SHORT COMMUNICATION

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Design and Development of Bioinspired Guanine-Based Organic Catalyst for Asymmetric Catalysis

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Design, preparation, and studies of a family of new organic catalysts are presented. The design of the catalysts is inspired by the ability of DNA nucleobases to develop precise and explicit hydrogen bonds. We have shown that this phenomenon can be used to create a useful organic catalyst that demonstrates a recognition pattern similar to those of common organic substrates. A selected bifunctional catalyst based on a guanine structure has been shown to catalyze the conjugate addition of 1,3-dicarbonyl compounds to various nitroalkenes, providing the products in good yields and enantioselectivities.

Introduction

The use of small organic molecules to catalyze organic reactions (organocatalysis), with particular appeal to asymmetric catalysis, has gained much attention within the chemical community in recent years.[1] Although the area is relatively new, organocatalysis has become an attractive strategy for the catalytic preparation of chiral molecules complementary to valuable organometallic and enzyme-based approaches. The field can be classified according to generic modes of catalyst activation and induction,[2] whereas the activation of substrates by hydrogen-bond-donor organic molecules represents one of the major directions.[3] It has been demonstrated that, as in complex enzymatic systems, certain relatively simple organic scaffolds can efficiently activate the substrate and control stereoselectivity through well-defined hydrogen-bonding interactions. Undoubtedly, progress in the field relies on the discovery and design of both new modes of activation and new catalyst architectures. Development of new efficient and tunable organic catalysts is of conceptual and practical importance, as it might lead to the discovery of novel organic transformations and guide to a deeper understanding of mechanistic features of the studied activation mode. Here, we present the design and development of a new organic catalyst, inspired by the guanine nucleobase structure and its ability to develop explicit hydrogen bonds in biological systems. The capability of this robust and structurally simple catalyst to enantioselectively mediate the benchmark conjugate addition of 1,3-dicarbonyl compounds to nitroolefins is demonstrated.

Results and Discussion

Our approach to organic catalyst design was inspired by the phenomenon of specific molecular recognition of DNA bases. It is well recognized that guanine–cytosine (G–C) and adenine–thymine (A–T) exhibit relatively strong and selective pairing by formation of reciprocal hydrogen bonds (Figure 1a).[4] We assumed that if a nucleobase selectively recognizes its complementary counterpart by hydrogen bonding interactions, then it may also recognize certain organic molecules that possess a structural hydrogen-bonding motif similar to that of its complementary base. For example, precursors bearing ester or nitro functional groups are attractive candidates (Figure 1b). The notion that nucleobases such as guanine could recognize and activate electrophiles through a multiple-hydrogen-bonding mechanism finds solid support in the scientific literature: artificial receptors possessing electrophilic acceptor patterns (N–H units) similar to guanine and capable of selectively binding to carboxylic acids and carboxylates via multiple hydrogen bonds to their oxygen atoms (donor unit) have been reported.[5] In addition, the relatively strong and directional hydrogen bonds formed by guanine and its structurally closely related species in noncovalent assemblies represent an important facet of supramolecular chemistry.[6] It should be mentioned that structurally related, mainly bicyclic, *guanidines* have been shown to be efficient organocatalysts[7] (Figure 1c). It is suggested, however, that these molecules provide a single hydrogen bond (N–H) for electrophile binding, whereas the adjacent nitrogen atom serves as an internal base, thus making guanidine a bifunctional catalyst.[7a,8] Guanidinium salts have been shown to act as cata-

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lysts operating by presumably dual hydrogen-bond donation (Figure 1d).[9a] Such guanidinium ions are also suggested to be active catalysts formed by protonation of neutral guanidine during the course of the catalyzed reaction.[9b]

