Chapter 1

Recent Advances in the Stereoselective Synthesis of Chroman Derivatives via Ar–O, ArO–C, and Ar−C Bond-Forming Intramolecular Cyclizations of Epoxides, Aziridines, and Vicinal Diols

1.1. Introduction

Organic synthesis is a sub-discipline of chemical synthesis, and is concerned with the construction of organic compounds, natural or designed, via organic reactions [1]. Over the past two centuries, the contributions of organic synthesis in the welfare of human beings have been quite remarkable– although, unfortunately, these days most of the world population bonds this process with environment pollution [2]. In fact, advances in organic synthesis can be clearly sensed when one realizes the requirement of medicines for relief of human sufferings, from the easing of pain to cures for various infectious diseases. Thus, organic synthesis has a huge impact on public health where treatments for majority of life threatening diseases have been developed [3].

On the other hand, small molecules have been defined as low molecular weight (< 1500 Da) compounds that are potentially orally bioavailable [4]. They are distinct from biological macromolecules such as nucleic acids, proteins and polysaccharides. Thus, vast majority of synthetic drugs and naturally occurring secondary metabolites, lipids, monosaccharides, very small oligomers and second messengers are considered as small molecules. With small molecule drugs, globally countless lives are saved/extended, resulting in a steady increase in life expectancy. Small molecules have been utilized as powerful tools because of their ability to interact with biological macromolecules to exert specific effects, frequently in a selective and dose-dependent manner. In the fields of medicinal chemistry and chemical genetics, the use of small organic molecules to modulate biological functions deliberately and selectively has rapidly attracted immense scientific growth [5-7].

For small molecule collections, there are several sources among which *Mother Nature* has traditionally been a rich supplier of biologically active small molecules. However, organic synthesis also plays a major role in discovering new bioactive small molecules. For example, an important source of small molecules includes combinatorial libraries generated by applying combinatorial chemistry techniques wherein chemists can synthesize many hundreds or thousands of compounds on a given pharmacophore using the same reaction conditions in one time [8]. However, due to the lack of structural diversity of the products in a particular combinatorial library, this methodology has been not as successful as initially expected. In drug discovery research, synthesis of structurally diverse small molecules is very important because compounds that have the same structural diversity often have a similar biological profile [9]. Natural products and

combinatorial libraries thus provide only a small proportion of bioactive chemical space. Therefore, in order to exploit compounds from the unexplored areas of chemical space, synthesis of an array of small molecules with high level of structural diversity is required. Along this line, Schreiber introduced the concept of diversity-oriented synthesis (DOS) in 2000 [10]. The objectives of DOS involve the production of small molecule collections by varying the building blocks, the stereochemistry, the functional groups and the molecular frameworks.

1.2. Importance of Heterocycles

Heterocycles are arguably the most versatile and ubiquitous family of organic compounds found in a vast number of natural products and synthetic compounds. In fact, heterocyclic compounds make up more than half of all known organic compounds and have become essential tools, spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals. Almost every area of organic synthesis has been impacted by heterocycles. Heterocyclic compounds are related with almost all aspects of life processes, both undesirable (e.g., toxicity, carcinogenicity, environmental pollutant, etc.) and favorable ones (e.g., nucleobases, porphyrins, vitamin C, proline, tryptophan etc.), enabling life processes, and also those externally empowering the quality of life (medicines, foods, etc.). Indeed, the history, chemistry and biology of heterocycles are very rich [11-17].

As far as their biological applications are concerned, heterocyclic compounds exhibit broad spectrum of biological activities, including antimalarial, antibacterial, antitumor, antiviral, anti-HIV, anti-inflammatory, antimicrobial, antifungal, antidepressant activities and so on. Heterocycles constitute an integral part of majority of the marketed clinical drugs. Penicillin (antibiotic), sofusbuvir (hepatitis C), azidothymidine (HIV), and cyclosporine (immunosuppressant), to name a few, have increased the life expectancy of human population. Many heterocyclic agrochemical compounds also serve as pesticides, insecticides, fungicides, rodenticides and herbicides. Heterocyclic compounds are also used as solvents, copolymers, dyestuffs, photographic sensitizers and developers. Moreover, for the development of many organic conductors, semiconductors, molecular wires, and organic light-emitting diodes (OLEDs), heterocyclic building blocks are used. Finally, they also serve as valuable synthetic intermediates in organic synthesis.

Owing to the widespread applications, synthesis of heterocyclic compounds has been a subject of intensive investigations as revealed by mammoth literature enfolding the

subject. Despite the tremendous advances that have been made on the synthesis and functionalization of heterocycles, there remains a great need for further advances in this area. Specially, for the drug discovery and development process, access to a diverse collection of heterocyclic compounds is extremely important.

1.3. Benzoxacycles: the 2,3-Dihydrobenzofuran, Chroman, 1,4-Benzodioxane, and 1-Benzoxepane Scaffolds

Oxygen-containing heterocycles are an important class of the heterocyclic compounds. Almost all families of oxa-heterocyclic natural products, found in all kingdoms of life, display some level of biological activity [18,19]. A subgroup of oxygen atom-containing heterocycles is benzo-fused oxygen heterocycles (benzoxacycles) in which an oxa-heterocyclic ring is fused to a benzene ring. Benzoxacycles are of special interest due to their fascinating structural diversity and the interesting biological activities of molecules containing these heterocyclic units [20,21]. 2,3-Dihydrobenzofuran, chroman (also known as chromane, 3,4-dihydro-2*H*-1-benzopyran and 3,4-dihydro-2*H*-chromene), and 1,4-benzodioxane skeletons (Figure 1.1) constitute a large proportion of benzoxacycles. 1-Benzoxapane (also known as 2,3,4,5-tetrahydrobenzoxepine, Figure 1.1) is also a significant structural motif that is featured in several bioactive natural products and synthetic molecules. However, unlike 2,3-dihydrobenzofuran, chroman and 1,4-benzodioxane derivatives, 1-benzoxapane derivatives suffer from sparse occurrence in nature. Moreover, synthetic studies on 1-benzoxapanes also remain scarce.

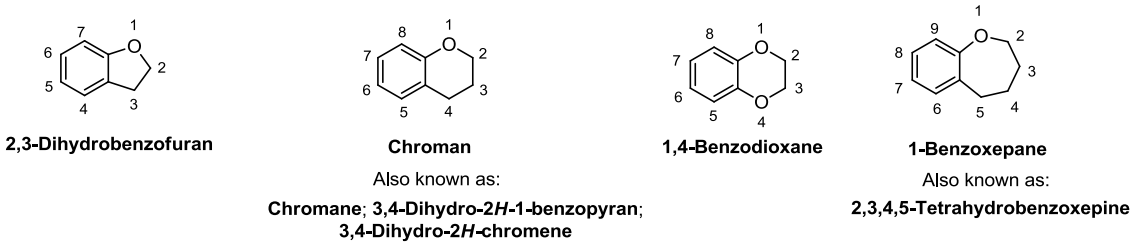


Figure 1.1. Structures of 2,3-dihydrobenzofuran, chroman, 1,4-benzodioxane, and 1-benzoxepane skeletons

Since the research work described in this thesis mainly involves the synthesis of chroman derivatives (together with a few related heterocycles which contain 2,3-dihydrobenzofuran, 1,4-benzodioxane, 1-benzoxepane scaffolds), biological importance

and recent synthetic developments of only chroman derivatives are discussed in the following sections.

1.4. Chroman as a Privileged Scaffold

The chroman core is a prevalent structural motif found in numerous biologically active natural compounds and pharmaceuticals. Chroman derivatives can interact with different types of enzymes, receptors and ion channels, thereby displaying a diverse array of biological activities, including anticancer activity, antioxidant activity, antihypertensive activity, antiestrogen activity, and antiviral activity and so on [22,23]. The recurring bioactivity found in chroman-containing molecules could be attributed to the conformational constraint provided by this cyclic scaffold, offering precise orientation of the substituents to interact with complex biological targets. The broad range of bioactivities exhibited by chroman containing compounds has made this ring system a "privileged structure" [24]. Representative examples of natural and synthetic compounds with a chroman scaffold are shown in Figure 1.2.

