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Catalytic Synthesis of 2H-Chromenes

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ABSTRACT: 2H-Chromenes (2H-1-benzopyran derivatives) display a broad spectrum of biological activities. The 2H-chromene substructure is an important structural motif present in a variety of medicines, natural products, and materials showing unique photophysical properties. Hence, the structural importance of the benzopyran moiety has elicited a great deal of interest in the field of organic synthesis and chemical biology to develop new and improved synthesis of these molecular skeletons. This review gives an up-to-date overview of different catalytic methodologies developed for the synthesis of 2H-chromenes and is structured around the three main approaches applied in catalytic 2H-chromene synthesis: (I) catalysis with (transition) metals, (II) metal-free Bronsted and Lewis acid/base catalysis, which includes examples of nonenantioselective organocatalysis, and (III) enantioselective organo-catalysis. The section in which the metal-catalyzed reactions are discussed describes different ring-closing strategies based on (transition) metal catalysis, including a few enantioselective approaches. For most of these reactions, plausible mechanisms are delineated. Moreover, synthesis of some natural products and medicinally important drugs are included. Specific advantages and disadvantages of the several synthetic methodologies are discussed. The review focuses on catalytic 2H-chromene synthesis. However, for a complete overview, synthetic routes involving some stoichiometric steps and reactions producing ring-scaffolds that are closely related to 2H-chromenes are also included.

KEYWORDS: 2H-chromenes, heterocycles, catalysis, metal-mediated, organo-catalysis, enantioselective, ring-closure, ortho-quinone methide

INTRODUCTION

Heterocycles are a broad spectrum of organic compounds and classifications. They are indispensable structural motifs not only because of their biological relevance but also given their diverse applications. Especially in medicinal chemistry and chemical biology, heterocycles are used extensively as valuable synthetic organic building blocks. Among the various classes of heterocyclic compounds, 2H-chromenes (2H-1-benzopyran derivatives) are present in a vast number of natural products (e.g., tannins and polyphenols found in teas, fruits, and vegetables), are used as building blocks in the synthesis of a variety of bioactive compounds, and find application as photochromic materials for a variety of applications. The 2H-chromene skeleton is an important substructure in a wide range of bioactive heterocyclic compounds showing anticancer, antioxidant, anti-inflammatory, antitubercular, antiviral, antitumor, antibacterial/antimicrobial, antidiabetic, anticoagulant, antianaphylactic, diuretic, fungicidal, and anti-HIV activity; additionally, other 2H-chromene compounds act as sex-pheromones, are activators of potassium channels, or inhibit the enzymes phosphodiesterase IV and dihydrofolate reductase (Figure 1). Furthermore, 2H-chromenes find interesting applications as photochromic materials, and they have been extensively used in diverse fields including laser dyes, organic light emitting devices (OLEDs), optical brighteners, organic scintillators, triplet sensitizer, fluorescence probes, and many more (Figure 2). They even play a key role as a regulator of numerous biopolymers.

The diverse array of biological activities of 2H-chromene-containing compounds and the structural importance of benzopyran moiety has elicited a great deal of interest in the field of organic synthesis and chemical biology to develop new and improved synthesis of these molecular skeletons. This review gives an up-to-date overview of different catalytic methodologies developed for the synthesis of 2H-chromenes. The number of publications on this issue is growing rapidly, especially over the past few years. This review is structured around the three main approaches applied in catalytic 2H-chromene synthesis: (I) catalysis with (transition) metals, (II) metal-free Bronsted and Lewis acid/base catalysis, which includes a few examples of nonenantioselective organocatalysis, and (III) enantioselective organo-catalysis. First the

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Metal-catalyzed reactions are discussed, then the metal-free catalytic reactions are described, and finally enantioselective organocatalytic approaches to functionalized 2H-chromene derivatives are recapitulated. The synthetic reactions along with plausible mechanistic aspects of the described 2H-chromene syntheses are discussed. Moreover, synthesis of some natural products and medicinally important drugs are included. Although the review focuses mainly on catalytic approaches toward 2H-chromenes, here and there a few reactions containing one or more stoichiometric steps are included, as well as a few reactions producing different ringscaffolds that are closely related to 2H-chromenes. We considered these examples important to provide a more complete overview of the field.

1. METAL-MEDIATED APPROACHES

Metal ions play a key role in bringing about different useful chemical transformations which are otherwise difficult or in some cases impossible to achieve. Over the years, different metal catalysts were successfully employed in the synthesis of 2H-chromenes. An up-to-date overview of the different metal catalyzed/mediated methodologies for chromene synthesis is presented in section 1 of this review.

1.1. Copper-Catalyzed 2H-Chromene Synthesis. 1.1.1. Recently, Liu and co-workers reported a copper-promoted...
Scheme 2. Proposed Mechanism of the Copper(II)-Promoted Synthesis of Isochromeno-[3,4-b]Chromenes

Scheme 3. Synthesis of 2H-Chromenes by Fe-Catalyzed Intramolecular Alkyne-Carbonyl Metathesis

Scheme 4. Proposed Mechanism of Fe-Catalyzed 2H-Chromene Synthesis Involving Intramolecular Alkyne-Carbonyl Metathesis

Scheme 5. 5H-Naphtho[1,2-c] Chromenes via Fe-Mediated [3 + 3]-Annulation

Scheme 6. Conversion of 8 to 9 and 10 to 11

tandem reaction of internal alkylnol and salicyl-N-tosylhydrazone to produce isochromeno[3,4-b]chromene (Scheme 1). This methodology works best with copper(II) perchlorate as the catalyst in a toluene/dioxane (1:4) solvent mixture at 60 °C. The reaction was found to work with a variety of substrates, both with respect to salicyl-tosylhydrazone and alkynols. Salicyl tosylhydrazone containing electron-donating or electron-withdrawing groups like Cl, Br at ortho, meta, or para position are effective. However, strong electron-withdrawing groups like a nitro moiety at the para position with respect to the hydroxy group makes the reaction sluggish. A naphthalene-based substrate generated the corresponding chromene in only 52% yield, whereas disubstituted substrates hampered the formation of the desired products; 3,5-disubstituted salicyl-N-tosylhydrazone produced the corresponding chromene only in 45% yield. Internal alkynols bearing electron-donating or -withdrawing groups at para or meta positions also react well, affording the chromene products in moderate to high yields. Naphthyl and 4-pentyphenyl alkynols are also tolerated, although leading to
quite low yields of the corresponding chromenes. Internal alkynols containing nonbenzenoid bridges such as cyclopentene and cyclohexene also produced the desired chromenes in 36% and 41% yields, respectively. However, the reaction does not proceed at all with alkynols substituted with an alkyl group like hexyl or an alkenyl group like 1-cyclohexene.

The proposed mechanism is outlined in Scheme 2. The reaction is suggested to proceed via an initial activation of the alkyne by \( \text{[Cu(ClO}_4\text{)]_2.6H}_2\text{O} \), which enhances the electrophilicity of the alkyne. In the next step, intramolecular addition of the hydroxyl group to the electron-deficient alkyne produces the vinyl-copper intermediate 1-B. Notably, in the presence of 3 equiv of tBuOK or Cs\(_2\text{CO}_3\), no chromene formation was observed. Moreover, the desired chromene was obtained in a lower yield when salicylaldehyde was used instead of salicyl-N-tosylhydrazone under optimal conditions. On the basis of these experimental findings, it was proposed that the intermediate 1-B is trapped by 2 to produce the intermediate 1-C rather than by a diazo compound generated in situ by the deprotonation of 2. The intermediate 1-D is then formed after the acetalization with subsequent release of a proton. Finally, cleavage of the carbon–copper bond followed by acid-promoted elimination of TsHNHN\(_2\) is proposed to produce the desired isochromeno-[3,4-b]chromene 3 with regeneration of the catalyst.

1.2. Iron-Catalyzed 2H-Chromene Synthesis. 1.2.1. In 2011, Jana and co-workers developed a catalytic methodology
for the synthesis of 3-substituted 2H-chromenes via an iron-catalyzed intramolecular alkyne-carbonyl metathesis reaction. The 3-substituted 2H-chromenes were obtained in high yields from the simple alkyne ethers of salicyaldehyde in the presence of 15 mol % FeCl₃ as catalyst in acetonitrile (Scheme 3). The intramolecular alkyne-carbonyl metathesis proceeds smoothly with a variety of substituents on the aromatic ring and on the alkyne affording the desired 3-substituted chromenes in high yields. Notably, the incorporation of Cl, Br, OMe, and Ph groups in salicylaldehyde does not alter the yield of the products. Reactions with naphthalene and biphenyl systems produced the corresponding chromenes in good yields. Alkyl-substituted alkyynes were also found to be suitable for this
reaction, but simple propargyl ethers with terminal alkyne units were unreactive.

A plausible mechanism, as proposed by the authors, is depicted in Scheme 4. The reaction is suggested to proceed via a [2 + 2] cycloaddition. Initially the carbonyl group is activated by coordination to the FeCl₃ catalyst, followed by nucleophilic attack of the terminal alkyne unit. The resulting enediyne intermediate undergoes intramolecular [2 + 2] cycloaddition to form a dihydroisoquinoline product.
attack of the alkyne on the aldehyde producing oxetene intermediates 1.2.1-C via the vinyl-cation intermediates 1.2.1-B. Finally, the 2H-chromenes 5 are formed via an electrocyclic ring-opening of the oxetene intermediates 1.2.1-C. Notably, the exact role of FeCl₃ in the process is yet to be understood in detail.

1.2.2. Recently, Li and co-workers reported an iron-mediated protocol for the synthesis of $\textit{SH}$-naphtho[1,2-$c$]chromenes using 2-(2-ethynyl) phenoxy-1-aryl ethanones in the presence of 1 equiv of FeCl₃ and 1 equiv of TMSCl at 100 °C in toluene (Scheme 5). The reaction proceeded following a [3 + 3] annulation strategy. Substrates bearing a three-membered carbocyclic ring on the alkyne participated in this [3 + 3] annulation. Substrates containing different substituents (formyl, methoxy, cyano, and halo groups) on both aromatic rings of 6 were found to be suitable for this reaction. Notably, substrates containing $p$- or $m$-methyl groups in the benzene ring attached to the carbonyl afforded only moderate yields of the desired chromenes.

Surprisingly, the reaction with substrate 8 containing a cyclobutane substituent on the alkyne gave a Friedel–Crafts alkylation product rather than the expected chloro ring opened product. The later has been observed in the product (X = Cl). The mechanism involves the initial activation of the alkyne by FeCl₃, followed by nucleophilic attack of the carbonyl on the activated alkyne. This leads to the formation of intermediate 1.2.2-B (Scheme 7). Subsequent electrophilic addition of the vinyl moiety to the aromatic ring is followed by ring-opening of the cyclopropane ring to produce intermediate 1.2.2-C. Finally, the products 7 (X = Cl) were obtained via nucleophilic addition along with concomitant dehydroxylation and rearrangement. Notably, no further intramolecular Friedel–Crafts alkylation was observed in the product (X = Cl).

1.2.3. Using FeCl₃ as catalyst, Li and co-workers developed a sustainable, environmentally friendly, regioselective intramolecular hydroaryloxylation protocol for the synthesis of densely substituted chromenes starting from 2-propargyl phenols and naphthols (Scheme 8). It is noteworthy that during metal-mediated hydroaryloxylation of propargyl phenols, usually five-membered rings are formed via an $\textit{exo}$-attack although according to Baldwin’s rules, both $\textit{exo}$-dig and $\textit{endo}$-dig are possible pathways in these types of reactions.

