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Novel *Cinchona*-Aminobenzimidazole Bifunctional Organocatalysts

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Abstract: Efficient *Cinchona*-derived chiral 2-aminobenzimidazole catalysts were prepared by the coupling of 5,7-bis(trifluoromethyl)-2-chlorobenzimidazole with C(9*S*)-aminodihydroquinine or C(9*R*)-aminodihydroquinidine and successively applied to the Michael addition of dimethyl malonate to nitroolefins as very efficient chiral Lewis acid bifunctional organocatalysts (up to >99% *ee*).

Keywords: 2-aminobenzimidazoles; bifunctional catalysts; *Cinchona* alkaloids; enantioselectivity; organocatalysts

Since Jacobsen's group first disclosed thiourea-based chiral ligands for the metal-free Strecker reaction in 1998, thioureas have been extensively studied as Lewis acid organocatalysts given their functionality as hydrogen bond donors, and successfully applied to various useful organic reactions.[1] Especially, thioureas conjugated with chiral amines have been developed as chiral bifunctional catalysts capable of simultaneously activating both nucleophiles and electrophiles in a reaction by their Brønsted/Lewis acidic (thiourea moiety) and basic (chiral amine moiety) functionalities. As such, they have successfully been applied to various asymmetric syntheses (Figure 1).[2]

The cumulative results reveal that the electron-withdrawing moiety, for instance, trifluoromethyl group not only increases N–H acidity, but also contributes to the conformational rigidity of the catalyst by polarizing the adjacent H atoms, which in turn facilitates a hydrogen bonding interaction with the sulfur atom in the thioureas.[3] The *N*-3,5-bis(trifluoromethyl)phenyl group, introduced by Schreiner's group in 2002, has been popularly employed in the design of thiourea-based organocatalysts thus far.[4]

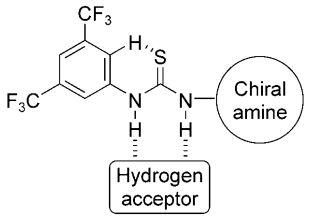

Figure 1. Thiourea-based bifunctional organocatalysts.

In 2005, Göbel's group introduced metal-free catalysts derived from 2-aminobenzimidazoles for the cleavage of RNA (Scheme 1).[5] The guanidine moiety in tris[2-(benzimidazol-2-ylamino)ethyl]amine (**1**) efficiently activated phosphates by hydrogen bonding, which could facilitate the cleavage of phosphate esters to cyclic phosphate **3** under neutral conditions (pH 7.0). Since the 2-aminobenzimidazole group is conformationally more rigid and bears a more acidic N–H compared to the corresponding thiourea group as in Figure 1, *N*-substituted-2-aminobenzimidazoles could serve as new Lewis acid organocatalysts.[6] In this paper, we report new *Cinchona* alkaloid-derived 2-aminobenzimidazole catalysts and their application in enantioselective Michael additions.[7]

First, the catalytic activity of a 2-aminobenzimidazole-containing compound in a Brønsted acid-catalyzed reaction was examined. Model compound **5** was prepared according to a known synthetic method[8]

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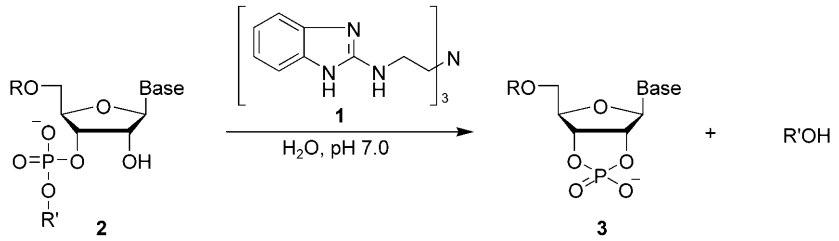
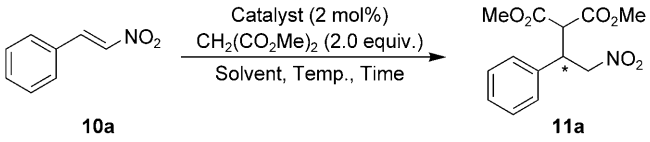


