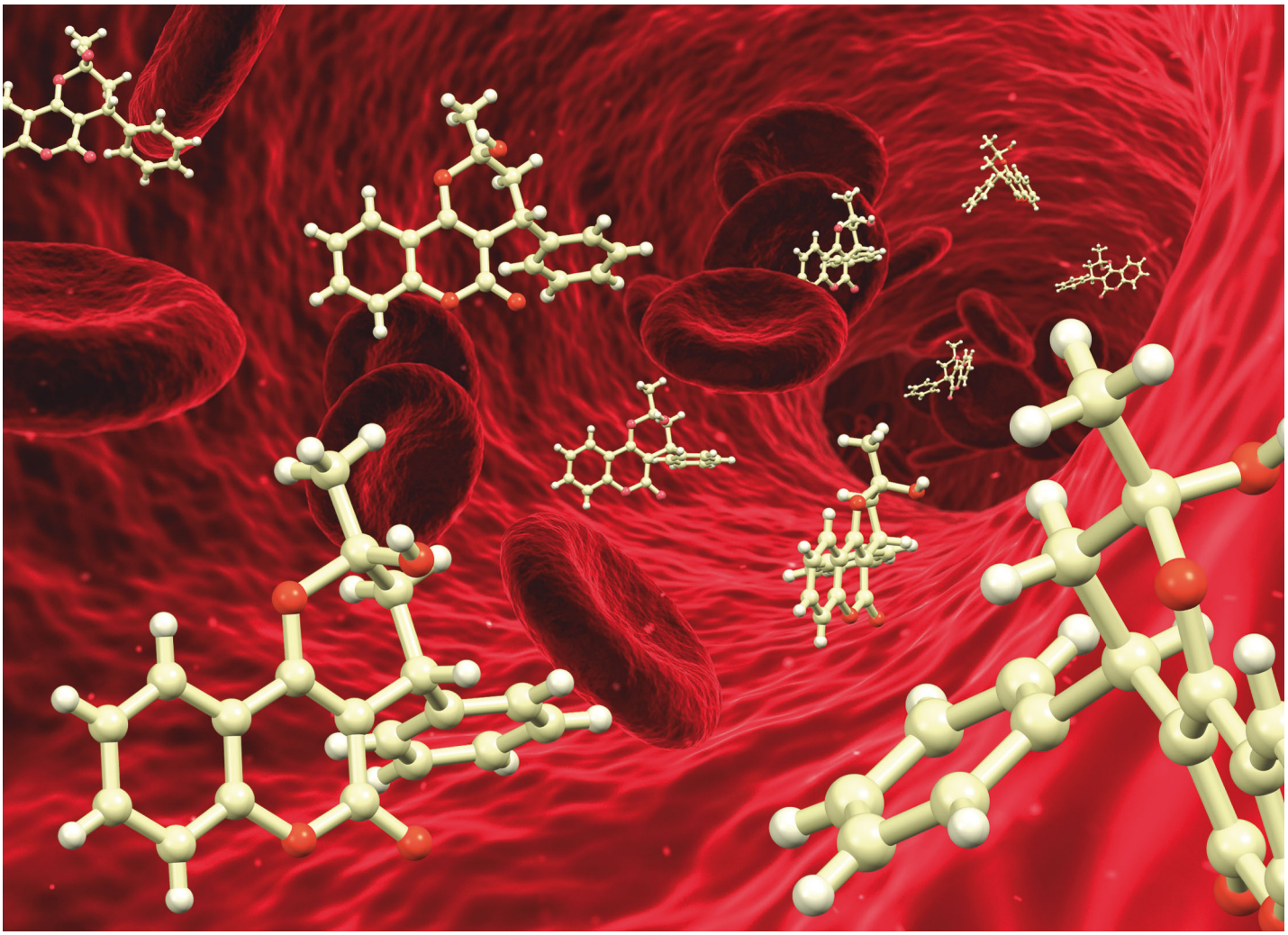

Showcasing research from Raquel P. Herrera's lab at the Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-University of Zaragoza, Spain

First aromatic amine organocatalysed activation of α,β-unsaturated ketones

We have developed the first example of a chiral aromatic amine used as an organocatalyst to activate α,β-unsaturated ketones in aminocatalysis. Additional experimental studies and the detection of important intermediates of the reaction supported a plausible bifunctional mode of activation by the catalyst *via* an aminocatalytic pathway. This pioneering work contributes to the scarcely developed field of aromatic amines as chiral organocatalysts and opens a door for further studies in this area of research.

As featured in:

See Raquel P. Herrera *et al.*, *New J. Chem.*, 2019, **43**, 12233.

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First aromatic amine organocatalysed activation of α,β-unsaturated ketones†

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This work provides an unprecedented example of a chiral aromatic amine used to activate α,β-unsaturated ketones in asymmetric aminocatalysis. Chiral aromatic diamine **VII** has been efficiently employed, as a proof of concept, in the Michael addition reaction between benzylideneacetones (**1a–f**) and coumarins (**2a–d**). The reaction gives rise to warfarin derivatives **3** with promising results using this family of catalysts for the first time. The additional studies performed supported the bifunctional mode of activation of the chiral catalyst **VII** and the covalent nature of the interactions between the catalyst **VII** and benzylideneacetones **1**.

