Tetrahedron: *Asymmetry* 25 (2014) 923–935

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of novel cinchona-amino acid hybrid organocatalysts for asymmetric catalysis

Pedro Barrulas [a], Maurizio Benaglia [b,†], Anthony J. Burke [a,*]

[a] *Universidade de Évora e Centro de Química de Évora, Rua Romão Ramalho 59, 7000 Évora, Portugal*
[b] *Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, I-20133 Milano, Italy*

ARTICLE INFO

Article history:
Received 26 February 2014
Revised 5 May 2014
Accepted 9 May 2014
Available online 18 June 2014

ABSTRACT

Three novel subclasses of cinchonidine derivatives coupled to diverse amino acids were prepared in very good overall yield and tested in a benchmark organocatalytic aldol reaction, between acetone and aromatic aldehydes. These subclasses are a family of amino acid-cinchonidine (subclass A), *N*-formamides-cinchonidine (subclass B) and dipeptide-cinchonidine (subclass C) hybrids. Our main goal, besides obtaining very good yields and enantioselectivities, was to understand the influence of the amino acid side chain residues on the enantioselectivity of the asymmetric aldol reactions. Different amino acid tethered cinchonidine hybrids were compared and their catalytic behaviour was evaluated, allowing good enantioselectivities to be achieved, 92% ee in one case. Other reactions such as Biginelli, Michael addition and ketimine hydrosilylation reactions were screened with these ligands, but the outcome was less successful.

1. Introduction

One of the most powerful means for obtaining enantiomerically enriched compounds is via asymmetric catalysis.[1,2] The most common way of achieving this is with metal based catalysts or enzymes. Over the last 15 years, organocatalysts have become important alternatives to these traditional catalysts.[2,3]

In the early 70s, Eder et al.[4a] and Hajos and Parrish[4b] reported ground-breaking work on the proline catalysed Robinson annulation, thus giving rise to the field of organocatalysis. However, only in 2000 did this field experience a remarkable renaissance, with key reports by List[5a] (aldol condensation with L-proline) and MacMillan[5b] (Diels–Alder reaction with imidazolidinone). From this time this field has witnessed significant and exponential growth.

Due to their considerable success, cinchona alkaloid based organocatalysts are considered to be 'privileged chiral catalysts'.[6,7] Cinchona alkaloids are recognized as having many medicinal applications, particularly with regard to malaria,[8] and also functioning as antiarrythmics,[9] sodium-channel blockers[10] as well as potential cytostatic agents.[11]

On the other hand, due to their structural complexity and ready availability, they can be used as chiral resolving agents, ligands for asymmetric catalysis,[12–14] and also as NMR discriminating agents.[15] Cinchona alkaloids have a bifunctional nature, which is apparent in the case of both quinine **QN** and cinchonidine **CD** (Fig. 1).

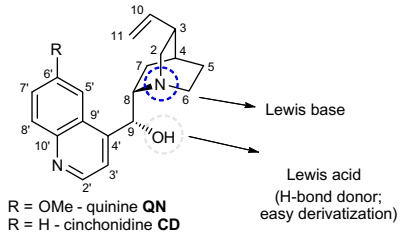


Figure 1. Structural attributes of quinine **QN** and cinchonidine **CD** alkaloids.

One of the beneficial characteristics of these molecules is the presence of a chiral cavity, and the potential to functionalize the 9-OH group; for instance, the functionalization of the OH group into more acidic groups or ones which are more effective as hydrogen bond donors. With regard to their organocatalytic activity, several key reactions can be successfully carried out, such as: Michael additions, Mannich, aldol, Baylis–Hillman, cycloadditions and Henry reactions.[12–14]

Amino acids are another class of natural compounds that play a very important role in asymmetric synthesis.[16,17] They have many

* Corresponding author. Tel.: +351 266745310; fax: +351 266744971.
E-mail addresses: maurizio.benaglia@unimi.it (M. Benaglia), ajb@uevora.pt (A.J. Burke).
† Tel.: +39 025031 4171; fax: +39 025031 4159.

http://dx.doi.org/10.1016/j.tetasy.2014.05.003
0957-4166/

diverse applications, and have been successfully applied in asymmetric organocatalytic reactions such as: Michael additions,[18] ketimine reductions with trichlorosilane,[19,20] multicomponent Biginelli reactions[21] and aldol reactions.[22–26]

Our main goal herein was the synthesis of three novel subclasses of cinchonidine-amino acid hybrids for asymmetric organocatalysis, using a benchmark aldol condensation as the test reaction. The subclasses that we targeted were amino acid hybrids based on cinchonidine (subclass A), *N*-formamides of some compounds from subclass A (subclass B) and dipeptide hybrids based on cinchonidine (subclass C) (Fig. 2).

Subclass A, has already been reported on,[27] however, our goal was to develop further specific examples of this class, with diverse amino side-chains. Subclass B is currently unknown in the literature, although *N*-formylated amine organocatalysts have already been extensively studied for organocatalyzed imine hydrosilylation reactions. Some molecules belonging to subclass C, are already known,[28] but to the best of our knowledge have not been exploited in catalysis to date. Our main motive was to carefully study and compare these three structural subgroups in a bench-mark aldol reaction (and other reactions) with a view to obtaining: (a) new efficient modular catalytic systems whose reactivity and asymmetry inducing capabilities could be easily tuned, and (b) to gain an insight into the most basic structural requirements within the molecule's chemical structure for controlling the reaction enantioselectivity. These molecules contain a number of structural and functional group diversity points, such as: the amino acid side-chain (aliphatic, aromatic or hydrogen), the amino acid nitrogen (primary, secondary cyclic or acyclic), as well as the incorporation of a carbonyl group or a new amino acid residue, which all have a potential influence on the stereochemical outcome of the reaction.

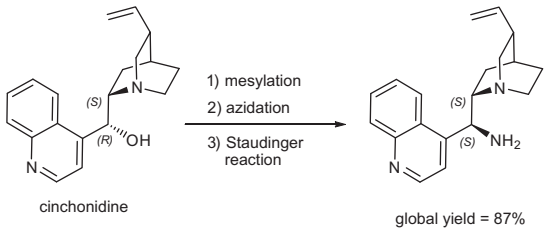
The first organocatalytic application of this type of compound was published by Chen et al.[27b] in 2008 when they synthesized Cinchona-(cinchonidine, cinchonine, quinidine and quinine)proline (D and L) hybrids, and applied them to enantioselective aldol reactions, affording very good results (97% yield and 98% ee).

Zhao et al.[27c] suggested a transition state model for the same prolinamides synthesized by Chen et al. that involves hydrogen bonding interactions between the protonated organocatalyst and the electrophile.

Recently, Huang et al.[29] reported on the synthesis of a small library of cinchona alkaloids (cinchonine and quinine) with a diverse range of amino acid residues in their structure (Ala, Val, Leu). They were screened in a series of asymmetric aldol reactions, giving very good yields (up to 96%) and enantioselectivities (up to 92% ee).

2. Results and discussion

The synthesis of all subclasses A, B and C was achieved using a common precursor; the amine (8S,9S)-9-amino(9-deoxy)-epi-cinchonidine, which was easily obtained in three reaction steps according to the literature from commercially available cinchonidine[30–32] (Scheme 1).



Scheme 1. General synthesis of amine (8S,9S)-9-amino(9-deoxy)-epi-cinchonidine.

With amine **4** in hand, we proceeded with the synthesis of our first library of cinchonidine derivatives: subclass A, and for this purpose we used the mixed anhydride method of Girgis and Prashad (Scheme 2).[33]

With this method we were able to successfully obtain a library of eight compounds with good results for subsequent screening in asymmetric aldol reactions (Fig. 3).

After concluding the synthesis of subclass A, we advanced with the synthesis of the respective *N*-formamide derivatives, subclass B, which were prepared (with the exception of compounds **1g** and **1h**) by *N*-formylation, including **2g** the formamide of amine **4**. Malkov and Kočovský have shown the importance of the presence of an *N*-formyl group in a variety of organocatalysts used in this reaction.[34] We wished to determine if the presence of this group might enhance the catalytic activity for other reaction types, such as: asymmetric aldol reactions,[35,36] Biginelli,[21] Michael[18] and ketone hydrosilylation reactions.[34,37,38,41,42]

Accordingly, based on the method used by Malkov and Kočovský[34a] for the *N*-formylation of L-valine derivatives, we created a library of amino acid cinchonidine *N*-formamide hybrids in good to excellent yields 62–99%, with overall yields of between 43% and 77% (Fig. 4).

Finally, subclass C was easily obtained in good yields using **1a** as the substrate by the mixed anhydride method (Fig. 5).

At this point, we started to evaluate the organocatalytic potential of these catalysts. Based on the pioneering work of Xiao[27] and Liu[27c] on the synthesis and application of prolinamides derived from Cinchona alkaloids in the asymmetric aldol reaction, we began studying the influence of various amino acid units on the outcome of a bench-mark aldol reaction. This was followed by their evaluation in various other asymmetric catalytic reactions such as Michael, Biginelli and hydrosilylation reactions.

In the case of the aldol reactions, we examined the bench-mark aldol reaction between acetone and *p*-nitrobenzaldehyde (Table 1) using the three subclasses of catalysts (see Table 1). It was possible to verify the reliability of our results; in the case of the cinchonidine-amino acid hybrids (subclass A) the results compared well to those of Xiao[27b] for the same reaction with prolinamide **1f**. Using the same conditions, Xiao obtained the desired product **6a**

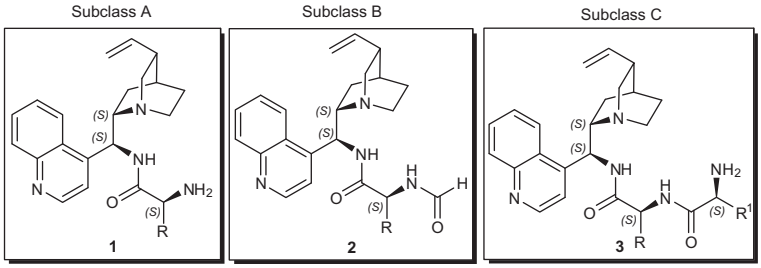
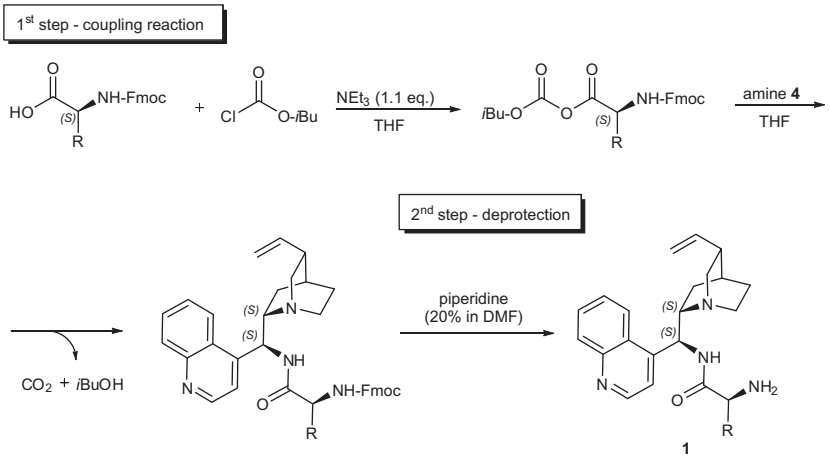


Figure 2. Novel subclasses of cinchonidine derivatives synthesized in this work.



Scheme 2. Synthesis of compounds of subclass A.

