Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5079

www.rsc.org/obc

PAPER

First asymmetric cascade reaction catalysed by chiral primary aminoalcohols†‡

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Received 14th March 2011, Accepted 11th April 2011
DOI: 10.1039/c1ob05400g

Readily available chiral primary 1,2-aminoalcohols and diamines have been explored as organocatalysts for a domino Michael–aldol reaction. Their application in this organocascade process afforded cyclohexanone **A** with high levels of reactivity (up to 91% yield) and stereoselectivity (>97 : 3 d.r., up to 93% *ee*). Depending on the acid cocatalyst different chiral species (cyclic secondary amines *vs*. acyclic primary amines) might catalyse the process. In order to shed light on the catalytic activation, several experiments were carried out and a detailed possible reaction mechanism is proposed. Theoretical studies support the stereochemical outcome of the process.

Introduction

In the last decade, organocatalysis has emerged as one of the most exciting and rapidly expanding fields in organic chemistry.[1] In particular, aminocatalysis has provided the life sciences with easy and environmentally friendly access to important building blocks.[2] Secondary amines have played a key role within this field due to their efficient activation of carbonyl compounds such as aldehydes, α,β-unsaturated aldehydes and ketones. Moreover, the past few years have witnessed the rapid development of chiral primary amine-based organocatalysts[3] owing to their extraordinary usefulness and versatility as activators of α,β-unsaturated ketones in asymmetric catalysis.[4]

In parallel with the advances in the use of primary amine organocatalysts, significant developments in asymmetric organocascade reactions have also been reported.[5] It is not surprising that domino processes represent a flourishing area in organic chemistry since they allow a number of bonds and stereocenters to be efficiently created in a single operation. These straightforward routes to molecular complexity are important in green chemistry for their atom economy, reduction of synthetic steps, and minimization of solvents and waste.[6] It is thus highly desirable to provide readily available molecules able to promote asymmetric cascade reactions.

In this context, chiral primary 1,2-aminoalcohols, easily accessible from inexpensive natural amino acids, are valuable small molecules that have been efficiently used as chiral auxiliaries in the preparation of enantiomeric scaffolds giving access to structurally complex bioactive and natural products.[7] Furthermore, a large number of vicinal amino alcohol derivatives have successfully acted as ligands in a great variety of transition metal catalytic reactions.[8] Although both these applications are well documented, chiral primary 1,2-aminoalcohols have been scarcely studied as "metal-free catalysts"[9] and, to the best of our knowledge, their application in asymmetric cascade reactions remains unexplored.

Going a step further in the study of chiral aminoalcohols in asymmetric synthesis, we herein examine their usefulness as organocatalysts for the enantioselective production of compounds by a cascade reaction. The structural requirements of the catalyst for efficient stereoselective catalysis are discussed. Finally, computational studies are performed to identify clues about the origin of the stereoselectivity.

Results and discussion

In a seminal study by Jørgensen's group, a phenylalanine-derived imidazolidine **1** was shown to catalyze a highly enantio- and diastereoselective domino Michael–aldol reaction of acyclic β-ketoesters and α,β-unsaturated ketones to form optically active cyclohexanones (Scheme 1).[10]

An initial screening was carried out to optimize the reaction conditions of benzylideneacetone with benzyl benzoylacetate using 10 mol% of **1**. The highest reaction rates were observed in EtOH at room temperature for 44 h (89% yield), with excellent diastereoselectivity (>97 : 3 d.r.) and good enantiomeric excess (89% *ee*). This transformation was also performed at 10 °C (80% yield, >97 : 3 d.r., 95% *ee*), although the reaction time increased to 190 h. The reaction also proceeded under solvent-free conditions, even though the yield was significantly lower (60%). Notably,

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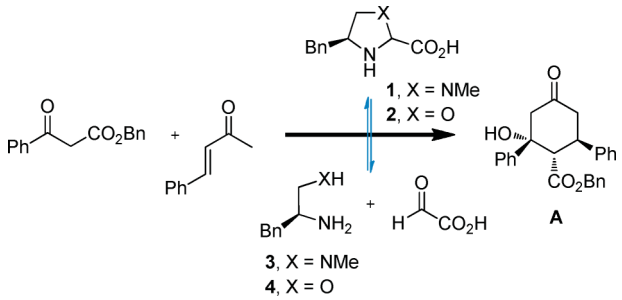
† Dedicated to the memory of Prof. Rafael Suau.

‡ Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of new products **1** and **13**, copies of the HPLC chromatograms, representation of alternative conformations for the products with *R* and *S* configuration, and optimized geometries of the structures shown in Fig. 4, 5, S1 and S2. See DOI: 10.1039/c1ob05400g



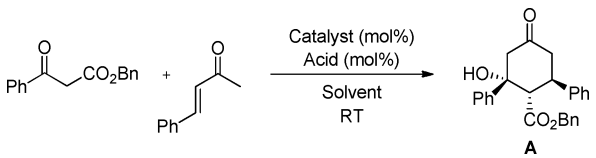
Scheme 1 Organocatalytic asymmetric domino Michael–aldol reaction.

a single enantiomer (**A**) precipitated from the reaction mixture, which was isolated in a pure form simply by filtration, suggesting that a continuous recrystallization took place during the process.