In the presence of aniline as additive, the best selectivity of benzopyran over the benzofuran was obtained. The six-membered heterocycles were obtained in good yields when 20 mol % iron(III)chloride catalyst and 2 equiv of aniline were used in the reaction mixture (Scheme 9). A variety of 2-propargylphenol and naphthol derivatives were found to produce the corresponding chromenes in good yields. Notably, the 6-$\textit{endo}$-dig mode of cyclization consistently predominated over the 5-$\textit{exo}$-$\textit{dig}$ mode of cyclization except for a few cases where both five- and six-membered rings were obtained.

1.3. 2H-Chromenes Synthesized from Chromium-Carbenes. In 2012, Wulf and co-workers reported a new route to synthesize 2H-chromenes from the reaction of an $\alpha\beta$-unsaturated Fischer-type carbene complex of chromium with a propargyl ether bearing an alkynyl group on the propargylic carbon (Scheme 10). This approach is noteworthy in that both rings of the chromene are generated in a single step.

The reaction of a chromium carbene complex with 3-siloxypent-4-en-1-ynes proceed via an initial benzannulation reaction that produces a chromium tricarbonyl complexed benzopyran over the benzofuran was obtained. The six-membered rings of the chromene are generated in a single step.

Unlike the mechanism proposed by Jana et al., this reaction mechanism involves the initial activation of the alkyne by FeCl₃, followed by nucleophilic attack of the carbonyl on the activated alkyne. This leads to the formation of intermediate 1.2.2-B (Scheme 7). Subsequent electrophilic addition of the vinyl moiety to the aromatic ring is followed by ring-opening of the cyclopropane ring to produce intermediate 1.2.2-C. Finally, the products 7 (X = Cl) were obtained via nucleophilic addition along with concomitant dehydroxylation and rearrangement. Notably, no further intramolecular Friedel–Crafts alkylation was observed in the product (X = Cl).
Notably, a chromium tricarbonyl complexed chromene can be isolated as the primary product of the reaction, which during the workup by an oxidizing agent loses the metal to produce the chromene (Scheme 11). The authors also extended the synthetic protocol for the synthesis of 2H-benzo[h]chromenes. To further extend the synthetic utility, racemic vitamin E was synthesized in overall 73% yield.

1.4. Cobalt-Catalyzed 2H-Chromene Synthesis. Recently, de Bruin and co-workers developed a new Co(II)(porphyrin) catalyzed synthetic route to 2H-chromenes. The reaction involves the use of salicyl-N-tosylhydrazones and terminal alkynes (Scheme 12). The synthetic protocol was found to tolerate a wide range of substrates, containing both electron-donating and -withdrawing substituents on both the salicyl-N-tosylhydrazones and the terminal alkynes.

The reaction proceeds via a metallo-radical activation of salicyl-N-tosylhydrazones by cobalt(II) complexes of porphyrins affording Co(III)-carbene radical intermediate 1.4.1-C. Subsequent radical addition of terminal alkynes produce salicyl-vinyl radical intermediates 1.4.1-D. Subsequent hydrogen atom transfer (HAT) from the hydroxy group of the salicyl moiety to the vinyl radical leads to the formation of 2H-chromenes. The proposed metallo-radical mechanism was further supported by EPR and DFT calculations. Notably, EPR spectroscopy and controlled radical-trapping experiments with TEMPO are in agreement with the proposed radical mechanism. Moreover, DFT calculations reveal the formation of the salicyl-vinyl radical intermediate by a metallo-radical-mediated process. However, the subsequent HAT from the hydroxy moiety to the vinyl radical leads to formation of an ortho-quinone methide intermediate (1.4.1-E), which dissociates spontaneously from the cobalt center. Finally, this ortho-quinone methide intermediate undergoes an endo-cyclic, sigmatropic ring-closing reaction to form the final 2H-chromene (Scheme 13). Notably, even in the presence of chiral porphyrin catalysts, no enantioselectivity was obtained.

1.5. Gold-Catalyzed 2H-Chromene Synthesis. Stratakis and co-workers synthesized 2H-chromenes form propargyl aryl ethers using Ph3P[AuNTf2] as a catalyst (Scheme 14). The reaction was found to be versatile, affording good to high yields with a wide variety of substituents consisting of both electron-rich and electron-deficient functional groups at 25 °C. Although the reaction rates with electron-deficient arenes are significantly slower, the corresponding chromenes were nonetheless obtained in excellent yields using slightly higher catalyst loadings (4 mol %) and elevated temperatures (70 °C). Notably, the yields of the densely substituted 2H-chromenes are high in comparison to that of unsubstituted 2H-chromenes. Moreover, in the cases of substrates bearing strong-electron-withdrawing groups (viz., NO2, CN, and CO2Me), 7% benzofuran was obtained in addition to the formation of the desired chromenes. The catalyst worked with high efficiency when the starting ether has an internal alkyne moiety. The reaction also proceeds smoothly for naphthyl ethers producing naphthopyran products in excellent yields, even when more hindered gem-dimethyl derivatives were used.
To showcase the applicability of this protocol, the synthesis of some chromene containing natural products was explored. Compound 24 (Precocene I) was prepared from the propargyl ether 23 and was obtained in a 3:1 ratio with its regioisomer 25. Notably, under thermal conditions (boiling in N,N-diethylani-line) the same reaction produced a 1:1 mixture of the two regioisomers. Similarly, the same catalyst produced exclusively 26 (Precocene II) from 23 in excellent yield. Xanthyletin 28 and Seselin 29 were also synthesized in a 40:60 ratio (Scheme 15).

Moreover, the authors have also used the same catalyst in the concise synthesis of the naturally occurring 2,2-dimethyl-8-prenyl chromene-6-propenoic acid 31 in 50% yield using five linear steps starting from p-iodophenol. The cycloisomerization step afforded the 2H-chromene 33 in almost quantitative yield (Scheme 16).

1.5.2. In a recent report, Aponick and co-workers disclosed a very effective Au(I)/AgOTf catalyzed protocol for the synthesis of a variety of chromenes via dehydrative endo-cyclization of o-(1-hydroxyallyl)phenols (Scheme 17). This reaction was carried out in refluxing THF for 5 h. Notably, other Lewis acids were found to be ineffective for this reaction.

The reaction was found to proceed smoothly with substrates containing both electron-donating and electron-withdrawing substituents, affording the corresponding 2H-chromenes in good yields. Introduction of substituents on the pyran-ring can also be easily achieved by using substituted alkenes. The method is quite general, except for the fact that inclusion of a dioxe-lane moiety fused to the benzene ring led to decomposition of the products.

1.5.3. Another gold catalyst, [(Ph3P)Au(Cl)] was used by Echavarren and co-workers for the synthesis 2H-chromenes via cycloisomerization reaction of aryl propargyl ethers (Scheme 18). Notably, a stoichiometric silver salt was required to activate the catalyst. The main drawback of this method is that the silver salts required for catalyst activation are often hygroscopic and frequently make the reaction medium acidic. On the other hand, the silver cocatalyst also promotes the unwanted side reactions. To overcome these drawbacks, Banwell and co-workers employed a commercially available catalyst 37 as a solution. Notably this catalyst is far more active than the previous catalyst, [(Ph3P)Au(Cl)] and it also does not require in situ activation by Ag+ salts.

The efficiency of this modified catalyst was examined on a variety of aryl propargyl ethers, and chromenes could be synthesized in high yields. In some cases, a mixture of benzopyrans and benzofurans formed as side products, lowering the 2H-chromene yields. However, this protocol lost some of its appeal since there was no definite relationship found between the structure of the starting compound and the selectivity in product formation.

1.5.4. Very recently, Wang and co-workers reported a gold(I)-catalyzed reaction of water with o-acetylenyl-substituted phenyldiazoacetates affording 1H-isochromene derivatives in good yields (Scheme 19). The reaction proceeds via insertion/cyclization cascade, which involves gold carbene formation followed by water O—H insertion and finally alcohol-alkyne cyclization. The electron-rich ligand coordinated gold(I)
complexes [(PMe₃)Au(Cl)] and [(IPr)Au(Cl)] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine) were found to be more effective in this reaction. Notably, [(IPr)Au(Cl)] produces the best results for both carbene transfer and cyclization. However, product 39 via 6-endo-dig cyclization and product 40 via 5-exo-dig cyclization were both obtained in nearly equal amounts in combined yield of 95%. Interestingly, in a mixture of H₂O and DMF (v/v = 1:1) the ratio of 39 to 40 increases to 4:1, with slightly diminished overall yield. Moreover, the overall yield decreases when carried out at a temperature higher or lower than 80 °C.

The proposed mechanism is depicted in Scheme 20. The reaction proceeds via a gold carbene intermediate 1.5.4-A, which inserts into the O−H bond of H₂O to form the chelating intermediate 1.5.4-B. Subsequently, 6-endo-dig attack of the Au(I)-activated triple bond produces the vinyl gold intermediate 1.5.4-C, which upon protonation produces the final desired 1H-isochromene 39 with regeneration of the catalyst.

1.6. Palladium-Catalyzed 2H-Chromene Synthesis. 1.6.1. Very recently, Scheidt and co-workers developed an enantioselective Pd-catalyzed 6-endo-trig reaction for the synthesis of 2-aryl-chromenes (Scheme 21). A monodentate phosphoramidite–palladium catalyst obtained from a TAD-DOL-derived ligand produced the 2-aryl-2H-chromenes with high yield and enantioselectivity under mild conditions. The reaction tolerates a wide variety of substituents affording the desired 2-aryl-chromenes in moderate to high yield with high enantioselectivity.
The allyl bromides react with reagents and a palladium-catalyzed intramolecular Heck asymmetric copper-catalyzed allylic substitution with Grignard enantioselective synthesis of chiral chromenes by combining magnesium bromide in CH2Cl2 in the presence of catalytic intermediate (nucleophilic phenoxide in situ via deacylation) with either enantiomer of the proximal phenoxide to produce the desired chromene generation is claimed to be faster than addition of the π-allyl intermediate (1.6.1-C), after bond rotation, gets attacked by the proximal phenoxide to produce the desired chromene. Notably, for this pathway the trans-ortho-quinone methide formation is claimed to be faster than addition of the palladium–ligand complex to 1.6.1-A (or 42). Another alternative pathway involving the generation of diastereomeric π-allylpalladium complexes (1.6.1-C or 1.6.1-C’) from each enantiomer of 41 was also discussed. However, on the basis of experimental results, coupled with the available literature data, Path A was proposed to be most relevant under the experimental conditions. More extensive research is needed to distinguish between either one of these plausible mechanistic pathways.

1.6.2. In 2012, Feringa and co-workers reported a highly enantioselective synthesis of chiral chromones by combining asymmetric copper-catalyzed allylic substitution with Grignard reagents and a palladium-catalyzed intramolecular Heck reaction. The allyl bromides 43, when subjected to methylmagnesium bromide in CH3Cl2 in the presence of catalytic amounts of CuBr2 and LiBr, were proposed. Intermediate 44 was observed. Surprisingly, under slightly modified reaction conditions (compound 44 in a molten mixture of tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAAC) as the base under ligand-free conditions) affords the cyclized product 46 in excellent yields with high enantioselectivity; only 4% of isomerization of the double bond to the internal position was observed.

