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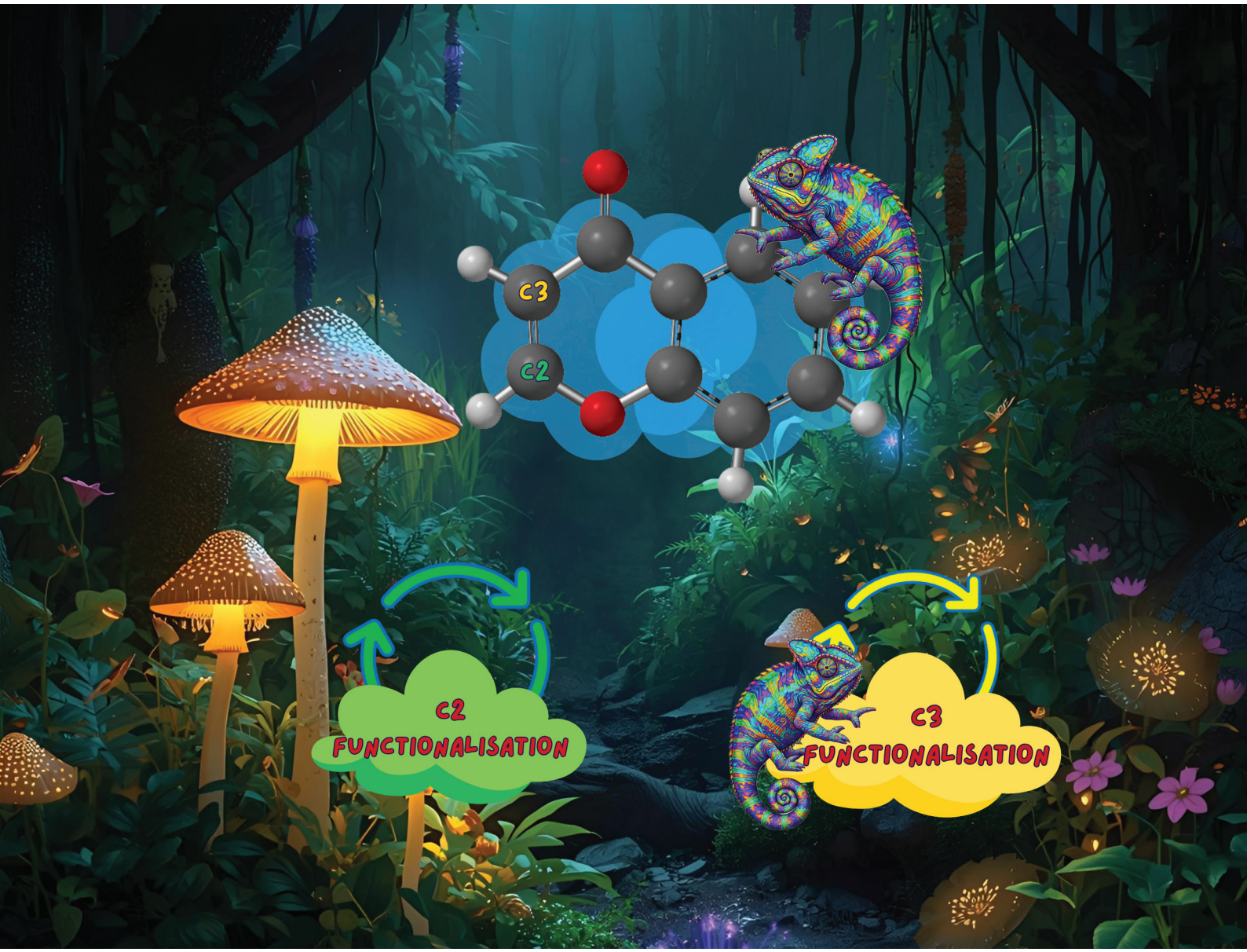

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REVIEW ARTICLE
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REVIEW

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Organocatalysed C-2 and C-3 functionalisation of chromones

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This review highlights the recent advancements in organocatalysed Michael addition reactions involving chromones, an important class of heterocyclic compounds with significant biological and pharmacological properties. Chromones, with their versatile conjugated structure, act as both electrophilic and nucleophilic partners, providing an ideal platform to synthesise diverse stereochemically enriched molecular frameworks. The work highlights various organocatalysed examples using chiral carbenes, phosphoric acids, thioureas and squaramides, that have demonstrated high efficiency and stereocontrol in a range of reactions. Mechanistic insights into how these catalytic systems activate the chromone scaffold and promote enantioselective transformations are also discussed in detail. Finally, we underline emerging trends and future directions in this research area, addressing current limitations, such as the need for more efficient catalytic systems and broader substrate compatibility.

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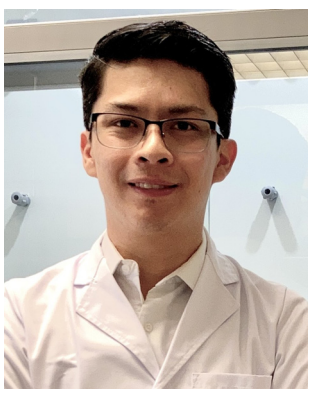
Introduction

The field of organocatalysis has gained significant attention since the early 2000s.[1] Organocatalytic methods represent an exciting and sustainable approach to chemical synthesis of complex and chiral molecules, which are particularly impor-



Juan Carlos Morales-Solís

Juan Carlos Morales-Solís was born in Mexico in 1996. He graduated with honors in Medicinal Chemistry (QFB) from Universidad Veracruzana in 2019. He obtained his Master's degree with honors from Universidad Autónoma del Estado de Morelos (UAEM) supervised by Prof. Mario Ordoñez, working on diastereoselective synthesis of heterocyclic aminophosphonic acids analogs of the hydroxypipecolic acid. He is currently completing his PhD through a cotutelle program between UAEM and the University of Zaragoza (Spain) at the HOCA group (ISQCH-CSIC), under the joint supervision of Prof. Mario Ordoñez and Dr. Eugenia Marqués-López, respectively. His research focuses on the enantioselective synthesis of hydroxyphosphonates derived from chromones, using organocatalysed strategies.

Mario Ordoñez

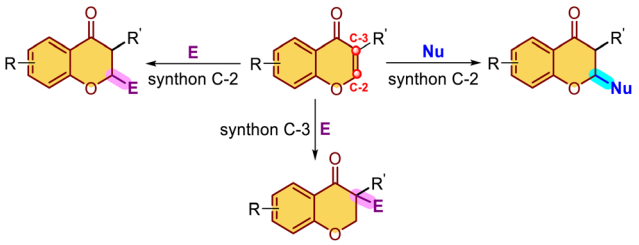
Mario Ordoñez born in Tlaxcala, Mexico. Received his Ph.D. in Chemistry from the University of Sevilla (Spain) in 1995. Since 1998 is Full Professor of Organic Chemistry at the University of Morelos State (Mexico). His research interests include the racemic and stereoselective synthesis of heterocyclic α-aminophosphonates and α-aminophosphinates through phosphonylation of N-acyliminium ions and Kabachnik–Fields reaction using new catalysts and their applications in medicinal and organic chemistry. Current research interests also involves the synthesis of a wide variety of α,β-unsatutared amides bearing α-aminophosphonates via Horner–Wadsworth–Emmons reaction, as well as the synthesis of isoindolin-2-ones and 2-phospho-4-oxochromanes.

tant in medicine and the pharmaceutical industry,[2] where the stereochemistry of a molecule can drastically affect its biological activity.[3] Additionally, this field is recognised for its advantages in terms of environmental impact, reaction versatility, and access to enantiomerically enriched products, making it a valuable tool for chemists in academic, industrial, and pharmaceutical research.

Among the plethora of organic reaction developed in this field, the Michael addition reaction is a cornerstone transformation in organic chemistry, particularly valued for its ability to create carbon–carbon and carbon-heteroatom bonds.[4] This kind of reaction provides a powerful alternative for building complex molecular frameworks, especially in the synthesis of natural products, pharmaceuticals, and advanced materials. One interesting application of the Michael addition involves the use of chromones as electrophilic (nucleophilic) partners.[5]

Chromones (1-benzopyran-4-ones) are heterocyclic compounds containing a benzopyran core with a ketone group. The chromone skeleton is found in a wide variety of naturally occurring compounds, including flavonoids, coumarins, and certain alkaloids, many of which exhibit valuable pharmacological properties.[6] These properties make chromones an attractive target for chemical modification through reactions like the Michael addition, enabling the construction of new molecules with potential biological activity. In the context of the Michael reaction, chromones can act as both nucleophiles and electrophiles, although they are more commonly employed as electrophilic partners. The most reactive site in chromones for nucleophilic additions is the C-2 position, which is activated due to electron withdrawal from the carbonyl group at C-4 (Scheme 1). Therefore, in this review, we aim to highlight the chameleonic behaviour exhibited by these fascinating structures.

One key feature of chromones is the conjugation between the carbonyl group at C-4 and the adjacent double bond. This



Scheme 1 Activated electrophilic/nucleophilic **C-2** and **C-3** positions for conjugated addition reactions in chromones.

conjugation not only stabilises the molecule but also broadens the reactivity potential of the chromone nucleus.

The resulting chromanone adducts also constitute an important structural motif found in many bioactive and natural compounds, making this reaction valuable for the synthesis of pharmacologically active molecules (Fig. 1). This reaction opens new pathways for constructing complex molecules, including those with potential anticancer, antiviral, or anti-inflammatory properties,[7] further highlighting the importance of the Michael addition reaction in the context of chromone chemistry.[8]

Recent advances in asymmetric Michael additions using chromones have focused on the development of enantioselective variants, allowing for the creation of chiral centres in a controlled manner. In this context, asymmetric transition-metal complexes have also been employed to achieve high enantioselectivity, leading to significant advancements in this area of research.[9] The racemic approach using silyl compounds to activate the carbonyl group of this structure also deserves special mention, as it represents a pioneering approach for activating this conjugated skeleton and has served as a source of inspiration for further research in this area.[10]

Eugenia Marqués-López

Dr. Marqués-López obtained her degree in Chemical Sciences from the University of Seville (2002), where she also earned her PhD in the Department of Organic Chemistry (2007). Her research has focused on the development of asymmetric synthetic methodologies using chiral auxiliaries and catalysis. She conducted research stays at the University of Oxford (2005) and TU Dortmund (2008–2010), the latter supported by a Humboldt Fellowship. Since 2011, she has been based at the University of Zaragoza, where she has held the position of Associate Professor since 2020. Her scientific output includes numerous publications, book chapters, a patent, and active international collaborations.