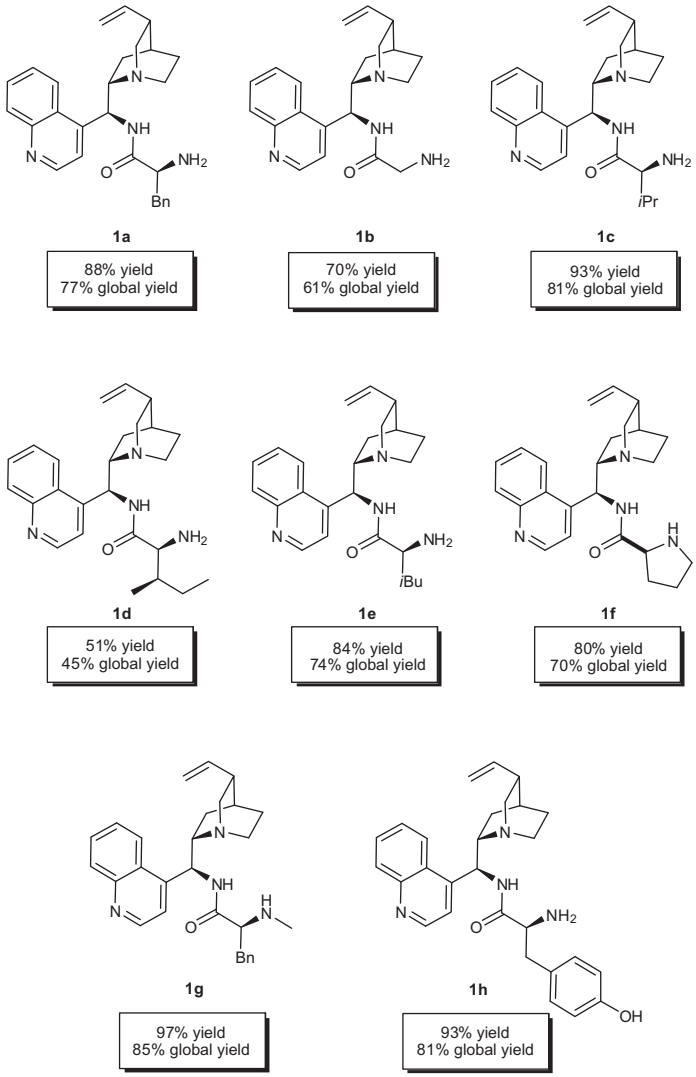


Figure 3. Organocatalyst candidates of subclass A synthesized herein.

in 79% yield with an enantiomeric excess of 44% for the (*R*)-enantiomer, (see entry 6, Table 1).

The results were very encouraging; subclass A gave the best results with yields of between 28% and 96% and with a highest enantioselectivity of 77% ee with catalyst **1e** (Table 1, entry 5). Subclass C was the next best type of catalyst, giving yields of 13–89%, and enantioselectivities of up to 45% ee (with catalyst **3c**, entry 18).

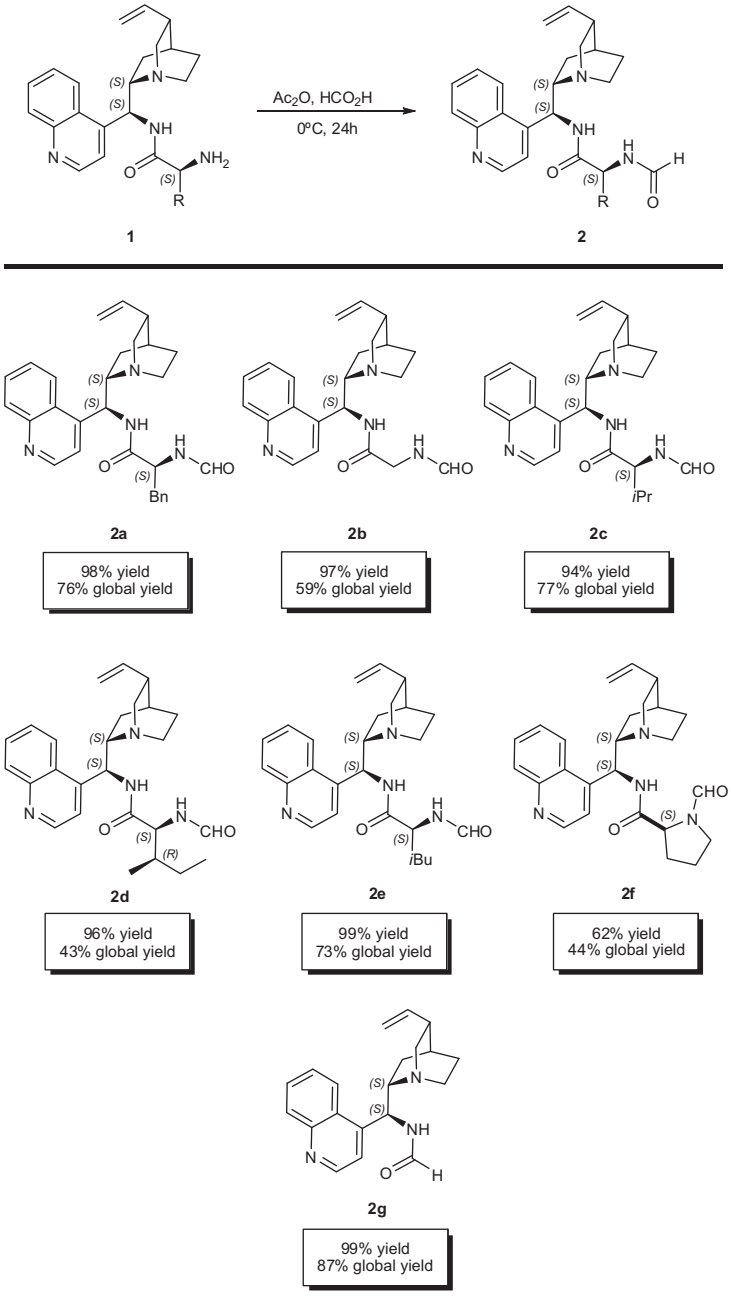


Figure 4. Generic synthesis of compounds of subclass B including the respective yields.

After careful analysis of the results, we found that the nature of the amino acid side chain, incorporated into the 9-amino-(9-deoxy)-*epi*-cinchonidine, was of great importance with regard to the enantioselectivity. Catalyst **1h** was the only example that gave the aldol product **6a** in racemic form (entry 8, Table 1) and this was presumed to be due to the nature of its side-chain: that is, it was the only one that contained a functional group, i.e. a phenol group (Fig. 3). Opposing internal competition between H-bonding (due to the phenolic hydroxyl group) and π–π interactions between the aryl groups might generate two distinct diastereomeric transition states leading to no overall enantioselectivity in the reaction.

The presence of a side chain in the amino acid structure plays an important role with regard to the enantioselectivity of the reaction. This deduction was related to the low ee observed for **1b** (entry 2, Table 1), since it was the only candidate containing an achiral amino acid residue (i.e., glycine). However, not only does the amino acid side chain play a vital role in the asymmetric induction process, but so does the nature of the amino nitrogen.

We observed that **1g**, which contains an *N*-methylated L-phenylalanine residue (entry 7, Table 1), affords a lower enantioselectivity when compared with its unmethylated counterpart **1a** (entry 1, Table 1) affording enantioselectivities of 28% and 36% ee, respectively.

As expected, the catalysts containing aliphatic and bulky side chains gave **6a** with the highest enantioselectivities. For example, **1e** (entry 5, Table 1) gave the desired aldol product in moderate yield but with high enantioselectivity (77% ee), even exceeding the results achieved when using the prolinamide derivative as reported by Xiao's group.[27b]

For the remaining subclasses, the results were conclusive. The incorporation of a carbonyl group or a second amino acid unit is disadvantageous, as the enantioselectivities revealed an abrupt

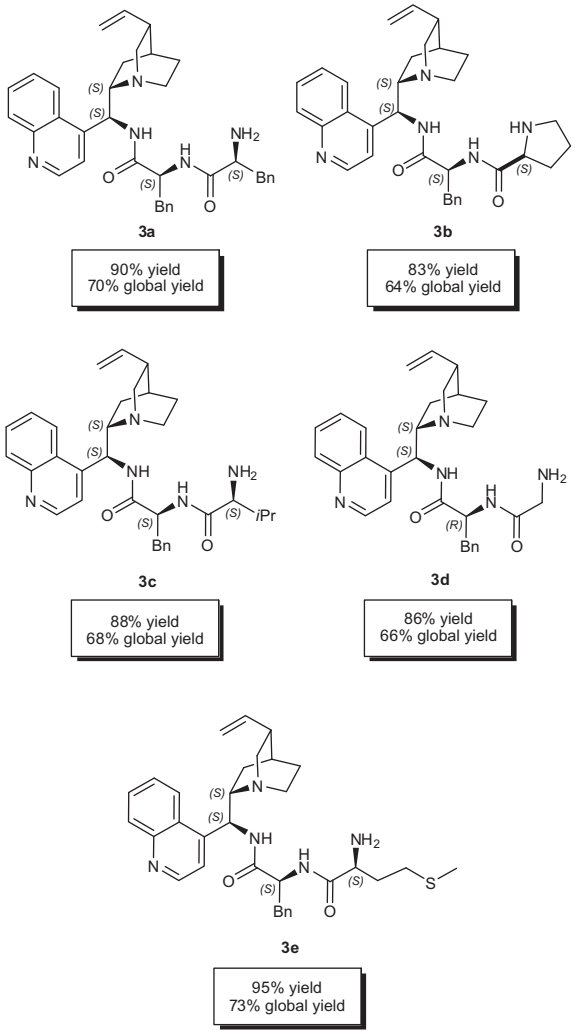


Figure 5. Organocatalyst candidates of subclass C synthesized herein.

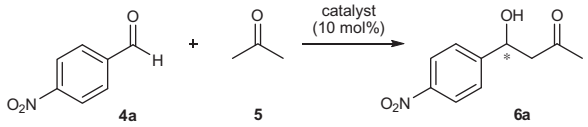
decrease (Table 1). All of the results obtained for these two subclasses were lower than those observed with the simpler hybrid structures (subclass A).

Zhao et al.[27c] proposed a transition state for the asymmetric aldol reaction involving **1f** that only comprises of one hydrogen bonding interaction between the aldehyde and the organocatalyst. However in our opinion, this mechanistic proposal appears to be incomplete. The hydrogen bond needed for the relevant stereocontrol seems to be insufficient to warrant a specific orientation of the aldehyde. This single hydrogen bond does not limit free rotation around its own axis, and in our opinion is insufficient to induce the high enantioselectivities reported (Fig. 6).

Another limitation of the proposed model is based on the lack of information on the hypothetical effect that the protonated amine could have on activation of the aldehyde unit for enantioselective nucleophilic attack. We also note that inadvertently Zhao et al.[27c] have mentioned that the attack of the enamine nucleophile to the aldehyde was *Re*-face and not *Si*-face (although this was correctly indicated in the figure) which gives the desired product with an (*R*)-absolute configuration.

We thus propose a slightly different transition state model with hydrogen-bonding and other stabilizing interactions (Fig. 6). According to this hypothetical model, the organocatalyst should form a chiral cavity defined by the perpendicular relationship between the quinoline and prolinamide units.

Table 1
Results for the aldol reaction using aldehyde **4a** and acetone **5**. Entries 1–8: subclass A; entries 9–15: subclass B; entries 16–20: subclass C



Entry[a]	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1a**	89	36 (*R*)
2	**1b**	28	11 (*S*)
3	**1c**	42	42 (*R*)
4	**1d**	49	74 (*R*)
5	**1e**	42	77 (*R*)
6	**1f**	96	44 (*R*)
7	**1g**	74	28 (*R*)
8	**1h**	59	Rac.
9	**2a**	6	12 (*S*)
10	**2b**	28	12 (*S*)
11	**2c**	20	12 (*S*)
12	**2d**	6	10 (*S*)
13	**2e**	44	13 (*S*)
14	**2f**	13	33 (*R*)
15	**2g**	9	11 (*S*)
16	**3a**	35	34 (*R*)
17	**3b**	89	37 (*R*)
18	**3c**	13	45 (*R*)
19	**3d**	14	10 (*S*)
20	**3e**	16	Rac.

[a] Reaction proceeded at room temperature in the presence of 0.53 mmol of aldehyde, 10 mol % of catalyst and 1 mL of acetone over 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC.

Contrary to the model proposed by Zhao et al.[27c] we suggest a double interaction via two hydrogen bonds involving the nitro group of the aldehyde simultaneously with π–π interactions between the aromatic ring of the substrate and the quinoline ring of the alkaloid, resulting in the exposure of the *Si*-face of the aldehyde to the enamine and thus the formation of the (*R*)-enantiomer of the product.

Computational studies will be required to gain a better insight into the nature of this mechanism.

In light of these results, substrate screening was performed using **1e** and the results are given in Table 2.

We found that the presence of a substituent on the aromatic ring was a key factor in obtaining the products with the highest enantioselectivities, for example benzaldehyde gave racemic aldol-product (entry 2, Table 2). It seems that the presence of strong electron-withdrawing groups in the *para*-position gave the best results (Table 2, entries 1 and 6). The presence of a nitro-group at the *para*-position seems to be crucial for the formation of critical H-bonds, thus enabling high enantiofacial selectivity (our model, Fig. 6). However, electron-donating substituents at the *ortho* positions gave racemic products (Table 2, entries 4 and 8). This might be due to critical steric hindrance issues that remove the transition state from that which gives the best enantiofacial selectivity.

This assay allowed us to conclude that the deactivating substituents on the ring of the aromatic aldehydes provide better enantioselectivities (e.g., NO_2 and Br), while substitution at the *ortho* and *meta* positions has a negative effect on the enantioselectivity.

Following the strategy of Chen[27b] and Liu[27c] we were curious to know the precise effect of an acid in the reaction medium and whether protonation of the quinuclidine nitrogen could improve the reaction enantioselectivity, by establishing crucial hydrogen bonds. Thus we decided to test different organic and inorganic Brønsted acids with counter-anions of different sizes and basicities (Table 3).