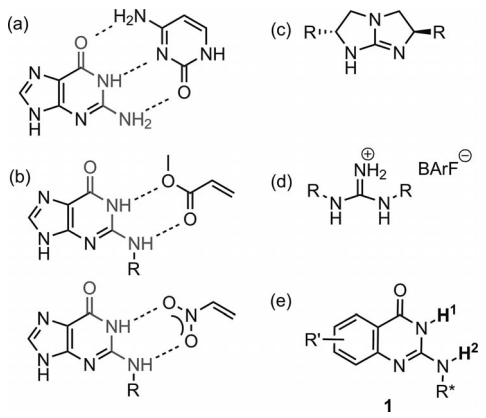
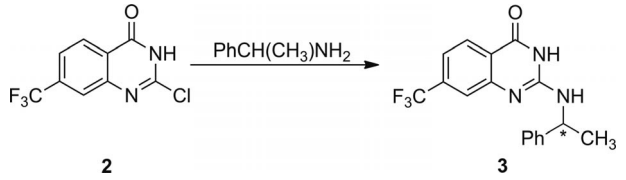


Figure 1. (a) The guanine–cytosine pair. (b) The hypothesized mode of substrate–catalyst binding. (c) A representative guanidine-based catalyst. (d) A representative guanidinium catalyst. (e) Catalyst **1**.

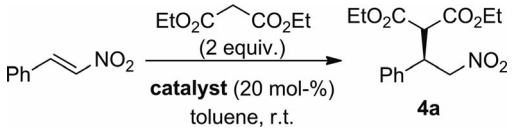
The generic structure of the proposed neutral guanine-based catalyst **1** is presented in Figure 1e. Several features make this scaffold attractive as a potential organocatalyst. Compound **1** can donate *two hydrogen bonds* simultaneously for use in electrophile binding and activation. This two-point binding, which might be important for a rigid transition state and hence improved stereoselectivity, has proven to be a highly successful strategy for electrophile activation, both in enzymes and in synthetic catalytic systems.[1,3] N–H protons, which are supposed to be responsible for the hydrogen bonding to the substrate, are considerably acidic.[10] Recently, it was demonstrated that the maximum possible rate acceleration is observed in some organocatalyst-mediated reactions when a catalyst with more acidic hydrogen bonding is utilized.[11] The ability to prepare various chiral catalysts by a single reaction of **2** (Scheme 1) with chiral amines offers tunability to the basic structure. The fused aromatic ring (installed instead of the imidazole unit of the original guanine) in catalyst **1** allows the introduction of various functionalities in its backbone and provides better solubility in common organic solvents.



Scheme 1. Synthesis of molecule **3**.

To test our ideas, molecule **3** was prepared from readily available chloride **2** (see Supporting Information) and phenylethylamine (Scheme 1). The latter was used in order to introduce both an N–H donor unit and asymmetry in the potential catalyst **3**. The trifluoromethyl group in **3** was installed for solubility reasons. We examined the catalytic properties of **3** in the conjugate addition of malonates to nitroalkenes. This carbon–carbon-bond-forming reaction leads to valuable building blocks in synthetic chemistry.[12] Recently, several hydrogen-donor organic molecules have proven to be efficient catalysts in this reaction,[13] and as such it might serve as a benchmark for the evaluation of the activity of new organocatalytic systems. When diethylmalonate was added to nitrostyrene in the presence of 20 mol-% of **3** and 1 equiv. of triethylamine in toluene at room temperature, the formation of addition product **4a** was observed in 60% yield after 24 hours (Table 1, entry 1). No product was observed when the reaction was performed without triethylamine, despite the addition of **3**. This control experiment indicates that molecule **3** has no suitable basic moiety for the activation of malonate. On the other hand, when the reaction was run under identical conditions in the presence of 1 equiv. of triethylamine and without **3**, product **4a** was formed in 17% yield only, which clearly indicates the rate enhancement with catalyst **3**. Disappointingly, analysis of the product exhibited no enantiomeric excess when enantiopure catalyst **3** was applied.