Raquel P. Herrera

Raquel P. Herrera completed her Ph.D. (1999–2003) under the supervision of Prof. Guijarro and Prof. Yus, at the University of Alicante. She then took up a European postdoctoral contract with Prof. Ricci (Bologna, Italy) until March 2006. Then, joined Prof. Lassaletta's and Fernández's group at the IIQ-CSIC (Seville, Spain). She was appointed to her present position at the ISQCH-University of Zaragoza in January 2008, first as ARAID Researcher, since 2012 as Tenured Scientist and currently, as Scientific Researcher (2021). In 2012 she was awarded with the Lilly Prize for the best young scientist less than 40 years, in Spain. She is the head of the Asymmetric Organocatalysis research group.

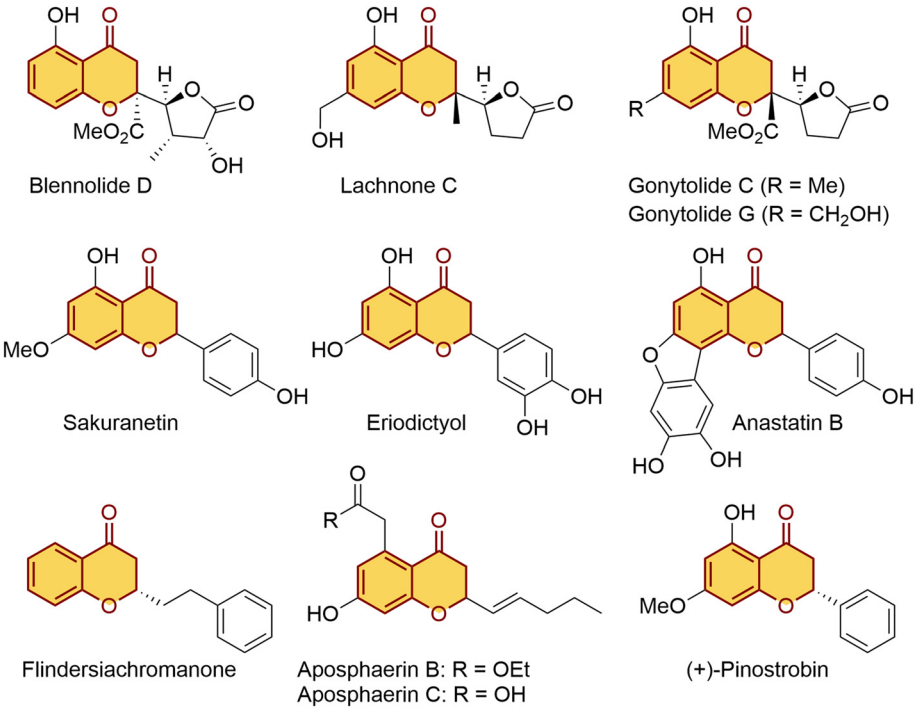


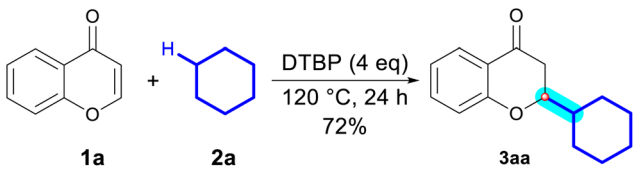
Fig. 1 Structure of bioactive chromanone natural products.

In addition, organocatalysts have been successfully developed to enhance the efficiency and selectivity of Michael additions with chromones. These catalytic strategies allow for mild reaction conditions, improved yields, and stereocontrol over the product, making them highly attractive for large-scale and industrial applications.

Although other valuable reviews have been published covering various aspects of chromone chemistry,[5] such as annulation reactions and C–H activation processes, there remains a lack of a comprehensive overview specifically focused on organocatalytic approaches. This gap has motivated us to undertake the present review, with a particular emphasis on the use of chiral organocatalysts. Our aim is to highlight recent advances and provide a detailed analysis of the progress made in organocatalysed C-2 and C-3 functionalisation of chromones.

Michael addition reactions using chromones as electrophilic C-2 synthons

In the context of chromones acting as electrophilic C-2 synthons, the Michael addition reaction is an interesting synthetic approach that usually requires organometallic reagents, as in the Zimmerman's strategy, which uses $Zn(OTf)_2$ as a catalyst,[11] or in Feringa's method,[9c] which employs a copper catalyst to produce 2-alkylchromanones. However, recent advances in the C–H functionalisation of chromones under metal-free conditions, which deserve special mention, have been developed by Han's group in 2014.[12] They demonstrated that the reaction of chromone **1a** and cyclohexane (**2a**) in the presence of 4 eq. of di-*tert*-butyl peroxide (DTBP) at 120 °C for 24 h, yielded 2-cyclohexylchroman-4-one (**3aa**) in 72% yield (Scheme 2).



Scheme 2 Synthesis of 2-cyclohexylchroman-4-one (**3aa**) *via* sp^3 C–H functionalisation.

Attempts to increase the yield by using additional DTBP or alternative oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), NaClO, $K_2S_2O_8$, 1,4-benzoquinone (BQ), or O_2 were unsuccessful. The method exhibited broad applicability, tolerating a variety of chromones **1a–h** and alkanes **2a–d**. Chromones bearing a methyl or bromine substituent at the C-6 position, as well as methoxy groups at the C-5 and C-7 positions, afforded the corresponding chromanones **3** with yields ranging from 58% to 83% (see the original article for a complete scope of the process).[12] Notably, the electron-withdrawing nature of the bromine at C-6 enhanced the yield, whereas steric hindrance and electron-donating groups, such as a methoxy substituent at C-5, seemed to have a moderate impact on the yield (Fig. 2).

The proposed mechanism proceeds through a radical pathway (Scheme 3). Initial homolysis of DTBP **4** would generate a *tert*-butoxy radical **5**$^{\bullet}$, which would abstract a hydrogen atom from cyclohexane **2a** to form a cyclohexane radical **2**$^{\bullet}$. This radical would add to chromone **1a**, yielding an intermediate **6aa** that would react further with the *tert*-butanol to form

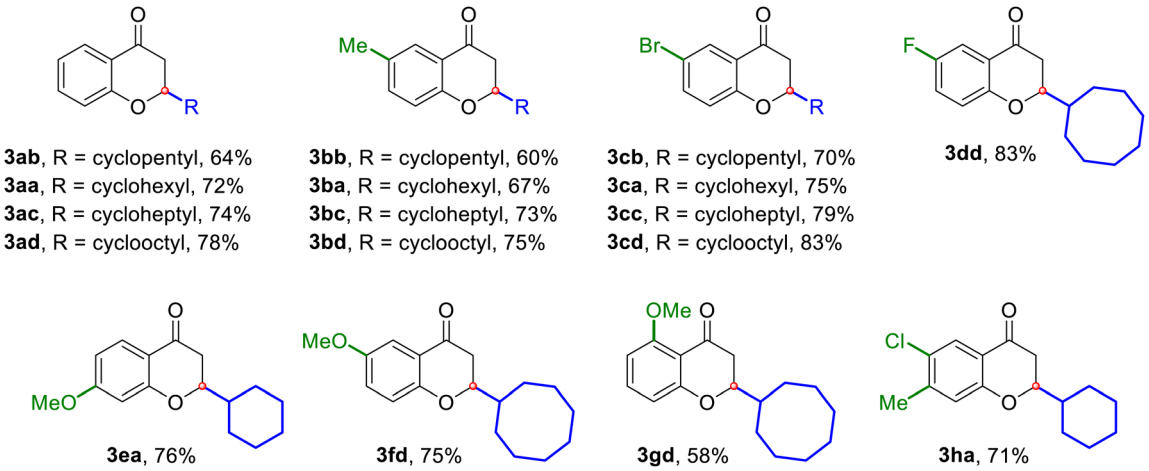
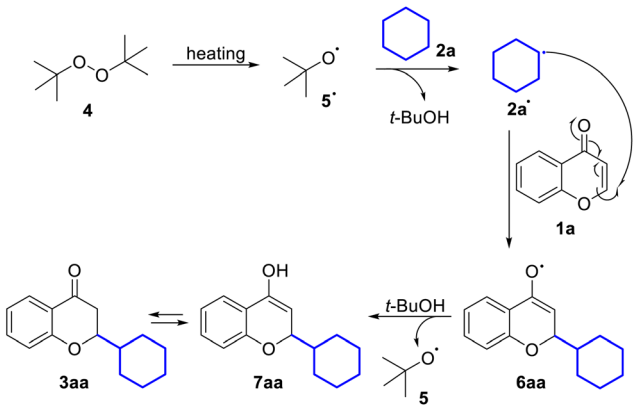


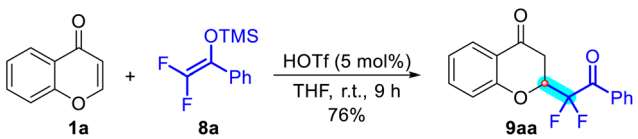
Fig. 2 Selected examples from the general scope for the synthesis of 2-alkylchroman-4-ones **3**.



Scheme 3 Mechanism *via* radical course.

an enol intermediate **7aa**. Subsequent keto–enol tautomerisation would produce the final 2-alkylchromanone product **3aa**.

In other hand, the *gem*-difluoroalkyl moiety have shown great importance in drug design to enhance the metabolic stability and biological properties of molecules.[13] Therefore, Hao and co-workers have selectively introduced a *gem*-difluoroalkyl moiety by developing an efficient metal-free Michael addition of difluoroenoxysilanes **8a** to chromone **1a**, using trifluoromethanesulfonic acid (HOTf) as a catalyst (Scheme 4).[14] Initially, the reaction of chromone **1a** with the difluoroenoxysilane **8a** in dichloromethane was tested with 10 mol% of different Lewis acids as $Fe(OTf)_3$, $Al(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_3$,



Scheme 4 Highly efficient Michael addition of difluoroenoxysilane **8a** to chromone **1a**.

and trimethylsilyl trifluoromethansulfonate (TMSOTf) over 72 h, obtaining the 2-difluoroalkylated chroman-4-one **9aa** in moderate yields. Notably, among all of them, the best yield was obtained with TMSOTf (72%), prompting further exploration to enhance the yields by exploring the Brønsted acid catalyst HOTf in dichloromethane (78%) and hexane (85%) over 27 h. However, the optimal reaction conditions were established using 5 mol% of HOTf in THF as solvent, after 9 h of reaction, resulting in the synthesis of 2-difluoroalkylated chroman-4-one **9aa** with 76% yield (Scheme 4).

