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Catalytic Synthesis of 2*H*-Chromenes

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ABSTRACT: 2*H*-Chromenes (2*H*-1-benzopyran derivatives) display a broad spectrum of biological activities. The 2*H*-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 2*H*-chromenes and is structured around the three main approaches applied in catalytic 2*H*-chromene synthesis: (I) catalysis with (transition) metals, (II) metal-free Brønsted 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 2*H*-chromene synthesis. However, for a complete overview, synthetic routes involving some stoichiometric steps and reactions producing ring-scaffolds that are closely related to 2*H*-chromenes are also included.

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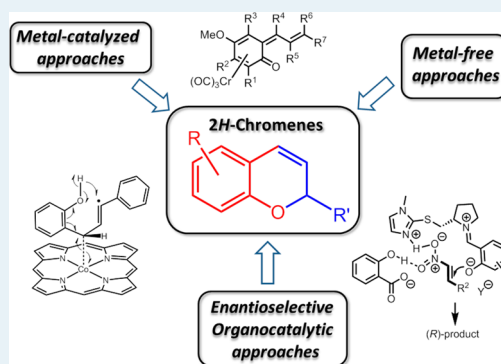
INTRODUCTION

Heterocycles[1] represent 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, 2*H*-chromenes (2*H*-1-benzopyran derivatives) are present in a vast number of natural products[2] (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 2*H*-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, antianaphylatic, diuretic, fungicidal, and anti-HIV activity; additionally, other 2*H*-chromene compounds act as sex-pheromones, are activators of potassium channels, or inhibit the enzymes phosphodiesterase IV and dihydrofolate reductase (Figure 1).[3] Furthermore, 2*H*-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).[4] They even play a key role as a regulator of numerous biopolymers.[5]

The diverse array of biological activities of 2*H*-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 2*H*-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 2*H*-chromene synthesis: (I) catalysis with (transition) metals, (II) metal-free Brønsted and Lewis acid/base catalysis, which includes a few examples of nonenantioselective organocatalytic reactions, and (III) enantioselective organo-catalysis. First the
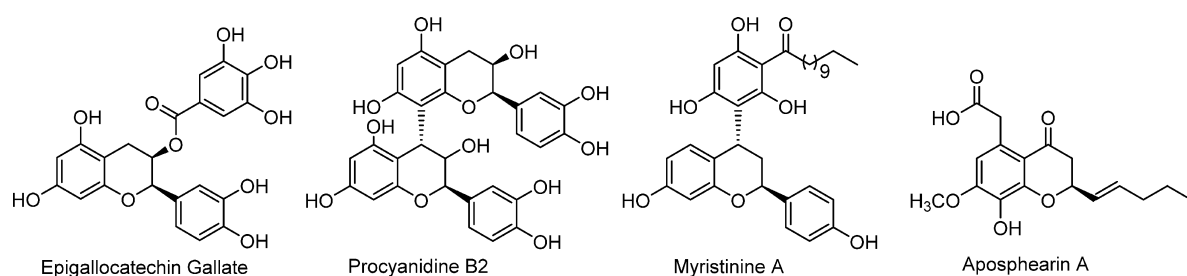
Figure 1. Selected examples of natural products containing 2H-chromenes and related scaffolds.
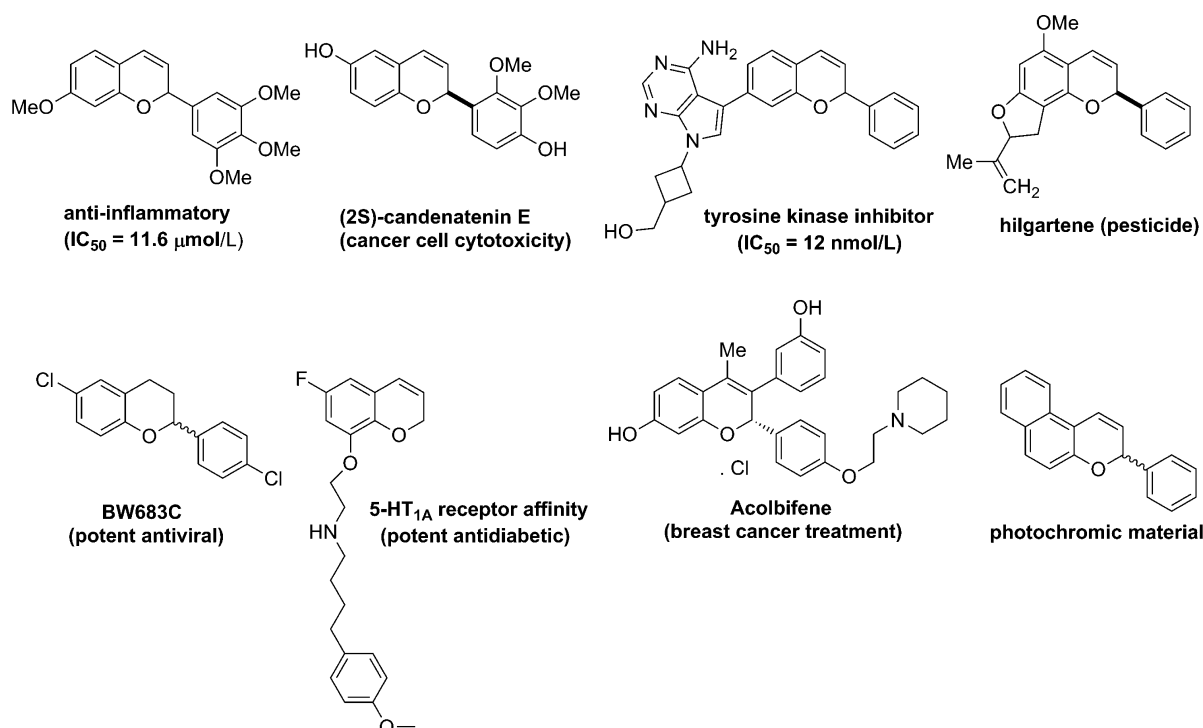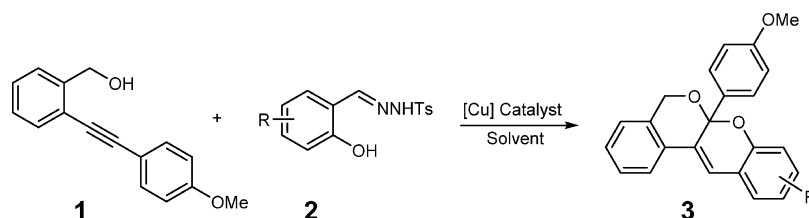

Figure 2. Selected examples of pharmacologically active and photochromic compounds based on 2H-chromenes and related scaffolds.

Scheme 1. Synthesis of Isochromeno[3,4-b] Chromenes via a Copper(II)-Promoted Tandem Reaction of an Internal Alkynol and Salicyl N-tosylhydrazone


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 ring-scaffolds 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
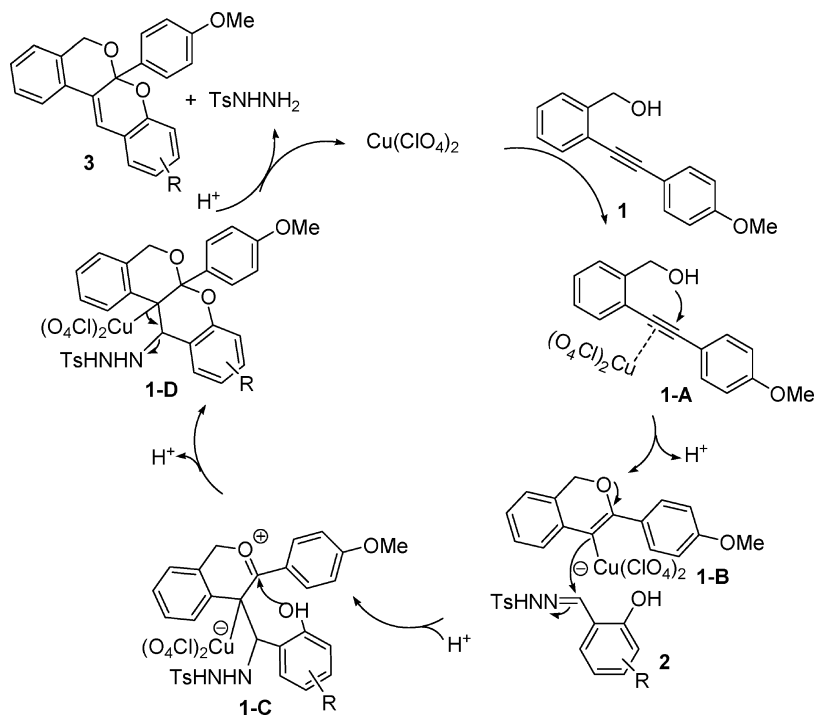
Scheme 3. Synthesis of 2H-Chromenes by Fe-Catalyzed Intramolecular Alkyne-Carbonyl Metathesis
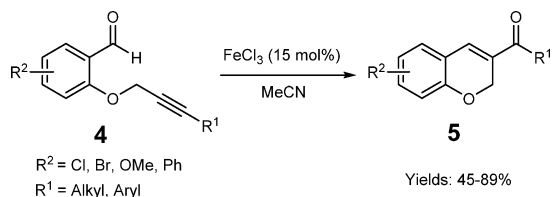
Scheme 4. Proposed Mechanism of Fe-Catalyzed 2H-Chromene Synthesis Involving Intramolecular Alkyne-Carbonyl Metathesis
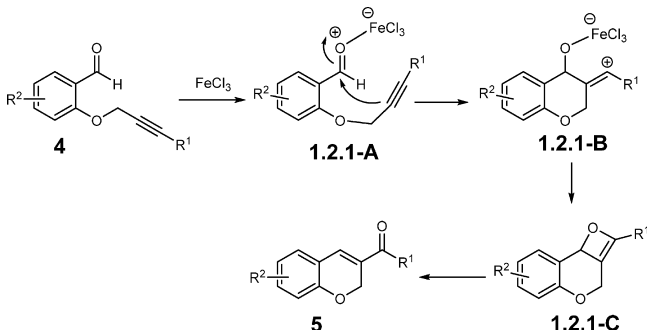
Scheme 5. 5H-Naphtho[1,2-c] Chromenes via Fe-Mediated [3 + 3]-Annulation
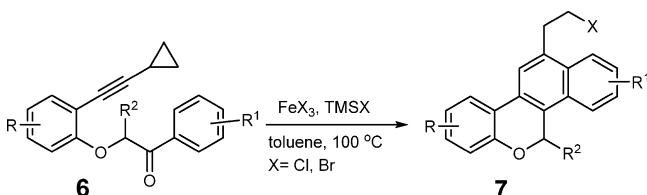
Scheme 6. Conversion of 8 to 9 and 10 to 11
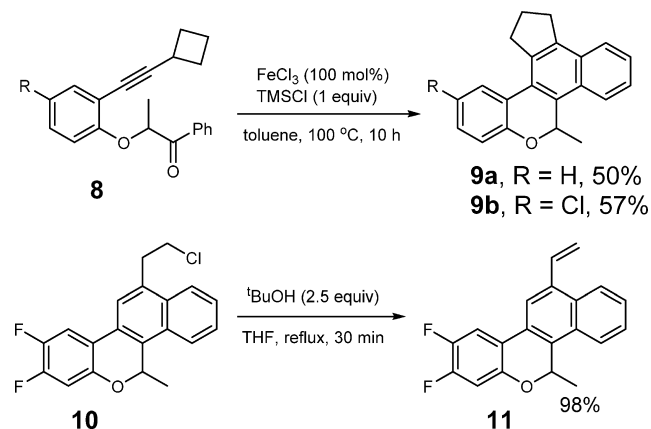
tandem reaction of internal alkynol and salicyl-N-tosylhydrazone to produce isochromeno[3,4-b]chromene (Scheme 1).[6] This methodology works best with copper(II)perchlorate as the catalyst in a toluene/dioxane (1:4) solvent mixture at 60 °C.

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, para, or at meta 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-pentylphenyl alkynols are also tolerated, although leading to

Scheme 7. Proposed Mechanism for the Formation of 5H-Naphtho[1,2-c] Chromenes via Fe-Mediated [3 + 3]-Annulation
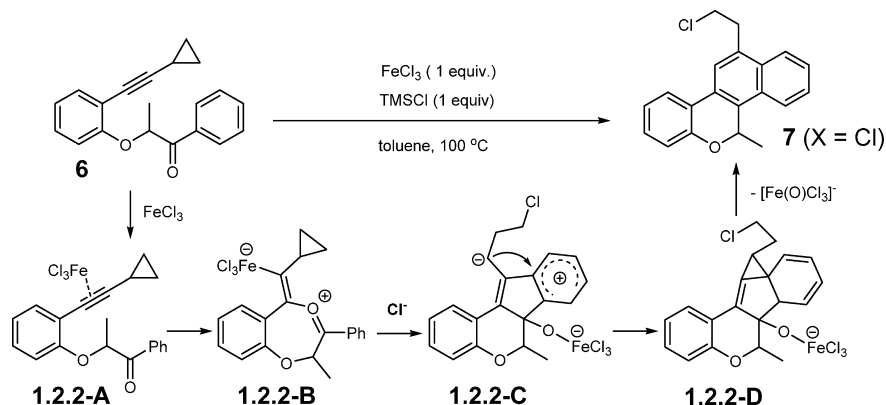
Scheme 8. Possible Pathways for Metal-Mediated Hydroaryloxylation
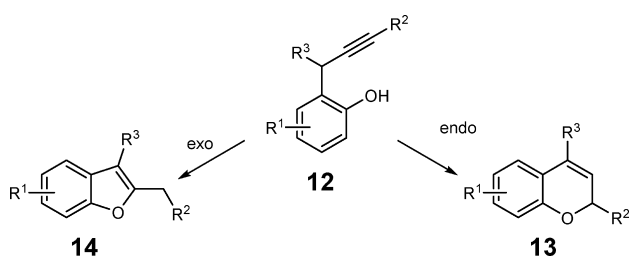
Scheme 9. 2H-Chromenes Obtained by Fe-Catalyzed Hydroaryloxylation
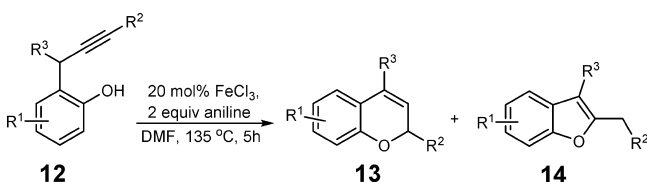
Scheme 10. Synthesis of 2H-Chromenes by Reaction of an α,β-Unsaturated Fischer Carbene Complex of Chromium with a Propargyl Ether

Scheme 11. Plausible Mechanism of 2H-Chromene Formation from Chromium Fischer-Type Carbenes
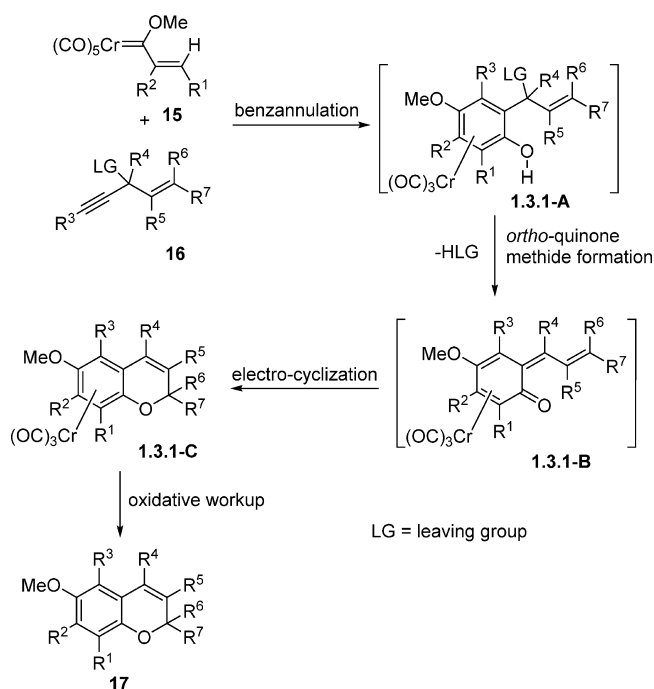
The proposed mechanism is outlined in Scheme 2. The reaction is suggested to proceed via an initial activation of the alkyne by $[Cu(ClO_4)_2 \cdot 6H_2O]$, which enhances the electrophilicity of the alkyne. In the next step, intramolecular addition of the hydroxyl group to the electron-deficient alkyne produces the vinyl-copper intermediate **1-B**. Notably, in the presence of 3 equiv of ^tBuOK or Cs_2CO_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 $TsNHNH_2$ 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

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.

