CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF C3-SUBSTITUTED DIHYDROCOUMARINS

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Abstract. *Given the interest of coumarin-derived architectures as bioactive compounds and/or naturally occurring products, the synthetic chemists have developed enantioselective syntheses of chiral derivatives with a focus on 3,4-disubstituted dihydrocoumarins. Nevertheless, essentially during the last decade, several reports highlighted the catalytic enantioselective syntheses of C3-substituted and C3-disubstituted analogues which encompass interesting synthetic and reactivity challenges. In this review, we have described the developments in that field of research with a focus on asymmetric sequences to have access to chiral dihydrocoumarins highlighting their useful synthetic transformations.*

Contents

1. Introduction

Amongst the family of privileged heterocycles in medicinal chemistry, the coumarin derivatives are frameworks of upmost importance. The 3,4-dihydrocoumarins or chroman-2-ones belong to a subfamily whose architectures have been encountered within naturally occurring products and bioactive compounds (Figure 1).[1-4] Furthermore, this heterocyclic motif is a useful building block which affords diverse opportunities to carry out synthetic transformations towards more complex coumarin-based products and derivatives resulting from ring-opening sequences.

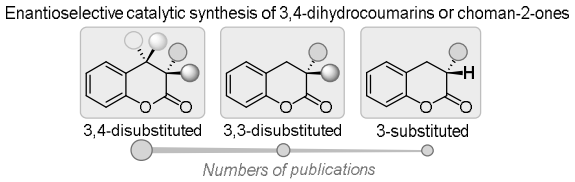


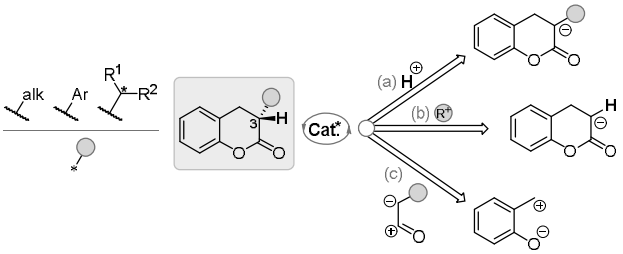
Figure 1. Enantioselective catalytic synthesis of 3,4-dihydrocoumarins or chroman-2-ones.

Generally speaking, it is currently recognized that the use of sp^3-rich biorelevant architectures, thereby "escaping from the flat land", belong to the strategies which increase the chance of success along the adventure leading to a drug development, by addressing better selectivity while decreasing the toxicity issues.[5,6] Accordingly, there is modern impetus for the construction of nonracemic molecules in the field of drug discovery in order to further populate the 3D-chemical space. In that context, the construction of nonracemic dihydrocoumarins has met a great interest with the emphasis given, in the recent years, on the

asymmetric catalysis. From an historical point of view, most of the catalytic synthetic strategies have addressed the elaboration of 4-substituted and 3,4-disubstituted chroman-2-ones,[3,4] while the syntheses of 3-substituted and 3,3-disubstituted chroman-2-ones have remained elusive up to recently. However, essentially during the last decade, several research efforts have successfully addressed the catalytic enantioselective synthesis of such heterocyclic frameworks which, from our opinion, deserve to be covered in a dedicated review. Hereby, we will describe the catalytic enantioselective syntheses of 3-substituted and 3,3-disubstituted chroman-2-ones by highlighting either the asymmetric synthetic methodology or the mode of activation (metal- or organic-catalysis) when the catalytic tools are key elements to overcome the synthetic challenge of a given structure.

2. Enantioselective synthesis of C3-substituted dihydrocoumarins

The catalytic asymmetric syntheses of C3-substituted dihydrocoumarins, depending on the nature of the substituent eventually present in the product, have been mainly based on three distinct strategies (Scheme 1). For the first two approaches, the enantioselective construction of the C3-stereocenter was considered either by the enantioselective protonation reaction of an α-substituted precursor (Scheme 1a), or by the α-alkylation process of an unsubstituted derivative (Scheme 1b). For the third strategy, an annulation sequence was applied allowing the creation of the stereocenter while the ring was constructed (Scheme 1c). We will describe these strategies in the following paragraph and highlight the metal- or organic-based catalytic asymmetric modes of activation in action. For the sake of comparison, the same general number was used for a series of dihydrocoumarins depending on the general nature of the C3-substituent, as depicted in Schemes 1 and 15.

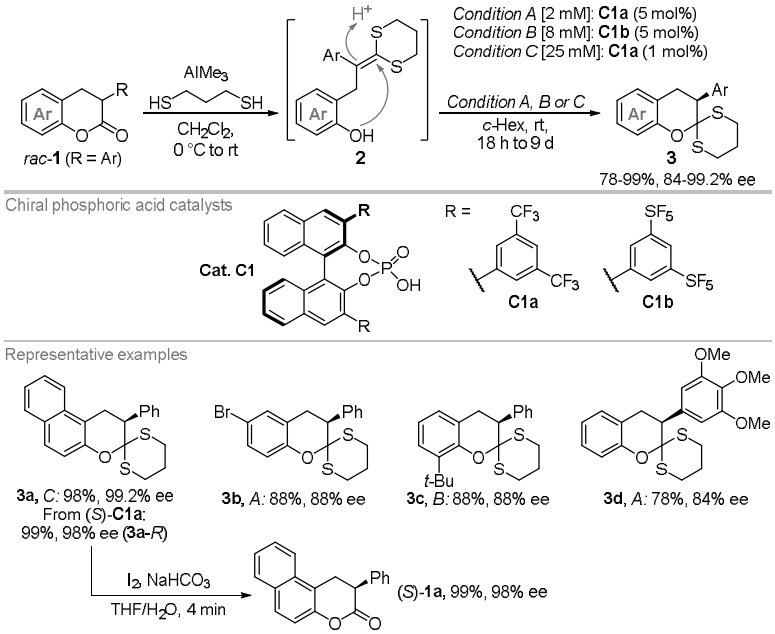


Scheme 1. Enantioselective strategies towards C3-substituted dihydrocoumarins.

2.1. Catalytic syntheses involving an enantioselective protonation reaction

The catalytic asymmetric protonation of enolates or equivalents offers a straightforward access to enantioenriched α-tertiary carbonyl compounds, however this sequence remains very challenging.[7-12] In fact, the introduction of a proton in an enantio-controlled fashion is not a trivial task due to the small size and high reactivity of the formal H^+ species, associated with the delicate management of the O *versus* C-protonation events. By the end of the 90s, pioneering radical-mediated enantioselective protonation sequences of α-alkyl-α-iododihydrocoumarins were reported by Murakata and Hoshino,[13,14] by means of a stoichiometric amount of a chiral Lewis acid complexes, and by Curran thanks to an excess of C_2-symmetric germanium hydride reductant.[15] Nonetheless, until the work of List and co-workers in 2012 (Scheme 2),[16] the catalytic version remained unexplored to elaborate 3-substituted dihydrocoumarins. The authors proposed an overall deracemization sequence, whereby the racemic α-aryl dihydrocoumarins *rac*-**1** were converted into the corresponding ketene dithioacetals **2** in the presence of trimethylaluminium. The rather unstable compounds **2** were directly subjected to the key asymmetric catalytic protonation-induced cyclization reaction, affording enantioenriched dithioacetal-protected product **3**. This step was promoted by phosphoric acids **C1**, as chiral Brønsted acid catalysts, including the unprecedented chiral phosphoric acid **C1b**. Despite the use of very low concentrations (2-25 mM) and long reaction time up to several days, this transformation required only low catalyst loading and provided a very effective access to chromane derivatives **3** with excellent yields (78-99%) and ee ranging from 84 to >99%. As shown with the representative examples in Scheme 2, various substituents on the aryl moieties of **3a-d** were well-tolerated.

Noteworthy, access to both enantiomers of **3a** (99.2% and 98% ee for the (*S*) and (*R*) compounds respectively) was demonstrated when using (*R*) or (*S*)-catalyst **C1a**. Finally, the authors completed the deracemization sequence (a single example) by a simple hydrolysis of **3a** leading to the formation of dihydrocoumarin (*S*)-**1a** with an excellent yield and enantioselectivity (99%, 98% ee).

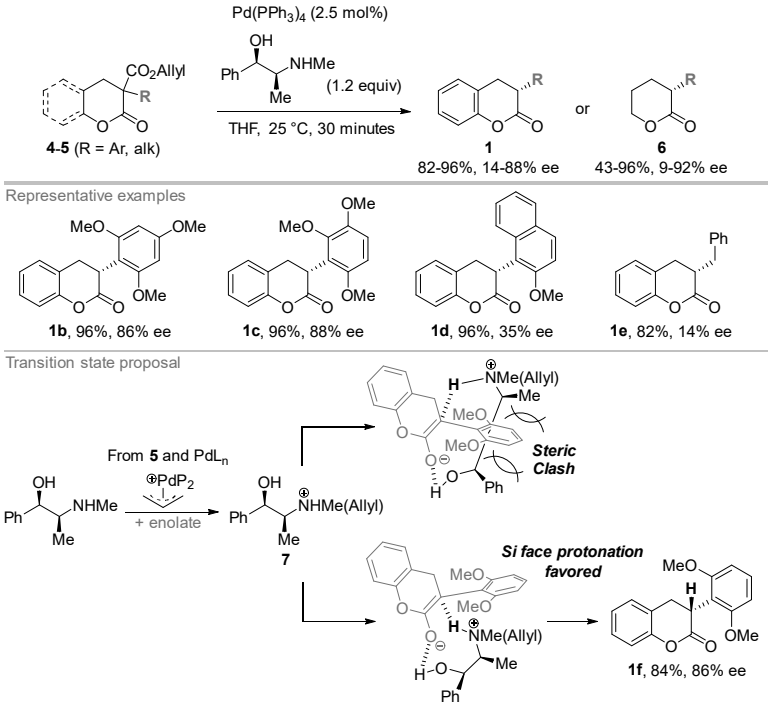


Scheme 2. Deracemization of dihydrocoumarins *via* catalytic asymmetric protonation.

