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Asymmetric Methods for the Synthesis of Flavanones, Chromanones, and Azaflavanones

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Abstract

Flavanones, chromanones, and related structures are privileged natural products that display a wide variety of biological activities. Although flavanoids are abundant in nature, there are a limited number of available general and efficient synthetic methods for accessing molecules of this class in a stereoselective manner. Their structurally simple architectures belie the difficulties involved in installation and maintenance of the stereogenic configuration at the C2 position, which can be sensitive and can undergo epimerization under mildly acidic, basic, and thermal reaction conditions. This review presents the methods currently used to access these related structures. The synthetic methods include manipulation of the flavone/flavanone core, carbon-carbon bond formation, and carbon-heteroatom bond formation.

Keywords

Natural products; Total synthesis; Asymmetric synthesis; Flavanones; Chromanones; Azaflavanones

Introduction

Flavanoids are plant metabolites that have been credited with many diverse key functions in plant growth and development, including stress protection, reproduction, signaling, and protection from insect and mammalian consumption.^[1] In addition to their biological roles in plants, these phytochemicals have been studied for potential human health benefits. Flavanones have been characterized as “privileged structures,”^[2] due to their ability to interact with a number of different receptors in the body, thereby precipitating a wide range of biological responses. These natural products have been shown to exhibit biological activities including anticancer, antitumor, antibacterial, antimicrobial, antioxidant, estrogenic and anti-estrogenic properties.^[1]

Many books and review articles have been written on the flavanoids and their related compounds, including references on their isolation and structural elucidation,^[3] biosynthesis, biological activity, metabolism, chemical synthesis, and other points of interest. Much focus has been placed on the relationship between the biological activities and structures of these molecules.^[4]

The flavanone structure is characterized by a benzopyranone core substituted at the C2 position with possible substitution on the aryl backbone of the benzopyranone core (Figure 1). Many flavanoids containing phenolic or prenyl substitution around the flavanone core have been isolated and both have been implicated in the bioactivities of these natural products.^[3g,3h,4a,4c] A literature search for compounds based on the flavanone core reveals that more than three thousand members of the flavanoid family of natural products have been identified as possessing some biological activity (Figure 2), but there remains a dearth of stereoselective methods to access enantio-enriched flavanoids. These methods are especially important in the current context because although flavanones themselves are important phytochemicals, they are also precursors to a number of other plant metabolites such as flavanols, dihydroflavanols, and deoxyantocyanidins, which are themselves important pharmacophores.^[1,3a–3f]

In nature, chalcone isomerase (CHI) is responsible for the cyclization of 2'-hydroxychalcones to (2*S*)-flavanones, and a number of different enzymes are responsible for the conversion of flavanones into other plant metabolites.^[1,4d,5] Synthetic methods for cyclization of 2'-hydroxychalcones are biomimetic and include general acid or base catalysis, with the most common method for accessing flavanones being the base-catalyzed cyclization of 2'-hydroxychalcones. Base-catalyzed cyclization can be potentially problematic for stereoselective syntheses of flavanones, however, due to the potential for reversible elimination of phenoxide and racemization of the flavanone (Scheme 1).^[6] Because of this inherent liability and the need for generating enantio-enriched flavanoids, a number of asymmetric methods have been developed.^[7]

This microreview summarizes the current cache of *stereo-selective* methods for the construction of flavanones and related structures. A comprehensive compilation of every approach (including racemic strategies), as well as of the biological activities of those compounds, is beyond the scope of this review. The synthetic routes for accessing flavanoids are organized in terms of the bond formed to generate the flavanoid core. Methods that detail the synthesis of these structures through manipulation of the flavone or flavanone core are detailed first. Convergent methods of C2–R bond formation through the intermolecular conjugate addition of metal species to chromanones are discussed second. Cyclization reactions that form the C2–Y bond are compiled at the end.

General Methods for Accessing Enantio-enriched Flavanoids

The approaches most commonly applied to the synthesis of flavanones and related structures fall into three basic categories: 1) reduction of a flavone or chromone, or resolution of a racemic flavanone or derivative, 2) C2–R bond formation through the intermolecular conjugate addition of a metal nucleophile to a 4-chromone, and 3) C2–Y bond formation through intramolecular conjugate addition or Mitsunobu inversion (Figure 3). In general, early work in this field focused on enzymatic resolution of racemic flavanoids and intramolecular Mitsunobu reactions whereas later work has focused on catalytic intra- and intermolecular conjugate addition reactions to form the flavanoid core.

Manipulation of Flavone/Flavanone Core

Two of the earliest methods for accessing enantio-enriched flavanoids are either through the asymmetric reduction of the parent flavone or through the resolution of racemic flavanones. These methods are straightforward because many racemic flavanones and achiral flavones are commercially available.

