RECENT ADVANCES IN THE ASYMMETRIC SYNTHESIS OF CHROMANE DERIVATIVES

DOI: http://dx.medra.org/10.17374/targets.2021.24.227

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Abstract. *Chromane derivatives are the core structure of many natural products, most of them having nutraceutical properties. As many natural products, this scaffold often carries out asymmetric carbon atoms. Therefore, asymmetric syntheses are of great importance in order to prepare these important building blocks. Our aim is to collect the asymmetric methods and some examples of total syntheses of natural product appeared in the literature in the last three years.*

Contents

Abbreviations

Binap, (1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine); **BINOL**, 1,1′-bi-2-naphthol; **Boc**, *t*-BuOCO; **Cbz**, BnOCO; **Cod**, 1,5-cyclooctadiene; **Cp***, pentamethylcyclopentadienyl; ***m*-CPBA**, *m*-chloroperbenzoic acid; **DBU**, 1,5-diazabicyclo(5.4.0)undec-7-ene; **DFT**, Density Functional Theory; **$(DHQD)_2PYR$**, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether; **DIBAL**, $(i\text{-}Bu_2AlH)_2$; **DIPEA**, *N,N*-diisopropylethylamine; **DMAP**, 4-(dimethylamino)pyridine; **DMF**, *N,N*-dimethylformamide; **β-ICD**, β-isocupreidine; **Mes**, $MeSO_3$; **MNP**, magnetic nanoparticles; **MOM**, $MeOCH_2$; **MS**, molecular sieves; **NBS**, *N*-bromosuccinimide; **NHC**, *N*-heterocyclic carbene; **NIS**, *N*-iodosuccinimide; **PCC**, pyridinium chlorochromate; **PPTS**, pyridinium *p*-toleuensulfonate; **$(QD)_2PHAL$**, quinidine-1,4-phthalazinediyl diether; **Segphos**, 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole; **TBS**, *t*-$BuMe_2Si$; **Tf**, CF_3SO_2; **TMS**, Me_3Si; **Ts**, $MeC_6H_4SO_2$.

1. Introduction

The chiral chromane skeleton is a motif present in a plethora of natural products and, in particular, in flavonoids.[1] These substances contribute to organoleptic and nutritional quality of many vegetables and fruits and often act as nutraceutical substances. In fact, they can show anti-HIV, antitumor, anticancer, antioxidant, anti-aging, anti-inflammatory, antibacterial properties.[2] Natural flavonoids are generally complex molecules; however, simpler chromanes can maintain the biological properties.[3] Commonly,

chromanes are prepared starting from benzene derivatives, annulating the pyran moiety in several steps. Clearly, such a procedure sets the challenge to perform enantioselective reactions in case enantiomerically pure chromanes are needed. Therefore, the asymmetric synthesis approach has been extensively studied over the years and a plethora of methodologies are now available, applying chiral catalysis to the classical reaction. Many chemists have already ventured in summarizing asymmetric synthesis of these compounds.[1,4] However, in the last three years, new synthetic methods for the preparation the chromane nucleus have appeared in the literature, and we aim to give an overview of these recent synthetic methods and also we wish to report some application to the total synthesis of complex molecules.

Asymmetric syntheses can be performed by chiral metal catalysts or by organocatalysis. Metal ions have variable oxidation states, thus they can form σ or π complexes with substrates and accommodate chiral ligands, which can hide one of the faces of the substrate, inducing enantioselectivity. However, the best catalysts are elements situated in the middle of the periodic table, the ions of which with higher oxidation state are toxic. Therefore, if their trace remains in the product, they can make unusable as drugs. In Italy every year, many drugs are removed from the commerce due to the presence of trace toxic substances.[5]

On the other hand, organocatalysis uses small organic molecules, often from non-toxic natural sources, the organocatalysts have many simultaneous activation modes for substrates and reagents allowing easy cascade reactions, they are easy available and cheap, and they operate at very mild conditions. However, these advantages do not impede the possible formation of toxic by-products.

2. DFT studies on the reaction mechanisms

Many authors explained their results envisaging plausible mechanisms for their reactions and they will be pictured in the reaction scheme, sometimes supported by theoretical calculations. However, there are also some general theoretical studies about asymmetric syntheses of chromane derivatives, and in last few years some examples have been reported.

Among them, a DFT study was carried out for the mechanism of the asymmetric intramolecular nucleophilic substitution of *ortho*-allyloxy benzaldehydes catalyzed by NHCs.[6] The reaction proceeds through three stages: (i) the combination of NHC with the substrate from the Si face; (ii) the SN2′ reaction, which is the rate- and enantioselectivity-determining step giving the stereocenter in the favored *R* configuration; and (iii) the release of the product.

Another DFT study was performed for the addition of arylboronic acid to coumarin substrates, catalyzed by a chiral rhodium catalyst.[7] The calculations showed that the best ligands for the acceleration of the insertion of $ArB(OH)_2$ should carry electron-withdrawing substituents and should give CH–π interactions with coumarin substrates. From the computational information, a rhodium ligand which worked at only 0.025 mol% catalysts loading was designed and successfully tested (see section 5).

Also the mechanism of the reaction of *ortho*-hydroxystyrene and azlactone catalyzed by chiral (BINOL)-phosphoric acid with and without chiral guanidine as the co-catalyst was studied in detail with the DFT method.[8] Both reactions were found to proceed stepwise and not by a classical [4+2] Diels-Alder reaction. The steps are: C–C then C–O bond formation and, finally, azlactone ring-opening.

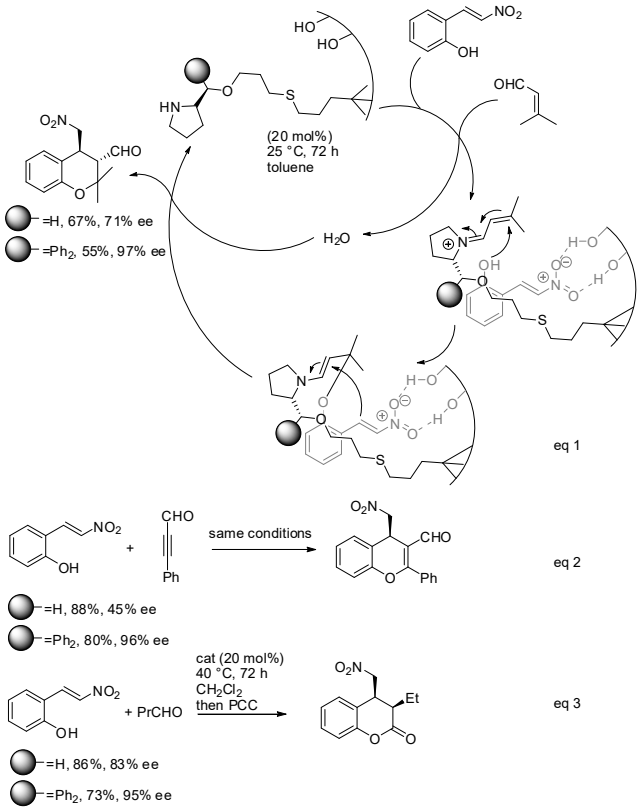
3. Cyclization of hydroxystyrene derivatives

o-Hydroxystyrene derivatives are certainly one of the most useful starting materials for building the chromane nucleus. Since 1999,[9] many nonracemic metal complexes and organocatalysts later have been introduced to catalyze the asymmetric version of this reaction, and the reader can find a detailed overview in the review cited in the introduction. However, the interest of chemists goes on and also in the last years other interesting papers have appeared in the literature.

3.1. From 2-nitrovinylphenols

In the last three years this reaction was essentially developed under organocatalysis and bifunctional catalysts have been revealed the best choice. Thus, An and co-workers prepared a heterogeneous catalyst, in which the silanol groups of mesoporous silica are the achiral acid site and an immobilized chiral amine is the basic site.[10] In Scheme 1[11] is reported the mechanism envisaged by the authors. It is very similar to the proposed mechanism for homogenous catalysis. By this hypothesis, the surface silanols bind and activate the

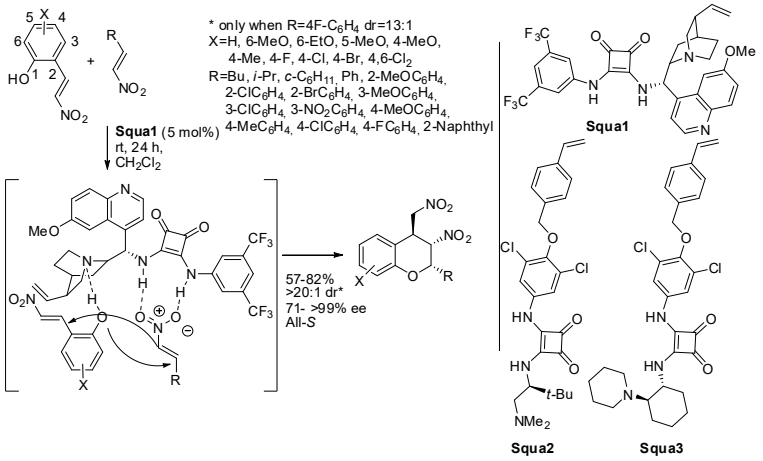
nitro group, while the proline forms an iminium ion intermediate with the aldehyde, which is attacked from the less hindered face by the hydroxy framework. Then, C-1 of the nitro-olefin closes the six-membered ring. Also the pore wall concurs to enhance the enantioselectivity, as demonstrated by the higher enantioselectivity obtained with larger groups adjacent to the nitrogen atom in the catalyst. The reaction was also extended to the Michael-hemiacetalization reaction followed by oxidation, with good results (Scheme 1, eq. 3). The heterogeneous catalyst was reused up to five times without significantly affecting the yield and enantioselectivity.



Scheme 1. Heterogeneous enantioselective synthesis of chromanes.

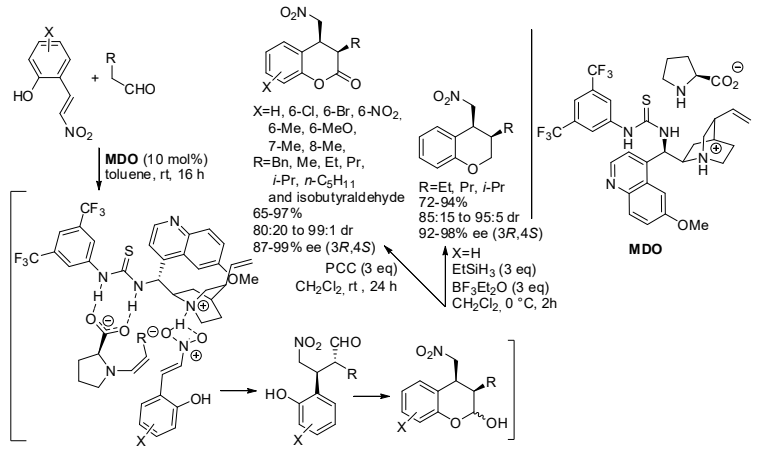
In principle, two molecules of nitrostyrene could react together, but this oxa-Michael-Henry reaction was never observed. In fact, also Xia, Xu and co-workers, who performed an enantioselective, organocatalytic oxa-Michael-nitro-Michael reaction, observed only the reaction with β-nitroolefins different from nitrovinylphenols.[12] The reaction afforded chiral chromane derivatives bearing three contiguous stereogenic centers (Scheme 2). The stereochemistry was assigned by X-ray analysis. Then, Andrés, Pedrosa and co-workers tested the reaction onto polymer-supported squaramides.[13] They prepared some monomers and found **Squa2** (Scheme 2) as the best. In fact a 5 mol% catalyst loading in dichloromethane at room temperature provided products in 65-88% yields with 63:27 to >99:1 dr, 70-> 99% ee (13 examples) after 12-72 h. The absolute configuration of the major isomer was once more (2*S*,3*S*,4*S*) and was established by X-ray analysis. The configuration of the minor isomer was instead established as (2*S*,3*R*,4*S*) by comparison of the ^{1}H-NMR coupling constants of the two diastereomers. Then **Squa2** was co-polymerized with styrene and divinylbenzene and the experiments were repeated (65-86% yields, 58:42 to >99:1 dr, 56-74% ee). The polymer-supported catalyst was also recovered and recycled five times without affecting yields and

selectivity. Authors were able to obtain the enantiomers by using **Squa3** (Scheme 2). The opposite stereochemistry was very likely due to a different assembly of the ternary complex formed by catalyst, nitroalkene and 2-hydroxynitrostyrene.



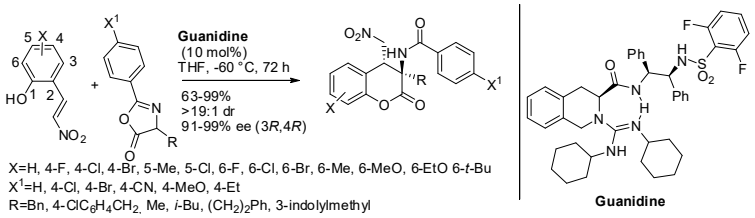
Scheme 2. Organocatalytic oxa-Michael nitro-Michael domino reaction.

A more general domino Michael/hemiacetalization with respect to that reported in Scheme 1 was reported by Zhao and co-workers (Scheme 3).[14] The hemiacetal intermediate was either oxidized to *cis*-3,4-disubstituted chroman-2-ones or dehydroxylated to chromanes. The reaction was scaled up to 0.5 mmol scale, without significant modification of yield and selectivity. The absolute stereochemistry was determined by the optical rotation of known compounds.



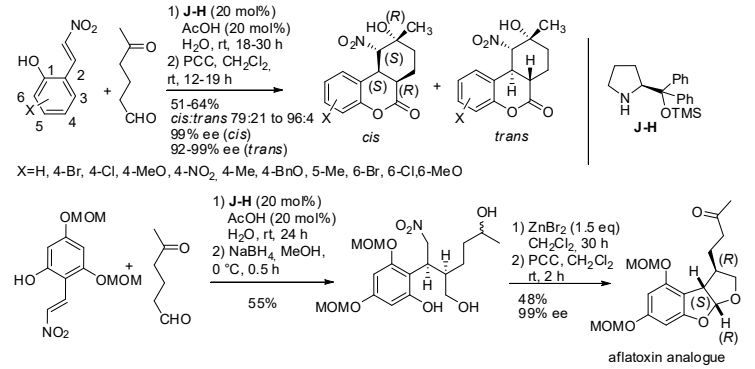
Scheme 3. Domino reaction catalyzed by **MDO** organocatalysts.

(*E*)-2-(2-Nitrovinyl)phenols were also allowed to react with azalactones (Scheme 4).[15] The required high excess (twelve-fold) of azlactone is certainly a drawback of this reaction. However, the reaction was also performed at a gram scale and 1.06 g were recovered in 84% yield with 92% ee and >19:1 dr. The absolute configuration was determined by X-ray analysis. It is noteworthy that these compounds have the opposite configuration at the 4-position with respect to all those reported in the above reactions.



Scheme 4. Chiral guanidine catalyzed cascade reaction of azalactones.

The Jørgensen-Hayashi catalyst allowed the enantioselective Michael-acetalization-Henry reaction of (*E*)-2-(2-nitrovinyl)phenols and 5-oxohexanal followed by oxidation with PCC, affording hexahydro-6*H*-benzo[c]chromenones with four stereogenic centers (Scheme 5).[16] Longer reaction times were required with electron-donating groups on the phenyl ring. During the reaction course three stereogenic centers were produced almost in single configuration, while the fourth stereogenic center was obtained in both configurations. However, the *cis* diastereomer was predominant. The aflatoxin skeleton was then obtained after reduction of these products, followed by Nef-cyclization with $ZnBr_2$.



Scheme 5. Cascade reaction of 2-hydroxynitrostyrene and 5-oxohexanal.

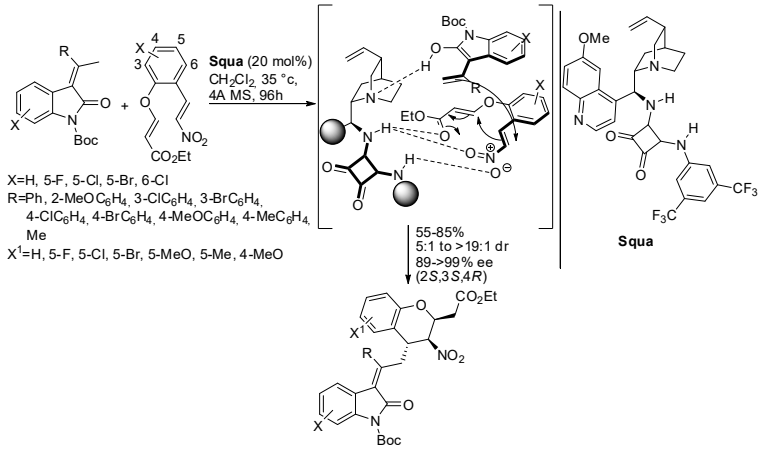
Recently, a reaction involving alkoxy nitrostyrenes instead of hydoxynitrostyrenes has been reported: that is the vinylogous Michael-Michael cascade reaction of 3-alkylidene oxindoles, with nitroolefin enolates (Scheme 6).[17] The reaction was also successfully extended to isopropylidene benzofuran-2-one and the desired was recovered in 59% yield with 10:1 dr and 93% ee. A gram-scale reaction afforded 1.23 g of the (67% yield, with 14:1 dr and 94% ee). The absolute configuration was determined by X-ray analysis. Finally, the reduction by $SnCl_2$ proceeded without affecting selectivity and affording an interesting chiral γ-amino acid ester structure.

3.2. From chalcones

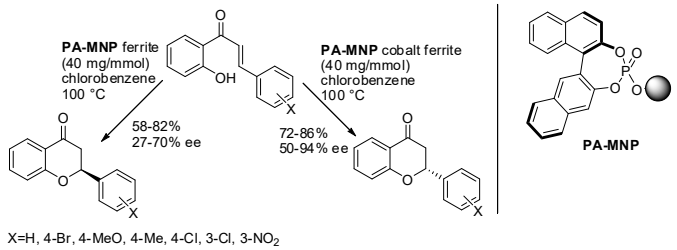
An interesting reaction was reported by Ranganath and co-workers in 2017 staring from 2′-hydroxychalcones [1-(2-hydroxyaryl) α,β-unsaturated aliphatic ketones.[18] They were able to obtain both enantiomers of the product with high enantioselectivity by employing two heterogeneous catalysts prepared from magnetite and cobalt ferrite nanoparticles with a binaphthol phosphate as the chiral ligand and confined into nanotubes (Scheme 7). The authors attributed the different stereochemistry to the confinement effect of the two different nanoparticles and to the π-interactions of aromatic groups with cobalt ferrite. No reaction was observed with 1-(2-hydroxyaryl) α,β-unsaturated aliphatic ketones. The catalyst can be easily recovered by external magnet and reused five times without a decrease in yield and selectivity.

A quite long asymmetric synthesis of 4-amino-3-hydroxybenzopyrans was performed starting from chalcones.[19] The asymmetric step was the synthesis of epoxy alcohols by a Corey-Bakshi-Shibata reduction

followed by Sharpless asymmetric epoxidation. Then alcohol protection, regioselective ring-opening with various amines, orthogonal protection of the new free alcohol group, deprotection of the other alcohol moiety, intramolecular nucleophilic aromatic substitution provided the products (Scheme 8). The reaction is quite complex, overall yields are low, authors do not explain if they deduced the configuration and ee from optical rotation and from what previous data and, finally, they did not give any information if the last steps affect either the diastereomeric or the enantiomeric excesses.



Scheme 6. Michael-Michael cascade reactions of 3-alkylidene oxindoles and nitroolefin enoates.



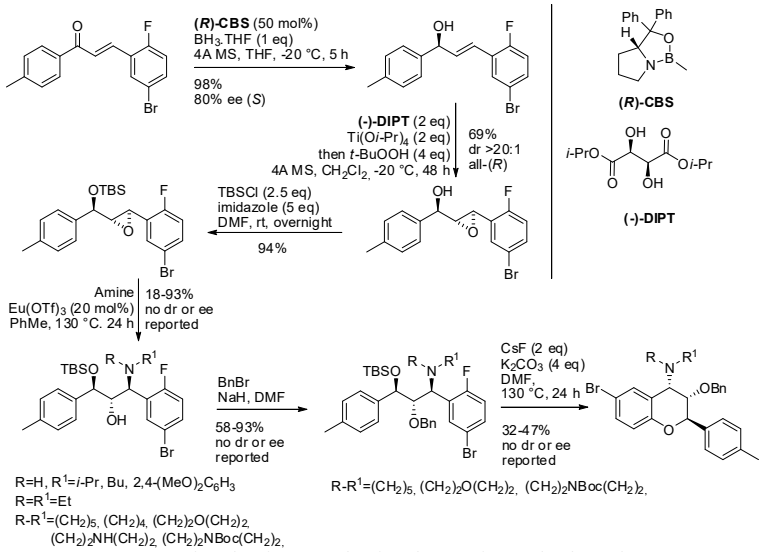
Scheme 7. Oxa-Michael addition of 2′-hydroxychalcones in carbon confined spaces.