Perhaps, the most well-known member of chroman-bearing biologically active natural compounds is **α-tocopherol** which serves as a natural lipophilic antioxidant and radical scavenger [25-27]. **Visnadine** is a natural chroman derivative that is used as vasodilator in vascular disorders [28,29]. **Nabilone**, a synthetic cannabinoid containing chroman skeleton, is used as an antiemetic as well as an analgesic for neuropathic pain [30,31]. **Equol** is a chroman-based non-steroidal estrogen produced from the metabolism of the isoflavonoid phytoestrogen daidzein by human intestinal microflora [32,33]. **Centchroman**, a selective estrogen receptor modulator, is best known as a nonsteroidal oral contraceptive [34]. **Englitazone** is an antidiabetic agent (hypoglycemic agent) [35]. **Cromakalim**, an ATP-dependent potassium channel opening vasodilator, is used to treat hypertension [36]. **(+)-Nebivolol**, a potent β_1-adrenergic receptor blocker, is available in the market as an antihypertensive drug [37]. **Catechin** is a naturally occurring flavan-3-ol having antioxidant property [38,39]. Finally, **(-)-heliannuol E** has a novel heliannane-type sesquiterpenoid structure and is involved in the allelopathic action of cultivated sunflowers [40].

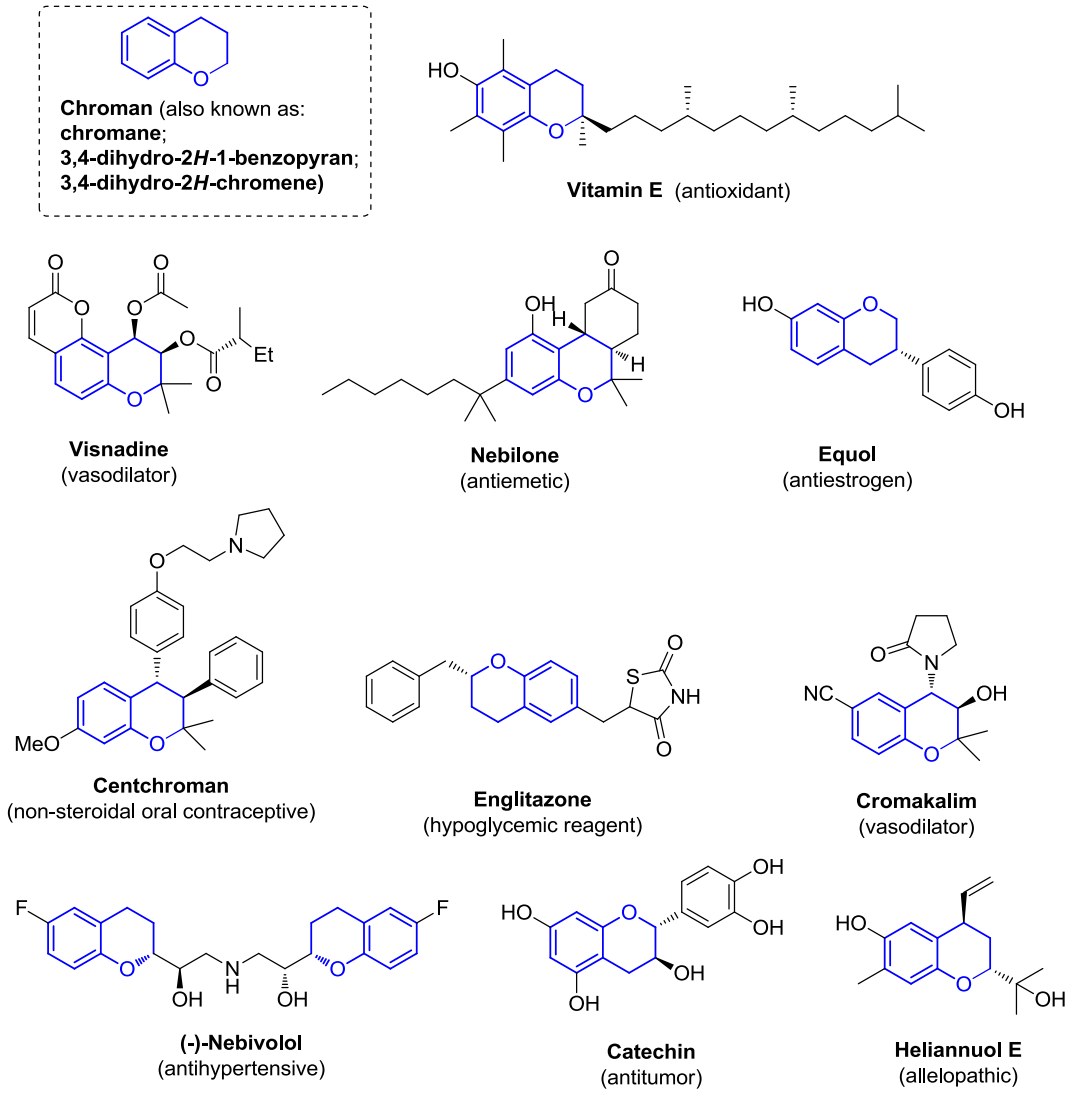


Figure 1.2. Representative examples of biologically active chroman derivatives

1.5. Synthetic Strategies towards Chromans

Owing to the widespread applications, synthesis of chroman derivatives has been a subject of intensive investigations as revealed by mammoth literature enfolding the subject [22,23]. Common synthetic approaches for construction of the chroman skeleton are depicted in Figure 1.3. One of the most widely used strategies involves Ar–O bond formation (route **I**, e.g., intramolecular transition metal-catalyzed cross-coupling and S_NAr reactions). However, perhaps the most common strategy involves formation of the ArO–C bond (route **II**, e.g., intramolecular Mitsunobu reaction, Williamson etherification, and epoxide/aziridine ring-opening). The construction of the C_3–C_4 bond is another approach that has been applied, but less frequently, in chroman synthesis (route **III**, e.g., ring closing metathesis).

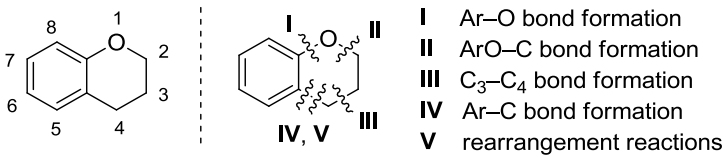


Figure 1.3. The most well-known strategies used for constructing the chroman ring

In contrast, the construction of the Ar–C bond is a well-explored approach (route **IV**, e.g., intramolecular Friedel–Crafts alkylation). Finally, the rearrangement of a preformed spirocyclic ring system can also be employed to construct the Ar–C bond (route **V**, e.g., dienone-phenol rearrangement). Despite the tremendous advances that have been made on the synthesis of chroman derivatives, there remains a great need for further advances in this area, especially for improving the scope and stereocontrol of constructing new classes of functionalized chroman derivatives.

1.6. A Brief Introduction to Epoxides, Aziridines, and Vicinal Diols

1.6.1. Epoxides

Epoxides, also called oxiranes, are three-membered heterocycles having one oxygen atom and two carbon atoms (Figure 1.4), and are among the most intensively studied building blocks in organic synthesis [41]. The C—C—O and C—O—C bond angles of the ring are 60°, a considerable deviation from the tetrahedral bond angle of 109.5°, or the divalent C—O—C angle of 110° for open chain ethers, resulting in a great deal of angle strain as in the comparable cyclopropane ring. To minimize this bond-angle strain, epoxide rings adopt a change in hybridization at the atoms which form the ring. In fact, epoxides can be considered as being constructed of bent or "banana" bonds (Figure 1.4). Nevertheless, the strain energy of ethylene oxide has been found to be 115 kJ mol^{-1}, compared with 114 kJ mol^{-1} for cyclopropane. The origin of the high reactivity of epoxides is based on this inherent strain, which provides a sufficient driving force for cleavage of the C–O bonds of the ring under either acidic or basic conditions.

