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Review

Recent advances in the diversification of chromones and flavones by direct C—H bond activation or functionalization

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ABSTRACT

Chromone and flavone are both central backbones of natural products and clinical medicines. Synthesis of diversely functionalized chromones and flavones constitutes significant research contents of the modern synthetic science because abundant molecular libraries of such types are crucial in providing candidate compounds for the discovery of new pharmaceuticals and functional materials. The direct C—H bond activation or functionalization on these heterocyclic backbones provides highly powerful tools for the rapid accesses to densely functionalized chromone and flavone derivatives. Considering the importance of the functionalized chromone and flavone compounds as well as the notable advances in the synthesis of such products by direct C—H activation or functionalization, we review herein the research advances in the C—H bond activation and functionalization reactions of chromone and flavones, in hope of showing the current states and promise of the research domain.

1. Introduction

The chromone and its derivatives such as flavones are heterocyclic system with strategic importance in a number of research and industrial domains. Chromone has been identified as the central backbone in a number of functional organic compounds, including natural products such as flavones, isoflavones as well as other natural molecules featured with chromone fragment [1–10]. What is more, many chromone-based compounds have also been identified with interesting optical as well as chelating functions, enabling their broad application in the designation of organic materials [11–15]. Moreover, on the basis of those well documented utilizations and activities, much more novel bioactivities and other utilities are yet to explore and discover weith these heterocyclic derivatives because of their intrinsically enriched functions [16–18]. By analyzing the structures of the chromone/flavone-based natural products, drugs and other functional molecules, it can be found that the common feature is that multiple substituents exist in both the heteroaryl ring and the phenyl fragments of the central backbone (Fig. 1). Therefore, the synthesis of chromones and flavones with diversely functionalized substructures has accordingly become attractive topic in the area of organic synthesis [19–21].

Typically, the synthesis of chromones can be accessed by two different tactics: One is the synthesis *via* reactions involving the hetero-ring construction. The other is the direct bond elaboration on the readily available chromones/flavone substrates. For the former strategy, the substrate sources as well as reaction pathways are considerably more abundant and flexible, thus enables the synthesis of the target product with highly divergent catalytic methods as well as substitution styles [22–29]. The synthetic methods by the direct elaboration on chromones/flavones, on the other hand, features the major advantages of more flexibly tunable site selectivity, and the step economy resulting from the straightforward C—H bond transformation or functionalization [30–40] in constructing both C—C [41–50], and C-heteroatom bonds [51–56]. Considering the importance of the synthetic methods toward these titled molecules as well as the notable advances taking place in the synthetic research area of C—H bond elaboration of chromones and flavones, we present herein the research advances on chromones and flavones synthesis by focusing on the direct C—H activation and functionalization of the readily available chromones/flavones substrates. On the basis of the actual reports, the reactions transforming the C—H bonds both in the heterocycle and phenyl ring fragments in these molecules are covered.

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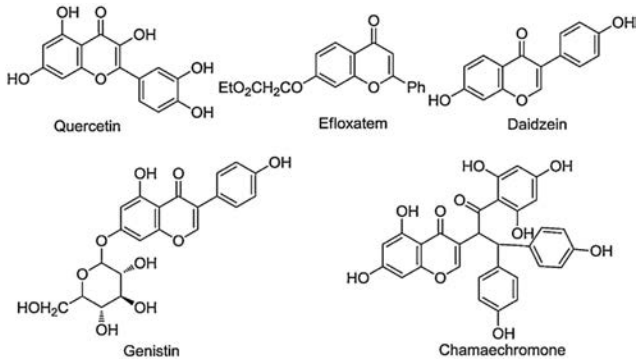
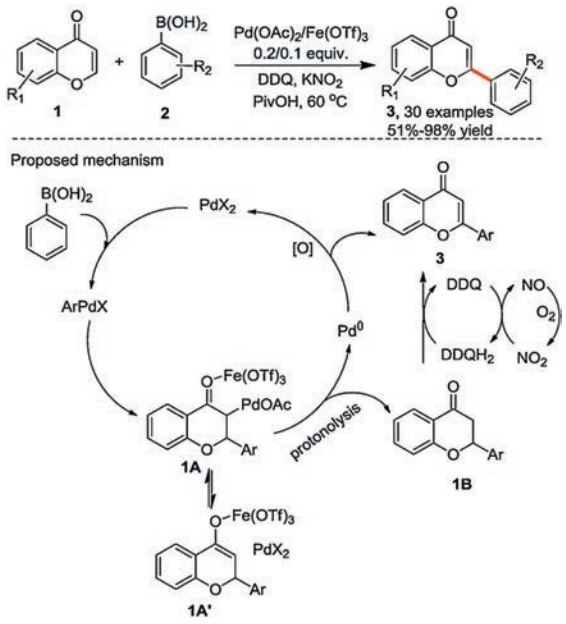


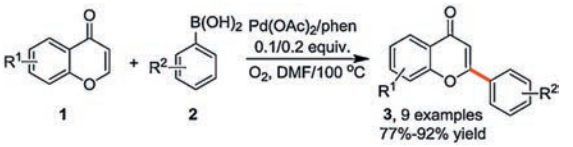
Fig. 1. The structures of typical chromone- and flavone-based natural products.

2. C—H elaboration on the heterocyclic fragment of chromones

The C(sp^2)—H bonds in the pyranone ring of chromone or related derivatives are intrinsically more reactive than conventional aryl or alkenyl C—H bonds. Therefore, the direct transformation on the C2— and C3—H bonds in chromones constitutes the reliable and powerful routes to access chromones bearing functional substitution in the C2 and/or C3 site. In 2012, Hong's group [57] reported the $Pd(OAc)_2/Fe(OTf)_3$-cocatalyzed synthesis of flavonoids *via* the C2-arylation of chromones. The reactions of chromones **1** and phenyl boronic acids **2** in the presence of $Pd(OAc)_2/Fe(OTf)_3$ catalyst and oxidant additive of DDQ/KNO_2 to provide flavones **3** with broad scope in PivOH at 60 °C heating. The reactions were proposed to be initiated by the aryl palladation of the C=C bond in chromone with the *in situ* generated ArPdX species by which the intermediate **1A**/**1A'** was generated *via* the assistance of Fe(III). The subsequent protonolysis led to the formation of chromanone **1B** which underwent oxidation to afford products **3** (Scheme 1).



Scheme 1. Pd(II)/Fe(III)-co-catalyzed C2-ayrylation of chromones.