3.3. From 2'-hydroxycinnamaldehydes

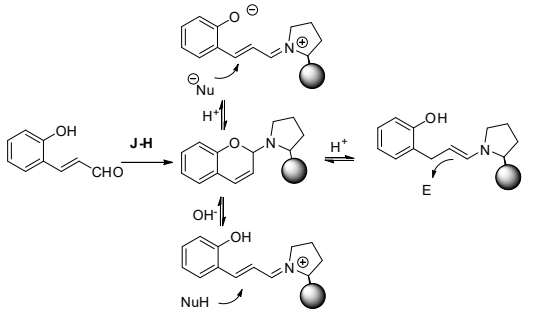
Many asymmetric synthesis of chromane derivatives have been performed starting from *o*-hydroxycinnamaldehydes. The Jørgensen-Hayashi class of catalysts is the best choice. In fact, it easily forms a relatively stable cyclic aminal, which, under basic conditions, is converted into a zwitterionic intermediate, or, under acidic conditions, into the iminium ion. Then both open-chain intermediates can be attacked by nucleophiles from the less hindered face. Alternatively, the acidic conditions can form an enamine that can attack electrophiles (Scheme 9).

An example of a reaction carried out under acidic conditions is the formal cycloaddition of *trans*-β-nitrostyrenes.[20] Recently, a diversity-oriented version of this reaction allowed preparing some different compounds (Scheme 10).[21] The Hantzsch ester can reduce either the 2-hydroxycinnamaldehyde or the *trans*-β-nitrostyrene. When the double bond of the aldehyde was reduced (Scheme 10, eq. 1), the reaction proceeded *via* enamine intermediate. The chroman-2-ol intermediate could be oxidized with PCC or treated with a base leading to chroman-2-ones or to polycyclic *O,O*-acetals with five adjacent stereocenters, respectively. It should be noted that significant amounts from iminium ion pathway (Scheme 10, eq. 2) lowered the yields with aliphatic *trans*-β-nitrostyrenes. If the nitrostyrene was reduced before adding the *o*-hydroxycinnamaldehydes (Scheme 10, eq. 2), the reaction exclusively occurred *via* iminium ion

intermediate, leading to open-chain compounds as a mixture of two diastereomers in different ratios, in which only the stereochemistry of the benzyl position is defined. The absolute configuration was determined by X-ray analysis of one of the tricyclic *O,O*-acetals and the other attributed by analogy.



Scheme 8. Enantioselective Synthesis of 4-Amino-3-hydroxybenzopyran.

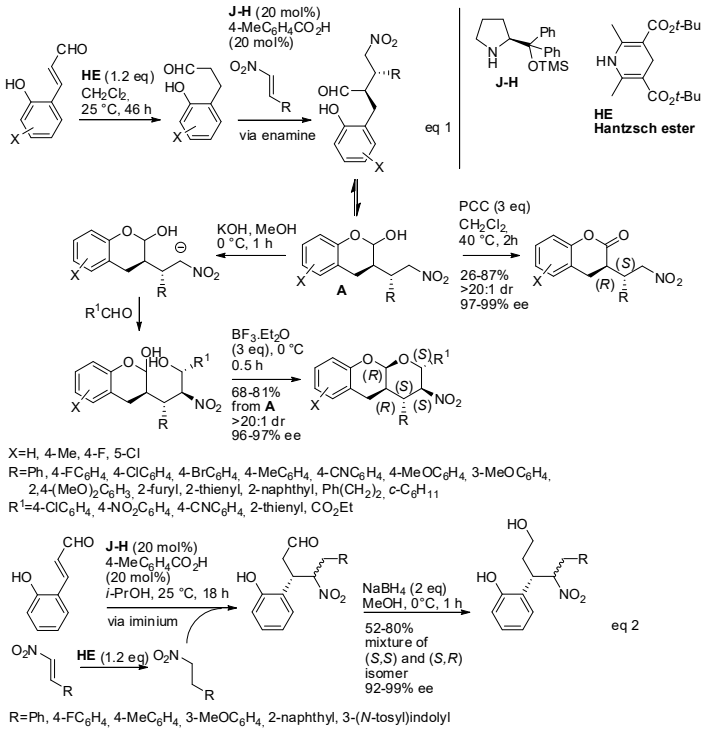


Scheme 9. The accepted mechanism for asymmetric reactions of *o*-hydroxycinnamaldehydes.

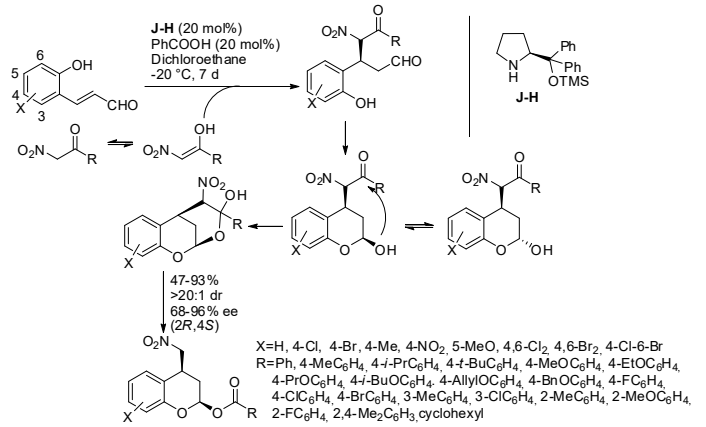
The synthesis of 4-(nitromethyl)chroman-2-ols can arise from *o*-hydroxynitrostyrene and aldehydes (Scheme 3) or from *o*-hydroxycinnamaldehydes and α-nitroalkanes *via* iminium ion pathway. In particular, with α-nitroketones (Scheme 11),[22] an acyl transfer can occur, thus avoiding the protection or the transformation of the unstable chroman-2-ol. However, the reaction suffered from steric reason: in fact, a *t*-butyl group in the 6 position of cinnamaldehyde impeded the reaction. Products were also successfully employed in further transformations. The absolute configuration was established by X-ray analysis.

The addition of diphenylphosphine oxide to *o*-hydroxycinnamaldehydes *via* zwitter ion pathway afforded 4-diphenylphosphinyl chroman-2-ols (Scheme 12).[23] Although yields are only moderate or good, the stereoselectivities are much higher diasteroselectivity with respect to the same reaction with nitromethane[24] or malonates.[25] The unstable chroman-2-ols were protected as acetates. The stereochemistry was determined by X-ray analysis. The asymmetric (*o*-anisyl)phenylphosphine oxide was also tested, and a 1:1 mixture of separable diastereomers was obtained in 84% yield with 85% and 94% ee, but the absolute

configuration of the chiral phosphorus was not identified. Some transformations of the products were also successfully carried out.



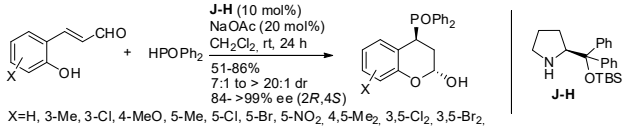
Scheme 10. Diversity-oriented one-pot syntheses starting from *o*-hydroxycinnamaldehydes.



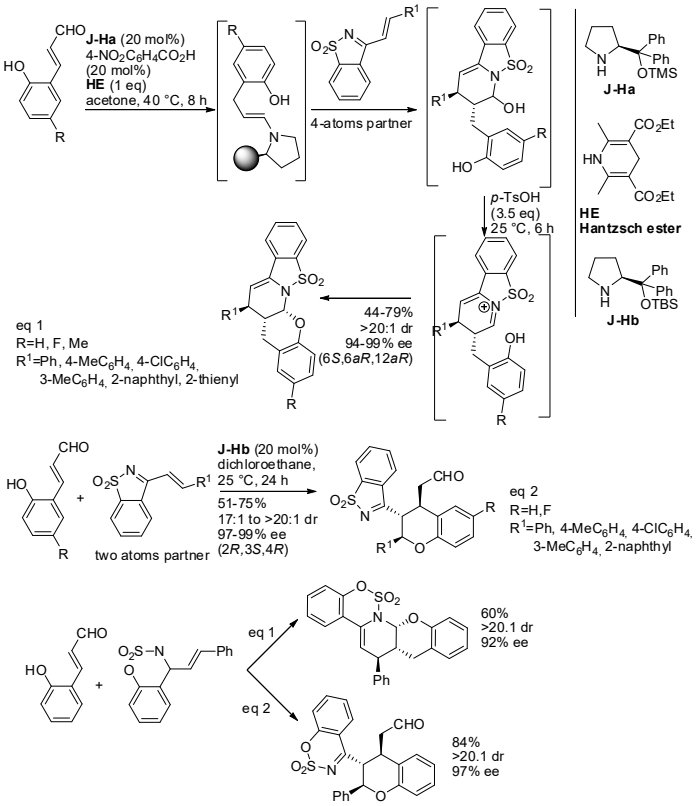
Scheme 11. Asymmetric Michael/hemiacetalization/acyl transfer reaction.

1-Aza-1,3-butadienes can work both as the four-atom and the two-carbon unit in the cycloaddition with *o*-hydroxycinnamaldehydes (Scheme 13).[26] As already depicted in Scheme 10, eq. 1, the Hantzsch ester reduced the 2-hydroxycinnamaldehydes to chroma-2-ols, which are the two-atoms partner in the cycloaddition reaction, then, the aminal intermediate was cyclized by medium acidification. On the other

hand, 2-hydroxycinnamaldehydes could work as a four-atom partner. This second reaction was also carried out in 0.5-mmol scale, and the product was successfully used for further transformations. The structure was determined by X-ray analysis on a product of each reaction.



Scheme 12. Asymmetric cyclization of *o*-hydroxycinnamaldehydes with diphenylphosphine oxide.

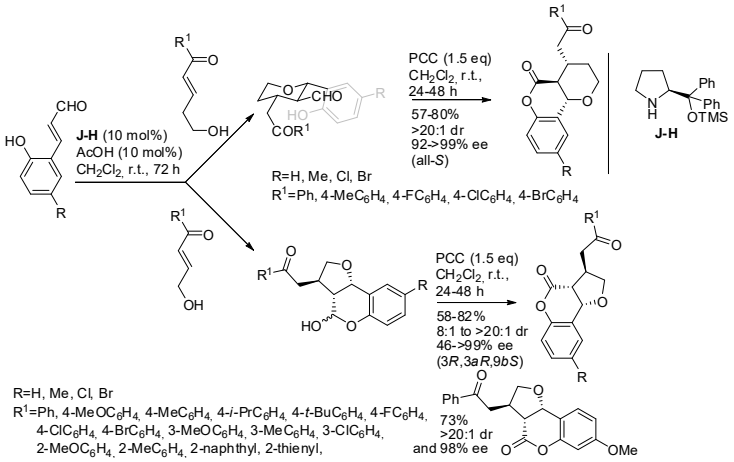


Scheme 13. Synthesis of chiral chromane-containing polyheterocyclic compounds.

2-Hydroxycinnamaldehydes and γ/δ-hydroxy enones reacted under iminium ion catalysis followed by oxidation with PCC and afforded tetrahydrofuran/tetrahydropyran-fused 3,4-dihydrocoumarin (Scheme 14).[27] The absolute configuration of products was determined by X-ray analysis. The hemiacetal intermediates arising from aliphatic γ-hydroxy enones could not be oxidized. However, they could be converted in acetals, or submitted to Wittig-Michael reaction without affecting the ArCO moiety, or converted into an allyl derivative with allyl trimethylsilane and $BF_3.Et_2O$. Finally, they could be also reduced with triethylsilane and $BF_3.OEt_2$ with the exclusive reduction of the hemiacetal group at -78 °C, and also of the ArCO moiety at 0 °C. All these reaction maintained high enantiopurity.

Some papers on the reaction of 2-hydroxycinnamaldehydes and bis-indolyl derivatives have been recently reported. In the most ancient paper, the target spiro-bridged compounds were obtained as a mixture of the diastereomers (3*R*,6′*S*,13′*S*) and (3*S*,6′*S*,13′*S*) with high enantiomeric excess (Scheme 15, eq. 1),[28]

because the organocatalyst only controlled the stereochemistry of the 4-position of the chroman-2-ol intermediate (see also Scheme 10, eq. 2). The preparation of chroman-2-ols before submitting them to the reaction with 3-indolyl-3-methoxyoxindoles and the use of a different catalyst (Scheme 15, eq. 2) did not overcome this drawback. In fact, a mixture of the diastereomers (5a*R*,11*R*,11a*R*) and (5a*R*,11*S*,11a*R*) with high enantiomeric excess was once more obtained. The absolute configurations of both spiro-bridged and spiro-fused products were determined by X-ray analysis. The synthetic utility of these compounds was also tested, and some transformations were successfully carried out.



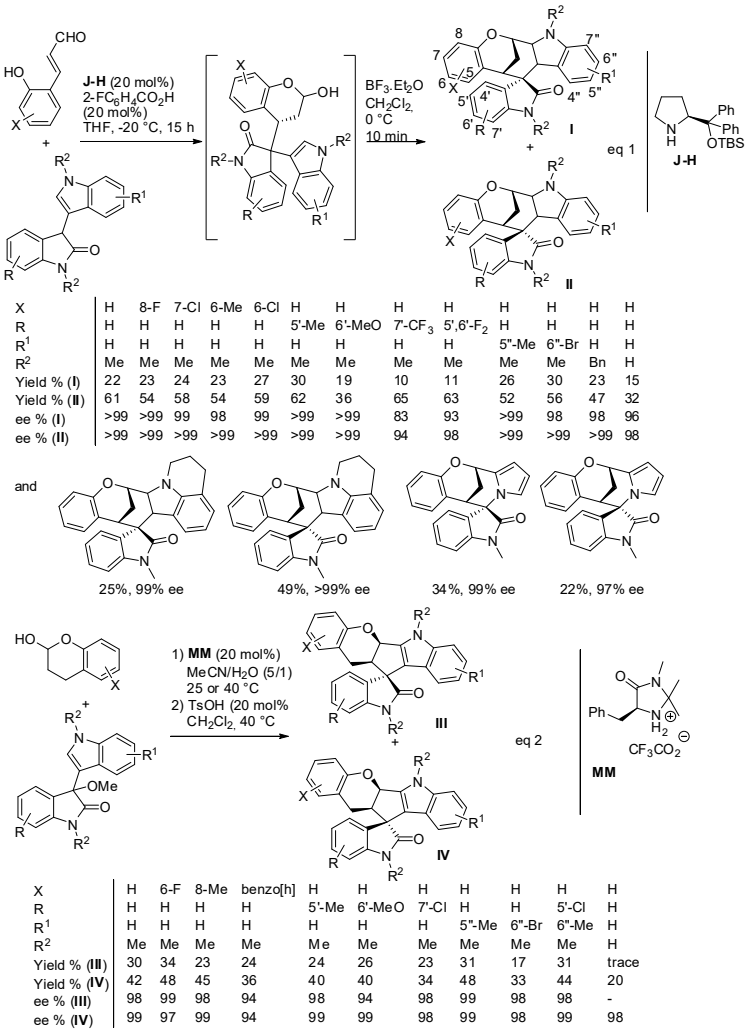
Scheme 14. Synthesis of tetrahydrofuran/tetrahydropyran-fused 3,4-dihydrocoumarins.

Then the research group studied the reaction with *N*-sulfonyl ketimines (Scheme 16).[29] Comparing this reaction with that depicted in Scheme 13, it is clear the role of the exocyclic double bond in the governance of the reaction pathway. The conjugate addition of *N*-sulfonyl ketimines to 2-hydroxycinnamaldehydes gave an inseparable equilibrating mixture of isomers, but the oxidation with PCC or the dehydration of this mixture led to bridged benzo-fused aminals. The reaction can be scaled up to 1 mmol with similar results and extended to *N*-protected 2-amino cinnamaldehydes. It should be noted that the reaction of the six-membered cyclic *N*-sulfonyl ketimine did not give any bridged compound after oxidation. To increase the significance of the reaction some chemical transformations of these compounds were successfully carried out.

Then the authors set up the reaction with acyclic *N*-tosyl ketimines (Scheme 17).[30] Interestingly, the scarcely reactive acyclic *N*-tosyl ketimine reacted without the addition of a base for their deprotonation. The reaction was solvent dependent: in CH_2Cl_2 provided bridged hemiaminals with excellent enantioselectivity as a single diastereomer; in acetone/H_2O, 4:1 open-chain product were recovered, which can be treated with $BF_3{\cdot}Et_2O$ at -20 °C to furnish bridged aminals. In the former conditions, NAc or NCbz ketimines gave low yields and selectivity, while NSO_2Ph gave similar results. Bulky ketimines did not provided bridged cycloadducts, but chromane aminals, which were characterized after Wittig reaction with $Ph_3P{=}CHCO_2Et$. The bridged hemiaminals can be efficiently opened with $BF_3{\cdot}Et_2O$ at -20 °C. The absolute configuration depicted in Scheme 16 was assigned by means of TD-DFT calculations of the electronic circular dichroism spectra. In acetone/H_2O, 4:1, 2-amino cinnamaldehyde also reacted leading to the product in 60% yield and 96% ee. Many transformations were carried out on these products without affecting enantioselectivity. The absolute configuration depicted in Scheme 16 was assigned by X-ray analysis.

A fourth synthesis allowed the preparation of a 6,6,5-bridged or a 6,6,6-bridged ring system from β-oxoesters (Scheme 18).[31] The 6,6,5-bridged compound was obtained after oxidation of the oxoester with *m*-CPBA. Conversely from many reactions involving the Jørgensen-Hayashi catalyst, in which an acidic additive must activate the catalyst, in the present reaction the reduced *m*-chlorobenzoic acid must be neutralized in order to obtain the products. 2-Furyl substituted oxoester afforded an inseparable 3:1 mixture

of epimers. The 2:1 mixture of epimers from aliphatic oxoester is instead separable. The reaction with *N*-protected 2-amino cinnamaldehydes gave worse yields. The structure depicted in Scheme 18 was determined by X-ray analysis. Moreover, several transformations were successfully attempted on these products.



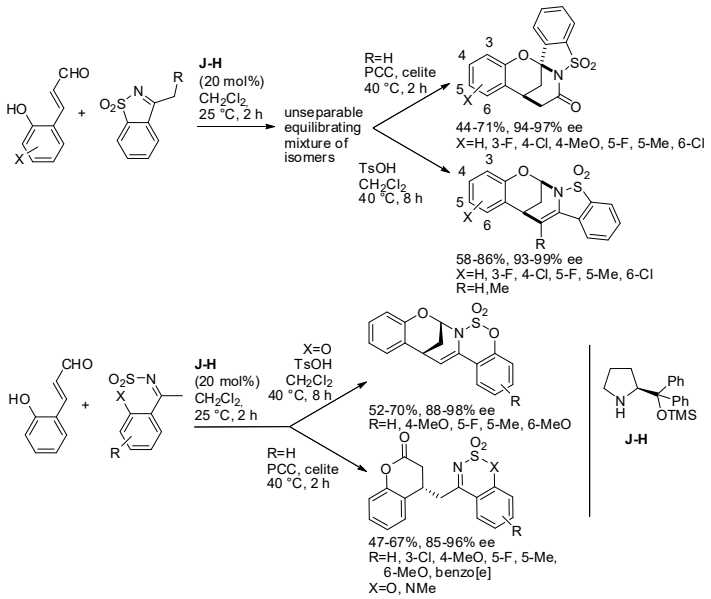
X	H	8-F	7-Cl	6-Me	6-Cl	H	H	H	H	H	H	H	H
R	H	H	H	H	H	5'-Me	6'-MeO	7'-CF_3	5',6'-F_2	H	H	H	H
R^1	H	H	H	H	H	H	H	H	H	5''-Me	6''-Br	H	H
R^2	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Bn	H
Yield % (**I**)	22	23	24	23	27	30	19	10	11	26	30	23	15
Yield % (**II**)	61	54	58	54	59	62	36	65	63	52	56	47	32
ee % (**I**)	>99	>99	99	98	99	>99	>99	83	93	>99	98	98	96
ee % (**II**)	>99	>99	>99	>99	>99	>99	>99	94	98	>99	>99	>99	98

X	H	6-F	8-Me	benzo[h]	H	H	H	H	H	H	H
R	H	H	H	H	5'-Me	6'-MeO	7'-Cl	H	H	5'-Cl	H
R^1	H	H	H	H	H	H	H	5''-Me	6''-Br	6''-Me	H
R^2	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	H
Yield % (**III**)	30	34	23	24	24	26	23	31	17	31	trace
Yield % (**IV**)	42	48	45	36	40	40	34	48	33	44	20
ee % (**III**)	98	99	98	94	98	94	98	99	98	98	-
ee % (**IV**)	99	97	99	94	99	99	98	99	98	99	98

Scheme 15. Synthesis of spiro-bridged and spiro-fused chromane derivatives.