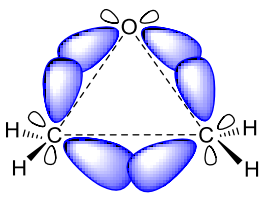


Figure 1.4. Bent bonding in ethylene oxide (the parent epoxide)

For the generation of racemic and enantiopure epoxides, several methods are well-established. Among them, epoxidation by peroxycarboxylic acids (for relatively electron rich alkenes), hydroperoxides in the presence of transition metal catalysts (for relatively electron rich alkenes), H_2O_2/NaOH (for electron-deficient alkenes), intramolecular S_N2 reaction (for halohydrins and related molecules), and sulfur ylides (Corey-Chaykovsky reaction for aldehydes/ketones) are routinely used in organic laboratories for accessing racemic epoxides (asymmetric versions are also known for all these methods excluding the first one) [41]. A number of asymmetric epoxidation methods are also available ─ among which Sharpless asymmetric epoxidation (for *E*-allylic alcohols) [42], Jacobsen asymmetric epoxidation (for unfunctionalized olefins) [43] and Shi epoxidation, [44] are the most celebrated ones.

Due to the ease of opening of the highly strained three-membered ring, epoxides can undergo ring-opening reactions with a wide range of nucleophiles such as halides, alcohols/alkoxides, thiols/thioalkoxides, azides, amines etc. as well as carbon-based nucleophiles, furnishing precious β-substituted alcohols towards the synthesis of a plethora of compounds. This topic has been the subject of a large number of reviews over the years [45-49]. It is important to mention that the S_N2 opening of epoxides has been widely studied and is tremendously utilized with high regio- and stereocontrol. By contrast, however, the S_N1 opening of epoxides is still not completely understood by chemists, and therefore remains a fascinating and very challenging area of study [41].

1.6.2. Aziridines

Aziridines are the nitrogenous analogues of epoxides with a strain energy of 113 kJ mol^{-1} for an unsubstituted aziridine (Figure 1.5). Like epoxides, aziridines are long established and powerful building blocks in the toolbox of organic chemists and have found applications in diverse sub-disciplines of organic chemistry for synthesizing nitrogen-containing compounds.

Compared to the diversity of epoxidation methods, however, the scope of the synthetic methods available for the preparation of aziridines is rather narrow [41] ─ this is especially true when enantioselective methods are considered [50]. Classical methods for the synthesis aziridines include ring closure of β-amino alcohols [51,52] and β-azido alcohols [53,54], transition metal-catalyzed nitrene transfer to alkenes [55], and carbene/carbenoid transfer to imines [56].

Due to lower electronegativity of nitrogen compared to oxygen, ring-opening reactions of aziridines are less effective than the corresponding reactions of epoxides. The reactivity of aziridines is dependent upon the nature of the substituent on the N atom. Aziridines with withdrawing groups such as carbonyl, sulfonyl or phosphoryl group are highly reactive (even more than epoxides in some cases) while those with *N*-hydrogen, alkyl or aryl are less reactive (Figure 1.5). Consequently, a large number of nucleophilic ring-opening reactions have been studied on activated aziridines while fewer such examples are known on non-activated aziridines [41]. Many reviews dealing with potential applications of aziridine ring-opening chemistry have been published over the past few decades [57-60].

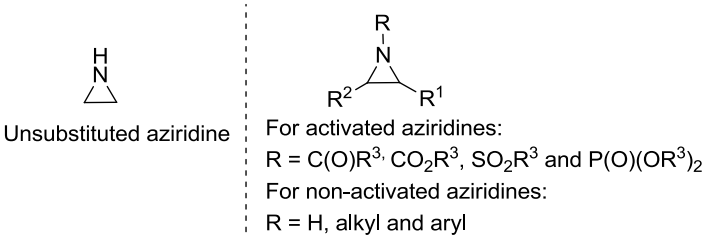


Figure 1.5. Unsubstituted-, activated- and non-activated aziridines

1.6.3. Vicinal Diols

Vicinal diols (also known as 1,2-diols, Figure 1.6) occupy a prominent place in organic chemistry as they are ubiquitous in natural products and are frequently used as starting materials for the synthesis of natural products, pharmaceuticals and agrochemicals [61-63]. Owing to the high richness of alcohol chemistry, numerous synthetic transformations are possible with vicinal diols. In fact, many transformations which were initially developed for carbohydrates have also been applied to non-carbohydrate vicinal diols.

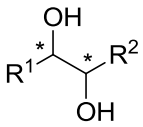


Figure 1.6. Vicinal diols

There are various methods for the preparation of vicinal diols. Among them, OsO_4-catalyzed dihydroxylations of alkenes (Upjhon dihydroxylation and Sharpless asymmetric dihydroxylation) are more commonly used [64]. Other methods for the asymmetric synthesis of vicinal diols include asymmetric hydrogenation of α-

hydroxyketones, hydrolysis of enantioenriched/enantiopure epoxides, α-oxyamination/reduction of carbonyls, diboration/oxidation of alkenes, kinetic resolution etc. [65].

1.7. Synthesis of Chroman Derivatives Using Epoxides, Aziridines and Vicinal Diols

As already mentioned, stereoselective synthesis of chroman derivatives has gained significant attention in recent decades. In this context, the ubiquity, relative ease of synthesis and versatile reactivity of epoxides, aziridines and vicinal diols bring about a good opportunity for organic chemists to utilize them in the synthesis of chroman derivatives. This section is intended to concentrate specifically on the recent development on the stereoselective synthesis of chroman derivatives using epoxides, aziridines and vicinal diols as building blocks. Recent literature reports are selected to illustrate the exploitation of each of the aforementioned three building blocks to synthesis of chromans. The synthetic approaches are classified according to the building block with the use of which the chroman ring has been constructed.

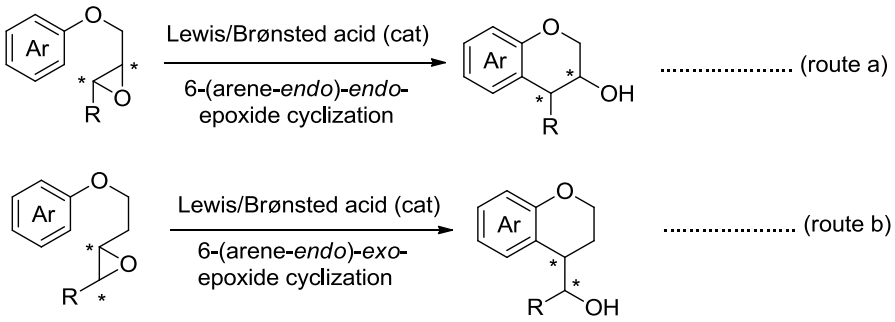
1.7.1. Using Epoxides

The literature deviates into two general strategies towards the chroman ring. These are: (i) construction of the Ar–O bond via intramolecular Friedel-Crafts epoxide-arene cyclization of aryl glycidyl ethers, and (ii) construction of the ArO–C bond via intramolecular ring-opening of epoxides by tethered phenols [22,41].

