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# Graphical abstract

## Bifunctional primary amine 2-aminobenzimidazole organocatalyst anchored to *trans*-cyclohexane-1,2-diamine in enantioselective conjugate additions of aldehydes

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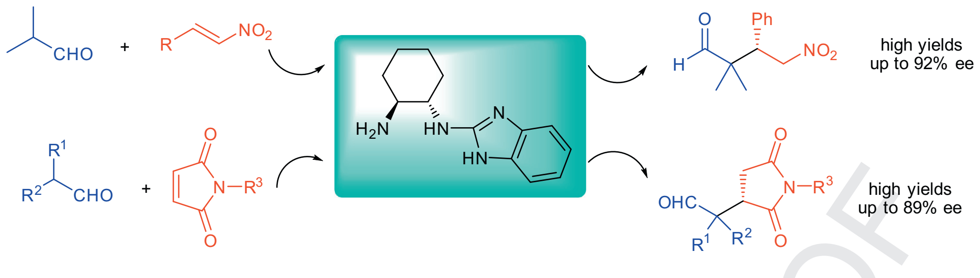

high yields
up to 92% ee

high yields
up to 89% ee

Tetrahedron: *Asymmetry* xxx (2015) xxx–xxx

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# Bifunctional primary amine 2-aminobenzimidazole organocatalyst anchored to *trans*-cyclohexane-1,2-diamine in enantioselective conjugate additions of aldehydes

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ABSTRACT

Bifunctional chiral primary amine **8** containing an (*S*,*S*)-*trans*-cyclohexane-1,2-diamine scaffold and a 2-benzimidazole unit is used as a general organocatalyst for the Michael addition of α,α-branched aldehydes to nitroalkenes and maleimides. The reactions take place, with 20 mol % of catalyst in dichloromethane at rt for nitroalkenes and with 15 mol % catalyst loading in toluene at 10 °C for maleimides, in good yields and enantioselectivities. DFT calculations demonstrate the bifunctional character of this organocatalyst activating the aldehyde by enamine formation and the Michael acceptor by double hydrogen bonding.

## 1. Introduction

The use of bifunctional organocatalysts bearing an amino group and a hydrogen bonding unit has become a very efficient strategy in many enantioselective transformations.[1–5] These two functionalities work in a cooperative manner when they are present in a rigid 1,2-diamine skeleton such as *trans*-cyclohexane-1,2-diamine. Different hydrogen bonding moieties, such as thiourea **1**,[6–8] sulfinyl urea **2**,[9,10] squaramides **3**[11–15] and 2-aminobenzimidazoles **4**–**6**[16–18] are privileged structures in asymmetric organocatalysis (Fig. 1). The 2-aminobenzimidazole group is structurally similar to a rigid guanidine and can act as a base and also as a hydrogen bond donor, especially after protonation.[19] Compounds **4**[16] and **5**–**6**,[17,18] bearing a tertiary amino group acting as a Brønsted base and a 2-aminobenzimidazole group as a hydrogen bonding donor, can efficiently catalyze the enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes. Compound **4** (R = Me, X = H) has been used in the amination of ethyl 2-oxocyclopentanecarboxylate with di-*tert*-butylazodicarboxylate.[20] A system bearing a *trans*-cyclohexane-1,2-diamine scaffold and two benzimidazoles units **7** has been used in the enantiocatalyzed Michael addition of 1,3-dicarbonyl compounds to maleimides.[21,22] In this case, one 2-aminobenzimidazole acts as a base (p$K_a$ ~7) and the other as a hydrogen bonding donor. Organocatalyst **7** also promotes the enantioselective alkylation of 1,3-dicarbonyl compounds with benzylic and allylic alcohols.[23] Chiral organocatalysts bearing a primary amine are especially important for the enamine formation of α,α-disubstituted aldehydes.[24]

We envisaged that compounds of type **4** bearing a primary amino group and a benzimidazole unit, such as **8**,[16] would be efficient bifunctional catalysts for the conjugate addition of aldehydes to electrophilic alkenes, combining the covalent (enamine) and non-covalent (hydrogen bonding) activation modes.

