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A Facile and Promising Synthetic Strategy toward Functionalized 2*H*-Chromenes from Aryl Propargyl Ethers. A Review

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Introduction

2H-Chromenes (2H-1-benzopyrans) are a vitally important class of flavonoid compounds, which are present in a vast number of natural products and pharmaceutically active molecules.[1,2] For example (*Figure 1*), Lonchocarpin **1**, which has significant antiplatelet effects, was isolated from the ether extract of the seeds and roots of *Lonchocarpus Scericeus*.[3,4] Quercinol **2**, isolated from the wood-rotting fungus *Daedalea quercina* (Oak Mazegill), has *in vitro* anti-inflammatory activity against the enzymes cyclooxygenase 2 (COX-2), xanthine oxidase (XO), and horseradish peroxidase (HRP).[5] Rottlerin **3** (mallotoxin) is a highly functionalized 2H-chromene-based natural product isolated from the Asian tree *philippensis Mallotus*. Rottlerin displays strong inhibition toward the protein kinase Cdelta (PKCdelta).[6,7] Recently, Mao and co-workers were able to synthesize 6-bromo-8-ethoxy-3-nitro-2*H*-chromene **4** that exhibited potent antiproliferative activities against a panel of twelve tumor cell lines.[8] In addition to their biological applications, 2*H*-chromene derivatives are also valuable intermediates in organic synthesis[9–13] and have been widely used as photochromic materials.[14–17] Consequently, many efforts have been made to develop efficient synthetic methodologies to access functionalized 2*H*-chromene derivatives.[18,19]

One of the most important aims within modern organic synthesis is to develop new highly efficient single-step methods for the preparation of diverse molecules, methods that benefit from simple, inexpensive, and readily available starting materials. Intramolecular cyclization reactions are particularly important tools for the construction of synthetically challenging heterocycles, allowing the generation of at least one ring in a single step with high atom economy.[20–23] In connection with our series of review

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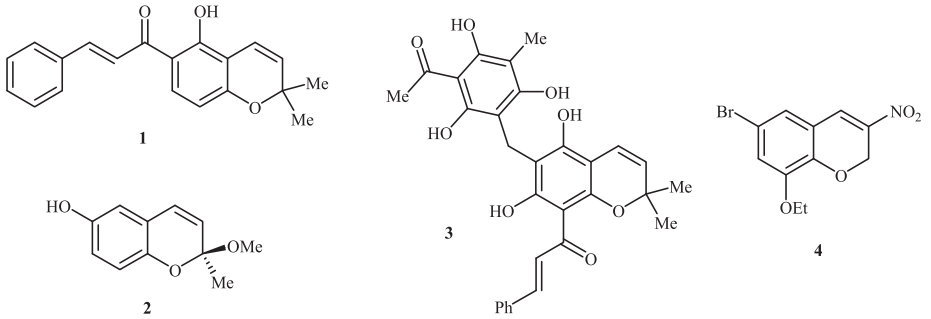


Figure 1. Selected examples of biologically active compounds containing a 2*H*-chromene core.

papers in the synthesis of heterocyclic compounds through intramolecular cyclization of heteroatom containing alkynes,[24–34] we summarize here a variety of methods for the synthesis of functionalized 2H-chromenes from inexpensive and readily accessible propargylic ethers. This approach to 2*H*-chromene synthesis presents many advantages, including cost, steps, and time benefits, as well as operational simplicity. We have classified these synthetic routes based on the type of reactions (hydroarylation, halocyclization, and thermal cyclizations), and the type of catalysts (Ag, Au, and In). The most detailed discussion is focused on the synthesis of 2*H*-chromene cores *via* hydroarylation reactions. It should be noted that we have not discussed the synthesis of coumarins, since it has very recently been described in another publication.[35]

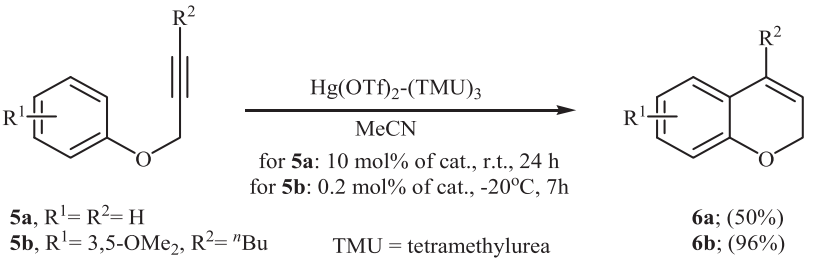
I. Hydroarylation Reactions

1. Mercuric

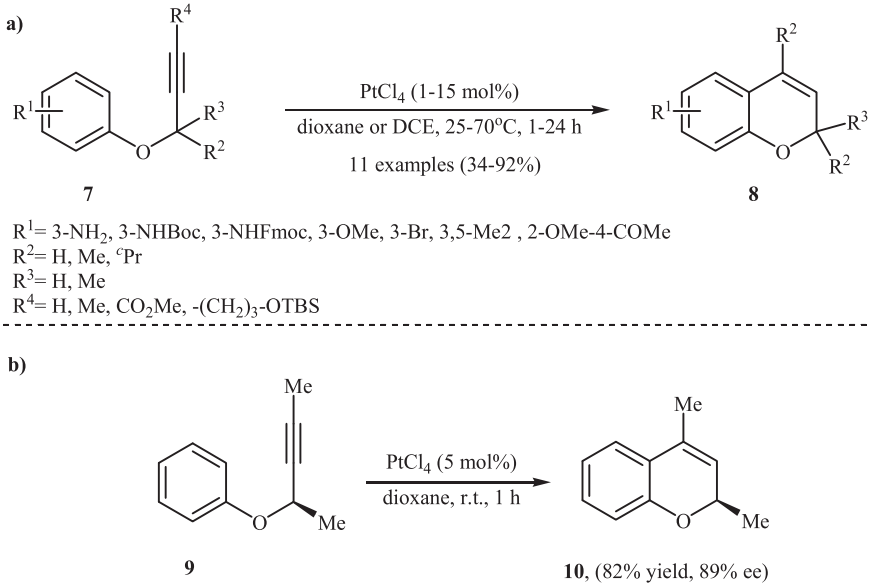
Mercuric-catalyzed cyclization of aryl propargyl ethers into 2H-chromenes has been scarcely studied; in fact, only one example of such a reaction was reported in the literature. In 2003, the group of Nishizawa was able to demonstrate that a mercuric complex can efficiently catalyze the intramolecular hydroarylation of substituted aryl propargyl ethers **7** to the corresponding 4-substituted-2*H*-chromenes **8** in moderate to excellent yields (*Scheme 1*). The catalysts studied includeed $Hg(OTf)_2$, $Hg(OAc)_2$, $Hg(OCOCF_3)_2$, $Hg(OTf)_2$-$(TMU)_n$ (n = 1–5), $Hg(OCOCF_3)_2$-TMU; and $Hg(OTf)_2$-$(TMU)_3$ was the most efficient for this reaction. The authors also successfully applied this methodology to the preparation of 1,2-dihydroquinoline and 1,2-dihydronaphthalene derivatives through the cyclization of the corresponding propargyl anilines and 1-(but-3-ynyl)benzenes, respectively. The results showed that substrates with internal alkyne units gave higher yields than those with terminal units.[36]

2. Platinum

In 2003, Pastine, Youn, and Sames synthesized a series of functionalized 2H-chromenes **8** through intramolecular hydroarylation of aryl propargyl ethers **7** employing $PtCl_4$ as catalyst and dioxin or DCE as solvent. $PtCl_2$ was also found to promote the reaction in lower yields. The reaction was carried out under mild conditions (25–70 °C) for 1–24 h and provided the expected products in moderate to high yields (*Scheme 2a*). With



Scheme 1. $Hg(OTf)_2$-$(TMU)_3$-catalyzed intramolecular hydroarylation of aryl propargyl ethers **5**.

