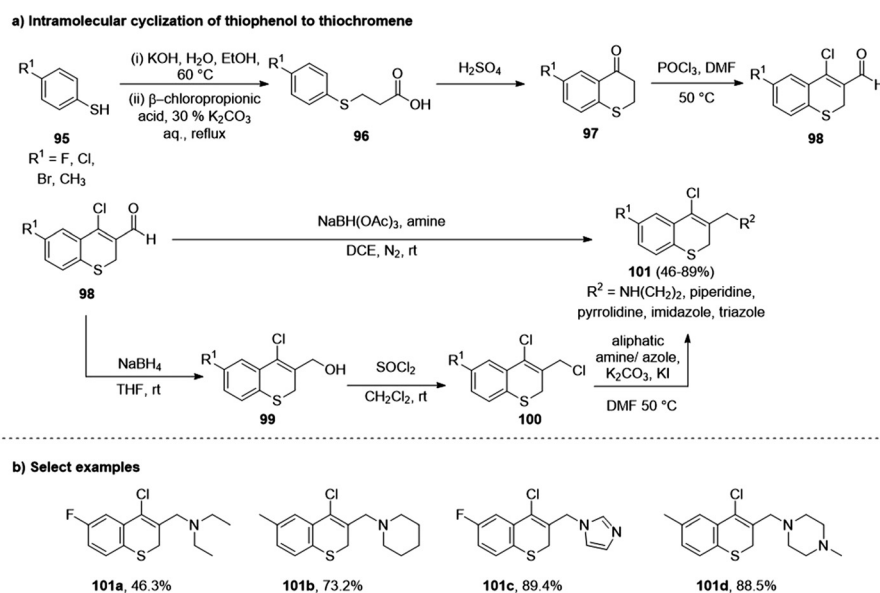
electronic properties of both substrates complemented each other (Scheme 29).

Yang *et al.* also put forth a single electron transfer (SET) cyclization method for the synthesis of similar thiochromene





**Scheme 24** (a) Brønsted acid-mediated formation of thiochromenes; (b) mechanism of cyclization; (c) select examples.



**Scheme 25** (a) Intramolecular cyclization of thiophenol to synthesize thiochromenes; (b) select examples.

molecules (**120**) from 1-thiomethyl naphthalene (**118**) in a *peri*-selective manner.<sup>58</sup> The actualized reaction differed intrinsically from the conventional methods owing to the selective heteroarylation at the *peri*-position rather than at the C2 position, which is usually involved due to the steric effect. This approach gave rise to good yields with various substrates but failed to discern the by-products formed, excluding the heteroaryl sulfides and unreacted starting materials. Mechanistically, it was observed that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was essential for the cyclization as it was postulated to have a stabilizing effect on the cation-radical intermediate (**118a**) to aid in the single electron transfer cum annulation approach (Scheme 30).

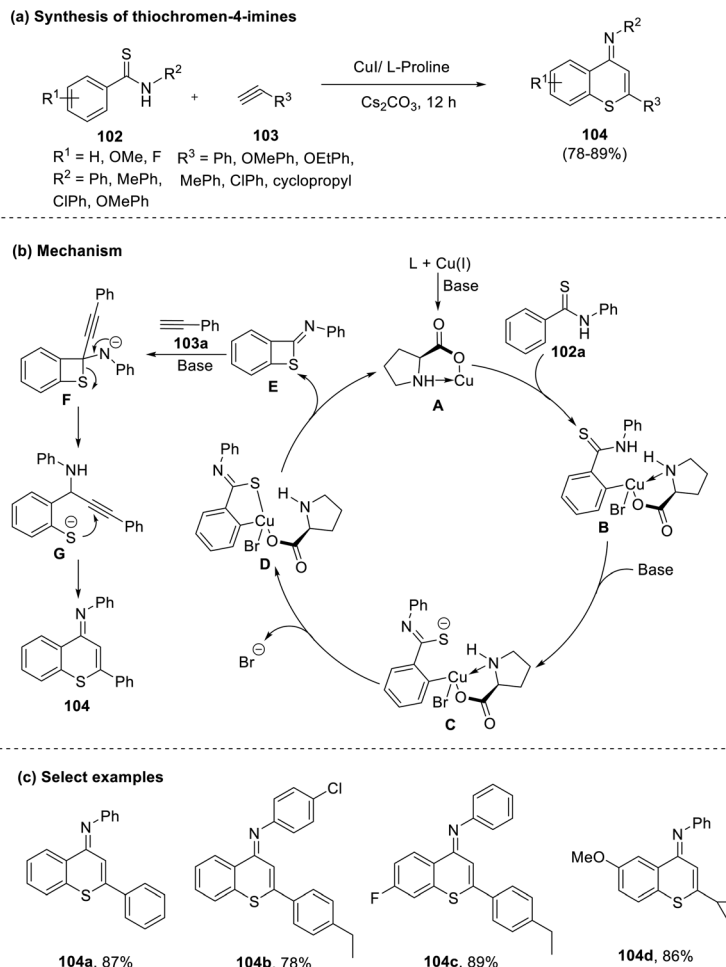
Velasco and co-workers explored the possibility of achieving thiochromene rings (**122**) by intramolecular cyclization of *S*-aryl propargyl thioethers (**121**) with *N*-iodosuccinimide (NIS)

as the electrophilic reagent.<sup>59</sup> Concomitantly, reactions using other catalysts that might act as iodonium agents were also attempted, with silver triflate identified as the most appropriate one on account of its ability to engender good coordinating counterions in comparison with other silver salts. This protocol was, however, incompatible with electron-withdrawing functionalities. *meta*-Substitution of the thioether led to a mixture of regioisomers in a ratio of 2 : 1 by 6-*endo* cyclization. In contrast, using the naphthol derivative of thioether corresponded to the generation of linear and angular thiochromenes in a ratio of 1.2 : 1 (Scheme 31).

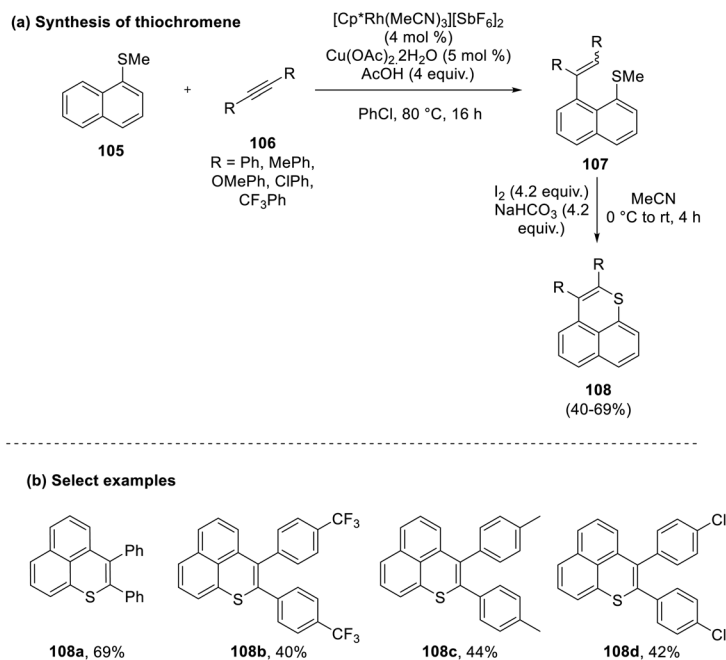
In 2021, Wang *et al.* impelled the synthesis of thiochromenones (**125**) by developing a carbonylative reaction utilizing aromatic sulfonyl chlorides (**123**) and alkynes (**124**) in the presence of a nickel catalyst. This one-pot reaction used sulfonyl chloride as the sulfur surrogate and proceeded through a







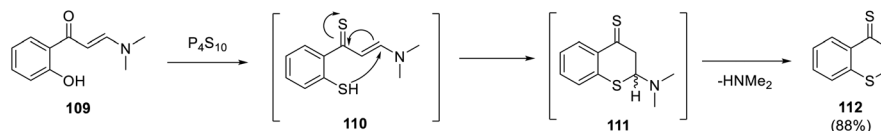
**Scheme 26** (a) Proline-catalyzed cyclization to synthesize thiochromenes; (b) mechanism of cyclization; (c) select examples.