A bifunctional tertiary amine-thiourea catalyst activated cyclic β-oxoaldehydes in the reaction with the iminium ion from 2-hydroxycinnamaldehyde (Scheme 19).[32] Benzofused oxoaldehydes led to spiro-bridged hemiacetal products, and the reaction was scaled up to a 1 mmol scale without affecting yields and selectivity. The less reactive aliphatic cyclic oxoaldehydes gave cage-like polycyclic hemiacetal products in longer reaction times. Further chemical transformations on the products did not affect stereoselectivity. The absolute configuration of both spiro-bridged and cage-like products was determined by X-ray analysis. Attempts to recover the catalyst were unsuccessful. Thus, the authors set up a rather curious procedure: they charged 100 mol% catalysts and added the reactants, waited the complete consumption of reactants, added

fresh reactants and repeated the procedure five times. Product was recovered with a slightly lower average yield and comparable stereochemistry, and the reaction was faster. However, in our opinion, this procedure did not demonstrate the recyclability of the catalyst, but that, at the last stage, a 20 mol% was still active. They should have loaded only 20 mol% of catalyst and then add fresh portions of reactants and see if the reaction went on. The higher reaction rate was obvious because in the first steps the catalyst is much more abundant.



Scheme 16. Divergent synthesis of chiral bridged and spiro-bridged benzofused aminals.

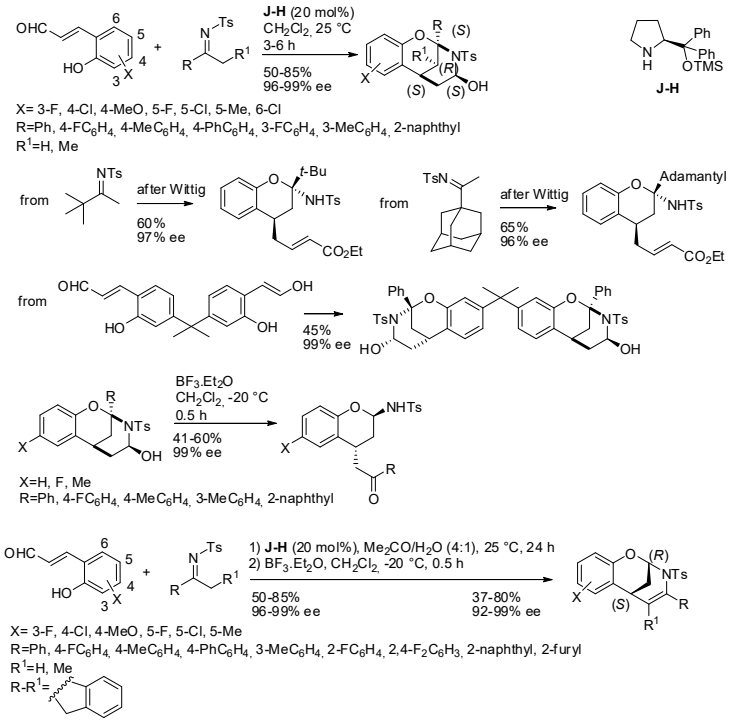
Finally, the same research group reported another asymmetric multi-catalytic tandem Michael/cyclization reaction, that is the reaction between 2-hydroxycinnamaldehydes and 4-hydroxycoumarins leading to enantioenriched chiral benzofused 2,8-dioxabicyclo[3.3.1]nonanes (Scheme 20).[33] It should be noted that 6-substituted 2-hydroxycinnamaldehydes gave the corresponding products with low enantioselectivities (6-23% ee). The absolute configuration of both spiro-bridged and cage-like products was determined by X-ray analysis. Some useful transformations of the products were performed without affecting stereoselectivity. A 1-mmol scale reaction provided 220 mg of product with 75% yield and 96% ee. In this paper authors provided experiments to elucidate the mechanism and then proposed that the Jørgensen-Hayashi catalysts formed the iminium intermediate according to Scheme 9, while the thiourea catalyst served the dual function of activating the phenoxide anion and the enolic 1,3-dicarbonyl substrate through three hydrogen bonds.

3.1. From other derivatives

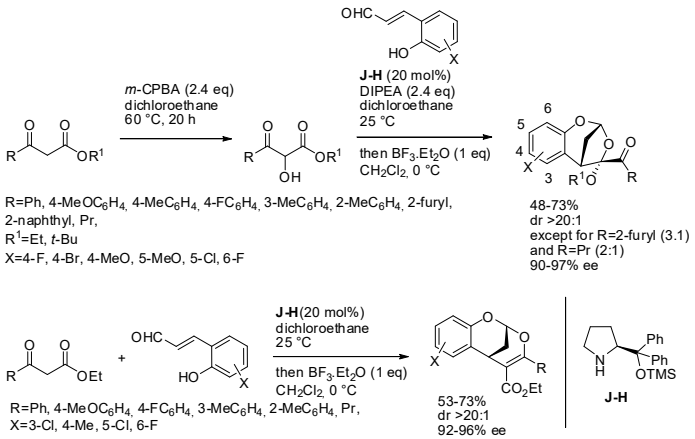
The imine from salicylaldehyde can be deprotonated by a base leading to an azomethine ylide, which in turn can undergo 1,3-dipolar cycloaddition, for instance with 2-hydoxybenzylidene indandiones.[34] Among the racemic examples, authors also tried a organocatalyzed reaction by a squaramide chiral base (Scheme 21). The absolute configuration of products was established via X-ray analysis. *Ortho*-substituted salicylaldehyde derivatives were unreactive, perhaps for steric hindrance. Authors did not report mechanisms.

A malonate bearing an *ortho*-hydroxybenzoyl group, having one electrophilic and three nucleophilic sites, is a great candidate for cascade reactions. Thus an *N*-heterocyclic carbene is able to catalyze the synthesis of enantioenriched cyclopenta[c]-fused chromenones by reaction of these substrates with

α,β-unsaturated aldehydes (Scheme 22).[35] It is worth noting the control of the reactivity of the substrate, which led to a very high chemoselectivity. The reaction did not work with pent-2-enal or phenyl rings with three consecutive substituents. The absolute configuration of compounds was determined by X-ray analysis. DFT calculations demonstrated that the δ-lactonization mechanism is more thermodynamically favored with respect to the β-lactonization analysis, thus authors envisaged the mechanism depicted in Scheme 22.

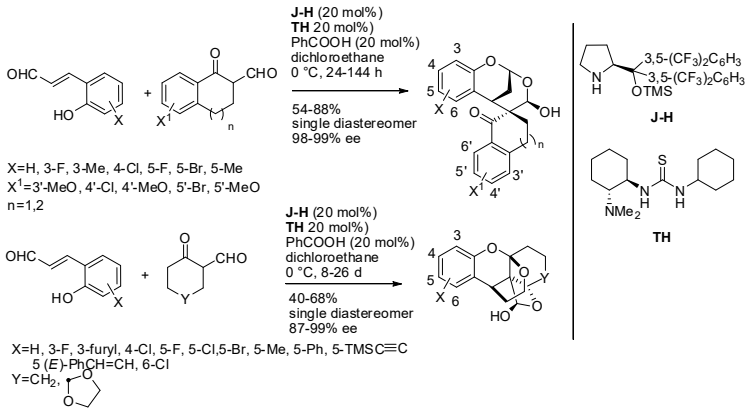


Scheme 17. Reaction of 2-hydroxycinnamaldehydes and acyclic *N*-tosyl ketimines.

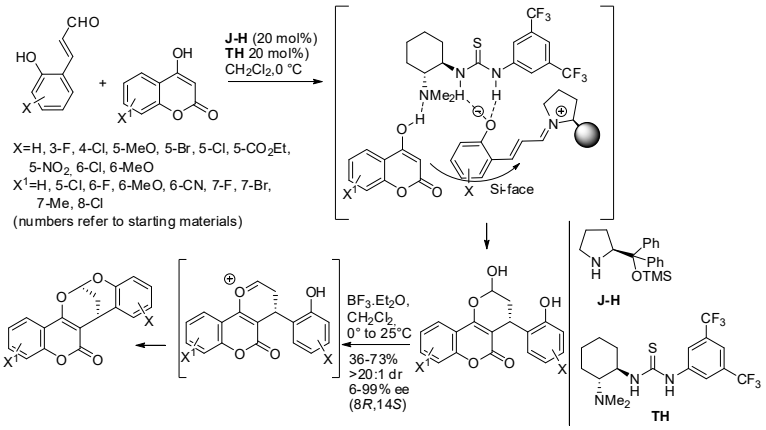


Scheme 18. Synthesis of chiral acetal-containing bridged cyclic compounds.

The intramolecular Alder-ene reaction of 1,7-dienes is a useful method for the synthesis of nonracemic functionalized heterocyclic compounds. Recently, it was applied to the synthesis of chromane derivatives (Scheme 23).[36] It was found that: (i) increasing steric hindrance of the ester group the diasteroselectivity increased; (ii) long chain olefin needed 10 mol% catalyst loading; (iii) lower yields and dr values were obtained with 5- or 6-substituted phenyl rings; (iv) naphthyl ring gave only 49% yield, with 6:1 dr and 20% ee. The absolute configuration of compounds was determined by X-ray analysis. When diastereomeric ratios are low, the enantiomeric excess of the minor isomer is reported in the paper, but they are not copied here for sake of simplicity. The reaction was also extended to the synthesis of benzothiopyran and tetrahydroquinolines, and in this last case the reaction was also scaled up to gram scale. Interestingly one of the compounds was efficiently transformed into a tetrahydropyranochromene skeleton typical of potentially antiproliferative, polyphenolic compounds isolated from *Alpinia blepharocalyx*.



Scheme 19. Construction of spiro-bridged or cage-like polyheterocyclic compounds.



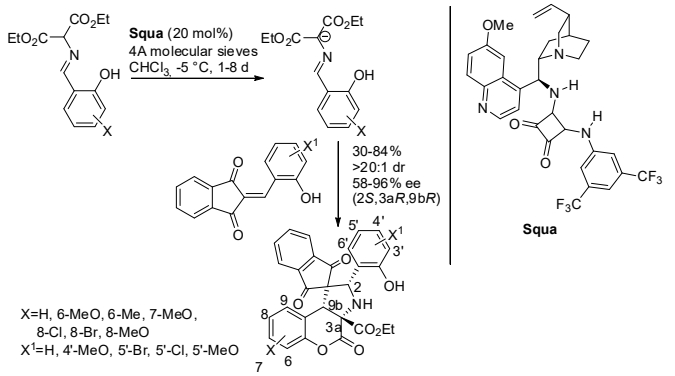
Scheme 20. Asymmetric multicatalytic reaction sequence to construct bridged bicyclic acetals.

4. Cycloaddition of *ortho*-quinone methides

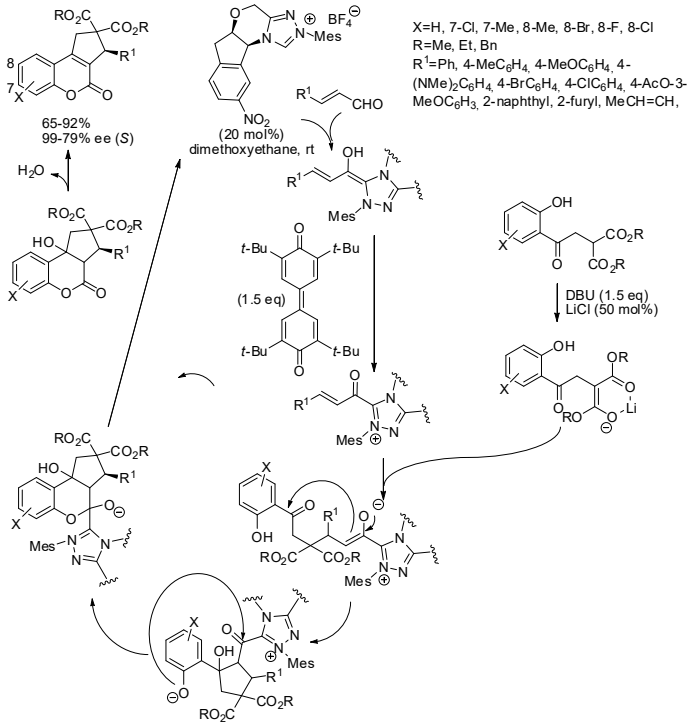
The cycloaddition of both stable and *in situ* prepared *o*-quinone methides is a classical method for preparing the benzopyran nucleus.[37]

In the last years, two papers described this reaction referring to chiral reactions but, actually they are only diasteroselective reactions. Those are: (i) the organocatalytic dearomative [4+2] cycloadditions of biomass-derived 2,5-dimethylfuran with (-)-camphor sulfonic acid as the catalyst, in which authors reported

excellent diasteroselectivities but not enantiomeric excesses;[38] (ii) the Diels-Alder reaction between the *o*-quinone methides of resorcin[4]arene and styrenes, which provided only two of the possible diastereoisomers but in a racemic form.[39]



Scheme 21. Chromenopyrrolidines from azomethine ylides and 2-hydroxybenzylideneindandiones *via* [3+2] cycloaddition.

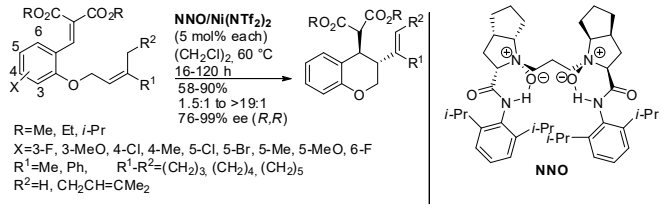


Scheme 22. Quadruple domino reactions for the asymmetric synthesis of cyclopenta[c]chromenones.

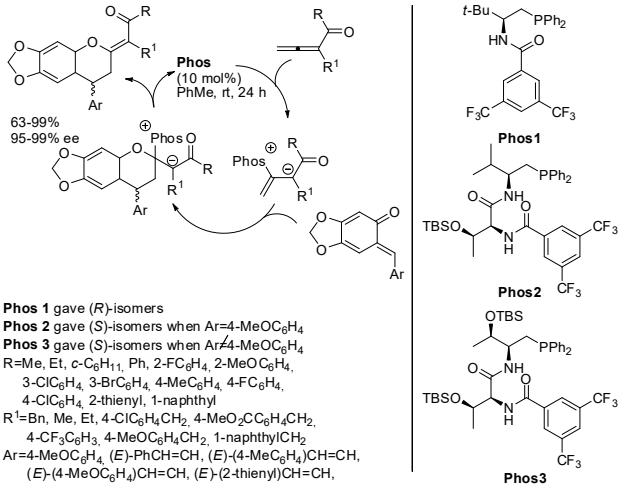
Some reactions were set up with stable *o*-quinone methides, but the useful substrates are very scarce, thus the reactions are not widely applicable even if highly efficient.

For instance, allene ketones were allowed to react with stable *o*-quinone methides (Scheme 24).[40] Interestingly, changing the catalyst both enantiomers can be obtained. However, a particular catalysts had to

be used when Ar=4-MeOC$_6$H$_4$ in the quinone methides in order to obtain the (*S*)-isomer. The (*S*)-configuration was determined by X-ray analysis and the (*R*) deduced as a consequence. The reaction worked also with *in situ* prepared *o*-quinone methides, thus enlarging the scope of the reaction. Moreover, the reaction was successfully scaled up to 1 mmol. The mechanism suggested by the authors was not supported by experimental evidence or *ab initio* calculations.



Scheme 23. Chromanes from Alder-ene reaction of 1,7-dienes

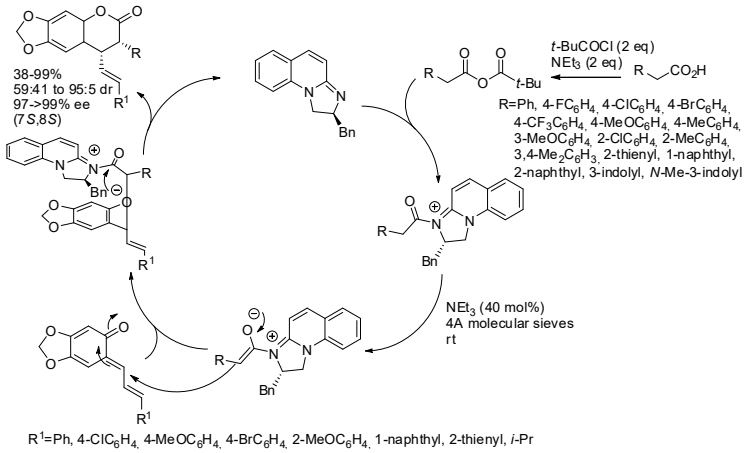


Scheme 24. Asymmetric [4+2] annulation of allenic ketones with *ortho*-quinone methides.

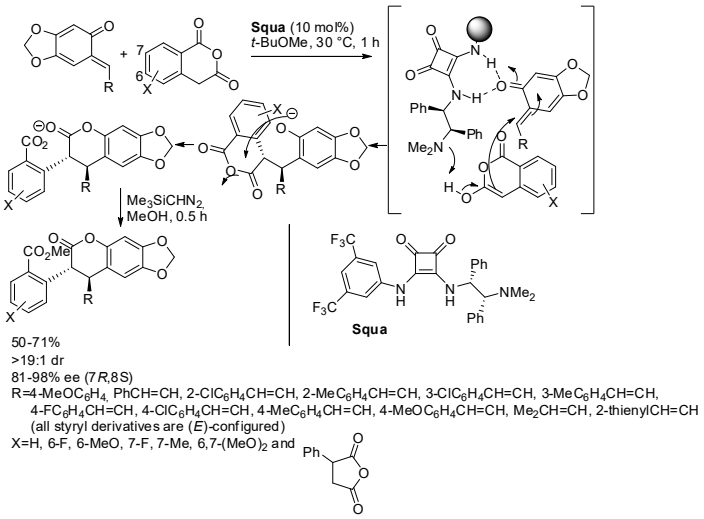
Some examples are applied to enolizable ketones as the two-atom partner. Among them a chiral amidine-derivative catalyzed tandem Michael addition-lactonization of enolizable carboxylic acids (Scheme 25).[41] Unfortunately, all diastereomeric mixtures were inseparable except that arising from the reaction of indole-3-acetic acid. *N*-protected indole gave better results than *N*-H indole. The absolute configuration of products was determined by X-ray analysis. The authors envisaged the mechanism depicted in Scheme 25, without providing evidence for it.

Chiral squaramides with a tertiary amine framework are other useful catalysts, because they can deprotonate the carbonyl compound generating an enolate and an ionic interaction catalyst-substrate and, at the same time, link the *o*-quinone methides by hydrogen bonds. These catalysts were used in the reaction both of enolizable homophthalic anhydrides or a succinic anhydride (Scheme 26).[42] and of aryl β-keto acylpyrazoles (Scheme 27).[43] The absolute configuration of products in both reactions was determined by X-ray analysis. Although these reactions are formal asymmetric [4+2] cyclization, they are actually stepwise reactions (see the mechanism envisaged by authors depicted in Schemes 26).

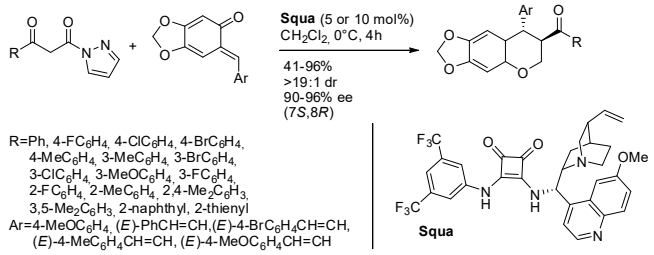
The first reaction was scaled up to 1 mmol with a slight decrease in yield while maintaining excellent stereoselectivity. The second one could bot applied to aliphatic β-keto acylpyrazoles, which were unreactive. The reaction was also attempted on an *o*-quinone methide generated *in situ*, but, albeit it proceeded smoothly, both yield and enantioselectivity were low.