At the outset of our studies, we planned to explore the influence of an oxygen atom within the cyclic catalyst. Thus, 4-benzyloxazolidine-2-carboxylic acid **2**, an analogue of the Jørgensen imidazolidine **1**, was used as an organocatalyst in the model reaction.[11] Satisfactorily, novel oxazolidine **2** was indeed able to catalyse the reaction (Table 1, entry 1), thus indicating its capacity to activate α,β-unsaturated ketones.[12] In this context, it is known that cyclic secondary amines are reluctant to react with α,β-unsaturated ketones due to the formation of congested iminium adducts, and that primary amines can easily overcome such steric difficulties.[4] Interestingly, some authors consider that one of the many imidazolidines that catalyse 1,4-additions is in fact a precatalyst,[13] since the primary amine derived from its hydrolysis can catalyse the conjugate addition.[14]

Bearing this case in mind, additional experiments were envisaged considering that imidazolidine **1** and oxazolidine **2** may be in equilibrium with the diamine **3** and aminoalcohol **4**, respectively.

Table 1 Optimization of the diastereo- and enantioselective domino Michael–aldol reaction by **2**–**4**[a]



Entry	Catalyst [mol%]	Acid [mol%]	Solvent	Time/d	Yield (%)[b]	*ee* (%)[c]
1	**2** [20]		EtOH	7	65	70
2	**3** [10]	Glyoxylic [10]	EtOH	3	70	89
3	**4** [20]	Glyoxylic [20]	EtOH	6	77	73
4	**4** [20]	Glyoxylic [10]	EtOH	6	88	82
5	**3** [10]	Benzoic [10]	EtOH	4	82	93
6	**4** [20]	Benzoic [20]	EtOH	6	66	66
7	**4** [20]	Acetic [20]	EtOH	6	60	53
8	**4** [20]	Glyoxylic [20]	H_2O	5	42	86
9	**4** [20]	Glyoxylic [20]	neat	6	70	86
10	**4** [20]	Benzoic [20]	neat	6	82	81
11	**4** [20]	Glyoxylic [20]	neat	2	90	75[d]
12	**4** [20]	Benzoic [20]	neat	3	91	78[d]

All the reactions were performed on a 0.5 mmol scale at room temperature unless indicated otherwise (see Experimental section).[a] Diastereoisomeric ratio in all reactions showed to be >97 : 3 determined by ^{1}H NMR spectroscopy of the crude product. [b] Yields of isolated product. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed at 40 °C.

Thus, when we directly used diamine **3** in the presence of an equimolecular amount of glyoxylic acid (Table 1, entry 2), we obtained **A** with the same optical purity (89% *ee*) as when using preformed imidazolidine **1** (*vide supra*). In order to elucidate the existing species in the reaction media, equimolecular amounts of diamine **3** and glyoxylic acid were mixed in EtOH, the solvent of the domino reaction. Under these conditions, total conversion to imidazolidine **1** was observed after 1 h.[15] Additionally, the mixture of equimolecular amounts of both reagents, **3** and glyoxylic acid, in CD_3OD in an NMR tube allowed us to confirm that the formation of **1** was instantaneous. These findings indicate that the phenylalanine-derived imidazolidine **1** is likely to be present in the domino reaction media (EtOH). Similarly, oxazolidine **2** is also rapidly formed in EtOH from glyoxylic acid monohydrate and (*S*)-phenylalaninol **4**. Thus, the previous preparation of cyclic catalysts **1** and **2** is not required since *in situ* formation can occur in the reaction media.

With this information in hand, we turned our attention to the study of primary aminoalcohols as organocatalysts, carrying out a screening of the reaction conditions. The use of 20 mol% of (*S*)-phenylalaninol (**4**) and glyoxylic acid furnished cyclohexanone **A** in 77% yield and 73% *ee* (Table 1, entry 3). Interestingly, an optimal ratio of the aminoalcohol and the acid (20 and 10 mol%, respectively) significantly increased the yield and enantioselectivity of the process (Table 1, entry 4). This result prompted us to explore the role of the acid in the reaction.

With the results obtained so far we assumed that the catalyst of the reaction could be either the heterocycles (**1** or **2**) or the primary amines (**3** or **4**), with the glyoxylic acid acting as a cocatalyst. To discard the former possibility, glyoxylic acid was substituted by other acids that prevent the *in situ* formation of the five-membered ring derivatives **1** and **2** from diamine **3** and aminoalcohol **4**, respectively.

The use of benzoic acid as the cocatalyst in the presence of diamine **3**, gave the product **A** in 82% yield and 93% *ee* (Table 1, entry 5). Aminoalcohol **4** was also able to catalyse the reaction in the presence of benzoic acid (Table 1, entry 6). These experiments proved that primary amines **3** and **4** are able to catalyze the domino Michael–aldol reaction on their own. However, it can not be completely excluded that reactions performed with glyoxylic acid (Table 1, entries 2–4) are not catalyzed by heterocycle **1** or **2**.

The product **A** was also obtained by using AcOH as the cocatalyst, although the yield and the *ee* decreased to 60 and 53%, respectively (Table 1, entry 7). Other acids with lower pK_a such as oxalic and trifluoroacetic acids turned out to be ineffective and the reaction did not progress at all.

In order to provide a more environmentally friendly procedure, water and neat conditions were considered. Although previous studies using **1** in water were not successful,[10] (*S*)-phenylalaninol (**4**) enabled the reaction to take place in water with high selectivity but moderate reactivity (Table 1, entry 8), the latter probably due to the low solubility of the reagents in the aqueous media.

Neat conditions in the presence of glyoxylic acid resulted in an improved enantioselectivity (Table 1, entry 9 *vs.* entry 3), whereas with benzoic acid, the absence of solvent enhanced both the reaction rate and enantioselectivity (Table 1, entry 10 *vs.* entry 6).