Asymmetric Reduction

Recent developments in asymmetric hydrogenation have made it possible to carry out the chemoselective saturation of the C2=C3 alkene component of a flavone without reduction or loss of the carbonyl group. Although there are methods to saturate the flavone C=C bond (such as 1,4-hydride addition,^[8] hydrogenation with H₂ and Pd/C,^[9] or transfer hydrogenation^[10]) few of them perform this reduction with high levels of enantioselectivity without over-reduction of the benzocyclic ketone and/or elimination of phenoxide.^[6,11]

Asymmetric reductions of C2-substituted chromones to afford chromanones have not been used extensively, perhaps due to the tendencies towards overreduction to the chromanol or chromane skeletons. In their investigation of chromanones and related structures as treatments for central nervous system disorders, Bokel and co-workers reported the asymmetric reduction of chromone **1** to afford chromanone **2** (Scheme 2).^[12] Extensive optimization of their rhodium and iridium systems, including the metal counterion, chiral ligand, solvent, and pressure, led to the synthesis of enantio-enriched chromanone **2**.

A related report by Gontcharov and co-workers described two general methods for accessing chromanones and pharmaceutically acceptable salts: 1) hydrogenation of chromone **3** and chemical resolution, and 2) asymmetric hydrogenation of chromone **3**. After optimization of the late transition metal species and chiral ligands, they were able to carry out the reduction of 2-carboxy-4-chromone **3** with H₂ gas in the presence of a chiral rhodium complex to generate the saturated product **4** with 81% *ee* (Scheme 3).^[13] This chromanone could be elaborated to generate 5-HT_{2C} agonists for serotonin receptors, which treat a variety of central nervous system disorders including schizophrenia. The fact that only two reports on the efficient asymmetric hydrogenation of chromones (> 80% *ee*) exist, coupled with the lack of reports for flavones, highlights the need for further development of a general, efficient method for hydrogenation of these heterocycles.

Flavanones can be accessed through the asymmetric hydrogenation of 2-arylchromenes to 2-arylchromanes and subsequent oxidation to flavanones.^[14] We consider syntheses that generate dihydrobenzopyrans – such as Fu and Chung's synthesis^[15] – to be formal syntheses of these structures. Similarly, generation of enantio-enriched tetrahydroquinolines can also be considered a formal synthesis of azaflavanones and azachromanones.^[16,17]

Chemical Resolution

Because of the ease of reaction setup and the generally high yields and selectivities of enzymatic processes, enzymatic kinetic resolution, particularly in the synthesis and purification of optically pure pharmaceutical agents, has been widely reported in the literature.^[18] The discovery that enzyme catalysis can be carried out in organic solvents allowed for further development in this field.^[19] Chemical resolution has been reported less frequently. Both processes allow for up to a theoretical 50% yield of the desired enantiomer, with high enantioselectivity, together with recovery of the undesired enantiomer. However, a more desirable method would generate an excess of a desired enantiomer.

In 1962, Corey and Mitra reported a method for the chemical resolution of racemic ketones by use of (+)-butane-2,3-dithiol and applied it to the resolution of racemic flavanone (Scheme 4).^[20] Treatment of (±)-flavanone (**5**) with (+)-butane-2,3-dithiol generates a mixture of diastereomeric ketals (**6a** and **6b**), which can be easily separated by recrystallization (the ketals have differential solubility in benzene and methanol). Hydrolysis affords optically pure flavanones (2*R*)-**5** and (2*S*)-**5**.

Later work by Bognár, Rákosi, and Tökés was based on a multistep sequence to generate enantio-enriched flavanones from racemates (Scheme 5).^[21] After oxime formation from

(±)-flavanone (**5**) and reduction to the secondary amine, the mixture of *cis*- and *trans*-amines could be resolved by use of (+)-camphor-10-sulfonate and (–)-dibenzoyl-tartrates. These salts could be converted into the free amines **7a** and **7b**, which upon deamination with nitrous acid yielded flavanols that were subsequently oxidized to give both enantiomers of flavanone.

Enzymatic Kinetic Resolution

In 1992, Kasahara and co-workers reported the enzymatic kinetic resolution of flavanone and *cis*-flavanol acetate. The resolution of flavanone was accomplished by first reducing the carbonyl with baker's yeast (*Saccharomyces cerevisiae*). After separation of the enantio-enriched flavanol from the flavanone, oxidation provided the opposite enantiomer of flavanone. However, enzymatic kinetic resolution of racemic flavanols proved to be more difficult.

An enzymatic transesterification of (±)-**8** (Scheme 6) with lipase PS afforded flavanol acetate **9**, but in racemic form. However, enzymatic kinetic resolution of (±)-**9** at ambient temperature provided a mixture of *cis*-flavanol acetate **9** and enantio-enriched *cis*-flavanol **8**.^[22] After eight days, hydrolysis of acetate **9**, followed by oxidation with manganese dioxide, led to the formation of (2*S*)-**5**, whereas oxidation of flavanol **8** led to the formation of (2*R*)-**5**.

