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Metal-catalyzed synthetic strategies toward coumarin derivatives

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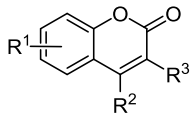


Modern approaches toward coumarin ring construction based on metal-catalyzed reactions significantly complement and extend the applicability of classical methods by increasing the reaction rates and product yields. The present review summarizes various approaches to the synthesis of coumarin derivatives catalyzed by different metals – palladium, gold, copper, silver, platinum, iron, cobalt, rhodium, gallium, nickel, and zinc. Among these, palladium-catalyzed reactions are the most numerous and significant in many aspects. The review covers literature over the last 20 years.

Keywords: coumarins, palladium, Knoevenagel condensation, metal catalysis, Pechmann condensation, synthetic routes.

The biological significance of coumarin scaffold is well established because of its diverse pharmacological activities. Numerous coumarin derivatives of natural and synthetic origin possess different kinds of biological activities. The pharmacological profile of coumarin derivatives includes anticancer,[1] antidiabetic,[2] antiHIV,[3] antioxidant,[4] antimicrobial,[5] anti-inflammatory,[6] vasodilator,[7a] anticoagulant,[7b] and other bioactivities (Fig. 1). Coumarin derivatives are used as fluorescent materials in diagnostics and monitoring of physiological disorders.[8] They also have an application in the agrochemical, food, and cosmetic industries as aroma enhancers, flavorants, dyes, and additives.[9] It has been reported that therapeutic applications of coumarins depend on the nature of the substitution pattern present on the benzene and pyrone rings.[10] Various substitution sites possible on coumarin core are represented in Figure 2.

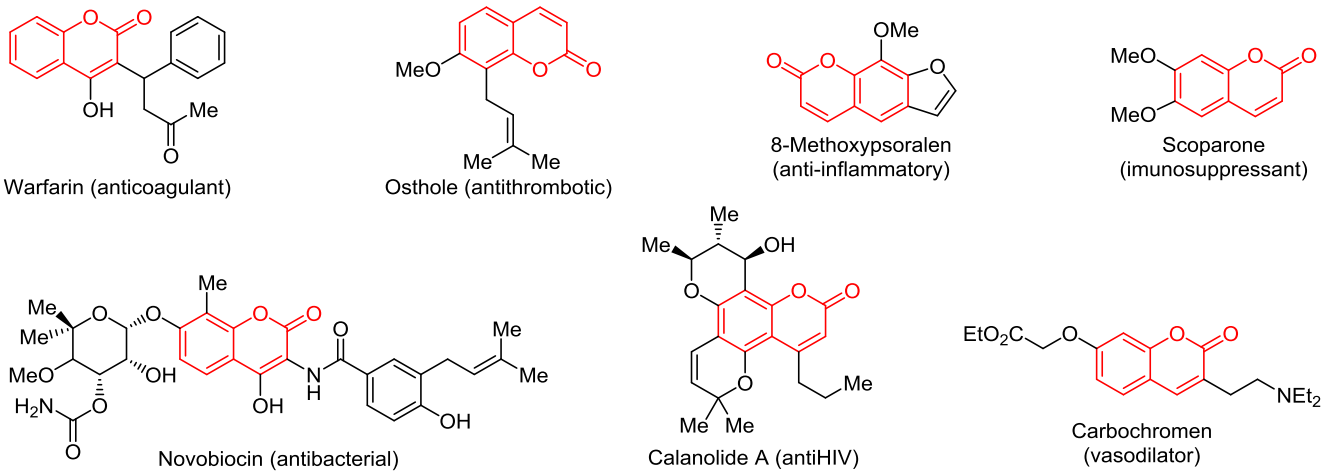


Figure 1. Examples of biologically active coumarin derivatives.

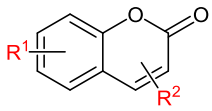


Figure 2. Possible coumarin substitution sites.

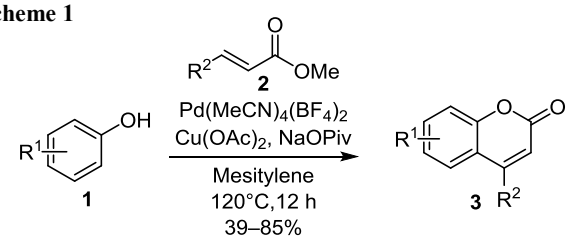
Numerous synthetic approaches have been reported for the synthesis of coumarin derivatives. Classical synthetic methods, such as Pechmann condensation,[11] Knoevenagel condensation,[12] and Perkin reaction[13] may be associated with the certain limitations such as requirement of large amounts of corrosive chemicals. Sometimes these are multistep or time-consuming processes that lack stereoselectivity. These problems are partially solved by metal-catalyzed intermolecular or intramolecular coupling reactions. Metals reported for the synthesis of coumarins include palladium, gold, copper, silver, platinum, iron, cobalt, rhodium, gallium, nickel, and zinc. Various synthetic approaches using different metals as catalysts will be discussed in the next sections of this review article.

1. Pd-catalyzed synthesis of coumarins

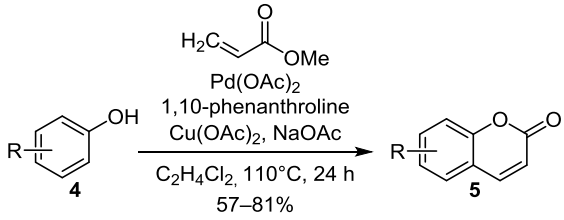
1.1. Pd-catalyzed synthesis of coumarins by C–H alkenylation of phenols

C–H activation is a type of reaction in which a C–H bond is cleaved and replaced with C–X-type bond, where X may be carbon, oxygen, or nitrogen. In such type of reactions, the hydrocarbon firstly reacts with the metal catalyst to create an organometallic complex. By utilizing the properties of this reaction, Zhang et al. reported synthesis of coumarin derivatives by Pd-catalyzed base-accelerated *ortho*-selective C–H alkenylation of phenols.[14] The synthesis of various coumarin derivatives was carried out by stirring substituted phenols **1** in the presence of $Cu(OAc)_2$ as an oxidant and sodium pivalate (NaOPiv) as a base. Phenol **1**, acrylate **2**, catalyst $Pd(MeCN)_4(BF_4)_2$, and

Scheme 1



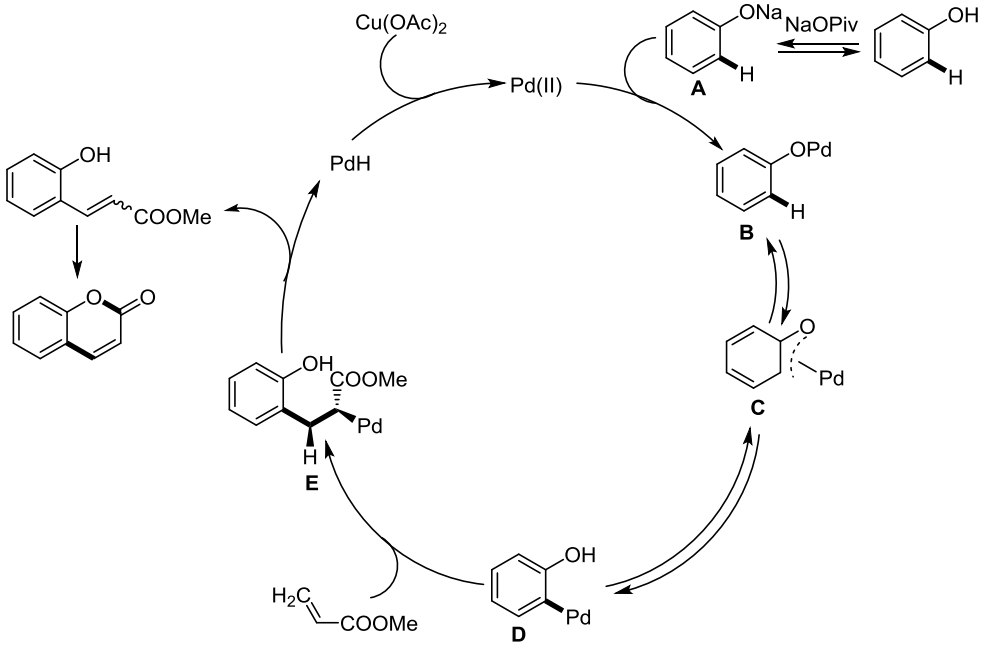
R^1 = H, Me, *t*-Bu, Ph, NO_2, OMe, F, Cl, Br, Ac, CHO, CO_2*n*-Pr, CF_3, OTs; R^2 = H, Me, *n*-Pr, Ph