## 2. Results and discussion

### 2.1. Conjugate addition of aldehydes to nitroalkenes

Nitroalkenes are one of the most used Michael acceptors for different nucleophiles, especially 1,3-dicarbonyl compounds and aldehydes.[25–29] The corresponding adducts namely γ-nitrocarbonyl compounds, can be further transformed into many important biologically active compounds generally by reduction of the

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† Corresponding author for computational data.

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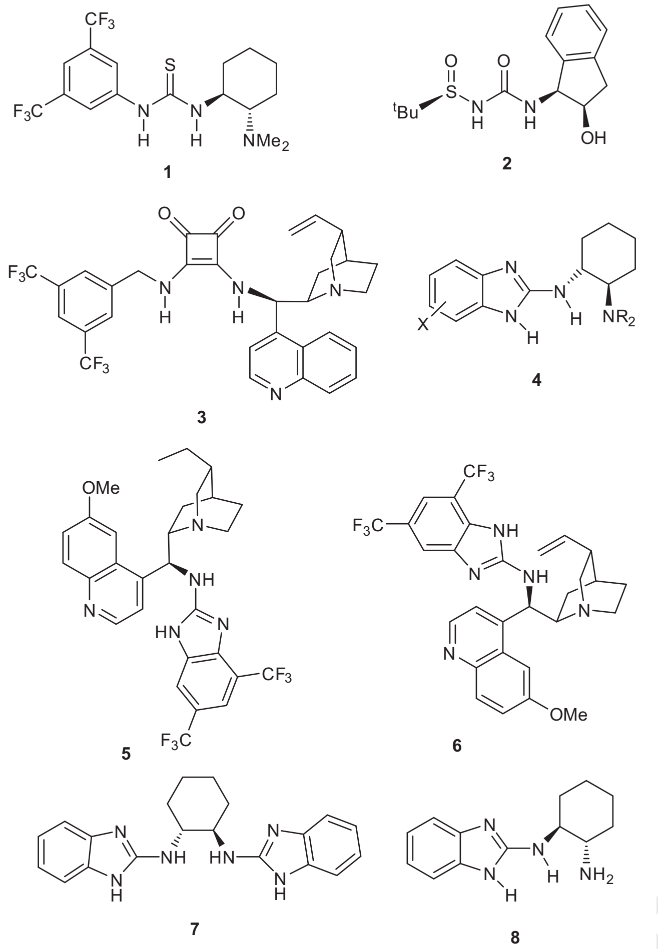
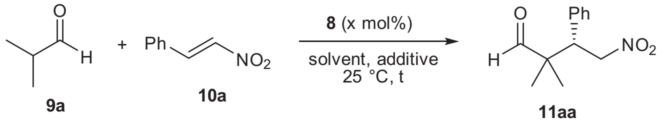


**Figure 1.** Selected chiral bifunctional organocatalysts.

nitro to an amino group. Initially, we studied the conjugate addition of isobutyraldehyde to β-nitrostyrene using organocatalyst **8**[16] (10 mol %). Compound **8** can be easily prepared in one step by reaction of 2-chlorobenzimidazole with (*S*,*S*)-*trans*-cyclohexane-1,2-diamine.[16] Initially, different solvents were assayed at room temperature (Scheme 1 and Table 1). In the case of toluene, 60% ee and a moderate 40% yield of product **11a** after reaction time of 4 days were obtained (Table 1, entry 1). However, with more polar solvents, such as DMF or water, lower enantioselectivities were observed (Table 1, entries 2 and 3). The best enantioselectivity (85% ee) was obtained with dichloromethane (DCM) as the solvent, but a low 11% yield was obtained (Table 1, entry 4). Increasing the catalyst loading to 20 mol % and the amount of isobutyraldehyde to 2 equiv gave the best results, with 87% yield and 92% ee being obtained after 3 days reaction time (Table 1, entry 5). The presence of 10 or 20 mol % of Et$_3$N as base accelerated the process while maintaining 90% ee, but the formation of byproducts was observed (Table 1, entries 6 and 7). Therefore, the reaction conditions of entry 5 were chosen for studying the scope of the reaction.