In the domino reaction, heating the mixtures at 40 °C in solvent-free conditions reduced the reaction times and increased the yields

(>90%), but slightly decreased enantioselectivities (Table 1, entries 11 and 12).[16]

Other vicinal diamine and aminoalcohols as domino Michael–aldol reaction catalysts

Since diamine **3** and (*S*)-phenylalaninol (**4**) are good candidates for the model domino reaction, other 1,2-aminoalcohol derivatives with different structural features were studied (Fig. 1). Representative results are summarized in Table 2.

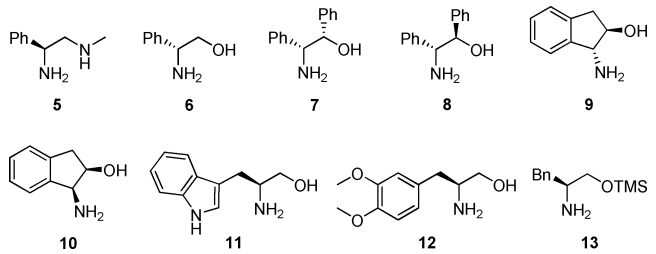
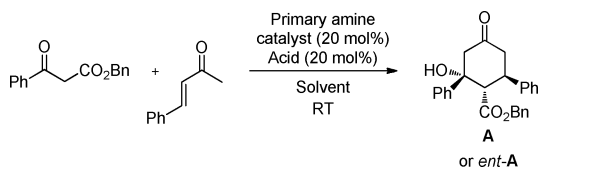


Fig. 1 Diamine **5** and aminoalcohols **6–13** used in this study. TMS = trimethylsilyl.

We first examined the influence of the aromatic ring arrangement within the catalyst. Thus, when the aromatic substituent was directly linked to the chiral stereocenter of the diamine (**5**) the effect was considerable, with the *ee* dropping from 89 to 68% (Table 1, entry 2 *vs.* Table 2, entry 1). However, such a phenyl substituent within an aminoalcohol moiety (**6**) affected the reaction outcome only slightly (Table 2, entry 2 *vs.* Table 1, entry 3), this compound thereby showing more tolerance to structural modifications.

As expected, the use of (*R*)-phenylglycinol (**6**) as the catalyst led to the enantiomer (*ent*-**A**) of the final product obtained in all the aforementioned studies using compounds **3–5** as the chiral source (Table 2, entry 3).

Table 2 Domino Michael–aldol reaction catalysed by diamine **5** and aminoalcohols **6–13**[a]



Entry	Catalyst	Acid	Solvent	Time/d	Yield (%)[b]	*ee* (%)[c]
1	**5**	Glyoxylic	EtOH	3	70	68[d]
2	**6**	Glyoxylic	EtOH	6	71	−80
3	**7**	Glyoxylic	EtOH	6	67	−73
4	**7**	Benzoic	EtOH	4	55	−63
5	**8**	Glyoxylic	EtOH	6	55	−77
6	**9**	Glyoxylic	EtOH	6	65	−70
7	**10**	Glyoxylic	EtOH	6	28	86
8	**11**	Glyoxylic	EtOH	4	42	56
9	**12**	Glyoxylic	neat	3	50	79[e]
10	**13**	Glyoxylic	EtOH	6	77	61

All the reactions were performed on a 0.5 mmol scale at room temperature with 20 mol% of the cocatalyst and catalysts unless indicated otherwise (see Experimental section).[a] Diastereoisomeric ratio in all reactions showed to be >97 : 3 determined by ^{1}H NMR spectroscopy of the crude product. [b] Yields of isolated product. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed with 10 mol% of both diamine **5** and glyoxylic acid. [e] Reaction performed at 40 °C.

An additional stereocenter with a tethered phenyl group was included in the catalyst, and (1*S*,2*R*)-2-amino-1,2-diphenylethanol **7** was examined with either glyoxylic or benzoic acid as the cocatalyst. Such conditions afforded *ent*-**A** in moderate yield and enantioselectivity (Table 2, entries 3 and 4). Running the reaction in the presence of its 1*R*, 2*R* diastereoisomer **8** did not significantly improve the rate or selectivity of the process (Table 2, entry 5). These results indicated that only the stereocenter bearing the primary amino group has a significant influence on the stereochemical outcome of the reaction. These observations were confirmed by the different behavior of the constrained diastereoisomers **9** and **10**. Using *trans*-(*R*,*R*)-aminoindanol **9**, *ent*-**A** was formed in 65% yield and 70% *ee*, whereas with *cis*-(*S*,*R*)-aminoindanol **10**, low conversion to the opposite enantiomer (**A**) occurred, albeit with a higher *ee* value (Table 2, entries 6 and 7).

When bearing a 3-indolyl substituent the primary aminoalcohol catalyst [(*S*)-tryptophanol, **11**] was ineffective (Table 2, entry 8). Electron-donating groups in the phenyl substituent hampered the reaction evolution as (*S*)-3,4-dimethoxyphenylalaninol (**12**) needed a higher temperature in solvent-free conditions to yield 50% of **A** (Table 2, entry 9).

The above results show that, in the aminoalcohol series, the optimal aromatic substituent for an efficient domino Michael–aldol reaction is a phenyl or benzyl group.

Alcohol protection of (*S*)-phenylalaninol (**4**) gave trimethylsilyl ether derivative **13**, which catalyzed the cascade reaction in good yield. Nevertheless, the absence of a hydrogen-bonding donor decreased the reaction enantioselectivity (Table 2, entry 10).

Mechanistic and theoretical considerations

Based on our experimental observations and previous considerations,[10] a putative mechanism can be proposed for the Michael–aldol reaction.