R = H, Me, OMe, CHO, NO_2, CN, COMe, CH_2CN

mesitylene as a solvent were heated at 120°C for 12 h to afford substituted coumarins **3** (Scheme 1). Sharma et al. reported similar approach for the synthesis of coumarin derivatives **5** from phenols **4** and methyl acrylate using $Pd(OAc)_2$ as a catalyst in the presence of 1,10-phenanthroline, NaOAc, $Cu(OAc)_2$, and 1,2-dichloroethane at 110°C.[15] The important finding in these reactions was the tolerance of various electron-withdrawing groups, such as NO_2, CN, CHO, COMe, and other groups such as CH_2CN, toward the reaction conditions. The yields of obtained coumarins were good. On the basis of the studies carried out by Zhang group, the possible mechanism of the reaction is outlined in Scheme 2. In the presence of a base, phenol gets converted to its sodium salt **A** which forms an intermediate **B** with Pd(II) catalyst. Then 1,3-migration occurs *via* intermediate **C** to generate C–H bond metalation intermediate **D**. The alkene insertion occurs, followed by

Scheme 2



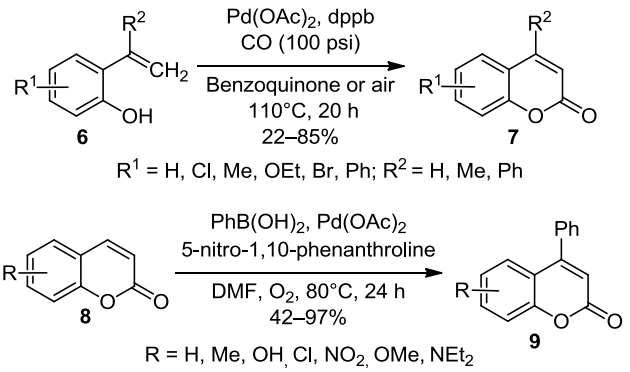
β-H elimination which releases alkenylated product **E** and PdH species. The catalytic cycle finishes by oxidation of PdH to Pd(II) in the presence of copper(II) acetate, and final product is produced by intramolecular esterification. This kind of C–H activation reactions have a large number of applications in synthesis of various products like (+)-lithospermic acid,[16] calothrixin A and B,[17] mescaline analogs,[18] etc.

1.2. Synthesis of coumarins by Pd-catalyzed oxidative processes

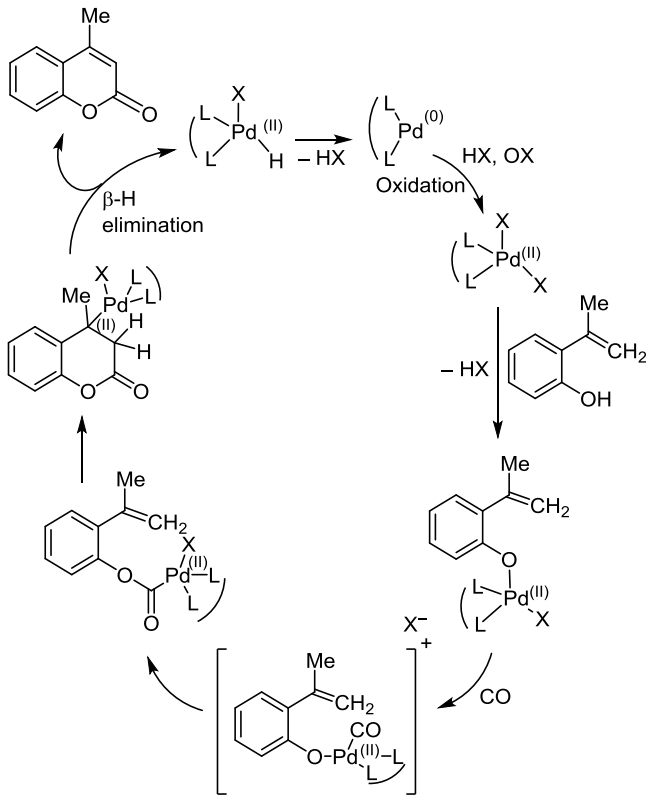
Metal-catalyzed oxidative carbonylation involves coupling of two components through carbonyl group in the presence of an oxidant. This methodology is an important route for the synthesis of many natural products. Ferguson et al. reported a direct method for the synthesis of coumarins by Pd-catalyzed oxidative cyclocarbonylation.[19] A substituted vinylphenol **6** was used as a model substrate to optimize the oxidative Pd-catalyzed cyclocarbonylation. The reaction was catalyzed by $Pd(OAc)_2$ in the presence of carbon monoxide (CO) at low pressure and air or 1,4-benzoquinone as oxidant to yield various substituted coumarin derivatives **7** (Scheme 3). The possible mechanism of oxidative cyclocarbonylation is similar in several aspects to that of proposed by Bianchini and coworkers for the oxidative carbonylation of styrene in methanol[20] and is briefly outlined in Scheme 4. The catalysis begins with generation of a palladium phenoxide species by exchange of ligand with an anionic ligand with loss of HX. Then insertion of CO into the PdO bond affords a phenoxycarbonyl palladium species. Next alkene insertion occurs into the Pd–CO bond to generate an alkylpalladium intermediate. After that coumarins are released by β-H elimination and the resulting palladium(II) hydride may be reduced to a palladium(0) species through the loss of HX. Finally, palladium(II) is regenerated by the oxidant, either 1,4-benzoquinone or molecular oxygen to complete the catalytic cycle.

Metal-catalyzed oxidative Heck reaction is an approach which involves formation of C–C bond. Utilizing this approach Duan et al. reported Pd-catalyzed oxidative Heck coupling reaction for direct synthesis of 4-phenylcoumarins using coumarins and phenylboronic acid.[21] It involved direct oxidative coupling by the C–H bond activation of coumarins. Coumarin derivatives **8** reacted with phenylboronic acid in the presence of $Pd(OAc)_2$, 5-nitro-1,10-phenanthroline, DMF, and O_2 at 80°C for 24 h to yield various 4-aryl coumarin derivatives **9** (Scheme 3). This method was found to be atom economic and convenient approach with broad functional group tolerance.

Scheme 3



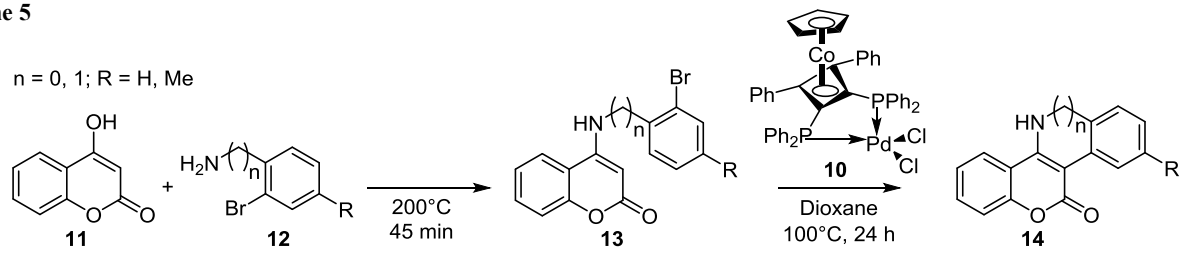
Scheme 4



1.3. Synthesis of coumarins by Pd complex-catalyzed intramolecular Heck reaction

The intramolecular Heck reaction involves coupling of an aryl or alkenyl halide with an alkene of the same molecule. These reactions are utilized to give carbocyclic or heterocyclic organic compounds with different ring sizes. For the synthesis of chiral intramolecular Heck reaction products in nonracemic form, chiral palladium complexes can be used. Chang et al. reported an efficient method for the synthesis of coumarin derivatives by palladium complex-catalyzed intramolecular Heck reaction.[22] First, a cobalt sandwich diphosphine-chelated palladium complex **10** was prepared by the reaction of a cyclopentadienylcobalt-cyclobutadiene diphosphine and dichloro(1,5-cyclooctadiene)palladium(II) ($Pd(cod)Cl_2$). Then 4-hydroxycoumarin **11** was allowed to react with 2-bromobenzylamines **12** at 200°C for 45 min to give the corresponding substituted chromen-2-one derivatives **13**. Further, compounds **13** were treated with complex **10** in presence of dioxane at 100°C for 24 h to yield substituted coumarin derivatives **14** (Scheme 5). In this one-pot reaction, a cyclization into an annulated heterocycle took place. This process is significant route for the synthesis of cyclized coumarin derivatives fused with five-membered or extended rings at the C-2 and C-3 positions of the molecule. Other reported applications of intramolecular Heck reaction