1.7.1.1. Intramolecular Friedel-Crafts Epoxide-Arene Cyclization

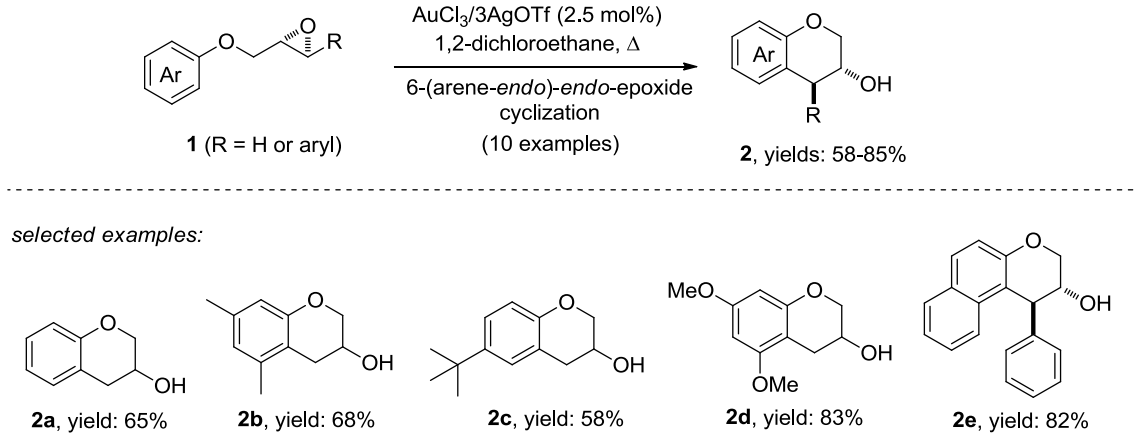
In this strategy, an aryloxy moiety undergoes Friedel-Crafts alkylation by a tethered epoxide ring in the presence of a suitable Brønsted/Lewis acid (Scheme 1.1, route a) [49]. For the convenience of discussion, throughout this section such a reaction is termed as intramolecular Friedel-Crafts epoxide-arene cyclization (IFCEAC). With a 1-carbon link between the aryloxy moiety and the epoxide ring, 6-(arene-*endo*)-*exo*-epoxide cyclization leads to the formation of chroman ring. On the other hand, this ring can also be constructed by 6-(arene-*exo*)-*endo*-epoxide cyclization, provided the aryloxy moiety and the epoxide ring are separated by 2-carbon link (Scheme 1.1, route b). However, since 2000, no examples of the 6-(arene-*exo*)-*endo*-epoxide cyclization have been reported.

Although chroman derivatives, especially the chiral ones, can be constructed through a number of highly efficient methodologies, additional synthetic efforts using readily available substrates with high product selectivity (chemo-, regio-, and stereoselectivity) are always adored. IFCEAC reactions appear to be one such type of reactions with high potential to realize the above-mentioned requirements.



Scheme 1.1. Schematic representation of the synthesis of chroman derivatives via IFCEAC reactions

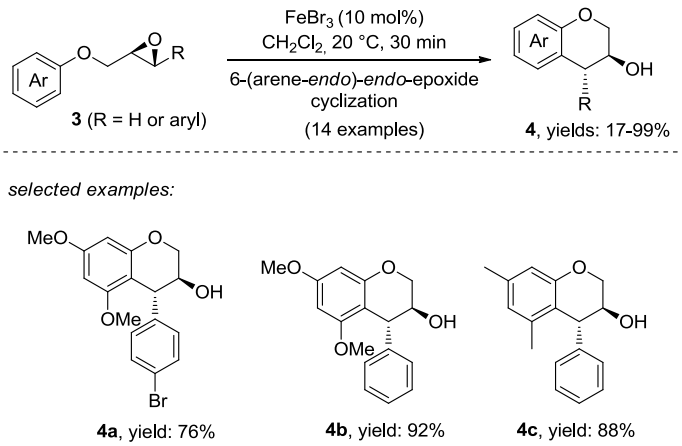
The first utilization of IFCEAC in the synthesis of 3-chromaols was reported by Shi and He in 2004 [66]. The authors synthesized 3-chromaols **2** in moderate to high yields via regio- and stereoselective IFCEAC of aryl glycidyl ethers **1** catalyzed by $AuCl_3$/3AgOTf (2.5 mol% based on gold) in 1,2-dichloroethane (Scheme 1.2).



Scheme 1.2. $AuCl_3$/3AgOTf-catalyzed IFCEAC of aryl glycidyl ethers

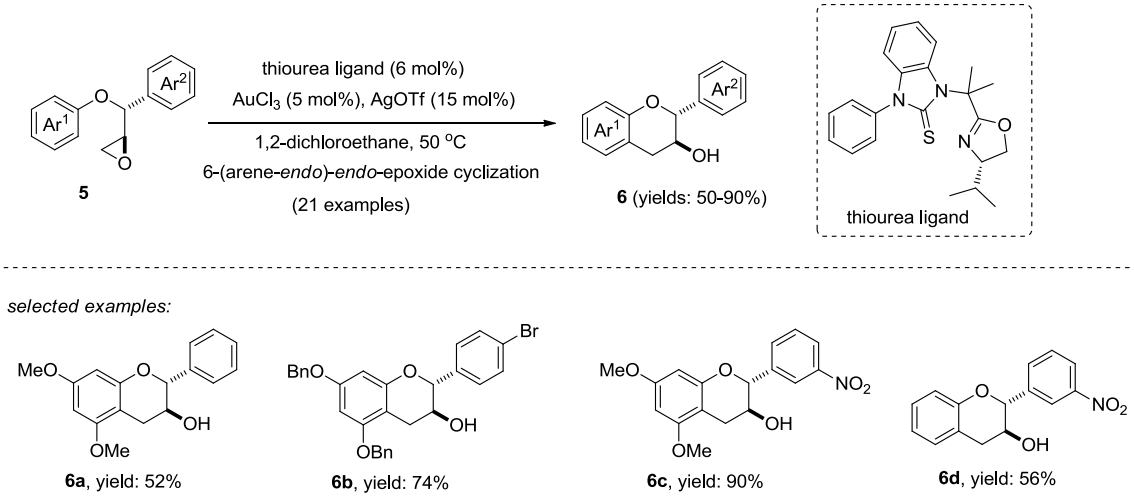
Pericàs et al. subsequently investigated the similar reactions of optically active aryl glycidyl ethers **3** under mild conditions in the presence of a catalytic amount of $FeBr_3$ (Scheme 1.3) [67]. A set of other catalytic systems ($BF_3{\cdot}Et_2O$, $FeBr_3$/3AgOTf, $AuCl_3$/3AgOTf) were also examined, all of which gave the desired products **4**, albeit in variable yields. The authors noted a significant influence of the R group on the product yield. With R = aryl, high yields were observed; however, these reactions were low

yielding with unsubstituted aryl glycidyl ethers (R = H), obviously due to the lack of aryl group-induced activation of the epoxide ring toward the ring-opening process.



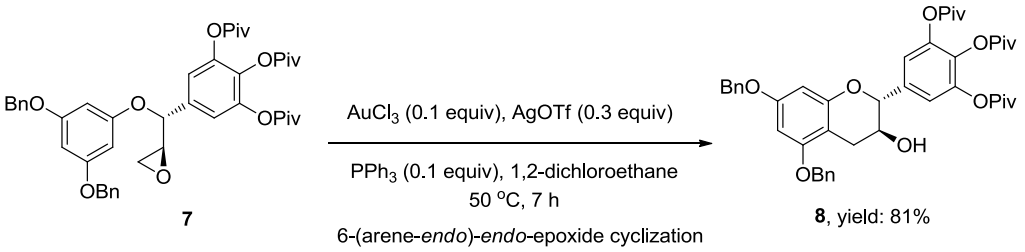
Scheme 1.3. $FeBr_3$-catalyzed IFCEAC of aryl glycidyl ethers

The groups of Chen and Yang described the synthesis of structurally diverse catechins **6** via thiourea/$AuCl_3$/AgOTf-catalyzed IFCEAC of aryl glycidyl ethers **5** under mild conditions (Scheme 1.4) [68].