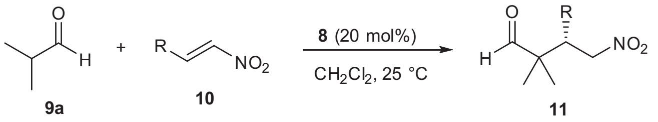
**Scheme 1.** Reaction condition studies for the addition of isobutyraldehyde to β-nitrostyrene.

**Table 1**
Optimization of the addition of isobutyraldehyde to β-nitrostyrene[a]

| Entry | **8** (mol %) | Solvent | Additive | *T* (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 10 | PhMe | – | 96 | 40 | 60 |
| 2 | 10 | DMF | – | 120 | 30 | 37 |
| 3 | 10 | $H_2O$ | – | 120 | 84 | 26 |
| 4 | 10 | DCM | – | 72 | 11 | 85 |
| 5[d] | 20 | DCM | – | 72 | 87 | 92 |
| 6[d] | 20 | DCM | Et$_3$N[e] | 30 | 99 | 90 |
| 7[d] | 20 | DCM | Et$_3$N[f] | 20 | 99 | 90 |

[a] Reaction conditions: **9a** (1 mmol), **10a** (0.5 mmol), **8** (see column), solvent (0.5 mL).
[b] Crude isolated yield determined by $^1$H NMR.
[c] Determined by using analytical SFC with a chiral coated column (Phenomenex Lux 5u Cellulose-1).
[d] **9a** (2 mmol) and **10a** (1 mmol) were used.
[e] 10 mol %.
[f] 20 mol %.

The scope of the reaction was next studied. Isobutyraldehyde **9a** was allowed to react with several nitroalkenes **10** in DCM at rt for 3–4 days (Scheme 2 and Table 2). Products **11** were obtained pure in moderate to high yields after adding ether to the reaction mixture followed by filtration over a pad of Celite. Only aromatic nitroalkenes **10a**–**10f** gave the corresponding adducts in good yields (52–99%) and enantiomeric excesses (74–92%) (Table 2, entries 1–6). In the case of heteroaromatic nitroalkenes, the 2-furyl derivative **10g** gave product **11ag** in high yield and with 82% ee (Table 2, entry 7). However, the reaction with 1-(3-pyridyl)-2-nitroethylene was unsuccessful. This process only took place with isobutyraldehyde with these types of conjugate additions. The absolute configuration of products**13** was assigned according to the literature data for identical products.[31]



**Scheme 2.** Michael addition of isobutyraldehyde to nitroalkenes.

**Table 2**
Conjugate addition of isobutyraldehyde **9a** to nitroalkenes[a]

| Entry | R | No. | *T* (d) | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | **10a** | 3 | **11aa** | 69 | 92 |
| 2 | 4-MeC$_6$H$_4$ | **10b** | 4 | **11ab** | 52 | 81 |
| 3 | 2-BrC$_6$H$_4$ | **10c** | 3 | **11ac** | 94 | 74 |
| 4 | 3-BrC$_6$H$_4$ | **10d** | 3 | **11ad** | 99 | 76 |
| 5 | 4-BrC$_6$H$_4$ | **10e** | 3 | **11ae** | 99 | 88 |
| 6 | 4-FC$_6$H$_4$ | **10f** | 3 | **11af** | 87 | 80 |
| 7 | 2-furyl | **10g** | 3 | **11ag** | 99 | 82 |

[a] Reaction conditions: **9a** (1 mmol), **10** (0.5 mmol), **8** (20 mol %), DCM (0.5 mL).
[b] Isolated yield after ether addition followed by filtration over a path of Celite and evaporation.
[c] Determined by using analytical SFC with a chiral coated column (Phenomenex Lux 5u Cellulose-1).