Later work by Izumi and Suenaga detailed the enzymatic kinetic resolution of flavanone oximes (Scheme 7).^[23] The enzymatic hydrolysis of flavanone oxime acetate (±)-**10** afforded a mixture of flavanone oxime **11** and flavanone oxime acetate **10**. Acid hydrolysis of both compounds afforded each enantiomer of flavanone (**5**).

During an investigation of the α-hydroxylation of flavanones by Tanaka and co-workers, they realized that they required a more efficient method for the preparation of the parent enantiomerically enriched flavanones.^[24] Prior to this report, there were three viable reported methods for accessing chiral 3-hydroxyflavanones: enzymatic resolution of racemic 3-hydroxyflavanones,^[25] conversion of epoxy-ketones,^[26] and synthesis through asymmetric dihydroxylation of cinnamic esters.^[27] All of these methods required multistep sequences and yielded materials with low enantiomeric excesses. Tanaka and co-workers carried out initial studies to investigate the feasibility of the use of lipases, including PS, M, A, R, and AY lipases, to resolve flavanones. These studies revealed that lipase AY was superior for kinetic hydrolysis and transesterification (Scheme 8). Treatment of racemic flavanol **8** with lipase AY and vinyl acetate generated a mixture of *cis*-flavanol acetate **9** and *cis*-flavanol **8**, which could be converted into (2*R*)-**5** or (2*S*)-**5** in one or two steps. It is interesting to note that kinetic hydrolysis of racemic *cis*-flavanol acetate **9** in phosphate buffer (pH 6.8) with lipase AY gave **8** and unreacted **9**.

Kawasaki and co-workers carried out a combination Mitsunobu reaction/enzymatic resolution to access enantio-enriched 2-methylchroman-4-one (Scheme 9).^[28] Mitsunobu inversion of homoallylic alcohol **12** with phenol generated the alkyl phenyl ether **13**, which was then oxidized to the carboxylic acid and subjected to enzymatic transesterification to generate a mixture of butyl ester **14** and acid **15**. Enzymatic hydrolysis of butyl ester **14** and subsequent Friedel–Crafts acylation generated (2*S*)-chromanone **16**, whereas acylation of **15** allowed for generation of the enantiomeric chromanone **16**.

Earlier work on the resolution of secondary alcohols (similar to 1-phenylbut-3-en-2-ol) by lipase-catalyzed transesterification^[29] led Kawasaki and co-workers to adopt an alternative route for the synthesis of 2-phenylchroman-4-one (flavanone).^[28] Similarly to the steps detailed above, the first step of their synthesis involved enzymatic transesterification of the

arylhomomoallylic alcohol and a subsequent Mitsunobu reaction, which unfortunately involved minor racemization. Oxidation of the terminal alkene to the carboxylic acid, followed by Friedel–Crafts acylation, produced enantio-enriched flavanone. Although these highly tuned enzymatic resolution processes can deliver the desired flavanones and chromanones with excellent enantioselectivities, enzymatic kinetic resolution remains inherently inefficient due to a maximum theoretical yield of 50% for the resolution process.

Non-Enzymatic Kinetic Resolution

Metz and Schwab have developed a transfer hydrogenation method for producing enantiopure flavanones, in particular prenylated flavanones.^[30] In the presence of a chiral catalyst, a racemic mixture of a flavanone can be selectively reduced with a mixture of formic acid and base to produce one enantiomer of the flavanone, together with the other enantiomer as the *cis*-flavanol. The flavanol can be oxidized to produce the flavanone, and selectivities in excess of 95% *ee* can be achieved for the flavanones (not shown).

Recently, Hou and co-workers reported the first non-enzymatic kinetic resolution of 2-substituted 2,3-dihydro-4-quinolones **17** through palladium-catalyzed asymmetric allylic alkylation (Scheme 10).^[31] Although palladium-catalyzed allylic substitution reactions have been successfully applied to kinetic resolutions, the majority of studies until the disclosure of this work and a related report^[32] had focused on the resolution of allyl substrates.^[33]

Carbon–Carbon Bond Formation

Carbon–carbon bond formation through the intermolecular conjugate addition of a nucleophilic metal–carbon species (i.e., arylboronic acid, dialkylzinc, cuprate, aryllithium) to a 4-chromone is the most convergent of the approaches to flavanones listed above. Although this approach has been employed extensively in syntheses of compounds in which Y = CH₂ (tetralones)^[34] it has been less frequently utilized with 4-chromones, due to the ease of phenoxide elimination after enolate formation.^[6,11] Until recently, these methods for accessing flavanoids required capture of the newly formed enolate with a suitable electrophile such as benzaldehyde or chlorotrimethylsilane. In light of the concern of problematic phenoxide elimination, the development of suitable metal complexes with chiral ligands have made it possible to access the desired products in good yields and with high selectivities.