After establishing the optimal reaction conditions, the scope of the reaction was evaluated (Fig. 3). It was found that chromones substituted at the C-7 position (**1h,i**) with electron-donating groups (Me, OMe) led the desired products **9ha** and **9ia** at higher yields compared to those bearing electron-withdrawing groups (F, Cl, Br) (**9ja**, **9ka**, **9la**). Furthermore, electron-withdrawing groups (F, Cl, Br, NO_2) at the C-6 position (**9da**, **9ea**, **9fa**, **9ga**) resulted a higher yield than those with electron-donating groups (Me, OMe) (**9ba**, **9ca**). Subsequently, the scope of phenyl-substituted difluoroenoxysilanes **8b–e** was evaluated, revealing that substituents in *para* position improved the yield, achieving values between 89 and 93% (**9ab**, **9ac** and **9ad**) (Fig. 3).

However, the need to prepare enantiomerically pure compounds requires new stereoselective strategies that consider both environmental impact and reaction versatility. Consequently, as illustrated in the following methods, asymmetric organocatalysis has played a crucial role in addressing this challenge.

Enantioselective Michael addition reactions using chromones as electrophilic C-2 synthons

This approach enables the synthesis of highly functionalised, stereochemically enriched compounds that are crucial intermediates in pharmaceuticals, natural products, and advanced materials.[2,3]

Interestingly, based on the anion-binding ability of silanediols as catalysts,[15] Mattson and co-workers pioneered the first

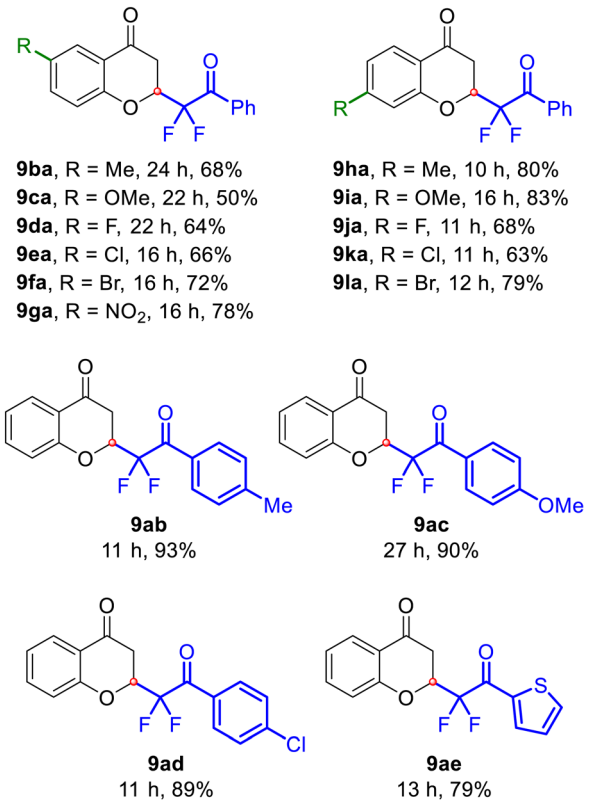


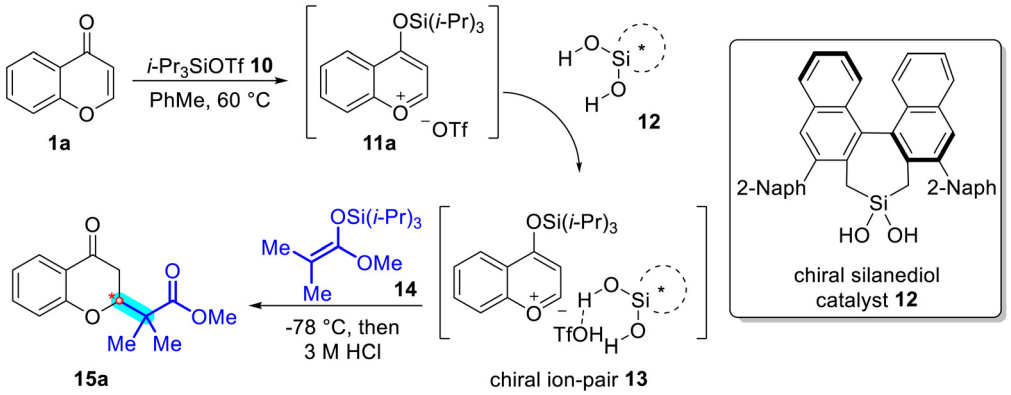
Fig. 3 Highly efficient Michael addition of difluoroenoxysilane **8a–e** to chromones **1a–l**.

enantioselective C-2 functionalisation of chromones.[16] Their approach uses enolsilyl acetals as nucleophiles within a catalytic silanediol ion-pair strategy. In this methodology, the reaction of chromone **1a** with a trialkylsilyl triflate **10** in toluene, at 60 °C, afforded its 4-siloxybenzopyrylium triflate **11a**, which was captured with the silanediol catalyst **12** to form a chiral ion pair **13**.[16] Subsequently, the addition of the silyl acetal **14** at −78 °C provided the corresponding 2-alkylchroman-4-one **15a** (Scheme 5). Notable, the nature of silyl group present on both the silyl acetal **14** and the silyl triflate **10** significantly influenced the enantioselectivity of the reaction, where the tri-*iso*-propyl group was better than *tert*-butyldimethylsilyl group.

Further studies exploring the scope of this reaction, using 20 mol% of catalyst **12**, provided evidence about the effect of the substituents on the chromone backbone (Fig. 4). In fact, electron-withdrawing substituents such as Br, F, and Cl at the C-6 position (**15c**, **15e**, **15f**) led to higher yields compared to electron-donating groups like H and Me (**15a**, **15b**). Notably, the highest yield was achieved when a CF_3 group was introduced at the C-7 position (**15h**). Additionally, the enantioselectivity improved in the presence of electron-withdrawing groups (Br, F, Cl, NO_2) at the C-6 position (**15c**, **15e**, **15f**, **15g**). The best enantiomeric excess (ee) was observed for the 3,5-(F_3C)Ph-substituted derivative (**15d**) (Fig. 4).

The absolute configuration of the newly formed stereogenic centre at the C-2 position of chromanones **15** was determined by X-ray crystallography of its iminochromanone derivative **16a** (Scheme 6). This derivative was obtained by reacting a racemic (*rac*) mixture of 2-substituted chromanone **15c** with (*R*)-2-methylpropane-2-sulfinamide using $Ti(OMe)_4$ as catalyst in THF at reflux, affording the iminochromanone **16a** in 80% yield and a diastereomeric ratio (dr) of 55 : 45. The diastereoisomers were then separated by crystallisation from dichloromethane and hexanes. Finally, the X-ray analysis and the deprotection of the iminochromanone **16a** revealed the absolute configuration (*S*) of its chromanone **15c** (Scheme 6).

In the context of chromone as C-2 electrophilic synthon, the presence of a carboxylic acid at the C-3 position has demonstrated significant potential in enhancing the activation of the Michael acceptor, facilitating the synthesis of novel 2-substituted chroman-4-ones. Albrecht's group has been a pioneer in developing a decarboxylative Michael addition using malonic acid half-thioesters in their first enantioselective approach.[17] Subsequently, Albrecht and co-workers explored the Michael addition of azlactones **18** to chromone-3-carboxylic acids **17** to synthesise novel α-amino acid moieties.[18] Initially, the reaction between chromone **1a** with azlactone **18a** was carried out in the presence of 20 mol% of quinine in THF at room temperature. However, no reaction was observed under these conditions. Introducing a carboxylic



Scheme 5 Enantioselective C-2 functionalisation of chromones **1a** *via* chiral ion-pair **13**.

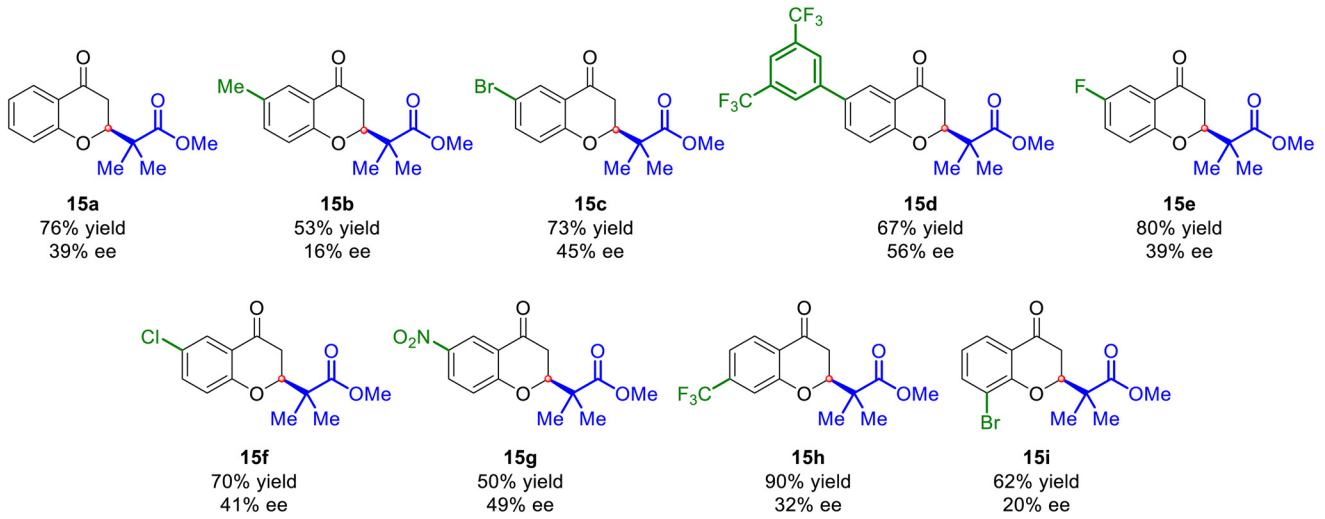
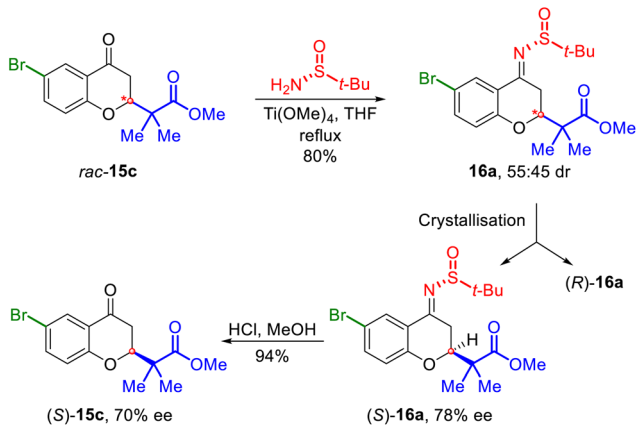
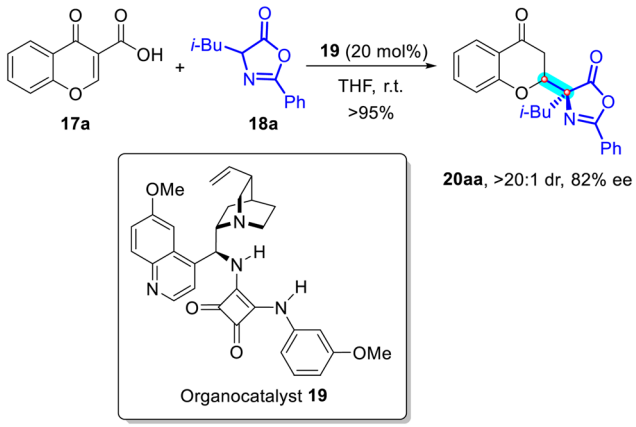