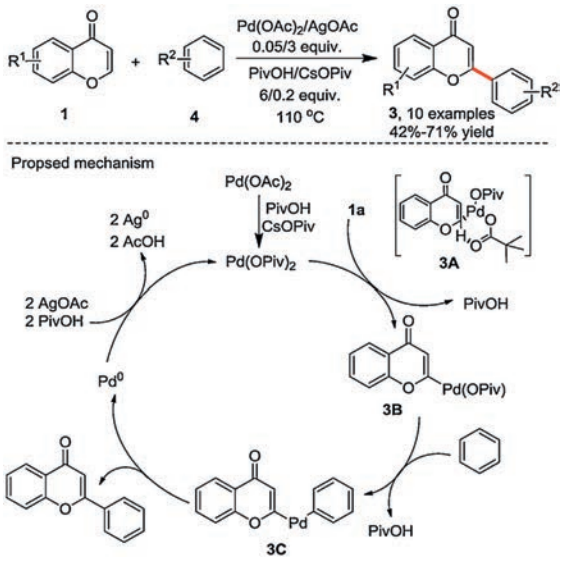


Scheme 2. Pd-catalyzed C2-arylation of chromones using aryl boronic acids.

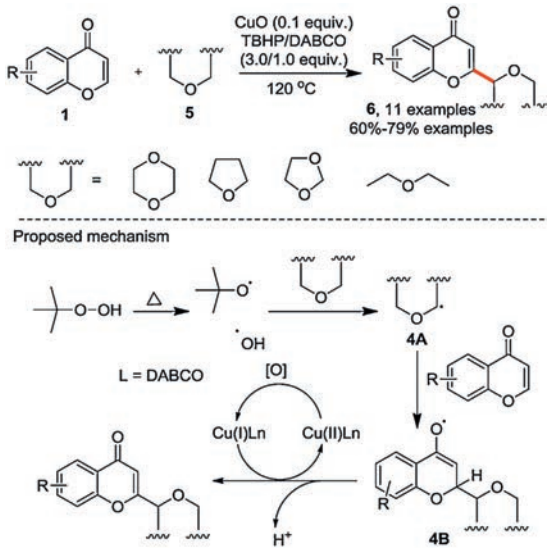
In the same year, Shafiee and Jafapour *et al.* [58] reported the $Pd(OAc)_2$-catalyzed C—H arylation reactions of coumarins and chromones by oxidative C—H bond transformation. The reactions involving chromone substrates were run under balloon O_2 with the assistance of 1,10-phenanthroline (phen) ligand, which allowed the synthesis of 2-aryl chromones with good to excellent yield (Scheme 2).

On the other hand, Kim and co-workers [59] developed a different method for the synthesis of compounds **3** by employing directly arenes **4** as the aryl sources. Under the catalysis of $Pd(OAc)_2$, a series of products were provided with moderate to good yields in the presence of AgOAc terminal oxidant as well as PivOH and CsOPiv. Because arene component also served the solvent, the application scope of arene was not as broad as the boronic acid-based synthesis (Scheme 3). The Pd-complexes **3A**-**3C** were the key intermediates throughout the reaction process. Notably, by incorporating experimental and computational investigation on the site selectivity of the chromone arylation, Hong, Peng and Paton *et al.* [60] disclosed that the selective C2-arylation of chromones with palladium catalysis could be ascribed to the favorable C2 carbopalladation *via* the strong interaction of the neighboring C3 site and the Pd-species.

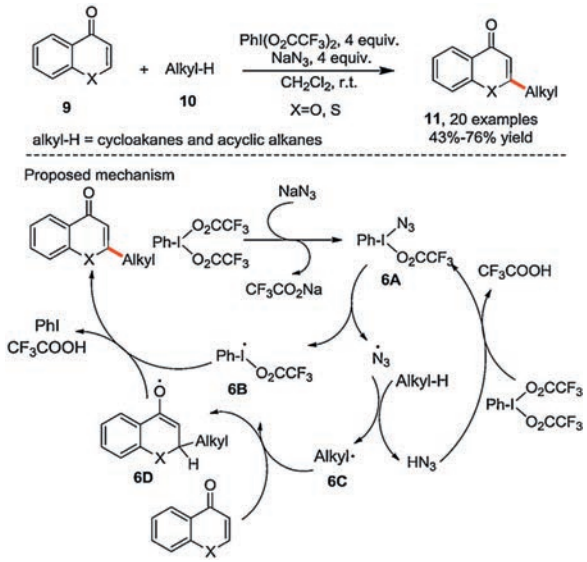
Alongside the arylation, other carbon functionalization in the chromone C2 site were also realized. Zhou and Ge *et al.* [61] achieved the synthesis of ether functionalized chromones **6** *via* the reactions of chromones **1** and ethers **5** *via* CuO catalysis in the presence of TBHP/DABCO. The reactions took place selectively in the carbon site adjacent to the oxygen in the ether. In terms of mechanism, the reactions were proposed to proceed *via* a free radical pathway involving the *O*-centered free radical from TBHP. The free radical **4A** was first generated from the coupling of TBHP-



Scheme 3. Pd-catalyzed C2-arylation of chromones with arenes.



Scheme 4. Cu-catalyzed C2-coupling of chromones and ethers.

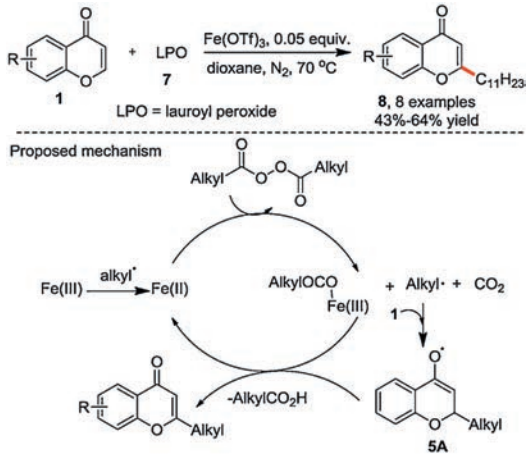


Scheme 6. Transition metal-free C2-alkylation of chromones.

derived free radical and ether **5**. The addition of **4A** to chromone gave rise to free radical intermediate **4B** which was transformed into a cation species and gave the product successively *via* SET by the oxidation of Cu(II) (Scheme 4).

As another example of transition metal-catalyzed chromone C2 elaboration, Jin and co-workers [62] reported recently the C2-alkylation reaction of chromones *via* Fe(III)-catalyzed reactions of chromones and diacyl peroxides. While the reactions of coumarins and different peroxides forming diverse 3-alkyl coumarins were defined *via* the catalytic protocol, the reactions of chromones and lauroyl peroxide (LPO) **7** were conducted to provide 2-alkylated chromones **8** with fair to good yields. The generation of alkyl radical was a key transformation in the reactions, which enabled the formation of intermediate **5A** to mediate the product generation and the formation of Fe(II) species for the catalytic cycle (Scheme 5).