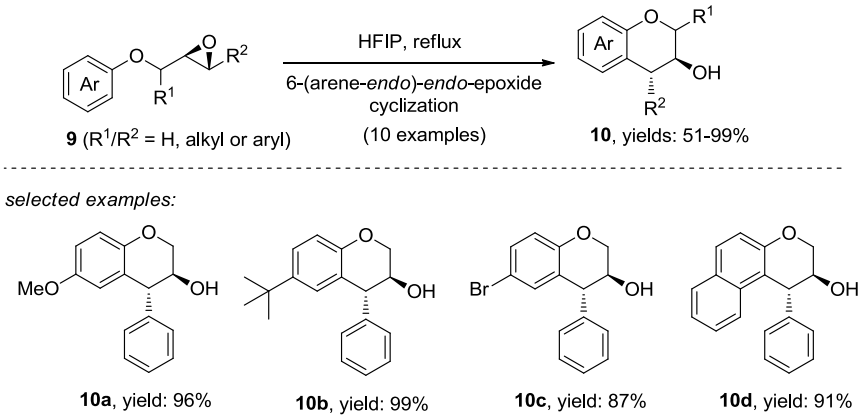
Scheme 1.4. Synthesis of catechins via thiourea/$AuCl_3$/3AgOTf-catalyzed IFCEAC of aryl glycidyl ethers

In their efforts for the total synthesis of (±)-gallocatechin, (-)-epigallocatechin, and 8-C-ascorbyl-(-)-epigallocatechin, the same research group achieved high yielding (81%) synthesis of catechin derivative **8** via IFCEAC of enantiomerically pure *anti*-epoxyether **7** in the presence of an $AuCl_3$/AgOTf/PPh_3 catalytic system (Scheme 1.5) [69].



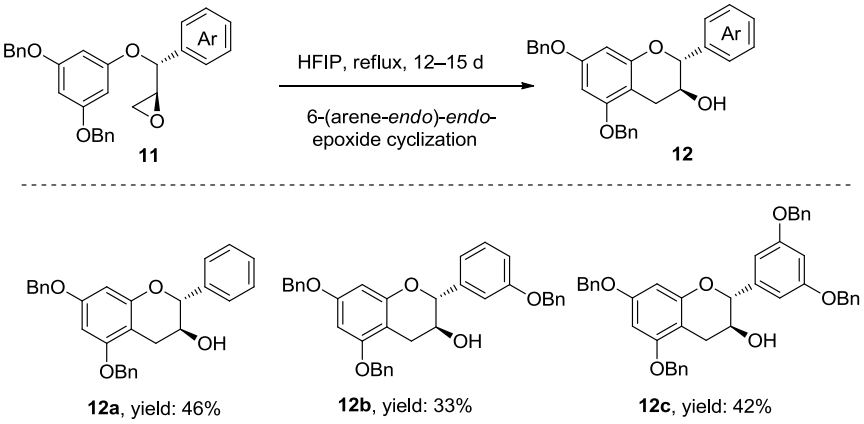
Scheme 1.5 Synthesis of a catechin derivative via $PPh_3/AuCl_3/3AgOTf$-catalyzed IFCEAC of aryl glycidyl ethers

The IFCEAC reactions as described above could be further modified by employing 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as both promoter and reaction medium, thus enabling the synthesis of 3-chromaols **10** in high yields under metal-free conditions (Scheme 1.6) [70].



Scheme 1.6. HFIP-promoted IFCEAC reactions

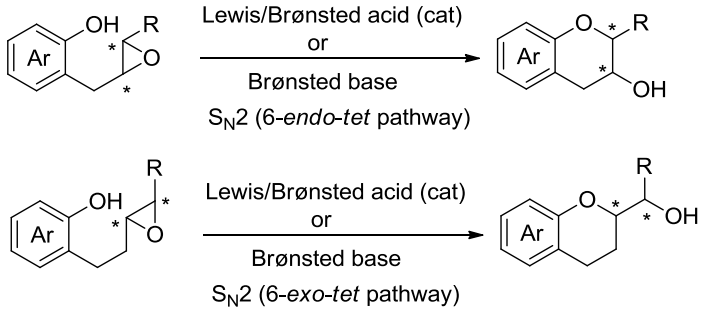
This method was subsequently applied by Anderson et al. in a key step while studying the synthesis of structural analogues of (−)-epicatechin gallate (Scheme 1.7) [71].



Scheme 1.7. Further application of HFIP-promoted IFCEAC reactions

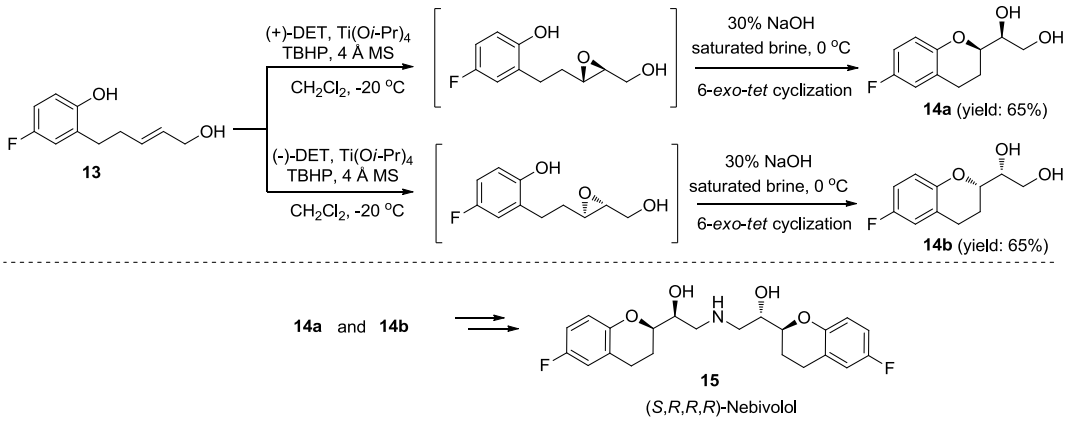
1.7.1.2 Intramolecular Ring-Opening of Epoxides by Tethered Phenols

In these reactions, an epoxide moiety undergoes ring-opening ─ cyclization induced by a tethered phenolic-OH group (Scheme 1.8). Such reactions require the presence of either a suitable Brønsted/Lewis acid (to activate the epoxide ring) or a Brønsted base (to convert less nucleophilic phenolic-OH group to more nucleophilic phenolate ion). Like in IFCEAC reactions, to construct a chroman ring, epoxide ring has to undergo *exo* or *endo* ring-opening ─ cyclization, depending on length of tether.



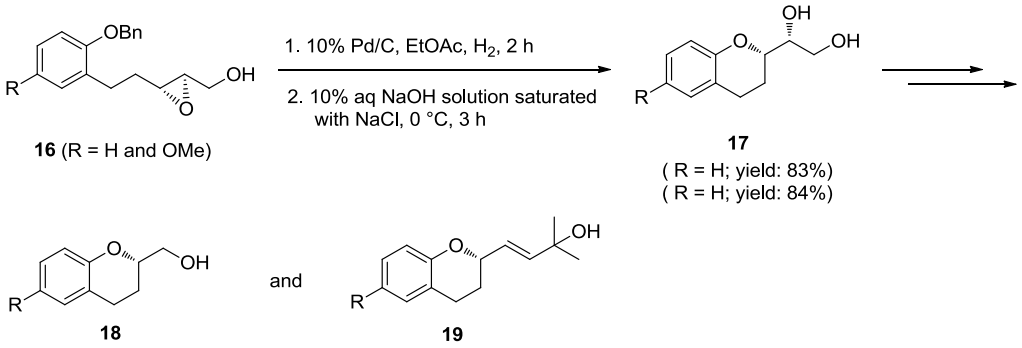
Scheme 1.8. Strategies for chromans via intramolecular ring-opening of epoxides by phenols

The first example of this section is shown in Scheme 1.9. In an approach to (*S*,*R*,*R*,*R*)-nebivolol **15**, which is potent and selective β_1-adrenergic blocker with antihypertensive activity, Chandrasekhar et al. subjected *E*-allylic alcohol **13** to Sharpless asymmetric epoxidation, and then treated the resulting crude chiral epoxides with 30% NaOH in saturated brine to obtain the corresponding chroman derivatives **14a** and **14b** [72]. The cyclization was clearly induced by phenolate ion and occurred through 6-*exo*-*tet* pathway.