Fig. 4 Highly efficient enantioselective Michael addition of difluoroenoxysilane **14** to chromones **1a–i**.



Scheme 6 Chiral resolution of chroman-4-one **15c** by formation of the iminochromanone **16a**.



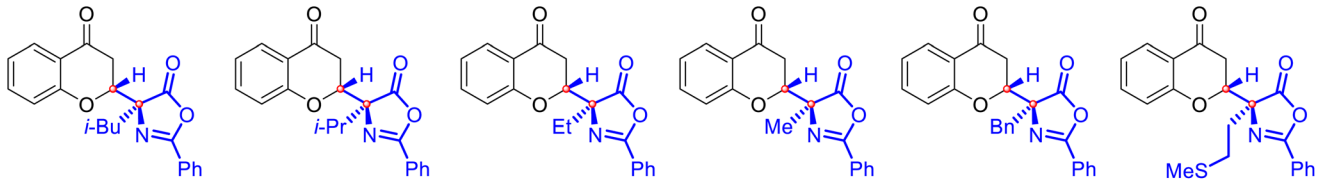
Scheme 7 Decarboxylative Michael addition of azlactone **18a** to chromone-3-carboxylic acid **17a**.

acid moiety at the C-3 position of chromone **17a** successfully facilitated the formation of the desired product **20aa** in over 95% yield *via* a decarboxylative Michael addition, albeit initially with low diastereoselectivity. In this context, to improve the enantioselectivity of the process, they conducted a screening of different organocatalysts. Notably, cinchonidine-derived squaramide **19** significantly improved the stereoselectivity, yielding the 2-substituted chromone **20aa** with >95% yield, a diastereomeric ratio of >20 : 1, and 82% enantiomeric excess (Scheme 7).[18]

The method showed a broad scope in the preparation of 2-substituted chromanones **20** (Fig. 5 and 6). In all cases, the final products were obtained with moderate-to-high yields. Notably, good diastereoselectivities were achieved with the model azlactone **18a**, although lower enantioselectivity was observed in all cases compared to product **20aa** (Fig. 5). Additionally, electron-withdrawing groups (Br, F, Cl) in the chromone-3-carboxylic acid (**17c–17e**) gave the products **20** in higher yield than those with an electron-donating group (Me) in **17b** (Fig. 6). Despite these variations, the best outcome in this series was still achieved with the reaction model, leading to the formation of product **20aa** (see the original article for a complete scope of the process).

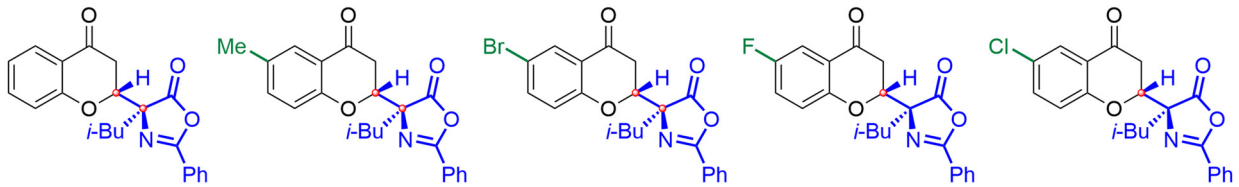
Furthermore, the absolute configuration of the newly formed stereogenic centre was confirmed by X-ray crystallographic analysis of one of the chromanones **20**. Finally, the hydrolysis of the azlactone **20aa** using TsOH in a MeOH : $CHCl_3$ (2 : 1) at 40 °C produced the α,α-disubstituted amino acid **21aa** (Scheme 8).

Additionally, a transition state model **22** was proposed by the authors to explain the observed stereoselectivity (Fig. 7). It is suggested that the chromone-3-carboxylic acid **17** would interact with the cinchona catalyst **19** *via* hydrogen bonding with the NHs of the squaramide. At the same time, the tertiary amine moiety, on the quinuclidine ring of **19**, would promote the deprotonation of the azlactone **18**. The simultaneous inter-



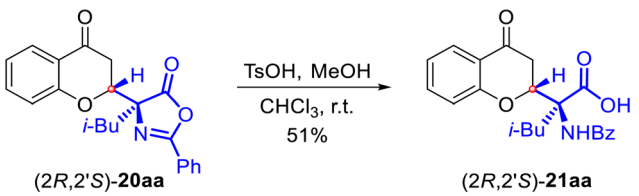
20aa, 81% yield, >20:1 dr, 82% ee; **20ab**, 42% yield, 3:1 dr, 66% ee; **20ac**, 80% yield, 2.5:1 dr, 56% ee; **20ad**, 81% yield, >20:1 dr, 44% ee; **20ae**, 74% yield, 4:1 dr, 48% ee; **20af**, 81% yield, 5:1 dr, 46% ee

Fig. 5 Selected examples from the general scope of the decarboxylative Michael addition of azlactones **18a–f** to chromone-3-carboxylic acid **17a**.



20aa, 81% yield, >20:1 dr, 82% ee; **20ba**, 34% yield, 19:1 dr, 60% ee; **20ca**, 70% yield, 19:1 dr, 54% ee; **20da**, 65% yield, 19:1 d.r., 58% ee; **20ea**, 73% yield, 10:1 d.r., 59% ee

Fig. 6 Selected examples from the general scope of the decarboxylative Michael addition of azlactone **18a** to chromone-3-carboxylic acids **17a–e**.



(2*R*,2'*S*)-**20aa** (2*R*,2'*S*)-**21aa**

Scheme 8 Azlactone-ring opening to afford protected α,α-disubstituted amino acid **21aa**.

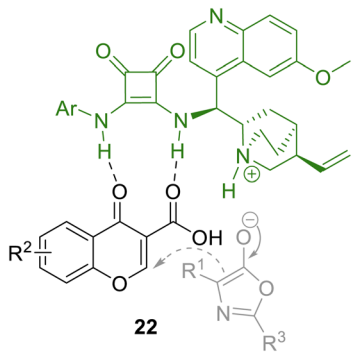


Fig. 7 Proposed transition state **22** to explain the observed stereochemistry in **20**.

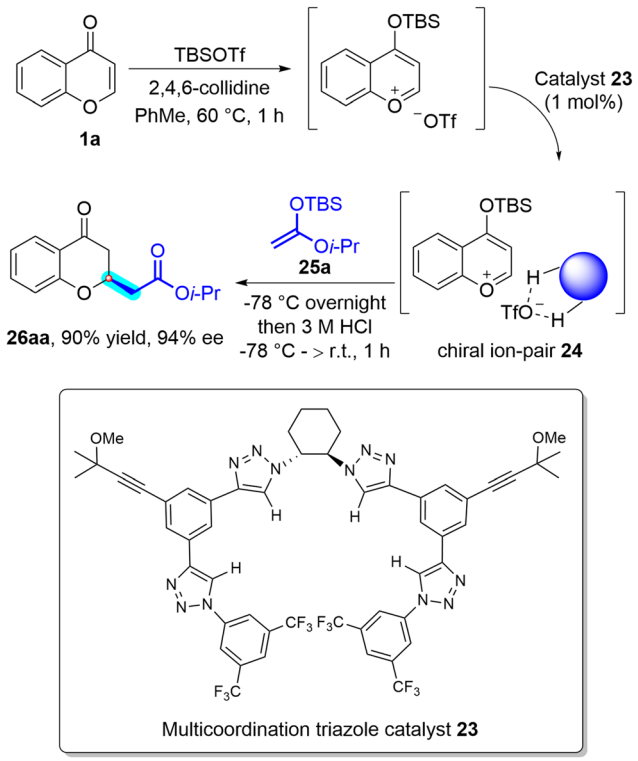
action between the protonated catalyst and the resulting enolate, forming an ion pair, would facilitate the enantioselective Michael addition.

Contemporaneously, García Mancheño and co-workers reported a highly enantioselective nucleophilic dearomatisation reaction of pyrylium salts using a chiral multicoordination triazole anion-binding catalyst **23** to afford 2-alkyl chromanones **26**.[19] Initially, the reaction was performed as previously described by Akiba,[10a] wherein the active benzopyrylium ion was generated through the reaction of chromone **1a** with a silyl derivative [*tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)] in the presence of catalytic amounts of chiral H-donor catalyst **23** and 2,4,6-collidine at 60 °C in toluene. The optimal conditions involved the use of TBSOTf with a remarkably low catalyst loadings (1 mol%) of the multicoordination triazole **23**, followed by the reaction with a silyl ketene acetal **25a** at −78 °C, affording the 2-alkyl chromanone **26aa** in 90% yield and 94% ee (Scheme 9).

