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Modern and Advanced Approaches for Catalytic Synthesis of Coumarin Derivatives

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Coumarin is an important pharmaceutical structural motif, abundantly found in numerous now-used drugs. Compounds containing this core show a broad spectrum of medicinal properties and biological activities. The increasing importance and wide usages of coumarin derivatives have gained much attention to its synthetic methods, among which metal-catalyzed and organo-catalyzed methods have proven the most effective. Several metal- and/or organo-catalyzed synthetic strategies for coumarin have been investigated and reported in recent decades. This review focuses on more recent reports on catalyzed methods of synthesizing coumarin and coumarin-like structures, from both synthetic and mechanistic aspects.

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1. Introduction

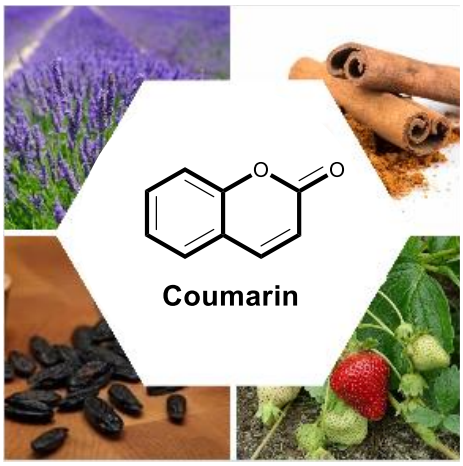

Figure 1 Coumarin structure and some coumarin-containing plants

Coumarin (2H-1-benzopyran-2-one) or 2H-chromen-2-one (Figure 1) is an aromatic organic chemical compound belonging to the subgroup of lactones. Coumarin can be also be referred to as 1,2-benzopyrone or o-hydroxycinnamic acid-8-lactone [1]. The nomenclature owes to the scientific name of Tonka plant, *Coumarouna odorata Aube*, which for the first time, a very simple coumarin was derived from it[2]. This structure is made of fused benzene and α-pyrone rings. Coumarin and its derivatives are abundant in nature and are found in lots of plants including strawberries, lavenders, and cinnamons (Figure 1). Coumarins have also been detected in microorganisms and animal sources[3]. Coumarin can be found in nature either solely or as coumarin glycoside. it has a sweet scene and has been used in perfumes since 1882[4].

Through the years after its discovery, coumarin has been a subject to numerous pharmaceutical studies. This penzopyrone structure can easily interact with a wide range of enzymes and receptors in organisms with weak bonds[5], and therefore has shown various bioactivities as anti-inflammatory [6,7,8,9,] antioxidant[6], anti-cancer [10,3,11,12], anti-HIV[3,13,14], anti-fungal[15,16], anti-diabetic[17], antibacterial[18,19,20], antiviral[21,22], anti-proliferative[23], and anticoagulant[24] agent, and also useful in Alzheimer's treatment [25,26], as fluorescence chemo-sensors[27] and as dyes in dye lasers[28]. Additionally, due to its electron-reach conjugated system, coumarin can show good charge-transport activities[29] (Figure 2). Recent researches on coumarin derivatives were more focused on their promising anticancer activities[30]. Antibiotics like novobiocin (Figure 2, **A**)[31], antivirals like Calanolide A (Figure 2, **B**)[32], and psoralens like

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Trioxsalen (Figure 2, **C**)[33] can be good examples of coumarin-containing drugs.

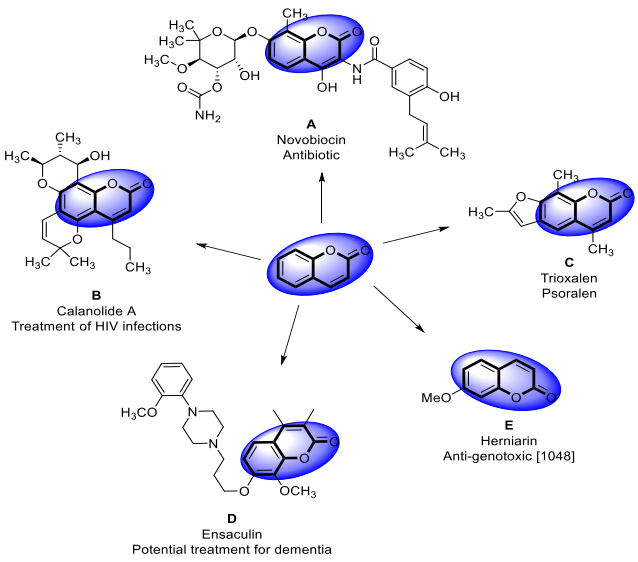


Figure 2 Examples of coumarin-containing drugs

Coumarin-based drugs and pharmaceutical structures are abundant in both literature and medical applications. For instance, numerous derivatives of coumarins such as Warfarin (Figure 3, **A)** , Acenocoumarol (Figure 3, **C)** and Phenprocoumon (Figure 3, **B)** have been used as anticoagulant agents, vitamin K antagonists, due to their resemblance to the structure of vitamin K [34,35] (Figure 3). Warfarin **A** is a world-famous anticoagulant, widely used for the treatment of thromboembolic disease[36]. Warfarin, also known as "Coumadin", was first introduced as a rat poison, but after reporting its lack of toxicity in humans and its anticoagulant activity in 1955, it stood amongst the top 20 used drugs in the United States for so many years[37].

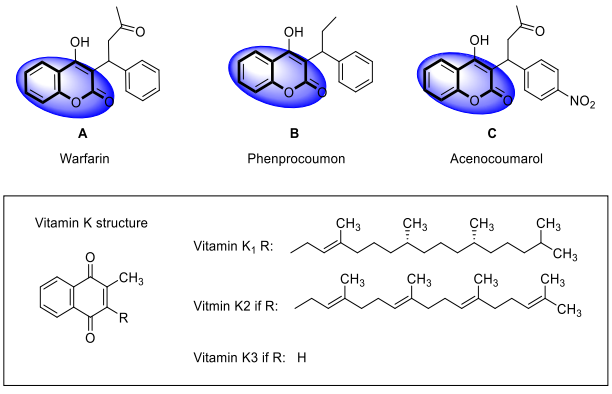


Figure 3 Anti-coagulant coumarin derivatives and their resemblance to vitamin K

Given the high importance and wide applications of coumarin derivatives, much research was devoted to developing newer and more effective synthetic methods for these.

structures[1,38,39,4,40,41,42]. More basic and less effective classic synthetic methods like Knoevanagel, Pechman, and Perkin condensations were used for the synthesis of coumarin derivatives for so many years[43,44,40]; however, recent advances in transitional-metal-catalyzed C-O and C-C bond formation[42,45], and organo- and photo-catalyzed mechanisms have increased the efficiency of synthetic methods used for the preparation of coumarins. The necessity of energy economy, sustainability, and protecting the environment along with increasing the production efficiency has caused catalytic studies to be of high importance[46]. Additionally, transition-metal-catalyzed cross-coupling reactions has become a potent tool in designing organic scaffolds, and the formation of C–C, and C-X bonds[47]. More recently, with the discovering and increasing the usage of metal-catalyzed C-H activation and C-H functionalization methods, more economic and efficient synthetic paths has become available[48,49,50].

Organic synthesis can be catalyzed by either homogenous, heterogeneous, or biocatalysts, however, the role of homogenous catalysts has been more investigated and more focused on. Transition metals by using their d orbital vacancy can accelerate catalytic reactions by coordination, ligand exchange, insertion, and elimination processes, and assisting in forming or cleaving of C-H or C-C bonds. Transition metals bearing different ligands can show varying activity[46,51]. Metals such as palladium, cupper, gold, iridium, iron, manganese, nickel, platinum, rhenium, ruthenium, scandium, silver, titanium, tungsten, zinc, and zirconium[42] have been extensively explored in the literature. Additionally, using organic compounds as catalysts has always been a useful tool in organic synthesis. Although with the advent of transition-metal-catalyzed reactions, organo-catalyzed paths were overshadowed by them, they never lose their importance in organic synthesis. Specially phosphorus and carbene-based organocatalyst has shown perfect effectivity in modern syntheses[46]. Organo-catalysts can also act *via* two mechanisms. They can be potential photocatalysts, or they can act as redox catalysts.

In this review, synthetic methods for coumarin under the effect of three types of catalysts, metal, organo-, and photo-catalysts, have been investigated. Reviewing the recent literature illustrated that metals can participate in the catalytic cycles with direct coordination, 1 electron- or 2 electron-charge transfer, or as oxidant, metals like cupper, rhodium, and iridium can take part in either photo-induced or irradiation-free radical mechanisms. They can readily act as photocatalysts, as they lose an electron in the presence of irradiation, and subsequently, start the radical mechanism by the radicalization of the starting material. They can also act as redox catalysts to start radical mechanisms. Additionally, metals like cupper and iridium can act as oxidants simultaneous to their catalytic role, or as an additive beside other metal catalysts.

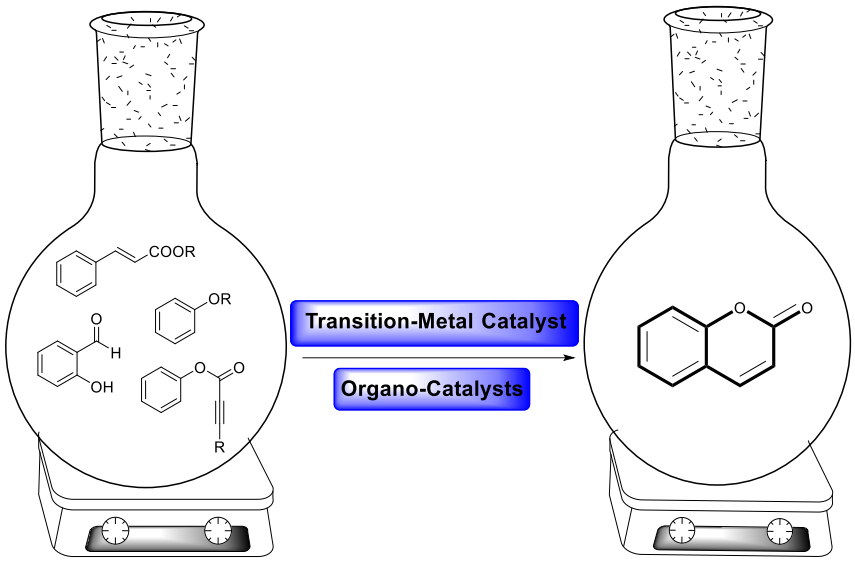


Figure 4 Synthesis of coumarin from various starting materials is possible by various catalytic systems

2. Transition-metal catalyzed synthesis of coumarins

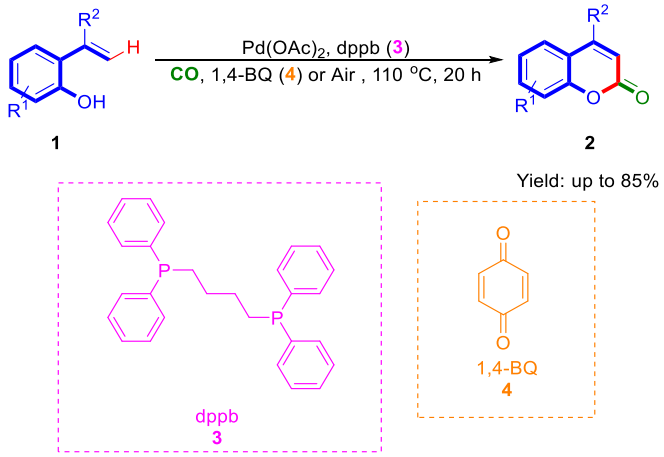
2.1 Palladium

Palladium (II)-catalyzed C-H Activation/C-C cross-coupling reactions are well-known, and frequently-used methods to form C-C, and C-Heteroatom bonds *via* Pd(II)/Pd(0), Pd(II)/Pd(IV), Pd(0) /Pd(II)/Pd(IV), and Pd(0) /Pd(II) catalytic cycles[52], namely some previously reported methods by the current research group[53,54,55] Palladium-assisted methods have also been used numerously for the synthesis of coumarin derivatives. Extensive efforts have been made in developing feasible routes for the preparation of coumarin scaffolds by three main strategies: CO insertion followed by a cyclization step, intermolecular annulation, and intramolecular annulation. Followed more recent examples of these methods have been reviewed.

2.1.1 Through Carboxylation

Employing CO gas as a cheap and abundant carbon source in the presence of a transition-metal catalyst such as palladium can be considered as a facile, direct, and economic strategy for the synthesis of a wide range of carbonyl-containing products. This method can be mentioned as one of the most important industrial, and academic tools. Various examples of using this method for the synthesis of coumarin derivatives can be found in the literature.

In 2012, a palladium-catalyzed oxidative cyclocarboxylation was performed by *Howard Alper* and his research group to achieve 3-fused coumarin derivatives. (Scheme 1)



Scheme 1 Palladium-catalyzed carboxylation/cyclization of 2-vinylphenol

In this study, 2-vinylphenols **1** were used as the precursor to undergo palladium-catalyzed cyclization in the presence of $Pd(OAc)_2$ as the sole catalyst, dppb (1,4-Bis(diphenylphosphino)butane) **3** as the ligand, and 1,4-benzoquinone **4** or air as the oxidant under low pressure of CO gas. The reaction was heated up to 110 °C and was proceeded for 20 hours. The catalytic process went through intramolecular oxidative carbonylation of 2-vinylphenols followed by a Pd(II)-P(0) catalytic cycle to produce desired product [56]. Due to the proposed mechanism, under optimized condition, carbon monoxide was coordinated into palladium phenoxide **5** to generate **6**, which subsequently underwent a CO insertion through Pd-oxygen bond **7** followed by the addition of Pd-coordinated carbon atom to the vinyl group to generate intermediate **8**. The intermediate transformed to the coumarin product by β-hydride elimination, through which Pd(0) was released, and oxidized to Pd(II) to start over the catalytic cycle (Figure 5).

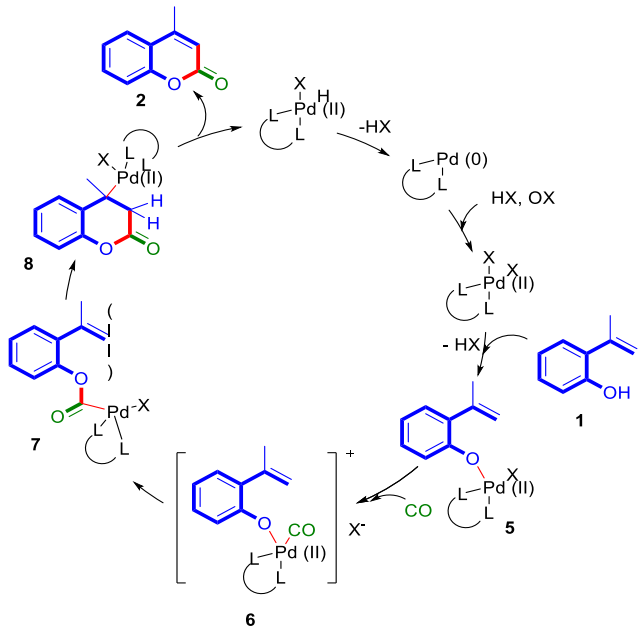
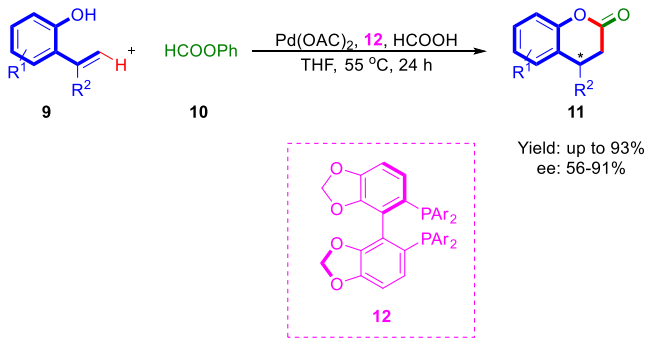


Figure 5 Proposed mechanism for formation of coumarin from CO-insertion into 2-vinylphenol

A variety of 2-vinylphenols were tested in the process and the result showed that *1*) in most cases, the process has worked better with air as oxidant, *2*) substituents in the 3-,4- and 5-positions were well tolerated on both vinyl group or the aromatic ring; however, steric hindrance proved to decrease the result in the presence of both oxidants[57].

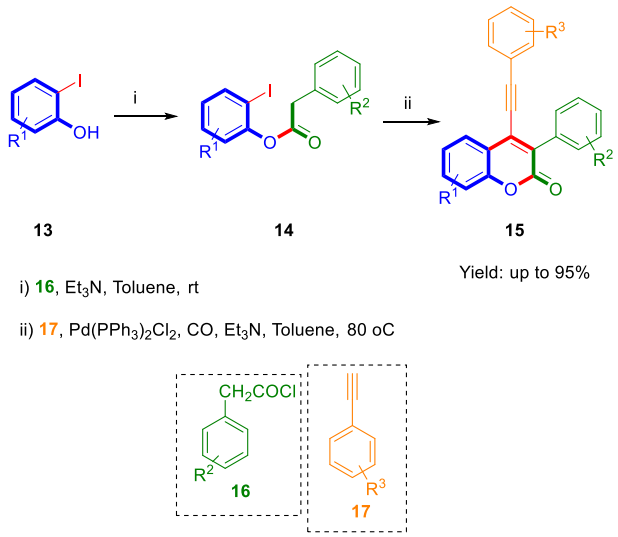
In another report in 2015, the high efficacy of palladium-catalyzed methods for synthesizing coumarin derivatives **11** was again proved by *Yian Shi* and his co-workers. They introduced a palladium-catalyzed enantioselective hydroesterification on alkenylphenols **9**, by using phenylformate **10** as an efficient CO surrogate, $Pd(OAc)_2$ as the catalyst, **12** as ligand, HCOOH as additive under mild conditions. The group has proposed two plausible mechanisms both proceeded through Pd(0)-Pd(II) cycle (Scheme 2).



Scheme 2 Using benzoic acid as carboxylating agent for synthesis of coumarin

The scope of the reaction was also investigated through the production of more than fifteen different derivatives of **11**. Alkenylphenols with various substituents on phenolic ring were well-tolerated in the procedure. Substituents like Me, halogens, phenyl, substituted arenes, thiophen, and furan groups were tested as R^1 and acted efficaciously. Double substituting *ortho* and *para* positions of phenolic moiety with 2-NP, *para*-CF_3-phenyl, and 2,4-dimethylphenyl was also tested and proved successful. Moreover, the effect of different substituents like Me, Et, and phenyl on vinylic moiety (R^2) was investigated. The result showed that despite expectations, the increased steric hindrance caused by the R^2 substituents did not affect negatively on neither effectivity nor enantioselectivity of the reaction, and moderate to excellent yields were produced[54].

In 2016, 3-aryl-4-arylethynylcoumarin **15** as another strongly applicable derivatives of coumarins were synthesized through a novel Pd-catalyzed method by *Sankararaman et al*. (Scheme 3). In this study, the research group performed a carbonylative Sonogashira coupling-intramolecular aldol cascade reaction on 2-iodoaryl-2-arylacetyl **14** and phenylacetylene **17** in the presence of palladium as the catalyst, Et_3N as the base under CO atmosphere. The group has achieved 2-iodoaryl-2-arylacetyl **15** from a reaction between 2-iodophenols **13** and 2-arylacetyl chloride derivatives **16** in toluene. The two-step reaction was performed one-pot, but the second step needed 80 °C heat to proceed.

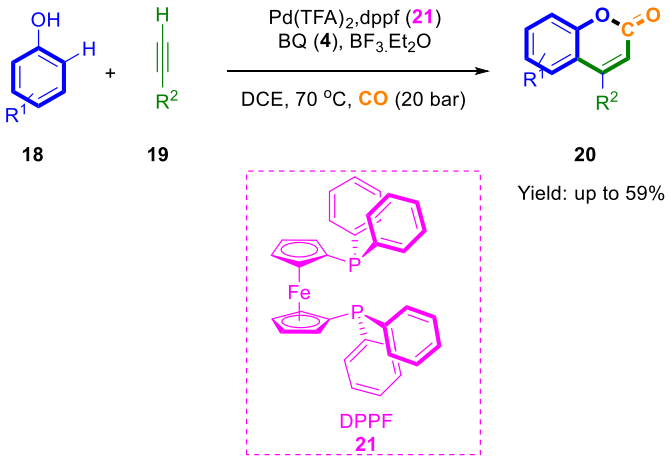


Scheme 3 A cascade reaction starting from 2-iodophenol to produce 2,3-substituted coumarin

Regarding the scope of the reaction, various substituents were examined in all three positions R^1, R^2, and R^3, and all were well-tolerated. Notably, the reaction was performed efficiently in the presence of strong electron-withdrawing group NO_2 in *para* position of aryl acetyl ring of **15** and the product was gained up to 75% yield. Moreover, the bulky t-Bu group as R, electron-donating OMe and Br as R^1, and electron-donating Me and OMe as R^2 were successfully yielded with up to 90% effectivity[59].

Fengxiang Zhu and *Xiao-Feng Wu* in 2018 reported another palladium-catalyzed oxidative carbonylation method for the synthesis of 3-substituted coumarin derivatives (Scheme 4). In this strategy, acetylene **19** and phenol **18** derivatives were used

in the presence of $Pd(TFA)_2$ as the catalyst, dppf (1,1'-Bis(diphenylphosphino)ferrocene) **21** as the ligand, benzoquinone (BQ) **4** as the oxidant, and $BF_3.Et_2O$ as an effective additive in dichloroethan in 70 °C, and yielded up to 59% effectivity.



