Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides Using a Chiral C$_2$-Symmetric Bis(2-aminobenzimidazole) as Recyclable Organocatalyst

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ABSTRACT
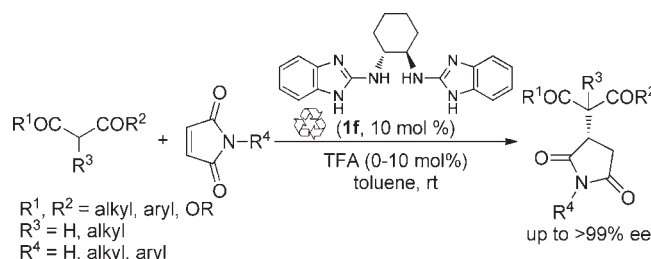
The recyclable chiral 2-aminobenzimidazole-derived organocatalyst 1f efficiently promotes the room temperature asymmetric conjugate addition of 1,3-diketones, β-ketoesters, and malonates to maleimide and N-substituted maleimides, affording the corresponding Michael adducts in excellent yields and enantioselectivities even at gram scale.

In recent years, organocatalytic enantioselective conjugate addition reactions have been subjected to intensive investigations,[1] enals, enones, and nitroolefins generally being used as Michael acceptors. In sharp contrast, maleimides have been used to a lesser extent as electrophiles,[2–4] despite the broad synthetic and biological utilities of chiral α-branched succinimides.[5] Furthermore, the nature of the substituent on the N atom of the maleimide has been shown to be a critical parameter for the stereochemical outcome of the process. In particular, the development of a general and highly enantioselective

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organocatalyst for the asymmetric conjugate addition to maleimide still remains a challenging goal.[6]

The utility of chiral 2-aminobenzimidazoles as organocatalysts has been recently disclosed by our group[7] and others[8] showing the benefits from 2-aminobenzimidazole's characteristic dual hydrogen-bonding catalysis.[9] Thus, **1b**, in which the distance between hydrogen atoms H_a and H_b is in between the reported distances for the thiourea[10] and squarimide-derived organocatalysts,[11] is a very active and general catalyst for the enantioselective addition of malonates, β-ketoesters, and 1,3-diketones to nitroalkenes in the presence of TFA as cocatalyst.[7] Herein, we describe the use of chiral 2-aminobenzimidazoles to promote the asymmetric conjugate addition of 1,3-dicarbonyl compounds to maleimides.

Initially, the challenging maleimide Michael acceptor (0.15 mmol) was chosen to study the conjugate addition of acetylacetone (0.3 mmol) in toluene at 30 °C using 10 mol % of chiral 2-aminobenzimidazole organocatalysts **1** (Figure 1) in the presence of TFA (10 mol %) as cocatalyst (Table 1).
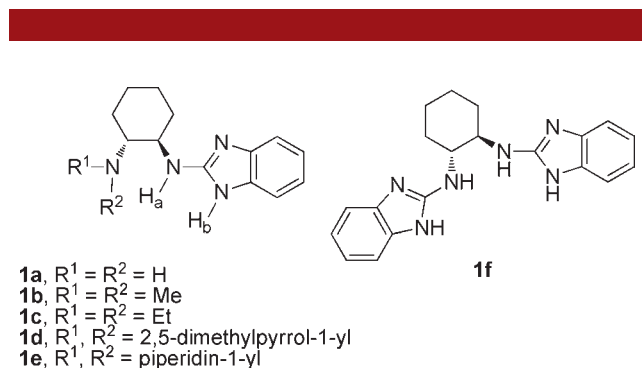

Figure 1. Hydrogen bond donor catalysts.

1a, R^1 = R^2 = H
1b, R^1 = R^2 = Me
1c, R^1 = R^2 = Et
1d, R^1, R^2 = 2,5-dimethylpyrrol-1-yl
1e, R^1, R^2 = piperidin-1-yl