1.6.3. 4-Substituted-3-bromo-2H-chromenes were synthesized via a simple cyclization reaction of simple aryl propargyl ethers using Pd(OAc)2 as catalyst with stoichiometric quantities of CuBr2 and LiBr. Using this reaction protocol, a variety of benzopyranes with bromine at the 3-position and different alkyl and aryl groups in the 4-position could be synthesized in good yields (Scheme 25). To extend the substrate scope, the method was applied to a variety of naphthopyrans in a similar way starting with naphthyl propargyl ethers.

Notably, both [Pd(OAc)2] and [CuBr2] are essential for this reaction to work at all, whereas the presence of LiBr makes the reaction more efficient and selective. The proposed mechanism involves the activation of the alkyne via coordination to palladium(II), followed by cyclization to form the intermediate 1.6.3-B. Starting from this intermediate, two plausible pathways were proposed. Intermediate 1.6.3-B may convert to palladium(IV) intermediate 1.6.3-C, which by reductive elimination converts to the desired 2H-chromene 49. On the other hand, it is also possible that the oxidation state of palladium remains unaltered and that product 49 is formed from intermediate 1.6.3-D by Cu(II)-assisted ligand transfer (Scheme 26). The latter process could involve homolysis, disproportionation, and/or bromide radical transfer.

Two plausible mechanisms (Path A and Path B) for this particular reaction are displayed in Scheme 22. The reaction is believed to proceed with the reaction of either enantiomer of 41 with potassium carbonate and methanol producing the nucleophilic phenoxide in situ via deacylation (1.6.1-A, Path A). In the next step, ejection of the secondary acetate forms the achiral trans-ortho-quinone methide (π-QM, 1.6.1-B). Subsequent coordination of the chiral catalyst derived from ligand complex to the π-allyl intermediate (1.6.1-C). The π-allyl intermediate (1.6.1-C), after bond rotation, gets attacked by the proximal phenoxide to produce the desired chromene 42. Notably, for this pathway the trans-ortho-quinone methide formation is claimed to be faster than addition of the palladium–ligand complex to 1.6.1-A (or 42). Another alternative pathway involving the generation of diastereomeric π-allylpalladium complexes (1.6.1-C or 1.6.1-C’) from each enantiomer of 41 was also discussed. However, on the basis of experimental results, coupled with the available literature data, Path A was proposed to be most relevant under the experimental conditions. More extensive research is needed to distinguish between either one of these plausible mechanistic pathways.

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1.6.4. Hu and co-workers synthesized poly substituted furo[3,2-c]chromenes 53 via a palladium catalyzed multi-component reaction involving 1,4-addition and cyclization cascade.20 This method requires three precursors including 3-(1-alkynyl)chromones 50, aryl iodides 51, and alcohols 52. The reaction proceeds smoothly at 45 °C in the presence of Pd2(dba)3 catalyst (10 mol %), DIPEA as base and DMF as solvent. The corresponding furan-fused chromenes were obtained in moderate to good yields. It was observed that an aryl iodide containing electron-withdrawing groups are favored because of a faster oxidative addition step. Electron-donating groups on the alkyne of the chromone precursor increase the product yield considerably, and electron-withdrawing groups have a negative effect (Scheme 27).

The proposed mechanism involves the oxidative addition of aryl iodide to palladium to produce an aryl-Pd(II) species, which in the subsequent step activates the chromones C=O and promote the 1,4-addition of alcohol. In the next step, palladium migrates to the alkyne to give intermediate 1.6.4-D. Thus, the alkyne also gets activated. The intermediate 1.6.4-D undergoes cyclization to produce the intermediate 1.6.4-E, which upon reductive elimination produced the desired chromenes 53 with the regeneration of Pd(0) (Scheme 28).

1.6.5. Substituted chromenes like 2,2-dialkyl-2H-chromenes with an aryl or a vinyl substituent at the 4-position were synthesized from the readily available tertiary 3-(o-bromophenyl) propynols via a hydroarylation/C–O coupling reaction sequence mediated by a palladium-catalyst (Scheme 29).21 [Pd(OAc)2] was used as the catalyst. The cyclization step proceeds through an intramolecular Buchwald–Hartwig C–O bond forming reaction. Reaction with different types of aryl iodides, vinyl triflates, and propynols produced the corresponding chromenes and spirochromenes in moderate yield.

Because both steps involve a palladium catalyst, attempts were made to simplify the overall reaction. At the beginning, the reaction was carried out at the optimized hydroarylation conditions, but no cyclization was observed even after prolonged reaction times or even at higher reaction temperatures. Combination of cyclization and hydroarylation also failed to give the desired products. However, it was found that simply omitting the workup between two steps led to the expected chromene product in good yield. It was obvious from this observation that addition of fresh [Pd(OAc)2] was necessary for the second step to give good yields of the desired chromenes. This is probably because of the irreversible precipitation of the majority of the catalyst in the first step.

Because chloride ions stabilize low-ligated Pd(0) species, 1 equiv of Bu4NCl was added at the beginning instead of the addition of fresh [Pd(OAc)2] after the first step, and the reaction seemed to work nicely. However, as a generalized procedure, the reaction required the presence of Bu4NCl and the addition of fresh [Pd(OAc)2], NaOBU and dpff in the second step.

1.6.6. Pan et al. reported the synthesis of 6H-naphtho[2,3-c]chromenes by a palladium-catalyzed reaction of 2-haloaryl...
allene 59 with 2-alkynylphenol 60 (Scheme 30). This transformation proceeds efficiently with excellent chemoselectivity and regioselectivity. The reaction between phosphonated 2-bromoaryl allene 59 and 2-(phenylethynyl)-phenol 60 proceeds most efficiently in the presence of Pd(dppf)Cl2 as catalyst in dioxane solvent, affording the desired chromene 61 in 67–93% yield.

The proposed mechanism is shown in Scheme 31. The first step proceeds via an oxidative addition to afford Pd(II) species 1.6.6-A. In the next step insertion of Pd(II) takes place into the triple bond of 2-alkynylphenol, which eventually produces the vinyl palladium(II) intermediate 1.6.6-B. Regioselective intramolecular coordination followed by insertion of Pd(II) into the double bond of the allene produced the intermediate 1.6.6-C. Finally, the desired chromene 61 was formed via base promoted C–O bond formation with subsequent release of Pd(0), which re-entered the catalytic cycle.

1.6.7. Malinakova and co-workers disclosed a polymer-supported palladacycle mediated 2H-chromene synthesis (Scheme 32). The palladacycles 62, attached to a variety of resins, were found to react with dimethyl acetylene dicarboxylate (DMAD) 63 in DCE to afford the 2H-chromene 64. Notably, the yield of the 2H-chromene obtained via this method was found to be superior to those of analogous solution phase reactions. Small amounts of the 4H-chromene 65 as a side-product was also detected. Under the applied reaction conditions, in the presence of high local concentrations of the phosphine and the palladacycle at elevated temperature, the main 2H-chromene product possibly isomerizes to the detected 4H-chromene side-product.

1.7. Gallium-Catalyzed 2H-Chromene Synthesis. A multicomponent one-pot approach for the synthesis of naphthopyrans was reported by Yadav and co-workers, using gallium(III) chloride as a catalyst which allows the coupling of naphthol, alkynes, and aldehydes (Scheme 33). Similar types of other metal halides, for example, [FeCl₃], [BiCl₃], [InCl₃], [ZnCl₂], [CeCl₃·7H₂O], and metal triflates such as [In(OTf)₃], [Bi(OTf)₃], [Sc(OTf)₃], and [Yb(OTf)₃] were tested, but all of them failed to give the desired product. To explore the scope of the reaction a variety of combination of substrates, namely, α- and β-naphthol, aromatic as well as aliphatic alkynes, aromatic aldehydes and cyclic and acyclic aliphatic aldehydes were also tested. Notably, the desired
naphthopyrans were obtained in good yields from all combinations of substrates. The reaction also works nicely with simple phenols.

The proposed mechanism of this reaction is displayed in Scheme 34. During the course of the reaction, Ga(III) first activates the alkyne to promote the nucleophilic attack of naphthol on the coordinated alkyne forming organometallic intermediate 1.7.1-B, which then undergoes proto-demetalation to produce intermediate 1.7.1-C. In the next step, a Ga(III)-activated aldehyde is proposed to be attacked by intermediate 1.7.1-C, followed by E2 elimination of Ga(III)-hydroxide and cyclization of the resulting ortho-quinone methide to form the desired chromene moiety.

1.8. Rhenium-Catalyzed 2H-Chromene Synthesis. Hua and co-workers reported the synthesis of 2,2-dimethyl-2H-chromenes via Re-catalyzed one-pot cyclocondensation of phenols and 2-methyl-3-butyne-2-ol at 60 °C in hexane (Scheme 35). Re(CO)Cl was used as the catalyst. The reactions were tested with simple phenols, p-, o-, m-cresols, as well as with other substituents on the aromatic ring, and in every case, the corresponding chromenes were obtained in moderate to good yields. Notably, the naphthopyran derivatives were also obtained in moderate yields from β- and α-naphthols, although α-naphthol showed a relatively lower reactivity.

Considering the high chemo- and regio-selectivity of the hydroarylation at the ortho position of the phenols, the reaction is believed to proceed via dehydration followed by intramolecular hydroarylation (Scheme 36).

1.9. Ytterbium-Catalyzed 2H-Chromene Synthesis. Starting from a salicylaldehyde and an olefin, Janin and co-workers reported a two-step synthesis of 2,2-dimethyl-2H-chromenes using ytterbium triflate as a catalyst. The first step of the reaction of salicylaldehydes 73 and 2-methyl propene 74 produced two intermediates, 1.9.1-A and 1.9.1-B, in 27% and 14% yield, respectively. Both of these two intermediates can be converted to the desired chromene 75 by refluxing with p-toluenesulfonic acid in toluene (Scheme 37). The reaction was found to work with a variety of substituents on the salicylaldehyde, containing both electron-withdrawing and electron-donating substituents, but the overall yield is moderate. The reaction fails to produce chromenes from substituted salicylaldehydes containing a OMe group in the ortho or para positions to the aldehyde. To explore the applicability of this protocol, the authors also explored the preparation of the spirochromene II compound 78, but in this case the yield was quite low (10%) (Scheme 38).

1.10. Aluminum-Catalyzed 2H-Chromene Synthesis. Laurent and co-workers found that 3-(perfluoroalkyl)-3-phenoxypypropan in the presence of [AlCl3] undergoes intramolecular cyclization to produce 2-(fluoromethyl)- and 2-(perfluoroalkyl)-2-hydroxy-2H-chromenes in moderate to high yield (Scheme 39). Overall, this method is quite general and tolerates the use of a large number of substituted 2-(perfluoroalkyl)-2-hydroxy-2H-chromenes 80. The reaction involves a dehydration–hydration rearrangement sequence after formation of the initial 2-(perfluoroalkyl)-4H-chromen-4-ol intermediate (see also section 2.4).