Two different pathways may be considered depending on the catalytic participation of cyclic secondary amine $\mathbf{I_A}$ (cycle A depicted in Fig. 2) or acyclic primary amine $\mathbf{I_B}$ (cycle B). Using catalysts **3** or **4** with glyoxylic acid as the cocatalyst, the reaction can progress through both primary amine catalysis[17] (cycle B) and secondary amine catalysis[18] (cycle A). However, when the reaction was performed in the presence of other acid cocatalysts such as benzoic acid, the reaction course would only follow cycle B (X = NCH_3, O; R^1 = Bn; R^2 = Ph) since the absence of aldehyde functionality within the acid would avoid the cyclic secondary amine formation.

The iminium/enamine cascade sequence would proceed through the initial activation of the unsaturated ketone by either the catalyst $\mathbf{I_A}$ or $\mathbf{I_B}$ to form iminium ions $\mathbf{II_A}$ and $\mathbf{II_B}$, respectively. The ketoester nucleophilic attack at the *Si* face of these activated eniminium ions would afford Michael adducts $\mathbf{III_A}$ and $\mathbf{III_B}$, with two new stereogenic centers, although one of them can probably epimerize in the reaction media. After an enamine isomerization, intermediates $\mathbf{IV_A}$ and $\mathbf{IV_B}$ can adopt a preferential pseudo-chair conformation where the bulky substituents are in equatorial disposition. Only these favourable conformers, probably assisted by a hydrogen-bonding interaction, would easily undergo the aldol reaction. Finally, subsequent hydrolysis of $\mathbf{V_A}$ and $\mathbf{V_B}$ would afford cyclohexanone **A** and re-establish the catalysts.

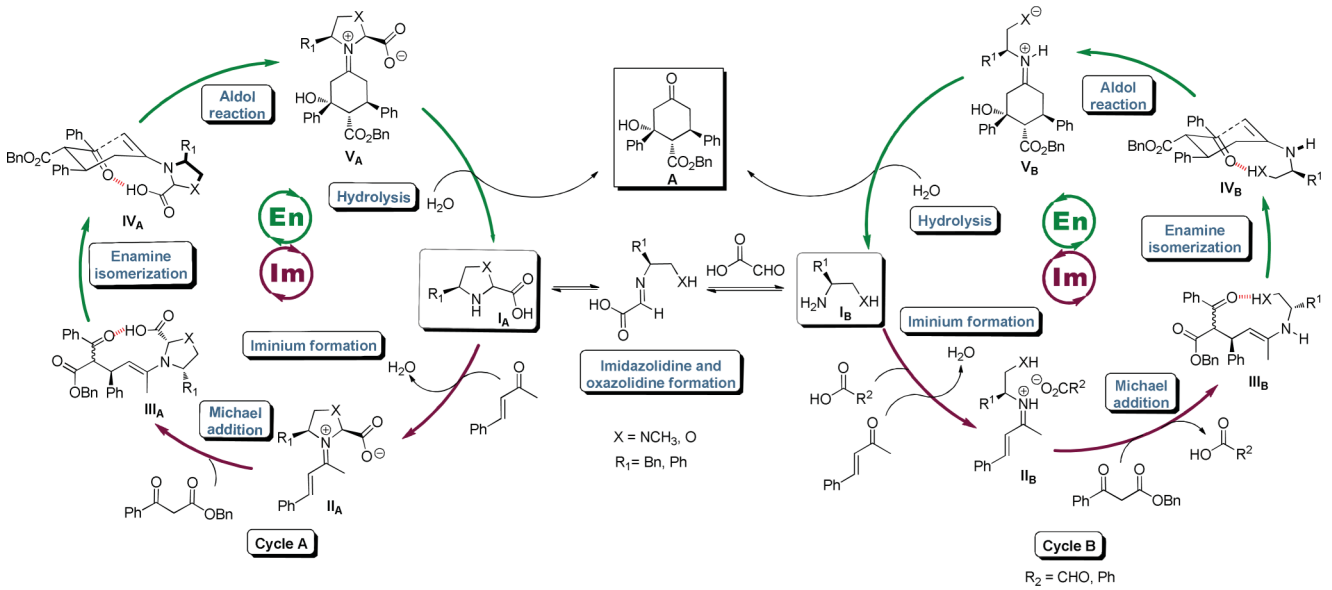


Fig. 2 Proposed Michael–aldol reaction mechanism catalysed by primary and secondary amines.

Interactions between catalysts and other carbonyl groups present in the mixture may produce reversible side reactions. However, these would not interfere with the organocascade reaction as the whole system is in equilibrium wherein the precipitation of the final product (**A**) from the reaction mixture acts as the driving force of the process.

Regarding the stereoselectivity in the domino Michael–aldol sequence, the key step for the asymmetric induction is the initial Michael addition, which involves the generation of the two first stereogenic centers. Since only one of them is configurationally stable, this one determines the configuration of other stereocenters present in the final product (**A**). Thus, we centered our attention on the stereochemical outcome during the formation of this stable stereocenter. To explain the stereochemistry of the Michael adduct $\mathbf{III_B}$, two main factors were considered: the stability of the iminium ion ($\mathbf{II_B}$) and the stereofacial selectivity in the ketoester attack.