The scope of the reaction was investigated by testing various silyl ketene acetals **25a–e**. The substitution pattern on the nucleophile was found to significantly influence on the enantioselectivity of the process, with more sterically hindered nucleophiles proceeding smoothly and exhibiting lower enantioselectivity (**25c–e**) than smaller nucleophiles (**25a–b**). Chromones substituted at C-6 position with either electron-donating and electron-withdrawing groups delivered final products **26** in high yields and with moderate to excellent enantioselectivities (Fig. 8). Interestingly, the method also proved effective for challenging thiochromones and 4-pyrones, producing final products with moderate yields but good to excellent enantioselectivity (see the original article for a complete scope of the process).[19]

Enantioselective conjugated addition reactions using chromones as nucleophilic C-2 synthons

Additionally, enantioselective Michael addition reactions using chromones as nucleophilic synthons are also of significant importance in synthetic organic chemistry, as they provide a powerful and efficient approach for constructing structurally complex and biologically relevant molecules with high stereocontrol.[20]



Scheme 9 General reaction by chiral ion-pair **24** to obtain chromanone **26aa**.

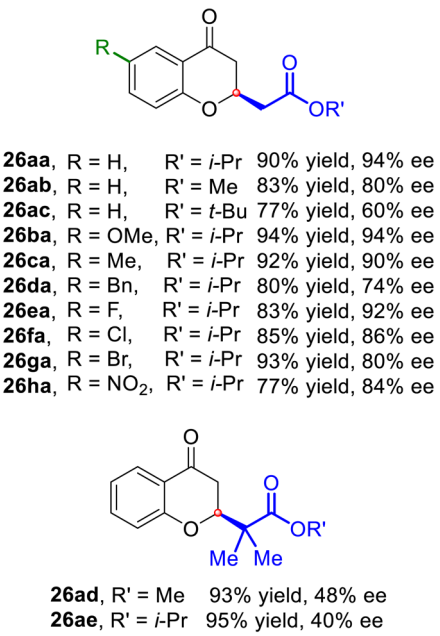


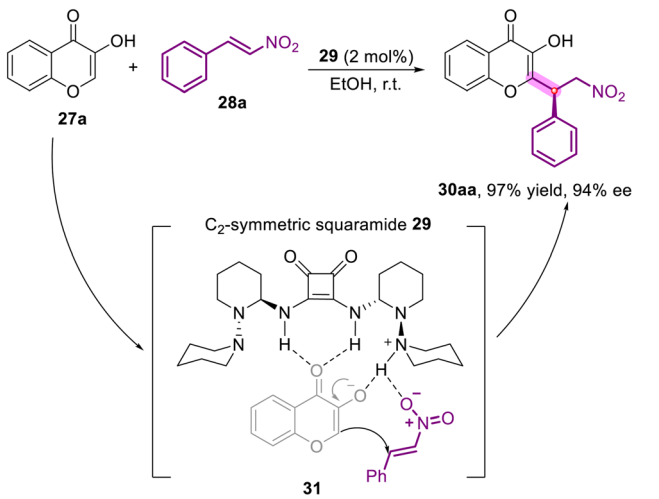
Fig. 8 Selected examples from the general scope using chiral ion-pair to obtain chromanones **26**.

Recently, in the field of C–H functionalisation to obtain new 2-functionalised chromones,[21] Zlotin and co-workers,[22] reported a metal-free C-2 functionalisation of 3-hydroxychromones **27** *via* electrophilic olefination with electron-deficient olefins, such as nitroolefins **28** (Scheme 10) or β,γ-unsaturated-α-keto esters **32** (Scheme 11), using a recyclable C_2-symmetric squaramide **29** as organocatalyst. The reaction was optimised between the 3-hydroxychromone **27a** and nitroolefin **28a** in the presence of 2 mol% of the chiral C_2-symmetric squaramide **29** at room temperature in EtOH (95%). This process afforded 2-alkyl-3-hydroxychromone **30aa** in 97% yield and 94% ee (Scheme 10). Transition state **31** was proposed by the authors to explain the absolute configuration observed in the final products **30**. In this mechanism, the bifunctional squaramide **29** would deprotonate the chromone **27a** through its tertiary amino group. Then, the catalyst would interact with the enolate to influence the geometry of the active complex. Simultaneously, strong hydrogen bonds formed between the electron-deficient olefins **28a** and the NH groups of the squaramide, would drive the nucleophilic attack determining the absolute configuration of final products **30**.

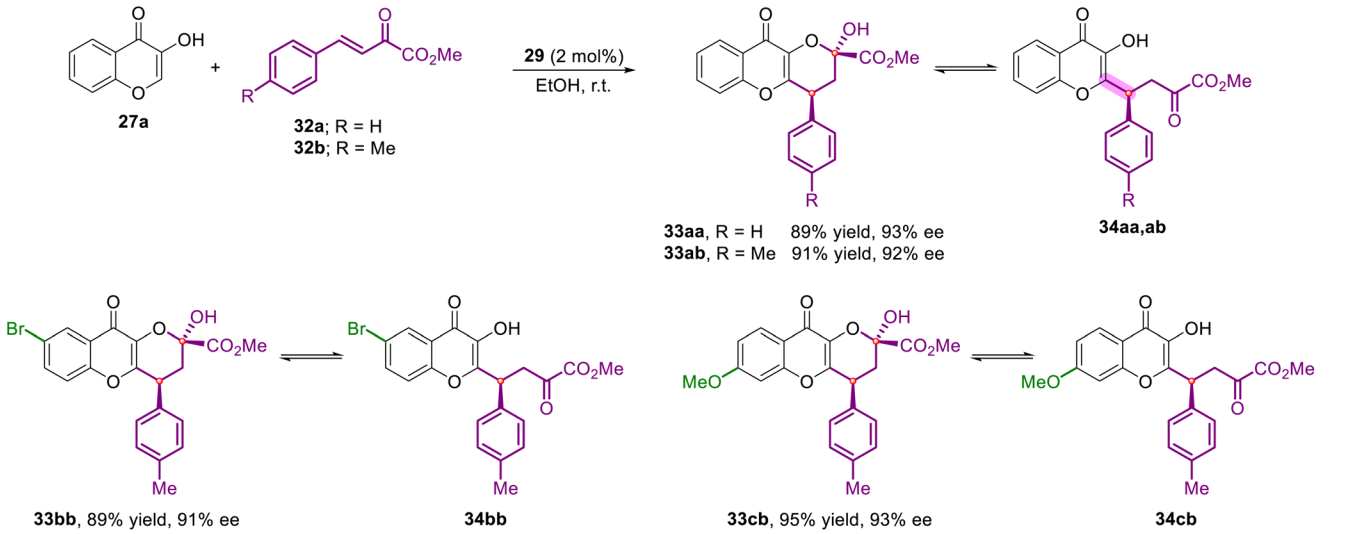
With the best reaction conditions established, the scope of this methodology was evaluated with various 3-hydroxychromones **27a–c** and several nitroolefins **28a–f**, leading to the corresponding 2-alkyl-chromones **30** with yields of up to 99% and excellent enantioselectivity (90–99% ee, see the original article for a complete scope of the process). In general, this method demonstrated an excellent tolerance to electronic effects of the substituents in the 3-hydroxychromones **27a–c** and nitroolefins **28a–f** (Fig. 9).[22]

Additionally, β,γ-unsaturated-α-keto esters **32a,b** showed almost quantitative yield and high enantioselectivity, leading to the formation of the corresponding Michael adducts **33** and **34** in a lactonisation/ring opening equilibrium (Scheme 11).

Following the same approach of chromones as nucleophilic C-2 synthon, Rafiński and co-workers reported a very interesting asymmetric organocatalysed conjugated addition of 3-hydroxychromones **27** *via* chiral α,β-unsaturated acyl azoliums.[23] In this methodology, initially, 3-hydroxychromone **27a**



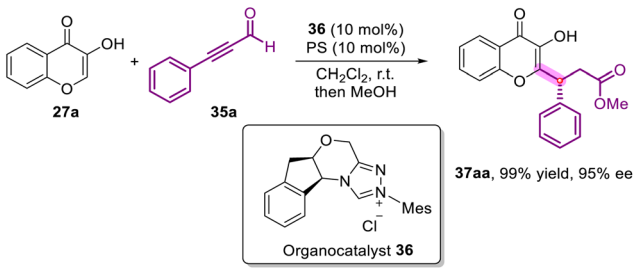
Scheme 10 Model reaction for the formation of chromenone **30aa** through C_2-symmetric squaramide catalyst **29**.



Scheme 11 General scope using β,γ-unsaturated-α-keto esters **32a,b** to obtain chromenone derivatives **33** and **34**.

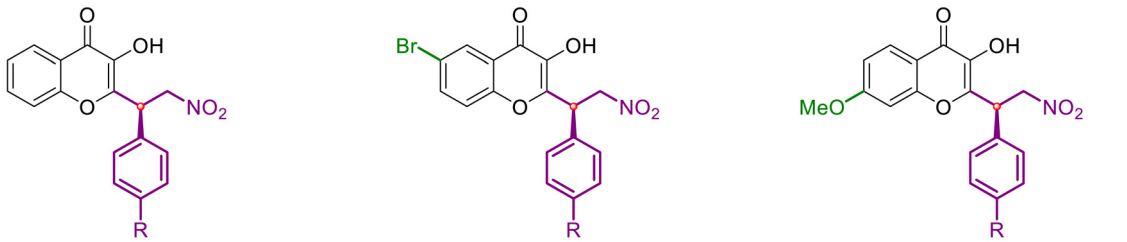
reacted with ynal **35a** in the presence of a carbene, generated from chiral aminoindanol-derived triazolium salt **36**, using a proton sponge (PS) as sterically hindered and non-nucleophilic base, in dichloromethane. Subsequent treatment with MeOH, afforded the *C*2-alkylated 3-hydroxychromone **37aa** in 99% yield (as determined by ^{1}H NMR analysis), and 95% ee (Scheme 12).