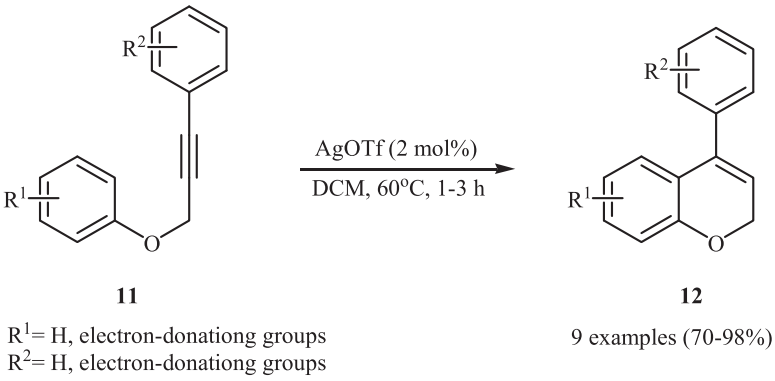


Scheme 2. (a) Pt(IV)-catalyzed cyclization of aryl propargyl ethers **7** reported by Sames; (b) Pt(IV)-catalyzed enantioselective synthesis of **10**.

regard to the electronic effects of substituents on the aryl ring, substrates with electron-donating groups gave higher yields than those with electron-withdrawing groups. As shown in *Scheme 2a*, the reaction displayed very good functional group tolerance, including bromo, alkoxy, amino, and ester functionalities that would allow further elaboration of the products. The authors also successfully utilized this catalytic system in the enantioselective synthesis of 2*H*-chromene **10** from the corresponding chiral propargylic ether **9** (*Scheme 2b*).[37,38]

3. Silver

In 2012, Arcadi and Fabrizi along with their co-workers demonstrated for the first time the usefulness of silver catalysts for the intramolecular hydroarylation of aryl propargyl ethers. Thus, in the presence of inexpensive and readily accessible AgOTf as catalyst in DCM at 60 °C, intramolecular cyclization of aryl-substituted aryl propargyl ethers **11** furnished the corresponding 4-aryl-substituted-2*H*-chromenes **12** in good to almost

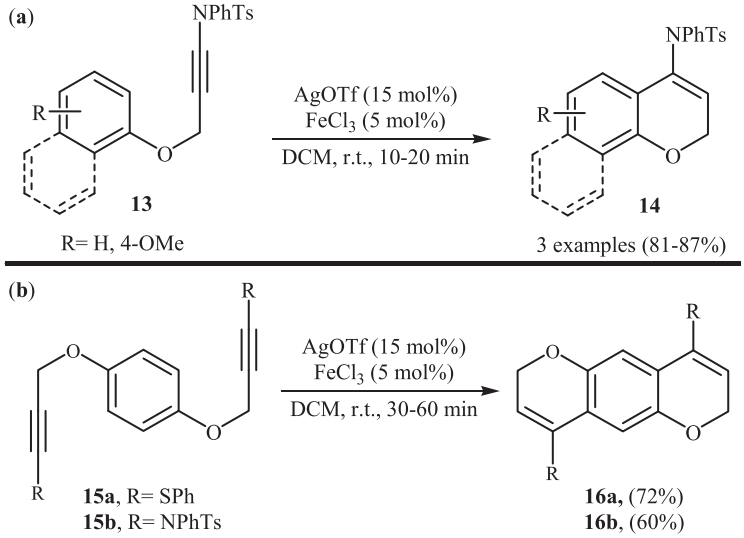


11 **12**

R^1= H, electron-donationg groups
R^2= H, electron-donationg groups

9 examples (70-98%)

Scheme 3. AgOTf-catalyzed synthesis of 4-aryl-substituted-2*H*-chromenes **12**.



13 **14**

R= H, 4-OMe

3 examples (81-87%)

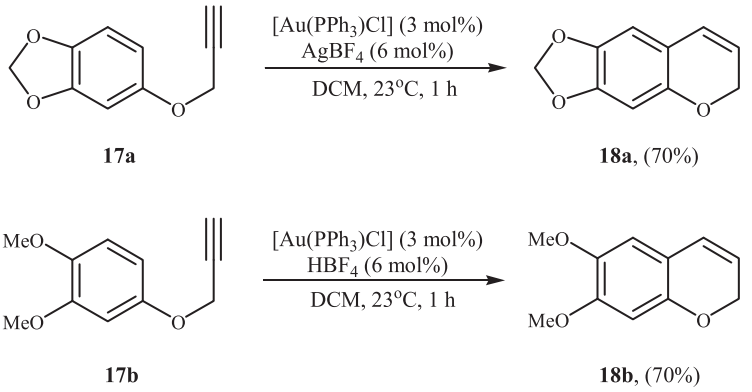
15a, R= SPh
15b, R= NPhTs

16a, (72%)
16b, (60%)

Scheme 4. (a) Fe/Ag-catalyzed hydroarylation of aryl propargyl ethers **13**; (b) Lee's synthesis of tricyclic ring systems **16**.

quantitative yields (*Scheme 3*). However, substrates bearing electron deficient arenes either failed to participate in this reaction or produced the corresponding products in low yields. It should be mentioned that in the case of *meta*-substituted aryl propargyl ethers, the mixture of both possible isomers (1:1 ratio) was obtained.[39]

In the same year, *N*-phenyl-*N*-tosyl-substituted aryl propargyl ethers **13** were found by Lee and co-workers to undergo intramolecular hydroarylation in the presence of 15 mol% of AgOTf and 5 mol% of $FeCl_3$, using dichloromethane as solvent at room temperature, to afford 4-*N*-phenyl-*N*-tosyl-substituted-2*H*-chromene derivatives **14** in 81-87% yields (*Scheme 4a*). The cyclization also allowed the synthesis of tricyclic ring systems **16** through double cyclization reactions of corresponding aryl di-propargylic ethers **15** (*Scheme 4b*). It is noted that similar reaction conditions were also successfully applied to the synthesis of 4-phenylsulfenyl-substituted-2*H*-chromenes from the corresponding propargylic ethers.[40]



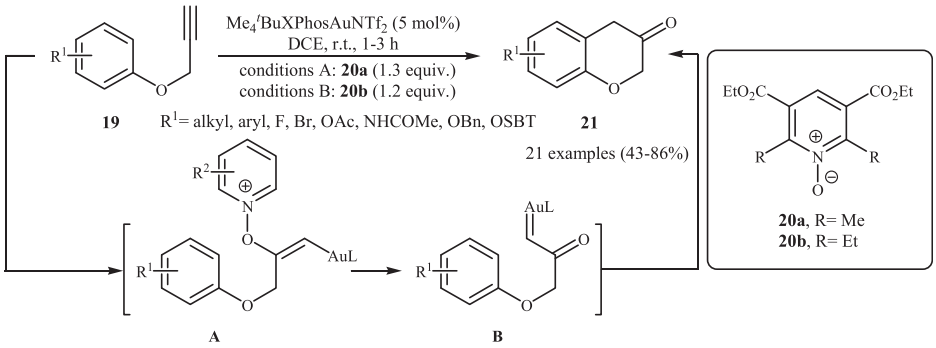
Scheme 5. Synthesis of 2*H*-chromenes **18** *via* gold-catalyzed cyclization of aryl propargyl ethers **17**.

4. Gold

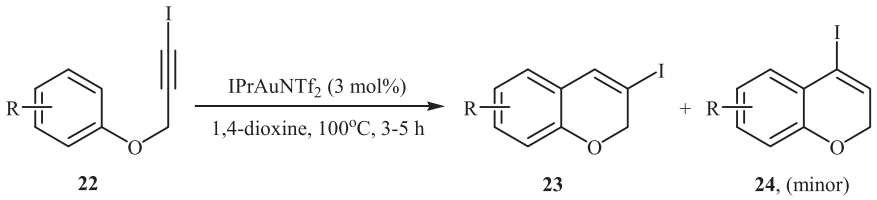
The use of gold catalysts for the intramolecular hydroarylation of aryl propargyl ethers has recently received increased interest. One of the earliest reports of the applicability of gold catalysts in this area had been reported by Nevado, Antonio, and Echavarren in 2005, when aryl propargyl ethers **17** underwent a cyclization reaction in the presence of [Au(PPh_3)Cl] in DCM to form the corresponding 2*H*-chromenes **18**. Some reported examples are shown in *Scheme 5*.[41] Inspired by this work, numerous gold-based catalytic systems have been developed. These include: [Au(PPh_3)NTf_2],[42,43] [Au(PPh_3)Cl]/$AgSbF_6$,[44–46] Au-nanoparticles supported on TiO_2,[47] and [Au(IPr)NTf_2].[48]