Intermolecular Conjugate Addition to 4-Chromanones

Wallace and Saengchantara employed enantio-enriched sulfoxide **20** in the first diastereoselective synthesis of chromanone **16** (Scheme 11).^[35] Treatment of **20** with lithium dimethyl cuprate afforded a separable mixture of chromanones, which produced the *cis* isomer **21** in 24% overall yield after flash column chromatography and crystallization. A desulfurization by use of an aluminium amalgam afforded the chromanol, which was oxidized with PDC to generate chromanone **16**. Their model for stereochemical induction invokes chelation of the oxygen atoms of **20** with a metallic species, which causes blocking of the front face of the molecule by the tolyl substituent. The incoming methyl group approaches from the less hindered (back) face and, after a reduction/oxidation sequence, affords (2*S*)-chromanone **16**. An attempt to apply this chemistry to synthesize flavanone (**5**) failed because of the lability of the intermediate 2-phenyl-3-(*p*-tolylsulfinyl)chromanone, which underwent sulfoxide elimination at ambient temperature to afford flavone.^[36] They also used this chemistry to synthesize (*S*)-2,3-dimethylchroman-4-one, which Hodgetts later synthesized by a Mitsunobu-based strategy.^[37]

Solladie and co-workers later employed this chemistry in the total synthesis of leridol (Scheme 12).^[38] Addition of lithium diphenyl cuprate to sulfoxide **22**, followed by flash column chromatography, allowed access to the 1,4-addition product **23**. Because of the instability of the addition product, desulfurization was carried out as quickly as possible to afford a flavanone later identified as (+)-dimethylcryptostrobin (**24**). Demethylation and hydroxymethylation afforded flavanone **25**, which has a melting point significantly lower than that of natural leridol, confirming that the structure of leridol was not flavanone **25**, as previously reported.

Hoveyda and co-workers reported the first effective and general highly enantioselective copper-catalyzed additions of dialkylzinc reagents to furanones and pyranones in 2005 (Scheme 13).^[39] Amino-acid-based phosphanes were employed as chiral ligands for asymmetric conjugate addition processes, affording products in moderate-to-good yields and with generally high enantioselectivities. To obtain higher yields, the reactions must be carried out in the presence of an aldehyde, presumably due to adventitious ketene formation (in the case of lactones) or intermolecular Michael addition (if the enolate is not trapped in situ). In the example above (the sole example of addition to a 4-chromanone in this report), treatment of 4-chromanone (**26**) with the chiral phosphane, dialkylzinc reagent, and benzaldehyde generated β -hydroxychromanones **27** and **28**, which underwent retro-aldol reactions to afford the desired chromanones **29** and **30** in good yields and with excellent enantioselectivities.

Later that year Hayashi and co-workers reported the first catalytic asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones **32** (Scheme 14).^[40] These compounds, although they have undergone limited biological studies, have been identified as a new class of antimitotic antitumor agents, one enantiomer of which is more potent than the other.^[41] Because of this novel mode of biological action, Hayashi and co-workers sought to develop a method for accessing these compounds. Their method, 1,4-conjugate addition of arylzinc reagents to substrates **31**, proceeds in the presence of a rhodium catalyst and chlorotrimethylsilane, which has a twofold purpose: to act as a Lewis acid, activating the substrate toward 1,4-addition, and to stabilize the product by intercepting the generated enolate as a silyl enol ether. The reaction accommodates both electron-deficient and electron-rich aromatic electrophiles and arylzinc reagents to afford products in good-to-excellent yields and with selectivities generally greater than 90%.

Inspired by these earlier reports, a general method for accessing flavanones **34** through a 1,4-conjugate addition variant that did not require trapping of the enolate intermediate was reported in 2010. Liao and co-workers developed asymmetric 1,4-additions of sodium tetraarylborates to 4-chromones **33** by employment of a novel C_2 -symmetric chiral bis-sulfoxide ligand (Scheme 15).^[42] This was the first report of a conjugate addition of an arylboron reagent to 4-chromenone (**26**), which had previously remained elusive.^[43] Although the reaction was initially optimized with phenylboronic acid, it was found to be easier with sodium tetraarylborates.^[44] This method can be used to access a wide range of optically pure (or very nearly so) flavanones **34**. Electron-deficient sodium tetraarylborates afford the poorest yields (25% yield, 97% *ee*) whereas more electron-rich substrates result in higher yields and enantioselectivities. Substitution on the aromatic portion of 4-chromone did not have a dramatic effect on the yield or selectivity of this process. This reaction required longer reaction times (24 h) than the originally optimized 3 h to afford modest yields of the flavanone products **34**. The 1,4-conjugate additions could be extended to substrates such as cyclopentenones, cyclohexenones, cycloheptenones, unsaturated lactones, and aliphatic enones.