Table 1. Enantioselective Michael addition of diethylmalonate to nitrostyrene in the presence of **3** and **5a**–**n**.



Entry	Catalyst	Time (days)	Yield (%)[a]	*ee* (%)[b]
1	**3**	1	60	0
2	**5a**	1	94	84
3	**5b**	4	54	68
4	**5c**	3	78	90
5	**5d**	1	23	80
6	**5e**	1	61	77
7	**5f**	1	84	82
8	**5g**	1	15	92
9	**5h**	7	30	n.d.[c]
10	**5i**	6	10	n.d.[c]
11	**5j**	6	11	11
12	**5k**	6	33	45
13	**5l**	6	n.r.[c]	n.d.[c]
14	**5m**	1	74	73
15	**5n**	1	27	0

[a] Isolated yield. [b] Enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [c] Abbreviations: n.d. (not determined); n.r. (no reaction).

In view of these results, we decided to covalently connect a base, which is required for the reaction, to the hydrogen-donor guanine-like backbone in order to form a bifunctional catalyst (Figure 2). Bifunctional organocatalysts capable of simultaneous activation of nucleophile and electrophile have proven very efficient for both enantioselectivity and rate enhancement.[14] As such, a series of bifunctional potential catalysts was conveniently prepared by starting from the same precursor **2** and utilizing various chiral diamines instead of phenylethylamine (Scheme 1 and Figure 2, **5a**–**l**; see Supporting Information for synthetic details

and X-ray crystallographic confirmation of the molecular structure for selected catalysts). These include basic functions bearing primary, secondary, and cyclic/acyclic tertiary amines, as well as chiral units based on *trans*-cyclohexane (**5a**–**h**),[15] diphenylethane (**5i,j**), and indane (**5k,l**) scaffolds. Structurally related molecules **5m**,**n** were also prepared for comparative studies. The behavior of compounds **5a**–**n** was examined in the above-mentioned reaction of nitrostyrene and diethylmalonate, and the results are summarized in Table 1. As can be seen from this data, the bifunctional approach proved distinctively superior in terms of enantioselectivity. Gratifyingly, when catalyst **5a** was used, product **4a** was isolated in 94% yield and 84% *ee* (enantiomeric excess) after 24 hours (entry 2). Modifications of the amine base gave usually lower yield and *ee* (entries 3–6), except for catalyst **5c**, for which a somewhat higher enantiomeric excess (90%) of product **4a** was obtained (entry 4). However, the reaction was slower and only 78% yield was obtained after three days. Other modifications involving substituents on the aromatic ring (entries 7–9) or in the chiral scaffold (entries 10–13) did not provide better reaction outcomes. Thus, installation of an additional trifluoromethyl group on the catalyst backbone did not improve the results (entry 7); however, a removal of the parent CF_3 greatly reduces the rate of the process (entry 9). The rate was also significantly reduced when the *trans*-cyclohexane diamine unit was replaced by a conformationally unrestricted, acyclic diphenylethylene diamine (allowing a stable *anti* conformation; entry 10). Interestingly, isocytosine-based catalyst **5m**, possessing no additional aromatic ring, brings notable but not dramatic changes (entry 14); however, installing an amide instead of the key guanine unit (**5n**; entry 15) significantly diminishes both yield and *ee*. The latter experiment indicated that the two-point hydrogen-binding fragment is crucial for activation of the substrate in order to provide good yield and *ee*.

Compound **5a** was selected as an optimal catalyst with respect to the reaction outcome, and it was used to study the reaction parameters (Table 2). We found that toluene proved to be superior for our model reaction over all other tested solvents. Additives such as water or molecular sieves did not improve the results (entries 6 and 9). The enantioselectivity can be slightly improved if the reaction is carried out at low temperatures, yet at the expense of a substantially longer reaction time (entry 8). Therefore, we decided to examine the scope of the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes by applying 20 mol-% of catalyst **5a** in toluene at room temperature.