In 2018 the group of Guiry developed a palladium-catalyzed decarboxylative asymmetric protonation leading to sterically hindered α-aryl lactones **6** and dihydrocoumarin derivatives **1** (Scheme 3).[17,18,19] Starting from the corresponding allyl esters **4** in the presence of palladium $Pd(PPh_3)_4$ and (–)-ephedrine as proton source, the optimized reaction conditions allowed to obtain an array of dihydrocoumarins **1** in very good yields with enantiomeric excesses ranging from 14 to 88%. Lactones **6** were also obtained from **5** with ee up to 92% following the same procedure. The critical factor for high enantioselectivity in this methodology appeared to be the bulkiness of the α-aryl substituent. As shown with some representative examples in Scheme 3, with di-*ortho* methoxy substituents very good enantioselectivities were reached (86% ee for **1b** and 88% ee for **1c**). By contrast, with less sterically hindered structures, the ee drastically dropped to 35 and 14% respectively as exemplified with α-naphtyl **1d** and α-benzyl derivative **1e**. From a mechanistic point of view, it was expected that (–)-ephedrine reacted first as a nucleophile towards η^3-[allyl]-Pd complex to form ammonium **7** as an active proton donor. The authors were able to establish the absolute configuration of compound **1b** from X-ray crystallographic analysis, allowing them to provide a stereochemical model in which the *Si* face protonation was favored.

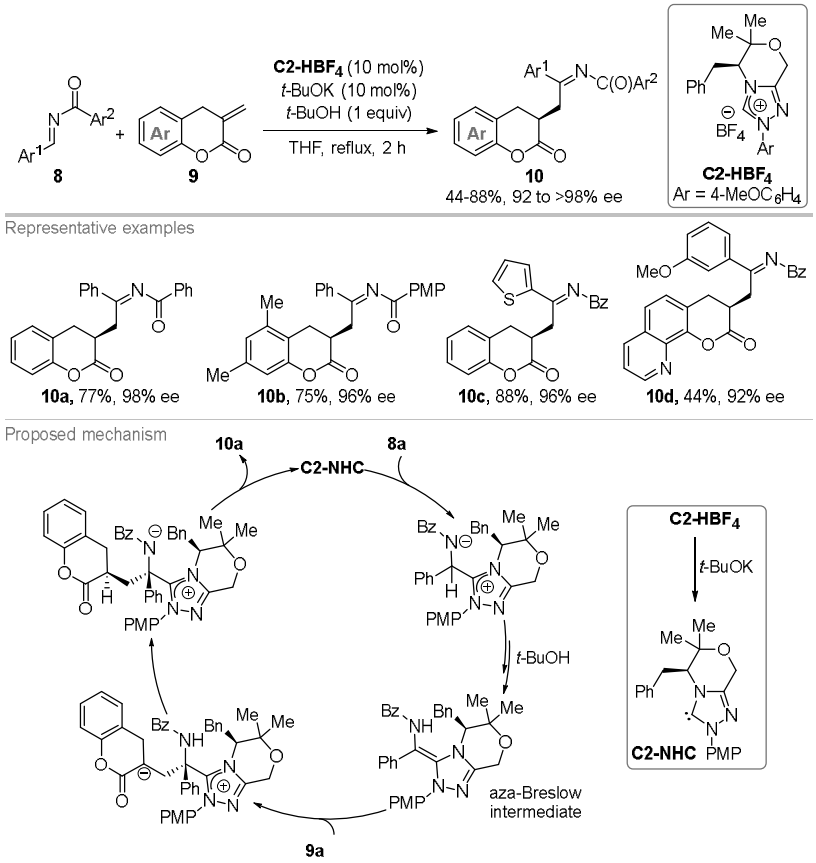
Another elegant way to access 3-substituted dihydrocoumarin derivatives was reported by Lupton and co-workers (Scheme 4).[20] They exploited a strategy from imines **8** for the development of an original *N*-heterocyclic carbene (NHC)-catalyzed enantioselective aza-Stetter reaction. The methodology was fairly general as a range of *N*-acyl imines **8** were successfully coupled with 3-methylene chroman-2-ones **9** to give a variety of γ-iminolactone **10** (21 examples) in excellent enantiomeric excesses of 92-98% and good yields of 44-88%. As illustrated with some representative examples (Scheme 4), the obtained dihydrocoumarins **10a-d** could be diversely substituted with aryl or heteroaryl moieties both on the imine and the aryl parts. However, it was showed that the reaction did not proceed with *N*-Boc, *N*-tosyl or *N*-phosphinyl protected

imines. A mechanistic investigation allowed to propose the catalytic cycle shown in Scheme 4. After deprotonation of the triazolium precatalyst **C2-HBF$_4$** in the presence of a base, the addition of the *in situ* generated **C2-NHC** onto benzoyl imine **8a** (turnover-limiting step) was followed by a *tert*-butanol-mediated tautomerization affording the corresponding aza-Breslow intermediate. The subsequent 1,4-addition to 3-methylene-chromanones **9a** followed by diastereoselective protonation of the enolate intermediate and elimination of the catalyst **C2-NHC**, released the corresponding dihydrocoumarin **10a**.



Scheme 3. Decarboxylative asymmetric protonation.

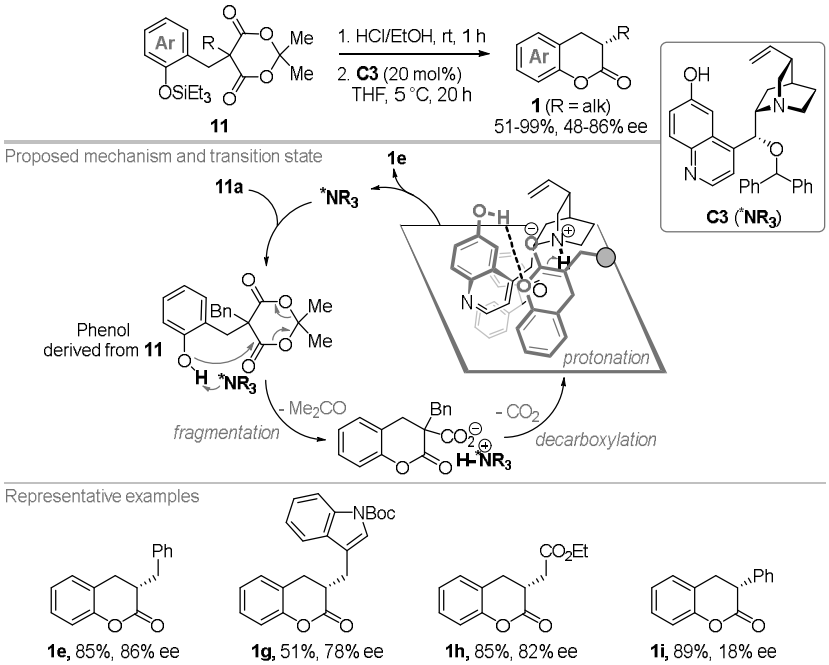
Recently, our research group also contributed to open an entry towards 3-substituted dihydrocoumarins (Scheme 5).[21] Exploiting the electrophilic properties of Meldrum's acid (MA) derivatives,[22,23] and inspired by our previous work on decarboxylative protonation triggered by the intermolecular addition of phenol,[24] we prepared the readily available C5-disubstituted MA platform **11** design for the enantioselective organocatalytic construction of dihydrocoumarins **1**. Indeed, the strategy is based on a sequential two-steps procedure, including desilylation of **11** upon acidic conditions, followed by a Brønsted base **C3**-promoted enantioselective cyclization-decarboxylative protonation sequence to afford the expected dihydrocoumarin **1**. Worthy of note, this transformation was promoted by a newly developed and original bifunctional cupreine-based catalyst **C3** bearing a *O*-benzhydryl moiety on the C9 position. This Brønsted base **C3** first activates the phenol group to lead to the addition onto the electrophilic carbonyl of the MA architecture giving rise to the fragmentation-decarboxylation events. Then, during the subsequent enantioselective protonation reaction by the transient tertiary ammonium, it is believed that a "rigidified" transition state was formed by means of hydrogen bonding with the C6' hydroxyl group and conformational constraint due to the bulky *O*-benzhydryl at C9 of **C3**. A large variety of 3-alkylated dihydrocoumarins **1** could be synthesized with this methodology in good yields (51-99%) and enantiomeric excesses up to 86% (see examples **1e** and **1g-h**), whereas their 3-aryl counterparts **1i** could only be obtained with a low level of enantioselectivity (**1i**, 18% ee), likely due to racemization events.



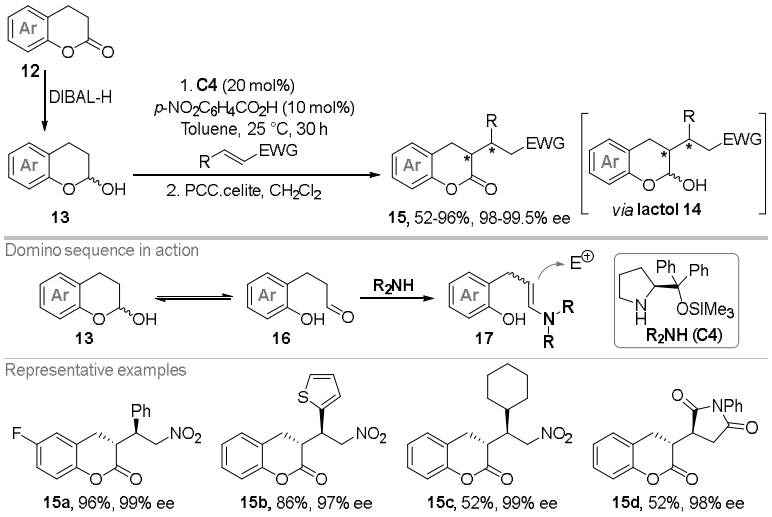
Scheme 4. NHC-catalyzed enantioselective aza-Stetter reaction.