Introduction

After the tragic effects caused by the prescription of thalidomide to pregnant women at the beginning of the 1960s, more efforts have been devoted to the synthesis and commercialisation of single enantiopure pharmaceuticals. The obtainment of a single enantiomer, as an optically active drug, is becoming progressively more vital for the treatment of many diseases. To achieve this pivotal goal, asymmetric catalysis has been employed as a powerful tool to develop new reactions affording enantioenriched compounds.[1] In this respect, one of the most important aims of organocatalysis has also been the preparation of new chiral biologically active compounds or natural products.[2]

Among the plethora of drug-based compounds, warfarin **3a** is one of the most widely used anticoagulants due to its advantages such as oral administration, low price and permanent effect. Like other pharmaceuticals, it is prescribed worldwide as a racemate. However, it is well-known that the anticoagulant activity of the *S* enantiomer is about 5–8 times higher than that of the *R* enantiomer.[3] Different catalytic asymmetric approaches towards the synthesis of optically active warfarin by means of enzymatic,[4] metal based[5] or organocatalytic procedures have been reported.[6] Among the organocatalytic approaches, the first example was reported by Jørgensen's group using a chiral imidazolidine organocatalyst following the Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated enones.[7] After this pioneering example, other organocatalytic procedures were reported with the main aim of obtaining better results for the enantiopure products. Some of these organocatalytic approaches have been developed using aliphatic amines as catalysts.[8] It is important to cite some of these pioneering examples using aliphatic primary chiral amines such as those reported by Chin[9] and Chen[10] or more recently, by Zlotin's group.[11]

In contrast, the use of chiral aromatic amines to promote organocatalytic reactions has been eclipsed by the corresponding chiral aliphatic amines, mainly due to the conjugation between the nitrogen lone pair and the aromatic ring. Consequently, this conjugation is responsible for their less nucleophilic behavior in comparison with aliphatic amines.[12] In fact, there are scarce organocatalytic examples where a chiral aromatic amine promotes the reaction by itself.[13,14] In addition to all reported examples for the preparation of warfarin and its derivatives, to the best of our knowledge there is not any example of a chiral aromatic amine used as an organocatalyst for the synthesis of these interesting molecules. Moreover, none of these previous examples using aromatic amines was involved in the activation of α,β-unsaturated ketones.

Hence, based on our continuous search for the discovery of new organocatalysts and catalytic reactions,[15] we have studied this alternative as a totally unexplored approach.

Results and discussion

To test the model process depicted in Scheme 1, simple chiral amine structures, non containing in their skeletons a proline,

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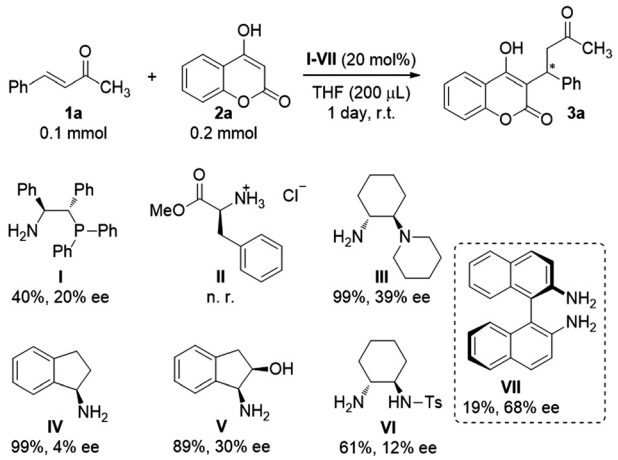


Scheme 1 Screening of catalysts in the Michael addition between 4-hydroxycoumarin (**2a**) and benzylideneacetone (**1a**).

an amino-cinchona or a DPEN moiety as is usual, were selected as promising catalysts. Interestingly, these simple amines have been overlooked so far in the literature for this process.

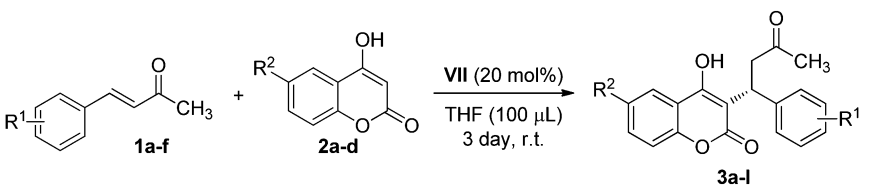
To our delight, all catalysts, except **II**, promoted the Michael addition reaction affording final desired product **3a** (Scheme 1). Primary amines exhibited higher reactivity in comparison with catalyst **VII** (as expected). Although catalyst **VII** was not the most reactive, it was surprisingly the most enantioselective. To the best of our knowledge this is the first time that this aromatic amine has been used to activate ketone electrophiles in asymmetric aminocatalysis.[16] Therefore, with these promising results of enantioselectivity in hand, a deep exploration of different parameters, in the previous model reaction, was carried out using catalyst **VII** (Tables S1 and S2, ESI†).

The study of the reaction conditions such as the amount of solvent or equivalents of reagents **1a** and **2a**, and catalyst **VII** loading, afforded smooth variations in both the yield and enantioselectivity of the reaction (Table S1, ESI†). In general, the concentration of the reaction led to better reactivity without impairing the enantioselectivity of the process (Table S1, entries 9–12, ESI†). Variations in the amount of coumarin **2a** did not afford an appreciable improvement neither in the reactivity nor in the enantioselectivity of the process. The exploration of a vast number of different solvents did not afford better results in comparison with those obtained with THF (Table S2, ESI†). With the best reaction conditions in hand (Table S1, entry 11), the scope of the reaction was explored for different benzylideneacetones (**1a–f**) and coumarins (**2a–d**) (Table 1).

