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Chiral 2-Aminobenzimidazoles as Recoverable Organocatalysts for the Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes†

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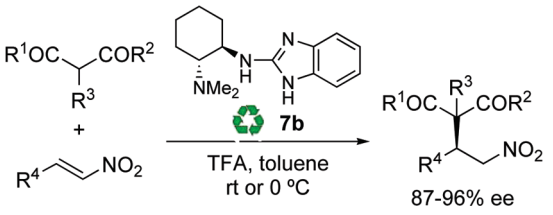

Chiral *trans*-cyclohexanediamine-benzimidazole organocatalysts promote the conjugate addition of a wide variety of 1,3-dicarbonyl compounds such as malonates, ketoesters, and 1,3-diketones to nitroolefins in the presence of TFA as cocatalyst in toluene as solvent at rt or 0 °C. The Michael adducts are obtained in high yield and enantioselectivity, using the chiral 2-aminobenzimidazole **7b** as hydrogen-bond-mediated chiral organocatalyst. This catalyst can be recovered by acid−base extractive workup in 94% yield. The proposed bifunctional Brønsted acid−base activation role of the catalyst and the origin of the stereoselectivity of the process is in agreement with DFT calculations. According to these calculations, the protonated tertiary amine from the cyclohexanediamine backbond activates the nitroolefin, while the benzimidazole unit activates the 1,3-dicarbonyl nucleophile.

Introduction

Asymmetric organocatalysis[1] is a powerful and environmentally friendly strategy for the stereoselective synthesis of highly valuable chiral building blocks. The development of a wide variety of new organocatalysts efficiently applied to numerous asymmetric transformations has been responsible for the impressive progress exhibited in the field of asymmetric organocatalysis during recent years. Particularly important has been the progress observed for enantioselective conjugate addition reactions.[2] The addition of 1,3-dicarbonyl compounds to nitroolefins provides access to synthetically useful enantioenriched nitroalkanes[3] under mild conditions. High yields and enantioselectivities have been obtained for the conjugate addition of activated methylenes (such as 1,3-diketones)[4] as well as β-ketoesters and derivatives[5] to nitrostyrenes; cinchona alkaloid derivatives represent the most commonly used chiral scaffolds. Few organocatalysts, such

† Dedicated to Josep Font on occasion of his 70th birthday.

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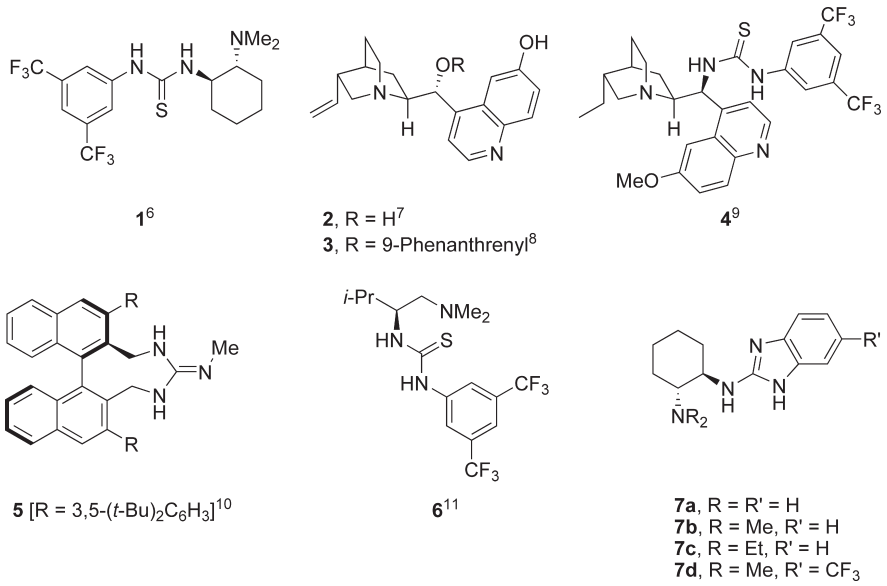

FIGURE 1. Hydrogen bond donor catalysts.

as **1**−**6** (Figure 1),[6−11] have been shown to efficiently promote the addition of malonate esters to nitroolefins with high enantioselectivity at typical catalyst loadings between 2 and 10 mol %. Essential to the overwhelming success of these catalysts is their ability to activate reactants through hydrogen bond interactions[12] producing well-defined orientation required for the transition state of the process.