In addition to these transition metal-catalyzed methodologies, the C2—H functionalization of chromones was also proved to be applicable under transition metal-free conditions. As one representative example of such type, Antonchick *et al.* [63] developed

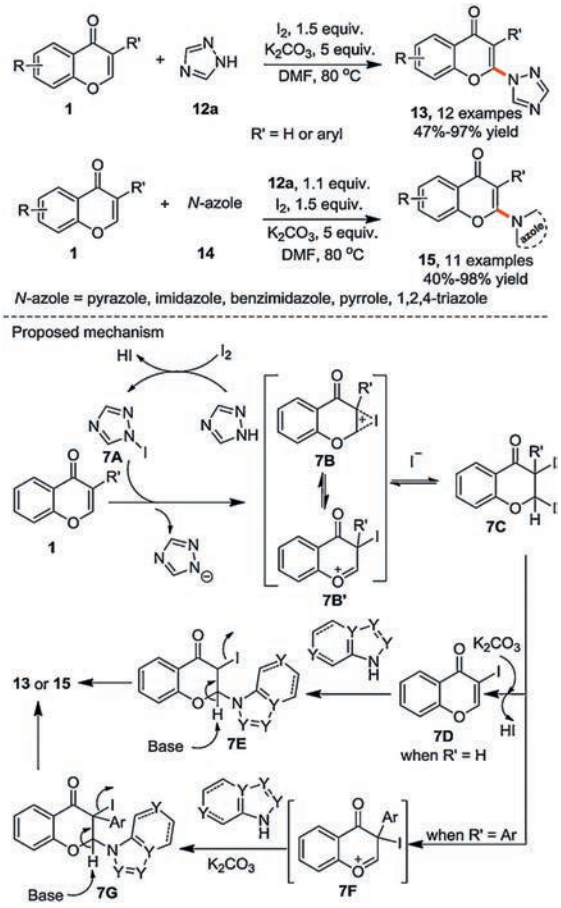


Scheme 5. Fe(III)-catalyzed C2-alkylation of chromones.

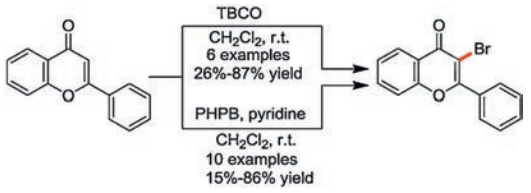
the $PhI(CF_3CO_2)_2/NaN_3$ mediated C2-alkylation of chromones the thiochromones **9** by employing a series of cycloalkanes and acyclic alkanes **10** as coupling partners. Under the promotion of $PhI(CF_3CO_2)_2$ and NaN_3, divergent 2-alkylated chromones and thiochromones **11** were practically afforded at room temperature. A free radical-based reaction mechanism was proposed for the titled reactions. First, the coupling of $PhI(CF_3CO_2)_2$ and NaN_3 provided intermediate **6A**, which generated azide free radical and iodine centered $PhICF_3CO_2$ free radical **6B** *via* homo-cleavage of the N—I bond. The reaction of azide free radical and alkane C—H bond led to the production of alkyl free radical **6C** which could couple chromone/thiochromone to provide free radical intermediate **6D**. The coupling of **6D** with **6B** then yielded products **11** by releasing PhI and TFA (Scheme 6).

Later on, the same group [64] reported the C2-azolation reactions of chromones *via* the promotion of molecular iodine and K_2CO_3. For the reaction of 1,2,4-triazole **12a**, the reactions took place directly in the presence of I_2 and K_2CO_3 to afford products **13**. On the other hand, when other azoles such as pyrazole, (benz) imidazole, pyrrole and substituted 1,2,4-triazole were used, the stoichiometric **12a** should be additionally employed. The authors hypothesized that the **12a** played a key role to promote the reaction by coupling iodine to generate reactive *N*-iodoazole **7A** to mediate the formation of the ionic intermediate **7B**/**7B'**. The subsequent incorporation of **7B** with anionic iodine then afforded **7C**. Depending on the structure of **R'**, the transformations *via* intermediates **7D** and **7E** (**R'** = H), or **7 F** and **7 G** (**R'** = Ar) then gave the target products **13** and **14** (Scheme 7).

Alongside the functionalization reactions of the C2—H bond of chromones, corresponding functionalization reaction in the C3—H bond of chromones also received splendid advances for the synthesis of diverse C3-functionalized chromones. As fundamental intermediates for the synthesis of numerous C3-substituted chromone *via* C-halogen bond cross coupling, the 3-halogenated chromones constituted one of the major targets in the chromone C—H functionalization reactions. While the synthesis of 3-halochromones by cascade chromone ring formation and C—H halogenated were realized [25,65,66], the direct C—H halogenation of chromones made up the other major strategy.

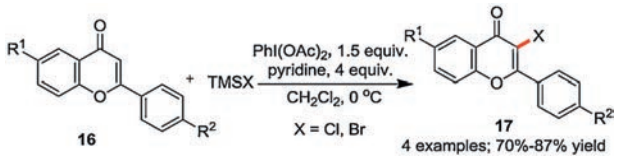


Scheme 7. Transition metal-free C2-azolation of chromones.

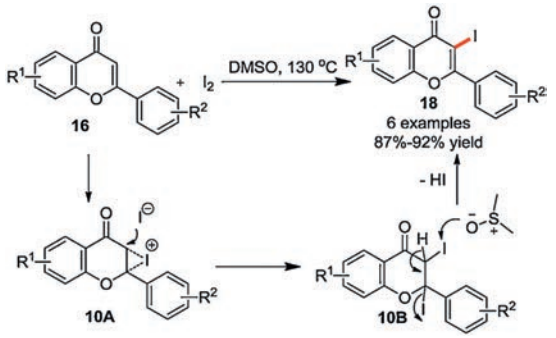


Scheme 8. C3-bromination of flavones.

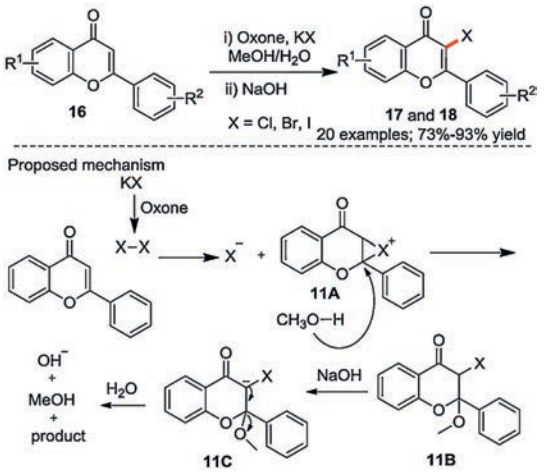
In 1998 and 2002, Joo and co-workers reported successively the C-3 bromination of flavones by employing pyridinium bromide perbromide (PHPB) [67] and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) [68] as the brominating reagent, respectively (Scheme 8). In order to developed synthetic methods using more stable reagents and of broader substrate scope, continuous efforts were made toward 3-halochromone and related flavone synthesis.



Scheme 9. TMSX-based synthesis 3-haloflavones.