### 2.2. Conjugate addition of aldehydes to maleimides

The conjugate addition of aldehydes to maleimides using chiral organocatalysts enables the synthesis of enantioenriched succinimides, structures that can be found in several natural products and pharmaceuticals.[30] Initial optimization studies for the addition of isobutyraldehyde **9a** to *N*-phenylmaleimide **12a** in acetone, aqueous DMF (1:2) or toluene indicated that toluene was the

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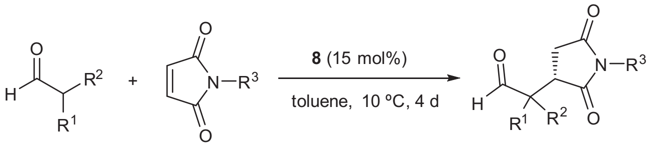
solvent of choice using 15 mol % of catalyst **8** at 10 °C. Thus, the scope of the reaction was performed under the mentioned reaction conditions using different aldehydes **9** and maleimides **12** (Scheme 3 and Table 3).



**9** **12** **13**

**Scheme 3.** Conjugate addition of aldehydes to maleimides.

**Table 3**
Organocatalyzed conjugate addition of aldehydes to maleimides[a]

| Entry | R$^1$ | R$^2$ | R$^3$ | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Me | Me | Ph | **13aa** | 59 | 77 |
| 2[d] | Me | Me | Ph | **13aa** | 79 | 89 |
| 3 | Me | Me | 3-ClC$_6$H$_4$ | **13ab** | 99 | 60 |
| 4 | Me | Me | 4-BrC$_6$H$_4$ | **13ac** | 67 | 80 |
| 5 | Me | Me | 2-MeOC$_6$H$_4$ | **13ad** | 63 | 78 |
| 6 | Me | Me | Bn | **13ae** | 63 | 89 |
| 7[e] | Me | Me | H | **13af** | 65 | 55 |
| 8 | Me | H | Ph | **13ba**[f] | 47 | 83[g] |
| 9 | —[h] | —[h] | Ph | **13ca** | 67 | 80 |
| 10 | —[h] | —[h] | Bn | **13ce** | 83 | 58 |

[a] Reaction conditions: **9** (1.5 mmol), **12** (0.5 mmol), **8** (15 mol %), toluene (1 mL) at 10 °C during 4 d.
[b] Isolated yield after purification.
[c] Determined by using analytical chiral coated HPLC columns (Chiralcel OD-H and Chiralpak AS).[31]
[d] 3 mmol of **9** and 1 mmol of **12a** in 2.3 mL of toluene were used.
[e] 2 mmol of **12** and 6 mmol of **9**were used.[32]
[f] A 2:1 mixture of diastereomers was obtained.
[g] 77% ee for the minor diastereomer.
[h] Cyclohexanecarbaldehyde (**9c**) was used.

The reaction of isobutyraldehyde **9a** with different *N*-arylmaleimides afforded the corresponding succinimides **13aa–13ad** in good yields and ee (60–89%) (Table 3, entries 1–5). In the case of *N*-benzylmaleimide **12e**, succinimide **13ae** was obtained in 63% yield and 89% ee (Table 3, entry 6). However, maleimide **12f** reacted with isobutyraldehyde in a similar 65% yield, but with a lower enantioselectivity (55%) (Table 3, entry 7). The addition of propanal with *N*-phenylmaleimide took place in a lower 47% yield, giving succinimide **13ba** as a 2:1 mixture of diastereoisomers with 83%/77% ee (Table 3, entry 8). However, the addition of α-phenylpropanal to *N*-phenylmaleimide was unsuccessful. Finally, when cyclohexanecarbaldehyde **9c** was allowed to react with *N*-phenylmaleimide **12a** and *N*-benzylmaleimide **12e**, the corresponding succinimides **13ca** and **13ce** were obtained in good yields and with 80% and 58% ee, respectively (Table 3, entries 9 and 10). The absolute configuration of products **13** was assigned according to the data already reported.[32]