Scheme 5

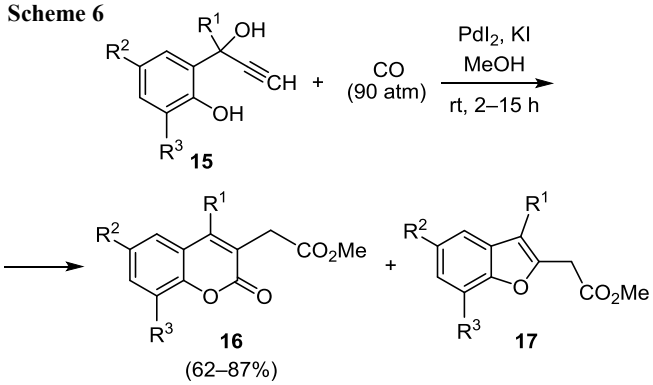


are syntheses of different natural products – terpenoids, alkaloids, polyketides, etc.[23]

1.4. Synthesis of coumarins by Pd-catalyzed dicarbonylation

Gabriele et al. reported synthesis of coumarin derivatives by dicarbonylation reaction catalyzed by palladium.[24] Starting materials used in this reaction were 2-(1-hydroxyprop-2-ynyl)phenols **15**, which in the presence of catalytic amounts of PdI_2 in conjunction with an excess of KI in MeOH as solvent at room temperature and under 90 atm of CO pressure afforded 3-[(methoxycarbonyl)methyl]coumarins **16** in good yields (62–87%) as depicted in Scheme 6.

Scheme 6



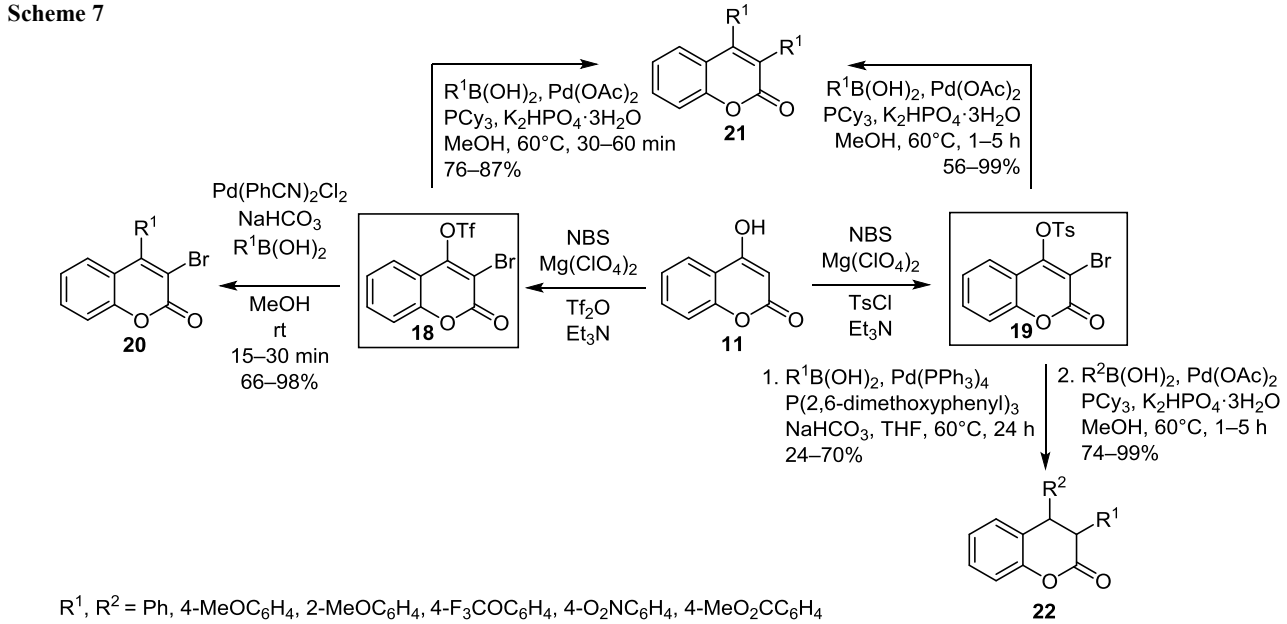
R^1 = H, Me, Ph; R^2 = H, Cl, OMe, R^3 = H, OMe

Unfortunately, the reaction was not selective, and beside coumarins **16**, methyl 1-benzofuran-2-ylacetate derivatives **17** were formed. But the selectivity toward compounds **17** could be significantly improved by raising the CO pressure, decreasing the reaction temperature, and increasing the substrate concentration.

1.5. Synthesis of 3,4-disubstituted coumarins by Pd-catalyzed site-selective cross-coupling reactions

Zhang et al. developed a new Pd-catalyzed approach for the synthesis of 3,4-disubstituted coumarins by site-selective cross-coupling reaction.[25] 4-Hydroxycoumarin **11** upon treatment with Tf_2O, NBS, and magnesium perchlorate in the presence of Et_3N afforded 3-bromo-2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**18**) and reaction with TsCl afforded 3-bromo-2-oxo-2*H*-chromen-4-yl methylbenzenesulfonate (**19**) (Scheme 7). Then compound **18** was coupled with arylboronic acids under nitrogen atmosphere in the presence of $Pd(PhCN)_2Cl_2$ to yield 4-aryl-3-bromocoumarins **20**. In a different procedure, compounds **18** and **19** were treated with arylboronic acids in the presence of $Pd(OAc)_2$, PCy_3, and $K_2HPO_4 \cdot 3H_2O$ in methanol at 60°C to afford various 3,4-diarylcoumarins **21**. Unsymmetrically substituted compounds **22** were synthesized from tosylates **19** sequentially applying different experimental conditions. A one-pot synthesis for the preparation of bisarylated coumarins **22** was also carried out using compounds **18** and **19** as starting materials under

Scheme 7



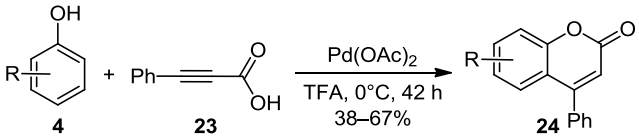
R^1, R^2 = Ph, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$F_3COC_6H_4$, 4-$O_2NC_6H_4$, 4-$MeO_2CC_6H_4$

different set of experimental conditions, but only a few examples with quite low yields were reported. The main idea of the whole strategy was to introduce various substituents to the C-3 and C-4 positions of the coumarin scaffold.

1.6. Synthesis of coumarins by Pd(II)-catalyzed reaction of phenols with propiolic acids

Kotani et al. proposed a direct route toward coumarin derivatives from phenols and propiolic acids in the presence of $Pd(OAc)_2$ as a catalyst.[26] The synthetic procedure involves reaction of substituted phenols **4** with phenylpropiolic acid **23** in the presence of $Pd(OAc)_2$ and TFA to give substituted coumarin derivatives **24** (Scheme 8). This synthesis was totally regioselective and atom economic as no additives were required and water was the side product.

Scheme 8



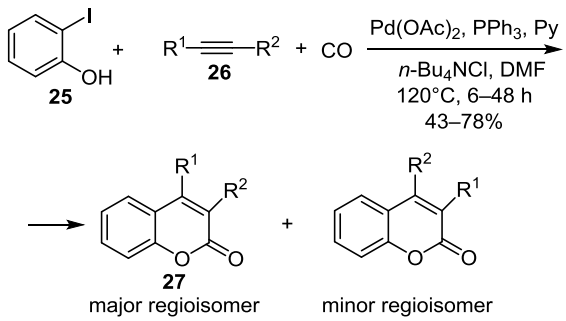
4 **23** **24**

R = Me, MeO, Ph, naphthyl, 1,3-dioxalanyl

1.7. Synthesis of coumarins *via* Pd-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols

Kadnikov et al. reported variety of substituted coumarins **27** obtained in good yields by Pd-catalyzed coupling of *o*-iodophenol with internal alkynes at 1 atm of CO pressure.[27] Unlike most of the previous work on the Pd-catalyzed carbonylation of alkynes, the insertion of the internal alkyne occurs in preference to the insertion of CO. Synthetic procedure involved a reaction of *o*-iodophenol (**25**), alkyne **26**, 1 atm of CO, 5 mol % of $Pd(OAc)_2$, PPh_3, pyridine, and *n*-Bu_4NCl in DMF at 120°C to yield various substituted coumarin derivatives **27** as depicted in Scheme 9. Pyridine base plays a crucial role in completion of the reaction. The use of higher pressures of CO resulted in the formation of a large number of unidentified products. The reactions were mostly regioselective, only in few cases mixtures of regioisomers were obtained, which were then separated by HPLC. The synthesis employs mild conditions and is compatible with a wide variety of functional groups.