Under the best reaction conditions, this strategy showed a great scope as shown in Fig. 10 (see the original article for a complete scope of the process). Notably, various 3-hydroxychromones **27** were tested with different substituents at C-6 and C-7 position (**27a–i**), affording the desired products **37** in 66–99% yield and excellent enantioselectivities (56–99% ee). Notably, a methoxy group at C-5 position (**27h**) gave its respective chromone **37ha** in 97% yield and 99% ee. Additionally, a series of ynals with electron-withdrawing (**35b–d**) and electron-donating groups (**35e–g**) on the *para* position of the phenyl ring worked well. However, the CF_3 moiety (**35h**) exhibited only



Scheme 12 General reaction by chiral carbene to obtain chromenone **37aa**.

moderate selectivity. A similar trend was observed for the phenyl *ortho*-substituted ynals (**35i–l**) giving high stereoselectivities. However, phenyl *meta*-substituted ynals (**35m** and **35n**) showed slightly lower enantioselectivity without affecting the yield (**37am** and **37an**). The reaction also showed good toler-



30aa, R = H	97% yield, 94% ee	**30ba**, R = H	92% yield, 91% ee	**30ca**, R = H	89% yield, 95% ee
30ab, R = Me	95% yield, 92% ee	**30bc**, R = OMe	88% yield, 90% ee	**30cc**, R = OMe	91% yield, 92% ee
30ac, R = OMe	98% yield, 92% ee	**30be**, R = Cl	80% yield, 95% ee	**30ce**, R = Cl	99% yield, 93% ee
30ad, R = F	95% yield, 92% ee	**30bf**, R = Br	84% yield, 92% ee	**30cf**, R = Br	91% yield, 98% ee
30ae, R = Cl	90% yield, 95% ee				
30af, R = Br	92% yield, 95% ee				

Fig. 9 Selected examples from the general scope using chiral squaramide **29** to obtain chromenone derivatives **30**.

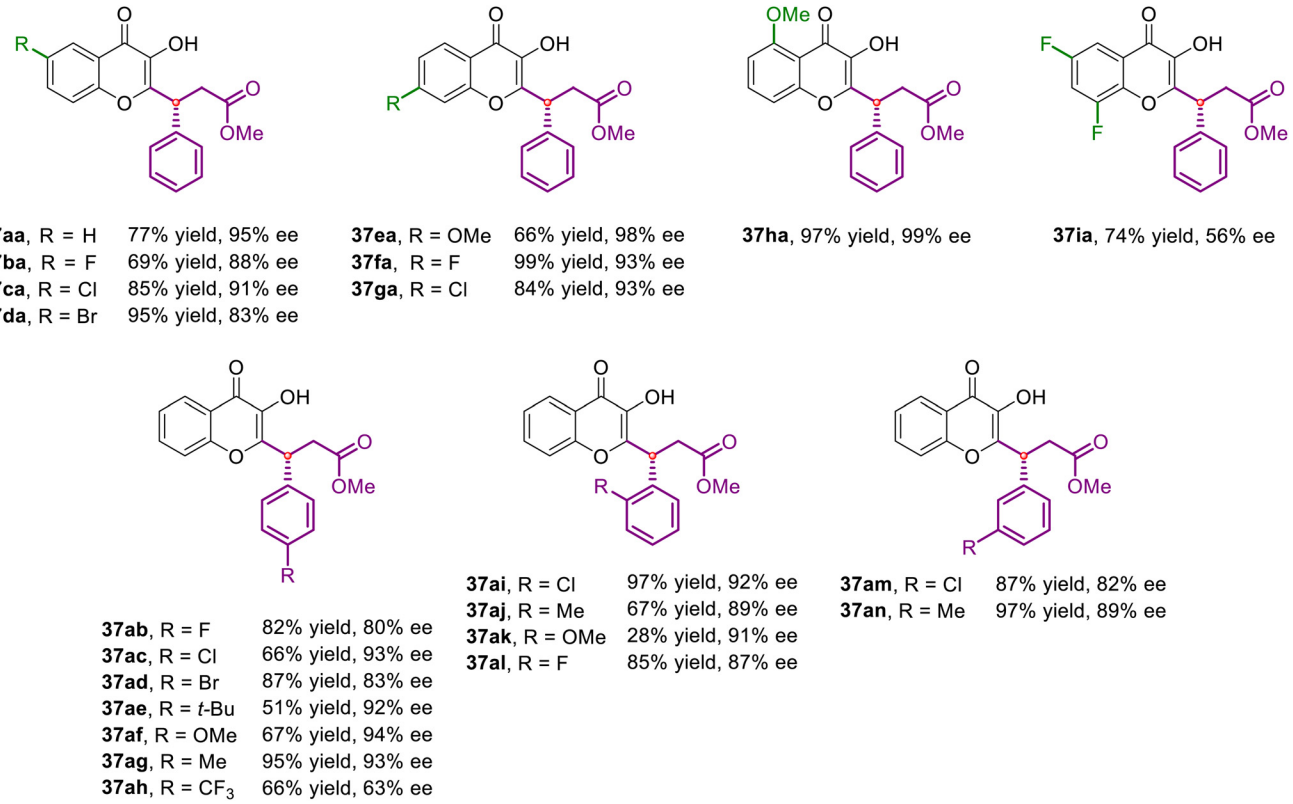


Fig. 10 Selected examples from the general scope using chiral carbene **36** to obtain chromenone derivatives **37**.

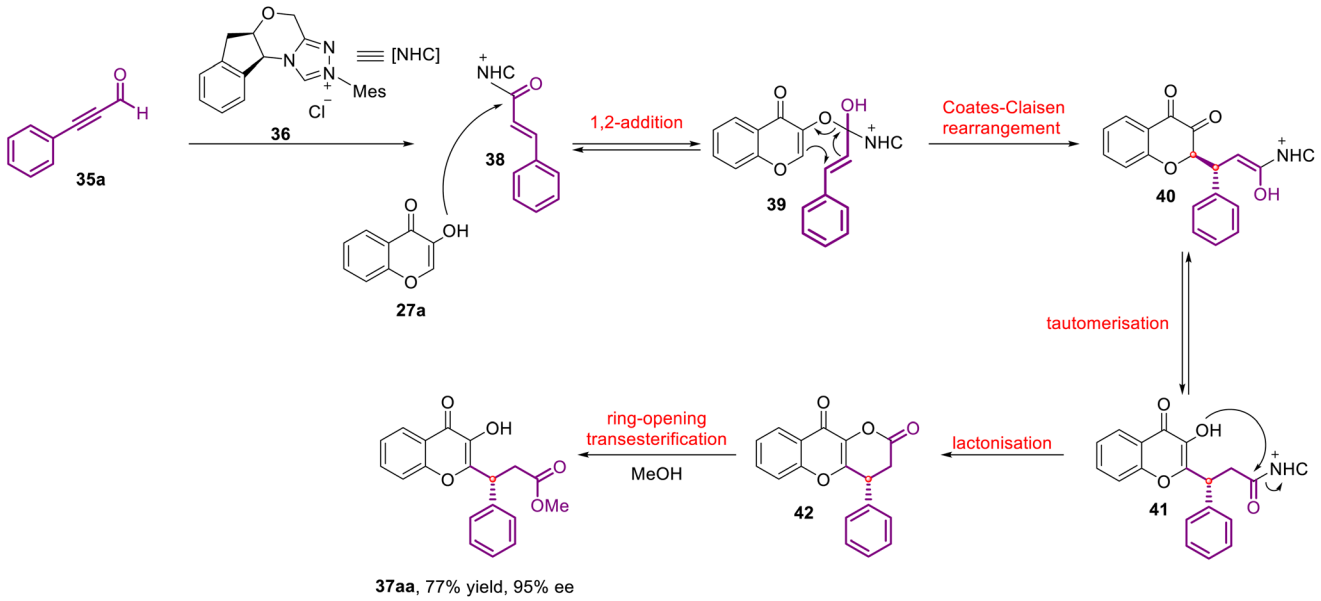
ance for challenging ynals bearing alkyl substituents, yielding the desired *C*2-alkylated chromenones in moderate to high yields with consistent enantioselectivities. To further extend this approach, the ring opening was performed using different oxygen or nitrogen nucleophiles, successfully generating the corresponding chromenones without compromising the enantioselectivity (see the original article for a complete scope of the process).[23] Notably, trimethylsilylpropynal, used as precursor for α,β-unsaturated acyl azolium, efficiently produced the *C*2-alkylated product **37**, despite undergoing complete desilylation under the reaction conditions. In this regard, the silyl derivative serves as a safer alternative to propynal, which is known for its explosive nature.

The absolute stereochemistry of the chiral centre was determined through single-crystal X-ray analysis.

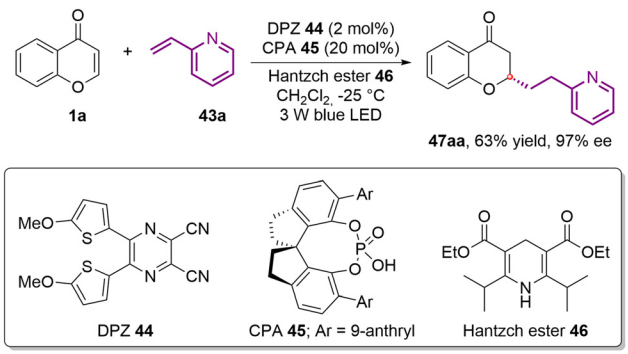
The authors propose a reaction mechanism that begins with the formation of the α,β-unsaturated acyl azolium **38** *via* redox isomerisation of ynal **35a**. This intermediate undergoes a 1,2-addition with 3-hydroxychromone **27a**, yielding intermediate **39**. A subsequent Coates–Claisen rearrangement generates the 2-alkyl-chroman-3,4-dione **40**, which, through tautomerisation and lactonisation of amide **41**, forms the tricyclic chromone **42**. Finally, reaction with a nucleophile (MeOH) produces the *C*2-functionalised 3-hydroxychromone **37aa** with high enantioselectivity (Scheme 13). The authors proposed this mechanism based on common experimental observations, particularly the formation of esterification by-products, which is typically associated with 1,2-addition pathways. This behaviour is consistent with the involvement of an NHC catalyst. In their study, esterification side reactions were also observed, supporting the idea that the reaction does not proceed *via* a nucleophilic 1,4-addition of the enol to the catalytically generated α,β-unsaturated acyl azolium. Instead, it likely follows a 1,2-addition route, leading to *O*-acylation products. Additionally, based on the [3,3]-sigmatropic rearrangement mechanism previously described by Bode for kojic acid derivatives,[24] the authors suggest that a similar rearrangement could be occurring in the reaction between 3-hydroxychromenones **27** and α,β-unsaturated acyl azoliums **38.**

Simultaneously, Jiang and co-workers design an enantioselective reductive cross coupling of chromones **1** and electron deficient olefins **43**, applying a visible-light-driven cooperative photoredox system in combination with a chiral Brønsted acid catalyst.[25] The reaction was performed using chromone **1a** and 2-vinylpyridine **43a** as model substrates. A dicyanopyrazine-derived chromophore (DPZ) **44** (2 mol%) was employed as photoredox catalyst in the presence of 20 mol% of the chiral phosphoric acid (CPA) **45** and the Hantzsch ester **46** in dichloromethane at −25 °C. The reaction was conducted under 3 W blue LED light in an oxygen-free environment for 60 hours, affording the 2-alkylchromanone **47aa** with a 63% yield and 97% of enantiomeric excess (Scheme 14).