Scheme 10. I_2-based synthesis of 3-iodoflavones.



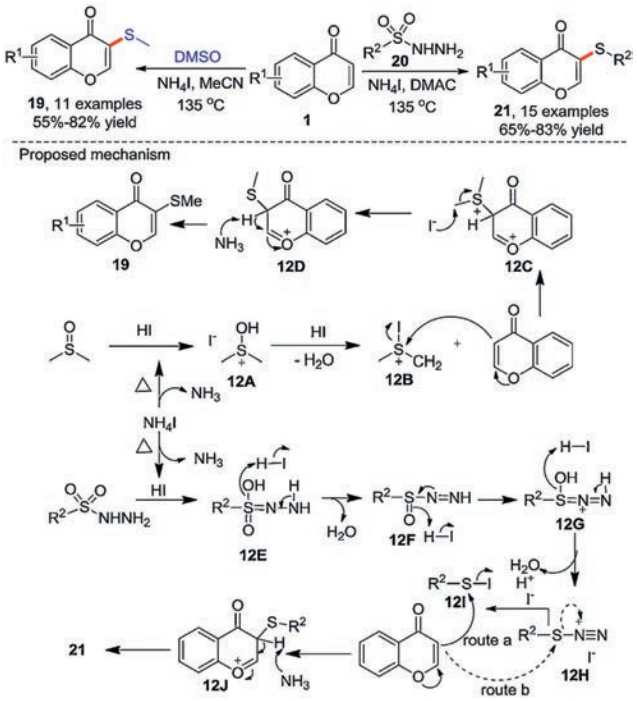
Scheme 11. Synthesis of 3-haloflavones with KX/Oxone system.

Rho *et al.* [69] reported an alternative method to access 3-haloflavones **17** *via* hypervalent iodine ($PhI(OAc)_2$ promoted reactions of flavones **16** and trimethyl silyl halide (X = Cl or Br). The reactions were run at 0 °C, and 3-bromo-/chloroflavones could be synthesized, but broad scope of synthesis was not yet defined (Scheme 9).

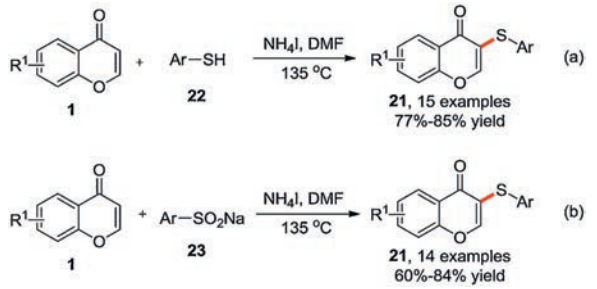
In their work of synthesizing 3-iodoflavones *via* the reactions of chalcone precursors, Lokhande *et al.* [70] disclosed that the reactions of flavones **16** and molecular iodine could also afford 3-iodoflavones **18** by heating at 130 °C in DMSO. The formation of iodonium ion **10A** and diiodochromanone intermediate **10B** were proposed as the main stages during the formation of **18** (Scheme 10).

Recently, Wang and Liu *et al.* [71] developed a new approach for the synthesis of halogenated flavones **17** and **18** (X = Cl, Br, I) by employing potassium halide (KX) as halogen source in the presence of Oxone. The key process was the *in situ* oxidation of Oxone to KX to provide reactive molecular halogen. The formation of halogenium ion **11A**, intermediates **11B** and **11C** constituted as additional main transformations enabling the generation of the target products (Scheme 11).

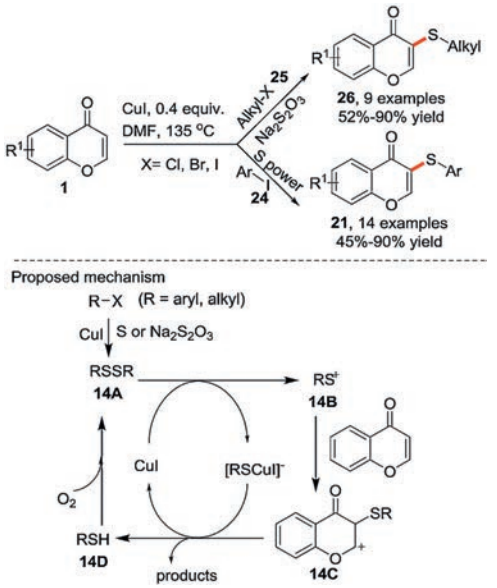
The formation of C—S bond in the C3 site of chromones constituted a highly practical tactic in the decoration of chromones for the synthesis of their sulfur derivatives. In 2015, Zhou and Ge *et al.* [72] reported the synthesis of 3-methylthiolated chromones **19** and 3-sulfenylated chromones **21** by reacting chromone with



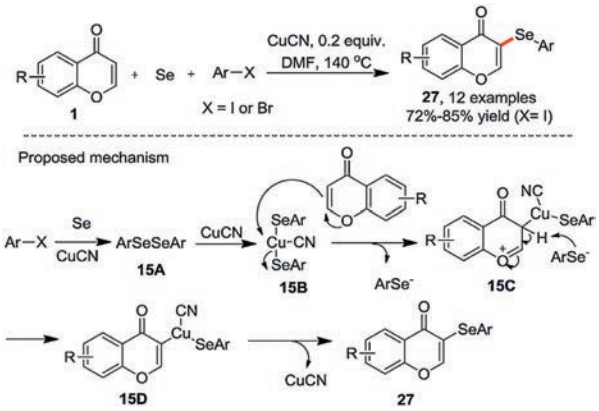
Scheme 12. C3-methylthiolation and sulfenylation of chromones.



Scheme 13. Different sulfenyl sources for the synthesis of 3-sulfenyl chromones.



Scheme 14. Synthesis of 3-sulfenyl and 3-alkylthiochromones.

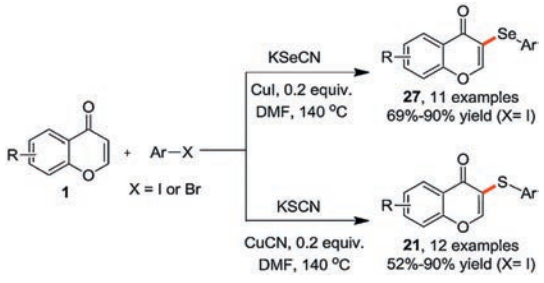


Scheme 15. Synthesis of 3-arylselenyl chromones.