2.2. Catalytic syntheses involving an enantioselective alkylation reaction

The enantioselective α-alkylation-based methodology is indubitably one of the most straightforward C–C bond formation approach to construct nonracemic α-substituted dihydrocoumarin derivatives. However, despite its apparent simplicity, this strategy has to address some reactivity issues of transient reactive enolates, and to be able to limit the introduction of only one alkyl group without further racemization events. In order to allow such formal α-alkylation reaction of dihydrocoumarin derivatives **12**, the group of Liu proposed in 2015 the so-called open-close strategy (Scheme 6).[25] The synthetic approach stemmed from the readily access to lactol **13** by a simple diisobutylaluminium hydride (DIBAL-H) reduction of dihydrocoumarin **12** as starting material. Then, in the presence of the Hayashi-Jørgensen organocatalyst **C4**, a highly enantioselective and diastereoselective Michael addition took place on **13** to eventually provide the α-alkylated dihydrocoumarins **15** with up to 99.5% ee, after a PCC-based oxidation of the lactol intermediate **14** used as a crude product. This domino sequence took advantage of an equilibrium between lactol **13** and the corresponding hydroxyaldehyde **16**, which can be trapped by the secondary amine catalyst **C4**. Then, an amino-catalytic process involving the formation of a nucleophilic enamine **17** allows the stereoselective 1,4-conjugate addition reaction. As representative examples (Scheme 6), this sequence was successfully applied to a range of aliphatic or aromatic derived nitroalkenes, as Michael acceptors, to afford the corresponding products **15a-c**, as well as with *N*-phenyl-maleimide in one case to give product **15d** with 52% yield in 98% ee.



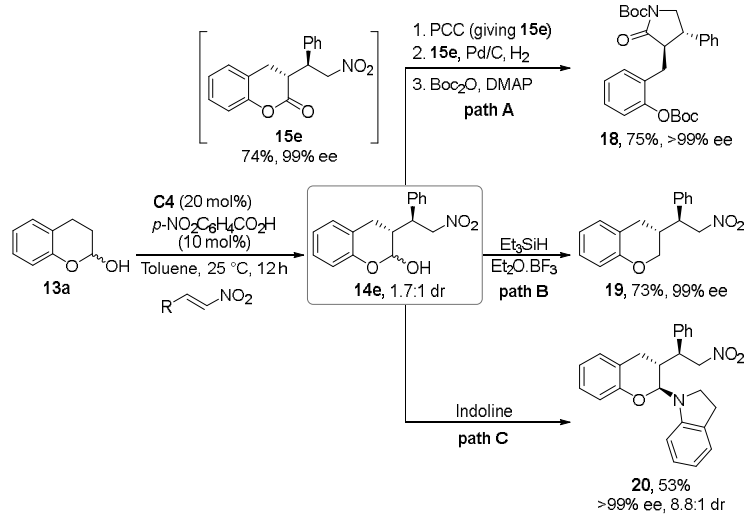
Scheme 5. Enantioselective organocatalytic decarboxylative protonation.



Scheme 6. An open-close strategy.

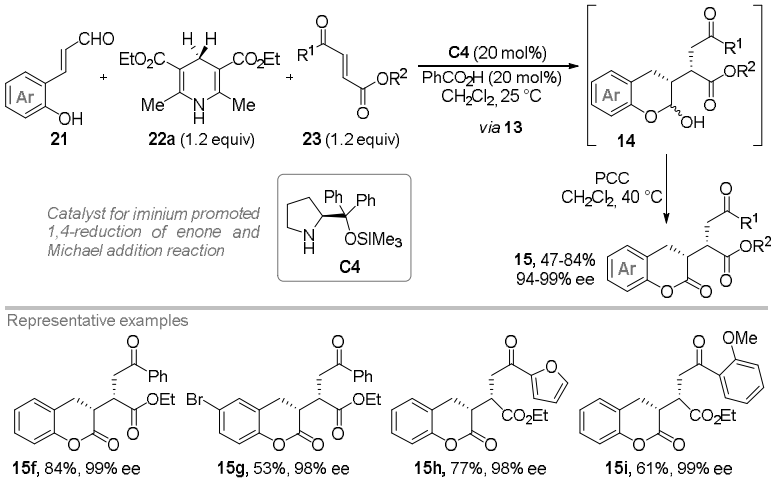
During this investigation, the authors carried out some useful synthetic transformations of lactol **14e**, which is readily accessible from its counterpart **13a** and used without further purification (Scheme 7). First of all, the dihydrocoumarin **15e** was synthesized after PCC oxidation of **14e** (Path A). Then, a cyclization reaction took place, after reduction of the nitro functional group into NH_2, to furnish the corresponding pyrrolidine as a Boc-protected product **18** (75% yield and 99% ee). The reduction of the lactol substrate **14e** was also carried out with triethylsilane in the presence of BF_3 as Lewis acid to give chromane **19** in 73%

yield (Path B), a substructure encountered within naturally occurring products. Eventually, the addition of indoline onto the likely oxonium species afforded product **20** as a mixture of 8.8:1 epimers (Path C).



Scheme 7. Useful transformations.

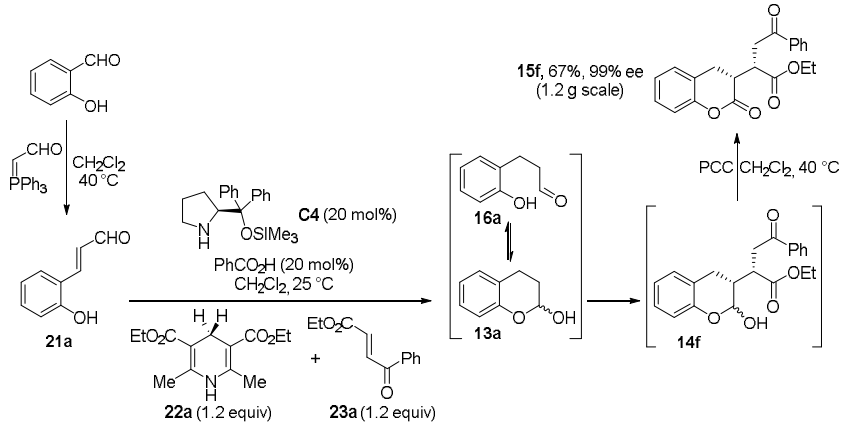
The group of Liu have pushed the limit of the organocatalyzed open-close strategy by performing a multicomponent reaction (MCR) involving 2-hydroxycinnamaldehydes **21**, the Hantzsch ester **22a** and *trans*-benzoylacrylic ester derivatives **23** (Scheme 8) giving rise to the formation of lactols **14**.[26] These Michael adduct intermediates **14** were oxidized *in situ* by PCC to afford chroman-2-ones **15** with excellent ee (>94%) and good yields described as single diastereoisomers. The chemoselective MCR was conducted thanks to the capability of prolinol type catalyst **C4** to promote both the Hantzsch ester-based reduction of enals **21** into hemiacetal compounds **13** at first (*via* an iminium intermediate) and the enantioselective Michael addition reaction to **13** (*via* an enamine intermediate **17**, see Scheme 6).



Scheme 8. A multicomponent reaction.

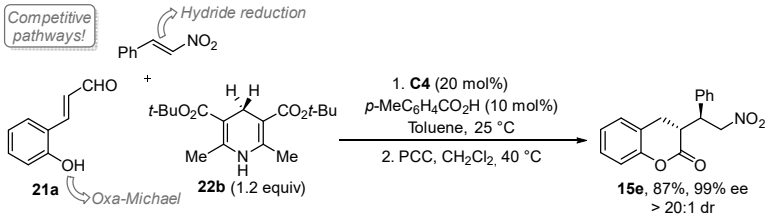
This one-pot sequence could be applied to a range of enal **21** and enone **23** partners as depicted in Scheme 8 with the selected products **15f-i**.

The authors then proved that this reaction could start from salicylaldehyde which easily underwent a Wittig olefination in order to synthesize *in situ* the required 2-hydroxycinnamaldehyde **21a** (Scheme 9).[26] Then, upon the addition of the others components, *i.e.* Hantzsch ester **22a** and the crude *trans*-benzoylacrylic ethyl ester **23a** in the presence of the organocatalyst **C4**, the reduction into intermediates **13a** and **16a**, the Michael addition and lactol **14f** formation took place, as a domino process. Then, the one-pot addition of PCC allowed the transformation of **14f** into the dihydrocoumarin **15f** with a remarkable 67% yield over the five steps performed in one-pot and on 1.2 grams scale.



Scheme 9. A five steps sequences.

In line with these achievements, this group of research undertook an investigation of a diversity-oriented synthesis (DOS) approach by started from a mixture 2-hydroxycinnamaldehyde **21a**, nitrostyrene and Hantzsch ester **22b** (Scheme 10).[27] Contrary to previous achievements that made use of benzoylacrylic esters **23** as Michael acceptors, the authors faced the competitive reduction of nitrostyrene by Hantzsch ester **22a**. Furthermore, as previously observed by Wang and colleague,[28] another competitive pathway took place which encompasses an oxa-Michael reaction of 2-hydroxycinnamaldehyde **21a** to nitrostyrene. However, by adapting the reaction conditions, namely by means of the more sterically hindered Hantzsch *tert*-butylester **22b** and *para*-methylbenzoic acid as additive, the corresponding chroman-2-one **15e** was obtained, after a one-pot PCC oxidation, with excellent yields and selectivities. The MCR was applied to a range of aldehydes and nitrostyrene derivatives en route to DOS.

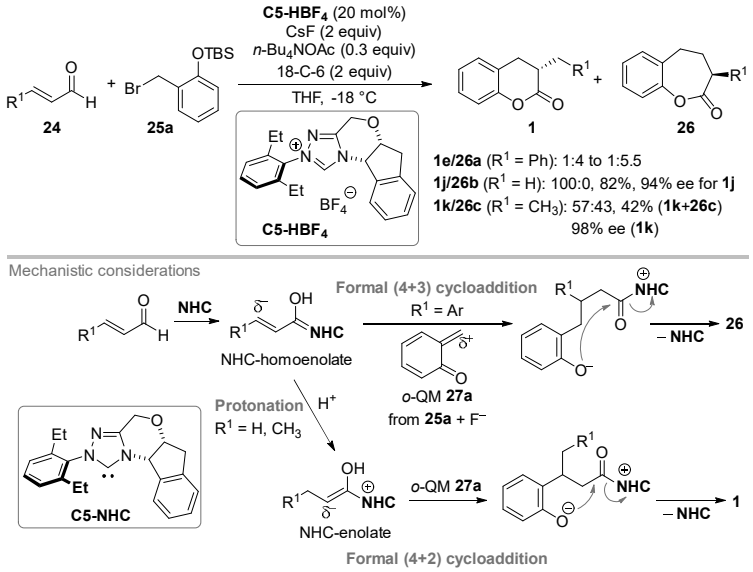


Scheme 10. An open-close strategy.