1.11. Eco-Zinc Catalyzed 2H-Chromene Synthesis. In 2014, Escande et al., reported a general and efficient method to synthesize 2H-chromenes on the basis of the concept of eco-catalysis, which involves the use of biomass-derived metallic elements for chemical synthesis. In this process, phytoextraction processes are used to obtain valuable metals. The Eco-Zn was extracted from Zn-hyperaccumulating plant leaves derived from Noccaea caerulescens (Brassicaceae). Notably, this methodology was claimed to be superior to other known methods affording 2H-chromenes in excellent yields.

The methodology involves catalysis with Eco-Zn, with or without montmorillonite K10 support. The reaction of α,β-unsaturated aldehydes with phenol derivatives works best in the presence of the Eco-Zn catalyst at 110 °C in anhydrous toluene (Scheme 40). Notably, under heterogeneous conditions, with montmorillonite K10 supported Eco-Zn catalyst, a slight loss of yield was observed. A wide variety of differently substituted 2H-chromene derivatives were synthesized in excellent yield from differently substituted phenols and the corresponding α,β-unsaturated aldehydes, including the preparation of precocene I 24 (a natural insect growth regulator) in 91% yield.

1.12. 2H-Chromene Synthesis from Chromene Acetals. In addition to the above-mentioned metal mediated/catalyzed 2H-chromene synthesis, very recently Doyle and co-workers reported the synthesis of a wide variety of substituted 2H-chromenes via a Ni-catalyzed cross coupling reaction between chromene acetics and boronic acids (Scheme 41).

A somewhat related approach was followed by Hiemstra and co-workers, who reported a multistep, multicatalytic approach to synthesize 2H-chromenes, involving a combination of Pd-catalyzed addition of allenes to 2-vinyl-phenols, ring-closing metathesis, and nucleophilic addition to the resulting (BF3 activated) acetal.

1.13. Metal-Catalyzed Synthesis of Selected Chromene-Containing Natural Products and Medicinally Important Compounds. 1.13.1. Sasai and co-workers reported an enantioselective synthesis of (−)-cordiachromene 92 by using 6-endotrig-Wacker-type oxidative cyclization of 2-geranylphenols without using any protecting groups. Before they started the actual synthesis of cordiachromene, the reaction condition was optimized using 2-geranyl phenol 86 as the starting compound, which produced the corresponding chromene 88 in 55% yield with 54% ee in the presence of 11 mol % iPr-SPRiX 87, 10 mol % Pd(OCCF3)2 and 4 equiv of p-benzoquinone in dichloromethane as solvent at 60 °C. Notably, the S-exo-trig cyclization product 89 was also obtained in 11% yield with 18% ee (Scheme 42).

During the actual synthesis and under the optimized conditions 91, oxidizes to 2-geranylbenzoquinone. Therefore, the actual synthesis required some modification of the optimized conditions. Stoichiometric use of the Pd catalyst turned out to be the best solution to this problem, affording 42% yield with 54% ee of (R)-cordiachromene 92 (Scheme 43).

According to the proposed mechanism, the reaction proceeds through an initial activation of the double bond by coordinating to Pd(II) followed by the nucleophilic attack and subsequent β-hydrate elimination. Notably, the positive charge generated after the activation of double bond would be more stabilized at a tertiary center compared to a secondary center. As a consequence, 6-endotrig cyclization was favored in this case compared to S-exo-trig (Figure 3).

1.13.2. Moody and co-workers reported the synthesis of two chiral chromene-based natural products likonide B and smenochromene D (Figure 4) using a Claisen rearrangement followed by intramolecular Mitsunobu reaction.

Starting from the simple allylic alcohol 95, in a few steps the chromene precursor 96 was synthesized in high yields. In the next step, the compound 96 furnishes the chromene moiety 97.
via intramolecular Claisen rearrangement (Scheme 44). Notably, with an unprotected hydroxyl group on the phenyl ring, the desired chromene 97 was obtained exclusively in higher yield (87%). On the contrary, protection of the hydroxyl group with TBS or mesylate groups leads to a significant lowering of the desired chromene. Finally, compound 97 undergoes macrocyclization via a Mitsunobu reaction to produce smenochromene D.

1.13.3. Correia and co-workers reported the synthesis of natural product flavone 99 via the sequential employment of (i) o-allylation of phenols, (ii) Claisen rearrangement, (iii) O-vinylolation and (iv) ring-closing metathesis (RCM), followed by (v) Heck arylation (Scheme 45).32 Notably, during the Heck arylation of the enol ether, the authors have successfully used arenediazonium tetrafluoroborate as an alternative reagent, which produces the corresponding chromene with high regioselectivity. It is noteworthy that the flavone 99 possesses leishmanicidal activity.

1.13.4. Tahtoui and Schneider and co-workers reported an enantioselective synthesis of iclaprim enantiomers 100 (Scheme 46).33 Both the enantiomers are dihydrofolate reductase (DHFR) inhibitors and are known to be active against a broad range of bacteria.

The total synthesis was carried out according to the retro-synthetic plan shown in Scheme 47. Starting from the chiral homoallylic alcohol (S)-105, the chiral ether (R)-103 could be easily obtained via a Mitsunobu reaction. Next, the diaminopyrimidine moiety was incorporated before the cyclization step to avoid recemization. Oxidative cleavage of the C=C double bond followed by ring-closure of the aldehyde produces the final target compound (S)-100. Using this retro-synthetic approach, iclaprim was obtained in a moderate yield with moderate enantioselectivity (70% ee for (R)-100 and 50% ee for (S)-100) (Scheme 48).

2. METAL-FREE BRøNSTED AND LEWIS ACID/BASE CATALYTIC APPROACHES TO 2H-CHROMENES

Transition metal catalysts can be expensive, especially those based on noble metals. Furthermore, for the synthesis of bioactive/pharmaceutical compounds, preventing product contamination with potentially toxic metal traces can be of importance. Hence, metal-free methodologies to synthesize 2H-chromenes are of interest and have already received quite some attention. Such protocols are summarized in section 2 of this review.

2.1. Larock and co-workers reported34 a mild synthetic methodology for the synthesis of 3,4-disubstituted 2H-benzopyrans in excellent yields via electrophilic cyclization of substituted propargyl aryl ethers by I2, IC1, or PhSeBr (Scheme 49). The metal-free methodology was found to be effective over a range of functional groups including both electron donating and electron withdrawing substituents. The introduction of electron-donating groups on the aromatic ring was found to render a positive effect on the yield, while electron-withdrawing groups had the opposite influence. Notably, under the optimized reaction conditions, when I2 was used as electrophile, addition of NaHCO3 becomes essential for cyclization, whereas IC1 as an electrophile produced the desired product even in the absence of NaHCO3. In both cases, nitromethane proved to be the best solvent choice. The reaction also worked well with PhSeBr as the electrophile in dichloromethane solvent at low temperature (−78 °C). A range of substituted aryl propargyl ethers containing either an aryl or olefinic group at the alkyne terminus were found to undergo smooth cyclization in the presence of I2 or IC1 as electrophiles. The cyclization was unsuccessful for substrates with an alkyl group on the alkyne terminus for I2 or IC1 as electrophile but was successful with PhSeBr. Interestingly, the hydroxy-methyl-substituted propargyl aryl ether successfully reacted with both I2 and IC1. Both were also successful in the synthesis of naphthochromene derivatives in a modest yield starting from the corresponding α-naphthyl propargyl ether. Unfortunately, the simple phenyl propargyl ether failed to produce the desired chromene under the optimized reaction conditions.

The proposed mechanism involves the addition of the electrophile to the triple bond to produce an iodonium or selenonium intermediate first, which then undergoes cyclization with the aromatic ring (Scheme 50). Finally, loss of a proton results in the formation of the desired 2H-chromenes.

This methodology has an added advantage that the chromenes obtained from this route can be easily functionalized via replacement of the iodine moiety present in the 2H-chromene ring. Further functionalization using a Sonogashira reaction produced the alkynyl chromene 112 in 87% yield and a Pd-catalyzed CO insertion reaction on the chromene 113 produced the lactone 114 in 72% yield (Scheme 51).

2.2. In a related approach to the above example, Zeni and co-workers used organochalcogen-substituted propargyl aryl ethers to synthesize 3- and 4-substituted chromenes via the same type of electrophilic cyclization.35 The authors used 3 equiv of I2 and Na2CO3 in THF or CH3CN, and the reactions
proceeded smoothly to give a wide range of 3- and 4-substituted chromenes in moderate to high yields (Scheme 52). Notably, they also studied these same reactions employing Larock’s conditions in nitromethane to find that no reaction occurred. The proposed mechanism is quite similar to that of the Larock’s proposal, except for the first step, which was proposed to involve the usual reaction of organochalcogen propargyl aryl ethers with I₂ to give selenium(IV) intermediates. The next steps were proposed to proceed through the formation of an iodonium intermediate involving addition of iodine to the triple bond, which then undergoes cyclization with the aromatic ring to produce the intermediate 2.2-C. Loss of a proton restores the aromaticity of the cyclized organochalcogen(IV) species 2.2-D, which is finally reduced to an organochalcogen(II) species by sodium thiosulfate used in the workup procedure (Scheme 53).

2.3. Synthesis of functionalized 2H-chromenes was reported by Shi et al., who demonstrated a simple reaction between salicylaldehyde 117 and allenic ketones 118 or esters 121 catalyzed by potassium carbonate (Schemes 54 and 55). For a variety of salicylaldehydes 117 and allenic ketones 118 bearing methyl or benzyl groups at the 3-position, this reaction appears to be general. Chromenes of the type 119 were obtained from this method in high yields, but they were obtained as a mixture of E and Z-isomers. For allenic esters of the type 121, the chromene products were formed in remarkably high yields, exclusively as the E-isomer (Scheme 55). Notably, salicylaldehyde containing electron-donating groups favored higher yields. However, although the reaction with 2-hydroxyacetophenone and allenic ester 121 produced the expected chromene product 122 in 79% yield, the same reaction with an allenic ketone failed to produce any desired product.

According to the authors, the proposed mechanism involves deprotonation of salicylaldehyde followed by attack of the phenoxide moiety on the allenic ester to form intermediate 2.3-C. This intermediate undergoes an aldol condensation with salicylaldehyde to produce the final chromene 122-A (Scheme 56).

2.4. One year later, the Shi group revisited their 2H-chromene synthesis using unsubstituted allenic esters or ketones in the presence of K₂CO₃ as catalyst. Notably, the use of elevated temperatures (120 °C) in the first report by Shi et al. was found to be unnecessary for unsubstituted allenic ketones and esters, and in fact, these reactions can be run at room temperature (Scheme 57). The reaction of salicylaldehydes 117 with unsubstituted allenic esters interestingly produced different products compared to α-substituted allenic esters. Depending upon the isolation methodology, these reactions produced two types of products, either 120 or 121, in moderate to good yields. Purification of reaction mixture using neutral Al₂O₃ column chromatography gave only product 121, whereas purification using silica gel column chromatography exclusively gave product 120 (Scheme 58).

Moreover, compound 122 converts to compound 123 under acidic conditions within 2 days at room temperature in the absence of any other reagents (Scheme 59).
The proposed mechanism is depicted in Scheme 60. Initially, deprotonation of salicylaldehyde 117 by K2CO3 leads to the phenolate anion 2.4-A, which attacks the allenic ester producing the carbanion intermediate 2.4-B. Subsequent attack of this carbanion intermediate on the aldehydic C=O completes the cyclization reaction. On the other hand, oxyanion intermediate 2.4-D abstracts a proton from salicylaldehyde to afford compound 2.4-E and regenerates 2.4-A. After isomerization, compound 2.4-E is converted to 2.4-F, and subsequent dehydration produces the pyrylium intermediate 2.4-G, which is then attacked by H2O to form the final product 120.