1f

Table 1. Enantioselective Conjugate Addition of Acetylacetone to Maleimide Catalyzed by Catalysts **1**[a]

entry	**1** (mol %)	cocatalyst (mol %)	solvent	conversion (%)[b]	ee (%)[c]
1	**1a** (10)	TFA (10)	toluene	42	41
2	**1b** (10)	TFA (10)	toluene	>99	15
3	**1c** (10)	TFA (10)	toluene	90	13
4	**1d** (10)	TFA (10)	toluene	<5	
5	**1e** (10)	TFA (10)	toluene	89	11
6	**1f** (10)	TFA (10)	toluene	>99 (94)	97
7	**1f**·TFA (10)[d]		toluene	99	95
8	**1f** (10)	TFA (10)	benzene	>99	90
9	**1f** (10)	TFA (10)	xylene	>99	44
10	**1f** (10)	TFA (10)	MeOH	68	55
11	**1f** (10)	TFA (10)	H$_2$O	>99	0
12	**1f** (10)		toluene	>99	51
13	**1f** (10)	TFA (10)	toluene[e]	>99 (81)[f]	>99
14	**1f** (10)	TFA (10)	toluene[g]	45	90

[a] Reaction conditions: acetylacetone (0.3 mmol), maleimide (0.15 mmol), **1** (10 mol %, 0.015 mmol, 0.05 M), TFA (10 mol %, 0.015 mmol), solvent (0.3 mL), 30 °C, 24 h. [b] Determined by ^{1}HNMR on the crude reaction mixture. In brackets: isolated yield after flash chromatography. [c] Chiral HPLC [OD-H, hexane/i-PrOH: 85/15, 1 mL/min]. [d] Carried out with 10 mol % of preformed bench stable salt **1f**•TFA. [e] Reaction conditions: acetylacetone (10 mmol), maleimide (5 mmol), **1f** (10 mol %, 0.5 mmol, 0.05 M), TFA (10 mol %, 0.5 mmol), toluene (10 mL), 30 °C, 20 h. [f] Isolated yield of **2a** after filtration of the crude reaction mixture. [g] Reaction performed under MW irradiation conditions (40 W, 25 °C, 1 h).

Regarding catalyst study, C$_2$-symmetric catalyst **1f** proved to be the most promising and afforded the 1,4-adduct **2a** in an excellent isolated yield (94%) and enantioselectivity (97% ee) (Table 1, entries 1−6). A similar level of enantioselection (95% ee) was observed when the preformed bench-stable salt **1f**·TFA was used as catalyst (entry 7). Further optimization confirmed toluene for optimal selectivity (Table 1, entries 8−11). The use of hydrogen-bond accepting solvents such as H$_2$O or MeOH led to a drastic decrease in stereoselectivity, especially H$_2$O that afforded racemic **2a** (entry 11). Finally, a significant decrease in the enantioselectivity of the reaction (51% ee) was observed in the absence of TFA (Table 1, entry 12), a result that evidenced the higher ability of the protonated catalyst for hydrogen-bonding activation.

The synthetic utility of the catalytic approach was confirmed by a gram-scale experiment (5 mmol of maleimide), which gave optically pure (>99% ee) **2a** in 81% yield after filtration of the crude reaction mixture (Table 1, entry 13).[12] The reaction could be also performed at rt under microwave irradiation conditions, affording succinimide **2a** in a moderate conversion and 90% ee in only 1 h (entry 14).

Under the optimized reaction conditions (Table 1, entry 6), the generality of the conjugate addition reaction with respect to the nucleophile and the maleimide acceptor was investigated. The conjugate addition of acetylacetone to different N-alkyl- and N-aryl maleimides afforded compounds **2b**−**2e** in good yields and excellent enantioselectivities

(6) Only one example of organocatalyzed conjugate addition to maleimide has been reported using methyl 2-oxo-2,3-dihydro-1H-indene-1-carboxylate as nucleophile and quinine as catalyst at −20 °C with limited success in terms of diastereoselectivity and enantioselectivity (up to 81% ee). See ref 4a.

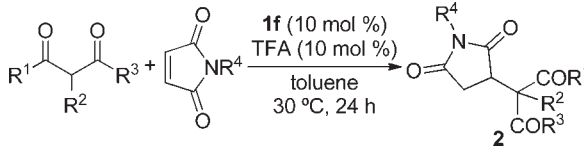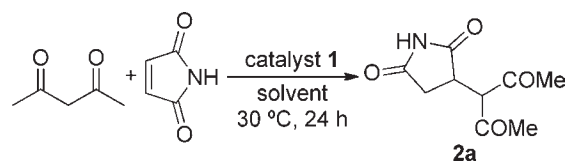(7) Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. J. Org. Chem. **2009**, 74, 6163–6168.