Scheme 1.9. Strategies for chromans via intramolecular ring-opening of epoxides by phenols

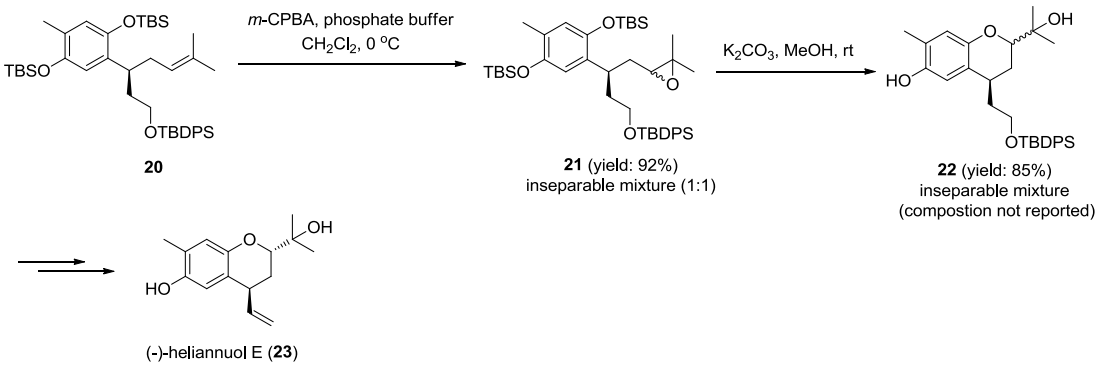
This methodology was subsequently utilized by Panda et al. to prepare 1-(chroman-2-yl)ethane-1,2-diols **17a**,**b** as advanced intermediates in the synthesis of 2-hydroxymethyl chromans and 4-chroman-2-yl-2-methylbut-3-en-2-ols (Scheme 1.10) [73].



Scheme 1.10. Synthesis of chroman derivatives by Panda et al.

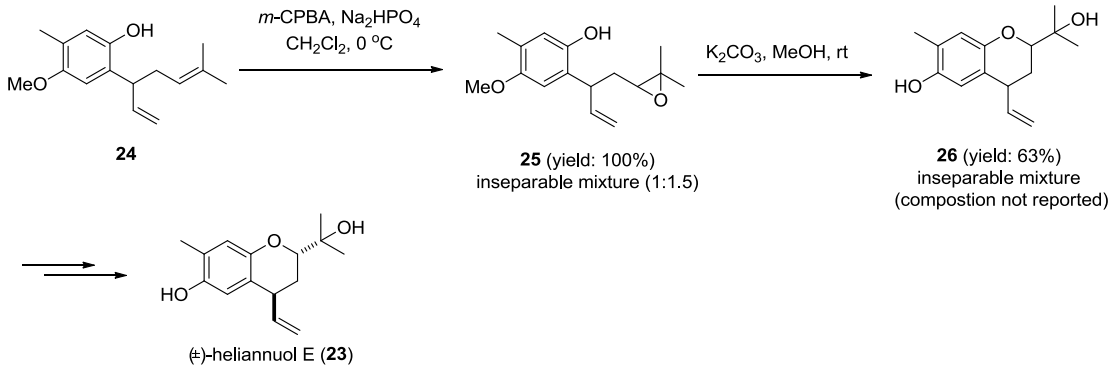
More recently, Jas, Schinzer et al. exploited 1-(chroman-2-yl)ethane-1,2-diol **17** (R = H) and its enantiomer, also prepared by the same methodology, to synthesize all possible stereoisomers of desfluorinated nebivolol [37].

Shishido et al. utilized phenolate-induced intramolecular epoxide ring-opening reaction to prepare chroman derivative **22** as a late-stage intermediate in the first total synthesis of a novel heliannane sesquiterpenoid (−)-heliannuol E **23** (Scheme 1.11) [74]. The starting epoxide **21** was synthesized by *m*-CPBA mediated epoxidation of olefin **20**, and was isolated as an inseparable mixture of the corresponding diastereomeric epoxides in a 1:1 ratio in 92% yield. Treatment of **21** with K_2CO_3 in MeOH again provided an inseparable mixture of the corresponding diastereomeric chromans **22** in 85% yield. This crucial chroman skeleton formation reaction involved double desilylation followed by 6-*exo-tet* epoxide ring-opening ─ cyclization.



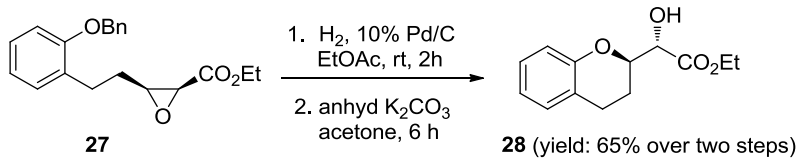
Scheme 1.11. Phenolate-induced epoxide ring-opening ─ cyclization as a key step for the synthesis of (−)-heliannuol E

The research group of Vyvyan also used a similar strategy in their synthesis of (±)-heliannuol E (Scheme 1.12) [75].



Scheme 1.12. Phenolate-induced epoxide ring-opening ─ cyclization as a key step for the synthesis of (±)-heliannuol E

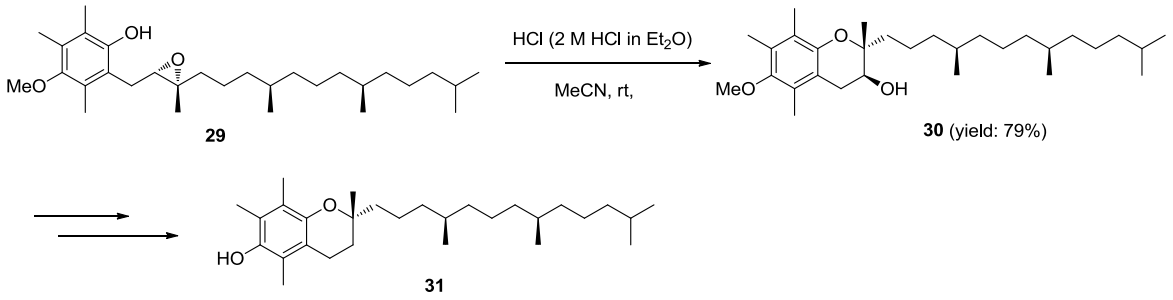
Panda et al. also reported the propensity of phenolate-induced 6-*exo*-*tet* epoxide ring-opening ─ cyclization in their study on the synthesis of benzoxacycles using β-hydroxy-α-tosyloxy esters as chiral building blocks [76]. In their work, debenzylation of *syn*-epoxy ester **27** with Pd-C and hydrogen followed by treatment of the resulting phenolic derivative with anh. K_2CO_3 in dry acetone afforded chroman derivative **28** in 68% yield (Scheme 1.13).



Scheme 1.13. Phenolate-induced ring-opening ─ cyclization of *syn*-epoxy ester

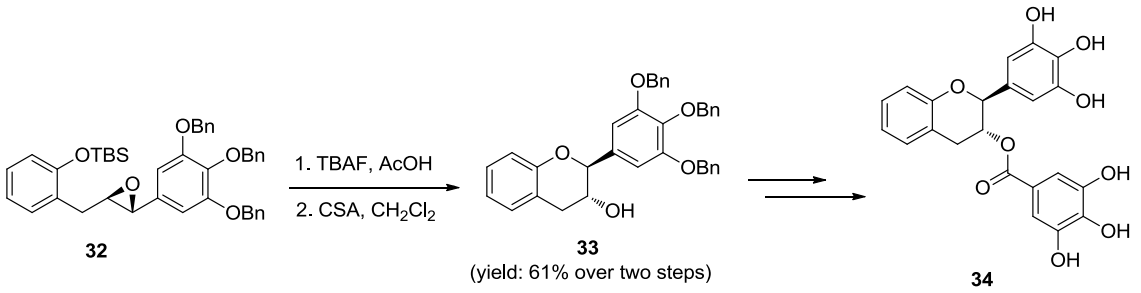
An example of the use of acid catalyzed intramolecular ring-opening of epoxide by tethered phenolic-OH group is the synthesis of chroman derivative **30** from chiral epoxide **29** ─ a crucial step in the synthesis of α-tocopherol **31** by the Woggon group (Scheme 1.14) [77]. Treatment of **29** with 2 M HCl in diethyl ether caused deprotective 6-*endo* ring-opening ─ cyclization to furnish **30** in 79% yield.