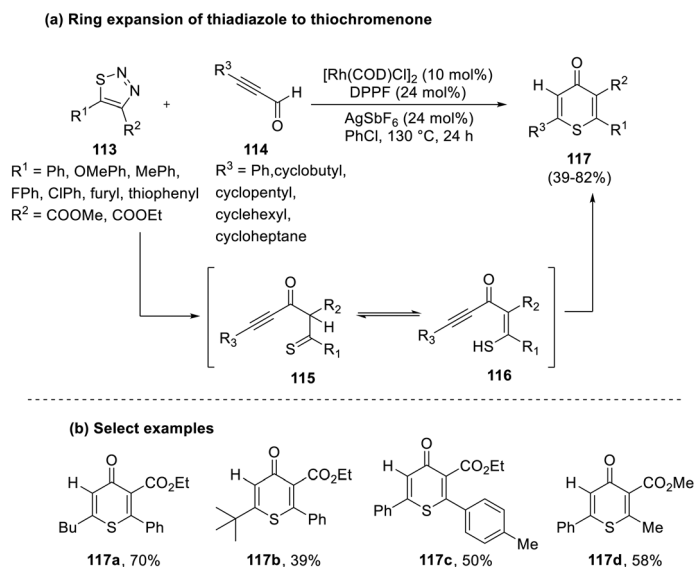
**Scheme 27** (a) *Peri*-selective cyclization of bicyclic systems to synthesize thiochromenes; (b) select examples.







Scheme 28 Lawesson's reagent mediated generation of thiochromenes.



Scheme 29 (a) Ring expansion of thiadiazoles to synthesize thiochromenones; (b) select examples.

6-*endo-dig* cyclization pathway.<sup>60</sup> Interestingly, this reaction generated lower yields with *o*-substituted alkynes compared with *m*- or *p*-substituted alkynes, which is ascribed to the steric effects seen in the case of the former. Through control experiments, two mechanistic cycles were postulated bearing a common intermediate II as the starting point. This intermediate is generated by the migratory insertion of CO into nickel complex I and then reacts with terminal alkynes to produce alkynones that, on cyclization, generate thiochromenones (**125a**); similarly, when the same intermediate reacted with internal alkynes, ring expansion followed by reductive elimination furnished the final product (**125**) (Scheme 32).

Ahlemeyer *et al.*, in 2021, attempted the cascade cyclization of cinnamic acid thioesters (**126**), which proceeded *via* aldol cyclization cum lactonization to generate thiochromenes (**130**) under neat reaction conditions.<sup>61</sup> The asymmetric synthetic protocol envisaged by this group demonstrated good yields (up to 79%) with an ee of 96% using electron-rich amidine-based catalysts (Scheme 33).

The conventional synthesis of thiochromene-containing polycyclic systems often necessitates transition metal catalysts and proceeds through multiple steps.<sup>62,63</sup> These approaches,

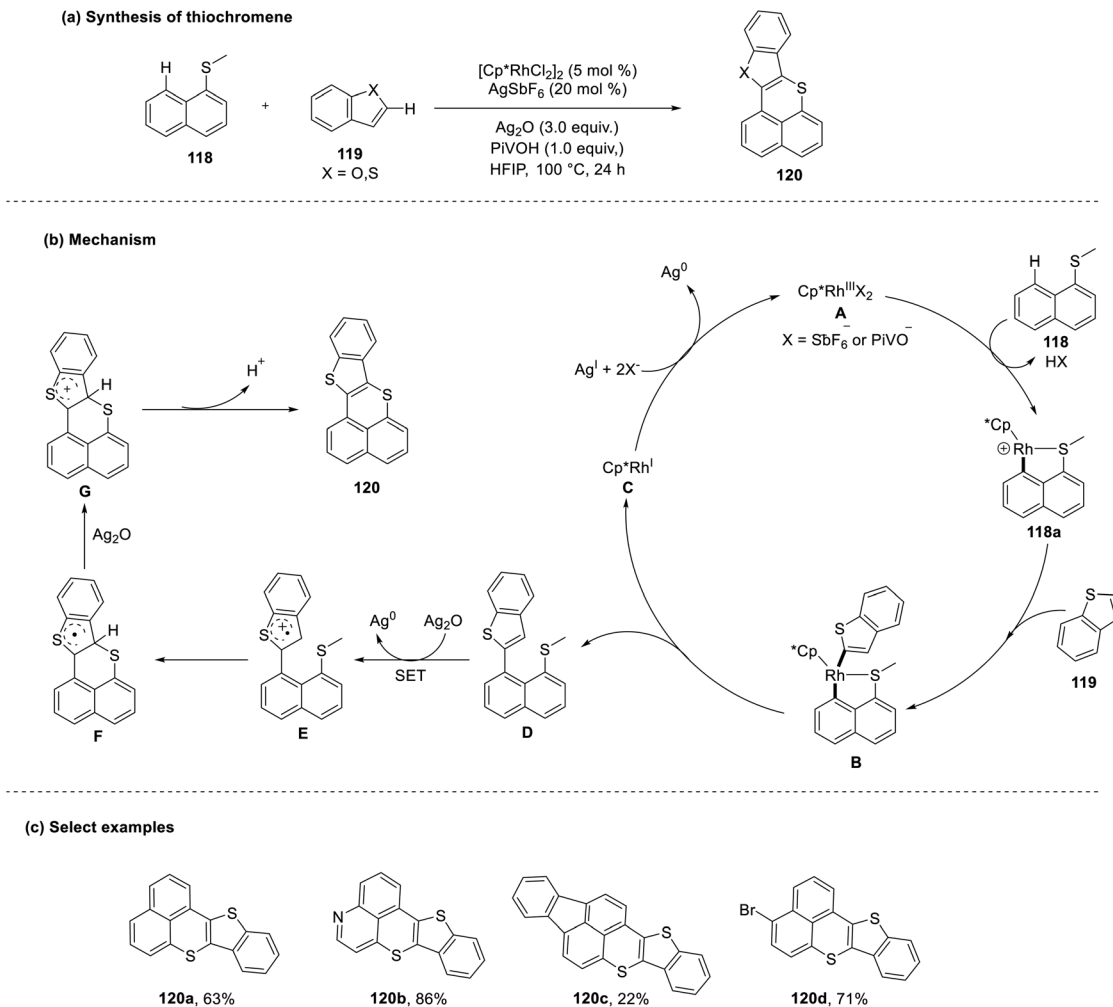
while feasible, are constrained by restricted substrate compatibility and reliance on environmentally harmful catalysts. Prompted by this challenge, Deng and co-workers (2021) streamlined the synthetic approach to present a sustainable base-catalyzed domino reaction of thioisatin (**131**) with bromo-ketone (**132**) to achieve thiochromene-fused furan scaffolds (20–80%) (**133**) (Scheme 34).<sup>64</sup>

Song *et al.* (2021) adopted mild reaction conditions to actualize the synthesis of highly stereoselective (>19:1 *Z/E* ratio) thiochromene dioxides (**137**) through visible light-mediated photocatalysis.<sup>65</sup> This approach utilized sodium metabisulfite as the sulfur dioxide surrogate and reacted it with terminal alkynes (**136**) in the presence of a phenyl ethynyl derivative of a diazonium coupling agent (**135**). Examination of the substrate scope revealed that the reaction was impeded when strong electron-withdrawing groups were substituted in the aryl rings attached to the coupling agent. This was ascribed to the formation of an unstable intermediate (alkenyl radical) *in situ* (Scheme 35).

In 2023, Davoine and co-workers synthesized carboxy-(thio)chromenes (**142**) by the cyclization of substituted mercapto-benzaldehyde (**138**) under optimum reaction conditions.<sup>66</sup> This reaction was facilitated by the formation of an

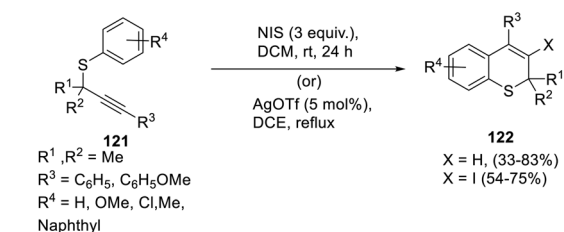






**Scheme 30** (a) HFIP-mediated single electron transfer annulation to synthesize thiochromenes; (b) mechanism of cyclization; (c) select examples.

**(a) NIS-facilitated cyclization to thiochromene**



**Scheme 31** (a) *N*-Iodosuccinimide (NIS)-facilitated cyclization to synthesize thiochromenes; (b) select examples.

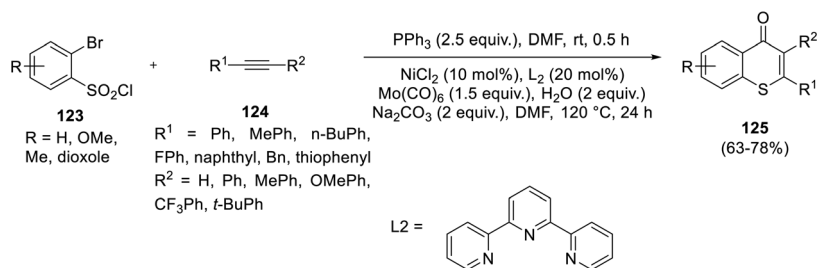
$\alpha,\beta$ -unsaturated ketone (**140**) or a dioxane-dione intermediate (**139**) that undergoes annulation to give the desired product (Scheme 36).