Scheme 25. [4+2] Cycloadditions of *o*-quinone methides catalyzed by amidine.



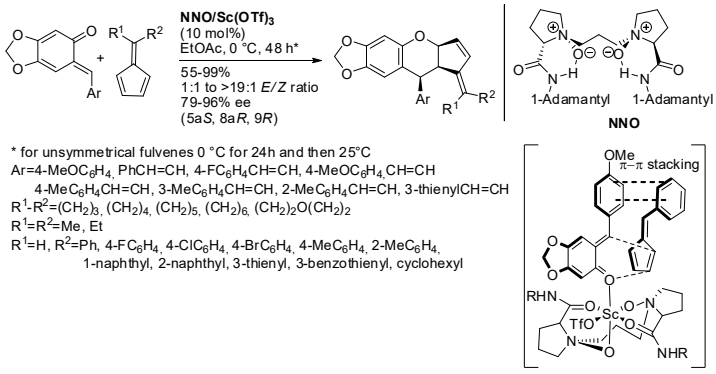
Scheme 26. Asymmetric [4+2] addition of enolizable homophthalic anhydrides to *ortho*-quinone methides.



Scheme 27. Asymmetric [4+2] addition of aryl β-keto acylpyrazoles to *ortho*-quinone methides.

Instead chiral metal complexes catalyzed true enantioenriched [4+2] cycloadditions. In fact, a chiral *N,N'*-dioxide/Sc(III) complex allowed the asymmetric reaction of *o*-quinone methides with fulvenes

(Scheme 28).[44] Unsymmetrical fulvenes gave poor *E/Z* ratios (1:1 to 4:1 instead of >19:1 for symmetrical fulvenes), but the substrates containing aliphatic cyclohexyl groups have better ratios than those containing aromatic rings. Thus authors envisaged a π–π stacking between *o*-quinone methides and fulvenes in the transition state to account for these low ratios. The absolute configuration of products was determined by X-ray analysis. In a gram-scale reaction 1.153 g (99% yields with 92% ee) were obtained from a symmetrical fulvene.



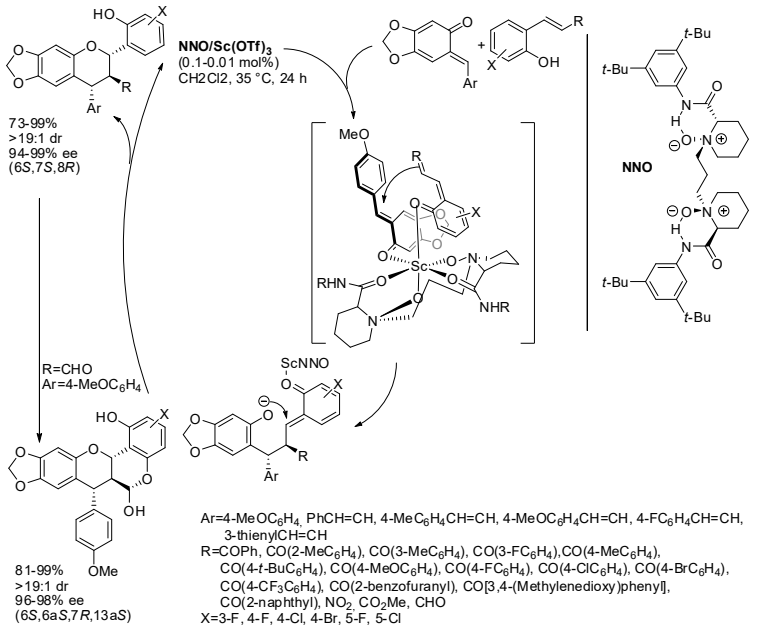
Scheme 28. Reaction of *o*-quinone methides with fulvenes.

The same research group found that another scandium chiral *N,N′*-dioxide complex (0.1-0.01 mol %) allowed the reaction of *o*-quinone methides with *o*-hydroxyphenyl α,β-unsaturated compounds (Scheme 29).[45] 2-Hydroxychalcones, 2-hydroxynitrostyrenes, 2-hydroxyphenyl-acrylate and 2-hydroxyphenylacroleins worked as two atom partner in this reaction. In the last substrate a double cyclization occurred and hexahydropyrano[4,3-b]chromanes with four adjacent stereocenters were obtained. The absolute configuration of products was determined by X-ray analysis. A gram-scale reaction produced 1.41 g (98% yield) of the product in 99% ee. Some control experiments were carried out to elucidate the reaction mechanism, and on these basis authors proposed the mechanism depicted in Scheme 29. Finally, *in situ* generated *o*-quinone methides from *ortho*-hydroxybenzyl alcohols were tested and products were obtained in 70-99% yields, with >19:1 dr and 98-99% ee (6 examples). If stable *o*-quinone methides are rare, *ortho*-alkylphenols, bearing a leaving group in the benzylic position, can *in situ* form *o*-quinone methides by acid or basic catalysis. If the catalyst is a chiral acid or base, we can obtain enantioenriched product.

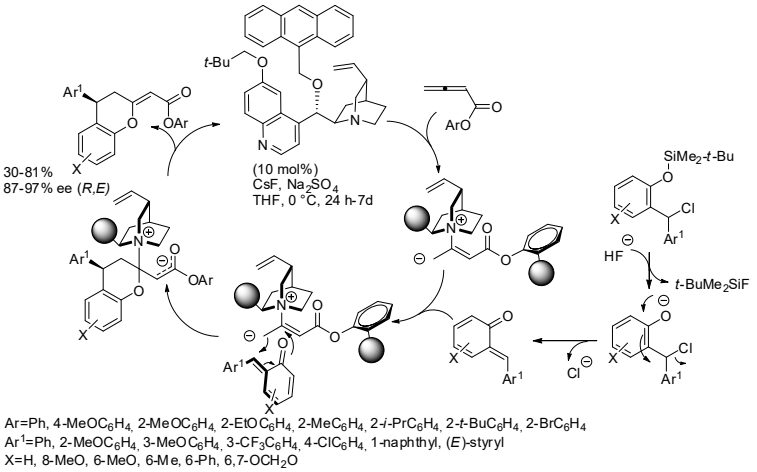
In the reactions described above, authors sometimes attempted the reaction with *in situ* generated *o*-quinone methides,[40,43,45] but there are also successful reactions completely devoted to *in situ* generated *o*-quinone methides. The reaction with allenoates, reported by Fan and co-workers, is an example.[46] *o*-Quinone methides were generated by fluorine deprotection of 2-silyloxybenzyl chlorides and allowed to react with *ortho*-substituted aryl butadienoates (Scheme 30). Phenyl- and 4-methoxyphenyl-butadienoates gave the expected products, but in lower yields, while 2,6-dimethylphenylbutadienoate was unreactive, perhaps for steric hindrance. The absolute configuration was determined by X-ray analysis. It should be noted that 6-arylmethylidenebenzo[*d*][1,3]dioxol-5(6*H*)-ones are stable, while their precursors are not.

However, *o*-hydroxybenzhydryl alcohols are the more classical starting material for the *in situ* preparation of *o*-quinone methides. For instance, they are widely employed in the reaction with enolizable carbonyl compounds. All these reactions required significant amounts of enol in the keto-enol tautomerism for their occurrence; used chiral phosphoric acids as the catalysts, which had to form at least two hydrogen bonds to give the three-membered *o*-quinone methide-catalyst-enol intermediate responsible of the enantioselectivity. The reaction of *o*-hydroxybenzhydryl alcohols with β-keto acids follows this pattern to give 2,4-diaryl-1-benzopyrans after decarboxylation and dehydration (Scheme 31).[47] The absolute configuration of products was determined by comparison of their optical values with the literature. The reaction was scaled up to gram scale with a 78% yield and 91% ee. In the mechanism proposed by authors, the chiral phosphoric acid promoted the dehydration of the *o*-hydroxybenzhydryl alcohols, the

decarboxylation of the β-keto acids and determined the stereochemistry, while scandium triflate promoted cyclization and dehydration of the lactol intermediate.



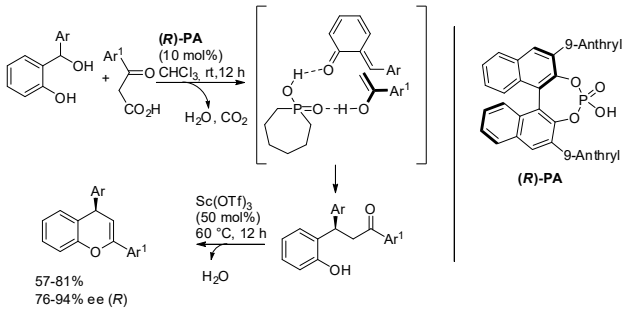
Scheme 29. Reaction of *o*-quinone methides with *o*-hydroxyphenyl α,β-unsaturated compounds.



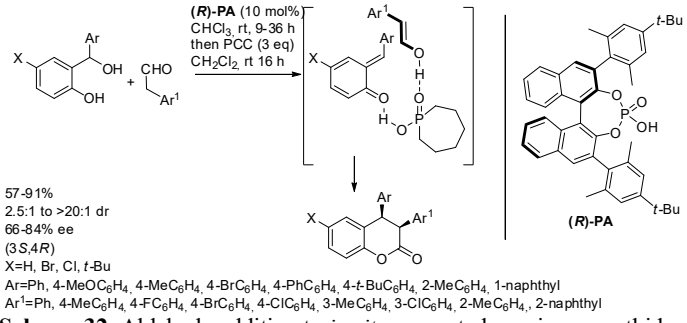
Scheme 30. Asymmetric [4+2] annulation of allenic esters with *ortho*-quinone methides.

The group of Schneider group prepared *cis*-3,4-diarylchromanols from acetaldehydes (Scheme 32).[48] Also in this reaction, *ortho* substitution in the aryl group of *o*-hydroxybenzhydryl alcohol enhanced the enantioselectivity (see also above ref. 46). Diasteroselectivity was generally low (only 3-4:1), because the acidic conditions could open the lactol intermediate, so that the *cis/trans* ratio was dynamic. However, authors found that a 4-methoxy group in the *o*-hydroxybenzhydryl alcohol locked the equilibrium leading to a >20:1 *cis/trans* ratio, but they did not give an explanation. The very low enol content in the keto-enol

tautomerism of aliphatic aldehydes did not allow the reaction occurrence. Then the lactol intermediate was transformed into a variety of other useful compounds.

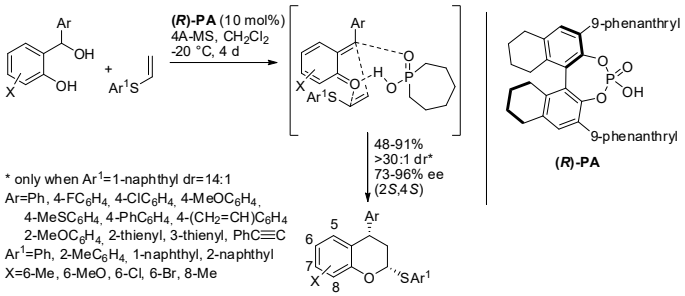


Scheme 31. Decarboxylative alkylation of β-keto acids to *o*-quinone methides.



Scheme 32. Aldehyde addition to *in situ* generated *o*-quinone methides.

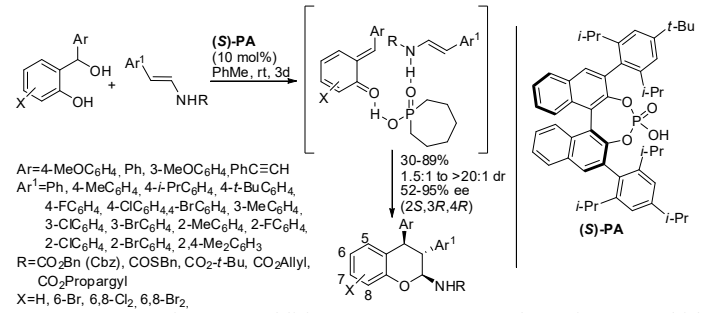
Also stable alkenes have been employed as partner in the [4+2] cycloaddition with *o*-quinone methides. An example was the reaction of vinyl sulfides setup by Wang and Sun (Scheme 33).[49] The absolute configuration was determined by X-ray analysis. The absence of sites for hydrogen bond interaction between vinyl sulfides and the catalysts made the authors speculate a transition, in which only the *o*-quinone methide has effective interaction with the catalyst. A gram-scale synthesis allowed the recovery of 1.41 g of product (88% yield, >30:1 dr, 91% ee).



Scheme 33. Vinyl sulfides addition to *in situ* generated *o*-quinone methides.

The products were efficiently oxidized to sulfone and then some transformations were performed essentially maintaining the enantiopurity of the products. In particular, the syntheses of 2,3-unsubstituted chromane and chromenes are interesting, because the direct cycloaddition with ethylene and acetylene cannot be performed.

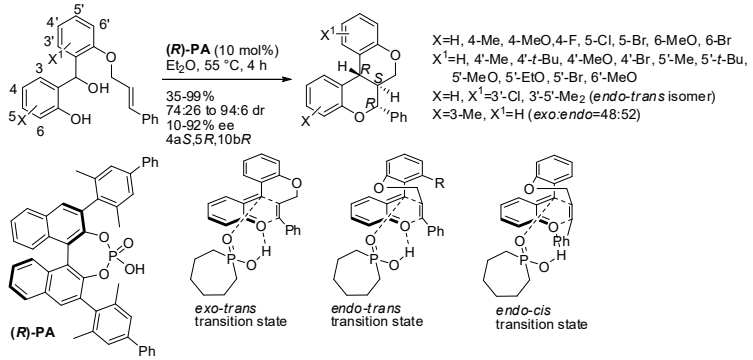
Acyclic enecarbamates are another simple alkene, which can undergo to [4+2] cycloaddition with *o*-quinone methides (Scheme 34).[50] The reaction was sluggish when Ar=4-$MeOC_6H_4$, X=6,8-Cl_2, 6,8-Br_2, R=Cbz (only 30-33% yields after 3-6 days at 50 °C). The absolute configuration was determined by the Mosher amide method.



Scheme 34. Enecarbamates addition to *in situ* generated *o*-quinone methides.

Very recently, a reaction, in which the staring material provided the chirality, has been reported[51] that is the $FeCl_3$ catalyzed synthesis of enantioenriched benzopyran from a (*S,E*)-crotyl silane. However, the catalyst promoted both a [4+2] cycloaddition and a 1,4-addition reaction; therefore a mixture of products was obtained, albeit the benzopyrans are always recovered as a single diastereomer, while conjugate addition products were recovered as a mixture of diastereomers.

Benzhydryl alcohols with a double bond at a suitable distance to give stable five- or six-membered can give an intramolecular version of this reaction (Scheme 35).[52] The phenyl ring denoted with the index "prime" in Scheme 35 is peculiar for the reaction occurrence; in fact, simple benzyl alcohols with suitable double bonds were unreactive. On the other hand, also cinnamyl ether is peculiar to the reaction, because prenyl and phenylpropargylic ethers gave very low enantioselectivity, while other allyl- or vinyl ethers did not react at all. (*E*)-Cinnamyl ethers led to *exo-trans* compounds, while the (*Z*)-cinnamyl ethers led to the *endo-cis* product, but with very low ee's.

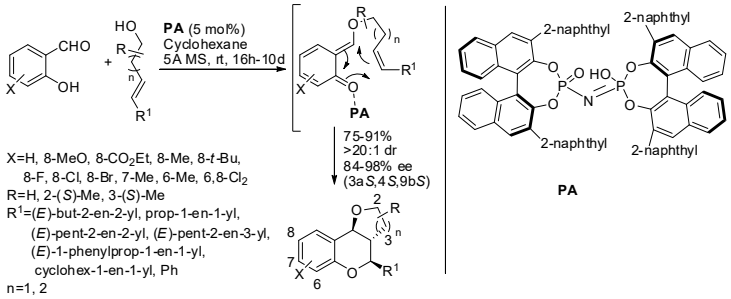


Scheme 35. Intramolecular oxa-Diels-Alder reaction of *ortho*-quinone methides.

When the 3′-position (see Scheme 34) was occupied, the *endo-trans*-isomers were recovered from (*E*)-cinnamyl ethers. On the other hand, when the 3-position (see Scheme 34) was occupied, a fast

equilibrium between *E*- and *Z*-configured *o*-quinone methide occurs, thus the *endo*-*exo*-selectivity was completely lost. The absolute configuration of products was determined by X-ray analysis. In a large-scale experiment (3.30 mmol) 913 mg (80% yield, 92:8 dr, 92% ee), and 530 mg, (51% yield, single diastereomer, 50% ee) were recovered from (*E*)- and (*Z*)-products respectively.

A particular *o*-quinone methides arose from salicylaldehydes and they were allowed to react with unsaturated alcohols (Scheme 36).[53] The absolute configuration of products was determined by X-ray analysis. Chiral unsaturated alcohols retained the configuration, thus authors setup a kinetic resolution from racemic chiral unsaturated alcohols. Moreover, some experiments allowed envisaging a [4+2] addition mechanism, but the authors did not rule out a stepwise mechanism.



Scheme 36. Furano- and pyrano-chromanes from asymmetric intramolecular [4+2] cycloaddition.

2,6-Di-*t*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dienone is a stable *p*-quinone methide, which under acidic conditions, is in equilibrium with an *o*-quinone methide structure, and, consequently it can undergo [4+2] addition as above. The isomerization energy was calculated by DFT and was found to be very low (7.0 kcal/mol).[54] However, also a 1,6-conjugated addition can explain the reactivity of this compound, so that all papers generally justified the observed stereochemistry with both mechanisms (Scheme 37). For instance, this substrate allowed the preparation of dihydrocoumarins from azlactones (Scheme 37).[55] A gram-scale reaction worked with a lower loading of the catalyst (3 mol% *vs.* 5 mol%) and gave the product in higher yield (87% *vs.* 65%), but with little low enantiomeric excess (95% *vs.* 98%). The products were also submitted to some transformation in order to discover the potentiality of the reaction. The absolute configuration of products was determined by X-ray analysis.

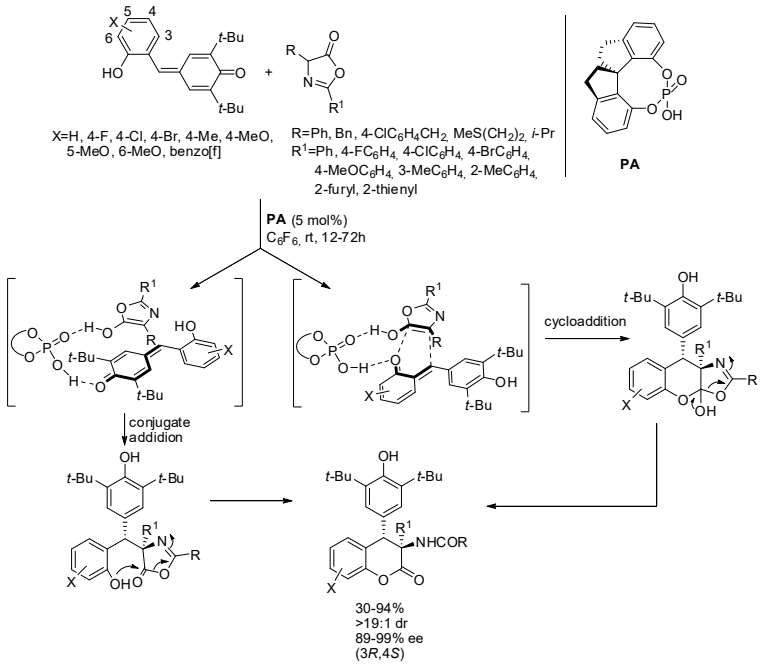
Another example from the same research allowed the synthesis of spiro-dihydrocoumarins (Scheme 38).[56] If all *p*-quinone methides gave high diasteroselectivity (>19:1) in the reaction with 1-oxotetralin-2-carbaldehyde, varying the aldehydes diasteroselectivity ranged from 1.5:1 to >19:1. The absolute configuration of products was determined by X-ray analysis. The reaction was scaled up to gram-scale, without significant modification of yield and selectivity. The products were also submitted to some transformation in order to discover the potentiality of the reaction and only the de-*tert*-butylation (Tf_2O/TfOH at 60 °C) gave racemization, very likely for the higher required temperature.