In all cases, the Michael addition reaction took place smoothly giving rise to the desired final products **3** with moderate to good yields and with promising enantioselectivities. This proof of concept is well accounted for a variety of coumarins **2a–d** and benzylideneacetones **1a–f**, and the crude products of the reactions are very clean. Although the values of enantioselectivity did not show a clear correlation with the electronic environment of the reagents, the reactivity suggests a dependence on the electronic environment in the aromatic ring of coumarins **2** and benzylideneacetones **1**. Therefore, deactivated benzylideneacetones **1e, f** (with electron-donating groups) led to lower reactivities (entries 5, 10–12). Furthermore, coumarin **2d**, with a methyl group, seems to decrease the reactivity of the process (entry 8). The absolute configuration was determined to be *R* by comparison of the optical rotation of products **3a** and **3b** with those reported in the literature.[6b,17] Therefore, the same stereochemical outcome was assumed for all products **3**.

Additionally, we have found some inconsistences regarding the sign of the values previously reported for the optical rotation of some of these products. In order to also support the absolute configuration of our products, single crystals were

Table 1 Scope of the Michael addition reaction[a]



Entry	R^1	R^2	Prod.	Yield[b] (%)	ee[c] (%)
1	H (**1a**)	H (**2a**)	**3a**	68	64
2	4-Cl (**1b**)	H (**2a**)	**3b**	76	64
3	4-Br (**1c**)	H (**2a**)	**3c**	85	66
4	4-CN (**1d**)	H (**2a**)	**3d**	92	50
5	4-Me (**1e**)	H (**2a**)	**3e**	62	58
6	H (**1a**)	Cl (**2b**)	**3f**	57	67
7	H (**1a**)	Br (**2c**)	**3g**	53	67
8	H (**1a**)	Me (**2d**)	**3h**	25	61
9	4-Cl (**1b**)	Br (**2c**)	**3i**	25	62
10	4-Me (**1e**)	Cl (**2b**)	**3j**	20	62
11	4-OMe (**1f**)	Cl (**2b**)	**3k**	52	54
12	4-OMe (**1f**)	Br (**2c**)	**3l**	40	54

[a] To a mixture of catalyst **VII** (20 mol%, 0.02 mmol) and coumarins **2a–d** (0.2 mmol) in THF (100 μl), benzylideneacetones **1a–f** (0.1 mmol) were added at room temperature. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis.

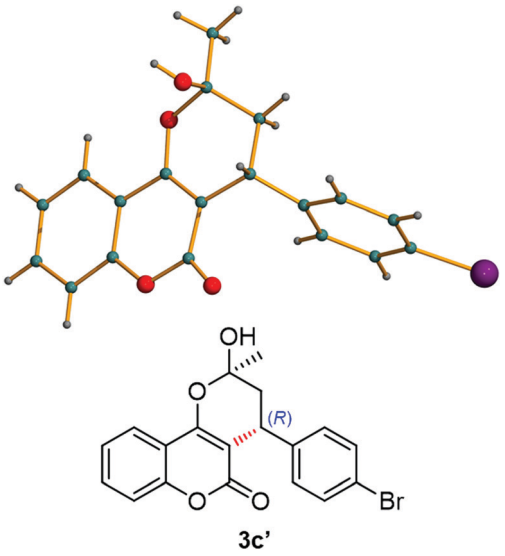
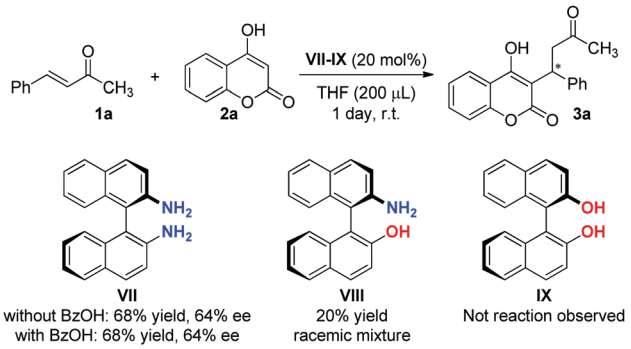


Fig. 1 X-ray crystal structure of (*R*)-**3c**′.



Scheme 2 Study of the bifunctional role of the catalyst **VII**.

grown from adduct **3c**′ and the stereochemical outcome was determined to be also *R* for this product (Fig. 1).[18] It is worth noting that product **3c** was crystallised as its pseudo-diastereomeric hemiketal form **3c**′.

In order to gain insights into the mode of activation by the catalyst **VII** in this Michael reaction, additional experiments were performed. First, ESI-MS analysis was carried out (Fig. 2). ESI-MS has been considered as an important technique for mechanistic studies of organic reactions.[19] The presence of plausible intermediates in the solution of the reaction mixture was analysed directly (**VII** (20 mol%, 0.02 mmol), coumarin **2a** (0.15 mmol) and benzylideneacetone **1a** (0.1 mmol), in THF (100 μl) at room temperature) (Fig. 2).

In the cationic ESI spectrum recorded directly from the solution to the gas phase, several important mass peaks related to some plausible intermediates of the reaction, such as the imine between catalyst **VII** and benzylideneacetone **1a** (*m*/*z* 413.2, **Int. 1**, and *m*/*z* 451.2, **Int. 1**′) were found. The resulting enamine intermediates (**Int. 2** and **Int. 3**), generated after coumarin **2a** attacks **Int. 1**, were also found. From this observation, it can be assumed that catalyst **VII** gives rise an imine with benzylideneacetone **1a** before the attack of the nucleophile **2a**.