Acid catalyzed intramolecular ring-opening of epoxide by tethered phenolic-OH group constitutes the key step in Hirooka's synthesis of (−)-5,7-dideoxy gallocatechin 3-*O*-gallate **34** (Scheme 1.15) [78]. Desilylation of chiral epoxide **32** followed by treatment of the resulting epoxy alcohol with CSA led to the formation of *trans*-chroman derivative **33** via 6-*endo* ring-opening ─ cyclization in 61% yield (over two steps).



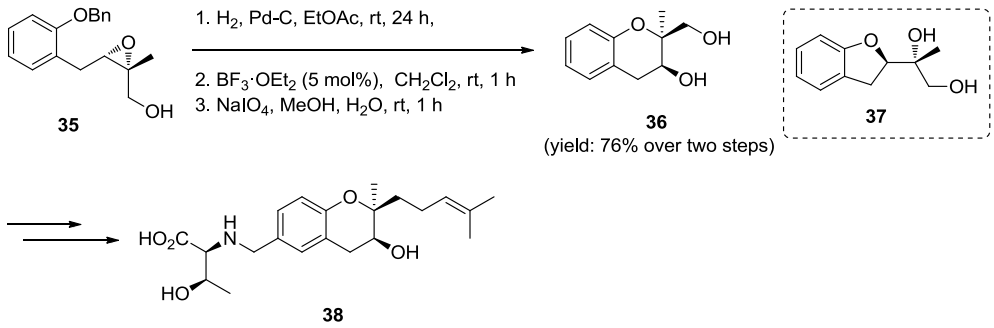
Scheme 1.14. Acid catalyzed intramolecular ring-opening of epoxide by tethered phenolic-OH

In contrast, the *cis*-counterpart of **32** furnished only a 1 : 1 mixture of *trans*/*cis* isomers of **33** (not shown here). Nevertheless, compound **33** was subsequently converted into (−)-5,7-dideoxy-gallocatechin 3-*O*-gallate **34**.



Scheme 1.15. Synthesis of (−)-5,7-dideoxy-gallocatechin gallate via acid catalyzed intramolecular ring-opening of epoxide by tethered phenolic-OH

In their total synthesis of xiamenmycin A **37**, a chroman derivative isolated from *Streptomyces xiamenensis* 318 with a highly potent anti-fibrotic activity, Xu, Xie et al. reported that chroman derivative **36** could be synthesized from epoxy alcohol **36** in 76% overall yield over three steps (Scheme 1.16) [79].



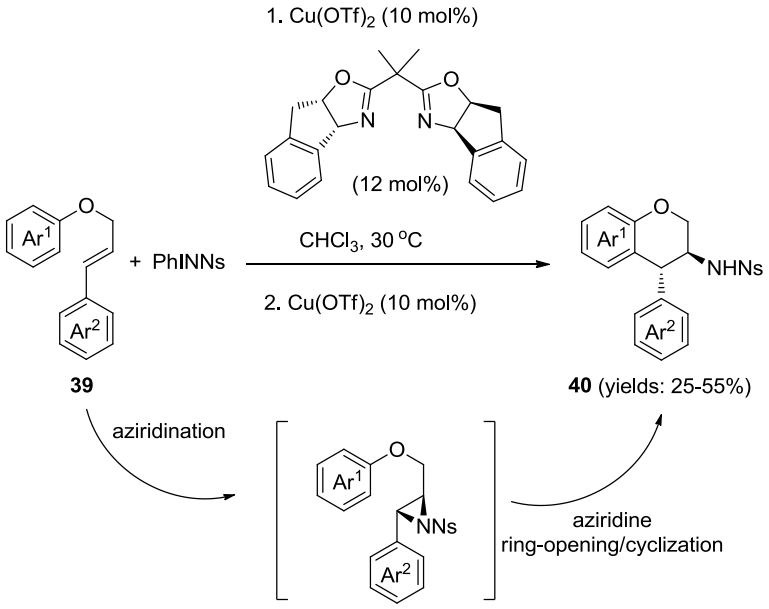
Scheme 1.16. Use of acid catalyzed intramolecular ring-opening of epoxide in the synthesis of xiamenmycin A

First two reactions of the sequence involved debenzylation of **35** by hydrogenolysis under standard conditions and a subsequent $BF_3 \cdot OEt_2$-promoted cyclization of the resulting epoxy phenol to furnish chroman derivative **36** (arose via 6-*endo* epoxide ring-opening ─ cyclization) and 2,3-dihydrobenzofuran derivative **37** (arose via 5-*exo* epoxide ring-opening ─ cyclization) as an inseparable mixture (**36** : **37** = 7.36 : 1). In the last step of this sequence, this mixture was treated with $NaIO_4$ to facilitate the purification process of **36**, by converting **37** into the corresponding less polar aldehyde compound.

1.7.2. Using Aziridines

1.7.2.1. Intramolecular Friedel-Crafts Aziridine-Arene Cyclization

While intramolecular Friedel-Crafts epoxide-arene cyclization reactions have been utilized for the assembly of chroman skeleton on several occasions, a similar strategy with aziridines has been rarely studied. For the synthesis of chroman derivatives via intramolecular Friedel-Crafts aziridine-arene cyclization, only one example, as shown in Scheme 1.17, has been reported to date. This contribution came from the research group of Hajra who reported the synthesis of *trans*-3-amino-4-arylchromans via one-pot sequential asymmetric aziridination/Friedel–Crafts reactions of aryl cinnamyl ethers. The reactions involved 6-(arene-*endo*)-*endo*-aziridine cyclization and furnished the products in high regio-, diastereo-, and enantioselectivities of up to >98% de and 95% ee [80].



Scheme 1.17. Synthesis of chromans via intramolecular Friedel-Crafts aziridine-arene cyclization

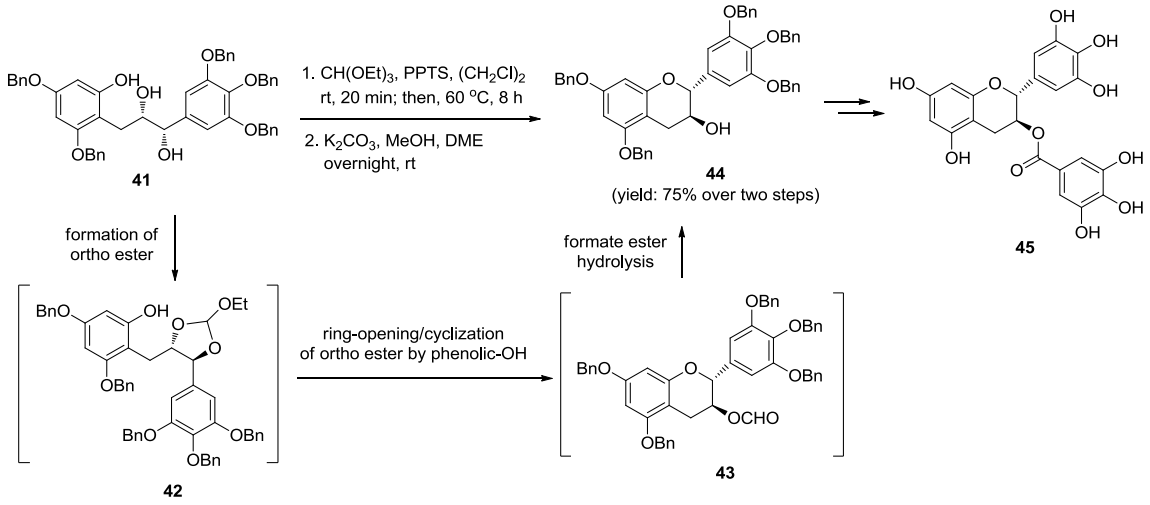
1.7.2.2. Intramolecular Ring-Opening of Aziridines by Tethered Phenols

To the best of our knowledge there have been no such reports in the literature.

