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Enantioselective Synthesis of Succinimides by Michael Addition of 1,3-Dicarbonyl Compounds to Maleimides Catalyzed by a Chiral Bis(2-aminobenzimidazole) Organocatalyst

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A wide variety of chiral succinimides have been prepared in high yields and enantioselectivities by asymmetric conjugate addition of 1,3-dicarbonyl compounds to maleimides under very mild reaction conditions using a bifunctional benzimidazole-derived organocatalyst. Computational and NMR studies support the hydrogen-bonding activation role of the catalyst and the origin of the stereoselectivity of the process.

Introduction

Cyclic imides play a vital role in polymer, biological, medicinal, and synthetic chemistry.[1] In particular, succinimides are important building blocks that are often present in natural products and drugs such as phensuximide,[2] ethosuximide,[3] and andrimid[4] (Figure 1).

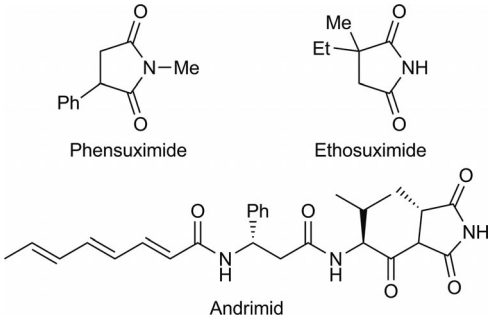

Figure 1. Succinimides in pharmaceuticals and drugs.

Chiral succinimides are valuable synthetic intermediates[5] and structural motifs in molecules with interesting biological activities.[4,6] Among the different methodologies available for the synthesis of chiral α-substituted succinimides,[7] the asymmetric conjugate addition to maleimides[8] has emerged as a powerful tool for the synthetic chemist, especially using chiral organocatalysts.[9] Thus, very high enantioselectivities have been obtained in the conjugate addition of ketones,[10] aldehydes,[11] and a wide variety of activated methylenes and methines,[12] to *N*-substituted maleimides. Regarding activated nucleophiles, 1,3-diketones,[12a] malonates,[12c] β-keto esters,[12a,12c,12d] anthrones,[12b,12g] oxindoles,[12f] α-cyanoacetates,[12j,12k] α-nitroacetates,[12l] α-isocyanoacetates,[12m] azlactones,[12i] pyrazolones,[12n] and oxazolones,[12o] have been successfully used as Michel donors, typically employing bifunctional chiral Brønsted base/hydrogen-bonding organocatalysts (Figure 2).[9f]

Very recently, the utility of chiral 2-aminobenzimidazoles as organocatalysts for the asymmetric conjugate addition to nitroolefins has been disclosed by our group[13] and others,[14] which benefits from 2-aminobenzimidazole's characteristic dual hydrogen-bonding catalysis.[15] Thus, catalyst **5b** (Figure 2), in which the distance between hydrogen atoms H_a and H_b is between the reported distances for the highly enantioselective thiourea[16] and squarimide-derived organocatalysts,[17] is a very active and general catalyst for the enantioselective conjugate addition of malonates, β-keto esters, and 1,3-diketones to a wide range of conjugated nitroalkanes in the presence of trifluoroacetic acid (TFA) as cocatalyst.[13]

Regarding the addition to maleimides, we have recently demonstrated that the recyclable chiral 2-aminobenzimidazole catalyst **5f** efficiently catalyzes the direct conjugate addition of different 1,3-dicarbonyl compounds to maleimides to give the corresponding chiral (*S*)-succinimides with very high enantiocontrol.[18] For this process, we tentatively proposed a transition state model in which the benzimidazole-derived organocatalyst **5f** carried out a bifunctional activation of the nucleophile and the electrophile.[18]