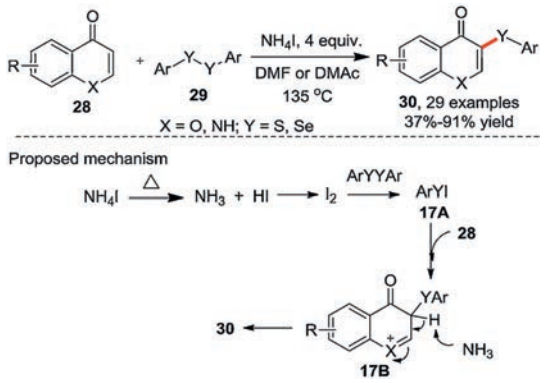
DMSO and sulfonyl hydrazines **20**, respectively. In the reaction conditions consisted of NH_4I/MeCN and 135 °C heating in DMSO, the methylthiolated products **19** were provided *via* key intermediates **12A**-**12D**. On the other hand, by the reactions employing sulfonyl hydrazines conducted in DMAC in the presence of NH_4I, **21** were synthesized *via* a plausible process involving intermediates **12E**-**12J**. Notably, when **12H** was generated, it might be further transformed into **12I** to enable the subsequent transformation (Scheme 12, route a), or directly incorporate chromones to yield the target products (Scheme 12, route b).

Following the work on the successful synthesis of 3-sulfenyl chromones, the group developed later different methods for the synthesis of such functionalized chromones by employing thiophenols **22** (Scheme 13a) [73] and sodium benzenesulfinates **23** (Scheme 13b) [74] as sulfenylation reagents, respectively. The Ar-S-I intermediate **12J** (Scheme 12) was also proposed as the key intermediate in these reactions.

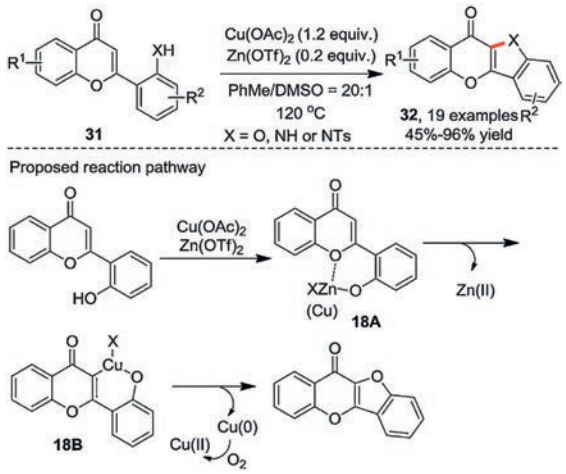
In addition, Zhou *et al.* [75] realized also the synthesis of 3-sulfenyl and 3-alkylthiochromones *via* the chromone C3—H bond functionalization with different sulfur sources by the catalysis of CuI. The reactions employing chromones, aryl iodide **25** and sulfur powder led to 3-sulfenyl chromones **21** *via* CuI catalysis by heating at 135 °C in DMF. On the other hand, the reactions of chromones, alkyl halides **25** and $Na_2S_2O_3$ led to 3-alkylthiochromones **26** under identical conditions. The CuI-catalyzed generation of aryl/alkyl disulfide intermediate **14A** was proposed as the initial step in the reactions. The formation of sulfur cation **14B** *via* CuI incorporation



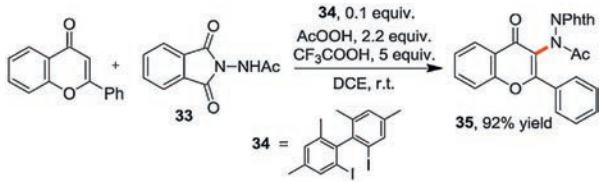
Scheme 16. Synthesis of 3-sulfenyl/selenyl chromones with KYCN (Y = Se or S).



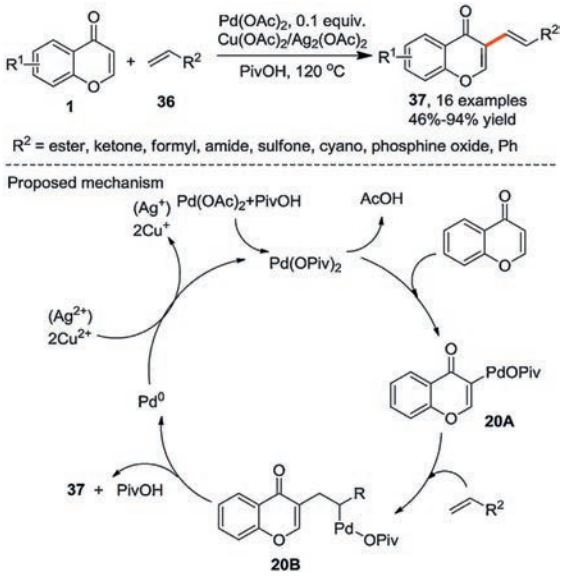
Scheme 17. C3—H sulfenylation/selenylation of chromones and quinolinones.



Scheme 18. Intramolecular C—O bond formation reactions of functionalized flavones.



Scheme 19. Organocatalytic flavone C3—H hydrazination.



Scheme 20. Pd-catalyzed C3—H bond alkenylation of chromones.

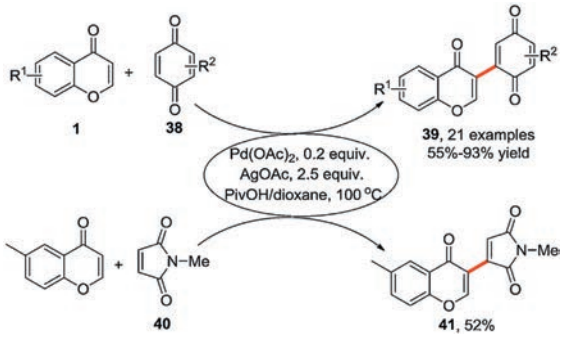
and its electrophilic addition to chromone generating intermediate **14C** enabled the formation of target products *via* proton elimination. The simultaneously produced RSH could be easily oxidized to regenerate the reactive disulfide species (Scheme 14).

By similar method employing elemental selenium and aryl halide as reaction partners, they also established the synthetic method to 3-arylselenyl chromones **27** *via* CuCN-catalyzed C—H bond transformation [76]. According to the proposed mechanism, the formation of aryl diselenide **15A** was also the initiating step, which mediated the formation of **15B** by coupling CuCN. The further addition of **15B** to chromone gave **15C**, and the successive elimination of proton led to **15D** which subsequently yielded **27** by the elimination of CuCN (Scheme 15).