Scheme 4 A Pd(0)-mediated carboxylative method to synthesize coumarin

The group successfully separated the propiolate intermediate **22** in the same condition, but without $BF_3.ET_2O$ (Figure 6). However, by using various control reactions the group proved that the conversion of propiolate to coumarin did not happen solely under the effect of $BF_3.Et_2O$, and the reaction of acetylene and phenol derivatives to produce coumarin has happened in one concerted step.

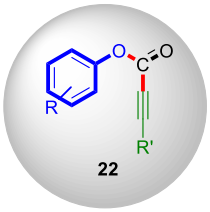
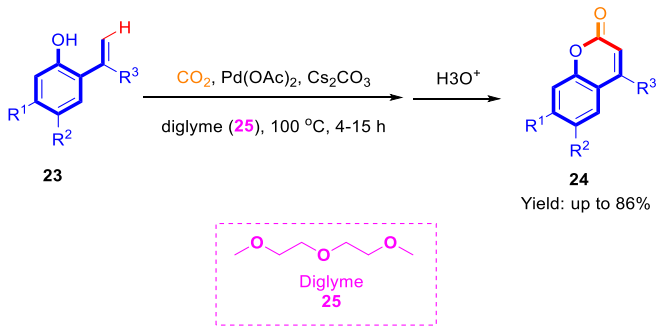


Figure 6 the product in the absence of $BF_3.ET_2O$

The scope of the reaction was also explored. It is reported that nine coumarin derivatives were synthesized using this method with moderate effectivities. Me, F, and t-Bu were tested as R^2, and slightly higher outcome was produced compared to those of simple acetylene. *Ortho-*, *meta-*, and *para*-substituted phenols were also applied in the reaction, and all produced the corresponding products in 43-54% yield. similarly, in this case, simple unsubstituted phenol produced weaker results[60].

Although CO_2 gas is a kinetically and thermodynamically stable material, its application as a building block in organic synthesis has attracted high attention in last decades. Transition metal-catalyzed carboxylation reactions of organic substrates using benign CO_2 gas can provide a route to install carboxylic acids and their derivatives under mild conditions *via* carbon-carbon bond formation. In 2013, *Iwasawa et al*. demonstrated a palladium-catalyzed C-H activation/carboxylation on 2-hydroxystyrenes **23** with carbon dioxide as the carboxylation agent, followed by an acidic hydrolysis for direct synthesis of coumarins **24**. The reaction was proceeded in the presence of $Pd(OAc)_2$ as the catalyst, and Cs_2CO_3 as the base in diglym at 100 °C in sealed tubes and the desired product were obtained with up to 86% yield (Scheme 5).

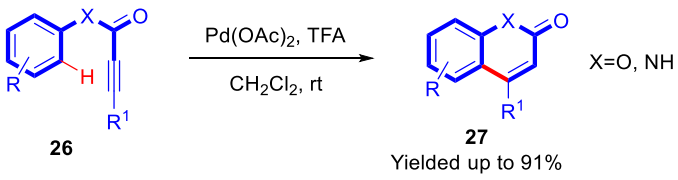


Scheme 5 Using carbon dioxide gas to produce coumarin from 2-hydroxystyrenes

The scope of this reaction was investigated with substituted 2-hydroxystyrenes **23**. The author reported that a wide range of substitutions with electron-donating or electron-withdrawing activities were beard on the phenyl ring of 2-hydroxystyrene and in the α position of the double bond, providing the corresponding coumarins with good yields up to 90%. In addition, substituents such as 4-cyanophenyl, 3,4-methylene dioxyphenyl, pyrrole, and thiophene on the 2-hydroxystyrene's double bond also provided the corresponding products with the yield up to 88%. The author also reported that the presence of methyl or methoxy groups as R^1 or R^2 slightly reduced the efficiancy of the reaction. Unfortunately, coumarin derivatives with substituent on C3 position could not obtain from this protocol.

Unfortunately, employing 2-hydroxystyrene bearing substituents on the β-position as the substrate did not provide the desired product under the same condition[61].

Palladium-catalyzed intramolecular cyclization through C-H activation can be a useful method to access coumarin scaffolds. For instance, starting from aryl propiolates **26**, *Fujiwara* and his research group reported a palladium-catalyzed procedure to access coumarin and quinolone derivatives in 2000 (Scheme 6).



Scheme 6 Intramolecular annulation/C-H activation of aryl propiolate **26**

The reaction was conducted in the presence of palladium acetate as the catalyst, triflouroacetic acid as the essential additive and dichloromethane as the solvent in room

temperature. The results indicated that presence of TFA is vital for the formation of cationic Pd(II) and completion of the catalytic cycle. The group also has successfully achieved up to 91% effectivity in synthesizing several derivatives of both coumarin and quinolone through reported protocol. Interestingly, the steric hindrance of trimethoxy- or *para*-t-Bu-substituted phenyl propiolates did not affect the efficacy of the reaction negatively. Propiolates substituted with CHO, or i-Pr on the *ortho* position were also applied to the reaction condition and produced the corresponding products in good yields[62]. The proposed mechanism (Figure 7) began with electrophilic attack of cationic Pd(II) to the aromatic C–H bond to form IMa which is coordinated to alkyne group in next step to give **29**. Subsequently, the **30** species was generated through a trans insertion of **29** on C-C triple bond. Finally, the desired product was produced through protonation of **30**, Pd(II) was released to start over the catalytic cycle.

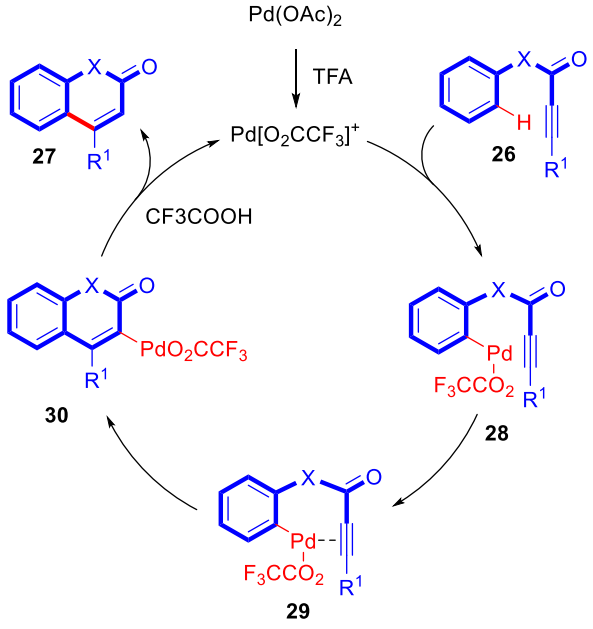
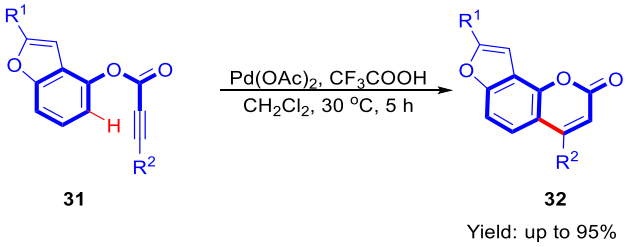


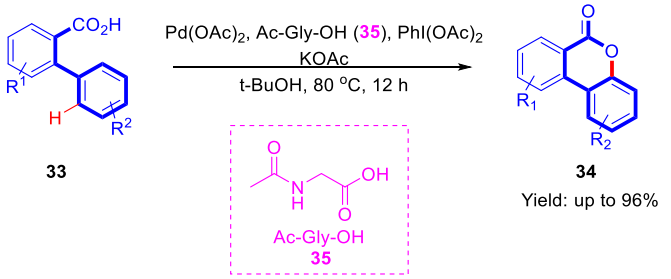
Figure 7 proposed mechanism for the palladium-catalyzed C-H activation of aryl propiolate to synthesize coumarin

Kitamura et al. in 2012, introduced a Pd-catalyzed procedure for synthesizing angelicin **32**, a class of fused coumarin derivatives (Scheme 7). In this report, an intramolecular hydroarylation-cyclization happened on 4-benzpfuranyl alkynoates **31**. This reaction was proceeded with activation of triple bond by palladium. The group has produced 12 derivatives of angelicin with aromatic or long chain and short chain aliphatic substituents on the starting alkynoate. The best result was produced with hydrogen as R^1 and phenyl as R^2. Besides, n-C_6H_{13} and phenyl were both applied as R^1 and produced the desired result in moderate yields. Me, H and n-C_5H_{11} were also appropriate substituents for R^2. Overall, there was no meaningful pattern in the efficacy of reaction of different derivatives[63].



Scheme 6 A novel method to produce angelicin derivatives **32** reported by *Kitamura et al.*

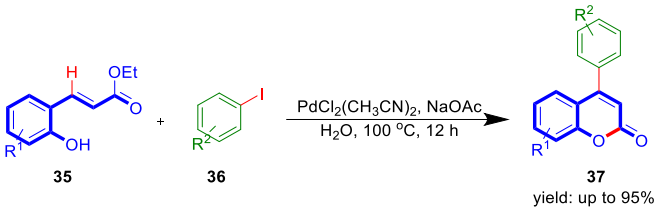
In 2013, *Xi-Sheng Wang* and his group described another palladium-catalyzed reaction to produce biaryl lactones **34**, another multicycle structure containing coumarin motif (Scheme 8). This C-H functionalization/O-cyclization was started from biphenyl carboxylic acid **33** and was proceeded with $Pd(OAC)_2$ as the catalyst, Ac-Gly-OH **35** as the ligand, KOAc as the base, $PhI(OAc)_2$ as the additive and tert-Buyl alcohol as the solvent in 80 °C.



Scheme 7 Palladium-catalyzed intramolecular annulation of biphenyl carboxylic acid **33**

This mechanism went through a Pd(II)-Pd(IV) catalytic cycle which activated the C(4)-H bond to result in an intramolecular cyclization. The scope of the reaction was also explored. The reaction was able to tolerate various EWGs and EDGs on both phenyl rings. Halogenated products of this reaction are potential to be substrate of further cross-coupling reactions. when *meta*-substituted biaryl carboxylic acids were applied to the protocol, the C-H bond that was farther to the substitute acted in the reaction (the product was achieved in 100% regioselectivity). The group has also reported that *ortho*-substitutions did not have negative effect on the efficiency of the reaction. They have tested replacing free phenyl ring (ring which does not bear the acidic moiety) with other aromatic rings like naphthalene and thiophen and observed that the desired result was produced in moderate to high yields[64].

In another attempt in 2018, Junmin Chen's research group, coupled ethyl *ortho*-hydroxy cinnamate **35** with phenyl iodide *via* a Pd-catalyzed arylation-intramolecular cyclization to produce 4-arylcoumarins **37** (Scheme 9).



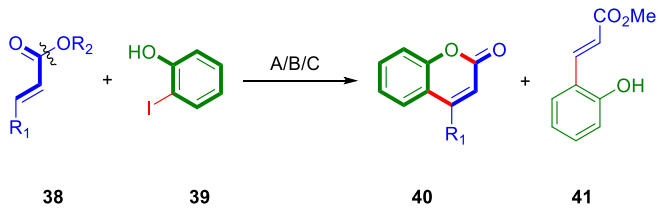
Scheme 8 Coupling ethyl *ortho*-hydroxycinnamete with phenyl iodide to produce 3-phenylcoumarin

In this method, $PdCl_2(CH_3CN)_2$ was used as an efficient catalyst and NaOAc as the base in water at 100 °C. Having the optimized condition in hand, the group researched about the scope of the reaction. Their studies showed that aryliodide can tolerate various functional groups as substitutes on its aromatic ring, showing small effects on the reaction's effectivity. Aryliodide's aromatic hydrogens were successfully replaced with methyls, methoxies, halogens, CF_3, Acyl and COOMe (the later three being strong EWGs) and the reaction's efficiency did not fall under 80%, unless with the presence of two *meta*-flourines. However, the presence of strongly electron donating NH_2 on the aromatic ring and nitrogen and sulfur heterocycles or naphthalene in place of the aromatic ring lowered the effectivity by an average of 10 units. The group also reported that relocating methyl and methoxy groups to *ortho*, *meta* and *para* positions did not affect the results.

Furthermore, various *ortho*-hydroxycinnamates **35** were examined in the reaction's optimized condition. It was observed that the presence of methyl group and halogens in the 3 or 4 position is well-tolerated. However, substituting *para* position of aryl iodide with strong EWGs like CN and NO_2 , and also substituting C5 of cinamates with methoxy group was shown to have destructive effects[65].

2.1.3 Through Intermolecular annulation

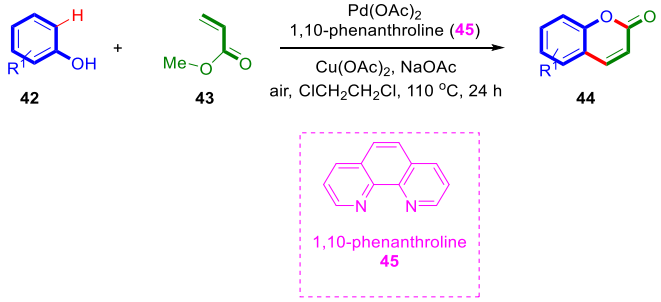
Silva, *Costa*, and colleagues in 2010 reported a tandem Heck-lactonization reaction between E- and Z-enoats **38**, and *ortho*-iodophenol **39** (Scheme 10). In this report, palladium(II) salts were used as catalyst, in the presence of suitable base and in aqueous atmosphere; and coumarin **40** was produced, alongside cynnamate **41** as the side product. The group has investigated and compared three different methods mechanistically. The scope was also tested using all three conditions, and no meaningful pattern was observed. Reportedly, steric hindrance around the enoate's double bond affected the result negatively[66].



Conditions A: $Pd(OAc)_2$, H_2O, Et_3N, 80 °C
Conditions B: $PdCl_2$, H_2O, Et_3N, 80 °C
Conditions C: $Pd(OAc)_2$, in the presence or absence of PPh_3, acetone, Ag_2CO_3, reflax

Scheme 9 Comparing three palladium-catalyzed methods to produce coumarins from orth-iodophenol **39**, and enoats **38**

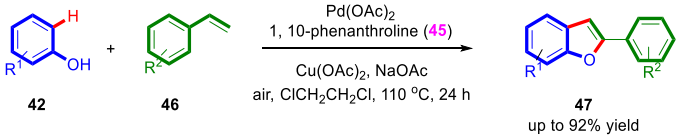
In 2013, another palladium-catalyzed method for synthesis of simple coumarins was introduced by *Maiti* and his team (Scheme 11). In this method, phenols **42** were coupled with methyl esters **43** under the effect $Pd(OAc)_2$ and 1,10-phenanthroline **45** as the catalytic system, $Cu(OAc)_2$ as the co-catalyst and oxidant, NaOAc as base, and $ClCH_2CH_2Cl$ as solvent under air in 110 °C.



Scheme 11 using Palladium-cupper catalytic system to synthesize coumarins **44** from phenols **42**

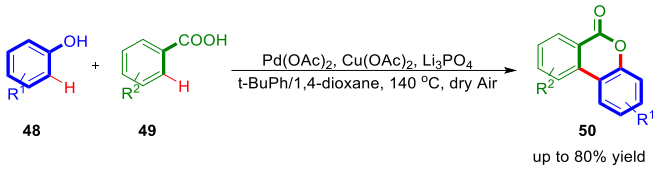
The author reported synthesis of fifteen different coumarin variants using this protocol. Phenols with *para*-substituted electron-withdrawing groups; namely NO_2, CH_2CN, $COCH_3$, CN, and CHO proved less efficient than the ones with electron-donating groups, like OMe. Di-substituted and *meta*-substituted phenols were also successful in producing the yield with both EDGs and EWGs.

The group also reported using the same method for synthesis of 2-arylbenzofuranes **47** from the reaction of phenols **42** and styrenes **46** with up to 92% effectivity and excellent regioselectivity[67] (Scheme 12).



Scheme 10 Synthesis of benzofurran derivatives **47** in a report from *Maiti et al.*

Another palladium-catalyzed method to synthesis fused coumarin derivatives was introduced by *Shi* research group in 2017 (Scheme 13)



Scheme 11 Introduction of a palladium-catalyzed CDC method for synthesizing coumarin by *Shi et al.*

The group coupled phenol derivatives **48** with benzoic acids **49** in the presence of $Pd(OAC)_2$ as catalyst, $Cu(OAc)_2$ as oxidant, Li_3PO_4 as base, and a mixture of t-BuPh and 1,4-dioxane as base in 140 °C under dry air. t-buPh and dioxane separately did not produce good yields. A single silver salt was also tested as oxidant and did not result in the desired product. The proposed mechanism contained addition of Cu(II) to the phenol **48** and its replacement with palladium through a transmetalation. The acid was coordinated to palladium through a ligand exchange in the next step. A subsequent C-H activation followed by a reductive elimination of Pd(0) (which was oxidized to Pd(II) and went back to the cycle), formed intermediate **51** and an intramolecular lactonization on **51** gave the final product.

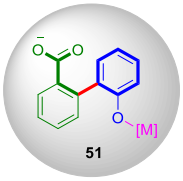
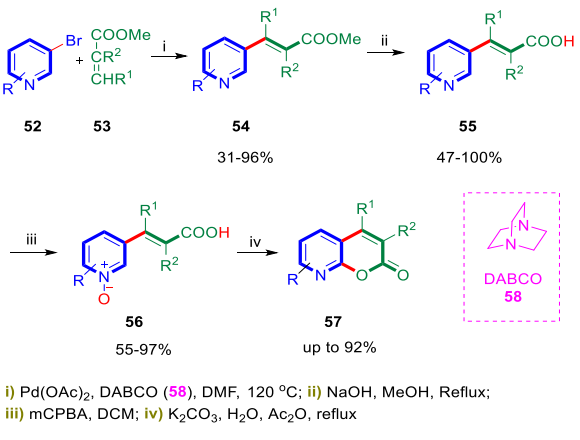


Figure 8 O-metal coordinating in the synthetic process of Scheme 13

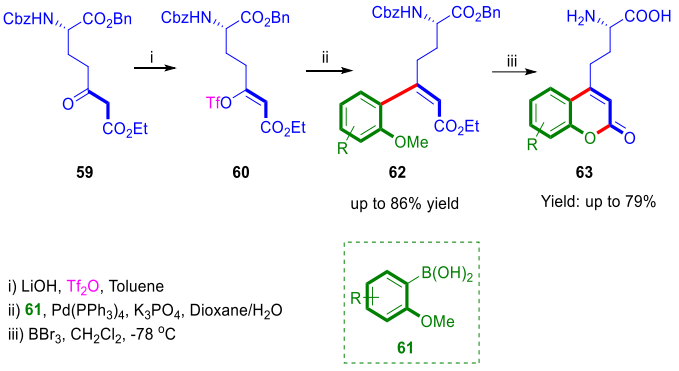
The protocol was used to synthesize 24 different derivatives of **50** and gave up to 80% effectivity. The best result was obtained from methyl-4-hydroxybenzoate and 4-methoxybenzoicacid, showing positive effect of electron-richness of the benzoic acid (better coordination to metal) on the effectivity[68].



Scheme 12 Total synthesis of 3,4-disubstituted 8-azacoumarins

In 2016, *Wang* and *Yu et al.* reported a novel method for the total synthesis of 8-azacoumarins **57**, starting from 2-bromopyridine **52** (Scheme 14). The key step includes a palladium-catalyzed Heck coupling in the presence of $Pd(OAc)_2$ as the catalyst, DABCO (1,4-diazabicyclo[2.2.2]octane) **58** as base, and DMF as solvent in 120 °C (i). In the following steps, the esteric group was hydrolyzed in reflux with methanol and NaOH (ii), the pyridine moiety was then oxidized to pyridine N-Oxide (iii) and the final lactonization-cyclization (iv) happened in the presence of K_2CO_3 and Ac_2O. Two pathways were suggested for the final step, first including coordination of OAc to nitrogen atom and second including coordination of OAc to the ring itself, both ways followed by intramolecular lactonization and departure of HOAc.

Less than 20 different derivatives of 8-azacoumarin **57** were synthesized, derived from substituted 2-bromopyridines **52** and methyl acrylates **53.** 2-bromopyridines bearing halogens, phenyl, and alkyl groups at the *meta* position were successful in giving the final product in good yields. However, the ones with the strong electron-donating group OMe and the strong electron-withdrawing groups COOEt and CF_3 contributed in the reaction with lower efficiencies. Also, methyl acrylates with phenyl or methyl substituent on both R^1 and R^2 successfully proceeded to the corresponding products[69].