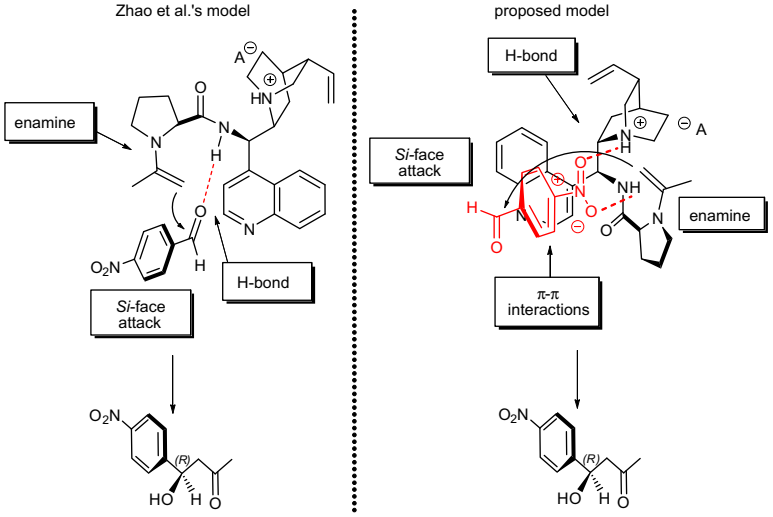
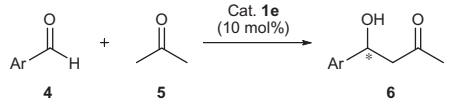


Figure 6. Comparison of Zhao et al.'s[27c] and our transition state models.

Table 2
The aldol reaction using aldehydes **4** and acetone **5** in the presence of catalyst **1e**



4 **5** **6**

Entry[a]	Aldehyde	Aryl	Product	Yield[b] (%)	ee[c] (%)
1	**4a**	*p*-NO_2–C_6H_4	**6a**	42	77 (*R*)
2	**4b**	Ph	**6b**	25	*rac*
3	**4c**	*p*-MeO–C_6H_4	**6c**	2	44 (*R*)
4	**4d**	*o*-MeO–C_6H_4	**6d**	71	*rac*
5	**4e**	2,4-$(MeO)_2$–C_6H_3	**6e**	5	49[d]
6	**4f**	*p*-Br–C_6H_4	**6f**	19	56 (*R*)
7	**4g**	*m*-Me–C_6H_4	**6g**	11	35 (*R*)
8	**4h**	*o*-Me–C_6H_4	**6h**	2	*rac*
9	**4i**	*o*-Cl–C_6H_4	**6i**	14	22 (*R*)
10	**4j**	*p*-BnO–C_6H_4	**6j**	11	27[d]

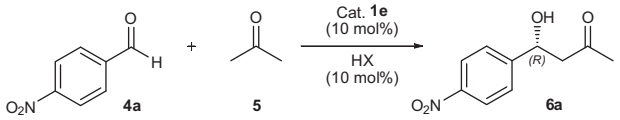
[a] Reaction proceeded at room temperature in the presence of 0.53 mmol of aldehyde, 10 mol % of catalyst and 1 mL of acetone over 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] No available data in the literature for the attribution of the absolute configuration.

In a similar test, Chen et al.[27b] observed an approximate 25% increase in the enantioselectivity of the product when using 10 mol % of an acid additive (i.e., acetic acid). Contrary to this, our results using various acid additives revealed a decrease in the enantioselectivities and in fact no reaction occurred in the presence of phosphoric acid (entry 5, Table 3).

We then carried out some solvent screening studies to determine if the solvent might affect the enantiocontrol of the reaction (Table 4). We observed no particular correlation between the solvent polarity and enantioselectivity, as both polar (DMF, entry 7 Table 4) and apolar (toluene, entry 6), gave good enantioselectivities. In fact, with the exception of methanol, DMF and water, all other solvents allowed us to obtain the desired product with enantiomeric excesses of 70–79% ee. THF (entry 3, Table 4) provided the best enantioselectivity (79% ee), but with a modest yield. It is noteworthy that the catalyst was also active in water (entry 9, Table 4), giving an enantioselectivity of 49% ee and 45% yield.

The reaction could also be conducted under solvent free conditions (entry 10, Table 4), giving an enantioselectivity of 77% ee and 42% yield.

Table 3
The acid effect on the aldol reaction between aldehyde **4a** and acetone **5** in the presence of catalyst **1e**

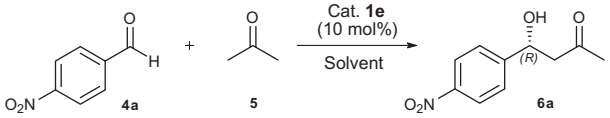


4a **5** **6a**

Entry[a]	Acid (HX)	pK_a[39]	Yield[b] (%)	ee[c] (%)
1	HCl	<1	36	Rac.
2	AcOH	4.75	46	37
3	TFA	<1	15	20
4	*p*-TsOH	<1	40	5
5[d]	H_3PO_4	2.12	0	-
6	$HClO_4$	<1	42	5

[a] Reaction proceeded at room temperature in the presence of 0.53 mmol of aldehyde, 10 mol % of catalyst, 10 mol % of acid and 1 mL of acetone over 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] No reaction.

Table 4
The solvent effect on the aldol reaction between aldehyde **4a** and acetone **5** in the presence of catalyst **1e**

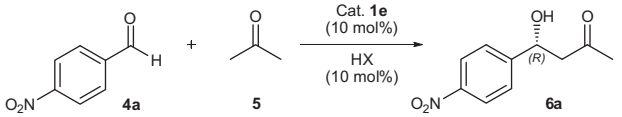


4a **5** **6a**

Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	20	73
2	$CHCl_3$	20	70
3	THF	36	79
4	Et_2O	30	73
5	MeOH	57	59
6	Toluene	30	73
7	DMF	42	Rac.
8	DMSO	27	70
9	H_2O	45	49
10	Neat	42	77

[a] Reaction proceeded at room temperature in the presence of 0.53 mmol of aldehyde, 10 mol % of catalyst, 0.5 mL of acetone and 0.5 mL of solvent over 24 h.
[b] Isolated yield.
[c] Enantiomeric excess determined by chiral HPLC.

Table 5
The temperature effect on the aldol reaction between aldehyde **4a** and acetone **5** in the presence of catalyst **1e**



Entry[a]	Solvent	T (°C)	Yield[b] (%)	ee[c] (%)
1	Neat	0	50	78
2	THF	0	47	68
3	Neat	−40	24	92
4	THF	−40	29	87

[a] Reaction proceeded in the presence of 0.53 mmol of aldehyde, 10 mol % of catalyst, 0.5 mL of acetone and 0.5 mL of solvent over 24–72 h.
[b] Isolated yield.
[c] Enantiomeric excess determined by chiral HPLC.

With these optimized conditions already in hand, we investigated the effect of temperature on the reaction (Table 5).

At low temperatures (−40 °C) the highest enantioselectivities were obtained, either under solvent free conditions or with THF (Table 5, entries 3 and 4, giving 92% and 87% ee, respectively).

These catalysts were also screened in other asymmetric catalytic reactions, notably in Biginelli, Michael and in ketimine hydrosilylation reactions.[40] Unfortunately the results were not encouraging. For the Biginelli reaction[40] with methyl acetoacetate, benzaldehyde and urea, the best results were achieved with **3d**, giving an enantioselectivity of 23% ee and the best yield (44%) with **1b**. This catalyst only provided a highest enantioselectivity of 32% ee for the Michael addition[40] between β-nitrosyrene and acetylacetone with moderate to very good yields. Finally, for the hydrosilylation reactions of *N*-(1-(4-nitrophenyl)ethylidene)-aniline with trichlorosilane,[40] a highest enantioselectivity of 45% ee was obtained with a yield of 84%.

3. Conclusions

Herein our aim was the synthesis of a new series of organocatalysts derived from a combination of various L-amino acids with cinchonidine and their exploitation in a series of bench-mark reactions. These organocatalysts were obtained using very simple strategies and synthesized in overall moderate to high yields (43–87%).

We have found that the presence of non-functionalized, aliphatic and bulky side chains, as well as primary amines are essential requirements for obtaining high enantiomeric excesses in the bench-mark aldol reaction of acetone with aromatic aldehydes. We also found that using **1e** at −40 °C, in the aldol reaction gave high enantioselectivities (up to 92% ee).

Other reactions such as the Biginelli and Michael additions and ketimine hydrosilylations were also investigated, but the results were less satisfactory.

4. Experimental

4.1. General

Cinchonidine, L-amino acids and all other reagents and solvents used herein were purchased from Sigma–Aldrich, Fluka or Acros Organics and were used as received.

Column chromatography was carried out on silica gel (sds, 70–200 μm) or on reverse phase C_{18}-silica gel (40–63 μm). Thin-layer chromatography (TLC) was carried out on aluminium backed Kieselgel 60 F254 plates (Merck). Plates were visualized either by UV light (254 e 366 nm), developed with phosphomolybdic acid in ethanol or with a Drangendorff reagent followed by heating. Melting points were determined on a Barnstead/Electrothermal 9100 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument (^{1}H: 400 MHz; ^{13}C: 100 MHz) at FCT-UNL (Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa), using $CDCl_3$, DMSO-d_6 or D_2O as solvents and TMS as internal standard. All chemical shifts (δ) were expressed in ppm and the coupling constants, expressed in Hz. Mass spectra were recorded on a Waters–Micromass spectrometer. The specific rotation determinations were performed in LNEG (Laboratório Nacional de Energia e Geologia, Lisbon) on a Perkin–Elmer 241 at the temperatures indicated. High performance liquid chromatography (HPLC) was performed on a Agilent 1110 Series instrument using Chiralcel OD-H (0.46 cm × 25 cm) or an AD-H (0.46 cm × 25 cm) as chiral columns both equipped with a pre-column.

4.2. General procedure for the synthesis of (8*S*,9*R*)-9-*O*-mesylcinchonidine

Based on Hoffmann's method,[31] to a stirred solution of cinchonidine (10.032 g, 34.08 mmol) in 350 mL of dry THF was added triethylamine (15 mL, 107.60 mmol) and then the solution was cooled in an ice bath to 0 °C. Methanesulphonyl chloride (5.3 mL, 68.48 mmol) dissolved in a small volume of THF was added dropwise to the previous solution, and then the mixture was allowed to react at room temperature over 2 h. Next, the reaction was quenched with saturated aqueous sodium bicarbonate (80 mL) and then extracted with CH_2Cl_2 (2 × 20 mL). The resulting crude product was purified by column chromatography on silica gel using ethyl acetate as eluent to give the title compound as a white solid with a sweet aroma (11.76 g, 93%), mp 107.2–108.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.94 (d, 1H, J = 4 Hz, H2′), 8.28 (d, 1H, J = 8 Hz, H5′), 8.15 (d, 1H, J = 8 Hz, H8′), 7.75 (t, 1H, J = 8 Hz, H7′), 7.66 (t, 1H, J = 8 Hz, H6′), 7.52 (br s, 1H, H3′), 6.59 (br s, 1H, H9), 5.73 (m, 1H, H10), 5.00 (m, 2H, H11), 3.45–3.32 (m, 2H, H6, H8), 3.11 (br s, 1H, H2), 2.76 (br s, 5H, H6, H2, CH_3), 2.38 (br s, 1H, H3), 1.96–1.65 (m, 5H, H7, H5, H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 150.0 (C2′), 148.8 (C10′), 142.4 (C10), 140.1 (C4′), 130.8 (C8′), 129.9 (C7′), 127.9 (C9′), 125.0 (C6′, C5′), 122.9 (C3′), 115.6 (C11), 59.9 (C9), 56.04 (C8, C2), 39.3 (C6, C3, C-mesyl), 27.2 (C7, C4, C5).