In early 2011, Korenaga and co-workers reported similar 1,4-conjugate addition reactions of arylboronic acids to chromones **33** (Scheme 16).^[45] These reactions also employ a rhodium catalyst, but with lower catalyst loadings than under Liao's conditions (0.5–3 mol-% Rh, compared to 5 mol-%). Korenaga's reactions proceeded in up to three hours to afford flavanone products **34** in moderate yields and with excellent enantioselectivities. During the course of the reaction, mixtures of both 1,4-addition and 1,2-addition products were observed. It was found that use of toluene as a solvent greatly increased the catalytic activity of rhodium complex and therefore resulted in a faster rate of 1,2-addition. Use of a halogenated solvent such as dichloromethane decreased the catalytic activity of the rhodium complex, suppressed the formation of the 1,2-addition products (up to 10% yields), and afforded moderate yields of the desired flavanones. With these optimized reaction conditions, electron-rich and -deficient arylboronic acids underwent addition to electron-rich and -deficient 4-chromones **33** to provide enantiopure flavanones **34**.

Korenaga applied this methodology to the synthesis of (*S*)-pinostrobin (**38**, Scheme 17), a biologically active flavanone that had been synthesized only once previously.^[46] Because 4-chromone **36** was not a very reactive substrate, use of CH₂Cl₂ as the solvent resulted in poor yields. Switching to toluene increased the yield of the reaction, without generation of the undesired 1,2 adduct (due to the steric repulsion between the *o*-methoxy substituent and the rhodium center). This synthesis was the first to employ asymmetric catalysis to access enantiopure pinostrobin (**38**), which was accomplished in four steps and 74% overall yield. The opposite enantiomer of the natural product could also be synthesized simply by using the opposite enantiomer of the chiral ligand.

Carbon–Heteroatom Bond Formation

The methods most commonly used to generate asymmetric flavanoids proceed by formation of the C2–Y bond. This strategy of cyclizing the flavanone core is generally based either a) on an intramolecular conjugate addition reaction of a 2'-hydroxy- or 2'-aminochalcone to form the C2–Y bond of the flavanoid core, or b) on the Mitsunobu inversion of a β -hydroxyketone (Figure 3). Although both methods can generate enantio-enriched flavanoids, the former method requires the use of a chiral catalyst for asymmetric induction at C2 and the latter requires the generation of an enantio-enriched aldol or Mannich adduct to introduce stereochemistry at C2.

Intramolecular conjugate additions have been used extensively to form racemic flavanones, but the conditions required for their cyclization are not always tolerant of functional groups and can result in reversible ring-opening and closing for the chalcone.^[6,11] Aqueous alkali-mediated aldol condensation of a 2'-hydroxyacetophenone with an aldehyde will generate the 2'-hydroxychalcone. Acid-mediated or base-mediated cyclization of the chalcone can generate the desired flavanone (or chromanone, if the aldehyde is an alkyl aldehyde). Successful intramolecular conjugate addition methods that have been developed for the asymmetric generation of flavanoids require more strongly activated substrates such as α -carboxychalcones.

The Mitsunobu reaction^[47] has also become a popular intramolecular alternative for the formation of flavanoids.^[48] Although the intramolecular variant of the Mitsunobu reaction forms the same C2–Y bond as the intramolecular conjugate addition reactions, it requires the stereoselective installation of the secondary alcohol in the appropriate configuration for inversion by the C2'-phenol in an S_N2-type displacement. The enantiomeric excess of that alcohol should thus determine that of the Mitsunobu inversion. Producing an enantio-enriched β -hydroxyketone can be problematic, because there are no reports of stereoselective aldol reactions with 2'-hydroxyacetophenones and few reports featuring 2'-

alkoxyacetophenones.^[49] The desired β -hydroxy ketone can also be accessed through the addition of a lithiated phenoxide to a β -siloxy Weinreb amide and subsequent desilylation,^[46] but the generation of the amide requires several synthetic steps.

Intramolecular Conjugate Additions of 2'-Hydroxychalcones

In 1999 Ishikawa and co-workers reported studies directed towards the total synthesis of (+)-calanolide A and (+)-inophyllum B, coumarin natural products with anti-HIV activity (Scheme 18).^[50] The key step of the synthesis was the construction of the chromanone core through intramolecular conjugate addition of an *o*-tigloylphenol in the presence of triethylamine. Use of quinine as the base led to an asymmetric cyclization, the first effective asymmetric conjugate addition of its type.^[24,51] Treatment of phenol **39** with quinine afforded a quantitative yield of a mixture of *cis*-**40** and *trans*-**40**. The *cis* isomer could be converted into the *trans* isomer by heating at reflux in $\text{MgI}_2 \cdot 6\text{H}_2\text{O}$ to afford a 50% yield of *trans*-**40** with recovery of 50% of the *cis* isomer, and no erosion of enantiomeric excess. Finally, reduction of *trans*-**40** afforded (+)-calanolide A.