Scheme 12. Co^{II}(porphyrin)-Catalyzed Synthesis of 2H-Chromenes from the Reaction of N-Tosylhydrazones and Terminal Alkynes
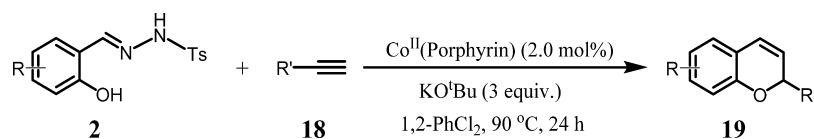
Scheme 13. Proposed Mechanism for Cobalt-Porphyrin-Mediated 2H-Chromene Synthesis by Coupling Salicyl-tosylhydrazones with Terminal Alkynes
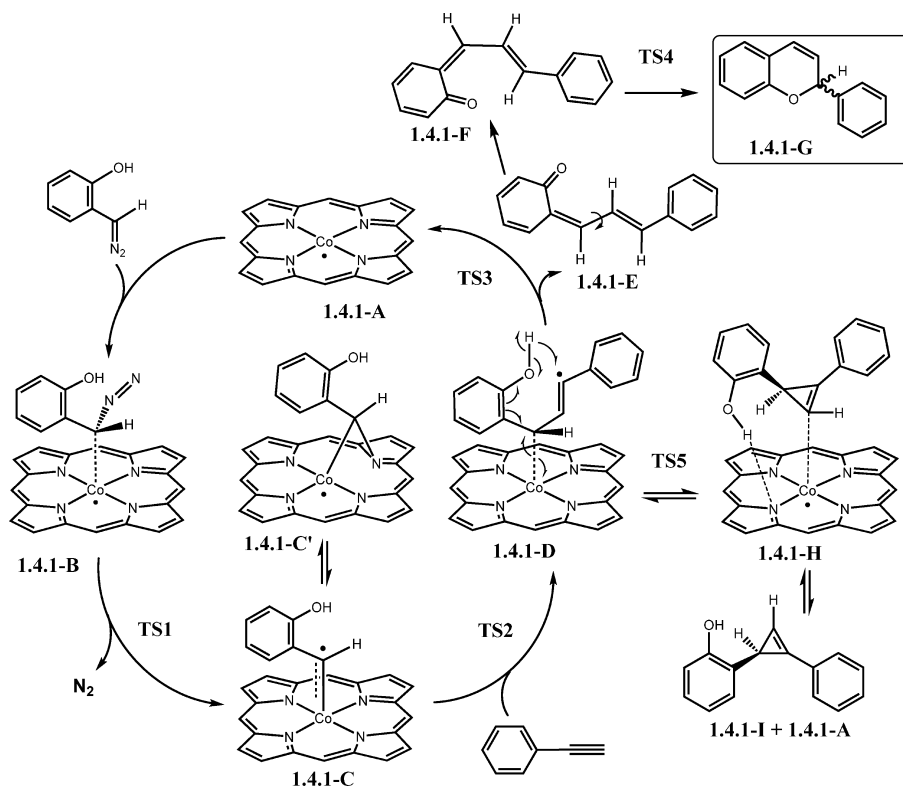
Scheme 14. Au-Catalyzed Synthesis of 2H-Chromenes from Aryl Propargyl Ether
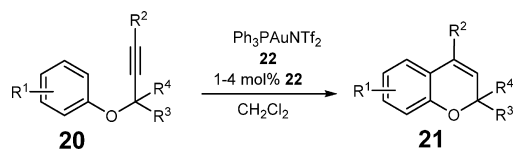
for the synthesis of 3-substituted 2H-chromenes via an iron-catalyzed intramolecular alkyne-carbonyl metathesis reaction.[7] The 3-substituted 2H-chromenes **5** were obtained in high yields

from the simple alkynyl ethers of salicyaldehyde **4** in the presence of 15 mol % FeCl$_3$ 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 salicyldehyde does not alter the yield of the products. Reactions with naphthalene and biphenyl systems produced the corresponding chromenes in good yields. Alkyl-substituted alkynes were also found to be suitable for this

Scheme 15. Synthesis of 24−26, 28, and 29
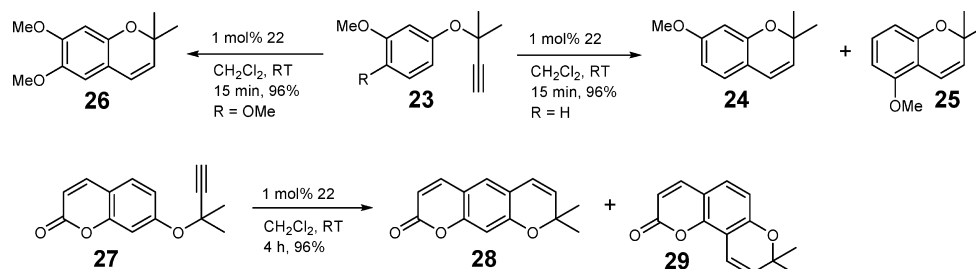
Scheme 16. Synthesis of Chromene-Containing Natural Products 31 and 33
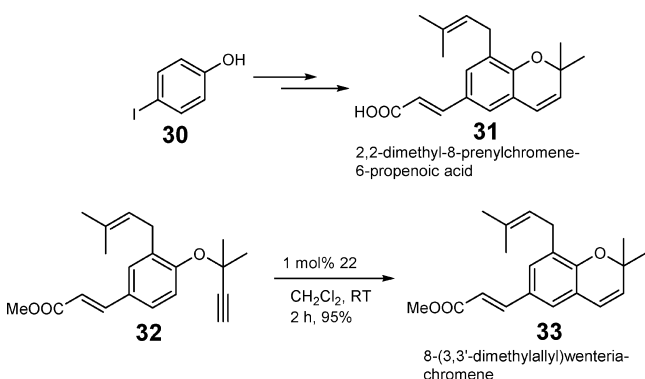
Scheme 17. Au-Catalyzed Dehydrative *Endo*-Cyclization
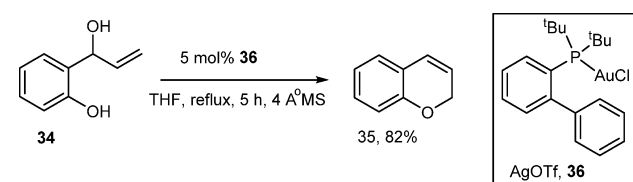
Scheme 18. Au-Catalyzed Synthesis of 2*H*-Chromenes via Cycloisomerization
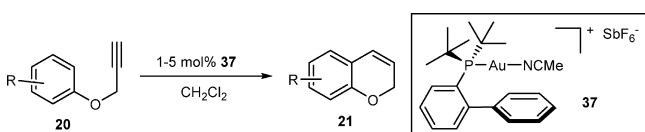
Scheme 19. Gold(I)-Catalyzed Synthesis of 1*H*-Isochromenes via Insertion/Cyclization of *o*-Acetylenyl-Substituted Phenyldiazoacetates
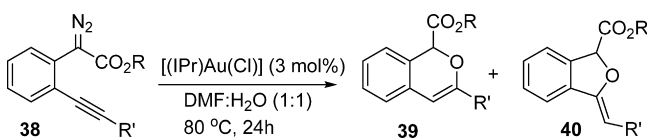
Scheme 20. Proposed Mechanism for the Gold(I)-Catalyzed Synthesis of 1*H*-Isochromenes
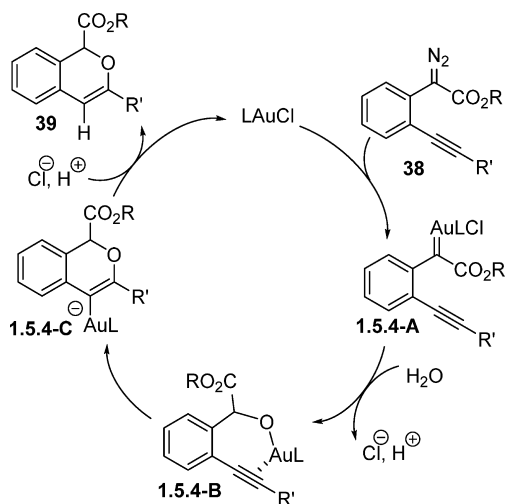
Scheme 21. Pd-Catalyzed Enantioselective Synthesis of 2-Aryl-Chromenes
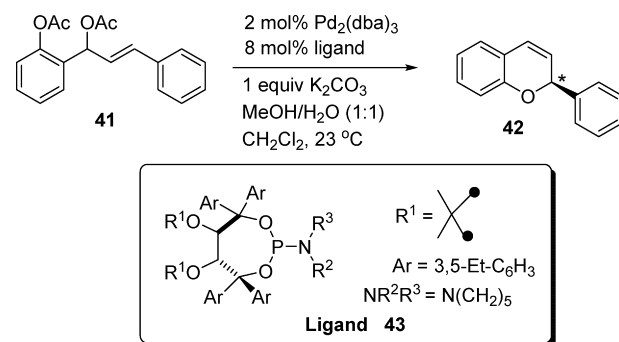
Scheme 22. Proposed Mechanisms for Pd-Catalyzed Enantioselective Synthesis of 2-Aryl-Chromenes
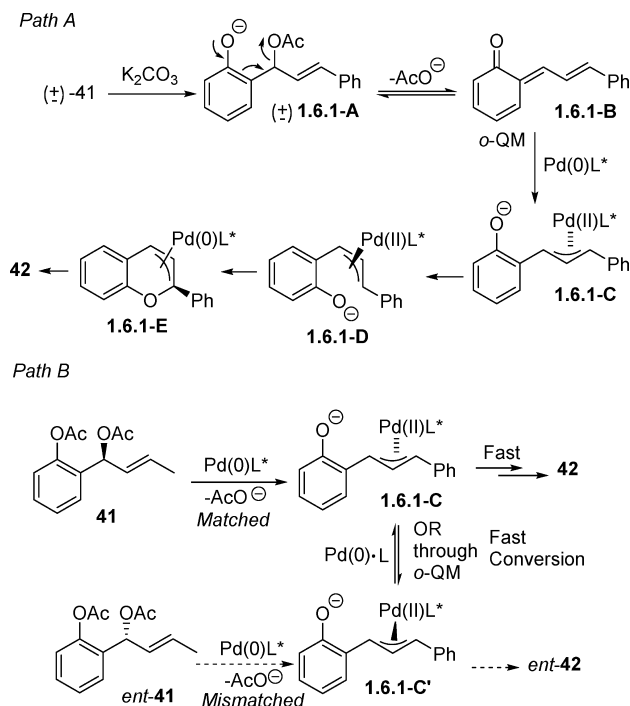
Scheme 23. Cu-Catalyzed Enantioselective Allylic Alkylation of 43 with Cu/Taniaphos ((R,R)-45) and Grignard Reagents
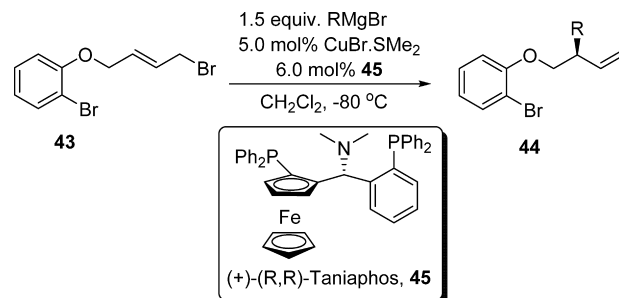
reaction, but simple propargyl ethers with terminal alkyne units were unreactive.

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 FeCl$_3$ catalyst, followed by nucleophilic

Scheme 24. Intramolecular Heck Reaction on Chiral Substrate 44
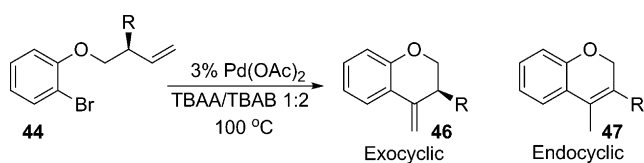
Scheme 25. Pd-Catalyzed Cyclization of Aryl Propargyl Ethers
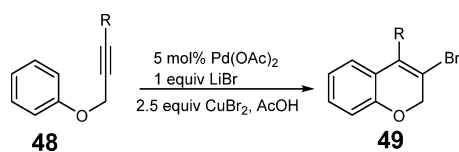
attack of the alkyne on the aldehyde producing oxetene intermediates **1.2.1-C** via the vinyl-cation intermediates **1.2.1-B**. Finally, the 2*H*-chromenes **5** are formed via an electrocyclic ring-opening of the oxetene intermediates **1.2.1-C**. Notably, the exact role of FeCl$_3$ in the process is yet to be understood in detail.

1.2.2. Recently, Li and co-workers reported an iron-mediated protocol for the synthesis of 5*H*-naphtho[1,2-*c*] chromenes using 2-(2-ethynyl) phenoxy-1-aryl ethanones in the presence of 1 equiv of FeCl$_3$ and 1 equiv of TMSCl at 100 °C in toluene (Scheme 5).[8] 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 with substrate **6**. The resultant products from the cyclopropyl substituents **6** contain an interesting halo-ethyl group on the naphthalene moiety. One can use this halo-ethyl group for the incorporation of new functionalities in these systems such as dehydrohalogenation of product, which gives an alkene in near quantitative yield for **11** (Scheme 6).

Unlike the mechanism proposed by Jana et al.,[7] this reaction mechanism involves the initial activation of the alkyne by FeCl$_3$ 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 FeCl$_3$ 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).[9] It is noteworthy that during metal-mediated hydroaryloxylation of propargyl phenols, usually five-membered rings are formed via an *exo*-attack although according to Baldwin's rules, both *exo-dig* and *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-*endo-dig* mode of cyclization consistently predominated over the 5-*exo-dig* mode of cyclization except for a few cases where both five- and six-membered rings were obtained.

1.3. 2*H*-Chromenes Synthesized from Chromium-Carbenes. In 2012, Wulff and co-workers reported[10] a new route to synthesize 2*H*-chromenes from the reaction of an α,β-unsaturated Fischer-type carbene complex of chromium with a propargyl ether bearing an alkenyl 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-yne proceed via an initial benzannulation reaction that produces a chromium tricarbonyl complexed phenol **1.3.1-A**. Subsequently, loss of a silanol generates an *o*-quinone methide intermediate **1.3.1-B**, which then undergoes a six-electron electrocyclic ring closure to furnish the desired 2*H*-chromene. The reaction is found to be general, affording good to high yields of a variety of 4-alkoxychromenes with mono- and disubstituted alkenyl carbene complexes as well as with mono-, di-, and trisubstituted 3-silyloxypent-4-en-1-ynes.

Scheme 26. Proposed Mechanisms for Pd-Catalyzed Cyclization of Aryl Propargyl Ethers
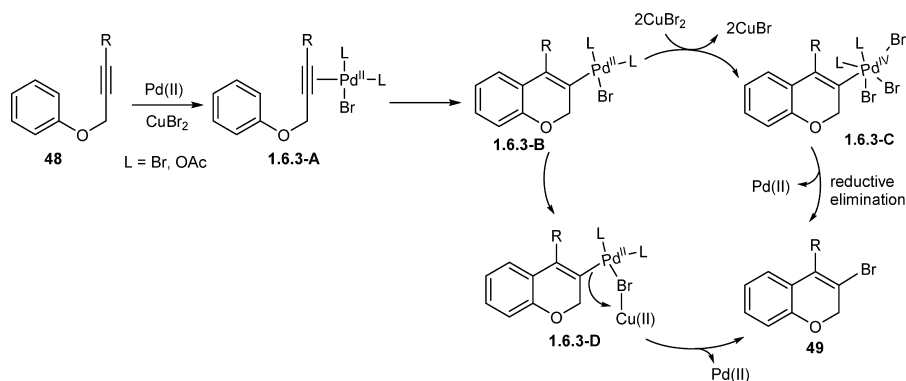
Scheme 27. Pd-Catalyzed Multicomponent Synthesis of Chromenes

R^1 = C_6H_5, 4-OMe-C_6H_4, 2-F-C_6H_4, 4-CF$_3$-C_6H_4, (CH$_2$)$_3$CN, ^{t}Bu, (CH$_2$)$_4$CH$_3$, cyclic secondary alcohol, tertiary alcohol
Ar = aryl, het-aryl
R^2 = Me, iPr, t-Bu, Bn, 4-NO$_2$-C_6H_4
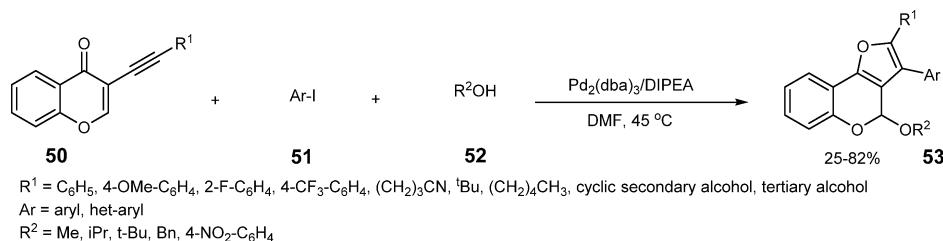
Scheme 28. Proposed Mechanism of the Pd-Catalyzed Multicomponent Synthesis of Chromenes

Notably, a chromium tricarbonyl complexed chromene can be isolated as the primary product **1.3.1-C** of the reaction, which during the workup by an oxidizing agent loses the metal to produce the chromene **17** (Scheme 11). The authors also extended the synthetic protocol for the synthesis of 2*H*-benzo[h]-chromenes. To further extend the synthetic utility, racemic vitamin E was synthesized in overall 73% yield.

1.4. Cobalt-Catalyzed 2*H*-Chromene Synthesis.
Recently, de Bruin and co-workers developed a new [Co^{II}(porphyrin)] catalyzed synthetic route to 2*H*-chromenes. The reaction involves the use of salicyl-*N*-tosylhydrazones and terminal alkynes (Scheme 12).[11] 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** (see Scheme 13). Treatment of tosylhydrazone with base affords the corresponding diazo compounds, which in the presence of [Co^{II}(porphyrin)] as the catalyst produce the corresponding Co(III)-carbene radical intermediates. Subsequent radical addition of terminal alkynes produce salicyl−vinyl radical intermediates **1.4.1-D**. Subsequent hydrogen at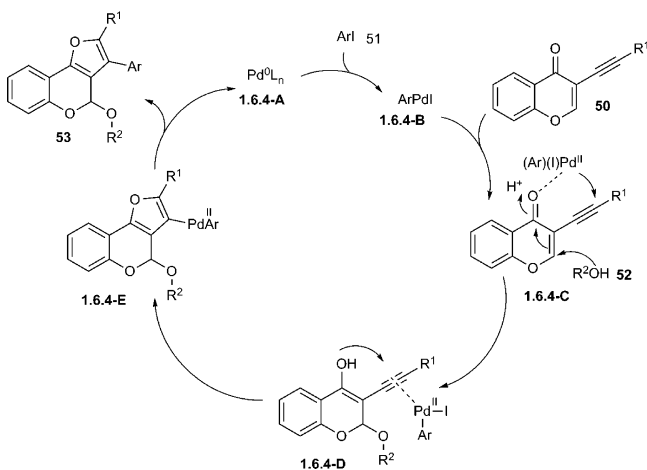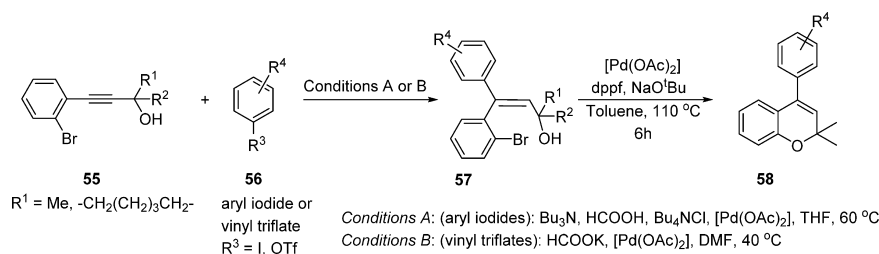om transfer (HAT) from the hydroxy group of the salicyl moiety to the vinyl radical leads to the formation of 2*H*-chromenes. The proposed metallo-radical mechanism was further supported by EPR and DFT calculations. Notably, EPR spectroscopy and controlled radical-trapping experiments with TEMPO are in agreement with the proposed radical mechanism. Moreover, DFT calculations reveal the formation of the salicyl−vinyl radical intermediate by a metalloradical-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 2*H*-chromene (Scheme 13). Notably, even in the presence of chiral porphyrin catalysts, no enantioselectivity was obtained.

1.5. Gold-Catalyzed 2*H*-Chromene Synthesis.
1.5.1. Stratakis and co-workers synthesized 2*H*-chromenes form propargyl aryl ethers using Ph$_3$PAuNTf$_2$ **22** as a catalyst (Scheme 14).[12] 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 2*H*-chromenes are high in comparison to that of unsubstituted 2*H*-chromenes. Moreover, in the cases of substrates bearing strong-electron-withdrawing groups (viz., NO$_2$, CN, and CO$_2$Me), ∼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.

