SYNTHETIC APPROACHES TO 4-ARYL-3,4-DIHYDROCOUMARINS

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Abstract. *The transformations mediated by transition metals or organocatalyzed or metal-free strategies have become crucial tools for the synthesis of natural products and valuable scaffolds that have important biological activities. 4-Aryl-3,4-dihydrocoumarin compounds with diverse functionalities are also synthesized by employing these strategies. Many of the catalytic methods have revolutionized synthetic chemistry programme providing an efficient and sustainable approach for the synthesis of complex compounds that are important in pharmaceuticals, materials science, and agrochemicals fields. The newly discovered transition metal-catalyzed, organocatalyzed approaches and also many metal-free methods are compiled in this chapter toward the synthesis of 4-aryl-3,4-dihydrocoumarins with recent literature covering close to a decade.*

Contents

1. Introduction

Coumarins are heterocyclic compounds that belong to the benzopyrone family and are found abundantly in nature.[1] In 1820, a coumarin molecule was first isolated by Vogel from plant species *Coumarouma odorate* and till now more than 1400 types of natural coumarins have been identified.[2] Coumarins possess a wide range of biological properties, including antioxidant, antiviral, anti-inflammatory, antifungal, anticancer, neuroprotective, and anticoagulant properties.[3] Dihydrocoumarins are widely used in various fields of flavouring food, fragrances in cosmetics, as well as perfumery industries.[4] They contain the core skeleton of 4-aryl-3,4-dihydrocoumarin and have been isolated from various classes of plants (neoflavanoids) and fruits like *Polygonum erfoliatum*[5a], *Dorstenia poinsettifolia*,[5b] *Pityrogramma calomelanos*,[5c] *Gnetum montanum* Markgr. f. megalocarpum Markgr,[5d] and Clusiaceae, Fabaceae, Rubiaceae, Asteraceae, Thelypteridaceae, Passifloraceae, and Rutaceae families,[5e-g] which exhibit intriguing biological activities like anti-herpetic,[6a] aldose reductase inhibition,[6b] and protein kinase inhibition[6c] Moreover, some tannins containing the dihydrocoumarin unit have been used in the treatment of infections and diseases. Naturally occurring dihydrocoumarins like **I**[7] and **II**[7] obtained from *Aloe vera*[8] and *Gnetum cleistostachyum*,[5d] respectively, display anti-inflammatory and antioxidant activities[9] (Figure 1). The compounds **I** and **II** protect low-density lipoproteins from oxidative attack[10] and have shown potential in controlling chronic heart and colon-rectal cancers. Specifically, dihydrocoumarin molecule **III** is an essential intermediate for endothelin antagonists[11] and the drug tolterodine **V**,[12a] which is employed in the treatment of overactive bladder.[12b] Moreover, the dihydrocoumarin **IV** exhibits bactericidal activity in vitro against the *Trypanosoma* family,[10] offering the

potential for the treatment of related infections. Vismiaguianone D **VI** and E **VII** were isolated from roots of *Vismia guianesis* and have moderate cytotoxicity.[13a] Poinsettifolactone **VIII** is a biologically active natural product and typically a precursor for many prospective therapeutic compounds.[5b,13b]

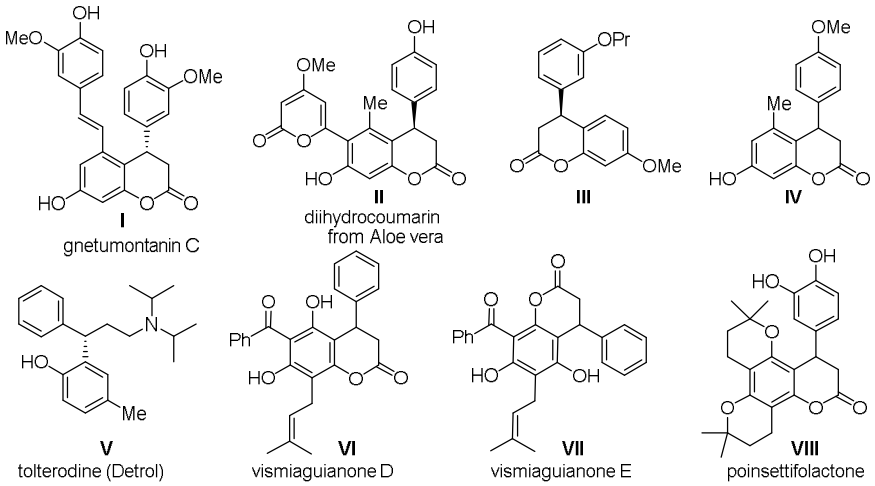


Figure 1. Some 4-aryl-3,4-dihydrocoumarins and derivatives.

The synthetically prepared 4-aryl-3,4-dihydrocoumarins have received significant attention due to diverse bioactivities. Several approaches have been reported, including transition metal-mediated or catalytic hydrogenations,[11,14] protic acid-assisted hydroarylation of cinnamic acids with phenols,[15] Lewis acid-mediated rearrangements,[16] the use of oxidants on acids,[17] synthesis from ionic liquids and solid-states catalysts, utilization of molecular iodine as catalyst, 5-alkylidene Meldrum's acids[18] and microwave-assisted synthesis from phenols and cinnamoyl chlorides in the presence of montmorillonite K-10 catalyst.[16a] Coumarins and their derivatives have a wide range of applications across various industries due to their unique chemical properties and pleasant aromatic characteristics. Coumarins have been used as intermediates in the production of various dyes and pigments. They could impart specific colours and properties to the final products, making them valuable components in the textile and dye industries. Many have sweet, hay-like scent, which makes them popular ingredients in perfumes, colognes, and other fragrances. Coumarin derivatives, such as ethyl coumarin, are used in the production of toothpaste and oral care products to provide a pleasant flavour and aroma. Coumarin compounds can act as plasticizers in the production of synthetic rubbers and plastics, improving their flexibility and other properties. Some coumarins possess insecticidal properties, and they are used in the formulation of insecticides and repellents to control pests. Coumarin-based compounds can be incorporated into detergents and cleaning products to enhance their fragrance and appeal to consumers. They have also applications in various essence formulations and spray products, contributing to characteristic fragrance.[19]

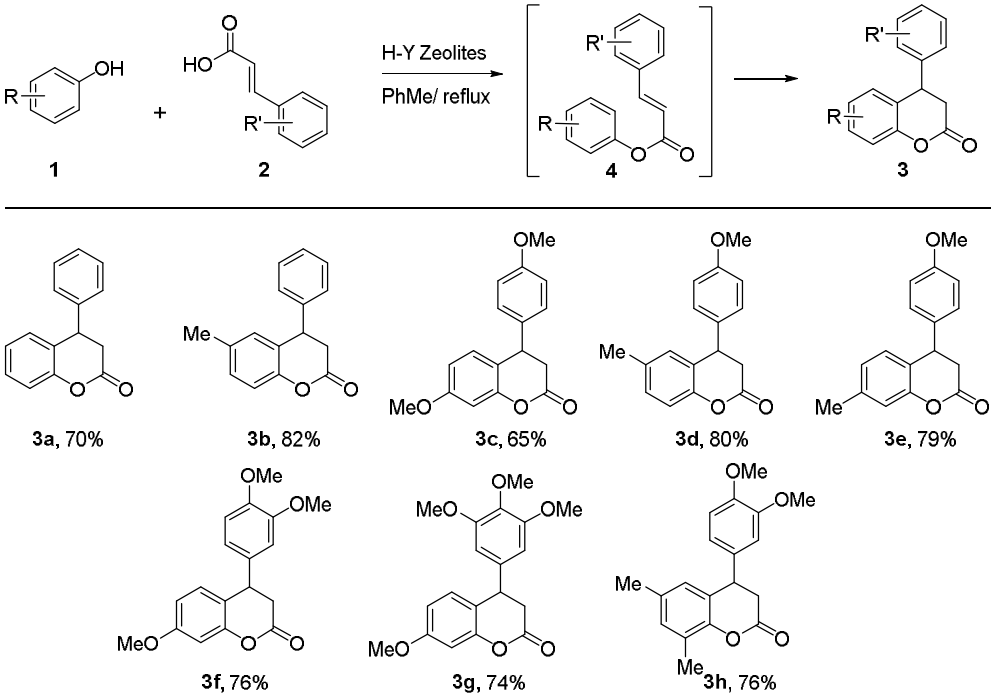
2. Metal-free approaches

Over the years, several transition metal-catalyzed, metal-free, and organocatalyzed synthetic methods have been developed for the synthesis of 4-aryl-3,4-dihydrocoumarins. There are inherent limitations involved in some of these protocols that include long reaction times,[11,15c,15e,20] use of costly, irreversible, and toxic catalysts,[15c,15e,18,20] complex starting materials,[15c] and lack of substrate generality. Metal-free synthetic strategies are in demand and for coumarins synthesis, these involve heterogeneous catalysts like zeolites, clays, and ion exchange resins.[18] The advantage of using metal-free catalysts was that they simplify product recovery and reduce undesirable waste compared to traditional Lewis acid-catalyzed methods that involve transition metals. Metal-free approaches are also preferred for their economic viability, non-toxic nature, versatility, ease of handling, and environmentally friendly characteristics. By using metal-free catalysts, researchers can

develop more sustainable and greener synthetic routes for the preparation of dihydrocoumarins. These methods may become a valuable contribution to the field of organic synthesis, as they address some of the limitations associated with traditional transition metal-catalyzed protocols. Some of the metal-free interesting methods developed in 4-aryl-3,4-dihydrocoumarins syntheses are discussed below.

2.1. Zeolites

Salunkhe and co-workers[21] in 2000 reported the synthesis of substituted 4-aryl-3,4-dihydrocoumarins using H-Y Zeolites. The dihydrocoumarins have been prepared by reacting various cinnamic acids **2** with phenols **1** on H-Y Zeolites (Si/AI = 2.45) by refluxing in toluene (Scheme 1). The reaction proceeds first by esterification to **4** followed by the alkylation of the ring giving the products **3a-h** in good yields.



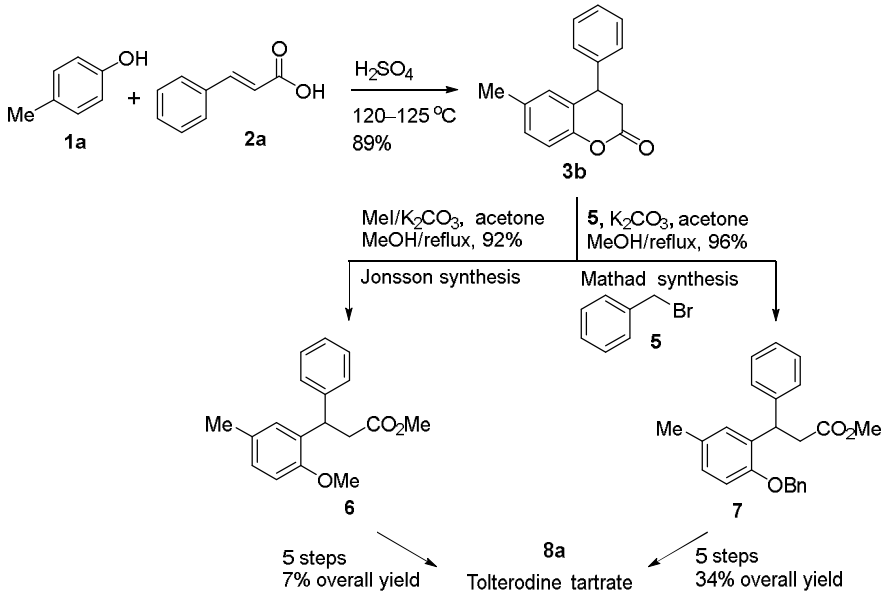
Scheme 1. Synthesis of substituted 4-aryl-3,4-dihydrocoumarins using H-Y Zeolites by Salunkhe.

2.2. Protic acids

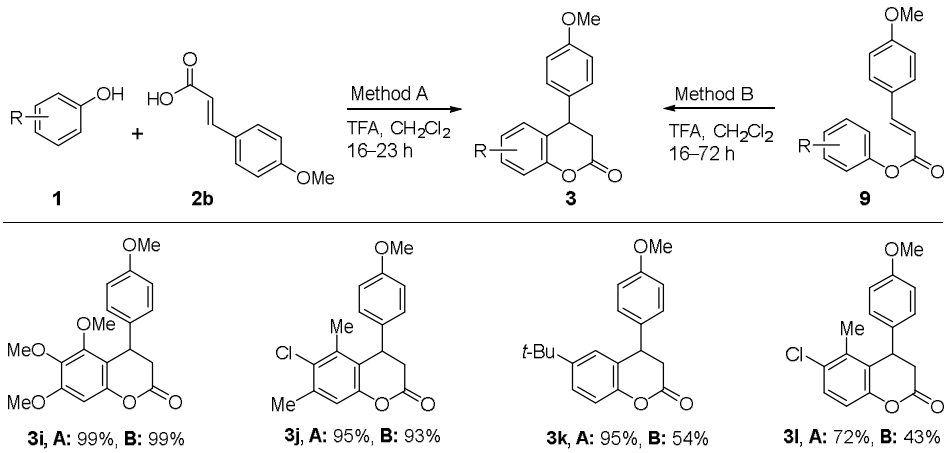
In 2005, Mathad and co-workers[22] developed cost-effective and impurity-free, improved route for tolterodine by modifying the original Jonsson's synthetic route (Scheme 2). Previously, in 1995, Jonsson and co-workers[23] synthesized tolterodine tartrate *via* acid-catalyzed condensation of cinnamic acid **2a** and 4-methylphenol **1a** in neat sulfuric acid to afford 4-aryl-3,4-dihydrocoumarin **3b**, which was further used for the synthesis of tolterodine tartrate **8a** *via* **6**. Similarly, Mathad also prepared 4-aryl-3,4-dihydrocoumarin **3b** utilizing the Jonsson route and further tolterodine tartrate **8a** *via* **7** (obtained by benzyl bromide **5** addition) by using an eco-friendly reagents and overall good yields.