Scheme 1. Cleavage of RNA by tris[2-(benzimidazol-2-ylamino)ethyl]amine.

and its catalytic efficiency compared with that of the corresponding thiourea analogue **4** (Figure 2) in the Michael addition of dimethyl malonate to nitroolefin **10a** (Table 1). The reaction was performed with dimethyl malonate (2.0 equiv.), triethylamine (10 mol%), and catalysts (10 mol%) in toluene at 0 °C. As shown in Table 1, the 2-aminobenzimidazole catalyst **5** (entry 2, 85%) afforded adduct **11a** in higher chemical yield than the thiourea catalyst **4** (entry 1, 71%), which could prove the potentiality of a 2-aminobenzimidazole group as a Brønsted acid organocatalyst.

The successful model study with the simple achiral 2-aminobenzimidazole organocatalyst **5** prompted the preparation of chiral bifunctional organocatalysts by conjugation of a chiral amine to the 2-aminobenzimidazoles. There have been many chiral amines employed for the design and preparation of thiourea-based chiral bifunctional catalysts.[2] In 2005, Connon's group reported *Cinchona* alkaloid-derived thiourea catalysts as highly efficient chiral bifunctional organocatalysts[2i] and demonstrated that the C(9)-NH_2 epimer of *Cinchona* alkaloids is an excellent chiral amine resource. This approach was adopted herein by employing C(9*S*)-aminodihydroquinine and C(9*R*)-aminodihydroquinidine as chiral amines to prepare novel "*Cinchona*-aminobenzimidazole" chiral bifunctional organocatalysts. Three benzimidazole derivatives **6**–**8** (Figure 2) were prepared by coupling 2-chlorobenzimidazoles (**9**) with the corresponding amines under microwave irradiation at 170 °C (**6**, 42%; **7**, 47%; **8**, 40%) (Scheme 2).[8]

Table 1. Screening and optimization.[a]



Entry	Cat.	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1[d]	**4**	PhMe	r.t.	24	71	–
2[d]	**5**	PhMe	r.t.	24	85	–
3	**6**	PhMe	r.t.	24	98	83 (*S*)[e]
4	**7**	PhMe	r.t.	7	99	91 (*S*)
5	**8**	PhMe	r.t.	7	99	93 (*R*)
6	**7**	CH_2Cl_2	r.t.	7	99	91 (*S*)
7	**7**	THF	r.t.	24	99	91 (*S*)
8	**7**	PhMe	0	24	89	94 (*S*)
9	**7**	CH_2Cl_2	0	24	98	94 (*S*)
10	**7**	CH_2Cl_2	-20	40	98	95 (*S*)
11	**7**	CH_2Cl_2	-40	144	95	95 (*S*)

[a] Reaction was performed with 2 equivalents of of dimethyl malonate and 2 mol% of catalyst under the given conditions.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] 10 mol% of triethylamine and 10 mol% of catalyst were used.
[e] Absolute configurations were determined by comparison of the optical rotation of **11a** with reported values.[9]

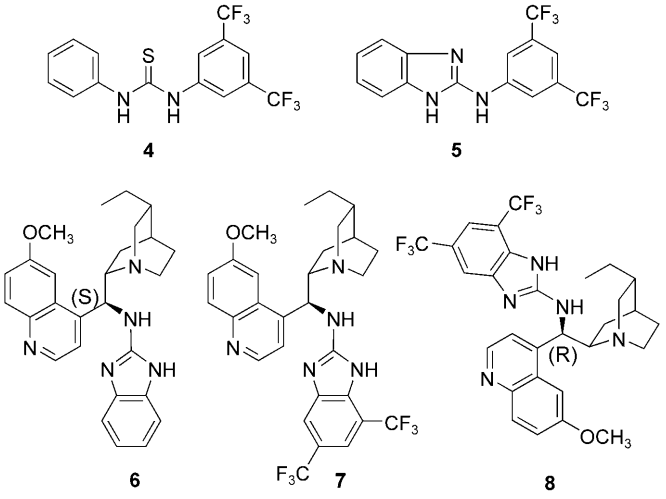


Figure 2. 2-Aminobenzimidazole-containing organocatalysts.