Scheme 29. Pd-Catalyzed Hydroarylation/C−O Coupling Sequence To Produce 2*H*-Chromenes

R^1 = Me, -CH$_2$(CH$_2$)$_3$CH$_2$-

aryl iodide or vinyl triflate
R^3 = I, OTf

Conditions A: (aryl iodides): Bu$_3$N, HCOOH, Bu$_4$NCl, [Pd(OAc)$_2$], THF, 60 °C
Conditions B: (vinyl triflates): HCOOK, [Pd(OAc)$_2$], DMF, 40 °C

Scheme 30. Palladium-Catalyzed Synthesis of Phosphonated Naphthol[2,3-*c*] Chromenes from 2-Bromoaryl Allene and 2-Alkynylphenol
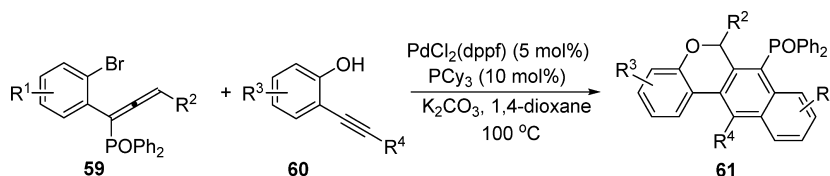
Scheme 31. Proposed Mechanism of the Palladium-Catalyzed Synthesis of Phosphonated Naphthol[2,3-*c*]Chromenes
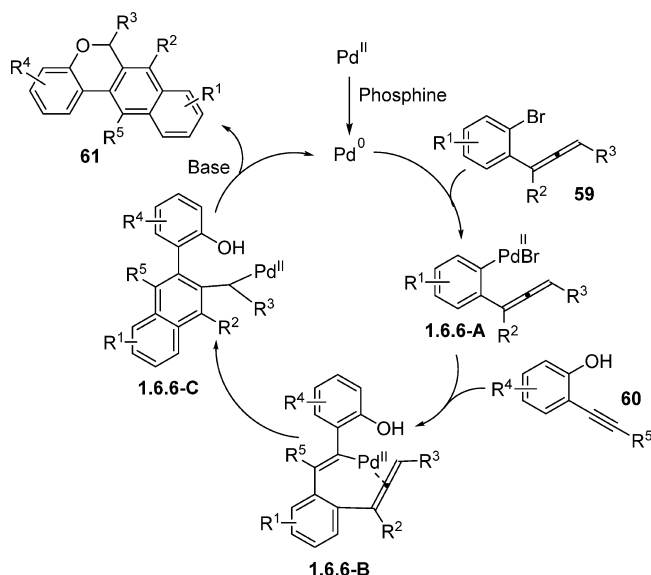
To showcase the applicability of this protocol, the synthesis of some chromene containing natural products was explored. Compound **24** (Precocene I) was prepared from the propargyl ether **23** and was obtained in a 3:1 ratio with its regioisomer **25**. Notably, under thermal conditions (boiling in *N,N*-diethylaniline) 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 2*H*-chromene **33** in almost quantitative yield (Scheme 16).

1.5.2. In a recent report,[13] 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 2*H*-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 dioxolane 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[14] for the synthesis 2*H*-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[15] 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 2*H*-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[16] a gold(I)-catalyzed reaction of water with *o*-acetylenyl-substituted phenyldiazoacetates affording 1*H*-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)

Scheme 32. Polymer Supported Pd-Mediated Synthesis of Chromenes
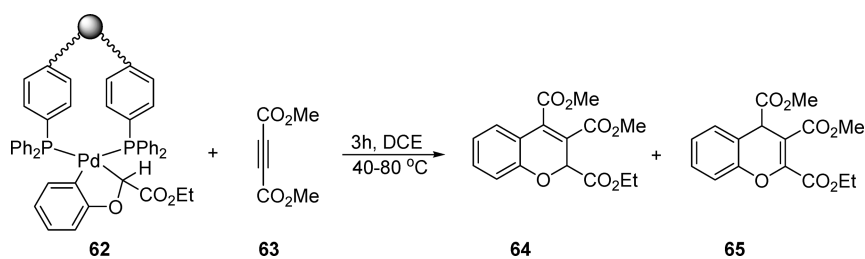
Scheme 33. Synthesis of 2H-Chromenes in a Ga-Catalyzed Multicomponent Reaction
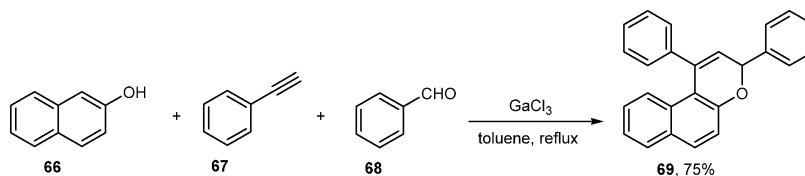
Scheme 34. Proposed Mechanism of the Ga-Catalyzed Multicomponent Synthesis of 2H-Chromenes
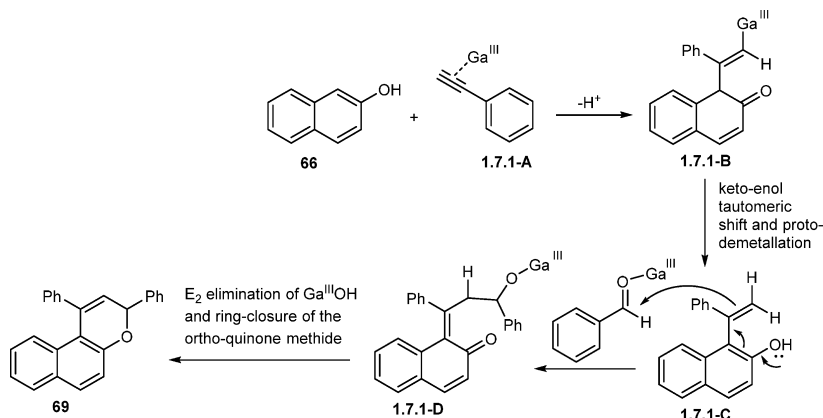
Scheme 35. Synthesis of Chromenes via Re-Catalyzed Cyclocondensation

Scheme 37. Yb-Catalyzed Synthesis of 2H-chromenes
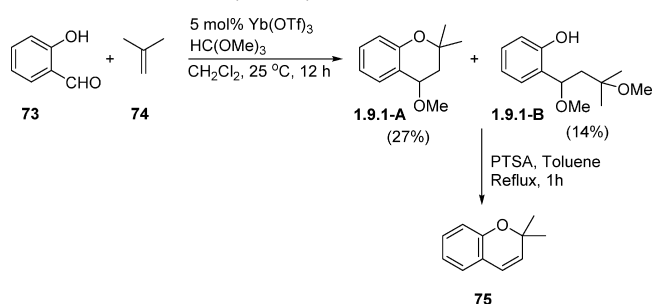
Scheme 38. Yb-Catalyzed Synthesis of Spirochromene

complexes [(PMe$_3$)Au(Cl)] and [(IPr)Au(Cl)] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) 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 from 5-exo-dig cyclization were both obtained in nearly equal amounts in combined yield of 95%. Interestingly, in a mixture of H$_2$O 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 H$_2$O 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[17] 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.

Scheme 36. Proposed Mechanism of Re-Catalyzed Cyclocondensation to form 2H-Chromenes
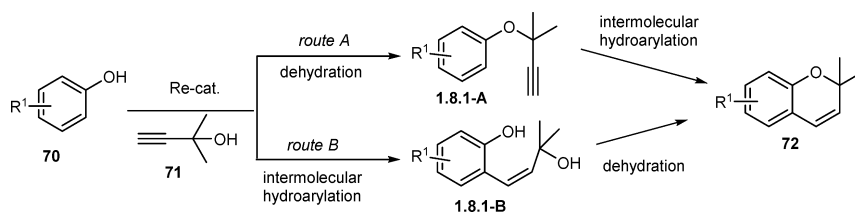
Scheme 39. AlCl$_3$-Catalyzed Synthesis of Chromenes via Intramolecular Cyclization

R = H, OMe, Me, Cl, CN, NO$_2$
R' = CF$_3$, C$_3$F$_7$, C$_5$F$_{11}$
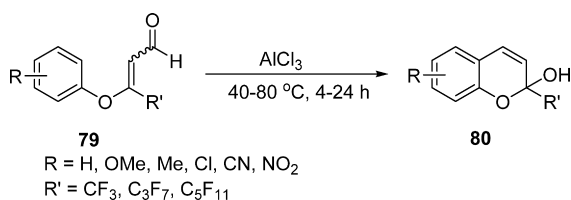
Scheme 40. Eco-Zn-Catalyzed Synthesis of 2H-Chromenes from Biomass

Scheme 42. Synthesis of (−)-Cordiachromene Analogue 88

88 55%, 54% ee   89 11%, 18% ee

87
(P,R,R)-iPr-SPRIX
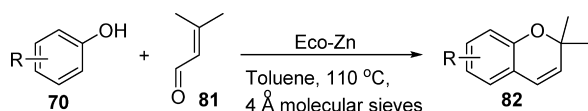
Two plausible mechanisms (**Path A** and **Path B**) for this particular reaction are displayed in Scheme 22. The reaction is believed to proceed with the reaction of either enantiomer of **41** with potassium carbonate and methanol producing the nucleophilic phenoxide in situ via deacylation (**1.6.1-A, Path A**). In the next step, ejection of the secondary acetate forms the achiral *trans-ortho*-quinone methide (*o*-QM, **1.6.1-B**). Subsequent coordination of the chiral catalyst derived from ligand **43** generates 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 diasteromeric 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[18] a highly enantioselective synthesis of chiral chromenes 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 CH$_2$Cl$_2$ in the presence of catalytic amounts of CuBr·SMe$_2$ and (R,R)-(+)-Taniaphos **45** at −80 °C, produce **44** in high yields with excellent enantioselectivity (99% ee) (Scheme 23).
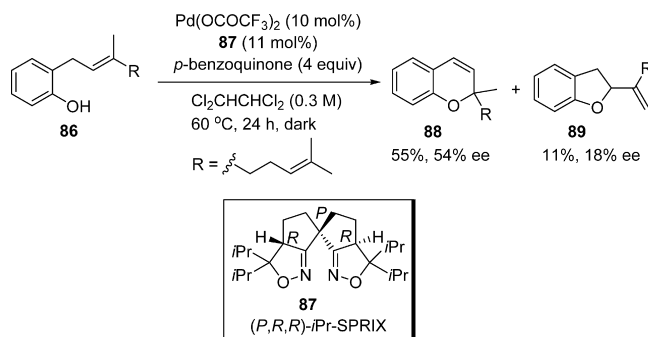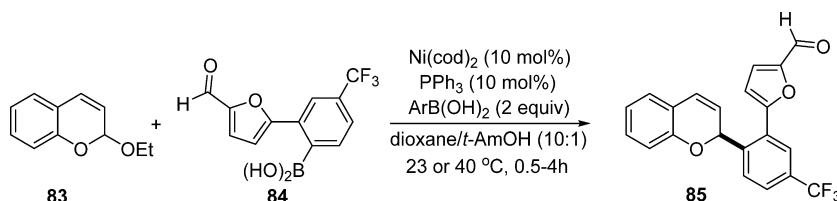
Notably, few linear products were formed (branched vs linear ratios >20:1). Reactions with functionalized alkenyl Grignard reagents also affords the corresponding products **44** in high yields, which also allows further ring closing metathesis

functionalization after the Heck reaction. In the next step, during Heck reaction under standard conditions (catalytic amounts of Pd(OAc)$_2$ and PPh$_3$ and Bu$_4$NBr as an additive in MeCN or DMF), compound **44** is converted to a mixture of the bicyclic compounds **46** and **47** (37% yield) (Scheme 24). The obtained product mixture always consisted of an approximately 70:30 mixture of the expected *exo*-cyclic olefin **46** and its isomer **47** with the olefin in the internal position. Surprisingly, under slightly modified reaction conditions (compound **44** in a molten mixture of tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAA) 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 (**47**) was observed.

1.6.3. 4-Substituted-3-bromo-2H-chromenes were synthesized[19] via a simple cyclization reaction of simple aryl propargyl ethers using Pd(OAc)$_2$ as catalyst with stoichiometric quantities of CuBr$_2$ 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 [CuBr$_2$] 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.

Scheme 41. Ni(0)-Catalyzed Synthesis of 2H-chromenes via Cross-Coupling of Chromene Acetals and Boronic Acids

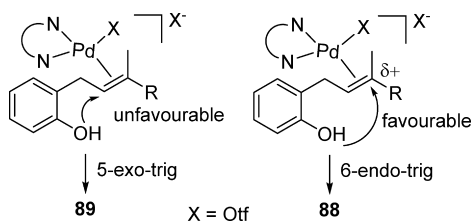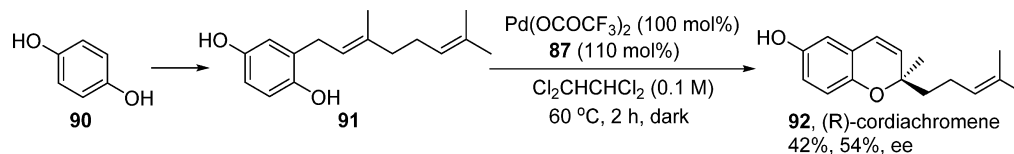**Scheme 43. Synthesis of (−)-Cordiachromene via Modified Conditions**

Pd(OCOCF$_3$)$_2$ (100 mol%)
87 (110 mol%)
Cl$_2$CHCHCl$_2$ (0.1 M)
60 °C, 2 h, dark

90   **91**   **92**, (R)-cordiachromene
42%, 54%, ee

Figure 3. 5-Exo-trig versus 6-endo-trig cyclization.

5-exo-trig   6-endo-trig
89   X = Otf   **88**

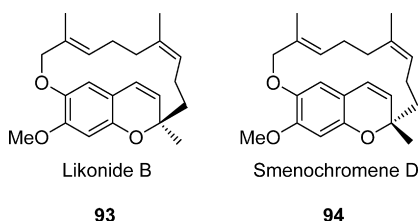**Figure 4.** Likonide B and smenochromen D.

Likonide B   Smenochromene D
93   **94**

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 Pd$_2$(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-bromophen-yl) 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 Bu$_4$NCl 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 Bu$_4$NCl and the addition of fresh [Pd(OAc)$_2$], NaO^{t}Bu and dppf 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

Scheme 44. Synthesis of Likonide B

PhNEt$_2$, MW
140 °C, 40 min

95   **96**   **97**, 87%

Likonide B
(Smemochromene D)
94
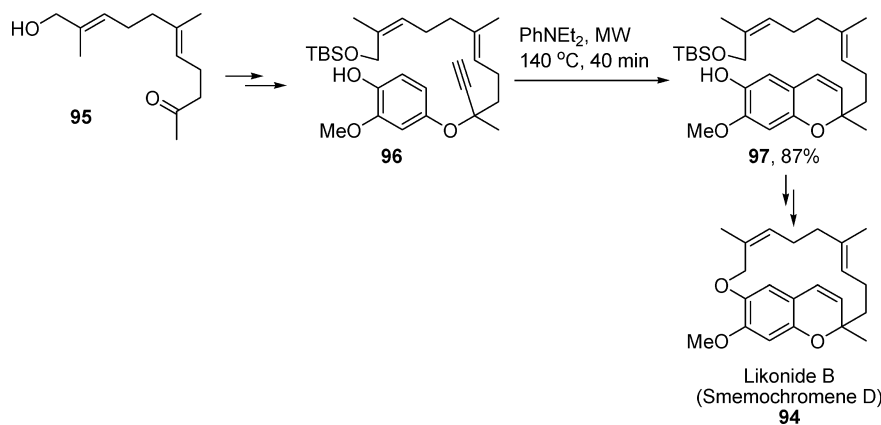
Scheme 45. Synthesis of a Natural Flavone
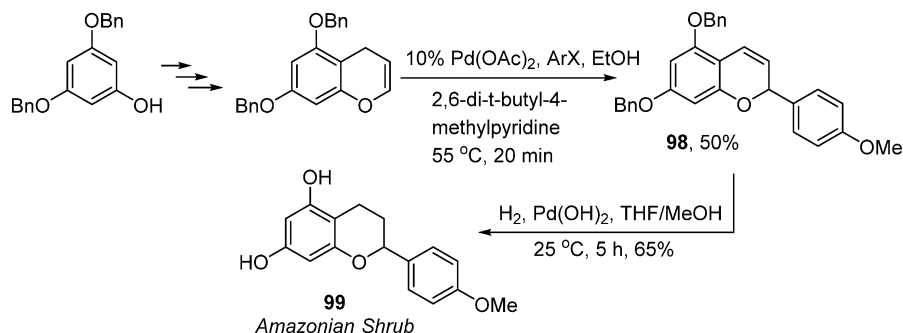
Scheme 46. Iclaprim Enantiomers
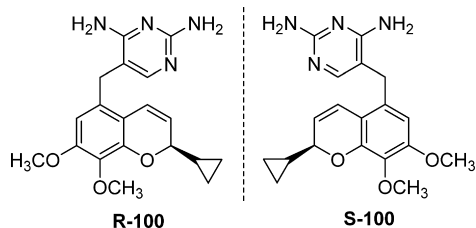
Scheme 47. Retro-Synthetic Pathway for the Synthesis of Iclaprim
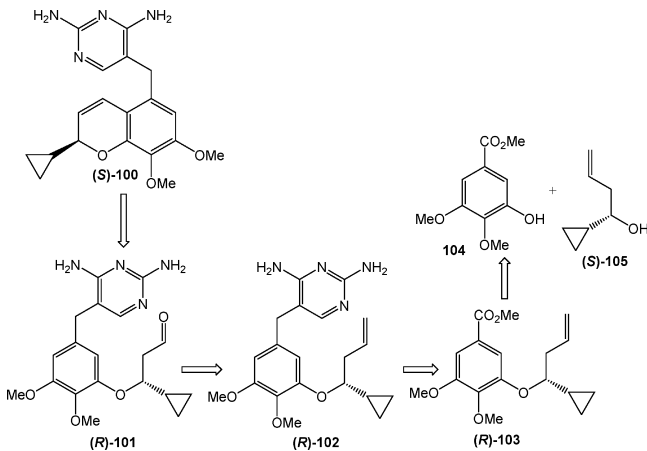
allene **59** with 2-alkynylphenol **60** (Scheme 30).[22] This transformation proceeds efficiently with excellent chemoselectivity and regioselectivity. The reaction between phosphonated 2-bromoaryl allene **59** and 2-(phenylethynyl)-phenol **60** proceeds most efficiently in the presence of Pd(dppf)Cl$_2$ 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 coor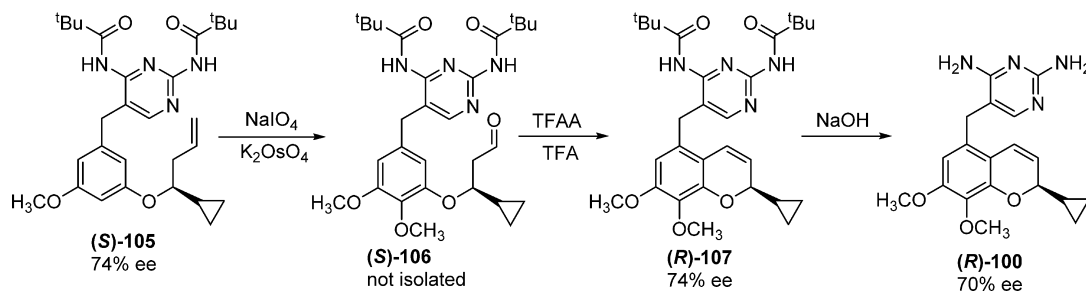dination followed by insertion of Pd(II) into the double bond of the allene produced the intermediate **1.6.6-C**. Finally, the desired chromene **61** was formed via base promoted C−O bond formation with subsequent release of Pd(0), which re-entered the catalytic cycle.