Tunge and co-workers[15c] in 2005 described hydroarylation of *p*-methoxycinnamic acid **2b** with various substituted phenols **1** in the presence of trifluoroacetic acid (TFA) and dichloromethane (4:1) to give 4-aryl-3,4-dihydrocoumarin derivatives **3**, obtained in efficient yields (Scheme 3). They also performed the reaction with pre-formed aryl esters **9** under the same reaction conditions to afford the products with excellent yields. It was noted that the reaction proceeds *via* both intra- and intermolecular cyclizations with substituted phenols. This means that the reaction can form cyclic structures either within the same molecule (intra) or

between two different molecules (inter). However, when substituted aniline was used in the reaction, only intramolecular cyclization occurred, leading to the formation of the desired dihydroquinolone products (not shown). The failure of intermolecular reaction in this case is attributed to the protonation of nitrogen leading to decreased nucleophilicity of the aryl ring.



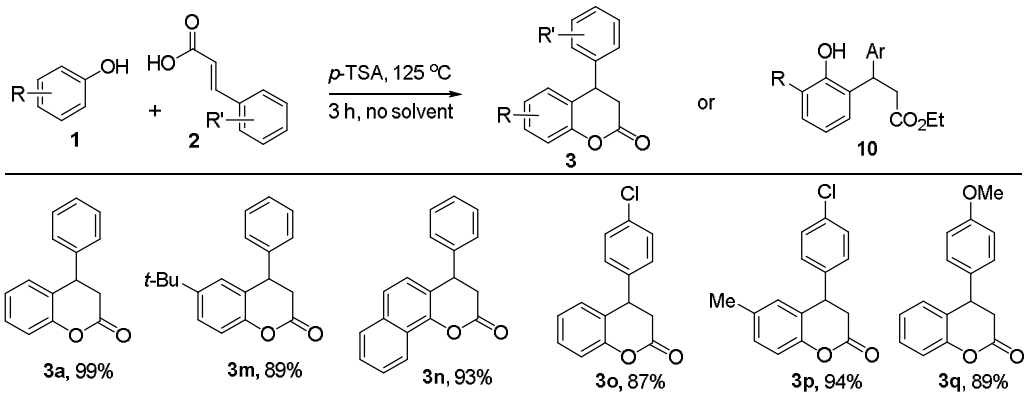
Scheme 2. Tolterodine tartrate synthesis from cinnamic acid and 4-methylphenol by Mathad.



Scheme 3. TFA-mediated hydroarylation for the synthesis of 4-aryl-3,4-dihydrocoumarins by Tunge.

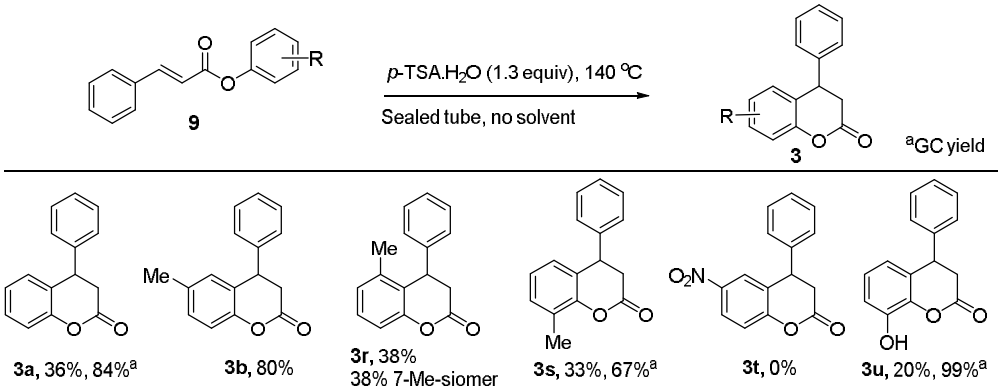
In 2007, Jagdale and Sudalai[15d] reported *p*-toluenesulfonic acid-mediated hydroarylation of various cinnamic acids **2** with phenols **1** (under metal and solvent-free conditions) to afford 4-aryl dihydrocoumarins **3** in good to excellent yields (Scheme 4). The formation of dihydrocoumarins was proposed to occur *via* an intramolecular Friedel-Craft type cyclization of phenolic esters facilitated by the presence of *p*-toluenesulfonic acid. Interestingly, when phenols with *ortho*-substituents such as Cl, Br, OMe, and CO_2Me, were subjected to

the reaction, a distinct behaviour was observed. In these cases, the reaction selectively produced the corresponding esters **10**.



Scheme 4. *p*-TSA-mediated hydroarylation of various cinnamic acids with phenols to afford 4-aryl-3,4-dihydrocoumarin derivatives by Sudalai.

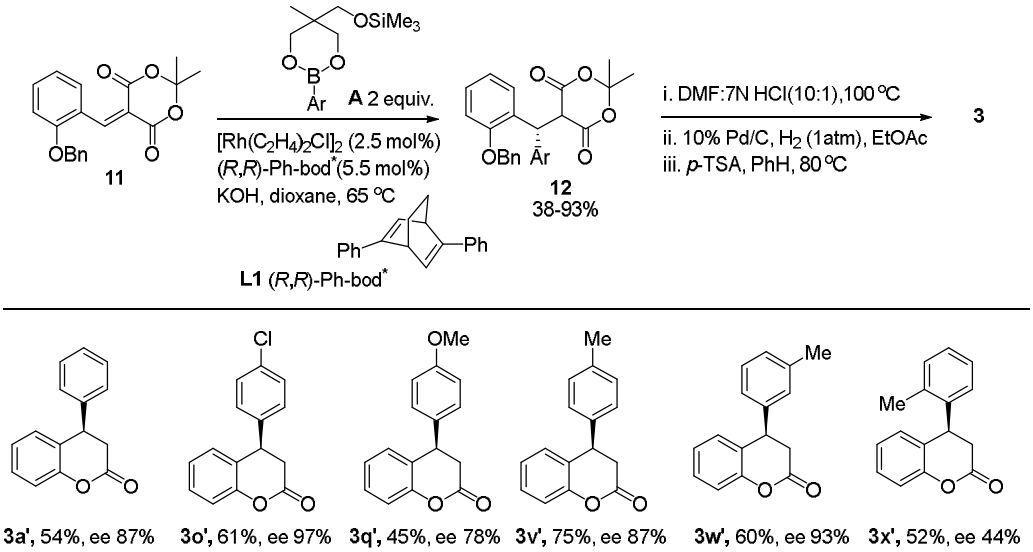
Based on the above discussed reports by Tunge[15c] and Sudalai[15d] wherein TFA and *p*-TSA-mediated synthesis of 4-phenyl-3,4-dihydrocoumarins by intermolecular approach, in 2011, Jun and co-workers[24] observed the high cost and use of more equivalents of TFA being involved and this proved to be disadvantageous. Therefore, they considered to use *p*-TSA-mediated intramolecular hydroarylation of cinnamate esters **9** for the synthesis of 4-aryl-3,4-dihydrocoumarins **3** (Scheme 5). Aryl cinnamates **9** were obtained by reaction of cinnamoyl chloride and substituted phenols. Then, among different Lewis acids investigated such as *p*-TSA, $SnCl_4$, $TiCl_4$, $InCl_4$, and others, the use of *p*-TSA proved to be best as it afforded higher yields. The substrates possessing an electron-donating group formed the desired products with good to excellent yields, whereas those possessing strong electron-withdrawing group did not form the desired product (for example **3t**). In the case of $TiCl_4$, the chalcone derivative was formed instead of the desired product, which could be due to thermodynamically controlled formation of an acylium carbocation intermediate.[25] Also in the case of catechol-based cinnamate though the GC yield of **3u** was 99%, the isolation yield was only 20%.



Scheme 5. Synthesis of 4-aryl-3,4-dihydrocoumarins by intramolecular hydroarylation using *p*-TSA by Jun.

Frost and co-workers[26] in 2012 investigated Rh-catalyzed enantioselective aryl addition to arylidene Meldrum's acid derivatives **11** and subsequent asymmetric synthesis of 4-aryl-3,4-dihydrocoumarin derivatives (Scheme 6). Enantiopure diene ligands proved to be effective substitutes for chiral phosphines in

enantioselective processes, demonstrating higher reactivity and enantioselectivity.[27] One such ligand, (*R,R*)-Ph-bod* **L1**, developed by Hayashi, enabled successful arylations under anhydrous conditions.[28] The isolated yields of **12** obtained using the enantiopure diene ligand were comparable to those achieved with racemic protocols. Notably, substituting the silyl-protected dioxaborinane **A** at the *para*-position resulted in excellent product yields while lower yields were observed for the *meta* or *ortho*-substituted aryl groups. Enantioselective 1,4-addition takes place with only Meldrum's acid derivatives possessing electron-donating group, otherwise, the reaction did not occur due to inductive deactivation of the hindered trisubstituted alkene in carbometallation. Next, the carboxylic acid was produced by heating the enantioenriched Meldrum's acid derivatives **12** by stirring in DMF and aqueous HCl. Further, debenzylation under catalytic hydrogenation conditions resulted in substituted phenols that underwent cyclization on heating in the presence of catalytic *p*-toluenesulfonic acid to afford 4-aryl-3,4-dihydrocoumarins **3a′**, **3o′**, **3q′**, **3v′**, **3w′** and **3x′** over three steps in good yields and enantioselectivities.



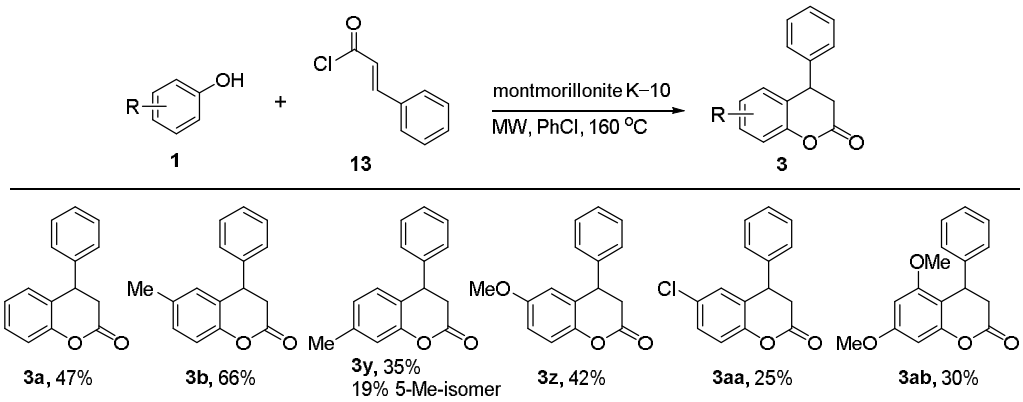
Scheme 6. (*R,R*)-Ph-bod* ligand and Rh-catalyzed asymmetric aryl addition to Meldrum's acids derivatives and synthesis of 4-aryl-3,4-dihydrocoumarins by Frost.

2.3. Solid acids

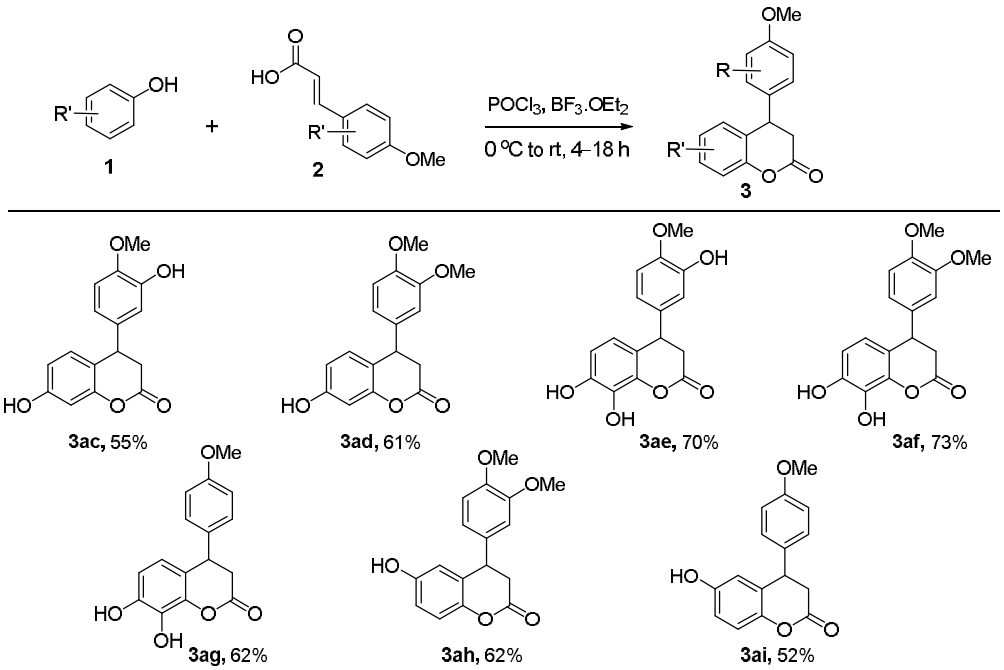
In 2008, Ma and co-workers[18] developed a facile one-pot temperature-controlled microwave irradiation assisted synthesis of 4-aryl-3,4-dihydrocoumarins **3** with solid-acid montmorillonite K-10 catalyst (Scheme 7). Various substituted phenols **1** and cinnamyl chloride **13** underwent tandem esterification-Friedel-Crafts alkylation under microwave irradiation in the presence montmorillonite K-10 in chlorobenzene solvent to deliver 4-aryl-3,4-dihydrocoumarins in moderate yields. The reaction had distinguished features like inexpensive and recyclable catalyst, easy handling, less reaction time and easy product purification.

