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Asymmetric synthesis of chiral chromans

Hong C. Shen

Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., Rahway, NJ 07065-0900, United States

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Contents

1. Introduction

Chiral chromans (Fig. 1) constitute the core of numerous natural products and synthetic analogs (Scheme 1) displaying an extensive array of biological activities. As such, chiral chroman small molecules have played an important role in various therapeutic areas including cardiovascular diseases, diabetes, obesity, hypertension, cancer, central nerve system and endocrine disorders, and infectious diseases.

The most well-known chiral chroman is α-tocopherol (**1**), which is also the most significant member of the vitamin E family serving as a natural lipophilic antioxidant and radical scavenger.[1] In addition, trolox (**2**)[2] and MDL-73404 (**3**),[3] analogs of α-tocopherol (**1**), are believed to play a beneficial role against cardiovascular diseases presumably due to their antioxidant activity. In particular, MDL-73404 (**3**) exhibits cardioprotective effects during a myocardial infarction.

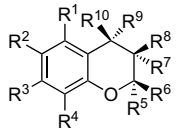

Figure 1.

E-mail address: hong_shen@merck.com

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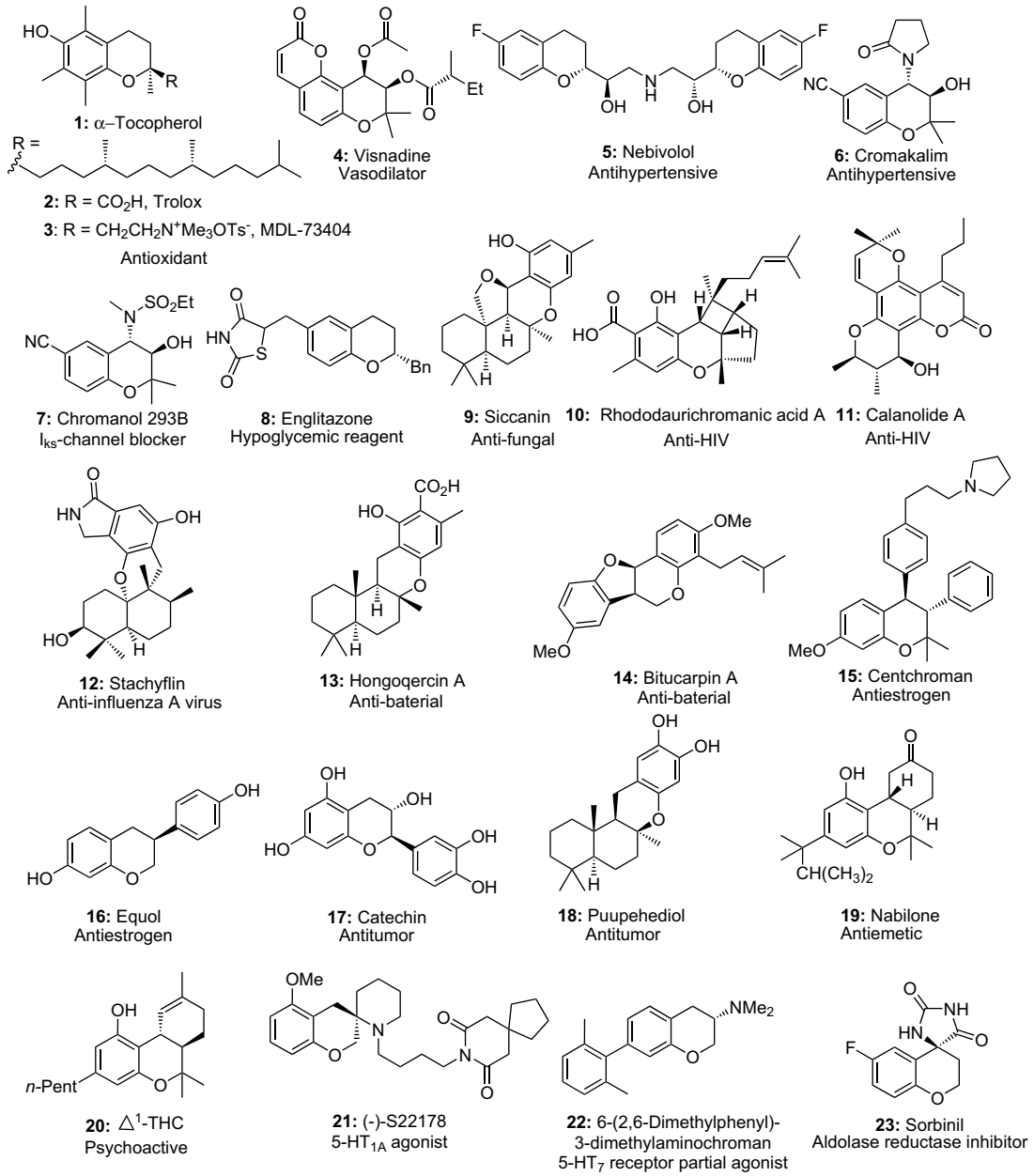


Scheme 1.

Other chiral chromans have also displayed important biological properties. For example, visnadine (**4**),[4] nebivolol (**5**), and cromakalim (**6**) have demonstrated vasodilatory or anti-hypertensive effects.[5] Mechanistically, the promising anti-hypertensive activity of cromakalim (**6**) is due to its activation of potassium channels.[6] Conversely, chromanol 293B (**7**) leads to a selective IK_s-channel blockade.[7]

Besides hypertension, another manifold of metabolic disorder is diabetes. Englitazone (**8**)[8] and its analog troglitazone, both agonists of PPARs, have been developed as clinical candidates to control the glucose level in diabetic patients.

In the arena of infectious diseases, siccanin (**9**) is a potent antifungal drug;[9] rhododaurichromanic acid A (**10**) shows anti-HIV activity;[10] calanolides A (**11**) and B demonstrate excellent inhibition toward HIV-1 reverse transcriptase;[11] stachyflin (**12**) exhibits potent antiviral effect against influenza A/WSN/33 (H1N1) virus by inhibiting the fusion between the viral envelop and the endosome of the host cell membrane;[12] hongoquercin A (**13**)[13] and bitucarpin A (**14**)[14] elicit antibacterial effects.

As an example of a potential application in endocrinology, centchroman (**15**) is an estrogen antagonist with antifertility properties.[15]

With respect to biological activity related to oncology, (*S*)-equol (**16**) was found to give higher estrogenic activity than daidzein, and may increase the proliferation of breast-cancer cells.[16] Formerly used as an antidiarrhoeal, (+)-catechin (**17**) inhibits intestinal tumor formation and suppresses focal adhesion kinase activation in the min/+ mouse.[17a] Additionally, it also reduces atherosclerotic plaques in animal models.[17b] Puupehediol (**18**) and several other analogs of puupehedione have shown various cytotoxic, antifungal, immunomodulatory and CETP (cholesteryl ester transfer protein) inhibitory effects.[18] Recently, they have also been shown to exhibit a good inhibitory effect against several cancer cell lines.

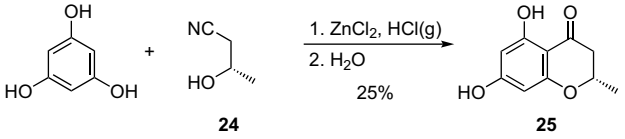
In CNS drug discovery, nabilone (**19**) is a synthetic cannabinoid with antiemetic, antiglaucoma, and CNS effects.[19] The δ-1-tetrahydrocannabinol (THC) (**20**) binds to the cannabinoid receptor CB_1, and exerts analgesic effects that, even at low doses, could be used for the treatment of pain. Other CNS effects of CB_1-activation by

THC analogs including relaxation, euphoria, altered space-time perception, disorientation, fatigue, alteration of senses, and appetite stimulation have also been reported.[20] Compound S22178 (**21**) was developed as a potent 5-HT_{1A} agonist (IC_{50}=8.8 nM) to potentially treat anxiety and depression.[21] 6-(2,6-Dimethylphenyl)-3-dimethylaminochroman (**22**) was identified as a 5-HT_7 receptor partial agonist, therefore it may modulate cognitive and behavior functions. Sorbinil (**23**) functions as an aldolase reductase inhibitor and has been shown to improve nerve conduction velocity in diabetic patients.[22]

The significant and diverse biological profiles of chiral chromans have kindled enormous interest in academia and pharmaceutical industry to develop efficient asymmetric synthesis of this class of molecules. The methods described herein can be classified into five categories based on how chiral centers in chromans are introduced.[23] The first strategy entails readily available chiral reagents as building blocks, and usually allows concise synthesis. These chiral reagents could be derived from natural sources, kinetic resolution or catalytic asymmetric transformations performed by chemical companies. Sometimes this approach can be limited by the cost, and the challenge of accessing both chroman enantiomers as only one starting enantiomer may be available.

The second approach relies on kinetic resolution of racemic chromans, or their precursors by either enzymatic or non-enzymatic means. In a conventional kinetic resolution, racemic mixtures are treated with a chiral resolving agent such as a chiral acid or base, followed by a separation, such as crystallization or chromatography, to obtain a single enantiomer. To secure a high level of enantiopurity, a recrystallization process is often adopted. For conventional kinetic resolution of racemic material, the maximum yield of the desired enantiomer is 50%. To improve the yield, dynamic kinetic resolution protocols, whenever possible, have been utilized to convert racemic mixtures into a single enantiomer.[24] Additionally, the use of stoichoimetric resolution agent could be circumvented by enzyme- or metal-catalyzed kinetic resolution methods, which have demonstrated excellent selectivity factors.[25]

The third method to synthesize chiral chromans involves desymmetrization, in which a *meso* or prochiral starting material is desymmetrized with the aid of a chiral reagent or catalyst, thereby potentially allowing for complete conversion of the starting material into a single enantiomer.[26]



24 **25**

Scheme 2.

The fourth approach utilizes chiral auxiliaries to construct chiral centers of chromans. The asymmetric induction by a chiral auxiliary can be very effective, however synthetic operations required to install and remove chiral auxiliaries may potentially diminish their practicality, particularly in large-scale industrial operations.

Lastly, the asymmetric catalysis has evolved into an atom-economical and effective strategy to prepare chiral chromans. In this approach, only catalytic amount of chiral material (usually as ligands) is required to produce a large quantity of enantiomerically pure products. In addition, asymmetric catalysis can provide access to either enantiomer by simply employing ligands of opposite configuration.

2. Synthetic strategies toward chiral chromans

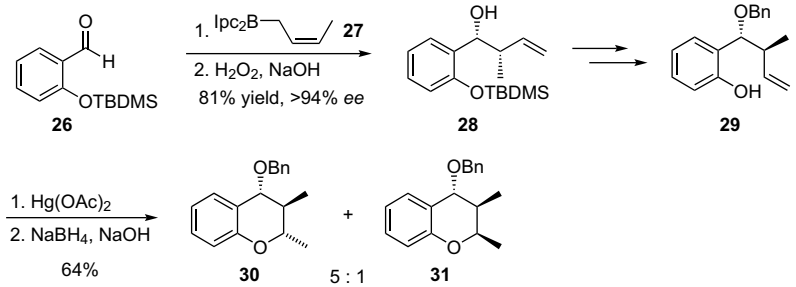
Several examples were selected to illustrate each of the aforementioned five approaches to chiral chromans. In particular, every approach has been employed in the asymmetric synthesis of α-tocopherol (**1**), which initially prompted extensive synthetic studies of chiral chromans. In this context, the asymmetric total syntheses of several other representative targets, such as nebivolol (**5**), siccanin (**9**), rhododaurichromanic acid A (**10**), calanolide A (**11**), hongoquercin A (**13**), equol (**16**), catechin (**17**), and many others will also be reviewed.

2.1. Chiral building blocks

Chiral building blocks could be naturally occurring substances, or simple and readily available chiral compounds that may be directly employed in the synthesis of more complex target molecules. Using (*S*)-3-hydroxy butyronitrile **24** as a chiral building block, the Rao group employed a Houben–Hoesch reaction to build chiral chromanone **25** toward the synthesis of calanolide A (**11**) (Scheme 2).[27] Despite the low yield, the reaction efficiently provided the chiral chromanone moiety in one step.