In 2012, an interesting and elegant approach for the construction of synthetically challenging chroman-3-one derivatives **21** through gold-catalyzed oxidation of the corresponding terminal aryl propargyl ethers **19** was demonstrated by Zhang and co-workers. The optimum conditions for this novel oxidative cyclization reaction used the combination of $Me_4{}^t$BuXPhosAuNTf_2 (5 mol%) as catalyst and pyridine *N*-oxide derivatives **20** (1.2–1.3 equiv) as oxidants with DCE as the solvent, at room temperature. It should be mentioned that other gold catalysts such as ^{t}BuXPhosAuNTf_2 and BrettPhosAuNTf_2 were also found to promote the reaction but in lower yields. Under optimized conditions, the expected chroman-3-ones **21** were obtained in moderate to high yields (*Scheme 6*). The reaction showed excellent functional group tolerance, including fluoro, bromo, methoxy, amide and ester functionalities that would allow further elaboration of the products.[49]

Shortly afterwards, Poladura, Rubio, and González reported an elegant approach for the synthesis of synthetically important 4-unsubstituted-3-iodo-2*H*-chromenes **23** *via* a gold-catalyzed iodine-shift hydroarylation of 1-(3-iodoprop-2-ynyloxy)benzenes **22**. The optimum conditions for this reaction utilize 3 mol% of IPrAuNTf_2 as the catalyst and 1,4-dioxane as the solvent. Under optimized conditions, the reaction tolerates both electron-rich and electron-poor substrates and gives the corresponding 3-iodo-2*H*-chromenes **23** in good to excellent yields (*Scheme 7*). It is noted that in some cases mixtures of the desired product **23** and trace amounts of 4-iodo-2*H*-chromenes **24** were formed. Beside good yields, short reaction times and broad substrate scopes were other advantages of this synthetic procedure. Notably, the use of chiral starting materials in this reaction led to the chiral products with retention of configuration in up to 99% *ee*.



Scheme 6. Synthesis of chroman-3-ones **21** through gold-catalyzed oxidation of aryl propargyl ethers **19**.



R= 4-CN, 4-CHO, 4-CO_2Et, 4-NO_2, 3-Br, 2-Cl-4-F, 2-Me-5-Br, 2,4,5-Cl_3

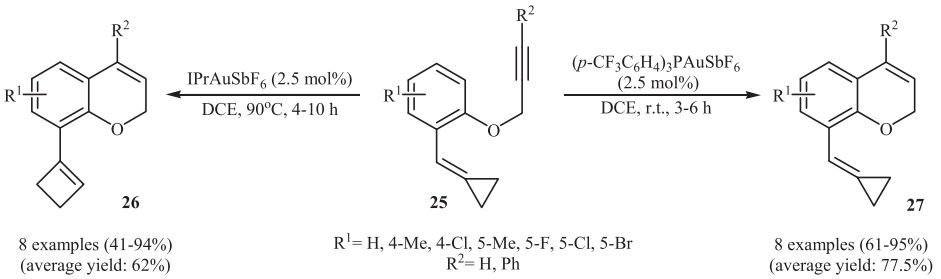
Scheme 7. Gold(I)-catalyzed hydroarylation reaction of 1-(3-iodoprop-2-ynyloxy)benzenes **22**.

Interestingly, this process can also be scaled up to provide multigram quantities of the desired product without obvious loss in the yield or outcome.[48]

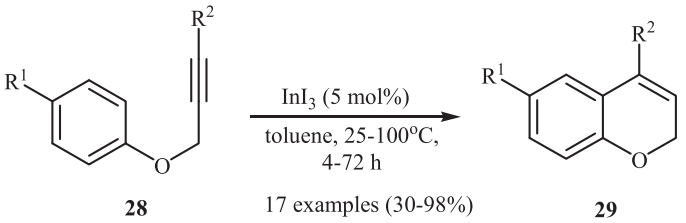
Recently, Fang, Tang, and Shi demonstrated an elegant sequential Au(I)-catalyzed intramolecular hydroarylation/ring enlargement of methylenecyclopropanes containing aryl propargyl ethers **25** to cyclobutene containing 2*H*-chromene derivatives **26**. They observed that the use of 2.5 mol% of $IPrAuSbF_6$ as catalyst in DCE was the best system for the transformation. Under the optimized conditions, an array of cyclobutene-containing 2*H*-chromene derivatives was successfully produced. Interestingly, when (p-$CF_3C_6H_4)_3PAuSbF_6$ (2.5 mol%) was used as the catalyst, methylenecyclopropanes containing 2*H*-chromenes **27** were formed in good to excellent yields at room temperature, without any **26** (*Scheme 8*).[50]

5. Indium

One of the latest metal catalysts to be used in the intramolecular hydroarylation of aryl propargyl ethers is indium. In 2015, Sestelo and co-workers showed that indium halides could regioselectively catalyze the intramolecular cyclization of aryl propargyl ethers to the corresponding 2*H*-chromenes. Among the common indium(III) halides, ($InCl_3$, $InBr_3$, and InI_3), InI_3 was the most efficient for this transformation. Interestingly, the use of $In(OTf)_3$ as catalyst led to decomposition of the aryl propargyl ethers. In their optimization study, they found that using a coordinating solvent such as THF or MeOH



Scheme 8. Gold-catalyzed selective synthesis of 2*H*-chromenes **26** and **27**.



Scheme 9. Indium(III)-catalyzed intramolecular hydroarylation of aryl propargyl ethers **28**.

gave trace amounts of the product and using a noncoordinating solvent (*e. g.* CH_2Cl_2 and toluene) gave 6-methoxy-2*H*-chromene in high yield. The results suggested that toluene exhibited relatively better performance than DCM. Under optimized conditions the reaction tolerates both internal and terminal aryl propargyl ethers **28** bearing electron-rich and electron-deficient substituents in the benzenes and alkynes and gave the expected 2*H*-chromenes **29** in moderate to excellent yields (*Scheme 9*). A sequential In(III)-catalyzed intramolecular hydroarylation/Pd-catalyzed Sonogashira coupling can be performed in one reaction vessel to produce more functionalized products.[51] Recently, Menkir and Lee investigated the detailed reaction mechanism of $InCl_3$-catalyzed hydroarylation of aryl propargyl ether **28a** with density functional theory (DFT). As shown in *Figure 2* this reaction is predicted to be a three-step process: (i) 6-*endo-dig* cyclization (TS-1); (ii) deprotonation (TS-2a); and (iii) protonation (TS-3a). The authors proposed that the reaction proceeds through the coordination of InI_3 to the triple bond of aryl propargyl ether **28**, following the regioselective 6-*endo dig* cyclization through nucleophilic attack of the aromatic ring onto the activated triple bond to give intermediate **A**, which after a deprotonation/protonation step affords intermediate **B**. Finally, the proto-demetalation of **B** yields the observed product **29** (*Scheme 10*).[52]

Very recently, Martínez and Sestelo along with their co-workers reported an efficient and elegant protocol for the synthesis of 4-substituted-2*H*-chromenes **32** through a sequential dual-catalyzed In/Pd intramolecular hydroarylation-cross-coupling reaction of bromopropargyl aryl ether **30** with electrophilic partners **31**. This process was run in toluene under relatively mild conditions and generally provided 2*H*-chromenes **32** in moderate to almost quantitative yields (*Table 1*).[53]