In the same context, Ortiz *et al.* (2023) proposed three novel methodologies for the synthesis of thiochromenes from thiophenol (**143**) and bromopropionic acid (**144**) or crotonic acid

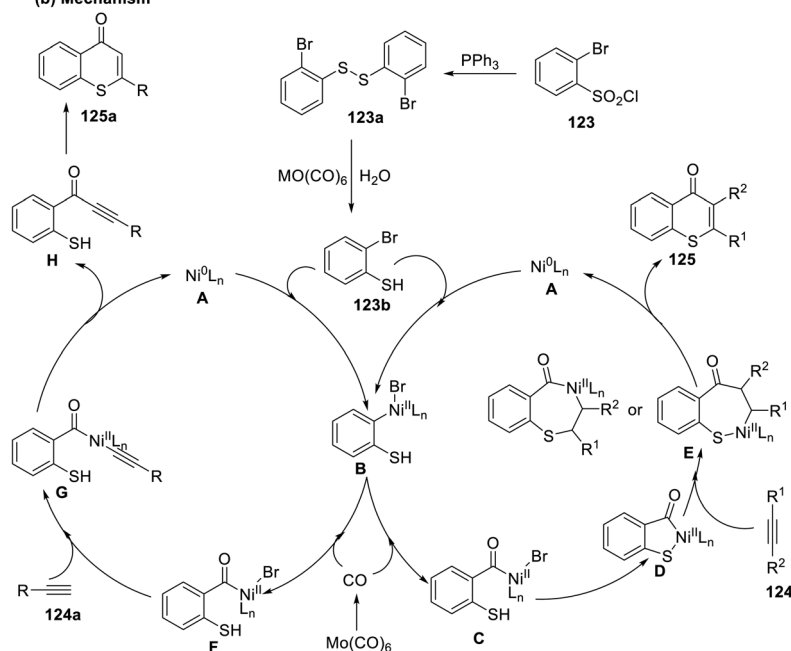




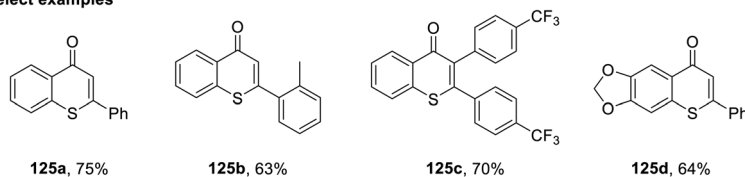
## (a) 6-endo dig cyclization of sulfonyl chloride to thiochromene



## (b) Mechanism

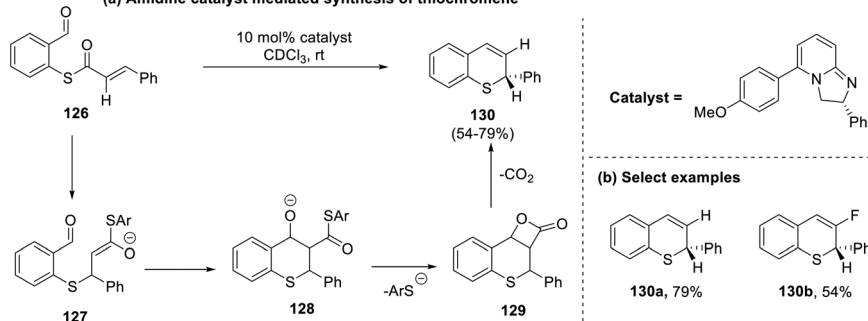


## (c) Select examples



Scheme 32 (a) 6-Endo-dig cyclization of sulfonyl chloride to synthesize thiochromenes; (b) mechanism of cyclization; (c) select examples.

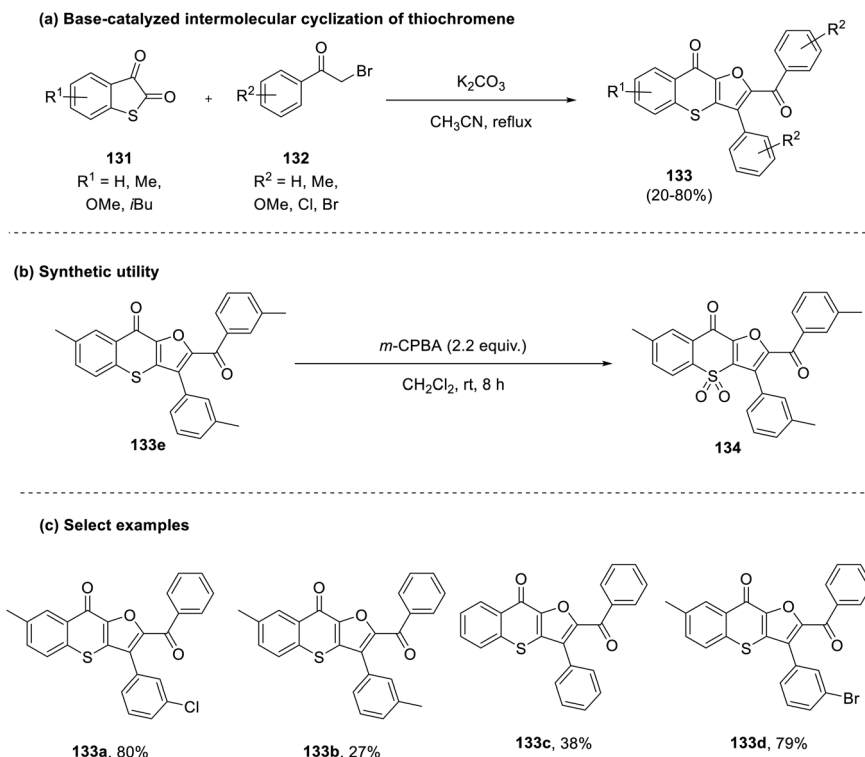
## (a) Amidine catalyst mediated synthesis of thiochromene



Scheme 33 (a) Amidine catalyst mediated synthesis of thiochromenes; (b) select examples.







**Scheme 34** (a) Base-catalyzed intermolecular cyclization of thiochromenes; (b) synthetic application; (c) select examples.

(145).<sup>67</sup> The reaction with bromopropionic acid was catalyzed by the use of a basic buffer solution. In contrast, the reaction with crotonic acid was facilitated by a phase transfer catalyst, tetra-*n*-butylammonium fluoride (TBAF) (Scheme 37).

Taking into account the widespread utility of thiochromenes, Bartz *et al.*, in 2023, devised a sustainable protocol for achieving sulfenyl thiochromenes (**154**) using thiols (**153**) and thioaryl nones (**150**) in the presence of visible light.<sup>68</sup> This work sought to improve the protocols reported by Xu's group (2019) and Ai's group (2020) in this area, which demanded oxidant species and excess solvent.<sup>69,70</sup> Besides offering sustainable reaction conditions, the recently reported method commenced with light irradiation to generate an intramolecular complex (**B**), which, in the presence of a thiol, triggers Hydrogen Atom Transfer (HAT) to give a thiyl radical (**C**). This radical initiates chain propagation and undergoes intramolecular ring cyclization to afford the final product (**154**) (Scheme 38).

### 1.6. Diels–Alder reactions

Wang's group laid the foundation for the synthesis of 3-substituted thiochromenes, which was then explored by Rios *et al.*<sup>71,72</sup> These asymmetric catalytic methods activated by iminium ions or thiourea facilitated the substitution of an electron-withdrawing functionality at the C3 position of the thiochromene, thereby limiting its further extension. Inspired