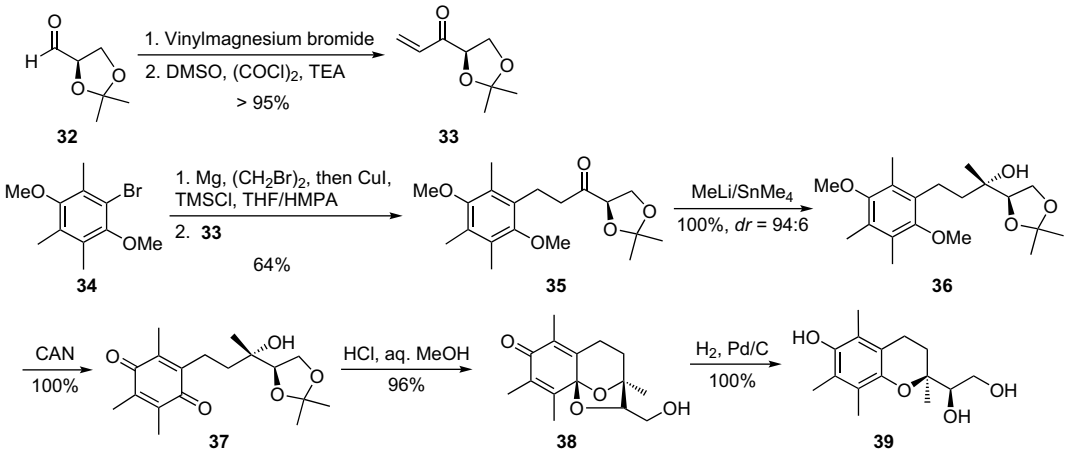
Baker's group utilized Brown's allyl borane **27**[28] as a chiral reagent for allylation of aldehyde **26** (Scheme 3). The resulting highly enantiomerically pure homoallylic alcohol **28** was subsequently converted to intermediate **29**, which, upon exposure to a Hg(II)-promoted diastereoselective cyclization and demercuration, afforded chiral chromans **30** and **31** at a 5:1 ratio.[29]

The Nakai group developed a synthetic route featuring the aryl cuprate addition to vinyl ketone **33**, which was obtained in two steps from aldehyde **32** (Scheme 4).[30] By employing a 'glycerketone's methylation' protocol developed by this group, the chelation-controlled diastereoselective methylation of the resulting ketone **35** provided tertiary alcohol **36**, thereby establishing the pivatol quaternary chiral center of the chroman framework. The following oxidation, monoketal formation and hydrogenation afforded chroman diol **39**. It should be noted that this sequence was first described by Cohen's group (vide infra) and later widely applied in the synthesis of α-tocopherol (**1**) by other labs.



26 **28** **29** **30** **31**

Scheme 3.

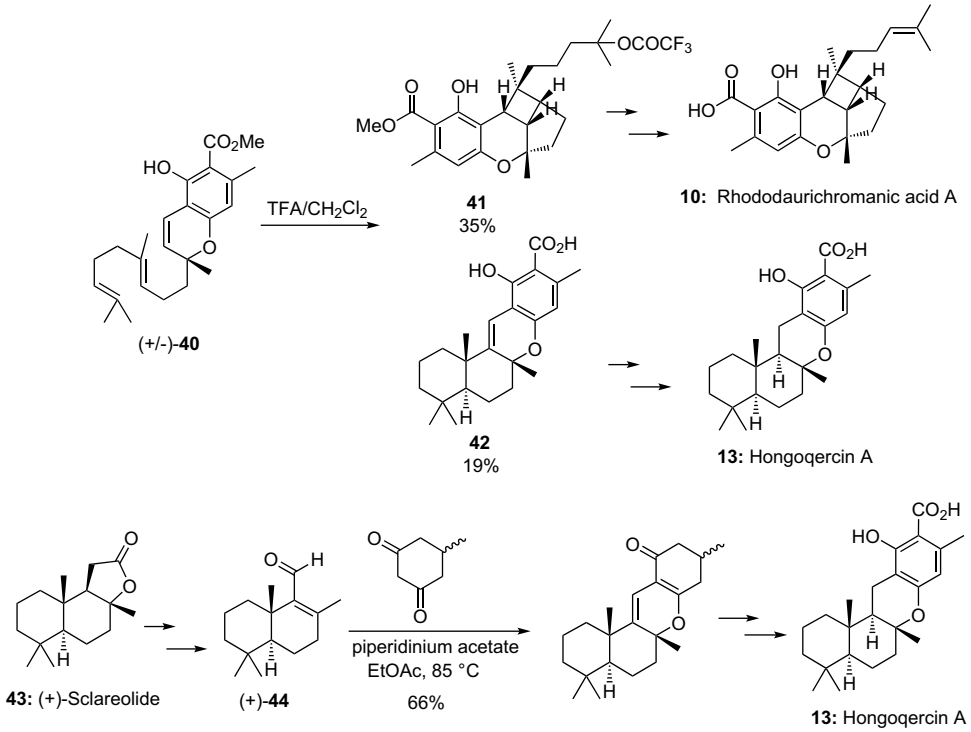


Scheme 4.

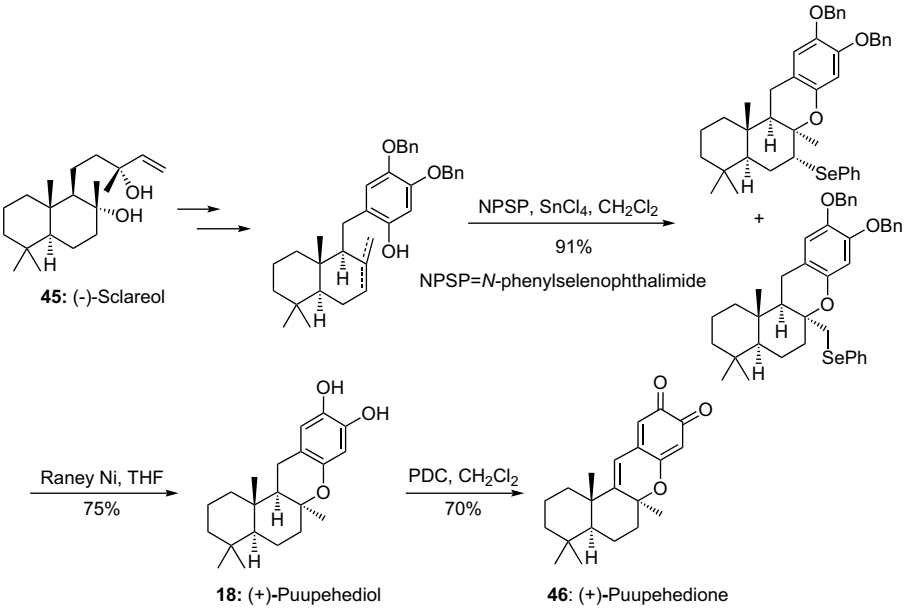
The Hsung group reported an acid-promoted cationic cyclization to construct polycyclic scaffolds, leading to divergent synthesis of rhododaurichromanic acid A (**10**) and hongoquercin A (**13**) (Scheme 5).[31] Remarkably, the stereochemical course during the key cyclization step was completely dictated by a single stereogenic center in racemic chromene **40**, therefore establishing the feasibility of asymmetric synthesis of rhododaurichromanic acid A (**10**) and hongoquercin A (**13**) from a single enantiomer of **40** through intermediates **41** and **42**. In a different approach starting with a single enal enantiomer **44** derived from a natural product called (+)-sclareolide (**43**), Hsung and Kurdyumov showcased their formal [3+3] cycloaddition which provided a mixture of two diastereomers but with complete control of the absolute configuration of the α-methyl group adjacent to oxygen of the pyran moiety. This approach eventually led to the enantioselective total synthesis of (+)-hongoquercin A (**13**).

The Barrero group developed an enantiospecific synthesis of (+)-puupehenone and puupehediol (**18**) starting from naturally occurring (−)-scareol (**45**) (Scheme 6).[32] The synthesis entails a diastereoselective organoselenium-induced cyclization as the key step to assemble the tetracyclic scaffold with the desired stereochemical outcome, and a subsequent Raney Ni-mediated hydrogenolysis of both benzyl ethers and phenylselenyl group to afford puupehediol (**18**) and further to puupehenone **46** upon a PDC oxidation.

(−)-Perrottetinene (**53**), a natural tetrahydrocannabinol, contains a cyclohexene cis-fused to chroman, as opposed to the trans-fused ring junction observed in most tetrahydrocannabinol natural products such as tetrahydrocannabionol **20**. The synthesis of perrottetinene featured a diastereoselective Ireland-Claisen rearrangement of ester **50** and a ring-closing metathesis reaction of diene **52** (Scheme 7).[33] A Stille coupling of enzymatic resolution-derived chiral building block **48**[34] and aryl iodide **47** incorporated the chiral center into allylic alcohol **49** that was later employed to dictate the absolute stereochemical course at the two adjacent stereogenic centers during the Ireland-Claisen rearrangement to furnish product **51** with >99% chirality transfer and >20:1 diastereoselectivity.



Scheme 5.



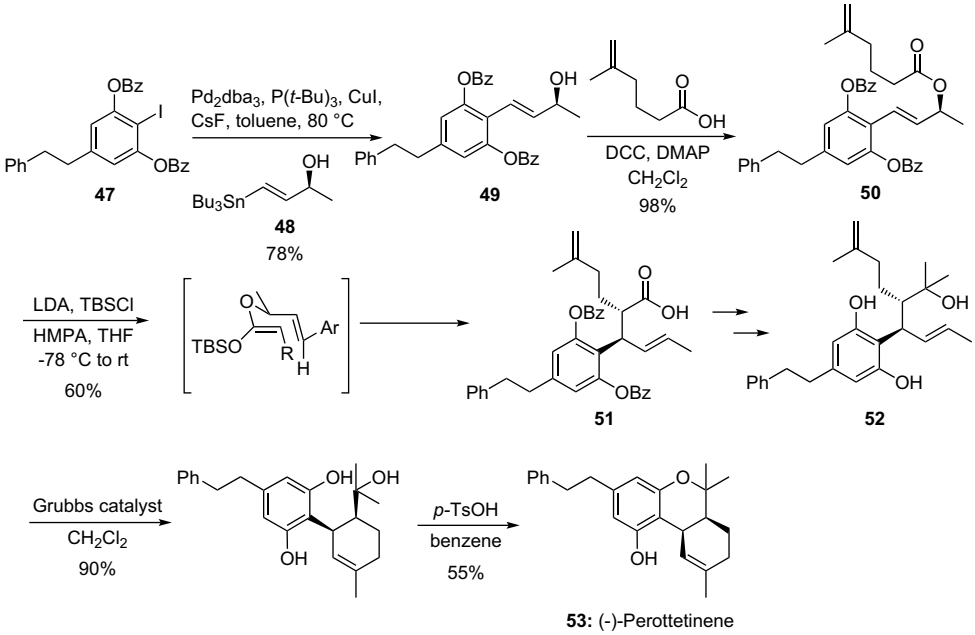
Scheme 6.

Based on the hypothesis that the clinical side effects of the aldolase reductase inhibitor (ARI) sorbinil (**23**) were due to its hydantoin fragment, the Lipinski group at Pfizer investigated a series of spirohydantoin bioisosteres, of which the chroman β-hydroxycarboxylic acid **55** demonstrated excellent in vitro and in vivo ARI activities.[35] It was also found that both chiral centers on the chroman of analog **55** were essential for achieving its excellent ARI activity (IC_{50}=46 nM) as its enantiomer was barely active (59% at 10 μM). Starting from chiral lactic acid **54**, the asymmetric synthesis of **55** was achieved through an 11-step sequence with 4.8% overall yield (Scheme 8). The first step involved a Mitsunobu reaction with a complete inversion of stereochemistry of lactic acid thus setting up the first chiral center of the final product.

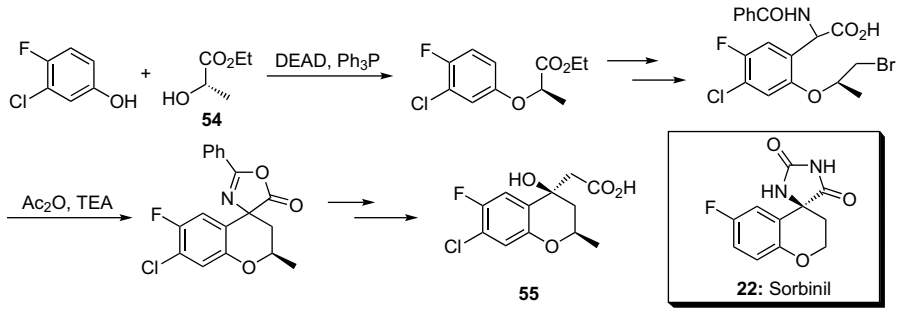
The Katoh group developed an efficient synthesis of (+)-aureol (**61**) via $BF_3{\cdot}Et_2O$-promoted cationic rearrangement/cyclization of (+)-arenarol (**57**) (Scheme 9),[36] which was derived from the enantiomerically pure (−)-Wieland–Miescher ketone derivative **56** as a chiral building block.[37] The remarkable stereoselectivity of the rearrangement/cyclization sequence presumably proceeded under kinetically controlled conditions involving three tertiary cationic intermediates **58**–**60**. The same strategy was later applied by the same group to the tetracyclic core of (+)-stachyflin (**12**).[38]