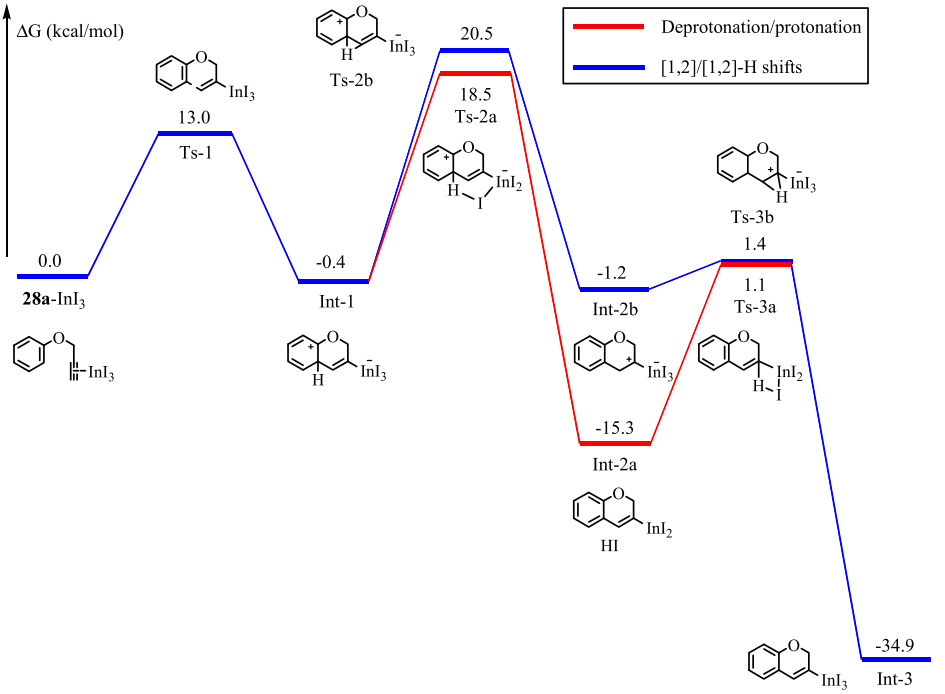
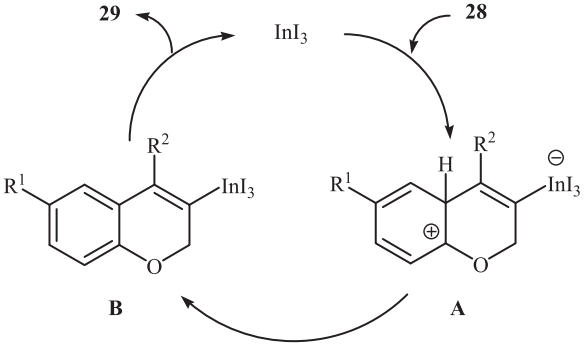


Figure 2. Potential energy profile of the In(III)-catalyzed intramolecular hydroarylation of aryl propargyl ether **28a** (energies are in kcal mol^{-1}). (Modified from reference 52.)

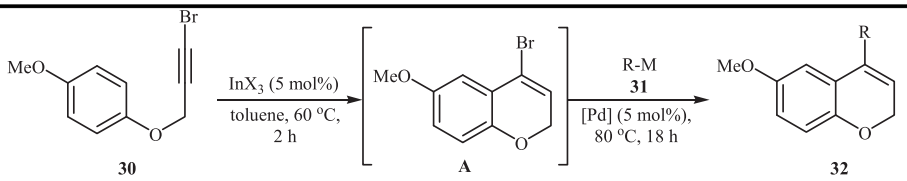


Scheme 10. Proposed mechanistic pathways for the formation of **29**.

6. Rhodium

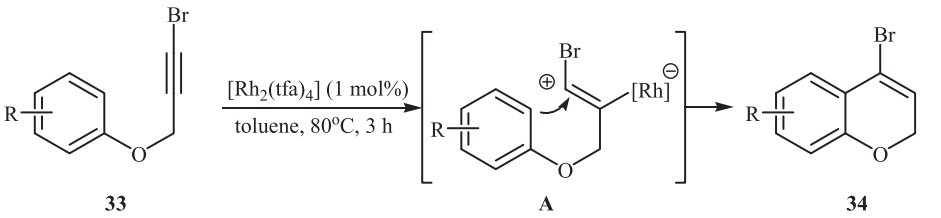
Recently, the first rhodium-catalyzed transformation of aryl propargyl ethers to obtain functionalized 2*H*-chromenes was described. H. Urabe and co-workers reported that bromopropargyl aryl ethers **33** were converted into 4-bromochromenes **34** *via* a regioselective 6-*endo-dig* hydroarylation by employing only 1 mol% of ($[Rh_2(tfa)_4]$, $tfa = CF_3CO_2$) as catalyst in toluene (*Scheme 11*). The isomeric five-membered products were not detected, and the structure of 4-bromochromenes **34** were unambiguously determined by their hydrogenation to the known 3,4-dihydro-2H-chromenes. A variety of protected amino-substituted chloropropargyl aryl ethers also react under analogous

Table 1
Sequential In-catalyzed Intramolecular Hydroarylation and Pd-catalyzed Cross-coupling of Bromopropargyl Aryl Ether **30**



Entry	InX_3	R-M (0.5 equiv.)	[Pd]	Yield (%)[a]
1	$InCl_3$	Ph_3In	$Pd(PPh_3)_2Cl_2$	95
2	$InBr_3$	Ph_3In	$Pd(PPh_3)_2Cl_2$	57
3	InI_3	Ph_3In	$Pd(PPh_3)_2Cl_2$	60
4	$InCl_3$	$(2\text{-thienyl})_3In$	$Pd(PPh_3)_2Cl_2$	85
5	$InCl_3$	$(Phc \equiv c)_3In$	$Pd(PPh_3)_2Cl_2$	72
6	$InCl_3$	Bu_3In	$Pd(PPh_3)_2Cl_2$	70
7	$InCl_3$	Me_3In	$Pd(PPh_3)_2Cl_2$	89
8	$InCl_3$	PhZnCl[b]	$Pd(PPh_3)_4$	40
9	$InCl_3$	$PhSnBu_3$[c]	$Pd(PPh_3)_4$	40
10	$InCl_3$	$PhB(OH)_2$[d]	$Pd(PPh_3)_4$	87

[a]Isolated yield.
[b]4.0 equiv of PhZnCl.
[c]4.0 equiv of $PhSnBu_3$ at 100 °C.
[d]2.2 equiv $PhB(OH)_2$, Na_2CO_3 (6 equiv.) in toluene:EtOH (2:1).

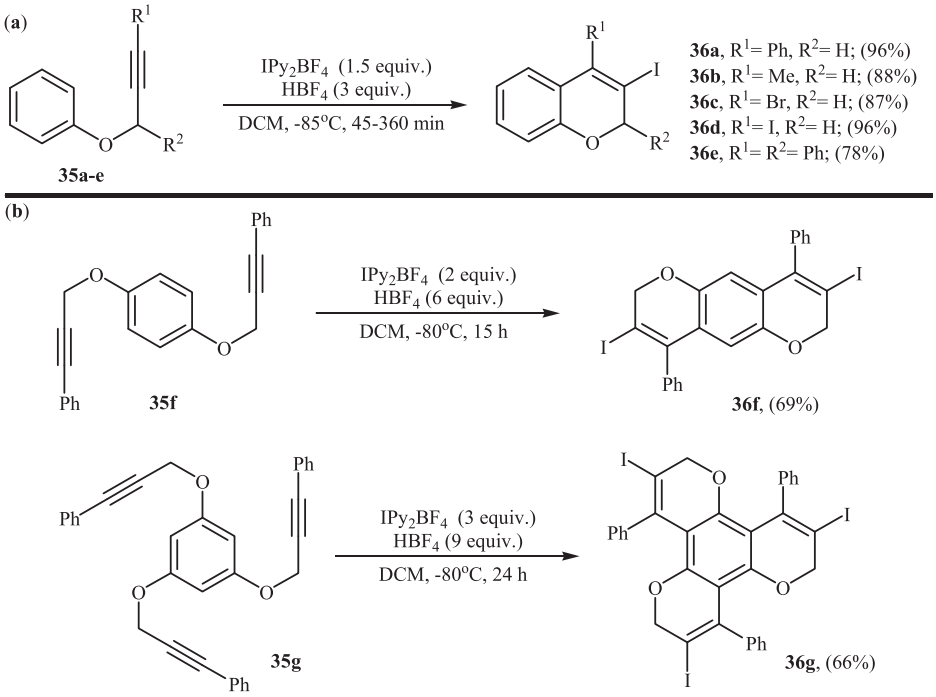


Scheme 11. Rh-catalyzed synthesis of 4-bromochromenes **34** developed by Urabe.