Catalytic efficiencies were evaluated by the Michael addition of dimethyl malonate to **10a** in toluene at room temperature. As shown in Table 1, both 5,7-bis-(trifluoromethyl)benzimidazole-2-aminodihydroquinine (**7**) (entry 4, 99%, 91% *ee*) and 5,7-bis(trifluoromethyl)benzimidazole-2-aminodihydroquinidine (**8**) (entry 5, 99%, 93% *ee*) afforded the adducts (*S*)-**11a** and (*R*)-**11a** in high enantioselectivity with high chemical yields, respectively. The lower catalytic efficiency of benzimidazole-2-aminodihydroquinine (**6**) (entry 3, 98%, 83% *ee*), relative to its trifluoromethyl analogue

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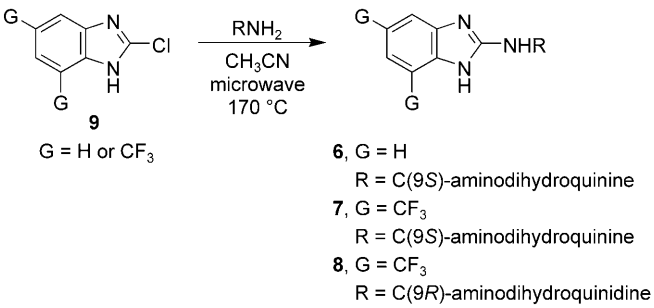


Scheme 2. Preparation of novel *Cinchona*-aminobenzimidazole bifunctional organocatalysts.

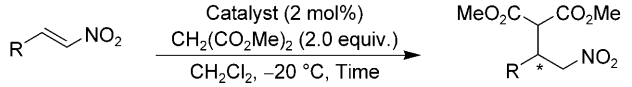
7, implies that the trifluoromethyl group plays an important role in enantioselectivity, which is in accord with previous results.[2i] Enantioselectivity seemed insensitive to the nature of the reaction solvent at room temperature (entries 4, 6, 7), but lower temperature provided increased enantioselectivities. Notably, the chemical yield was preserved with reaction temperature only in dichloromethane as solvent (entries 8, 9). The highest enantioselectivity was observed in dichloromethane at −20 °C, however, a lower reaction temperature (−40 °C) gave a reaction time three times longer with comparable enantioselectivity (entries 10, 11).

Further investigation into the scope and limitations was performed with various nitroolefins **10b–10l** under optimal reaction conditions (entry 10 in Table 1). Very high chemical yields (*S*-**11**, up to 99%; *R*-**11**, up to 99%) and enantioselectivities (*S*-**11**, up to >99% *ee*; *R*-**11**, up to >99% ee) were obtained (Table 2), which were slightly higher than those of thiourea-based catalysts.[2i]

A plausible transition state is proposed in Figure 3.[10] The nitro group of substrate **10a** forms hydrogen bonds with two N−H moieties from the catalyst **7** while the bridgehead nitrogen of the *Cinchona* moiety abstracts an α-proton from dimethyl malonate to form an ion-pair located downside to **10a**. As a consequence, the malonate anion can only approach the β-carbon of the nitroolefin from the downside during the 1,4-nucleophilic addition, affording the *S* isomer (**11a**). This is in agreement with the results.

In conclusion, chiral "*Cinchona*-aminobenzimidazole" catalysts **6–8** were designed, prepared and verified as efficient chiral Brønsted acid-base bifunctional organocatalysts in the Michael addition of dimethyl malonate to nitroolefins. The facile preparation and high enantioselective efficiency make these catalysts very efficient bifunctional organocatalysts. Further applications of these new catalysts are currently under investigation.