2.2. Kinetic resolution

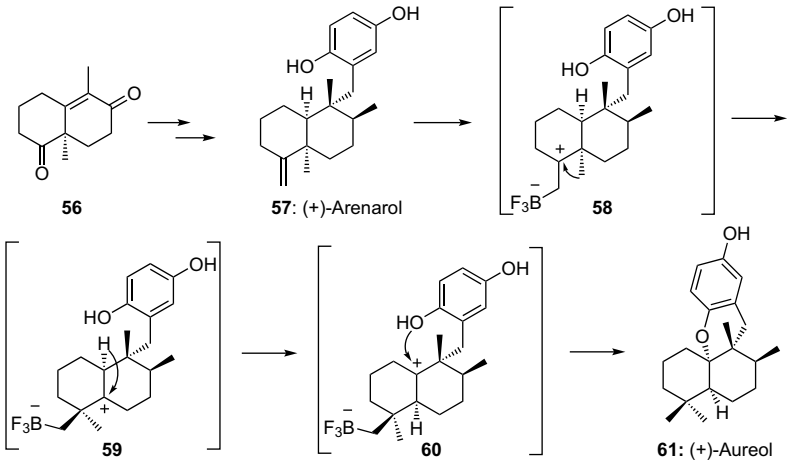
Kinetic resolutions originate from two enantiomers reacting at different rates in respond to a chiral environment provided by a chemical enzyme or enzymatic process, thereby leading one enantiomer to be recovered and the other kinetically derivatized. Conceptually relevant, two enantiomers may display different crystallization rates when exposed to an exogenous chiral substance. Despite the limitation that at least half of the racemic



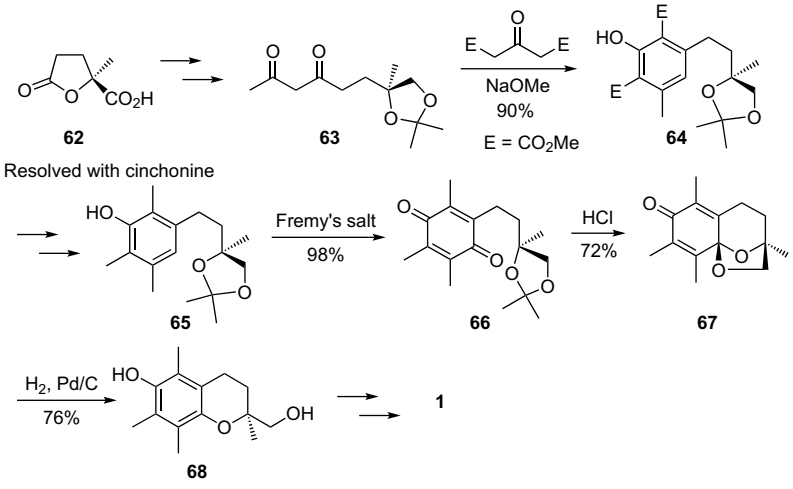
Scheme 7.



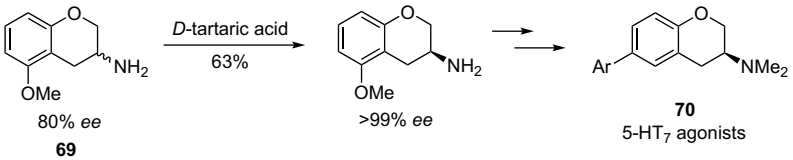
Scheme 8.



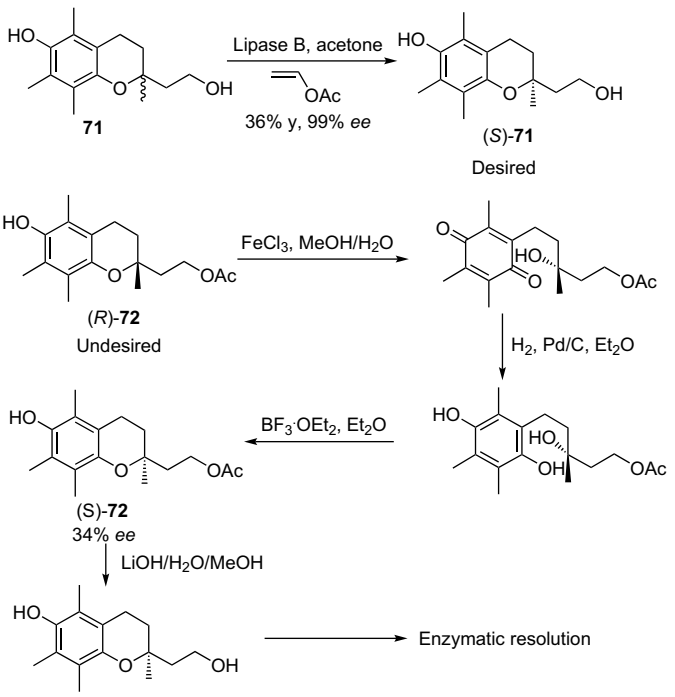
Scheme 9.



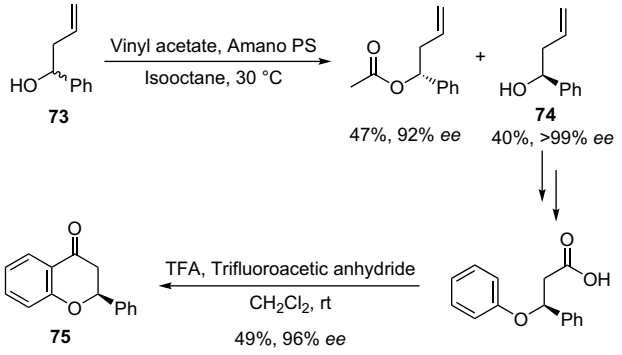
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

material could be scarified, such a strategy remains as a useful method, particularly when the selectivity factor is high and the added chiral material is inexpensive.

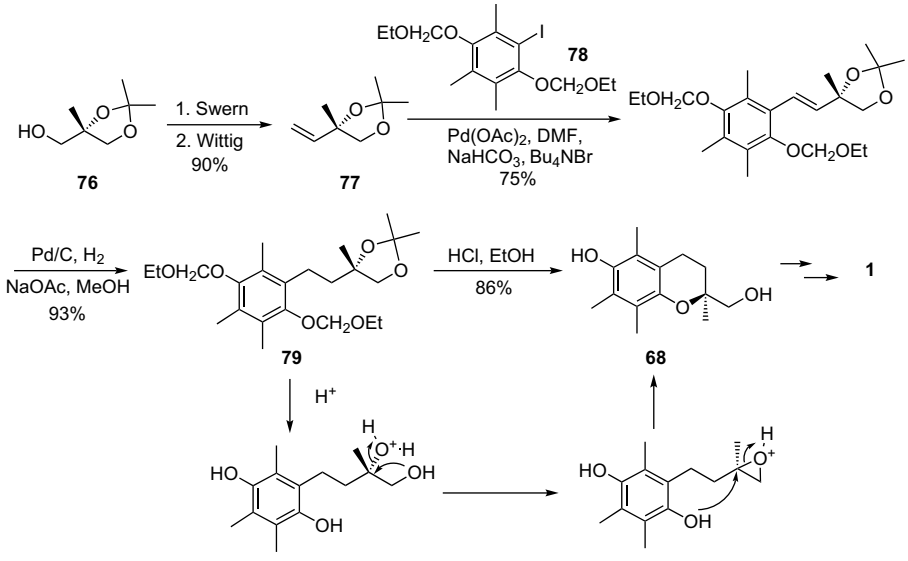
In this category, Cohen and co-workers at Roche utilized optically active lactone carboxylic acid **62** as a precursor in their total synthesis of α-tocopherol (**1**) (Scheme 10).[39] The enantiomerically pure starting material **62** was obtained through the resolution of its racemate with cinchonine.[40] The phenol moiety of intermediate **64** was assembled through a benzannulation of diketone **63** with acetonedicarboxylate in the presence of sodium methoxide. The oxidation of **65** by Fremy's salt resulted in nearly quantitative formation of quinone **66**, which was then cyclized to tricyclic quinone monoketal **67**. A subsequent reduction of **67** under Pd/C conditions readily produced chromanmethanol **68**, which upon further structural elaboration eventually led to the total synthesis of α-tocopherol (**1**). Such an efficient oxidation–reduction event implemented over a quinone–monoketal–chroman sequence provided the most popular approach for the chroman ring formation in the syntheses of α-tocopherol (**1**).

In an effort to discover serotonin 5-HT_7 agonists (**70**) for potential indications such as psychosis, hypertension and sleep disorder, a series of *C*6-aryl substituted derivatives of 3-(dimethylamino)chroman analogs were prepared. The synthesis commenced with chiral chroman amine **69**, which was readily obtained in enantiomerically pure form (>99% ee) through resolution of an enantiomerically enriched material (~80% ee) with D-tartaric acid (Scheme 11).[41]

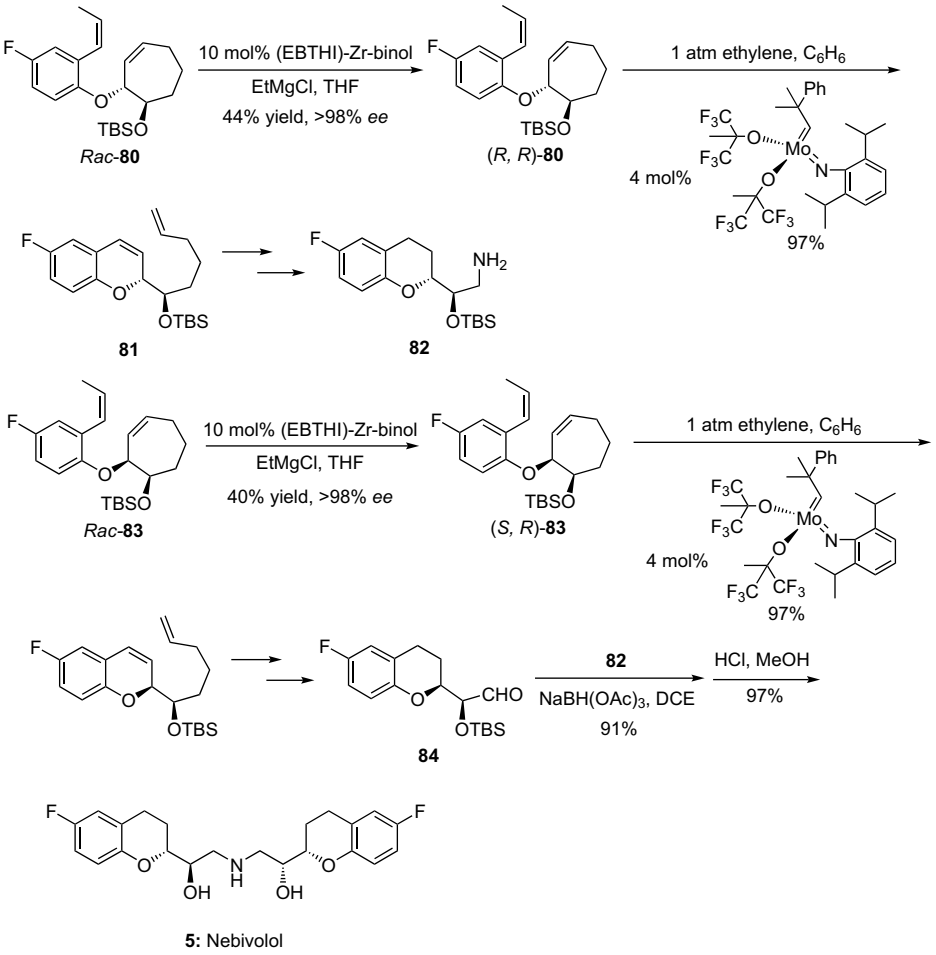
The Achiwa group reported an enzymatic kinetic resolution to provide chiral chromanethanol (*S*)-**71** with good enantioselectivity (Scheme 12).[42] To compensate for the loss of the other half of the material during the process, the undesired *R*-isomer **72** was inverted to the desired *S*-isomer in 34% ee over three steps. The resulting acetate could be hydrolyzed and resubmitted to the enzymatic resolution to improve the overall yield.

To prepare chiral chroman-4-ones, lipases were used to resolve racemic homoallylic alcohol **73**. The enantiomerically pure alcohol **74** then served as the starting material that contains the chiral center of chromanone **75** (Scheme 13). Due to the high substrate specificity of this approach, a lipase library screening is often required to achieve optimal ee.[43]

In another total synthesis of α-tocopherol (**1**), alcohol **76**, derived from an efficient enzymatic ester hydrolysis, could undergo an oxidation and a Wittig olefination to yield intermediate **77** (Scheme 14).[44] An ensuing Heck reaction with aryl iodide **78** under the Jeffery conditions and a subsequent hydrogenation provided



Scheme 14.