4.3. General procedure for the synthesis of (8*S*,9*S*)-9-azide(9-deoxy)-*epi*-cinchonidine

9-*O*-Mesylcinchonidine (2.06 g, 5.53 mmol) was dissolved at room temperature in anhydrous DMF (40 mL); this was followed by the addition of 2 equiv of NaN_3 (0.719 g; 11.06 mmol) and the mixture was heated to 80 °C over 24 h.[15,30] The formation of a yellow solution is an indication of azide formation. Monitoring the reaction by TLC analysis indicated the consumption of the substrate. The solvent was removed by distillation and the residue was re-suspended in H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL), then purified by column chromatography on silica gel with ethyl acetate to furnish the title compound as a yellowish dense oil (1.701 g; 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.95 (d, 1H, J = 4 Hz, H2′), 8.23 (d, 1H, J = 8 Hz, H5′), 8.18 (d, 1H, J = 8 Hz, H8′), 7.77 (t, 1H, J = 8 Hz, H7′), 7.65 (t, 1H, J = 8 Hz, H6′), 7.41 (d, 1H, J = 4 Hz, H3′), 5.76 (m, 1H, H10), 5.15 (d, 1H, J = 10 Hz, H9), 4.99 (m, 2H, H11), 3.35–3.21 (m, 3H, H6, H2, H8), 2.95–2.83 (m, 2H, H6, H2), 2.30 (br s, 1H, H3), 1.71–1.58 (m, 4H, H4, H7, H5), 0.77–0.72 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 149.9 (C2′), 148.7 (C10′), 142.2 (C10), 141.3 (C4′), 130.6 (C8′), 129.4 (C7′), 127.2 (C6′), 126.6 (C9′), 123.0 (C5′), 120.2 (C3′), 114.4 (C11), 59.5 (C9),

55.9 (C8), 53.4 (C2), 40.9 (C6), 39.3 (C3), 27.8 (C7), 27.1 (C4), 26.0 (C5).

4.4. General procedure for synthesis of (8*S*,9*S*)-9-amino(9-deoxy)-*epi*-cinchonidine

Based on a literature method,[30] (8*S*,9*S*)-9-azide(9-deoxy)-*epi*-cinchonidine (8.37 g, 26.2 mmol) was dissolved in dry THF (120 mL) followed by the addition of triphenylphosphane (10.31 g, 39.3 mmol) at room temperature. After the addition was complete, the mixture was heated to 48–52 °C in an oil bath and the mixture was allowed to react over 4 h. The mixture was then cooled to room temperature, H_2O (3 mL) was added and left stirring overnight. The crude product was concentrated and purified by column chromatography on silica gel with ethyl acetate followed by AcOEt/MeOH/NEt_3 (100:2:3) to furnish the title compound as a yellowish dense oil (7.07 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.92 (d, 1H, J = 4 Hz, H2′), 8.36 (br s, 1H, H5′), 8.15 (d, 1H, J = 8 Hz, H8′), 7.73 (t, 1H, J = 8 Hz, H7′), 7.60 (t, 1H, J = 8 Hz, H6′), 7.54 (br s, 1H, H3′), 5.82 (m, 1H, H10), 5.03–4.72 (m, 2H, H11), 4.72 (br s, 1H, H9), 3.33–3.22 (m, 2H, H6, H2), 3.10 (br s, 1H, H8), 2.85–2.82 (m, 2H, H6, H2), 2.42 (s, 2H, NH_2), 2.30 (br s, 1H, H3), 1.64–1.58 (m, 3H, H4, H7, H5), 1.43–1.41 (m, 1H, H5), 0.79–0.74 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 150.5 (C2′), 148.8 (C10′), 141.8 (C10, C4′), 130.6 (C8′), 129.2 (C7′), 128.0 (C6′), 126.7 (C9′), 123.4 (C5′), 119.7 (C3′), 114.6 (C11), 62.1 (C9), 56.4 (C8), 41.1 (C6), 39.9 (C2), 29.8 (C3), 28.2 (C7), 27.7 (C4), 26.2 (C5). The structure was confirmed by comparison with the literature data[30] for the same compound.

4.5. General procedure for the synthesis of the organocatalysts of subclass A 1

Using the method described by Girgis and Prashad,[33] to a stirred solution of the desired Fmoc-L-amino acid (1.02 mmol) in dry THF (10 mL) was added NEt_3 (0.16 mL, 1.12 mmol). In a two-necked flask, isobutylchloroformate (0.13 mL, 1.02 mmol) was diluted with THF (ca. 5 mL) and the solution cooled on an ice bath. The first mixture prepared was then slowly added via a syringe to the diluted isobutylchloroformate, after which the resulting mixture was allowed to react at room temperature for 2 h. (8S,9S)-9-Amino(9-deoxy)-epi-cinchonidine (0.3 g, 1.02 mmol) was then added and the reaction was stirred for 1 h at room temperature. The mixture was concentrated under vacuum and the resulting crude product was purified by column chromatography on silica gel with AcOEt/MeOH (4:1). The resulting intermediate was deprotected with 20% piperidine in DMF and purified by column chromatography on reverse phase silica to furnish the title compound.

4.5.1. (8*S*,9*S*)-9-L-Phenylalanylamide(9-deoxy)-*epi*-cinchonidine 1a

Using the method described above, **1a** was obtained as a white powder (395 mg, 88%), mp 98.7–99.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.88 (d, 1H, J = 4 Hz, H2′), 8.53 (m, 2H, H5′, NH-COR), 8.05 (d, 1H, J = 8 Hz, H8′), 7.77 (t, 1H, J = 8 Hz, H7′), 7.67 (t, 1H, J = 8 Hz, H6′), 7.57 (d, 1H, J = 4 Hz, H3′), 7.11 (m, 5H, Ph), 5.79 (m, 1H, H10), 5.52 (br s, 1H, H9), 4.99–4.89 (m, 2H, H11), 3.43–3.11 (m, 6H, H6, H2, H8, CH-Ph, NH_2), 2.88 (m, 1H, CH-NH_2), 2.63–2.50 (m, 3H, H6, H2, CH-Ph), 1.90 (br s, 1H, H3), 1.57–1.45 (m, 3H, H4, H7, H5), 1.22 (m, 1H, H5), 0.72 (m, 1H, H7). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 173.4 (C=O), 150.2 (C2′), 147.9 (C10′), 147.3 (C-Ph), 142.0 (C10), 138.2 (C4′), 129.7 (C8′), 129.3 (2C-Ph), 129.0 (C7′), 128.0 (2C-Ph), 127.1 (C-Ph), 126.5 (C6′), 126.0 (C9′), 124.1 (C5′), 119.8 (C3′), 114.2 (C11), 58.8 (C9), 55.7 (C8), 55.2 (C2), 40.5 (C6, *CH*-NH_2), (CH_2-Ph and C3 signals superimposed with DMSO), 27.3 (C7), 27.1 (C4), 25.7 (C5). ESI-TOF MS (m/z): 441.27 (M+1), 442.27 (M+2). HRMS (ESI) Found 441.26430, calcd for $C_{28}H_{33}N_4O$, 441.26489. $[\alpha]_D^{28}$ = +2.1 (c 1.05, MeOH).

4.5.2. (8*S*,9*S*)-9-Glicinylnamide(9-deoxy)-*epi*-cinchonidine 1b

Using the method described above, **1b** was obtained as a yellow oil (250 mg, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) = 8.89 (d, 1H, J = 4 Hz, H2′), 8.71 (br s, 1H, NH-COR), 8.48 (d, 1H, H5′), 8.04 (d, 1H, J = 8 Hz, H8′), 7.77 (t, 1H, J = 8 Hz, H7′), 7.67 (t, 1H, J = 8 Hz, H6′), 7.60 (br s, 1H, H3′), 5.83 (m, 1H, H10), 5.61 (br s, 1H, H9), 5.02–4.92 (m, 2H, H11), 4.51 (m, 2H, NH_2), 3.38–3.13 (m, 5H, H6, H2, H8, CH_2), 2.67 (m, 2H, H6, H2), 2.24 (br s, 1H, H3), 1.47 (m, 3H, H4, H7, H5), 1.17 (m, 1H, H5), 0.69 (m, 1H, H7). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 168.6 (C=O), 150.3 (C2′), 147.9 (C10′), 146.8 (C4′), 143.0 (C10), 142.0 (C8′), 129.7 (C7′), 129.2 (C9′), 126.9 (C6′), 126.7 (C5′), 120.0 (C3′), 114.3 (C11), 58.7 (C9), 55.3 (C8, C2), 42.2 (CH_2), 40.6 (C6), (C3 signal superimposed with DMSO), 27.2 (C7), 27.1 (C4), 25.8 (C5). ESI-TOF MS (m/z): 350.20 (M+), 351.23 (M+1), 352.22 (M+2). $[\alpha]_D^{28}$ = +15.9 (c 1.04, MeOH).

4.5.3. (8*S*,9*S*)-9-L-Valinylamide(9-deoxy)-*epi*-cinchonidine 1c

Using the previous method, **1c** was obtained as an oily yellow solid (372 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.88 (d, 1H, J = 4 Hz, H2′), 8.52 (d, 1H, J = 8 Hz, H5′), 8.48 (br s, 1H, NH-CO), 8.03 (d, 1H, J = 8 Hz, H8′), 7.76 (t, 1H, J = 8 Hz, H7′), 7.65 (t, 1H, J = 8 Hz, H6′), 7.60 (d, 1H, J = 4 Hz, H3′), 5.81 (m, 1H, H10), 5.52 (br s, 1H, H9), 5.00–4.90 (m, 2H, H11), 3.65 (s, 2H, NH_2), 3.23–3.12 (m, 3H, H6, H2, H8), 3.01 (d, 1H, J = 4 Hz, *CH*-NH_2), 2.68–2.58 (m, 2H, H6, H2), 2.22 (br s, 1H, H3), 1.92–1.86 (m, 1H, *CH*-(CH_3)$_2$), 1.52–1.45 (m, 3H, H4, H7, H5), 1.24 (m, 1H, H5), 0.83 (d, 3H, J = 8 Hz, CH_3), 0.67 (m, 1H, H7), 0.65 (d, 3H, J = 8 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 173.1 (C=O), 150.1 (C2′), 147.9 (C10′), 147.5 (C4′), 142.0 (C10), 129.7 (C8′), 129.0 (C7′), 127.1 (C9′), 126.5 (C6′), 124.2 (C5′), 119.8 (C3′), 114.2 (C11), 59.4 (C8, CH-NH_2), 58.9 (C9), 55.3 (C2), 40.6 (C6), (C3 signal superimposed by DMSO), 31.3 (*CH*-(CH_3)$_2$), 27.3 (C7), 27.1 (C4), 25.7 (C5), 19.3 (CH_3), 16.5 (CH_3). ESI-TOF MS (m/z): 393.27 (M+1), 394.27 (M+2). HRMS (ESI) Found 393.26424, calcd for $C_{24}H_{33}N_4O$, 393.26489. $[\alpha]_D^{27}$ = +13.7 (c 1.36, MeOH).

4.5.4. (8*S*,9*S*)-9-L-Isoleucinylamide(9-deoxy)-*epi*-cinchonidine 1d

With the aforementioned method, **1d** was obtained as a white solid (211 mg, 51%), 126.2–127.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.87 (d, 1H, J = 4 Hz, H2′), 8.53 (d, 1H, J = 8 Hz, H5′), 8.40 (s, 1H, NH-CO), 8.03 (d, 1H, J = 8 Hz, H8′), 7.76 (t, 1H, J = 8 Hz, H7′), 7.65 (t, 1H, J = 8 Hz, H6′), 7.60 (d, 1H, J = 4 Hz, H3′), 5.82 (m, 1H, H10), 5.50 (br s, 1H, H9), 5.00–4.90 (m, 2H, H11), 3.23–3.12 (m, 3H, H6, H2, H8), 2.98 (d, 1H, J = 4 Hz, *CH*-NH_2), 2.68–2.59 (m, 2H, H6, H2), 2.50 (s, 2H, NH_2), 2.21 (br s, 1H, H3), 1.45 (br s, 3H, H4, H7, H5), 1.24–1.15 (m, 2H, CH_2), 1.00–0.93 (m, 1H, CH-CH_3), 0.78 (d, 3H, J = 4 Hz, *CH*$_3$-CH), 0.69 (m, 4H, CH_3-CH_2, H7). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 173.9 (C=O), 150.1 (C2′), 147.9 (C10′), 147.5 (C4′), 142.0 (C10), 129.6 (C8′), 128.9 (C7′), 127.1 (C5′), 126.4 (C6′), 124.2 (C9′), 119.8 (C3′), 114.2 (C11), 66.4 (*CH*-NH_2), 59.1 (C8), 58.8 (C9), 55.4 (C2), 40.5 (C6), (*CH*-CH_3 signal superimposed with DMSO), 38.4 (C3), 27.3 (C4), 27.1 (C7), 25.7 (C5), 23.3 (CH_2-CH_3), 15.8 (CH_3), 11.5 (CH_3). ESI-TOF MS (m/z): 407.30 (M+1), 408.29 (M+2). HRMS (ESI) Found 407.28023, calcd for $C_{25}H_{35}N_4O$, 407.28054. $[\alpha]_D^{25}$ = +17.8 (c 1.11, MeOH).