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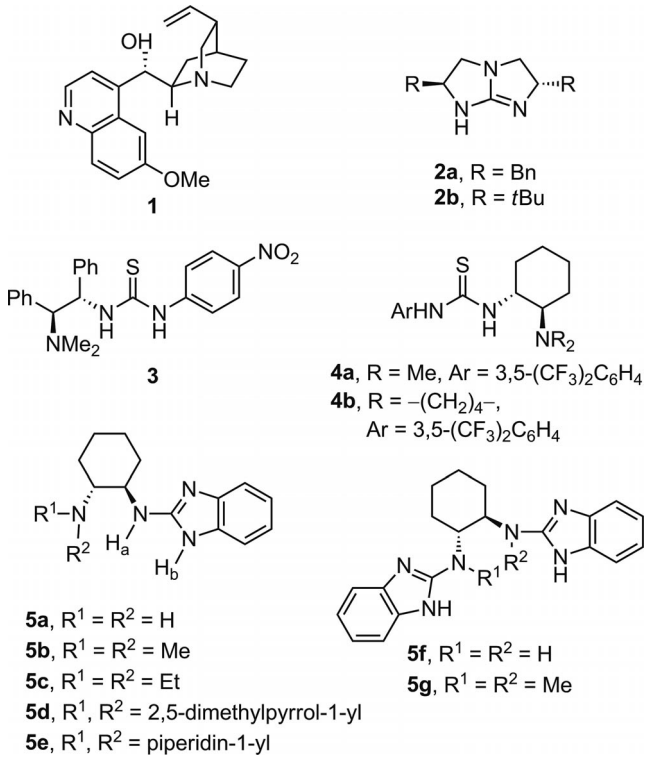


Figure 2. Chiral bifunctional Brønsted base/hydrogen-bonding organocatalysts.

Herein, we report the results of a full study on this reaction, including detailed NMR mechanistic investigations as well as DFT calculations to elucidate the catalytic active species and the H-bond network between catalyst, nucleophile and maleimide responsible for the observed reactivity and enantioselectivity.

Results and Discussion

The synthesis of catalysts **5a**–**e** has already been described[18a] and involves, as a common initial step, solvent-free aromatic nucleophilic substitution of (1*R*,2*R*)-1,2-diaminocyclohexane to 2-chlorobenzimidazole followed by derivatization of the primary amine. C_2-symmetric catalysts **5f**[18a] and **5g** were prepared by a twofold aromatic substitution with 2-chlorobenzimidazole and 1-methyl-2-chlorobenzimidazole, respectively.

In our previous optimization study,[18,19] we demonstrated the superiority of dimeric catalyst **5f** over benzimidazole-derived catalysts **5a**–**e** in the conjugate addition of a range of 1,3-dicarbonyl compounds to maleimides. For instance, the conjugate addition of acetylacetone (0.3 mmol) to maleimide (0.15 mmol) catalyzed by **5f** (10 mol-%) in the presence of TFA (10 mol-%) as cocatalyst and toluene as solvent, led to the formation of succinimide **6a** in an excellent 94% yield and *ee* = 97% (Figure 3). We also showed that the use of hydrogen-bond-forming solvents such as water or methanol, led to a drastic decrease in stereoselectivity.[18] Accordingly, and to confirm the hydrogen-bonding activation mode of catalyst **5f** in this reaction, we initially studied the aptitude of catalyst **5g** (Figure 2, $R^1 = R^2$ = Me) in the process under the previously optimized reaction conditions. As depicted in Figure 3, only 11% yield of succinimide **6a** was obtained in a lower *ee* value (48%), which confirms the importance of the presence of the secondary amine for optimal hydrogen-bonding catalyst performance.

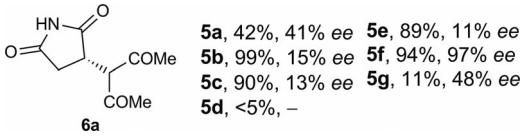
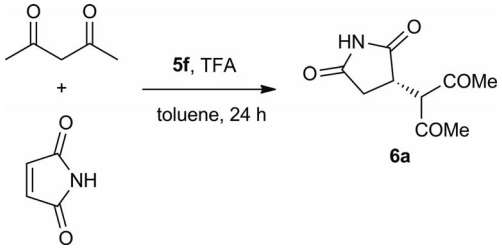


Figure 3. Conjugate addition of acetylacetone to maleimide catalyzed by **5f** and **5g**.