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(12) The enantioselectivity of **2a** was determined to be >99% ee on the crude reaction mixture, before filtration.

Table 2. Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides Catalyzed by **1f**

entry	product	no	yield (%)[a]	ee (%)[b]
1	R² = H, R⁴ = H	**2a**	94	97
2	R² = H, R⁴ = Me	**2b**	69	97[c]
3	R² = H, R⁴ = Bn	**2c**	69	95
4	R² = H, R⁴ = Ph	**2d**	100	97 (78)[d]
5	R² = H, R⁴ = 4-BrC₆H₄	**2e**	98[e]	96
6	R² = Me, R⁴ = Ph	**2f**	50	91[c]
7		**2g**	93[f]	95/98[g]
8		**2h**	98[h]	99/99[i]
9		**2i**	99[j]	98/98[k]
10	R⁴ = H	**2j**	23	81[c]
11	R⁴ = H	**2j**	74[d]	78[c]
12	R⁴ = Me	**2k**	7	99[l]
13	R⁴ = Me	**2k**	90[d]	99[l]

[a] Isolated yield after flash chromatography. [b] Chiral HPLC [OD-H, hexane/*i*-PrOH: 85/15, 1 mL/min]. [c] Chiral HPLC [AD-H, hexane/*i*-PrOH: 90/10, 1 mL/min]. [d] Reaction performed in the absence of TFA. [e] Isolated yield of pure compound after washing of the crude reaction mixture with *i*-PrOH. [f] dr: 93/7. [g] Chiral HPLC [IA, hexane/*i*-PrOH: 90/10, 1 mL/min]. [h] dr: 76/24. [i] Chiral HPLC [IA, hexane/*i*-PrOH: 95/5, 1 mL/min]. [j] dr: 87/13. [k] Chiral HPLC [AD-H, hexane/*i*-PrOH: 95/5, 1 mL/min]. [l] Chiral HPLC [AD-H, hexane/*i*-PrOH: 85/15, 1 mL/min].

(Table 2, entries 1−5). All of the studied substrates afforded levels of enantioselectivity similar to that of maleimide (95−97% ee).

The reaction was also applicable to α-substituted 3-methylpentane-2,4-dione, which afforded, after addition to *N*-phenylmaleimide, compound **2f** in 50% yield and 91% ee (Table 2, entry 6).

The addition of 2-acetylcyclopentanone to *N*-phenylmaleimide afforded compound **2g** in 93% yield as a 93:7 mixture of diastereomers, both of them obtained with very high enantioselectivity (entry 7). The protocol also proved to be effective for cyclic and acyclic β-ketoesters, the expected products being formed in high yields, good diastereoselectivity, and very high ee's (Table 2, entries 8 and 9). The synthesis of compounds **2g** and **2h** was especially interesting, since it evidenced the ability of the catalytic system to synthesize adjacent quaternary/tertiary stereogenic centers with excellent enantioselectivities.

When dimethyl malonate was reacted with maleimide, compound **2j** was obtained in an 81% ee and a very low 23% isolated yield (Table 2, entry 10). This was probably due to the lower acidity of the nucleophile compared to that of 1,3-diketones and β-ketoesters, thus requiring a catalyst with an stronger basic character. This was confirmed by performing the reaction in the absence of TFA, which afforded compound **2j** in a 78% ee and a higher 74% isolated yield (entry 11). With respect to yield, a similar tendency was observed in the reaction with *N*-methyl maleimide (Table 2, entries 12 and 13), and compound **2k** was quantitatively obtained in 99% ee in the absence of TFA (entry 13).

The absolute configuration of compound **2e**, generated by the **1f**-catalyzed conjugate addition of acetylacetone to *N*-(4-bromophenyl)maleimide, was assigned to be *S* by X-ray crystallography analysis (Figure 2).[13] The same crystal used for X-ray crystallography was analyzed by chiral HPLC, which confirmed the presence of the major *S* enantiomer in 97% ee. Since products **2** are generally solid substances, this also demonstrated that it is possible to obtain a single stereoisomer in essentially enantiomerically pure form after a single crystallization.[14]