4.5.5. (8*S*,9*S*)-9-L-Leucinylamide(9-deoxy)-*epi*-cinchonidine 1e

The product **1e** was obtained as a white solid (348 mg, 84%), mp 125.9–126.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.86 (d, 1H,

J = 4 Hz, H2′), 8.38 (d, 1H, J = 12 Hz, H5′), 8.18 (br s, 1H, NH-CO), 8.10 (d, 1H, J = 8 Hz, H8′), 7.69 (t, 1H, J = 8 Hz, H7′), 7.58 (t, 1H, J = 8 Hz, H6′), 7.38 (d, 1H, J = 4 Hz, H3′), 5.70 (m, 1H, H10), 5.45 (br s, 1H, H9), 4.99–4.93 (m, 2H, H11), 3.38–3.34 (m, 1H, H8), 3.27–3.20 (m, 3H, H6, H2, *CH*-NH_2), 2.76–2.71 (m, 2H, H6, H2), 2.38 (br s, 2H, NH_2), 2.28 (br s, 1H, H3), 1.64–1.41 (m, 6H, H5, H7, H4, *CH*-NH_2, *CH*$(CH_3)_2$, CH), 1.20–1.13 (CH), 0.91–0.86 (m, 1H, H7), 0.81 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 175.6 (C=O), 150.1 (C2′), 148.7 (C10′), 146.9 (C4′), 141.1 (C10), 130.4 (C8′), 129.3 (C7′), 127.4 (C5′), 126.9 (C6′), 123.6 (C9′), 119.3 (C3′), 114.8 (C11), 59.8 (C9), 55.9 (C2), 53.7 (C8), 51.7 (*CH*-NH_2), 41.1 (CH2), 41.0 (C6), 39.4 (C3), 27.6 (C7), 27.4 (C4), 26.2 (C5), 24.8 (CH$(CH_3)_2$), 23.3 (CH_3), 21.6 (CH_3). ESI-TOF MS (m/z): 407.30 (M+1), 408.29 (M+2). $[\alpha]_D^{25}$ = +12.4 (c 1.16, MeOH).

4.5.6. (8*S*,9*S*)-9-L-Prolinylamide(9-deoxy)-*epi*-cinchonidine 1f[27b,c]

With the aforementioned method, product **1f** was obtained as a white solid (319 mg, 80%), mp 174.3–175.6 °C; (Lit.[27c] 174.0–176.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.86 (d, 1H, J = 4 Hz, H2′), 8.46 (br s, 1H, NH-CO), 8.33 (d, 1H, J = 8 Hz, H5′), 8.09 (d, 1H, J = 8 Hz, H8′), 7.69 (t, 1H, J = 8 Hz, H7′), 7.58 (t, 1H, J = 8 Hz, H6′), 7.39 (d, 1H, J = 4 Hz, H3′), 5.71 (m, 1H, H10), 5.55 (br s, 1H, H9), 5.26 (br s, 1H, NH), 5.02–4.96 (m, 2H, H11), 3.74 (m, 1H), 3.48–3.42 (m, 1H), 3.38–3.32 (m, 2H), 2.97 (m, 1H), 2.83–2.73 (m, 3H), 2.35 (br s, 1H, H3), 1.97–1.93 (m, 1H), 1.72–1.46 (m, 7H), 0.93–0.88 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.9 (C=O), 150.1 (C2′), 148.7 (C10′), 146.0 (C4′), 140.3 (C10), 130.4 (C8′), 129.4 (C7′), 127.1 (C5′), 127.0 (C6′), 123.5 (C9′), 119.3 (C3′), 115.3 (C11), 60.6 (C8), 59.6 (C9), 55.5 (C2), 47.1 (CH_2), 44.5 (CH), 41.1 (C6), 38.8 (C3), 30.5 (CH_2), 27.3 (C4), 27.0 (C7), 26.0 (C6), 25.9 (CH_2). ESI-TOF MS (m/z): 391.25 (M+1), 392.25 (M+2). $[\alpha]_D^{24}$ = −3.5 (c 1.12, MeOH).

4.5.7. (8*S*,9*S*)-9-(*N*-Methyl)-L-phenylalaninylamide(9-deoxy)-*epi*-cinchonidine 1g

In the same manner, **1g** was obtained as an oily yellow solid (450 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.87 (d, 1H, J = 4 Hz, H2′), 8.42 (br s 1H, H5′), 8.14 (m, 2H, H8′, NH-CO), 7.71 (m, 1H, H7′), 7.60 (m, 1H, H6′), 7.33 (br s, 1H, H3′), 7.16 (m, 3H, Ph), 7.05 (m, 2H, Ph), 5.70 (m, 1H, H10), 5.38 (br s, 1H, H9), 4.98–4.91 (m, 2H, H11), 3.26–3.06 (m, 5H, H6, H2, H8, CH-Ph, NH), 2.86 (m, 1H, CH-NH_2), 2.72–2.62 (m, 3H, H6, H2, CH-Ph), 2.29 (s, 3H, CH_3-NH), 1.82 (br s, 1H, H3), 1.64–1.58 (m, 3H, H4, H7, H5), 1.39 (m, 1H, H5), 0.90 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.7 (C=O), 150.1 (C2′), 148.7 (C10′), 147.0 (C-Ph), 141.5 (C10), 137.5 (C4′), 130.5 (C8′), 129.2 (2C-Ph), 128.6 (C7′, C-Ph), 126.8 (2C-Ph), 123.6 (C6′, C9′, C5′), 119.6 (C3′), 114.6 (C11), 66.3 (C9), 60.0 (C8), 56.1 (C2), 44.7 (C6), 41.0 (*CH*-NH_2), 39.6 (CH_2-Ph), 39.1 (C3), 35.2 (CH_3-NH), 27.9 (C7), 27.5 (C4), 26.3 (C5). ESI-TOF MS (m/z): 455.29 (M+1), 456.29 (M+2). $[\alpha]_D^{24}$ = +17.4 (c 1.03, MeOH).

4.5.8. (8*S*,9*S*)-9-L-Tyrosinylamide(9-deoxy)-*epi*-cinchonidine 1h

Using the previous method, **1h** was obtained as an oily yellow solid (433 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.75 (d, 1H, J = 4 Hz, H2′), 8.42 (d, 1H, J = 8 Hz, H5′), 8.13 (d, 1H, J = 8 Hz, H8′), 7.73 (t, 1H, J = 8 Hz, H7′), 7.65 (t, 1H, J = 8 Hz, H6′), 7.33 (d, 1H, J = 4 Hz, H3′), 6.67 (d, 2H, J = 8 Hz, Ar), 6.42 (d, 2H, J = 8 Hz, Ar), 5.84 (br s, 1H, H9), 5.76–5.67 (m, 1H, H10), 5.06–5.02 (m, 2H, H11), 3.66 (m, 1H, H8), 3.54 (m, 1H, H6), 3.46 (m, 1H, H2), 2.93–2.88 (m, 3H, H6, H2, CH-Ar), 2.51–2.45 (m, 2H, H3, CH-Ar), 1.97 (m, 1H, *CH*-NH_2), 1.64–1.60 (m, 4H, H4, H7, H5), 0.93–0.90 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.7 (C=O), 155.9 (C-OH), 150.1 (C2′), 148.4 (C10′), 145.4 (C4′), 139.3 (C10), 130.4 (2C-Ar), 130.2 (C8′), 129.9 (C7′), 127.8 (C6′), 127.6 (C9′), 127.2 (C-Ar), 123.5 (C5′), 118.2 (C3′), 115.9 (C11), 115.6 (2C-Ar), 59.5 (C9), 56.4 (C8), 54.9 (C2), 41.3 (*CH*-NH_2), 39.4 (CH_2-Ar), 38.2 (C6), 29.8 (C3), 27.1 (C7), 26.4 (C4), 25.8 (C5). ESI-TOF MS (m/z): 457.26 (M+1), 458.27 (M+2). $[\alpha]_D^{24}$ = −0.7 (c 0.92, MeOH).

4.6. General procedure for synthesis of the subclass B derivatives 2

Using the method described by Malkov and Kocovský[42] for conducting *N*-formylation procedures; formic acid (1 mL, 26.5 mmol) was carefully added to a cooled mixture of acetic anhydride (0.450 mL, 4.76 mmol) and the desired compound from subclass A (0.68 mmol). The mixture was allowed to react at room temperature for 12 h, followed by removal of the volatiles in vacuo. The product was then purified by column chromatography on reverse phase silica with methanol.

4.6.1. (8*S*,9*S*,α*S*)-9-(*N*-Formyl)-L-phenylalanylamide(9-deoxy)-*epi*-cinchonidine 2a

Using the method above and starting with **1a**, **2a** was obtained as a yellow oil (312 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.87 (d, 1H, J = 4 Hz, H2′), 8.33 (m, 3H, 2NH-CO, H5′), 8.12 (d, 1H, J = 8 Hz, H8′), 7.95 (s, 1H, H-CO), 7.72 (t, 1H, J = 8 Hz, H7′), 7.63–7.58 (m, 2H, H6′, H3′), 6.90 (m, 5H, Ph), 6.04 (br s, 1H, H9), 5.66 (m, 1H, H10), 5.13–5.08 (m, 2H, H11), 3.64 (m, 1H, H8), 3.51 (m, 1H, *CH*-NH), 3.12 (m, 3H, H6, H2, CH-Ph), 2.92–2.80 (m, 3H, H6, H2, CH-Ph), 2,63 (br s, 1H, H3), 1.84–1.69 (m, 3H, H4, H7, H5), 1.05 (m, 1H, H5), 0.79 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 175.3 (C=O), 171.8 (C=O), 150.3 (C2′), 148.3 (C10′), 143.2 (C-Ph), 136.4 (C10), 135.8 (C4′), 130.2 (C8′), 129.9 (C7′), 129.1 (2C-Ph), 128.7 (C-Ph), 128.4 (2C-Ph), 127.9 (C6′), 126.9 (C9′), 123.1 (C5′), 120.4 (C3′), 117.9 (C11), 58.9 (C9), 54.8 (C8), 53.26 (C2), 41.5 (CH-NH), 37.2 (C6, C3), 36.6 (CH_2-Ph), 26.7 (C7), 24.4 (C4), 24.1 (C5). ESI-TOF MS (m/z): 469.26 (M+1), 470.26 (M+2). HRMS (ESI) Found 469.25982, calcd for $C_{29}H_{33}N_4O_2$, 469.26035. $[\alpha]_D^{24}$ = −16.1 (c 1.28, MeOH).

4.6.2. (8*S*,9*S*)-9-(*N*-Formyl)glicinylamide(9-deoxy)-*epi*-cinchonidine 2b

Using the method described above and starting with **1b**, **2b** was obtained as a yellow oil (250 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.94 (d, 1H, J = 4 Hz, H2′), 8.80 (br s, 2H, 2NH-CO), 8.42 (s, 1H, H-CO), 8.37 (d, 1H, J = 8 Hz, H5′), 8.15 (m, 1H, H8′), 7.76 (t, 1H, J = 8 Hz, H7′), 7.69–7.2 (m, 2H, H6′, H3′), 6.15 (br s, 1H, H9), 5.71 (m, 1H, H10), 5.20–5.15 (m, 2H, H11), 4.33 (m, 1H, H8), 4.05–3.62 (m, 4H, H6, H2, CH_2), 3.31–3.19 (m, 2H, H6, H2), 2.70 (br s, 1H, H3), 1.97 (m, 2H, H5, H7), 1.81 (m, 1H, H4), 1.12 (m, 1H, H5), 0.85–0.81 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 169.4 (C=O), 167.7 (C=O), 150.3 (C2′), 148.5 (C10′), 142.9 (C4′), 136.6 (C10), 130.5 (C8′), 130.1, (C7′), 128.1 (C6′), 126.8 (C9′), 122.9 (C5′), 120.0 (C3′), 117.9 (C11), 59.3 (C9), 53.7 (C8, C2), 41.8 (C6, C3), 41.5 (CH_2), 26.7 (C5), 24.5 (C7, C4). ESI-TOF MS (m/z): 379.21 (M+1), 380.21 (M+2). $[\alpha]_D^{23}$ = −8.6 (c 1.09, MeOH).

4.6.3. (8*S*,9*S*)-9-(*N*-Formyl)-L-valinylamide(9-deoxy)-*epi*-cinchonidine 2c

Using the same method and starting with **1c**, **2c** was obtained as a yellow oil (269 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.92 (s, 1H, H2′), 8.39 (br s, 3H, H5′, H8′, NH-CO), 8.13 (m, 2H, H7′, NH-CO), 7.74–7.66 (m, 3H, H6′, H3′, H-CO), 6.61 (br s, 1H, H9), 5.74 (m, 1H, H10), 5.19–5.15 (m, 2H, H11), 4.49 (br s, 1H, H8), 4.10 (m, 1H, *CH*-NH_2), 3.79 (br s, 1H, H6), 3.61 (m, 1H, H2), 3.27 (m, 2H, H6, H2), 2.69 (br s, 1H, H3), 2.05 (m, 1H, *CH*$(CH_3)_2$), 1.98–1.82 (m, 3H, H5, H7, H4), 1.13 (m, 1H, H5), 0.92

(m, 1H, H7), 0.75–0.70 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 175.4 (C=O), 171.9 (C=O), 150.3 (C2′), 148.3 (C10′), 143.1 (C4′), 136.5 (C10), 130.3 (C8′), 129.9 (C7′), 127.8 (C6′), 126.8 (C9′), 123.1 (C5′), 120.2 (C3′), 117.9 (C11), 59.5 (C8, C9), 59.0 (CH-NH), 53.7 (C2), 41.7 (C6), 36.7 (C3), 30.1 (*CH*-$(CH_3)_2$), 26.7 (C7), 24.4 (C4), 24.2 (C5), 19.2 (CH_3), 17.9 (CH_3). ESI-TOF MS (*m*/*z*): 421.26 (M+1), 422.26 (M+2). $[\alpha]_D^{23} = -9.4$ (*c* 1.23, MeOH).