1.6.7. Malinakova and co-workers disclosed a polymer-supported palladacycle mediated 2*H*-chromene synthesis (Scheme 32).[23] The palladacycles **62**, attached to a variety of resins, were found to react with dimethyl acetylene dicarboxylate (DMAD) **63** in DCE to afford the 2*H*-chromene **64**. Notably, the yield of the 2*H*-chromene obtained via this method was found to be superior to those of analogous solution phase reactions. Small amounts of the 4*H*-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 2*H*-chromene product possibly isomerizes to the detected 4*H*-chromene side-product.

1.7. Gallium-Catalyzed 2*H*-Chromene Synthesis. A multicomponent one-pot approach for the synthesis of naphthopyrans was reported[24] 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, [FeCl$_3$], [BiCl$_3$], [InCl$_3$], [ZnCl$_2$], [CeCl$_3$·7H$_2$O], 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

Scheme 48. Synthesis of Iclaprim

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 2*H*-Chromene Synthesis. Hua and co-workers reported the synthesis of 2,2-dimethyl-2*H*-chromenes via Re-catalyzed one-pot cyclocondensation of phenols and 2-methyl-3-butyn-2-ol at 60 °C in hexane (Scheme 35).[25] $Re(CO)_5Cl$ was used as the catalyst. The reactions were tested with simple phenol, *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 intra-molecular hydroarylation (Scheme 36).

1.9. Ytterbium-Catalyzed 2*H*-Chromene Synthesis. Starting from a salicylaldehyde and an olefin, Janin and co-workers reported[26] a two-step synthesis of 2,2-dimethyl-2*H*-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 2*H*-Chromene Synthesis. Laurent and co-workers found[27] that 3-(perfluoroalkyl)-3-phenoxypropenals in the presence of $[AlCl_3]$ undergoes intramolecular cyclization to produce 2-(fluoromethyl)- and 2-(perfluoroalkyl)-2-hydroxy-2*H*-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-2*H*-chromenes **80**. The reaction involves a dehydration−hydration rearrangement sequence after formation of the initial 2-(perfluoroalkyl)-4*H*-chromen-4-ol intermediate (see also section 2.4).

1.11. Eco-Zinc Catalyzed 2*H*-Chromene Synthesis. In 2014, Escande et al., reported[28] a general and efficient method to synthesize 2*H*-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, phytoex-traction processes are used to obtain valuable metals. The Eco-

Zn was extracted from Zn-hyperaccumulating plant leaves derived from *Noccaea caerulescens* (Brassicacae). Notably, this methodology was claimed to be superior to other known methods affording 2*H*-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 2*H*-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. 2*H*-Chromene Synthesis from Chromene Acetals. In addition to the above-mentioned metal mediated/catalyzed 2*H*-chromene synthesis, very recently Doyle and co-workers reported[29a] the synthesis of a wide variety of substituted 2*H*-chromenes via a Ni-catalyzed cross coupling reaction between chromene acetals and boronic acids (Scheme 41).

A somewhat related approach was followed by Hiemstra and co-workers, who reported a multistep, multicatalytic approach to synthesize 2*H*-chromenes, involving a combination of Pd-catalyzed addition of allenes to 2-vinyl-phenols, ring-closing metathesis, and nucleophilic addition to the resulting (BF$_3$ activated) acetal.[29b]

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-*endo-trig*-Wacker-type oxidative cyclization of 2-geranylphenols without using any protecting groups.[30] 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 % *i*Pr-SPRIX **87**, 10 mol % $Pd(OCOCF_3)_2$ and 4 equiv of *p*-benzoquinone in dichloromethane as solvent at 60 °C. Notably, the 5-*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*-hydride 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-*endo-trig* cyclization was favored in this case compared to 5-*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.[31]

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-vinylation 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. Tahtaoui 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 2*H*-CHROMENES

Transition metal catalysts can be expensive, especially those based on noble metals. Furthermore, for the synthesis of

Scheme 49. Synthesis of 2*H*-Chromenes via Electrophilic Cyclization of Propargylic Aryl Ethers
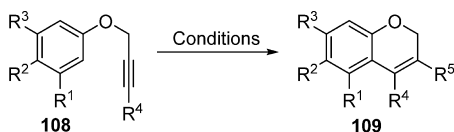
R^1 = ^{t}Bu, Cl, OMe
R^2 = Me, ^{t}Bu, OMe, Cl, CHO
R^3 = ^{t}Bu, Cl, OMe
R^4 = Ph, C$_6$H$_4$Me-p, C$_6$H$_4$OMe-p, C$_6$H$_4$NO$_2$-p, C$_6$H$_6$Me-o
cyclohexenyl, CH$_2$OH, Me
R^5 = I, SePh

109
38 examples
Yield: 39-96%

Conditions A: NaHCO$_3$ (0.50 mmol), I$_2$ (0.75 mmol), CH$_3$NO$_2$ (5 ml), 25 °C, 24
Conditions B: ICl (0.375 mmol), CH$_3$NO$_2$ (5 ml), -25 °C, 30 min
Conditions C: PhSeBr (1.2 equiv), CH$_2$Cl$_2$ (5 ml), 25 °C
Conditions D: ICl (0.375 mmol), CH$_2$Cl$_2$ (5 ml), -78 °C

bioactive/pharmaceutical compounds, preventing product contamination with potentially toxic metal traces can be of importance. Hence, metal-free methodologies to synthesize 2*H*-chromenes are of interest and have already received quite some

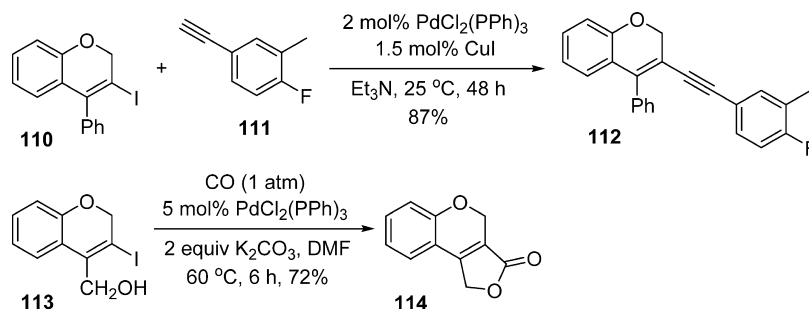**Scheme 50. Proposed Mechanism of Electrophilic Cyclization of Propargylic Aryl Ethers**
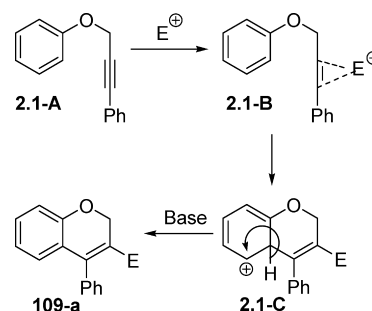
attention. Such protocols are summarized in section 2 of this review.

2.1. Larock and co-workers reported[34] a mild synthetic methodology for the synthesis of 3,4-disubstituted 2*H* benzopyrans in excellent yields via electrophilic cyclization of substituted propargylic aryl ethers by I$_2$, ICl, 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 I$_2$ was used as electrophile, addition of NaHCO$_3$ becomes essential for cyclization, whereas ICl as an electrophile produced the desired product even in the absence of NaHCO$_3$. 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 a 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 I$_2$ or ICl as electrophiles. The cyclization was unsuccessful for substrates with an alkyl group on the alkyne terminus for I$_2$ or ICl as electrophile but was successful with PhSeBr. Interestingly, the hydroxy-methyl-substituted prop-argylic aryl ether successfully reacted with both I$_2$ and ICl. 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.
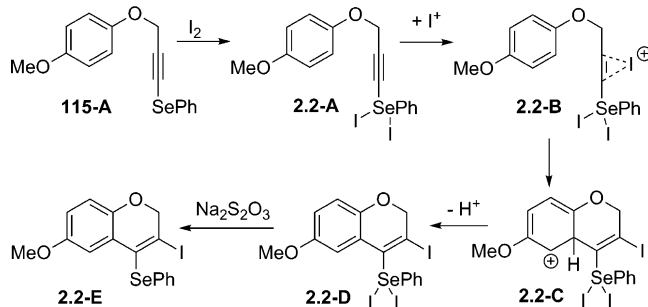
The proposed mechanism involves the addition of the electrophile to the triple bond to produce an iodonium or selenonium intermediate first, which then undergoes cyclization with the aromatic ring (Scheme 50). Finally, loss of a proton results in the formation of the desired 2*H*-chromenes.

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 2*H*-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 I$_2$ and Na$_2$CO$_3$ in THF or CH$_3$CN, and the reactions

Scheme 51. Further Functionalization of Iodine-Substituted 2H-Chromenes

Scheme 52. Synthesis of 2H-Chromenes via Electrophilic Cyclization of Organochalcogen Propargyl Aryl Ethers

R^1 = Me, ^tBu, OMe, Cl, Ph
YR^2 = Se-aryl, Se-alkyl, Te-aryl, Te-alkyl

30 examples
up to 83 % yields
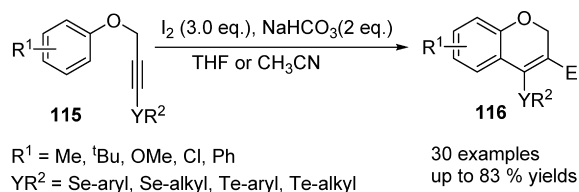
Scheme 53. Proposed Mechanism

Scheme 54. Synthesis of 2H-Chromenes via K$_2$CO$_3$-Catalyzed Coupling of Salicylaldehyde to Allenic Ketones
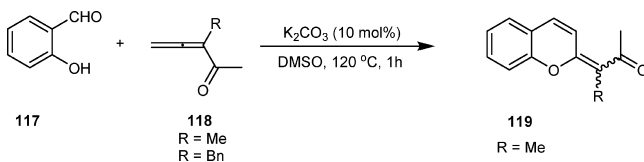
Scheme 55. K$_2$CO$_3$-Catalyzed Reaction of 2-Hydroxyacetophenone and Allenic Esters
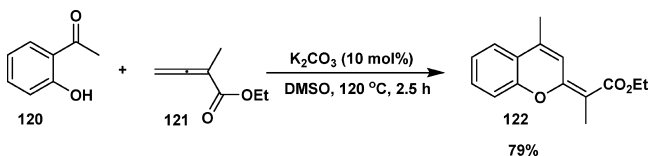
proceeded smoothly to give a wide range of 3- and 4-substituted chromenes in moderate to high yields (Scheme 52). Notably, they also studied these same reactions employing Larock's conditions in nitromethane to find that no reaction occurred.

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 I$_2$ 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).
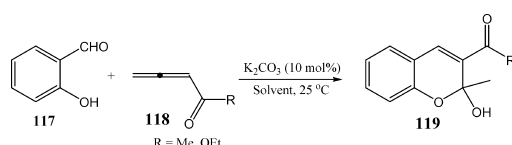
2.3. Synthesis of functionalized 2H-chromenes was reported by Shi et al.,[36] who demonstrated a simple reaction between salicylaldehyde **117** and allenic ketones **118** or esters **121** catalyzed by potassium carbonate (Schemes 54 and 55). For a variety of salicylaldehydes **117** and allenic ketones **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[37] their 2H-chromene synthesis using unsubstituted allenic esters or ketones in the presence of K$_2$CO$_3$ as catalyst. Notably, the use of elevated temperatures (120 °C) in the first report by Shi et al.[36] 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 Al$_2$O$_3$ 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).
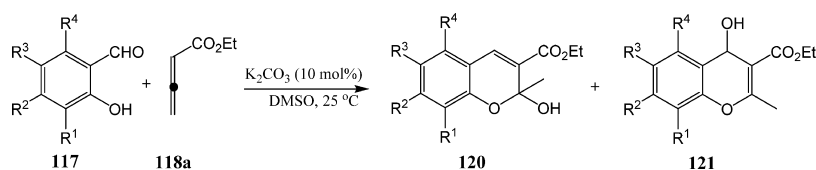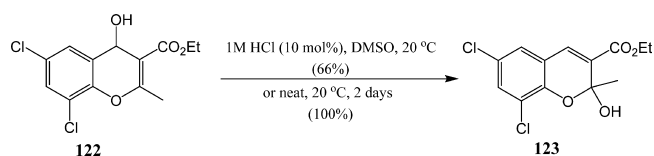
Scheme 56. Proposed Mechanism of K$_2$CO$_3$-Catalyzed Coupling of Salicylaldehyde to Allenic Ketones and Esters
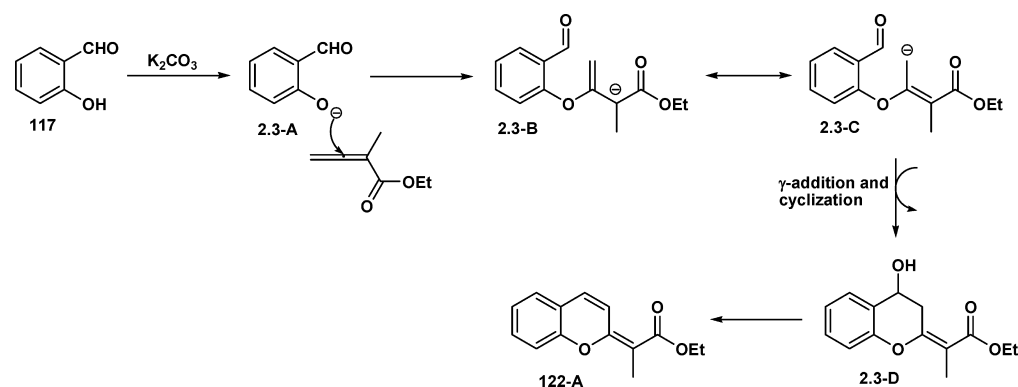
Scheme 57. Synthesis of 2H-Chromenes via K$_2$CO$_3$-Catalyzed Reaction of Salicylaldehyde and Allenic Ketones and Esters at Room Temperature

Scheme 59. Conversion of Compound 122 to 123

The proposed mechanism is depicted in Scheme 60. Initially, deprotonation of salicylaldehyde **117** by K$_2$CO$_3$ 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 H$_2$O to form the final product **120**.

2.5. In an unprecedented reaction, Tang and co-workers reported[38] 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 K$_2$CO$_3$, 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$2′ reaction of intermediate **2.5-D**, after which tetrahydrothiophene **128** is regenerated to close the catalytic cycle. Formation of the 4H-chromene **127** as minor product could be explained from the fact that 2H-chromene **126** slowly transformed to the more stable thermodynamic product in the presence of K$_2$CO$_3$, which is the 4H-chromene **127** (Scheme 62). Use of stronger bases like Cs$_2$CO$_3$ 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.[39] 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[40] 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

Scheme 58. Reaction with Unsubstituted Allenic Esters

Scheme 60. Proposed Mechanism of the Conversion of 117 to 120
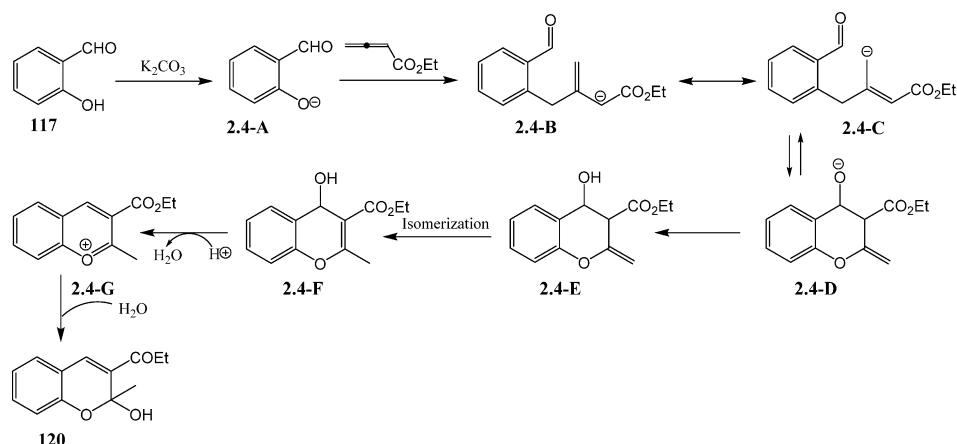
Scheme 61. Synthesis of Substituted 2H-Chromenes via Michael Addition/Reverse Michael/Allylic Substitution Cascade


126:127 = 33:1 (85%)
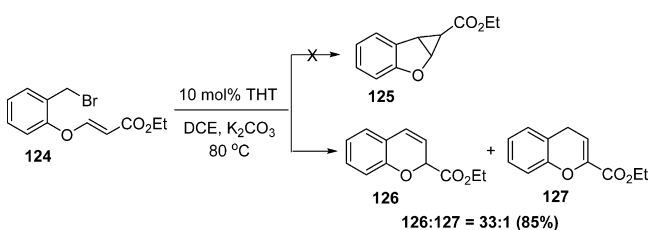
reactivity toward arynes to produce the σ-insertion *ortho*-disubstituted products (Scheme 65).

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

Scheme 63. Reaction between Salicylaldehyde and Cyclic Enones
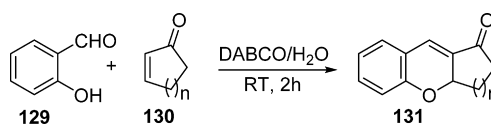
Scheme 64. Synthesis of Chromenes via Multicomponent Reaction between 132, 133, and 134
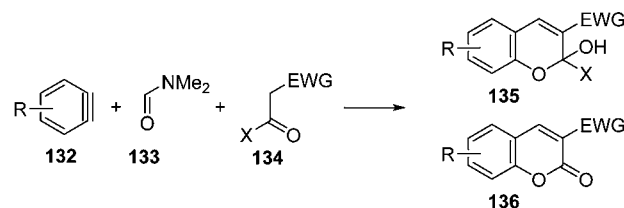

reacted under the optimized reaction conditions. The 4-methoxytriflate corresponding to **138** gave two regioisomers in a 6:5 ratio.

The authors successfully used this methodology for the one-pot synthesis of a neuropeptide YY5 acceptor antagonist **143** in

Scheme 62. Proposed Mechanism of THT-Catalyzed Formation of 2H-Chromenes 127 from Halide 124
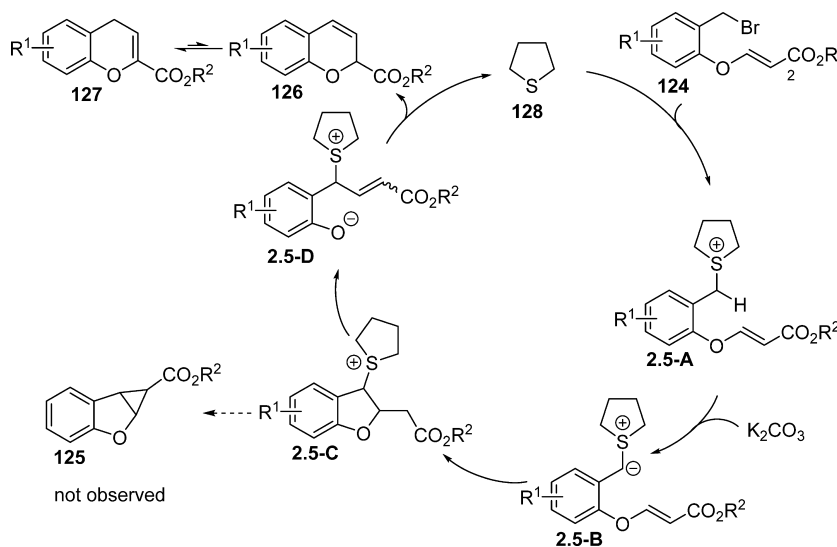
Scheme 65. σ-Bond Insertion between Arynes and Activated Methylenes

Scheme 67. Synthesis of Neuropeptide YY5 Acceptor Antagonist and Related Scaffolds
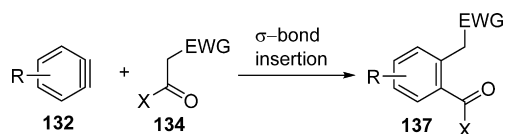
86% yield. Two similar products **144** and **145**, having different substitution on the aromatic ring, were also synthesized in 87% and 69% yields, respectively (Scheme 67).

