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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 (pK_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.[8,15,24]

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.[8,25–28] 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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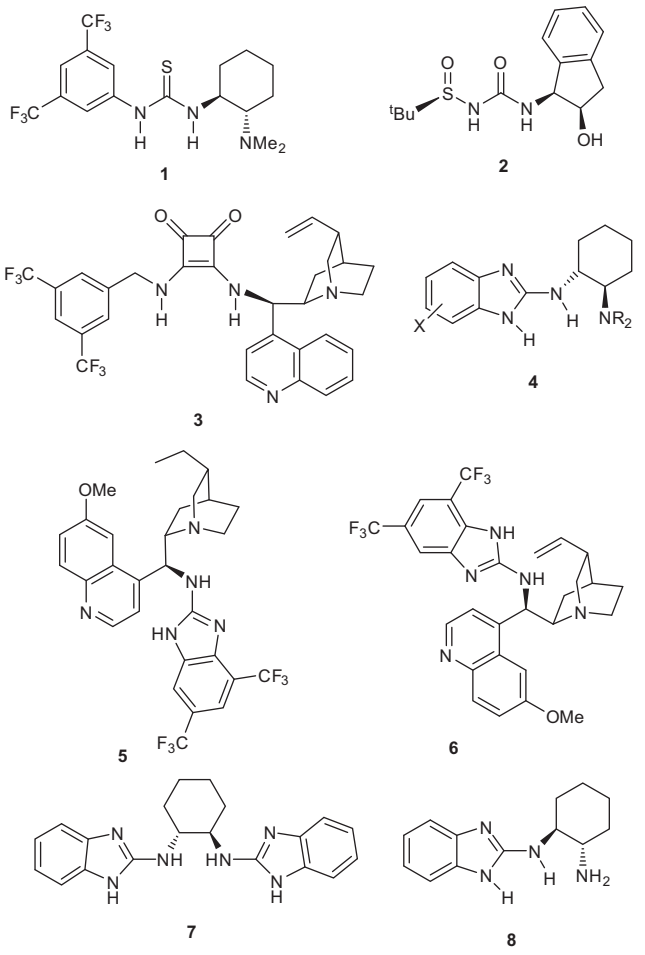
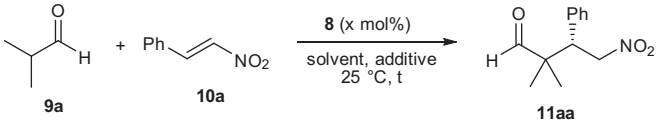


Figure 1. Selected chiral bifunctional organocatalysts.

nitro to an amino group. Initially, we studied the conjugate addition of isobutyraldehyde **9a** 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 **11aa** 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_3N as base accelerated the process while maintaining 90% ee, but the formation of by-products was observed (Table 1, entries 6 and 7). Therefore, the reaction conditions of entry 5 were chosen for studying the scope of the reaction.



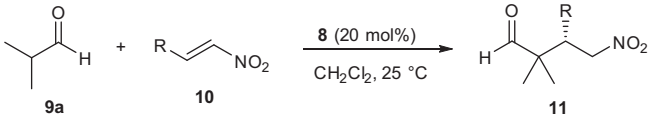
Scheme 1. Reaction condition studies for the addition of isobutyraldehyde to β-nitrostyrene.

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_3N[e]	30	99	90
7[d]	20	DCM	Et_3N[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 ^1H 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.[30]



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_6H_4	**10b**	4	**11ab**	52	81
3	2-BrC_6H_4	**10c**	3	**11ac**	94	74
4	3-BrC_6H_4	**10d**	3	**11ad**	99	76
5	4-BrC_6H_4	**10e**	3	**11ae**	99	88
6	4-FC_6H_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.[29] 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 solvent of choice using 15 mol % of catalyst **8** at 10 °C. Thus, the