Further optimization of the reaction conditions employing organocatalyst **5f** (Table 1) showed a slight decrease in the enantioselectivity of the process when the conjugate addition was performed at 0 °C, affording **6a** in a 94% *ee* (Table 1, entry 2). With respect to the role of the acid cocatalyst TFA in the reaction, a significant decrease in the enantioselectivity of the reaction (*ee* 51%) was detected in the absence of TFA (Table 1, entry 3). This result clearly evidenced the greater ability of the protonated catalyst for hydrogen-bonding activation. Notably, complete deactivation of the catalyst was observed when a twofold excess (20 mol-%) of cocatalyst was used (Table 1, entry 4). Furthermore, a dependence of the enantioselectivity of the process on catalyst loading was observed (Table 1, entries 5 and 6). Finally, further optimization of catalyst loading revealed that only 1 mol-% of **5f**/TFA was able to afford a highly efficient reaction, although the enantioselectivity of the process slightly decreased to 93% (Table 1, entry 7).

Table 1. Enantioselective conjugate addition of acetylacetone to maleimide catalyzed by chiral 2-aminobenzimidazole catalyst **5f**.[a]

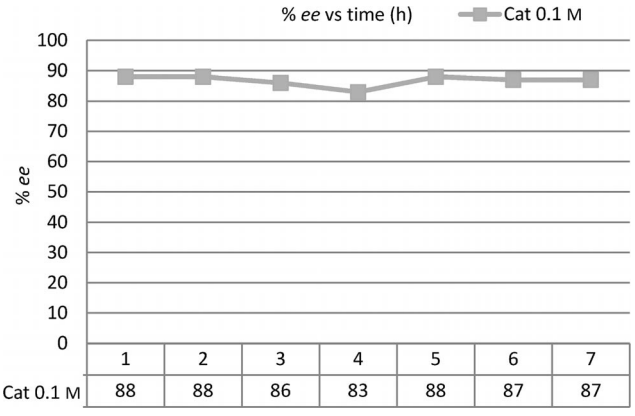


Entry	**5f** [mol-%]	TFA [mol-%]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	10	10	30	94	97
2	10	10	0	95	94
3	10	–	30	94	51
4	10	20	30	<5	–
5	30	30	30	85	87
6	100	100	30	81	83
7	1	1	30	96	93

[a] *Reaction conditions:* acetylacetone (0.3 mmol), maleimide (0.15 mmol), **5f** (10 mol-%, 0.015 mmol, 0.05 M), TFA (10 mol-%, 0.015 mmol), solvent (0.3 mL), room temp., 24 h. [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC [OD-H; hexane/*i*PrOH, 85:15; 1 mL/min].

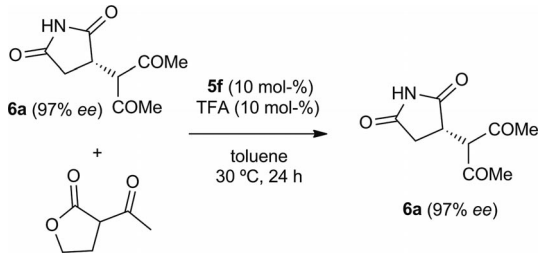
At high catalyst concentrations (Table 1, entries 5 and 6), product racemization due to thermodynamic control of the

process was discharged, since the enantioselectivity of the reaction remained constant within the course of the experiment when a 0.1 M catalyst concentration was used in the conjugate addition (Figure 4). This was also confirmed when succinimide **6a** (*ee* = 97 %) was submitted to the optimal reaction conditions [**5f** (10 mol-%), TFA (10 mol-%), toluene, 30 °C] in the presence of a different nucleophile such as 3-acetyldihydrofuran-2(3*H*)-one; under these conditions, compound **6a** was only detected in the crude reaction mixture (TLC and ^{1}H NMR analyses) with the same optical purity (Scheme 1).



	1	2	3	4	5	6	7
Cat 0.1 M	88	88	86	83	88	87	87

Figure 4. The *ee* vs. time for the conjugate addition of acetylacetone to maleimide catalyzed by **5f**/TFA.



Scheme 1. Racemization study with **6a**.