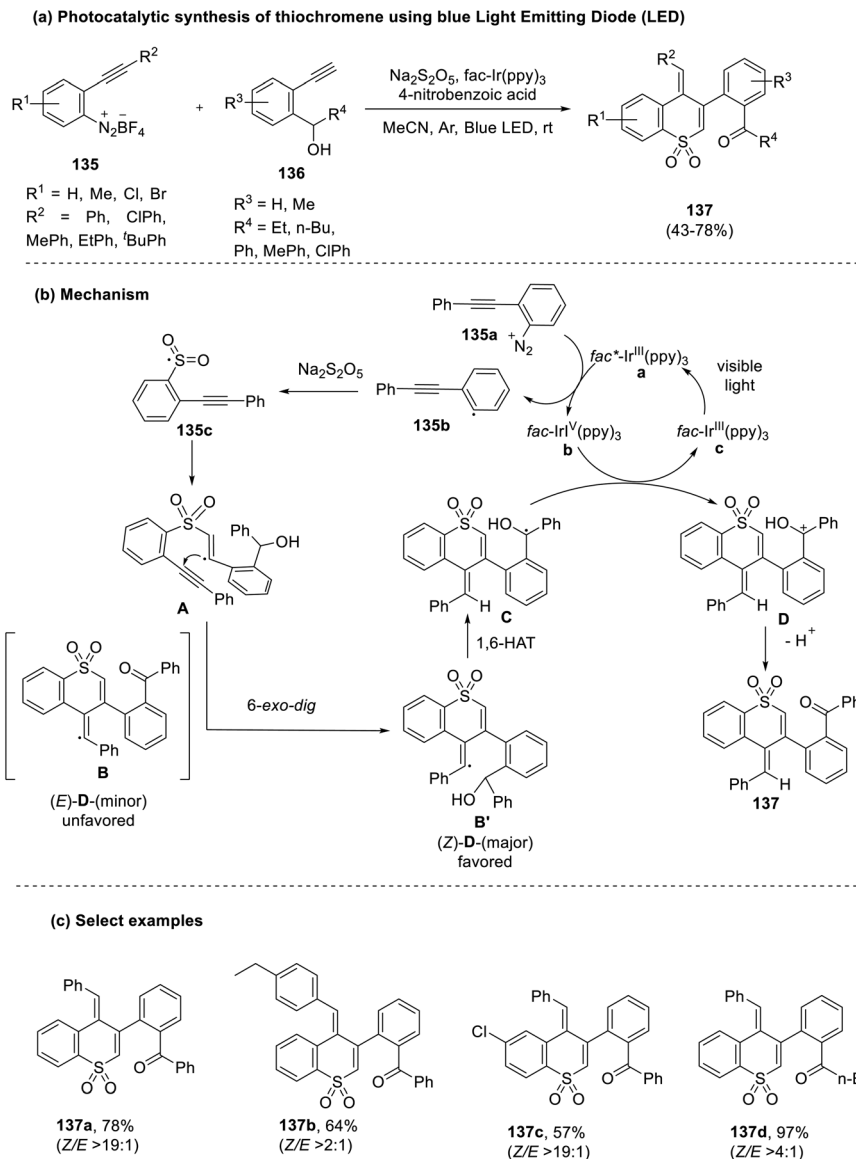
by this, Ahlemeyer *et al.* sought to design 3-unsubstituted thiochromenes (**156**) from thioesters of mercaptobenzaldehyde (**155**) by using a homobenzotetramisole derivative (HBTM-2), an amidine-based catalyst.<sup>73</sup> This protocol demonstrated an enormous substrate scope and offered products with high enantioselectivity (>99% ee), forming only carbon dioxide as the byproduct. Using transition state models, they proposed a hetero-Diels–Alder reaction, wherein C–S and C–C bond formation happens simultaneously, which is responsible for the absolute configuration of the thiochromene derivatives (Scheme 39).

Młostoń and co-workers in 2018 devised a thia-Diels–Alder protocol for attaining novel 4*H*-thiochromenes (**159** and **161**) from thiochalcones (**157**) and anthroquinones (**158** and **160**).<sup>74</sup> In this reaction, a highly regioselective [4 + 2] cycloaddition was observed between the two substrates to yield the desired product in 89–94% yields. Further investigation into the substrate scope revealed that the reaction was not bench-feasible with benzoquinones, as the pure synthesized product underwent decomposition under ambient conditions, posing a challenge for practical application. Besides this, the reaction showed compatibility issues with menadione as well owing to the extended time-frame needed and the formation of significant amounts of [4 + 2] decomposed products along with the product (Scheme 40).

Expanding further on this domain, An *et al.* leveraged aryne chemistry and C–S bond formation to streamline the synthesis







**Scheme 35** (a) Photocatalytic synthesis of thiochromenes using a blue Light Emitting Diode (LED); (b) mechanism of cyclization; (c) select examples.

of benzothiochromenes (**166**).<sup>75</sup> In particular, they addressed the requirement of excess base, harsh reaction conditions, and the use of costly catalysts through the use of Kobayashi's reagent, an aryne precursor (**163**) and a thionoester (**162**). This reaction employed a relatively inexpensive phase transfer catalyst (18-crown-ether-6) and made use of 4 Å (Angstrom) molecular sieves (MS) to selectively yield benzothiochromenes (**166**) (Scheme 41).

### 1.7. Miscellaneous reactions

Chanda *et al.*, in 2021, reported a straightforward approach for the synthesis of benzothiochromenes (**169**) *via* carboarylation of alkynes (**167**) with activated benzylic alcohols

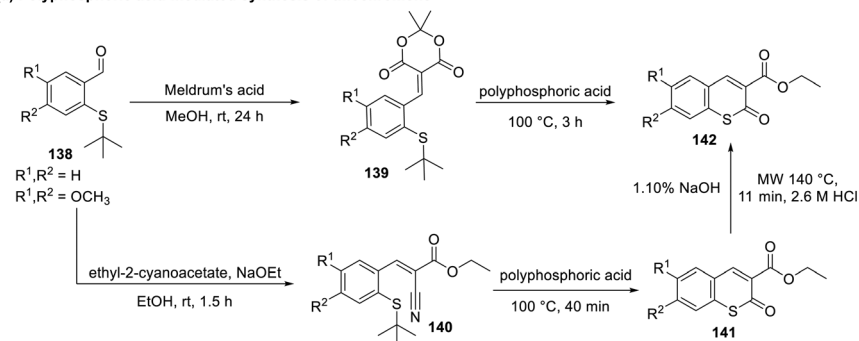
(**168**).<sup>76</sup> This reaction promoted the use of a cheaper and greener iron catalyst for actualizing the desired product with high chemo- and regio-selectivity. In accordance with the previous reports and control experiments, a plausible mechanism was outlined. Initially, a highly reactive benzylic carbocation (**B**) is generated by the activation of the alcohol (**168**) by the iron catalyst. This then transitions to form a stable aryl vinyl carbocation (**C**), which cyclizes and forms the final product by following the Friedel-Crafts alkylation pathway (Scheme 42).

In the same year, Shibata's group put forth an atom-economical protocol for the synthesis of indenothiochromene (**171**) by a Ni-catalyzed carbothioloation reaction of symmetric phenyl-substituted diynes (**170**).<sup>77</sup> This reaction took place in

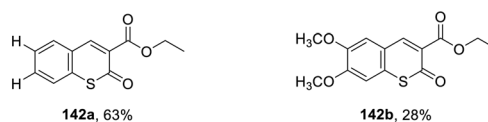




## (a) Polyphosphoric acid-mediated synthesis of thiochromene

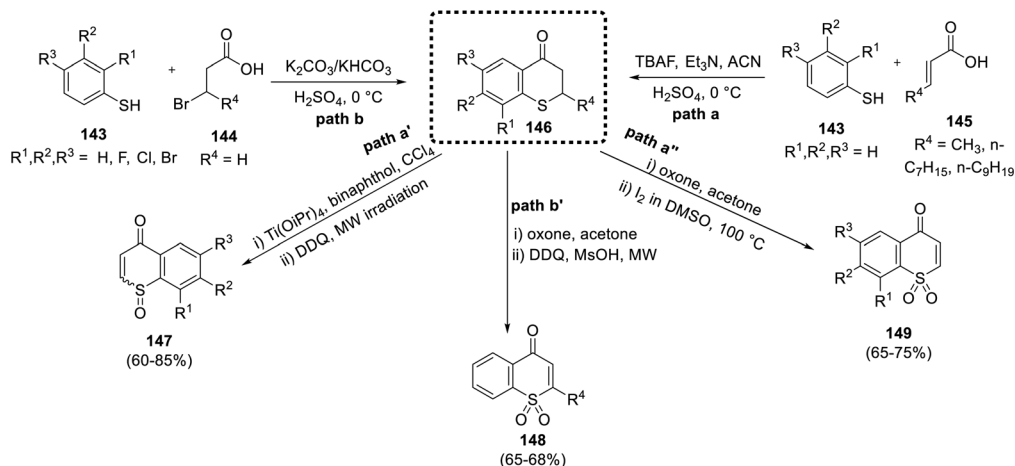


## (b) Synthesized molecules

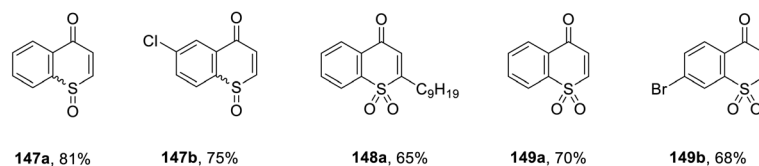


Scheme 36 (a) Polyphosphoric acid-mediated synthesis of thiochromenes; (b) synthesized molecules.