Scheme 9



25 **26** **27**

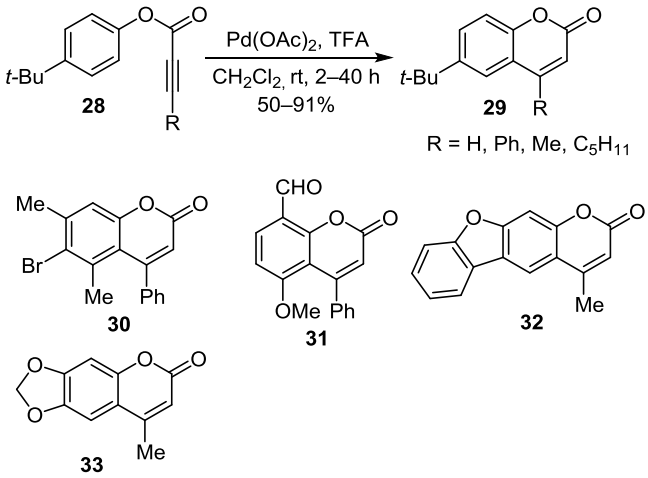
major regioisomer minor regioisomer

R^1, R^2 = Me, Et, *n*-Pr, *t*-Bu, Ph, MeCO, $SiMe_3$

1.8. Synthesis of coumarins by Pd-catalyzed intramolecular hydroarylation of C–C triple bonds

Intramolecular hydroarylation of C–C multiple bonds involves metalation of aromatic C–H bonds by oxidative insertion a transition metal, which is a significant approach in the synthesis of coumarins. Jia et al. reported Pd-catalyzed approach to synthesize coumarins by intramolecular hydroarylation of C–C triple bonds.[28] Various aryl alkynoates undergo fast intramolecular reaction at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$ in a mixed solvent containing TFA to afford coumarin derivatives. The synthetic process involves reaction of 4-*tert*-butylphenyl propiolates **28** and TFA in the presence of $Pd(OAc)_2$ giving various coumarin derivatives **29** in excellent yields (Scheme 10). Other derivatives **30**–**33** using different substrates were also prepared. No side reaction was observed. The cyclization was highly regioselective, affording kinetically favored six-membered rings. The reaction exhibited high chemoselectivity with groups like Br, CHO and heterocyclic moieties.

Scheme 10



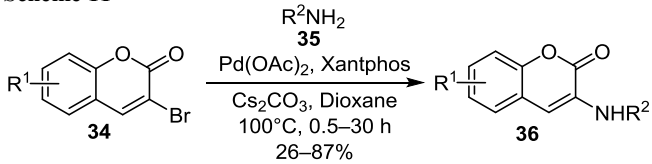
28 **29** **30** **31** **32** **33**

R = H, Ph, Me, C_5H_{11}

1.9. Synthesis of aminocoumarins *via* Pd-catalyzed Buchwald–Hartwig reaction

Buchwald–Hartwig reaction involves Pd-catalyzed formation of C–N bond by cross coupling of amines with aryl halides which is also a significant approach in the synthesis of aminocoumarins. Audisio et al. reported a convenient method for the synthesis of 3-aminocoumarins **36**[29] (Scheme 11). General synthetic procedure involves charging of dried resealable Schlenk tube with $Pd(OAc)_2$,

Scheme 11



34 **36**

R^1 = Me, OMe, Br, BnO; R^2 = Ph, CH_2Ph, CH_2CO_2Et, CO_2Bn, SO_2Me, SO_2Ph, COMe, (4-$MeOC_6H_4$)CO

Xantphos, Cs_2CO_3, 3-bromocoumarin **34**, and the corresponding nucleophile (amide, amine, carbamate, or sulfonamide) **35**. Then 1,4-dioxane is added through the septum and the mixture is stirred at 100°C. The resulting suspension is purified by column chromatography to obtain various 3-aminocoumarins **36**. This method has wide applications in the synthesis of diversified 3-aminocoumarins and compounds related to novobiocin, which is a target compound in anticancer drug discovery.

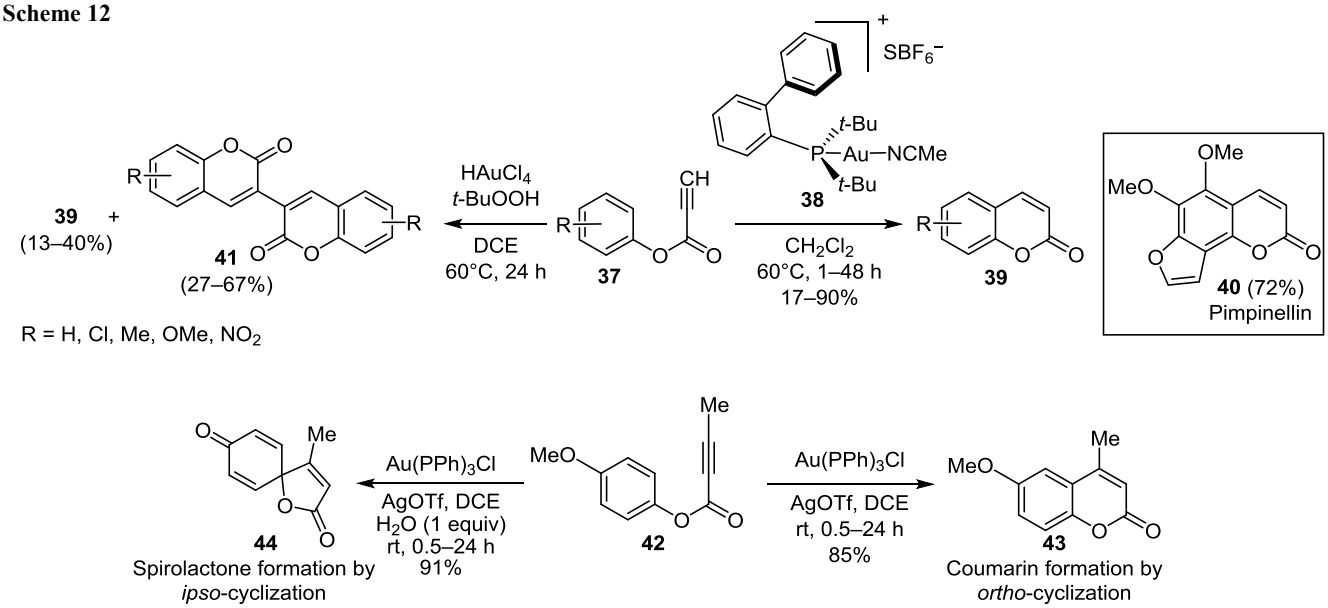
2. Au-catalyzed synthesis of coumarins

Gold was initially believed to be a nonreactive metal, although the first Au-catalyzed reaction was reported more than 40 years ago.[30] In recent years, the catalytic properties of gold have attracted attention due to its unique π-Lewis acid properties. Its catalytic properties have also been explored by some researchers to synthesize coumarin derivatives. Menon et al. reported Au(I)-catalyzed intramolecular hydroarylation of terminal alkynes under mild conditions to synthesize various coumarin derivatives.[31] A characteristic feature of this reaction was low catalyst loadings, mild reaction temperatures, short reaction times, no requirement of cocatalysts and additives. The synthetic procedure for coumarins involved reaction of aryl propargylates **37** and gold catalyst [(acetonitrile)[(2-biphenyl)di-(*tert*-butyl)-phosphine]gold(I)] hexafluoroantimonate **38** at ambient temperature in dichloromethane to yield various coumarin derivatives **39** in good yields as depicted in Scheme 12. Another application of Au(I)-catalyzed intramolecular hydroarylation was the synthesis of coumarin-containing natural product pimpinellin **40** which was reported by Cervi et al.[32] This method has proven to be operationally simple with mild reaction conditions and time-efficient. Au(I)-catalyzed intramolecular hydroarylation is highly useful for the synthesis of various scaffolds like 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines.