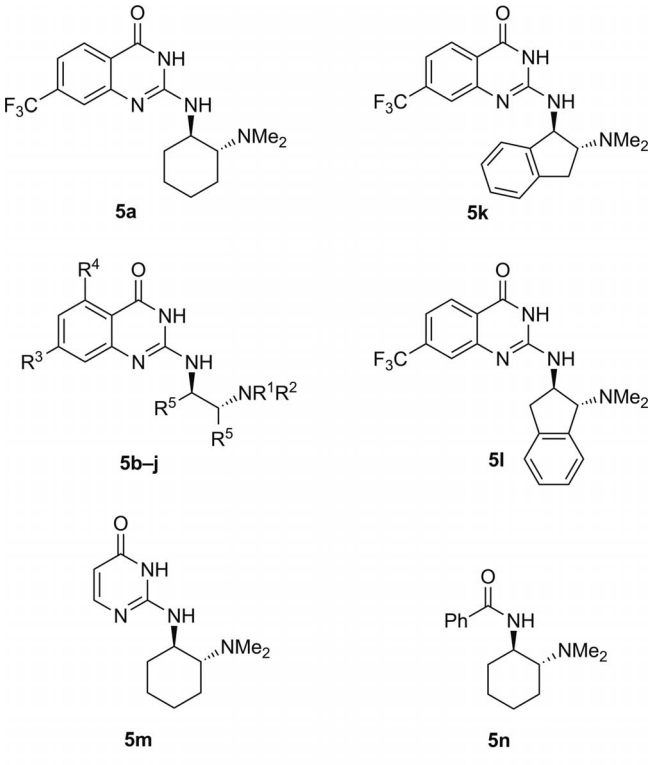
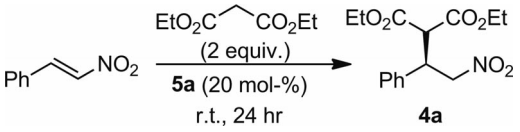


Figure 2. Structures of bifunctional catalysts.

Table 2. Enantioselective Michael addition of diethylmalonate to nitrostyrene in the presence of **5a** under various conditions.



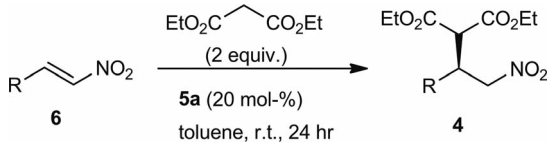
Entry	Solvent	Yield (%)[a]	*ee* (%)[b]
1	toluene	94	84
2	hexane	75	80
3	CH_2Cl_2	62	78
4	THF	n.d.	49
5[c]	THF/H_2O	22	45
6[d]	toluene	32	48
7[e]	toluene	60	86
8[f]	toluene	94	87
9[c]	toluene/H_2O	45	84

[a] Isolated yield. [b] The enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [c] The reaction was conducted with 20 mol-% of H_2O. [d] The reaction was conducted with 4 Å molecular sieves. [e] The reaction was conducted with 10 mol-% of **5a**. [f] The reaction was carried out at 0 °C for 4 d.

We were pleased to find that various nitroalkenes are suitable substrates for this catalytic reaction: substituted aromatic, heterocyclic, and aliphatic nitroalkenes afforded moderate to excellent yields and very good *ee* values (Table 3).

Moreover, a number of 1,3-dicarbonyl compounds, including malonates and diketones, provided the products in high yields and very good levels of enantioselectivity upon addition to nitrostyrene (Table 4). Quite a rare example of

Table 3. Enantioselective Michael addition of diethylmalonate to various nitroalkenes **6a**–**h** in the presence of **5a**.