2.4. Lewis acids

Zou and co-workers[29] in 2012 reported the synthesis of 4-aryl-3,4-dihydrocoumarins **3** by condensation of substituted cinnamic acids **2** with phenols **1** in the presence of $BF_3{\cdot}OEt_2$ and $POCl_3$ under neat conditions (Scheme 8). They also evaluated the antimicrobial activity of synthesized compounds against four microorganisms, *Staphylococcus aureus* (ATCC2592) (Gram-positive), *Escherichia coli* (ATCC25922) (Gram-negative), *Bacillus dysenteriae* (Bacillaceae), and *Candida albicans* (ATCC2002) (fungus). These compounds exhibited a broad range of antimicrobial activities.



Scheme 7. Microwave irradiation-assisted synthesis of 4-aryl-3,4-dihydrocoumarins by Ma.

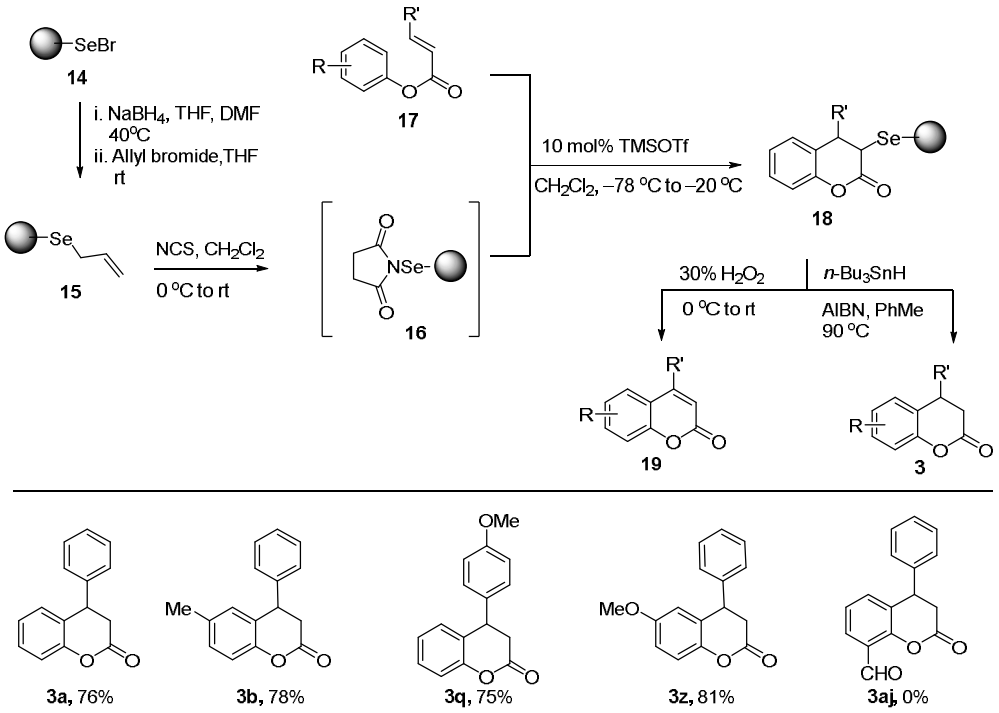


Scheme 8. $BF_3{\cdot}OEt_2$-mediated synthesis of 4-aryl-3,4-dihydrocoumarins by Zou.

In 2012, Tang and co-workers[17d] reported the solid phase synthesis of 4-aryl-3,4-dihydrocoumarins and coumarin derivatives *via* a highly regioselective selenium-induced intramolecular Friedel-Crafts alkylation of substituted phenyl acrylates **17** using a polymer-supported organoselenium reagent **16** (Scheme 9).

Solid-phase synthesis is an important tool with an obvious advantage in drug discovery because of its simplicity in workup procedures as well as characteristics for parallel synthesis.[30] Using Wang resin, the Knoevenagel condensation of ethyl malonate and 2-hydroxybenzaldehydes followed by cleavage with trifluoroacetic acid afforded 4-aryl-3,4-dihydrocoumarins and coumarins derivatives in low yield[31] (not shown here). On the other hand, the solid phase synthesis of 4-aryl-3,4-dihydrocoumarins and coumarin derivatives *via* highly regioselective selenium addition afforded the desired products in good to excellent yields. The reaction involves cyclization, oxidative elimination, and free radical hydrogenation steps. The substituted

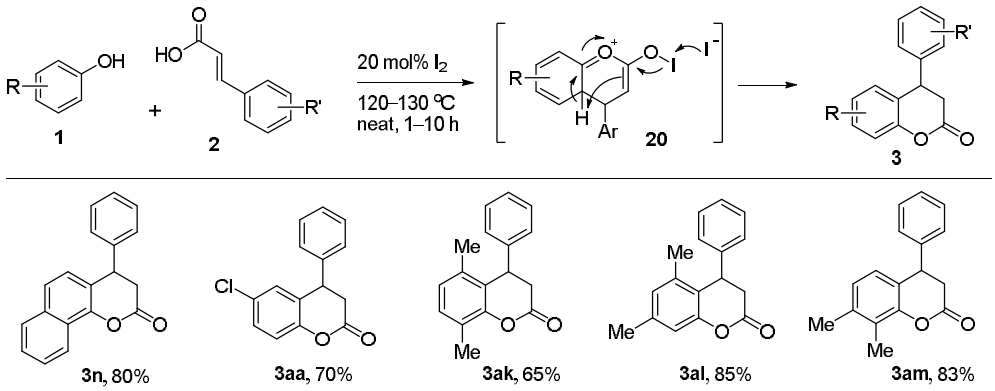
phenyl acrylates **17** were synthesized by reacting acryloyl chlorides with substituted phenols in the presence of NaOH at 40°C. Polystyrene-supported allyl selenide **15** was prepared in high yield by allylation of polystyrene-supported selenenyl bromide **14** using sodium borohydride and allyl bromide. Subsequent reaction of resin **15** with *N*-chlorosuccinimide yielded polystyrene-supported succinimidyl selenide **16** (PSSS), with 3-chloroprop-1-ene as the only by-product. PSSS resin **16** was moisture-sensitive, unlike the stable resin **15**. A one-pot synthesis of polymer-supported cyclized product **18** was carried out by subjecting **17** to cyclization using TMSOTf as a catalyst in presence of resin **16**. The reaction of **18** with 30% H_2O_2 afforded coumarins **19**. Alternatively, employment of 2,2′-azodiisobutyronitrile (AIBN) and tri-*n*-butylstannane led to 4-aryl-3,4-dihydrocoumarins **3** in good yields and purities. The method gave excellent results when substituted phenyl acrylates containing electron-donating groups were used, but with electron-withdrawing groups, no cyclization occurred, *e.g.* **3aj**.



Scheme 9. TMSOTf-catalyzed solid phase synthesis of 4-aryl-3,4-dihydrocoumarins by Tang.

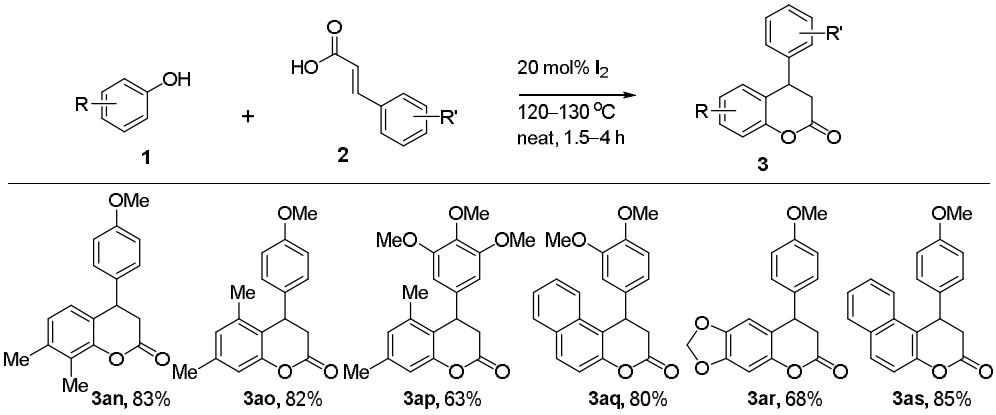
In 2012, Tilve and co-workers[17e] reported the synthesis of 4-aryl-3,4-dihydrocoumarins **3** *via* [3+3]-cyclo-coupling of phenols **1** with cinnamic acids **2** using 20 mol% of molecular iodine at 120 to 130 °C under solvent-free conditions through intermediate **20** (Scheme 10). Molecular iodine stood out as an excellent catalyst due to its remarkable characteristics. Firstly, it was economically viable, making it an attractive option for large-scale synthesis. Additionally, its non-toxicity, and high tolerance to air and moisture, simplifies the reaction conditions and thereby reducing the need for rigorous moisture-free environments.[32] They expanded the scope by carrying out the reaction with different substituted phenols wherein those possessing electron-donating groups exhibited high reactivity, leading to the desired products **3** with commendable yields. Also, *ortho*-substituted phenol delivered the desired product **3am** in good yield. One of the remarkable aspects of this method was the absence of solvents, which not only simplified the process but also had environmental benefits. However, when phenols with electron-withdrawing groups were employed, the reaction yielded lower amounts of the target compounds. Most intriguingly, the presence of strong electron-withdrawing groups, such as NO_2 and F proved detrimental to the reaction, as no desired products were obtained, however

phenol substituted with Cl group afforded the desired coumarin **3aa** in good yield. This observation highlighted the importance of substrate selection when applying this synthetic approach.



Scheme 10. Solvent-free synthesis of 4-aryl-3,4-dihydrocoumarins utilizing molecular iodine by Tilve.

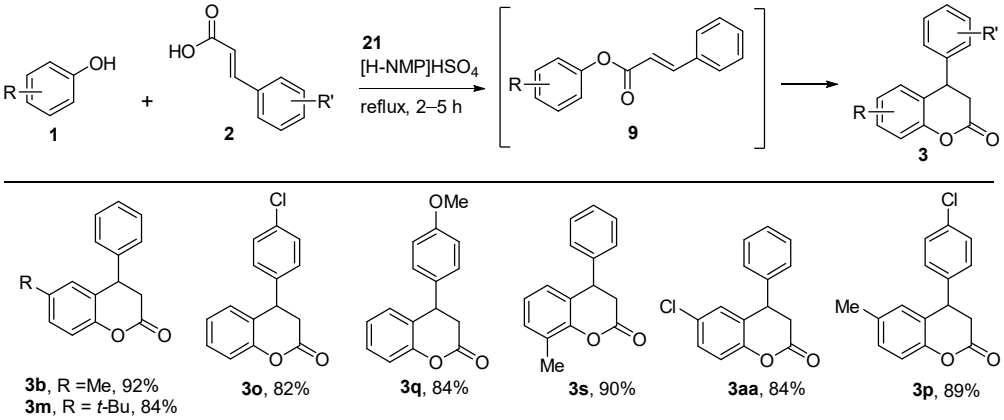
Tilve and co-workers[33] while continuing their above work, expanded the substrate scope of their study in 2014 and synthesized further examples of 4-aryl-3,4-dihydrocoumarins **3** from phenols **1** with cinnamic acids **2** using the same conditions of molecular iodine (20 mol%) catalysis under neat conditions (Scheme 11). They also synthesized chromans by using similar conditions (not shown here).



Scheme 11. Extended solvent-free synthesis of 4-aryl-3,4-dihydrocoumarins by utilizing molecular iodine catalysis by Tilve.