The interaction of the catalyst with the α,β-unsaturated ketone could originate four possible iminium derivatives (Fig. 3). The *transoid* iminium salts were expected to be more stable due to the larger steric hindrance in the *cisoid* derivatives. Indeed, B3LYP/6-31G(d) calculations (phenylglycinol chosen as model, Fig. 3 X = O) indicate that *transoid* forms were more stable by 2.4 kcal mol^{-1}. Among them, *trans-im***2** was more stable than *trans-im***1** by 0.7 kcal mol^{-1}. This effect can be ascribed to the balance of two opposite effects (Fig. 4): (i) the energetic stabilization due to the formation of an intramolecular hydrogen bond between the hydroxyl group and the iminium N–H, and (ii) the destabilization due to the proximity of the benzene ring to the carbon atom in the position β to the iminium nitrogen and *trans* to the iminium hydrogen (CH in *trans-im***2**; CH_3 in *trans-im***1**), which is larger in *trans-im***1** due to the presence of the methyl group. Relief of such steric hindrance, which is associated with the loss of the intramolecular hydrogen bond, does not afford a net gain in stability, as the corresponding conformations are destabilized by around 1.1 kcal mol^{-1} (Fig. 4).

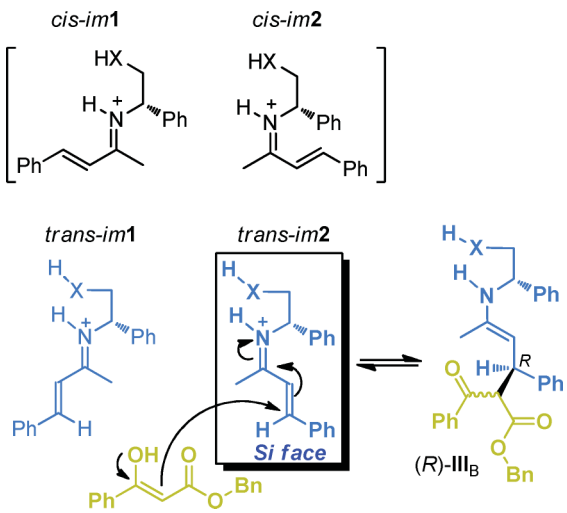


Fig. 3 Putative iminium salt derivatives and Michael adduct intermediate.

The nucleophilic attack of benzyl benzoylacetate at the *Si* face of the iminium intermediate (*trans-im***2**) will determine an *R* configuration in the newly created stereocenter [(*R*)-$\mathbf{III_B}$ where R^1 = Ph, Fig. 3]. In order to gain insight into the preference for the *Si* face, we determined the relative stability of the products formed from the attack of benzyl benzoylacetate at the two faces of *trans-im***2**. Exploration of the different conformational states for the products with *R* (*Si* face, (*R*)-$\mathbf{III_B}$) and *S* (*Re* face, (*S*)-$\mathbf{III_B}$) configurations indicated that the former is predicted to be more stable by 2.0 kcal mol^{-1} at the B3LYP/6-31G(d) level (Fig. 5). In the two cases an intramolecular hydrogen bond is formed between the hydroxyl unit and the carbonyl group of the keto or ester moieties upon attack *via Si* or *Re* faces, respectively (the alternative conformations where hydrogen bonding involves the ester (*Si* face) or keto (*Re* face) units are destabilized by 2.9 and 3.6 kcal mol^{-1}; see Fig. S1 in the ESI†). Inspection of Fig. 5 suggests that the preference for the product with *R* configuration

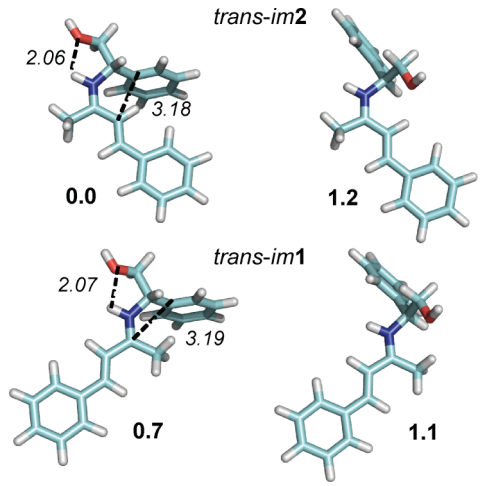


Fig. 4 Representation of the most favorable species of *trans-im***1** and *trans-im***2**, their relative energy (kcal mol^{-1}; in bold), and selected intramolecular distances (Å; in italics) determined from geometry optimizations at the B3LYP/6-31G(d) level.

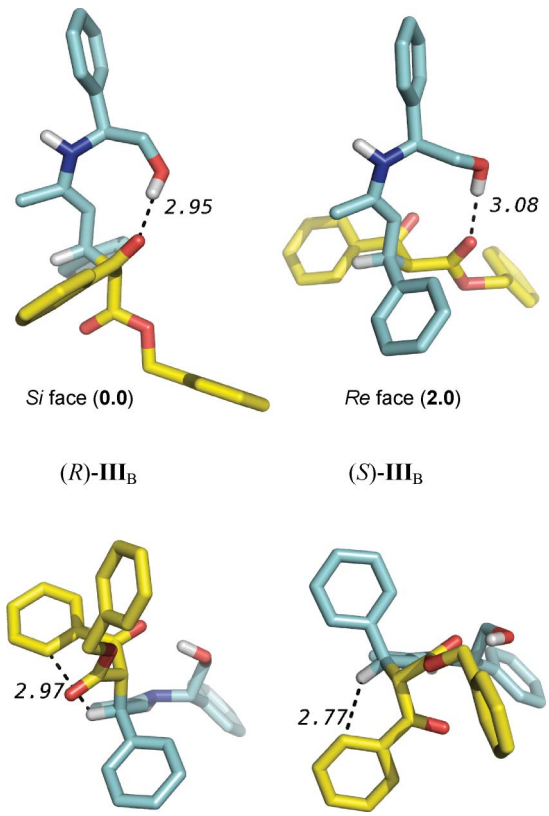


Fig. 5 Two views of the most stable products formed upon nucleophilic attack of the benzyl benzoylacetate (shown in yellow) to the *Si*/*Re* faces of the iminium intermediate *trans-im***2** (shown in blue). The relative energy (kcal mol^{-1}; in bold), and selected intramolecular distances (Å; in italics) determined from geometry optimizations at the B3LYP/6-31G(d) level are shown.