2.5. In an unprecedented reaction, Tang and co-workers reported an annulation reaction from an ylide generated from halide 124 and tetrahydrothiophene (THT) to produce 2-substituted 2H-chromenes (Scheme 61). The reaction involves tandem Michael addition/reverse Michael/allylic substitution. Formation of 2H-chromenes was rather unexpected because under the reaction conditions the cyclopropane 125 was the expected product. However, there was no trace of 125, and instead, chromene 126 was obtained in 85% yield.

The scope of the reaction was tested with a wide variety of unsaturated esters having different substituents on the phenyl ether ring. The desired chromenes were obtained in high yields, despite the fact that 4H-chromenes were obtained in some cases as minor side-products. The relative yield of 2H-chromenes to 4H-chromenes is likely to be substrate dependent, and according to the authors, an 8:1 ratio of 2H-chromenes 127 over the 4H-chromenes 126 is obtained in the worst case.

The plausible mechanism involves the reaction of tetrahydrothiophene 128 with bromide 124 to form sulfonium salt 2.5-A first, which after deprotonation by K2CO3 forms the sulfonium ylide 2.5-B. An intramolecular Michael addition, followed by a retro-Michael reaction produces intermediate 2.5-D. Finally, 2H-chromene 126 is formed via an intramolecular S$_{N}$$'$ reaction of intermediate 2.5-D, after which tetrahydrothiophene 128 is regenerated to close the catalytic cycle. Formation of the 4H-chromene 127 as minor product could be explained from the fact that 2H-chromene 126 slowly transformed to the more stable thermodynamic product in the presence of K2CO3, which is the 4H-chromene 127 (Scheme 62). Use of stronger bases like Cs2CO3 exclusively produced 4H-chromene 127 instead of 2H-chromene 126.

2.6. Ravichandran and co-workers described an easy one-pot synthesis of 2H-chromenes starting from cyclic enones and salicylaldehydes. This reaction is catalyzed by DABCO. They were successful in synthesizing the corresponding chromenes in moderate yields, starting from salicyldehydes containing both electron-donating and -withdrawing groups. Cyclohexenone and cyclopentenone both produced the desired chromenes (Scheme 63).

2.7. Miyabe and co-workers reported the synthesis of 2H-chromenes via a multicomponent reaction which involves insertion of arynes 132 into C=O bond of dimethylformamide 133 followed by the nucleophilic attack by active methylenes 134 to produce the desired products 135 in moderate to high yield (Scheme 64). Notably, active methylenes show high...
reactivity toward arynes to produce the $\sigma$-insertion ortho-disubstituted products (Scheme 65).

Reaction of the aryne precursor 138, DMF 133, and acetylacetone 139 produced 2H-chromene 140 (84% yield) in the presence of TBAF in DMF as the solvent (Scheme 66).

No undesired byproducts were observed, even though active methylene compounds 134 show high affinity toward arynes 132 giving ortho-disubstituted arene 137. This reaction is quite versatile and shows regioselectivity with substituted arynes. The corresponding chromenes were obtained in moderate to high yields when different aryne precursors and diketones were reacted under the optimized reaction conditions. The 4-methoxytrifluoroborate corresponding to 138 gave two regioisomers in a 6:5 ratio.

The authors successfully used this methodology for the one-pot synthesis of a neuropeptide YYS acceptor antagonist 143 in...
86% yield. Two similar products 144 and 145, having different substitution on the aromatic ring, were also synthesized in 87% and 69% yields, respectively (Scheme 67).

A plausible mechanism of the reaction was proposed on the basis of the experimental findings coupled with ab initio molecular orbital calculation (Scheme 68). The authors considered two possible reaction pathways; according to Path A, chromones were produced via addition of an enolate anion to unstable intermediates 146 or 147 followed by elimination of dimethylamine. Path B, on the other hand, involves hydrolysis of the unstable intermediate 146 or 147 to produce salicylaldehyde 148, which in a subsequent reaction with the enolate, resulted in the desired products (Scheme 68).

Notably, carefully controlled reactions even under anhydrous conditions could not exclude the possibility that the reaction follows Path B. To get further insight, the authors planned three test reactions with three different salicylaldehydes 150, 152, and 154 and acetylacetone 139 under optimized reaction conditions. Even after a much elongated reaction time, a significant amount of unreacted salicylaldehyde starting material was recovered, and a quite low yield of the desired chromones was obtained (Scheme 69). These experimental findings are in agreement with the thermodynamic data obtained from an ab initio molecular orbital calculation and suggest that the reaction mainly follows Path A. The step involving the formation of the unstable intermediate 157 is highly exothermic (\( \Delta H = -177 \text{ kJ mol}^{-1} \)) probably because of the release of the strain energy of aryne 156, which overcomes the entropy loss of the bimolecular coupling (\( -7 \Delta S^\circ = +65 \text{ kJ mol}^{-1} \)). The free energy changes (\( \Delta G^\circ = +65 \text{ kJ mol}^{-1} \)) in all these sequential reactions are thermodynamically favorable (Scheme 70), whereas in Path B, the reaction of 148 with 139 is thermodynamically uphill (\( \Delta G^\circ = +77 \text{ kJ mol}^{-1} \)).

2.8. Sridhar and Raju reported 41 an easy one-pot and mild synthesis of 2H-chromenes from the reaction of salicylaldehydes 160 and ethyl-4-chloro-3-oxobutanato 161 in the presence of piperidine as base and dichloromethane as the solvent (Scheme 71). This methodology is versatile and tolerates a wide range of substituents (both electron-donating and electron-withdrawing) on the phenyl ring. The yields were good in all cases. Notably, electron-withdrawing substituents render a positive effect on the yield of the desired chromenes, whereas a lower yield was obtained with electron-rich arenes.

A plausible mechanism proposed by the authors involves the formation of Knoevenagel product 2.8-A as a key intermediate. Then cyclization takes place by the nucleophilic attack of the phenolic OH onto the nearest C==O to Cl to produce the chromone product. The electron-withdrawing effect of CH_3Cl is believed to play an important role during the Knoevenagel condensation giving a cis-relationship of the chloromethyl ketone and arene ring on the double-bond, allowing for the cyclization to occur (Scheme 72).

2.9. A convergent method for the synthesis of a variety of fused 2H-chromenes was reported by Sosnovskikh and co-workers. 42 This methodology deals with oxa-Michael addition/Mannich condensation of salicylaldehydes with chromones, \( \gamma \)-pyrones, and \( \beta \)-furanones activated by the polyhaloalkyl groups. The substituted chromones 165 reacts smoothly with a number of salicylaldehydes in the presence of piperidine in refluxing benzene to afford the corresponding chromenes in moderate to high yields. Notably, no side products resulting from the Baylis–Hillman reaction nor any ring-opening of the pyrone ring were observed (Scheme 73). The reaction worked well with a wide range of substituents on both the salicylaldehydes and chromones, resulting in good to excellent yields of the desired chromenes. However, with 2-hydroxyacetophenone the reaction did not proceed at all. The presence of an electron-withdrawing group at the C6 position (R2) of the chromones greatly facilitates the rate limiting initial nucleophilic addition to the C2 carbon, whereas the electron-donating groups have a negative effect.

Similar reactions starting with various cyclic enones and different types of salicylaldehydes were also found to produce 2H-chromenes in moderate to high yields (Scheme 74). Activated 2,3-dihydro-4H-pyrane-ones and 2,2-dimethylfuran-3(2H)-ones also smoothly react under the optimized reaction conditions, affording good yields of the chromenes. Interest-
Interestingly, the desired chromene was obtained with a poor yield (8%) starting from the sterically hindered 2-hydroxy-1-naphthaldehyde. Interestingly, the same reaction with activated γ-pyrones containing two electron-withdrawing groups on the 2-and 6-positions produced double annulated polycyclic compounds, containing three oxygen atoms in the adjacent rings. Activated γ-pyrones with an excess of salicyaldehydes (3.0 equiv) in the presence of piperidine and p-TsOH in refluxing benzene produced the chromenes in 52–82% yields. Notably, in the absence of p-TsOH, the yields were poor (42–48%) (Scheme 75). However, the direct reaction of salicyaldehyde with 2 equiv of 170 in the presence of piperidine and p-TsOH failed to produce the corresponding monoadduct 173.

2.10. In a recent report, Bhar and co-workers disclosed a methodology for the synthesis of 2H-chromenes and 2H-thiochromenes through cyanuric chloride-dimethylformamide mediated cleavage of different spiro-4-hydroxychroman-3,1′-cyclopropanes and corresponding thiochroman analogues (Scheme 76). The plausible mechanistic proposition for this reaction is outlined in Scheme 77. In the first step, the substrate 174 reacts with the TCTDMF adduct 2.10-A to form the intermediate 2.10-B along with a byproduct 2.10-C. The cleavage of cyclopropane ring in 2.10-B produced the carbocationic intermediate 2.10-D as an intimate ion pair. Notably, the possibility of extended conjugation with the aromatic moiety facilitates this process. Moreover, the presence of electron-donating substituents at the para-position of the aryl moiety render additional stabilization to the carbocationic intermediate through canonical structure 2.10-E. Finally, compound 2.10-C deprotonates the rather acidic –CH2– group of 2.10-E to produce the desired chromenes 177.

2.11. Park and co-workers synthesized various chromene-containing heterocycles simply starting from s-cis-enones. The reaction of 3-methylenecromene-4-ones with various enamines in neat condition at 100 °C produced the pyridine-fused chromenes in high yields (Scheme 78). A wide range of electron-rich and -poor substrates reacted cleanly to produce the corresponding pyridine-fused chromene derivatives in high yields.
Similarly, pyrazolopyrimidine-fused chromenes were successfully synthesized from the reaction of \( \text{s-cis-enone} \) and 3-aminopyrazole derivatives under microwave irradiation (Scheme 79). The corresponding chromenes were obtained in excellent yields.

Corresponding pyrimidine-fused chromenes were also synthesized in moderate yield employing the same reaction methodology. The hydroxyl-substituted \( \text{s-cis-enone} \) reacts with a stoichiometric amount of pyrrolidine to produce the corresponding pyrimidine-fused chromenes via an enaminone intermediate (Scheme 80).

2.12. Koussini et al. reported a microwave-assisted synthesis of 3-nitro-2H-chromenes from the reaction of 2-hydroxybenzaldehydes and 2-nitroethanol supported on anhydrous potassium carbonate, in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB). This methodology involves simple mixing of salicyaldehyde derivatives with a 1.5-fold excess of 2-nitroethanol and a catalytic amount of tetraethylammonium bromide (TBAB). The mixtures were then adsorbed on dry potassium carbonate and irradiated in a small transparent polypropylene beaker in a domestic microwave oven for 2 min (Scheme 81). A plausible mechanism is depicted in Scheme 82. The reaction begins with proton abstraction from 2-nitroethanol using \( \text{K}_2\text{CO}_3/\text{TBAB} \) under microwave irradiation to form carbanion 2.12-A. A Henry reaction between the carbanion and salicylaldehyde then affords the benzylidene derivative 2.12-B as an intermediate, which subsequently undergoes cyclodehydration to produce the final products. Notably, a competitive polymerization of nitroethylene to poly-nitroethylene was also observed under the applied reaction conditions which accounts for the low yield of the chromenes obtained.