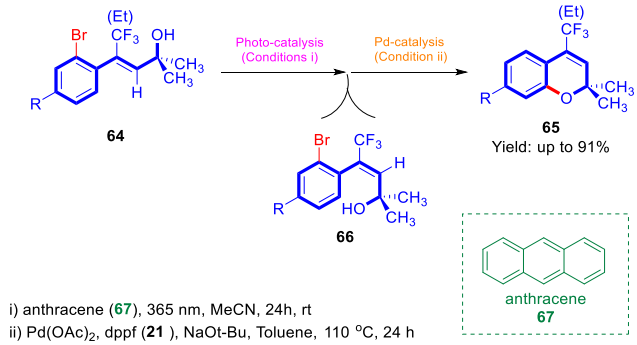


Scheme 13 Starting from vinyl triflates **59** to produce coumarin-fused amino acids

In 2017 *Moodie et al.* found a novel synthetic route for the synthesis of coumarin-functionalized amino acids (Scheme 15). In this method, coumarin derivatives **63** were produced from glutamic acid derived (Z)-vinyl triflates **59** in three steps. The initial step was done in the presence of LiOH as base, toluene as solvent and Tf_2O. In this step, Tf_2O was ionized in the presence of aqueous base, and Tf^+ was added to the stable enol confirmation of **59** turning it to **60**. subsequently, a Suzuki-Miyuara reaction was performed between *ortho*-methoxyboronic acid **61** and **60** in the presence of $Pd(PPh_3)_4$ as metal catalyst, K_3PO_4 as base and a mixture of dioxane and water as solvent. Finally, a demethylation with the help of BBr_3 in CH_2Cl_2 was conducted in -78 °C to give the desired product **63**.

Using this protocol, five different coumarin derivatives were produced in 53-79% yield through which the group tested boronic acid's scope using methoxy and fluorine as

substituents. The least effective result belonged to 2,6-dimethoxyboronic acid which can be simply explained by the steric hindrance near the reaction's site. The presence of fluorine as a substituent did not cause any dramatic difference in the yield[70].



Scheme 14 A novel two-step method, using tandem photo-catalyzed and Pd-catalyzed reactions to synthesis 4-trifloroumethylcoumarins

Gilmour and colleagues in 2017 introduced a method for preparation of 4-trifloroumethylcoumarin **65** from 3-CF_3-substituted *ortho*-bromocinnamyl alcohol **64** in two-steps (Scheme 16). The value of this method is because of the predominance of fluorine in bioactive molecules and existence of limited method for synthesize of CF_3-substituted coumarins. In this protocol, the readily available Z-cinnamylalcohol **64** was turned into the E-isomer *via* a photo-catalyzed isomerization in the presence of anthracene **67** as the catalyst, and 365 nm irradiation in methylcianide and room temperature for 24 hours. The author has also reported that the efficiency of benzophenone **68** (Figure 9) as a photocatalyst for this reaction was approximately equal to that of anthracene **67**.

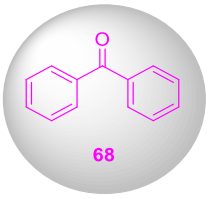
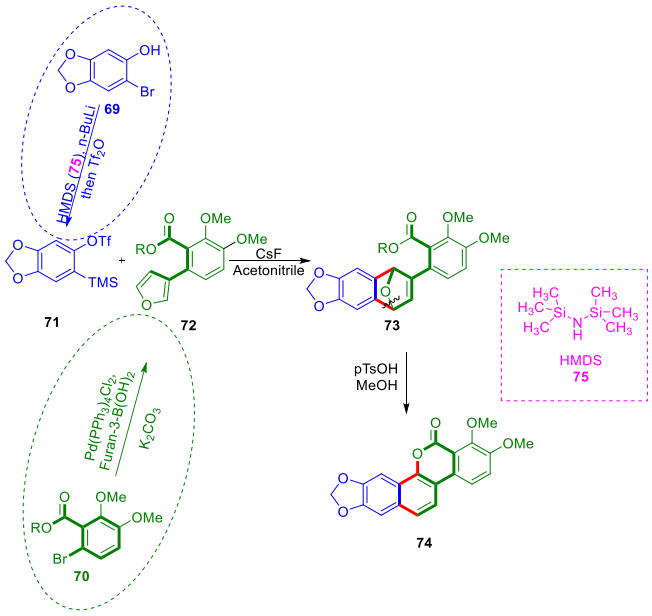


Figure 9 structure of benzophenone

Subsequently, the final product, coumarin **65,** was synthesized through a palladium-catalyzed cyclization in the presence of $Pd(OAc)_2$ as catalyst, dppf **21** as ligand, sodium tert-butoxide as base and toluene as solvent. The reaction was heated up to 110 °C and stirred for 24 hours. The initial isomerization went through a radical intermediate, made from radically breaking of the double bond, inspired by the 1,3-allylic strain. The second step went through activation of C-Br bond by the metal catalyst. The reaction's repeatability was tested by the group using various cinnamyl alcohols. Interestingly, the reaction was able to be performed with up to 70% effectivity when the triflouromethyl group was replaced with ethyl, given that these two groups possess very similar van der waals volumes. The phenyl group was substituted in the *para* situation with halogens and electron-donating groups like methyl and methoxy and yielded up to 95%. Additionally, replacing the phenyl group with naphthalene was a successful attempt and



Scheme 15 Preparation of Arnottin I **74** using a series of metal-catalyzed and catalyst-free reactions

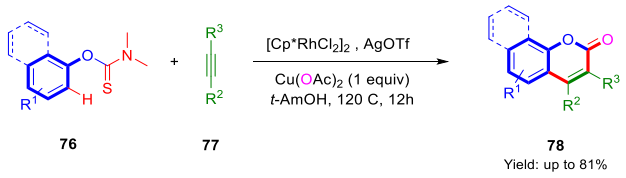
the final product was achieved in 81% yield[71].

In 2015, *Chad A. Lewis* and his co-workers performed a series of reactions to produce Arnottin I **74** starting from 2-bromobenzoate derivatives **70** and 6-bromobenzo[*d*][1,3]dioxol-5-ol **69** (Scheme 17). Arnottins are coumarin-containing natural products mostly known for their antibiotic features. In the first step, a palladium-catalyzed Suzuki reaction was performed on **70** using $Pd(PPh_3)_4Cl_2$ as catalyst and K_2CO_3 as base to achieve furyl-coupled **72**. Also, **71** was prepared by treatment of **69** with HMDS (Bis(trimethylsilyl)amine) **75**, n-BuLi and Tf_2O. Subsequently, in situ cycloaddition procedure proceeded under the effect of CsF in acetonitrile followed by intra-molecular lactonization of **73** to the final product **74**[72].

2.2 Rhodium catalyzed synthesis of coumarins

Rhodium(III)-catalyzed C–H bond activation under oxidative conditions has become one of the most remarkable methods to produce C–C, C–N, and C–O bonds, however most of rhodium(III)-catalyzed reports are limited to oxidative coupling of arenes with unsaturated molecules such as alkenes and alkynes[73]. Two types of mechanisms are possible for rhodium-catalyzed C-H bond functionalization *via* Rh(I)/Rh(III) catalytic cycles: with E-H directing groups or without E-H directing groups[74,75]. These strategies were employed as a practical and powerful tool to synthesized coumarin derivatives in multiple attempts.

For instance, in 2015, *Chungu Xia et al.* Proposed a new pathway for synthesizing coumarin through a Rh-catalyzed oxidative annulation protocol (Scheme 18). The reaction was performed using aryl thiocarbamates **76** and internal alkynes **77** as substrates in the presence of a catalytic amount of $[Cp^*RhCl_2]_2$, AgOTf as ligand, and $Cu(OAc)_2$ as oxidant (acted both as the oxidant for RhI and as the oxygen source of the carbonyl group) in tert-amyl alcohol at 120 °C under Argon atmosphere.



Scheme 16 Coupling of thiocarbamate **76** and internal alkynes in the presence of rhodium

The scope of the reaction was also investigated. The results showed that aryl thiocarbamates **76** substituted with electron-donating groups such as alkyl and methoxy at the *para* position of the phenyl ring produced the result in good yields. However, substituting the *ortho* position of **76**'s phenyl ring lowered the yield immensely. When aryl thiocarbamate **76** with a substitution *meta* to the oxygen group was used, regioselectivity was decreased, and both products **79** and **80** were produced in 5:1 ratio (Figure 10).

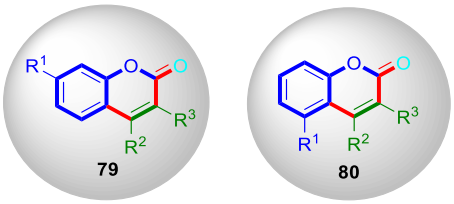
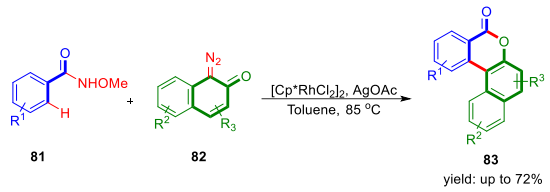


Figure 10 applying thiocarbamate **76** with substitution *meta* to the oxygen group produced two regioisomers

Halogen groups such as chlorine and bromine, when substituted on aryl thiocarbamate's phenyl ring were less effective regardless of their positions. The scope of the internal alkynes was also perused. It is reported that phenyls with *para*-substituents and alkyls acted suitably as alkyne's substituents. Additionally, alkynes substituted with *para*-methoxy phenols produced relatively lower efficacy[76].

In 2017, *Cui et al.* conducted a transition-metal-catalyzed C-H activation on benzamides **81** and diazonaphthalen-2(1H)-ones **82** to synthesize highly conjugated lactones **83** with a coumarin moiety (Scheme 19). In this mechanism Rh(III) was hired as a catalyst, AgOAc as additive and toluene as solvent heated up to 85 °C.



Scheme 17 Producing highly resonanced **83** using rhodium-catalyzed coupling of benzamides **81** and diazonaphtalen-2(aH)-ones **82**

The first step of this reaction was a Rh(III) catalyzed *ortho* C-H activation on **81** followed by addition of diazoketone to the complex, causing N_2 to leave, and coupling of the *ortho* carbon atom of **81** with carbon adjacent to diazo group (**84**, Figure 11). In the next step another organometallic complex **85** formed between N-Rh-O (sterically close and preferable) and the subsequent protonation with HOAc produced the intermediate **86** which later continued to form the final product **83**.

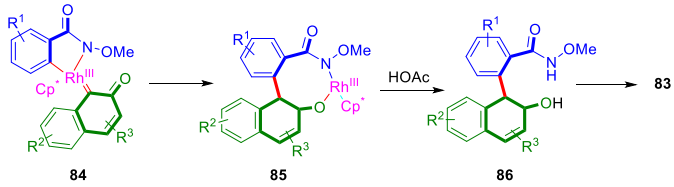
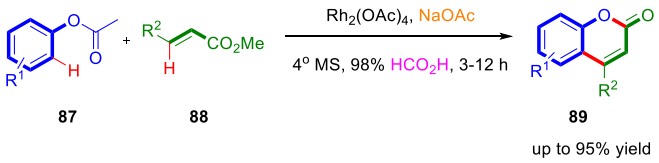


Figure 11 the proposed mechanism goes through coordination of rhodium into both starting materials

This reaction was able to be successfully performed with 20 different derivatives of the starting materials. Substituents like Me, Ph, MeO, NO_2 and halogens were well-tolerated on bezamides, although *para*-halogens and NO_2 are reported to produce relatively higher efficiencies. Replacing the phenyl ring of benzamides with aromatic heterocycles and other aromatic structures was also proved to be successful. Namely, thiophen, furan, benzofuran, and naphthalene were suitable replacements. Aliphatic benzamides were also tested and gave the corresponding products in 59-62% yields. Diazonaphtalene-2(1H)-ones **82** with substituents like CO2Me, Ph and Br on both phenyl rings also proved to act adequately in this process. Additionally, 2-diazonaphtalene-1(2H)-one was also able to participate in the reaction and give the corresponding product, which can be an interesting perspective for later researches[77].



Scheme 20 A rhodium-catalyzed CDC to produce coumarins with high effectivity

Sudalai and co-workers in 2015, suggested a rhodium-catalyzed C-H activation to produce coumarin derivatives **89** (Scheme 20). In this protocol phenolic acetates and acrylates **87** were used as the starting materials with rhodium acetate as catalyst, NaOAc as additive and HCO_2H as both reducing agent and solvent. The reaction

went through activation of *ortho* C-H bond of phenolic acetate by rhodium, followed by the insertion of alkenic ester **88** into Rh-C bond of the catalytic complex to produce intermediate **90** (Figure 12) subsequently a β-hydride elimination and an intermolecular cyclization of intermediate **91** gave the corresponding product.

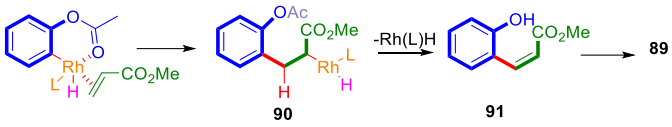
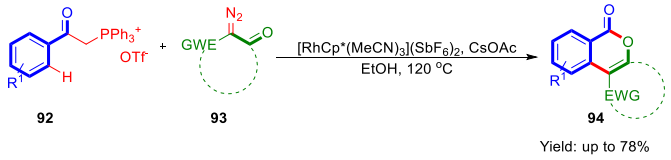


Figure 12 Rhodium-catalyzed C-H activation of phenolic acetates or acrylates

The scope of the reaction was investigated, and the result showed that plenty of substituents were tolerated at both R^1 and R^2 positions. The group has reported 26 different derivatives of the product successfully produced using this method in up to 95% yield. More precisely, EDGs like bromine, EWGs like CN, NO_2, COMe, CHO and bulky groups like t-Bu were well-tolerated at the *para* position of phenolic moiety. *meta* position of phenolic moiety was able to bear Me, OH and OMe as well. Likewise, phenolic acetates with di-substituted and tri-substituted phenyl rings gave the corresponding products in moderate yields. Acrylates substituted with either H, Ph, or Me participated in the reaction to give the product with good effectivity[78].



Scheme 18 Another rhodium-catalyzed method C-H activation to access fused coumarins

Another example of metal-catalyzed methods to synthesize coumarin derivatives was reported in 2017 by *Xingwei Li* and his research lab (Scheme 21). This Rh(III) catalyzed C-H activation of phenacyl phosphoniums **92** was mediated by phosphonium ylide and performed in the presence of CsOAc as base and ethanol as solvent heated to 120 °C. Based on the experiments the group conducted for illustrating the mechanism, they suggested a Rh(II)-Rh(III) catalytic cycle.

To check the reaction's generality, the group used various phenacyl phosphoniums **92** and diazocarbonyl compounds **93**. Among *para*-substituted phenacyl phosphoniums, those with electron-donating groups or neutral groups performed better than those with EWGs like CF_3 or CN. Chlorine and fluorine were also tested at the same position on **92** and the chloro-substituted one produced better yields. *meta*-substituted phenacyl phosphoniums were also proven adequate in this condition. Two types of corresponding products **95** and **96** were yielded when using *meta*-substituted phenacyl phosphoniums, with higher yields for regioisomer **95**.

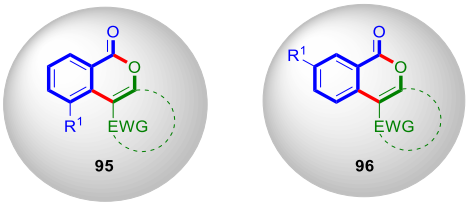
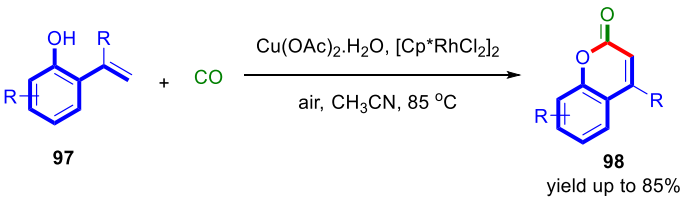


Figure 13 two possible regioisomers when *meta*-substituted phenacyl phosphoniums

ortho-methoxy and *ortho*-flouro **92**s were also applied to the protocol and gave the corresponding products in respectively 89% and 62% yield, showing that steric hindrance is well-tolerated in the protocol. Furthermore, replacing the phenyl ring with other aromatic rings like benzo[1,4]dioxepine, naphthalene and benzothiophen successfully gave the yields with up to 70% effectivity. All phenacyl phosphoniums reported had reacted with ethyl 2-diazo-3-oxobutanoate; however, other diazocarbonyl compounds were examined by the group and produced the result in moderate to excellent yields[79].



Scheme 19 Insertion of CO to *ortho*-vinylphenols using rhodium-based catalytic systems

Moiseś Gulías, José L. Mascareñas, and their group in 2013 developed a new way to synthesis coumarin derivatives **98** *via* a metal-catalyzed [5+2] cycloaddition, involving a C(sp2)–H activation (Scheme 22). The process was proceeded with [(pentamethylcyclopentadienyl) $RhCl_2]_2$ and $Cu(OAc)_2$ as catalyst, and carbon monoxide and *ortho*-vinylphenols **97** as reagents in CH_3CN and air. The protocol has successfully given up to 85% yield.

The existence of 3 different C-H positions susceptible to being activated in 2-vinylphenol **97**, could have led to the formation of 5-, 6-, or 7-membered rings, but the presence of Rh(III) catalysts has led to the formation of benzofuranes and eventually coumarins.

As the reaction was reported as a side reaction in the research of synthesizing benzoxepines, only four derivatives of the result were produced, but substituents with a wide variety of electronic activity were used. Satisfyingly, all substituents, including Me, OMe, and CO_2Me were perfectly tolerated[80].

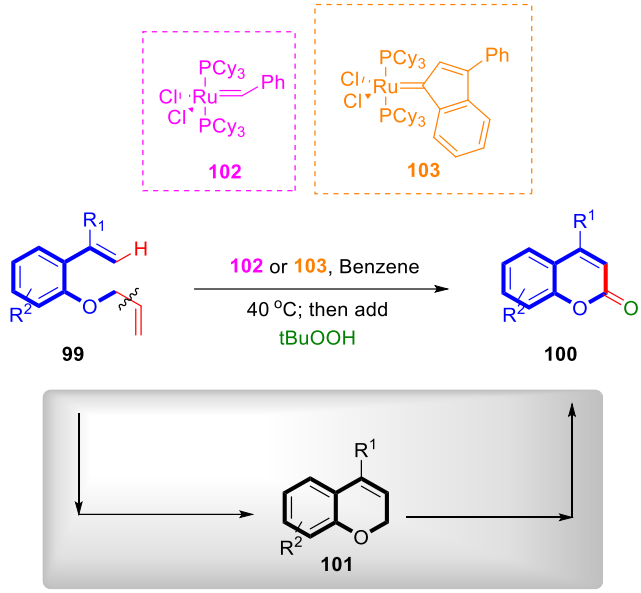
2.3 Ruthenium catalyzed synthesis of coumarins

Catalytic C-H bond activation/functionalization using Ru(0) was first introduces by *Murai, Chatani*, *Kakiuchi* group in 1993[81]. This procedure can go through insertion of ruthenium(0) to the C–H bond and further reaction of generated C–Ru–H species

with the other, unsaturated, substrate. In the recent decade, ruthenium(II) as a catalyst is more widely used, mostly because of some benefits it possesses such as low economy, efficiency, facility of access and preparation, and stability. Ruthenium (II)-catalyzed C–H bond functionalization of C(sp^2)-H bonds has contributed in so many cross-coupling C–C bond formations, especially in the arylation reactions in presence of suitable directing groups, and oxidative dehydrogenative cross coupling (CDC) reactions[82,83].

Additionally, ruthenium(II) polypyridine complexes can easily undergo single-electron-transfer (SET) processes by being exposed to visible light irradiation, that is why ruthenium-based photo-redox catalysts have become an effective tool in organic synthesis. Photoexcitation can happen in the presence of various sources of light, including LED lamps, fluorescent light bulbs, Xe lamps, and natural sunlight. Tris(2,2′-bipyridine) ruthenium ($[Ru(bpy)_3]^{2+}$) complex is widely used as a photo-redox catalyst. Herein, we have investigated recent methodologies using ruthenium(II) as either a direct catalyst or a photocatalyst for synthesizing coumarin derivatives[84].

2.3.1 As a Direct Catalyst

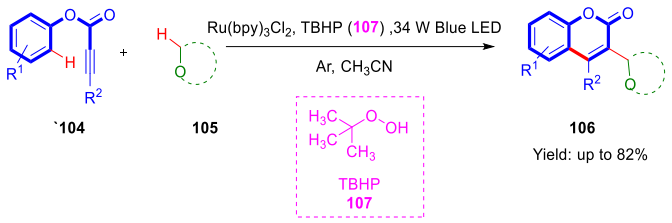


Scheme 20 Using two ruthenium complexes to convert allyl ethers **99** to coumarin scafold

In 2011 *Bernd Schmidt* and *Stefan Krehl* reportes an oxidative ruthenium-catalyzed C-H activation/C-C coupling for synthesis of multi-substituted coumarins **100** (Scheme 23). This method was performed by treatment of allyl ethers **99** with ruthenium salts **102** or **103** in 40 °C in benzene as solvent, followed by working up with *tert*-butyl peroxide. Accordingly, the product was produced *via* an initial ring closing metathesis of **99**, leading to intermediate **101,** the group was successful in isolating which, followed by a ruthenium-catalyzed allylic oxidation on **101** in the presence of t-BuOOH as oxidant. Trying to find the optimal condition, the group has found out that both catalysts **102**, a first-generation Grubbs' catalyst, and **103**, an Umicore M1 catalyst, were able to produce the final product in virtually identical yields.