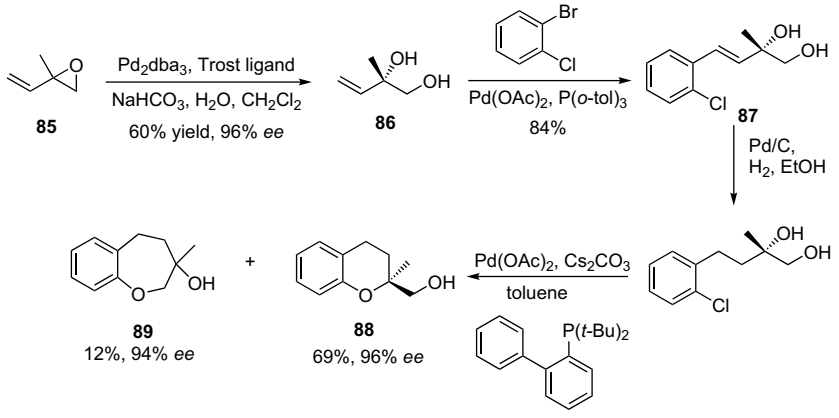


Scheme 15.

intermediate **79**. In the presence of a catalytic amount of acid, chroman **62** was formed with a complete retention of stereochemistry presumably due to a double-inversion mechanism.

Not only have enzymes been employed for kinetic resolution, transition metal catalysts have also be applied. For example, the enantioselective total synthesis of nebivolol (**5**) by the Hoveyda group featured a Zr-catalyzed kinetic resolution of racemic **80** to give the (*R*,*R*)-isomer with over 98% ee (Scheme 15). The Mo-catalyzed ring-closing metathesis (RCM) of (*R*,*R*)-**80** formed chiral chromene **81**, which then afforded intermediate **82**, the left-hand fragment of nebivolol (**5**). A similar sequence (**83** to **84**) led to the right-hand fragment, which was united with intermediate **82** by a reductive amination to finish the assembly of nebivolol (**5**).[45]

Palucki and Yasuda at Merck developed a highly efficient enantioselective synthesis of 2-methylchromans utilizing four sequential Pd-catalyzed transformations (Scheme 16).[46] The chiral center of the chroman core was established by a dynamic kinetic resolution of vinyl epoxide **85** developed by the Trost group.[47] The resulting chiral vinyl diol **86** underwent a Heck reaction with bromochlorobenzene to yield diol **87**. After hydrogenation, a Pd-catalyzed chemoselective O-arylation using Buchwald's conditions[48] afforded a mixture of two bicyclic compounds **88** and **89** containing a six- and seven-membered ring, respectively. Chiral chroman **88**, the major product, was obtained from the reaction of the tertiary alcohol, and its enantiomeric excess is identical to that of intermediate **86**.



Scheme 16.

2.3. Desymmetrization

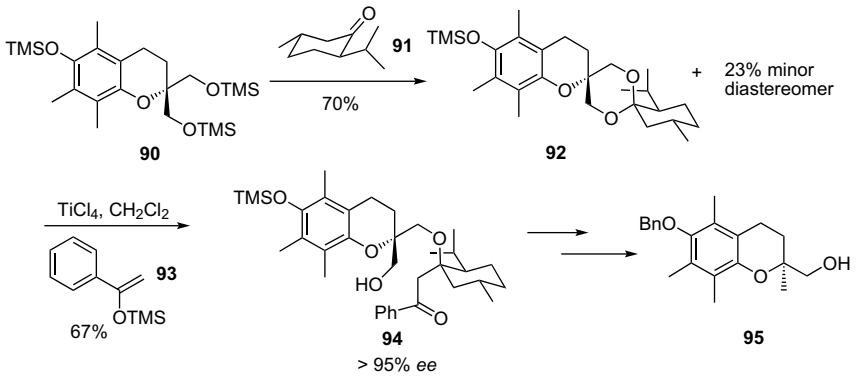
To synthesize α-tocopherol (**1**), Oku's group performed a desymmetrization of prochiral diol silyl ether **90** with chiral ketone **91** to form chiral spiroketal **92** as the major diastereomer. A subsequent $TiCl_4$-promoted equatorial C–O bond cleavage of the spiroketal produced chiral chroman **94** with remarkable stereoselectivity (>95% ee) (Scheme 17).[49] Presumably, $TiCl_4$ preferred coordination with the less hindered equatorial oxygen, thus the incoming nucleophile silyl enol ether **93** underwent an equatorial attack of the positively charged sp^2-hybridized C(1) carbon of the menthone skeleton leading to compound **94** essentially as a single diastereomer, which was transformed to chiral chroman **95** over several steps.

Lipases were also used for desymmetrization. For example, using two different types of lipases, desymmetrization of **96**[50] and **97**[51] for esterification and saponification, respectively, led to precursors of tocopherol (Schemes 18 and 19).

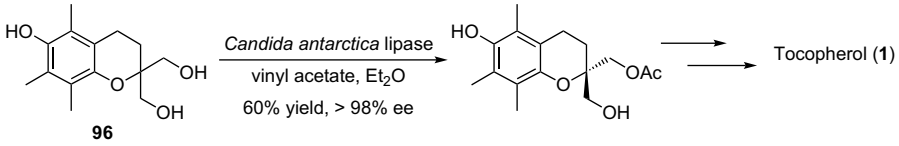
2.4. Chiral auxiliary

Chiral auxiliaries have been utilized extensively for asymmetric synthesis due to their generally high magnitude of asymmetric induction. Either nucleophiles or electrophiles may contain chiral auxiliaries to control the reaction stereoselectivities.

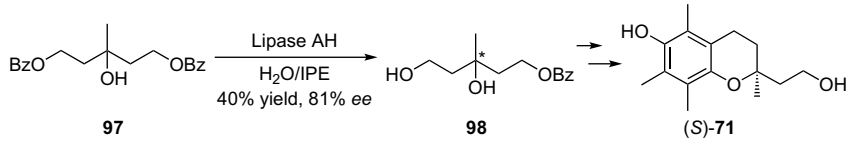
In the synthesis of α-tocopherol (**1**) by the Solladie group, a chiral sulfoxide lithium species **100** was employed to control the diastereoselectivity of addition to aldehyde **99** resulting in the formation of the chiral secondary alcohol **101** (Scheme 20).[52] To account for the stereospecific nucleophilic attack of phenol on the α,β-unsaturated sulfoxide **102**, the authors proposed a *syn* S_N2'



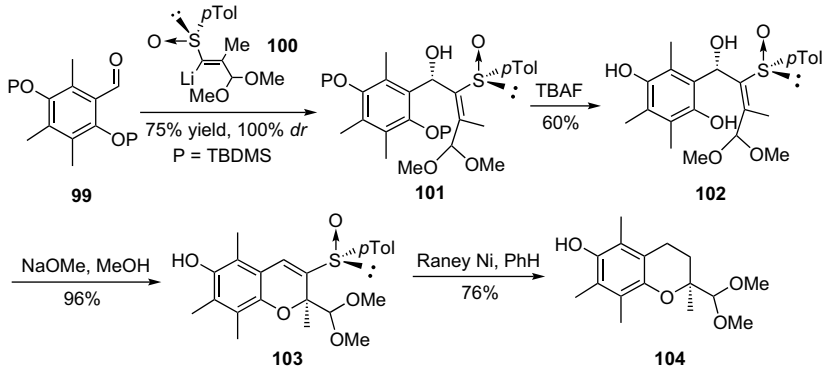
Scheme 17.



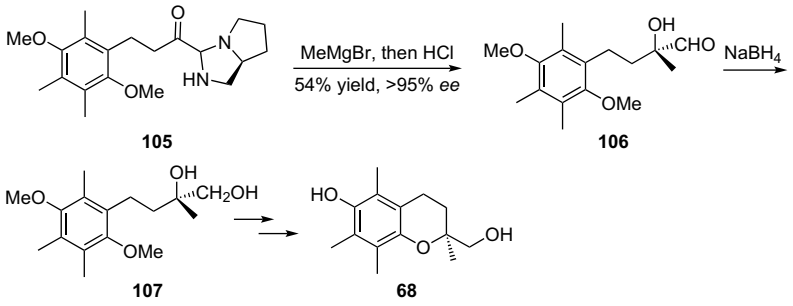
Scheme 18.



Scheme 19.



Scheme 20.



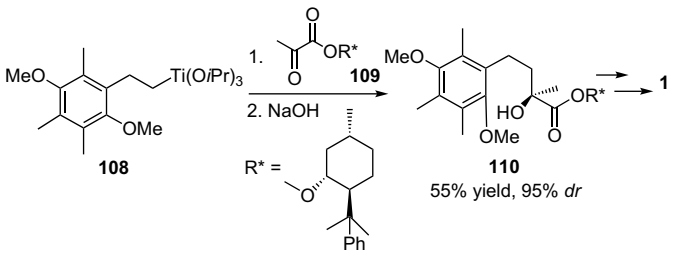
Scheme 21.

mechanism to form chromene **103** as a single diastereomer. The subsequent hydrogenation and reductive desulfurization then provided chiral chroman **104**.

The Sakito group utilized chiral ketone aminal **105** to control the asymmetric addition of methyl magnesium iodide to ketone with excellent diastereoselectivity (>95%) (Scheme 21).[53] The following steps to chromanmethanol **68** are similar to the sequence depicted in Scheme 10.

The Barner group explored a highly stereoselective addition of alkyl titanium **108** to ketone ester **109** bearing a chiral ester auxiliary. The resulting tertiary alcohol **110** eventually led to α-tocopherol (**1**) (Scheme 22).[54]

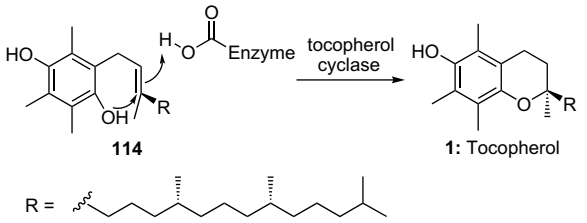
Another example of the use of chiral auxiliary in the formation of chiral chromans is the enantioselective synthesis of (*S*)-equol (**16**) (Scheme 23).[55] The alkylation of precursor **111** containing an Evan's auxiliary allowed the formation of intermediate **112** with



Scheme 22.

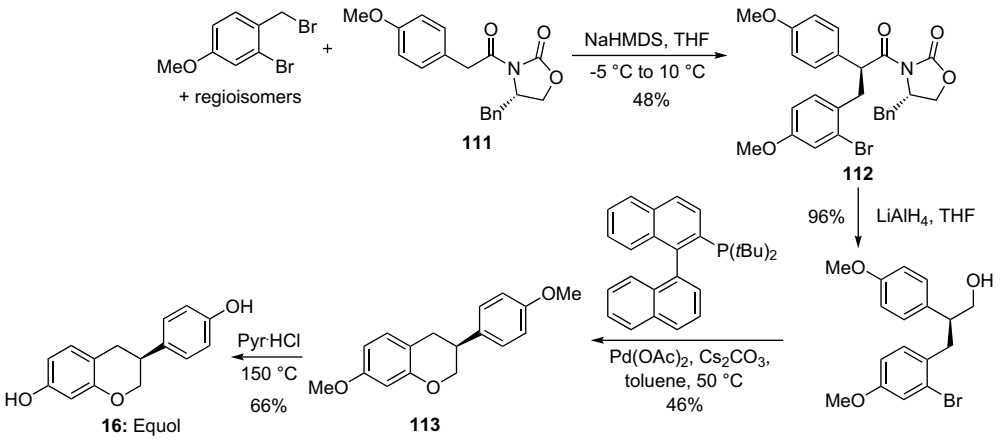
excellent diastereoselectivity. The best reaction conditions for this asymmetric alkylation entailed the mixing of the nucleophile and the electrophile prior to the addition of base. The removal of the auxiliary followed by a Pd-catalyzed O-arylation gave chroman **113**, which eventually led to multi-gram production of (*S*)-equol (**16**) with >99.8% ee.

The Woggon group discovered that the cyclization of phenol **114** to tocopherol (**1**) could be achieved in cyanobacteria (Scheme 24).[56] The tocopherol cyclase responsible for such activity was later cloned successfully. Subsequently, the same group developed a biomimetic chromanol cyclization reaction (Scheme 25).[57] The authors proposed a well-defined architecture involving proline–aspartate and *p*-TsOH, formed by multiple hydrogen-bond interactions, which direct the facial selective protonation of the double bond in substrate **115** by *p*-TsOH thereby leading to a diastereomerically enriched chroman **116**.

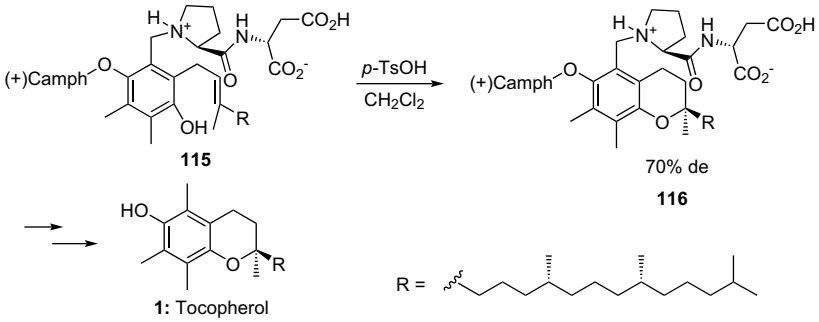


Scheme 24.