2.13. Similarly, under microwave conditions, 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate esters were synthesized under solvent-free conditions via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetate followed by intramolecular cyclization in the presence of silica-immobilized L-proline as the catalyst (Scheme 83). Notably, the catalyst can be recovered conveniently and reused without obvious loss of activity. A wide range of substituted salicylaldehydes reacted with ethyl trifluoroacetate to afford the corresponding chromenes in moderate to high yields. Both electron-withdrawing and electron-donating groups at various positions of the benzene rings are tolerated. The aromatic aldehydes with electron-withdrawing groups afforded higher yields in comparison with those with electron-donating groups. On the other hand, the same reaction under thermal condition at 80 °C in the absence of microwave irradiation produced relatively lower yields and longer reaction times were required.

The proposed catalytic cycle is shown in Scheme 84. The reaction proceeds via an enamine intermediate 2.13-A.
Subsequent reaction of the intermediate \textbf{2.13-A} with salicylaldehyde produces the intermediate \textbf{2.13-C}, which upon hydrolysis followed by dehydration produced another intermediate \textbf{2.13-E}. Subsequent cyclization by the addition of phenoxide ion to the more electrophilic carbonyl group rather than to the ester group affords the intermediate \textbf{2.13-G}. Finally, protonation of \textbf{2.13-G} affords the desired chromene 196.

2.14. Adler and Baldwin developed an efficient single-step method for the synthesis of 2,2-dimethyl-2H-chromenes from the corresponding phenols with 3-methylbutenal under microwave irradiation in CDCl$_3$ (Scheme 85). Unfortunately, the yield of this reaction is very poor, although the presence of an increasing number of electron-donating groups on the phenol ring increases the effectiveness of this method.

2.15. Ferreira and co-workers reported a simple one-pot synthesis of 2H-chromenes from \textit{ortho}-quinones and allyl-
triphenylphosphonium salts 200, in the presence of aqueous NaOH and chloroform as solvent (Scheme 86). The reaction proceeds smoothly at room temperature via the in situ-generated ylide, which subsequently reacts with the ortho-quinone to produce an ortho-quinone methide intermediate that eventually cyclizes to give the 2H-chromenes in moderate to high yields.

2.16. An enantioselective synthesis of a 2H-chromene from a β-hydroxy-unsaturated ketone (Scheme 87) was reported by Scheidt and co-workers,49 making use of a diastereoselective ring-closing step. The starting chiral β-hydroxy-unsaturated ketone was initially prepared from an α-acylvinylic anion generated from a silyloxyallene. Although the resulting chromene was obtained in good yield, the authors reported only one example using this methodology to synthesize chiral chromenes from β-hydroxy-unsaturated ketones.

2.17. Kureshy et al. successfully used sulfonic-acid-functionalyzed mesoporous SBA-15 silica for the high yield synthesis of chromenes 205 from chromanols 204 under heterogeneous reaction conditions (Scheme 88).50 The very short reaction time with the added advantage of the more than 10 times catalyst recyclability is noteworthy.

2.18. Petasis and Butkevich recently developed51 a one-step strategy for the synthesis of 2H-chromenes starting from salicylaldehyde 206, alkyl boronic acids 207 or alkynyl trifluoroborates 208, and an amine 209. The reaction of salicylaldehydes 206 with alkyl boronic acids 207 or alkynyl trifluoroborates 208 in the presence of an amine initially produced an aminophenol intermediate 2.18-A, which upon cyclization afforded the 2H-chromenes 210 (Scheme 89).

The reaction was found to be highly sensitive to the applied reaction conditions. The secondary amines show the highest reactivity, whereas tertiary amines as base can also mediate this transformation. However, tertiary amines are relatively less effective than the secondary amines, whereas tetrahydroammonium hydroxide, comparatively a stronger base, was observed to be entirely ineffective. The proposed mechanism (Scheme 90) proceeds via a direct nucleophilic attack of the amine 209 on the aldehyde to produce the intermediate 2.18-B, which then reacts with the boronic acid 212 to form an ion-pair 2.18-C consisting of an electrophilic ammonium species and a nucleophilic borate moiety. Subsequent conjugate addition of the alkenyl group within the ion-pair 2.18-C leads to an ammonium phenolate intermediate 2.18-D, which upon fragmentation produced another intermediate 2.18-E. Finally, intermediate 2.18-E upon electro-cyclization produces the 2H-chromenes 213 (Scheme 90).

This synthetic methodology was successfully used in the synthesis of vitamin E analogues, as an efficient application (Scheme 91). The reaction of 214 with boronic acid 215 and dibenzylamine afforded the corresponding chromene 216 in 57% yield, which upon catalytic hydrogenation was transformed to the tocopherol analogue 217.

2.19. Based on a modified Petasis reaction, Das et al. reported52 the synthesis of various 2-substituted-2H-chromenes starting with salicylaldehydes and vinylboronate salts. The reaction also requires catalytic amounts of dibenzylamine as the secondary base and DMF as the solvent (Scheme 92). Notably, these vinylboronate salts are much more stable, easier to use than the corresponding organoboronic acids and more
reactive. A wide range of substituted salicyaldehyde and the alkenyl trifluoroborate salts produced the corresponding substituted 2H-chromenes in moderate to high yields. Electron-withdrawing groups in the position para to the salicyaldehyde OH group have a somewhat positive influence on the product yield.

2.20. Sosnovskikh and co-workers reported a new synthetic method for the synthesis of highly substituted 2H-chromenes starting from N-unsubstituted imines of 2-hydroxyacetophenones and activated trihalomethyl substituted nitro alkenes. The reaction of N-unsubstituted imines of 2-hydroxyacetophenones with activated trihalomethyl substituted nitro alkenes in the presence of DABCO as base proceeds via a
tandem oxa-Michael/aza-Henry addition reaction in dichloro-
methane to produce the desired highly substituted 2H-
chromenes 224 in excellent yields (Scheme 93). The reaction
proceeds via an aza-Michael addition in benzene to produce the
compound 225. The reaction worked efficiently with DABCO
as the base, although use of other bases such as triethylamine
resulted in lower yields. The reaction is found to be highly
dependent on the substituent present on the aryl ring, which
controls the nucleophilicity of the phenolate anions.

2.21. Moustrou and co-workers developed54 an efficient and
highly selective two-step procedure for the synthesis of a
number of nitro-substituted 2,2-diphenyl-2H-1-benzopyrans,
starting from their brominated homologues. These were
obtained by a classical chromenization between the commer-
cially available 1,1-diphenyl-2-yn-ol and various brominated
phenols. Subsequently, the nitro chromenes were synthesized
from their boronic acids followed by the regioselective
electrophilic nitr ation (Scheme 94).

2.22. Uguen and co-workers used a protocol involving
pyridine-catalyzed condensation of phenolic compounds with
\( \alpha,\beta \)-unsaturated aldehyde dimethyl acetals to synthesize a
variety of chromenes.55 The highly substituted phenol 233 (R =
Me) reacts with 234a to produce the 2H-chromene 235 in 59%
yield. Also 1,4-hydroquinone 233 (R = H) was found to react
smoothly with 234b to produce 236, which was then protected
by routine acetyoxylation to a
ord 236. (Rac)-Cordiachromene
A 237 was obtained in 40% yield from the reaction of 1,4-
hydroquinone 233 (R = H) and 234a (Scheme 95).

2.23. Ramachary et al. reported56 a new method for the
synthesis of highly substituted (\( Z \))-2-(buta-1,3-dienyl)phenols
from highly substituted dienes by a combination of ring-closing
metathesis (i) and base-induced ring-opening (ii). The
corresponding phenol then transformed to the desired 2-
methyl-2H-chromenes via a [1,7]-sigmatropic H-shift reaction
followed by electrocyclic ring closure (Scheme 96). Two
different reaction conditions were employed: heating at 120–
140 °C and treatment with silica at room temperature. Under
these two conditions, the chromene products were obtained in
80–98% yield range. The versatility of this method was tested
using differently substituted substrates, and for both steps, the
yields were over 90%.

Also the C2-symmetric benzo[b]oxepine 241 on treatment
with 1.5 equiv of tBuOK followed by treatment with SiO2/
CHCl3 at 25 °C produced the nonsymmetric 2-methyl-2H-
chromene 242 in 70% yield. Notably, the same reaction
produced the C2-symmetric chromene 243 in 65% yield when
the reaction time for the base-induced ring-opening was
increased from 1 to 3 h and the amount of KO-
t-Bu was
increased from 1.5 to 5.0 equiv (Scheme 97).

The mechanism of these reactions involves the formation of
the ortho-quinone methide intermediates 2.23B
from a [1,7]-
sigmatropic H-shift followed by an electrocyclic ring closure to
give the desired chromene products (Scheme 98).

2.24. Wu and Chen recently reported57 the synthesis of a
variety of chromenes via a cascade reaction of \( \beta,\gamma \)-unsaturated-
\( \alpha \)-ketoesters with phenols in the presence of trityl chloride as
an oxidizing agent in TFA under refluxing conditions (Scheme
99). Initial optimization of the reaction conditions were
achieved with 4-tert-butylphenol 245 with (3E)-2-oxo-4-

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phenylbut-3-enoate methyl ester 246. The best yield of chromene 247 (90%) was obtained with 1.1 equiv of 246 and Ph3CCl as an oxidant in the presence of TFA. The reaction was found to be very general with respect to the \( \beta,\gamma \)-unsaturated-\( \alpha \)-ketoesters; \( \beta,\gamma \)-unsaturated-\( \alpha \)-ketoesters either

Scheme 93. Synthesis of Chromenes via a Tandem Oxa-Michael/Aza-Henry Reaction

Scheme 94. (Top) Retro Synthetic Approach for Chromene Synthesis; (Bottom) Synthesis of Nitro-Substituted 2,2-Diphenyl-2H-1-benzopyrans via the Ipso-Nitration Reaction

Scheme 95. Synthesis of Chromenes via Pyridine-Catalyzed Condensation of Phenolic Compounds with \( \alpha,\beta \)-Unsaturated Aldehyde Dimethyl Acetals

Scheme 96. Synthesis of Chromenes via RCM/Base-Induced Ring-Opening Reaction

Scheme 97. Transformation of C2-Symmetric Benzo[b]oxepine to Chromenes
with electron-withdrawing or -donating groups participate in this cascade cyclization, producing the corresponding chromenes in moderate to high yields. The substitution pattern of the aromatic phenol ring seems to have little effect on this cascade reaction. Notably, 1-naphthol and 2-naphthol also react with 246 to furnish the corresponding chromene derivatives in high yields.

The proposed mechanism is believed to proceed via Friedel-Crafts alkylation and cycloaddition of $\beta,\gamma$-unsaturated-$\alpha$-ketoesters 249 with phenols 248 to produce the intermediate 2.24-A (Scheme 100). Then benzopyrylium ions 2.24-B are formed by intermolecular hydride transfer from 2.24-A to trityl chloride, which on subsequent hydration with water during workup afforded the 4-aryl-2H-chromenes 250.

In a follow-up study, the authors also investigated further transformation of 2H-chromenes to their various synthetic derivatives (Scheme 101). Different amino-substituted chromenes were synthesized in good yields.