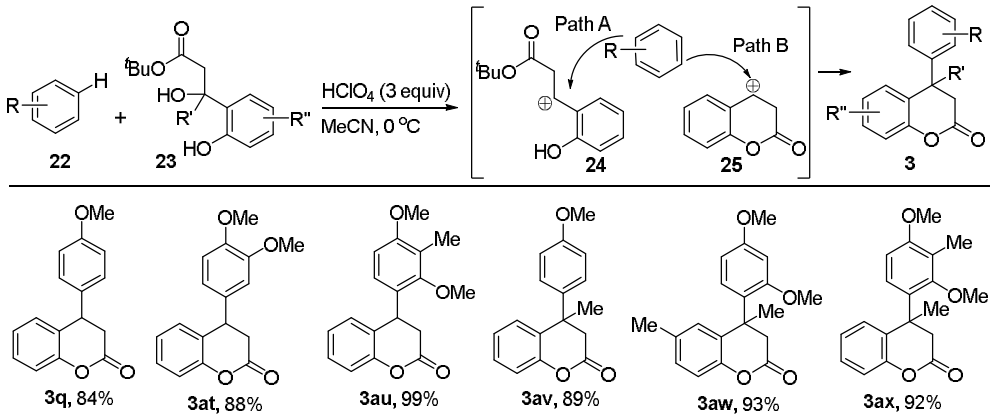
In 2016, Heravi and co-workers[34] reported the synthesis of 4-aryl-3,4-dihydrocoumarins **3** by hydroarylation of cinnamic acids **2** with substituted phenols **1** in the presence of acidic ionic liquid *N*-methyl-2-pyrrolidonum hydrosulphate ([H-NMP]HSO_4) **21** (Scheme 12). Ionic liquids can be used as both catalysts and solvents with the properties like high thermal and chemical stability, low vapour pressure, good solvating ability, ease of recovery, reusability, and controlled miscibility make them suitable for synthetic green chemistry.[35,36] They established the scope and generality of the reaction by using differently substituted phenols as shown in Scheme 12, wherein those bearing electron releasing groups such as Me, *t*-Bu easily delivered desired coumarins **3s**, **3m** in good yields. Similarly, phenol substituted with mild electron-withdrawing group such as Cl afforded the desired product **3aa** in high yield. However, phenol substituted with strong electron-withdrawing group such as NO_2 resulted in undesired esterification products.

The mechanism indicates that transesterification takes place first to form phenolic ester **9**, then Friedel-Craft type cyclization occurs leading to the formation of corresponding 4-aryl-3,4-dihydrocoumarins **3**. With the help of DFT and quantum chemistry computation methods, it was observed that the reaction of phenols bearing Me group **3b** was more energetically favoured in comparison to the phenols bearing NO_2 group. The *para*-methyl phenyl cinnamate has more electronic tendency to undergo an intramolecular cyclisation step to generate dihydrocoumarin in good yield.



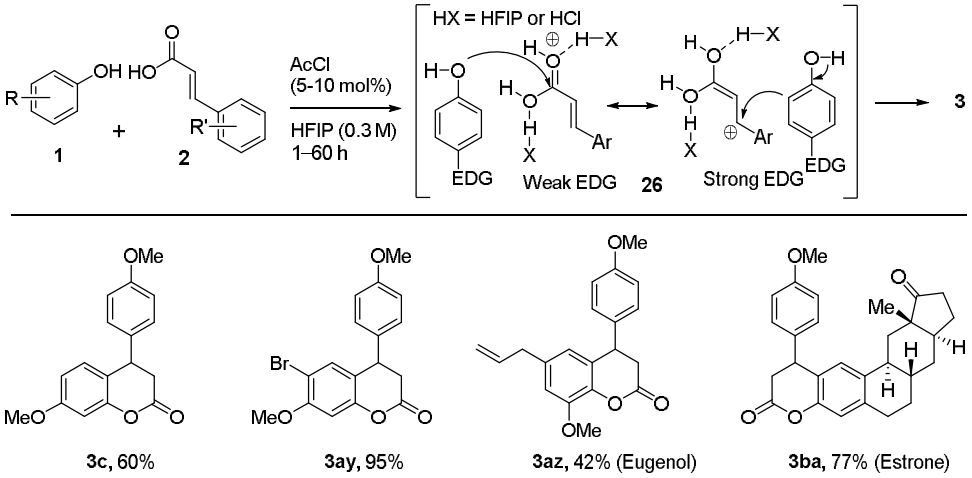
Scheme 12. [H-NMP]HSO_4-catalyzed synthesis of 4-aryl-3,4-dihydrocoumarins by Heravi.

Wu and co-workers in 2016[37] disclosed a facile and efficient one-pot synthesis of 4-aryl-3,4-dihydrocoumarin derivatives through a perchloric acid-mediated cyclization in acetonitrile solvent (Scheme 13). By utilizing the Brønsted acid ($HClO_4$), the intramolecular lactone formation followed by intermolecular arylation in a one-pot fashion provided a convenient approach to 4-aryldihydrocoumarins **3q**, **3at-3ax** in excellent yields. There were two possible pathways, first pathway A involves an S_N1-type alcohol **23** nucleophilic substitution (or Friedel-Crafts alkylation) *via* a benzylic carbenium species **24** followed by intramolecular cycloaddition to afford **3**. On the other hand, pathway B begins with Brønsted acid-aided intramolecular cycloaddition, leading to the formation of a carbenium ion **25**, which then reacts with **22** to yield the final product **3**.



Scheme 13. One-pot synthesis of 4-aryl-3,4-dihydrocoumarins using Brønsted acid by Wu.

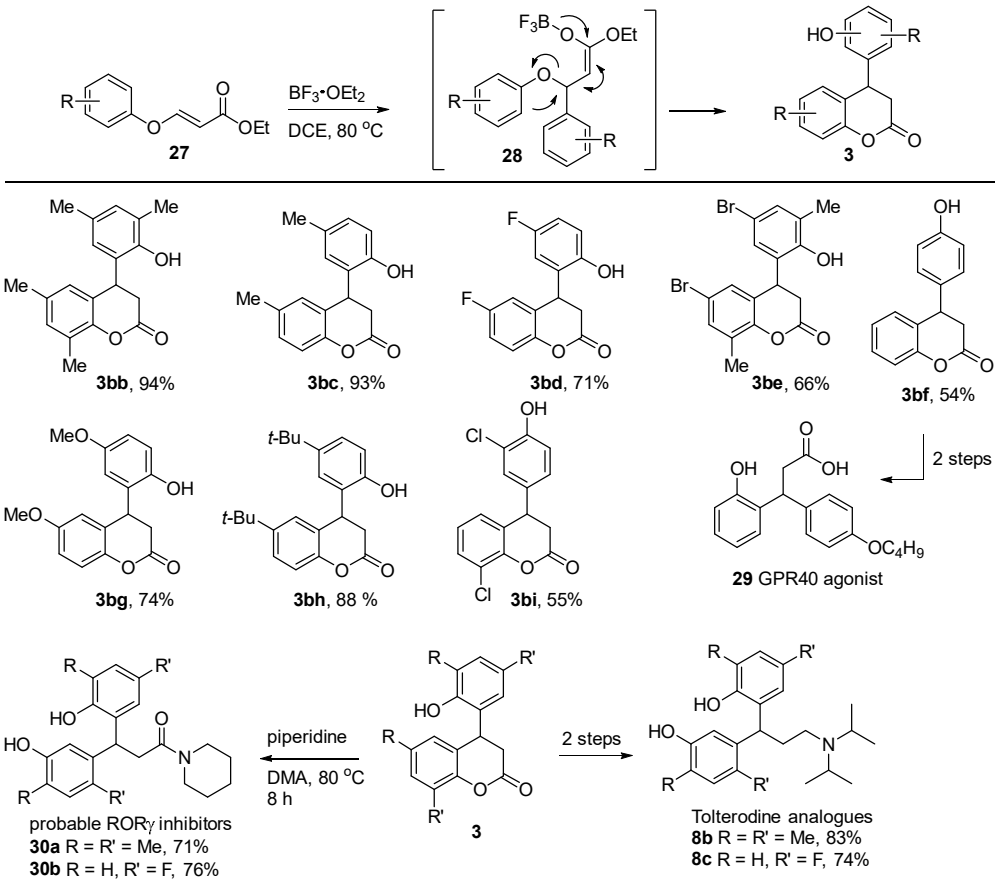
Aubé and co-workers[38] in 2018 investigated the catalytic hydroarylation of α,β-unsaturated acids **2** with phenols **1** to synthesise 4-aryl-3,4-dihydrocoumarins **3** by using acid generated from acetyl chloride (5-10 mol %) in the presence of hexaflouroisopropanol (HFIP) (0.3 M) as the solvent (Scheme 14). HFIP works as a good solvent for the reaction to generate *in situ* HCl for intramolecular Schmidt reaction[39] and Friedel-Craft acylation. The reaction afforded good to excellent yields when substrates possessing an electron-donating group and weak electron-withdrawing groups were used at ambient temperature. However, when phenol substrates containing strong electron-withdrawing groups were used, no desired product was formed, indicating that the reaction was selective and sensitive to the electronic properties of the substrates. To explain the mechanism, first, dissolution of *para*-substituted cinnamic acid **2** in HFIP and AcCl furnishes an oxocarbenium intermediate **26**, which was stabilised by HFIP or HCl or both. With phenols substituted with electron-donating groups like *p*-OMe, the desired product was formed *via* 1,4-addition of the *ortho* carbon of the phenol, followed by cyclisation. However, with weaker electron-donating groups like *p*-Me or H in *trans*-cinnamic acid, the reaction occurs slowly and a competing Fischer esterification side reaction occurs that results in a cinnamate ester instead of the desired product. To obtain 4-aryl-3,4-dihydrocoumarins **3** in these cases, AcCl in HFIP was needed. The reaction offered good to excellent yields and formed desired products **3c**, **3ay**, **3az** and **3ba**. This method was applied in synthesizing drug molecules like eugenol and estrone derivatives **3az** and **3ba**, which could be of significant interest in pharmaceutical research due to their biological activities and potential therapeutic properties.



Scheme 14. Hexafluoroisopropanol and acetyl chloride promoted synthesis of 4-aryl-3,4-dihydrocoumarins by Aubé.

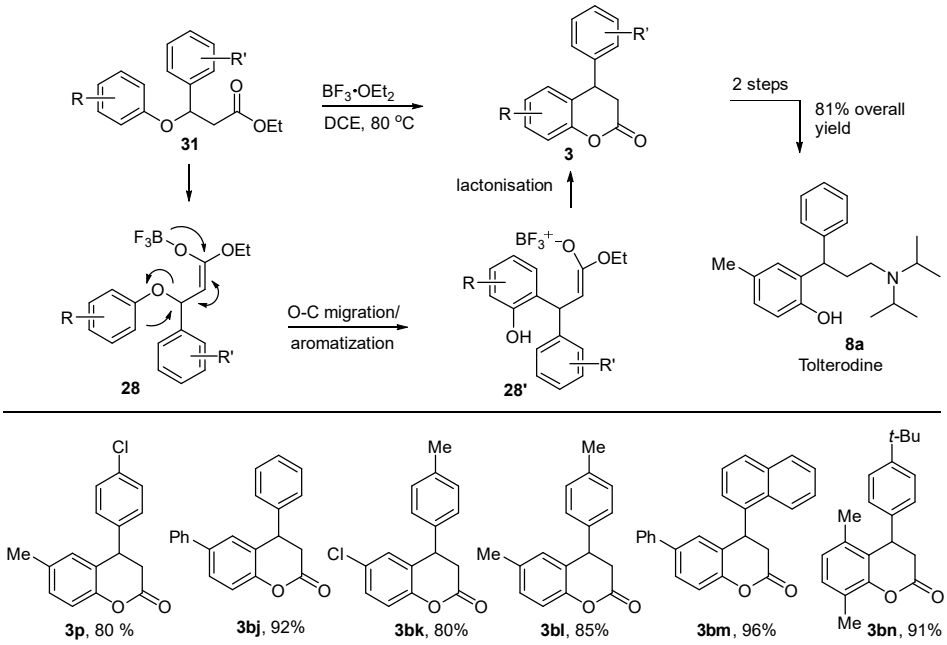
Fernandes and Kunkalkar[40] in 2019 discovered an interesting $BF_3{\cdot}OEt_2$-catalyzed annulative partial dimerization of 3-aryloxyacrylates **27** (Scheme 15). The reaction was carried out at 80 °C in dichloroethane (DCE) and resulted in the synthesis of 4-aryl-3,4-dihydrocoumarins **3** in good to excellent yields. The reaction mechanism proposed began with C−O bond cleavage of aryloxy esters followed by an electrophilic aromatic substitution reaction to **28**. Subsequently, an O−C aryl migration takes place leading to the formation of 4-aryl-3,4-dihydrocoumarins **3** through lactonization. The success of this reaction was dependent on the nature of the substrates used. The reaction proceeded smoothly when alkyl, aryl, or methoxy substituents were present on the aryloxy part of the substrate to afford desired dihydrocoumarins **3bb-bi** in good to excellent yields. The electrophilic substitution occurred at the *ortho* position when the *para* position was blocked for the substrates **3bb-be**, **3bg**, and **3bh**. However, if the *para* position was free, substitution occurred exclusively at this position (**3bf** and **3bi**). Substrates possessing halide groups showed excellent reactivity, resulting in the desired products in high yields. Conversely, substrates bearing electron-withdrawing groups did not undergo the same reaction pathway due to the electrophilic substitution involved, wherein the aryl ring need to be electron rich.

Acid-catalyzed rearrangements are atom-economic and resource efficient and therefore have wide applications in cascade reactions. Beyond its fundamental significance, this reaction holds practical value as it could be employed for the synthesis of compounds like tolterodine analogues **8b** and **8c**,[41] RORγ inhibitors **30** and a GPR40 agonist **29**[42] which have applications in pharmaceutical fields.



Scheme 15. Synthesis of 4-aryl-3,4-dihydrocoumarins *via* Lewis acid-catalyzed annulative partial dimerization of 3-aryloxyacrylates by Fernandes.