The group has also tested the scope of the reaction and reported that several mono- and multi-substituted aryl ethers can be hired in this protocol and lead to the corresponding products. most of all, the *para* position of the phenolic moiety was tested by the group, and the position proved compatible to alkyls, halogens, alkenyls, and EWGs like NO_2. Interestingly, in all the tested reactions, applying catalyst **102**, or **103** did not lead to more than 5% difference in the effectivities. The presence of both hydrogen and methyl as R^1 was tested and proved successful, although methyl had slightly lower results[85].

2.3.2 As a Photocatalyst



Scheme 21 A light-mediated novel method for synthesis of 2,3-disubstituted coumarins

A visible-light-promoted ruthenium-catalyzed radical method for synthesizing 3-functionalized coumarin derivatives was reported by *Weiwei Zhang* research group in 2016 (Scheme 24). The group coupled aromatic ethers **105** (important to have α-hydrogen) with alkynoates **104** in the presence of $Ru(bpy)_3Cl_2$ as photo-redox catalyst, TBHP (tert-Butyl hydroperoxide) **107** as oxidant and CH_3CN as solvent in argon atmosphere under 34W blue LED. According to the proposed mechanism, primarily under the effect of LED light the Ru(II)-based photo-redox catalyst converted to the excited state and underwent a single electron-transfer (SET) with TBHP to produce t-BuO radical, OH^- and Ru(III). This readily active radical absorbed a hydrogen radical from ether **105** which attacked the triple bond on the carbon adjacent to the carbonyl group to give the radical **108** (Figure 14). Subsequently, a radical cyclization happened to produce radical **109**, which in an electron-transfer process with Ru(III) formed carbocation **110**. This carbocation has formed the final product by reacting with OH^- ion.

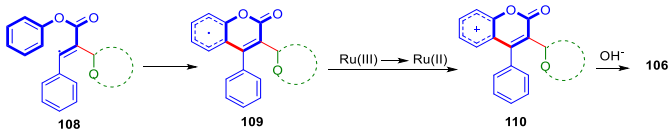


Figure 14 The process proceeded with assistance of ruthenium as oxidative catalyst

Regarding the generality of the reaction, *Zhang* group reported that various phenyl-3-arylpropiolates were tested and all reacted adequately. Among these reactants, *para*-substituted

ones had the best efficiencies and *ortho*-substituted ones had the least. EDGs, di-substitutions and halogens were well-tolerated. Also, bulky groups like t-Bu and i-Pr at the *para* position led the reaction to higher effectivities. Inserting *para*-methylphenyl, *para*-methoxyphenyl, *para*-cholorophenyl and 2-thiophen as R^2 was also a successful attempt and the reaction of these substrates gave up to 75% yield. Different ethers also were tested and proved successful in this protocol. Diethylether, tetrahydropyran, 1,4-dioxane and 1,3-dioxolane gave the corresponding product with high regioselectivity, while 1,2-dimethoxyethan gave two regioisomers **111** and **112** with a ratio of 1:0.65[86].

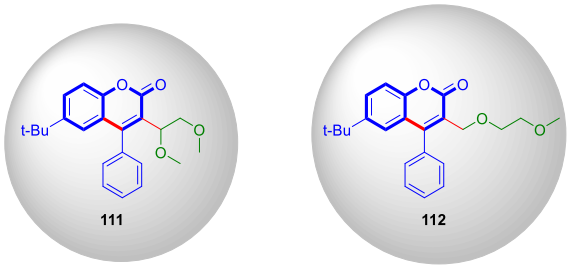
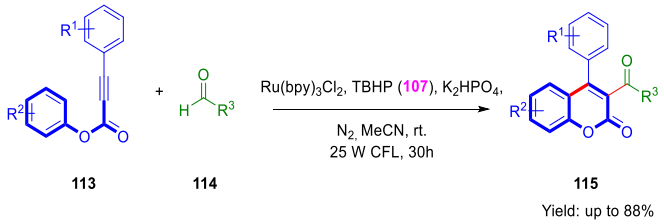


Figure 15 1,2-dimethoxyethan can cause in two regioisomers as the final product



Scheme 22 Ruthenium-catalyzed coupling of phenyl propiolate **113** and aldehydes in nitrogen atmosphere to produce 3-arylcoumarins

Another very similar ruthenium-catalyzed method was reported in 2018 by *Chao Jiang* and his group with ruthenium complexes as photocatalyst (Scheme 25). In this protocol, phenyl propiolate **113** was coupled with aliphatic or aromatic aldehyde **114** in the presence of $Ru(bpy)_3Cl_2$ as photocatalyst, TBHP **107** as oxidant, K_2HPO_4 as base and MeCN as solvent under nitrogen atmosphere in ambient temperature and under visible-light to produce 3-acylcoumarins **115**. It is noteworthy that the presence of photo-redox catalyst, oxidant, base and light source was necessary for this transformation. In this case as well, the substrates underwent a radicalization/5-exo cycle/ester migration to produce the final product and yields up to 88% were produced.

To examine the substrate scope, various aldehydes were tested with phenyl 3-phenylpropiolate under the optimized conditions. All of them fashioned the desired product with good yields in a range of 38-75%. Aromatic aldehydes such as benzaldehyde and 2-naphthalene aldehydes created the product with average yields 61% and 48%, respectively. Methyl-substituted benzaldehyde was well-tolerated and yielded 76%. However, this synthetic method performed poorly when ethyl- or isopropyl-substituted benzaldehydes were used. Also, chlorine and fluorine substitutions in *para* position of benzaldehyde were well-tolerated and produced moderate efficiency. Finally, cyclic, long-chained linear, and short-chained linear aliphatic benzaldehydes were examined and all produced good yields. A small decrease was observed when cyclopentanal was applied to the reaction.

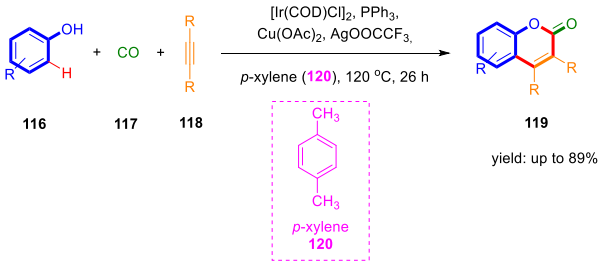
The scope of propiolates was also tested, and It is reported that phenyl and naphthalene both were able to act well as either R^1 or R^2. Generally, on propiolates, electron-donating groups were more successful than electron-withdrawing ones[87].

2.4 Iridium-catalyzed synthesis of coumarins

Iridium-catalyzed cross-coupling reactions provide valuable pathways for the formation of new carbon–carbon and carbon-heteroatom bonds under oxidative condition in the presence of nitrogen and/or oxygen directing groups.

Iridium-catalyzed reactions normally proceed *via* one of the two probable methods: 1) C–H bond activation by formation of C–Ir bond. Iridium-catalyzed C-H activation can go through Ir(I)-r(III) cycle, Ir(III)-Ir(V) cycle, or non-oxidative C–H activation by metalation-deprotonation (CMD) processes[88,89]. This mechanisms start with oxidative addition of C-H bonds to iridium(I) or iridium(III) followed by reductive elimination of the final product and regression of the active catalyst to restart the catalytic cycle. 2) Iridium is one of the most well-established photo-redox catalysts, and some of its complexes like tris[2-phenylpyridinato-C2 ,N]iridium(III) have been widely studied in this area. Using iridium complexes as photo-redox catalyst is attracting many attentions recently because of its low economicy and environmental friendliness. Iridium absorbs light in the visible region and participates in SET processes with organic substrates[90,91,92]. Following, we investigated recently-reported reactions hiring iridium as either direct catalyst or photo-catalyst.

2.4.1 As a Direct Catalyst



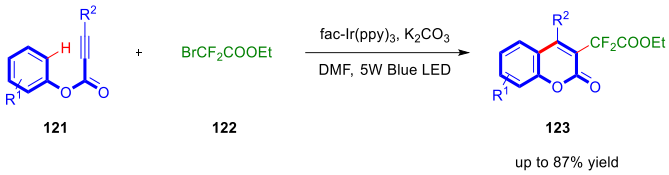
Scheme 23 Iridium can also act as an active catalyst to produce coumarins

A metal-catalyzed C(2p)-C(sp^2) coupling/C-H activation reaction on phenols was proposed by *Wu et al* in 2016 aiming to reach coumarin moiety (Scheme 26). In this method, they carboxylized phenols **116** with CO gas **117** and acetylene **118** in the presence of $[Ir(COD)Cl]_2$ and PPh_3 as catalytic system,

$Cu(OAc)_2$ as co-catalyst and $AgOOCCF_3$ as oxidant in *para*-xylene **120** and 120 °C for 26 hours. In this method activation of O-H bond, activation of C-H bond, C(benzene)-C(acetylene) coupling, and insertion of CO, all happened with the catalytic help of iridium and during ligand exchanges on it's complex.

The reaction proved repeatable by being applicable for synthesis of more than fifteen coumarin derivatives in up to 90% yields. substituents on both acetylene and phenol were perfectly tolerated. Both aromatic and aliphatic internal alkynes were able to be converted to their corresponding products. Unsymmetrical alkynes were also tested and proved thriving. In all these cases, good to excellent yields and regioselectivities were obtained. The scope of the phenols was also tested, and it was observed that the reaction is compatible with both EDGs and EWGs on phenols. However, terminal alkynes were not suitable for this procedure[93].

2.4.2 As a Photocatalyst



Scheme 24 Iridium acting as photocatalyst for intermolecular annulation of aryl propiolates

In 2015, a visible-light-mediated radical mechanism to synthesize coumarin derivatives **123** was reported by *Mei Zhu et al* (Scheme 27). The group used fac-$Ir(ppy)_3$ as catalyst, K_2CO_3 as base and DMF as solvent under 5W blue LED. In this mechanism, various alkynoates **121** were attacked on their triple bond carbon by CF_2COOEt radical (previously produced by excited Ir(III)) to produce radical **124**, followed by cyclization of the radical, converting it to carbocation **126** by an electron-transfer with Ir(IV) and further absorption of H^+ by the base which led to the production of the final product.

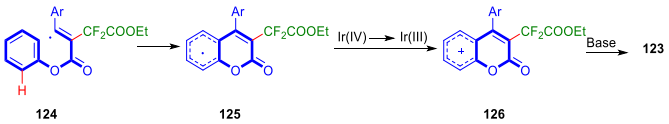
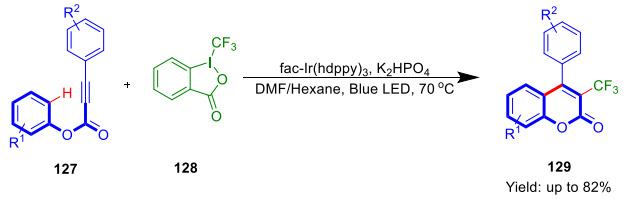


Figure 16 Radical mechanism proposed by *Zhu* group for reaction **27**

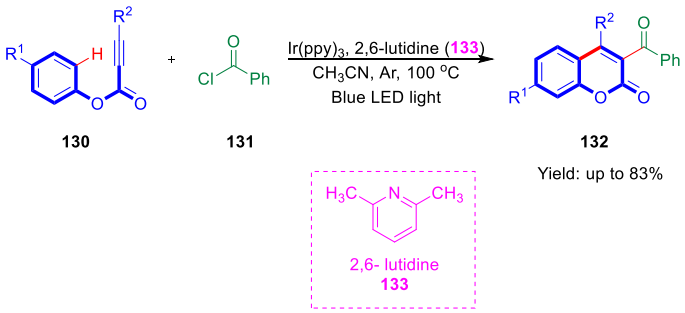
Among all alkynoates used, those substituted with halogens, t-Bu, methyl, Ph, OCH_3 and OCF_3 in *para* position of phenol moiety yielded the corresponding product in moderate to good yields. it is noteworthy that the best yield belonged to OMe and the least to iodine. Alkynoates with *ortho*-substituent did not produce any results. Regarding the R^2 position, it is reported that methyl was not a suitable substituent, but phenyl and its *para*- and *meta*-substituted derivative, with Me, halogens and phenyl were suitable[94].



Scheme 25 Fac-Ir(hdppy)3 in the presence of LED light can assist in the formation of coumarin from aryl propiolate

Duan and *Li* research group in 2018, introduced a visible-light photo-redox-catalyzed method for synthesizing coumarin derivatives (Scheme 28). fac-tris(heptadecanyl-2-phenylpiridine)iridium, used in this method as photo-redox catalyst, was synthesized starting from $IrCl_3$ and 4-methyl2-phenylpyridine. The details of this mechanism will not be related to the subject of this study. The synthesized fac-tris$(hppy)_3$ Was solved in hexane and added to DMF containing **127** and **128**, in hot water bath heated to 70 °C. Also, K_2HPO_4 was added as base, and the reaction was conducted under blue LED.

Researches on the scope of this reaction showed that, moderately electron-donating and electron-withdrawing groups on both R^1 and R^2 positions yielded the corresponding product with up to 82% effectivity. However, the presence of chlorine or bromine on aromatic rings was not in favor of the reaction's effectivity[95].



Scheme 26 Another example of converting aryl propiolates to coumarin using Ir-catalyzed light-assisted mechanisms

In 2018, *Liu* and *Tang et al.* suggested a new visible-light-mediated method to synthesize 3-acylcoumarine **132** derivatives (Scheme 29). In this method, one-pot radical cyclization of alkynoates **130** with acyl chlorides **131** happened in the presence of iridium salts as photocatalyst, 2,6-lutidine **133** as additive, and acetonitrile as solvent under argon atmosphere and Blue LED light for 24 hours. The author has collected evidence proving that the presence of $Ir(ppy)_3$ and light is both essential for the reaction to be completed. Furthermore, the scope of the reaction was investigated with various aryl 3-phenylpropiolate and acyl chloride derivatives. The results showed broad tolerate of substituents on aromatic ring of **130**. In this position, electron-donating groups produced better yields than electron-withdrawing ones. Various derivatives of **131** were also hired, showing that electron-donating and electron-withdrawing groups both can be suitable

substituents. However, the reaction showed better results in the presence of electron-rich aroyl chlorides. 4-nitrobenzoyl chloride was not successful in this reaction.

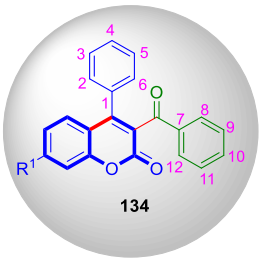
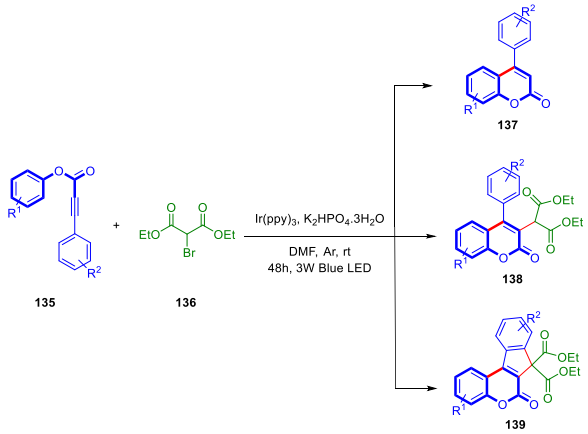


Figure 17 methyl substituents on C4, C5, and C2 has reduced the efficiency

The steric effects were also examined. The result showed that *ortho*-substituted alkynoates cannot perform well in this condition. Another example of steric hindrance effect was shown as follows: the efficiency of producing **134** (Figure 17) was decreased respectively when a methyl was placed on position 4 (83%), 5 (77%) and 2 (70%). The same goes with products with methyl group on position 10 (82%), 9 (78%) and 8 (72%)[96].



Scheme 27 A non-selective iridium-catalyzed method for intramolecular annulation of aryl propiolates

Kim, *Wu,* and their co-workers in 2012 introduced another radical cyclization of phenyl propiolates **135** with diethyl bromomalonate derivatives **136** (Scheme 30). This reaction was proceeded in the presence of $Ir(ppy)_3$ as both photocatalyst and oxidant, $K_2HPO_4.3H_2O$ as base, and DMF as solvent in argon atmosphere and ambient temperature under the effect of blue LED for 48 hours. The author has mentioned that the reaction failed in the dark, which is an illustration of the importance of light in starting the radical cycle. Also, to witness the proposed mechanism, testing reactions were performed in the presence of radical scavengers like TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl oxyl)) **140** or BHT (butylated hydroxytoluene) **141** and no product was observed.

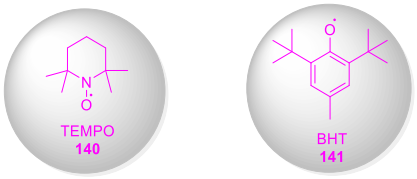
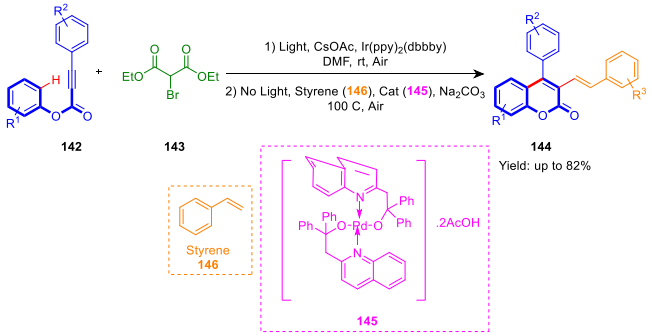


Figure 18 structures of two radical-scavengers BHT **141**, and TEMPO **140**

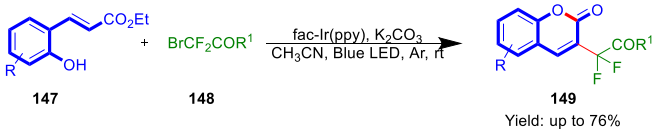
The scope of the reaction was also investigated, in most cases of which only products **139** and **137** were observed. The reaction showed perfect tolerance to both electron-withdrawing and electron-donating groups on the *para* position of the starting phenyl propiolate's phenolic ring, with EDGs favoring formation of **139** and EWGs for **137**. However, replacing the ring's *ortho* hydrogen with chlorine group was not a successful attempt. Also, *meta*-substituted phenolic ring on the phenyl propiolate produced lots of side products and reduced the efficacy of each product. Also when using phenyl propiolates with *para*-substitutions on the phenyl ring adjacent to the triple bond, the corresponding product was produced in good yields and better selectivity[97].



Scheme 28 A two-step light-mediated method for synthesis of highly-conjugated coumarin derivatives

A very similar two-step method for synthesizing 3-styryl coumarins **144** from aryl alkynoates **142**, diethyl bromomalonate **143** and styrene, in two steps, was found by *Li* and *Yin et al*. in 2019 (Scheme 31). The two steps performed were 1) a light-driven radical cyclization 2) a Pd-catalyzed cross-coupling in the absence of light.

The generality of this reaction was also examined. Various electron-donating, electron-withdrawing and halogen substituents on *para* and/or *meta* position of phenoxy ring of **143** were well-tolerated, although strong EWGs like CF_3 reduced the efficiency to a noticeable extent. Regarding the scope of aryl alkynoates also, it is reported that the presence of EWGs on the alkynyl phenyl produced higher effectivities than that of EDGs. Multiple derivatives of styrene bearing electron-withdrawing or electron-donating groups were also applied to the reaction. The result showed that regardless on the electronic activity of the substituent, styrenes **146** will act adequately in this process[98].



Scheme 29 Another example of light-mediated iridium-catalyzed coumarin synthesis introduced by *Xiang* and *Yang* research group

Hao-Yue Xiang, *Hua Yang,* and their co-workers in 2019 coupled *ortho*-hydroxycinnamic esters **147** with $BrCF_2COR^1$ **148** *via* a photo-redox-catalyzed cascade reaction in one-pot to produce 3-fluoroalkylated coumarins **149** (Scheme 32). This method is more facile and economic than the previous methods of reaching coumarin derivatives from *ortho*-hydroxycinnamic esters in harsh condition, because of using photoredox radical starter.

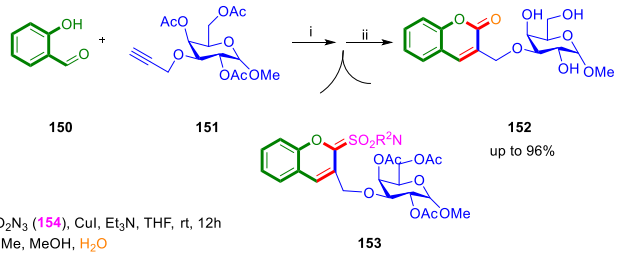
As for the studies of the scope, this reaction was examined with various functional groups on both starting materials. All *ortho*, *meta* and *para* positions of the phenol moiety of *ortho*-hydroxycinnamic esters were substituted and examined in the reaction. The results showed that methoxy substitution at the *para* position lowered the efficiency of producing coumarin, while other substitutions produced the result in moderate to good yields. Disubstituted **147**s were also applied to the protocol and performed successfully. Bromodifluoroamides and 2-(bromodifluoromethyl)benzoxazoles were also tested, but they participated in the reaction with efficiencies less than 51%.