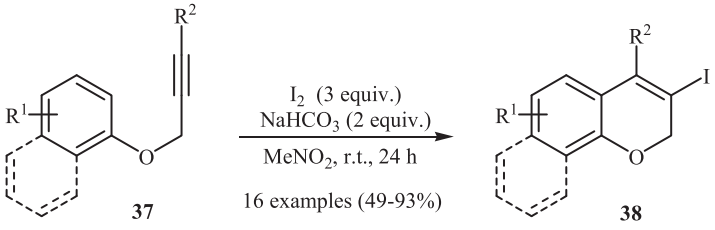
conditions to give good to excellent yields (62–97%) of the corresponding 4-chlorochromenes.[54]

II. Haloarylation Reactions

In 2005, Barluenga and co-workers reported the preparation of a variety of 3-iodo-2*H*-chromenes **36** in good to excellent yields *via* intramolecular iodoarylation of internal aryl propargyl ethers **35** (*Scheme 12a*). The reactions were carried out in DCM at −80 °C with 1.5 equiv of bis(pyridine)iodonium tetrafluoroborate (IPy_2-BF_4) as the electrophilic source. The reaction was highly regioselective, since the six-membered



Scheme 12. (a) The intramolecular iodoarylation reaction of aryl propargyl ethers **35a-e** reported by Barluenga; (b) double and triple cyclizations of propargyl ethers **35f, g**.

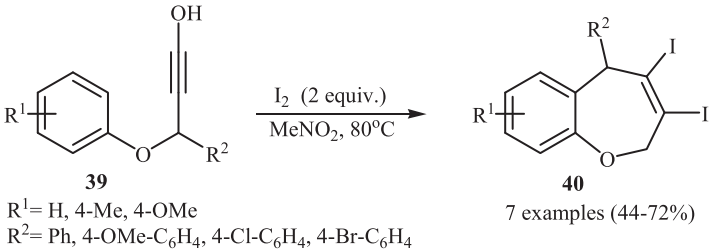


R^1= H, 4-Me, 4-^{t}Bu, 4-OMe, 4-COH, 4-Cl, 3-OMe, 3-^{t}Bu, 3-Cl, 3,5-^{t}Bu$_2$
R^2= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NO_2-C_6H_4, 1-^{c}Hex, CH_2OH

Scheme 13. Larock's synthesis of 3-iodo-substituted-2*H*-chromenes **38**.

ring 2*H*-chromenes were obtained in the complete absence of five membered product. Interestingly, the cyclization allowed additional substitution in the propargylic position, providing the possibility of double and triple cyclizations, quite useful for the quick assembly of systems with extended conjugation (*Scheme 12b*). They also found that the reaction of aryl propargyl ethers with iodine in water gave the corresponding 2*H*-chromenes in moderate to good yields.[55]

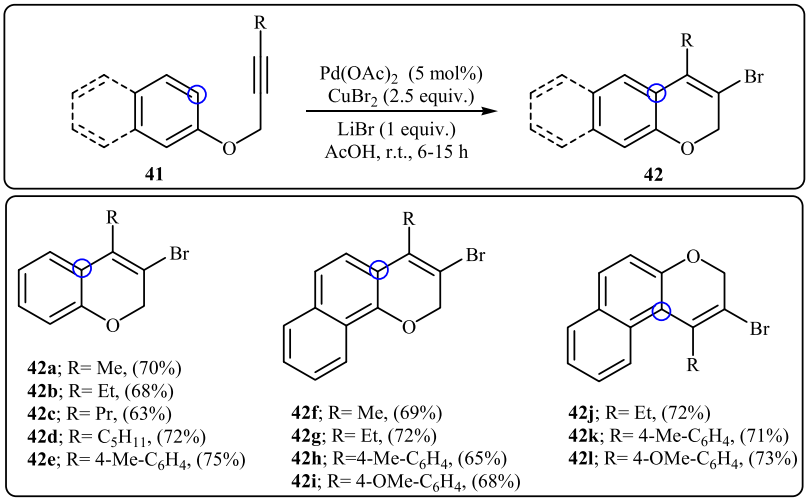
With the objective of designing a milder procedure to form 3-iodo-2*H*-chromenes through iodoarylation, Larock demonstrated that a wide variety of 3-iodo-substituted-2*H*-chromenes **38** could be obtained from the treatment of substituted aryl propargyl ethers **37** with I_2 (3 equiv.) as electrophilic source and $NaHCO_3$ (2 equiv.) as a base in $MeNO_2$ at room temperature (*Scheme 13*). The optimized protocol tolerated various functional groups,



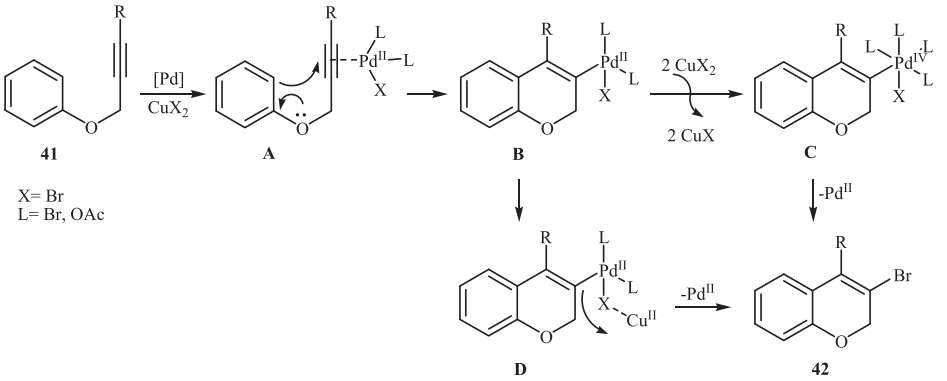
Scheme 14. Synthesis of 3,4-diiodophenyldihydrobenzo[b]-oxepines **40** through iodo-cyclization of aryl propargyl ethers **39**.

including hydroxyl, methoxyl, nitro, and alkyne, and generally provided the desired product in moderate to excellent yields. However, terminal propargylic ethers and methyl-substituted internal propargylic ethers failed to participate in this cyclization. It should be mentioned that no regioselectivity has been observed in the case of *meta*-substituted aryl propargyl ethers. The authors found that when ICl was used as the electrophilic source, the iodocyclization produced the expected 2*H*-chromenes even in the absence of $NaHCO_3$. It is noted that in many cases better yields were observed with ICl.[56,57] When aryl propargyl ethers **39** having a -CHROH group on the propargylic terminus were treated with I_2 in $MeNO_2$ at 80 °C, another type of cyclization reaction was observed. In these cases an unusual electrophile-promoted domino process occurred to give 3,4-diiodophenyldihydrobenzo[b]-oxepines **40** as sole products (*Scheme 14*).[58]

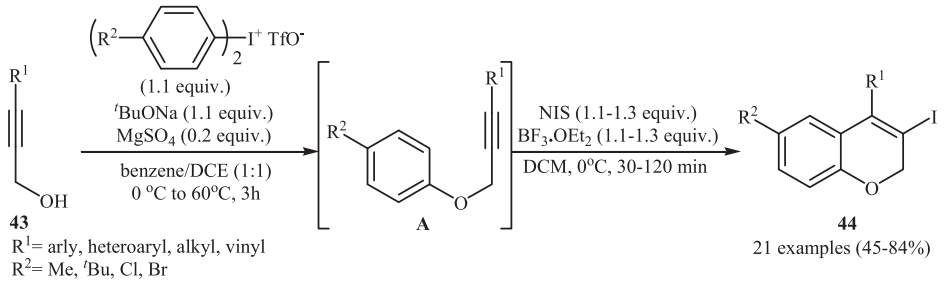
Internal aryl propargyl ethers **41** were found by the group of Perumal to undergo electrophilic cyclization in the presence of a catalytic amount of $Pd(OAc)_2$ in conjunction with a stoichiometric amount of $CuBr_2$ and LiBr, using acetic acid as solvent at room temperature, to afford 3-bromo-2*H*- chromenes **42** in 63-75% yield (*Scheme 15*). The reaction is noteworthy in that both aromatic and aliphatic substituted internal alkynes are tolerated. The presence of both $Pd(OAc)_2$ and $CuBr_2$ are crucial for the outcome of the cyclization and the presence of LiBr makes the cyclization more efficient and selective. A possible mechanism was also proposed (*Scheme 16*), whereby the



Scheme 15. Pd-catalyzed bromo-cyclization of aryl propargyl ethers **41**.



Scheme 16. Plausible mechanism for the formation of **42**.