It is remarkable that the formation of a diimine intermediate with the catalyst (**Int. 4**) was not observed in the ESI-MS spectrum, which could be due to the formation of an imine with each NH_2 group in the catalytic structure, as previously observed[20] or hypothesised[9] by other authors, using primary aliphatic amines.

Furthermore, some additional reactions were also performed in order to understand the role of the second NH_2 group in the catalyst (Scheme 2).

Some conclusions could be made from the results shown in Scheme 2: (1) first, the second **NH_2** group present in **VII** could

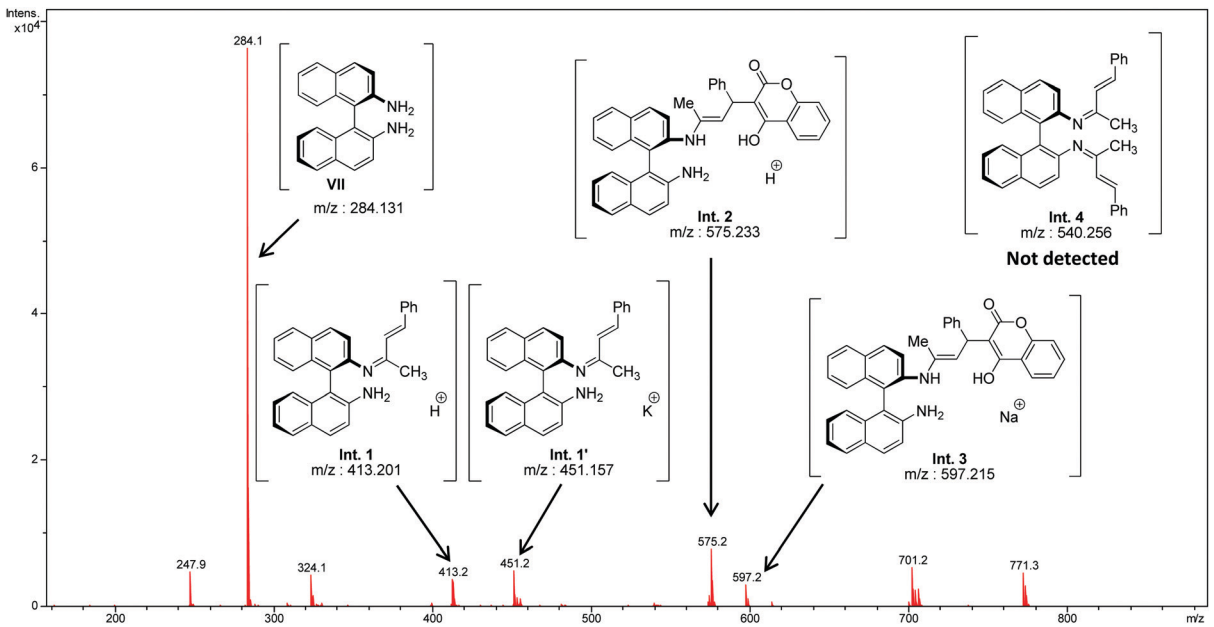


Fig. 2 Cationic ESI spectrum of the reaction mixture.

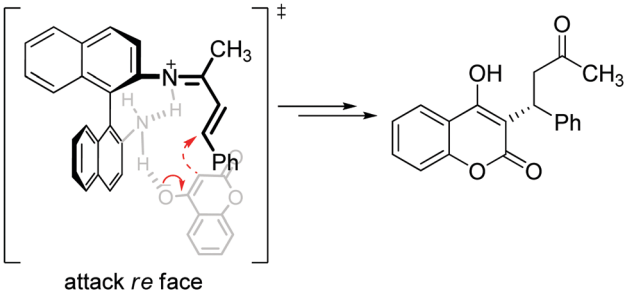


Fig. 3 Plausible TS to explain the bifunctional role of the catalyst.

not be involved in the generation of a second imine in agreement with the results found in the ESI-MS analysis (**Int. 1** and **Int. 1′**, Fig. 2). (2) Interestingly, the second NH_2 group in catalyst **VII** could play an important role in the enantioselection process, since when catalyst **VIII** is used, the enantioselectivity dramatically collapses and a racemic mixture is obtained. (3) The reaction seems to be mainly activated by an aminocatalytic approach more than hydrogen bond activation alone, which agrees with the intermediates (**Int. 1–3**) found in the ESI-MS spectra (Fig. 2). Hence, when catalyst **IX** (which is more acidic than **VII** and **VIII**) was employed the process did not work. (4) Moreover, the addition of an external Brønsted acid did not enhance the reactivity of the process when using **VII**. In the case of using catalyst **VII** alone, iminium ions would be formed after deprotonation of the coumarin substrate (Fig. 3). (5) A strange behaviour was observed with the low reactivity displayed by catalyst **VIII**, just with one NH_2 group in its structure, since a higher reactivity could be initially expected. Thus, it seems that the **OH** group is not involved in the enantioselection process and more importantly, it likely inhibits the reaction. This finding could be explained by assuming an intramolecular hydrogen bonding between RO-H$\cdots$$NH_2$R. This would make the NH_2 group in **VIII** less nucleophilic than in catalyst **VII**, avoiding the formation of the initial imine (**Int. 1** and **Int. 1′**, Fig. 2) and therefore, obstructing the reaction. A similar intramolecular hydrogen bonding, although weaker, between RHN-H$\cdots$$NH_2$R would also be possible.