## (a) Mild base-catalyzed reaction of thiophenol to thiochromenone



## (b) Select examples



Scheme 37 (a) Mild base-catalyzed reaction of thiophenol to synthesize thiochromenones; (b) select examples.

the presence of a non-activated C–S bond, which underwent cleavage in the presence of a catalyst and was subsequently difunctionalized to generate the thiochromene scaffold (171). In contrast, the use of unsymmetric diynes led to the gene-

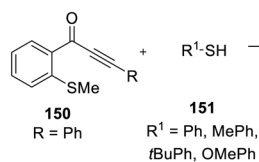
ration of a regioisomeric mixture of the product in lower yields (34%). Exploration of the synthetic scope of this work revealed the uniqueness of this substrate in undergoing self-coupling to produce thiochromene entities (172) when the



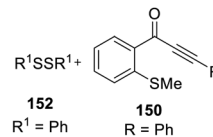


## (a) HAT-mediated synthesis of thiochromene

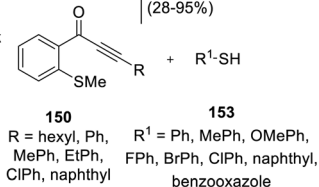
Song's work:



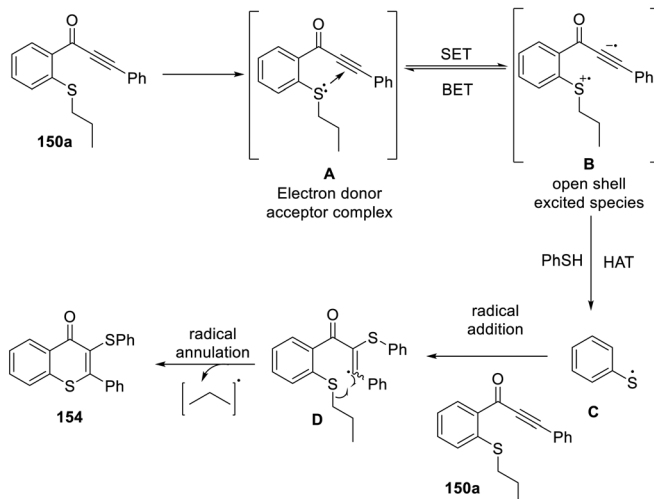
Zhao's work:



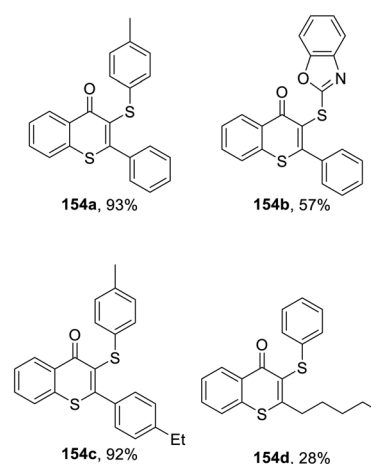
Bartz's work



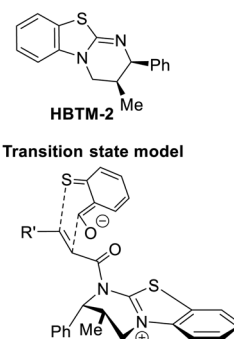
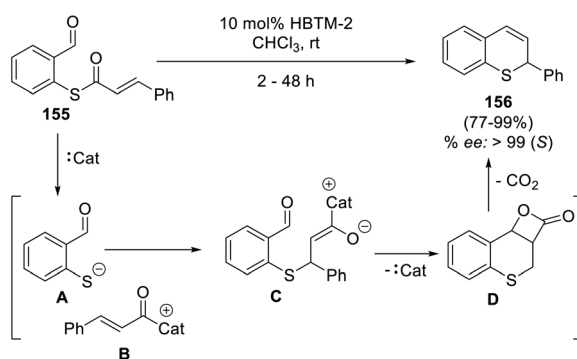
## (b) Mechanism



## (c) Select examples



Scheme 38 (a) Hydrogen Atom Transfer (HAT)-mediated synthesis of thiochromenes; (b) mechanism of cyclization; (c) select examples.



Scheme 39 Homobenzoetetramisole (HBTM-2) catalyzed synthesis of thiochromenes.

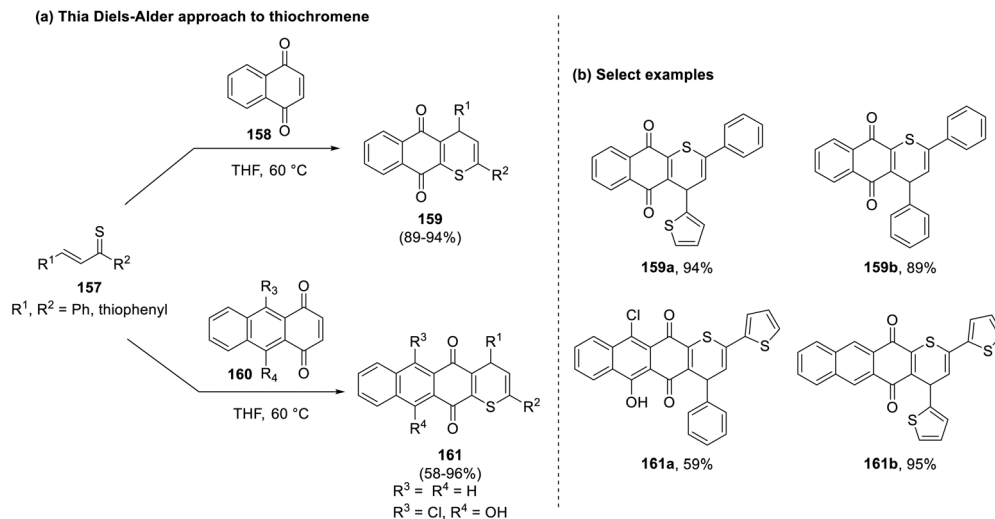
employed Ni-catalyst was reduced *in situ* during the reaction (Scheme 43).

Virumbrales *et al.*, in 2022, also focussed on the development of indenothiochromenes (174) by the use of a

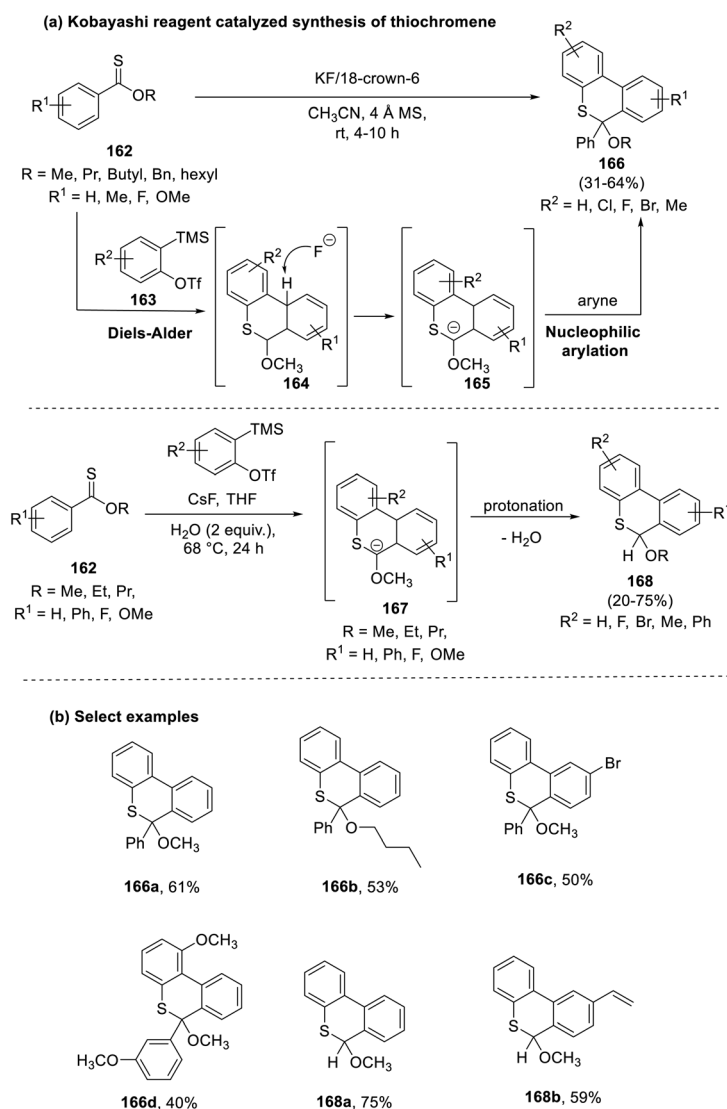
cyclopropyl gold catalyst.<sup>78</sup> The thio analog of (*E*)-(alkynyl)-styrene (173), used as a substrate for this reaction, participated in a cascade process wherein the styrene underwent intramolecular rearrangement and subsequent cyclization