Table 2. Scope and limitations.[a]



Entry	R	Cat.	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**10a**)	**7**	40	98	95 (*S*)[d]
2		**8**	40	99	97 (*R*)
3	4-Me-C_6H_4 (**10b**)	**7**	40	98	96 (*S*)
4		**8**	40	98	97 (*R*)
5	4-CN-C_6H_4 (**10c**)	**7**	40	97	92 (*S*)
6		**8**	40	94	95 (*R*)
7	4-Cl-C_6H_4 (**10d**)	**7**	40	97	95 (*S*)
8		**8**	40	95	94 (*R*)
9	4-Br-C_6H_4 (**10e**)	**7**	40	91	97 (*S*)
10		**8**	40	86	95 (*R*)
11	3-Br-C_6H_4 (**10f**)	**7**	40	90	>99 (*S*)
12		**8**	40	85	>99 (*R*)
13	2-Br-C_6H_4 (**10g**)	**7**	40	93	98 (*S*)
14		**8**	40	95	92 (*R*)
15	4-MeO-C_6H_4 (**10h**)	**7**	60	94	>99 (*S*)
16		**8**	60	95	97 (*R*)
17	3-MeO-C_6H_4 (**10i**)	**7**	40	99	97 (*S*)
18		**8**	40	99	>99 (*R*)
19	2-MeO-C_6H_4 (**10j**)	**7**	60	96	92 (*S*)
20		**8**	60	97	94 (*R*)
21	2-Naphthyl (**10k**)	**7**	40	93	94 (*S*)
22		**8**	40	91	94 (*R*)
23[e]	*n*-Hexyl (**10l**)	**7**	96	70	94 (*R*)
24[e]		**8**	96	67	91 (*S*)

[a] Reaction was carried out with 2 equivalents of dimethyl malonate and 2 mol% of catalyst under the given conditions.
[b] Isolated yields.
[c] Enantiopurity was determined by HPLC analysis of the corresponding addition adducts (**11**) on chiral columns with hexanes/2-propanol as an eluent.
[d] Absolute configurations were determined by comparison of the optical rotation of **11**.[9]
[e] Reaction was performed with 5 mol% of catalyst.

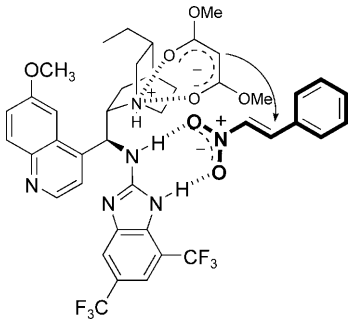


Figure 3. A plausible transition state between the catalyst **7**, an anion of dimethyl malonate, and (*E*)-(2-nitrovinyl)benzene **10a**.

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Experimental Section

Typical Procedure

To a cooled solution (−20 °C) of (*E*)-(2-nitrovinyl)benzene (**10a**) (50.0 mg, 0.335 mmol) and catalyst **8** (3.87 mg, 6.7 μmol) in anhydrous CH_2Cl_2 (0.67 mL) was added dimethyl malonate (76.6 μL, 0.67 mmol). After stirring for 40 h at −20 °C under an argon atmosphere, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 7:1) to afford the Michael adduct (*R*)-**11a** as a white solid; yield: 93.0 mg (98%). The enantiomeric excess was determined by chiral HPLC analysis [Chiral Technologies Inc., Chiralcel AD-H column, hexanes:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm]: retention times: 16.4 min (major), 26.3 min (minor), 97% *ee*. The absolute configuration of (−)-**11a** was determined to be *R* by comparing the specific optical rotation with the literature value, $[\alpha]_D^{23}$: −6.02 (*c* 1.0, $CHCl_3$) 97% *ee*, {lit (*S*)-(+), $[\alpha]_D^{25}$: +5.9 (*c* 1.0, $CHCl_3$) 96% *ee*}.[9]

Acknowledgements

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