Benzimidazole is a ubiquitous element in a wide variety of biologically relevant natural products[13] whose derivatives display a key role in pharmaceutical chemistry and in many biological processes.[14] In addition, benzimidazole derivatives are widely utilized in synthetic organic chemistry as the basis for ionic liquids[15] and as precursors for *N*-heterocyclic carbenes.[16] The basic character of benzimidazole derivatives [pK_a ($BzImH_2^+$) = 5.4],[17] their ability to act as recognition elements through hydrogen bond interactions,[13] and their high degree of stability and facile synthesis[13a,b] make these compounds an attractive alternative to thioureas and guanidines as organocatalysts. However, enantioselective organocatalysis using chiral benzimidazoles has enjoyed limited success so far.[18] Here, as part of our research program on the organocatalytic asymmetric conjugate addition to nitroalkenes,[19] we describe a new family of hydrogen bonding catalysts for the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins based on the benzimidazole moiety, which features the introduction of a rigid chiral *trans*-cyclohexanediamine scaffold **7** (Figure 1).

Results and Discussion

The synthesis of catalyst **7** started with a solvent-free aromatic nucleophilic substitution of (1*R*,2*R*)-1,2-diaminocyclohexane to 2-chlorobenzimidazole or 2-chloro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (obtained from 4-trifluoromethyl-1,2-phenylenediamine by urea formation with 1,1′-carbonyldiimidazole and further chlorination with $POCl_3$),[20] in the presence of triethylamine as base, yielding primary amine derivatives **7a** and **7e**, in 65% and 56% yields, respectively (Scheme 1). Reductive amination of formaldehyde in formic acid at 120 °C with **7a** and **7e** afforded organocatalysts **7b** and **7d** in 30% and 42% yield, respectively, after purification by flash chromatography and recrystallization (Scheme 1). Catalyst **7c** was prepared from **7a**

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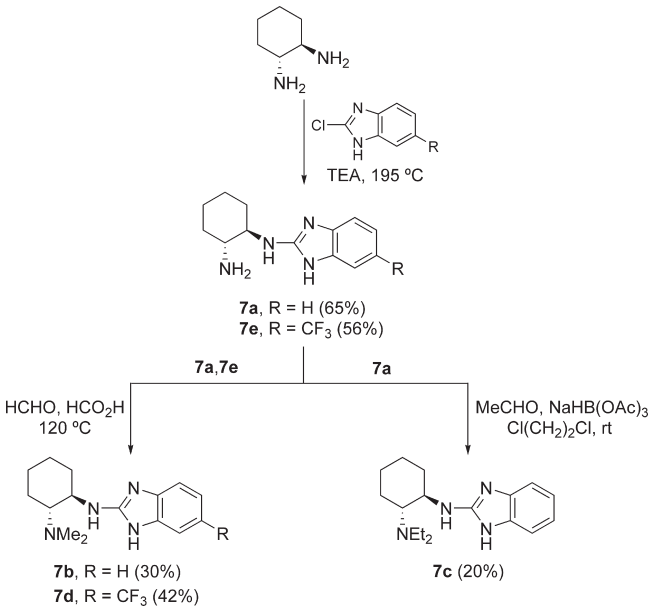
SCHEME 1. Synthesis of Organocatalysts 7



in 20% yield by reductive amination of acetaldehyde in the presence of $NaHB(OAc)_3$ (Scheme 1).

Examination of crystallographic[21] and computational data (see Supporting Information) on catalyst **7b** showed that the two H atoms of the aminobenzimidazole moiety are positioned 2.41 and 2.61 Å apart, respectively (Figure 2). The observed distance is in between the reported distances for the highly active thiourea-[6] and the recently described squaramide-derived organocatalysts[4e] (Figure 2), which should render benzimidazole-derived catalysts **7** efficient dual hydrogen-bonding activating systems. Therefore, the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins seemed to be an ideal test for the potential activity and selectivity of novel benzimidazole-derived catalysts **7**.