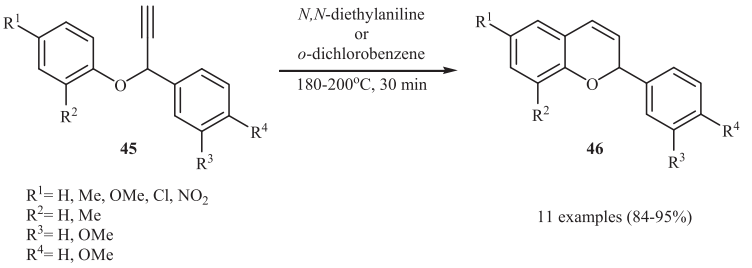
Scheme 17. One-pot transformation of propargyl alcohols **43** into 4-substituted-3-iodo- chromenes **44** developed by Togo.

reaction is initiated with coordination of palladium(II) to the triple bond of the alkyne **41** to give intermediate **A**, which undergoes nucleophilic attack by the arene affording organometallic intermediate **B**. The intermediate **B** is then convert to palladium(IV) intermediate **C**, which by reductive elimination affords the desired 2*H*-chromene **42**. In another possibility, the oxidation state of palladium intermediate **B** remains unaltered and product **42** is formed *via* intermediate **D** by Cu(II)-assisted ligand transfer.[59]

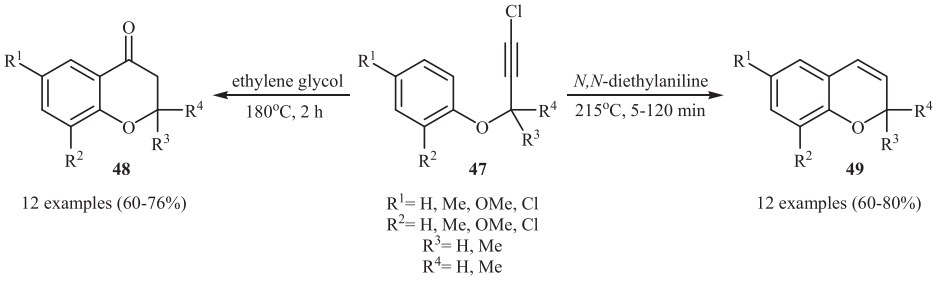
Recently, Togo and co-workers developed an interesting methodology toward 4-substituted-3-iodo-chromenes **44** through the reaction of internal propargyl alcohols **43** with diaryliodonium triflates and *t*-BuONa in benzene/DCE, followed by treatment with *N*-iodosuccinimide and $BF_3{\cdot}OEt_2$ in DCM under mild conditions. The results demonstrated that substrates bearing aryl or heteroaryl groups in the alkyne terminus gave higher yields than those bearing alkyl groups (*Scheme 17*). No reaction occurred in the absence of the additive.[60]

III. Thermal Cyclizations

One of the earliest reports on the synthesis of functionalized 2*H*-chromenes through thermal cyclization of aryl propargyl ethers was published by Subramanian and Balasubramanian in 1988. They showed that heating α-substituted terminal aryl propargyl ethers **45** at 180–200 °C in *N*,*N*-diethylaniline or *o*-dichlorobenzene for 30 minutes gave the corresponding 2-substituted-2H-chromenes **46** in high yields (*Scheme 18*).



Scheme 18. Synthesis of 2-substituted-2*H*-chromenes **46** *via* thermal cyclization of α-substituted terminal aryl propargyl ethers **45**.



Scheme 19. Thermal cyclization of aryl γ-chloropropargyl ethers **47**.

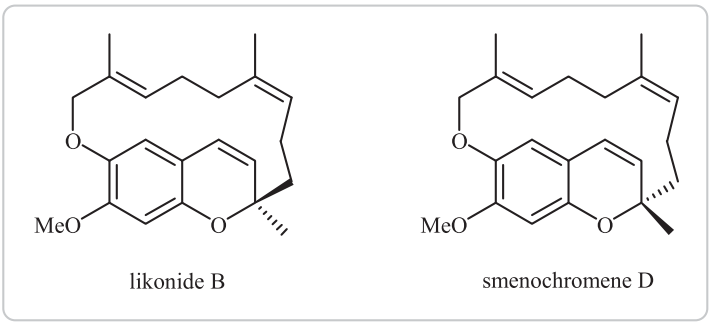
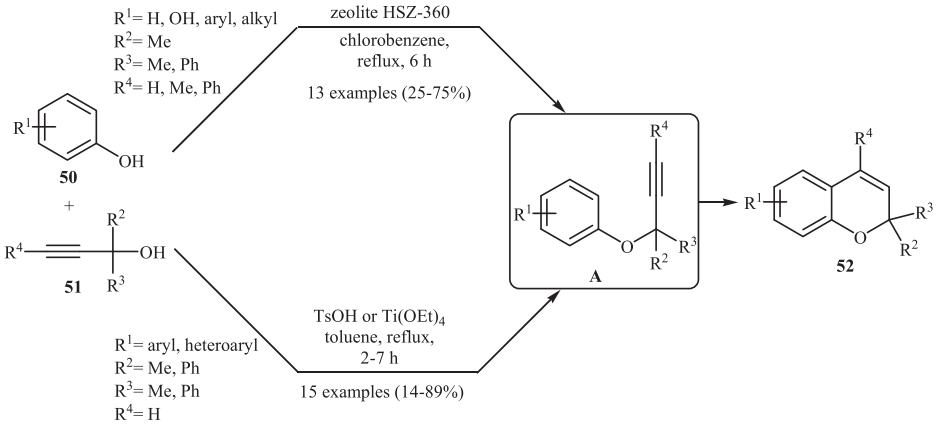


Figure 3. Chemical structures of Likonide B and smenochromen D.

High yields, short reaction times and broad substrate scope are the advantages of this synthetic process.[61] Chloro-substituted internal aryl propargyl ethers **47** were also found by the same group to undergo thermal cyclization at 215 °C in *N*,*N*-diethylaniline, to afford 4-chloro-2*H*-chromenes **48** in 60-80% yields. Interestingly, rearrangement of the same set of propargylic ethers in ethylene glycol led to the formation of 2*H*-chroman-4-ones **49** in good yields (*Scheme 19*). Aryl γ-bromopropargyl ether derivatives also worked well under these reaction conditions.[62] Yamaguchi and co-workers extended the scope of this methodology to a variety of *m*-acylaryl 1,1-dimethylpropargyl ethers and obtained a range of 5-acyl-2,2-dimethyl-2*H*-chromenes in moderate to high yields.[63] Later, the group of Mashelkar reinvestigated this reaction using α,α-unsubstituted propargylic ethers and good results were obtained.[64]



Scheme 20. Synthesis of 2*H*-chromenes **52** by Sartori and Guglielmetti group.

The Moody laboratory reported the synthesis of two chiral 2*H*-chromene-based natural products Likonide B and Smenochromene D (*Figure 3*) by a regioselective microwave-mediated thermal cyclization of the corresponding aryl propargyl ethers followed by intramolecular Mitsunobu reaction.[65]

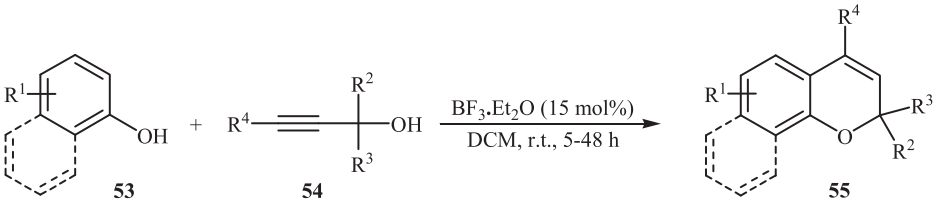
Recently, Kong, Meng, and Su reported the usefulness of silicone oil as an organic solvent for thermal cyclization of aryl propargyl ethers. Interestingly, their report is the first example of conducting an organic reaction using silicone oil as an organic solvent.[66]

IV. Cyclocondensation of Phenols with Propargyl Alcohols

In 1997, Sartori *et al.*[67] and Guglielmetti *et al.*[68] independently reported the synthesis of 2*H*-chromene derivatives **52** through cyclocondensation of phenols **50** with propargylic alcohols **51** using acidic catalysts in polar solvents (*Scheme 20*). In both cases functionalized 2*H*-chromenes were obtained in low to good yields. According to the author-proposed mechanisms, the formation of chromenes **52** involves the key aryl propargyl ether intermediate **A**, which undergoes intramolecular cyclization to produce the desired product. Subsequently, the groups of Carreira[69] and Hua[70] improved the efficiency of this protocol using either pyridinium *p*-toluenesulfonate (PPTS) or $ReCl(CO)_5$, respectively, as the catalyst.