In order to obtain a better understanding of the mechanism of these reactions, we carried out DFT theoretical investigations, with the aim of proving the bifunctional character of the catalyst (enamine formation and H-bond activation of the electrophile) and clarifying the role of the benzimidazole unit as a single or double H-bond donor. Structure optimizations were performed at the B3LYP/6-311+G$^{**}$ level, and refined by reoptimization at the M06-2X/6-311+G$^{**}$ level in order to determine accurate energies. In both cases, solvent effects were included (CPCM, toluene and CH$_2$Cl$_2$). We assumed that the reaction was initiated by the formation of a reactive nucleophilic enamine between the free NH$_2$ group of the catalyst **8** and isobutyraldehyde, and calculations were carried out for an attack of such enamine to the two most representative electrophiles used herein, nitrostyrene **10a** (Scheme 2), and *N*-phenylmaleimide **12a**. Based on our previous related work,[31–33] we located a number of distinct conformational transition states involving the two enantiotopic faces of the electrophiles. Special attention was paid to the *inter* and *intra* H-bond networks that can be formed between the benzimidazole, enamine and either the nitro group of **10a** or the maleimide/carbonyl of **12a**.

In light of the computational results, we anticipated that the most favoured structures computed for both electrophiles were those possessing the highest possible number of H-bonds within those networks, and that the reactivity and enantioselectivity of both types of electrophiles can be interpreted through a common mechanistic model.

The reactivity of maleimide **12a** was first examined, and we found that in the approach of the enamine to its *Re* face (*pro-S* transition state, **TS1-S**, Fig. 2), the two NH units of benzimidazole were involved in a double H-bond activation of the electrophilic carbonyl group, showing H-bond distances of 2.0 Å and 2.1 Å. Furthermore, the NH unit of the enamine is able to form a third H-bond with the free nitrogen of the benzimidazole with a distance of 2.0 Å. The latter interaction is noteworthy since it is responsible for an extra charge transfer from the benzimidazole to the enamine, making the enamine more electron-rich (and nucleophilic), while the benzimidazole becomes slightly more electron-poor and thus a better H-bond donor. In contrast, the spatial arrangement of the different groups in **TS1-R** (maleimide *Si*-face approach, Fig. 2) is not well suited for a multiple H-bond formation, and therefore, the most favoured transition state shows a single H-bond between the catalyst and the electrophile. Although it is true that this H-bond is slightly shorter (1.8 Å) than those present in **TS1-S**, the overall result is that **TS1-S** is energetically favoured over **TS1-R** with energy differences that range from 4.1 kcal/mol in the gas phase to 2.3 kcal/mol in toluene and 0.7 kcal/mol in dichloromethane. This decreasing energy trend is logical because H-bonds are known to be stronger in the gas phase and weaker as the polarity of the solvent increases. The prevalence of **TS1-S** in the outcome of the reaction also follows the same trend.