2-Aminobenzimidazoles **7** (10 mol %) were screened as catalysts in the diethyl malonate addition (2 equiv) to (*E*)-*β*-nitrostyrene in toluene at rt (Table 1). All benzimidazole-derived compounds **7** showed high catalytic efficiency, and complete conjugate addition was observed after 24 h (Table 1, entries 1−4). With respect to selectivity, organocatalysts **7b** and **7d** exhibited superior enantioselectivity and gave complete conversion of (*E*)-*β*-nitrostyrene into nitroalkane **8a** with 78% and 79% ee, respectively (Table 1, entries 1 and 4). Further solvent studies with other apolar, polar aprotic, and polar protic solvents were performed with the more accessible catalyst **7b**, indicating toluene to be the optimal solvent for the reaction (Table 1, entries 5−15). The effect of different acids as additives in the process was also investigated.[22] It was found that 2-aminobenzimidazole **7b** (10 mol %) in combination with TFA (10 mol %) exhibited high catalytic activity for the asymmetric conjugate addition in toluene at rt, affording **8a** in 74% yield with a promising 92% ee after 36 h (Table 1, entry 16). No further improvement could be achieved when the reaction was carried out in the presence of other acid additives; this afforded lower yields and/or enantioselectivities (see Supporting Information). In the presence of TFA as cocatalyst and reduced temperature (0 °C), the enantioselectivity decreased to 74% ee with no noticeable effect on conversion (Table 1, entry 17). Using 5 mol % of catalyst, high enantioselectively (93% ee) was still achieved albeit in a modest 40% yield after 36 h (Table 1, entry 18). At this point, the activity of catalyst **7d** was again tested under the optimal conditions (rt, TFA (10 mol %)) affording **8a** in lower conversion and similar enantioselectivity to **7b** (Table 1, compare entries 16 and 19).

We also studied the recyclability of benzimidazole-derived organocatalyst **7b** and were pleased to demonstrate that **7b** could be easily recovered (94%) from the reaction mixture after extractive acid/base workup with no loss of optical activity.

Under the optimized reaction conditions, the scope of this 2-aminobenzimidazole-catalyzed conjugate addition was examined next (Table 2). The size of the ester group of the malonate had a marginal effect on the selectivity of the Michael adducts (Table 2, entries 1−3) with the exception of the largest *tert*-butyl ester, which did not react (Table 2, entry 4). Different nitroolefins were allowed to react with diethyl malonate giving products **8e**−**8j** in high yield and good enantioselectivities (Table 2, entries 5−10). The reactions proceeded smoothly at rt whether neutral (Table 2, entry 1), electron-withdrawing (Table 2, entries 5−7), or electron-donating (Table 2, entries 8 and 9) groups were present in the aromatic rings, giving the desired adducts **8** in excellent yields and good enantioselectivities (88−94%). The reaction of 2-thienyl-substituted nitroolefin gave **8j** in excellent yield and good enantioselectivity (Table 2, entry 10).

The efficiency of **7b** was further evaluated with different types of 1,3-dicarbonyl compounds and nitroalkenes (Table 3). Acetylacetone proved to be a superior nucleophile: after conjugate addition to *β*-nitrostyrene, product **8k** was obtained in excellent 96% ee after only 7 h employing only 1 equiv of nucleophile and 5 mol % of **7b**/TFA (Table 3, entry 1). This result is similar in terms of yield and enantioselectivity to that obtained with the most efficient organocatalysts reported so far.[4a,c−e,10] Catalyst **7b**/TFA also showed high catalytic efficiency for the reaction of acetylacetone with challenging aliphatic nitroalkenes such as 1-nitro-4-phenylbut-2-ene affording compound **8l** in a 93% yield and 86% ee (Table 3, entry 2). The reaction between the acyclic, nonsymmetrical 1-phenyl-1,3-butanedione and *β*-nitrostyrene proceeded with low diastereoselectivity, as usually encountered for the most selective reported organocatalysts,[4e,6,7,10] to afford ca. a 1/1 diastereomeric mixture of compound **8m** with a 92% ee (Table 3, entry 3). In this case, the diastereomeric mixture could be separated by recrystallization in ether, which allowed us to assign, via X-ray analysis (see Supporting Information),[23] the absolute configuration for the stereocenter of the nucleophile in the major diastereomer to be *S*. Also, after recrystallization the ee of the (*S*,*R*)-diastereomer was improved to 99% (Table 3, entry 3).