The reaction with enamides afforded products in high yields and selectivity (Scheme 39).[54] The only exception was when X=H, X^1=4-MeO, in which the diastereomeric ratio was only 64:36. The absolute configuration of products was determined by X-ray analysis. A gram-scale reaction gave product in a 96% yield with 95:5 dr and 96% ee.

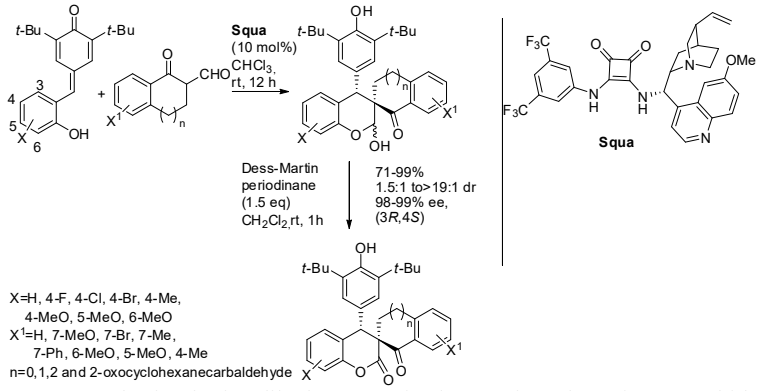
3-Alkyl-2-vinylindoles were also used as reactants and the NH group of indole was found to be very important, in fact, *N*-methyl-protected indole was unreactive (Scheme 40).[57] Clearly in the transition state, a hydrogen bond between the chiral phosphoric acid and the NH group of indole and another with the OH group of the substrate (in a fashion of a 1,6-conjugate addition), or with the OH group of the *o*-quinone methide form (in a fashion of a [4+2] cycloaddition) must be involved. The absolute configuration of products was determined by X-ray analysis. The reaction was scaled up to gram scale, and product was recovered in 96% yield with >95:5 dr and 96% ee.

Finally, two papers reported the reaction of 2,6-di-*t*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dienone with isocyanates[58] and isoxazolones,[59] affording benzoxazin-2-one and spiro-isoxazolonechromans,

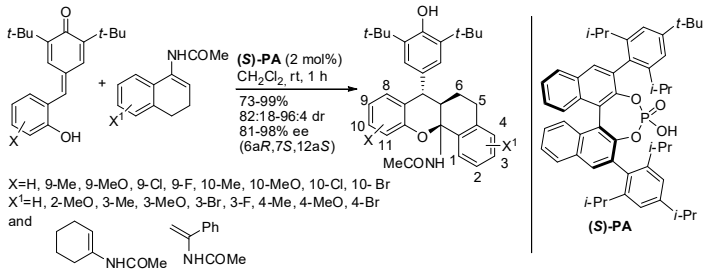
respectively. Both papers mainly described the reaction, under asymmetric conditions and envisaged a 1,6-conjugate addition mechanism. Only at the end of the papers, an example of the asymmetric version was reported. In the reaction with isocyanates, a series of chiral phosphoric acids gave the product in moderate to high yields, but without any enantioselectivity. On the other hand, a squaramide {namely 3-[(1*R*,2*R*)-2-(piperidin-1-yl)cyclohexylamino]-4-(4-(trifluoromethyl)phenylamino)cyclobut-3-ene-1,2-dione} gave 4-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-tosyl-3,4-dihydro-2H-benzo[1,3-e]oxazin-2-one in 98% yield with 56% ee, while the (*S,S*) squaramide led to the enantiomer in 95% yield with 30% ee (absolute configurations not reported). In the reaction with isoxazolones, the chiral catalyst was quinine and 4-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3′-methyl-2-(*p*-tolyl)-5′H-spiro[chromane-3,4′-isoxazol]5′-one was recovered in 82% yield with 21:79 dr and 11/48% ee (absolute configuration not reported).



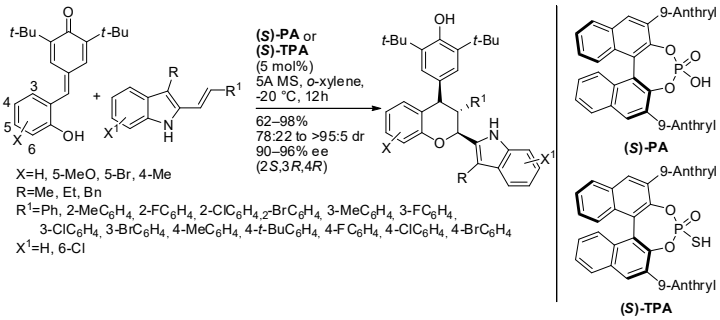
Scheme 37. Cycloannulation of *p*-quinone methides with azlactones.



Scheme 38. Synthesis of spiro-dihydrocoumarins by reaction of *p*-quinone methides and 1-oxotetralin-2-carbaldehydes.



Scheme 39. Acetamido-substituted tetrahydroxanthenes by reaction of *p*-quinone methides and enamides.

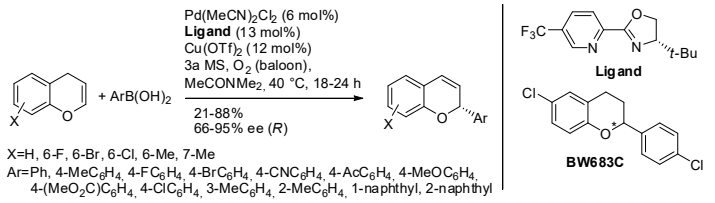


Scheme 40. Reaction of *p*-quinone methides with 3-alkyl-2-vinylindoles.

5. Asymmetric alkylation

The asymmetric synthesis of the benzopyran derivatives mainly contemplates the *de novo* construction of the pyran ring. However, some interesting asymmetric alkylations of the benzopyran ring have been reported in recent years and they are described in this section.

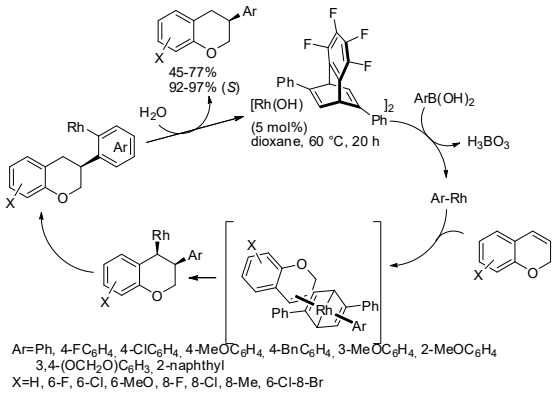
The Pd-catalyzed oxidative Heck reaction of 4*H*-chromenes and arylboronic acids in the presence of a chiral pyridine-oxazole ligand is an example of this reaction (Scheme 41).[60] It was found that 6- and 7-Me 4H-chromenes gave the lowest enantioselectivity, and that electron-withdrawing substituted arylboronic acids gave unknown side products. No envisaged mechanism or transition state was reported to explain the observed stereochemistry. The absolute configuration of products was determined by comparison of their optical values with the literature. One of the synthesized compounds was easily converted in the potent antiviral compound BW683C (4′,6-dichloroflavan).



Scheme 41. Palladium-catalyzed asymmetric redox-relay Heck reaction.

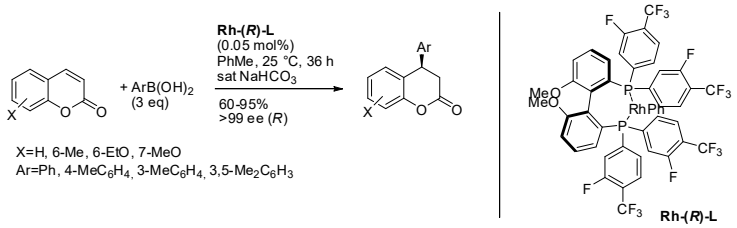
Arylboronic acids were also added to 2*H*-chromenes in the presence of a chiral rhodium catalyst to give 3-arylchromanes (Scheme 42).[61] The reaction was also unsuccessfully attempted with 2*H*-thiochromene or 1,1-dimethyl-1,2-dihydronaphthalene, while 1,2-dihydroquinoline afforded the expected product in 76% yields with 97% ee. The absolute configuration was attributed by comparison of optical rotation with the known values. The observed stereochemistry was explained by authors with a transition state, which

minimizes the steric repulsions between the substituent on the diene ligand and the benzo moiety. Moreover, deuterium-labeling experiments accounted for 1,4-Rh shift before the final protonolysis.



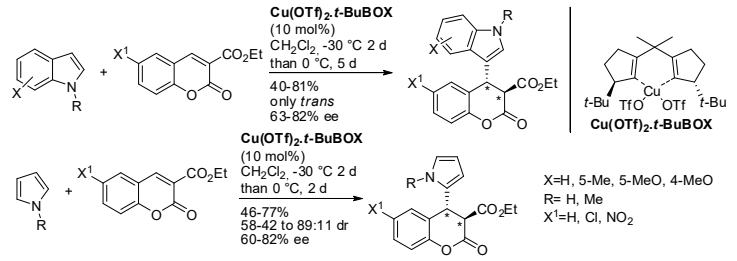
Scheme 42. Asymmetric addition of arylboronic acids to 2*H*-chromenes.

In section 2, we already reported that Korenaga and co-workers designed the best rhodium ligand for the alkylation of coumarins with boronic acids.[7] The catalyst was then tested and the good obtained results are reported in Scheme 43. It should be noted that a hydroxy group on the coumarin substrate inhibited the catalyst, while arylboronic acid bearing an electron-withdrawing group such as a chlorine atom competitively decomposed under the reaction conditions, drastically lowering yields (25%). The reaction was also successfully scaled up to 15-gram scale.



Scheme 43. Rhodium catalyzed alkylation of coumarins.

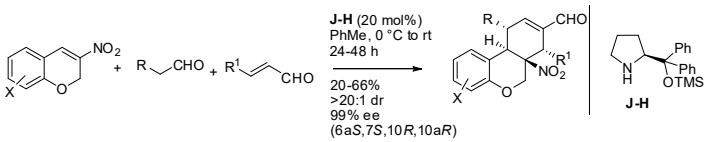
Indoles and pyrroles were added to coumarin-3-carbonylates under different chiral BOX complexes (Scheme 44).[62] Many combinations of triflate salts with different BOX compounds were tested. Among them a heterogeneous catalyst showed better yield than the homogeneous catalyst (80% vs. 59%) but it did not improve the enantioselectivity, so the reaction scope was carried out under the best homogeneous complex.



Scheme 44. Asymmetric addition of indoles and pyrroles to coumarin-3-carboxylates.

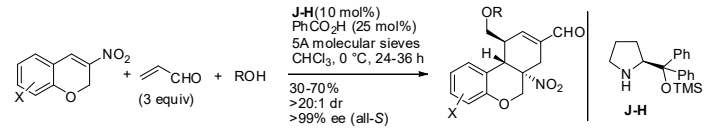
Authors did not report the absolute configuration of their products and only affirmed that a *trans* relationship is present.

Enders' group reported two asymmetric cascade reactions of nitro-chromenes: (i) with aliphatic aldehydes, and α,β-unsaturated aldehydes (Scheme 45),[63] or (ii) with two equivalents of α,β-unsaturated aldehydes and an alcohol (Scheme 46),[64] providing tricyclic compounds. In both reactions, the surmised reaction mechanism is a classical sequence of enamine, iminium ion, intermediates, some transformations of the products were successfully carried out without affecting stereoselectivity and the absolute configuration of products was determined by X-ray analysis. A gram-scale reaction provided 0.87 g of product (42% yields, with 20:1 dr and >99% ee) and 0.619 g of product (41% yields, with 20:1 dr and >99% ee), in reaction (i) and (ii), respectively. The drawbacks of the first reaction were: 2-nitro-3*H*-benzo[*f*]chromane gave product in only 20% yield; 7-(diethylamino)-3-nitro-2*H*-chromene, 1-nitrocyclohex-1-ene, 2*H*-chromene-3-carbonitrile, isovaleraldehyde and *t*-butyl acetaldehyde were unreactive. The drawbacks of the second reaction were: methyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate and 2*H*-chromene-3-carbonitrile as the substrate, as well as benzylthiol and dimethyl phosphite as the nucleophiles failed to give the products.



X=H, 6-F, 6-Cl, 6-Br, 6-NO_2, 6-MeO, 6-Me, 7-MeO, 6,8-Cl_2, 6,8-I_2, 6,8-(*t*-Bu)$_2$
R=Me, Et, Pr, Bn
R^1=Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-$MeOC_6H_4$, H, Me

Scheme 45. Triple domino reaction of nitro-chromenes with aliphatic aldehydes, and α,β-unsaturated aldehydes.



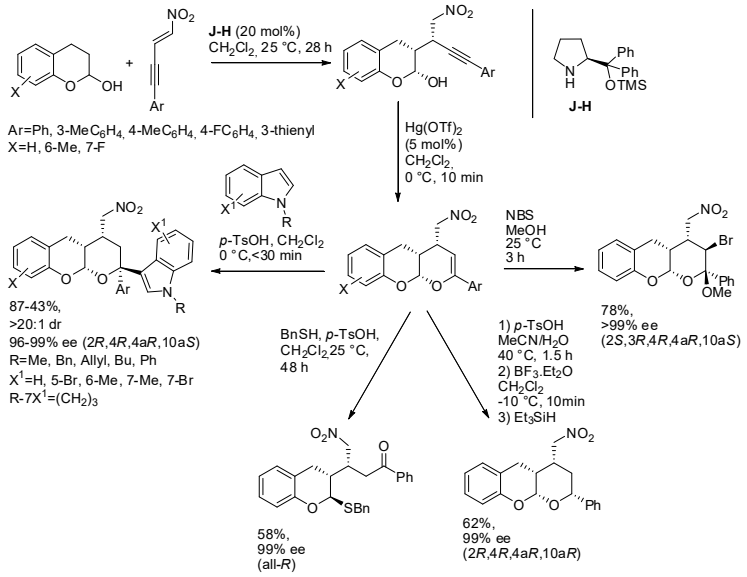
X=H, 6-F, 6-Cl, 6-Br, 6-NO_2, 6-MeO, 6-Me, 7-MeO, 7-Me, 8-MeO, 8-Allyl, 6,8-Cl_2, 6,8-Br_2, 6,8-I_2, 6,8-(*t*-Bu)$_2$
R=Me, Et, Pr, *i*-Pr, Bn, Ph_2CH, Allyl, Propargyl

Scheme 46. Quadruple domino reaction of nitro-chromenes with α,β-unsaturated aldehydes and alcohols.

The asymmetric reaction of chroman-2-ols and (*E*)-4-nitrobut-3-en-1-ynes led to an enantioenriched 3-alkyllactol, which can then undergo ring-closure to tricyclic compounds (Scheme 47).[65] The absolute configuration of products was determined by X-ray analysis. These compounds were then submitted to the addition of some nucleophiles: *N*-alkylindoles were the most efficient; benzyl mercaptan opened the cycle; triethylsilane reduced the double bond; and *N*-bromosuccinimide in methanol gave the addition of BrOMe; ethanol did not react.

4-Hydroxycoumarins were asymmetrically alkylated by oxidative β-functionalization of ketones in the presence of 2-iodoxybenzoic acid (Scheme 48, eq. 1).[66] Many cyclic and aliphatic ketones reacted, but not cyclopentanone. The reaction was scaled up and 1.23 g product (95% yield with 94% ee) was recovered. The desymmetrization of 4-methyl cyclohexanone was also performed in a one-pot two-stage reaction, leading to desired product in 86% yield and with 82% ee as a single diastereoisomer. The absolute configuration was determined by comparing optical rotation with literature and is described in the paper as (*S*)-(+) for cyclic ketones and (*R*)-(−) for acyclic ones. On the other hand, starting from α,β-unsaturated ketones the oxidation step is not required. Actually, C2-symmetric squaramide-based primary diamines allowed the Michael asymmetric addition of 4-hydroxycoumarin to α,β-unsaturated ketones (Scheme 48, eq. 2).[67] Both enantiomers of the anticoagulant warfarin and some its derivatives were prepared by this method. The absolute configuration was attributed by comparison of the product with known (*S*)-warfarin. Being the catalyst poorly soluble, catalyst recycles was attempted, but yield and enantioselectivity significantly decreased at every cycle. The catalyst deactivation was attributed by authors to by-side reactions of key

iminium ions. The reaction was also scaled up to 1.62 g of 4-hydroxycoumarin without affecting yields and enantioselectivity.



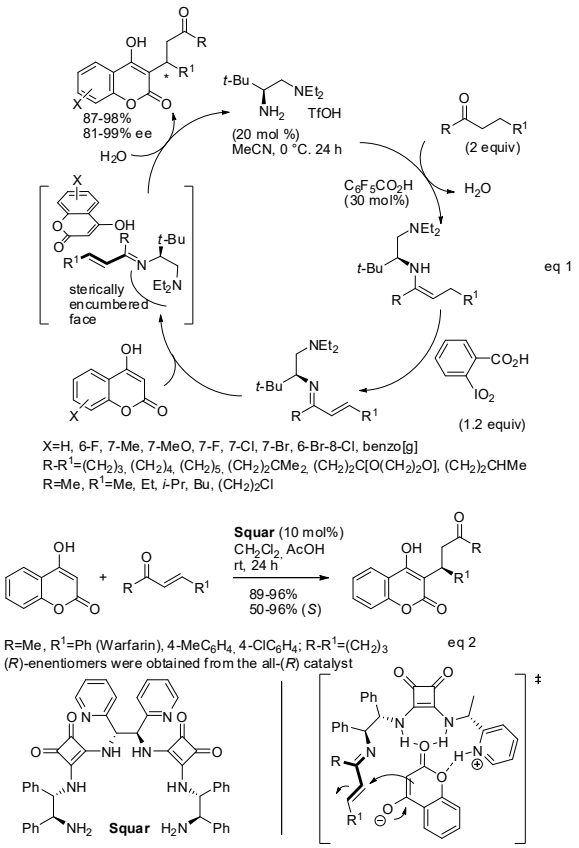
Scheme 47. Reaction of chroman-2-ols and (*E*)-4-nitrobut-3-en-1-ynes.

Bez and co-workers reported the multi-component reaction of 6-amino-1,3-dimethyluracil, 4-hydroxycoumarin and aldehydes with a L-proline derived bifunctional amidothiourea.[68] Although this catalyst is asymmetric, authors did not found any stereoselectivity in the final coumarin-based unsymmetrical trisubstituted methanes. In fact, at 10 °C, the reaction did not occur, while, at room temperature or higher, there was no enantioselectivity.

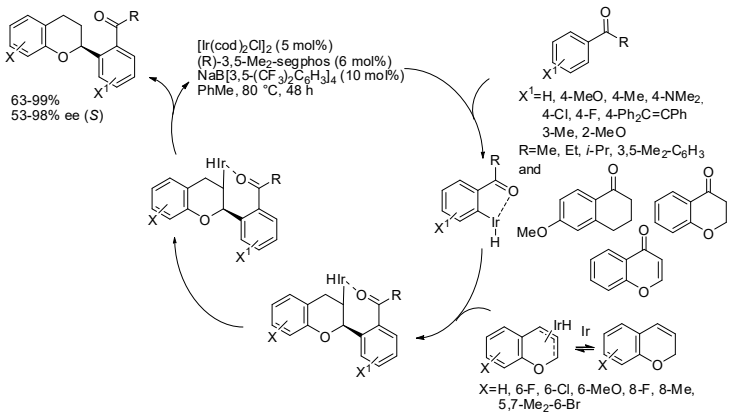
The research group of Nishimura performed the asymmetric hydroarylation of 2*H*-chromenes with aromatic ketones by an iridium/chiral phosphine complex (Scheme 49).[69] Authors provided evidences by deuterium labeling experiments and DFT calculations that the reaction proceeded via olefin isomerization, followed by enantioselective hydroarylation. When Ar=4-[Ph_2C=C(Ph)]C_6H_4; R=Me and Ar=4-$MeOC_6H_4$; R=3,5$Me_2C_6H_3CH_2$ (*R*)-Binap was used instead of (*R*)-3,5-dimethylsegphos and the products were recovered in 95% yield with 81% ee and 97% yield with 53% ee, respectively. The reaction was also successfully applied to benzodioxane (89% yields with 70% ee). The absolute configuration of the products was assigned by transforming into the known chiral flavan one of the products.