Scheme 30 Attempting the same method for synthesis of perfluoroalkyl **149** derivatives

Synthesis of 3-perfluoroalkyl coumarins is also possible using this method (Scheme 33). This method was tested with various perfluoroalkyl halides such as CF_3X, C_4F_9X, $C_6F_{13}X$, $C_8F_{17}X$ and $C(CF_3)_2F$ and producecd up to 80% effectivity[99].

2.5 Cupper catalyzed synthesis of coumarins

Cupper-catalyzed C–H functionalization methods have recently been recognized as an important pathway for formation of C-C and C-Heteroatom (C-N, C-O, C-X, C-P, C-S, ….) bonds. Cupper-based catalysts can assist in activation of C(sp)–H, $C(sp^2)$–H, and $C(sp^3)$–H bonds to produce various forms of new bonds[100]. Early studies proposed that Cu-catalyzed reactions for synthesis of heterocycles proceed via either a one-electron electron transfer, a two-electron electron transfer, or a combination of one and two-electron electron transfer processes[101]. Even with the wide and very beneficial applications of second-row metals like Palladium, cupper still holds its role in organo-metallic synthesis [102]. Followed, the authors have described more



Scheme 31 Metal-catalyzed fusion of coumarin moiety to carbohydrates

recent reports of Cu-Catalyzed C–H Functionalization to construct substituted coumarins.

In 2014, a biological modification/fused coumarin synthesis was done by *Mukhopadhyay et al.* (Scheme 34). In this method, the group synthesized coumaryl-substituted glycoside derivatives *via* a cupper-catalyzed multi-component reaction between glycoside propargyl **151**, salicylaldehydes **150**, and tosyl azides **154** (Figure 19) followed by a final hydrolysis in the presence of methanol, NaOMe and water. This multi-component reaction was advanced with the help of CuI as catalyst, triethylamine as base and THF as solvent in room temperature. Reportedly, the iminocoumarin glycoside **153** could be separated from the mixture of reaction i easily. Also, the hydroxylised imminocoumarin glycoside **155** (Figure 19) can be produced from treatment of **153** with very diluted mixture of MeOH and NaOMe in the absence of water.

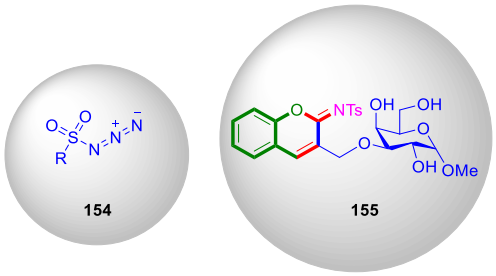
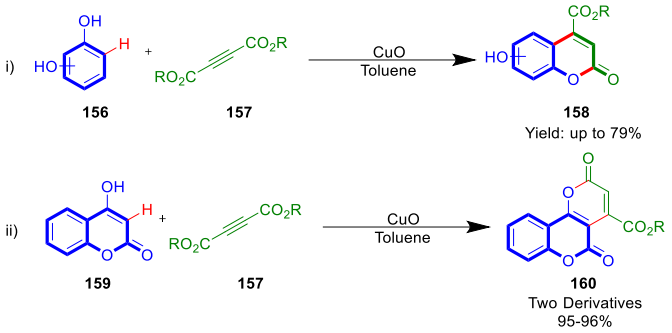


Figure 19 hydroxylised imminocoumarin glycoside **155** can be produced from treatment of **153** with very diluted mixture of MeOH and NaOMe in the absence of water

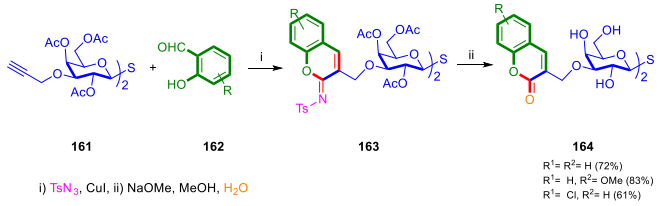
The reaction was also performed with various other carbohydrate propargyls and other tosyl azides and proved repeatable with up to 88% effectivity[103].

In 2014, *Maiti et al*. suggested a method for synthesis of polyhydroxy coumarins **158** using catalytic cyclization of polyhydroxy phenols **156** with alkynes (Scheme 35, i). In this mechanism, cupper oxide is used as a commercially available catalyst in toluene under reflux. The same method can be used for synthesis of alkyl 2,5-dioxo-2,5-dihydropyrano[3,2-c]chromene-4-carboxylate derivatives **160** from 4-hydroxy coumarin **159** (Scheme 35, ii).



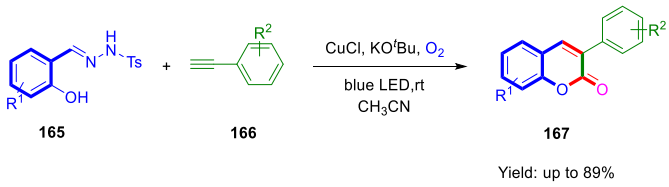
Scheme 32 Synthesis of polyhydroxy coumarins **158** and alkyl 2,5-dioxo-2,5-dihydropyrano[3,2-c]chromene-4-carboxylate **160** derivatives by a cupper-catalyzed method

Maiti research group investigated the scope of reaction (i). It can be inferred from the efficiencies, that the presence of electron-donating groups and the lack of electron-withdrawing groups on **156** as well as presence of less electron-donating groups on **157** can increase the yield[104].



Scheme 33 A series of tandem reactions to produce coumarin-fused carbohydrates introduced by *Nilsson et al*.

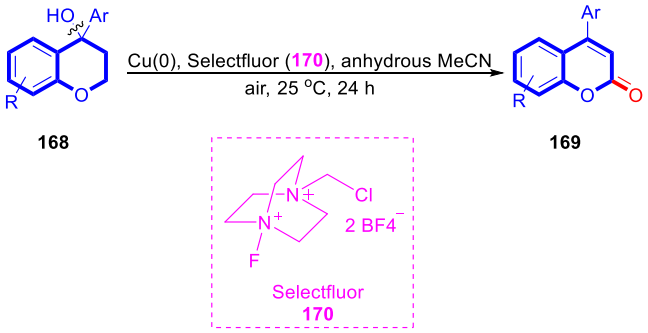
Nilsson and his co-workers in 2016 reported a synthetic method for 3-*ortho*-coumarinmethyl substituted thiodigalactosides **164** from bis-3-propargyl-thiodigalactoside **161** and salicylaldehyde **162** (Scheme 36). This two-step method was able to produce three different derivatives if **164** in up to 83% yield. In the first step, two substrates were coupled in the presence of TsN_3 and CuI in a solvent-free mechanism. *Via* this step, the propargyl moiety of the galactoside **161** took part in an oxidative addition/condensation to produce **163**. In the second step, in the presence of base NaOMe and solvent MeOH, water hydrolyzed the amine moiety to carbonyl to give the final coumarin[105].



Scheme 34 Cupper-catalyzed oxidative coupling of N-tosylhydrazone **165** and terminal alkynes **166**

In 2013, *Hwang* and co-workers performed a quiet novel cupper-catalyzed cyclization to produce 3-arylcoumarin derivatives choosing N-tosylhydrazone **165** and terminal alkynes **166** as substrates (Scheme 37). In this protocol, cupper chloride was used as catalyst, potassium tert-butoxide as base, molecular oxygen as oxidant, and acetonitrile as solvent under blue LED in ambient temperature; and up to 89% effectivity was obtained. The mild condition, reasonable effectivity and lack of the need for pre-protecting the hydroxyl group made this method advantageous.

Testing the scope of the reaction proved its compatibility to strong electron-donating groups like OMe, and strong electron-withdrawing ones like CF_3 on the phenyl group of phenyl acetylenes used. Replacing the phenyl group with other aromatic groups like pyridine, pipyridine, and thiophen was also a successful attempt, and the desired products were produced in good yields. The group also used naphthalene-based N-tosylhydrazones with various phenyl acetylenes and the result was satisfying[106].



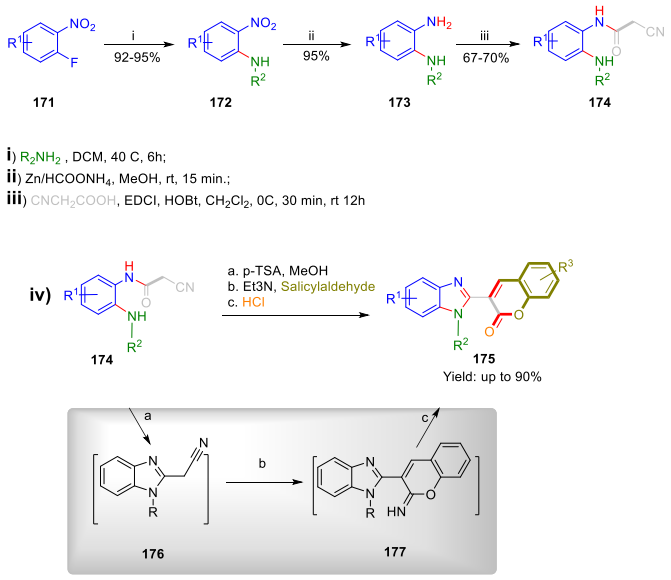
Scheme 35 Dehyroxylation/oxidation of oxabenzocyclohexanol in the presence of selectfluor to produce coumarin moiety

In 2015, a cupper-catalyzed dehyrogenative oxidation was performed on oxabenzocyclohexanol derivatives **168** to produce 4-arylcoumarins **169** (Scheme 38). In this method Cupper in its base oxidation level was used as catalyst, along with selectfluor **170** as oxidant. The reaction was proceeded in anhydrous MeCN as solvent, in air and ambient temperature.

The method was successful for synthesis of 12 different derivatives of 4-arylcoumarin **169**, substituted with alkyls, phenyl, and chlorine. Substituents on both aromatic rings of **168** were compatible. The best results were obtained in the presence of chloro group on the aromatic ring of coumarin. Also, the group has reported one example of synthesizing thia-4-arylcoumarin with 51% effectivity[107].

2.6 Zinc catalyzed synthesis of coumarins

Zinc salts are mostly known for being used as additives in C-H activation reactions catalyzed by other transition metals and for activating the electrophilic sites. However, they can also be employed alone or in combination with organometallic compounds as catalysts for C-C bond formation and/or cross-dehydrogenative couplings reactions [108,109]. In this regard we refer to some publications using Zn salts as direct catalysts.

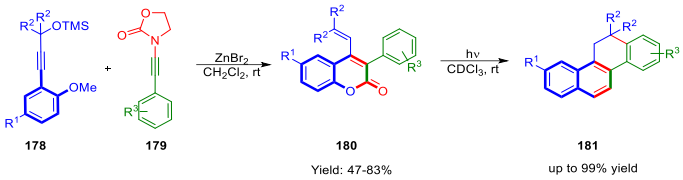


Scheme 36 synthesis of highly practical benzamidazol-linked coumarins *via* a series of tandem reactions

In 2017 *Yao et al.* worked on a diversity-oriented tandem synthetic method for benzamidazol-linked coumarin derivatives *via* a one-pot, four-step sequential method (Scheme 39). Through the first two steps, diaminobenzene **173** was synthesized from the reaction of o-nitrofluorobenzene **171** with amines in DMF at 40 °C for 6 hours, followed by reduction of nitro group by zinc /ammonium formate in methanol at ambient temperature in 15 minutes. In step **iii**, synthesis of N-(2-aminophenyl)-2-cyanoacetamides **174** from diaminobenzene **173** was done through a regioselective condensation in the presence of cyano acetic acid, EDCI, and HOBt in CH_2Cl_2 at 0 °C for 30 minutes and then in room temperature for 12 hours. Finally, an intramolecular cyclization of N-(2-aminophenyl)-2-cyanoacetamide **174** in the presence of PTSA (to give benzimidazole in situ), followed by a Knoevenagel condensation with salicylaldehyde (as the key step for synthesis of coumarin), and an acidic hydrolysis was performed and produced benzimidazole-linked coumarin **175**.

In more details, in the final step, **174** went through a dehydrative intramolecular cyclization reaction in the presence of PTSA in methanol at 50 °C within 4 hours to produce intermediate **176.** A subsequent nucleophilic addition with salicylaldehydes in the presence of Et_3N yielded intermediate **177** in 5 hours. Adding HCl to the same mixture and stirring for 2 hours afforded the final product **175** with 88% yield.

The group explored the scale of the reaction **iv** by using it in synthesizing various benzimidazole-linked coumarin derivatives. Various aliphatic substituents like long-chained and cyclic alkyls, benzyl, furan-2-ylmethyl, acetoxy alkyls, and hydroxyl alkyls were positioned on the amine and led to corresponding products. Substituents like COOMe and chlorine were perfectly tolerated on the starting *ortho*-nitrofluorobenzene. Additionally, electron-withdrawing substituents like NO_2, and electron-donating ones like Me or OMe on the salicylaldehyde's phenyl ring were both well-tolerated[110].



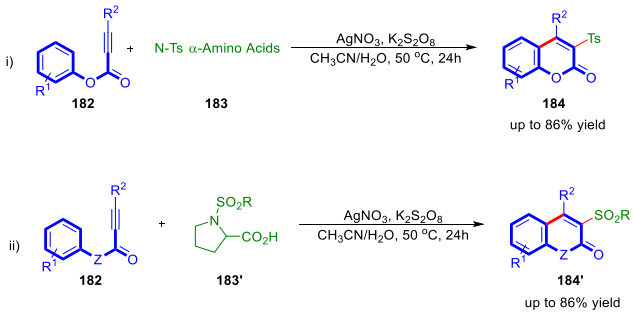
Scheme 40 An example of application of cycloaddition in producing coumarin motif

In 2016, *Zhan-Jiang Zheng*, *Li-Wen Xu* and their co-workers proposed a novel method for the synthesis of polycyclic coumarins **181** *via* a carbocation-initiated [4+2] cycloaddition followed by a photo-irradiated cyclization (Scheme 40). This protocol successfully gave the final product with up to 99% effectivity by using $ZnBr_2$ as Lewis acid and CH_2Cl_2 as solvent for the first step and UV photo-irradiation in $CDCl_3$ in room temperature for the second one.

To test the generality, this reaction was performed with various derivatives of propargyl silyl ether and ynamide. The [4+2] cycloaddition successfully proceeded with 16 different derivatives. The result showed that electron-donating groups like Me and OMe along with halogens were well-tolerated. replacement of ynamide's phenyl group with naphthalene, normal butyl and cyclopropyl gave **180** in respectively 69%, 56%, and 47% yields although they are not capable of running the second step to produce **181** derivatives. The photo-irradiated formation of polycyclic coumarins was also successful with **180**s substituted with Me, OMe, and halogens[111].

2.7 Silver catalyzed synthesis of coumarins

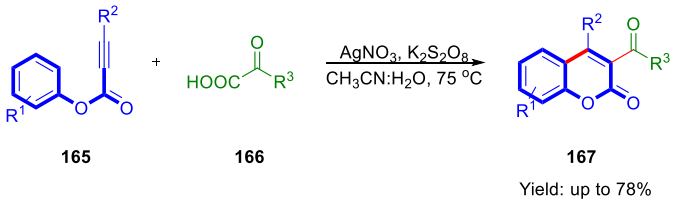
Within the last few years, silver, as a cheaper catalyst compared to other transition metals, has rapidly opened its way into the novel synthetic methods and research works on functionalization of C(sp^3)-H, C(sp^2)–H, and C(sp)–H bonds. Silver has proved strongly applicable for C-C bond functionalization by cleavage of strained and unstrained ring systems. silver-catalyzed C–H bond cleavage for formation of C–N, C–C, C–S, C–halogen, C–P, C–B, C–O, and C–Se bonds has been widely used in organic transformations. The mechanism studied indicated that a radical-chain mechanism may be involved in most of the transformations[112,113].



Scheme 37 Silver was used in the popular metal-catalyzed intramolecular annulation of phenyl propiolates in 2018

In 2018, *Shibata* group tried to introduce α-amino acid sulfonamides **183** as a sulfonylation agents in a procedure that led to formation of sulfonylated coumarin derivatives **184** (Scheme 41). The optimized condition of this reaction is $AgNO_3$ as catalyst, $K_2S_2O_8$ as base and a mixture of acetonitrile and water as solvent with 50 °C temperature within 24 hours. This radical cyclization is explained by the research group through radicalization of the amino acid in the presence of silver salts and further addition of **182** from Z atom, oxidation of the radical to carbocation, and migration of ester group to the α-carbon. Release of H^+ at the subsequent step has led to the final product.

These two reactions were tested with various amino acids and phenylpropiolates. N-Ts proline, and N-Ts 2-methylalanine acted the best among all-natural amino acids used including N-Ts glycine, N-Ts alanine, N-Ts phenylalanine, N-Ts valine, and N-Ts N-methylglycine. By using less amount of catalyst, higher amounts of amino acid and more time, the reaction of N-Ts proline was able to produce higher efficacy. Regarding reaction **ii** in (scheme 41), the scope was explored as well. Numerous substituents on the phenyl ring of phenyl propiolate were tested and the result showed that *ortho*-, *meta*- and *para*-methyl and *meta*-tBu, *meta*-flouro, and *meta*-CO_2Me can be effectively hired as propiolate substituents. In the place of R^2, naphthalene, phenyl, *para*-chlorophenyl, *para*-phenylphenyl, phenyl and Me were suitable to be used. Among the later mentioned, phenyl- and methyl-substituted phenylpropiolates were not able to afford the desired product in more than 30% yield. The scope of sulfonamides was also investigated. Among aromatic ones, those with *para*- or *meta*-substituents, whether electron-donating or electron-withdrawing were more thriving in the protocol than those of phenyl itself or *ortho*-substituted phenyl. Among aliphatic sulfonamides, benzyl sulfonamide did not act well (less than 5% effectivity) and methyl sulfonamide and isopropyl-sulfonamide produced the corresponding products in less than 50% yield[114].



Scheme 38 Another silver-catalyzed radical cyclization of alkynoates **165**

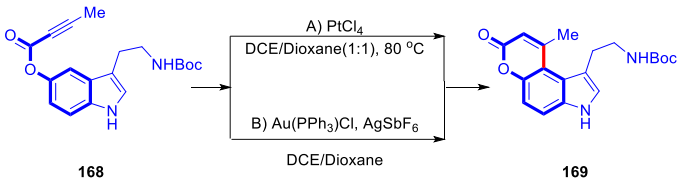
Another radical cyclization of alkynoates **165** was performed by *Hua Wang et al*. in 2015 using silver salts as the starter of radical cycle by radical decarboxylation of α-keto acids **166.** In this method 3-acylcoumarin derivatives **167** were produced in the presence of $AgNO_3$ as catalyst, $K_2S_2O_8$ as oxidant, and a mixture of acetonitrile and water as solvent heated up to 75 °C. The radical mechanism was proved when no product was achieved in the presence of radical scavengers like TEMPO **140** or BHT **141**.

The mechanism proved successful for synthesis of more than 20 different 3-acylcoumarins. The alkynoate's phenyl ring was substituted with alkyls like methyl, halogens like chlorine and bromine, and strong electron-withdrawing group CF_3, successful in producing the result in all cases. Also, alkynoates with unsubstituted or *para*-halo-substituted phenyl rings on their triple bond were used in the protocol and proceeded to the corresponding product. Furthermore, several aromatic α-keto acids with substitutions in all the positions of their phenyl ring were tested and produced moderate yields. on the other hand, aliphatic α-keto acids were not as successful and produced ignorable low yields. The reaction of phenyl methyl propiolate did not lead to the corresponding product, presumably because it lacked the aromaticity needed to stabilize the radical intermediates[115].

2.8 Other transition metals for synthesis of coumarins

In the recent decade, many metals other than above-mentioned ones, including Pt, Au, Fe and Co were used to perform C-H bond activation/functionalization for synthesize coumarin derivatives[116,117].

For instance, *Dalibor Sames and Paul A. Vadola* in 2012 produced fused coumarin derivatives from aryl alkynoate esters **168** using metal-catalyzed intramolecular coupling of C-H bond and triple bond (Scheme 43). The research group screened a range of metal complexes to find the best catalytic system. Accordingly, palladium was not a suitable catalyst for this procedure, but the reaction was able to progress well using both platinum and gold as catalyst (Condition **A** and **B**).



Scheme 39 Platinum can also act as an effective catalyst to synthesis coumarin derivatives

It is reported that the optimized conditions for platinum-catalyzed pathway was using of a 1:1 mixture of DCE and dioxane as solvent without any extra additive or oxidant. On the other hand, gold-catalyzed method needed a silver salt as oxidant, so the optimized condition went like: Au(PPh3)Cl as catalyst, $AgSbF_6$ as oxidant, and a mixture of DCE and dioxane as solvent. The group has also mentioned that NHBoc as an electron-rich substituent had no directing effect and was not necessary, although the reaction went on with perfect regioselectivity, showing that coordination of the metal produced intermediate **170** and not **171** (Figure 20).