2.3. Catalytic syntheses involving enantioselective annulation processes

Besides the functionalization of chroman-2-ones, the construction of this bicyclic architecture has appeared as an appealing alternative asymmetric approach. The [4+2] cycloaddition between various nucleophiles and *ortho*-quinone methide (*o*-QM) derivatives was used as a strategy of choice. In this regard,

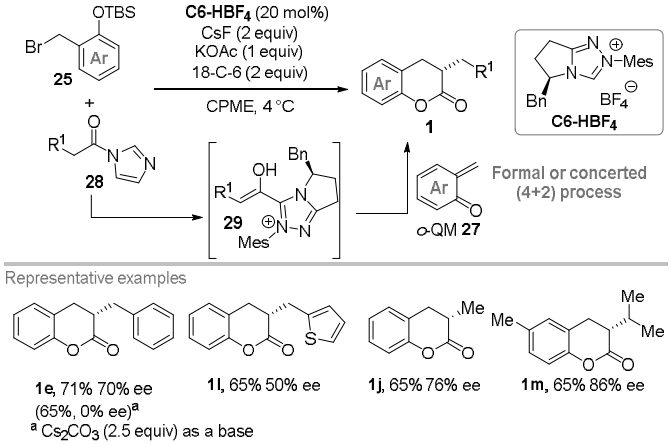
the group of Scheidt reported in 2013 the first synthesis of enantioenriched dihydrocoumarins **1** by means of a dual Lewis base activation strategy using a combination of a catalytic amount chiral azolium salt **C5-HBF4** (precursor of NHC catalyst **C5-NHC**) and an over-stoichiometric quantity of cesium fluoride (Scheme 11).[29] Starting from α,β-unsaturated aldehydes **24** and silylated phenols **25a**, as precursor of *o*-QM **27a**, the α-alkylated dihydrocoumarins **1** were initially identified as a side-products during the synthesis of 2-benzoxopinones **26**. During the setup of optimal reaction conditions with cinnamaldehyde **24a** (R^1=Ph), the corresponding products **1e/26a** was obtained with a ratio ranged from 1:4 to 1:5.5 regardless the reaction conditions (*i.e.* the nature of the chiral precatalytst azolium salt **C5-HBF4**, the base and the silylated phenol **25a**). The authors found that by using acrolein **24b** (R^1=H) instead of cinnamaldehyde **24a** (R^1=Ph) the dihydrocoumarin **1j** was synthesized as the only product in 82% yield and 94% ee. This result is surprising if one considers that acrolein is well known to oligomerize under nucleophilic conditions. However, crotonaldehyde **24c** (R^1=Me) gave a 57:43 ratio of **1k**/**26c** in 42% overall yield (**1k**+**26c**) but an excellent enantiomeric excess of 98% ee was measured for product **1k**. In order to gain insight into the mechanism and especially to the difference in reactivity between α,β-unsaturated aldehydes (*i.e.* with various R^1), DFT calculations were performed. The divergent reaction outcomes were attributed to a fast protonation event that takes place to the NHC-homoenolate intermediate with R^1=H, and to a lesser extend with R^1=alkyl, to furnish the NHC-enolate equivalent (Scheme 11). This latter species then undergoes a Michael addition/intramolecular *O*-acylation of the phenoxide anion to form the six-membered ring of the dihydrocoumarin **1**. On the other hand, in the presence of an α,β-unsaturated aldehyde having an aryl (R^1) substituent, the C-C bond formation is proposed to be faster than the competitive protonation thus resulting in the formation of the formal [4+3]-cycloaddition product **26**.



Scheme 11. Dual Lewis base activation strategy.

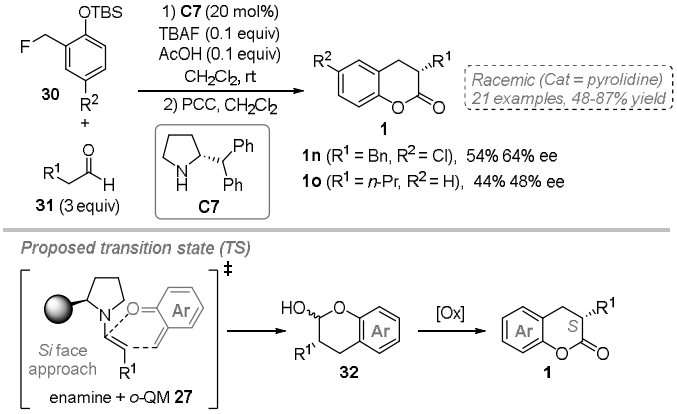
Later on, the same authors postulated that the use of acyl imidazoles should be of great interest in order to favor the selective formation of the NHC-enolate intermediate (Scheme 12).[30] Indeed, preliminary work demonstrated the feasibility of this approach starting from acyl imidazole **28a** (R^1=Ph) and the *o*-QM precursors **25** in the presence of a chiral imidazolium salt **C6-HBF4** as NHC pre-catalyst to provide the 3-benzyl dihydrocoumarin **1e** in 65% yield as a racemate. This lack of enantioselectivity was attributed to the slow racemization event occurring during the reaction conditions performed under the rather basic conditions (*e.g.* 2.5 equivalents of Cs_2CO_3). A change in both the amount and the strength of the base (1 equivalent of KOAc) allowed to solve this issue giving rise to the formation of dihydrocoumarin **1e** in 71%

yield and 70% ee. By applying these optimized conditions, 15 enantioenriched α-alkyl dihydrocoumarins **1** were obtained in fair to good yields and ee ranging from 50% to 86%. Regarding the mechanism, the authors postulated two plausible pathways. The first one is a formal [4+2] cycloaddition consisting of a domino Michael addition/annulation process as depicted in Scheme 11 while the second one would be a concerted (4+2)-process, both of them involving the same NHC-enolate intermediate **29**.



Scheme 12. Dual Lewis base activation strategy: extension to acyl imidazoles.

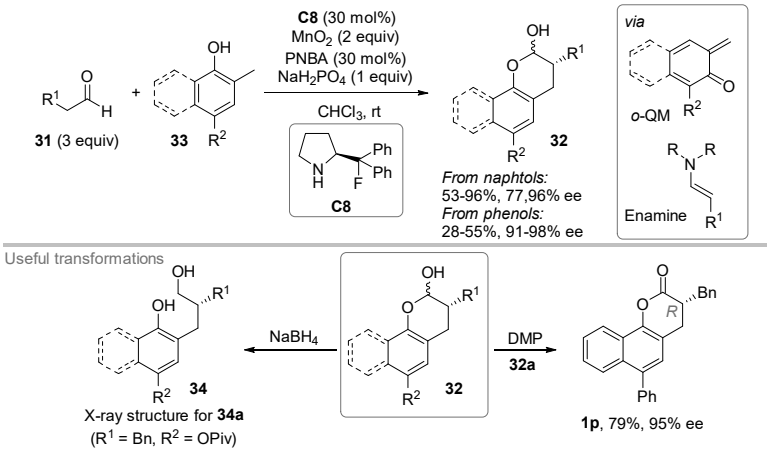
The group of Xie studied a two-steps sequence consisting of: 1) an enantioselecive [4+2] cycloaddition between *o*-QM **27** and aldehydes **31** to provide a transient hemiacetal **32**; 2) followed by an oxidation step to eventually afford dihydrocoumarins **1** (Scheme 13).[31] Indeed, starting from a silylated phenol **30**, as precursor of *o*-QM **27**, and aliphatic aldehydes **31**, the authors were able to obtain several racemic hemiacetals **32** under racemic aminocatalytic conditions (pyrrolidine used as catalyst) that, upon treatment with PCC as oxidant provided the corresponding 3-substituted dihydrocoumarins **1** with fair to high isolated yields. It is worth of noting that the presence of a fluorine atom as a living group on the silylated phenol **30** allows the use of only a catalytic amount of the external fluorine source for the *in situ* generation of the *o*-QM **27**. Moreover, acidic additives such as acetic acid was found to drastically improve the yield of the reaction.



Scheme 13. Aminocatalysis approach: [4+2] cycloaddition approach.

While 21 examples were obtained in racemic fashion, the authors successfully obtained two enantioenriched dihydrocoumarins **1n-o** by means of chiral benzhydryl pyrrolidine **C7** as a catalyst albeit in modest yields and enantioselectivities (**1g**, 54%, 64% ee; **1h**, 44%, 48% ee). Regarding the mechanism, both concerted (Hetero-Diels-Alder) or formal (Michael addition/cyclization) [4+2] cycloaddition processes were envisioned. To account for the stereochemical outcome of the reaction, a TS model was proposed whereby the *o*-QM **27** approaches from the *Si* face of the enamine intermediate affording the corresponding *S*-dihydrocoumarin **1** as the major enantiomer after the oxidation step (Scheme 13).