A thorough investigation of asymmetric cyclizations of 2'-hydroxychalcones catalyzed by chiral Brønsted acids and bases was reported by Hintermann and co-workers in 2007.^[5a] A wide range of catalytic conditions were employed to induce cyclization, but none of those conditions provided useful levels of enantioselectivity. Hintermann discusses two such apparent cases: the first with use of camphorsulfonic acid (CSA, Fujise et al.)^[52] and the second with use of cinchona alkaloids for the cyclization of *o*-tigloylphenols to 2,3-dimethylchroman-4-ones (Ishikawa et al.).^[24,50-51,53] In their investigation of Ishikawa's work (Scheme 19) they found that although cinchona alkaloids could be employed as catalysts to generate enantio-enriched chromanones, they could not be used in the asymmetric synthesis of flavanones. It was discovered that 2',6'-dihydroxychalcones cyclized more readily than their monohydroxy counterparts, perhaps as a result of destabilization due to steric repulsion between the C6'-substituents and the α -CH bonds of the chalcones. This report disclosed the first asymmetric cyclizations of 2',6'-dihydroxychalcones in the presence of cinchona alkaloids. The cyclization of chalcone **42** in the presence of quinine generated flavanone **43** with up to 64% *ee* (Scheme 19). Whereas employment of CH_2Cl_2 as a solvent resulted in fast reaction times but low enantioselectivities, chlorobenzene and *o*-dichlorobenzene were suitable solvents in terms of polarity and solubility. The quinine/quinidine alkaloids gave higher selectivities than the cinchonine/cinchonidine pseudoenantiomeric pair. Interestingly, the cinchonine/cinchonidine catalysts produced the same enantiomer in excess. Direct and efficient asymmetric cyclization of 2'-hydroxychalcones to match nature's chalcone cyclization process continues to be a synthetic transformation yet to be realized.

Intramolecular Conjugate Addition of Alkylidenes

In 2007, our group reported the first general catalytic enantioselective synthesis of flavanones and chromanones from alkylidenes with the general structure **44** (Scheme 20).^[6c,11] These intramolecular conjugate additions are catalyzed by a chiral thiourea derived from quinine. Our strategy was to incorporate on the chalcone substrate a functional group that would enhance the reactivity, favor flavanone products over chalcone starting materials, and provide a second Lewis basic site for potential interaction with the catalyst. These requirements were met by a *tert*-butyl ester that could also be easily removed under mild conditions with minimal impact on the C2 stereochemistry. The alkylidenes **44** were accessed by Knoevenagel condensations, from which the *E*-alkenes could be isolated by crystallization in >95:5 *E/Z* ratios. Both electron-rich and extended aromatic systems are suitable substrates, and flavanones and chromanones **45** are accessed with excellent enantioselectivities.

Because the Knoevenagel and conjugate addition reactions are both performed in toluene, these reactions can be combined in a single reaction flask (Scheme 21). Upon completion of the Knoevenagel condensation between β -keto ester **46** and hydrocinnamaldehyde and cyclization, *p*TsOH is added for the decarboxylation to afford the natural product flindersiachromanone (**47**) in 77% overall yield and with 80% *ee*. We were also able to apply our chemical method to the first total syntheses of four members of the abyssinone family of natural products: abyssinones I, II (see Figure 2), III, and IV-4'-OMe and their unnatural enantiomers. These syntheses allowed us to determine not only the absolute stereochemistry of the abyssinones, but also that the abyssinones selectively and differentially inhibit cell growth and downregulate matrix metalloproteinase-2 expression.^[6c]

Shortly after our report in 2007, Feng and co-workers reported an analogous reaction based on transition metal catalysis (Scheme 22).^[54] This asymmetric intramolecular conjugate addition is catalyzed by a chiral *N,N'*-dioxide nickel(II) complex to afford flavanones **45** (and a single example of a chromanone). It is important to note that although the yields for this process were generally high, use of substrates containing an electron-donating group resulted in decreased enantioselectivities of the flavanone products, possibly due to quinone methide formation.^[6c,11]

Most reports on the cyclization of alkylidenes are based on catalysis by cinchona alkaloid derivatives. ShuLi and co-workers reported the first use of chiral phosphoric acids and *N*-triflyl phosphoramides for the cyclization of alkylidenes **44** (Scheme 23).^[55] When they employed 2'-hydroxychalcones as substrates and a chiral *N*-triflyl phosphoramide as catalyst, ShuLi and co-workers were unable to generate any flavanone, due to the inactivity of the substrate. However, alkylidenes such as **44** introduced by us afforded 3-carboxyflavanones in good yields and with moderate selectivities. Although all chiral phosphoric acids examined provided low yields of flavanones **45**, the more acidic chiral *N*-triflyl phosphoramides catalyzed the reaction well, improving the yields. The size of the ester on the alkylidene has a marked effect on the selectivity of the reaction, with the bulkier *tert*-butyl ester affording products with higher selectivities. Flavanones can be generated with up to 74% *ee* values under two sets of reaction conditions. Electron-donating substituents significantly increase the reaction yields but decrease the enantioselectivities.

Lu and Liu reported the synthesis of azaflavanones, based on our alkylidene cyclization strategy (Scheme 24).^[56] Until this report was published, there were only two reports of accessing asymmetric azaflavanones: the rhodium-catalyzed 1,4-additions of arylzinc reagents to 4-quinolones reported by Hayashi and co-workers^[40] and the kinetic resolutions of 2,3-dihydro-substituted 4-quinolones by palladium-catalyzed asymmetric allylic alkylation reported by Hou and co-workers.^[31] The optimal substrates were alkylidenes **48**, which after treatment with a bifunctional thiourea could be converted into azaflavanones **49** and azachromanones (a single example) in good yields. Although aryl substitution (*R* = aryl) afforded products **49** with high selectivities, alkyl substitution produced a chromanone with significantly lower selectivity.