The asymmetric hydroboration of 2*H*-chromenes was performed with a chiral copper complex (Scheme 50).[70] Conversely, from the above reported hydroarylation, no double bond isomerization was observed, and therefore the 3-substituted chromane was recovered. The electronic property of the substituents on the phenyl ring influenced the enantioselectivity: electron-withdrawing groups, benzo[h]- and benzo[g]chromenes gave lower enantioselectivities than electron-donating substituents. Authors did not give product stereochemistry but only a positive optical rotation.[71] Some transformations of the products were successfully carried out without affecting stereoselectivity.

Finally, in a paper aimed at enhancing the properties of chiral silanediols as chiral catalysts, the addition of ketene acetals to chromanones was realized.[72] The reaction conditions allowed the *in situ* generation of benzopyrylium ions, which are hydrogen bonded to the silanediol before addition of the ketene acetal. Authors reported a 50-90% yield range and up to 56% ee, but they reported neither what nor how many substrates submitted to neither the reaction nor the stereochemistry of the main enantiomer (only a positive optical rotation was given for the sole product reported in the experimental section).



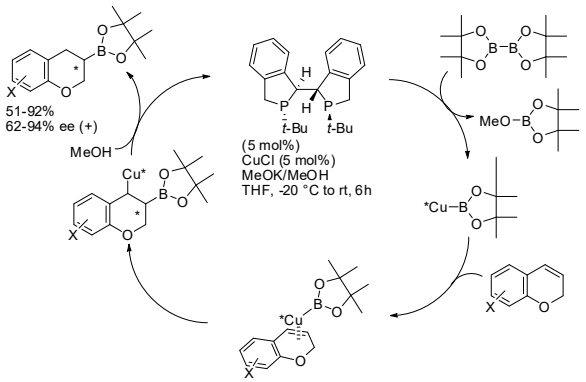
Scheme 48. Reaction of 4-hydroxycoumarins and ketones.



Scheme 49. Iridium-catalyzed asymmetric hydroarylation of chromanes.

6. Desymmetrization

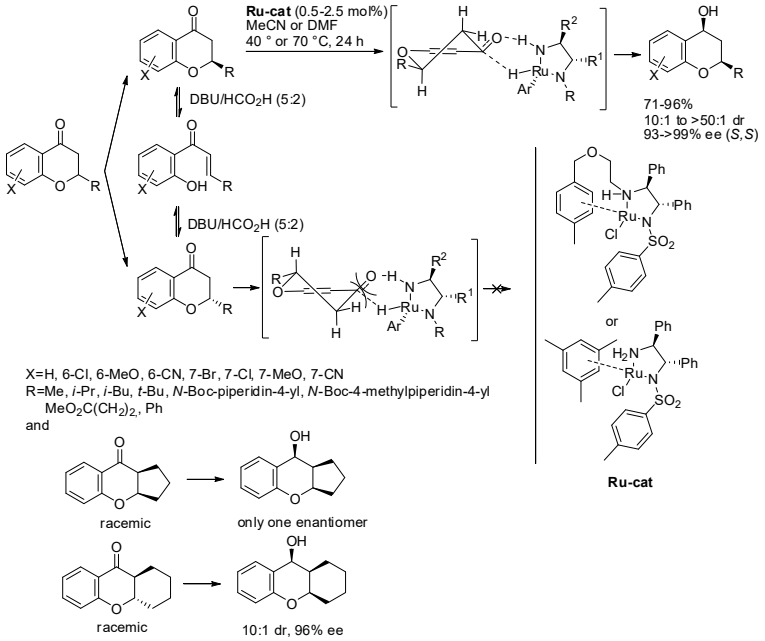
Another method to obtain chiral benzopyran derivatives was the desymmetrization of racemic compounds.



X=H, 8-Cl, 8-Me, 8-MeO, 8-*i*-Pr, 8-*t*-Bu, 8-Ph, 7-Me, 7-MeO, 7-*t*-Bu, 6-Br, 7,8-Me_2, 6,8-Me_2, 5,8-Me_2, 5,7,8-Me_3, benzo[g], benzo[h]

Scheme 50. Copper-catalyzed asymmetric hydroboration of 2*H*-chromenes.

Ashley and co-workers surmised that a chiral ruthenium complex could be able to reduce (*S*)-chromanones to *cis* (*S,S*)-chromanols, leaving the (*R*)-enantiomer untouched for torsional strains (Scheme 51).[73] However, they also thought that a base-catalyzed β-epimerization via open-chain intermediate allowed a dynamic kinetic resolution driving both substrate enantiomers to a single product stereoisomer. Only 6-chloro-2-isopropyl-2-methylchroman-4-one gave a 2.3:1 diastereomeric ration albeit both isomers have a >99% ee. Authors supported their experimental data with computational analysis. However, to obtain the best results the reaction conditions (catalyst type and loading, solvent, and temperature) should be adapted to every substrate.

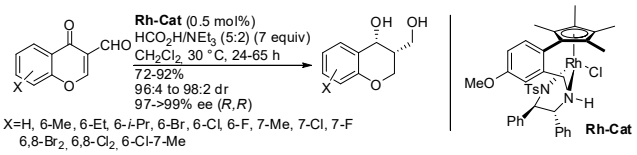


X=H, 6-Cl, 6-MeO, 6-CN, 7-Br, 7-Cl, 7-MeO, 7-CN
R=Me, *i*-Pr, *t*-Bu, *t*-Bu, *N*-Boc-piperidin-4-yl, *N*-Boc-4-methylpiperidin-4-yl $MeO_2C(CH_2)_2$, Ph
and

Scheme 51. Ruthenium-catalyzed dynamic kinetic resolution asymmetric transfer hydrogenation of β-chromanones.

Authors also found that one-pot condensation-dynamic kinetic resolution-asymmetric transfer hydrogenation from acetophenones and aldehydes occurred in high yield and stereoselectivity, and that products can be further manipulated without affecting selectivity.

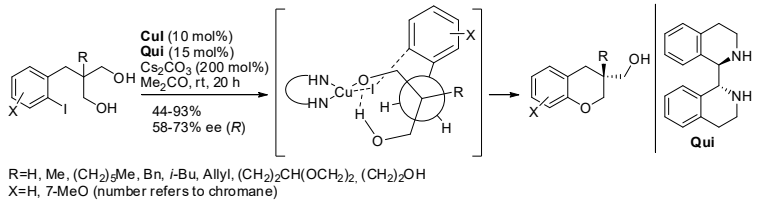
Another example of dynamic kinetic resolution-asymmetric transfer hydrogenation allowed the enantioenriched synthesis of *cis*-3-(hydroxymethyl)-chroman-4-ols under chiral rhodium catalysis (Scheme 52).[74] The absolute configuration of products was determined by X-ray analysis. A 1.0 gram-scale reaction afforded the product in 81% yield with 96:4 dr and >99% ee. Some reactions were carried out to the products without affecting stereoselectivity.



Scheme 52. Rh-mediated asymmetric-transfer hydrogenation of 3-substituted chromones.

Maguire and co-workers attempted the enzymatic acetylation of some chroman-2-ols, testing over than 50 different enzymes.[75] The best results for chroman-2-ol, 6-methylchroman-2-ol and 6-methyl-4-phenylchroman-2-ol were respectively: lipase B from *Alcaligenes sp* (77% ee (*R*) with 76% conversion in the presence of 4.2 equivalents of vinyl acetate in toluene); lipase from *Thermomyces lanuginosus* (92% ee (+) with 88% conversion in the presence of 100 equivalents of vinyl acetate in hexane); acylase from *Aspergillus sp* [>98% ee, (2*S*,4*S*) with only 6% conversion in the presence of 100 equivalents of vinyl acetate without solvent].

A chiral complex between octahydro-1,1'-biisoquinoline and CuI allowed the enantioselective desymmetric aryl C−O coupling of different 2-(2-iodoaryl)-1,3-diols.[76] Among other oxygen-containing heterocycles, chromanes bearing quaternary chiral centers at the 4- or 3-position were prepared. However, the two synthesized 4-substituted chromanes were recovered in 85 and 89% yields, but the enantiomeric excesses were only less than 5% and 10%. More successfully was the synthesis of 3-substituted chromanes (Scheme 53). Aryl bromides gave only trace amounts of desired coupling products. The absolute configuration was assigned by comparison with literature data. Authors calculated the most stable transition states by DFT calculations.

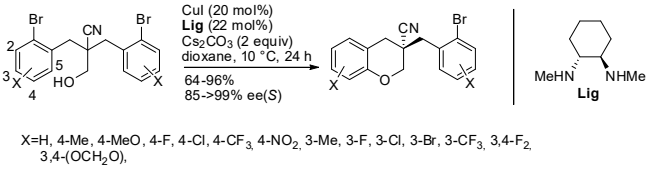


Scheme 53. Asymmetric desymmetrization of different 2-(2-iodoaryl)-1,3-diols.

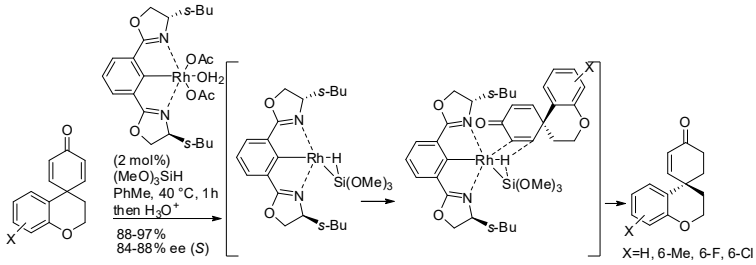
Another similar enantioselective desymmetric aryl C−O coupling involved 2,2-bis(2-bromobenzyl)-3-hydroxypropanenitriles (Scheme 54).[77] It should be noted that, conversely from the previous reaction, aryl iodides gave very low enantioselectivity. The absolute configuration was determined by X-ray analysis. A gram-scale reaction provided 1.28 g of the product (93% yield, 92% ee). Some transformations of the products were successfully carried out without affecting stereoselectivity. The reaction can be extended to some alkenyl bromide, thus affording hexahydro-2*H*-chromenes and octahydrocyclohepta[b]pyran. However, tetrahydrocyclopenta[b]pyran, decahydrocycloocta[b]pyran, dihydropyran and products arising from 2- or 5-substituted aryl bromides were recovered with very low enantiomeric excesses. Dihydrodibenzo[b,f]oxepine was recovered in only 17% yield.

In a feature article devoted to the hydrosilylation of differently γ,γ-disubstituted cyclohexadienones catalyzed by chiral rhodium complexes,[78] four examples were reported for the synthesis of spiro-chromane

derivatives (Scheme 55). The absolute configuration of products was determined by X-ray analysis. DFT calculations of different reaction pathways allowed explaining the observed asymmetric induction and the substituent effect on enantioselectivity.

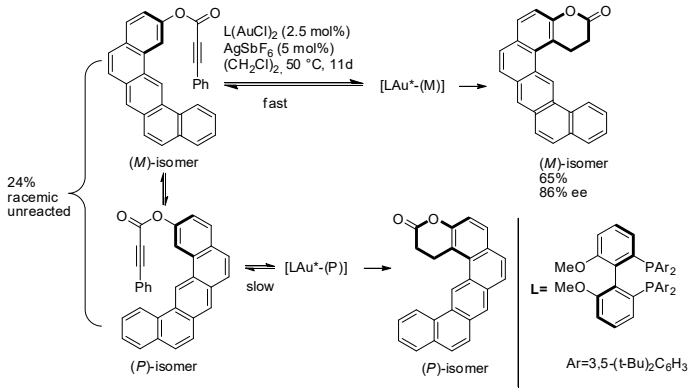


Scheme 54. Synthesis of β-quaternary carbon-containing chromanes.



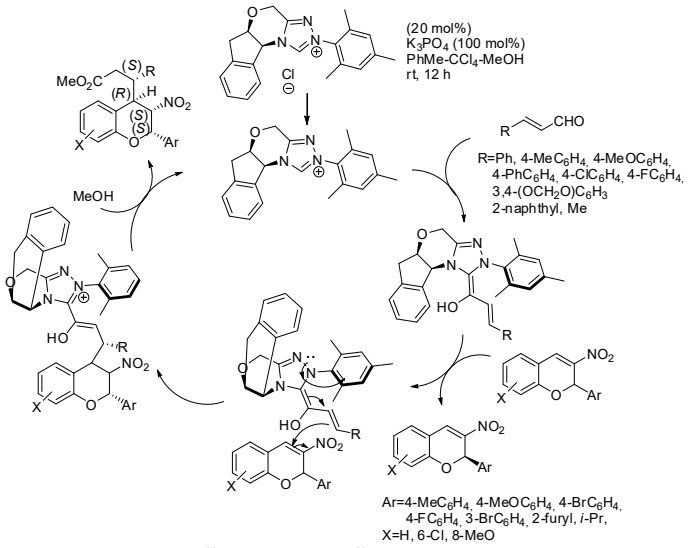
Scheme 55. Asymmetric desymmetrization of spiro-chromanes by rhodium catalyst.

[5]Helicenyl propiolates were converted onto coumarin-fused helicenes by gold catalysis.[79] Besides the racemic reactions, authors reported a dynamic kinetic resolution using an Au/chiral bis(phosphine) complex (Scheme 56). Under the reaction conditions the two enantiomeric staring materials rapidly interconverted and the (*M*)-isomer is formed from the most stable transition state, as demonstrated by authors.



Scheme 56. Dynamic kinetic resolution of helicene.

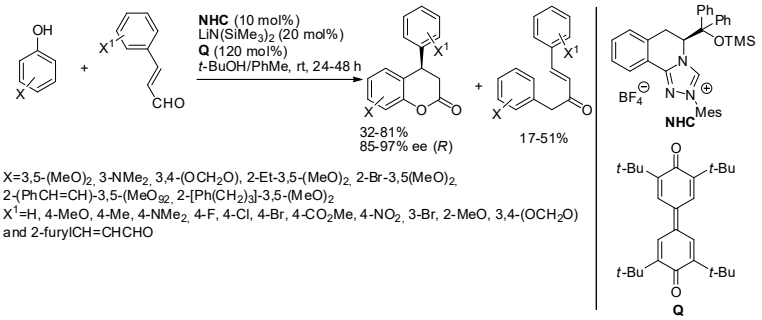
2-Aryl-3-nitro-chromenes were allowed to react with α,β-unsaturated aldehydes under *N*-heterocyclic carbene catalysis.[80] With a 2:1 chromene:aldehyde ratio, addition products were obtained in good to excellent yield and stereoselectivity (Scheme 57). An aliphatic unsaturated aldehyde such as crotonaldehyde gave product in a very poor diasteroselectivity (3:1 dr). With a stoichiometric ratio, the kinetic resolution of the starting chromene was achieved; in fact, (*R*)-2-aryl-3-nitro-2*H*-chromenes were recovered unreacted. The absolute configuration of products was determined by X-ray analysis. Some useful transformations of the products were performed without affecting stereoselectivity.



Scheme 57. Kinetic resolution of 2-aryl-3-nitro-2*H*-chromenes.

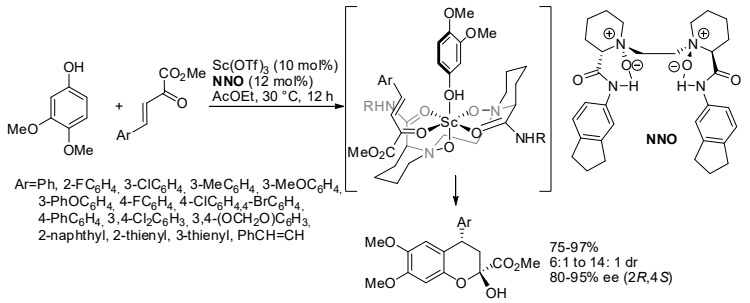
7. Reaction of phenols with activated alkenes

Some additions of phenols to activated alkenes can afford the construction of the benzopyran nucleus. For example 4-aryl-3,4-dihydrocoumarins can be obtained by reaction of phenols with α,β-unsaturated arylaldehydes, catalyzed by NHC. Then the hemiacetal intermediates were oxidized with 3,3′,5,5′-tetra-*t*-butyldiphenoquinone (Scheme 58).[81] As in the reaction described above (Scheme 57),[80] aliphatic aldehydes such as crotonaldehyde gave a sluggish reaction. Unfortunately, all reactions give a mixture of the desired products and open-chain byproducts. The absolute configuration of products was determined by X-ray analysis. Some useful transformations of the products for the synthesis of key intermediates of natural products were performed without affecting stereoselectivity.



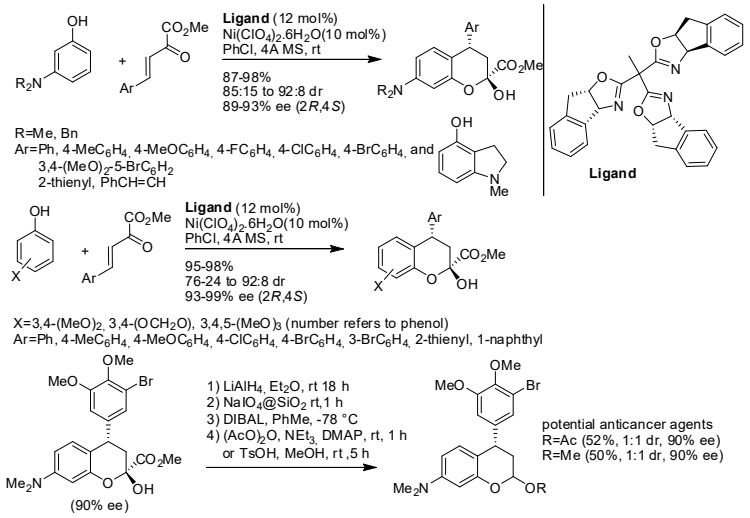
Scheme 58. Synthesis of 4-aryl-3,4-dihydrocoumarins by *N*-heterocyclic carbene catalyst.

Electron-rich phenols underwent a formal Diels-Alder reaction with and β,γ-unsaturated α-ketoesters under a chiral *N,N′*-dioxide-scandium(III) complex catalysis (Scheme 59).[82] The absolute configuration of products was determined by X-ray analysis. *Ortho*-substituted phenyl groups in the β,γ-unsaturated α-ketoesters did not react for steric reasons, except the little fluorine. 3-(Dimethylamino)phenol afforded the expected product in 93% yield, with 10:1 dr, but as a racemic mixture. Phenol, resorcinol and 2-naphthol did not react. A gram-scale reaction afforded 2.02 g of product (92% yield, 14:1 dr, 90% ee).



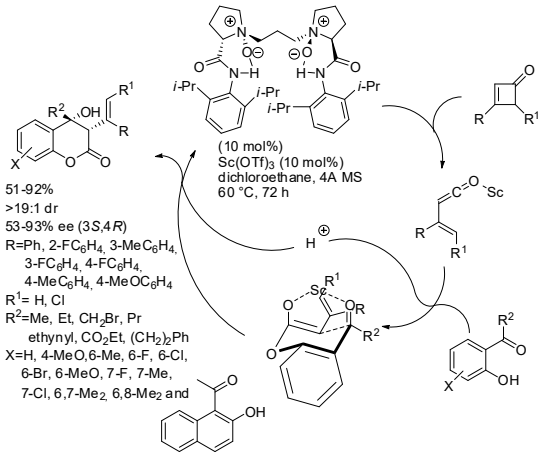
Scheme 59. Oxa-[3+3] annulation of phenols with benzylidene pyruvates.

Then the synthesis of enantioenriched 7-aminated chromanes has been successfully performed under a chiral nickel complex catalysis (Scheme 60).[83] The absolute configuration was determined by comparing optical rotation values with literature. A gram scale reaction provided 2.16 g of chromane (93% yield with 91:9 dr and 90% ee). Two potential antitumor drugs were then prepared in a four-step-one-pot synthesis, which provided the desired products in 50 or 52% overall yields without loss of enantiopurity at the 4-position of the chromane ring and with 50:50 diastereomeric ratio at the 2-position.