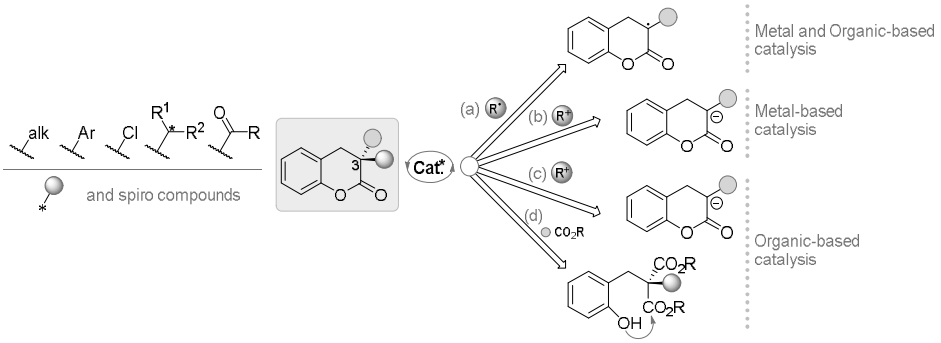
Two years later, the same group reported an original enantioselective formal [4+2] cycloaddition between *o*-QM, formed *in situ* from the corresponding phenol or naphtol derivatives **33**, and aldehydes **31** in the presence of a fluorine-containing chiral pyrolidine aminocatalyst **C8** to provide an entry to tricyclic hemiacetals **32** as precursors of dihydrocoumarins **1** (Scheme 14).[32] The basic idea of this work was to design experimental conditions that allow the similar rate of formation for both the enamine and the *o*-QM intermediates thus limiting the possible generation of by-products. The *o*-QM **27** was thus generated *in situ* from the corresponding phenol derivatives **33** by an oxidation reaction with MnO_2 under inert atmosphere in $CHCl_3$ at rt. It is worth of noting that the reaction media needs to be buffered (NaH_2PO_4) in order to maximize the formation rate of the enamine intermediate. Thus, by implementing these optimized reaction conditions (*i.e.* **C8** 30 mol%, MnO_2 2 equivalents, *p*-nitrobenzoic acid (PNBA) 30 mol%, NaH_2PO_4 1 equivalent), several enantioenriched hemiacetals **32** were obtained in high yields (53-96%) and enantiomeric excesses (77-96% ee) when naphtol derivatives where used, whereas phenol analogues gave almost the same level of enantioselection (91-98% ee) but at the expense of a drastically drop of yield (28-55%). In order to avoid epimerization issues, the enantiomeric excesses were measured on the corresponding diols **34** obtained after reduction of **32** with $NaBH_4$. The absolute configuration was ascertained by X-ray diffraction analysis of compound **34a** (R^1=Bn, R^2=OPiv). In order to demonstrate the synthetic utility of the chiral hemiacetals **32**, a chemical transformation of **32** (R^1=Bn, R^2=Ph, 95% ee) into dihydrocoumarin **1p** was achieved without racemization (95% ee) in 75% isolated yield. The same transition state (*Si* face approach) as the one described above in Scheme 13 was proposed to account for the stereochemical outcome of the reaction.



Scheme 14. Aminocatalysis approach: an entry to tricyclic dihydrocoumarins.

3. Enantioselective catalytic synthesis of C3-disubstituted dihydrocoumarins

The catalytic asymmetric syntheses of C3-disubstituted dihydrocoumarins were essentially conducted by alkylation reactions of α-substituted dihydrocoumarins as starting materials (Scheme 15). At the origin radical processes were initially envisaged (Scheme 15a), while ionic pathways either though metal (Scheme 15b) or organic (Scheme 15c) mediated catalysis were developed thereafter. More recent reports started considering other electrophiles than the alkyl-ones or cyclization-based sequences as alternatives methodologies (Scheme 15d).

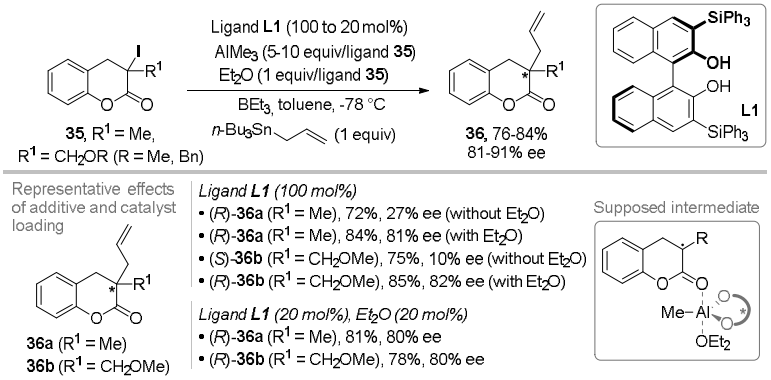


Scheme 15. Enantioselective strategies towards C3-disubstituted dihydrocoumarins.

3.1. Asymmetric radical alkylation reaction

The catalytic radical-based alkylation syntheses of nonracemic α,α-disubstituted dihydrocoumarins were reported in the 90s.[33-35] Despite inefficient catalytic cycles and high catalyst loading generally required, these achievements, essentially reported by the group of Hoshino and Murakata, constitute pioneering and inspiring contributions in that field of research both addressing the construction of chiral dihydrocoumarins with an all-carbon quaternary stereocenter and developments in catalytic radical chemistry at that time.

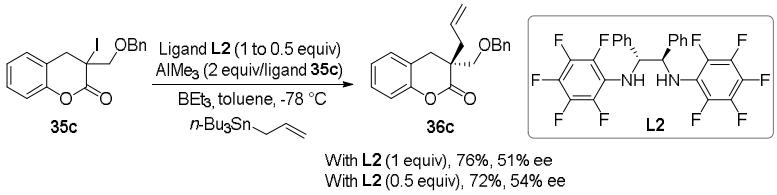
In 1997, Hoshino and coworkers demonstrated an enantioselective allylation of 3-iodo-3,4-dihydrocoumarins **35** by allyltributyltin to afford the corresponding lactone product **36** with the construction of a tetrasubstituted stereocenter with up to 91% ee in the presence of the chiral binaphtol ligand **L1** (Scheme 16).[33] Although the generation of a radical intermediate was initiated by means of triethylborane facing **35**, a marked acceleration of the reaction was only secured in the presence of a Lewis acid. Indeed, after the screening of various metal complexes (MgI_2, $Zn(OTf)_2$, Et_2AlCl, *etc.*) and additives, it was demonstrated that $AlMe_3$ was the best Lewis acid provided that the reaction was performed in the presence of diethylether as described in Scheme 16. The most remarkable outcome was observed with starting materials such as **35b**, having an ether pendant (R^1=CH_2OMe). Without Et_2O, the (*S*)-product **36b** was obtained in 75% yield and 10% ee, but improved ee of 82% and yield of 85% were measured in the presence of Et_2O for the (*R*)-product **36b**. This outcome was explained by a competitive complexation of the ether-pendant of **35b** which led to inverse enantioselectivity without Et_2O. Eventually, the authors demonstrated that the nonracemic Lewis acid loading could be decreased to 20 mol% to furnish for instance products **36a-36b** with similar ee of 80%, albeit a slight erosion was observed in the presence of 10 mol% of catalyst.



Scheme 16. Pioneering catalytic radical-mediated process.

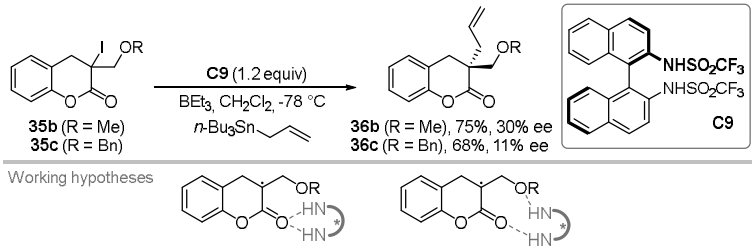
To account for these observations, it was proposed that a nonracemic aluminum MeAl-Lewis acid complex originated from ligand **L1** (pre-formation by adding **L1** and Me_3Al before **35**) led to a five-coordinate trigonal bipyramide aluminum intermediate (Scheme 16) with an Et_2O ligand and the carbonyl functional group of coumarin derivative being at the apical positions.

Murakata and Hoshino have investigated the use of a different class of C_2-symmetric diamine ligand **L2** for a similar nonracemic Lewis acid-mediated asymmetric allylation reaction of substrate **35c** (Scheme 17).[34] In this case the diethylether-effect was not reported and an enantiomeric excess of 51% was measured for product **36c** with 1 equivalent of ligand. It was also mentioned that a sub-stoichiometric amount of nonracemic Lewis acid could be used (0.5 equivalent) which, in principle, led to similar outcomes (72% yield and 54% ee).



Scheme 17. Use of diamine ligand in radical chemistry.

Although the term organocatalyst might be a bit too overestimated by means of an excess of a nonracemic entity, the demonstration that a C_2-symmetric diamine **C9** is able to promote a radical-mediated allylation reaction of 3-iodo-3,4-dihydrocoumarins **35b** or **35c** into the corresponding products **36b** and **36c** in up to 30% ee was already an important achievement in 2008, and worth being mentioned (Scheme 18).[35] The authors ruled out the possible implication of triethylborane, or complexes derived thereof, as Lewis acids by performing the reaction in the absence of this radical initiator, but by using azobisisobutyronitrile (AIBN) under light irradiation instead. This led to similar results. Then, it was supposed (working hypothesis, Scheme 18) that organic chiral promoter **C9** could create hydrogen bonding interactions either exclusively with the carbonyl functional group or by additionally involving the ether-pendant of dihydrocoumarin radical species.

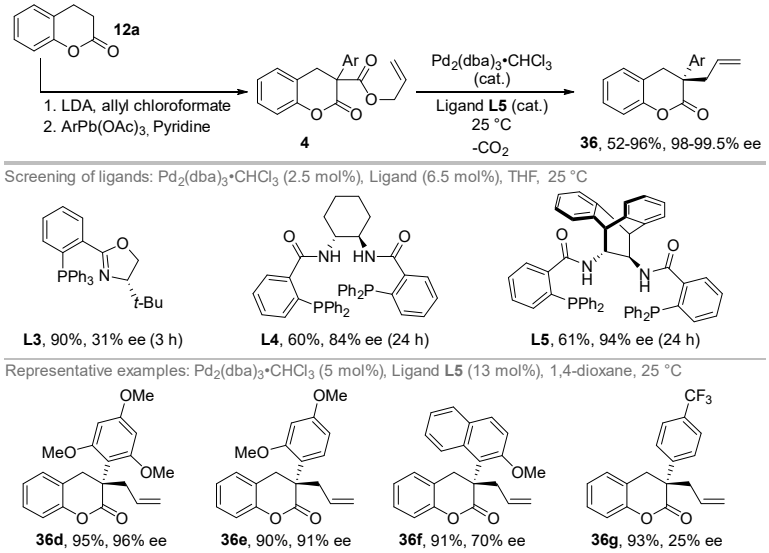


Scheme 18. Diamine ligand as "organocatalyst" in radical chemistry.