In 2012, Madabhushi and co-workers reinvestigated this reaction using $BF_3{\cdot}Et_2O$ as a catalyst under very mild reaction conditions (DCM, room temperature). The results indicated that both internal and terminal propargylic alcohols and a variety of phenols could be used in this procedure (*Scheme 21*). However, the authors found some limitations in their methodology when they used phenols having strong electron-withdrawing groups such as 4-nitrophenol and 4-trifluoromethylphenol. Unfortunately, in these cases the expected 2*H*-chromenes were not observed even under reflux for 24 h in 1,2-dichloroethane. The authors also found that primary and secondary propargylic alcohols failed to participate in this reaction.[71]

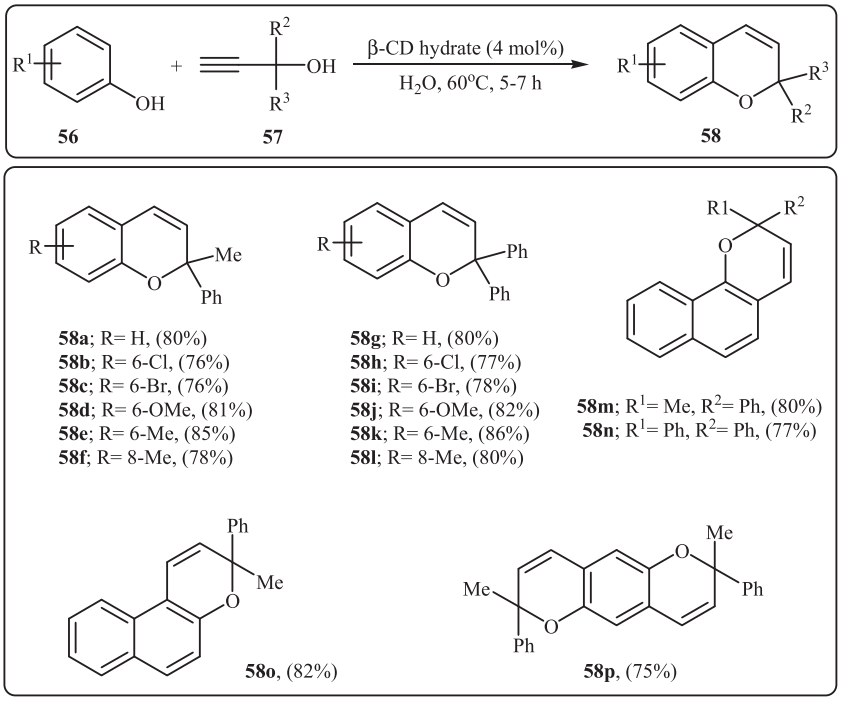
Very recently, Ghatak, Khan, and Ghar reported a promising green protocol for the synthesis of functionalized 2*H*-chromenes **58** by the treatment of phenols **56** with propargylic alcohols **57** in the presence of *β*-cyclodextrin hydrate as a catalyst in the most environmentally benign solvent, water, under an ambient atmosphere (*Scheme 22*). The



R^1= H, 4-Me, 4-OMe, 4-F, 4-Br, 3-Me, 3,5-Me_2, 2-Me, 2,5-Me_2
R^2= Me, Ph, CF_3
R^3= Me, Ph, CF_3
R^2+R^3= -$(CH_2)_6$-
R^4= H, Me, Ph, TMS

20 examples (64-90%)

Scheme 21. BF_3Et_2O catalyzed cyclocondensation of phenols **53** with propargylic alcohols **54**.



58a; R= H, (80%)
58b; R= 6-Cl, (76%)
58c; R= 6-Br, (76%)
58d; R= 6-OMe, (81%)
58e; R= 6-Me, (85%)
58f; R= 8-Me, (78%)

58g; R= H, (80%)
58h; R= 6-Cl, (77%)
58i; R= 6-Br, (78%)
58j; R= 6-OMe, (82%)
58k; R= 6-Me, (86%)
58l; R= 8-Me, (80%)

58m; R^1= Me, R^2= Ph, (80%)
58n; R^1= Ph, R^2= Ph, (77%)

58o, (82%)

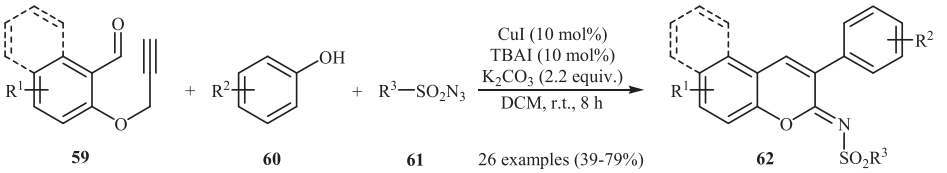
58p, (75%)

Scheme 22. *β*-cyclodextrin hydrate catalyzed synthesis of functionalized 2*H*-chromenes **58** in water.

authors claimed that this is the first report where *β*-cyclodextrin hydrate acted as a catalyst for an organic synthesis. It should be mentioned that *β*-cyclodextrin alone failed to promote the transformation.[72]

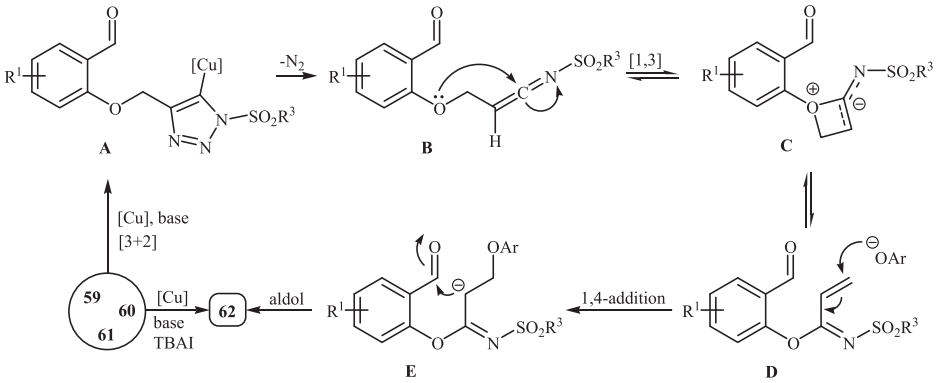
V. Multicomponent Reactions

An elegant one-pot three-component synthesis of synthetically challenging 2*H*-chromene derivatives **60** from easily available *O*-propargyl salicylaldehydes **59**, phenols **60**, and sulfonyl azides **61** has been reported by Murugavel and Punniyamurthy (*Scheme 23*). The



R^1= H, 3-OMe, 4-OMe, 5-Me, 5-OMe, 5-Br, 3,5-^{t}Bu$_2$
R^2= H, 2-Me, 2-I, 3-Me, 3-Br, 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CHO, 2,3-Me$_2$, 3,4-Me$_2$, 3,5-Me$_2$
R^3= Me, Ph, 4-Me-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$

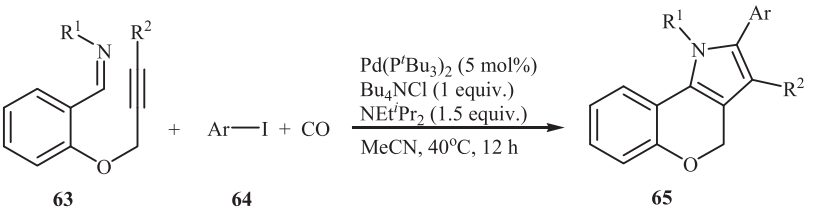
Scheme 23. Cu(I)-catalyzed multicomponent cascade synthesis of iminocoumarin aryl methyl ethers **62** developed by Punniyamurthy.