The scope of this asymmetric cross coupling protocol was evaluated using several chromones **1a–i** containing electron-



Scheme 13 Proposed mechanism for obtaining *C*2-functionalised chromenone derivative **37aa**.



Scheme 14 Model enantioselective reductive cross coupling of chromone **1a** with 2-vinylpyridine **43a**.

withdrawing and electron-donating substituents, affording the 2-alkylchromanones **47** in moderate to high yields with excellent enantioselectivities. Furthermore, to improve the yield of the reaction, 2-vinylpyridines substituted with a methyl group at the C-3 and C-4 position were tested (**43b** and **43c**). The best result (93% yield, 96% ee) was obtained with the pyridine substituted at C-3 (**47ab**). On the other hand, when the reaction was performed with a thiochromone, the best result was using the 2-vinylpyridine **43c** bearing a methyl group at C-4 position affording thiochromanone **48ic**. Moreover, different substituted thiochromones exhibited excellent enantioselectivities, albeit with lower yield (**48aa–ga**, **48hb** and **48ic**) (Fig. 11).

Based on the success of this process, the authors proposed a reaction mechanism involving radical intermediates generated under photoredox conditions (Scheme 15). Simultaneously, the chiral phosphoric acid **45** would form hydrogen-bonding interactions with the substrates, stabilising the intermediate and organising the reactive components in a well-defined transition state (TS **51**). This precise arrangement ensures enantioselective C-2 functionalisation of the chromone **1a**. This dual catalytic system, combining photoredox and CPA catalysis, enables effective control over both reactivity and selectivity, facilitating the formation of *C*2-functionalised chromones **47** with excellent stereochemical outcomes.

Chromones as nucleophilic C-3 synthons and ulterior Michael addition reactions

Addition reactions using chromones as nucleophilic C-3 synthons are highly valuable in organic synthesis, offering a versatile strategy to access diverse, stereochemically enriched scaffolds that are crucial for the development of bioactive compounds and natural product derivatives.

In this context, homoisoflavonoids[26] are an important subclass of flavonoids with significant potential in drug design due to their demonstrated biological activities, including antioxidant,[27] cytotoxic[28] or antimicrobial effects (Fig. 12).[29]

In this framework, Seo and co-workers[30] have established a diastereodivergent synthesis of *anti*- and *syn*-9-hydroxyflavanones **54** and **58**, respectively, starting from chromones **1** and carbaldehydes **52** *via* a reductive aldol reaction or the Morita–Baylis–Hillman (MBH) reaction, followed by a *syn*-selective Michael reduction. Initially, they demonstrated the feasibility of the 3,9-*anti* selective synthetic route. Under reductive conditions, the enolate of chromone **1** was generated using Na, K or Li tri-*sec*-butylborohydride (Selectride) in THF at −78 °C, which provided the (*E*)-enolate. This enolate subsequently reacted with arylaldehydes **52**, affording the *anti*-3,9-hydroxyflavanones **54** through a Zimmerman–Traxler transition state **53**, giving the products from 68 to 97% yield and up to 1 : 14 diastereomeric ratio (Scheme 16 and Scheme 18).

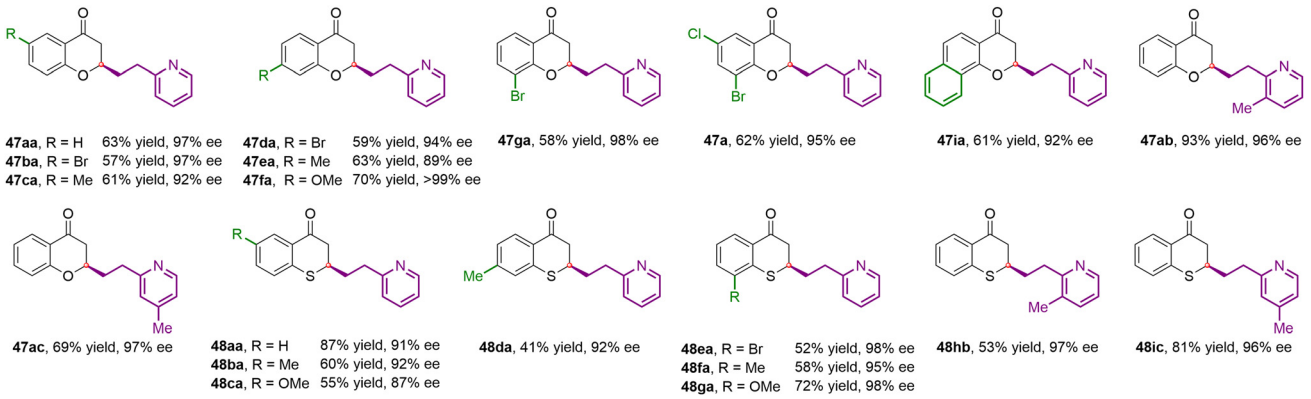
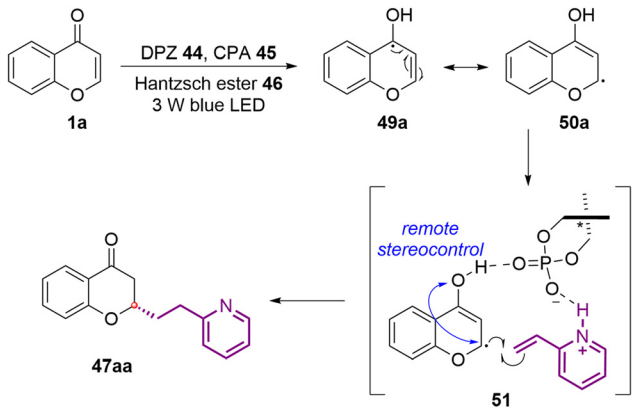
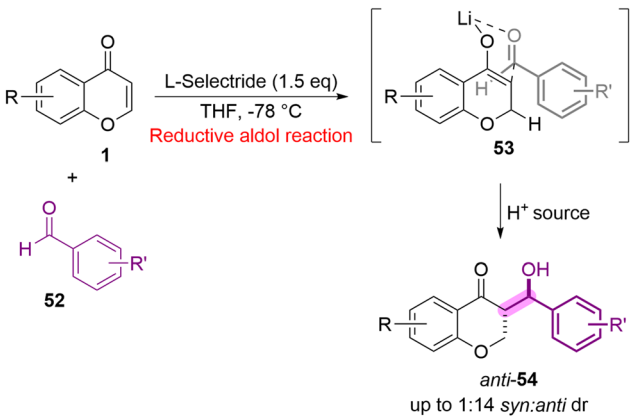


Fig. 11 Scope of the enantioselective reductive cross coupling of chromones **1** to obtain 2-alkylchromanone derivatives **47** and 2-alkylthiochromanones **48**.



Scheme 15 Proposed mechanism through radical intermediates.



Scheme 16 Transition state **53** in the reductive aldol reaction conducting to the *anti*-product **54**.

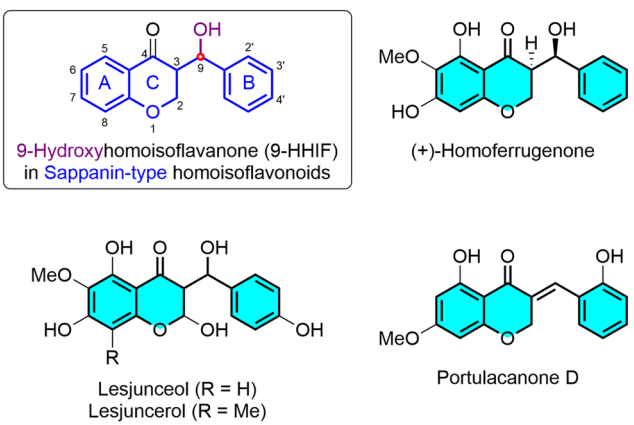
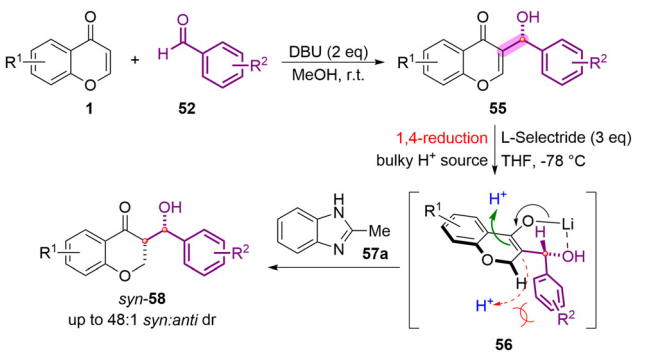


Fig. 12 Potential homoisoflavonoids with biological properties.