3.2. Metal-catalyzed alkylation reaction

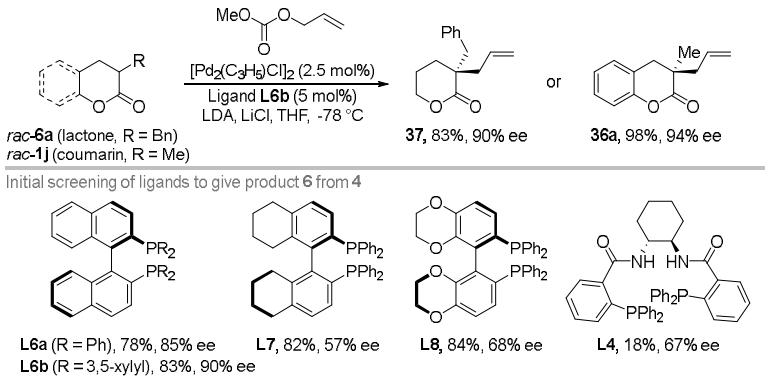
In 2016, the group of Guiry reported on an enantioselective synthesis of α-allyl-α-aryldihydrocoumarins **36** displaying an all-carbon quaternary stereocenter (Scheme 19).[36] The strategy was based on the so-called palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) reaction starting from starting material **4**. The authors developed a straightforward access to **4** from dichroman-2-one **12a** by means of a two-step sequence which began by the introduction of the allylic ester (LDA, allyl chloroformate). Then, an arylation reaction using aryllead triacetate reagents proved to be efficient to introduce sterically hindered arene moieties. With these precursors in hand, a screening of ligand **L3**-**L5** showed that *P*,*P*-bidendate ligand were the most competent to perform the DAAA reaction with high enantiomeric excesses reaching 94% with the (*R*,*R*)-DACH-phenyl Trost ligand **L5**. Further optimization

allowed to improve the ee up to 96% using dioxane as solvent thus giving rise to the formation of several sterically hindered dihydrocoumarins such as **36d-f** having *ortho* or di-*ortho*-substituted aryl moieties, especially with electron-donating properties (Scheme 19). However, a drop in the ee was measured starting from precursors **4** lacking *ortho*-substituent on the arene part as testified by the *para*-CF_3 phenyl product **36g** (25% ee). In the same paper, Akula and Guiry extended this protocol to the asymmetric synthesis of other lactones such as 3-isochromanones.[36]



Scheme 19. DAAA reaction towards allylic dihydrocoumarins.

The same years, Fang, Hou and coworkers published palladium-catalyzed asymmetric allylic alkylation (AAA) reaction of various lactones namely an intermolecular variant of this powerful alkylation reaction (Scheme 20).[37,38]During the optimization of the allylation of 3-benzyltetrahydro-2*H*-pyran-2-one **6a**, by allyl methyl carbonate to furnish product **37**, it was shown that lithium diisopropylamide (LDA) turned out to be the most suited base (*versus* NaHMHS, LiHMDS) provided that LiCl was used as an additive to improve both yields and ee. In THF at -78 °C, a series of bidentate C_2-symmetric ligands **L4** and **L6**-**L8** (to name a few) was investigated and this screening revealed that BINAP derived phosphine **L6b** provided the corresponding lactone **37** in up to 90% ee and with an excellent 83% yield.

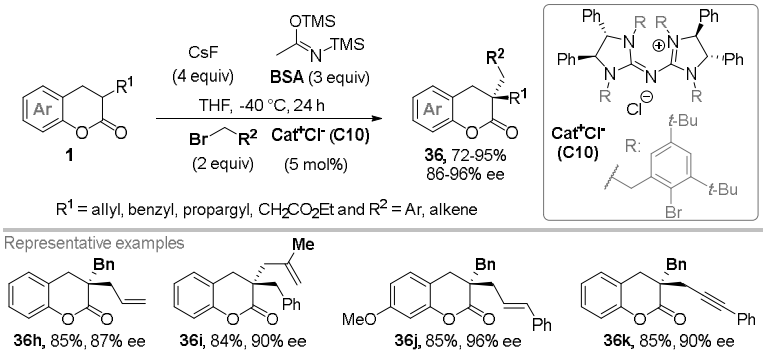


Scheme 20. AAA reaction towards allylic a dihydrocoumarin.

As seen with ligand **L7**-**L8**, the dihedral angle and the electronic of these phosphines are key features for the success of this reaction. Despite a single example was reported, these conditions were extended to the racemic α-methyldihydrocoumarin **1j** to provide the corresponding allylic product **36a** with 94% ee in excellent 98% yield (Scheme 20).

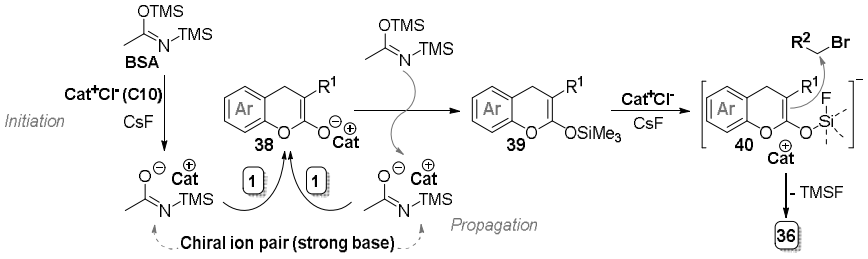
3.3. Organocatalyzed alkylation reaction

During preliminary investigations, Teng, Tan and colleagues have pointed out how challenging the direct alkylation reaction of α-substituted dihydrocoumarin **1** is, especially under regular basic conditions even upon Phase-Transfer Catalysis (PTC) conditions.[39] Upon these conditions indeed, either a lack of reactivity or an extensive decomposition occurred due to the sensitivity of the lactone moiety in the presence of a base. Consequently, the authors developed the so-called probase approach,[40] a process whereby *bis*(trimethylsilyl)acetamide (BSA) undergoes a desilylation by CsF to form *in situ* a strong amide base (Scheme 21). In the presence of the home-made pentanidiums **C10** as a PT-organocatalyst, the alkylation of a large array of α-substituted dihydrocoumarins **1** takes place and allows the formation of the corresponding product **36** with high ee and yields along with the challenging construction of an all-carbon quaternary stereocenter. Starting materials **1** having allylic, benzylic, propargylic and ester pendants (R^1) at C3 were nicely compatible with this enantioselective process, and allyl together with benzyl bromide electrophiles (R^2CH_2Br) could be introduced (Scheme 21). The yields and ee were not affected by the substitution pattern of the aromatic ring of the chroman-2-ones **1**.



Scheme 21. A probase approach.

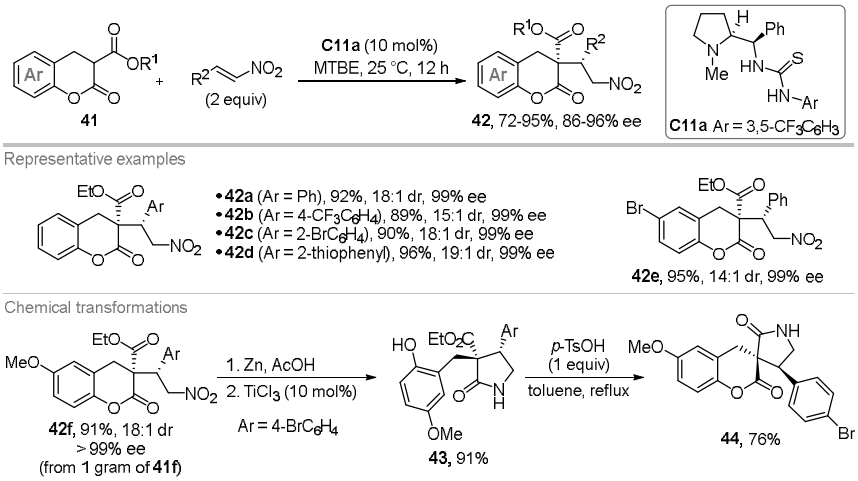
During preliminary mechanistic investigations, it was observed that the stoichiometrically pre-formed silyl ketene acetal **39**, a supposed key intermediate in this sequence, furnished a similar outcome than the probase sequence Scheme 22.[39] Accordingly, and although the authors mainly conducted the mechanistic investigations on indanone derivatives, the following sequence could be proposed as depicted in Scheme 22. BSA undergoes a desilylation event by CsF leading, after ion metathesis with pentanidiums catalyst **C10** (Cat^+Cl^-), to the *in situ* formation of the chiral ammonium amide ion pair as a strong base.



Scheme 22. Proposed intermediates.

Then, a deprotonation of the dihydrocoumarin **1** gives the ketene acetal **38** (initiation pathway) which is subsequently silylated by BSA into the silyl ketene acetal **39** while generating another equivalent of ammonium amide base (propagated pathway). This strategy prevents the accumulation of an otherwise destructive strong base. Then, it is believed that silyl precursor **39** is activated by the addition of a fluoride addition (likely vectorized by the ammonium Cat^+) to form the hypervalent silicate derivative **40** flanked by the chiral ammonium (Cat^+). This ion pair species would lead to the enantioselective alkylation reaction while recycling the ammonium-based catalyst (Scheme 22).