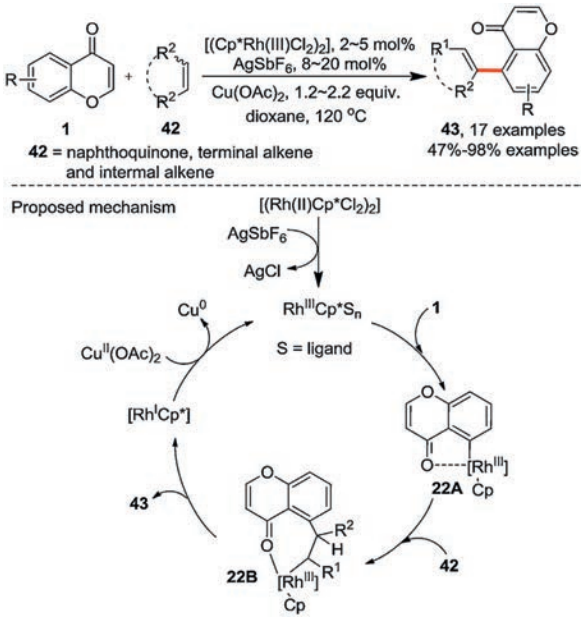
Moreover, Zhou's [77] subsequent work on this area disclosed that the reactions of chromones, aryl halides and KSeCN, by which products **27** could be efficiently accessed with the catalysis of CuI by heating at 140 °C in DMF (X = I). Notably, similar reactions using KSCN providing 3-sulfenyl chromones **21** was also practical by using CuCN as the alternative copper catalyst (Scheme 16).

Alternatively, by employing directly disulfides and diselenides **29** as substrates, Guo [78] realized the synthesis of 3-sulfenyl/3-selenyl chromones **30** *via* NH_4I-promoted C—H sulfenylation and selenylation. Besides chromones, the aza-equivalent quinolinones (X = NH in **28**) were also applicable substrates for the synthesis of corresponding C3-functionalized quinolinones. The ArY-I (**17A**) and cationic heterocycle **17B** were believed as the key intermediate during the reaction process (Scheme 17).

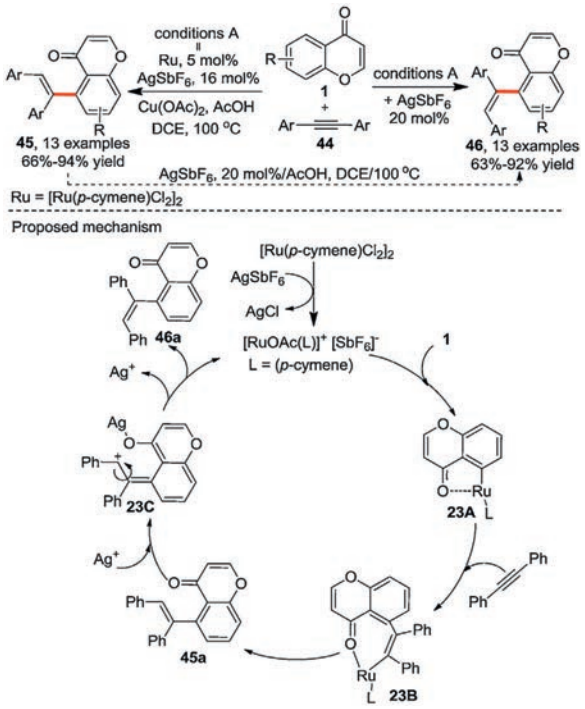
Unlike the relatively enriched reports in the C3—H sulfenylation/thiolation and selenylation *via* new C—S/Se bond formation, corresponding reports on the C—O bond formation *via* the chromone C—H functionalization or activation was rather hardly available. The typical example on the chromone C3—H bond oxygenation was reported by Hong *et al.* in their work synthesizing chromone fused benzofurans [79]. By employing *o*-hydroxyphenyl functionalized flavones **31** as starting materials, the co-catalysis of $Cu(OAc)_2/Zn(OTf)_2$ and heating at 120 °C in mixed toluene and DMSO enabled the intramolecular C—O bond formation to provide products **32**. The species of Zn(Cu)-complex **18A** and Cu-complex



Scheme 21. C—H activation reactions of chromones with quinones.



Scheme 22. Rh(III)-catalyzed C5—H alkeneylation of chromones.



Scheme 23. Ru-catalyzed C5—H alkenylation of chromones by addition to alkynes.

18B were hypothesized as the major intermediates in the general reaction pathway (Scheme 18).

As another type of typical C-heteroatom bond, the C—N bond had also received sound concerns in the domain of chromone C3—H bond functionalization. However, successful method for such transformation remained yet as a challenge. Besides the examples of two products reported in Hong's intramolecular annulation *via* substrates of type **31** (Scheme 18), Antonchick *et al.* [80] reported the synthesis of product **35** as a single example in their work of arene C—H hydrazination by using biaryl **34** as organocatalyst (Scheme 19).

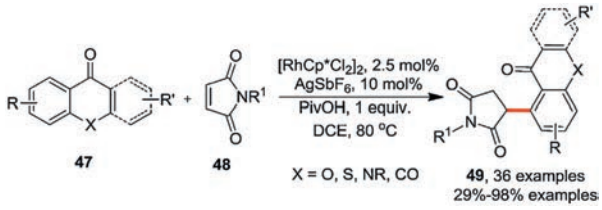
In parallel with the C-heteroatom bond construction *via* the chromone C3—H bond activation and functionalization, the equivalent C—H bond transformation enabling C—C bond generation has also received extensive concern. Hong and co-workers [81] developed an interesting method for the synthesis of 3-alkenyl chromones **37** *via* the direct C—H alkenylation of chromones and terminal alkenes **36** *via* the catalysis of $Pd(OAc)_2$ using $Cu(OAc)_2$ and Ag(I) as terminal oxidants. The reactions were proposed to proceed *via* intermediate **20A** by the insertion of Pd(II) to C—H bond as well as the formation of intermediate **20B** resulting from carbopalladation of alkenes. The elimination of Pd(0) and PivOH from **20B** then led to the production of alkenyl chromones **37** (Scheme 20).

On the basis of this C—C bond forming reaction, the same group [82] again reported the reactions of chromones and quinones for the synthesis of quinone functionalized flavones **39** by employing quinones **38** as reaction partners using the catalyst system consisted of $Pd(OAc)_2$ and AgOAc. In addition, this C—H activation protocol could also be expanded to the synthesis of product **41** by employing *N*-methylmaleimide **40** as alternative reaction partners (Scheme 21).

3. Activation of the phenyl C—H bond

In parallel with the elaboration on the C—H bond located in the heteroaryl fragment, the activation of the phenyl C—H bond in the chromone constituted the other major route to access chromone derivatives with expanded molecular diversity. In 2012, Antonchick and co-workers [83] reported the C5—H and alkenylation of chromone *via* oxidative coupling by employing alkenes **42** as reaction partners *via* Rh(III) catalysis. The C5-alkenylated chromones **43** were synthesized with high efficiency under the catalytic conditions consisting of $[(Rh(II)Cp^*Cl_2)_2]$, $AgSbF_6$ and $Cu(OAc)_2$ by heating in dioxane. As alkene substrates, naphthoquinone, terminal alkenes and dimethyl but-2-enedioate could be tolerated. The reactions were proposed to start from the $Rh^{III}Cp^*S_n$ given by the interaction of $[(Rh(II)Cp^*Cl_2)_2]$ and $AgSbF_6$. The assistance of the carbonyl group in **1** then enabled the insertion of Rh(III) to the C5—H bond of chromone to generate intermediate **22A**, which coupled the alkene and led to the formation of intermediate **22B**. The reductive elimination of Rh(I) from **22B** gave rise to products **43**. And the Rh(III) could be regenerated by the oxidation of Cu(II) to Rh(I) (Scheme 22).