In continuation to above, in 2019, Fernandes and co-workers[43] reported the synthesis of 4-aryl-3,4-dihydrocoumarins *via* $BF_3{\cdot}OEt_2$-catalyzed O-C aryl migration of *β*-aryloxy-*β*-aryl esters **31** to *β,β*-bis-aryl esters that lactonized to **3** (Scheme 16). Firstly, $BF_3{\cdot}OEt_2$ coordinates with *β*-aryloxy-*β*-aryl esters **31** and forms enolate **28**, which undergoes 'O' to 'C' aryl migration to form *β,β*-bis-aryl esters **28′** that cyclizes with free OH group to form 4-aryldihydrocoumarins in good yields. $BF_3{\cdot}OEt_2$ showed best results when used in DCE solvent and among various Lewis and Bronsted acids like $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, and $Ag(OTf)_2$ investigated. One notable aspect of this synthesis is its versatility when it comes to substituents on the β-aryloxy part. Different groups such as Me, *t*-Bu, Ph, and Cl could be accommodated, yielding the desired products **3p**, **3bj**-**3bn** in good to excellent yields. However, it was observed that the presence of a CO_2Me group at the aryloxy part impedes product formation. This approach could potentially be utilized for the preparation of tolterodine **8**, an antimuscarinic drug available under the trade names Detrol and Detrusitol.[44] This highlights the utility and importance of the developed method in the context of pharmaceuticals synthesis.



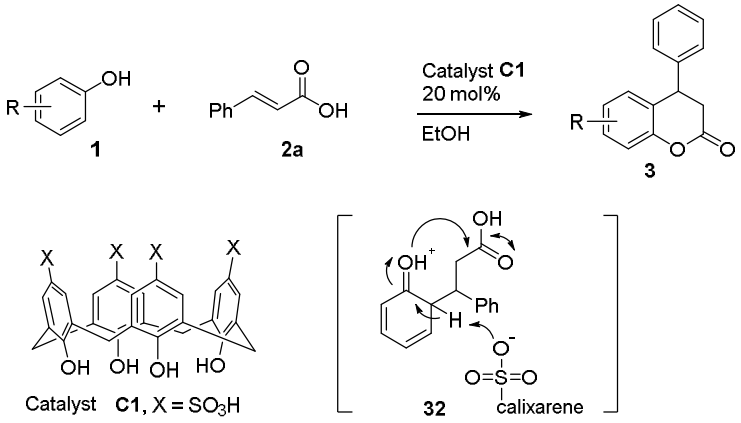
Scheme 16. Synthesis of 4-aryl-3,4-dihydrocoumarins *via* Lewis acid-catalyzed phenolic ether 'O' to 'C' rearrangement by Fernandes.

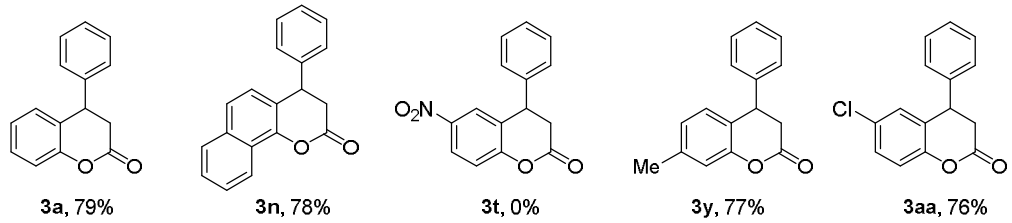
2.5. Other metal-free catalysts

In 2021, Rawat and co-workers[13b] reported the synthesis of 4-aryl-3,4-dihydrocoumarins **3** using 20 mol% of calixarene-based catalysts **C1** with phenols **1** and cinnamic acid **2a** in ethanol solvent under reflux conditions involving Michael addition-intramolecular lactonization pathway (Scheme 17). The shape, conformational flexibility, easy synthesis, and functionalisation make calixarenes attractive ligands in organometallic catalysis.[45,46] In the first step, *p*-sulfonic acid calixarene **C1** provides a proton which facilitates Michael addition of phenols **1** to the cinnamic acid **2a**, followed by re-aromatisation **32** and regeneration of the Brønsted catalyst followed by intramolecular condensation/lactonization to form 4-aryl-3,4-dihydrocoumarins **3**. The reaction was investigated with several substituted phenols that underwent reaction smoothly to deliver 4-aryl-3,4-dihydrocoumarins **3a**, **3n**, **3t**, **3y** and **3aa** in good to excellent yields. Phenols with an electron-donating group resulted in good yields, while with electron-withdrawing groups like NO_2, no desired product was formed. This strategy provides an efficient, economical, high yielding and metal-free approach for the synthesis of 4-aryl-3,4-dihydrocoumarins. The catalyst can be recovered and reused at least 5 times, which makes this method a desirable way in the synthesis of **3**. The sulphonic acid calixarene can be obtained in a one-step protocol from *p-t*-butylcalix[4]arene.

Luu and co-workers[47] in 2021 reported the microwave-assisted synthesis of 4-aryl-3,4-dihydrocoumarins **3** *via* solvent-free tandem reaction of cinnamic acids **2** with phenols **1** using Amberlyst 15 resin **C2** as catalyst *via* the intermediate **33** (Scheme 18). Microwave irradiation assistance decreased the reaction time for the formation of products. Amberlyst 15 is a macro reticular polystyrene-based ion exchange resin with strongly acidic sulfonic groups. Eco-friendliness, economic nature, efficiency, easy storage and high recyclability makes Amberlyst 15 a good choice of catalyst.[48,49] The scope of the reaction was established by using different phenols **1** and cinnamic acids **2**. The nucleophilic addition of phenol to the carbon atom of C=O of carboxylic acid proves to be difficult due to the acidity of the phenol. Therefore, phenols bearing the electron-donating group (EDG) reacted smoothly to afford dihydrocoumarins **3a** and **3b** with high yields, possibly due to the resonance or inductive effect of the EDG. On the other hand, when the phenyl group was present at the *ortho* position of phenol, the yield of the desired product **3bp** decreased due

to steric hindrance. While carrying out the reaction with phenols substituted with electron-withdrawing groups, the products were obtained in lower yields, which might be attributed to the decreased nucleophilicity of the substrate. A comparison of the reaction carried out under microwave irradiation at 130 °C (**Method A**) and the conventional method (**Method B**) indicated that with former method, the reaction took a much smaller time while the yields were more or less similar. This approach was useful for reactions which require activation by heating.[50-52]





Scheme 17. Calixarene-catalyzed synthesis of 4-aryl-3,4-dihydrocoumarins by Rawat.

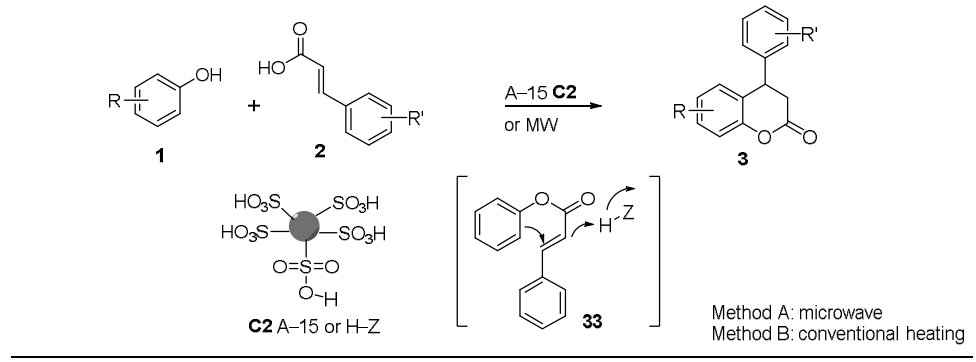
3. Transition metal-mediated or -catalyzed approaches

Catalysis is an important aspect of modern science, revolutionizing the construction of complex molecules with high selectivity and efficiency. The inheritance of catalysis in organic synthesis has a major impact as many transition metals and organocatalysts can catalyze efficient transformations, though it is difficult to compare which catalysis is more efficient due to their distinctive reactivity profile. Transition metals can form different complexes by shuttling the oxidation state and with the reagent in the catalytic cycle, enabling them to achieve unprecedented and unconventional transformations. Consequently, transition metal catalysis offer highly efficient processes with significant potential for developing new methodologies.[53] A number of different metals have been employed in the synthesis of 4-aryl-3,4-dihydrocoumarins as discussed below.

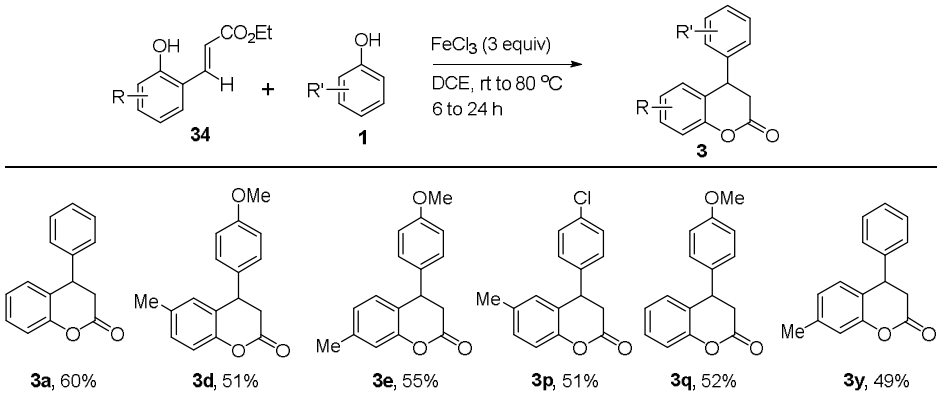
3.1. Iron-mediated or -catalyzed methods

Satyanarayana and co-workers[54] in 2014 developed an Fe-based Lewis acid-mediated synthesis of 4-aryl-3,4-dihydrocoumarins (Scheme 19). The cinnamic esters **34** and substituted phenols **1** reacted in the presence of ferric chloride in dichloroethane solvent to afford 4-aryl-3,4-dihydrocoumarins along with Michael addition product as by-products. The reaction conditions were temperature and system-dependent because the reaction is slow at ambient temperature, while it works well at 80 °C. This methodology was

applied on highly electronically rich aromatic rings of cinnamates with the appropriate position of the electron-donating group to afford desired products **3a**, **3d**, **3e**, **3p**, **3q** and **3y** in moderate yields.



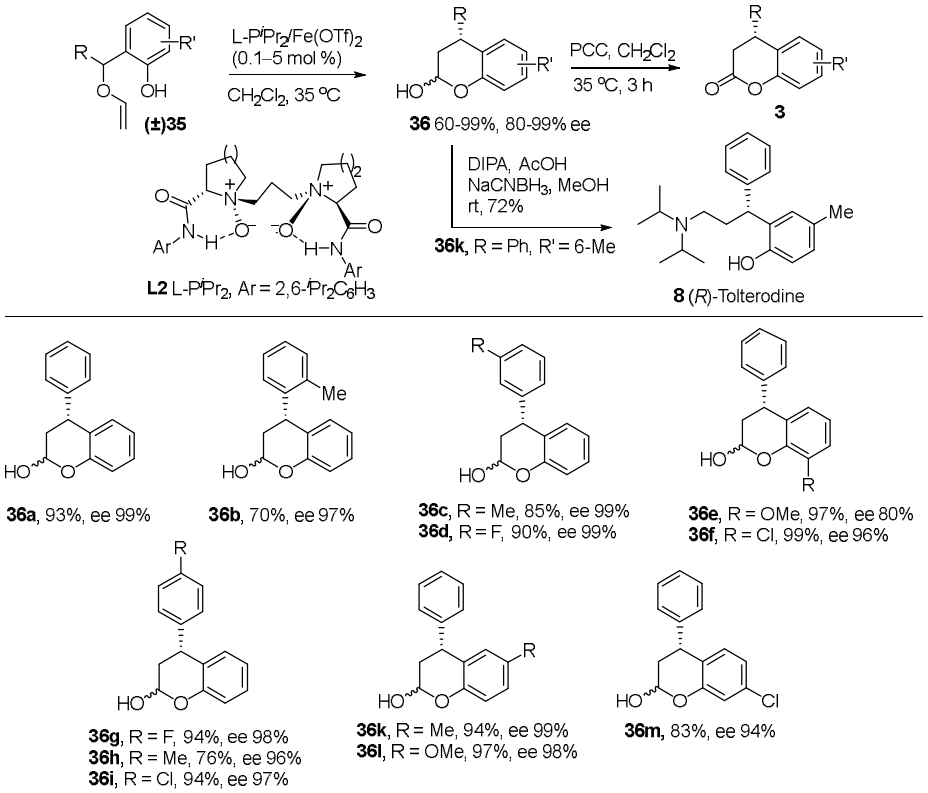
Scheme 18. Solvent-free microwave assisted synthesis of 4-aryl-3,4-dihydrocoumarins using Amberlyst 15 resin as catalyst by Luu.



Scheme 19. $FeCl_3$-mediated synthesis of 4-aryl-3,4-dihydrocoumarins by Satyanarayana.

In 2020, Feng and co-workers,[55] developed mild conditions for highly enantioselective [1,3]-O to -C rearrangement in the presence of chiral *N,N′*-dioxide **L2**/$Fe(OTf)_2$ catalyst system on racemic vinyl alkyl ethers **35** to afford broad scope for chromanols **36a-m** with excellent yields and enantioselectivities (Scheme 20). This methodology was applied for the synthesis of dihydrocoumarins **3** *via* PCC oxidation in efficient yields. The catalytic loading was very low (0.1-5.0 mol%) in most of the cases. They have also synthesized a crucial urological drug (*R*)-Tolterodine **8** using the above-mentioned strategy. The chroman-2-ol **36k** was subjected to a reductive amination reaction in the presence of diisopropylamine and sodium cyanoborohydride. This transformation resulted in the formation of (*R*)-tolterodine **8** with a yield of 72%. The absolute configuration of (*R*)-Tolterodine was determined by comparing its optical rotation with the literature value.