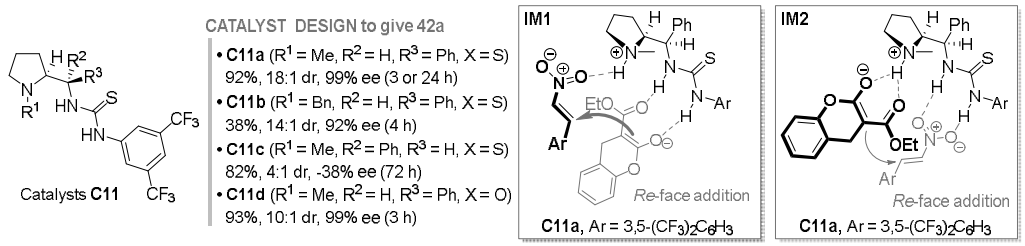
Hwang, Ryo and co-workers have developed another synthesis of α,α-disubstituted dihydrocoumarins **42** with the challenging control of two adjacent stereocenters (Scheme 23).[41] By means of 10 mol% of the bifunctional Brønsted base organocatalyst **C11a**, the rather acidic dihydrocoumarin derivatives **41** (in contrary of the aforementioned example), akin to a masked malonate, underwent a Michael addition to nitro olefins to afford the dihydrocoumarins **42** along with the formation of an all-carbon quaternary stereocenter with high yields, enantiomeric excesses and diastereoisomeric ratios. Although aliphatic nitroalkenes proved to be poorly reactive substrates, the aromatic counterparts led to corresponding products **42a**-**42d** with excellent outcomes irrespective of the substitution pattern on the aryl moiety, albeit a longer reaction time was required in the latter case. Furthermore, starting materials **41e-f**, substituted on the aromatic ring, were nicely tolerated as exemplified by the synthesis of adduct **42e**-**42f**. It is worth of noting, that this process could be performed on 1 gram scale with the use of 2 mol% of catalyst **C11a** to give product **42f** in 99% ee (Scheme 23). As an application, the nitro group of **42f** was then reduced by zinc in acidic conditions to furnish, after a titanium-promoted cyclization, the pyrrolidinone **43**. This compound **43** was subsequently recyclized into the original spiranic dihydrocoumarin **44** in 76% yield.



Scheme 23. A Brønsted base Michael addition.

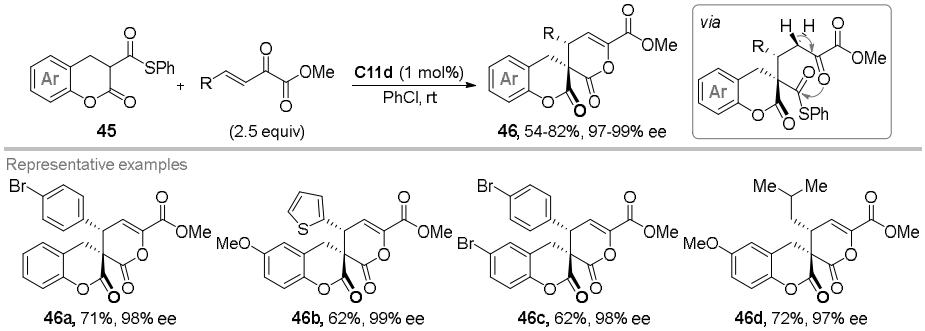
During this investigation, Ryu have designed a pyrrolidine-based organocatalyst **C11a** which outperformed the cinchona derived ones.[41,42] Under closely related conditions as those depicted in Scheme 23, it was shown that sterically more hindered *N*-benzyl catalyst **C11b** not only provided a lower yield of product **42a** than the *N*-methyl catalyst analogue **C11a** (38% *versus* 99%), but also achieved a lower ee (92% versus 99% ee, Scheme 24). Interestingly, the so-called *epi*-catalyst **C11c** led to both modest reaction rates (72 hours were needed to get 82% yield) and enantiomeric excess (38% ee), showing the key role of the stereocenter carried by the phenyl ring. On the other hand, the urea derived catalysts **C11d** also led to excellent results (93% yield and 99% ee) albeit in lower dr of 10:1. The authors proposed an induction model **IM1** obtained after deprotonation of the dihydrocoumarins **41a** by the amine catalyst **C11a** (Scheme 24). Thus, the so-obtained enolate intermediate would be complexed by the thiourea moiety of catalyst **C11a** while the tertiary ammonium salt part allows, thanks to hydrogen bonding interactions, its addition onto the

Re-face of nitrostyrene electrophile during the C–C bond formation, thus controlling both the absolute and relative configuration of the Michael adduct. As pointing out by the authors, another induction model **IM2** may account for this stereochemical outcome through the complexation of the nitro functional group by the thiourea group which also allows the incoming enolate nucleophile to attack the *Re*-face of the Michael acceptor thanks to hydrogen bonding with the ammonium moiety of the catalyst **C11a**.[41]



Scheme 24. Proposed induction model and catalyst design.

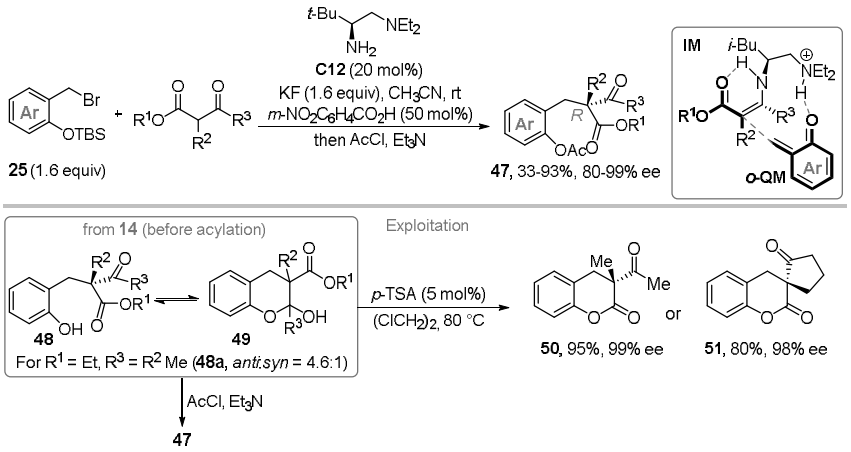
Inspired by the biosynthesis of chiral dihydropyranones from thiomalonates, the same group made use of dihydrocoumarins **45** as nucleophiles to perform an enantioselective domino Michael addition/cyclization reaction to β,γ-unsaturated α-keto esters (Scheme 25).[43] Thanks to the previously developed urea derived organocatalyts **C11d**, the corresponding spiranic dihydropyranones-dihydrocoumarin derivatives **46** were obtained in excellent yields and ee (>98%). In order to observe a productive cyclization onto the thioester moiety, the use of aromatic thioether instead of aliphatic ones were preferred. As long as the asymmetric induction was concerned, it was assumed that a similar induction model **IM2** (Scheme 24), previously proposed for nitrostyrene as Michael acceptors, might account for the enantio- and diastereoselectivity.



Scheme 25. Synthesis of spiranic pyranone.

In the context of methodology developments in amino catalysis, aiming at tackling the use of neutral super-electrophiles like *ortho*-quinone methides (*o*-QM), the group of Luo has achieved a highly enantioselective benzylation reaction of keto-esters to give, after acylation reaction, the enantioenriched products **47** with the construction of an all-carbon quaternary stereocenter (Scheme 26).[44] This transformation started from benzyl bromide derivatives **25**, as precursors of *o*-QM upon desilylation events promoted by KF. However, the known competitive benzylation of primary amine organocatalyst **C12** had to be prevented. Thanks to the use of *meta*-nitro benzoic acid as key additive, the benzylation of the catalyst **C12** in the presence of the base (KF) alone was indeed prevented while facilitating the enamine formation was facilitated (see induction model **IM** in Scheme 26). This benzylation reaction furnished at first the formation of phenol-derived products **48** which are in equilibrium with the cyclized hemi-acetal adducts **49**. Upon treatment with acetyl chloride the mixtures **48**/**49** eventually allow the formation of products **47**. On the other hands, the authors demonstrated that crude mixtures of **48**/**49** could be cyclized onto the ester moiety, under forced conditions in the presence of *para*-toluene sulfonic acid (*p*-TSA at 80 °C in

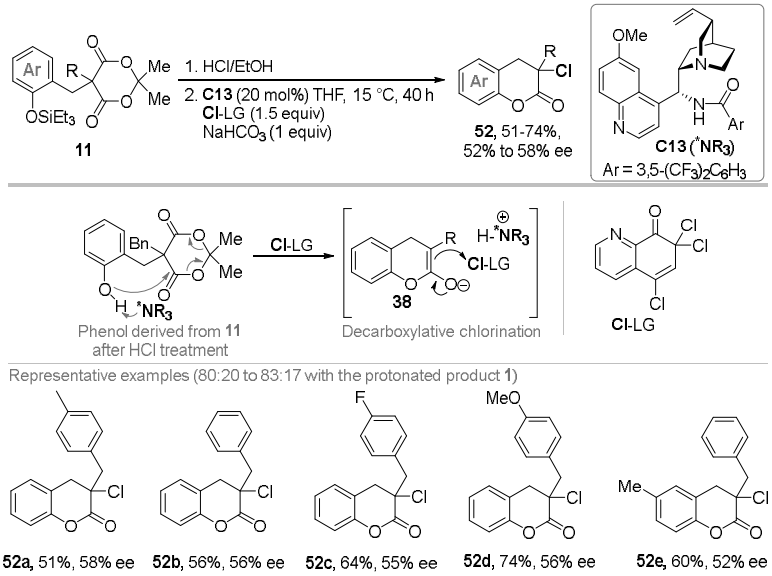
dichloroethane), to provide the corresponding dihydrocoumarins **50** and **51** in good yields and without erosion of the enantiomeric excesses.



Scheme 26. The *ortho*-quinone methide approach.

3.4. Miscellaneous

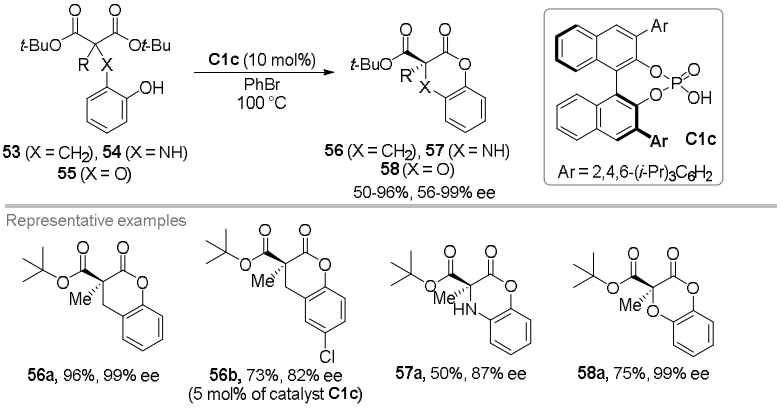
Our research group exploited the above-mentioned strategy (see Scheme 5 in section 2.1.) making use of C5-disubstituted Meldrum's acid platforms **11** for the synthesis of chlorinated dihydrocoumarin derivatives **52** displaying a tetrasubstituted stereogenic center at C3 (Scheme 27).[21] Pleasingly, in the presence of trichloroquinolinone as an electrophilic chlorine source (Cl-Leaving Group), a mineral base and upon the use of the bifunctional *epi*-amino quinine derived catalyst **C13**, a faster chlorination reaction of the enolate **38** intermediate occurred in place of the protonation event (with less of 20% of relative ratio was observed).