Based on all these experiments, **VII** would act as a bifunctional catalyst,[21] activating at the same time the electrophile, by the generation of an imine or iminium ion, and driving the attack of the nucleophile (Fig. 3).

According to the above outcomes, a stereochemical model is proposed in Fig. 3.[22] The approach of the coumarin **2** to the *in situ* generated imine (**Int. 1**) would be driven by an RHN–H$\cdots$$^{-}$OR′ bond, resulting in the addition to the *re* face (lower face) of the imine (or iminium ion, Fig. 3). Moreover, we could not ignore the possibility of an intramolecular hydrogen bond between the second amino group and the iminium ion, giving rise to a more rigid transition state. Hence, the enantiomer obtained would agree with the absolute configuration (*R*) found in final products **3**.

Conclusions

In conclusion, we have developed the first example of a chiral aromatic amine used as an organocatalyst to activate α,β-unsaturated ketones in aminocatalysis. This Michael addition reaction is efficiently catalysed by the simple diamine catalyst **VII**, which can be easily accessed in both enantiomeric forms from commercially available sources. Final warfarin derivatives **3** are obtained with good results, as a proof of concept. The additional ESI-MS and experimental studies performed supported a plausible bifunctional mode of activation by catalyst **VII**. The detection of important and crucial intermediates of the reaction strongly supports the role of the diamine catalyst **VII** in the activation mechanism *via* aminocatalysis. This work contributes to the scarcely developed field of aromatic amines as organocatalysts and opens a door for further studies in this area of research.

Experimental

General experimental methods and instrumentation

Starting materials **1a** and **2a–d**, as well as amine catalysts **I–IX**, are commercially available and were employed as received without further treatment or purification. In the case of solvent, commercial tetrahydrofuran (THF, HPLC grade) was transferred to a new recipient and molecular sieves (4 Å) were added.

All reactions were performed at room temperature under ambient conditions. The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets recoated with silica gel and a fluorescent indicator (60 F254, 0.2 mm). Compounds were visualised at 254 nm by using UV light. Products **3** were isolated by flash chromatography using silica gel (0.06–0.2 nm) as the stationary phase and a mixture of commercial dichloromethane and ethyl acetate as an eluent.

The chiral HPLC analysis of products **3** was performed using a Waters 600 system, with a Daicel ChiralPak IC column as the stationary phase and a mixture of commercial *n*-hexane and isopropyl alcohol as an eluent. The specific rotation of products **3** was determined using a Jasco P-1020 polarimeter, in acetonitrile of HPLC grade as the solvent. The absolute configuration of products **3a** and **3b** was assigned comparing their specific rotation with those reported in the literature.

The NMR spectra of the reagents and products were recorded at 300 MHz (Bruker ARX300 spectrometer) or 400 MHz (Bruker AV400 spectrometer), in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 ($(CD_3)_2SO$) as the deuterated solvent. The infrared spectra of the starting materials and products were obtained employing attenuated total reflection infrared (ATR-FTIR) spectroscopy using a PerkinElmer FTIR spectrometer equipped with a universal ATR sampling accessory. The HRMS analysis of the reagents and products was performed using a MicroTof-Q mass spectrometer and electrospray (ESI) as the ionisation method. The melting point of the reagents and products was determined using a Gallenkamp MPD 350 BM 2.5 device.

Materials. The spectroscopic data recorded for synthesised starting materials **1b**,[23] **1c**,[23] **1d**,[23] **1e**,[23] and **1f**,[23] and products obtained **3a**,[7] **3b**,[7] **3c**,[6b] **3e**,[6b] **3f**,[20] **3g**,[6e] **3h**,[10] **3i**[6e] and **3j**[6e] are in agreement with the values previously reported by other authors.

Synthesis of benzylideneacetone derivatives 1b–f

The substrates **1b–f** were synthesised from the corresponding commercial aldehydes **4b–f** and the phosphonium ylide **5**, which was previously prepared following the procedure reported in the literature using commercially available reagents (Scheme S1, ESI†).[24] The respective yields after purification are shown in Scheme S1 (ESI†). The ratio (*E*)/(*Z*) of products **1b–f** was determined by ^{1}H-NMR spectroscopy, using DMSO-d_6 as the solvent.

(*E*)-4-(4-Chlorophenyl)-3-buten-2-one (1b)[23]. To a suspension of phosphonium ylide **5** (955 mg, 3 mmol, 1.2 eq.) in toluene (4 ml) at room temperature, 4-chlorobenzaldehyde (**4b**) (357 mg, 2.5 mmol) was added. The reaction mixture was stirred overnight at reflux temperature. After cooling down the reaction to room temperature, the corresponding residue was purified by flash chromatography using a mixture of *n*-hexane and ethyl acetate 8 : 2 as an eluent. The mixture of isomers obtained was washed with cold *n*-hexane, affording 320 mg of compound **1b** (71% yield, (*E*)/(*Z*) > 99 : 1).

(*E*)-4-(4-Bromophenyl)-3-buten-2-one (1c)[23]. To a suspension of phosphonium ylide **5** (955 mg, 3 mmol, 1.2 eq.) in toluene (4 ml) at room temperature, 4-bromobenzaldehyde (**4c**) (467 mg, 2.5 mmol) was added. The reaction mixture was stirred overnight at reflux temperature. After cooling down the reaction to room temperature, the corresponding residue was purified by flash chromatography using a mixture of *n*-hexane/ethyl acetate 8 : 2 as an eluent. The mixture of isomers obtained was further purified by recrystallisation in methanol, affording 203 mg of compound **1c** (36% yield, (*E*)/(*Z*) > 99 : 1).