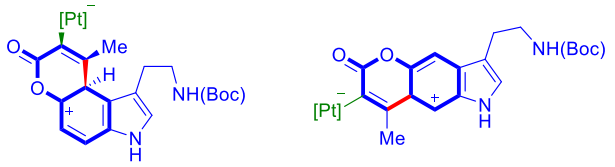
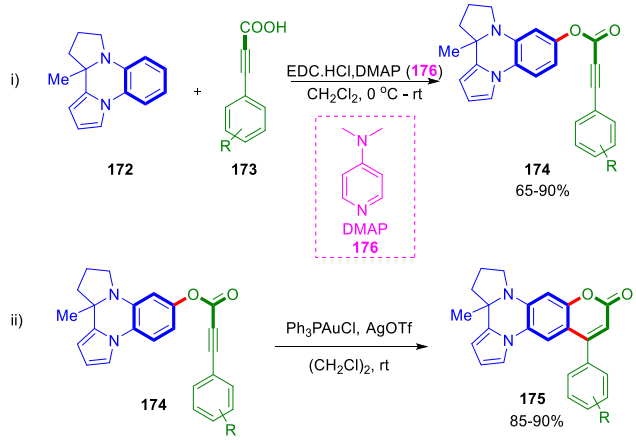


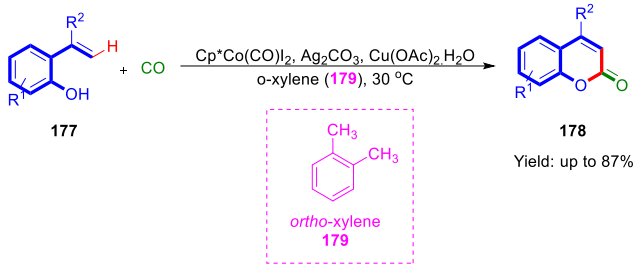
Figure 20 Regioselectivity of the reaction **43**

The scope of the reaction was examined with both indole-derived aryl alkynoate esters and aniline derived alkynoate ethers **168**. In most cases, the result was obtained in more than 50% yield. However, in some cases, the desired product was obtained in the presence of Au or Pt only. generally, aniline-derived alkynoate ethers possessed higher effectivities in this protocol[118].



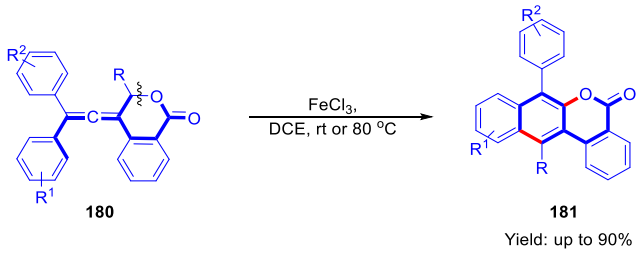
Scheme 44 A two-step gold-catalyzed method for synthesis of fused coumarins

Trying to explore luminescent properties of pyrrolo-quinoxaline embedded coumarin PQC derivatives**175**, *Patil* research group introduced a gold-catalyzed intramolecular hydroarylation to produce them (Scheme 44). The group started from pyrrolo[1,2-a]quinoxalines **172** and propiolic acids **173** in the presence of EDC.HCl to produce the desired alkynoates **174** (Reaction **i**). In this reactio DMAP (4-Dimethylaminopyridine) **176** is used as base and CH_2Cl_2 as solvent in 0 °C. Subsequently at reaction **ii**, the previously produced alkynoates **174** went through an intramolecular C-H activation-cyclization under catalytic effect of gold to produce PQCs **175**. In this second step, Ph_3PAuCl was used as catalyst, AgOTf as oxidant, and $(CH_2Cl)_2$ as solvent in room temperature. The group tested this method using 8 different derivatives of propiolic acid **173** with short-chained and long-chained alkyls, CF_3, OMe, and secondary amines, and achieved the corresponding results in all cases[119].



Scheme 45 Carboxylation of 2-alkeylphenols to achieve coumarin in the presence of cobalt salts as catalyst

In 2015, *Wang* research group introduced a new cobalt-catalyzed method to synthesize coumarin derivatives **178** (Scheme 45). This method included insertion of CO into 2-alkenylphenols **177** in the presence of catalytic amounts of $Cp^*Co(CO)I_2$ as catalyst, Ag_2CO_3 and $Cu(OAc)_2.H_2O$ as oxidant, and *ortho*-xylene **179** as solvent. The group has reported production of up to 87% yield with more than twenty derivatives upon a Co(I)-Co(II) catalytic cycle. Inserting substituents at the *para* position of phenolic moiety of **177** resulted in moderate to good yields. Noticeably, the presence of strong electron-withdrawing groups like NO_2 led to more effective production of the result. Halogens at the same position were also successful, however, electron rich groups like Me and OMe were proven to reduce the effectivity. 2-alkenylphenols **177** with fluorine, methoxy and chlorine substituents *meta* to the phenolic moiety also gave the result in up to 77% yield with again less effectivity in the presence of methoxy. 2-alkenylphenols **177** with multi-substituted phenyl rings were also applied in the reaction condition and the yield was achieved with the least efficacy when the *ortho* position of OH was substituted and OEt is used. Substituents on alkenyl were also tested and both aromatic and aliphatic groups proved effective, with better result for aromatics. EWGs like CN and CF_3 were effective here, but CF_3 with more electron-withdrawing power led to lower result. The group also tested replacing OH with groups like NH_2, NHAc, NHBoc and NHTs to try producing 2-quinolone derivatives but failed to do so. Trying 1,1,2-trisubstituted alkene and 2-allylphenol was also unproductive[120].



Scheme 46 Iron-catalyzed methods can also be used for preparation of coumarin

In 2018, *Hongjun Ren* and co-workers introduced a $FeCl_3$-catalyzed method to synthesize 5H-dibenzo[c,g]chromen-5-ones **181** from 1-isochromanones **180** in dichloroethane. In this reaction, first the cleavage of C-O bond happened in the

presence of $FeCl_3$, making the rotation of phenyl group possible to help it place in a suitable position for reacting with the allylic moiety. A 6π-electrocyclization on intermediate **182** followed by a final aromatization produced the final product **180**.

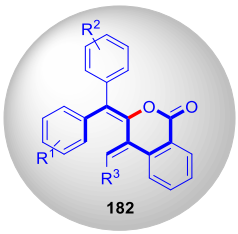


Figure 21 The last step intermediate leading to the final product after a final aromatization

The repeatability of the reaction was also explored. Reportedly, various aromatic and aliphatic groups were able to act well when put in the place of R^3. 1-isochromanones having aromatic rings like thiophene, naphthalene, and 9H-carbazole in the place of R^3, were potential to produce the result in satisfying yields, though not very high for the latter. Testing phenyl rings with substituents of different electron-activity as R^3 had shown that the presence of electron-donating groups on the *para* position of the ring has made the reaction more efficient, and the presence of any group at *ortho* position (obviously because of the steric hindrance) or electron-withdrawing groups at *para* position has lowered the efficacy. Same studies were conducted on the effect of R^1 and R^2 showing that the reaction was able to tolerate substituents at these positions as well[121].

3. Organo-catalyzed synthesis of coumarins

Organo-catalysts have been widely used for regio- and enantio-selective and asymmetric organic transformations in the past few decades. Currently, the organo-catalyzed reactions are one of the frontier areas in the synthesis of chiral molecules. Cost, time, and energy saving; suitable experimental condition; and less waste of reactants are some of the main reasons for rapid expansion of using organo-catalysts in the synthetic methods[122].

3.1 NHCs catalyzed synthesis of coumarins

In 1991, *Arduengo* and co-workers isolated crystalline N-Heterocyclic Carbene (NHC IAd) with extraordinary stability and storability. This new discovery provided a new electronically and sterically stable carbene, in contradiction to the old very active and unstable ones, which subsequently found lots of applications in chemical synthesis[123]. Due to the high electron-richness of NHCs, many of their catalysts have ability to reverse electrophiles (umpolung). NHCs have been broadly used as either direct organo-catalysts or as Ligands in transition-metalcatalyzed reactions. Amongst various types of carbene-based catalysts, carbenes made of imidazolium **183**, thiazolium **184**, imidazolinium **185**, and triazolium **186** are most abundantly found in organocatalyzed processes (Figure 22).

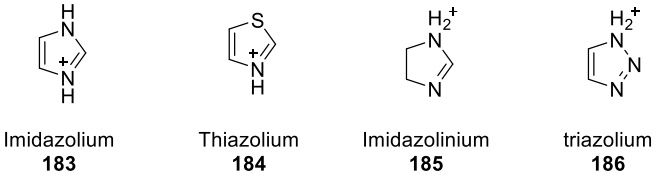
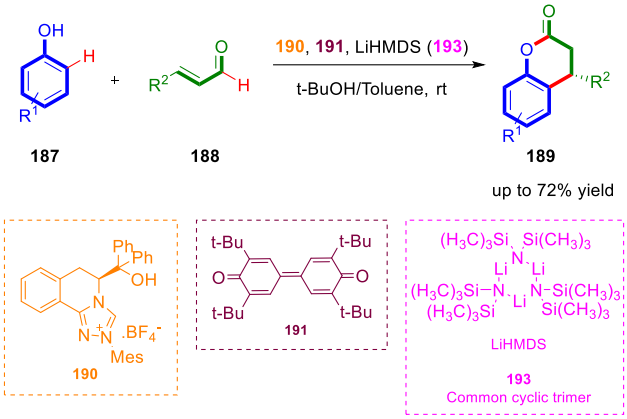


Figure 22 some famous nitrogen-based carbenes

These NHCs are all easy to access/synthesize. for example, condensation of α-chloro ketone with an N-substituted thioformamide is a proven method for thiazoliums synthesis. Preparation of thiazoliums from their corresponding thiazolin-2-thione with hydrogen peroxide under acidic conditions is another example of its synthetic methods. Some of the well-studied reactions employing NHCs as organocatalysts are characterization of the Breslow Intermediate, the benzoin reaction, the Stetter reaction and hydroacylation of double and triple Bonds[124,125].



Scheme 47 Various NHCs can act as organo-catalysts for synthesis of coumarin

Shu-Li You et al. in 2017 reported a carbene-catalyzed annulation reaction on phenols leading to 4-functionalized-3,4-dihydrocoumarins **189** (Scheme 47). In this method, NHC **190** is used as catalyst, 3,3',5,5'-*tetra*-*tert*-butyldiphenoquinone **191** as additive, LiHMDS (Lithium bis(trimethylsilyl)amide) **193** as base and a mixture of *tert*-butylalcohol and toluene as solvent, and the reaction is proceeded in ambient temperature. This condition was successfully used for synthesis of nineteen different derivatives of **189**. Enantioselectivity of the product was negatively affected by the presence of strongly electron-withdrawing group NO_2 in *para* position of cinnamaldehyde. In other cases, almost excellent enantioselectivity was obtained. Moreover, *para*-halogens, Me, NMe_2, COOMe, OMe and hydrogen were all well tolerated on cinnamaldehyde. Regarding the scope of phenols, NMe_2 at *meta* position of phenolic moiety was proved efficient.

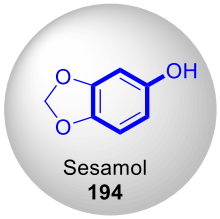


Figure 23 the structure of sesamol

When sesamol **194** (Figure 23) was applied in the reaction condition, 36% of the coumarin derivative was produced with 94% ee.

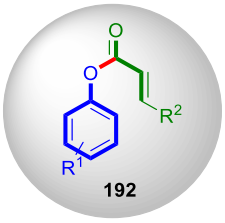
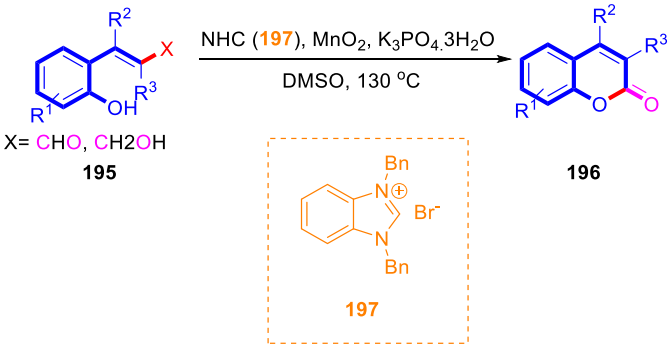


Figure 24 **192** was produced as side product in this procedure

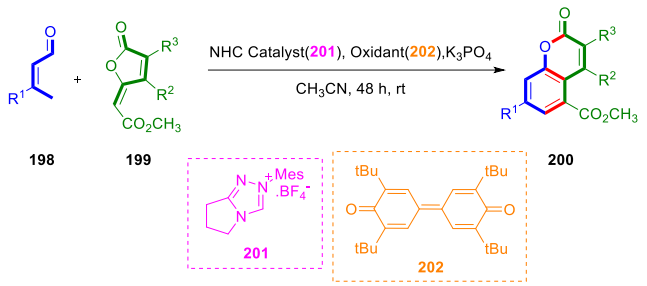
Multi-substitution on phenols was also examined and resulted in the desired products. It is notable that in all the tests, this reaction condition produced compound **192** (Figure 24) as side product[126].



Scheme 48 NHC-catalyzed intramolecular oxidative annulation of 2-vinylphenol **195** derivatives

Once again, an NHC-catalyzed method to synthesize coumarin derivatives was proposed in 2017 by *Kai Guo et al*. This group performed an intramolecular lactonization on *o*-hydroxycinnamaldehyde or o-hydroxycinnamyl alcohol derivatives **195** in the presence of NHC **197** as catalyst, MnO_2 and air as oxidant, $K_3PO_4.3H_2O$ as additive in DMSO. The mechanisms proposed by this group has gone through either formation of a carbanion or an acyl azolium in conclusion of the interaction between substrate **195** with **197**.

The scope of the reaction was also explored using several *o*-hydroxycinnamaldehyde derivatives with multiple substituents on the phenyl ring. Alkyls, alkoxys, phenyl ring, halogens and fused lactone were proved to act as suitable substituents on phenyl ring at all *ortho*, *meta* and *para* positions of phenyl moiety. The presence of EDGs at *ortho* position or EWGs at *para* position decreased the reaction's efficacy. The reaction could also be performed with hydroxycinnamyl alcohol derivatives, with good tolerance of various functional groups on both the aromatic ring and the double bond. In this case, efficiency of reaction was generally lower than that of hydroxycinnamaldehydes, and the presence of EWGs lowered it more intensely[127].



Scheme 49 NHC-catalyzed [5+5]cycloaddition between enals **198**, and furanones **199**

In 2017, *Robin Chi* and his group suggested a carbene-catalyzed [5+5]cycloaddition between enals **198** and furanones **199** to access coumarin derivatives in one-step (Scheme 49). NHC catalyzed this reaction through attaching to the carbon atom in carbonyl bond of enals and replacing the hydrogen atom (Figure 24). In further steps, regioselective 1,6-addition of furanone to the structure, gave intermediate **201**, which released NHC to produce intermediate **202**. subsequent tautomerization of the structure gave intermediate **203** which led to the final product *via* a transesterification and a dehydration.

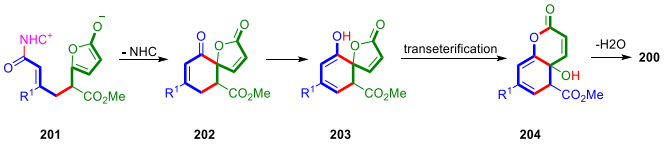
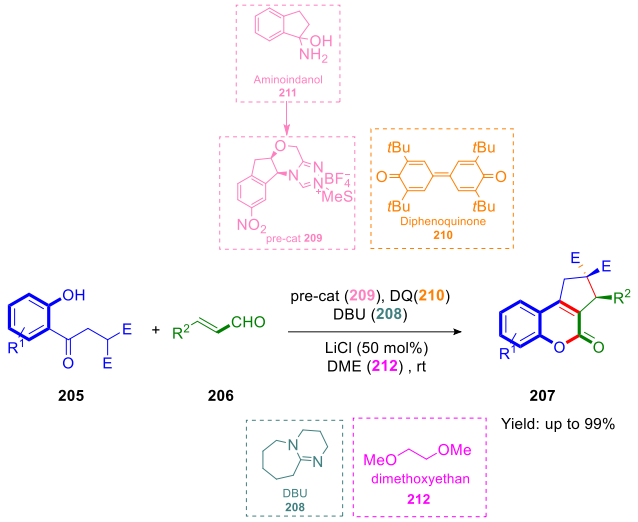


Figure 24 The proposed mechanism for reaction of Scheme 51

The scope of the reaction was also investigated. Reportedly, a variety of substituents were tolerated on both enals and furanones. Both EWGs and EDGs on *para* position of phenyl group on enals acted as adequate substituents, whereas *ortho*-substituents decreased the efficiency to a notable extent, obviously as an effect of steric hindrance. On the other hand, phenyl ring with *meta*-methoxy as R^1 acted better than the one with *para*-methoxy. Hiring 1-furan, 1-pyrol, 3-naphthalene and 2-naphthalene as R^1 was successful and produced the corresponding products with moderate to excellent efficiencies. Non-aromatic substituents like Me and styryl at the same position were also proven effective. Other than furanone itself, furanones with methyl groups as R^2 and R^3 were also able to produce the desired product[128].



Scheme 50 NHC-catalyzed domino reactions to provide tri-cyclic coumarin derivatives by *Enders et al.*

In 2018, *Dieter Enders et al.* worked on NHC-catalyzed domino reactions to provide tri-cyclic coumarin derivatives **207** *via* an α,β-unsaturated acyl azolium intermediate (Scheme 50). In this procedure, the product was achieved through a domino sequence of Michael addition / Aldol condensation / intramolecular lactonization/dehydration. The coupling process of α,β-unsaturated aldehydes **206** and salicylaldehyde esters **205** was performed in the presence of NHC-catalyst **209** (derived from aminoindanol **211**) diphenoquinone **210** as oxidant, LiCl as a cooperative Lewis acid, and DBU (1,8-Diazabicyclo[5.4. 0]undec-7-ene) **208** as the base in DME **212** in ambient temperature, while up to 99% effectivity, and perfect enantioselectivity was obtained. The reaction produced the desired product with TMEDA (tetramethylethylenediamine) **213** (Figure 25) as base, but the best results were achieved with DBU **208**.

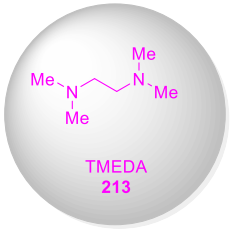
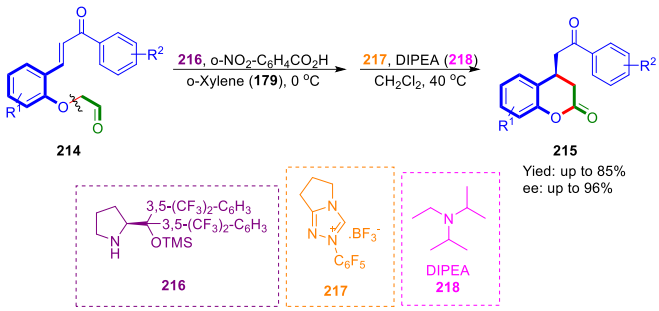


Figure 25 The structure of bulky base TMEDA

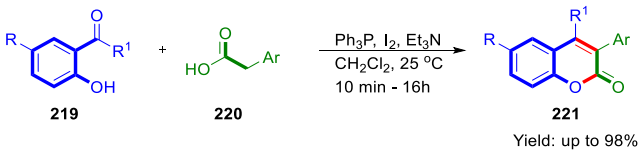
The scope of the reaction was also investigated. It was observed that the procedure was compatible with aromatic and aliphatic substituents on **206**, halogens and alkyls on the benzene ring of **205**, and various esteric moieties as E. CO_2ME, CO_2Et, and CO_2Bn were examined as E, all of which produced the result in excellent yields. Substituents on both *para* and *meta* positions of **205**'s phenyl ring were tolerated, and no meaningful difference existed between their effectivities. Among the halogens replaced as R^1, Cl had the best performance and respectively after that Br, and F. Various α,β-unsaturated aldehydes were tested as well. Hiring ethyl group as R^2 was not successful, however, ethylene and aromatic rings like thiophen, naphthalene, *para*-Cl-phenyl, *para*-Br-phenyl, *para*-N(Me)2-Phenyl, *para*-methoxyphenyl, *para*-methylphenyl, and other aromatic groups all acted efficiently in the reaction's condition[129].



Scheme 51 A multi-catalytic one-pot synthetic method for achieving of 3,4-dihydrocoumarins **215**

In 2012, a multi-catalytic one-pot synthetic method for achieving 3,4-dihydrocoumarins was discovered by *Jorgensen* and his research group (Scheme 51). This method is another good example of vast applications of organo-catalysts in synthesizing coumarin derivatives. Amino-catalyst **216** is reported to be highly potential of inducing enantio-selectivity as an applicable catalyst (along with NHC) to be used for producing enantioselective products in NHC-catalyzed reactions. The optimized condition that the group proposed was *ortho*-nitrobenzoic acid in catalytic amount, in *ortho*-xylene **179** in 0 °C for the first step, enantioselective 1,4-addition, with **216** as amino-catalyst. The second step has had its best result with DIPEA (N,N-di-isopropylethylamine) **218**, **217** as catalyst, and CH_2Cl_2 as solvent in 40 °C. The reaction was performed using various derivatives of **214**. Reportedly, *para*-OMe, Br, and F as R^2 can act as successful substituents along with *meta*-flouro although they produce less efficiency than the simple **214**. Also, *meta*-flouro substituted **214** produced the result with respectively lower enantioselectivity (70%). *para*-hydrogen of the phenolic moiety of **214** can be replaced with strongly EWG NO_2 to produce the corresponding result in 41% yield. Bromine also was able to act as a useful substituent at the same position. Additionally, *meta*-OMe and 3,5-dimethoxy substituents on the same ring did not lower the efficiency nor the enantioselectivity, but *ortho*-methyl apparently because of the steric hindrance it has, has lowered the enantioselectivity to a great extent[130].