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**, chromenes 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 chromenes 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 ($\Delta H = -177$ kJ mol^{-1}) probably because of the release of the strain energy of aryne **156**, which overcomes the entropy loss of the bimolecular coupling ($-T\Delta S° = +65$ kJ mol^{-1}). The free energy changes ($\Delta G°_{298\ K} < 0$ 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 ($\Delta G° = +77$ 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-oxobutanoate **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
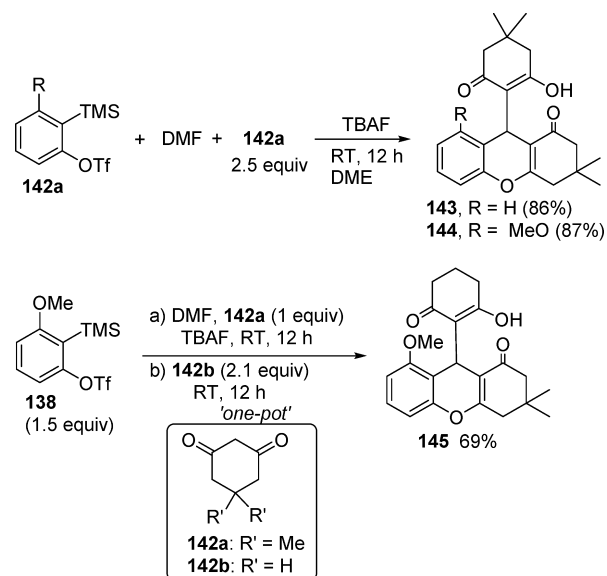
phenolic OH onto the nearest C=O to Cl to produce the chromene product. The electron-withdrawing effect of CH$_2$Cl is believed to play an important role during the Knoevenagel condensation giving a *cis*-relationship of the chloromethyl ketone and arene ring on the double-bond, allowing for the cyclization 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, γ-pyrones, and β-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 (R^2) 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-pyran-4-ones and 2,2-dimethylfuran-3(2H)-ones also smoothly react under the optimized reaction conditions, affording good yields of the chromenes. Interest-
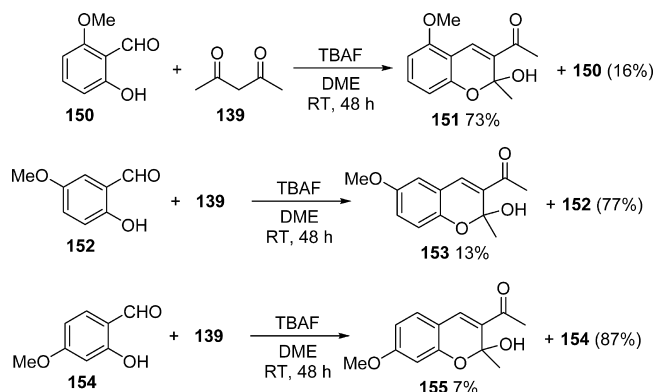
Scheme 66. Competitive Insertion of DMF and Activated Methylenes into Arynes
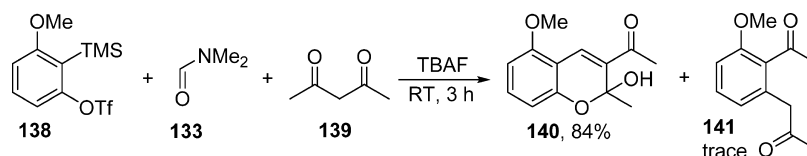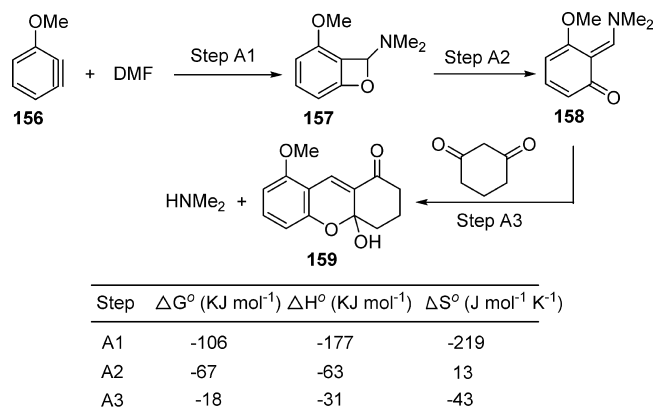
Scheme 68. Proposed Mechanisms for Formation of Chromenes 149 from 132, 133, and 139
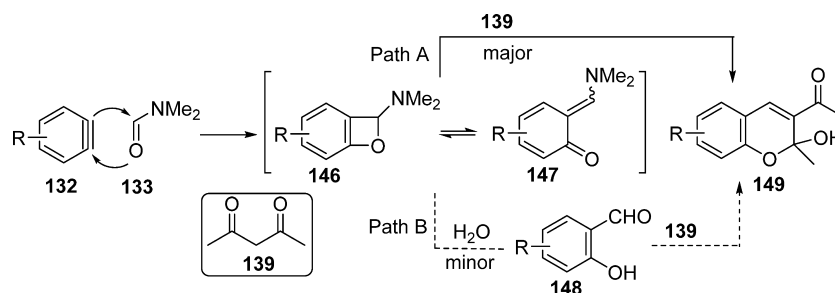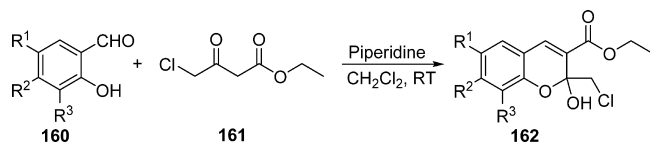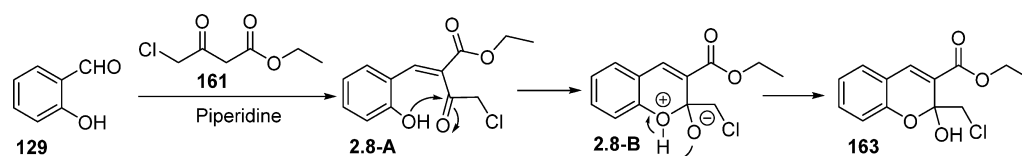

Scheme 69. Control Reactions Used To Exclude Path B

Scheme 70. Mechanistic Investigation and Ab Initio Results

Step	$\triangle G^o$ (KJ mol^{-1})	$\triangle H^o$ (KJ mol^{-1})	$\triangle S^o$ (J mol^{-1} K^{-1})
A1	−106	−177	−219
A2	−67	−63	13
A3	−18	−31	−43

Scheme 71. Synthesis of 2H-Chromenes via Knoevenagel Condensation of Salicylaldehydes with Ethyl-4-chloro-3-oxobutanoate

ingly, the desired chromene was obtained with a poor yield (8%) starting from the sterically hindered 2-hydroxy-1-naphthaldehyde.
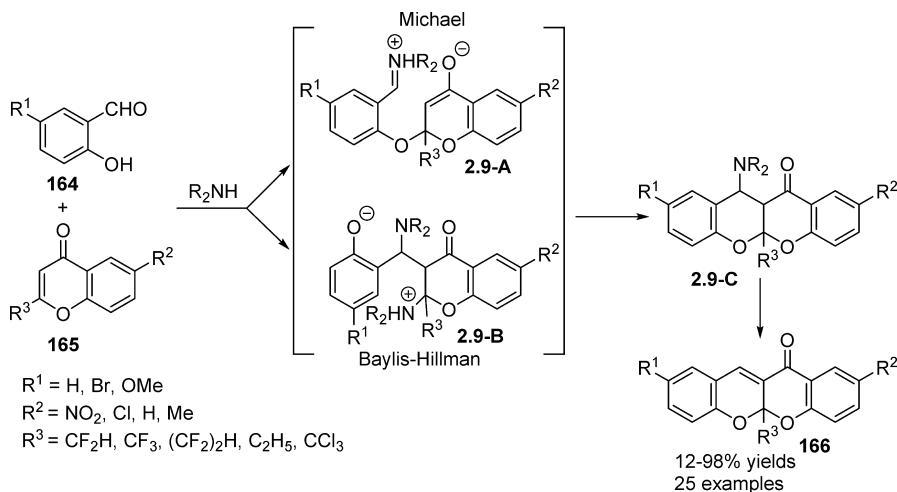
Interestingly, the same reaction with activated γ-pyrones **170** containing two electron-withdrawing groups on the 2-and 6-positions produced double annulated polycyclic compounds **172**, containing three oxygen atoms in the adjacent rings. Activated γ-pyrones with an excess of salicyaldehydes (3.0 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 salicylaldehyde 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[43] 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).
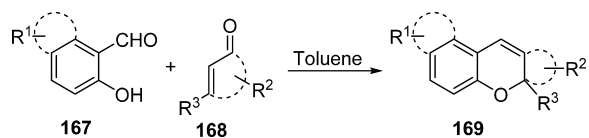
The plausible mechanistic proposition for this reaction is outlined in Scheme 77. In the first step, the substrate **174** reacts with the TCTDMF adduct **2.10-A** to form the intermediate **2.10-B** along with a byproduct **2.10-C**. The cleavage of cyclopropane ring in **2.10-B** produced the carbocationic 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 −CH$_2$− 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-methylenechromene-4-ones **178** with various enamines in neat condition at 100 °C produced the pyridine-fused chromenes in high yields (Scheme 78).[44] A wide range of electron-rich and -poor substrates reacted cleanly to produce the corresponding pyridine-fused chromene derivatives in high yields.

Scheme 72. Plausible Mechanism of the Knoevenagel Condensation of Salicylaldehydes with Ethyl-4-chloro-3-oxobutanoate

Scheme 73. Synthesis of Fused Chromenes via a Convergent Methodology

R^1 = H, Br, OMe
R^2 = NO$_2$, Cl, H, Me
R^3 = CF$_2$H, CF$_3$, (CF$_2$)$_2$H, C$_2$H$_5$, CCl$_3$

12-98% yields
25 examples **166**

Scheme 74. Reaction between Salicylaldehyde and Cyclic Enones

Similarly, pyrazolopyrimidine-fused chromenes were successfully synthesized from the reaction of *s-cis*-enone **181** and 3-aminopyrazole **182** derivatives under microwave irradiation (Scheme 79). The corresponding chromenes **184** were obtained in excellent yields.
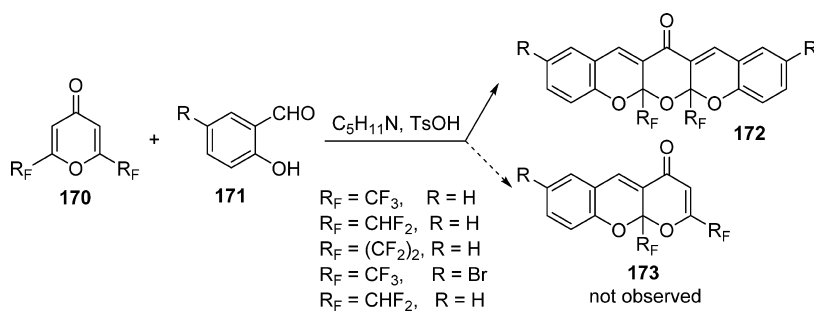
Corresponding pyrimidine-fused chromenes **188** were also synthesized in moderate yield employing the same reaction methodology. The hydroxyl-substituted *s-cis*-enone **185** reacts with a stoichiometric amount of pyrrolidine **186** to produce the corresponding pyrimidine-fused chromenes **188** via an enaminone intermediate **187** (Scheme 80).

2.12. Koussini et al. reported a microwave-assisted synthesis of 3-nitro-2*H*-chromenes from the reaction of 2-hydroxy benzaldehydes and 2-nitroethanol supported on anhydrous potassium carbonate, in the presence of a catalytic amount of tetrabutylammmonium bromide (TBAB).[45] This methodology involves simple mixing of salicylaldehyde derivatives with a 1.5-fold excess of 2-nitroethanol and a catalytic amount of tetrabutylammonium 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 **190** using K$_2$CO$_3$/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)-2*H*-chromene-3-carboxylate esters were synthesized under solvent-free conditions via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate followed by intramolecular cyclization in the presence of silica-immobilized L-proline as the catalyst (Scheme 83).[46] Notably, the catalyst can be recovered conveniently and reused without obvious loss of activity. A wide range of substituted salicylaldehydes reacted with ethyl trifluoroacetoacetate 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**.

Scheme 75. Double Annulation of γ-Pyrones with Salicylaldehyde

R$_F$ = CF$_3$, R = H
R$_F$ = CHF$_2$, R = H
R$_F$ = (CF$_2$)$_2$, R = H
R$_F$ = CF$_3$, R = Br
R$_F$ = CHF$_2$, R = H

173 not observed

Scheme 76. Synthesis of 2H-Chromenes and 2H-Thiochromenes via Cyanuric Chloride-Dimethylformamide Mediated Cleavage of Different Spiro-4-hydroxychroman-3,1′-cyclopropanes and Corresponding Thiochroman Analogues
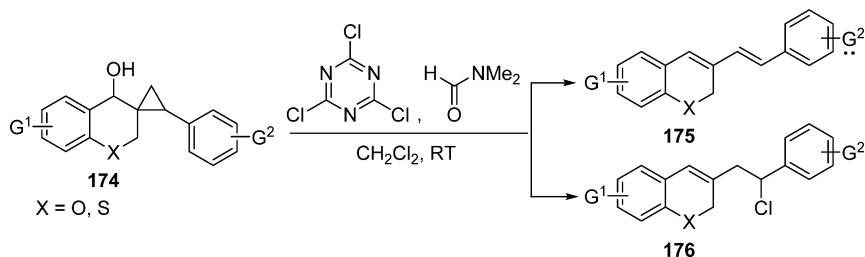
Scheme 77. Proposed Mechanism for the Synthesis of Substituted 3-(E)-Styryl-2H-chromenes
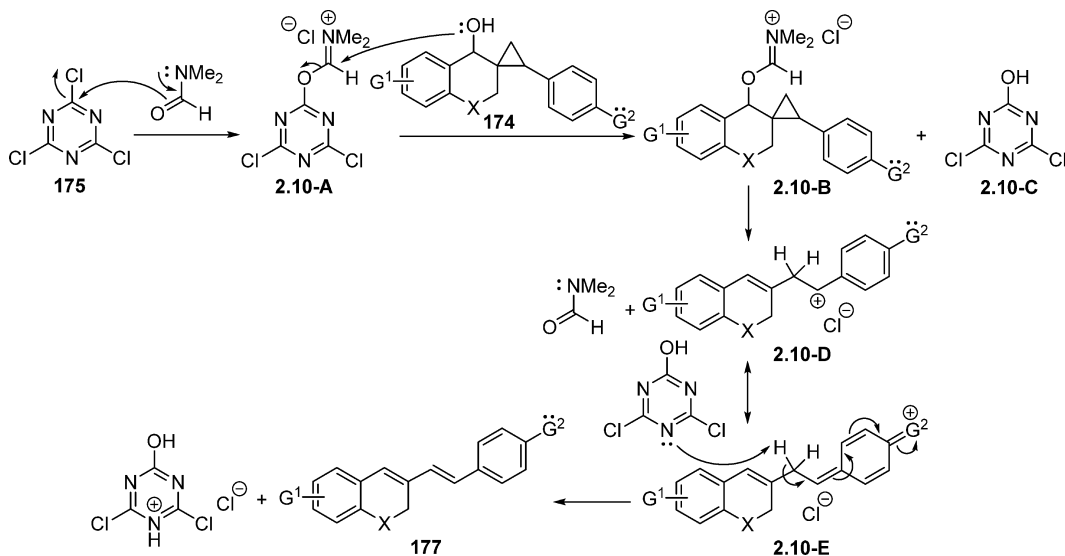
Scheme 78. Synthesis of Chromenes from s-cis-Enones

R1 = Me, 4-F-C$_6$H$_4$, C$_6$H$_5$, 4-Br-C$_6$H$_4$, n-Bu
R2 = CO$_2$Me, CO$_2$Et
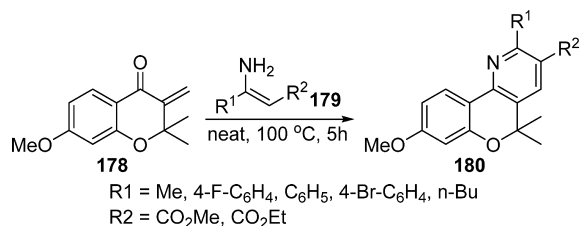
Subsequent reaction of the intermediate **2.13-A** with salicylaldehyde produces the intermediate **2.13-C**, which upon hydrolysis followed by dehydration produced another intermediate **2.13-E**. Subsequent cyclization by the addition of phenoxide ion to the more electrophilic carbonyl group rather than to the ester group affords the intermediate **2.13-G**. Finally, protonation of **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 micro-wave irradiation in CDCl$_3$ (Scheme 85).[47] 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.