(*E*)-4-(4-Cyanophenyl)-3-buten-2-one (1d)[23]. To a suspension of phosphonium ylide **5** (955 mg, 3 mmol, 1.2 eq.) in toluene (4 ml) at room temperature, 4-bromobenzaldehyde (**4d**) (345.1 mg, 2.5 mmol) was added. The reaction mixture was stirred overnight at the reflux temperature. After cooling to room temperature, the corresponding residue was purified by flash chromatography using a mixture of *n*-hexane and ethyl acetate 8 : 2 as an eluent. The mixture of isomers obtained was purified by recrystallisation in methanol, affording 230 mg of compound **1d** (54% yield, (*E*)/(*Z*) > 99 : 1).

(*E*)-4-(4-Methylphenyl)-3-buten-2-one (1e)[23]. To a suspension of phosphonium ylide **5** (955 mg, 3 mmol, 1.2 eq.) in toluene (4 ml) at room temperature, 4-methylbenzaldehyde (**4e**) (304 μl, 2.5 mmol) was added. The reaction mixture was stirred overnight at reflux temperature. After cooling down the reaction to room temperature, the corresponding residue was purified by flash chromatography using a mixture of *n*-hexane and ethyl acetate 8 : 2 as an eluent. The mixture of isomers obtained was purified by flash chromatography using *n*-hexane/diethyl ether 9 : 1 as an eluent, affording 205 mg of compound **1e** (51% yield, (*E*)/(*Z*) > 99 : 1).

(*E*)-4-(4-Methoxyphenyl)-3-buten-2-one (1f)[23]. To a suspension of phosphonium ylide **5** (955 mg, 3 mmol, 1.2 eq.) in toluene (4 ml) at room temperature, 4-methoxybenzaldehyde (**4f**) (304 μl, 2.5 mmol) was added. The reaction mixture was stirred overnight at reflux temperature. After cooling to room temperature, the corresponding residue was purified by flash chromatography using a mixture of *n*-hexane and ethyl acetate 8 : 2 as an eluent. The mixture of isomers obtained was purified by recrystallisation in methanol, affording 191 mg of compound **1f** (43% yield, (*E*)/(*Z*) > 99 : 1).

General procedure for the enantioselective synthesis of warfarin derivatives 3a–l catalysed by the chiral aromatic diamine VII

To a mixture of benzylideneacetone derivative **1a–f** (0.1 mmol) and catalyst **VII** (5.74 mg, 0.02 mmol, 20 mol%) in THF (100 μl) at room temperature, the corresponding 4-hydroxycoumarin **2a–d** (0.2 mmol, 2 eq.) was added. The reaction mixture was stirred at room temperature for three days, leading to the final desired product with the lack of by-products. After this reaction time, the residue obtained was purified by flash chromatography using the gradient from CH_2Cl_2 : AcOEt, 99 : 1 to CH_2Cl_2 : AcOEt, 94 : 6 as the eluent, affording the corresponding pure product **3**. The different yields and enantioselectivities obtained are collected and compared in Table 1 of the manuscript.

(*R*)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one (3a) (warfarin)[7]. Starting from benzylideneacetone **1a** (14.92 mg, 0.1 mmol) and coumarin **2a** (33.09 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 20.94 mg of compound **3a** was obtained (68% yield). The corresponding ee (64%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 282.5 nm): τ_{major} = 16.7 min; τ_{minor} = 24.3 min. $[\alpha]_D^{23}$ = +8.7 ± 0.1 (*c* 0.75, acetonitrile, 64% ee). {lit.,[6b] $[\alpha]_D^{23}$ = −9.4 (*c* 0.4, acetonitrile, 83% ee, *S*-**3a**)}.

(*R*)-3-[1-(4-Chlorophenyl)-3-oxobutyl]-4-hydroxychromen-2-one (3b) (coumachlor)[7]. Starting from benzylideneacetone **1b** (18.06 mg, 0.1 mmol) and coumarin **2a** (33.09 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 26.03 mg of compound **3b** was obtained (76% yield). The corresponding ee (64%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 279.4 nm): τ_{major} = 10.5 min; τ_{minor} = 21.3 min. $[\alpha]_D^{25}$ = −6.1 ± 0.1 (*c* 0.60, acetonitrile, 64% ee). {lit.,[17] $[\alpha]_D^{25}$ = −8.8 (*c* 0.27, acetonitrile, 79% ee, *R*-**3b**)}.

(*R*)-3-[1-(4-Bromophenyl)-3-oxobutyl]-4-hydroxychromen-2-one (3c)[6b]. Starting from benzylideneacetone **1c** (22.50 mg, 0.1 mmol) and coumarin **2a** (33.09 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 33.04 mg of compound **3c** was obtained (85% yield). The corresponding ee (66%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 279.4 nm): τ_{major} = 11.7 min; τ_{minor} = 23.0 min. $[\alpha]_D^{23}$ = −10.0 ± 0.1 (*c* 0.60, acetonitrile, 66% ee).

(*R*)-3-[1-(4-Cyanophenyl)-3-oxobutyl]-4-hydroxychromen-2-one (3d). Starting from benzylideneacetone **1d** (17.12 mg, 0.1 mmol) and coumarin **2a** (33.09 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 30.65 mg of compound **3d** was obtained (92% yield). The corresponding ee (50%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 250.0 nm): τ_{major} = 20.8 min; τ_{minor} = 26.5 min.