In the case of the conjugate addition of acyclic *β*-ketoesters such as ethyl 3-oxobutenoate to *β*-nitrostyrene catalyzed by **7b**, the ester moiety seemed to have little influence on

(21) Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre (CCDC 680867).

(22) For a review about protonated chiral organocatalysts, see: Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763.

(23) Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre (CCDC 723644).

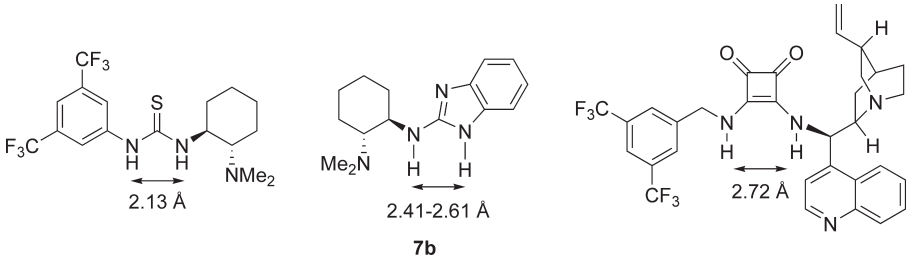
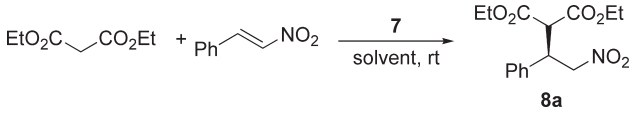


FIGURE 2. Hydrogen bond distances in hydrogen donor catalysts.

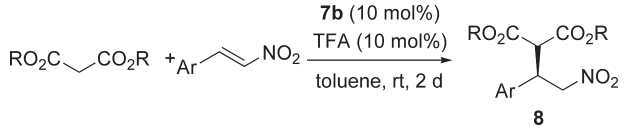
TABLE 1. Screening of Reaction Conditions for the Conjugate Addition of Diethyl Malonate to β-Nitrostyrene Catalyzed by 7[a]



entry	7 (mol %)	solvent	cocatalyst (mol %)	*t* (h)	yield (%)[b]	ee (%)[c]
1	**7a** (10)	toluene		24	99	60
2	**7b** (10)	toluene		24	99	78
3	**7c** (10)	toluene		24	99	66
4	**7d** (10)	toluene		24	99	79
5	**7b** (10)	benzene		24	99	72
6	**7b** (10)	xylenes		24	99	72
7	**7b** (10)	pentane		24	99	67
8	**7b** (10)	Et_2O		24	99	64
9	**7b** (10)	THF		24	99	30
10	**7b** (10)	CH_2Cl_2		24	99	70
11	**7b** (10)	NMP		24	99	28
12	**7b** (10)	DMSO		24	99	2
13	**7b** (10)	MeOH		24	99	36
14	**7b** (10)	H_2O		24	99	56
15	**7b** (10)	neat		36	74	52
16	**7b** (10)	toluene	TFA (10)	36	74	92
17	**7b** (10)[d]	toluene	TFA (10)	36	99	74
18	**7b** (5)	toluene	TFA (5)	36	40	93
19	**7d** (10)	toluene	TFA (10)	36	67	91

[a]The reaction was performed with β-nitrostyrene (1.16 mmol), diethyl malonate (2.32 mmol), catalyst **7** (0.116 mmol), and TFA (0.116 mmol) at rt in the corresponding solvent (2.3 mL) at the time indicated. [b]Yield of the crude product determined by ^{1}HNMR. [c]Determined by chiral HPLC analysis (Chiralpack AD, hexane/*i*-PrOH 90/10) of the crude reaction mixture. [d]The reaction was performed at 0 °C.