4.6.4. (8*S*,9*S*)-9-(*N*-Formyl)-L-isoleucinylamide(9-deoxy)-*epi*-cinchonidine 2d

Using the same method and starting with **1d**, **2d** was obtained as a yellow oil (283 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.93 (d, 1H, *J* = 4 Hz, H2′), 8.39 (m, 2H, H5′, NH-CO), 8.16–8.11 (m, 2H, H8′, CH-CO), 7.74 (t, 1H, *J* = 8 Hz, H7′), 7.68–7.63 (m, 2H, H6′, H3′), 6.10 (br s, 1H, H9), 5.73 (m, 1H, H10), 5.20–5.16 (m, 2H, H11), 4.47 (m, 1H, H8), 4.16 (m, 1H, *CH*-NH), 3.79 (m, 1H, H6), 3.63–3.57 (m, 1H, H2), 3.29–3.20 (m, 2H, H6, H2), 2.70 (m, 1H, H3), 1.32–1.00 (m, 3H, H4, H5, H7), 0.95–0.81 (m, 2H, CH_2), 0.78–0.75 (m, 1H, H7), 0.73–0.68 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.8 (C=O), 167.7 (C=O), 150.4 (C2′), 148.5 (C10′), 143.1 (C4′), 136.6 (C10), 130.4 (C8′), 129.9 (C7′), 127.8 (C6′), 126.9 (C5′), 123.1 (C9′), 120.3 (C3′), 117.9 (C11), 60.5 (*CH*-NH_2), 59.1 (C9), 58.6 (C8), 53.8 (C2), 41.7 (C6), 36.8 (*CH*-CH_3), 36.5 (C3), 26.7 (CH_2-CH_3), 25.1 (C4), 24.5 (C5), 24.3 (C7), 15.5 (CH_3), 11.1 (CH_3). ESI-TOF MS (*m*/*z*): 435.28 (M+1), 436.28 (M+2). $[\alpha]_D^{23} = -6.8$ (*c* 1.24, MeOH).

4.6.5. (8*S*,9*S*)-9-(*N*-Formyl)-L-leucinylamide(9-deoxy)-*epi*-cinchonidine 2e

Using the same method and starting with **1e**, **2e** was obtained as a yellow oil (294 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.92 (d, 1H, *J* = 4 Hz, H2′), 8.39–8.35 (m, 3H, H5′, 2NH-CO), 8.13 (d, 1H, *J* = 8 Hz, H8′), 8.05 (s, 1H, CH-CO), 7.73 (t, 1H, *J* = 8 Hz, H7′), 7.67–7.62 (m, 2H, H6′, H3′), 6.08 (br s, 1H, H9), 5.73 (m, 1H, H10), 5.19–5.14 (m, 2H, H11), 4.44 (m, 1H, H8), 4.27 (m, 1H, *CH*-NH), 3.77 (m, 1H, H6), 3.61 (m, 1H, H2), 3.30–3.19 (m, 1H, H6, H2), 2.69 (m, 1H, H3), 2.08–2.06 (m, 1H, *CH*$(CH_3)_2$), 1.83–1.77 (m, 1H, H4), 1.56–1.53 (m, 2H, H5, H7), 1.43–1.41 (m, 2H, CH_2), 0.93–0.91 (m, 1H, H5), 0.85–0.83 (m, 1H, H7), 0.80–0.76 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.0 (C=O), 163.7 (C=O), 150.3 (C2′), 148.3 (C10′), 143.1 (C4′), 136.5 (C10), 130.3 (C8′), 129.9 (C7′), 127.9 (C6′), 126.9 (C5′), 123.0 (C9′), 120.3 (C3′), 117.9 (C11), 59.1 (C9), 53.7 (C2), 52.7 (C8), 48.7 (CH-NH), 41.7 (CH_2), 40.3 (C6), 36.7 (C3), 26.7 (C7), 24.7 (C4), 24.4 (C5), 24.2 (*CH*$(CH_3)_2$), 22.9 (CH_3), 21.4 (CH_3). ESI-TOF MS (*m*/*z*): 435.28 (M+1), 436.28 (M+2). $[\alpha]_D^{24} = +29.8$ (*c* 1.8, MeOH).

4.6.6. (8*S*,9*S*)-9-(*N*-Formyl)-L-prolinylamide(9-deoxy)-*epi*-cinchonidine 2f

Using the same method and starting with **1f**, **2f** was obtained as a yellow oil (176 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.94 (d, 1H, *J* = 4 Hz, H2′), 8.42 (d, 1H, *J* = 8 Hz, H5′), 8.19 (m, 2H, H8′, NH-CO), 7.98 (s, 1H, CH-CO), 7.93 (br s, 1H, H7′), 7.74 (m, 1H, H6′), 7.66 (m, 1H, H3′), 6.12 (br s, 1H, H9), 5.75 (m, 1H, H10), 5.19–5.12 (m, 2H, H11), 4.10–4.05 (m, 1H, H8), 3.80 (m, 2H, H6, H2), 3.54 (m, 2H, CH_2), 3.44 (m, 1H, CH), 3.29 (m, 2H, H6, H2), 2.70 (br s, 1H, H3), 1.96–1.64 (m, 7H, H4, H5, H7, CH_2, CH_2), 1.53–1.50 (m, 1H, H5), 1.10–1.07 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.5 (C=O), 164.2 (C=O), 150.2 (C2′), 147.8 (C10′), 143.9 (C4′), 136.8 (C10), 130.4 (C8′), 129.7 (C7′), 128.3 (C6′), 127.4 (C5′), 123.5 (C9′), 121.2 (C3′), 118.1 (C11), 59.8 (C8), 59.2 (C9), 54.0 (C2), 47.6 (CH_2), 42.2 (CH), 41.2 (C6), 37.0 (C3), 29.9 (CH_2), 27.1 (C7), 24.6 (C5, CH_2), 24.5 (C4). ESI-TOF MS (*m*/*z*): 419.25 (M+1), 420.25 (M+2). $[\alpha]_D^{24} = +65.2$ (*c* 1.01, MeOH).

4.6.7. (8*S*,9*S*)-9-(*N*-Formyl)amino(9-deoxy)-*epi*-cinchonidine 2g

Using the same method and starting with (8S,9S)-9-amino(9-deoxy)-epi-cinchonidine, **2g** was obtained as a yellow oil (217 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.93 (d, 1H, *J* = 4 Hz, H2′), 8.38 (m, 1H, H5′), 8.15–8.11 (m, 2H, H8′, NH-CO), 7.75 (t, 1H, *J* = 8 Hz, H7′), 7.66 (m, 1H, *J* = 8 Hz, H6′), 7.62 (d, 1H, *J* = 4 Hz, H3′), 6.16 (br s, 1H, H9), 5.69 (m, 1H, H10), 5.16–5.10 (m, 2H, H11), 4.22 (m, 1H, H8), 3.77–3.61 (m, 2H, H6, H2), 3.39–3.21 (m, 1H, H6), 3.11–3.07 (m, 1H, H2), 2.69 (br s, 1H, H3), 2.09–1.96 (m, 3H, H4, H5, H7), 1.77 (m, 1H, H5), 1.14 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.7 (C=O), 150.2 (C2′), 148.4 (C10′), 143.3 (C4′), 136.6 (C10), 130.3 (C8′), 130.1 (C7′), 128.0 (C6′), 126.6 (C5′), 123.0 (C9′), 120.0 (C3′), 117.8 (C11), 58.9 (C8), 53.2 (C9), 46.8 (C2), 41.0 (C6), 36.5 (C3), 26.8 (C7), 24.5 (C5), 24.3 (C4). ESI-TOF MS (*m*/*z*): 322.19 (M+1), 323.19 (M+2). $[\alpha]_D^{23} = -28.5$ (*c* 1.15, MeOH).

4.7. General procedure for synthesis of subclass C derivatives 3

Using the same method as described for the synthesis of subclass A, compound **1a** (0.3 g, 0.68 mmol) was coupled with a second amino acid furnishing the dipeptide hybrid compounds.

4.7.1. (8*S*,9*S*)-9-(L-Phenylalanyl-L-phenylalanineamide)-(9-deoxy)-*epi*-cinchonidine 3a

Using Fmoc-L-phenylalanine (263 mg, 0.68 mmol), **3a** was obtained as an oily yellow solid (400 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.82 (d, 1H, *J* = 4 Hz, H2′), 8.29 (m, 1H, NH-CO),8.09 (d, 1H, *J* = 8 Hz, H5′), 7.69–7.56 (m, 4H, NH-CO, H8′, H7′, H6′), 7.31 (d, 1H, *J* = 4 Hz, H3′), 7.26–7.08 (m, 10H, 2Ph), 5.66–5.57 (m, 1H, H10), 5.20 (br s, 1H, H9), 4.93–4.87 (m, 2H, H11), 4.69–4.64 (m, 1H, CH), 3.45 (m, 1H, H8), 3.17–3.11 (m, 1H, CH), 3.06–2.96 (m, 4H, H2, H6, CH_2, CH_2), 2.60 (m, 2H, H2, H6), 2.42 (m, 1H, CH), 2.24 (br s, 1H, H3), 1.60–1.55 (m, 4H, H4, H5, H7, CH), 1.23 (m, 1H, H5), 0.87–0.85 (m, 2H, H7, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.4 (C=O), 170.8 (C=O), 150.1 (C2′), 148.6 (C10′), 146.7 (C-Ph), 141.0 (C10), 137.6 (aromatic), 136.6 (aromatic), 130.5 (aromatic), 129.4 (2C), 129.3 (2C), 129.2 (aromatic), 128.7 (2C), 128.5 (2C), 126.9 (2C), 126.7 (aromatic), 123.3 (aromatic), 119.7 (aromatic), 114.8 (C11), [60.2, 56.4, 55.8, 53.8, 40.8, 40.7, 39.4, 37.6, 29.8, 27.7, 27.3, 25.9 (8C quinuclidine, 4C L-Phe)]. ESI-TOF MS (*m*/*z*): 588.33 (M+1), 589.33 (M+2). HRMS (ESI) Found 588.33229, calcd for $C_{37}H_{42}N_5O_2$, 588.33330. $[\alpha]_D^{24} = +24.6$ (*c* 1.4, MeOH).

4.7.2. (8*S*,9*S*)-9-(L-Prolinyl-L-phenylalanineamide)-(9-deoxy)-*epi*-cinchonidine 3b

Using Fmoc-L-proline (229 mg, 0.68 mmol), **3b** was obtained as a white solid (303 mg, 83% yield), mp 138.0–140.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.83 (d, 1H, *J* = 4 Hz, H2′), 8.32 (m, 1H, NH-CO), 8.10 (d, 1H, *J* = 8 Hz, H5′), 7.91 (d, 1H, *J* = 8 Hz, H8′), 7.68 (m, 2H, H7′, NH-CO), 7.57 (m, 1H, H6′), 7.31 (s, 1H, H3′), 7.23–7.11 (m, 5H, Ph), 5.68–5.60 (m, 1H, H10), 5.23 (br s, 1H, H9), 4.94–4.87 (m, 2H, H11), 4.63–4.61 (m, 1H, CH), 3.17 (m, 1H, CH), 3.07–3.03 (m, 2H, H2, H6), 3.66–3.60 (m, 3H, H2, H6, CH), 2.23 (m, 2H, CH, H3), 1.98–1.93 (m, 1H, CH), 1.66–1.54 (m, 6H, H4, H5, H7, CH_2, CH), 1.35–1.29 (m, 2H, H5, CH), 0.86 (m, 2H, H7, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 175.5 (C=O), 170.9 (C=O), 150.1 (C2′), 148.6 (C10′), 146.8 (C-Ph), 141.3 (C10), 136.8 (C4′), 130.5 (C8′), 129.3 (2C-Ph), 129.1 (C7′), 128.5 (2C-Ph), 126.8 (C9′), 127.2 (CH-Ph), 126.7 (C6′), 123.4 (C5′), 119.6 (C3′), 114.6 (C11), [60.3, 55.9, 53.6, 47.1, 40.8, 39.6, 37.2, 30.6, 29.8, 27.9, 27.4, 25.9 (8C quinuclidine, 2C L-Phe, 4C L-Pro)]. ESI-TOF MS (*m*/*z*): 538.32 (M+1), 539.32 (M+2). HRMS (ESI) Found 538.31705, calcd for $C_{33}H_{40}N_5O_2$, 538.31765. $[\alpha]_D^{23} = -40.4$ (*c* 1, MeOH).