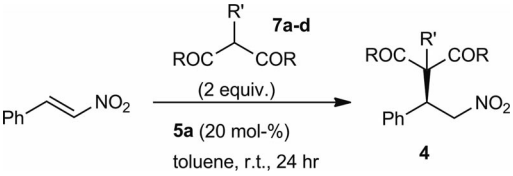


Entry	6	R	4	Yield (%)[a]	*ee* (%) [b]
1	**6a**	C_6H_5	**4a**	94	84
2	**6b**	4-ClC_6H_4	**4b**	41	88
3	**6c**	4-$OMeC_6H_4$	**4c**	82	84
4[c]	**6d**	2,6-$(OMe)_2C_6H_3$	**4d**	57	88
5	**6e**	2-BrC_6H_4	**4e**	76	89
6	**6f**	2-thienyl	**4f**	60	88
7	**6g**	2-naphthyl	**4g**	82	80
8[d]	**6h**	pentyl	**4h**	88	88

[a] Isolated yield. [b] The enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [c] The reaction was carried out for 3 d. [d] The reaction was carried out for 4 d.

diethylbromomalonate, compound **7d** (entry 4), offers an additional facet in a possible further functionalization of product **4k**.[13e]

Table 4. Enantioselective Michael addition of various 1,3-dicarbonyl compounds **7a**–**d** to nitrostyrene in the presence of **5a**.



Entry	7	R	R′	4	Yield (%)[a]	*ee* (%)[b]
1	**7a**	OEt	H	**4a**	94	84
2	**7b**	OMe	H	**4i**	90	86
3	**7c**	Me	H	**4j**	98	83
4	**7d**	OEt	Br	**4k**	62	85

[a] Isolated yield. [b] The enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column.

Interestingly, the related guanidinium species **8**, prepared by protonation of compound **3** with triflic or tetrafluoroboric acids (Figure 3), exhibited low catalytic activity and

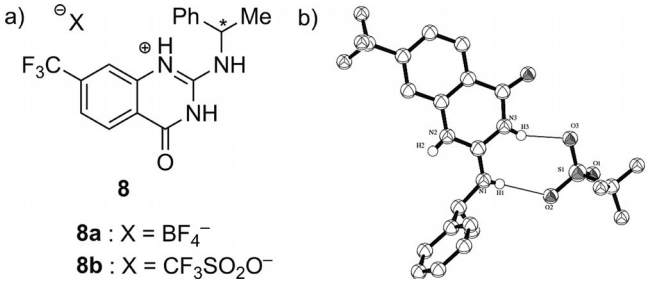


Figure 3. (a) Structure of **8**. (b) X-ray structure of **8b** (ORTEP drawing). Hydrogen bonds between N–H units and triflate groups are indicated.

no enantioselectivity in the model reaction of nitrostyrene and diethylmalonate.

A molecular structure of **8b** obtained by X-ray analysis of its single crystals demonstrates two well-defined hydrogen bonds between N–H groups and oxygen atoms of the triflate counterion.[16] This observation might indicate a general ability of our catalysts to make a two-point binding via N–H groups as hydrogen-bond donors to the substrates possessing hydrogen-bond acceptors.

Conclusions

In conclusion, we have designed, prepared, and studied a series of new organic catalysts inspired by the phenomenon of specific molecular recognition of DNA bases. A selected bifunctional catalyst based on a guanine structure has been shown to catalyze the conjugate addition of 1,3-dicarbonyl compounds to various nitroalkenes, providing the products in good yields and enantioselectivities. Further studies on the catalyst structure and its application to challenging asymmetric transformations as well as studies concerning the mechanism of substrate activation are underway in our laboratories.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of all new compounds, X-ray structures of **5c**, **8a**, and **8b**, copies of HPLC chromatograms and NMR spectra.

Acknowledgments

We are thankful to Prof. Amir H. Hoveyda for valuable discussions. Financial support from the United States–Israel Binational Science Foundation (BSF-grant no. 2008391) is acknowledged.

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[16] CCDC-855444 (for **8b**), -855445 (for **8a**), and -855446 (for **5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See ORTEP drawings in the Supporting Information.

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