After the preparation of compound **2e**, we also studied the recyclability of organocatalyst **1f** and were pleased to demonstrate that **1f**·TFA could be easily recovered (99%) from the crude reaction mixture just by washing with *i*-PrOH (see Supporting Information) (Scheme 1). The recovered **1f**·TFA was employed in a second run of the reaction, affording **2e** in 99% yield and 93% ee.
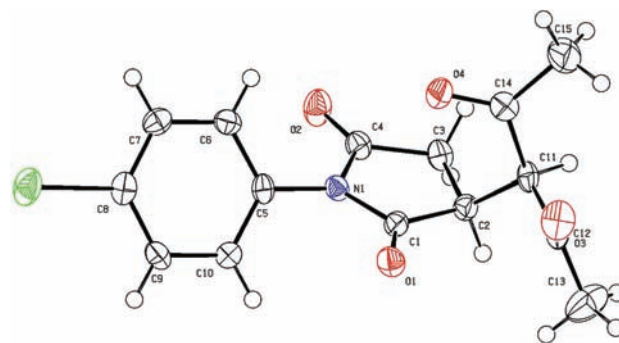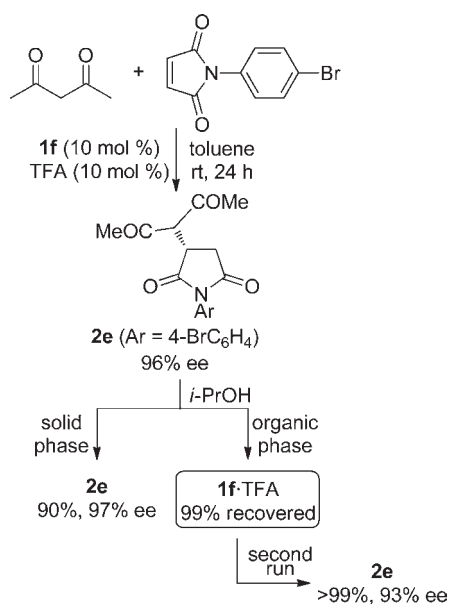

Figure 2. X-ray structure for compound **2e**.

In light of the performed experiments, we tentatively propose the transition state model shown in Figure 3 for the conjugate addition of acetylacetone to maleimide in the presence of TFA as cocatalyst. The neutral portion of the

(13) Compound **2e**, obtained in 98% yield and 96% ee, was crystallized from a CH_2Cl_2 solution to give fine colorless crystals of a single enantiomer with the configuration shown in Figure 2. Crystal data for **2e**: CCDC 846922.

(14) Compounds **2g** (89%, dr 100/0, ee 99%) and **2d** (87%, ee 99%) could be also obtained in a gram-scale experiment using, respectively, 5 mol % and 2 mol % of catalyst by just filtering off from the reaction media.

Scheme 1. Recyclability and Reuse of Benzimidazole-Derived Catalyst **1f**

Figure 3. Plausible transition state for the **1f**-catalyzed conjugate addition in the presence of 1equiv of TFA.

direct conjugate addition of different 1,3-dicarbonyl compounds to maleimide and *N*-substituted maleimides to give the corresponding Michael adducts with very high enantiocontrol. Further studies are in progress to study by computational methods the H-bond network between catalyst, nucleophile, and maleimide responsible for the observed reactivity/enantioselectivity and to explore the scope of organocatalyst **1f** in other catalytic asymmetric reactions.

catalyst deprotonates the nucleophile that performs a *si* face attack to the maleimide electrophile, which is activated by the protonated benzimidazole moiety via single hydrogen bonding interaction with the carbonyl group (Figure 3). In this structure, the activation of the maleimide is achieved by a single NH bond, and two other NH groups bind the nucleophile.[15]

In summary, we have designed a recyclable chiral 2-aminobenzimidazole catalyst **1f**, which catalyzes the

Supporting Information Available. Experimental procedures, spectroscopic data for all the products, and X-ray structure for compound **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Tighter H-bonding to the nucleophile than to the electrophile during the transition state have also been observed in related addition reactions; see: (a) Hamza, A.; Schubert, G.; Soós, T.; Papai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160. (b) Gómez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem.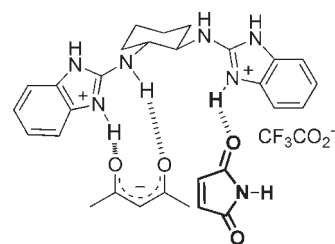 Soc.* **2008**, *130*, 7955–7966.