4.7.3. (8*S*,9*S*)-9-(L-Valinyl-L-phenylalanineamide)-(9-deoxy)-*epi*-cinchonidine 3c

Using Fmoc-L-valine (231 mg, 0.68 mmol), **3c** was obtained as an oily solid (323 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.82 (br s, 1H, H2′), 8.30 (m, 1H, NH-CO), 8.10 (br s, 1H, H5′), 7.97 (br s, 1H, H8′), 7.68 (m, 1H, H7′), 7.57 (m, 2H, H6′, NH-CO), 7.29 (br s, 1H, H3′), 7.22–7.13 (m, 5H, Ph), 5.67–5.59 (m, 1H, H10), 5.17 (br s, 1H, H9), 4.93–4.87 (m, 2H, H11), 4.63 (m, 1H, CH), 3.42 (s, 1H, CH), 3.18–3.12 (m, 1H, CH), 3.06–3.00 (m, 3H, H2, H6, CH), 3.65–3.56 (m, 2H, H2, H6), 2.22 (br s, 1H, H3), 2.09 (br s, 1H, CH), 1.59 (m, 4H, H4, H5, H7, CH), 1.28–1.23 (m, 1H, H5), 0.85–0.80 (m, 4H, H7, CH_3), 0.53–0.52 (m, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.6 (C=O), 170.9 (C=O), 150.0 (C2′), 148.6 (C10′), 146.9 (C-Ph), 141.3 (C10), 136.8 (C4′), 130.5 (C8′), 129.3 (2C-Ph), 129.1 (C7′), 128.6 (2C-Ph), 127.2 (CH-Ph), 126.8 (C9′), 126.6 (C6′), 123.3 (C5′), 119.5 (C3′), 114.6 (C11), [60.2, 55.9, 53.8, 40.8, 39.6, 37.4, 30.8, 29.8, 27.8, 27.4, 26.0 (8C quinuclidine, 2C L-Phe, CH)], 19.5 (*i*Pr), 19.1 (*i*Pr), 15.8 (*i*Pr). ESI-TOF MS (*m*/*z*): 540.33 (M+1), 541.32 (M+2). HRMS (ESI) Found 540.33285, calcd for $C_{33}H_{42}N_5O_2$, 540.33330. $[\alpha]_D^{24} = -17.9$ (*c* 1.28, MeOH).

4.7.4. (8*S*,9*S*)-9-(Glycinyl-L-phenylalanineamide)-(9-deoxy)-*epi*-cinchonidine 3d

Using Fmoc-glycine (202 mg, 0.68 mmol), **3d** was obtained as an oily white solid (291 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.81 (br s, 1H, H2′), 8.30 (m, 1H, H5′), 8.08 (br s, 1H, H8′), 8.00 (br s, 1H, NH-CO), 7.68 (m, 2H, H7′, NH-CO), 7.56 (m, 1H, H6′), 7.45 (br s, 1H, H3′), 7.14–7.08 (m, 5H, Ph), 5.65–5.62 (m, 1H, H10), 5.43 (br s, 1H, H9), 4.99–4.92 (m, 2H, H11), 4.58 (m, 1H, CH), 3.23–2.97 (m, 6H, H2, H6, H8, CH_2, CH), 2.68 (m, 2H, H2, H6), 2.30 (br s, 1H, H3), 1.65 (m, 4H, H5, H4, H7, CH), 1.37 (m, 1H, H5), 0.86–0.80 (m, 1H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.9 (C=O), 170.9 (C=O), 150.2 (C2′), 148.4 (C10′), 145.7 (C-Ph), 140.1 (C10), 136.4 (C4′), 130.3 (C8′), 129.2 (C7′, 2C-Ph), 128.5 (2C-Ph), 127.4 (C-Ph), 126.9 (C6′, C9′), 123.3 (C5′), 119.9 (C3′), 115.3 (C11), 59.6 (C8), 55.2 (C9), 54.4 (CH), 50.4 (C2), 41.0 (C6), 38.8 (CH_2), 37.6 (C3), 29.7 (CH_2), 27.1 (C7), 26.9 (C4), 25.5 (C5). ESI-TOF MS (*m*/*z*): 498.28 (M+1), 499.29 (M+2). HRMS (ESI) Found 498.28622, calcd for $C_{30}H_{36}N_5O_2$, 498.28635. $[\alpha]_D^{24} = -14.5$ (*c* 1.3, MeOH).

4.7.5. (8*S*,9*S*)-9-(L-Methioninyl-L-phenylalanineamide)-(9-deoxy)-*epi*-cinchonidine 3e

Using Fmoc-L-methionine (253 mg, 0.68 mmol), **3e** was obtained as an oily yellow solid (370 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ (ppm) = 8.61 (br s, 1H, H2′), 8.11 (m, 1H, H5′), 7.82 (br s, 1H, H8′), 7.73 (br s, 2H, 2NH-CO), 7.45 (m, 1H, H7′), 7.35 (m, 1H, H6′), 7.16 (m, 1H, H3′), 6.94–6.90 (m, 5H, Ph), 5.43 (m, 1H, H10), 5.09 (br s, 1H, H9), 4.72–4.65 (m, 2H, H11), 4.39 (m, 1H, CH), 3.06–2.4 (m, 6H), 2.43–2.31 (m, 3H), 2.16–2.01 (m, 3H), 1.81 (m, 1H), 1.58 (m, 2H), 1.44–1.32 (m, 4H), 0.99 (m, 1H), 0.63–0.59 (m, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ (ppm) = 174.4 (C=O), 170.3 (C=O), 149.5 (C2′), 147.9 (C10′), 146.5 (C-Ph), 140.6 (C10), 136.5 (C4′), 129.7 (C8′), 128.8 (2C-Ph), 128.6 (C7′), 127.8 (2C-Ph), 126.7 (C-Ph), 126.2 (C6′, C9′), 123.0 (C5′), 119.2 (C3′), 114.1 (C11), 59.2 (C8), 55.1 (CH), 53.7 (C9), 53.3 (CH), 43.8 (C2), 37.1 (C6), 33.5 (C3), 29.9 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 27.0 (C7), 26.8 (C4), 25.3 (C5), 14.7 (CH_3). ESI-TOF MS (*m*/*z*): 572.31 (M+1), 573.31 (M+2). HRMS (ESI) Found 572.30486, calcd for $C_{33}H_{42}N_5O_2S$, 572.30537. $[\alpha]_D^{24} = -19.6$ (*c* 1.13, MeOH).

4.8. Catalytic reactions

4.8.1. General procedure for the aldol reaction[27]

The organocatalyst (0.053 mmol) was dissolved in 1 mL of acetone in a 10 mL round bottom flask and the solution was allowed to stir at room temperature for 10 min. The aldehyde (0.53 mmol) was then added to the reaction mixture and allowed to stir for 24–72 h. The volatiles were removed under reduced pressure and the product was purified by column chromatography on silica gel eluted with hexane/AcOEt (5:1), to furnish the desired aldol product **6**.

4.8.1.1. 4-Hydroxy-4-(4-nitrophenyl)butan-2-one[27] 6a

This was obtained as a brown oil (47 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (d, 2H, *J* = 4 Hz, Ar), 7.51 (d, 2H, *J* = 8 Hz, Ar), 5.23 (br s, 1H, OH), 3.75 (s, 1H, CH), 2.84 (d, 2H, *J* = 4 Hz, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 208.5 (C=O), 150.3 (Ar), 147.3 (Ar), 126.5 (2C-Ar), 123.8 (2C-Ar), 68.9 (CH), 51.6 (CH_2), 30.7 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/EtOH = 70:30, flow rate 0.7 mL/min), λ = 254 nm: t_r = 12.2 min (*S*), t_r = 13.1 min (*R*).

4.8.1.2. 4-Hydroxy-4-phenylbutan-2-one[43–45] 6b

This was obtained as an orange oil (22 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33–7.25 (m, 5H, Ph), 5.12 (m, 1H, CH), 3.31 (br s, 1H, OH), 2.89–2.73 (m, 2H, CH_2), 2.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 209.1 (C=O), 142.9 (Ar), 128.5 (2C-Ar), 127.7 (Ar), 125.7 (2C-Ar), 69.8 (CH), 52.0 (CH_2), 30.8 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 90:10, flow rate 1 mL/min), λ = 230 nm: t_r = 5.4 min (*R*), t_r = 6.6 min (*S*).

4.8.1.3. 4-Hydroxy-4-(4-methoxyphenyl)butan-2-one[45] 6c

This was obtained as an orange oil (2 mg, 2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.29 (m, 2H, Ar), 6.90 (m, 2H, Ar), 6.89, 5.14–5.11 (m, 1H, CH), 3.86 (s, 3H, CH_3), 2.94–2.78 (m, 2H, CH_2), 2.21 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 198.5 (C=O), 161.7 (Ar), 143.3 (2C-Ar), 127.1 (Ar), 125.1 (2C-Ar), 60.5 (CH), 29.8 (OCH_3), 21.1 (CH_2), 14.3 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 90:10, flow rate 1 mL/min), λ = 230 nm: t_r = 14.5 min (*R*), t_r = 16.6 min (*S*).

4.8.1.4. 4-Hydroxy-4-(2-methoxyphenyl)butan-2-one 6d

This was obtained as yellow oil (73 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44 (d, 1H, *J* = 8 Hz, Ar), 7.25 (t, 1H, *J* = 8 Hz, Ar), 6.97 (t, 1H, *J* = 8 Hz, Ar), 6.86 (d, 1H, *J* = 8 Hz, Ar), 5.41 (d, 1H, *J* = 8 Hz, CH), 3.82 (s, 3H, CH_3), 3.61 (br s, 1H, OH), 2.93–2.74 (m, 2H, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 209.3 (C=O), 155.7 (Ar), 130.9 (Ar), 128.3 (Ar), 126.3 (Ar), 120.7 (Ar), 110.2 (Ar), 65.4 (CH), 55.2 (OCH_3), 50.4 (CH_2), 30.5 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 85:15, flow rate 1 mL/min), λ = 230 nm: t_r = 9.9 min, t_r = 11.3 min.

4.8.1.5. 4-(2,4-Dimethoxyphenyl)-4-hydroxybutan-2-one 6e

This was obtained as yellow oil (6 mg, 5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.27 (d, 1H, *J* = 8 Hz, Ar), 6.45–6.40 (m, 2H, Ar), 5.30 (d, 1H, *J* = 4 Hz, CH), 3.76 (s, 6H, 2CH_3), 3.43 (br s, 1H, OH), 2.85–2.72 (m, 2H, CH_2), 2.14 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 209.4 (C=O), 160.1 (Ar), 156.9 (Ar), 127.1 (Ar), 123.5 (Ar), 104.2 (Ar), 98.4 (Ar), 65.4 (CH), 55.3 (OCH_3), 55.2 (OCH_3), 50.6 (CH_2), 30.6 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 85:15, flow rate 1 mL/min), λ = 230 nm: t_r = 13.9 min, t_r = 19.1 min.

4.8.1.6. 4-(4-Bromophenyl)-4-hydroxybutan-2-one[45] 6f

This was obtained as yellow oil (25 mg, 19% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 (d, 2H, *J* = 8 Hz, Ar), 7.19 (d, 2H, *J* = 8 Hz, Ar), 5.07 (m, 1H, CH), 3.73 (br s, 1H, OH), 2.85–2.71 (m, 2H, CH_2), 2.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 208.7 (C=O), 142.0 (Ar), 131.5 (2C-Ar), 127.4 (2C-Ar),

121.3 (Ar), 69.1 (CH), 51.8 (CH_2), 30.7 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 95:5, flow rate 1 mL/min), λ = 262 nm: t_r = 18.2 min (*R*), t_r = 19.9 min (*S*).

4.8.1.7. 4-Hydroxy-4-m-tolylbutan-2-one[43] 6g

This was obtained as a red oil (10 mg, 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.26–7.09 (m, 4H, Ar), 5.10 (m, 1H, CH), 3.65 (s, 1H, OH), 2.91–2.74 (m, 2H, CH_2), 2.37 (m, 3H, CH_3), 2.17 (m, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 208.9 (C=O), 142.9 (Ar), 138.0 (Ar), 128.3 (Ar), 128.3 (Ar), 126.3 (Ar), 122.6 (Ar), 69.7 (CH), 52.0 (CH_2), 30.6 (CH_3), 21.3 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 95:5, flow rate 1 mL/min), λ = 257 nm: t_r = 16.5 min (*R*), t_r = 17.8 min (*S*).