TABLE 2. Conjugate Addition of Dialkyl Malonates with Nitroalkenes Catalyzed by 7b[a]

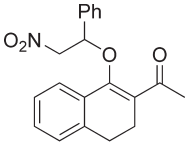


entry	R	Ar	no.	yield (%)[b]	ee (%)[c]
1	Et	Ph	**8a**	97	92
2	Me	Ph	**8b**	95	89
3	*i*-Pr	Ph	**8c**	42	89
4	*t*-Bu	Ph	**8d**	< 5	nd
5	Et	4-ClC_6H_4	**8e**	95	88
6	Et	2-$CF_3C_6H_4$	**8f**	97	90
7	Et	2,4-$(Cl)_2C_6H_3$	**8g**	96	94
8	Et	4-MeC_6H_4	**8h**	98	88
9	Et	4-$MeOC_6H_4$	**8i**	98	88
10	Et	2-thienyl	**8j**	98	87

[a]The reaction was performed with the nitroolefin (1.16 mmol), dialkyl malonate (2.32 mmol), catalyst **7b** (0.116 mmol), and TFA (0.116 mmol) at rt in toluene (2.3 mL) for 2 d. [b]Isolated yield after flash chromatography. [c]Determined by chiral HPLC analysis on the crude reaction mixture (see Supporting Information).

the selectivity of the process since very low diastereoselectivity was observed again, with good enantioselectivities for both isomers of **8n** (90% and 88% ee, Table 3, entry 4). Acyclic β-ketoesters seem to be challenging substrates since only catalysts **1**[6] and **5**[10] (Figure 1) have so far been reported to efficiently promote the conjugate addition of this type of activated methylenes to nitrostyrenes. Moreover, these processes have been found to be non-diastereoselective.

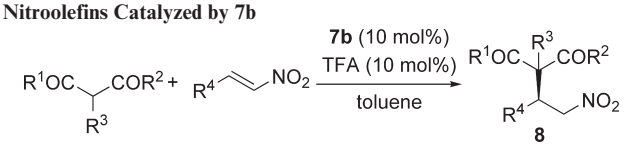
Conversely, α-substituted dicarbonyl compounds afforded, in general, good yields and enantioselectivities at the β-position to the nitro group for the quaternary stereocenter-containing derivatives **8o−q** (Table 3, entries 5−7).[24] The observed diastereoselectivities were usually higher than those observed for the acyclic nucleophiles (compare entries 3 and 4 with 5−7). Thus, compound **8o** was isolated after 24 h at rt in a 42% yield as a 84/16 mixture of diastereomers with 85% ee being observed for the major one (Table 3, entry 5). Again, the enantiomeric excess could be improved by recrystallization in ether to 98%. The low yield obtained in this particular reaction was due to the formation of compound **9** from conjugate addition of the enol form of the 1,3-diketone nucleophile to the β-nitrostyrene.

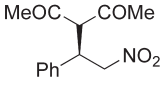
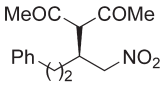
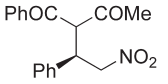
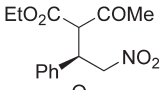
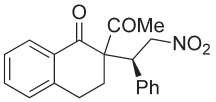
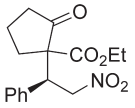
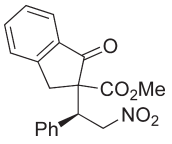


Cyclic β-ketoesters were also suitable partners for conjugate addition to β-nitrostyrene, affording nitro derivatives **8p** and **8q** in 95% and 92% isolated yields, respectively, at 0 °C and in short reaction times (3−6.5 h). The addition product **8p** (Table 3, entry 6), derived from ethyl 2-oxocyclopentanecarboxylate, was obtained in high diastereoselectivity (dr = 91/9) with the enantioselectivity being higher for the minor enantiomer (ee_{major} = 70%, ee_{minor} = 93%). Lower diastereoselectivity (dr = 62/38) was seen for compound **8q**, obtained with only 1 equiv of methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate, with a high ee (90%) for the major diastereomer (Table 3, entry 7). The level of selectivity for compound **8q** is similar to the best results

(24) For a recent review about organocatalytic formation of quaternary stereocenters, see: Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583–1614.

TABLE 3. Conjugate Addition of 1,3-Dicarbonyl Compounds to Nitroolefins Catalyzed by 7b



ent.	t (h)	T	product	no.	yield (%)[a]	dr (%)[b]	ee (%)[c]
1	7	rt		**8k**	96[d,e]	–	96
2	72	rt		**8l**	93	–	86
3	6	rt		**8m**	96	59/41	92[f,g]/92
4	6.5	0 °C		**8n**	96	53/47	90/88
5	24	rt		**8o**	42[e,h]	84/16	85[i]/nd
6	6.5	0 °C		**8p**	95	91/9	70/93
7	3	0 °C		**8q**	92[e]	62/38	90/78