1.7.3. Using vicinal 1,2 diols

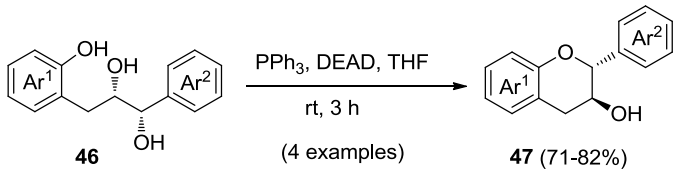
In this section, selected literature reports, illustrating the use of the chiral vicinal diols in the preparation of various chroman derivatives, are described.

In 2001, Chan and Li used Sharpless asymmetric dihydroxylation-derived vicinal diol **41** to construct chroman derivative **44** as a late-stage intermediate in the enantioselective synthesis of epigallocatechin-3-gallate **45** (Scheme 1.18) [81]. In their approach, treatment of diol **41** with triethyl orthoformate and PPTS in 1,2-dichloroethane (r.t.→ 60 °C) provided chroman derivative **43**, via orthoester **42**, in stereo- and regioselective fashion. Saponification of crude **43** by K_2CO_3 in MeOH/DME gave **44** in 75% yield over two steps.



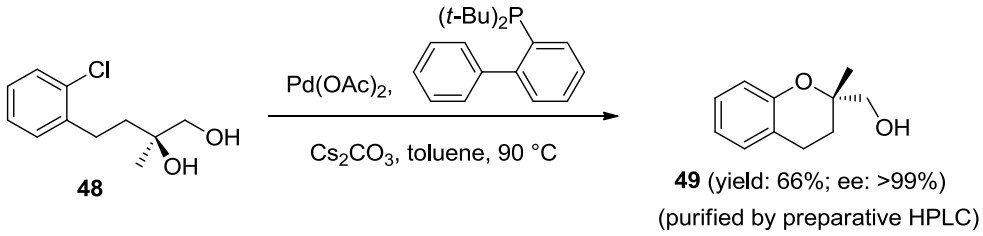
Scheme 1.18. Synthesis of epigallocatechin-3-gallate via chiral vicinal diol

Krohn et al. reported enantioselective syntheses of 2,3-*trans*-flavan-3-ols **47**, with different substitution patterns and electron densities, via stereo- and regioselective intramolecular Mitsunobu etherification of Sharpless dihydroxylation-derived vicinal diols **46** (Scheme 1.19) [82].



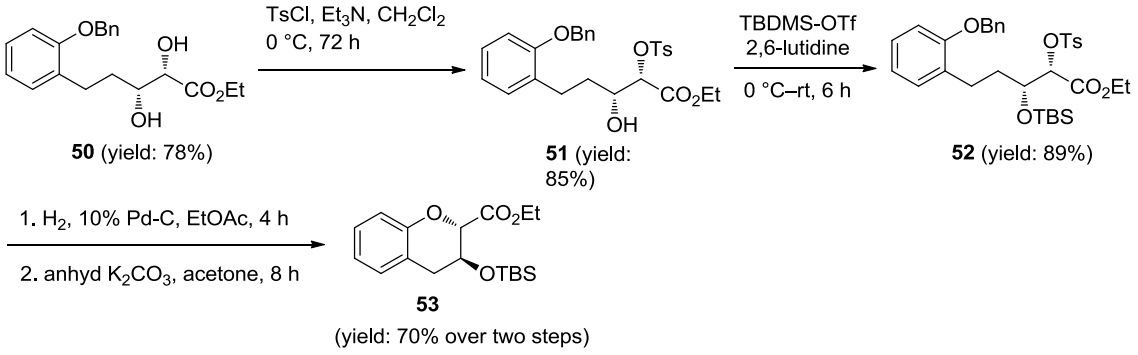
Scheme 1.19. Enantioselective Synthesis of flavan-3-ols using chiral vicinal diols

In 2005, Palucki and Yasuda utilized chiral vicinal diol **48** for the synthesis of chroman derivative **49** via Pd-catalyzed intramolecular ArC─O bond-forming etherification reaction (Scheme 1.20) [83].



Scheme 1.20. Synthesis of (*S*)-(2-methylchroman-2-yl)methanol using chiral vicinal diol

Panda and Das converted Sharpless asymmetric dihydroxylation-derived diol **50** into the β-hydroxy-α-tosylxy ester **51** via regioselective α-tosylation (Scheme 1.21). TBS-protection of **51** furnished compound **52** which on debenzylation ─ etherification gave chroman derivative **53** [76]. This was the first report of utilization of a *syn*-2,3-dihydroxy ester for the synthesis of a chroman derivative.



Scheme 1.20. Synthesis of chroman derivative from *syn*-2,3-dihydroxy ester

1.8. Conclusion

In summary, this chapter begins by highlighting the importance of organic synthesis for the welfare of human beings. Along this line, a brief discussion about the role of small molecules derived from natural products, combinatorial chemistry, and diversity oriented synthesis (DOS) is made. Next, importance of heterocycles as a special class of small organic molecules is demonstrated. As this thesis mainly involves the synthesis of chroman derivatives, special emphasis is given on the biological and medicinal importances of chroman derivatives. This chapter also summarizes the most common synthetic routes to chroman derivatives. One subsection is dedicated to the properties,

syntheses, and importances of epoxides, aziridines, and vicinal diols. Finally, an overview of the recent synthetic developments of chroman derivatives using epoxide, aziridine, and vicinal diol building blocks is given, covering representative reports from the literature since the beginning of 2000.

1.9. Thesis Overview

Synthesis of chroman derivatives is one of the major research endeavors in organic chemistry research due to their fascinating biological activities. A plethora of methods is available for the stereo- and regioselective synthesis of this privileged heterocyclic system, but the most commonly reported methods are intramolecular S_NAr reaction, transition-metal-catalyzed C-O bond formation reaction, and Mitsunobu reaction, with each approach having its own advantages and disadvantages. As an alternative to these methods, ArO–C/Ar−C bond-forming intramolecular cyclization of epoxides, aziridines, and vicinal diols is undoubtedly an attractive and efficient synthetic methodology. Ready accessibility (in racemic as well as enantiomerically pure forms) and ability to undergo regio- and stereoselective reactions make epoxides, aziridines, and vicinal diols three important tools in organic synthesis. Admittedly, however, these three building blocks still remain underutilized for the synthesis of chroman derivatives. Given the ever-increasing use of chroman derivatives in organic and medicinal chemistry, further exploitations of epoxides, aziridines, and vicinal diols for making such compounds are needed.

The general aim of my PhD research work, as described in the **Chapters 2-7** of **this thesis**, was to develop new/improved synthetic routes of functionalized chroman derivatives using epoxides, aziridines, and vicinal diols in chemo-, regio-, and stereoselective fashion. Specifically, the research work described in this thesis involves the synthesis of *trans*/*cis*-4-arylchroman-3-ols (**Chapter 2**), chroman-fused tetralins (**Chapter 3**), (+)-nebivolol intermediates (**Chapter 4**), 2-amino-2-(chroman-2-yl)ethanols (**Chapters 5 and 6**) and chroman-linked benzoxazepines (**Chapter 7**). Synthesis of a very few related heterocycles such as 2,3-dihydrobenzofuran, 1,4-benzodioxane,1-benzoxepane, and 1,4-benzoxazepine derivatives is also described in this thesis (**Chapters 6 and 7**).

1.10. References

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