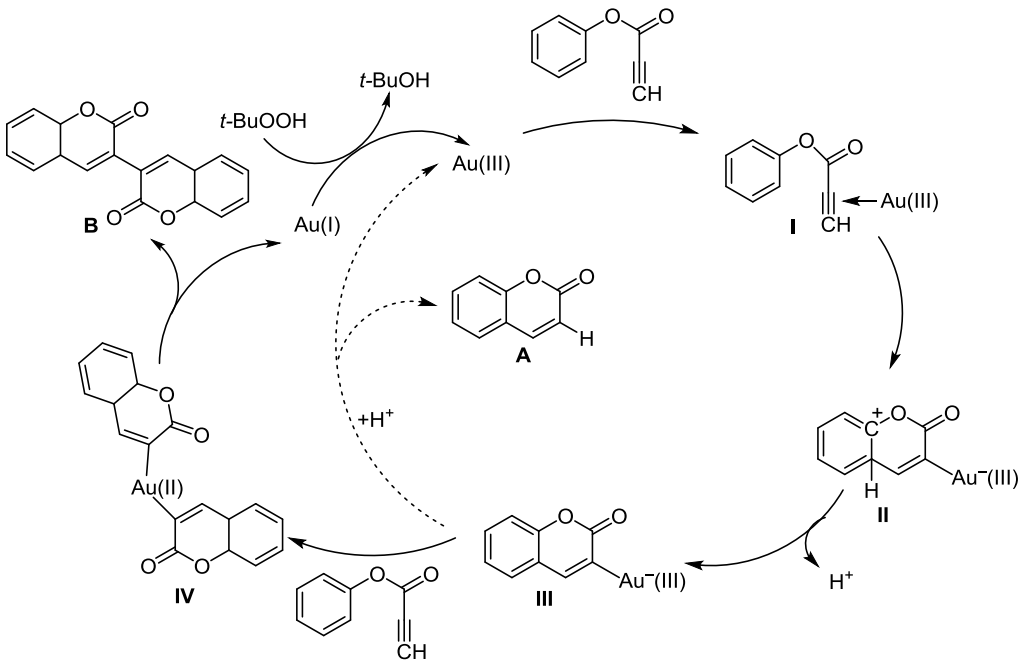
Another Au-catalyzed synthetic strategy was reported by Wegner et al. for the synthesis of coumarins *via* domino cyclization–oxidative coupling reaction.[33] This process involves cyclization followed by oxidative coupling of two coumarin subunits. The synthesis involved reaction of corresponding arylpropionic acid ester **37** with catalyst $HAuCl_4$ in presence of 1,2-dichloroethane (DCE), *tert*-butylhydroperoxide (*t*-BuOOH) at 60°C for 24 h to afford not only compounds **39**, but also coumarin dimers **41** as major products (Scheme 12). Based on these findings, the mechanism for the Au-catalyzed domino cyclization–oxidative coupling reaction can be explained (Scheme 13). First, the Au catalyst activates phenyl propiolate for electrophilic substitution to form complex **I** followed by cyclization to complex **II**. Then rearomatization results in the formation of complex **III** which again undergoes cyclization to produce complex **IV**. Protonation of complex **III** terminates the catalytic cycle and results in the formation of monomeric coumarin **A**. Complex **IV** undergoes oxidative coupling to form the dimeric coumarin **B** and an Au(I) species, which is subsequently reoxidized to Au(III), completing the catalytic cycle. This technique is highly significant in the synthesis of natural products with eminent biological activities.

Aparece et al. reported another Au-catalyzed strategy for the synthesis of coumarins which involved dearomative spirocyclization of aryl alkynoate esters.[34] Dearomative spirocyclization is an significant approach for the synthesis of biologically active compounds which involves electrophilic activation of functional groups triggering a Friedel–Crafts-type nucleophilic attack of arene leading to formation of C–C bond with dearomatization and formation of spirocyclic compounds. Water was found to play a critical role in govering the product selectivity. Anhydrous conditions lead selectively to coumarin products, while the addition of 1 equiv of water leads selectively to spirocycle **44** formation. The procedure involved reaction of 4-methoxyphenyl but-2-ynoate **42** with the catalyst in the presence of AgOTf and DCE to afford *ortho*-cyclized coumarin **43** as depicted in Scheme 12.

Scheme 12



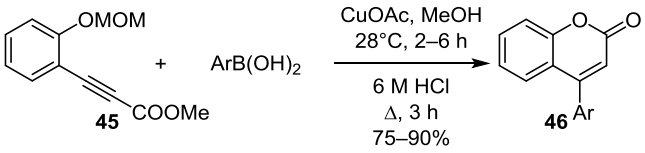
Scheme 13



3. Cu-catalyzed synthesis of coumarins

Literature reveals that copper has also played a crucial role in various methods for coumarin synthesis. Yamamoto et al. reported a Cu-catalyzed synthesis of coumarins **46** by reacting methyl phenylpropiolate having a MOM-protected hydroxyl group at *ortho* position **45** with various arylboronic acids in the presence of methanol and hydrochloric acid at 28°C (Scheme 14).[35] Coumarins **46** were obtained in excellent yields 75–90%. This methodology was compatible with a wide range of arylboronic acids bearing various functional groups including halogens. This approach was used for the synthesis of naturally occurring neoflavones.

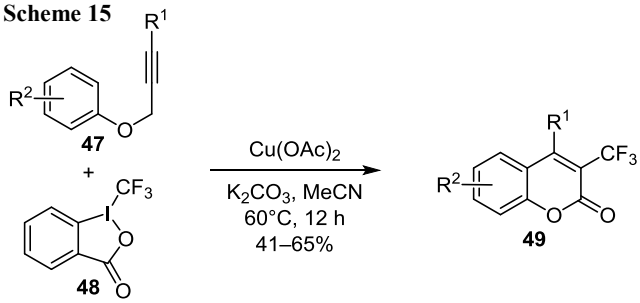
Scheme 14



Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-HOC_6H_4, 3-$O_2NC_6H_4$, 2-Naphth

In another approach, Li et al. reported Cu-catalyzed synthesis of trifluoromethylated coumarins **49** by trifluoromethylation of internal alkynes.[36] The reaction of propionic acid esters **47** with Togni's reagent **48** in the presence of K_2CO_3, MeCN, and $Cu(OAc)_2$ at 60°C gave trifluoromethylated coumarins **49** in good yields (Scheme 15). Mechanistic studies suggested that the reaction proceeds *via* radical formation and has good functional group tolerance. This technique was used for the synthesis of various coumarin derivatives of natural and synthetic origin.

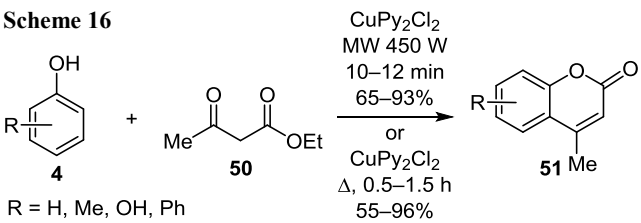
Scheme 15



R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, PMP, cyclopropyl
R^2 = H, Me, MeO, *t*-Bu, F, Cl, Br, I

Rajitha et al. prepared coumarin derivatives **51** by dipyridine copper chloride-catalyzed Pechmann condensation under conventional heating and microwave irradiation.[37] Conventional synthetic procedure involved reaction of phenolic compounds **4** and ethyl acetoacetate (**50**) under reflux in the presence of $CuPy_2Cl_2$ to obtain the corresponding coumarins **51** (Scheme 16). In microwave method, the mixture was heated at 450 W for 10–12 min. Substrates having electron-donating groups in the *para* position to the site of electrophilic substitution gave maximum yields under mild reaction conditions in a short period of time. This method was found to be one-pot condensation, just as traditional Pechmann reaction, that produces excellent yields of coumarin products without environmental pollution.