[a]Isolated yield after flash chromatography. [b]Determined by ^{1}HNMR on the crude reaction mixture. [c]Determined by chiral HPLC analysis on the crude reaction mixture (see Supporting Information). [d]5 mol % of **7b**/TFA was used. [e]1 equiv of nucleophile was used. [f]Absolute configuration for the new stereocenter in the major diastereomer was determined to be *S* by X-ray analysis[23] (see Supporting Information). [g] > 99% ee after recrystallization (Et_2O). [h]Reaction conversion. [i]98% ee after recrystallization (Et_2O).

previously obtained with the most active guanidine-derived catalyst **5**[10] and cinchona alkaloid-derived organocatalysts.[5c]

Finally, under the optimized reaction conditions, the **7b**-catalyzed conjugate addition of other activated methylenes such as malononitrile and ethyl 2-cyanoacetate afforded the corresponding products in high yields (>99%) but with negligible diastereo- and enantioselectivity (dr ≈ 1/1, <3% ee).

Finally, mechanistic studies were carried out to gain insight into the H-bond activation pattern of the electrophile and the origin of the observed stereoselectivities. Both substrates, the nucleophile (malonate or diketone) and the electrophile (nitrostyrene), bear polar groups capable of H-bond formation. In this regard, it has been generally accepted that the mechanism of the Michael addition involves nitrostyrene activation through binding to the Brønsted acidic N−H

(25) For an extensive theoretical study on the reaction mechanism in the presence of a chiral thiourea, see: Hamza, A.; Schubert, G.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

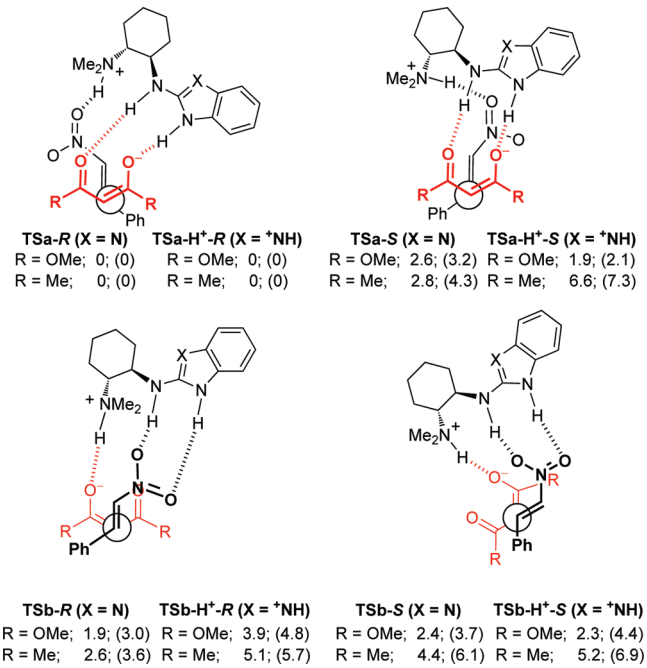


FIGURE 3. Representation of the computed transition states. Energies correspond to the B3LYP/6-311++G**// B3LYP/6-31G* level. Single-point values in a toluene model (IEF-PCM) are shown in brackets.

moieties of the catalyst. However, it has been recently reported[25,26] that an alternative H-bonding pattern between the nucleophile and a thiourea-catalyst leads to more stable complexes and transition states, and thus, lower activation barriers. In order to obtain insight about the two possible operational mechanisms for 2-aminobenzimidazole catalysts **7**, DFT calculations were performed at B3LYP/6-311++G**// B3LYP/6-31G* levels for the conjugate addition of 1,3-dicarbonyl compounds to *β*-nitrostyrene.

In our case, the deprotonation of the nucleophilic dicarbonyl compound renders a protonated catalyst that possesses three N−H units. Two competing mechanistic pathways were envisioned for the C−C bond-forming step,[27] differing on the N−H groups attached to the nucleophile and electrophile in the initial ternary complex and during the transition state. In **TSa**, the nitroolefin interacts with the protonated amine, while the two benzimidazole N−H units bind the deprotonated nucleophile (Figure 3). In **TSb**, the opposite binding pattern was computed. For each of them, the neutral and cationic forms of catalyst **7b**, and the two possible diastereoselective transition states providing the *R* or *S* enantiomers were considered. Dimethylmalonate and 2,4-pentanedione were chosen as nucleophiles.