Alternatively, Hong *et al.* [84] developed a synthetic routes to C5-alkenylated chromones by the Ru-catalyzed C5—H bond addition to symmetrical internal alkynes **44**. The $[Ru(p\text{-cymene})Cl_2]_2$ catalyst, $AgSbF_6$ as well as $Cu(OAc)_2$ and AcOH were required for the desired C—H addition to alkynes. Interestingly, modifying the loading of $AgSbF_6$ enabled the selective synthesis of *Z*-isomers **45** and *E*-isomers **46**. The control experiments proved that treating the *Z*-isomers with additional $AgSbF_6$ in AcOH promoted their transformation to corresponding *E*-isomers. The Ru-insertion to



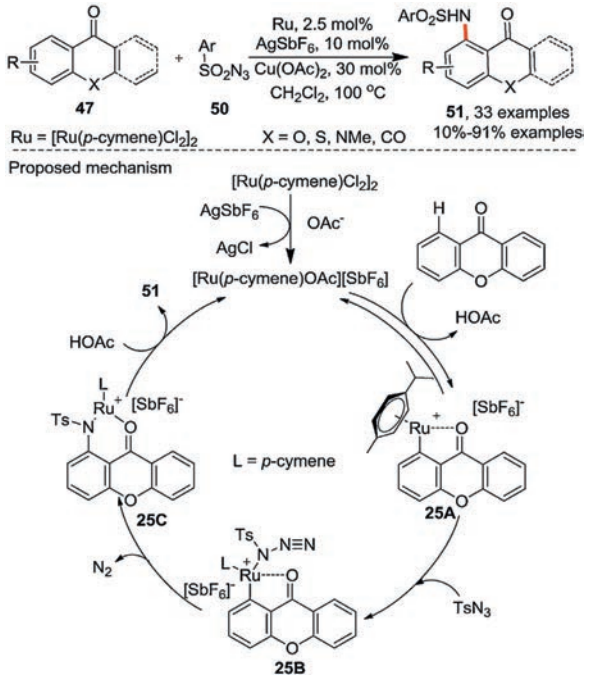
Scheme 24. C—H bond addition of chromones and analogous aryl cyclic enones to maleimides.

the C5—H bond forming intermediate **23A** and the subsequent alkyne insertion providing **23B** were believed to mediate the synthesis of *Z*-alkenylated products **45**. The transformation of this isomer to *E*-alkenylated products, on the other hand, was proposed to take place by forming cation intermediate **23C** in the presence of additional Ag^+ (Scheme 23).

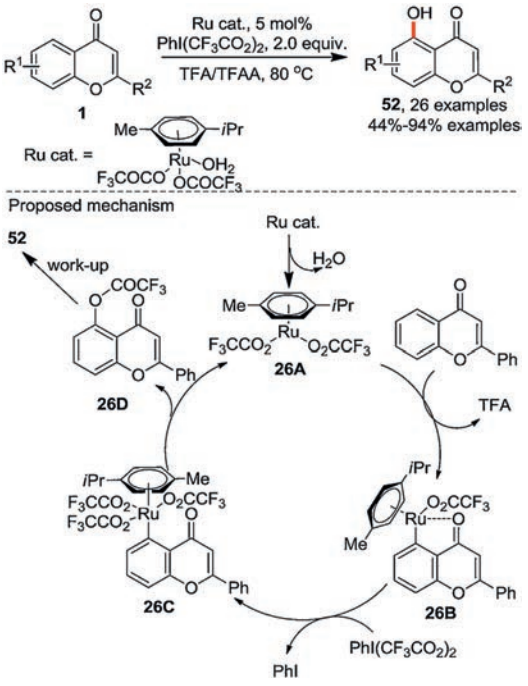
On the other hand, the C5—H bond addition of chromones and analogous benzoketone derivative to C=C double bond was realized by Kim *et al.* [85] With the co-catalysis of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ in the presence of PivOH, the addition of chromones and analogous cyclic enone substrates **47** to maleimides **48** proceeded practically to deliver diverse maleimide functionalized chromones, 1,4-naphthoquinones, and xanthones, *etc. via* the direction of the ketone carbonyl group *via* weak coordination (Scheme 24).

Moreover, the same group also reported the amination reactions of similar C—H bond in substrates **47**. The reactions of sulfonyl azides **50** with **47** provided aminated products **51** [86]. The main transformations were also proposed as the metal insertion to the reactive C—H bond, and the addition of coupling partners forming intermediates **25A** and **25B**, respectively. In addition, an additional migratory insertion of N atom providing intermediate **25C** by releasing nitrogen gas was believed to be involved to mediate the formation of products **51** (Scheme 25).

As a typical example on the aryl C—H oxygen functionalization, Hong and co-workers [87] disclosed the C5—H bond hydroxylation of chromones and flavones *via* Ru(II) catalysis. The Ru-species which was prepared by reacting $[Ru(p\text{-cymene})Cl_2]_2$ with trifluoroacetic acid (TFA) was discovered as the efficient catalyst for the reactions of chromones/flavones **1** and $PhI(CF_3CO_2)_2$ to provide 5-hydroxyl chromones/flavones **52** by heating at 80 °C in the presence of TFA/TFAA. According the proposed reaction mechanism, the reactions were initiated by the generation of Ru-species **26A** from the dehydration of the Ru cat. The insertion of **26A** to the C5—H bond gave **26B** which coupled $PhI(CF_3CO_2)_2$ to generate another Ru-complex **26C**. The elimination of Ru-catalyst **26A** from **26C** led to the production of intermediate **26D**. The aqueous work-up on **26D** yielded the final products **52** *via* hydrolysis (Scheme 26).



Scheme 25. C—H amination of chromones and analogous aryl cyclic enones.