Scheme 16



R = H, Me, OH, Ph

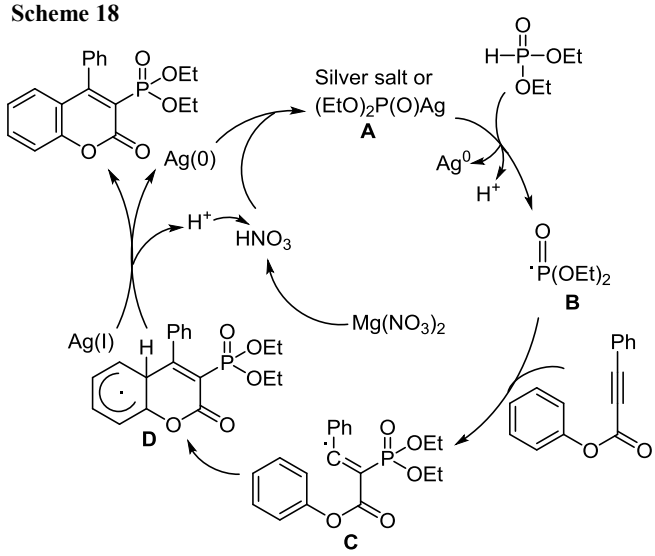
4. Ag-catalyzed synthesis of coumarins

Silver has tendency to catalyze the addition of phosphorous radical to alkynoates and to carry out direct cyclization to produce various phosphonated coumarins. Utilizing this property of silver, Mi et al. developed a process to synthesize 3-phosphonated coumarins by Ag-catalyzed difunctionalization of alkynes *via* a radical phosphonation and C–H functionalization.[38] Silver carbonate was employed in catalytic amount in the formation of C–P and C–C alkynoates to obtain coumarin derivatives with excellent yield. The typical experimental setup involved a reaction of substituted aryl alkynoates **52** with substituted phosphonates in the presence of Ag_2CO_3 catalyst, $Mg(NO_3)_2$, MeCN, and MS 4 Å at 100°C for 12 h to give various 3-phosphonated coumarin derivatives **53** (Scheme 17). Mechanistic studies indicate that the reaction pathway might proceed *via* generation and cyclization of a phosphonated vinyl radical intermediate. A plausible mechanism of the reaction is depicted in Scheme 18. First, a phosphorous radical **B** is generated from diethyl phosphonate by Ag_2CO_3 and the intermediate **A**. Then there is selective addition of P radical to the α-position of the C=O bond in phenyl 3-phenylprop-2-ynoate, which gives the vinyl radical **C** stabilized by the phenyl group. Then the intermediate **C** undergoes cyclization process to generate another intermediate **D**. Finally, a single-electron transfer from intermediate **D** to Ag(I) releases the product along with nitric acid and Ag(0) which is oxidized to Ag(I).[39]

In another approach, Yan et al. reported Ag-mediated radical cyclization of alkynoates and α-keto acids leading to coumarins *via* cascade double C–C bond formation.[40] The synthetic procedure involves reaction of aryl alkynoates **52** with α-keto acids **54** in the presence of catalytic amount of silver nitrate, potassium persulfate, and acetonitrile to afford difunctionalized coumarin derivatives **55** (Scheme 17). This procedure was completely regioselective and products were obtained in good yield.

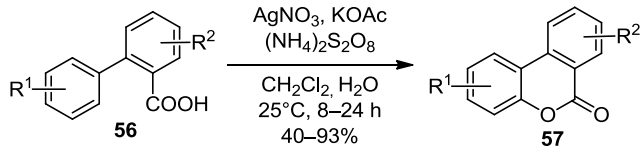
A different Ag-catalyzed strategy was proposed by Dai et al. which involved C(sp^2)–H functionalization – C–O cyclization reaction at room temperature. The synthetic procedure consisted of a reaction of biphenyl carboxylic acids **56** with $(NH_4)_2S_2O_8$ as oxidant in the presence of $AgNO_3$, CH_2Cl_2, H_2O at 25°C to afford various coumarin derivatives **57** (Scheme 19).[41] The kinetic isotope effect studies predicted that the reaction proceeds through the radical-mediated mechanism (Scheme 20). In the first step, Ag(I) is oxidized to Ag(II) which then reacts with an acid

Scheme 18



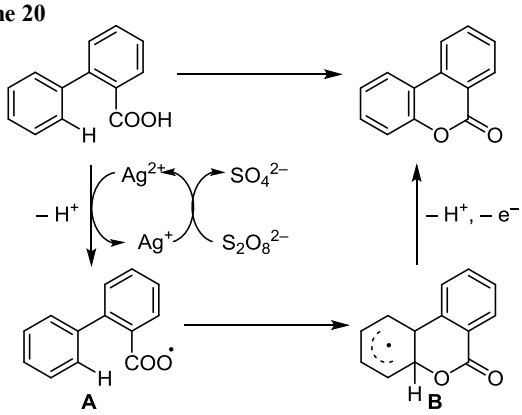
to give an intermediate – carboxy radical **A**. Then the carboxy radical **A** cyclizes into the aromatic ring to afford another intermediate **B** which further undergoes one-electron oxidation and proton loss to produce the final product. The advantage of this method is that it utilizes

Scheme 19

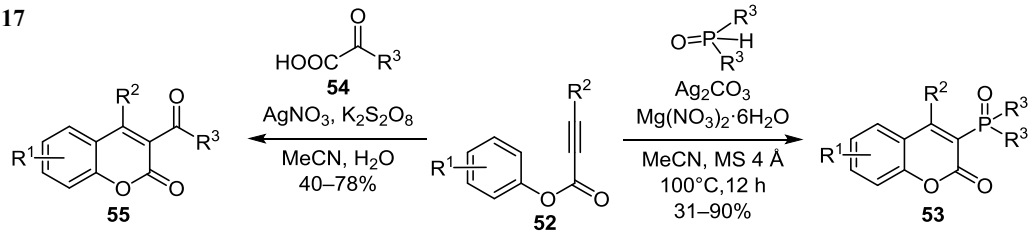


R^1 = Alk, Ar; R^2 = Alk, Ar, Het

Scheme 20



Scheme 17



R^1 = H, Me, CF_3, Cl, Br
R^2 = Ph, 4-BrC_6H_4, 4-ClC_6H_4
R^3 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 3-BrC_6H_4, 4-ClC_6H_4

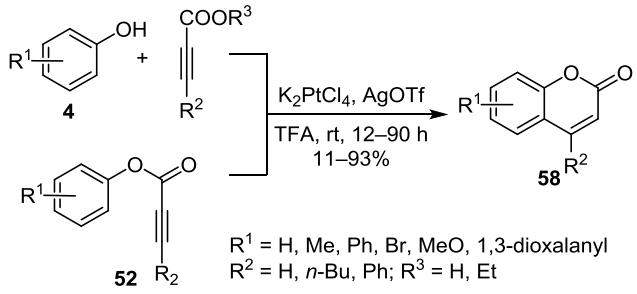
R^1 = H, Me, *n*-Bu, OMe, OPh, F,Cl,Br
R^2 = Ar, Alk
R^3 = Me, Et, *i*-Bu, Ph

inexpensive $AgNO_3$ catalyst and an environment-friendly $(NH_4)_2S_2O_8$ oxidant. Along with this, the reaction provides good substrate tolerance and chemoselectivity.

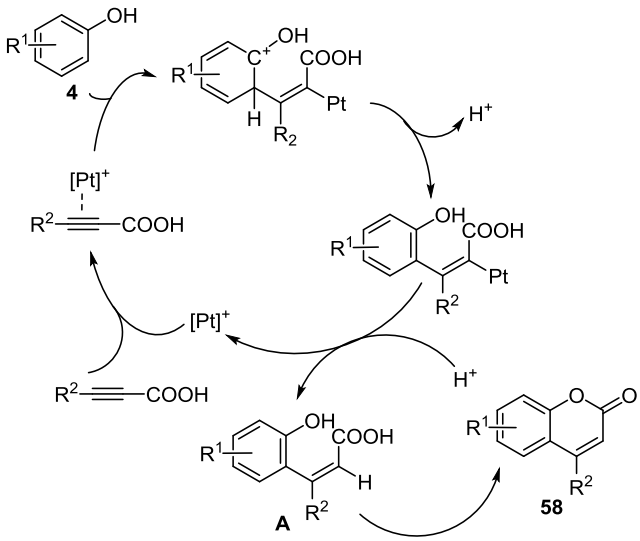
5. Pt-catalyzed synthesis of coumarins

Oyamada et al. reported the synthesis of coumarin derivatives by Pt-catalyzed hydroarylation of propiolic acid with phenols.[42] This reaction does not need any halogenated phenols. First, the synthesis of aryl-substituted alkenes was carried out by hydroarylation of alkynes using $PtCl_2$/AgOAc catalyst in TFA. This process of direct C–H functionalization was further expanded to synthesize newer coumarin derivatives by inter- or intramolecular hydroarylation of propiolates and substituted phenols. The K_2PtCl_4/AgOTf catalyst was found most effective for this hydroarylation. The typical synthetic procedure involved stirring of K_2PtCl_4/AgOTf and TFA at room temperature. Then significant amounts of corresponding phenol **4** and propiolic acid ester were added and stirred continuously to obtain the final product **58** (Scheme 21). The plausible mechanism for this reaction is depicted in Scheme 22. The reaction was thought to proceed through hydroarylation of phenol with propiolic acid, which gives *o*-hydroxy-substituted cinnamic acids **A** followed by the intermolecular esterification of the intermediate **A**. In another procedure, aryl alkynoates **52** were directly cyclized to coumarins **58** using the same catalyst (Scheme 21).