The results obtained for neutral (X = N) and protonated catalyst (X = NH^+) **7b** are very similar (Figure 3).[28] The lowest energy transition states correspond to the addition of

(26) For a related H-bonding activation pattern in an aza-Henry reaction, see: Gomez-Bengoa, E; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966.

(27) The participation of the enolic form of the nucleophile was also considered, but the activation energies are exceedingly higher than those found for the deprotonated nucleophiles.

(28) Activation energies computed at B3LYP/6-311++G**//B3LYP/6-31G* level versus the initial nucleophile-catalyst-electrophile H-bond ternary complexes. For computational details, see Supporting Information.

malonate or diketone to the nitrolefin with formation of two H-bonds between the nucleophile and the amino-benzimidazole and one H-bond between the nitroolefin and the protonated amine (**TSa-R** and **TSa-H$^+$-R**). These transition states were taken as relative $E = 0$. **TSb**-type transition states, which involve the opposite H-bonding pattern, are in general 2−6 kcal/mol higher in energy. This result is fully concordant with the previously reported examples,[25,26] in that it favors the alternative **TSa** activation mechanism over the classical **TSb**.

Notably, only pathway **a** is able to account for the experimental enantioselectivity, since **a-R** transition states lie an average of 3.8 kcal/mol lower in energy than **a-S** ones, predicting the formation of the experimental major *R* enantiomer. Meanwhile, **b**-type transition states present more similar activation energies (average $E_{b\text{-}S} - E_{b\text{-}R}$ of 0.6 kcal/mol), showing that, in this case, the formation of *quasi*-racemic products would be wrongly predicted. This finding can be taken as a further proof that activation mode **a** is probably responsible for the mechanism and the observed enantioselectivity. The fact that the conjugate addition performed with other activated methylenes such as malononitrile and ethyl 2-cyanoacetate afforded the corresponding products but with negligible selectivity would also support the activation mode of catalyst **7b** for the studied reaction.

Conclusions

We have developed a recyclable chiral 2-aminobenzimidazole-derived organocatalyst **7b**, bearing a chiral (1*R*,2*R*)-1,2-diaminocyclohexane moiety, which in the presence of TFA is a very active catalyst for the highly enantioselective conjugate addition of different 1,3-dicarbonyl compounds to a broad range of conjugated nitroalkenes. Unlike the majority of the most active organocatalysts reported so far, organocatalyst **7b** is not specific to one type of nucleophile but efficiently promotes the conjugate addition of different activated methylenes such as malonate esters, ketoesteres, and 1,3-diketones to nitroalkenes. Computational studies support the bifunctional Brønsted acid−base organocatalytic character of **7b** with the activation of the nitroolefin better achieved by the protonated tertiary amine motif. Further studies are in progress to explore the scope of organocatalysts **7** as hydrogen-bond donor scaffolds in other catalytic asymmetric reactions.

Experimental Section

For general experimental details, see Supporting Information.

Experimental Procedure for the Synthesis of 7b. A mixture of 2-chloro-1*H*-benzo[*d*]imidazole (233 mg, 1.53 mmol, 1 equiv), (1*R*,2*R*)-cyclohexane-1,2-diamine (698 mg, 6.12 mmol, 4 equiv), and TEA (213 μL, 1.53 mmol, 1 equiv) was heated under argon atmosphere at 195−200 °C during 16 h. The reaction mixture was then allowed to reach 50 °C, and water (20 mL) was added. The reaction was quickly extracted with CH_2Cl_2 (3 × 20 mL) before the temperature of the reaction reached rt in order to avoid solubility problems. The organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give a crude mixture, which was purified by flash chromatography (EtOAc/MeOH) to give pure **7a** (229 mg, 65%) as a pale yellow solid: mp 235−240 °C (Et_2O); $[\alpha]^{20}_D$ −55.0 (*c* 1.0, MeOH); IR (KBr) 2929, 2855, 1700, 1644, 1606, 1580, 1468, 1270, 1116, 1030; δ_H (CD_3OD) 1.19−1.49 (m, 4H), 1.74−1.77 (m, 2H), 1.98−2.11 (m, 2H), 2.50−2.58 (m, 1H), 3.34−3.40 (m, 1H), 6.93−6.97 (m, 2H), 7.15−7.18 (m, 2H); δ_C 26.0, 26.2, 33.8, 34.9, 55.6, 60.4, 112.7, 121.3, 139.1, 156.9; *m*/*z* 230 [M$^+$, 10%], 160 (24), 134 (100), 133 (59), 97 (28); HRMS calcd for $C_{13}H_{18}N_4$ [M]$^+$ 230.1531, found 230.1532.