Additional studies on catalyst concentration were performed with the model reaction. The *ee* values obtained at different catalyst concentrations (Table 2) were fairly consistent with the diffusion coefficients (*D*) of **5f**/TFA, strongly indicating that the degree of hydrogen-bonded self-association of bifunctional organocatalyst **5f**/TFA in solution plays a crucial role in determining the enantioselectivity of the process.[20]

Table 2. Diffusion coefficients of **5f**/TFA (10 mol-%) at different concentrations vs. enantioselectivities in the asymmetric addition of acetylacetone to maleimide.

Entry	**5f**/TFA conc. (molar)	D/D^{Tol}[a]	*ee* [%][b]
1	0.01	0.33	96
2	0.05	0.31	97
3	0.1	0.20	88

[a] Diffusion coefficients *D* (10^{-10} m^2 s^{-1}) at room temperature for **5f**/TFA corrected with respect to the solvent ([D_8]toluene) at different molar (M) concentrations. [b] Determined by chiral HPLC [OD-H; hexane/*i*PrOH, 85:15; 1 mL/min].

Under the optimized reaction conditions (Table 1, entry 1), the generality of the conjugate addition reaction with respect to the nucleophile and the maleimide acceptor was then investigated. As depicted in Figure 5, the conjugate addition of acetylacetone to different *N*-alkyl- and *N*-aryl maleimides afforded the corresponding 1,4-adducts **6b**–**g** in good yields and excellent enantioselectivities. All the studied substrates afforded similar levels of *ee* to those with maleimide (*ee* = 95–97 %). The **5f**-catalyzed conjugate addition reaction was also applicable to α-substituted 3-methylpentane-2,4-dione, which afforded, after addition to *N*-phenylmaleimide, compound **6h** in 50% yield and *ee* = 91 %. Regarding non-symmetrical β-diketones, the addition of 1-phenylbutane-1,3-dione to maleimide afforded compound **6i** in 97% yield as a 58:42 mixture of diastereomers, both of which were obtained with excellent enantioselectivity. Likewise, addition of the cyclic 2-acetylcyclopentanone to *N*-phenylmaleimide afforded **6j** in 93% yield as a 97:3 mixture of diastereomers, both of which were also obtained with very high enantioselectivity (Figure 5).

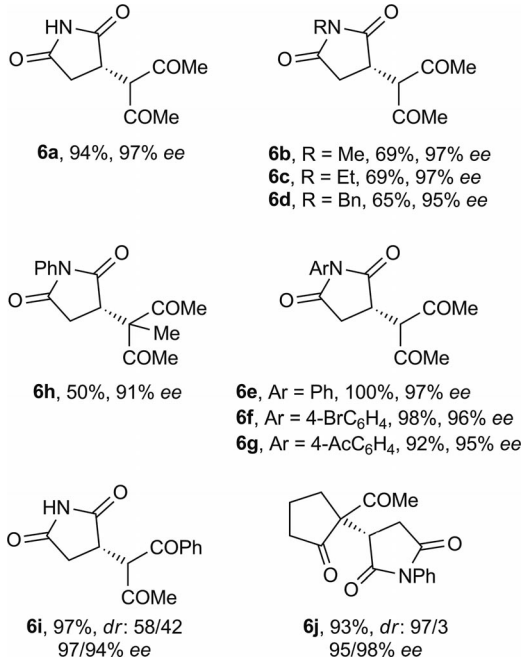


Figure 5. Conjugate addition of 1,3-diketones to maleimides catalyzed by **5f**.

The optimized catalytic system also proved to be effective for β-keto esters, giving the expected products in high yields, moderate to good diastereoselectivity, and very high levels of enantioselectivity (Figure 6). The synthesis of compounds **6j**–**n** was especially interesting because the results demonstrated the applicability of the catalytic system for the synthesis of adjacent quaternary/tertiary stereogenic centers with excellent enantioselectivities.