4.8.1.8. 4-Hydroxy-4-o-tolylbutan-2-one 6h

This was obtained as yellow oil (2 mg, 2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.28–7.10 (m, 4H, Ar), 5.37 (m, 1H, CH), 3.41 (br s, 1H, OH), 2.86–2.69 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 208.8 (C=O), 133.5 (Ar), 131.6 (Ar), 130.2 (Ar), 127.2 (Ar), 126.1 (Ar), 125.1 (Ar), 66.2 (CH), 50.6 (CH_2), 30.6 (CH_3), 18.8 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 90:10, flow rate 1 mL/min), λ = 257 nm: t_r = 8.6 min, t_r = 11.4 min.

4.8.1.9. 4-(2-Chlorophenyl)-4-hydroxybutan-2-one[43,45] 6i

This was obtained as yellow oil (15 mg, 14% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.28–7.14 (m, 4H, Ar), 5.55–5.46 (m, 1H, CH), 3.80 (br s, 1H, OH), 2.96–2.61 (m, 2H, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 209.0 (C=O), 129.3 (Ar), 129.3 (Ar), 128.5 (Ar), 127.2 (Ar), 127.2 (Ar), 127.1 (Ar), 66.5 (CH), 50.1 (CH_2), 30.5 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 95:5, flow rate 1 mL/min), λ = 262 nm: t_r = 13.0 min (*R*), t_r = 14.9 min (*S*).

4.8.1.10. 4-(4-(Benzyloxy)phenyl)-4-hydroxybutan-2-one 6j

This was obtained as an orange oil (16 mg, 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41–6.96 (m, 9H, Ar), 5.05 (m, 3H, CH, CH_2), 3.37 (br s, 1H, OH), 2.90–2.88 (m, 2H, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 209.1 (C=O), [158.3, 137.0, 135.3, 128.6 (2C), 128.0, 127.5 (2C), 127.0 (2C), 114.9 (2C) (aromatics)], 70.0 (CH), 52.0 (CH_2), 30.8 (CH_3). HPLC (Daicel Chirapak AD-H, hexane/ethanol = 80:20, flow rate 0.8 mL/min), λ = 257 nm: t_r = 19.9 min, t_r = 25.9 min.

4.8.2. General procedure for the Biginelli reaction[46]

Urea (0.116 g, 1.93 mmol) was dissolved in THF (2 mL) and to this solution were added benzaldehyde (0.197 mL, 0.206 g, 1.93 mmol), methyl acetoacetate (0.139 mL, 0.149 g, 1.29 mmol), 0.1 equiv of the organocatalyst **3d** and 0.1 equiv of HCl (65 μL of a 4 M solution in dioxane). The reaction was allowed to take place at room temperature over 6 days and then was quenched by evaporation of all the volatile compounds under reduced pressure.

4.8.2.1. Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate[46,47]

This was obtained as a white solid (mp 197.3–198.0 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.23 (s, 1H, NH), 7.77 (s, 1H, NH), 7.33–7.23 (m, 5H, Ph), 5.16 (s, 1H, CH), 3.52 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) = 165.9 (C=O), 152.3 (C=O), [148.7, 144.7, 128.5 (2C), 127.3, 126.2 (2C), 99.1 (phenyl and olefin)], 53.9 (CH), 50.8 (CH_3), 17.9 (CH_3). HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 80:20, flow rate 0.5 mL/min), λ = 254 nm: t_r = 15.8 min (*S*), t_r = 20.9 min (*R*).

4.8.3. General procedure for the Michael addition[48]

Organocatalyst **3d** (0.1 equiv) and 2,4-pentadione (2 equiv) were dissolved in CH_2Cl_2 (2 mL) in a 10 mL round bottom flask. After 10 min, *trans*-β-nitrostyrene (1 equiv) was added and the reaction was allowed to proceed at room temperature for 24 h under an atmosphere of nitrogen, after which the product was purified by column chromatography with silica gel and eluted with a mixture of hexane/ethyl acetate (5:1) to furnish the product.

4.8.3.1. 3-[1-(1-Phenyl-2-nitroethyl)]-2,4-pentanedione[49–52]

This was obtained as a white solid (mp 102.3–102–9 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35–7.19 (m, 5H, Ph), 4.66–4.64 (m, 2H, CH_2), 4.40–4.37 (m, 1H, CH), 4.28–4.22 (m, 1H, CH), 2.29 (s, 3H, CH_3), 1.95 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 201.9 (C=O), 201.1 (C=O), 136.1 (Ph), 129.4 (2C-Ph), 128.6 (Ph), 128.0 (2C-Ph), 78.3 (CH_2), 70.7 (CH), 42.9 (CH), 30.5 (CH_3), 29.7 (CH_3). HPLC: (Daicel Chirapak AD-H, hexane/isopropanol = 85:15, flow rate 0.8 mL/min), λ = 210 nm; t_r = 12.2 min (*S*), t_r = 16.3 min (*R*).

4.8.4. General procedure for the ketimine hydrosilylation reaction[53]

To a 10 mL round bottom flask were added 0.1 equiv of the organocatalyst **3d** and 1 equiv of *N*-(1-(4-nitrophenyl)ethylidene)-aniline (100 mg, 0.42 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 15 min, 3 equiv of $HSiCl_3$ (176 μL) was added dropwise, and after the addition was complete, the mixture was allowed to react at room temperature for over 21 h. The reaction was then quenched with a saturated solution of $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (10 mL × 3) and then $MgSO_4$ to remove the vestigial water that was present. The crude product was purified by column chromatography on silica gel and eluted with CH_2Cl_2 to furnish the desired chiral amine.

4.8.4.1. N-(1-(4-Nitrophenyl)ethyl)aniline[54]

This was obtained as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (d, 2H, *J* = 8 Hz, Ar), 7.55 (d, 2H, *J* = 8 Hz, Ar), 7.10 (m, 2H, Ph), 6.68 (t, 1H, *J* = 8 Hz, Ph), 6.45 (d, 2H, *J* = 8 Hz, Ph), 4.57 (d, 1H, *J* = 8 Hz, CH), 4.13 (br s, 1H, NH), 1.55 (d, 3H, *J* = 4 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = [153.3, 147.1, 146.6, 129.3 (2C), 126.8 (2C), 124.1 (2C), 118.0, 113.4 (2C) (aromatics)], 53.4 (CH), 25.0 (CH_3). HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 80:20, flow rate 1 mL/min), λ = 254 nm: t_r = 15.6 min (*R*), t_r = 18.6 min (*S*).

Acknowledgements

We are grateful for the award of a PhD Grant to P.B. (SFRH/BD/61913/2009) from the Science and Technology Foundation, Ministry of Science and Education (FCT) 2010. We also thank the FCT for funding through the strategic program PEst-OE/QUI/UI0619/2011. Dr. Olivia Furtado Burke, LNEG, Lisbon is acknowledged for performing the optical rotation measurements. The University of Vigo (Spain) is gratefully acknowledged for MS analysis. The NMR spectrometers are part of The National NMR Facility, supported by Science and Technology Foundation, Ministry of Science and Education (RECI/BBB-BQB/0230/2012).

References

1. Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8–27.
2. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
3. MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308.
4. (a) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

5. (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
6. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693.
7. Song, C. E. *Cinchona Alkaloids in Synthesis, Catalysis*; Wiley-VCH: Weinheim, 2009. pp 1–10.
8. Baraniak, D.; Kacprzak, K.; Celewicz, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 723–726.
9. Grace, A.; Camm, A. *Cardiovasc. Res.* **2000**, *45*, 43–51.
10. Liu, Y.; Li, L.; Zhang, H.; Fan, Z.; Guan, X. *Bioorg. Chem.* **2003**, *31*, 11–23.
11. Brunetti, I.; Falcone, A.; Calabresi, P.; Goulette, F. A.; Darnowski, J. W. *Cancer Res.* **1990**, *50*, 4026–4031.
12. Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007.
13. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.
14. Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748–9770.
15. He, W.; Zhang, B.; Liu, P.; Sun, X.; Zhang, S. *Chin. J. Catal.* **2006**, *27*, 527–531.
16. Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
17. Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495.
18. Meciarova, M.; Hubinska, K.; Toma, S.; Koch, B.; Berkessel, A. *Monatsh. Chem.* **2007**, *138*, 1181–1186.
19. Baudequin, C.; Chaturvedi, D.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 2623–2629.
20. Bonsignore, M.; Benaglia, M.; Raimondi, L.; Orlandi, M.; Celentano, G. *Beil. J. Org. Chem.* **2013**, *9*, 633–640.
21. Saha, S.; Moorthy, J. N. *J. Org. Chem.* **2010**, *76*, 396–402.
22. Pedrosa, R.; Andres, J. M.; Manzano, R.; Rodriguez, P. *Eur. J. Org. Chem.* **2010**, 5310–5319.
23. Tang, G. K.; Gun, U.; Altenbach, H. J. *Tetrahedron* **2012**, *68*, 10230–10235.
24. Tang, G. T.; Hu, X. M.; Altenbach, H. J. *Tetrahedron Lett.* **2011**, *52*, 7034–7037.
25. Tang, Z.; Cun, L. F.; Cui, X.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 1263–1266.
26. He, L.; Tang, Z.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron* **2006**, *62*, 346–351.
27. (a) Huang, W.-B.; Liu, Q.-W.; Zheng, L.-Y. *Catal. Lett.* **2011**, *141*, 191–197; (b) Chen, J.; An, X.; Zhu, X.; Wang, X.; Xiao, W. *J. Org. Chem.* **2008**, *73*, 6006–6009; (c) Zhao, J.; Chen, A. J.; Liu, Q. Z. *Chin. J. Chem.* **2009**, *27*, 930–936.
28. Sundermeirer, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality* **2003**, *15*, 127–134.
29. Huang, W.; Liu, Q.; Zheng, L.; Zhang, S. *Catal. Lett.* **2011**, *141*, 191–197.
30. He, W.; Liu, P.; Le Zhang, B.; Li Sun, X.; Zhang, S. Y. *App. Organomet. Chem.* **2006**, *20*, 328–334.
31. Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2003**, *68*, 4944–4946.
32. Dou, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18*, 8315–8319.
33. Chaudhary, A.; Girgis, M.; Prashad, M.; Hu, B.; Har, D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2003**, *44*, 5543–5546.
34. (a) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253–2256; (b) Malkov, A. V.; Figlus, M.; Cooke, G.; Caldwell, S. T.; Rabani, G.; Prestly, M. R.; Kočovský, P. *Org. Biomol. Chem.* **2009**, *7*, 1878–1883.
35. Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101–1103.
36. Revell, J. D.; Wennemers, H. *Tetrahedron* **2007**, *63*, 8420–8424.
37. Chen, Z.; Zhang, A.; Zhang, L.; Zhang, J.; Lei, X. *J. Chem. Res* **2008**, 266–269.
38. Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751–3754.
39. Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry and Molecular Biology*, 4th ed.; CRC Press, 2010. pp 595–635.
40. Barrulas, P. C. Ph.D. Dissertation, University of Évora, 2014.
41. Brunner, H.; Bugler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.
42. Malkov, A.; Figlus, M.; Stoncius, S.; Kocovský, P. *J. Org. Chem.* **2007**, *72*, 1315–1325.
43. Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097–4099.
44. Zhang, L.; Zhang, H.; Luo, H.; Zhou, X.; Cheng, G. *J. Braz. Chem. Soc.* **2011**, *22*, 1736–1741.
45. Tong, S.; Harris, P. W. R.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2008**, *2008*, 164–170.
46. Ding, D. R.; Zhao, C. G. *Eur. J. Org. Chem.* **2010**, 3802–3805.
47. Xu, F.; Huang, D.; Lin, X.; Wang, Y. *Org. Biomol. Chem.* **2012**, *10*, 4467–4470.
48. Puglisi, A.; Annunziata, R.; Benaglia, M.; Cozzi, F.; Gervasini, A.; Bertacche, V.; Sala, M. C. *Adv. Synth. Catal.* **2009**, *351*, 219–229.
49. Puglisi, A.; Benaglia, M.; Annunziata, R.; Rossi, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2258–2264.
50. Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713–4716.
51. Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, *2008*, 4563–4566.
52. Ma, Z.; Liu, Y.; Huo, L.; Gao, X.; Tao, J. *Tetrahedron: Asymmetry* **2012**, *23*, 443–448.
53. Guizzetti, S.; Benaglia, M.; Cozzi, F.; Annunziata, R. *Tetrahedron* **2009**, *65*, 6354–6363.
54. Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kocovský, P. *Org. Lett.* **2004**, *6*, 2253–2256.