A mixture of **7a** (168 mg, 0.73 mmol, 1 equiv), 80% HCO_2H (3.5 mL), and a 36% aqueous solution of HCHO (127 μL, 1.61 mmol, 2.2 equiv) was stirred at 120 °C for 16 h. Then, the solvent was removed under reduced pressure. Saturated $NaHCO_3$ solution (15 mL) and 10% NaOH solution (until pH 8) were added in this order, and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give a crude mixture, which was purified by flash chromatography (EtOAc/MeOH) and then recrystallized in CH_2Cl_2 to afford pure **7b** (87 mg, 46%) as a white solid; mp 248−250 °C (CH_2Cl_2); $[\alpha]^{20}_D$ −55.3 (*c* 1.0, CH_2Cl_2); IR (KBr) 2923, 2856, 2818, 2775, 1700, 1633, 1576, 1499, 1461, 1375, 1265, 1064; δ_H ($CDCl_3$) 1.09−1.42 (m, 4H), 1.65−1.70 (m, 1H), 1.82−1.87 (m, 2H), 2.22 (s, 6H), 2.33 (td, *J* = 10.9, 3.2 Hz, 1H), 2.65−2.69 (m, 1H), 3.44 (td *J* = 10.4, 4.0 Hz, 1H), 5.46 (br s, 1H), 6.91−6.96 (m, 2H), 7.14−7.20 (m, 2H); δ_C (CD_3OD) 23.7, 25.8, 26.4, 34.8, 40.5, 54.7, 67.7, 112.6, 121.2, 139.1, 156.6; *m*/*z* 258 [M+, 1.5%], 133 (30), 125 (100), 84 (20); HRMS calcd for $C_{15}H_{22}N_4$ [M]$^+$ 258.1844, found 258.1844.

Typical Experimental Procedure for the Conjugate Addition of Diethyl Malonate to β-Nitrostyrene Catalyzed by 7b. Synthesis of 8a. To a stirred solution of **7b** (30 mg, 0.116 mmol, 10 mol %) and β-nitrostyrene (173 mg, 1.16 mmol) in toluene (2.3 mL) were added trifluororacetic acid (8.7 μL, 0.116 mmol, 10 mol %) and then diethyl malonate (357 μL, 2.32 mmol). Once the reaction was completed (TLC), the mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give crude **8a**, which was purified by flash chromatography (EtOAc/hexane) to give pure **8a** (348 mg, 97%, er = 96/4) as a colorless oil: R_f 0.27 (hexane/EtOAc 4/1); $[\alpha]^{20}_D$ −3.5 (*c* 1.0, CH_2Cl_2); absolute configuration for **8a** was assigned as (*R*) by comparison of the optical rotation with reported literature[29] value: $[\alpha]^{23}_D$ +7.3 (*c* 1.07, $CHCl_3$), [95% ee, (*S*)-enantiomer]; δ_H (400 MHz) 1.04, 1,26 (2t, *J* = 7.1, 6H), 3.82 (d, *J* = 9.4 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.18−4.28 (m, 3H), 4.86 (dd, *J* = 13.1, 9.0 Hz, 1H), 4.93 (dd, *J*=13.1, 5.2 Hz, 1H), 7.22−7.37 (m, 5H); δ_C (100 MHz) 13.7, 13.9, 42.9, 54.9, 61.8, 62.1, 77.6, 128.0, 128.3, 128.9, 136.2, 166.8, 167.4; *m*/*z* 263, [M$^+$ − NO_2, 25%], 189 (100), 171 (44), 161 (43), 115 (54), 104 (26), 103 (28), 102 (26), 91 (29), 76 (37).

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Supporting Information Available: Experimental procedures and spectroscopic data for all the products and X-ray structures for compounds **7b** and (*S*,*R*)-**8m** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592.