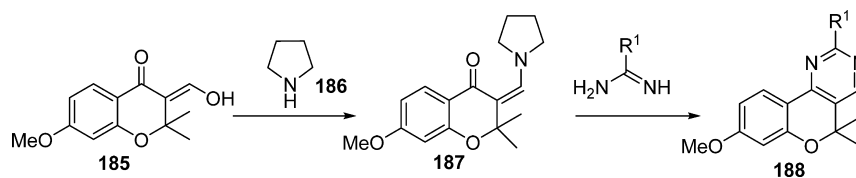**2.15.** Ferreira and co-workers reported[48] a simple one-pot synthesis of 2H-chromenes from ortho-quinones **199** and allyl-

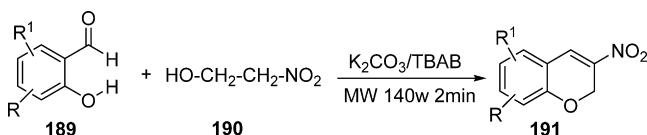**Scheme 79. Synthesis of Pyrazolopyrimidine-Fused Chromenes**
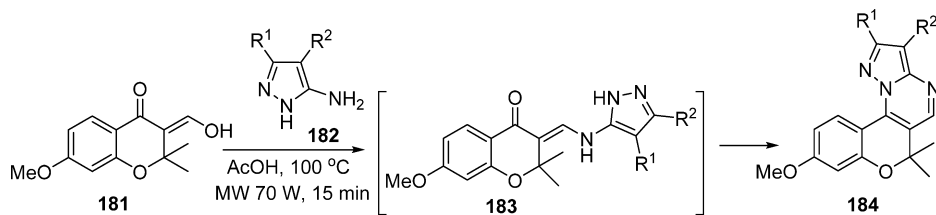
183a, R^1 = R^2 = H; 95%
183b, R^1 = H; R^2 = CO$_2$Et; 89%
183c, R^1 = Me; R^2 = H; 90%
183d, R^1 = C$_6$H$_5$; R^2 = H; 96%
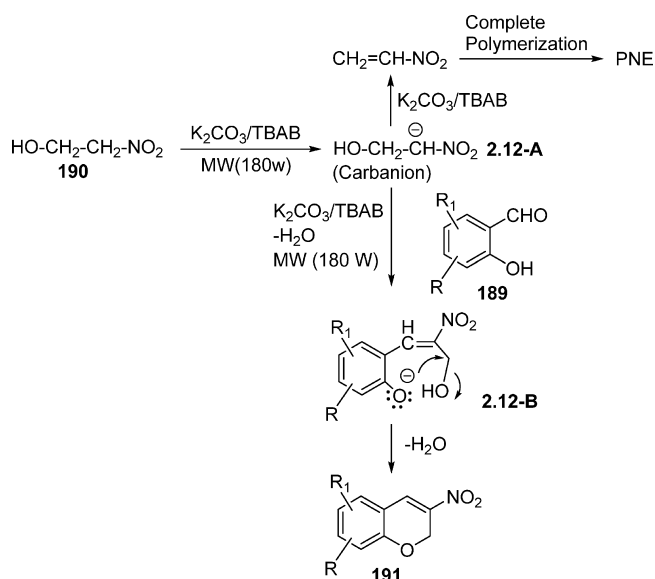**183e**, R^1 = 4-OMe-C$_6$H$_4$; R^2 = H; 95%

Scheme 80. Synthesis of Pyrimidine-Fused Chromenes

**Scheme 81. Microwave-Assisted Synthesis of 3-Nitro-2H-chromenes**

Scheme 82. Proposed Mechanism

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-acylvinyl anion generated from a silyloxyallene. Although the resulting chromene was obtained in good yield, the authors reported
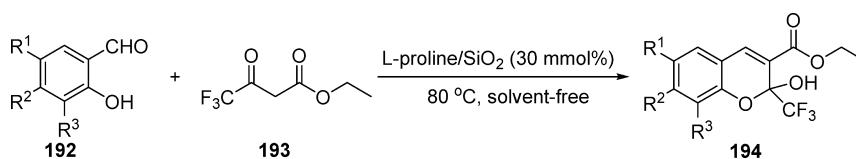
only one example using this methodology to synthesize chiral chromenes from β-hydroxy-unsaturated ketones.

2.17. Kureshy et al. successfully used sulfonic-acid-functionalized 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 developed[51] a one-step strategy for the synthesis of 2H-chromenes starting from salicylaldehyde **206**, alkenyl boronic acids **207** or alkenyl trifluoroborates **208**, and an amine **209**. The reaction of salicylaldehydes **206** with alkenyl boronic acids **207** or alkenyl 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 tetrabutylammonium 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. reported[52] 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 vinylborate salts are much more stable, easier to use than the corresponding organoboronic acids and more

Scheme 83. Microwave-Assisted Synthesis of Chromenes

Scheme 84. Proposed Mechanism
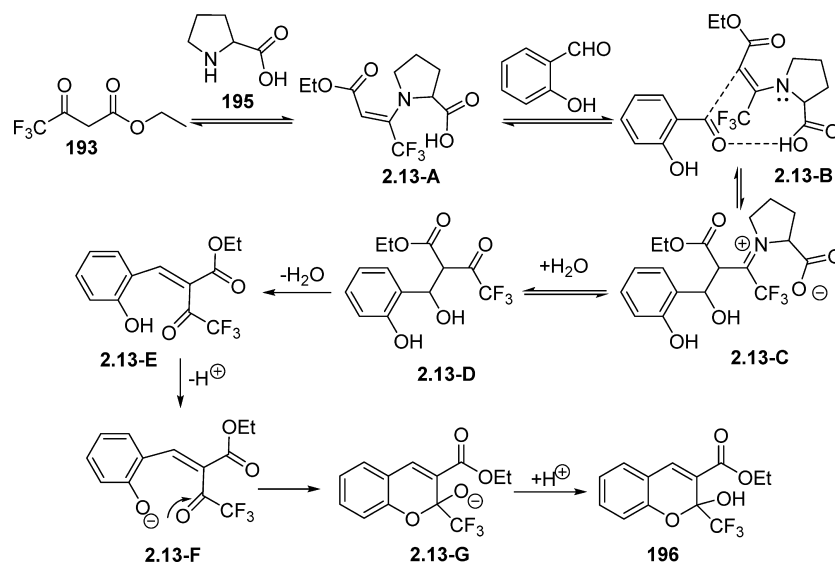
Scheme 85. Microwave-Assisted Synthesis of Chromenes
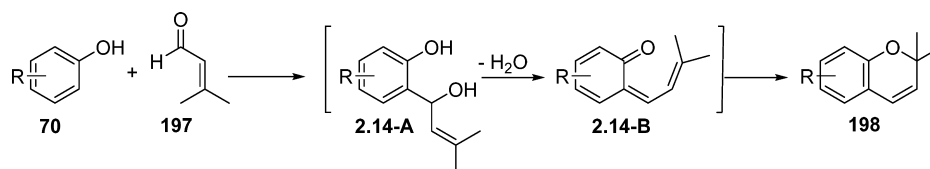
Scheme 86. Synthesis of Chromenes from the Reaction of *ortho*-Quinones and Allyltriphenylphosphonium Salts
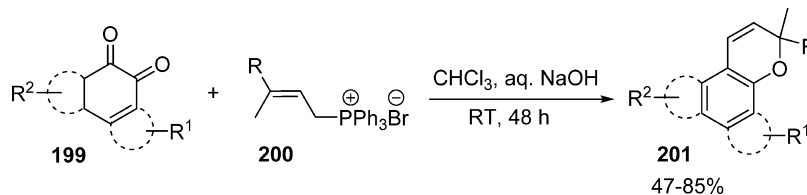
Scheme 87. Enantioselective Synthesis of 2H-Chromene 203 from 202
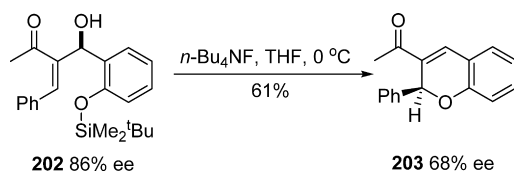
reactive. A wide range of substituted salicyaldehyde and the alkenyl trifluoroborate salts produced the corresponding

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.
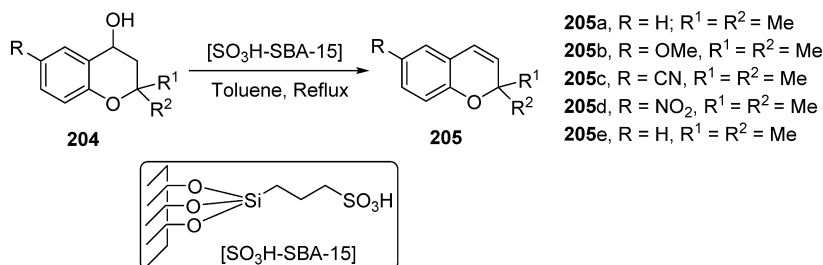
2.20. Sosnovskikh and co-workers reported[53] a new synthetic method for the synthesis of highly substituted 2H-chromenes starting from N-unsubstituted imines of 2-hydroxyacetophenones and activated trihalomethyl substituted nitro alkenes. The reaction of N-unsubstituted imines of 2-hydroxyacetophenones with activated trihalomethyl substituted nitro alkenes in the presence of DABCO as base proceeds via a

Scheme 88. Mesoporous-Silica-Supported Synthesis of Chromenes

205a, R = H; $R^1 = R^2 = Me$
205b, R = OMe, $R^1 = R^2 = Me$
205c, R = CN, $R^1 = R^2 = Me$
205d, R = NO_2, $R^1 = R^2 = Me$
205e, R = H, $R^1 = R^2 = Me$

Scheme 89. Synthesis of Chromenes via Petasis-Type Reactions
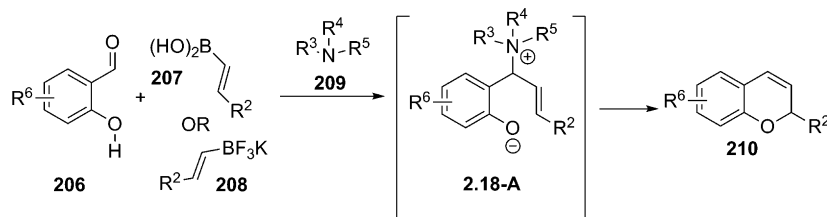
Scheme 90. Proposed Mechanism of 2H-Chromene Synthesis via Petasis-Type Reactions
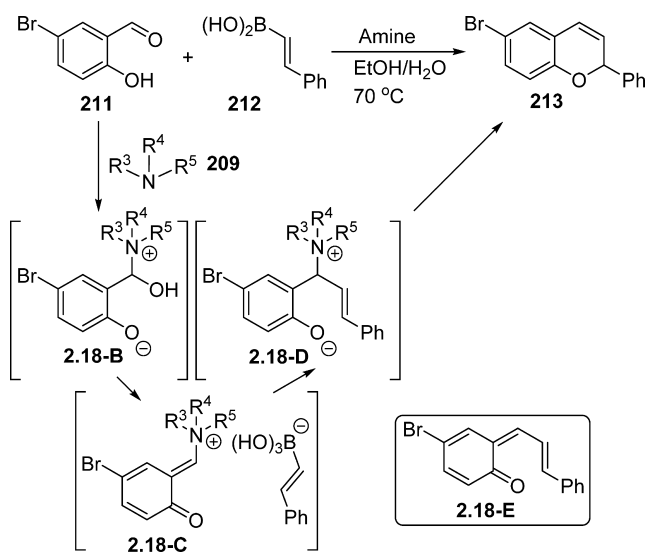
Scheme 91. Synthesis of Vitamin E Analogues

Scheme 92. Synthesis of Chromenes via a Modified Petasis Reaction

tandem oxa-Michael/aza-Henry addition reaction in dichloromethane to produce the desired highly substituted 2H-chromenes **224** in excellent yields (Scheme 93). The reaction proceeds via an 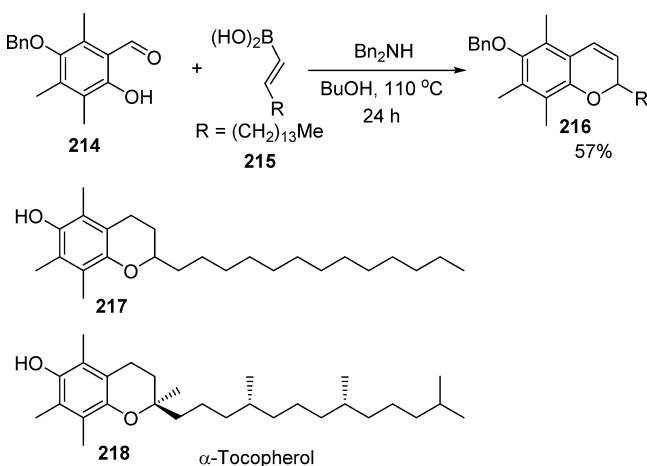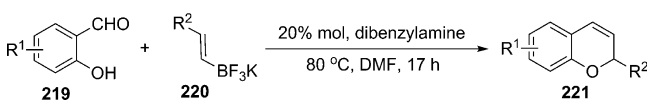aza-Michael addition in benzene to produce the compound **225**. The reaction worked efficiently with DABCO as the base, although use of other bases such as triethylamine

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 developed[54] 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 commercially 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 nitration (Scheme 94).

2.22. Uguen and co-workers used a protocol involving pyridine-catalyzed condensation of phenolic compounds with α,β-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 afford **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. reported[56] 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 ^{t}BuOK followed by treatment with SiO$_2$/CHCl$_3$ 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 reported[57] the synthesis of a variety of chromenes via a cascade reaction of β,γ-unsaturated-α-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-

Scheme 93. Synthesis of Chromenes via a Tandem Oxa-Michael/Aza-Henry Reaction
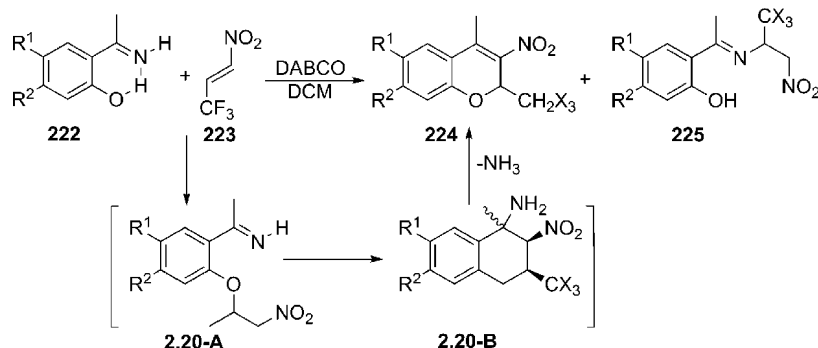
Scheme 94. (Top) Retro Synthetic Approach for Chromene Synthesis; (Bottom) Synthesis of Nitro-Substituted 2,2-Diphenyl-2H-1-benzopyrans via the Ipso-Nitration Reaction

X^1 = H, CH$_3$, NO$_2$; X^2 = H, CH$_3$; X^3 = NO$_2$, CH$_3$; X^4 = H, CH$_3$; PTSA = p-toluene sulfonic acid
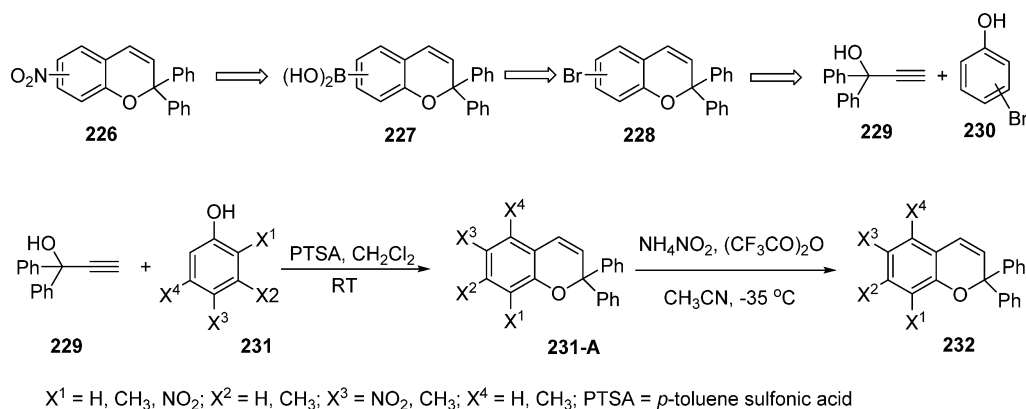
Scheme 95. Synthesis of Chromenes via Pyridine-Catalyzed Condensation of Phenolic Compounds with α,β-Unsaturated Aldehyde Dimethyl Acetals
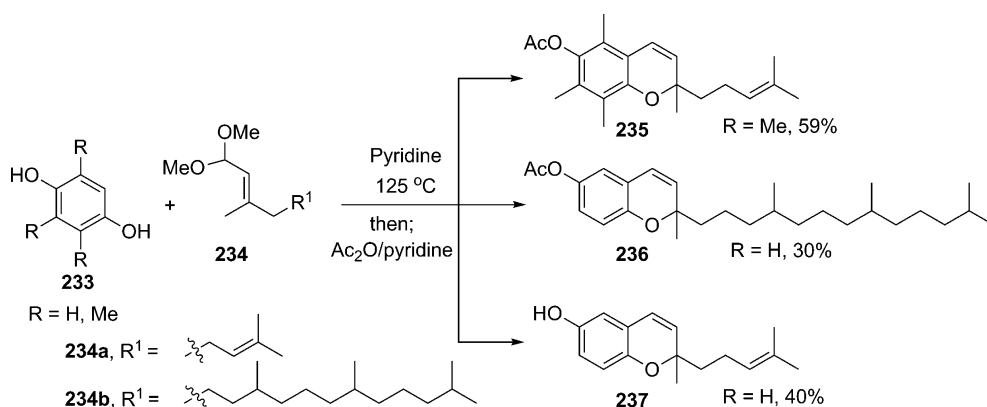
Scheme 96. Synthesis of Chromenes via RCM/Base-Induced Ring-Opening Reaction

Scheme 97. Transformation of C2-Symmetric Benzo[b]oxepine to Chromenes
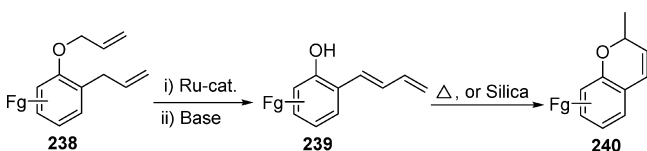
phenylbut-3-enoate methyl ester **246**. The best yield of chromene **247** (90%) was obtained with 1.1 equiv of **246** and Ph$_3$CCl as an oxidant in the presence of TFA. The reaction was found to be very general with respect to the β,γ-unsaturated-α-ketoesters; β,γ-unsaturated-α-ketoesters either
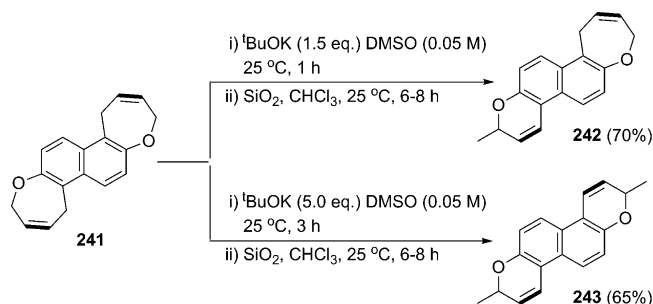
Scheme 98. Proposed Mechanism
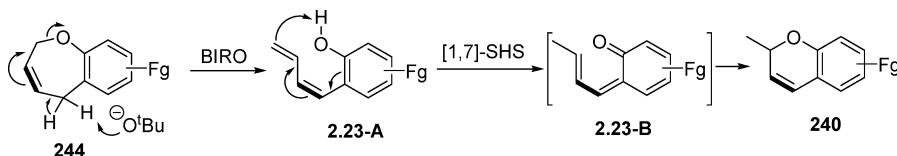
Scheme 99. Synthesis of Chromenes by Reaction of β,γ-Unsaturated-α-Ketoesters with Phenols

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 β,γ-unsaturated-α-ketoesters **249** with phenols **248** to produc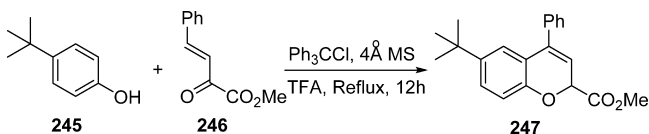e the intermediate **2.24-A** (Scheme 100). Then benzopyrylium ions **2.24-B** are formed by intermolecular hydride transfer from **2.24-A** to trityl chloride, which on subsequent hydration with water during workup afforded the 4-aryl-2H-chromenes **250**.