2.25. Recently, Rosenau and co-workers studied the bromination behavior of pyrano[1,3-α]chromene 263, which was obtained as the side product in 33% yield in the synthesis of $\gamma$-tocopherol model compound 2,2,7,8-tetramethylchroman-6-ol 260 (34%) from 260 with 1.0 equiv of alcohol 261. The reaction gives a 41% yield of 262 and 12% yield of 263 when 0.66 equiv of 261 is used. The compound 263 was formed by the double alkylation of the hydroquinone 260 with the 2-methylbut-3-en-1-ol, along with the monoalkylated compound 262. Finally, 263 upon reaction with 2 equiv of molecular bromine produced the chromone product 264 in 96% yield (Scheme 102).

The proposed mechanism is depicted in Scheme 103. Treatment of 263 with molecular bromine produced the corresponding 263-Br$_2$ complex 2.25-A. Elimination of two equivalents of HBr generates the pyranochromene 264, which upon further bromination produced 3-bromopyranochromene 266 after elimination of one equivalent HBr from 265.

2.26. Yadla and co-workers reported the synthesis of fluoro-substituted 2,2-dimethyl-2H-chromenes via microwave-assisted tandem intramolecular Wittig and Claisen rearrangement of [(2-(fluoroaryloxy)-2-methyl-propanoyl)-(cyan/o/ethoxy carbonyl)methylene]triphenyl phosphoranes followed by internal cyclizations (Scheme 104). The reaction proceeds through the formation of aryl propargyl ethers via Wittig reaction from the precursors 268. The propargyl ether 2.26-A then undergoes a Claisen rearrangement to produce the corresponding product 2.26-B, which tautomizes to the allenyl phenols 2.26-C. Finally, a [1,5]-sigmatropic migration of hydrogen gives an ortho-quinone methide 2.26-D which undergoes an electrocyclic ring closing reaction to yield the desired chromenes 269.

Notably, aryl propargyl ethers under thermal conditions in the presence of $N,N$-diethylaniline as a basic solvent smoothly rearrange to produce a wide range of 2H-chromenes in high yields (Scheme 105).60

2.27. Karami and co-workers developed a novel multi-component process involving the reaction of various aryl glyoxals with 4-hydroxy coumarin and malononitrile to synthesize pyrano[4,3-α]chromenes containing an aroyl group (Scheme 106).61 The reactions were catalyzed efficiently by ammonium dihydrogen phosphate to yield the desired products in good to excellent yields. The reaction has been found to be very sensitive to the applied reaction temperature, and best results were obtained when the reaction was stirred initially for 30–40 min followed by heating under reflux conditions. Aryl glyoxals containing either electron-withdrawing or electron-donating groups were successfully used in this reaction.

A plausible mechanism is shown in Scheme 107. The reaction proceeds via NH$_4$H$_2$PO$_4$ catalyzed cascade reaction in which the aryl glyoxal first condenses with malononitrile 274 to produce the corresponding aryloylidene malononitrile 272-A. Subsequent Michael-type addition of 272 to the intermediate 2.27-A affords another intermediate 2.27-B, which upon intramolecular heterocyclization forms the desired chromene 276.
3. ENANTIOSELECTIVE ORGANOCATALYTIC 2H-CHROMENE SYNTHESIS

Organocatalysis is one of the emerging fields of modern catalysis research. It plays a significant role in the asymmetric synthesis of 2H-chromenes. An up-to-date overview of organocatalytic methodologies developed for enantioselective synthesis of 2H-chromenes is described below.

3.1. Schaus and co-workers developed the new chiral Brønsted acid as a catalyst for the synthesis of chiral 2-substituted 2H-chromenes involving the enantioselective addition of alkenyl boronates to chromene acetals (Scheme 108). Although the organocatalyst could give the chromenes with good enantiomer ratios, a cocatalyst involving the combination of with a Lewis acid catalyst gave higher yields and enantioselectivities. The combination of the chiral tartaric amide with Ce(III), Ce(IV), or Yb(III)-triflate salts gave the best yields and enantioselectivities in this particular reaction. This methodology has a wide substrate scope; addition of a variety of differently substituted alkenyl boronates to the chromene acetals yielded the desired chromenes in a high enantiomeric ratio (up to 98:2), and high yields were obtained using slightly modified reaction conditions.

Scheme 102. Bromopyranochromene via Bromination of Pyranochromene

Scheme 103. Proposed Mechanism of Bromopyranochromene Formation
conditions. Although this synthetic method is found to be very efficient, unfortunately it could not be generalized as the conditions had to be optimized for each substrate (Scheme 108).
On the basis of spectroscopic observations and some controlled experimental findings, a plausible mechanism (Scheme 109) has been proposed. Formation of dioxaborolane 282 and pyrylium intermediate 284 were observed during the reaction. Complexation of Ce(OTf)₄ with theamide C—O of the tartaric acid catalyst and with the boronate oxygen atoms was noticed as well. The proposed catalytic cycle begins with the formation of dioxaborolane 282 from the boronate and tartaramide acid 279. As a result of complexation of 282 to...
Ce(OTf)$_4$, the acidity of the boronate moiety increases to some extent, which in turn facilitates the formation of pyrylium intermediate along with boronate complex $^{284}$. Finally, the activated complex $^{284}$ undergoes nucleophilic addition to the pyrylium intermediate yielding the desired chromene $^{285}$ (Scheme 109).

The proposed mechanism was further supported by the fact that the chromene acetal $^{283}$ and chiral dioxoborolane $^{282}$ react at $-40^\circ$C in the presence of Ce(OTf)$_4$ as catalyst in ethyl acetate as the solvent to produce the desired chromene $^{285}$ in 85% yield in a 98:2 enantiomeric ratio (Scheme 110).

3.2. Arvidsson and co-workers reported$^{63}$ the first organocatalytic asymmetric synthesis of benzopyrans via a one-pot oxa-Michael addition followed by an intramolecular aldol condensation between salicylaldehyde $^{286}$ and $\alpha,\beta$-unsaturated aldehydes $^{287}$ (Scheme 111). The catalyst diphenylprolinol trimethylsilyl ether $^{288}$ was found to be promising both for the initiation of the reaction and for the induction of chirality. Different organic acids and bases as additives had a positive influence on the enantioselectivity of the desired chromenes. Notably, in the presence of imidazole and $p$-chlorobenzoic acid as additives the enantioselectivity of the reaction increases, although in both cases the reaction became very sluggish producing the product in a much reduced yield.

The actual mechanism of this reaction was not clear at the time, but the rapid formation of the iminium ion $^{291}$ was detected, and the authors proposed an oxa-Michael addition reaction as the rate-determining step (Scheme 112).

3.3. At around the same time Córdova and co-workers independently developed almost the same organocatalytic methodology for the synthesis of optically active chromenes as described in section 3.2.$^{64}$ The authors also reported the chiral synthesis of 2-substituted-2H-chromene-3-carbaldehydes via an organocatalytic enantioselective domino oxa-Michael/aldol condensation reaction, using the same organocatalyst $^{288}$ as reported by Arvidsson. The reaction was found to proceed smoothly with a wide range of differently substituted $\alpha,\beta$-unsaturated aldehydes affording the desired chromenes in moderate to high yields with quite high enantiomeric excesses. The best enantioselectivities were obtained with electron-deficient aldehydes, although the yields were moderate. Interestingly, the use of molecular sieves for the removal of water led to higher yields for the same reactions without compromising the enantioselectivity (Scheme 113).

The proposed mechanism is shown in Scheme 114. The reaction proceeds through the initial iminium ion activation of intermediate along with boronate complex $^{284}$. Finally, the activated complex $^{284}$ undergoes nucleophilic addition to the pyrylium intermediate yielding the desired chromene $^{285}$ (Scheme 109).
α,β-unsaturated aldehyde 287 by the organocatalyst 293 followed by nucleophilic attack of the phenolic OH of salicylaldehyde 73. Then oxa-Michael addition takes place on the Re-face of the chiral iminium intermediate 294 to produce the enamine intermediate 295. Subsequently, the enamine attacks the C==O of salicylaldehyde to produce the cyclic iminium ion intermediate 296 which upon hydrolysis affords chromanol 297. Elimination of water produced the final chromene product 298. The proposed mechanism is in complete agreement with the experimental findings; the presence of organic acids as additives plausibly accelerates the reaction by stabilizing the iminium ion intermediate as well as by activating the benzaldehyde moiety for intramolecular 6-exo-trig aldol condensation. Similarly, addition of molecular sieves facilitates the removal of water from the reaction medium, thus driving the condensation forward to the product.

3.4. Using an almost identical approach, Wei and Wang reported the synthesis of chiral chromenes employing (S)-diphenylprolinol triethylsilylether 299 as the chiral organocatalyst and benzoic acid as the cocatalyst. This method also works efficiently with different salicylaldehydes and trans-
cinnamaldehydes, affording the corresponding chromenes in high yields (53–98%) with good to excellent enantioselectivity (75–99% ee) (Scheme 115). The enantioselectivity was found to be sensitive to the electronic nature of the cinnamaldehyde; a comparatively better enantiomeric excess was obtained with trans-cinnamaldehyde containing electron-withdrawing groups than the ones with electron-donating substituents. On the contrary, the substituents on the salicylaldehyde did not have much effect on the reaction.

3.5. Xu et al. described a one-pot asymmetric synthesis of 3-nitro-2H-chromenes via an enantioselective domino oxa-Michael/aza-Henry condensation between salicylaldehydes and nitro-olefins. They used a chiral secondary amine organocatalyst along with an organic acid as cocatalyst, which promotes the reaction via aromatic iminium activation. This is probably the first report of activation of aromatic aldehydes through iminium-formation in a domino oxa-Michael/aza-Henry condensation in which a bifunctional organocatalyst is used. It is noteworthy to mention that 3-nitro-2H-chromenes are very important compounds because they can be modified to flavonols, amines and other bioactive target compounds.

The catalyst and salicylic acid as cocatalyst afforded the highest yield and the highest enantiomeric selectivity of the desired chromenes in polar solvents. This method is quite versatile, producing high enantioselectivities (85%) with differently substituted salicylaldehydes (Scheme 116).

The proposed mechanism (Scheme 117) involves iminium activation of salicylaldehyde to produce intermediate which is also activated by the Lewis base moiety X present in the organocatalyst. The iminium intermediate then participates in a domino oxa-Michael/aza-Henry condensation with β-nitrostyrene to produce intermediate. Finally, product eliminates from intermediate, thus regenerat-
The proposed reaction proceeds over that in which only amine acid/base system (Scheme 119) not only increased the rate of catalyst and (conditions revealed that pipecolinic acid showed the highest dinitroguanidine (TMG) and pipecolinic acid for screening. No cocatalyst selected simple catalysts like guanidine, 1,1,3,3-tetramethylguanidine (TMG) and pipecolinic acid for screening. No cocatalyst was employed under reaction conditions that helped the formation of the iminium ion intermediate and activates the ω-nitrostyrene by H-bonding to the nitro oxygen (TS-308).

3.6. The enantioselective tandem oxa-Michael-aldol type reaction for the synthesis of optically active chromenes was further improved by the use of a combination of a chiral amine and a chiral acid organocatalytic system. After extensive screening, Xu and co-workers found67 that the combination of (S)-diphenylpropyltrimethylsilylether 288 as organocatalyst and (S)-Mosher acid 309 as cocatalyst produced the highest yields and enantioselectivities. Notably, this new chiral acid/base system (Scheme 119) not only increased the rate of the reaction but also improved the selectivity of the reaction over that in which only amine 288 was employed under identical reaction conditions. The proposed reaction proceeds via a similar pathway as the other oxa-Michael-aldol type reactions discussed above (Scheme 120).