We finished investigating the nucleophile scope with malonates. Interestingly, catalyst **5f** performed better in the absence of TFA for these nucleophiles. When dimethyl malonate reacted under the optimized reaction conditions with maleimide, compound **6o** was obtained in 81% *ee* but in

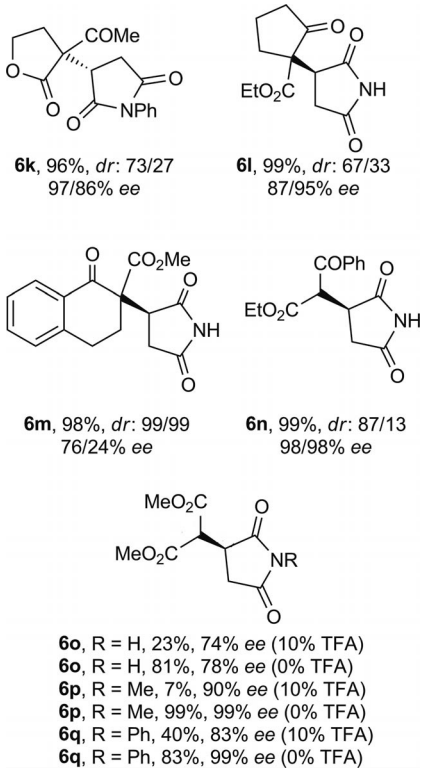


Figure 6. Conjugate addition of β-keto esters and dimethyl malonate to maleimides catalyzed by **5f**.

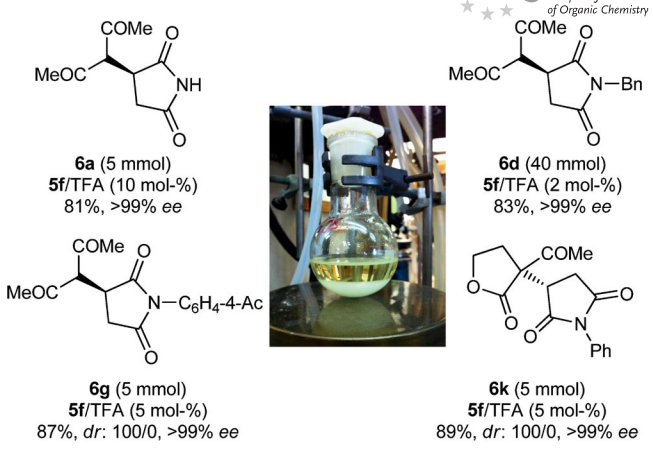
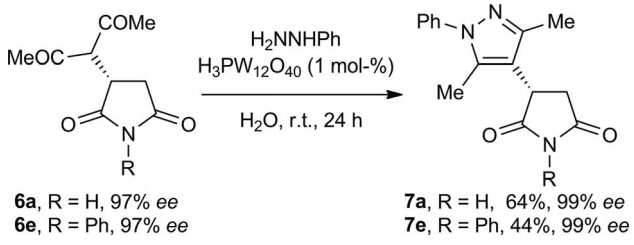


Figure 7. Gram-scale synthesis of chiral succinimides **6**.



Scheme 2. Synthesis of chiral pyrazol-derived succinimides **7**.

very low isolated yield (23%; Figure 6). This was probably due to the lower acidity of the nucleophile compared with 1,3-diketones and β-keto esters, thus requiring a catalyst with a stronger base character. This was confirmed by performing the reaction in the absence of TFA, which afforded compound **6o** in *ee* = 78 % and with a higher isolated yield (74%). With respect to yield, a similar tendency was observed in the reaction with *N*-methyl- and *N*-phenylmaleimides, which afforded compounds **6p** and **6q**, in *ee* = 99 % and high yields in the absence of TFA (Figure 6).

The synthetic utility of the catalytic methodology was confirmed by gram-scale experiments (5–20 mmol of Michael acceptor) for the synthesis of succinimides **6a**, **6d**, **6g**, and **6k**, which were obtained as optically pure compounds (*ee* >99 %) in high yields after filtration from the crude reaction mixture (Figure 7).[21]

The functional characteristics of the synthesized chiral 1,3-dicarbonyl compounds **6** was used for the synthesis of optically active pyrazol-derived succinimides.[22] Thus, compounds **6a** (*ee* = 97 %) and **6e** (*ee* = 97 %) were transformed into succinimides **7a** (*ee* = 99 %) and **7e** (*ee* = 99 %), respectively, by treatment with *N*-phenylhydrazine in the presence of phosphotungstic acid as catalyst (1 mol-%) in water at room temperature (Scheme 2).