Zhao and co-workers developed another asymmetric variant of our reaction in which excellent yields and enantioselectivities were achieved by use of a quinidine catalyst (Scheme 25). The authors postulate that the quinidine-derived catalyst serves as a bifunctional catalyst for the reaction.^[57]

Intramolecular Mitsunobu Inversion

In 1994, Rao and co-workers demonstrated the first single-flask enantioselective synthesis of 5,7-dihydroxy-2-methylchroman-4-one (Scheme 26), which served as a model substrate

for the anti-HIV agent (+)-calanolide A (see Scheme 18).^[58] (This compound was later methylated for analytical purposes.) In the intermolecular version of this reaction, phloroglucinol (**52**) and (*S*)-3-hydroxybutyronitrile (**53**) were subjected to Houben–Hoesch conditions, which generated chromanone **54**. Although the yield for this process was only 25%, the simplicity of the operation and the availability of pure β -hydroxy nitriles made this process attractive for the generation of racemic chromanones. The intramolecular version of this reaction employed a Mitsunobu reaction between phenol **55** and chiral secondary alcohol **56** for the stereospecific aryl ether bond formation. Ishikawa and co-workers later published reports on the enantioselective construction of the 2,3-dimethyl-4-chromanone ring^[50,53a] and of (+)-calanolide A (Scheme 18).^[24,51] In an approach similar to Rao's work, Lipinski and co-workers were able to employ alcohol **56**, an intermediate in their synthesis of spiro hydroxy acetic acids (not shown), in their synthesis of chromanones.^[8a]

In the first asymmetric total synthesis of (–)-pinostrobin (**38**), Hodgetts carried out the addition of *ortho*-lithiated **57** to a Weinreb amide to generate β -siloxy ketone **58** (Scheme 27).^[46,59] Removal of both the silyl and the MOM ethers and intramolecular Mitsunobu inversion generated (–)-pinostrobin. To date, the synthesis of (–)-pinostrobin has only been carried out in one other instance.^[45,60]

Similarly, 2-arylchromanes can be synthesized through intramolecular Mitsunobu inversion and subsequently oxidized to produce flavanones and chromanones (not shown).^[46,59] Syntheses of 2-aryl- and 2-alkyl-4*H*-chromenes can also be considered formal syntheses of these molecules.^[61]

Until Noda and Watanabe's report on the synthesis of flavanone and 2-methylchromanone,^[62] there had only been five reports of syntheses of enantio-enriched flavanones and 2-methylchromanones.^[35b,36,38,46,58] In their synthesis, Noda and Watanabe generated dithiane **59**, which was lithiated with *n*BuLi and added to either (*S*)- or (*R*)-styrene oxide to generate diol **60** (Scheme 28).^[62] Finally, Mitsunobu inversion and desulfurization generated the enantio-enriched flavanone. By treatment of dithiane **59** with either enantiomer of styrene oxide or propylene oxide, both flavanone (**5**) and 2-methylchromanone (**16**) could be accessed with high levels of enantiomeric excess.

Tandem Intramolecular Conjugate Addition/Functionalization

In an approach based on the quinine-catalyzed cyclizations of alkylidenes reported by our group in 2007,^[11] Zhao and co-workers reported tandem intramolecular conjugate addition/electrophilic fluorination sequences starting from alkylidenes **61** to generate 3-fluorocarboxyflavanones **62** (Scheme 29).^[63] They were able to access a variety of 3-fluorocarboxyflavanones and chromanones **62**, which included activated and deactivated substitution patterns at R. It is important to note that chromanones generally gave lower selectivities than flavanones and that the 2-furanyl substrate represented the most weakly performing of the aromatic substrates, with a yield of 56% and a selectivity of 73% *ee*.

Zhao and co-workers followed their earlier tandem work^[63a] with a recent report on the tandem intramolecular cyclization/functionalization of alkylidenes **63** (Scheme 30).^[57] They found that modified cinchona alkaloids were suitable catalysts for the reactions and provided products in good yields and with high enantioselectivities. Whereas treatment of the reaction mixtures with *p*TsOH upon completion of cyclization led to decarboxylation and the formation of flavanones, treatment with electrophilic agents such as methyl vinyl ketone, *N*-bromosuccinimide, or *N*-chlorosuccinimide generated functionalized flavanones **64**, **65**, and **66**, respectively.