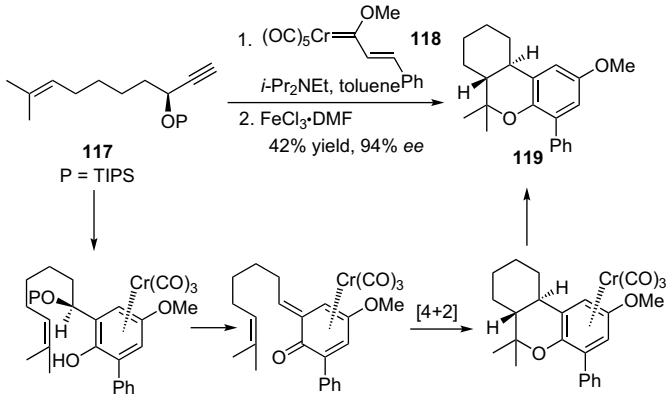
A novel sequential Wulff benzannulation, *o*-quinone methide formation, and intramolecular Diels–Alder reactions of enynyl ether **117** and carbene chromium complex **118** demonstrated an interesting strategy in assembling all three rings of hexahydrodibenzopyrans in one-pot (Scheme 26).[58] The stereochemistry was introduced via a 'traceless stereoinduction'. In this sequence, the chromium tricarbonyl moiety was installed with excellent diastereoselectivity directed by the propargylic chiral center. The chromium unit subsequently controlled the diastereoselectivity of



Scheme 23.



Scheme 25.



Scheme 26.

the Diels–Alder reaction before it was removed by the treatment of the DMF complex of iron trichloride to afford tricyclic product **119**. Therefore, the chromene tricarbonyl complex could be considered as a chiral auxiliary directing the stereochemistry of the Diels–Alder reaction.

2.5. Asymmetric catalysis

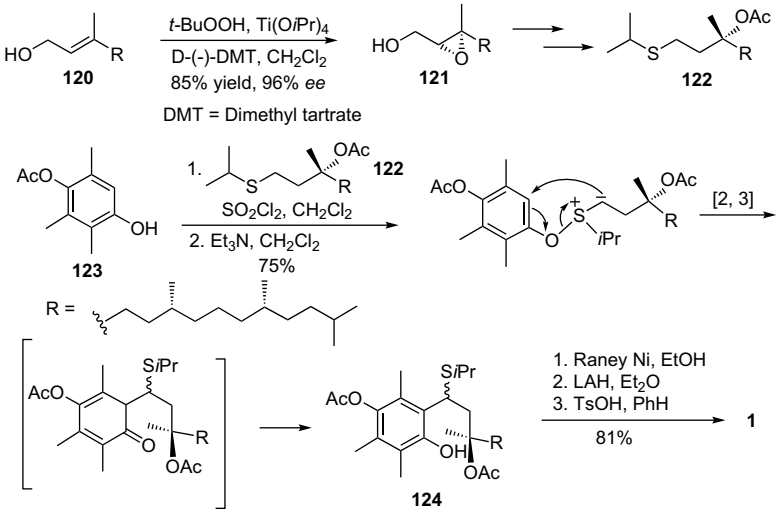
Despite remarkable ability in asymmetric induction, the chiral auxiliary strategy requires steps to install and later remove auxiliary, which becomes less desirable. Catalytic asymmetric methods have therefore emerged as better alternatives due to their atom-economical nature. To date several important catalytic asymmetric methodologies have been applied in synthesis of chiral chromans, including asymmetric epoxidation, dihydroxylation, hydrogenation, ketone alkylation, oxidative cyclization, allylic alkylation, chiral Brønsted acid-mediated cyclization, aldol reaction, enyne cyclization, etc.

2.5.1. Asymmetric epoxidation

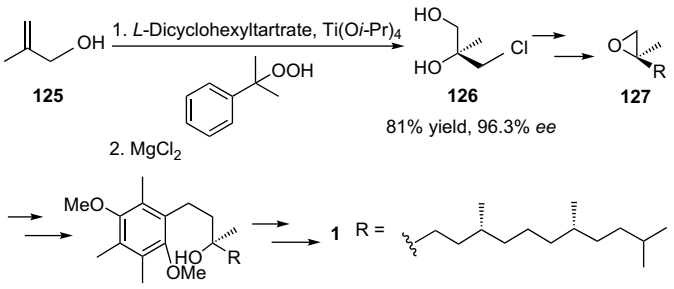
A novel [2,3] sigmatropic rearrangement of phenoxysulfonium ylides, originally developed by the Gassman group,[59] was applied by the Sato group for the *ortho*-alkylation of phenol **123**. This protocol gave intermediate **124**, which was subsequently converted to α-tocopherol (**1**) (Scheme 27).[60] The key intermediate sulfide **122** was derived from epoxide **121**, a product resulted from a standard Sharpless asymmetric epoxidation (SAE) protocol using allylic alcohol **120**.

The Barner group also employed the Sharpless asymmetric epoxidation of allylic alcohol **125** followed by an epoxide ring opening by chloride to give chlorodiol **126**.[54] The resulting chiral tertiary alcohol **126** was then transformed to epoxide **127**, of which the chiral center was eventually incorporated in the chroman unit of α-tocopherol **1** (Scheme 28).

The Achiwa group applied the Sharpless asymmetric epoxidation of substrate **128** to form epoxide **129** in 78% ee, which was opened regioselectively to afford 1,3-diol **130** and further to chiral chroman **132** following an acid-promoted cyclization (Scheme 29).[61] The observation of complete retention of absolute configuration of **132** with respect to diol **130** can be rationalized invoking a double-inversion mechanism via the oxetane intermediate **131**.



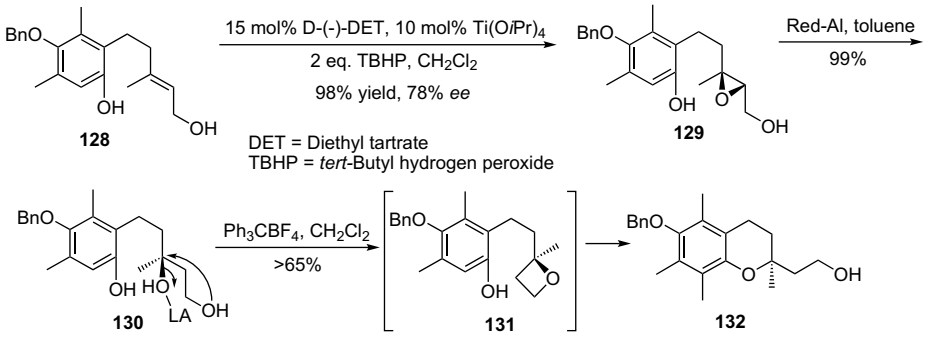
Scheme 27.



Scheme 28.

138 with a modest yield and ~94% ee. The subsequent Lewis acid-promoted cyclization proceeded smoothly to construct the tricyclic scaffold **139** by sequential epoxide ring opening and terminal phenoxide oxygen ring closure.

Another example of the use of the Shi epoxidation is the very recent synthesis of α-tocopherol by the Woggon group (Scheme 32).[66] The Shi epoxidation[64] of the trisubstituted olefin in substrate **141** (>98:2, *E*/*Z*) provided epoxide **142** in 81% yield and 97% de. The removal of the silyl group from a phenol hydroxy group was followed by an interesting epoxide opening-cyclization process to yield predominantly the desired 'anti-Baldwin' chromanol **143** using 2 M HCl in diethyl ether.[67] It should be noted that choice of acids and solvents



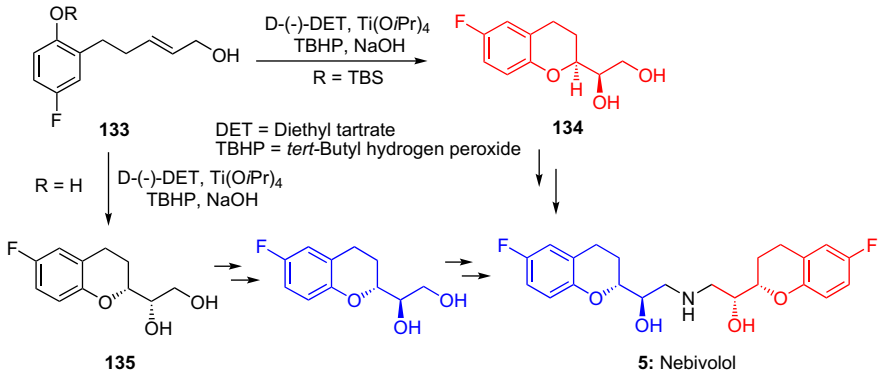
Scheme 29.

The same strategy was also applied to the enantioselective synthesis of chroman-2-ylmethanol by Kirschleger later.[62]

Another example of applications of the Sharpless asymmetric epoxidation is the total synthesis of nebivolol (**5**) (Scheme 30).[63] The epoxidation of the disubstituted trans alkene **133** directed by the allylic alcohol proceeded smoothly, followed by a one-pot treatment of sodium hydroxide work-up to afford two chromans **134** and **135**. Both chroman intermediates were utilized to assemble nebivolol. The chirality of the each chroman moiety was controlled by the epoxidation catalyst.

significantly impacted the ratio of the desired pyran over the undesired furan by-product. However, it should be pointed out that when involving nearly carbocation-like intermediates such those in Lewis acid or Brønsted acid-activation of epoxide ring opening, Baldwin's rules are not as predictive or much less strictly followed.

Very recently the Sharpless asymmetric epoxidation products such as aryl glycidyl ether **144** were shown to undergo a Lewis acid-catalyzed stereospecific ring closure to form 3-chromanol **145** in an enantiomerically pure form (Scheme 33).[68] The reaction could be effected using $F_3B{\cdot}OEt_2$ at −55 °C, or more conveniently, employing $FeBr_3$ at 20 °C.

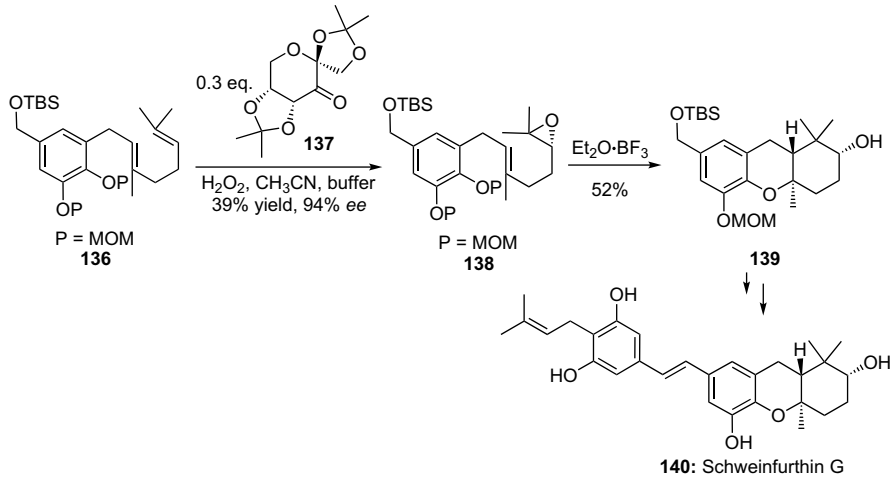


Scheme 30.

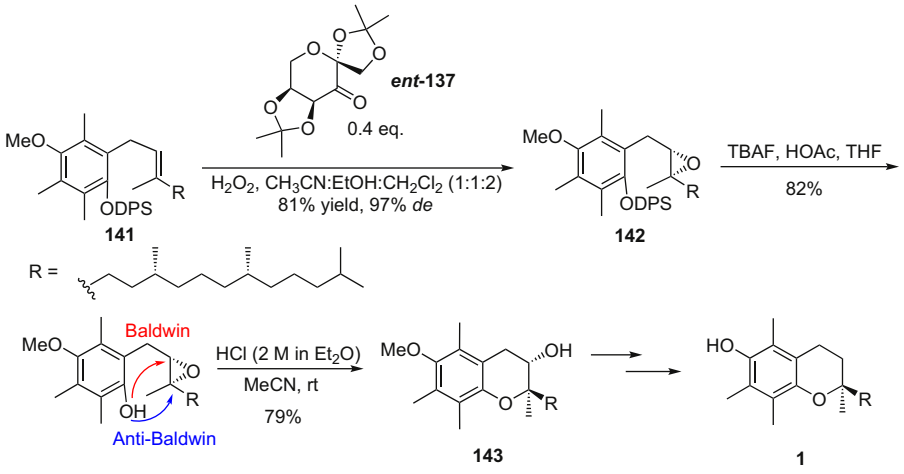
Recently, the Wiemer group reported a $BF_3{\cdot}Et_2O$-mediated cascade cyclization to furnish a tricyclic core with an embedded chiral chroman (Scheme 31). This transformation was crucial to their successful total synthesis of schweinfurthins F and G (**140**).[64] To install the chiral epoxide precursor for the cationic cyclization, a Shi epoxidation[65] of trisubstituted alkene **136** using sugar-derived ketone catalyst **137** was executed to provide the desired epoxide

2.5.2. Asymmetric dihydroxylation

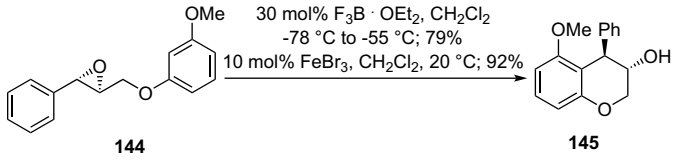
Tietze and Gorlitzer utilized the Sharpless asymmetric dihydroxylation[69] of enyne **146** to give diol **147** in high yield and ee, which constructed the quaternary chiral center.[70] In contrast, the *Z*-trisubstituted alkene isomer of **144** gave substantially lower ee. A sequence similar to a previous example (Scheme 4) afforded diol **148**, and thus accomplished the



Scheme 31.