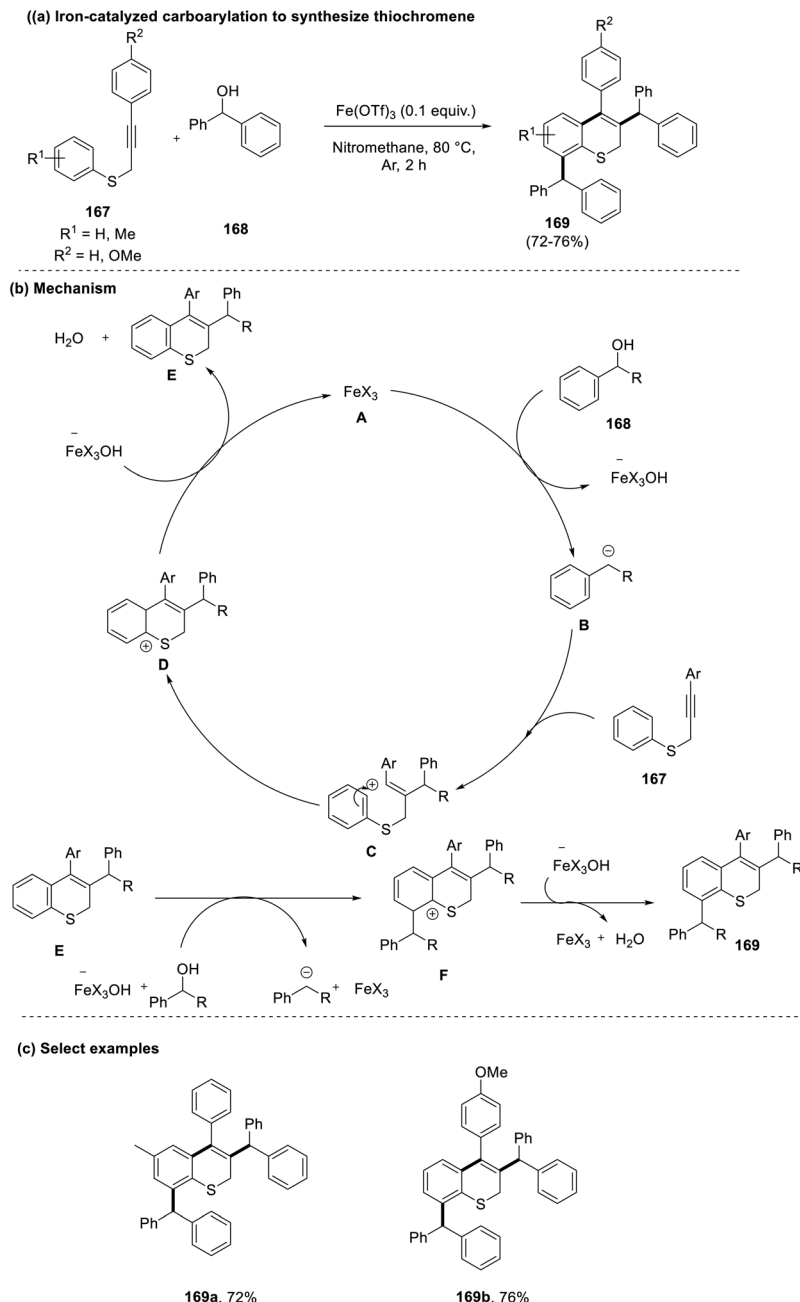
Scheme 40 (a) Thia-Diels-Alder approach to thiochromene synthesis; (b) select examples.



Scheme 41 (a) Kobayashi's reagent catalyzed synthesis of thiochromenes; (b) select examples.







**Scheme 42** (a) Iron-catalyzed carboarylation to synthesize thiochromenes; (b) mechanism involved; (c) select examples.

by following the Friedel-Crafts pathway. The use of the cyclopropyl gold catalyst with the *Z*-configuration of the substrate, however, led to the formation of diastereoisomers (dr value: 1:1.6 to 4:1) (Scheme 44).

## 2. Functionalization of thiochromenes

Mahato *et al.*, in 2017, reported a mild [3 + 2] cycloaddition reaction for the synthesis of thiochromenones bearing an

oxime functionality (178) from thiocoumarin (176) and styrenes (177).<sup>79</sup> The reaction tolerated a wide range of substituents in both substrates and proceeded *via* a regioselective annulation as sulfur serves as a better nucleophile in contrast to its oxygen counterpart, as the former has a larger size and better polarizability. Furthermore, the final product was utilized as the synthon for Beckmann rearrangement and Semmler-Wolf type reactions to generate the corresponding products (179 and 180), as shown in Scheme 45.

The late-stage functionalization of thiochromenones attempted by Barakat's group in 2021 further explored the syn-

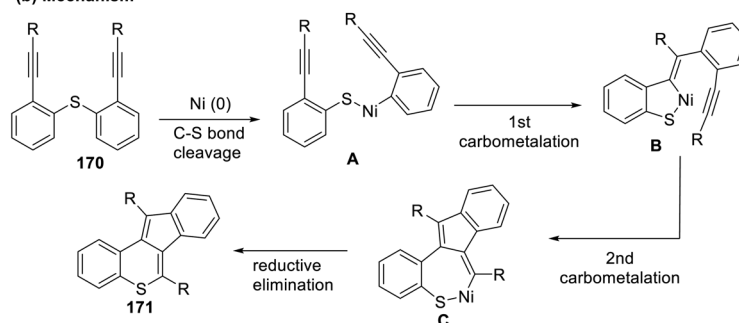




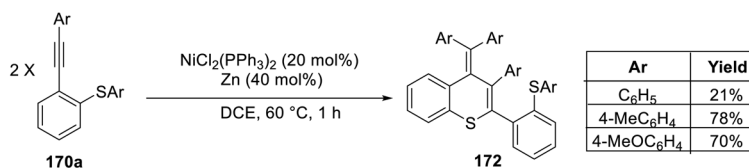
## (a) Nickel-catalyzed carbosulfuration to thiochromene



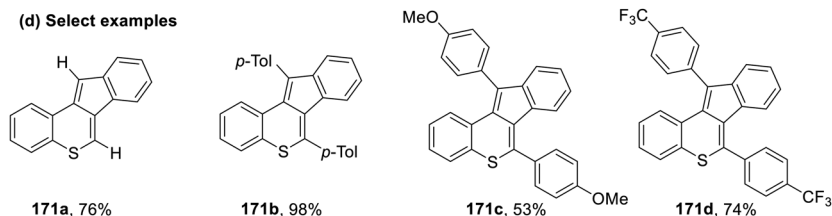
## (b) Mechanism



## (c) Synthetic application



## (d) Select examples



**Scheme 43** (a) Nickel-catalyzed carbosulfuration to synthesize thiochromenes; (b) mechanism involved; (c) synthetic application; (d) select examples.

thetic utility of these reactions.<sup>80</sup> In particular, the synthetic transformation of a natural compound, D-10-camphorsulfonyl chloride (**183**), was facilitated using the previously optimized reaction conditions to generate a thiochromenone-bearing derivative (**185**), as shown in Scheme 46.

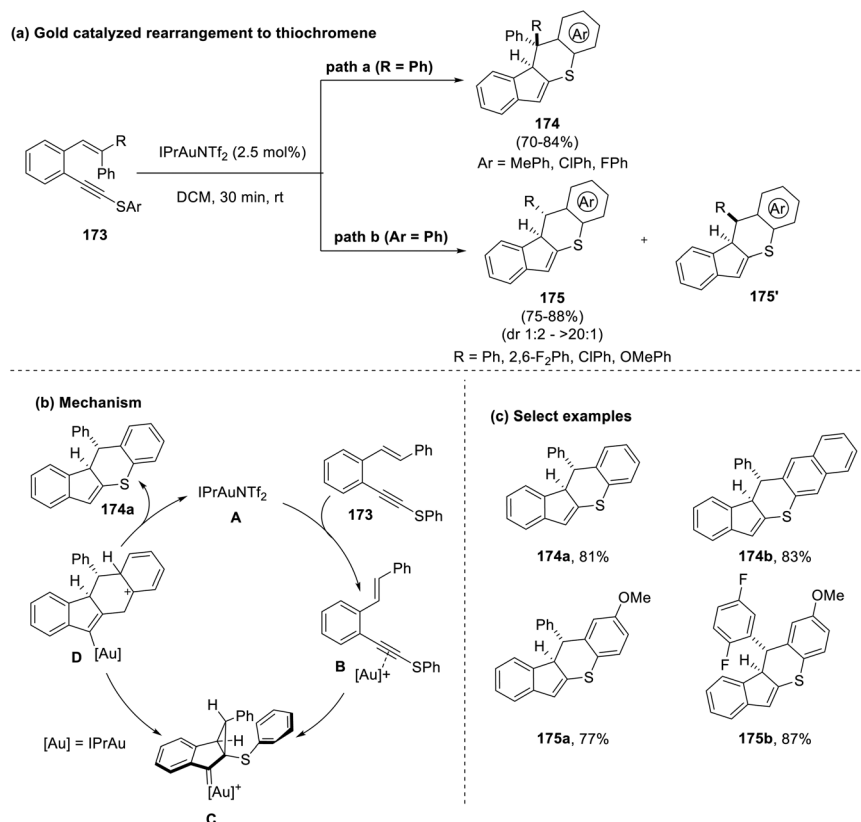
Barakat *et al.*, in 2021, devised a 1,3-dipolar cycloaddition approach for the synthesis of thiochromenones tethered with a spiroindole motif (**188**) in a wholly stereoselective and regioselective manner.<sup>81</sup> This reaction used L-proline as the catalyst, which initially reacts with isatin (**187**) to yield a cyclic lactone (**A**), which then undergoes cycloaddition with the chalcone (**186**) in a *trans*-selective manner to minimize the steric repulsion that usually arises when the carbonyl groups of isatin are *cis* to the chalcone moiety. The molecular electron density theory study also validated this unique *ortho*-*endo*-selective

nature of the reaction carried out by the same group in the year 2023 (Scheme 47).<sup>81</sup>