Scheme 21



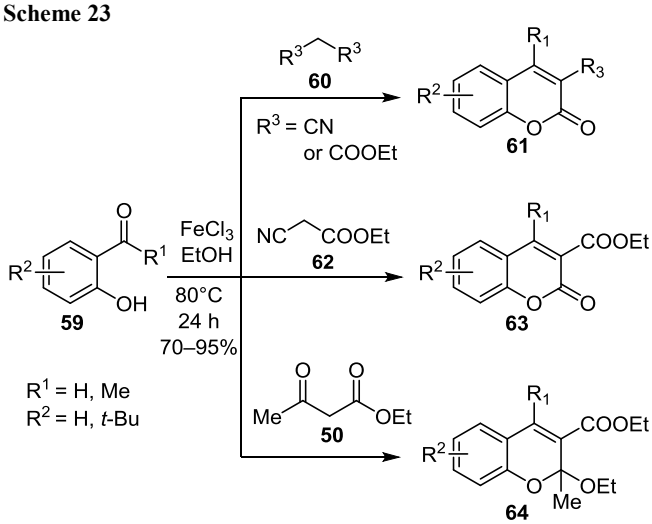
Scheme 22



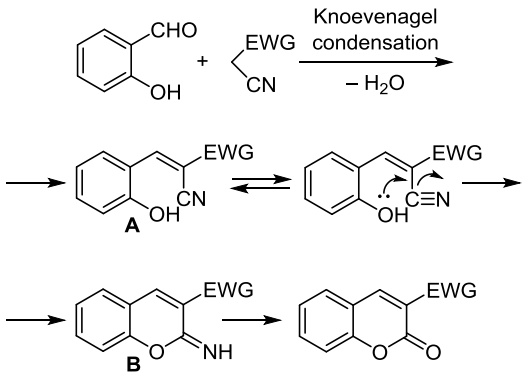
6. Fe-catalyzed synthesis of coumarins

Iron has found its prominent role as catalyst in the synthesis of various heterocycles, and recently iron trichloride ($FeCl_3$) has emerged as an ideal catalyst. He et al. reported the synthesis of new coumarin derivatives by cascade reactions of salicylaldehydes or acetophenones **59** and activated methylene compounds in presence of $FeCl_3$ catalyst.[43] The reaction is clean, preceeds under mild reaction conditions to provide the desired coumarin derivatives in good to excellent yields (70–95%). Compound **59** and malonate derivative **60** were heated at 80°C for 24 h in the presence of $FeCl_3$ and ethanol to afford the desired product **61** (Scheme 23). Similarly, compounds **63** and **64** were obtained using ethyl 2-isocyanoacetate (**62**) or ethyl acetoacetate (**50**), respectively. A plausible mechanism for the synthesis of compound **61** is depicted in Scheme 24. First, salicyladehyde reacted with activated methylene compounds in the presence of $FeCl_3$ to form benzylidene compounds **A** (Knoevenagel condensation). Subsequently, the oxygen of hydroxyl attacked the cyano group of the intermediate **A** to form the intermediate **B**, which then underwent hydrolysis to give the corresponding coumarin products. This approach is operationally simple and can be utilized to synthesize corresponding chromenols by utilizing ethyl acetoacetate.

Scheme 23



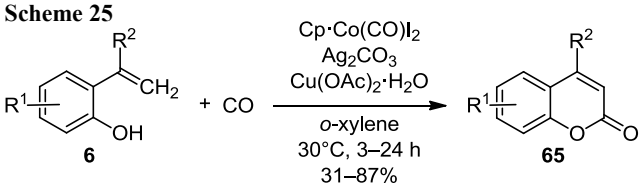
Scheme 24



7. Cocatalyzed synthesis of coumarins

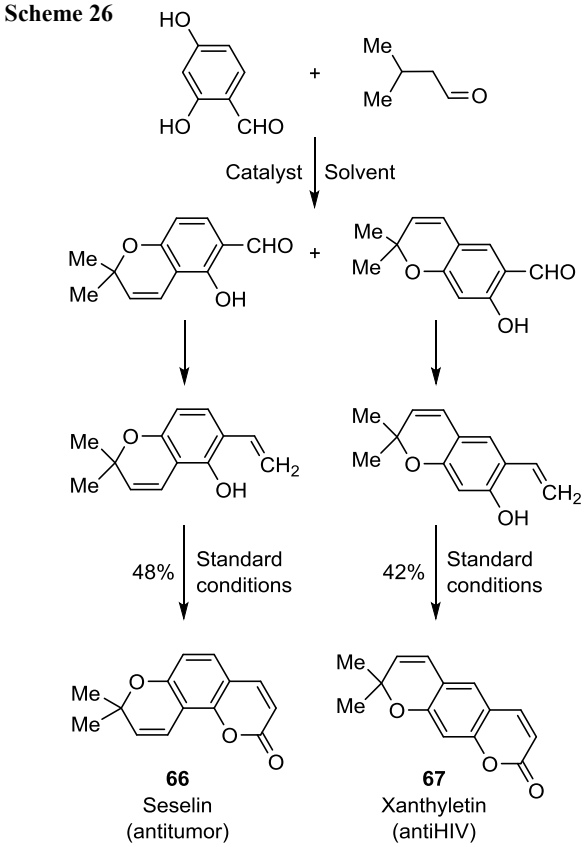
Liu et al. reported the synthesis of new coumarin derivatives by Cp·Co(III)-catalyzed annulations of 2-alkenylphenols with carbon monoxide.[44] The pleasant characteristics of this approach were mild reaction conditions, broad substrate scope, and good functional group tolerance. The typical synthetic procedure involved reaction of 2-alkenylphenol derivatives **6** with CO in the presence of $Cp·Co(CO)I_2$ catalyst at 30°C to afford substituted coumarins **65** (Scheme 25). Ag_2CO_3 as oxidant and *o*-xylene as solvent afford products in good yields 31–87%. A wide range of substrates was applicable in the optimized reaction conditions. This synthetic strategy was further utilized in the total synthesis of xanthyletin **67** and seselin **66**, which possess promising biolological activities, with good yields (Scheme 26). The plausible mechanism of annulations of 2-alkenylphenols and carbon monoxide was proposed on the basis of kinetic isotope effect (KIE) study. It was found that C–H bond cleavage was the turnover-determining step (Scheme 27). The active catalyst **A** is

Scheme 25

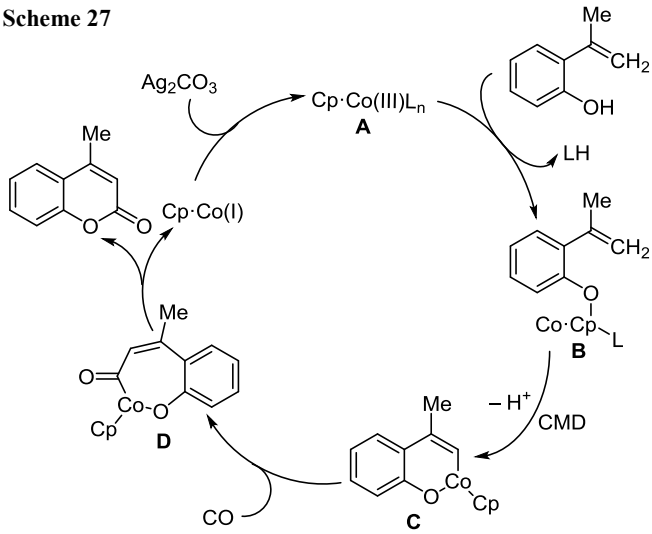


R^1 = H, Me, Cl, F, Br, NO_2, OMe, CF_3
R^2 = H, Me, Et, $(CH_2)_2Ph$, Ph, 4-CNC_6H_4, 4-$CF_3C_6H_4$

Scheme 26



Scheme 27

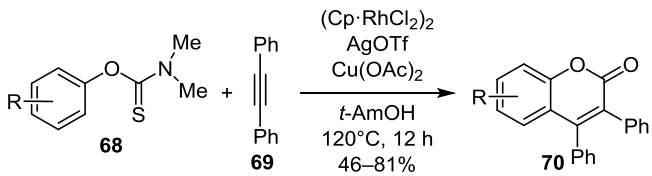


generated by reaction of $Cp·Co(CO)I_2$ with Ag_2CO_3. The ligand replacement takes place with vinylphenol to give an intermediate **B** which is converted to cyclometalated intermediate **C** by a concerted metalation deprotonation (CMD) process. After that, there is coordination of CO followed by a migratory insertion to generate compound **D**. Then final product coumarin is formed by reductive elimination.