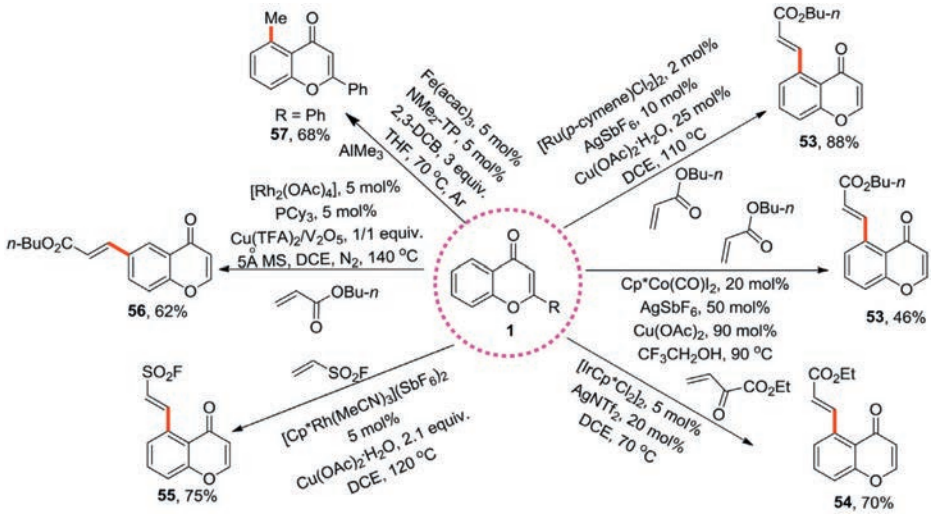


Scheme 26. Ru-catalyzed C5—H hydroxylation of chromones/flavones.

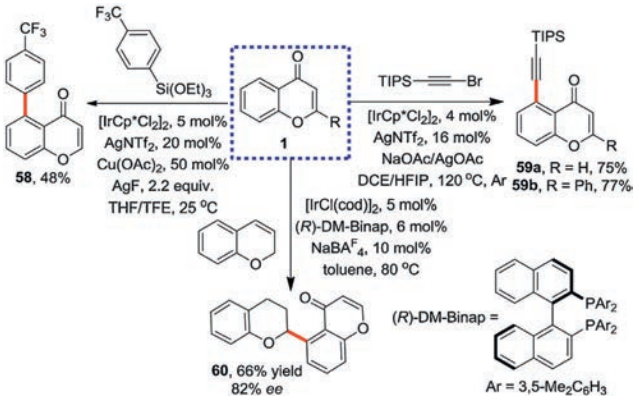
In addition to the systematic investigation in the phenyl C—H activation and functionalization of chromones and its derivatives, as specific example(s) of cyclic enone compounds, chromones were also frequently used in the methodologies of catalytic C—H activation reactions directed by ketone carbonyl. For example, Padala and Jeganmohan [88] reported that 5-alkenyl chromone **53** could be accessed *via* $[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$ and $Cu(OAc)_2$-co-catalyzed C—H alkenylation reactions (Scheme 27). Maji *et al.* [89] reported the same reaction synthesizing **53** in the catalyst system of $Cp^*Co(CO)I_2$, $AgSbF_6$ and $Cu(OAc)_2$ in 2,2,2-trifluoromethyl ethanol (Scheme 27). Chang and co-workers [90] reported the synthesis of alkenylated chromones **54** *via* C5—H alkenylation of chromone with the catalysis of $[IrCp^*Cl_2]_2$ and $AgNTf_2$ (Scheme 27). In addition, Huestis and Ncube [91] realized the synthesis of 5-fluorosulfonylvinyl chromone **55** *via* corresponding arene C—H 5-fluorosulfonylvinylation of chromones by the catalysis of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ in the presence of $Cu(OAc)_2{\cdot}H_2O$ by using ethenesulfonyl fluoride as coupling partner (Scheme 27). Interestingly, in a catalytic nondirected oxidative C—H alkenylation method, Yu *et al.* [92] disclosed the synthesis C6-alkenyl chromone **56** *via* the catalysis of $Rh_2(OAc)_4$ catalysis, and PCy_3 ligand, $Cu(TFA)_2$ as well as V_2O_5 were also required to performed the reaction under nitrogen atmosphere (Scheme 27).

By means of a phosphine ligand NMe_2-TP (4-(bis(2-(diphenylphosphanyl)phenyl)phosphanyl)-*N*,*N*-dimethylaniline) assisted $Fe(acac)_2$-catalysis in the presence of 2,3-dichlorobutane (2,3-DCB) additive, Nakamura *et al.* [93] realized the synthesis of 5-methyl flavone **57** by C5—H methylation of flavone (Scheme 27).

In addition to these C—H alkenylation and methylation protocols, the $[IrCp^*Cl_2]_2/AgNTf_2/Cu(OAc)_2$-co-catalyzed arene C—H arylation developed by Chang *et al.* [94] enabled the synthesis of C5-arylated chromone **58** by employing triethoxy (aryl)silane as aryl source (Scheme 28). In addition, Li, Huo and Jiang *et al.* [95] reported earlier the synthesis of C5-alkynyl chromone **59a** and flavone **59b** *via* their $[IrCp^*Cl_2]_2/AgNTf_2$/-co-catalyzed arene C—H alkynylation method with (bromoethynyl) triisopropylsilane as the coupling partner (Scheme 28). Moreover, the synthesis of optically pure cyclic ether functionalized



Scheme 27. Arene C—H alkenylation and methylation of chromone/flavone as specific examples.



Scheme 28. Arylation, alkynylation and hydroarylation of chromone/flavone C5—H bond.

chromone **60** was successfully accessed by the enantioselective hydroarylation reaction to 2*H*-chromene involving the transformation of stable arene C—H bonds [96]. The product **60** was afforded with good yield and high *ee* value *via* the catalysis of $[IrCl(cod)]_2$ and chiral ligand (*R*)-DM-Binap (Scheme 28). Although the reaction of chromone or flavone was reported as just specific examples, it should reasonable to deduce that most of the above C—H activation reactions in Schemes 27 and 28 would be applicable for other chromone and flavone derivatives bearing similar reactive C–H bond, thus provided potentially applicable routes to access chromones with more diverse substructures.

4. Conclusion and outlook

In conclusion, as well documented privileged heterocyclic motifs, the structurally diverse chromones and flavones are inarguably the longstanding targets of organic synthesis. The application of the powerful C—H bond activation and functionalization has brought tremendous advances in the synthesis of chromone and flavone derivatives elaborated with various carbon- and heteroatom-based functional structure by direct transformation on either the heterocyclic $C(sp^2)$—H bonds or the arene C—H bond in the readily available chromone/flavone substrates. On the other hand, the presently known literatures in this research area deliver also some challenges for future research efforts. One is the flexible control of the selective reaction of the C2—H and C3—H bonds of in heterocyclic fragment. Most known transformations take place either on the C2- or C3-site depending on the property of the coupling reagent. Tunable transformations on the chromone C2- and C3-sites with identical or similar reaction partners are yet rather difficult task. In addition, for the activation reactions in the arene part, the known reactions generally take place in the C5-site for both chromones and flavones because of the inherent direction of the carbonyl group. The C—H activation reaction in other sites of the arene moiety remains rigorously restricted. Therefore, applicable arene C—H activation methods in other sides beyond C5 of chromones and flavones are yet highly desirable. Of course, developing low cost metal-catalysis to enable the arene C—H activation in these scaffolds constitutes also important target for future research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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