DFT computational studies[23] were conducted with the aim of detailing the H-bond network between catalyst, nucleophile, and maleimide responsible for the observed reactivity/enantioselectivity. It was assumed that the reaction is initiated by deprotonation of the pronuclephile (2,5-pentadione) by the aminobenzimidazole catalyst to form an enolate/protonated catalyst binary complex (Figure 8). Further hydrogen bonding with maleimide renders a ternary complex that evolves into the final products through the corresponding transition state. We found that the minimum Gibbs free energy along the reaction coordinate always corresponded to the sum of the energies of the free maleimide and the binary complex, which was thus taken as the ground $G = 0$ energy level.

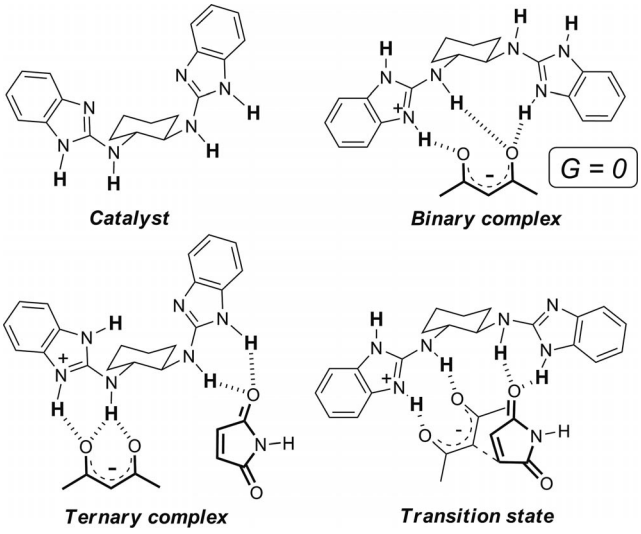


Figure 8. Main structures proposed along the reaction coordinate.

Three possible mechanistic scenarios were considered: (1) in the absence of acid, the base catalyst deprotonates

and binds the nucleophile (**A**; Figure 9). Four NH groups are available for Nu/maleimide activation, arranged in a flexible and open reactive site; (2) when partial protonation (1 equiv. of acid) of the catalyst is considered, the neutral portion of the catalyst deprotonates the nucleophile, leading to structure **B**, which possesses a tighter reactive space decorated with three or four NH groups for reagent activation; (3) further protonation of the catalyst with a second molecule of acid would cancel the basicity of the catalyst, and only the enol form of the nucleophile could act as a nucleophile, as in structure **C**, lowering its reactivity.

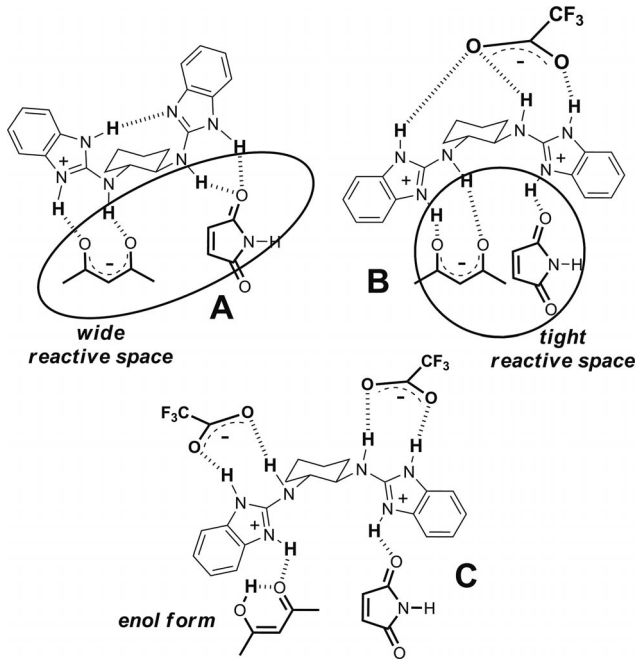


Figure 9. Computed mechanistic alternatives **A**, **B**, and **C**.