Scheme 27. Organocatalytic cyclization-decarboxylative-chlorination sequence.

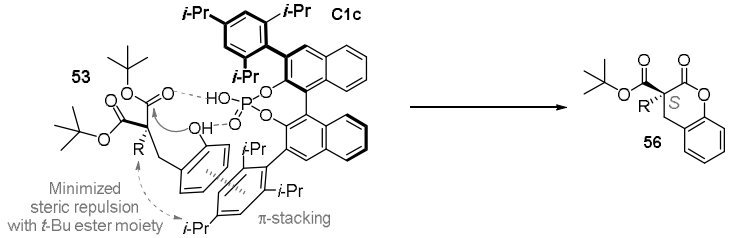
Although the yields and enantiomeric excesses (up to 58% ee) remain moderate, this sequence opens a new access to original enantioenriched chlorinated dihydrocoumarins **52** and constitutes a rare example of an enantioselective decarboxylative chlorination reaction (Scheme 27).[45]

Petersen and coworkers exploited their previously developed organocatalytic enantioselective desymmetrization reaction of disubstituted malonates,[46] to open an access to enantioenriched 3,4-dihydrocoumarins **56** and analogous heterocycles such as 1,4-morpholinones and 1,4-dioxanones **57**-**58** (Scheme 28).[47] The lactonization reaction took place on di-*tert*-butylester malonate derivatives **53**-**55** and was catalyzed by 5-10 mol% of BINOL derived phosphoric acid **C1c**, namely the so-called TRIP catalyst. The authors were able to obtain a range of dihydrocoumarin-derived heterocycles **56**-**58** with good yields and excellent enantiomeric excesses up to 99% despite the high temperature (100 °C) required to carry out this reaction.



Scheme 28. Organocatalyzed desymmetrization reaction.

Based on previously investigated specific interaction developed by TRIP type catalyst **C1c**, the authors suggested a bifunctional role of the phosphoric functional group both activating the phenol (Brønsted base activation) while a strong hydrogen bonding with one *tert*-butyl ester favors the lactonization reaction (Scheme 29). As long as the asymmetric induction is concerned, the authors proposed that a π-stacking interaction takes place between aryl pendants of both the axially chiral catalyst **C1c** and malonate **53**. Furthermore, the depicted conformation in Scheme 29 allows to keep away from each other the sterically bulky 2,4,6-tri-*iso*-propylphenyl moiety of catalyst **C1c** and the non-activated *tert*-butyl ester of **53**.



Scheme 29. Transition state proposed by Peterson and his co-workers

4. Conclusions

As testified by the results which have emerged since the last ten years, the catalytic asymmetric synthesis of chiral 3-substituted and 3,3-disubstituted dihydrocoumarins has led to significant achievements. The enantioselective α-substitution reaction of chroman-2-one platforms, essentially based on C–C bond construction, has been successfully executed by means of powerful organometallic or organic-based catalytic

tools. Then, the researchers have carried out various synthetic strategies. It is also important to point out that, in spite of important realization in annulation processes involving *ortho*-quinone methide derivatives to construct the dihydrocoumarin core, most of the proposed methodologies started from an existing dihydrocoumarin scaffolds. In search of product diversity, many opportunities remain to initiate new methodologies making use of more divers and original starting materials and, eventually, to go beyond the C–C bond construction to tackle more challenging C–heteroatom bond formation. We do hope that this review might be a useful background for the chemists interested in catching new opportunities for the elaboration of original dihydrocoumarin derivatives in heterocycles synthesis.

Acknowledgements

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References

1. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887-916.
2. Semeniuchenko, V.; Groth, U.; Khilya, V. *Synthesis* **2009**, *2009*, 3533-3556.
3. Kamat, D. P.; Tilve, S. G.; Kamat, V. P.; Kirtany, J. K. *Org. Prep. Proced. Int.* **2015**, *47*, 1-79.
4. Leitis, Z. *Chem. Heterocycl. Compd.* **2016**, *52*, 527-529.
5. Lovering, F. *MedChemComm* **2013**, *4*, 515-519.
6. Schneider, P.; Schneider, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 7971-7974.
7. Aurelie, C.; Sylvain, O.; Vincent, L. *Curr. Org. Chem.* **2012**, *16*, 2192-2205.
8. Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, *2014*, 6103-6119.
9. Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394-405.
10. Frongia, A.; Secci, F.; Melis, N. *Comptes Rendus Chimie* **2015**, *18*, 456-467.
11. Phelan, J. P.; Ellman, J. A. *Beilstein J Org Chem* **2016**, *12*, 1203-28.
12. Fu, N.; Zhang, L.; Luo, S. *Org Biomol Chem* **2018**, *16*, 510-520.
13. Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481-482.
14. Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshino, O. *Tetrahedron* **1999**, *55*, 10295-10304.
15. Gualtieri, G.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **2003**, *68*, 5013-5019.
16. Lee, J.-W.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 18245-18248.
17. Muzart, J. *Adv. Synth. Catal.* **2019**, *361*, 1464-1478.
18. James, J.; Akula, R.; Guiry, P. J. *Adv. Synth. Catal.* **2018**, *360*, 3138-3149.
19. Kingston, C.; James, J.; Guiry, P. J. *J. Org. Chem.* **2019**, *84*, 473-485.
20. Fernando, J. E. M.; Nakano, Y.; Zhang, C.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2019**, *58*, 4007-4011.
21. Martzel, T.; Annibaletto, J.; Levacher, V.; Brière, J.-F.; Oudeyer, S. *Adv. Synth. Catal.* **2019**, *361*, 995-1000.
22. Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2009**, *43*, 440-454.
23. Pair, E.; Cadart, T.; Levacher, V.; Brière, J.-F. *ChemCatChem* **2016**, *8*, 1882–1890.
24. Legros, F.; Martzel, T.; Brière, J.-F.; Oudeyer, S.; Levacher, V. *Eur. J. Org. Chem.* **2018**, *2018*, 1975-1983.
25. Liu, Y.-K.; Li, Z.-L.; Li, J.-Y.; Feng, H.-X.; Tong, Z.-P. *Org. Lett.* **2015**, *17*, 2022-2025.
26. Sun, X.-L.; Chen, Y.-H.; Zhu, D.-Y.; Zhang, Y.; Liu, Y.-K. *Org. Lett.* **2016**, *18*, 864-867.
27. Chen, Y.-H.; Sun, X.-L.; Guan, H.-S.; Liu, Y.-K. *J. Org. Chem.* **2017**, *82*, 4774-4783.
28. Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627-1630.
29. Izquierdo, J.; Orue, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 10634-10637.
30. Lee, A.; Scheidt, K. A. *Chem. Commun.* **2015**, *51*, 3407-3410.
31. Zhou, D.; Mao, K.; Zhang, J.; Yan, B.; Wang, W.; Xie, H. *Tetrahedron Lett.* **2016**, *57*, 5649-5652.
32. Zhou, D.; Yu, X.; Zhang, J.; Wang, W.; Xie, H. *Org. Lett.* **2018**, *20*, 174-177.
33. Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713-11714.
34. Murakata, M.; Jono, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1998**, *9*, 2087-2092.
35. Murakata, M.; Jono, T.; Shoji, T.; Moriya, A.; Shirai, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2479-2483.

36. Akula, R.; Guiry, P. J. *Org. Lett.* **2016**, *18*, 5472-5475.
37. Yamamoto, H.; Samanta, R. C. *Synfacts* **2016**, *12*, 0811-0811.
38. Li, X.-H.; Wan, S.-L.; Chen, D.; Liu, Q. R.; Ding, C.-H.; Fang, P.; Hou, X.-L. *Synthesis* **2016**, *48*, 1568-1572.
39. Teng, B.; Chen, W.; Dong, S.; Kee, C. W.; Gandamana, D. A.; Zong, L.; Tan, C.-H. *J. Am. Chem. Soc.* **2016**, *138*, 9935-9940.
40. Claraz, A.; Oudeyer, S.; Levacher, V. *Adv. Synth. Catal.* **2013**, *355*, 841-846.
41. Jin, H.; Cho, S. M.; Hwang, G.-S.; Ryu, D. H. *Adv. Synth. Catal.* **2017**, *359*, 163-167.
42. Jin, H.; Cho, S. M.; Lee, J.; Ryu, D. H. *Org. Lett.* **2017**, *19*, 2434-2437.
43. Jin, H.; Lee, J.; Shi, H.; Lee, J. Y.; Yoo, E. J.; Song, C. E.; Ryu, D. H. *Org. Lett.* **2018**, *20*, 1584-1588.
44. Zhu, Y.; Zhang, W.-Z.; Zhang, L.; Luo, S. *Chem. Eur. J.* **2017**, *23*, 1253-1257.
45. First enantioselective decarboxylative chlorination of β-ketocarboxylic acids: Shibatomi, K.; Kitahara, K.; Sasaki, N.; Kawasaki, Y.; Fujisawa, I.; Iwasa, S. *Nat. Commun.* **2017**, *8*, 15600.
46. One example of a multi-step enantioselective synthesis of a dihydrocoumarins in this paper: Kelley, A. M.; Minerali, E.; Wilent, J. E.; Chambers, N. J.; Stingley, K. J.; Wilson, G. T.; Petersen, K. S. *Tetrahedron Lett.* **2019**, *60*, 1262-1264.
47. Kelley, A. M.; Haywood, R. D.; White, J. C.; Petersen, K. S. *ChemistrySelect* **2020**, *5*, 3018-3022.