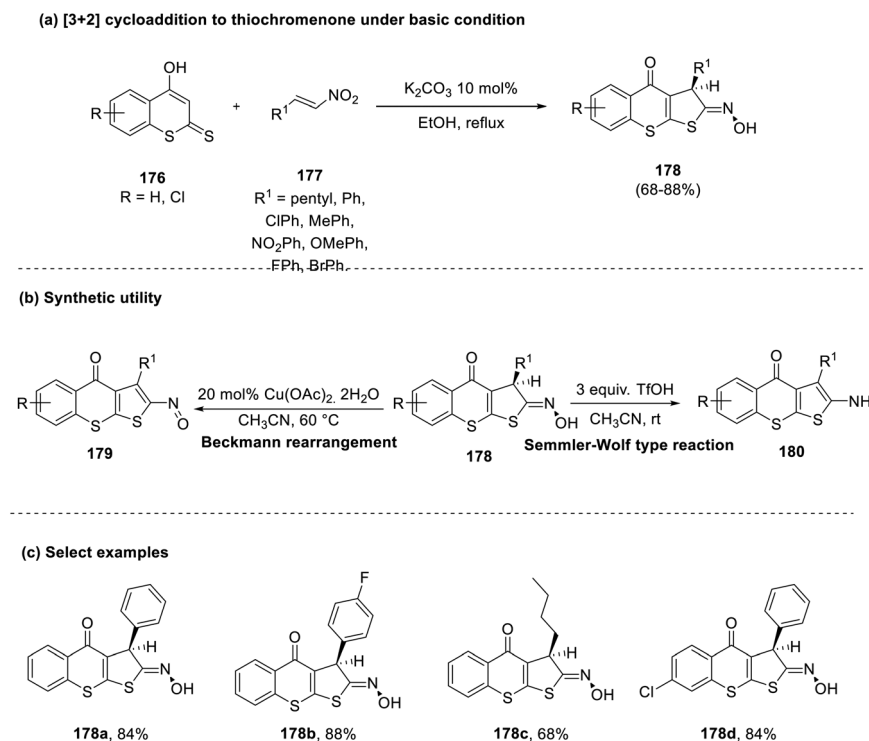
Das *et al.*, in 2022, ventured into the development of novel protocols for actualizing double intramolecular cyclization in a one-pot, atom-economical manner to attain polycyclic benzo-fused systems (**190**).<sup>82</sup> The use of thiobutanal with boron trifluoride etherate (**189**) smoothly delivered the products in good yields with the exception of substrates bearing halogens in the *ortho* position, as the inductive effect of the latter reduced the reactivity of the *S*-aryl ring for double cyclization. In addition, the presence of the *m*-methoxy functionality also served to highlight an anomaly as this substrate gave rise to a mixture of regioisomers that could not be separated (10:1). Mechanistic investigation revealed the formation of a carbenium ion, which depicted three possible conformational







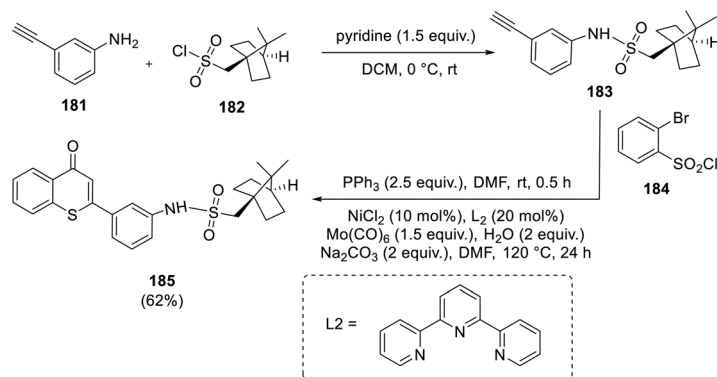
**Scheme 44** (a) Gold-catalyzed rearrangement to synthesize thiochromenes; (b) mechanism involved; (c) select examples.



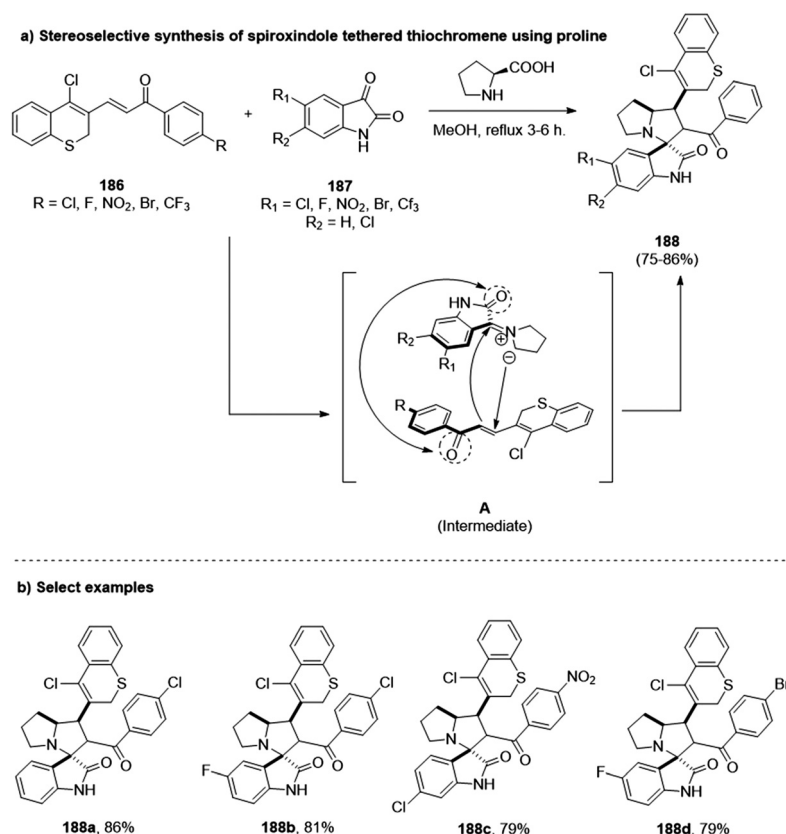
**Scheme 45** (a) [3 + 2] Cycloaddition to synthesize thiochromenones under basic conditions; (b) synthetic application; (c) select examples.







**Scheme 46** Late-stage functionalization of D-10-camphorsulfonyl chloride.



**Scheme 47** (a) Stereoselective synthesis of spiroindole tethered thiochromenes using proline; (b) select examples.

isomers, one *trans* and two *cis* forms; despite the existence of three conformers, the *cis*-fused axial conformer (**D'**) with enhanced hyperconjugative stabilization triumphed over the other two due to its minimal energy requirement for cyclization and the absence of the 1,3-allylic strain witnessed in the *trans*- and *cis*-conformers (equatorial) (Scheme 48).

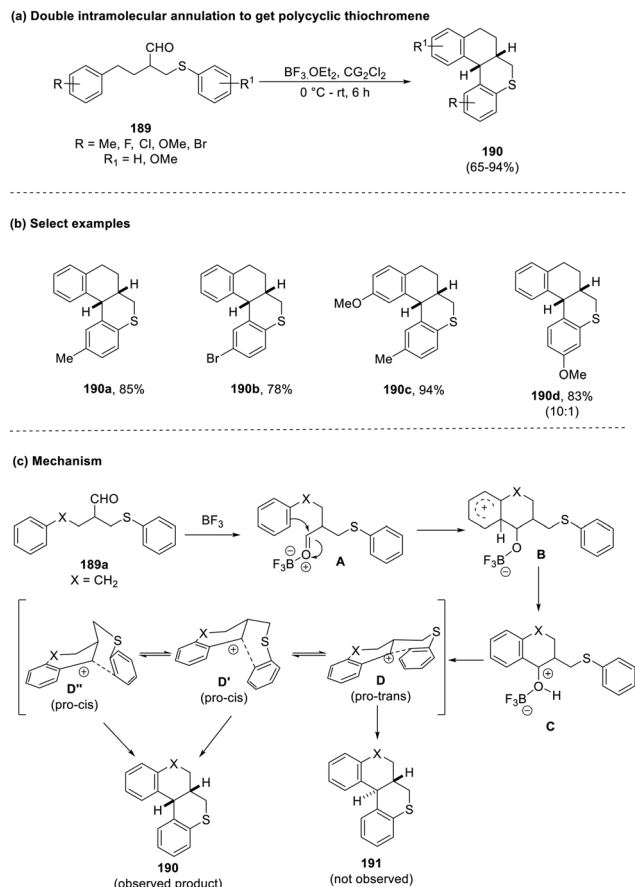
Etsè and co-workers in 2021 designed a series of thiochromane dioxides (**195** and **196**), which were envisioned to be the bio-isosteric replacement of nitrogen in the thiadiazine ring to explore the bioactive potential of this scaffold.<sup>83</sup> To attain this,

thiochromanone (**192**) was reacted with a Grignard reagent, dehydrated, and subsequently oxidized to generate the final product (**195** and **196**). During this reaction, palladium on carbon was used for hydrogenation in the final step to generate the final product. However, this Pd/C hydrogenation condition rendered the reaction with the use of the chloro-substituted substrate, aiding in removing the chlorine atom (Scheme 49).