As already mentioned, a similar reasoning can be applied to the reaction with nitrostyrene **10a**, with a few slight differences (Fig. 3). For example, the H-bond networks in **TS2**-type structures resemble the previous ones, although in general, the H-bonds formed with the nitro group are slightly weaker than with the carbonyl group in their **TS1** counterparts. Thus, an increase of an average of 0.1 Å was computed for both isomeric transition states **TS2-S** and **TS2-R**, compared to **TS1** structures. This effect is more significant in **TS2-R**, whose unique H-bond has a length of 2.0 Å, while it was 1.8 Å in **TS1-R**. This is probably the underlying reason for the higher energy difference between **TS2-R** and **TS2-S**, which amounts to ca. 7.0 kcal/mol, depending on the computational conditions used. As shown before for *N*-phenylmaleimide **12a**, there is a decreasing gradient on the energy gap with the polarity of the medium, ranging from 7.4 kcal/mol, in the gas phase, to 7.2 kcal/mol in toluene and 6.9 kcal/mol in CH$_2$Cl$_2$. These results are again in agreement with the experiments, although it is worth mentioning that these energy differences are too large to explain the actual experimental selectivity. In this regard, we have found that **TS2-R** is not the only transition state that accounts for the formation of the (*R*)-adduct in this case. At least two other transition states of comparable energy (ca. +7 kcal/mol) might participate in the reaction, and help decrease the energy gap between the (*S*)- and (*R*)-enantiomers. These additional structures show either one or no H-bonds in their structures, which is in line with the arguments detailed herein. These findings are in full agreement with the

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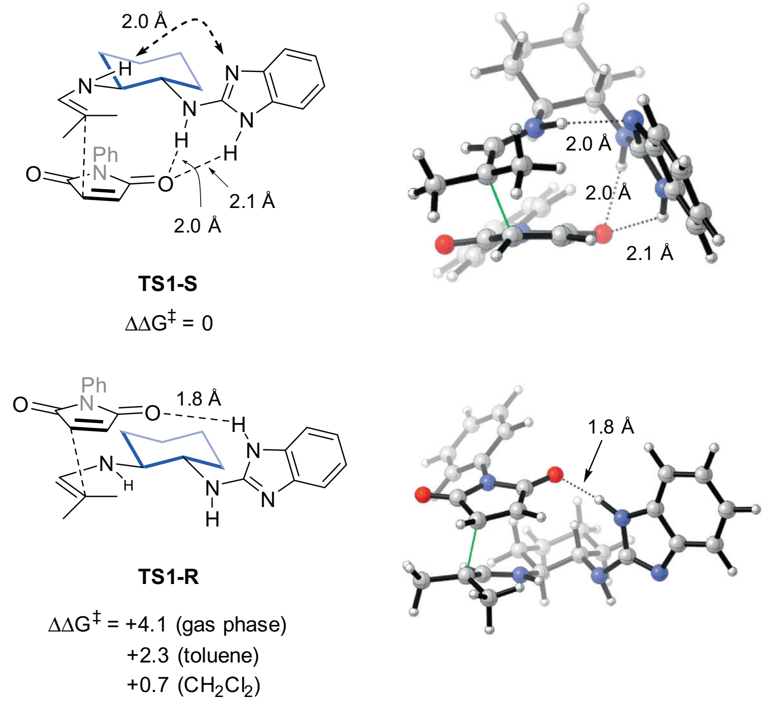

**Figure 2.** Most favoured transition states for the *pro-R* and *pro-S* attack to the maleimide. Free Gibbs energy values of **TS1-R** are relative to **TS1-S** and correspond to gas phase, toluene and $CH_2Cl_2$ models at M06-2X/6-311+G(d,p) level of theory.