Based on this comparison, the stereochemistry of both the starting material **36k** and the product **8** was assigned as (*R*)-isomers.



Scheme 20. The [1,3]-O to -C rearrangement of racemic vinyl alkyl ethers in the presence of $Fe(OTf)_2$ and proline-based ligand followed by PCC oxidation to afford 4-aryl-3,4-dihydrocoumarins by Feng.

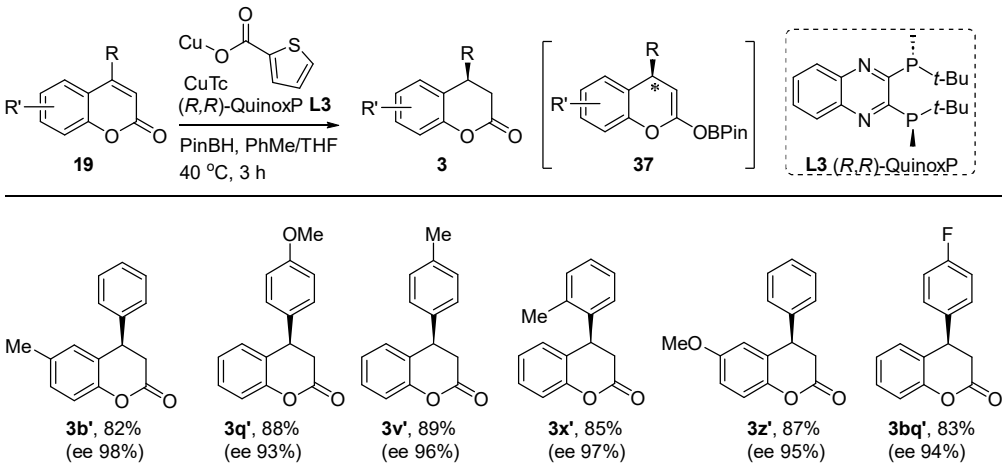
3.2. Copper-catalyzed method

Kim and Yun[56] in 2010 have introduced facial and an efficient asymmetric 1,4-hydroboration reduction of coumarins **19** by utilizing Cu(I)-QuinoxP catalyst and pinacolborane (Pin-BH) in toluene or mixture of toluene and THF (1:1) depending on the solubility of the coumarins to deliver the 4-substituted (aryl and methyl)-3,4-dihydrocoumarins **3b′**, **3q′**, **3v′**, **3x′**, **3z′**, **3bq′** in high enantioselectivities (93-98% *ee*)[57] and yields (82-89%) (Scheme 21). The P-chiral QuinoxP ligand **L3** plays an important role in delivering higher enantiomeric excesses and yields. They also signify that 1,4-hydroboration intermediate was exploited in the production of biologically active target compounds. The stereoselective reduction product without any isolation, directly on treatment with intermediate **37** with the electrophile delivered the enantioenriched 4-aryl-3,4-dihydrocoumarins. The high enantioselectivity was observed in **3b′** and **3x′** cases.

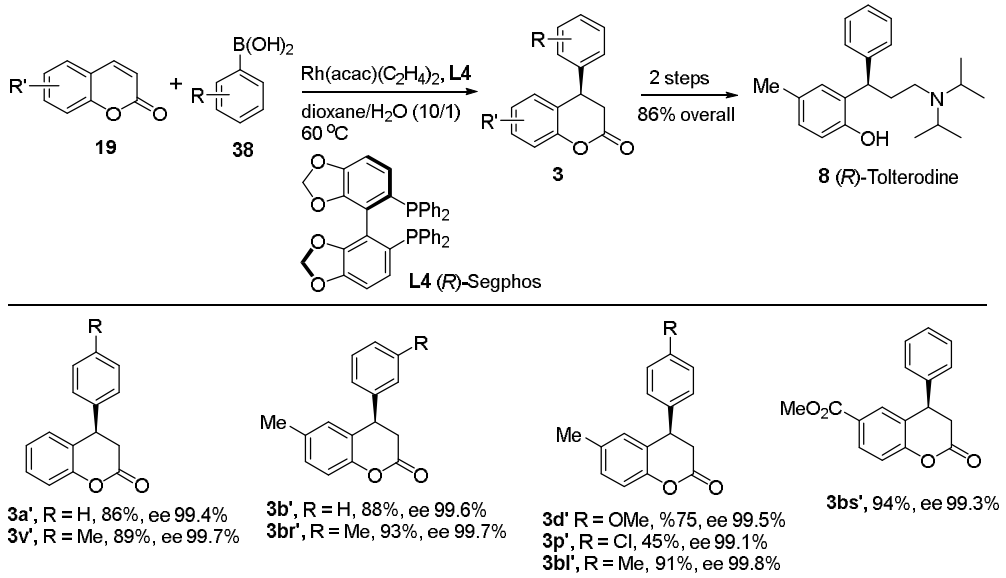
3.3. Rhodium-catalyzed methods

In 2005, Hayashi and co-workers[12] introduced Rh-catalyzed asymmetric conjugate addition of aryl-boronic acids **38** to coumarins **19** to afford (*R*)-4-aryl-3,4-dihydrocoumarins **3** (Scheme 22). Their optimized conditions included 3 mol% of $Rh(acac)(C_2H_4)_2$ and (*R*)-Segphos **L4** as chiral ligand to acquire asymmetric conjugate addition of phenylboronic acid to 6-methylcoumarin in dioxane/H_2O (10/1) as solvent at 60 °C for 8 h to obtain 88% yield of **3b′** (99.6% *ee*). They also explored other ligands like (*R*)-BINAP and (*R*)-P-Phos but the best results were obtained with (*R*)-Segphos. Under optimized conditions they successfully

explored various substituted coumarins and boronic acids to afford enantiomerically enriched (*R*)-4-aryl-3,4-dihydrocoumarins **3** in excellent yields. They have also demonstrated the asymmetric synthesis of (*R*)-Tolterodine **8** by utilizing 6-methyldihydrocoumarin **3b′**. Thus, the latter was reduced with DiBAL-H to provide lactol, which on reductive amination with diisopropylamine furnished (*R*)-Tolterodine **8**.[58,59]



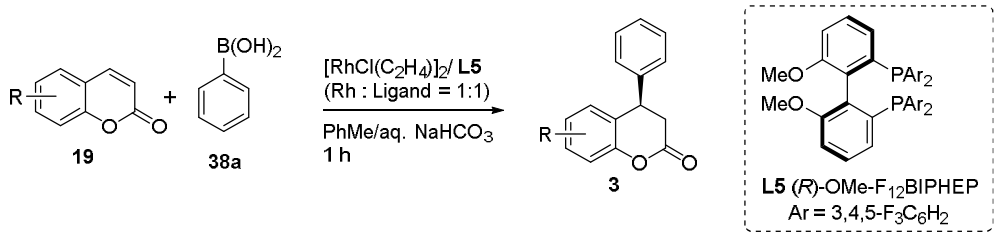
Scheme 21. Cu-catalyzed asymmetric hydroboration-reduction of coumarins with pinacolborane by Kim and Yun.

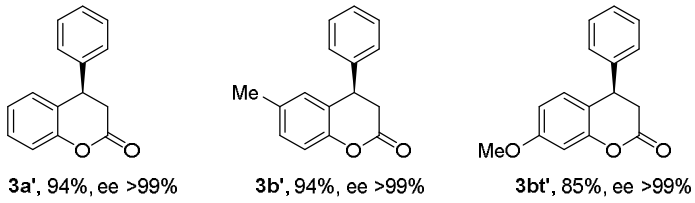


Scheme 22. Rh-catalyzed methodology using (*R*)-Segphos for the synthesis of substituted (*R*)-4-aryl-3,4-dihydrocoumarins and (*R*)-Tolterodine by Hayashi.

Korenaga and co-workers[60] in 2010 introduced a Rh-catalyzed methodology with electron deficient diphosphine (MeO-F_{12}-BIPHEP) ligand **L5** for the synthesis of chiral 4-phenyl-3,4-dihydrocoumarins **3**. The electron-deficient ligand elevated the asymmetric 1,4-addition of arylboronic acid to the coumarins in the presence of Rh catalyst (Scheme 23). The coumarins **19** reacted with phenylboronic acid **38a** in the presence

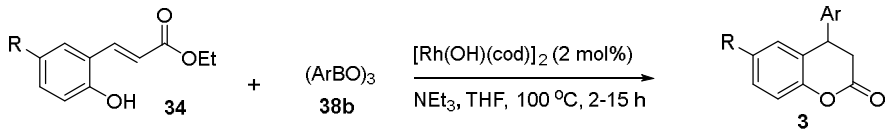
of 1 mol% Rh catalyst in toluene/saturated aq. $NaHCO_3$ (1:1) at 30 °C for 1 h to give (*R*)-4-phenyl-3,4-dihydrocoumarins **3** in good to excellent yields and high >99% *ee*.

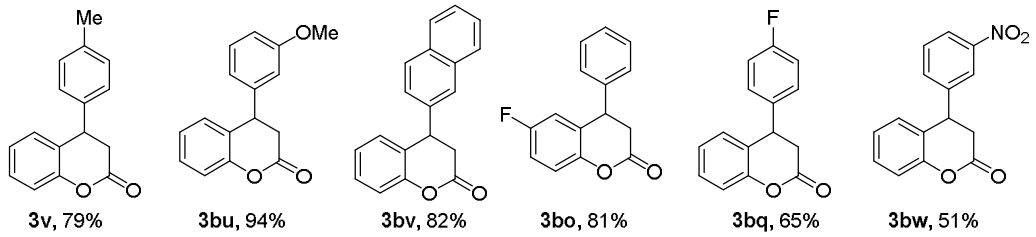




Scheme 23. Rh-catalyzed methodology for the synthesis of substituted 4-phenyl-3,4-dihydrocoumarins by Korenaga.

In 2010, Youn and co-workers[14] disclosed an efficient Rh-catalyzed (2 mol%) domino conjugate addition-cyclization reaction of arylboroxines **38b** to *ortho*-hydroxy cinnamate esters **34** in THF solvent and triethylamine as a base at 100 to afford 4-aryl-3,4-dihydrocumarins **3** in good to excellent yields (Scheme 24). In this work, both *ortho*-hydroxy cinnamate esters, as well as *ortho*-amino cinnamate esters were treated with organoboroxines in presence of Rh(I) catalyst to generate various *N*- and *O*-heterocycles which compose the crucial biologically active natural and synthetic compounds like 3,4-dihydroquinolin-2(1*H*)-ones, 3,4-dihydrocoumarins, and pyrrolidin-2-ones. This methodology demonstrated the distinctive functional group tolerance.

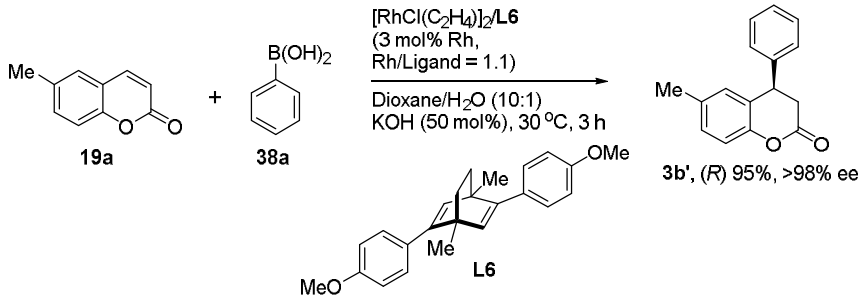




Scheme 24. The domino conjugate addition-cyclization utilizing Rh(I) catalyst for the synthesis of 4-aryl-3,4-dihydrocoumarins by Youn.

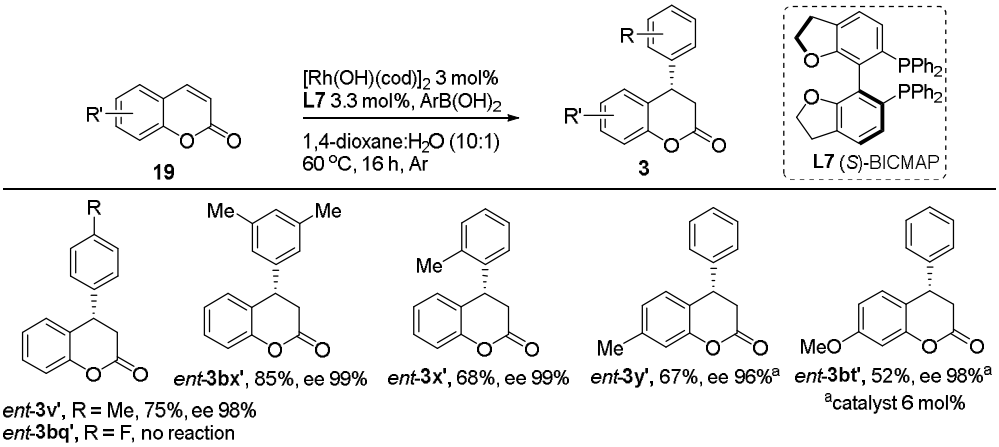
Carnell and Luo[61] in 2010 developed a Rh-catalyzed asymmetric conjugate addition of phenylboronic acid **38a** to 6-methylcoumarin **19a** in dioxane/H_2O (10:1) solvent with potassium hydroxide as a base to deliver chiral 4-phenyl-6-methyl-3,4-dihydrocoumarin **3b′** with high enantiomeric excess (98% *ee*) (Scheme 25). The

developed 1,4-dimethyl-2,5-diarylbicyclo[2.2.2]octadiene ligand **L6** facilitates the catalytic performance through its significant electronic effect. The ligand provided excellent enantioselectivity with high atom efficiency as compared to others, like Hayashi's[12] and Carreira's ligands.[62]



Scheme 25. Rh-catalyzed asymmetric conjugate addition to 6-methylcoumarin for the synthesis of 4-phenyl-3,4-dihydrocoumarin by Carnell.