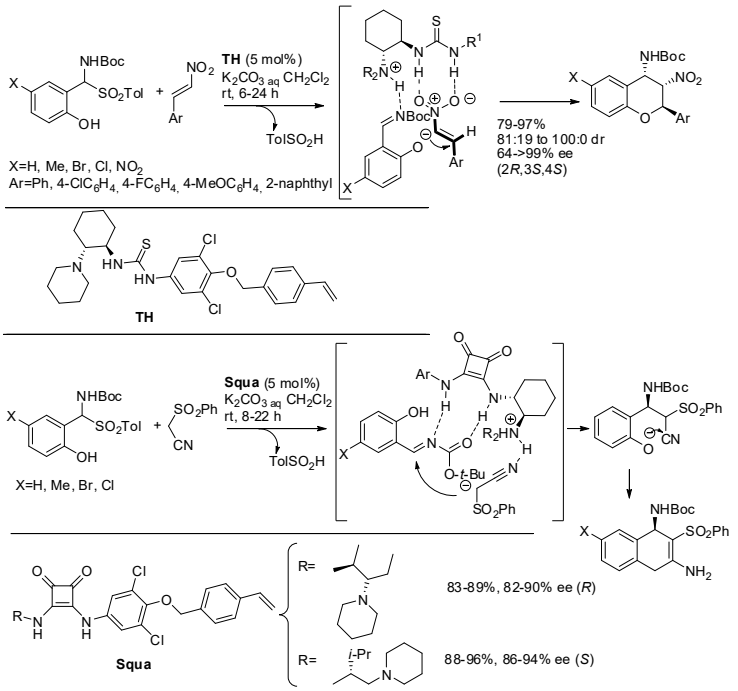
Scheme 60. Another oxa-[3+3] annulation of phenols with benzylidene pyruvates.

The reaction of 2-hydroxyacetophenones with cyclobutenones was carried out under a chiral *N,N'*-dioxide-scandium(III) complex catalysis (Scheme 61).[84] The enantioselectivity suffered from steric hindrance, in fact 2-hydroxybenzophenone gave the product in 90% yield with only 20% ee and a substituent in the *ortho*-position with respect to the hydroxyl group lowered enantiomeric excess to 55%. The reaction with salicylaldehyde needed a slightly great catalyst loading (15 mol%) and afforded product in 40% yield with >19:1 dr and 88% ee. The absolute configuration of products was determined by X-ray analysis. Several control experiments were carried out by authors to elucidate the mechanism depicted in Scheme 60, and they ruled out the formation of *o*-quinone methides, conversely from what found in Scheme 36 for 2-hydroxysalicylaldehyde.[53] The transition state leading to the products should minimize the steric shield between the diene moiety of the substrate and the amide subunit of the ligand.



Scheme 61. Catalytic ring opening/cycloaddition of cyclobutenones to 2-hydroxyacetophenones.

2-Hydroxy-*N*-Boc-α-amidosulfones can undergo a cascade oxa-Michael-aza-Henry reaction and a cascade Mannich cyclization-tautomerization with *trans*-β-nitrostyrenes or amidosulfones, respectively (Scheme 62).[85]

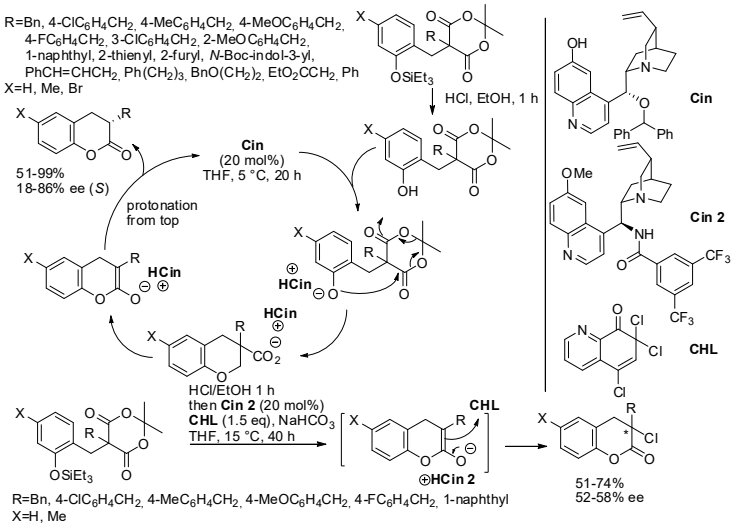


Scheme 62. Stereoselective synthesis of 2-substituted 4-amino-3-nitrobenzopyrans and 3-functionalized 3,4-diamino-4H-chromenes.

A thiourea was the most efficient catalysts for the reaction of *trans*-β-nitrostyrenes, while two squaramides allowed the preparation of both enantiomers in the reaction of amidosulfones. Both catalysts

were also co-polymerized with styrene divinylbenzene and tested in the reactions; products were recovered in 91-96% yield with 82:18 to 99:1 dr and 86->99% ee for polymeric thiourea and 78-84% yield, with 78-88% ee for polymeric squaramide, and the polymeric catalysts were recovered and reused five times without loss of efficiency. A mechanism, in which 2-hydroxy-*N*-Boc imine was initially formed by the aqueous solution of K_2CO_3, was also hypothesized. Then hydrogen bonds, in which the nitro group and the acyl imine functionality found the optimum distance in the thiourea and squaramide moieties, respectively, were formed and the tertiary amines deprotonated the phenol framework.

An intramolecular cyclization/decarboxylation can occur in *ortho*-hydroxyphenyl substituted Meldrum's acids (Scheme 63).[86] Owing to the difficult purification of these phenols, authors used the corresponding pure silyl ethers, which were efficiently *in situ* desylilated. When the R group is a 4-methoxy substituted benzyl moiety, the reaction time was prolonged to 60 h in order to increase yield from 61 to 99%. The absolute configuration of products was determined by X-ray analysis. The reduction of the carbonyl group to (*S*)-3-benzylchromane did not affect the enantiomeric excess. The chlorination instead of protonation of the intermediate was also performed, but some amounts of protonated by-product were always recovered by an independent pathway (from 83:17 to 80:20), as proved by control experiments. The absolute configuration of the chlorinated product was not determined.



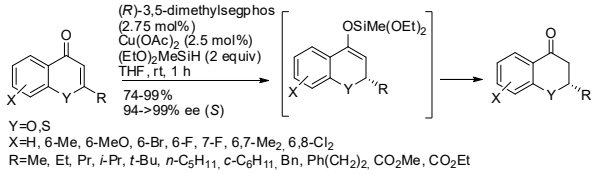
Scheme 63. Synthesis of C3-alkylated dihydrocoumarins from C5-disubstituted Meldrum's acids.

8. Reduction of chromones

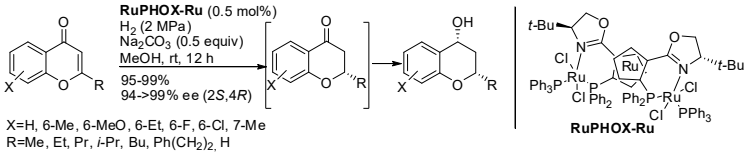
The asymmetric reduction of 4-chromones is another travelled way to obtain enantioenriched benzopyran derivatives. For instance a Cu-chiral complex allowed their asymmetric reduction in the presence of diethoxymethylsilane as the reductant (Scheme 64).[87] One of the reported examples was the natural product flindersiachromanone [R=Ph(CH$_2$)$_2$], which was recovered in 97% yield with 98% ee. The absolute configuration of chromanones was assigned as (*S*) by comparison with literature data for the known (*R*)-compounds and confirmed by X-ray analysis. Moreover, the silyl enol ether intermediates can react with electrophiles such as bromine of NBS or aldehydes to give 2,3-disubstituted products in 40% yield, 97% ee and in 75% yield, 17:1 dr, respectively. The reaction was also successfully applied to thiochromones, despite the affinity of sulfur to transition metals, which generally deactivates the catalysts.

An asymmetric Ru-complex allowed instead the complete reduction of chromones to enantioenriched chromanols (Scheme 65).[88] The absolute configuration of products was determined by X-ray analysis. A gram-scale hydrogenation starting from 1.87 g of reactant afforded product in 99% yield and with 96% ee, with 0.1 mol% of catalyst and 5 MPa H_2 at room temperature over 12 h. Some modifications of reaction

product were carried out without affecting selectivity; in particular flindersiachromanone was obtained in 92% after two steps with 98% ee. Some control experiments allowed authors envisaging a mechanism in which the C=C double bond was firstly reduced.



Scheme 64. Copper-catalyzed asymmetric reduction of chromones and thiochromones.



Scheme 65. Ru-catalyzed asymmetric hydrogenation of chromones.

9. Spiro, fused and bridged chromane-indoles

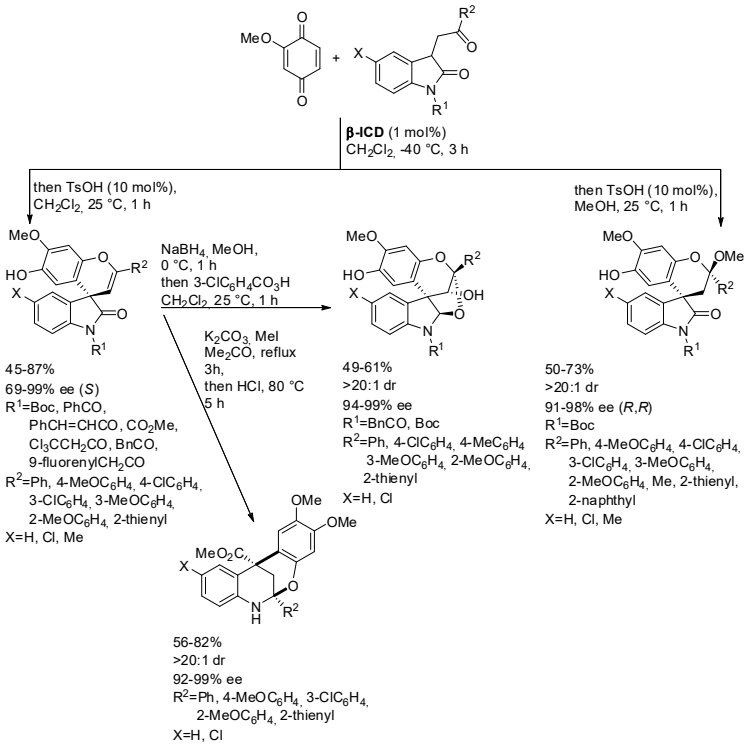
Oxindoles, chromanes and polycyclic compounds featuring their combination have many interesting biological and pharmacological properties, thus their synthesis fascinated many research groups. For example, the group of Li and Liu prepared a series of spiro-, dispiro-, fused, and bridged heterocycles by the reaction of quinones and 3-keto-oxindoles catalyzed by β-isocupreidine (Scheme 66).[89] The absolute configuration of products was determined by X-ray analysis. Authors carried out some control experiments to elucidate the mechanism and found that the free hydroxy group of the catalyst played a key role in the catalytic process (the methoxy derivative is much more efficient) and that the two spiroxindoles arose both from the hemiacetal intermediate by dehydration or ketalization, respectively.

Another organocatalytic synthesis of spiro oxindole-chromane derivatives was described by Wang and co-workers (Scheme 67),[90] that is and asymmetric [3+2] cycloaddition of oxindole azomethine ylides with 3-nitro-2*H*-chromenes. It should be noted that the reaction of 3-aminooxindole and aldehyde is more efficient than that of isatin and benzylamine. *N*-Unsubstituted oxindoles exhibited inferior reactivity and *N*-benzyl-protected ones gave the best results. The absolute configuration of products was determined by X-ray analysis. Also 3-nitro-2*H*-thiochromene and 3-nitro-1,2-dihydronaphthalene afforded products in 96% (>20:1 dr, 90% ee) and 95% (>20:1 dr, 94% ee). A gram-scale synthesis produced 0.79g of spiro [pyrrolidine-2,3′-oxindole] (78% yield, >20:1 dr, 76% ee).

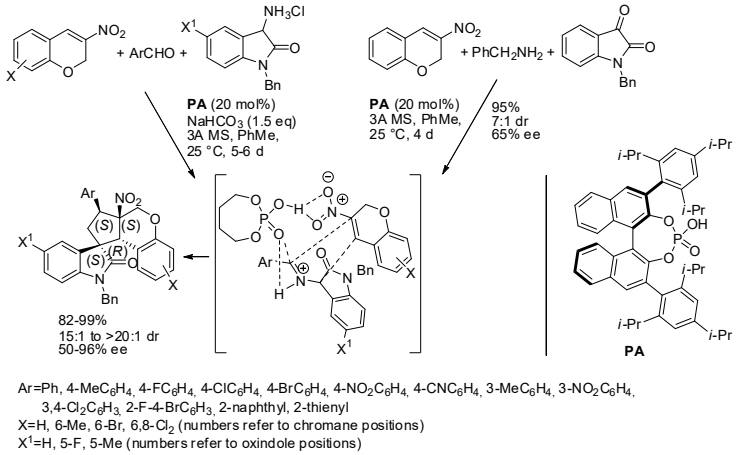
Spirooxindole-based hexahydroxanthones with five adjacent stereocentres have been prepared with a thiourea catalyst. The reaction was performed with nitroolefins (Scheme 68, eq. 1),[91] or 3-methyl-4-nitroisoxazole substituted alkylidenoxindoles (Scheme 68, eq. 2).[92] Boc protection of the oxindole-chromene starting material was found to be crucial for obtaining good results in terms of electrophilicity and efficiency. The absolute configuration of products was determined by X-ray analysis. In the reaction with nitroolefins, a gram-scale experiment provided 1.07 g of the desired product (77% yield with >20:1 dr and 98% ee). A tentative transition state, proposed by authors to explain the observed stereochemistry, is shown in eq. 1. In the reaction with 3-methyl-4-nitroisoxazole substituted alkylidenoxindoles, the most interesting feature was the *trans*-relationship between the C1′ and C2′ as in the natural products of the diversonol class, while all the other reported synthesis of this building block have a *cis*-relationship.[93] Some useful transformations of the products were performed without affecting stereoselectivity.

10. Miscellaneous

Other asymmetric reactions afforded benzopyran nucleus that cannot be listed in the above sections.

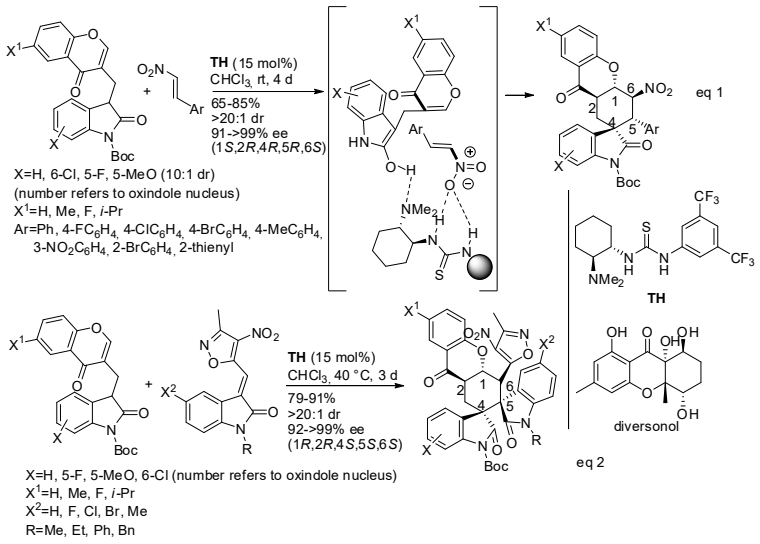


Scheme 66. Synthesis of spiro-, dispiro-, fused, and bridged heterocycles by the reaction of quinones and 3-keto-oxindoles.

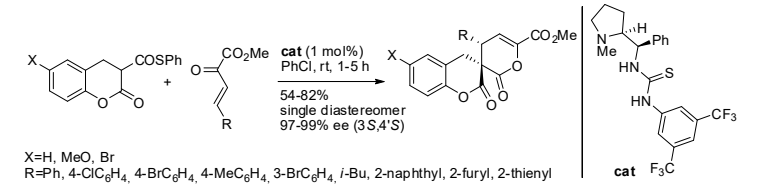


Scheme 67. Synthesis of enantioenriched polycyclic spirooxindole-chromane adducts.

In a paper mainly devoted to the asymmetric synthesis of dihydropyranones, some examples of spirochromanes are reported by Michael addition-lactonization reactions of β,γ-unsaturated α-keto esters with chromanone thioesters (Scheme 69).[94] The absolute configuration was determined by X-ray analysis. A gram-scale reaction provided the product in 76% yield and 99% ee.

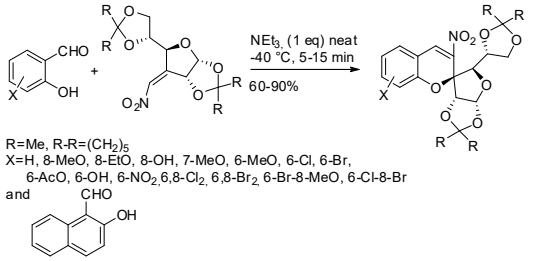


Scheme 68. Asymmetric synthesis of spirocyclic hexahydroxanthones.



Scheme 69. Synthesis of spiro-3,4-dihydrocoumarin-fused 3′,4′-dihydropyranones.

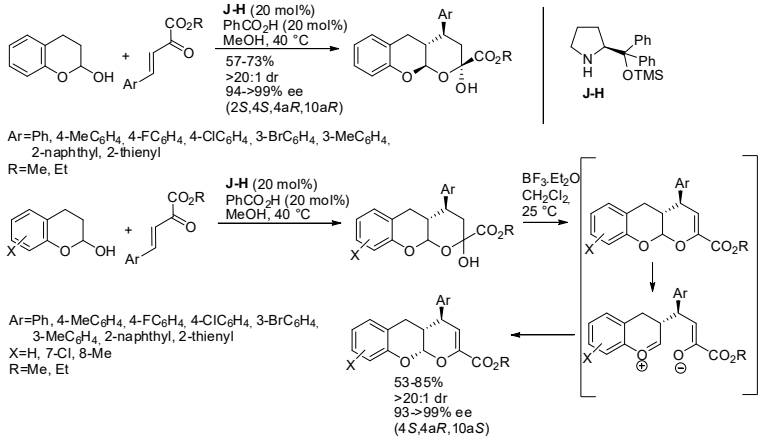
Salicylaldehydes have been already used as a starting material for the synthesis of chromane derivatives (see Scheme 21[34] and Scheme 36).[53] However, salicylaldehydes also reacted with 3-C-vinyl sugar nitro olefins prepared from protected glucofuranose (Scheme 70).[95] This is not an asymmetric catalyzed reaction, but actually a chiral pool reaction. In fact, the exclusive formation of the new chiral center at the C2 position of the chromane ring is due to the chiral sugar and not to the catalyst, which is triethylamine. The reaction is fast, affording exclusively (2*S*)-2-C-spiro-glycosyl-3-nitrochromenes.



Scheme 70. Synthesis of enantiopure 2-C-spiro-glycosyl-3-nitrochromenes.

Some formal Diels-Alder reaction of β,γ-unsaturated α-ketoesters for the synthesis of chromanes have been already encountered in this review (Schemes 59[82] and 60).[83] Recently this reaction was extended to chroman-2-ols by enamine catalysis (Scheme 71).[96] The products from chroman-2-ol and different β,γ-unsaturated α-ketoesters precipitated as a single diastereomer from the reaction mixture when using

MeOH as the solvent. As the catalyst remained in the filtrate, it was efficiently recycled eight times on a 1.5 mmol scale without significantly affecting yield and selectivity, but longer reaction times are required along with the number of recycling increased. The products arising substituted chroman-2-ols did not precipitate and were recovered after chromatography as a mixture of isomers. However, acidic treatment of the reaction mixture allowed dehydration and only the *cis*-configured product was recovered. Authors surmised that, in the acidic medium, a ring opening of the acetal moiety occurs and then the subsequent closure is obtained from the attack of oxygen anion at the *Si*-face of the oxocarbenium ion. The absolute configuration of both acetals and dehydrated products was determined by X-ray analysis. Finally, some transformations of both products were successfully carried out without affecting stereoselectivity.



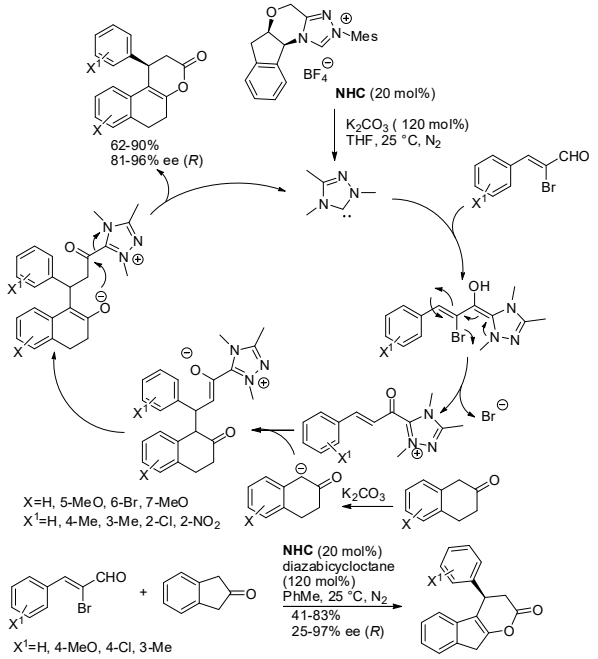
Scheme 71. Synthesis of both *cis*- and *trans*-configured pyrano[2,3-*b*]chromenes.