3.2 Other Organo-Catalysts



Scheme 52 Triphenylphosphine can act as organo-catalyst and assist formation of coumarin derivatives

Phakhodee's research group in 2017, synthesized coumarin derivatives *via* a two-step one-pot mechanism catalyzed by triphenyphosphine and iodine with trimethylamine as base in CH_2Cl_2 in ambient temperature, starting from aryl acetic acids **220** and 2-hydroxybenzaldehydes or 2'-hydroxyacetophenone derivatives **219** (Scheme 52). The group has proposed a plausible mechanism which started with the formation of PPh_3I_2 subsequently coordinating to the OH group of both substrates at the same time, forming intermediate **222** (Figure 26). Aryl group transformation in the **222** followed by an intramolecular base-catalyzed cyclization produced the final product **221**.

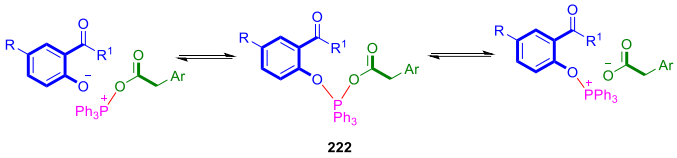
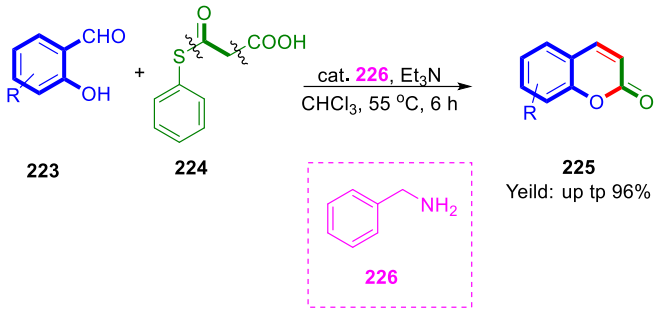


Figure 26 Three coordination states of intermediate **222**

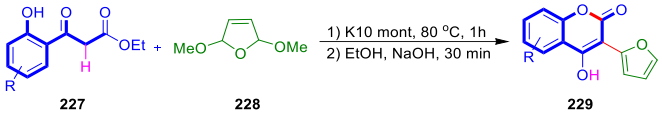
As for the scope of the reaction, it is reported that the reaction proceeded successfully in the presence of various electron-donating and electron-withdrawing groups on both hydroxyacetophenone **219** and aryl acetic acid **220**'s aromatic ring. Interestingly, the presence of hydroxyl group on either starting materials, though reduced the effectivity, made the process successful in achieving the result and did not cause any side products or undesired reactions. Strong EDGs like OMe and strong EWGs like NO_2 were also well-tolerated[131].



Scheme 53 Using amines as organo-catalysts for synthesis of coumarin derivatives

In 2013, *Jian Wang* of the national university of Singapore along with his research group developed an efficient way to synthesize 3,4-diunsubstituted coumarins through a cascade organo-catalyzed reaction (Scheme 53). The reaction was proceeded through coupling of salicylaldehyde **223** derivatives with malonic acid half-thioester **224** in the presence of a mixture of benzylamine **226** and triethylamine as the catalytic system. The method produced corresponding coumarin derivatives in $CHCl_3$ as solvent in 55 °C. The research group has proposed two plausible mechanisms, both through a Knoevenagel reaction, a decarboxylation step, and a lactonization step. Using different amine catalysts, it was found that bases as co-catalysts have important effect on the performance of the reaction.

Various salicylaldehydes were tested, and the corresponding coumarin products were obtained in good to high yields. Salicylaldehydes having both electron-donating and electron-withdrawing substituents were efficiently catalyzed in this transformation[132].



Scheme 54 Synthesis of furan-substituted coumarins by assistance of K10 montmorillonite as catalyst

In 2018, *Zunting Zhang* and co-workers proposed a method for synthesis of furan-substituted coumarin derivatives starting from ethyl 3-(2-hydroxyphenyl)-3-oxopropanoate **227** and 2,5-dimethoxy-2,5-dihydrofuran **228**, using K10 montmorillonite clay as catalyst (Scheme 54). This method consisted of two steps, 1) treatment of substrates in K10 montmorillonite clay in 80 °C for 1 hour, 2) 30 min refluxing of the mixture with ethanol and sodium hydroxide. The advantage of this method can be application of less-toxic and less-expensive K10 montmorillonite as catalyst instead of transition-metals.

It is noteworthy that intermediate **230** could be separated from the reaction in different conditions (Figure 27).

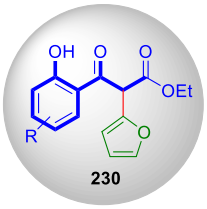


Figure 27 Intermediate **230** can be separated from the reaction mixture

Examination of the scope of the reaction showed that the presence of electron-donating groups gave the products in better yields (87-93%) than that of electron-withdrawing groups (65-78%). The reaction was also performed on multi-hydroxy-ethyloxopropanoate and moderate to good yields were obtained (64-76%)[133].

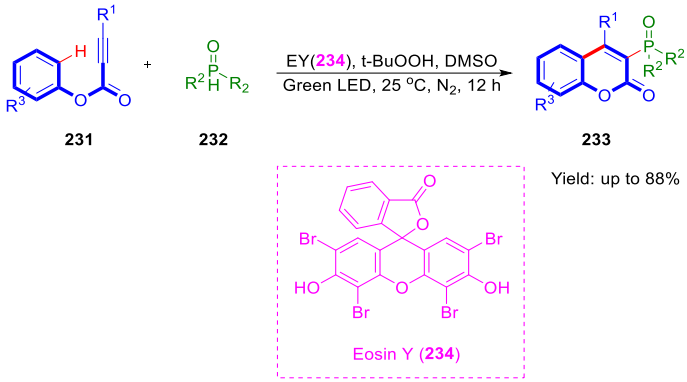
4. Photo-organo-catalyzed synthesis of coumarins

nowadays, synthesis of chiral organic compounds by visible-light photo-catalysts has been largely developed. this strategy stands on the tendency of metal complexes such as $[Ru(bpy)_3]$ and organic dyes such as Eosin Y to participate in single-electron transfer (SET) mechanisms with organic molecules. These catalysts can absorb light in the visible region to give stable, long-living photo-excited states. Photo-redox organo-catalysts

have some advantages including low-cost and stereo-chemical control in synthetic rout[134].

4.1 Eosin Y

Eosin is a fluorescent red dye, consisting of two closely related compounds, eosin Y and eosin B. Eosin Y is more commonly used in the photo-organo-catalyzed reactions. There are two kinds of Eosin Ys, water-soluble and ethanol-soluble. Eosin Y is a well-known and low-cost organic dye and photo-catalyst which can absorbs green light at 539 nm, and catalyze synthetic routes in organic chemistry for different kinds of transformations in asymmetric fashion[134].



Scheme 55 An example of using Eosin Y as a photo/organo-catalyst in preparation of coumarin

For example, a report of using eosin Y as the photo-catalyst in synthesis of coumarin was reported by *Peng-Fei Xu* and his co-workers in 2017 (Scheme 55). They coupled phenyl alkynoates **231** with phosphine oxides **232** using eosin Y **234** as photocatalyst, TBHP as oxidant and DMSO as solvent in 25 °C under nitrogen atmosphere and green LED. Same as other photo-catalyzed mechanisms, here as well eosin Y in its excited form started the reaction by making the phosphoryl radical which later attacked the triple bond to produce radical **235** (Figure 28). Further intramolecular cyclization of this radical with a subsequent single electron transfer with tBuO radical gave the product **233**.

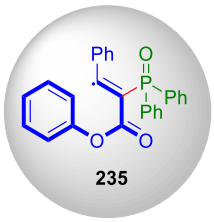


Figure 28 radical intermediate of reaction in Scheme **59**

The scope of the reaction was also examined, and the result was as follows: More than 30 different derivatives of reactants were used and most of them gave the corresponding results with up to 88% effectivity. In case of testing various groups as R^1, it was observed that phenyl rings with *ortho*, *para*- and *meta*-substitutions were able to act well in this position. More precisely, *para*-substituted phenyl rings with electron-withdrawing substituents or halogens were able to produce noticeably better results than the ones with electron-donating groups. Phenyls with *meta*-halogens and methyl at their *meta* position also gave subsequent amount of result, however, *meta*-methoxy phenyl as substituent decreased the result noticeably. *ortho*-Cl and *ortho*-Me were also examined as R^1 and gave respectively 68% and 77% of effectivity which proved good tolerance of steric hindrance in the reaction condition. Normal hexane as an example of aliphatic substituents was proven insufficient. Phosphine oxides with aromatic and aliphatic substituents were also used in the reaction condition and the *para*-methyl phenyl- and *para*-chlorine phenyl-substituted ones acted better than ethoxy-substituted ones.

The phenyl ring of alkynoates also showed tolerance toward a variety of substituents, including alkynes, halogens, EWGs like CF_3 and EDGs like OMe at *para* position of esteric moiety. Substituting *ortho* position of the same moiety was not a thriving effort, but naphthalene acted well when replaced with the simple phenyl ring. *meta*-substituted phenyls gave two regio-isomers **236** and **237** with more selectivity towards **237**[135] (Figure 29).

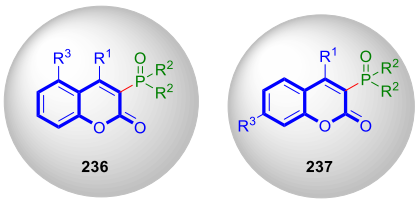
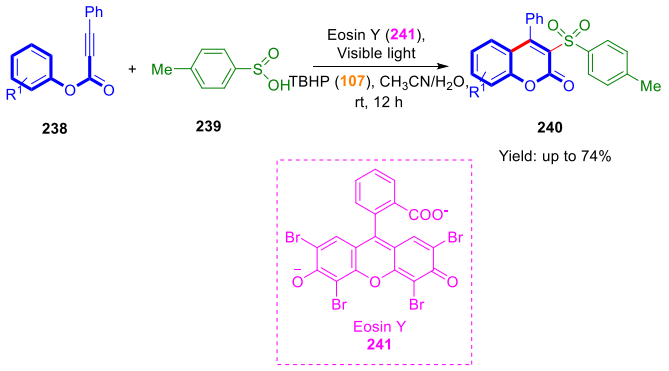


Figure 29 *meta*-substituted phenyls gave two regioisomers **236** and **237** with more selectivity towards **238**



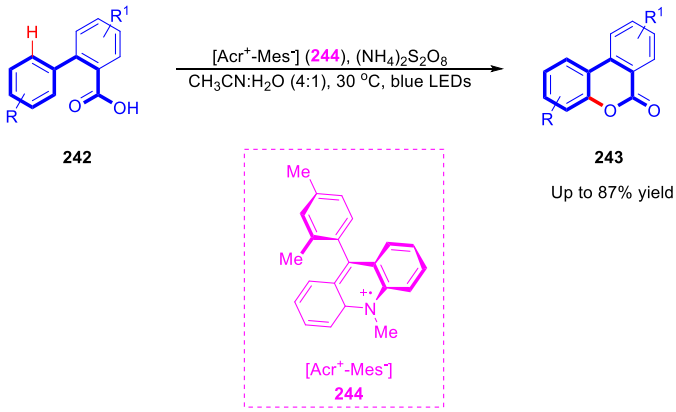
Scheme 56 Coupling aryl propiolates **238** with sulfinic acid under catalytic effects of Eosin Y

In 2015 *Wenchao Yang et al.* reported a novel visible-light-induced Eosin Y **241** catalyzed di-functionalization of alkynes with sulfinic acids *via* C–C and C–S bond formation for the synthesis of 3-sulfonated coumarins at room temperature

under metal-free conditions (Scheme 56). 3- phenylpropiolate **238** and 4-methylbenzenesulfinic acid **239** were chosen as substrates, Eosin Y **241** as a photo-redox catalyst, TBHP **107** as additive/oxidant and the 1:1 mixture of CH_3CN–H_2O as solvent in room temperature under the irradiation of 18 W fluorescent lamp for 12h. this reaction provided a novel and direct approach to the preparation of 3-sulfonated coumarins. The reactions generated the corresponding products in up to 74% yield, and the reaction proved compatible with various functional groups such as alkyls and halogens[136].

4.2 [Acr+-Mes-]

[Acr^+–Mes^-], 9-mesityl-10-methylacridinium **244** (Scheme 57) is a potential photo-catalyst widely used in synthesis of various compounds. The oxidizing ability of [Acr^+–Mes^-] can be increased by its photoexcitation in the presence of irradiation, and *via* SET process. The excited state of [Acr^+–Mes^-] is a strong electron acceptor, that effectively oxidize substrates by photo-induced SET. The created radical cations can participate in bond formation reactions with various nucleophiles. Reports showed that [Acr^+–Mes^-] provides the long-lived electron-transfer (ET) state (Acr+•–Mes•+), which has a high oxidizing ability (Ered = 1.88 V) and reducing ability (Eox = −0.49 V)[137].



Scheme 57 Nitrogen-based bulky salt [Acr^+-Mes^-] **244** as catalyst for intramolecular dehydrogenative lactonization of 2-arylbenzoicacids **242**

In 2015, *Gonzalez-Gomez* and co-workers worked on a metal-free dehydrogenative intra-molecular lactonization on 2-arylbenzoicacids **242** to produce benzo-3,4-coumarin derivatives (Scheme 57). In this method, [Acr^+-Mes^-] was used as photocatalyst under blue LED, ammonium persulfate as oxidant and a 4:1 mixture of acetonitrile and water as solvent in 30 °C. The plausible mechanism went through radicalization of the photocatalyst in the presence of LED light, which in next step produced the intermediate **245** (Figure 30) with inducing a single-electron transfer (SET) in **242**.

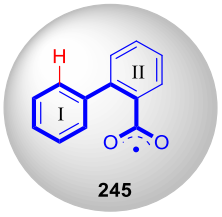
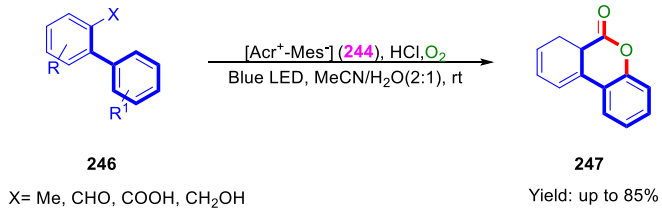


Figure 30 radical intermediate produced by dehydrogenation of 2-arylbenzoicacid **242**

The next step was intramolecular radical cyclization which ruined the aromaticity of ring **I**. To gain back the aromaticity, another SET happened with departure of a hydrogen atom. $S_2O_8^{2-}$ acted as oxidant for bringing the catalyst back in the catalytic cycle producing $SO_4^{-\cdot}$ radical anion which can assist in the final SET to reach the product **243**.

The group has also explored the repeatability of the reaction. The results indicated that the reaction was able to tolerate substituents like Cl, F, OMe, COOH, CF_3 and Ph in all positions of both aromatic rings of the initial biphenyl. However, 2-(pyridin-3-yl)benzoic acid was not successful in producing the final yields through this mechanism, which was probably because of less tolerance of nitrogen in having positive charge[138].



Scheme 58 Using biaryls 20A as substrate in [Acr^+-Mes^-]-catalyzed synthesis of benzocoumarins **247**

An oxidative lactonization on 2-methyl-1,1'-biaryls **246** to synthesize benzocoumarin **247** derivatives was reported by *Song Ye* and co-workers in 2013 (Scheme 58). The reaction was performed under the effect of visible light using HCl as acid and O_2 gas in a 2:1 mixture of MeCN and water. Benzocoumarin derivatives have reports of biological activities such as anti-proliferation, anti-fungal and anti-bacterial. The reaction went through oxidation of X group to COOH followed by intramolecular lactonization (Figure 31).

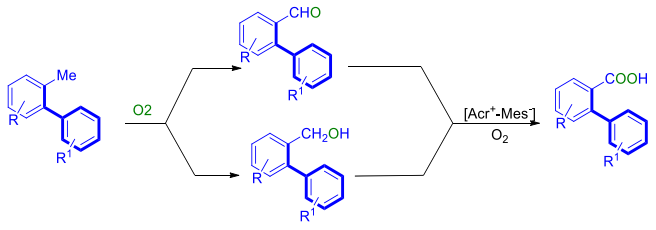


Figure 31 two proposed oxidation pathes of the reaction 62

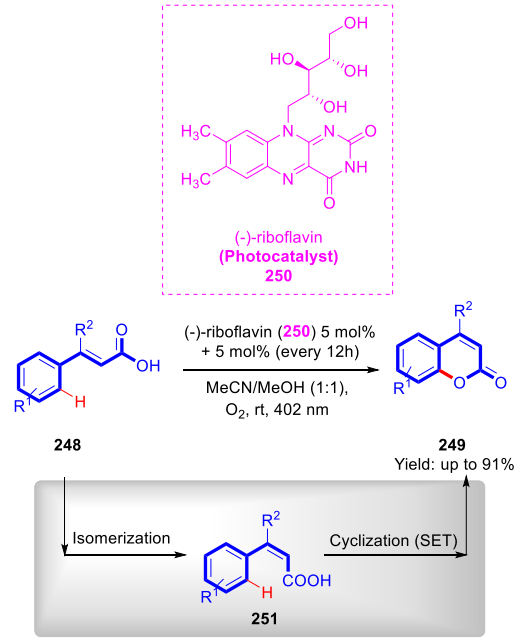
The scope of the reaction was also examined. regarding the reaction of 2-methyl-1,1'-biphenyl, the result showed that electron-withdrawing-substituted biphenyls reacted well in this

protocol and produced the corresponding products in good yields; however, hydrogen-substituted 2-methyl-1,1'-biphenyl gave a weaker result than those of the later. When 2-aldehyde, alcohol and carboxylic acid were used as **246** also the desired product was produced. Using 2-aldehyde-1,1'-biphenyl with Me, CF_3, Cl, and H as substituents on both phenyl rings gave the product with up to 75% effectivity. The alcohol was also successful in this method and tolerated CF_3 as a strong electron-withdrawing substituent well[139].

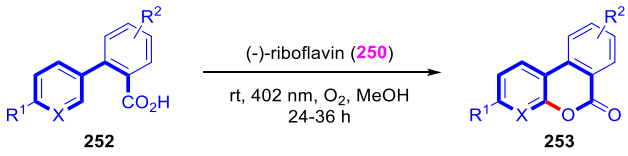
4.3 Riboflavin

(−)-riboflavin (vitamin B2) **250** as a photocatalyst have opened new avenues in the advancement of organic photochemistry by inducing cyclization and isomerization to generate the heterocyclic core under two possible pathwayw including energy transfer or single-electron transfer mechanism[140,141,142] *Gilmour and Matternich* in 2015, designed a new method for synthesizing 4-substituted coumarin derivatives using photocatalyst activities of (-)-riboflavin (Scheme 59). The protocol started from E-cinnamic acid (E:Z-20:1) **248**, and proceeded with an isomerization to Z-cinnamic acid followed by an intramolecular C-O coupling/Cyclization in a mixture of methylcianide and methanol, and in an atmosphere of oxygen in ambient temperature. Interestingly and satisfyingly in this reaction, both the isomerization and the cyclization stepsproceeded under catalytic effect of (-)-riboflavin (RF). First, the photocatalyst got activated (RF → RF^*) through its exposure to 420nm light and radically broke the double bond of **248** leading to the formation of the Z-isomer **251** and departure of RF. In the next step, the RF or RF^* present, absorbed the hydrogen of the Z-acid radically and $RFH^\bullet$ was produced. The $RFH^\bullet$ subsequently catalyzed the radical addition of oxygen to the benzene ring and the re-aromatization.

The procedure proved useful for synthesis of more than fifteen derivatives of **249**. First the α-flouro-substituted cinnamic acid was tested and exhibited lower efficiency in comparison with the β-flouro-substituted one (38:77%). Other than that, various cyclic and linear alkyls were tested on the β-position, and all produced the corresponding product in moderate to good yields. Cinnamic acids with halogens, alkyls, EDGs and EWGs as a replacement for R1 also acted thriving in this protocol. The *para*-CF_3-cinnamic acid gave intensely lower yield than *para*-OCH_3 (positive effect of EDGs and negative effect of EWGs). The efficacy of production of coumarins was increased from β-methylcinnamic acid to β-ethyl and β-propyl respectively, which can be related to the groups' effect on stability of the radical intermediate of isomerization reaction[143].