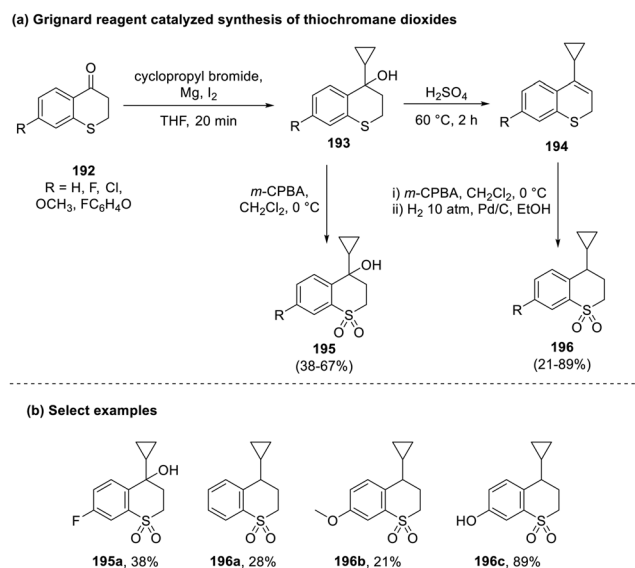
Recently, in 2024, Ali *et al.* explored the thia-Michael addition reaction of hydroxyl thiocoumarin (**197**) with cinn-







**Scheme 48** (a) Double intramolecular annulation to obtain polycyclic thiochromenes; (b) select examples; (c) mechanism involved.



**Scheme 49** (a) Grignard reagent catalyzed synthesis of thiochromane dioxides; (b) select examples.

maldehyde (**198**) using an organocatalyst (L-proline) to synthesize novel thiopyranthiochromenone products (**199**) in a one-pot reaction.<sup>84</sup> This reaction proceeded in the presence of

protic solvents while using aprotic non-polar solvents hindered the reaction. Furthermore, the reaction showed excellent compatibility with cinnamaldehyde substituted with electron-donating functionalities yet failed to proceed when they were replaced with electron-withdrawing groups. Mechanistic investigation proposed the abstraction of a proton from hydroxythiocoumarin by the zwitterionic form of proline to form a nucleophile (**B**) that tautomerizes to form **B'** and reacts with cinnamaldehyde (**198**) to form a Mannich intermediate (**D**) which finally undergoes ring cyclization to yield the product with the removal of proline (Scheme 50).

### 3. Conclusion

Various approaches have been explored, ranging from catalytic asymmetric reactions to aryne-chemistry-based reactions, for constructing a diverse portfolio of thiochromene derivatives. In the past decade, thiol surrogates have been extensively explored with newer alternatives like disulfides, thionoesters, and thioamides, aiding in developing cleaner reaction outcomes with minimal by-product generation, as discussed earlier. Concurrently, several greener methodologies have also been accomplished, highlighting greener catalysts like iron catalysts for the chemoselective synthesis of benzothiochromenes or D-glucosamine to drive the sustainable synthesis of thiochromene-4-imines. In addition to these noteworthy improvements, chalcones might be involved in improving atom economy as reactions employing these substrates have resulted in higher yields of up to 95%. Furthermore, this review also emphasizes that while the use of expensive metal catalysts like gold and rhodium is beneficial, relatively more straightforward reaction conditions employing *p*-toluene sulfonic acid, tetramethyl guanidine, PPh<sub>3</sub>, or potassium iodide offer a more practical approach for synthesizing the desired thiochromene derivatives.

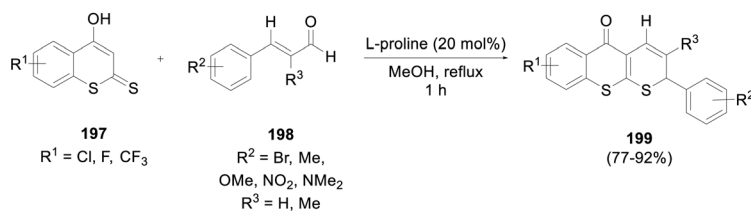
Despite the advancement in synthetic chemistry, the synthesis of thiochromenes can be streamlined and optimized even further. Given the importance of heterocyclic molecules in developing phytopharmaceuticals, synthetic methods to obtain enantioenriched thiochromenes as intermediates during complex natural product development require further work, as only one such work has been reported. Moreover, despite the exploration of metal catalysts and phase transfer catalysts, the use of enzyme catalysis, sonochemical methods, ionic liquids, and electrochemical catalysis still needs to be explored and, therefore, needs more attention. In addition, while several protocols attempted in this area show good substrate compatibility, specific methods suffer from limited substrate scope, emphasizing the need for newer reactions to diverge this aspect.

While the synthesis of thiochromenes has made strides in the recent decade, ample opportunities for refining and optimizing synthetic methodologies still exist. Therefore, the continued exploration of the design of eco-friendly and diverse

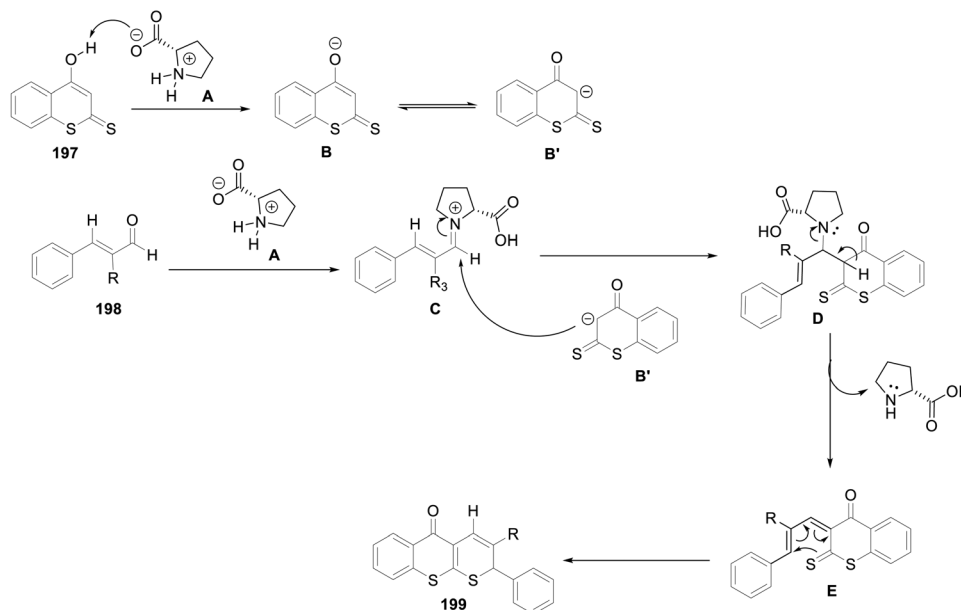




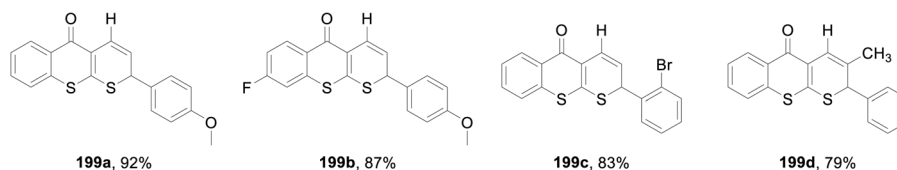
## (a) Proline catalyzed synthesis of thiopyranothiochromene from thiocoumarin



## (b) Mechanism



## (c) Select examples



**Scheme 50** (a) Proline catalyzed synthesis of thiopyranothiochromene from thiocoumarin; (b) mechanism involved in ring cyclization; (c) select examples.

catalytic approaches holds the potential to advance the synthetic methods of thiochromenes and their derivatives.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review titled "Recent Developments in Thiochromene Chemistry".

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

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