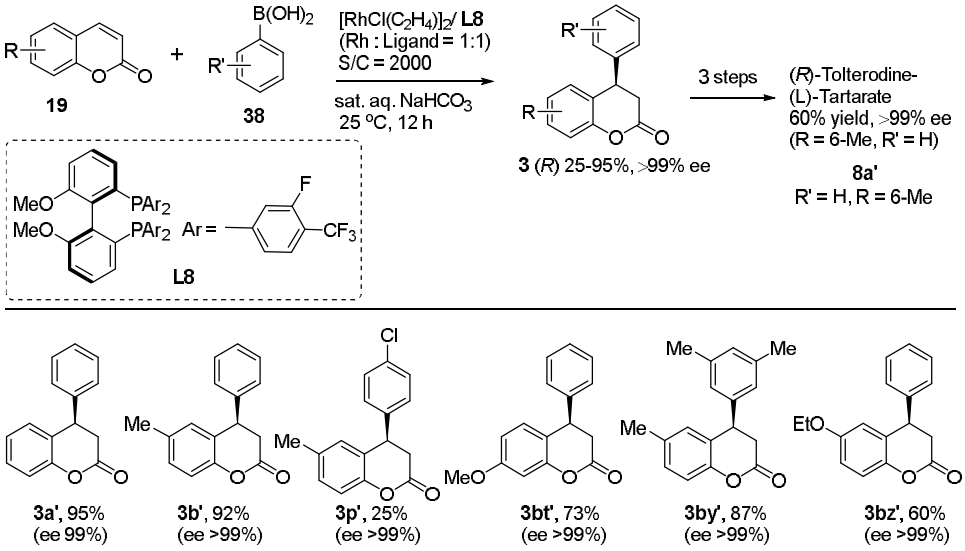
In 2015, Sakamoto and co-workers[63] illustrated the synthesis of 4-aryl-3,4-dihydrocoumarins **3** by asymmetric Michael-type addition of aryl boronic acids to coumarins **19** (Scheme 26). The Rh(I) catalyst with (*S*)-BICMAP **L7** as a ligand in 1,4-dioxane/H_2O (10:1) as solvent at 60 °C was found to be the best conditions for the addition of the boronic acids. The arylboronic acid added to different coumarins like 6-methyl-, 7-methyl- and 7-methoxycoumarins to deliver corresponding products with high enantioselectivities utilizing 6 mol% of the Rh(I) catalyst.



Scheme 26. Rh-catalyzed Michael addition of aryl boronic acids to coumarins by Sakamoto.

Korenaga and co-workers,[64] in 2018 reported the chiral biarylphosphine ligand **L8** for Rh-catalyzed asymmetric 1,4-addition of arylboronic acids **38** to coumarins **19** with low catalyst loading with substrate to catalyst molar ratio (S/C) of 2000 to afford (*R*)-4-aryl-dihydrocoumarins **3** in good to excellent yields along with >99% enantioselectivities (Scheme 27). The ligand was designed through a combination of theoretical and experimental approaches, which resulted in significantly reduced catalyst loading while improving the reaction efficiency. The electron-poor nature of the ligand and CH-π interaction with the coumarin substrates were identified as critical factors for accelerating the insertion step and inhibiting protodeboronation. They have also achieved the gram-scale synthesis of urological drug, *i.e.* Detrusitol [(*R*)-Tolterodine (L)-tartrate] **8a′**. The DiBAL-H reduction[12] of **3b′** afforded crude lactol, which on reductive amination with

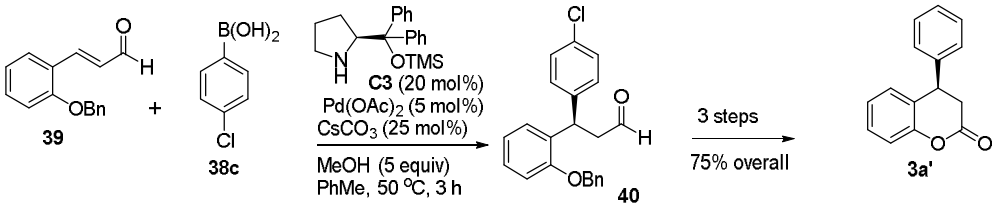
diisopropylamine in the presence of Cp*IrCl[8-quinolinolate] catalyst[65] gave crude (*R*)-Tolterodine that was further reacted with (L)-tartrate to obtain the salt with 60% total yield. In this synthesis, the intermediate purification was not required, so it can be expanded to industrial-scale process.



Scheme 27. Rh-catalyzed asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins and (*R*)-Tolterodine-(L)-tartrate by Korenaga.

3.4. Palladium-catalyzed methods

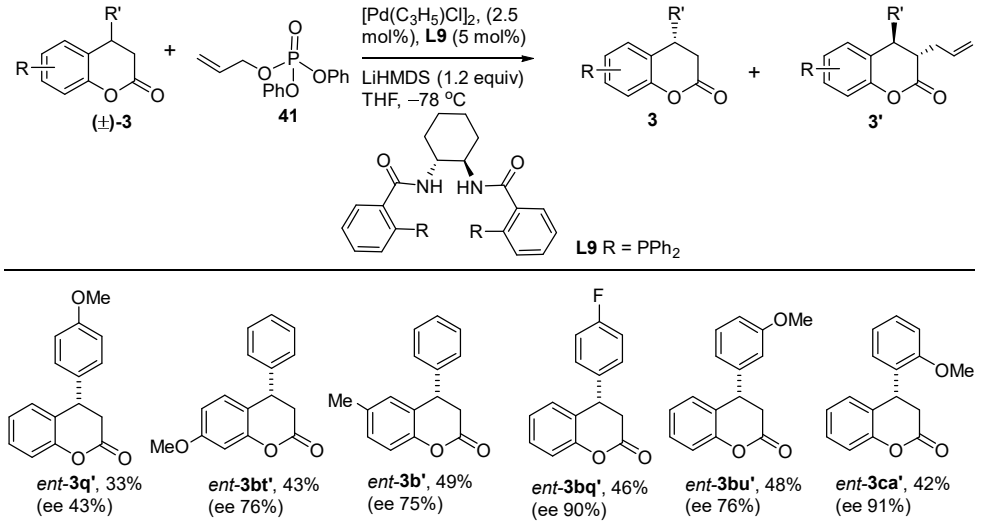
In 2013, Córdova and co-workers[66] introduced a method for addition of boronic acids to *α,β*-unsaturated aldehydes utilizing **C3** as catalyst and $Pd(OAc)_2$ as co-catalyst with methanol and cesium carbonate as additives in toluene solvent for the synthesis of *β*-arylated or 3,3-diaryl substituted aldehydes in high yield (Scheme 28). The 3,3-diaryl substituted aldehyde **40** was an important intermediate in the synthesis of 4-aryl-3,4-dihydrocoumarin **3a′** and tolterodine.[67] They synthesized **3a′** by utilizing their methodology as discussed above. The 2-OBn-substituted cinnamic aldehyde **39** reacted with 4-chlorophenyl boronic acid **38c** to give 3,3-diaryl substituted aldehyde **40** in 71% yield and further oxidation afforded corresponding acid, debenzylation/dechlorination and acid-catalyzed lactonization in the presence of *p*-toluenesulphonic acid afforded (*R*)-4-phenyl-3,4-dihydrocoumarin **3a′**.



Scheme 28. Asymmetric synthesis of (*R*)-4-phenyl-3,4-dihydrocoumarin by Córdova.

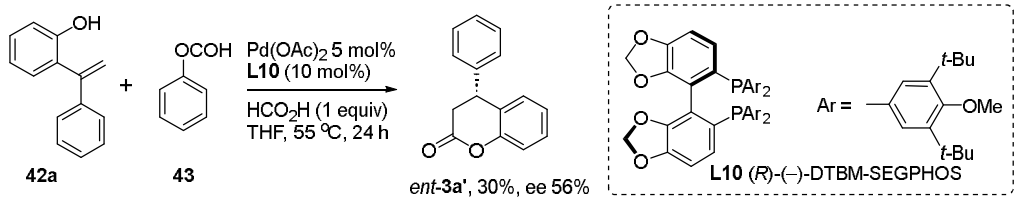
Hou and coworkers[68] in 2014 introduced Pd-catalyzed methodology utilizing Trost's chiral ligand **L9** for asymmetric allylic alkylation (AAA)/substitution to afford resolved **3** along with *trans*-3,4-disubstituted dihydrocoumarin derivatives **3′** in good yields (Scheme 29). The Pd-catalyzed AAA reaction of (±)-**3** in presence of **41** advanced in high diastereo- and enantioselectivities with various types of "hard" carbanion nuclieophiles,[69] in addition to the resolution of racemic starting material. The presence of different

electron-donating or electron-withdrawing groups on aryl part of the dihydrocoumarin core had smaller effect on the yield and enantioselectivity.



Scheme 29. Kinetic resolution of (*R*)-4-aryl-3,4-dihydrocoumarins *via* Pd-catalyzed AAA reaction by Hou.

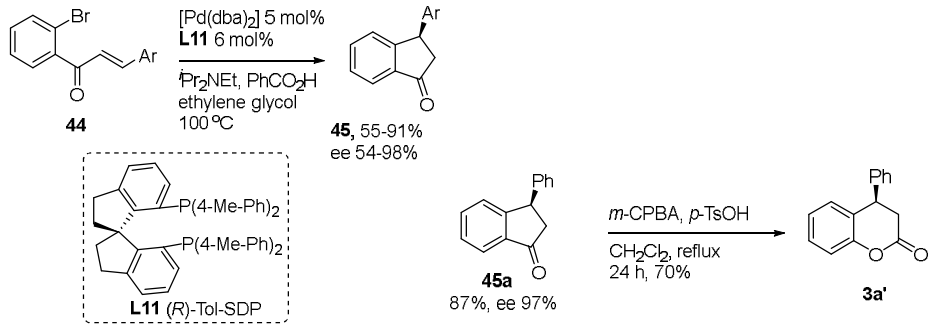
In 2015, Shi and coworkers[70] introduced an efficient Pd-catalyzed enantioselective hydroesterification of 2-(1-phenylethenyl)phenol **42a** with phenyl formate **43** as a CO source in the presence of formic acid and (*R*)-(−)-DTBM-SEGPHOS **L10** as chiral ligand in THF solvent at 55 °C to afford 4-phenyl-3,4-dihydrocoumarin *ent*-**3a′** in 30% yield and 56% ee (Scheme 30). This method represents the first procedure of hydroesterification of alkenyl phenols without the addition of external CO gas.



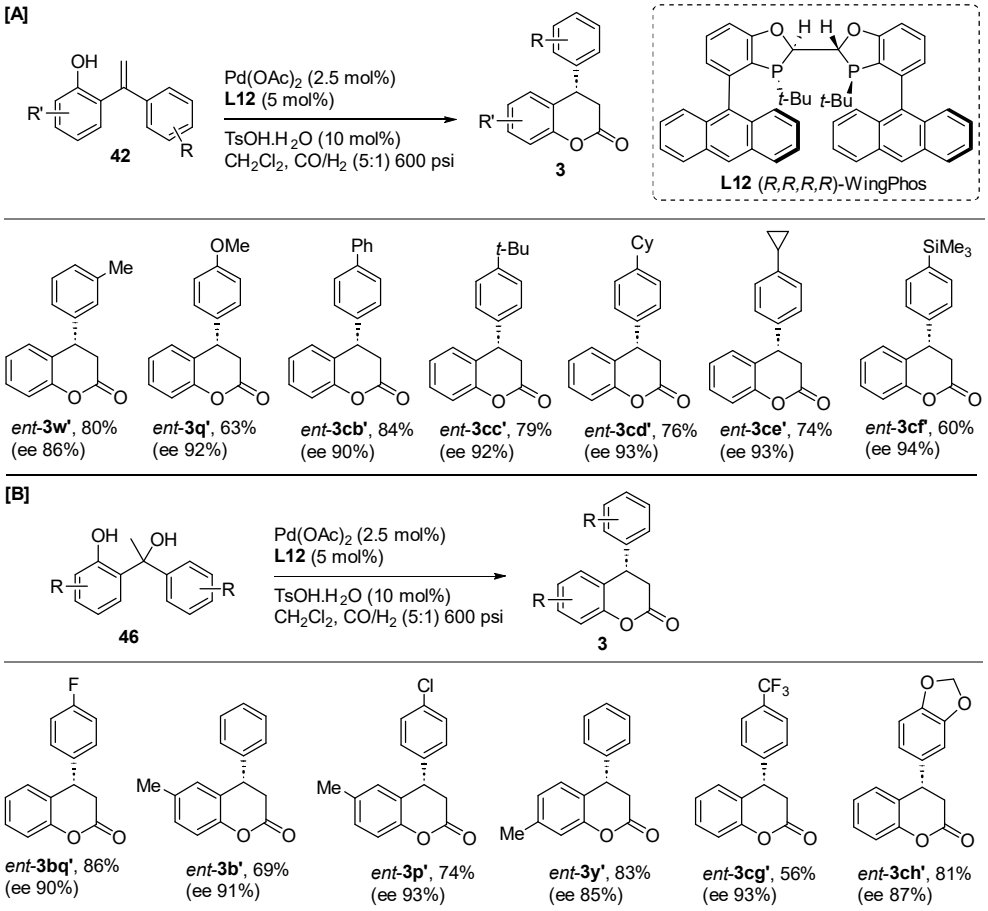
Scheme 30. Pd-catalyzed asymmetric hydroesterification of 2-(1-phenylethenyl)phenol by Shi.