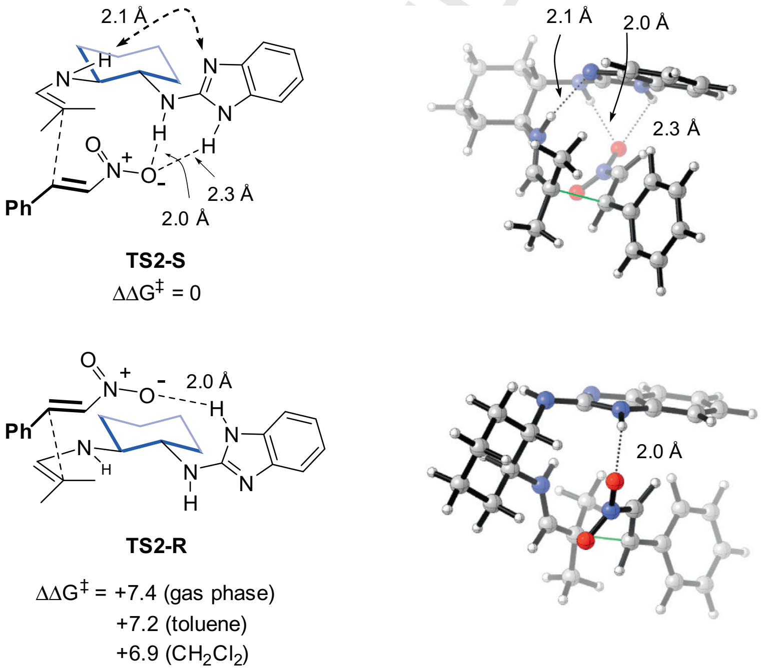

**Figure 3.** Most favoured transition states for the *pro-R* and *pro-S* attack to nitrostyrene. Free Gibbs energy values of **TS2-R** are relative to **TS2-S** and correspond to gas phase, toluene and $CH_2Cl_2$ models at M06-2X/6-311+G(d,p) level of theory.

experimental results, since (*S*) is the major enantiomer of the reaction, and the ee decreases as the polarity of the solvent increases.

## 3. Conclusions

Herein we have demonstrated the efficiency of the chiral primary amine benzimidazole **8** as a bifunctional organocatalyst for the enantioselective addition of aldehydes to nitroalkenes and maleimides. These processes took place efficiently in apolar organic solvents without additives. The enantioselection observed and the bifunctional character of this organocatalyst have been explained by DFT calculations, which show the significance of the H-bond network that the benzimidazole unit is able to form with the electrophiles. For *N*-phenyl maleimide **12a** and nitrostyrene **10a**, up to three H-bonds are formed when the reaction takes place through their *Re* face (pro-*S* transition state), while a maximum of

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a single H-bond is observed in the opposite face approach, leading to the minor experimental (*R*)-enantiomer. The decreasing enantioselectivity trend with the polarity of the solvent is related to the relative strength of the H-bonds in different polar media.

## 4. Experimental

### 4.1. Synthesis of γ-nitroaldehydes: general procedure

Q3 To a mixture of organocatalyst **8** (23 mg, 0.10 mmol), nitroalkene **10** (0.5 mmol) and isobutyraldehyde (93 μL, 2 mmol) was added dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for the time indicated in Table 2 (completion of the reaction was checked by TLC). Next, ethyl ether (30 mL) was added and the resulting suspension was filtered off over a pad of Celite. After solvent evaporation, the pure products **11** were obtained.[31] Enantiomeric excesses were determined by using analytical SFC with a chiral coated column (Phenomenex Lux 5u Cellulose-1, 210 nm, at 40 °C oven temperature, $CO_2$/MeOH).

### 4.2. Synthesis of succinimides; general procedure

A suspension of the organocatalyst **8** (18 mg, 0.075 mmol) and maleimides **12** (0.5 mmol) in PhMe (1 mL) was cooled for 5 min at 10 °C. Next, aldehyde **9** (3 mmol) was added and the mixture was stirred at the same temperature for 4 d (completion of the reaction was checked by TLC). Afterwards, aq 1 M HCl (30 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with $H_2O$ (2 × 15 mL) and 15 mL of brine, dried ($MgSO_4$), filtered and evaporated. The resulting crude was purified by flash chromatography to afford pure products **13**.[32] Enantiomeric excesses were determined by using analytical HPLC with chiral coated columns (Chiralcel OD-H or Chiralpak AD-H, 210 nm, hexane–isopropanol).[33]

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