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[58] the bromination behavior of pyrano chromene **263**, which was obtained as the side product in 33% yield in the synthesis of γ-tocopherol model compound 2,2,7,8-tetramethylchroman-6-ol **262** (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 chromene 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**-Br₂ 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[59] 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}-(cyano/ethoxycarbonyl)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 tautomerizes 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-hydroxycoumarin and malononitrile to synthesize pyrano[c]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 NH₄H₂PO₄ catalyzed cascade reaction in which the aryl glyoxal first condenses with malononitrile **274** to produce the corresponding aryloylidene malononitrile. 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**.

Scheme 100. Plausible Mechanism
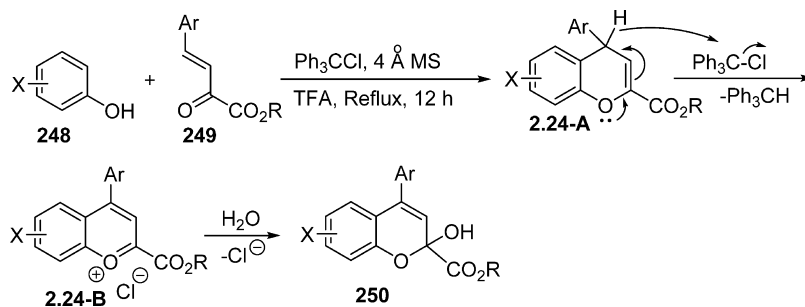
Scheme 101. Synthetic Transformations of 2H-Chromenes
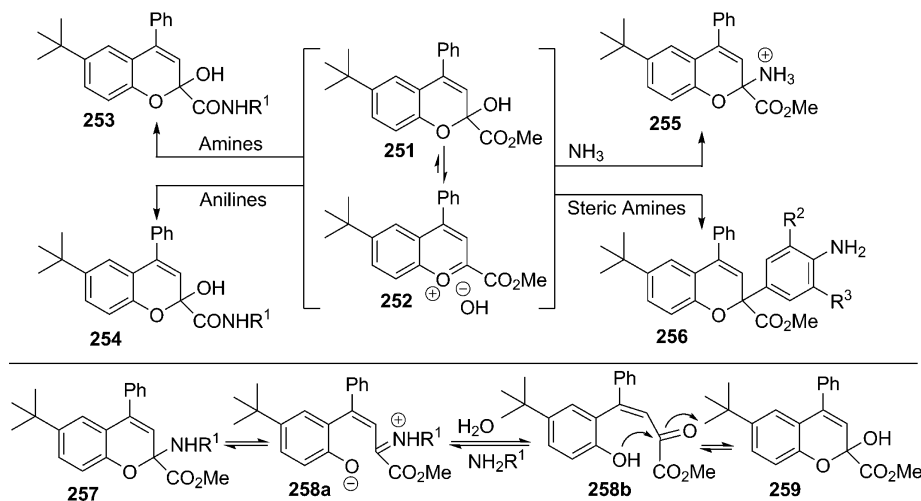
Scheme 102. Bromopyranochromene via Bromination of Pyranochromene
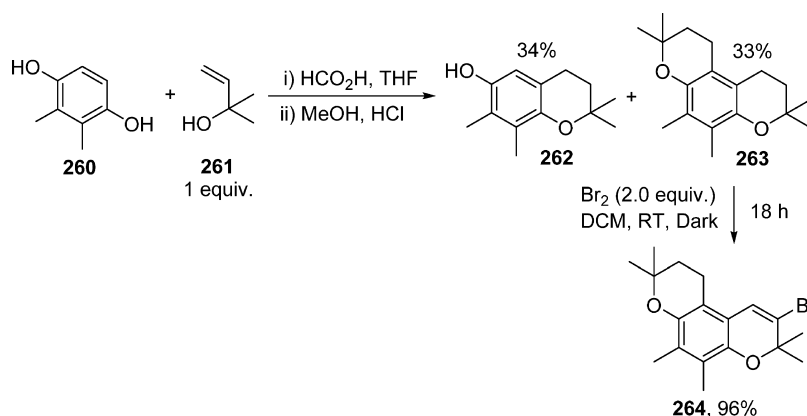
Scheme 103. Proposed Mechanism of Bromopyranochromene Formation

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[62] the new chiral Brønsted acid **279** as a catalyst for the synthesis of chiral 2-substituted 2H-chromenes involving the enantioselective addition of alkenyl boronates to chromene acetals (Scheme

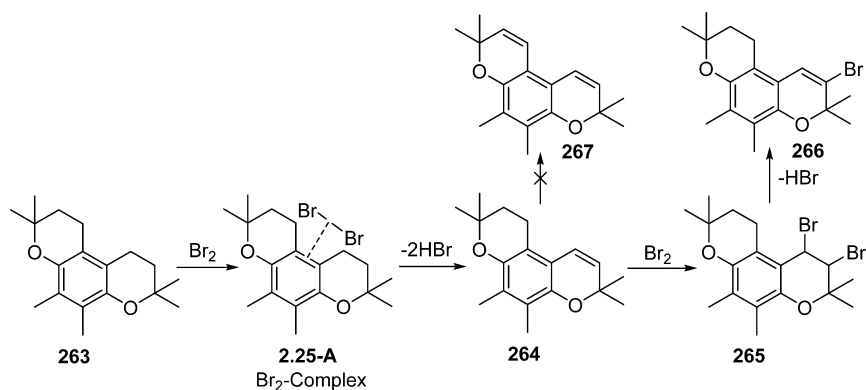108). Although the organocatalyst **279** could give the chromenes **280** with good enantiomer ratios, a cocatalyst involving the combination of **279** with a Lewis acid catalyst gave higher yields and enantioselectives. The combination of the chiral tartaric amide **279** with Ce(III), Ce(IV), or 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

Scheme 104. Synthesis of Chromenes via Microwave-Assisted Intramolecular Wittig and Claisen Rearrangement Followed by Internal Cyclizations
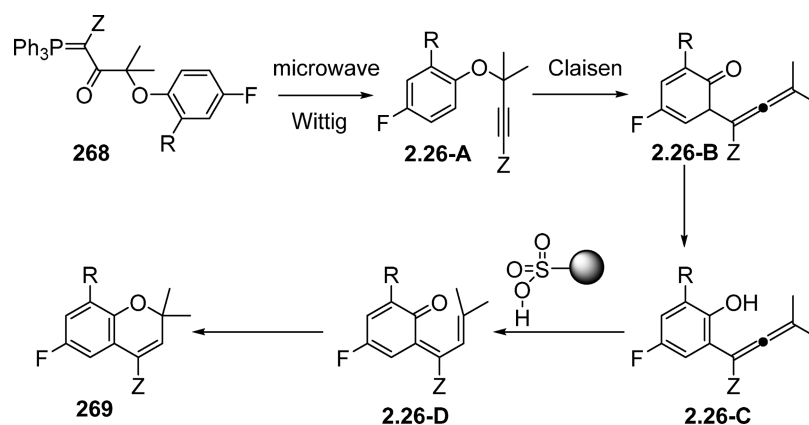
Scheme 105. Thermal Rearrangement of Aryl Propargyl Ethers

R^1 = H, Ph
R^2 = H, Ph
R^3 = H, Ph, 4-BrPh
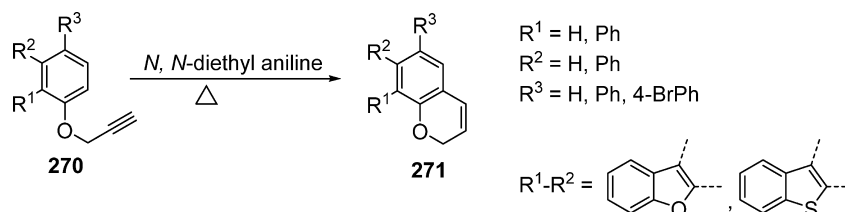
Scheme 106. Synthesis of Pyrano[c]Chromenes via Multicomponent Reaction
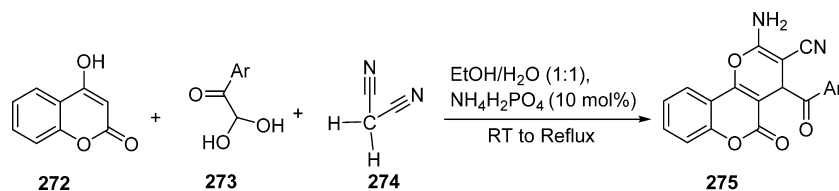
Scheme 107. Plausible Mechanism of the Multicomponent Synthesis of Pyrano[c]Chromenes
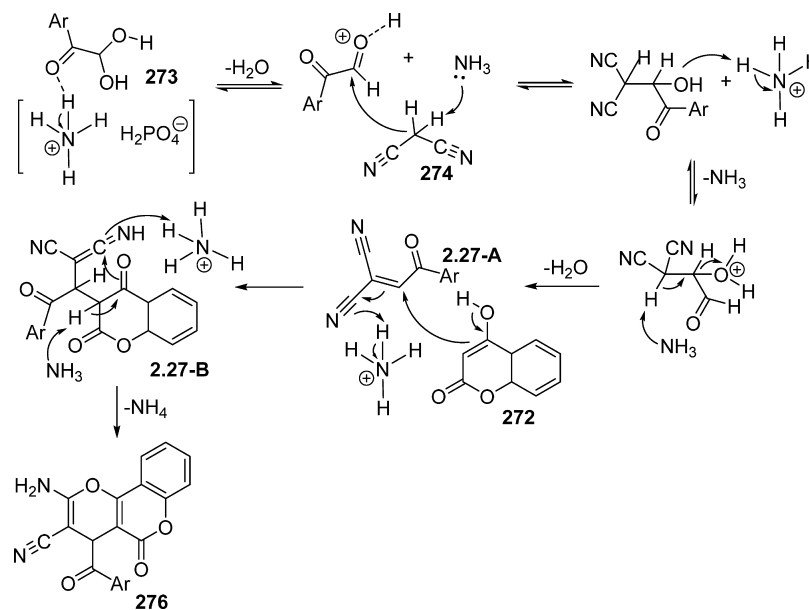
conditions. Although this synthetic method is found to be very efficient, unfortunately it could not be generalized as the conditions had to be optimized for each substrate (Scheme 108).

Scheme 108. Brønsted Acid/Lewis Acid-Catalyzed Asymmetric Synthesis of Chromenes
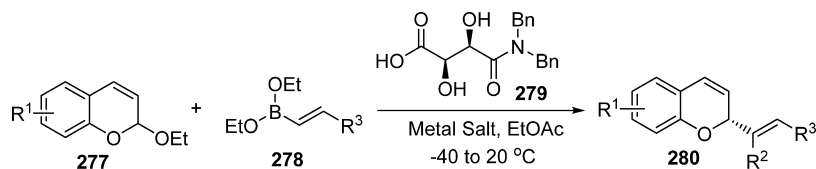
Conditions A: 1.5 equiv boronate, 5 mol% **279**, 4.5 mol% Ce(OTf)$_4$
Conditions B: 1.5 equiv boronate, 5 mol% **279**, 4.5 mol% Ce(OTf)$_4$, 1 equiv ^{t}BuOH
Conditions C: 1.5 equiv boronate, 5 mol% **279**, 4.5 mol% Yb(OTf)$_3$, 1 equiv ^{t}BuOH
Conditions D: 3.0 equiv boronate, 10 mol% **279**, 9.0 mol% Yb(OTf)$_3$

Scheme 109. Proposed Catalytic Cycle
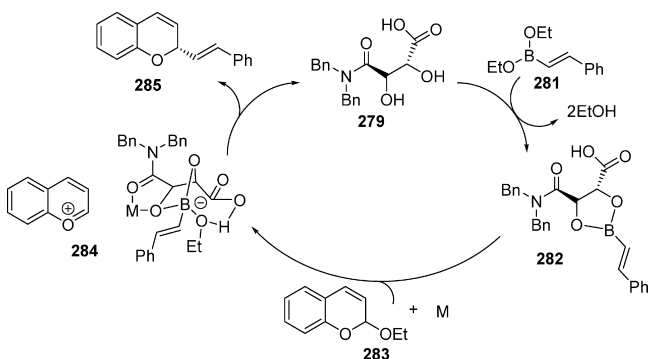
Scheme 110. Control Reaction in Support of the Proposed Mechanism
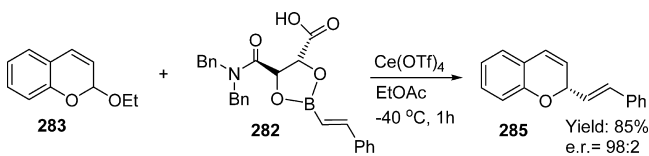
Scheme 111. Organocatalytic Asymmetric Oxa-Michael Addition for the Synthesis of 2*H*-Chromenes
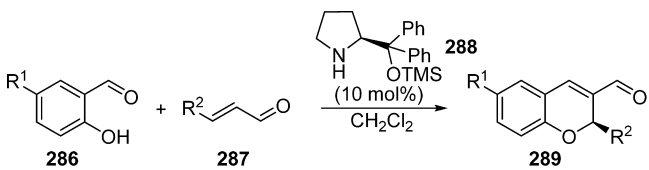
Additive	Conversion (%)	ee (%)
None	90	60
Imidazole	10	69
p-Chlorobenzoic acid	52	72

On the basis of spectroscopic observations and some controlled experimental findings, a plausible mechanism (Scheme 109) has been proposed. Formation of dioxaborolane

Scheme 113. Enantioselective Domino Oxa-Michael/Aldol Condensation
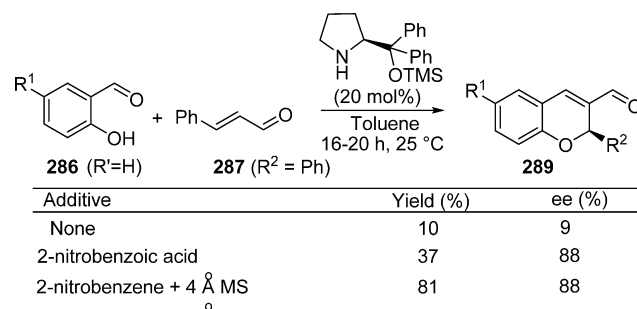

Additive	Yield (%)	ee (%)
None	10	9
2-nitrobenzoic acid	37	88
2-nitrobenzene + 4 Å MS	81	88

Scheme 114. Proposed Mechanism
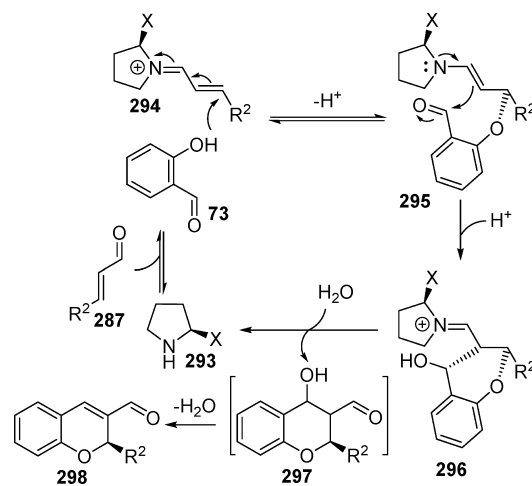
282 and pyrylium intermediate **284** were observed during the reaction. Complexation of Ce(OTf)$_4$ with the amide C=O of the tartaric acid catalyst and with the boronate oxygen atoms was noticed as well. The proposed catalytic cycle begins with the formation of dioxaborolane **282** from the boronate and tartaramide acid **279**. As a result of complexation of **282** to

Scheme 112. Proposed Mechanism of the Organocatalytic Asymmetric Oxa-Michael Addition
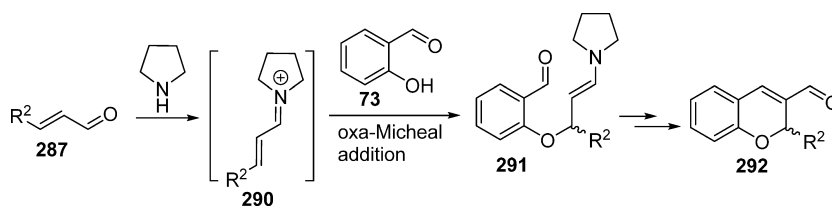
Scheme 115. Organocatalytic Enantioselective Domino Oxa-Michael/Aldol Condensation in the Presence of Benzoic Acid as Co-Catalyst
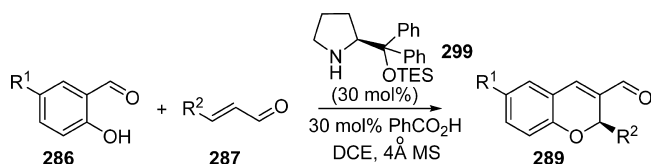
Scheme 116. Organocatalytic Enantioselective Domino Oxa-Michael/Aza-Henry Condensation in the Presence of Salicylic Acid as Co-Catalyst
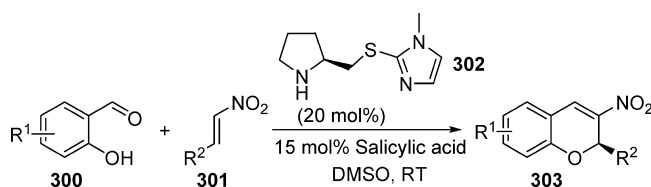
Scheme 117. Proposed Mechanism
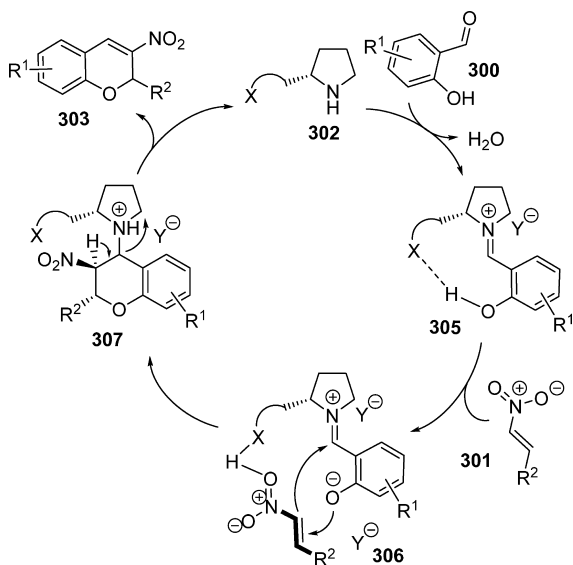
Scheme 118. Proposed Transition States
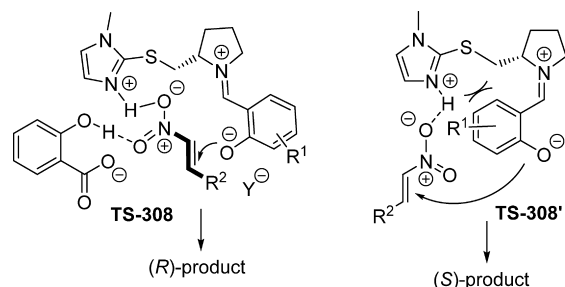
Scheme 119. Combination of Chiral Acid and Chiral Base
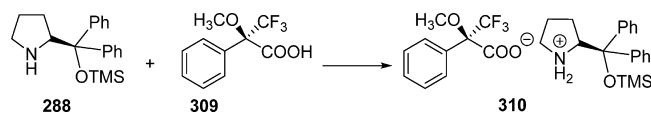
Ce(OTf)$_4$, the acidity of the boronate moiety increases to some extent, which in turn facilitates the formation of pyrylium

Scheme 120. Chiral Acid/Chiral Base-Catalyzed Chromene Synthesis
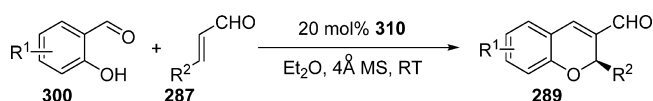
Scheme 121. Synthesis of 2-Substituted-3-Nitro-2H-Chromenes via a Domino Organocatalytic Oxa-Michael/Aldol Reaction
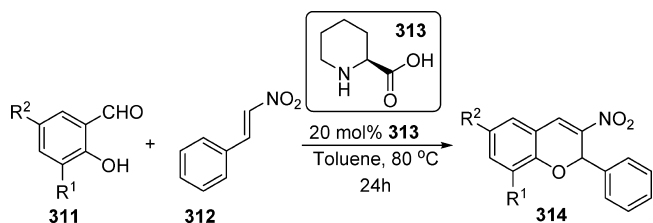
intermediate along with boronate complex **284**. Finally, the activated complex **284** undergoes nucleophilic addition to the pyrylium intermediate yielding the desired chromene **285** (Scheme 109).