Naphthopyran is another skeleton widely found in natural products. Its assembly has been made,[97] but in the last three years, the asymmetric assembly of tetrahydro-3*H*-benzo[f]chromen-3-one derivatives has been reported only from the reaction of bromoenal and β-tetralone or β-indanone catalyzed by *N*-heterocyclic carbene (Scheme 72).[98] 2-Bromobut-2-enal and α-bromoenals containing heterocycles as well as α-tetralone did not give the expected products. The absolute configuration was assigned observing an opposite optical rotation of products with respect to that reported in the literature.[97b]

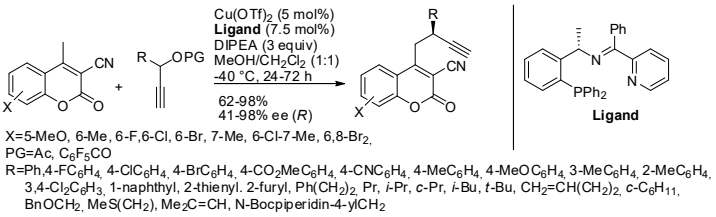
At the end of this section, some enantioselective remote formations of bonds will be collected, namely the enantioselective vinylogous γ-allylic alkylation of 4-methylcoumarins. It should be noted that the control of this remote formation is generally difficult. However, in 2017 the group of Antonchick and Waldmann reported an enantioselective copper-catalyzed vinylogous propargylic substitution of coumarins (Scheme 73).[99] Aromatic propargylic acetates reacted smoothly, but aliphatic propargylic acetates did not. On the other hand, perfluorobenzoates efficiently provided the products. The absolute configuration was determined by X-ray analysis. Then some transformations were carried out to prepare a set of derivatives for biological tests, which revealed a novel class of autophagy inhibitors.

Another vinylogous reaction of 3-cyano-4-methylcoumarins involved Morita-Baylis-Hillman carbonates. Two different papers described this reaction with $(QD)_2PHAL$[100] and $(DHQD)_2PYR$[101] catalysts (Scheme 74). Both reactions afforded (*R*)-isomers as determined by X-ray analysis. The former reaction was also carried out at a 1.0 mmol scale leading to 250 mg (67% yield with 92% ee). Some substrates were unreactive (see Scheme 74). In the latter reaction, a cyano-substituted MBH carbonate showed a lower enantioselectivity. Albeit 6-chloro-3-cyano-4-methylcoumarin was selected as model reactant, benzo unsubstituted coumarin successfully reacted. A tentative mechanism was also suggested.

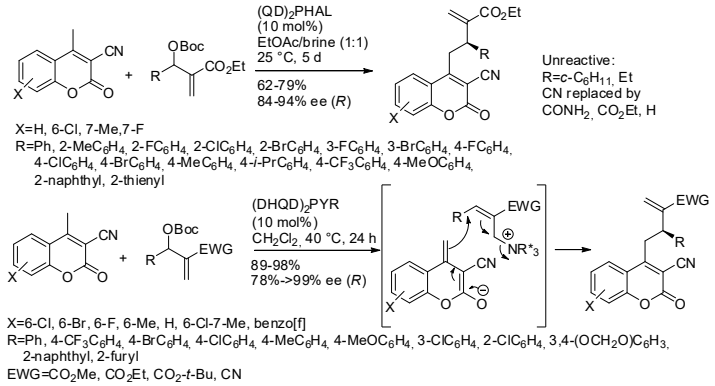
The vinylogous reaction of 3-cyano-4-methylcoumarins with allyl carbonates afforded the expected products under iridium complex with chiral ligands (Scheme 75).[102] The gram-scale reaction gave 1.08 g (90% yield with 94% ee) of the product. The absolute configuration was determined to be *S* by the comparison of optical rotation value with reported data.



Scheme 72. [3+3] Annulation of bromoenals with β-tetralones and β-indanone.

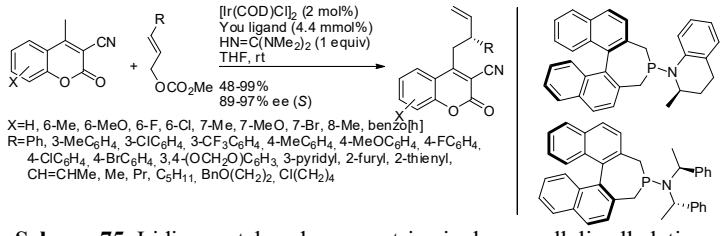


Scheme 73. Vinylogous propargylation of coumarins.



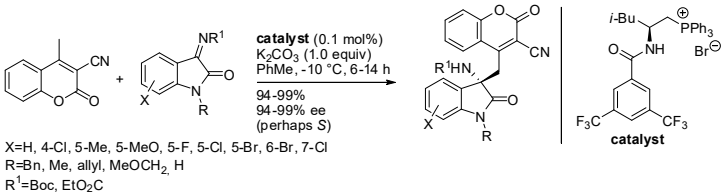
Scheme 74. Vinylogous allylic alkylation with Morita-Baylis-Hillman carbonates.

The products were then submitted to some transformations without affecting enantioselectivity. Some interesting feature must be outlined: (i) only this reaction was successfully carried out on isocoumarin (48% yield with 95% ee); (ii) coumarins, in which the CN group was replaced with CO_2Et or $CONH_2$ frameworks, unreactive in the previous reaction, (see Scheme 73), reacted smoothly leading to 54% yield with 99% ee and 83% yield with 97% ee, by using Feringa ligand instead of You-ligand.



Scheme 75. Iridium-catalyzed asymmetric vinylogous allylic alkylation.

Very recently, the enantioselective vinylogous Mannich addition of 3-cyano-4-methylcoumarins to isatin imines was reported by Wu and co-workers (Scheme 76).[103] The reaction worked with very low catalyst loading (0.1 mol%) and can be scaled up to 1.44 g (92% yield with 99% ee). It should be noted that the large scale reaction did not require chromatographic separation, but product was isolated in pure form after filtration through a short silica gel pad. Both *N*-protections could be efficiently removed with only a slight decrease of the ee. The reaction with *N*-Boc imine of benzaldehyde was also carried out, but the enantioselectivity was moderate (75% ee) albeit in 97% yield. Unfortunately, authors were unable to establish the configuration of the chiral center, which was tentatively assigned as *S* by analogy with similar reactions.



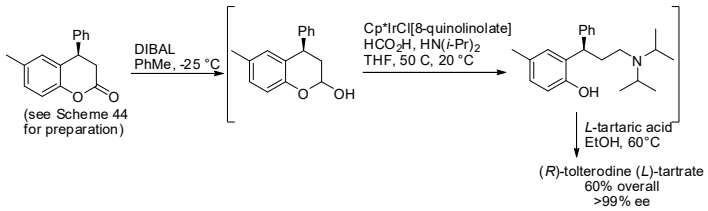
Scheme 76. Vinylogous allylic alkylation with isatin imines.

11. Examples of total syntheses

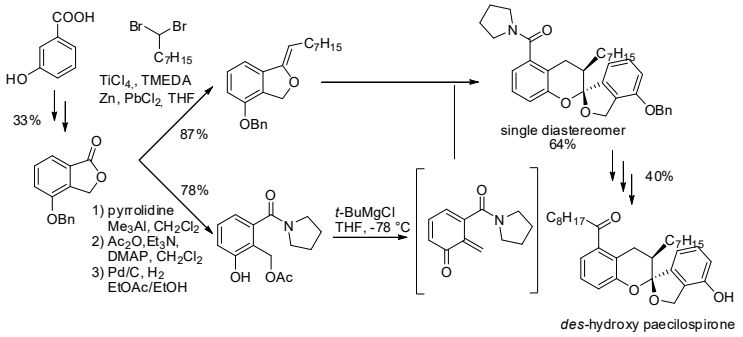
Being chromane a "privileged structure", that is a molecular framework able to provide a series of molecules with potent biological activities; it is not surprising that many above-described reactions have been used in the total syntheses of natural products or drugs.

The alkylation methods described in section 5 (Schemes 44 and 45) has been applied to the total synthesis of (*R*)-tolterodine by Korenaga and co-workers, applying their computationally designed catalyst (Scheme 77).[7] The alkylated chromane derivative was reduced with DIBAL and then the reductive amination was carried out with an Ir catalyst and HCO_2H as hydrogen source. Finally, the crude product, without further purification, was reacted with (L)-tartrate affording the salt in >99% ee. With respect to other syntheses of this product, this preparation shows some advantages: no use of hydrogen gas and large amounts of palladium catalyst and no need of intermediate purification.

Paecilospirone was isolated from the marine fungus *Paecilomyces* sp. near Yap Island (Micronesia). Being the molecular core a chromane moiety, Pettus and co-workers reported a synthetic strategy for the synthesis of *des*-hydroxy paecilospirone in ten steps, in which the key step was the reaction of an enol ether and an *ortho*-quinone methide, each derived from the same lactone (Scheme 78).[104] The synthesis is not enantioselective, but authors envisaged that the approach may become enantioselective by using a chiral amine instead of pyrrolidine.

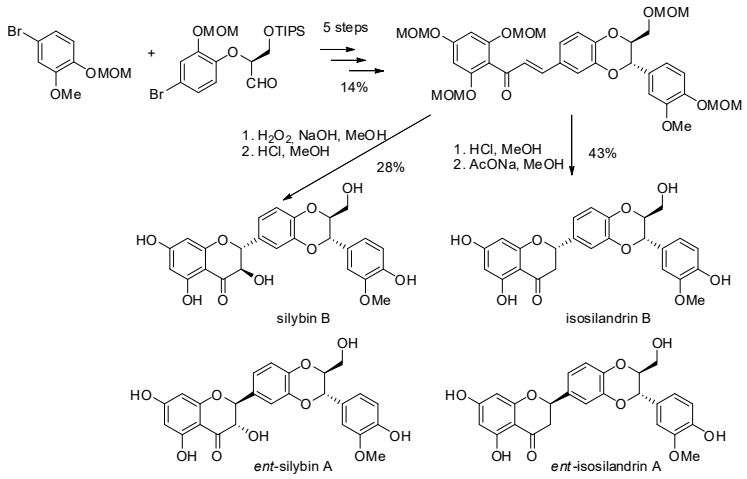


Scheme 77. Total synthesis of Detrusitol® [(*R*)-tolterodine (*L*)-tartrate)].



Scheme 78. Total synthesis of *des*-hydroxy paecilospirone.

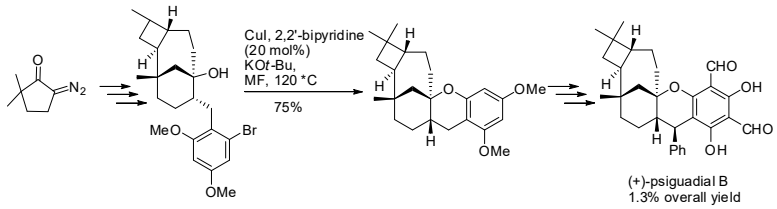
From the seeds of *Silybum marianum* were isolated silymarin a complex mixture of flavonolignans, with bioactive properties. The total synthesis of silybin B and isosilandrin B was performed by Barker and co-workers.[105] The key step converted a chalcone into equimolecular mixtures of *ent*-silybin A and silybin B or *ent*-isosilandrin A, and isosilandrin B (Scheme 79), because, unfortunately, the fixed chirality at the C-2′ and C-3′ atoms was not able to address the stereochemistry on the distant dihydroflavonol fragment.



Scheme 79. Total synthesis of some flavonolignans.

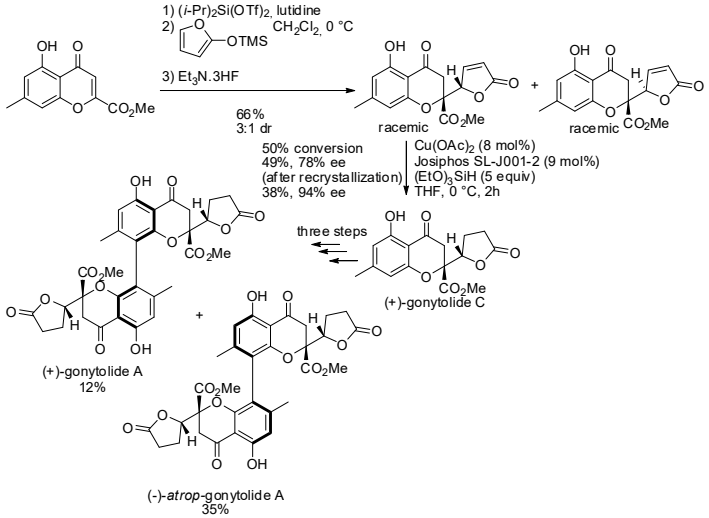
(+)-Psiguadial B is a diformyl phloroglucinol with activity against some cancer cell line. The total synthesis reported by Reisman and co-workers accounted for 15 steps, in which the enantioselectivity is governed by the ring contraction of the starting cyclic diazoketone.[106] Then three routes were attempted for

the synthesis of the chromane framework and the most efficient employed an intramolecular *O*-arylation reaction (Scheme 80).



Scheme 80. Total synthesis of (+)-psiguadial B.

(+)-Gonytolide A is a potent innate immune promoter from the fungus *Gonytrichum* sp. Its synthesis together with its atropisomer was achieved in five steps from a chromone ester monomer.[107] The key steps were the vinylogous addition of chromone to furan and the kinetic resolution by hydrogenation (Scheme 81). It should be note that the kinetic resolution of the stable (±)-gonytolide C was less efficient than the kinetic resolution of the less stable butenolide, which decomposed during silica gel chromatography, but can be isolated by crystallizations.



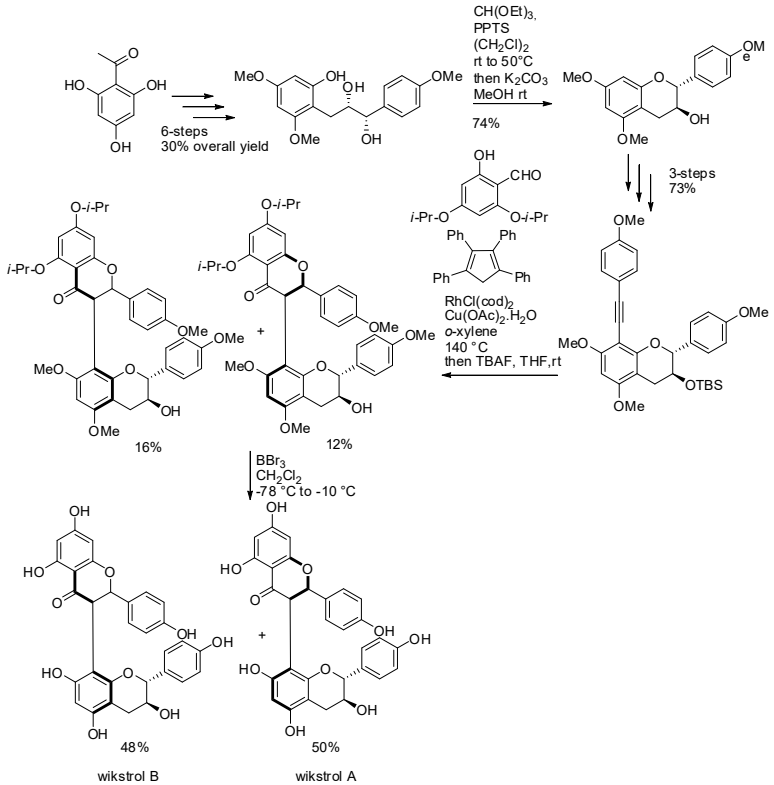
Scheme 81. Total synthesis of (+)-gonytolide A.

Other atropisomeric flavonoid dimers are wikstrol A and wikstrol B isolated from the root of *Wikstroemia sikokiana.* A 12 step total synthesis was described starting from 2′,4′,6′-trihydroxyacetophenone.[108] Sharpless asymmetric dihydroxylation was the asymmetric step, while the two chromane nuclei were prepared by acid-catalyzed cyclization with triethyl orthoformate and by hetero Diels-Alder cyclization (Scheme 82).

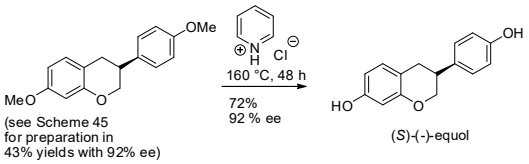
Nishimura and co-workers applied their method to the preparation of (*S*)-equol, a natural isoflavonoid found in soybeans and urine, used for the treatment of menopausal symptoms (Scheme 83).[61] After the addition of 4-methoxyphenylboronic acid to 7-methoxy-2H-chromene the product was then deprotected affording equol.

Phomoarcherins are tetracyclic terpenes isolated from *Phomopsis archeri,* with moderate to excellent anticancer properties. A nine-steps total synthesis of (−)-phomoarcherin C, was described staring from the

chiral Wieland-Mischer ketone, in which the key step for the formation of the chromane nucleus was a 6π-electrocyclization catalyzed by boronic acid-Bronsted acid cocatalyst (Scheme 84).[109]



Scheme 82. Total synthesis of wikstrol A and wikstrol B.



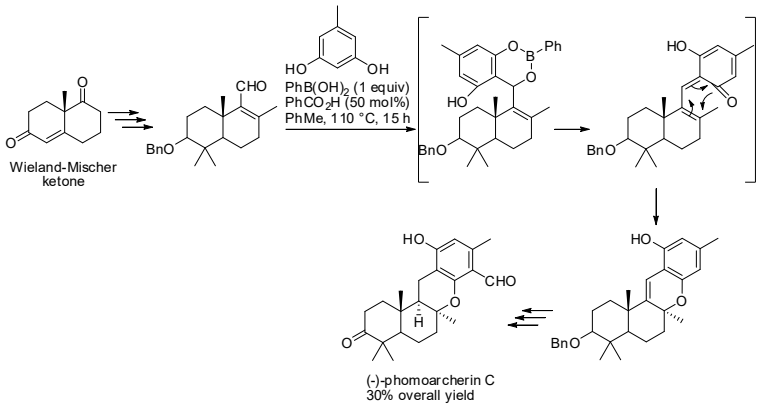
Scheme 83. Total synthesis of (*S*)-equol.

Preussochromones are isolated from the endolichenic fungus, *Preussia Africana.* Koert and coworkers performed a total 11-step synthesis of (−)-preussochromone D from the commercially available 5-hydroxy-4H-chromen-4-one. The asymmetric alkylation was carried out in the presence of a phenylglycine derivative and afforded the product in 73% yield and 77% ee (Scheme 85).[110]

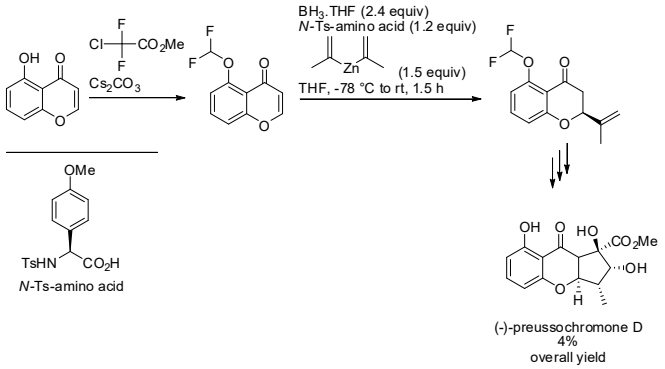
12. Conclusions

Despite the numerous reported examples, the asymmetric synthesis of chromanes remains a challenge for organic chemists. Actually, researchers have obtained multiple stereogenic centers with excellent levels of stereocontrol. These methods have been successfully applied to the synthesis of complex molecules with biological activity and in the total syntheses of natural products. This review, describing the already known

methods, aims to encourage scientists to explore new avenues for the synthesis of these biological important heterocycles.



Scheme 84. Total synthesis of (−)-phomoarcherin C.



Scheme 85. Total synthesis of (−)-preussochromone D.

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