Scheme 32.



Scheme 33.

enantioselective formal total synthesis of α-tocopherol (**1**) (Scheme 34).

In an enantioselective synthesis of (2*R*,3*S*)-(+)-catechin (**17**) by the group of Park and Jew (Scheme 35),[71] the asymmetric dihydroxylation (**149** to **150**) again demonstrated its utility in installing both chiral centers of this natural product with quantitative yield and >99% ee. The ensuing Barton–McCombie deoxygenation and intramolecular Mitsunobu reaction completed the natural product.

In the total synthesis of (−)-glyceollin I (**154**), Erhardt and Khupse also employed the Sharpless asymmetric dihydroxylation protocol to furnish chiral diol **152** from chromene **151** in 70% yield and >99% ee (Scheme 36).[72] The subsequent benzyl group deprotection, elimination of the benzylic hydroxy group, followed by ring closure in the presence of polymeric base offered the tetracyclic core **153**, which then led to (−)-glyceollin I (**154**) in a straightforward fashion.

2.5.3. Asymmetric hydrogenation

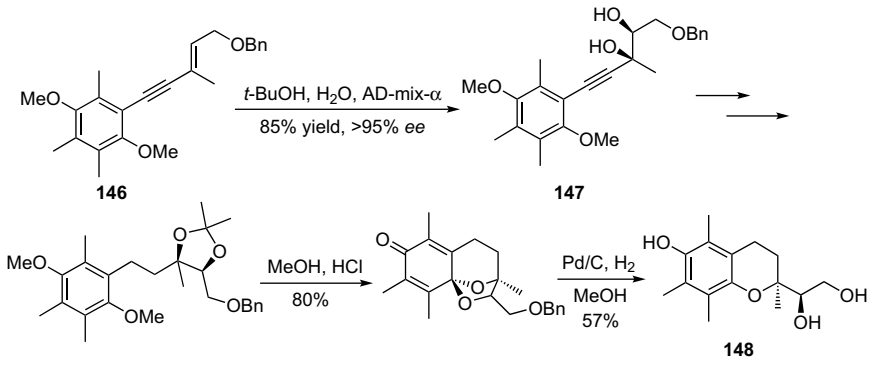
Barner's group reported that the Rh-catalyzed asymmetric hydrogenation of the ketone group with the concomitant hydrogenation of C=C double bond in substrate **155** afforded α-hydroxyacid **156** in excellent yield and good ee.[54] A methyl group was then introduced diastereoselectively via an α-methylation of intermediate **157** to give hydroxyacid **158**, which was eventually converted to α-tocopherol (**1**) (Scheme 37).

2.5.4. Asymmetric addition to aldehyde

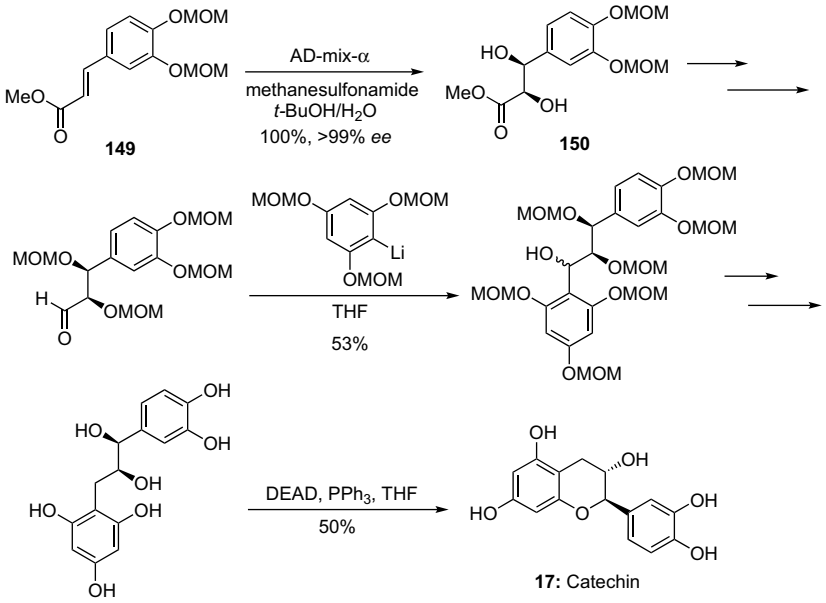
In another efficient approach to α-tocopherol by Barner's group,[54] following the Noyori protocol,[73] the addition of aryl zinc species **159** to enal **160** in the presence of a catalytic amount of chiral amino alcohol **161** provided allylic alcohol **162** in 92% diastereomeric excess. Subsequent cyclization of **162** in the presence of HCl led to chiral chromene, which upon hydrogenation gave α-tocopherol (**1**) (Scheme 38).

2.5.5. Asymmetric oxidative cyclization

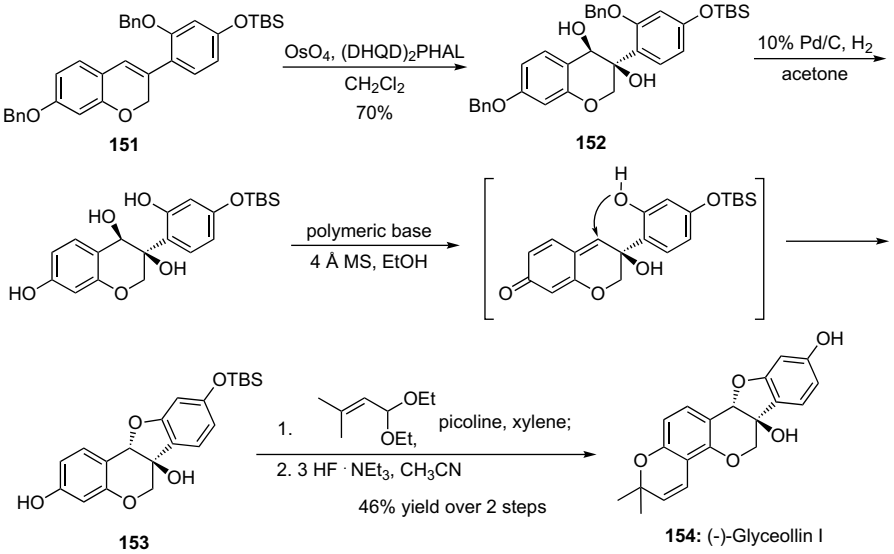
Hayashi and co-workers developed a powerful Pd-catalyzed asymmetric Wacker-type cyclization of alkenyl phenol **163** to form



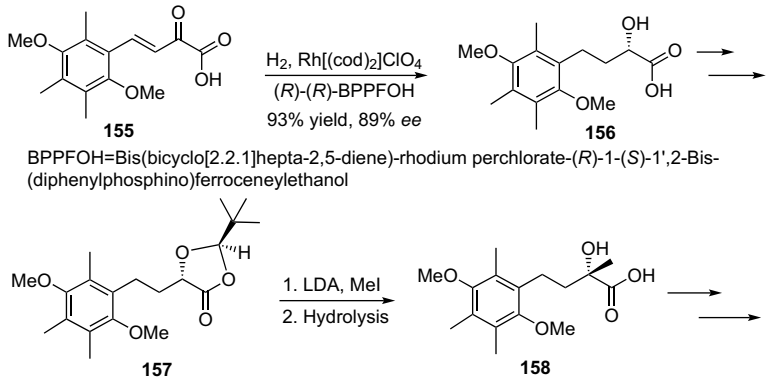
Scheme 34.



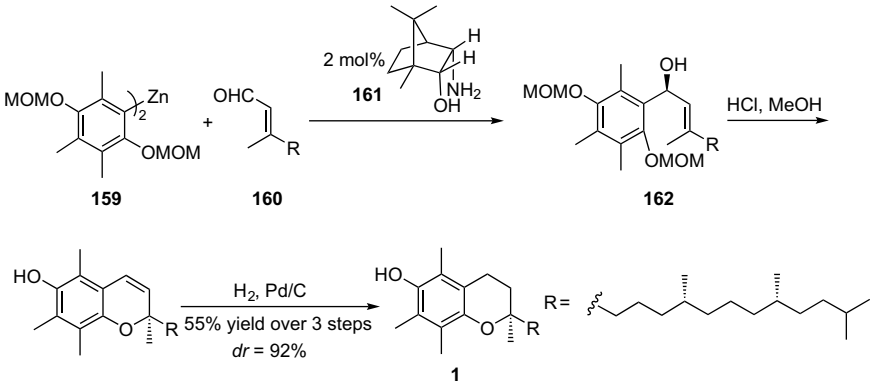
Scheme 35.



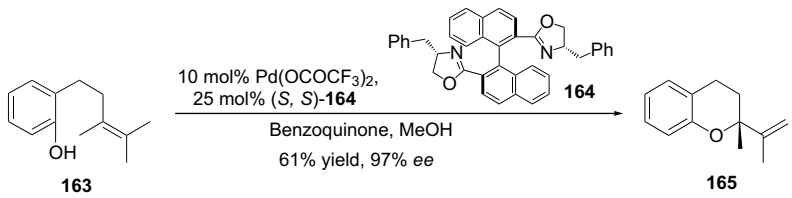
Scheme 36.



Scheme 37.

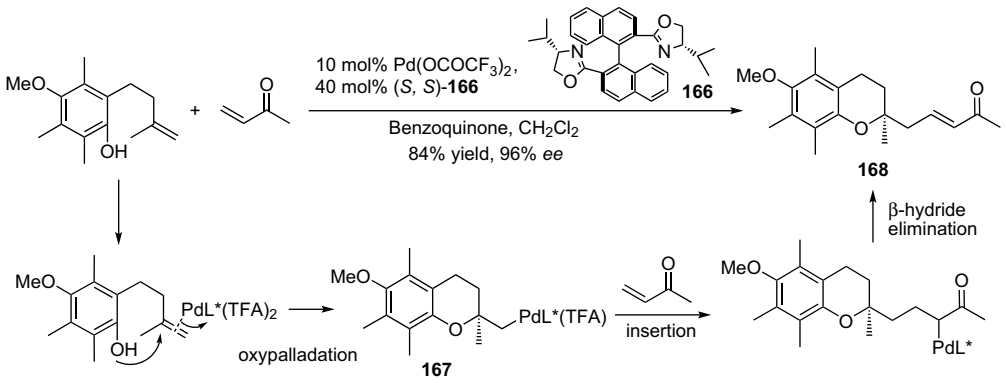


Scheme 38.

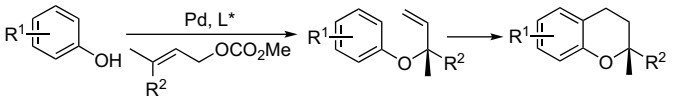


Scheme 39.

chiral vinylchroman **165** with excellent enantioselectivity using a C_2-symmetric bisoxazoline ligand **164** (Scheme 39).[74] An elegant extension of such strategy was employed in the concise enantioselective total synthesis of α-tocopherol (**1**) by the Tietze group (Scheme 40).[75] This efficient strategy involves a domino Wacker–Heck reaction to form not only the chiral chroman framework but also a portion of the side chain of α-tocopherol (**1**). As in the Hayashi system, it was proposed that the chiral catalyst **166** preferentially coordinated with one enantiotopic face of the substrate olefin forming chiral oxypalladation intermediate **167**. The ensuing



Scheme 40.



Scheme 41.

intermolecular Heck reaction afforded chiral chroman **168**, a key intermediate leading to α-tocopherol (**1**).