Zhou and co-workers[71] in 2015 demonstrated the asymmetric intramolecular reductive Heck reaction of aryl halides **44** for the synthesis of 3-arylindanones **45** with high selectivities (Scheme 31). One of the indanone **45a** was further transformed into 4-aryl-3,4-dihydrocoumarin **3a′**. The neutral aryl-Pd-catalyst along with chiral ligand (*R*)-Tol-SDP **L11** was utilized to detach the halide to access the cationic pathway in presence of trialkylammonium salt which was hydrogen−bond donor in glycol solvent to afford 3-arylindanones **45** in good to excellent yields and good enantioselectivities. The 3-arylindanone **45a** was oxidized through Baeyer-Villiger oxidation to afford 4-aryl-3,4-dihydrocumarin **3a′**.

In 2021, Tang and co-workers,[72] developed the first asymmetric Pd-WingPhos **L12**-catalyzed hydro esterification of 1,1-diaryl olefins **42** and tertiary alcohols (diarylmethyl carbinols) **46** under mild conditions with low catalyst loading to afford chiral 4-aryl-3,4-dihydrocoumarins **3** with efficient yield and enantioselectivities (Schemes 32). The methodology was efficient for the synthesis of biologically stimulating compounds or therapeutic agents like (*R*)-Tolterodine and GPR40 agonist (not shown here).



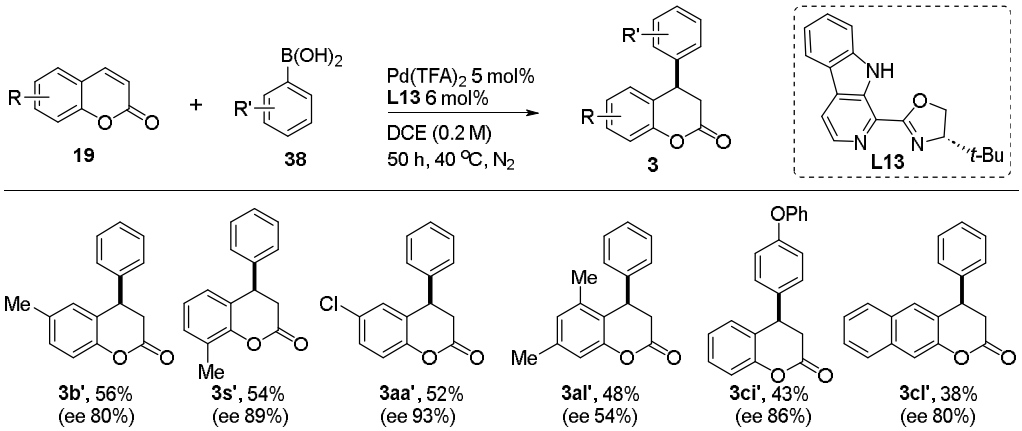
Scheme 31. Asymmetric reductive Heck approach towards the synthesis of 4-aryl-3,4-dihydrocumarin by Zhou.



Scheme 32. Asymmetric hydroesterification of [A] 1,1-diaryl olefins and [B] diarylmethyl carbinols with Pd-WingPhos catalyst by Tang.

Li and co-workers[73] in 2022 established Pd-catalyzed asymmetric addition of aryl boronic acids **38** to coumarins **19** in the presence of ligand **L13** for the synthesis of 4-aryl-3,4-dihydrocoumarins **3** (Scheme 33).

The reaction worked well with varying electron-withdrawing or electron-donating groups substituted on the coumarins and boronic acids to deliver chiral 4-aryl-3,4-dihydrocoumarins with good to excellent enantioselectivities and yields. This methodology featured with mild reaction conditions like air-stable and smoothly approachable chiral nitrogen-containing ligand leads to pharmaceutically crucial 4-aryl-3,4-dihydrocoumarins.



Scheme 33. Pd-catalyzed asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins by Li.

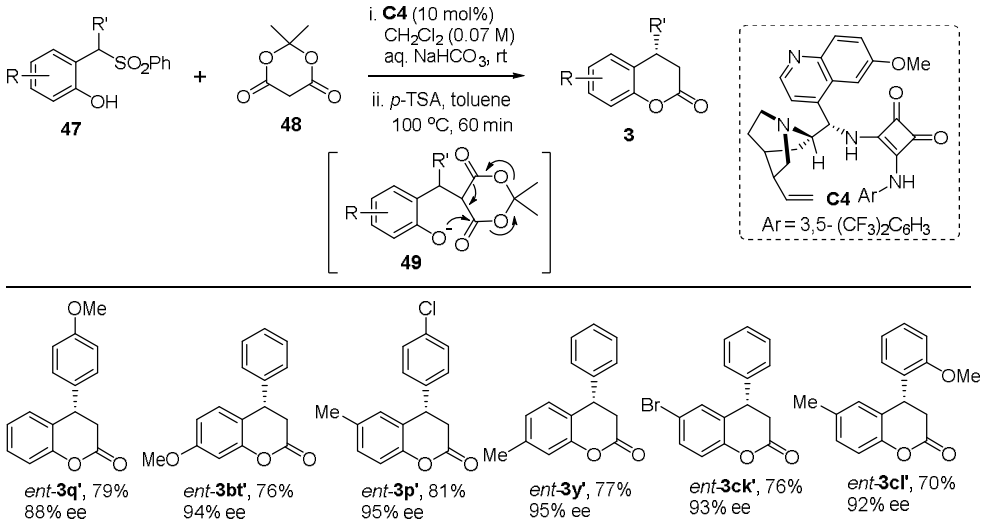
4. Organocatalysis approaches

The asymmetric organocatalysis is a valuable approach in organic synthesis. This approach employs small chiral organic molecules as catalysts for the stereoselective reactions besides enzymes and metal-based catalysts that are frequently used.[74] Metal-based catalysts possess several limitations such as high cost, toxicity, difficulty in preparation, and lack of orthogonality with a wide range of functional groups that can be solved using organocatalysts to some extent. The use of organocatalysts provide a different approach for the synthesis of complex compounds[75] with several advantages that include stability in air and water, easy handling experimentally, relatively non-toxicity, and easy separability from the crude reaction mixture.[76] In 2021 List and Macmillan won Nobel prize for "*the development of asymmetric organocatalysis*" which is the recognition of the importance of asymmetric organocatalysis in organic synthesis.[74]

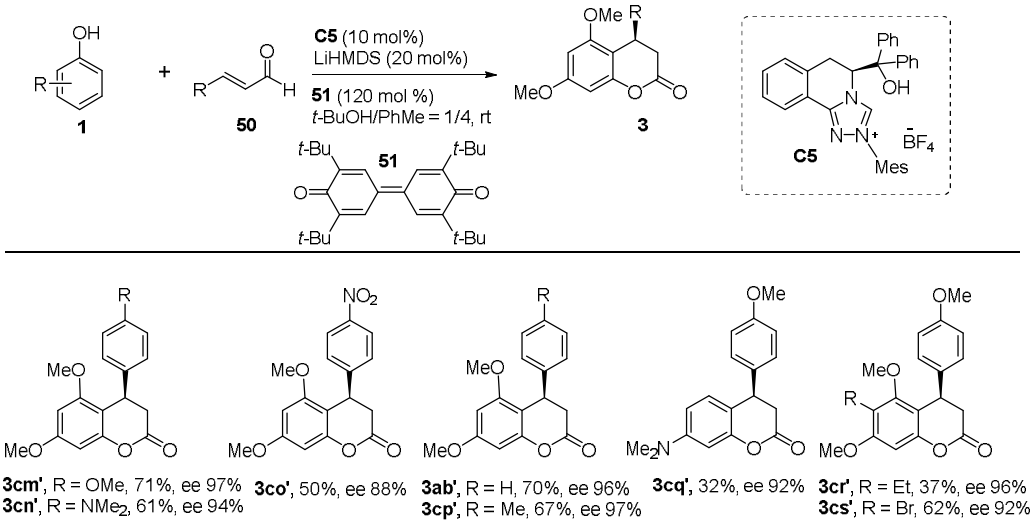
In 2015, Bernardi and co-workers[77] reported the synthesis of 4-aryl-3,4-dihydrocoumarins *via* organo-catalytic asymmetric addition of Meldrum's acid **48** to the *ortho*-quinone methides generated *in situ* from 2-sulfonylalkyl phenols **47** by base-promoted elimination of sulfinic acid (Scheme 34). The cyclization at the phenolic oxygen followed by decarboxylation of intermediate adducts **49** resulted in the formation of 4-aryl-3,4-dihydrocoumarins **3**.[78] Quinone methides are highly reactive as their reaction with 2π systems result in high energy gain due to aromatisation.[79,80] They are also stable when substituted with electron-donating groups. A base stronger than bicarbonate resulted in lower enantioselectivity, while a non-aqueous base resulted in less yield due to its poor efficiency in catalyst regeneration.[81] Thus at optimized reaction conditions with **C4** catalyst (10 mol %) in DCM (0.07 M), aqueous $NaHCO_3$, room temperature and *p*-TSA in toluene at 100 °C, in 60 min most substrates with different groups formed 4-aryl-3,4-dihydrocoumarins **3** in good yields along with good enantioselectivities.

You and co-workers[82] in 2017 introduced a methodology for the synthesis of 4-aryl-3,4-dihydrocoumarins **3** utilizing phenols **1** and enals **50** in the presence of dihyroisoquinoline-type *N*-heterocyclic carbene catalyst **C5** along with LiHMDS as base, quinone **51** as oxidant and *t*-butanol/toluene (1/4) as solvent (Scheme 35). However, phenols have been rarely utilized as nucleophiles despite the fact that such a reaction provides direct access to 4-aryl-3,4-dihydrocoumarins. Hydrogen bonding between *t*-butanol and the carbonyl group facilitates the conjugate addition of phenol to the acyl-azolium intermediate and the use of LiHMDS increases the yield of the annulation product. The reaction of phenols **1** with substituted cinnamaldehydes **50** with both electron-donating and electron-withdrawing groups resulted in the formation

of the desired products **3** in good yields and high enantioselectivities. The presence of a strong electron-withdrawing group like NO_2 on cinnamaldehyde decreased yield and enantioselectivity **3co′**.



Scheme 34. Organocatalytic asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins by Bernardi.



Scheme 35. Asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins using *N*-heterocyclic carbene by You.

5. Conclusions and outlook

The biological importance of 4-aryl-3,4-dihydrocoumarins, along with the increasing use of these structures in medicinal and pharmaceutical fields have motivated the organic chemist to develop synthetic strategies toward these important molecular motifs. 4-Aryl-3,4-dihydrocoumarin based natural products and related derivatives have significant bioactivities, including aldose reductase inhibition, antiherpetic properties, and protein kinase modulation. The 4-aryldihydrocoumarin moiety also served as intermediate for the synthesis of many drug molecules, including tolterodine, GPR40 agonists, and RORγ inhibitors. Tolterodine

is an antimuscarinic drug used for urinary incontinence. The synthetic methodologies utilized encompass transition metal catalysis, organocatalysis, acid catalysis and metal-free approaches to achieve the required 4-aryldihydrocoumarin derivatives. In most cases, the cinnamic acid derivatives and the substituted phenols were the substrates of choice for both inter and intramolecular cyclization approaches. In the latter case a preformed or *in situ* derived cinnamate ester was of choice. The methods utilizing the arylboronic acids addition in presence of various chiral ligands enabled asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins and these approaches were predominantly metal-catalyzed. Apart from this many metal-free methods were extensively used that are discussed in this chapter. Remarkably, the acid-catalyzed cyclization methods emerged as the conventional choice. Protic acids such as trifluoroacetic acid (TFA) or *para*-toluenesulfonic acid (*p*-TSA), solid acids like montmorillonite K-10, Lewis acids including $POCl_3$, I_2, and $BF_3{\cdot}OEt_2$, as well as other metal-free catalysts, have emerged as significant contributors to the synthesis of 4-aryl-3,4-dihydrocoumarins. These catalysts have effective characteristics such as easy recovery, non-toxic nature, and reusability, enhancing their attractiveness in the synthesis of 4-aryl-3,4-dihydrocoumarins.

Although several methods have been developed, there is still room for further improvements, especially in the asymmetric synthetic methods to target better enantioselectivities with simplified and easily available ligands. The organocatalytic methods would be of primary importance, and many known best performing catalysts like chiral thioureas and squaramides need to be explored. Also, suitable atropochiral ligands can be designed through computational means with appropriate metal for better efficiency, reusability and heterogenous catalysis can be explored. With the emergence of flow chemistry, electro-, and photochemistry, greener way of synthesizing these interesting 4-aryl-3,4-dihydrocoumarins appear promising and would pave a modern approach in their synthesis in the future.

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