After an extensive conformational search, the calculated energies for the optimal transition states in model **A** predict a high reactivity and a moderate selectivity [1.7 kcal/mol energy difference between $\mathbf{TS}_{A2}(S)$ and $\mathbf{TS}_{A2}(R)$; Figure 10], which is in fair agreement with the experimental results in the absence of acid (94% yield, *ee* = 51 %; Table 1, entry 4). The privileged transition structures for each enantiomer [$\mathbf{TS}_{A2}(S)$ and $\mathbf{TS}_{A2}(R)$] bear an intramolecular H bond between the protonated and the neutral benzimidazole portions of the catalyst. As a consequence, a quite open reaction space is formed in which the remaining four NH bonds are involved in a low-selective binding of the nucleophile and electrophile, see also the 3D picture for $\mathbf{TS}_{A2}(S)$ in Figure 10.

In contrast, the inclusion of one molecule of trifluoroacetic acid might produce a fast protonation of the catalyst (model **B**). The CF_3COO^- anion is able to bind the two imidazole units, eliminating the possibility of an intramolecular H-bonding between them. Optimal transition structures were found in which three of the NH groups are exposed to the trifluoroacetate anion and solvent. In this structure, the activation of the maleimide is achieved by a single NH bond, and two other NH groups bind the nucleophile[24] in a tight, concave reaction site. This effect increases the energy difference between the diastereomeric forms $\mathbf{TS}_{B(S)}$ and $\mathbf{TS}_{B(R)}$ (24.7 and 29.3 kcal/mol respectively), predicting a high reactivity and very good enantioselectivity, as experimentally found (94% yield, *ee* = 97 %; Table 1, entry 1).

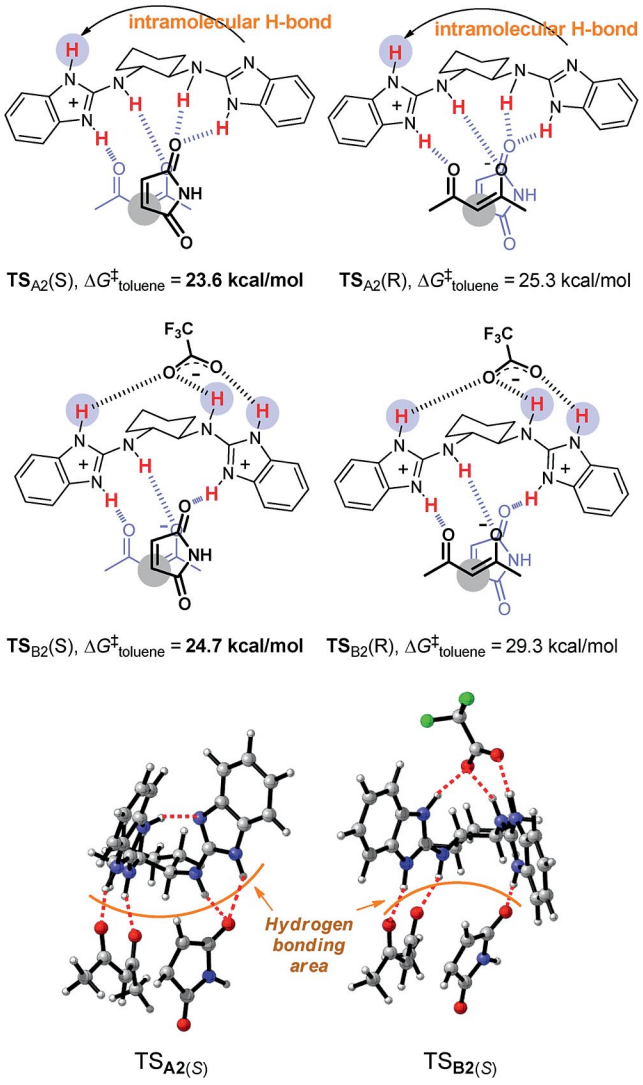


Figure 10. Main transition structures computed in models **A** and **B**.