8. Rh-catalyzed synthesis of coumarins

Zhao et al. reported a Rh-catalyzed synthetic pathway for the synthesis of coumarin derivatives by oxidative annulation of aryl thiocarbamates with internal alkynes.[45] This process exploits thiocarbamate group-directed C–H bond activation, annulation with an alkyne, and a desulfurization. Aryl thiocarbamate **68** with aromatic alkyne **69** in the presence of catalytic amounts of $(Cp·RhCl_2)_2$ and AgOTf with $Cu(OAc)_2$, added as oxidant as well as oxygen source, in *tert*-amyl alcohol (*t*-AmOH) at 120°C for 12 h gave final coumarin products **70** (Scheme 28).

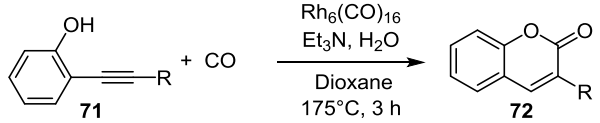
Scheme 28



R = H, Me, Et, OMe, Ph, Cl, Br, COMe, CO_2Me

Carbonylation of alkenes and alkynes catalyzed by transition metals is an important technique due to its wide industrial applications. The following approach was developed by Yoneda et al. for the synthesis of coumarins through Rh-catalyzed cyclic carbonylation of 2-alkynylphenols *via* water-gas shift reaction.[46] The mixture of 2-alkynylphenol **71**, $Rh_6(CO)_{16}$, catalyst, Et_3N, and water in 1,4-dioxane at 175°C for 3 h under 100 atm of carbon monoxide pressure gave the corresponding coumarin product **72** (Scheme 29). The hydroxy group adjacent to the C–C triple bond participated in the cyclic carbonylation.

Scheme 29



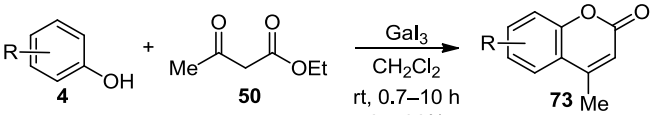
R = Me, *n*-Bu, *t*-Bu, Ph, 4-$MeOC_6H_4$, 4-CNC_6H_4

This method may be useful for the synthesis of diversified coumarin and benzofuranone (which is a major by-product in this reaction) derivatives directly from 2-alkynylphenols.

9. Ga-catalyzed synthesis of coumarins

Pechmann condensation involves formation of coumarins from phenol and carboxylic acid or ester containing a β-carbonyl group under acidic conditions. Sun et al. reported gallium triiodide-catalyzed synthesis of coumarin derivatives by Pechmann condensation.[47] The synthesis involved the reaction of phenols **4** with ethyl acetoacetate (**50**) in the presence of gallium triiodide in dichloromethane to form 4-methylcoumarins **73** (Scheme 30). This method was adaptive to the substrates with electron-donating groups and offered several advantages such as mild reaction conditions, short reaction times, high yields, and a simple experimental operation. It also revealed that GaI_3 is an effective and useful Lewis acid catalyst.

Scheme 30

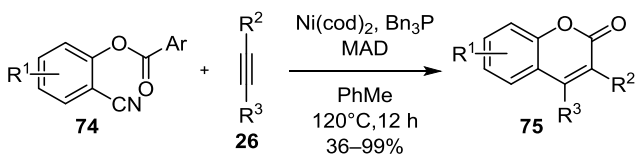


R = H, OH, OMe, NH_2, Ph

10. Ni-catalyzed synthesis of coumarins

Cycloaddition reaction involves combination of two or more unsaturated molecules leading to formation of a cyclic adduct with reduction in bond multiplicity. Nakai et al. reported Ni-catalyzed synthesis of coumarin derivatives by an intermolecular cycloaddition reaction.[48] The reaction showed an unusual mechanistic feature that is the cleavage of two independent C–CN and C–CO bonds. The synthetic strategy involved a catalytic system consisting of $Ni(cod)_2$, phosphine ligand Bn_3P, cocatalyst methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD). This system catalyzed the reaction of *o*-arylcarboxybenzonitriles **74** with internal alkynes **26** in the presence of PhMe at 120°C for 12 h to afford 3,4-disubstituted coumarins **75** in good yields (Scheme 31). A range of electron-donating and

Scheme 31

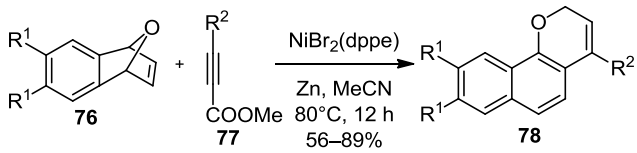


R^1 = H, OMe, Me, CF_3, F; R^2 = Me, Pr, Ph
R^3 = Pr, *i*-Pr, $(CH_2)_2OMe$, *n*-C_5H_{11}, $SiMe_3$
Ar = 4-$Me_2NC_6H_4$, 4-MeC_6H_4

electron-withdrawing ring substituents were tolerated under the optimized reaction conditions.

Another Ni-catalyzed method for the synthesis of benzocoumarin derivatives was developed by Rayabarapu et al. They have reported highly regioselective and stereoselective cyclization of substrates in a one-pot reaction.[49] The synthetic strategy involved the reaction of oxanorbornenes **76** with alkyl propiolates **77** in the presence of $NiBr_2$(dppe) (dppe = bis(diphenylphosphanyl)ethane), Zn powder, and acetonitrile at 80°C for 12 h to afford benzocoumarin derivatives **78** (Scheme 32).

Scheme 32

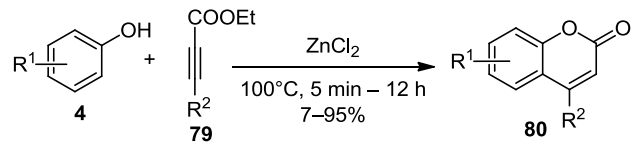


R^1 = H, OMe, Ph, 1,3-dioxalanyl
R^2 = H, Me, *n*-Bu, CH_2OMe, $(CH_2)_4Me$, $CH{=}CHCO_2Me$, Ph, $SiMe_3$

11. Zn-catalyzed synthesis of coumarins

Leao et al. reported Zn-catalyzed synthesis of coumarin derivatives by hydroarylation of acetylenic esters with phenols.[50] Zinc chloride was selected as catalyst on the basis of its ability to coordinate to both acetylenic esters (lowering its LUMO energy) and to the phenol which appears to be responsible for the regio- and stereoselectivity of the electrophilic aromatic substitution step. The catalytic amount of $ZnCl_2$ was added to the solution of appropriate phenol **4** and then mixed with suitable amount of acetylenic esters **79** at 100°C to afford substituted coumarin derivatives **80** (Scheme 33). This method provided an atom-economic synthesis of coumarins in acceptable yield (7–95%) using inexpensive Lewis acid catalyst. This method is of utmost importance for the synthesis of many coumarins and neoflavones.

Scheme 33



R^1 = H, OH, OMe, OBn, 1,3-dioxalanyl; R^2 = H, Me, Ph

Use of metals as catalysts have emerged as a very significant tool in the synthesis of coumarins and their derivatives. Palladium metal is the most widely used as catalyst in synthesis of various coumarins. Metals have catalyzed various synthetic reactions *via* different kinds of routes and mechanisms such as C–H alkenylation, oxidative cyclocarbonylation, oxidative Heck coupling, dicarbonylation, site-selective cross coupling, carbonylative annulations, intramolecular hydroarylation, Buchwald–Hartwig coupling, Pechmann condensation, difunctionalizations, cascade reactions, oxidative annulations, and cycloaddition reaction, etc. These synthetic strategies have

led to the development of new synthetic protocols for the total synthesis of many naturally occurring coumarins. Although metals have given excellent results as catalysts, they are associated with use of harmful oxidants, solvents, and complex procedures. So there is a dire need to develop new, eco-friendly and simple procedures by keen investigation of the existing strategies.

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