The proposed mechanism was further supported by the fact that the chromene acetal **283** and chiral dioxoborolane **282** react at −40 °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 organo-catalytic asymmetric synthesis of benzopyrans via a one-pot oxa-Michael addition followed by an intramolecular aldol condensation between salicylaldehyde **286** and α,β-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 α,β-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 enantioselectivy (Scheme 113).

The proposed mechanism is shown in Scheme 114. The reaction proceeds through the initial iminium ion activation of

Scheme 122. Modified Domino Oxa-Michael/Aza-Henry Condensation
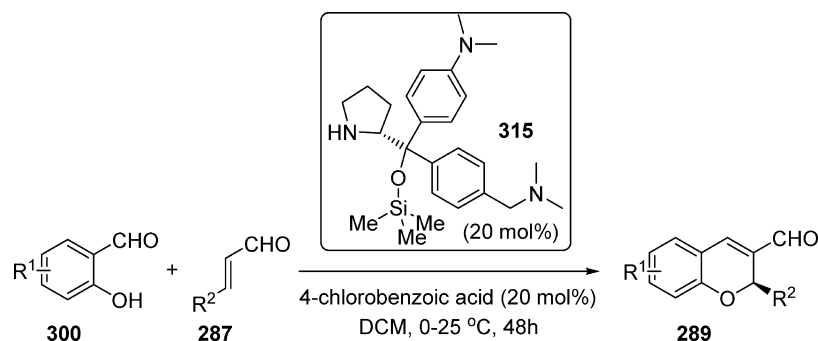
Scheme 123. Organocatalytic Synthesis of Chromenes via an Asymmetric Oxa-Michael/Henry Condensation Reaction Using a Bifunctional Thiourea Catalyst
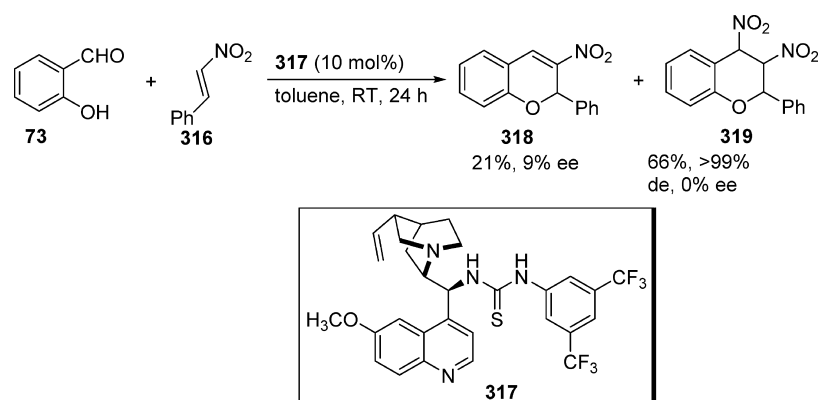
Scheme 124. Asymmetric Chromene Synthesis Using Organocatalyst 317
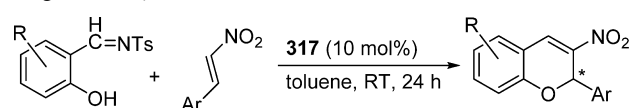
Entry	R	Ar	Yield[b]	ee (%)[b]
1	H	Ph	52 (31)	49 (92)
2	H	2-MeOPh	70 (22)	29 (66)
3	H	4-MeOPh	56 (23)	50 (80)
4	H	4-MePh	69 (22)	39 (96)
5	H	4-BrOPh	83	35
6	H	2,3-(MeO)₂Ph	81 (42)	48 (97)
7	H	2,6-Cl₂Ph	34 (23)	37 (52)
8	H	3,4-Cl₂Ph	93 (68)	31 (46)
9	H	furyl	87 (54)	43 (51)
10	5-MeO	Ph	20	80
11	4-Br	Ph	75	41

[b] Values between parentheses obtained in reactions performed at 0 °C

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

Scheme 125. Chiral Pool Synthesis of Chromenes
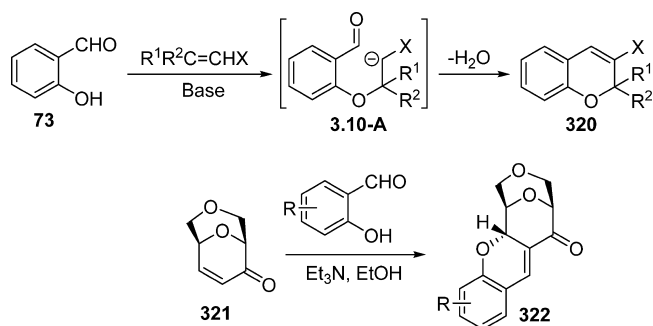
the *Re*-face of the chiral iminium intermediate **294** to produce the enamine intermediate **295**. Subsequently, the enamine attacks the C=O of salicylaldehyde to produce the cyclic iminium ion intermediate **296** which upon hydrolysis affords chromanol **297**. Elimination of water produced the 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[65] 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-*

Scheme 126. Kinetic Resolution of Racemic 3-Nitro-2H-Chromenes
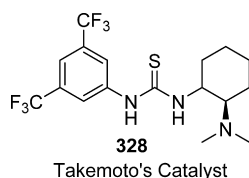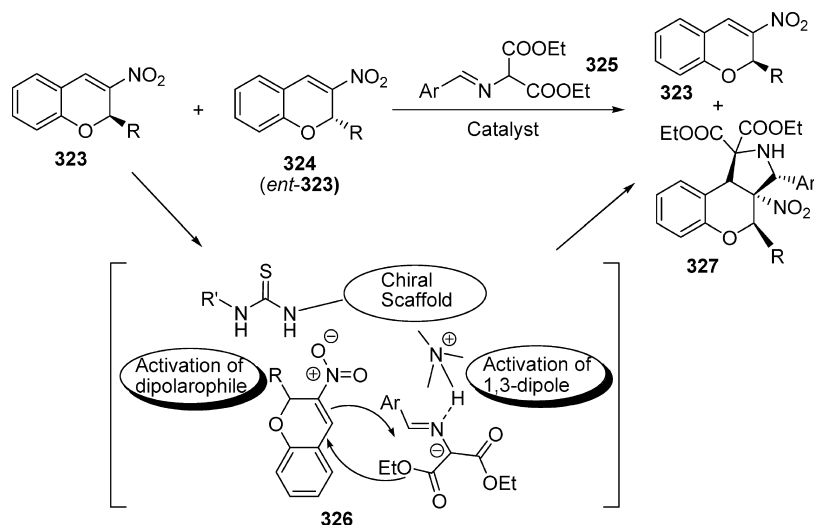
Figure 5. Takemoto's catalyst.

Scheme 128. Chiral Brønsted Acid-Catalyzed Synthesis of Chromenes

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[66] 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 organo-catalyst 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-ion 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 **302** and salicylic acid as cocatalyst afforded the highest yield and the highest enantioselectivity of the desired chromenes in polar solvents. This method is quite versatile,

Scheme 129. Reactions of Various Brønsted Acid Catalysts with Different Aryl Substituents

Ar = Ph, p-FC₆H₄, p-OMeC₆H₄, 2,4,6-Me₃C₆H₂, H, Me, phenanthryl, 1-naphthyl, p-ClC₆H₄
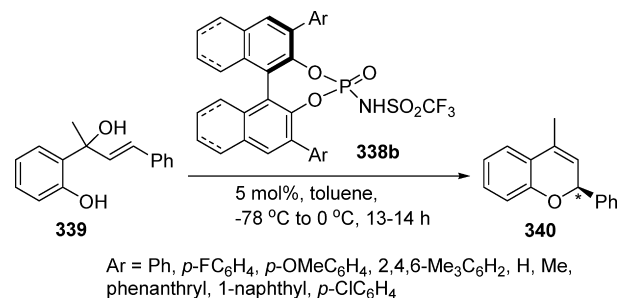
producing high enantiosectivities (85%) with differently substituted salicylaldehydes (Scheme 116).

The proposed mechanism (Scheme 117) involves iminium activation of salicylaldehyde to produce intermediate **305**, which is also activated by the Lewis base moiety X present in the organocatalyst **302**. The iminium intermediate then participates in a domino oxa-Michael/aza-Henry condensation with β-nitrostyrene to produce intermediate **307**. Finally, product **303** eliminates from intermediate **307**, thus regenerat-

Scheme 127. Organocatalytic Kinetic Resolution of Chromenes Using Takemoto's Catalyst
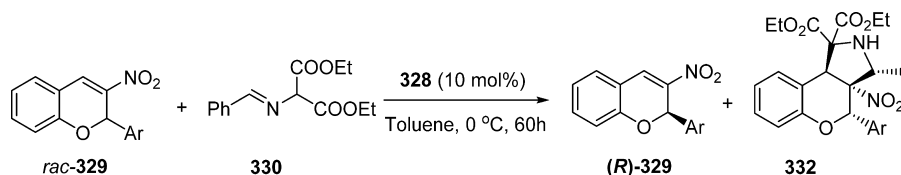
Scheme 130. Ionic-Liquid-Catalyzed Synthesis of Chromenes
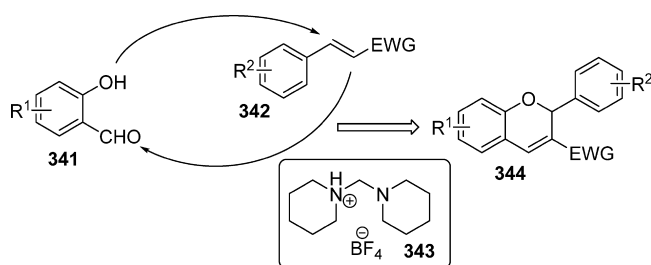
ing the catalyst. Two important transition states were proposed for this reaction: **TS-308** and **TS-308′**. **TS-308** seemed to be more favored compared to **TS-308′** for steric reasons. In **TS-308** the oxa-Michael addition take place to the *re* face of β-nitrostyrene leading to (*R*)-products (Scheme 118). Notably, both the catalyst and cocatalyst play a dual role in this reaction. Catalyst **302** not only acts as an activator of salicylaldehyde via iminium ion formation but also facilitates deprotonation of its OH group to promote the Michael addition. Salicylic acid, on the other hand, helped the formation of the iminium ion intermediate and activates the β-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 found[67] that the combination of (*S*)-diphenylprolinol trimethylsilyl ether **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 reported[68] another related organocatalytic domino oxa-Michael/aldol reaction for the synthesis of 2-substituted-3-nitro-2*H*-chromenes by employing some selected simple catalysts like guanidine, 1,1,3,3-tetramethylguanidine (TMG) and pipecolinic acid for screening. No cocatalyst was used during the reaction. Optimization of the reaction conditions revealed that pipecolinic 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 diarylprolinol 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 to increased up to 94% ee with improved yields with catalyst **315** (Scheme 122).

3.9. Another useful organocatalytic method was developed[70] using bifunctional thiourea as catalyst to synthesize chiral 2-aryl-3-nitro-2*H*-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*-tosylimine 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*-tosylimine 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. developed[71] 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-unsaturated ketone called evoglucosenone **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-salicylaldehyde, which showed exceptionally slow reactions leading to a low yield.

3.11. The synthesis of 3-nitro-2*H*-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-2*H*-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 developed[73] 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 Brønsted 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*-trifluorophosphoramide **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 carbinol carbon in **339**, producing chromenes in excellent yields and with high ee.

3.13. Very recently, Sabater and co-workers reported[74] another organocatalytic approach to 2*H*-chromenes involving the coupling of salicylaldehyde 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 nucleophilic attack compared to other electron-withdrawing groups. A wide range of substituted salicylaldehyde as well as *trans*-nitrostyrenes were found to produce the corresponding 2*H*-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 2*H*-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 2*H*-chromene syntheses. Other recurring mechanistic aspects in 2*H*-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.
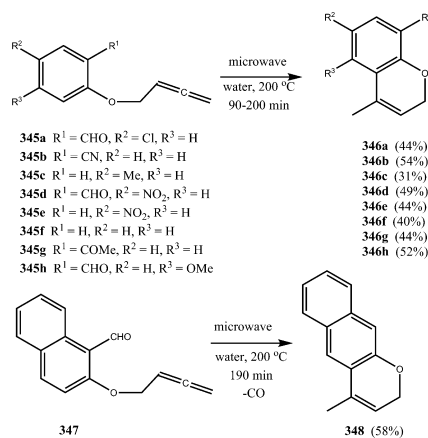
5. CONCLUSIONS

Several catalytic methods for the synthesis of 2*H*-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 2*H*-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 enanatioselective 2*H*-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 2*H*-chromene syntheses. High enantioselectivities can be achieved with the reported organo-catalytic approaches, but most of these methods are only suitable for the synthesis of 2,3-disubstituted 2*H*-chromenes. A more general approach to chiral 2*H*-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 2*H*-chromene scaffolds. In particular, trans-formations of simple 2*H*-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 2*H*-chromenes, which are

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

345a R¹ = CHO, R² = Cl, R³ = H
345b R¹ = CN, R² = H, R³ = H
345c R¹ = H, R² = Me, R³ = H
345d R¹ = CHO, R² = NO₂, R³ = H
345e R¹ = H, R² = NO₂, R³ = H
345f R¹ = H, R² = H, R³ = H
345g R¹ = COMe, R² = H, R³ = H
345h R¹ = CHO, R² = H, R³ = OMe

346a (44%)
346b (54%)
346c (31%)
346d (49%)
346e (44%)
346f (40%)
346g (44%)
346h (52%)

347

348 (58%)

included here as a note added in proof. The group of Alcaide reported the microwave-assisted synthesis of 2*H*-chromenes **346a−h**, starting from allene-substituted aryl ethers **345a−h** (Scheme 131).[75] In an analogous reaction using **347**, decarbonylation occurs leading to formation of **348**.

Scheme 132. Synthesis of Chromenopyridines

R^1 = Br, OMe
R^2 = Me, Ph, Py
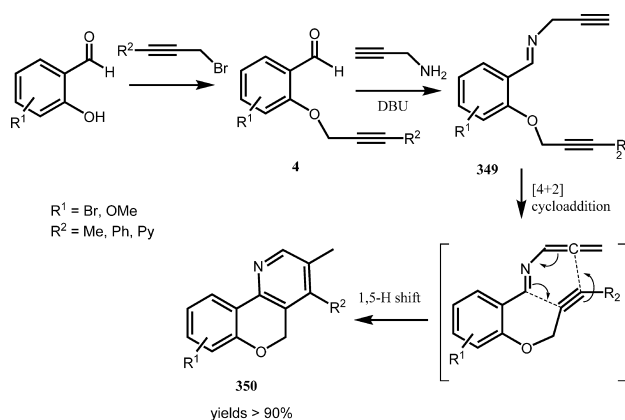
Scheme 133. Synthesis of Chromenopyridines

yields: 43–98%

The group of Balci reported an interesting metal-free regioselective approach to synthesize chromenopyridines.[76] The synthetic method involves O-propargylation of aromatic hydroxyaldehydes (such as salcylaldehyde) 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).

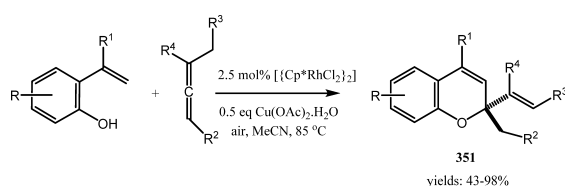Gulías and co-workers recently reported the Rh/Cu-mediated oxidative coupling of alkenylphenols and allenes to form 2,2-disubstituted 2H-chromenes **351** (Scheme 133).[77] The reaction tolerates a broad range of substituents both in the alkenylphenol and in the allene and most probably proceeds through 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).[78] 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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Notes
The authors declare no competing financial interest.

Scheme 134. Palladium-Catalyzed Formation of 2H-Chromenes Involving Using Migratory Carbene Insertion Protocol
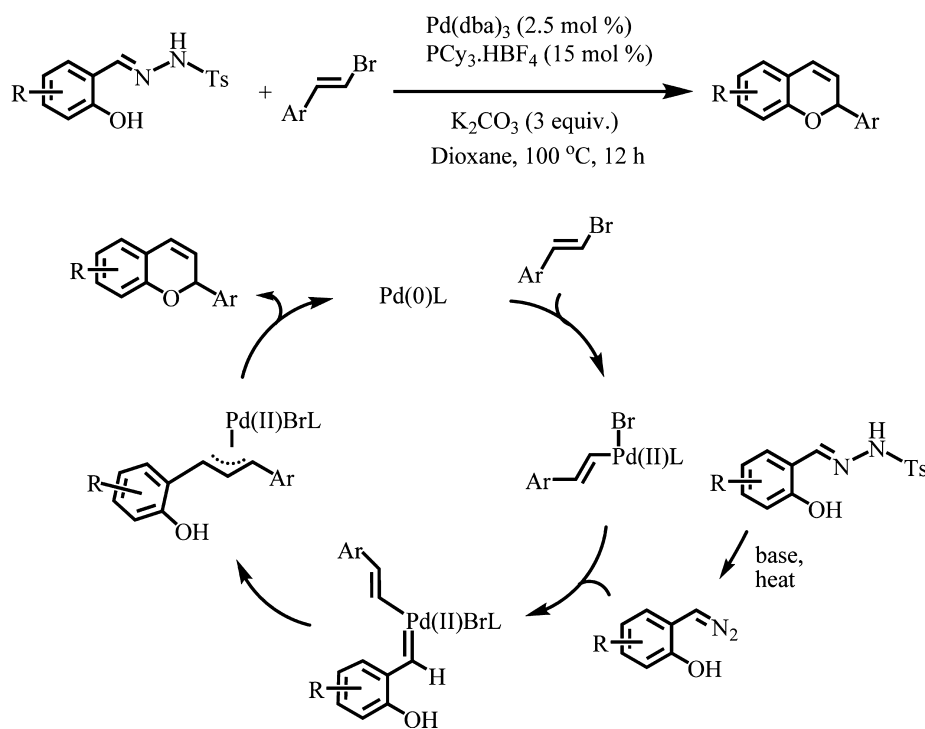
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