$[\alpha]_D^{23} = -10.9 \pm 0.1$ (*c* 1.37, acetonitrile, 50% ee). M.p. 105–107 °C. IR (cm^{-1}) 3353 (OH), 2226 (CN), 1680 (C═O), 1608 (C═O), 1381, 1068, 759, 727, 563. In $CDCl_3$, the product was found to exist in a fast equilibrium between its open chain form **3d** (≈10 mol%) and both pseudo-diastereomeric hemiketals **3d′** (≈30 mol% and ≈60 mol%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.72 (s, $0.9H_{3d'[a]}$, RCH_3), 1.77 (s, $1.8H_{3d'[b]}$, RCH_3), 1.92 (dd, J^1 = 10.4 Hz, J^2 = 8.9 Hz, $0.6H_{3d'[a]}$, RCH_2R'), 2.32 (s, $0.3H_{3d}$, RCH_3), 2.37–2.49 (m, $1.2H_{3d'[b]}$, RCH_2R'), 3.01 (br s, $0.3H_{3d'[a]}$, ROH), 3.23–3.33 (m, $0.1H_{3d}$, RCH_2R'), 3.33 (br s, $0.6H_{3d'[b]}$, ROH), 3.86 (dd, J^1 = 14.5 Hz, J^2 = 8.0 Hz, $0.1H_{3d}$, RCH_2R'), 4.19–4.24 (m, $0.6H_{3d'[b]}$ + $0.3H_{3d'[a]}$, RCHR′R″), 4.68–4.71 (m, $0.1H_{3d}$, RCHR′R″), 7.22–7.24 (m, $0.1H_{3d}$, Ar-H), 7.27–7.37 (m, $2.4H_{3d'[b]}$ + $1.2H_{3f'[a]}$, Ar-H), 7.41–7.43 (m, $0.2H_{3d}$, Ar-H), 7.50–7.60 (m, $1.8H_{3d'[b]}$ + $0.9H_{3d'[a]}$ + $0.4H_{3d}$, Ar-H), 7.81–7.83 (m, $0.6H_{3d'[b]}$, Ar-H), 7.86–7.88 (m, $0.3H_{3d'[b]}$, Ar-H), 7.95–7.98 (m, $0.1H_{3d}$, Ar-H), 9.64 (br s, $0.1H_{3d}$, ROH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 28.2, 28.4, 35.1, 35.2, 35.8, 39.6, 42.0, 44.9, 98.9, 100.0, 101.0, 103.3, 110.4, 110.5, 115.5, 115.8, 116.5, 116.8, 116.9, 119.1, 122.9, 123.0, 124.0, 124.2, 128.1, 128.5, 129.1, 132.0, 132.1, 132.3, 132.4, 132.7, 148.4, 149.3, 153.1, 159.4, 161.3. HRMS (ESI+) calcd for $[NaC_{20}H_{15}NO_4]^+$ ($[M + Na]^+$) 356.0899; found 356.0893.

(*R*)-4-Hydroxy-3-[1-(4-methylphenyl)-3-oxobutyl]-chromen-2-one (3e)[6b]. Starting from benzylideneacetone **1e** (16.32 mg, 0.1 mmol) and coumarin **2a** (33.09 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 20.10 mg of compound **3e** was obtained (62% yield). The corresponding ee (58%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 279.4 nm): τ_{major} = 17.3 min; τ_{minor} = 33.2 min. $[\alpha]_D^{23}$ = +3.3 ± 0.2 (*c* 0.37, acetonitrile, 58% ee). {lit.,[6a] $[\alpha]_D^{25}$ = +16.6 (*c* 1.0, dichloromethane, 96% ee, (*R*)-**3e**)}.

(*R*)-6-Chloro-4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one (3f)[20]. Starting from benzylideneacetone **1a** (14.92 mg, 0.1 mmol) and coumarin **2b** (40.53 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 19.41 mg of compound **3f** was obtained (57% yield). The corresponding ee (67%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 13.1 min; τ_{minor} = 18.3 min. $[\alpha]_D^{23} = -22.1 \pm 0.1$ (*c* 0.69, acetonitrile, 67% ee).

(*R*)-6-Bromo-4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one (3g)[6e]. Starting from benzylideneacetone **1a** (14.92 mg, 0.1 mmol) and coumarin **2c** (49.19 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 20.69 mg of compound **3g** was obtained (53% yield). The corresponding ee (67%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 13.7 min; τ_{minor} = 18.9 min. $[\alpha]_D^{23} = -24.3 \pm 0.1$ (*c* 1.00, acetonitrile, 67% ee).

(*R*)-4-Hydroxy-6-methyl-3-(3-oxo-1-phenylbutyl)chromen-2-one (3h)[10]. Starting from benzylideneacetone **1a** (14.92 mg, 0.1 mmol) and coumarin **2d** (35.95 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 8.04 mg of compound **3h** was obtained (25% yield). The corresponding ee (61%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 271.0 nm): τ_{major} = 20.0 min; τ_{minor} = 30.7 min. $[\alpha]_D^{23} = -4.9 \pm 0.1$ (*c* 0.31, acetonitrile, 61% ee).