Scheme 24. Mechanistic proposal for the reaction in *Scheme 23*.

iminocoumarins **62** thus obtained in moderate to good yields were considered of interest in view of their pharmacological importance. The reaction was catalyzed by the system CuI/K_2CO_3/tetrabutylammonium iodide (TBAI) in DCM at ambient conditions. The authors found that other copper catalysts also promoted the reaction (*e. g.* CuBr, CuCl, Cu_2O), albeit in lower yields. No reaction occurred in the absence of the copper catalyst. The electronic character of the substituents in both *O*-propargyl salicylaldehydes and phenols had remarkably little effect on the facility of reaction. However, the reaction does not give good yields with electron-poor sulfonyl azides. The authors proposed the mechanistic pathway shown in *Scheme 24* that involves [3 + 2]-cycloaddition/1,3-pseudopericyclic ketenimine rearrangement/1,4-conjugate addition/aldol condensation.[73]

More recently, Arndtsen and co-workers studied the possibility of synthesizing pyrrole-fused chromene systems **65** through a Pd-catalyzed three-component reaction between aryl propargyl ethers **63**, (hetero)aryl iodides **64**, and carbon monoxide. Careful analysis revealed that the optimum conditions for this multicomponent reaction was the addition of Pd(P^tBu_3)$_2$ (5 mol%), Bu_4NCl (1 equiv.), and NEt^iPr_2 (1.5 equiv.), at 40 °C, to a solution of aryl propargyl ethers **63** and aryl iodides **64** in MeCN under a carbon monoxide atmosphere. Under the optimized conditions, the reaction showed good functional group tolerance, including fluoro, chloro, iodo, methoxy, and ester functionalities, and gave the corresponding pyrrole-fused chromenes in good to excellent yields (*Scheme 25*). The results demonstrated that aryl iodides with electron-donating substituents gave higher yields of products than aryl iodides with electron-withdrawing substituents. In the case of aryl propargyl ethers, terminal alkynes gave lower yields of the desired products.[74]

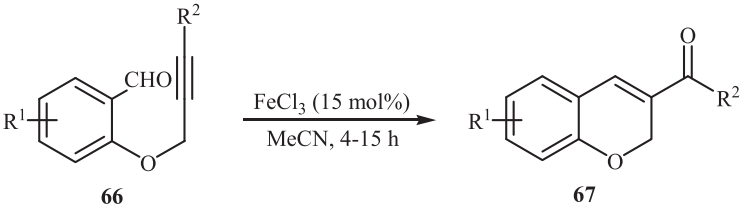


63 **64** **65**

R^1= Et, Bn
R^2= H, Me, Ph
Ar= Ph, 4-OMe-C_6H_4, 4-Me-C_6H_4, 4-F-C_6H_4, 4-C-C_6H_4, 3-OMe-C_6H_4, 3-CO_2Me-C_6H_4, 3,5-Me_2-C_6H_4, 3-thienyl, 5-N-Ts-indolyl

18 examples (57-95%)

Scheme 25. Arndtsen's three-component synthesis of pyrrole-fused chromenes **65**.

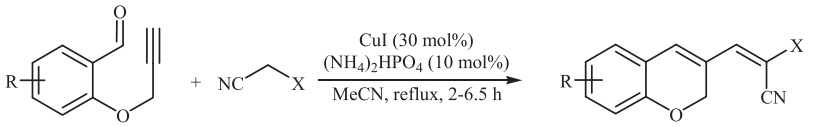


66 **67**

12 examples (45-89%)

R^1= H, 3-OMe, 5-Br, 5-Cl, 5-Ph, 3,5-Cl_2
R^2= Me, ^{n}Pr, Ph, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4

Scheme 26. Fe(III)-catalyzed synthesis of functionalized 2*H*-chromenes **67** *via* intramolecular alkyne-carbonyl metathesis.



68 **69** **70**

R= H, 3-OMe, 3-OEt, 5-Br, 5-NO_2
X= CN, CO_2Et, $CONH_2$

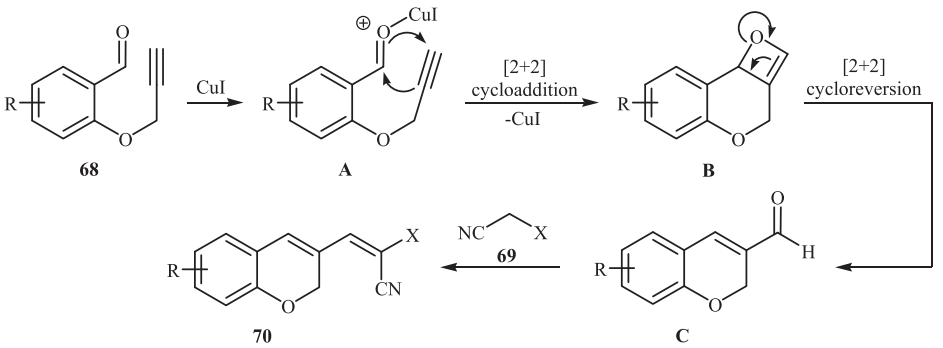
15 examples (59-90%)
(average yield: 76%)

Scheme 27. Synthesis of 2*H*-chromen-3-yl derivatives **70** *via* CuI/$(NH_4)_2HPO_4$ catalyzed reaction of O-propargyl salicylaldehydes **68** with active methylene compounds **69**.

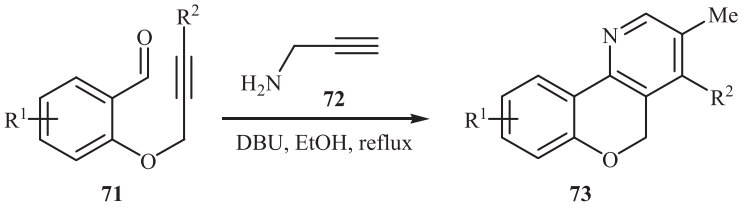
VI. Miscellaneous Reactions

In 2011, Jana and co-workers showed that the treatment of the propargylic ether of salicylaldehyde derivatives **66** with a catalytic amount of inexpensive and environmentally friendly $FeCl_3$ in MeCN afforded 3-acyl-substituted-2*H*-chromenes **67** through an intramolecular alkyne-aldehyde metathesis process. This metathesis reaction was successfully extended to bicyclic systems. Both aryl- and alkyl-substituted alkynes were well tolerated, providing the corresponding 2*H*-chromenes in 45–89% yield (*Scheme 26*). However, the reaction fails for terminal propargylic ethers.[75]

Shortly afterwards, Singh's research team reported a useful protocol for the synthesis of 2*H*-chromen-3-yl derivatives **70** *via* the reaction of *O*-propargyl salicylaldehydes **68** with active methylene compounds **69** using CuI/$(NH_4)_2HPO_4$ as a catalytic system



Scheme 28. Proposed mechanistic pathways for the formation of **70**.



Scheme 29. Balci's synthesis of chromenopyridines **73**.

in refluxing MeCN (*Scheme 27*). The results showed that the electronic character of the aryl propargyl ethers had little effect on the rate of the reaction. Both electron-donating and electron-withdrawing groups were well tolerated, providing the corresponding 2*H*-chromenes **70** in 59-90% yield. The author-proposed mechanism to explain this reaction is based on the formation a 2*H*-chromene-3-carbaldehyde intermediate **C** *via* an intramolecular alkyne-aldehyde metathesis in *O*-propargyl salicylaldehyde **68**, followed by nucleophilic addition of methylene compound **69** to the carbonyl group of **C** (*Scheme 28*).[76]

Keskin and Balci successfully synthesized a series of substituted chromenopyridines **73** from the reaction of corresponding *O*-propargyl salicylaldehydes **71** with *N*-propargylamine **72** in good to excellent yields, using DBU as a catalyst under ethanol reflux (*Scheme 29*). Mechanistically, the reaction proceeded *via* a condensation/isomerization/[4 + 2]-heterocycloaddition/hydrogen migration.[77]

Summary and Outlook

2*H*-Chromene derivatives have been identified as having antibacterial, antioxidant, antiviral, antifungal, anticancer, anti-HIV, anti-inflammatory, antidiabetic, and antihypertensive activities. Consequently, many efforts have been made to develop efficient synthetic methodologies to access this heterocycle. These efforts have included the reaction of *N*-tosylhydrazones and terminal alkynes, intramolecular hydroarylation of 2-propargyl phenols, intramolecular cyclization of 3-phenoxyacrylaldehydes, and the

reaction of 2-hydroxyacetophenone and allenic esters, among others. As illustrated, the one-pot synthesis of 2*H*-chromene cores through the cyclization of corresponding inexpensive and easily available aryl propargyl ethers has attracted a lot of attention in recent years. Broad substrate scope, simplicity and high yields are other advantages of this interesting synthetic process. We hope that this review will be beneficial in eliciting further research in this domain and encourage synthetic organic chemists to employ this valuable methodology in the preparation of important natural and biologically active 2*H*-chromene derivatives.

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