On the other hand, it is very important to consider that α-substituent-β-hydroxy ketones, such as the aldol chromone derivatives **55**, are highly prone to H-3 deprotonation (pK_a 14.8), which lead to β-elimination or *retro*-oxa-Michael reaction. To optimise the reaction conditions to obtain the desired *syn*-products **58**, the MBH reaction was carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeOH at room temperature to produce the enone intermediates **55**. A subsequent Michael reduction with 3 eq. of L-selectride facilitated the formation of a highly organised chelated transition state **56**, positioning H-3 on the opposite face of the phenyl group. Various proton sources were then tested, with phenol giving rise to the highest product

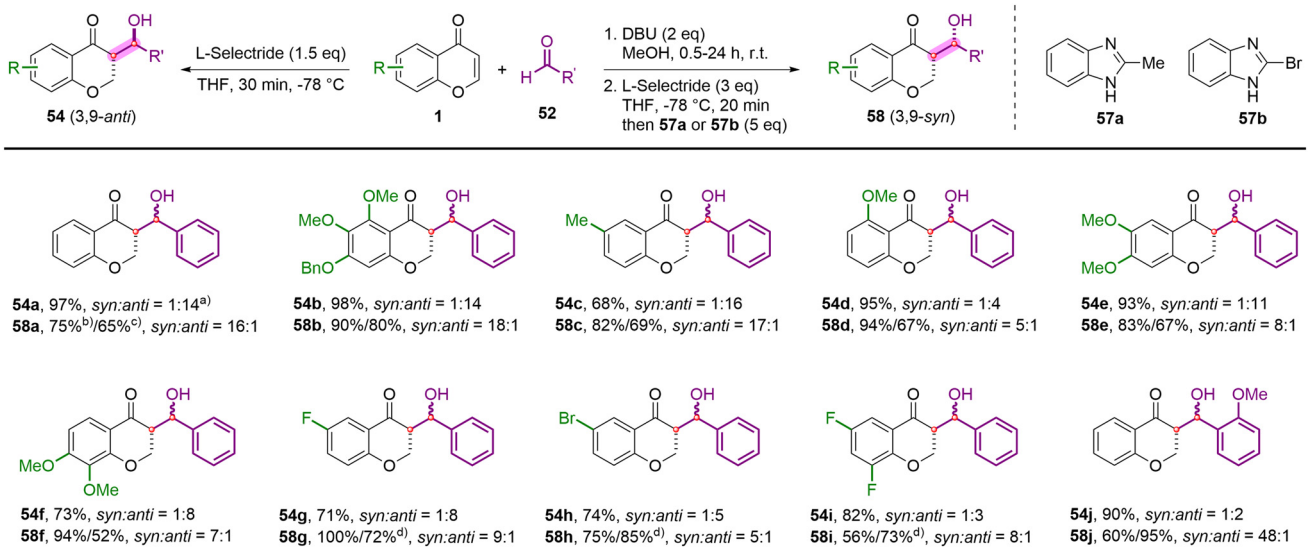


Scheme 17 Synthesis of the *syn*-product **58** by MBH/Michael reduction strategy.

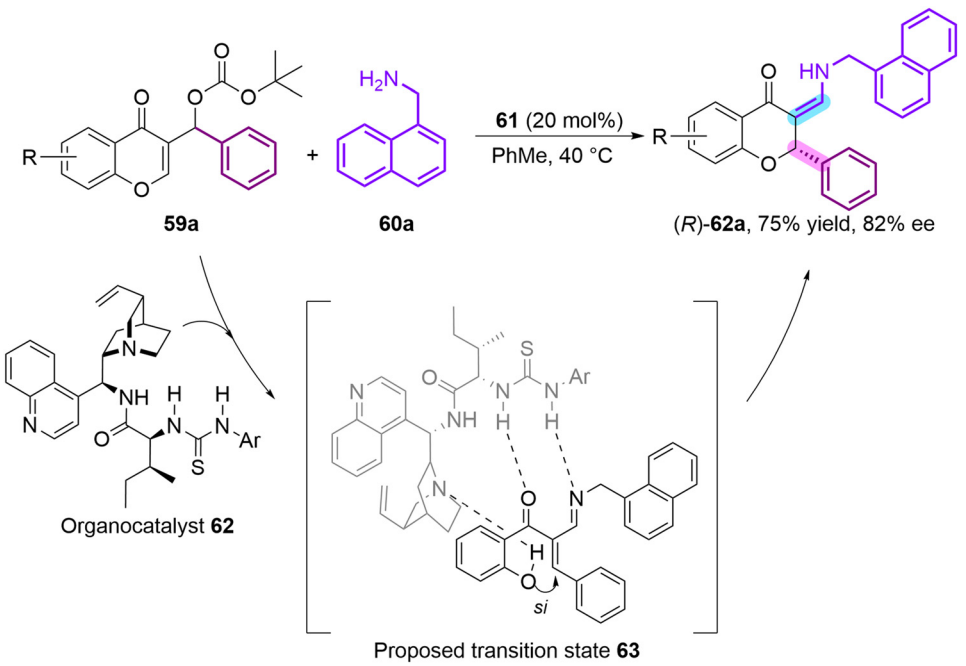
formation. Additionally, 2-methylbenzimidazole (**57a**) provided a comparable yield and with an improved dr compared to MeOH, NH_4Cl or AcOH, which instead led to *retro*-aldol by-products or degradation (Scheme 17).

Finally, higher *anti*- and *syn*-selectivity was observed in both methods using electron-rich aromatic rings than electron-deficient aromatic rings. However, the MeO group located on the C-5 position of chromones and/or C-2′ position of the carbaldehyde got worse diastereoselectivity due to possible involvement in the cation chelation during the stereochemistry-determining step (Scheme 18, see the original article for a complete scope of the process).[30]

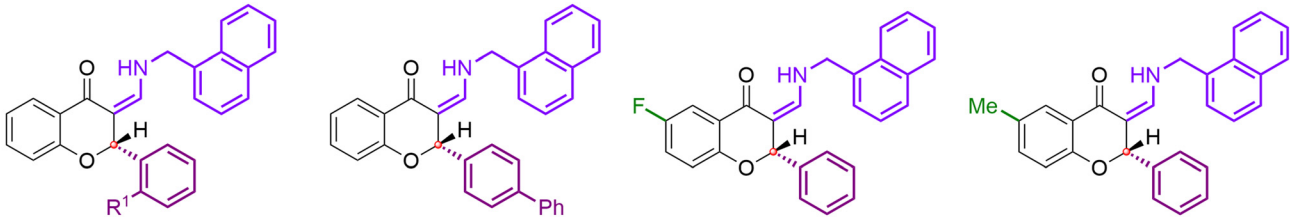
Furthermore, Chen and co-workers[31] initially reported the synthesis of chiral 3-aminomethylene-flavanones by In(III)-catalysed reactions of chromone-derived MBH adducts with amines *via* a tandem allylic amination/ring opening/oxa-Michael addition reactions in a one pot process.[32] In the next step of synthesis of this type of compounds, an organocatalytic oxa-Michael



Scheme 18 Selected examples from the general scope of the highly efficient MBH reaction for obtaining 3-alkylchromanones **54** and **58**; [a] For details in the SI of ref. 30. [b] Yield of the MBH; [c]Combined yield of both diastereoisomers of *syn*-selective 1,4-reduction; [d]Result obtained by using **52b** as a PS.



Scheme 19 Enantioselective organocatalytic synthesis of 3-aminomethylene-flavanones **62a**.



62b, R = H 75% yield, 82% ee
62c, R = Br 64% yield, 86% ee
62d, R = Cl 65% yield, 84% ee
62e, R = F 64% yield, 79% ee
62f, R = CF_3 80% yield, 85% ee
62g, R = Ph 84% yield, 89% ee
62h, R = Me 72% yield, 89% ee

62i, 78% yield, 80% ee

62j, 61% yield, 82% ee

62k, 60% yield, 77% ee

Fig. 13 Selected examples from the general scope for the enantioselective organocatalytic synthesis of 3-aminomethylene-flavanones **62**.

addition was employed.[33] This reaction began with the treatment of chromone-derived MBH carbonate **59a** with naphthylmethylenamine (**60a**) in the presence of 20 mol% of cinchonidine-derived thiourea catalyst in toluene at 40 °C for 60 h, affording the product **62a** in 74% yield and 36% ee. To improve the enantioselectivity, as reported by Zhu and Lu,[34] trifunctional catalysts containing primary amino acid units were found to be more effective for asymmetric conjugate addition than bifunctional thioureas. Following this method, different trifunctional catalysts were tested, resulting in a significant improvement in enantioselectivity when trifunctional cinchonidine-derived catalyst **61** was used, producing the 3-aminomethylene-flavone **62a** in 75% yield and 82% ee (Scheme 19).

With the optimal reaction conditions, several carbonates **59** and amines **60** were examined (Fig. 13), yielding moderate to high yields and enantioselectivities for all products **62** (see the original article for a complete scope of the process). The absolute configuration of the new stereogenic centre at C-2 position was then confirmed as *R* by X-ray crystallographic analysis of product **62c**. Drawing on these findings, the authors suggested a plausible transition state **63** for the tandem reaction (Scheme 19). Firstly, amines ($ArCH_2NH_2$) would react with the MBH carbonate, which is activated by the thiourea-based catalyst **61**, through hydrogen bond formation, leading to the generation of intermediate **63** (Scheme 19). This step is followed by an intramolecular oxa-Michael addition, stablishing multiple hydrogen bonds between the trifunctional catalyst and the intermediate **63**. These interactions enhance the reaction rate and ensure precise stereochemical control, facilitating the oxa-Michael addition to the α,β-unsaturated imine produced *in situ*, attacking from the *Si* face of the double bond.

Conclusions

The Michael addition reactions involving chromones represent a cornerstone in modern organic synthesis, offering an interesting alternative for the construction of complex, stereochemically enriched molecules. The remarkable versatility of chromones, acting as electrophilic or nucleophilic partners, has enabled the development of methodologies applicable in pharmaceuticals, natural products, and materials science.

Recent advancements have been driven by innovative organocatalytic systems that leverage non-metal-based strategies for asymmetric transformations, providing a sustainable and highly efficient approach to chemical synthesis. Despite these successes, several challenges remain, including improving the scalability of reactions, expanding the substrate scope to obtain more functionalised chromones, and achieving higher enantioselectivity even under milder or greener conditions. Future research in enantioselective Michael addition reactions involving chromones should focus on several key areas to address current challenges and unlock new opportunities. One priority is the development of novel organocatalysts with enhanced activity, selectivity, and environmental compatibility. These catalysts should not only improve reaction efficiency but also align with principles of green chemistry by reducing waste and utilising sustainable resources, such as greener solvents.

Additionally, a deeper understanding of the reaction mechanisms is essential. Employing advanced computational techniques could shed light on the underlying processes, helping to refine transition state models and guide the rational design of more effective catalytic systems.

Moreover, exploring tandem or cascade reactions to achieve multi-functionalised products in a single synthetic step could pave the way for even more complex and diverse molecular architectures.

By addressing these priorities, future research can further establish enantioselective Michael addition reactions as a cornerstone methodology in modern synthetic organic chemistry, with broad applications in both academia and industry.

Author contributions

All authors wrote and approved the paper.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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