As mentioned previously, the inclusion of a second molecule of TFA acid in the calculation has a deleterious effect on the reactivity of the catalyst (<5% conversion; Table 1, entry 4). We also offer an explanation for this effect: The double protonation of the catalyst cancels its basic character and prevents deprotonation of the nucleophile. Only the enol form of the nucleophile is available for the attack on the maleimide, and both enol and maleimide appear to be single bonded to the catalyst, as in model **C**. In this unfavorable scenario, it is not surprising to find a high computed activation energy (46.3 kcal/mol).

Finally, the distinct outcome shown by the malonates as nucleophiles might be related to the lower acidity of dimethyl malonate vs. acetylacetone [pK_a values in dimethyl

sulfoxide (DMSO) are 15.7 and 13.3, respectively]. In fact, deprotonation of dimethyl malonate by the TFA-protonated catalyst (mechanism B) is computed to be a disfavored process (Figure 11). Thus, reactions of malonate either in the presence or absence of TFA proceed through mechanism **A**, with a computed *ee* = 86 %, in fair agreement with the experimental results (*ee* = 74–78 %; Figure 6), but at different rates, since the acid exerts a negative effect by reducing the available amount of the necessary free imidazole.

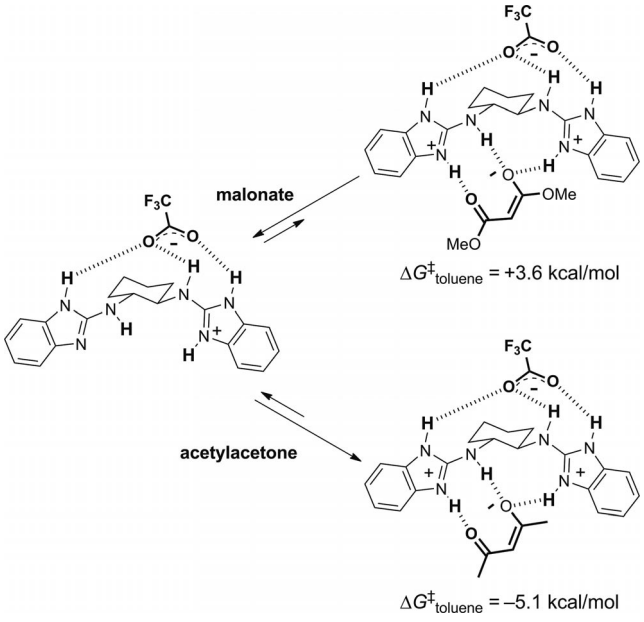


Figure 11. Different binding properties of the computed nucleophiles.

Conclusion

We have designed a chiral 2-aminobenzimidazole catalyst **5f** that catalyzes the direct conjugate addition of a range of 1,3-dicarbonyl compounds to maleimide and *N*-substituted maleimides to give the corresponding Michael adducts with very high enantiocontrol. The proposed hydrogen-bonding activation role of the catalyst and the origin of the stereoselectivity of the process have been confirmed by DFT calculations. Further studies are in progress to explore the scope of organocatalyst **5f** in other catalytic asymmetric reactions.

Experimental Section

Typical Experimental Procedure: To a stirred solution of catalyst **5f** (5.2 mg, 0.015 mmol, 10 mol-%) and maleimide (14.6 mg, 0.15 mmol) in toluene (185 μL), a 1 % (v/v) TFA solution in toluene (115 μL, 0.015 mmol) and acetylacetone (30.8 μL, 0.3 mmol) were added. The reaction mixture was stirred at 30 °C for 24 h, then the solvent was evaporated under reduced pressure to give the crude product that was purified by flash chromatography (EtOAc/hexane) to afford pure **6a** (27.8 mg, 94% yield). The selectivity of the reaction was determined by chiral HPLC before purification to be *ee* = 97 % (Chiralcel OD-H; 1 mL/min; hexane/*i*PrOH, 85:15; λ = 210 nm): t_R = 28.5, 33.4 min.

Supporting Information (see footnote on the first page of this article): Synthesis of new organocatalysts, general experimental procedures, physical and spectroscopic data for compounds **6** and **7**, computational data as well as HPLC and NMR spectra.

Acknowledgments

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