Wacker-Type Oxidative Cyclization

A variety of 2-methylchromanone derivatives were prepared through Wacker-type oxidative cyclizations of homoallylic alcohols such as **67** (Scheme 31).^[64] Wang and co-workers have proposed a 1,5-hydride shift as a key part of the mechanism. In enantio-enriched substrates, excellent chirality transfer was observed (Scheme 31). The aromatic rings accommodated both electron-rich and -deficient substituents to give products in moderate-to-good yields. Because of the natures of the substrates, this methodology is limited to the synthesis of substituted 2-methylchromanones.

Conclusions

Flavanone natural products remain attractive privileged structures for rapid library development, structure–activity studies, and optimization of drug-like properties, including potency and selectivity. Over the last decade, significant advances have been made in the field of asymmetric synthesis of flavanones and related molecules that have solved the issues of controlling the stereochemistry at C2, thereby allowing access to enantiopure or highly enantio-enriched flavanones. Despite these important advances, no general, asymmetric cyclization of unactivated 2'-hydroxychalcones has yet emerged. This cyclization strategy continues to remain elusive, perhaps because these substrates are less reactive than their α -carboxy counterparts. This most direct and biomimetic approach requires the development of more reactive and selective catalysts before it can be added to the list of general, efficient methods for the stereoselective synthesis of flavanones and related structures. Nonetheless, the examples and strategies outlined in this review show remarkable progress and collectively have greatly added to the arsenal of methods for the chemical community to synthesize this important class of compounds.

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Biographies

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Figure 1.
Flavanoid nomenclature.

Figure 2.
Representative biologically active flavanoid natural products.

Figure 3.
General methods for accessing enantio-enriched flavanoids.

Scheme 1.

Base-promoted racemization of enantio-enriched flavanones.

Scheme 2.
Asymmetric hydrogenation of 4-chromone **1**.

Scheme 3.
Asymmetric hydrogenation of 4-chromone **3**.

Scheme 4.
Resolution of (±)-flavanone (**5**) through the synthesis of ketals **6a** and **6b**.

Scheme 5. Resolution of (**±**)-flavanone (**5**) through conversion into *cis*-amines **7a** and **7b**.

Scheme 6.
Enzymatic kinetic resolution of racemic flavanol acetate **9**.

Scheme 7.
Enzymatic kinetic resolution of racemic flavanone oxime acetate **10**.

Scheme 8.
Lipase-catalyzed kinetic resolution of racemic flavanol **8**.

Scheme 9. Enzymatic resolution of flavanones via Mitsunobu construction of α -phenoxyester **14**.

Scheme 10.

Kinetic resolution of 2-substituted 2,3-dihydro-4-quinolones **17** through palladium-catalyzed asymmetric allylic alkylation.

Scheme 11.
Diastereoselective conjugate addition to sulfenylchromone **20**.

Scheme 12. Total synthesis of the originally proposed structure of leridol (**25**).

Scheme 13.

Highly enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to 4-chromanone (**26**).

Scheme 14.

Asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones **32** by rhodium-catalyzed 1,4-addition of arylzinc reagents in the presence of chlorotrimethylsilane.

Scheme 15.

Rhodium-catalyzed asymmetric 1,4-additions of sodium tetraarylborates to 4-chromones **33** in the presence of a C_2 -symmetric chiral bis-sulfoxide ligand.

Scheme 16.

Enantioselective synthesis of flavanones **34** through rhodium-catalyzed 1,4-additions of phenylboronic acid derivatives.

Scheme 17.

Enantioselective synthesis of (S)-pinostrobin (38) through a rhodium-catalyzed 1,4-addition of phenylboronic acid.

Scheme 18.

Quinine-catalyzed stereoselective cyclization of *o*-tigloylphenol **39**.

Scheme 19. Quinine-catalyzed asymmetric cyclization of 2',6'-dihydroxychalcone **42**.

Scheme 20.

Catalytic enantioselective synthesis of flavanones and chromanones **45** from alkylidenes **44**.

Scheme 21.

Total synthesis of flindersiachromanone (**47**) through a single-flask Knoevenagel condensation/cyclization/decarboxylation sequence.

Scheme 22.
 Ni^{II} -catalyzed cyclization of alkydienes **44**.

Scheme 23. Cyclization of alkylidenes **44** catalyzed by chiral *N*-triflyl phosphoramides.

Scheme 24.

Asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones **49** catalyzed by bifunctional thioureas.

Scheme 25.

Tandem intramolecular conjugate addition/decarboxylation reaction sequences from alkylidenes **50**.

Intermolecular Houben–Hoesch reaction

Intramolecular Houben–Hoesch reaction

Scheme 26.
Synthesis of chiral 2-methylchromanone **54**.

Scheme 27.
First total synthesis of (-)-pinostrobin (**38**).

Scheme 28.

Synthesis of (2R)-flavanone (**5**) through a dithiane addition/intramolecular Mitsunobu inversion sequence.

Scheme 29. Tandem cyclization/fluorination sequences starting from alkylidenes **61**.

Scheme 30.

Tandem intramolecular conjugate addition/Michael addition or halogenation sequences.

Scheme 31.

Oxidative cyclization of 2-(1-hydroxybut-3-en-1-yl)-phenol.