arises from two factors: (i) a stronger hydrogen bond between hydroxyl and carbonyl groups in the *R* product, as noted in the shorter O···H distance (2.95 and 3.08 Å for attack *via Si* or *Re* faces, respectively), and (ii) a larger steric clash between the benzyl ring and the hydrogen atom at the chiral center in the *S* product.

On the basis of these findings, it can be hypothesized that the formation of the transition state (TS) leading to the *R* product (*Si* face, (*R*)-**III$_B$**) will be energetically more favorable, which would thus justify the stereochemical outcome of the reaction. In order to confirm this hypothesis, the TS leading to the products were determined and confirmed by the presence of a single imaginary frequency, which mainly involves the displacement of the carbon atoms involved in the formation of the bond between *trans-im***2** and benzyl benzoylacetate (C–C distance of 2.31 and 2.33 for transition states *via Si* and *Re* faces, respectively; see Fig. S2 in the ESI†). Moreover, the TS yielding the *S* product is destabilized by 3.6 kcal mol^{-1} relative to the TS leading to the *R* product [(*R*)-**III$_B$**]. Notably, such a difference in stability can be attributed, at least in part, to the stronger intramolecular hydrogen bond in the *R* product-TS, as noted in a distance of 2.77 Å, which compares with a value of 3.02 Å found for the *S* product-TS (see Fig. S2 in the ESI†). Overall, these findings highlight the important role played by the hydroxyl group of the aminoalcohol catalyst. This observation is supported by our experimental results, comparing the *ee* in the reaction using **4** (Table 1, entry 4, *ee* 82%) and its silylated analogue **13** (Table 2, entry 10, *ee* 61%).

Finally, the α-dicarbonylic stereocenter is epimerizable and its configuration may be determined by the subsequent aldolic condensation step, taking into account that the most stable chair-like conformation for **IV$_A$** and **IV$_B$** would involve the pseudoequatorial disposition of all substituents (Fig. 2). In this last step, a hydrogen-bonding interaction between the hydroxyl group and the ketone is likely to be present, as indicated in the theoretical calculations for (*R*)-**III$_B$** (Fig. 5).

Conclusions

Chiral aminoalcohols and diamines, which are readily available from naturally occurring amino acids, have proven to be new, useful organocatalysts for a highly stereoselective domino Michael–aldol reaction, affording cyclohexanone **A** with excellent yields (up to 91%), diastereoselectivities (>97 : 3 d.r.) and enantioselectivities (up to 93% *ee*). Initial studies using cyclic secondary amines **1** and **2**, and acyclic primary amines **3** and **4**, in the presence of glyoxylic acid showed that two different types of catalysis might be involved. Benzoic acid cocatalysis pointed to primary amine catalysis, in which **3** and **4** acted as the real catalysts. However, when glyoxylic acid cocatalysed the reaction, the heterocyclic species present in the media could take part in the process through secondary amine catalysis. A detailed mechanism for the organocascade reaction was proposed.

All aminoalcohol derivatives studied were able to catalyse the domino process. However, few structural catalyst modifications allow an efficient reaction, thereby indicating that this transformation is very sensitive to the catalyst structure.

Finally, theoretical calculations have been performed to justify the stereochemical outcome of the Michael addition, which determines the configuration of the three contiguous stereogenic centres present in the final product. From these studies we can conclude that the preference for the product with *R* configuration (attack *via Si* face) can be attributed to the subtle balance

between (i) the hydrogen bonding between the hydroxyl group of the *transoid* iminium intermediate and the carbonyl unit of the benzyl benzoylacetate reagent, and (ii) the steric clash between the reacting partners.

Experimental

Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H) and 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (J) in hertz (Hz), integrated intensity. Multiplicities are reported using the following abbreviations: s, singlet; dd, doublet of doublets; m, multiplet; br s, broad signal. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IA column) with methyl *tert*-butyl ether/EtOH 98/2 as eluent. Analytical grade solvents and commercially available reagents were used without further purification. Benzyl benzoylacetate,[19] diamines **3** and **5**,[13a] aminoalcohols **4** and **6**,[20] and **12**[21] were prepared according to literature procedures.

(4*S*)-4-Benzyl-1-methylimidazolidine-2-carboxylic acid (1)

In a NMR tube glyoxylic acid monohydrate (4.6 mg, 0.05 mmol) was added to a solution of (*S*)-1-amino-2-methylamino-3-phenylpropane (**3**; 8.5 mg, 0.05 mmol) in CD_3OD (1 mL). The ^1H NMR spectrum was immediately recorded, indicating the presence of a 1 : 1 mixture of diastereoisomeric imidazolidines. ^1H NMR (400 MHz, CD_3OD) δ 2.64–2.75 (m, 2H), 2.82 (s, 6H, NCH_3), 2.86–2.94 (m, 2H), 3.03–3.09 (m, 2H), 3.15–3.20 (m, 2H), 3.52 (m, 1H, CH–N, one diastereoisomer), 3.82 (m, 1H, CH–N, one diastereoisomer), 4.34 (m, 1H. CH–N, one diastereoisomer), 4.38 (m, 1H, CH–N, one diastereoisomer), 7.23–7.33 (m, 10H, ArH); ^{13}C NMR (100 MHz, CD_3OD) δ 39.1. 39.6, 40.3, 40.7, 59.3, 59.8, 60.0, 60.3, 84.8, 86.6, 128.0, 128.4, 129.6, 129.8, 130.0, 130.1, 130.4, 130,5, 138.6, 138.7, 170.1, 170.6.