Scheme 59 Intramolecular annulation/C-H activation of E-cinnamic acids under the effect of (-)-riboflavin **250** as the photocatalyst



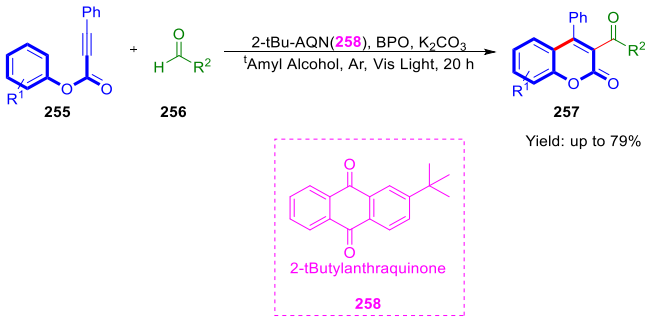
Scheme 60 Using (-)-riboflavin **250** as catalyst in another method for synthesis of coumarin structural motif

The same group in 2018, suggested a very similar photo-induced single electron-transfer to synthesize benzo-3,4-coumarin derivatives **253** directly from the lactonization of bi-aryl carboxylicacids **252** and without the need to isomerization (Scheme 60). In this method, (-)-riboflavin **254** assisted the electron-transfer process as a photoactive catalyst, O_2 as oxidant, and methanol as solvent in ambient temperature. The group's proposed mechanism started with the protonation of (-)-riboflavin (RF) with absorbing the acid **252**'s H^+ and continues with radicalization of the carboxylate ion in the presence of 402nm of light and RFH^+ which led to the radical lactonization. The group has found out that the best result was produced when the photocatalyst was added 5 mol% every 12 hours.

This reaction proved to be repeatable for synthesis of fourteen different derivatives of **253**. Halogens like fluorine and bromine, strong electron-donating group OCH_3, strong electron-withdrawing group CF_3 and alkyls like t-Bu were tested as R^1. The results showed that, the presence of EDGs and EWGs decreased the yield. Trying to extend the π-system, *para*-bromophenyl was used at this position and resulted in the corresponding product in 65% yield. The phenyl ring containing the acid residue was also substituted with EDGs, phenyl group

and halogens at both *meta* positions of the acidic moiety. The presence of methyl group at *meta* position of compound **254** showed interestingly low effectivity in producing the corresponding product, which the group has supposed to be a result of increasing 1,3-allylic strain near the reaction site[144].

4.4 Other Photo-catalysts



Scheme 61 2-tButylanthraquinone can act as an effective catalyst in synthesis of coumarin

In 2018, *Akichika Itoh*, *Eiji Yamaguchi* et al. reported a photo-catalysis, starting from aldehydes and ynoates to afford 3-acyl4-arylcoumarin **257** derivatives (Scheme 61). 2-tBuanthraquinone **255** was used as the photo-catalyst, BPO (benzoyl peroxide) **263** (Figure 33) as oxidant, K_2CO_3 as additive and t-amyl alcohol as solvent under argon atmosphere and visible light for 20 hours. The mechanism that the group has proposed and provided proofs for, is the detachment of aldehyde's hydrogen with one electron to produce an acyl radical at the starting point. Reportedly, this can happen with the attack of an AQN radical, which was made under the effect of visible light, or the attack of a $PhCO_2$ radical made from thermal or photo decomposition of BPO. Afterwards, the acyl radical reacted with the ynoate to produce intermediate **259**, which subsequently underwent an exo-cyclization to provide **260**. Oxidation of **260** gave carbocation **261**. A further ester migration along with the detachment of a hydrogen to produce aromaticity provided the final product (Figure 32).

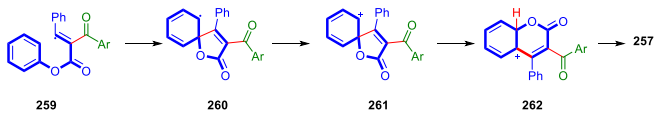


Figure 32 The process has gone through oxidation of radical intermediates

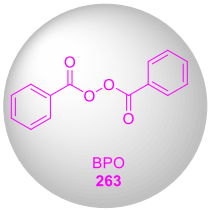


Figure 33 BPO as a light sensitive radical starter

Regarding the generality, this reaction is reported to proceed effectively with a wide variety of ynoates and aldehydes. No aliphatic aldehyde is used in this protocol whereas *para-*, *ortho-* and *meta-* substituted benzaldehydes with both electron-donating and electron-withdrawing substituents were used. Bulky groups like *t*-Bu at *para* position of the aromatic ring of benzaldehyde did not cause any noticeable decrease in efficacy. On the other hand, strong EDGs and EWGs like CF_3, OMe or Cl on the same ring are reported to produce lower yields. The phenolic aromatic ring of ynoates can be also substituted with various groups. Although ynoates with *para*-substituted phenyl provided regio-selectivity, *meta*-substituted ones were prone to produce 2 regio-isomers **264** and **265** (Figure 34).

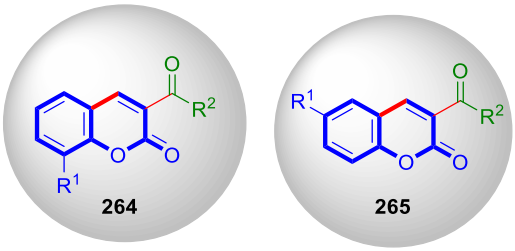


Figure 34 Two possible regio-isomers produced when *meta*-substitutions were used on 2-tBuanthraquinone **255**

when *para*-substituted ynoates were applied to the reaction, less electron-donating substituents were considered better options. In the other condition just electron-donating groups were tested and such a comparison was not possible[145].

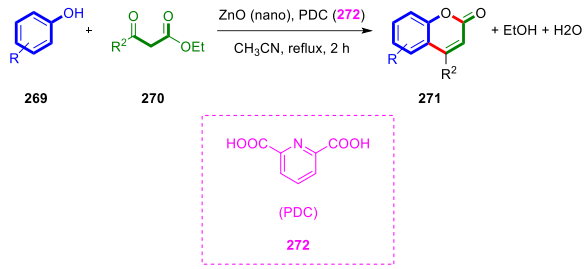
Scheme 62 Light-mediated coupling of aryl propiolates with α-keto acid **267**

Next year, the same reaction was tried by *Lei Wang et al.* with different radicalization mechanism (Scheme 62). In this method, BI-OH as the catalyst in the presence of blue LED light de-carboxylized the α-keto acid **267** and started the cycle. KPF_6 was added to the reaction as additive and the reaction went on in toluene in ambient temperature for 24 hours. The reaction did not produce the desired yield in absence of light irradiation. Interestingly, no other tried solvent, such as MeCN, DMSO or acetone, were successful in proceeding the reaction. This method was also effective for synthesizing various 3-acylcoumarin derivatives, substituted with halogens or alkyls with up to 81% yield[146].

5. Other Catalytic Systems

In the recent years, nanoparticle of metal salts such as zinc oxide being used as heterogeneous catalysts, apart from being a fundamentally interesting concept, has been employed as a

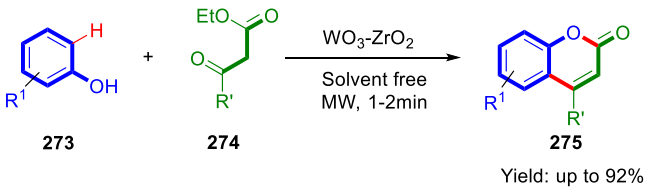
powerful strategy for the design and development of synthetic procedures for various organic molecules. Low-cost, low-waste, environmental friendliness, low-corrosion, and catalyst recycling ability are advantages of this catalytic reactions which has developed a cascade of innovative advancements in this area[147,148]. In 2009, *Papori Goswami* tried synthesizing coumarin derivatives **271** *via* a dually activated organo- and nano-cocatalyzed method (Scheme 63). Herein, phenols **269** and ethyl acetoacaetates **270** were used as substrates, PDC (pyridine dicarboxylic acid) **272** as organocatalyst, and nano ZnO as co-catalyst under reflux in acetonitrile.



Scheme 63 Using ZnO nanoparticles as nano-catalyst for synthesis of coumarins **271**

The scope of the reaction was tested *via* synthesis of various substituted coumarins. The result showed that *meta*-electron-donating-substituted phenols are relatively more successful and faster in producing coumarins *via* this protocol. Interestingly, reaction of simple phenol took a long time for completion, showing the substantial role of substituents in the kinetics of the reaction. phenols substituted with nitro, amino, and chloro also reacted smoothly to furnish the respective coumarins.

Regarding the scope of β-ketoesters **270**, it is reported that ethyl benzoylacetate, and ethyl acetoacetate both successfully created the corresponding products[149].



Scheme 64 nano-metal-catalyzed Pechman Condensation for synthesizing coumarins **275**

In 2007, *B. G. Mishra* and his research group proposed another nano-metal-catalyzed Pechman Condensation for synthesizing coumarins from the same reactants, phenols **273** and β-ketoesters **274** (Scheme 64). Here, the group have used nanoparticles of WO_3-ZrO_2 as catalyst, again in a very fast solvent-free mechanism in the presence of micro-wave irradiation. The method proved successful in producing fifteen different coumarin derivatives with up to 92% effectivity in one to two minutes. The catalyst has been reactivated after being used in the mentioned reaction and no dramatic loss of activity has been observed.

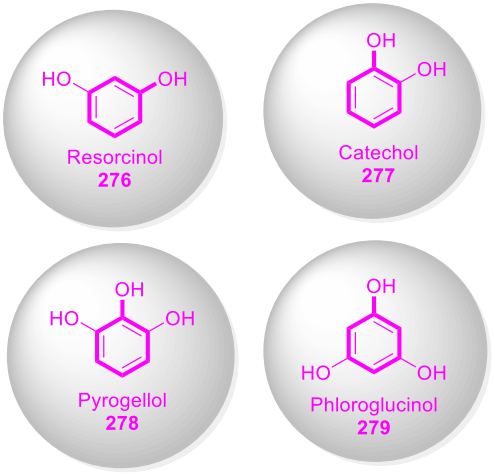
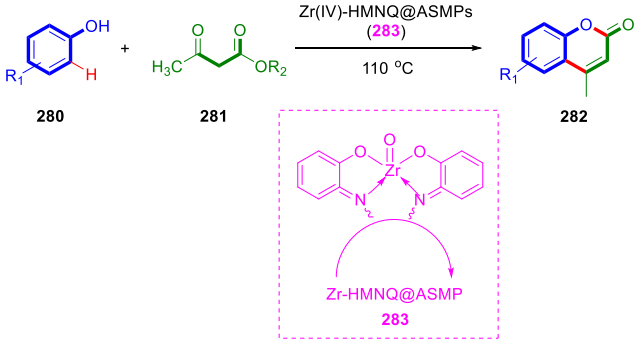


Figure 35 several poly-hydroxyphenols acted successfully in the reaction condition

For investigating the scope of the reaction Mishra group tried various phenol derivatives **273** with ethyl acetoacetate and benzoyl acetoacetate. Accordingly, the efficacies for all the tested reactions have been in a range of 74-92%, and poly-hydroxylphenols like resorcinol **276**, catechol **277**, pyrogellol **278**, and phloroglucinol **279** all performed successfully to obtain their corresponding product[150] (Figure 35).



Scheme 65 Application of magnetically retrievable HMNQ-coated zirconium (IV)-nanoparticles as catalyst for the synthesis of coumarin **282**

In 2013 *R.K. Sharma et al*. presented a report based on the use of magnetically retrievable HMNQ (Figure 36)-coated zirconium (IV)-nanoparticles as catalyst for the synthesis of various compounds *via* Friedel-Crafts reaction, Knoevenagel condensation, and Pechmann condensation (Scheme 65). The synthesis was performed in fast, simple, effective, and environmentally friendly conditions starting from phenols **280** and β-ketoesters **281**. The potential of the catalyst to be easily recycled made the protocol a greener option than other possible ones.

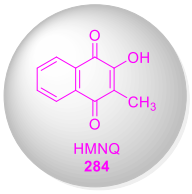
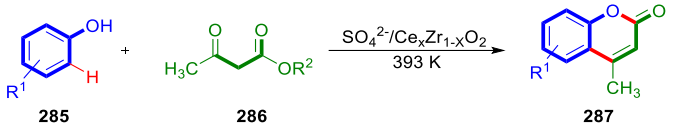


Figure 36 structure of single molecule of HMNQ

The group successfully synthesized six coumarin derivatives using this approach, and proved that the process can bear strong EDGs like OMe, amines, and hydroxyls[151].

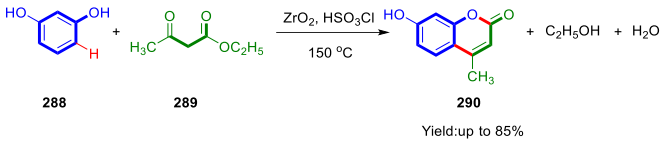


Scheme 66 Pechman condensation between phenols **285** and β-ketoesters **286** in the presence of $SO_4^{2-}/Ce_xZr_{1-x}O_2$ as catalyst

The sulfated metal oxides, based on zirconium oxide have been applied as effective catalysts in the organic transformations. This tactic can improve acid site availability, reactivity, acidity and increase the specific surface area of catalyst. The reactivity, selectivity and stability of sulfated zirconia catalysts were also increased by the coupling this structure to metals[152]. In 2006, *Reddy et al*. found a new effective catalytic system for synthesizing coumarin derivatives **287** (Scheme66). They used Pechman condensation between phenols **285** and β-ketoesters **286** in a solvent-free condition in the presence of $SO_4^{2-}/Ce_xZr_{1-x}O_2$ as catalyst and heated up to 393 K (≈ 120 °C). The acidic $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalyst was synthesized by primarily making Ce–Zr–hydroxide gel by a homogenous co-precipitation method and impregnating with sulfuric acid. The method produced up to 94% effectivity when used for synthesizing eight different coumarin derivatives. The author has compared the achieved efficacy with other recently published methods for the same reaction, proving that this catalyst can be counted as a highly effective one.

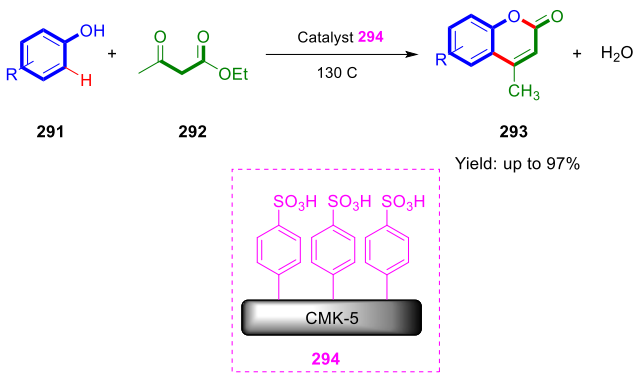
For investigating the scope, the reaction was performed with ethyl acetoacetate and methyl acetoacetate. They both proved successful, though generally the latter provided lower times and better effectivities. About the phenols, multiple hydroxy- or methyl-substituted phenols were tested and no dramatic differences in the efficacies was observed.

In 2012, *Yadav et al*. tried a Pechman-condensation between resorcinol **288** and ethyl acetoacetate **289** in the presence of zirconium-based catalysts synthesized by the group itself *via* a combustion method (Scheme 67). The group tried FLSZ (fuel-lean sulfated zirconia), and FRSZ (fuel-rich sulfated zirconia), and got the best result with FLSZ. The reaction produced its best result in 150 °C, in the presence of chlorosulfunic acid[153].



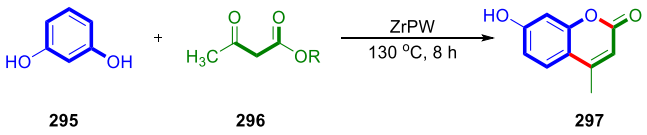
Scheme 67 Pechman condensation between resorcinol **288**, and ethyl acetoacetate **289** catalyzed by FLSZ

Another nano-catalyzed phenol **291** and ethyl acetoacetate **292** coupling to produce coumarin derivatives was done in 2014 by *Daryoush Zareyee* and his research group (Scheme 68). The group used ordered nanoporous carbonaceous sulfonic acid (CMK-5-SO_3H) with high surface area, narrow pore size distribution and large pore volume as a recoverable heterogeneous catalyst. The Pechmann condensation was done in 130°C, and the corresponding coumarin product was formed in 95% yield after 20 min.



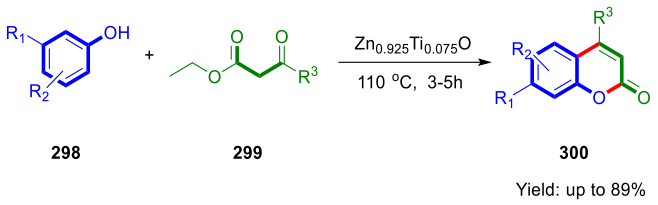
Scheme 68 nano-catalyzed phenol and ethyl acetoacetate coupling to produce coumarins **293** by Daryoush Zareyee

The advantages of using CMK-5-SO_3H as a solid acid catalyst includes thermal stability, high water tolerance ability, easy sedimentation property, and good catalytic activity, along with its reusability[154].



Scheme 69 Pechman condensation between resorcinol **295** and β-ketoesters **296** with Zirconium(IV) phosphotungstate as catalyst

In another research in 2013, *U. Chudasama et al*. tried another Pechman condensation between resorcinol **295** and β-ketoesters **296** to test the effect of ZrPW (Zirconium(IV) phosphotungstate) as a solid catalyst (Scheme 69). The group succeeded to produce coumarin derivatives in up to 65% effectivity in a solvent-free mechanism in 130 °C for 8 hours. The result did not have any difference in presence and absence of microwave irradiation[155].



Scheme 70 Another solvent-free Pechman condensation to test the effect of Ti(IV)-doped ZnO as catalyst

In a research in 2019, *Pawar* and co-workers used a solvent-free Pechman condensation to produce 4-substituted coumarin **300** derivatives (Scheme 70). In this attempt, the group used Ti(IV)-doped ZnO as catalyst/Lewis acid and 110 °C temperature in 3 to 5 hours. The catalysts were prepared by the solution-free mechanochemical method, and they had high surface, good Lewis acidity, and high activity. The reaction started with phenol derivatives **298**, and β-ketoesters **299** and proceeded with a nucleophilic attack from the hydroxyl group of **299** on the activated **298** to form intermediate **301**. Subsequently, the intramolecular cyclization of **301** followed by a dehydration in the presence of heat, produced the final product (Figure 37).

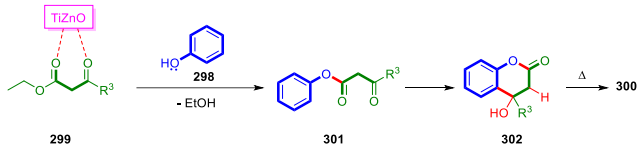


Figure 37 Some steps of the proposed mechanism

The scope of the reaction was also tested. More than twenty different derivatives of **300** were synthesized using this method. The protocol showed perfect tolerance for both aliphatic and aromatic substituents on both phenol and β-ketoester. The chloro-substituted phenols produced more than 87% effectivity. Methyl, propyl and phenyl were tested as R3 and produced the desired products efficiently, however the reaction of ethyl benzyl acetate took more time than others due to the lower electrophilicity of carbonyl adjacent to a benzene ring. The method also showed effectivity in synthesizing ayapin **303** (63-68%)[156] (Figure 38).

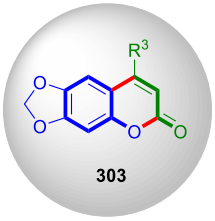


Figure 38 Ayapin **303** can also be produced using this method

Conclusions

As previously demonstrated, coumarin itself and other coumarin-like structures cover an important part of medicinal chemistry due to the wide pharmaceutical properties they possess. In this review, the author team tried to provide a more precise and more detailed insight into the catalytic methods applicable for the synthesis of mentioned structures. Metals can be divided into two groups, 1) the ones that act as catalyst by accepting electron-donation with coordination, 2) the ones that use their electron-deficiency to act as oxidants and help radical mechanism. In most cases, palladium, rhodium and ruthenium act like the first group, and gold, silver, and iridium act like the second. Metals can be also used for O-H activation which followed by a C-H coupling can produce many useful structures, including coumarin. Organo-catalysts also, although being overshadowed by metals in the recent years, still hold their importance and efficiency in the catalytic synthetic methods. Various number of organo-catalysts are investigated in the present paper for using in synthesis of coumarin derivatives. Both metal- and organo-catalysts provide good effectivities and regio-selectivity.

Abbreviation List

dppb	1,4-Bis(diphenylphosphino)butane
BQ	benzoquinone
Dppf	1,1′-Bis(diphenylphosphino)ferrocene
TFA	Trifluoroacetic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
HMDS	Bis(trimethylsilyl)amine
CDC	dehydrogenative cross coupling
SET	single-electron-transfer
TBHP	tert-Butyl hydroperoxide
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl oxyl
BHT	butylated hydroxytoluene
PQC	pyrrolo-quinoxaline embedded coumarin
DMAP	4-Dimethylaminopyridine
NHC	N-Heterocyclic carbene
DBU	1,8-Diazabicyclo[5.4. 0]undec-7-ene
TMEDA	tetramethylethylenediamine
DIPEA	N,N-di-isopropylethylamine
DMAP	4-Dimethylaminopyridine
BPO	benzoyl peroxide
PDC	pyridine dicarboxylic acid
HMNQ	8-Hydroxy-2-methoxy-1,4-naphthoquinone
FLSZ	fuel-lean sulfated zirconia
FRSZ	fuel-rich sulfated zirconia
ZrPW	Zirconium(IV) phosphotungstate

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