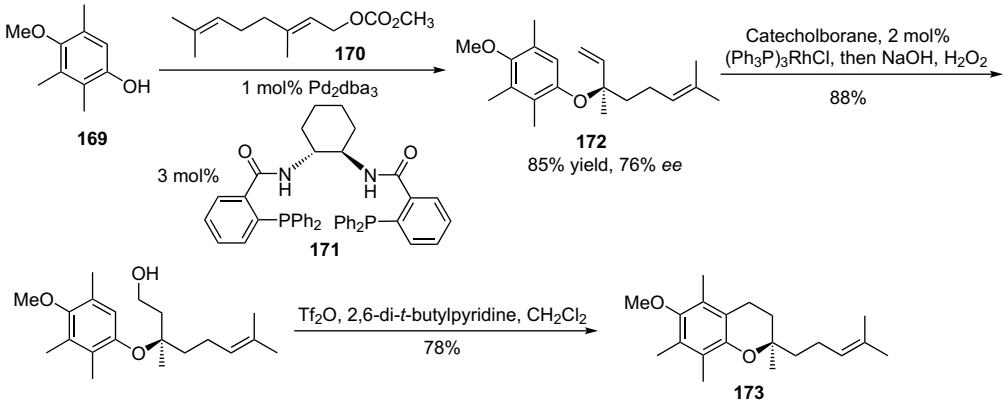
2.5.6. Asymmetric allylic alkylation

The Pd-catalyzed asymmetric allylic alkylation (AAA) of phenol allyl carbonate also constitutes an effective approach to chiral chromans. This transformation can be achieved both inter- and intramolecularly. The *intermolecular* version of this type of reaction leads to enantioselective formation of the allylic C–O bond, which was followed by a ring closure to give chiral chromans (Scheme 41). For example, phenol **169** reacted with allyl carbonate **170** to form the tertiary ether **172** using the Trost ligand **171** with excellent regioselectivity (92:8) and moderate ee (76%). The hydroboration, oxidation, and triflate formation, set the stage for electrophilic cyclization to assemble product **173**, the core of the tocopherol (Scheme 42).

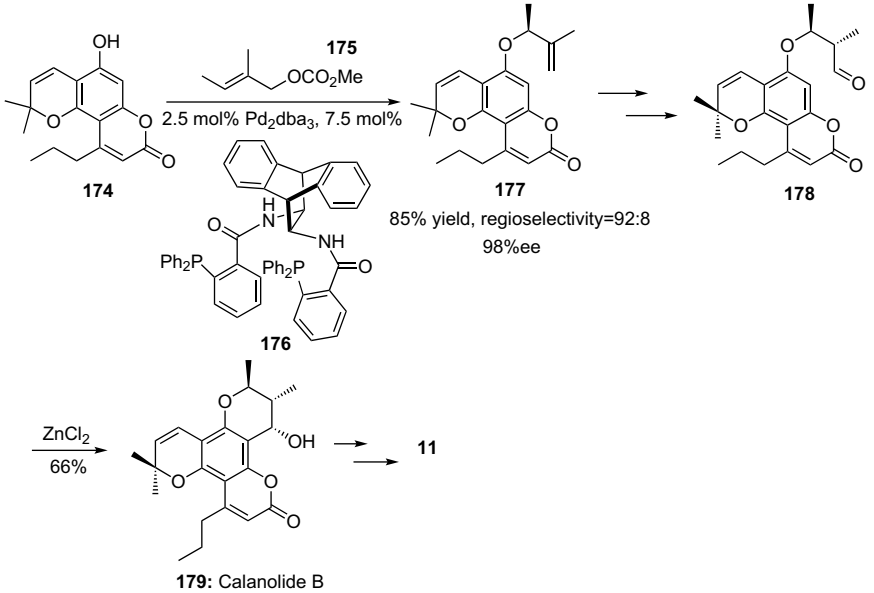
Such a strategy was also applied in the enantioselective total synthesis of calanolides A and B by Trost and Toste (Scheme 43).[76] The reaction of phenol **174** and carbonate **175** in the presence of Pd_2dba_3 and chiral ligand **176** generated allylic aryl ether **177** with excellent regio- and enantioselectivity. The $ZnCl_2$-promoted ring closure of intermediate **178** yielded calanolides B (**179**), which could be further converted to calanolide A (**11**).

In the Pd-catalyzed *intramolecular* AAA reaction of phenol allylic carbonates (Scheme 44), a chiral Pd complex initiates the ionization of a leaving group (**L**) such as a carbonate in precursor **180** to form Pd π-allyl intermediate **181**, which can be trapped by phenol intramolecularly to form chiral chroman **182**.

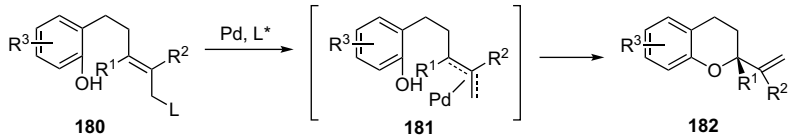
By using the Pd-catalyzed intramolecular AAA reaction of allyl carbonate **183**, the Achiwa group obtained chiral vinylchroman **185** with moderate ee using BFFPA ligand **184** (Scheme 45).[77] After screening a library of chiral phosphine ligands, the Sinou group obtained at best a 50% ee when employing a chiral monophosphine ligand **186** (NMDPP) for the same type of transformation but with usually high catalyst and ligand loading (Scheme 46).[78] Subsequently, the Trost group reported that cis-trisubstituted allylic carbonates, such as **187**, could undergo Pd-catalyzed AAA reaction using the Trost ligand ***ent*-171** to generate chiral chroman **188** in excellent ee, which then served as a key intermediate for the



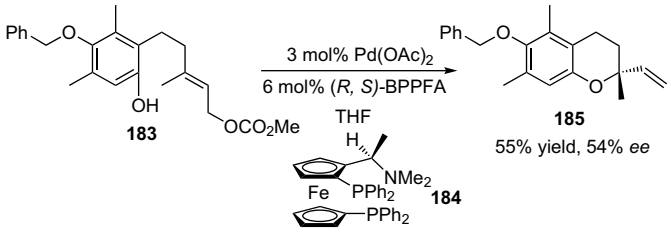
Scheme 42.



Scheme 43.



Scheme 44.



Scheme 45.

enantioselective total synthesis of siccanin (**9**) (Scheme 47).[79] The interesting effect of the olefin geometry, substitution pattern and acetic acid additive on the enantioselectivity of the reaction was particularly worth noting. For instance, the cis-disubstituted alkene substrates consistently gave chromans with much lower enantioselectivity than their trans counterparts, whereas the cis-trisubstituted alkenes substrates gave higher enantioselectivity than the trans counterparts.

2.5.7. Asymmetric allylation

In the total synthesis of (+)-epicalyxin F (**193**), Rychnovski and Tian established the first chiral center of the chroman moiety via a Keck allylation (**189** to **190**), and the second through a Lewis acid-promoted intramolecular conjugated addition of arene to enone in intermediate **191** to afford chroman **192** with moderate diastereoselectivity (5:1) (Scheme 48).[80] Interestingly, the TMSOTf is unique in providing a much higher diastereoselectivity than other Lewis acids such as $AuCl_3$ and $BF_3 \cdot Et_2O$.

2.5.8. Lewis acid assisted-chiral Brønsted acid-mediated cyclization

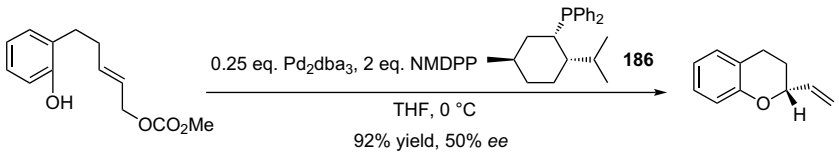
The Yamamoto group pioneered a Lewis acid assisted-chiral Brønsted acid (**195**)-promoted enantio- and diastereoselective cyclization of polyprenoid **194** as a remarkably efficient approach to tricyclic product **196** (Scheme 49).[81] It is likely that an abnormal Claisen rearrangement occurred first to yield the corresponding phenol, which then underwent a cyclization to afford chroman **196**. A similar strategy was also applied to the total synthesis of (−)-chromazonarol **200** from triene **197** employing chiral Brønsted acid **198** (Scheme 50).[82] This process was referred to as an artificial cyclase-induced cyclization (see also Scheme 24 for an enzymatic approach). The stereochemical outcome may be rationalized by invoking a linear OH/alkene π interaction between the Brønsted acid and the alkene of the substrate during the initial protonation step. Thus the steric bias for the terminal isoprenyl group to approach the Brønsted acid from the *re*-face (**201**) is different from the *si*-face (**202**). Consequently, compound **199** was obtained as the major product derived from the favorable *re*-face protonation. The development of a catalytic version of this transformation would be a particularly important extension of this strategy. Conceptually, this Lewis acid assisted-chiral Brønsted acid-promoted cyclization is similar to the biomimetic chromanol cyclization depicted in Scheme 25.

2.5.9. Asymmetric aldol reaction

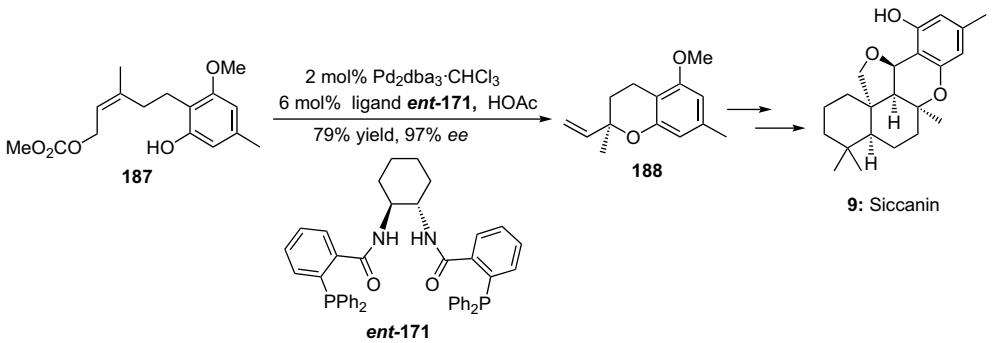
Recently Woggon and co-workers reported an elegant short asymmetric synthesis of α-tocopherol (**1**) utilizing the domino aldol and oxa-Michael reactions catalyzed by proline derivative (Scheme 51).[83] Despite the relatively high loading (30 mol%) of organocatalyst **203**, the reaction provided the tricyclic structure **204** with an embedded chiral chroman core in excellent de (97%). This example is the first application of organocatalysis in chiral chroman formation, which established a tetrasubstituted chiral carbon center.

2.5.10. Asymmetric enyne cyclization

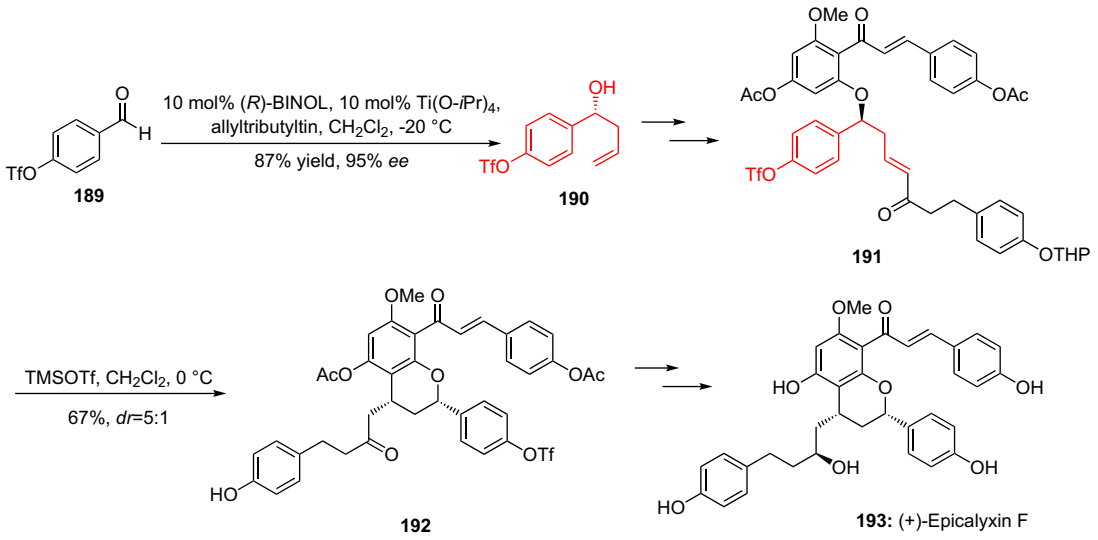
A ruthenium-catalyzed enantioselective cyclization of enyne **205** provided a novel approach to chiral chromans



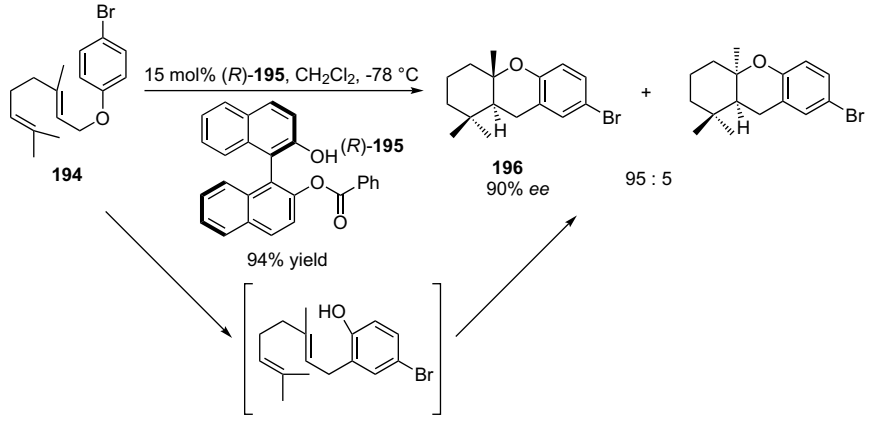
Scheme 46.