(*R*)-6-Bromo-3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxychromen-2-one (3i)[6e]. Starting from benzylideneacetone **1b** (16.06 mg, 0.1 mmol) and coumarin **2c** (49.19 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 10.54 mg of compound **3i** was obtained (25% yield). The corresponding ee (62%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 8.2 min; τ_{minor} = 13.6 min. $[\alpha]_D^{24} = -35.2 \pm 0.1$ (*c* 0.34, acetonitrile, 62% ee).

(*R*)-6-Chloro-4-hydroxy-3-(3-oxo-1-*p*-tolylbutyl)-2*H*-chromen-2-one (3j)[6e]. Starting from benzylideneacetone **1e** (16.32 mg, 0.1 mmol) and coumarin **2b** (40.53 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 7.14 mg of compound **3j** was obtained (20% yield). The corresponding ee (62%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 12.2 min; τ_{minor} = 19.4 min. $[\alpha]_D^{24} = -25.8 \pm 0.2$ (*c* 0.20, acetonitrile, 62% ee).

(*R*)-6-Chloro-4-hydroxy-3-[1-(4-methoxyphenyl)-3-oxobutyl]-chromen-2-one (3k). Starting from benzylideneacetone **1f** (17.62 mg, 0.1 mmol) and coumarin **2b** (40.53 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 15.62 mg of compound **3k** was obtained (42% yield). The corresponding ee (54%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 17.3 min; τ_{minor} = 31.6 min. $[\alpha]_D^{23} = -27.9 \pm 0.1$ (*c* 0.77, acetonitrile, 54% ee). IR (cm^{-1}) 3353 (OH), 1694 (C═O), 1614 (C═O), 1510, 1241, 824, 730, 535. In $CDCl_3$, the product was found to exist in a fast equilibrium between its open chain form **3k** (≈20 mol%) and both pseudo-diastereomeric hemiketals **3k′** (≈40 mol%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.68 (s, $1.2H_{3k'}$, RCH_3), 1.74 (s, $1.2H_{3k'}$, RCH_3), 2.00 (dd, J^1 = 14.0 Hz, J^2 = 11.5 Hz, $0.4H_{3k'[a]}$, RCH_2R'), 2.04 (s, $0.2H_{3k}$, RCH_3), 2.29 (s, $0.4H_{3k}$, RCH_3), 2.38 (dd, J^1 = 14.2 Hz, J^2 = 6.8 Hz, $0.4H_{3k'[b]}$, RCH_2R'), 2.47 (dd, J^1 = 14.1 Hz, J^2 = 6.9 Hz, $0.4H_{3k'[b]}$, RCH_2R'), 2.54 (dd, J^1 = 14.2 Hz, J^2 = 3.0Hz, $0.4H_{3k'[a]}$, RCH_2R'), 3.11 (br s, $0.4H_{3k'}$, ROH), 3.25–3.30 (m, $0.4H_{3k'}$ + $0.2H_{3k}$, ROH + RCH_2R'), 3.75–3.86 (m, $1.2H_{3k'[a]}$ + $1.2H_{3k'[b]}$ + $0.6H_{3k}$, $ROCH_3$), 4.09–4.15 (m, $0.4H_{3k'}$ + $0.2H_{3k}$, RCHR′R″ + RCH_2R'), 4.24 (dd, J^1 = 6.6 Hz, J^2 = 2.8 Hz, $0.4H_{3k'}$, RCHR′R″), 4.63 (dd, J^1 = 10.4 Hz, J^2 = 2.1 Hz, $0.2H_{3k}$, RCHR′R″), 7.12–7.31 (m, 2H, Ar-H), 7.12–7.31 (m, 3H, Ar-H), 7.41–7.44 (m, $0.4H_{3k'}$ + $0.2H_{3k}$, Ar-H), 7.51 (dd, J^1 = 8.8 Hz, J^2 = 2.5 Hz, $0.4H_{3k'}$, Ar-H), 7.78 (d, J^1 = 2.5 Hz, $0.4H_{3k'}$, Ar-H), 7.86 (d, J^1 = 2.5 Hz, $0.4H_{3k'}$, Ar-H), 7.91 (d, J^1 = 2.5 Hz, $0.2H_{3k}$, Ar-H), 9.56 (br s, $0.2H_{3k}$, ROH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.0, 28.5, 33.4, 34.7, 40.7, 42.6, 55.4, 55.4, 99.5, 101.0, 102.4, 113.8, 114.3, 114.9, 117.8, 118.2, 118.3, 122.5, 122.8, 123.7, 128.1, 128.2, 129.3, 129.3, 129.7, 131.6, 131.8, 132.1, 132.8, 134.8, 157.5. HRMS (ESI+) calcd for $[NaC_{20}H_{17}ClO_5]^+$ ($[M + Na]^+$) 395.0662; found 395.0657.

(*R*)-6-Bromo-4-hydroxy-3-[1-(4-methoxyphenyl)-3-oxobutyl]-chromen-2-one (3l)[6e]. Starting from benzylideneacetone **1f**

(17.62 mg, 0.1 mmol) and coumarin **2c** (49.19 mg, 0.2 mmol, 2 eq.), following the general procedure described above, 13.22 mg of compound **3l** was obtained (32% yield). The corresponding ee (54%) was determined by chiral HPLC analysis of the product (Daicel Chiralpak IC column, *n*-hexane/isopropyl alcohol 80 : 20, flow rate 1 ml min^{-1}, λ = 272.2 nm): τ_{major} = 19.5 min; τ_{minor} = 36.9 min. $[\alpha]_D^{24} = -34.3 \pm 0.1$ (*c* 0.61, acetonitrile, 54% ee).

Conflicts of interest

There are no conflicts to declare.

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