(4*S*)-4-Benzyloxazolidine-2-carboxylic acid (2)

An equimolecular mixture of (*S*)-phenylalaninol (151 mg, 1 mmol) and glyoxylic acid monohydrate (92 mg, 1 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. The solvent was evaporated to give quantitatively the desired product as a white solid as a mixture of diastereoisomers. HMRS $C_{11}H_{14}NO_3$ ($M + H^+$), 208.0968; found, 208.0968.

(*S*)-1-Phenyl-3-(trimethylsilyloxy)propan-2-amine (13)

Iodine (46 mg, 0.18 mmol) and hexamethyldisilazane (2.8 mL, 13.23 mmol) were added to a solution of (*S*)-phenylalaninol (2 g, 13.23 mmol) in anhydrous CH_2Cl_2 (45 mL). The resulting yellowish mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH (1 mL) and the mixture was evaporated to give a colourless oil that was dissolved in CH_2Cl_2 (45 mL). A solution of $Na_2S_2O_3$ (4 g) in water was added, the mixture was stirred for 5 min, and the phases were separated. The organic phase was dried, filtered and concentrated to give a pale yellow solid (2.52 g, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H, $3CH_3$), 1.30 (br s, 2H, NH_2), 2.38 (dd, J = 13.4, 8.4 Hz, 1H, CH_2Ph), 2.66 (dd, J = 13.4, 5.2 Hz, 1H, CH_2Ph), 2.99 (m, 1H, CH), 3.28 (dd, J = 9.8, 6.8 Hz, 1H, CH_2O), 3.44 (dd, J = 9.8, 4.3 Hz, 1H, CH_2O), 7.05–7.21 (m, 5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.6 (CH_3), 40.4 (CH_2Ph), 54.1 (CH), 67.2 (CH_2O), 126.2 (Ph), 128.4 (Ph), 129.2 (Ph), 139.1 (C-*i*); $[\alpha]_D^{22}$ –8.5 (*c* 1.0, $CHCl_3$); HMRS $C_{12}H_{22}NOSi$ ($M + H^+$), 224.1465; found, 224.1468.

General procedure for the domino Michael–aldol reaction

To a solution of benzylideneacetone (0.5 mmol) and benzyl benzoylacetate (1 mmol) in EtOH (1 mL), the appropriate catalyst (0.05–0.1 mmol) and acid cocatalyst (if appropriate) were added. The reaction mixture was stirred at the temperature and for the time indicated in the tables. The reaction mixture was diluted with Et_2O (2 mL) and filtered. The precipitate was collected to give the cyclohexanone product as a white solid. The enantiomeric excess (*ee*) was determined by HPLC analysis with an IA column (methyl *tert*-butyl ether/EtOH 98/2, 1.0 mL min^{-1}, λ = 210 nm).

Theoretical computations

Geometrical parameters and energy differences were determined from full geometry optimizations at the B3LYP/6-31G(d) level. For the (both *cis* and *trans*) iminium derivatives a conformational exploration was performed around the rotatable N–C bond in order to determine the minimum energy conformation. Regarding the products (with both *R* and *S* configuration) formed upon attack of the benzyl benzoylacetate to *trans*-*im***2**, a systematic exploration was performed to explore different hydrogen bonding patterns as well as the orientation of the benzyl and benzoyl moieties. The minimum energy nature of the stationary points was verified by inspection of the vibrational frequencies, which were positive in all cases with the exception of the transition states, which were characterized by a single imaginary frequency. Calculations were performed using Gaussian-03.[22]

Acknowledgements

Financial support from the Ministry of Science and Innovation, Spain (Projects CTQ2009-07021/BQU and SAF2008-05595), and the AGAUR, Generalitat de Catalunya (Grants 2009-SGR-111 and 2009-SGR-249) is gratefully acknowledged. C.A. thanks the Ministry of Education and Science for a predoctoral fellowship. The Centre de Supercomputació de Catalunya (CESCA) is acknowledged for computational facilities.

Notes and references

1 (*a*) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; (*b*) P. I Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, 2007; (*c*) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, RCS Publishing, 2010. For selected reviews, see: (*d*) Special Issue on Asymmetric Organocatalysis: *Acc. Chem. Res.*, 2004, **37**, ((8)); (*e*) Special edition on organocatalysis: *Chem. Rev.*, 2007, **107**; (*f*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308; (*g*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178–2189. For reviews on organocatalytic synthesis of drugs and natural products, see: (*h*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discov. Today*, 2007, **12**, 8–27; (*i*) R. M.

De Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 2575–2600; (*j*) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138–1167.
2 For selected reviews on asymmetric aminocatalysis, see: (*a*) B. List, *Chem. Commun.*, 2006, 819–824; (*b*) P. Melchiore, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138–6171. For an instructive essay on the aminocatalysis evolution, see: (*c*) B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 1730–1734.
3 For selected reviews on primary amine catalysis, see: (*a*) F. Peng and Z. Shao, *J. Mol. Catal. A: Chem.*, 2008, **285**, 1–13; (*b*) L.-W. Wu and Y. Lu, *Org. Biomol. Chem.*, 2008, **6**, 2047–2053; (*c*) L.-W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, 2009, 1807–1821. For a review on asymmetric primary amine catalysts based on *Cinchona* alkaloids, see: (*d*) Y.-C. Chen, *Synlett*, 2008, 1919–1930.
4 G. Bartoli and P. Melchiorre, *Synlett*, 2008, 1759–1772.
5 For reviews on organocatalytic domino/cascade reactions, see: (*a*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*b*) B. Westermann, M. Ayaz and S. S. van Berkel, *Angew. Chem., Int. Ed.*, 2010, **49**, 846–849; (*c*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178. For a review on asymmetric cascade reactions catalyzed by chiral secondary amines, see: (*d*) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037–2046. For a review on asymmetric cascade reactions catalyzed by chiral amines, see: (*e*) S. Vera and P. Melchiore, *An. Quím.*, 2010, **106**, 277–284.
6 (*a*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*b*) K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993–3009.
7 For a review on 1,2-aminoalcohols as chiral auxiliaries in asymmetric synthesis, see: (*a*) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835–875. For reviews on our work in the field, see: (*b*) C. Escolano, M. Amat and J. Bosch, *Chem.–Eur. J.*, 2006, **12**, 8198–8207; (*c*) M. Amat, M. Pérez and J. Bosch, *Synlett*, 2011, 143–160.
8 For a review on catalytic applications of nitrogen-containing ligands, including 1,2-aminoalcohols, see: F. Fache, E. Schultz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159–2232.
9 For examples on the use of chiral primary aminoalcohols as metal-free organocatalysts, see: (*a*) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Mayshev, K. Pluháčková and P. Kočovský, *Org. Lett.*, 2007, **9**, 5473–5476; (*b*) A. Russo and A. Lattanzi, *Eur. J. Org. Chem.*, 2008, 2767–2773; (*c*) T. E. Kristensen, K. Vestli, F. K. Hansen and T. Hansen, *Eur. J. Org. Chem.*, 2009, 5185–5191.
10 N. Halland, P. S. Aburel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 1272–1277.
11 Recently, a novel oxazolidine has been used as an organocatalyst for the first time: H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano and Y. Kohari, *Chem. Commun.*, 2010, **46**, 4827–4829.
12 At shorter reaction times (3 days), a decrease in yield (21%) is observed, although the *ee* was higher (89%). The use of ethyl benzoylacetate instead of benzyl benzoylacetate as starting material with **2** as catalyst provided lower yield (61%) and *ee* (44%). Comparable results were previously reported by Jørgensen and coworkers (ref. 10).
13 (*a*) N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331–8338; (*b*) N. Halland, P. S. Aburel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 661–665; (*c*) N. Halland, T. Hansen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4955–4957; (*d*) J. Pulkkinen, P. S. Aburel, N. Halland and K. A. Jørgensen, *Adv. Synth. Catal.*, 2004, **346**, 1077–1080.
14 A mechanism involving a diamine catalyst (diphenylethylenediamine), instead of the previously supposed imidazolidine catalyst, has been proposed: (*a*) H. Kim, C. Yen, P. Preston and J. Chin, *Org. Lett.*, 2006, **8**, 5239–5242. For selected organocascade reactions of enones catalysed by primary amines, see: (*b*) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7196–7199; (*c*) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200–7203; (*d*) Y.-Q. Yang, Z. Chai, H.-F. Wang, X.-K. Chen, H.-F Cui, C.-W. Zheng, H. Xiao, P. Li and G. Zhao, *Chem.–Eur. J.*, 2009, **15**, 13295–13298; (*e*) H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu and G. Zhao, *J. Org. Chem.*, 2010, **75**, 117–122. For an example of a primary amine (phenylethylamine) catalysed Michael reaction, see: (*f*) Y. Hirai, T. Terada, T. Yamazaki and T. Momose, *J. Chem. Soc., Perkin Trans. 1*, 1992, 509–516.
15 The preparation of **1** was previously reported by reaction of glyoxylic acid monohydrate and the corresponding diamine **3** in CH_2Cl_2 for 15 h (see ref. 10).
16 Performing the reaction at lower temperatures did not result in better reactivity or selectivity.
17 In the primary amine catalysis, the glyoxylic acid would only act as an acidic proton source, which would accelerate the iminium salt formation.
18 In the secondary amine catalysis, the *cis* heterocyclic diastereoisomer ($\mathbf{I_A}$) would play a major role as catalyst. In a related case, a 1,4-*cis* heterocyclic diastereoisomer was shown to be more reactive than the *trans* isomer in an *N*-acylation process. This can be rationalized taking into account that substituents in *trans* relationship shield the nitrogen inhibiting a nucleophilic attack. For the related example, see: W. Ando, Y. Igarashi and L. Huang, *Chem. Lett.*, 1987, 1361–1364See also ref. 11.
19 C.-Q. Sun, P. T. W. Cheng, J. Stevenson, T. Dejneka, B. Brown, T. C. Wang, J. A. Robl and M. A. Poss, *Tetrahedron Lett.*, 2002, **43**, 1161–1164.
20 S. E. Howson, L. E. N. Allan, N. P. Chmel, G. J. Clarkson, R. Gorkum and P. Scott, *Chem. Commun.*, 2009, 1727–1729.
21 S. M. Allin, S. L. James, M. R. J. Elsegood and W. P. Martin, *J. Org. Chem.*, 2002, **67**, 9464–9467.
22 *Gaussian 03*, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchsian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.