Scheme 47.

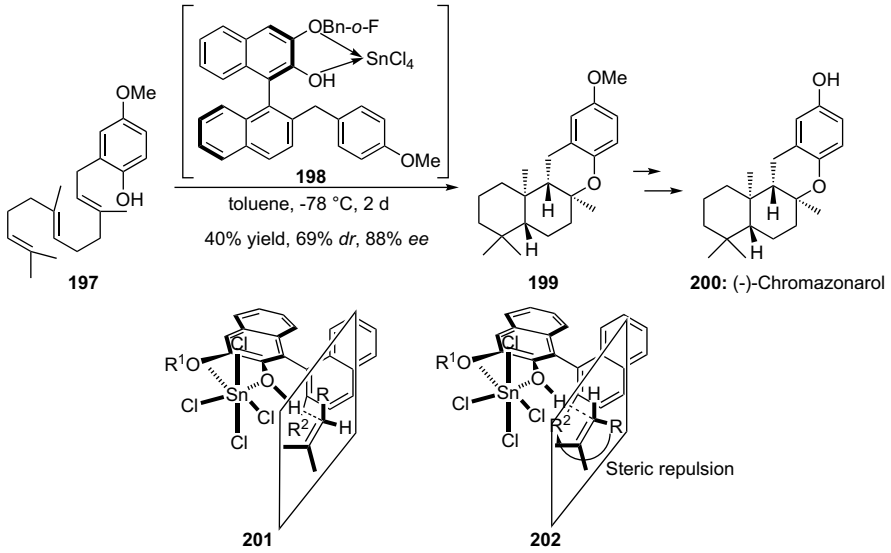


Scheme 48.

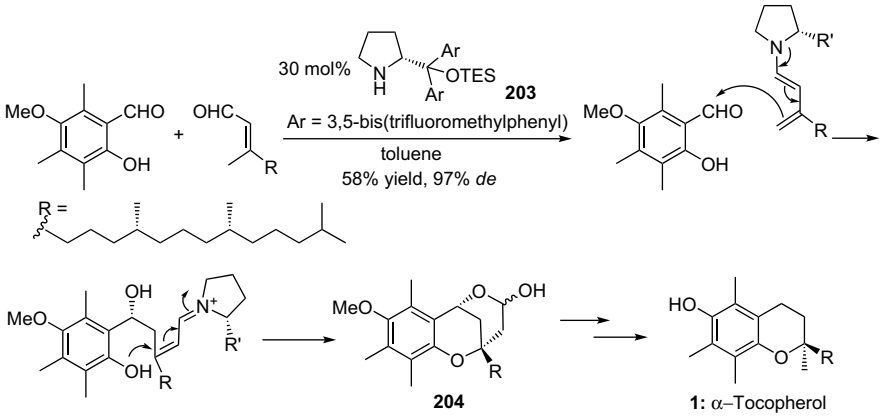


Scheme 49.

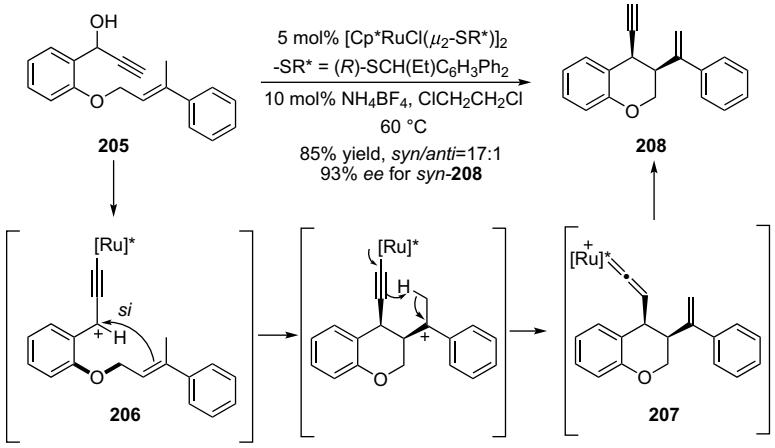
containing two stereogenic centers with good diastereo- and enantioselectivity (Scheme 52).[84] A theoretical study on the reaction of propargylic alcohol with 1,3-diene suggested that the allenylidene–ene reaction took place in a stepwise manner.[85] Presumably the ruthenium propargylic cation induced a nucleophilic attack of an alkene on the cationic γ-carbon in intermediate **206** from the *si*-face. The chiral diruthenium complex appeared to dictate the stereoselectivity



Scheme 50.



Scheme 51.



Scheme 52.

of this step. A smooth transfer of one of the methyl protons then led to the corresponding vinylidene complex **207**, followed by a proton-1,2 shift to give product **208** containing a 1,5-enyne moiety.

3. Conclusion

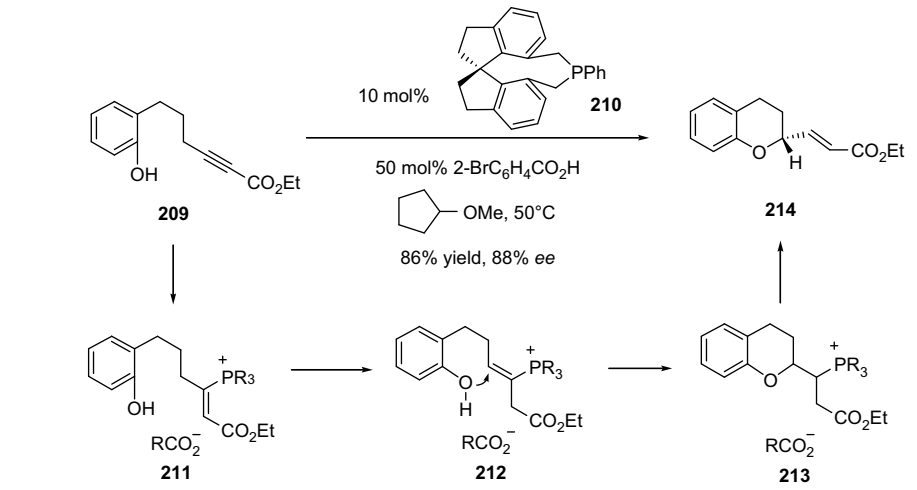
Chiral chromans represent a privileged structural motif that is ubiquitous in a range of natural products and drug candidates with broad biological implications. They interacted with a variety of enzymes, receptors, and ion channels, all of which show an extraordinary degree of recognition specificity for chiral molecules. As such, it is crucial to develop strategies to construct chromans with desired three-dimensional arrangements.

Over the past three decades, tremendous progress has been made in synthesis of chiral chromans. The examination of these research endeavors allows the identification of five general strategies toward chiral chroman targets. These include the use of chiral building blocks, kinetic resolution, desymmetrization and chiral auxiliary methods, which were employed to construct the quaternary chiral center in α-tocopherol, yet their efficiency and practicality are sometimes limited with respect to asymmetric catalysis, which typically possesses a broader scope and superior flexibility. Several representative applications of each strategy were presented for illustrative and informative purpose, although this review is not intended to be comprehensive. Fueled by these remarkable progresses, practical solutions have been developed to prepare chiral chroman moieties in natural products and drug candidates. These synthetic capabilities bodes discoveries of more chiral chroman molecules that can be harnessed to understand their biological course of action and/or developed for therapeutic purposes. In addition, chiral chromans are structurally related to chromenes and flavones, and the methodologies developed for chiral chroman synthesis could be readily applicable to these systems.

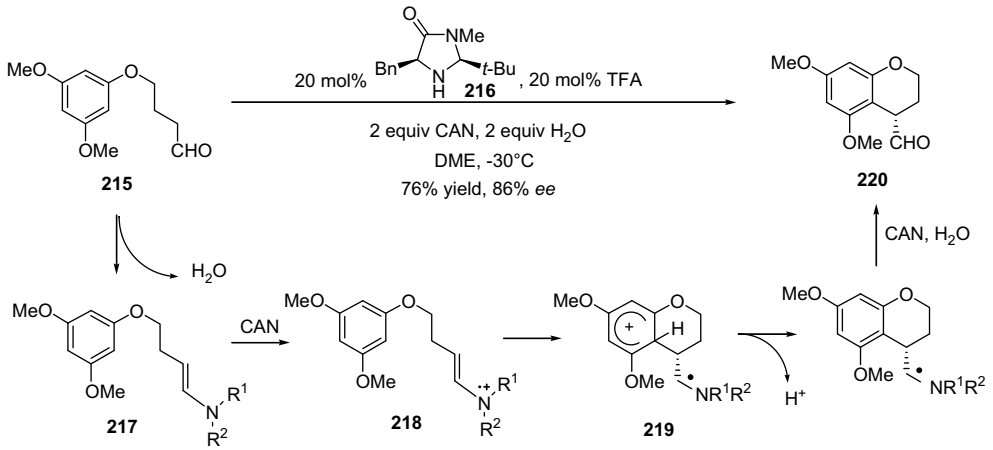
4. Addendum

After the acceptance of this review, three publications on chiral chroman synthesis emerged. Fu and Chung reported a chiral phosphine-catalyzed enantioselective cyclization to prepared chiral chromans in good ees (Scheme 53).[86] In this transformation, chiral phosphine **210** acted as a nucleophilic catalyst adding to alkynoate **209** to provide intermediate **211**. The subsequent proton shuffle led to intermediate **212**, which then underwent a ring closure to **213** and elimination to produce chroman **214**. This γ-addition of a phenol nucleophile to a 2-alkynoate represents an interesting chiral phosphine-catalyzed process furnishing products with good enantioselectivity.

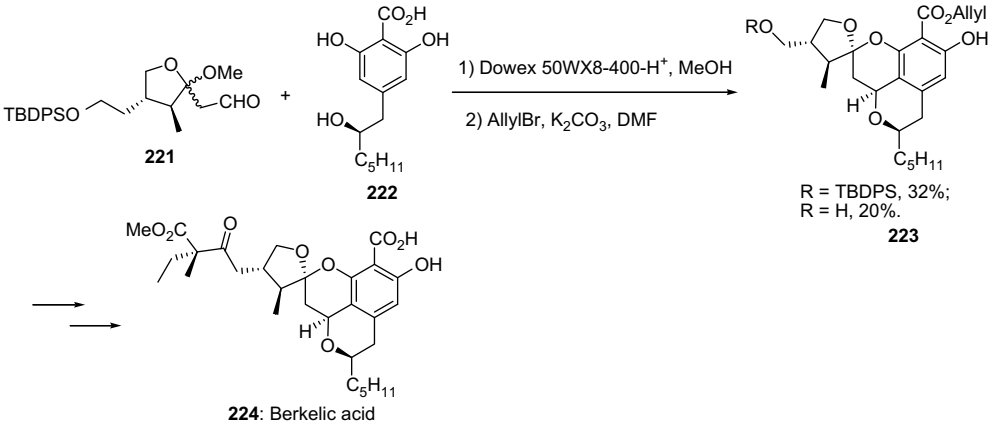
In a very recent report,[87] Nicolaou and co-workers utilized an enantioselective intramolecular Friedel–Crafts-type α-arylation of aldehyde **215** to access chiral chroman aldehyde **220** employing the organo-SOMO catalysis conditions developed by the MacMillan group (Scheme 54).[88] The proposed mechanism invokes the formation of enamine from aldehyde **215** and chiral amine **216**, and a single electron transfer in the presence of CAN leading to highly reactive radical cation **218**. The key step was proposed to be



Scheme 53.



Scheme 54.



Scheme 55.

a Friedel–Crafts type cyclization to generate intermediate **219**, which was followed by the removal of proton, a second electron transfer oxidation and hydrolysis to give chiral chroman aldehyde **220**. However, the exact nature of the cyclization step regarding whether it is a cationic or radical process may need further mechanistic studies.

Lastly, the Snider group accomplished a stereoselective total synthesis of (−)-berkelic acid (**224**), which involved an oxo-Pictet–Spengler reaction of secondary alcohol **222** and aldehyde **221** as a key step to assemble the tetracyclic core **223** with an embedded chroman ketal moiety (Scheme 55).[89]

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Biographical sketch

Hong C. Shen was born in Chengdu, China in 1974. In 1997, he received his B.S. degree in chemistry from Peking University under the direction of Professor Yunhua Ye. Hong Shen subsequently moved to University of Minnesota, where he developed a formal [3+3] cycloaddition with Professor Richard Hsung, and obtained his M.S. degree in 1998. Hong Shen then joined the research group of Professor Barry Trost at Stanford University. His work spanned from Ru- and Pd-catalyzed reactions to their applications in total syntheses of natural products. After obtaining his Ph.D. degree in 2003, Hong Shen assumed a senior research chemist position at Merck Research Laboratories, Rahway, New Jersey. He is currently a research fellow working on the discovery of novel drugs for treatment of cardiovascular and metabolic diseases. He has co-authored over 30 publications and held co-inventorship of 9 patents.