3.7. Das and Evans reported68 another related organocatalytic domino oxa-Michael-aldol reaction for the synthesis of 2-substituted-3-nitro-2H-chromenes by employing some selected simple catalysts like guanidine, 1,1,3,3-tetramethylguanidine (TMG) and pipercolinic acid for screening. No cocatalyst was used during the reaction. Optimization of the reaction conditions revealed that pipercolinic acid showed the highest efficiency, affording the best yields, but with poor enantioselectivity (5−17%). Substrate screening revealed that irrespective of the difference in the electronic nature of the substituents on the salicylaldehyde, the yields were high in all cases (70−80%) (Scheme 121).

3.8. The domino oxa-Michael/aza-Henry condensation of salicylaldehydes 300 with α,β-unsaturated aldehydes 287 was further improved by the use of a recyclable tertiary amine-modified diarylprolinyl silyl ether 315 as an effective organocatalyst.69 The reaction worked best in the presence of p-chlorobenzoic acid and molecular sieves. The enantioselectivity of previously reported prolinol catalysts for these reactions (72−90% ee) could be increased up to 94% ee with improved yields with catalyst 315 (Scheme 122).

3.9. Another useful organocatalytic method was developed70 using bifunctional thiourea as catalyst to synthesize chiral 2-aryl-3-nitro-2H-chromenes via a tandem oxa-Michael−aza-Henry-desulfonamidation reaction (Scheme 123). The initial exploration of the reaction of salicylaldehyde 73 and nitrostyrene 316, thiourea 317 showed the highest catalytic activity compared to other quinine derivatives although the yield (21%) and enantioselectivity (9% ee) were unsatisfactory (Scheme 123). The intermediate nitrochromane 319 was also isolated in 66% yield as a single diastereomer (>99% de) but with no enantioselectivity (Scheme 123).

By a slight modification of the reaction conditions, using activated aldimines as aldehyde surrogate, both the yield and enantioselectivity were significantly increased. Salicylaldehyde N-tosylamine reacts with nitrostyrene in the presence of thiourea 317 as organocatalyst to produce the desired chromene in 52% yield with 49% ee at room temperature (Scheme 124). Further modification by lowering the reaction temperature to 0 °C improved the ee to 92%, but the yield was compromised (31%). Both electron-donating and electron-withdrawing groups in nitrostyrene are tolerated, affording moderate to good yields. Interestingly, with salicylaldehyde N-tosylamine containing electron-withdrawing groups in the chromenes were produced in comparatively higher yields but with a moderate enantioselectivity, whereas electron donating groups gave lower yields with comparatively higher enantioselectivities (Scheme 124).

3.10. Recently, Samet et al. developed71 a chiral-pool synthetic strategy for the synthesis of optically active pyrano[3,4-b] chromenes 322 from the stereoselective domino oxa-Michael-aldol reaction between 2-hydroxy benzaldehyde and a chiral α,β-unaturated ketone called evogluconesene 321, well-known for its application in asymmetric synthesis (Scheme 125). Notably, the chirality in the chromene product originates from the attack of the phenolate anion occurring on the opposite side of the anhydro bridge. In general, the reaction proceeded smoothly with most of the substrates tested, except for 5-nitro-salicilaldehyde, which showed exceptionally slow reactions leading to a low yield.

3.11. The synthesis of 3-nitro-2H-chromenes via an enantioselective tandem oxa-Michael/Henry reaction using a chiral amine as the catalyst was reported simultaneously by Xu and co-workers (Scheme 116)66a and by Sankararaman and co-workers.66b However, their methods have several drawbacks such as low ee, low yields, and long reaction times (Scheme 116). In 2010, Xie et al. reported an efficient alternative route for the synthesis of optically active 3-nitro-2H-chromenes involving kinetic resolution (Scheme 126).72

The authors cleverly used a chiral thiourea-derived organocatalytic system, which renders selective asymmetric formal [3 + 2] cycloaddition of azomethine ylides with one enantiomer of nitro-chromene to form multifunctional benzopyrano-pyrrolidine derivatives leaving behind the other enantiomer. Several chiral thiourea catalysts were tested for this reaction and Takemoto’s catalyst 328 (Figure 5) was found to be most effective. Reactions with differently substituted chromenes and α-amino malonate imines in the presence of 10 mol % of Takemoto’s catalyst produced the desired chromenes with high enantioselectivity (77−85%) (Scheme 127).

3.12. Very recently, Rueping and co-workers developed73 a new synthetic methodology for the enantioselective synthesis of chromenes based on the concept of using chiral organic contact ion-pairs in metal-free catalytic allylic substitutions. The methodology involves the use of a chiral Brensted acid-catalyzed enantioselective allylic alkylation of alcohols, which delivers the substituted optically active product with regener-
ation of the chiral Brønsted acid catalyst. The regenerated catalyst could be utilized for the subsequent enantioselective synthesis of chromenes (Scheme 128 and 129).

Reaction of compound 339 in the presence of the highly acidic organo-catalyst N-trifluorophosphoramidate 338b (Ar = phenyl) at 0 °C in toluene produced the desired chromene 340 in 77% yield with 56% ee (Scheme 129). This could be improved to 76% yield and 88% ee with the same catalyst at −78 °C. Notably, a lower enantioselectivity was observed in any other solvent except toluene. Reactions with catalysts 338b with different substituents present on the BINOL ring exhibit very similar results at lower temperatures (Scheme 129).

This catalytic methodology was found to be quite general and tolerates a wide range of substituents. Both electron-donating and electron-withdrawing groups in the para-position of the aryl ring conjugated to the alkene moiety produced the desired chromenes in good overall yields. However, no chromene product was obtained when the reaction was carried out at −78 °C with meta-chloro substitution, but the reaction proceeded smoothly at −48 °C. The reaction can also tolerate other alkyl substituents at the carbonyl carbon in 339, producing chromenes in excellent yields and with high ee.

3.13. Very recently, Sabater and co-workers reported another organocatalytic approach to 2H-chromenes involving the coupling of salicyaldehyde with different electron-deficient alkenes in the presence of an ionic liquid catalyst 343 (Scheme 130). Although these particular reactions are not enantioselective, they are nonetheless included here in section 3 for completeness. A tandem reaction comprising a Michael addition followed by an intramolecular cyclocondensation produced chromenes in one-pot under solvent free conditions. The best results were obtained starting from salicylaldehyde derivatives and trans-nitrostyrenes as electron acceptors. Notably, in all cases, 100% selectivities toward the corresponding chromene derivatives was achieved. This exceptionally high selectivity can be explained on the basis of the strong electron-withdrawing effect of the nitro group on the double bond that makes the latter more prone to an nucelophilic attack compared to other electron-withdrawing groups. A wide range of substituted salicyaldehyde as well as trans-nitrostyrenes were found to produce the corresponding 2H-chromene in moderate to high yields. It is worth mentioning here that the catalyst can be reused; it retained its high activity and selectivity for at least three reaction cycles. Due to its ionic liquid characteristics, the catalyst can be efficiently extracted from the reaction media by using the appropriate solvent.

4. BRIEF COMPARISON OF MECHANISTIC ASPECTS ENCOUNTERED IN 2H-CHROMENE SYNTHESIS

The reported synthetic methods proceed via a variety of different reaction mechanisms. Especially the metal-catalyzed reactions involve a myriad of different mechanistic aspects. Nonetheless, there are quite a few similarities among the various reported mechanisms. Ring-closure of ortho-quinone methides is a strikingly frequent mechanistic feature in 2H-chromene syntheses. Other recurring mechanistic aspects in 2H-chromene syntheses are water elimination from chroman-4-ol intermediates, annulation reactions, carbene, alkyne, aldehyde, ketone and allene reactions. Friedel–Craft reactions, Diels–Alder reactions, and related cyclo-addition reactions involving salicyl-aldehyde derivatives are also quite common. In a few cases, the authors make efficient use of Pd-allyl reactivity. In the enantioselective organocatalytic approaches, formation of iminium ion intermediates in oxa-Michael/Aldol processes between salicylaldehydes and activated alkenes is a recurring theme.

5. CONCLUSIONS

Several catalytic methods for the synthesis of 2H-chromenes have been reported, each having their specific advantages and disadvantages. The method of choice will strongly depend on the substituents needed. Efficient metal-catalyzed processes are applicable to synthesize a wide variety of differently substituted 2H-chromenes, but only a few examples of enantioselective chromene formation using (transition) metals are reported. These are mostly restricted to palladium-catalyzed ring-closures using chiral catalysts. All other examples of enantioselective 2H-chromene syntheses involve reactions using organocatalysis, some of which give access to excellent enantioselectivities. Yet, there is still much to gain in the development of new enantioselective protocols in 2H-chromene syntheses. High enantioselectivities can be achieved with the reported organocatalytic approaches, but most of these methods are only suitable for the synthesis of 2,3-disubstituted 2H-chromenes. A more general approach to chiral 2H-chromenes remains a challenging but valuable goal, requiring the development of new transition-metal-catalyzed protocols. Furthermore, thus far only a few authors have focused on catalytic postfunctionalization of existing 2H-chromene scaffolds. In particular, transformations of simple 2H-chromene skeletons into more complex biologically active compounds is still in its infancy. Hence, although the catalytic methods developed thus far already have a quite broad applicability in organic synthesis, further development of novel, more general, efficient, and enantioselective methodologies is still warranted.

- NOTE ADDED IN REVISION

While this manuscript was in review, three additional papers appeared describing the synthesis of 2H-chromenes, which are included here as a note added in proof. The group of Alcaide reported the microwave-assisted synthesis of 2H-chromenes 346a–h, starting from allene-substituted aryl ethers 345a–h (Scheme 131). In an analogous reaction using 347, decarbonylation occurs leading to formation of 348.

Scheme 131. Microwave-Assisted 2H-Chromene Synthesis from Allene-Substituted Aryl Ethers

[Diagram showing the synthesis process]
The group of Balci reported an interesting metal-free regioselective approach to synthesize chromenopyridines. The synthetic method involves O-propargylation of aromatic hydroxyaldehydes (such as salicylaldehyde) followed by reaction of the aldehyde moiety with propargylamine. Subsequent intramolecular cycloaddition involving the alkyne and azadiene, which is formed as an intermediate, yields the desired chromenopyridine structures (Scheme 132).

Gulı̇as and co-workers recently reported the Rh/Cu-mediated oxidative coupling of alkenylphenols and allenes to form 2,2-disubstituted 2H-chromenes (Scheme 133). The reaction tolerates a broad range of substituents both in the alkenylphenol and in the allene and most probably proceeds through a mechanism involving a rhodium-catalyzed C–C coupling followed by a pericyclic ring-closing reaction.

The group of Wang and coworkers recently reported a new protocol for 2H-chromene synthesis, based on migratory carbene insertion (Scheme 134). The catalytic reactions have a broad substrate scope and lead to high isolated yields. The proposed reaction mechanism involves oxidative addition of vinyl-bromides followed by carbene formation and migratory insertion. The resulting allyl-palladium(II) compound then cyclizes to form the 2H-chromene products.

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